

Medicinal Plant Monographs



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Pictures on the front cover: *Silybum marianum* (L.) Gaertn., Asteraceae (milk thistle), *Borago officinalis* L., Boraginaceae (borage), *Malva sylvestris* L., Malvaceae (common mallow), *Matricaria recutita* L., Asteraceae (German chamomile). Photos by C.L. Quave.

TABLE OF CONTENTS

Preface	1
MEDICINAL PLANTS	
Allium sativum L., Amaryllidaceae	6
Aloe vera (L.) Burm. F., Xanthorrhoeaceae	20
Ananas comosus (L.) Merr., Bromeliaceae	30
Arctostaphylos uva-ursi (L.) Spreng., Ericaceae	42
Armoracia rusticana G. Gaertn., B. Mey. & Scherb., Brassicaceae	48
Artemisia absinthium L., Asteraceae	58
Atropa belladonna L., Solanaceae	66
Avena sativa L., Poaceae	75
Banisteriopsis caapi (Spruce ex Griseb.) C.V. Morton, Malpighiaceae	85
Camellia sinensis (L.) Kuntze, Theaceae	97
Capsicum annuum L., Solanaceae	111
Catharanthus roseus (L.) G. Don, Apocynaceae	121
Cimicifuga racemosa (L.) Nutt., Ranunculaceae	128
Cinnamomum verum J. Presl, Lauraceae	135
Coffea arabica L., Rubiaceae	146
Cola nitida (Vent.) Schoot & Endl, Malvaceae	156
Commiphora molmol (Engl.) Engl. ex Tschirch, Burseraceae	166
Croton lechleri Müll.-Arg., Euphorbiaceae	174
Curcuma longa L., Zingiberaceae	183
Digitalis purpurea L., Plantaginaceae	196
Echinacea purpurea (L.) Moench, Asteraceae	208
Ephedra sinica Stapf., Ephedraceae	218
Ficus insipida Willd., Moraceae	224
Ginkgo biloba L., Ginkgoaceae	231
Glycyrrhiza glabra L., Fabaceae	242
Hypericum perforatum L., Hypericaceae	252
Ilex paraguariensis A. St.-Hil., Aquifoliaceae	259
Lavandula angustifolia Mill., Lamiaceae	270
Linum usitatissimum L., Linaceae	279
Melaleuca alternifolia Cheel, Myrtaceae	289
Momordica charantia L., Cucurbitaceae	297
Panax ginseng C.A. Mey., Araliaceae	310
Papaver somniferum L., Papaveraceae	322
Passiflora incarnata L., Passifloraceae	330
Persea americana Mill., Lauraceae	341
Rosmarinus officinalis L., Lamiaceae	353
Sambucus nigra L., Adoxaceae	362
Silybum marianum (L.) Gaertn., Asteraceae	374
Solidago virgaurea L., Asteraceae	383
Taxus brevifolia Nutt., Taxaceae	390
Theobroma cacao L., Malvaceae	400
Thymus vulgaris L., Lamiaceae	409
Urtica dioica L., Urticaceae	421
Vaccinium macrocarpon Aiton, Ericaceae	426
Vaccinium myrtillus L., Ericaceae	436
Zingiber officinale Roscoe, Zingiberaceae	445
INDICES	
Index of Contributors	457
Index of Common Plant Names	458

PREFACE

Cassandra L. Quave, Ph.D.

Throughout history, mankind has utilized plants as a primary source of food, medicine, and shelter. This tradition continues today. In 2001, the World Health Organization estimated that approximately 80% of the world's population was directly dependent on plant-based medicines (Cox and Heinrich 2001). In contrast with most other organisms, plants have the ability to undergo a process of secondary metabolism, in which unique compounds are produced for the purposes of defense, pollinator attraction, and coloration, among others. Examples of these important secondary metabolites usually fall within the following natural product classes: alkaloids, non-protein amino acids, cyanogenic glycosides, coumarins, glucosinolates, monoterpenes, sesquiterpene lactones, diterpenoids, saponins, limonoids, carotenoids, phenols, flavonoids, and quinones (Dewick 2001).

These same compounds, which serve important roles in plant survival, are also useful in mammalian systems. For example, upon entry into the human body and an environment of physiological pH, the very structure of alkaloid compounds takes on a quaternary form, through which the compound can interact with human receptors – inhibiting or stimulating activity of the targeted site. This may have a medicinal, or even a toxic, effect on the body. For instance, the alkaloid strychnine acts as a glycine mimic, binding to glycine receptor sites in the spinal cord, and exhibiting a toxic effect. On the other hand, the alkaloid atropine can exert a medicinal anticholinergic effect by

competing with acetylcholine for the muscarinic receptor site in the parasympathetic nervous system (Dewick 2001).

Some notable plant-derived drugs still in use today include vincristine (*Catharanthus roseus* (L.) G. Don; Apocyanaceae), physostigmine (*Physostigma venenosum* Balf. f.; Fabaceae), pilocarpine (*Pilocarpus jaborandi* Holmes; Rutaceae), reserpine (*Rauvolfia serpentina* (L.) Benth. ex Kurz; Apocyanaceae), and digitalis (*Digitalis purpurea* L.; Scrophulariaceae) (Cox and Balick 1994; Cox and Heinrich 2001; Dewick 2001; Solomon 2004). Today, the search for new drugs coming from vascular plants continues with particular focus on plants exhibiting antimicrobial, anti-cancer, and antiviral effects. The need for new, structurally unique antimicrobials is of utmost importance in this era of widespread microbial resistance to existing therapies (Levy 2002; Smith and Coast 2002; Walsh 2003).

Many plants that are used for their antimicrobial activity contain polyphenolic compounds, which commonly act as antiviral agents, or essential oils, which often act as antiseptics (Heinrich et al. 2004). One of the best known antimicrobial plants is garlic, *Allium sativum* L., Amaryllidaceae. Garlic contains a wealth of sulphur compounds, glycosides, and monoterpenoids. These sulphur compounds have shown remarkable *in vitro* antibacterial, antiviral, and antifungal activity (Blumenthal, Goldberg, and Brinckmann 2000; Srinivasan et al. 2001; Zenner et al. 2003).

Another well-known plant with broad-spectrum antimicrobial activity is the tea tree, *Melaleuca alternifolia* Cheel., Myrtaceae. The monoterpenoids present in tea tree oil have demonstrated activity against a broad spectrum of microorganisms, including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Leishmania major*, and *Trypanosoma brucei* (Heinrich et al. 2004).

Secondary metabolites, or natural products, manufactured by plants as a means of defense against herbivory or microbial infection, have demonstrated potent activity against human pathogens. Yet, less than 0.5 % of the more than 265,000 flowering species that exist on earth have been exhaustively studied for their chemical composition and medicinal potential (Cox and Balick 1994). It is certain that a wealth of novel structures wait to be studied, and likely that some of these will, in fact, exhibit potential for medicinal applications.

EXPLANATION OF MONOGRAPH SECTIONS

In this e-book, I have compiled the medicinal plant monographs written by my students as their final paper for “Botanical Medicine and Health” course taught at Emory University and “Medical Botany” web-based course taught at the University of Arkansas at Little Rock. At the beginning of the semester, students were asked to select a medicinal plant and research its uses in CAM and traditional medicine, the mechanisms of action of its constituents, and assess the data reported in laboratory and clinical trials. Using this information, they each wrote a plant monograph which focuses on the medicinal

applications of their selected species. Each monograph has been formatted following these specifications:

Introduction

This section gives an introduction to the plant by listing its scientific name and family, common names, and a brief overview of how it is used, and what its main constituents are.

Description

This section contains a general description of the morphological characteristics of the plant. This includes its habit (tree, shrub, herb, etc.), its habitat (marshy areas, arid plains, etc.), and its flower and fruit characteristics (color, smell, shape).

Traditional Uses

This section pertains to the ethnomedical and other ethnobotanical applications of the species, including descriptions of its use as a food, decorative, construction, clothing, and etc.

Chemistry and Pharmacology

A description of the principle chemical constituents of the plant are given here.

Biological Activity

In this section, *in vitro* and *in vivo* laboratory studies conducted on extracts or fractions or purified compounds from the plant is described. Mechanisms of action are also discussed and issues with drug resistance are addressed.

Clinical Studies

When applicable, results from clinical studies are discussed in this section.

Contraindications

Drug contraindications (interactions with other CAM or allopathic medicines), side effects, toxicity and toxicology of the plant products are discussed here.

Current Use in Allopathic and CAM Therapies

In this section, the applications of the plant products in both CAM and allopathic medicine are discussed. Products on the market, including dietary supplements, OTC, and prescription medications are discussed.

Discussion

In this section, a summary of the utility of this medicinal species is given and the importance of its role in human health is discussed.

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Allium sativum L., Amaryllidaceae

Shannan Healy

Introduction

Allium sativum L., commonly known as garlic, is a member of the Amaryllidaceae family. More commonly known for its culinary role, *A. sativum* has many properties that are useful in medicine. Originally cultivated in central Asia, garlic is now cultivated throughout the world, but heavily in the Mediterranean and Asia (Brewster 2008). *A. sativum* is largely composed of sulfur compounds; the enzyme alliinase reacts with alliin upon crushing or chewing of the clove which results in the compound allinin (Block 2010). Allicin is a diallyl sulfinate that is recognized as the constituent responsible for many of garlic's medicinal properties, such as its preventative role in cardiovascular disease, antioxidant activity, and activity as a broad-spectrum antimicrobial. As people are more commonly seeking natural health care products, there has been extensive research done on *A. sativum* for its roles as a broad-spectrum antimicrobial, antioxidant, and for its overall effects on the cardiovascular system (Block 2010). Unfortunately, many trials report conflicting results and are not reliable because they do not specify the form of garlic used, which has tremendous effects on the release of active compounds.

Botanical Description

Other members of the onion genus, *Allium*, include *A. cepa* (onion), *A. schoenoprasum* (chives), *A. ascalonicum* (shallots), and *A. porrum* (leeks). *Allium sativum* is further divided into two subspecies, *A. sativum* var. *sativum*, also known as



Figure 1. A bulb of *Allium sativum* with some cloves removed to reveal membranous skin. (Image source: http://www.123rf.com/photo_3369595_a-white-clove-of-garlic-broken-open-and-isolated-on-a-white-back-ground.html)

softneck garlic, and *A. sativum* var. *ophioscorodon*, also known as hardneck garlic. Both varieties are composed of an underground bulb made up of cloves, which are prophylls enclosed by dry membranous skins and held together by a basal plate. A bulb with some cloves removed to reveal these skins can be seen in **Figure 1**. Flat leaves that point at the ends reach about two feet in length and arise from underground; they do not originate from the stalk (Brewster 2008).

The variations differ in that hardneck garlic's bulb is

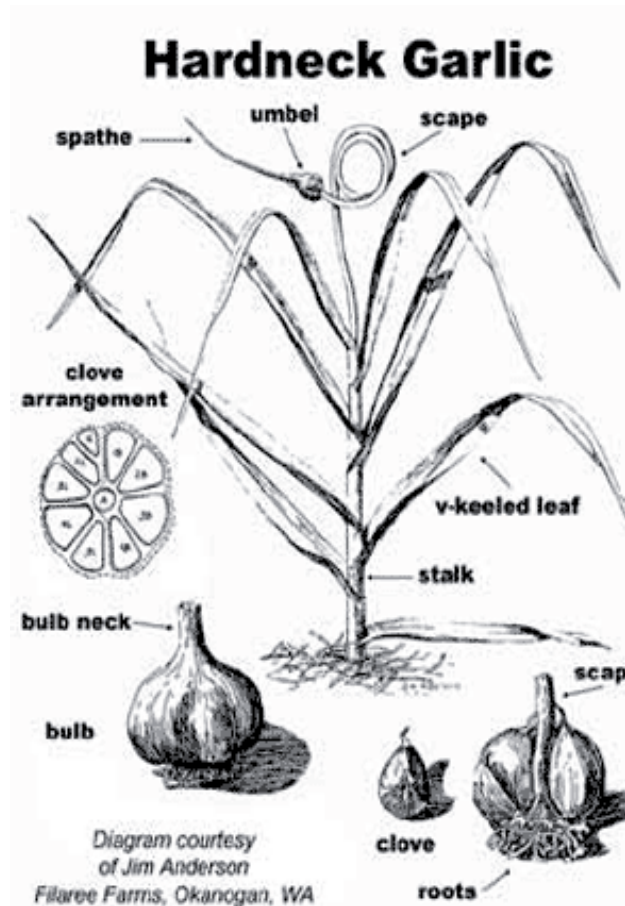


Figure 2. Diagram of *Allium sativum* spp. *ophioscorodon*. (Image source: http://saknoffel.co.za/garlic_cultivation.html)

composed of six to eleven cloves, circled around a centralized woody stalk (Block 2010). This variety of garlic has a scape that curls at the top, but it is generally removed after it curls one to three times. This is because if it continues to grow, less energy can be utilized towards the bulb (Block 2010). Eventually, the scape would give rise to bulbils, containing miniature cloves. The bulbils are occasionally accompanied by

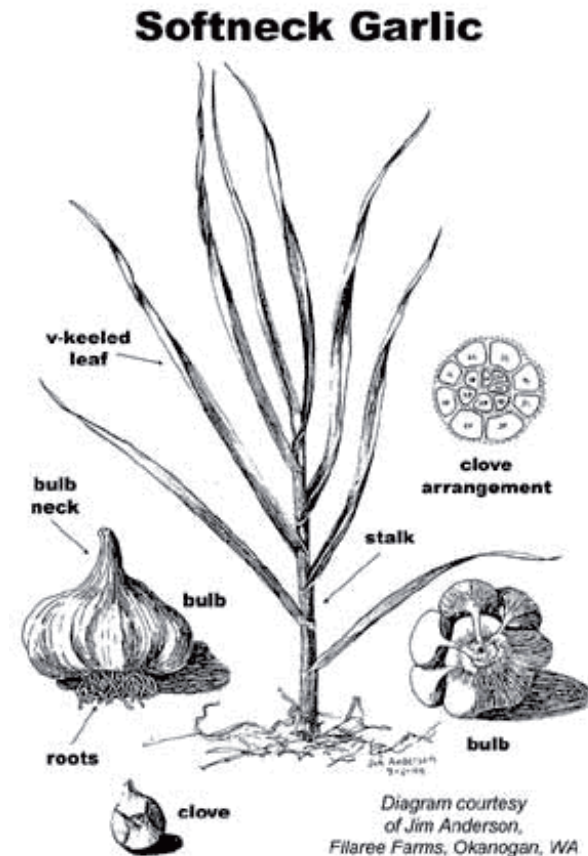


Figure 3. Diagram of *Allium sativum* spp. *sativum*. (Image source: http://saknoffel.co.za/garlic_cultivation.html)

white or light purple flowers, although these are sterile. Softneck garlic does not have a flowering top and contains up to twenty-four cloves per bulb (Block 2010). The stem is central and soft, hence the name, and the cloves are layered with larger ones on the outside (Block 2010). **Figures 2 and 3** illustrate the differences between the two subspecies and **Figure 4** shows an example of a flowering bulbil. While **A.**



Figure 4. Diagram of flowering bulbils. (Image source: <http://www.wegrowgarlic.com/7422.html>)

sativum sativum is the more common variation, many studies involving garlic do not specify which subspecies is used, but chemical and biological action are assumed to be similar.

A. sativum is sterile and hence is grown asexually from cloves, not requiring a pollinator (Block 2010). It grows best in mild climates, though hardneck varieties are better adapted to colder environments. *A. sativum* is a perennial species, as are most members of the genus. Garlic is composed of very strong organosulfur compounds that serve as secondary metabolites as described in the section entitled chemistry and pharmacology. These compounds are responsible for the very pungent smell and taste of raw garlic and act as defenses against predators (Block 2010).

Traditional Uses

Traditional Medicinal Uses

Medicinal uses of garlic are very prevalent in history, not only for the treatment of disease but also for the maintenance of health. Records date back to ~1550 BC: 22 of 875 therapeutic formulas in Ebers Papyrus contain garlic, including heart disease and abnormal growths, implying cancer (Block 2010). In Dioscorides' *De Materia Medica*, *Allium sativum* is mentioned 23 times and is listed as a remedy for driving out intestinal parasites, diarrhea and other gastrointestinal disorders and animal bites (Block 2010). Dioscorides also recommended garlic because it "cleans the arteries," and currently it is being investigated to help treat atherosclerosis, known as hardening of the arteries (Rivlin 2001). Hippocrates advised its use as a purgative agent and for pulmonary complaints (Moyers 1996).

It is suspected that historically, garlic was given mostly to laboring classes, as upper classes avoided the pungent smell. When King Tutankhamen's tomb was excavated (dating to ~1500 BC), garlic cloves were identified, although it was not evident what their use was (Kahn 1996). *A. sativum* was consumed by Egyptian slaves to increase their strength when building the pyramids (Kahn 1996). For similar reasons, it was given to Roman soldiers. In Ayurvedic medicine, garlic was used to warm the body, likely a result of improved blood circulation (Moyers 1996). In Traditional Chinese Medicine, garlic was used as an ailment for respiration and digestion discomfort, diarrhea, and worm infestation (Moyers 1996). In World War II, it was deemed Russian penicillin because it was used to fight infection and gangrene (Petrovska and Cekovska 2010). The Cherokees traditionally used it as a diuretic, expectorant, and for scurvy due to its high vitamin C content (Hamel and Chiltoskey 1975). It was also used to fight

Nutrient	Per Clove (3g)
Water	1.76g
Energy	4 kcal
Protein	0.19 g
Total lipid (fat)	0.02 g
Carbohydrate	0.99 g
Fiber, total dietary	0.1 g
Sugars, total	0.03 g
Calcium	5 mg
Iron	0.05 mg
Magnesium	1 mg
Phosphorus	5 mg
Potassium	12 mg
Sodium	1 mg
Zinc	0.03 mg
Vitamin C, total ascorbic acid	0.9 mg
Thiamin	0.006 mg
Riboflavin	0.003 mg
Niacin	0.021 mg
Vitamin B-6	0.037 mg
Vitamin K (phylloquinone)	0.1 mg

Table 1. Nutrient data in raw *Allium sativum* (USDA 2012)

infection during the Black Plague (Woodward 1996). Other traditional uses include infection, colds, diabetes and heart disease (Tsai et al. 2011). It is evident that ancient uses of *A. sativum* inspired many uses today in complementary and alternative medicine.

Traditional Culinary Uses

Allium sativum is a very nutritious food, but unfortunately this is not reflected since it is generally eaten in such small quantities. Nutrient information per clove of garlic can be seen

in **Table 1**. It is believed to have been a regular part of the diet in China since 2000 BC (Kahn 1996). Due to the overpowering taste, garlic does not have an extensive history of culinary use until the 20th century (Block 2010). In fact, monks, widows and children were forbidden from eating it in the Far East due to its aphrodisiac affects and the resulting odor was considered unsuitable for upper classes (Hospodar 2004). Perhaps the rise in consumption is correlated with cooking garlic, as heat mellows the flavor when it destroys the enzyme allinase so it cannot react with allin to form allinin, the sulfur compound responsible for the strong taste and smell (Block 2010). The role of these compounds will be further investigated in the section entitled chemistry and pharmacology.

Traditional Spiritual Uses

Allium sativum is involved in many religious and superstitious beliefs, and today is referenced in pop culture as a means to ward off vampires. In the Bible, the Jews are said to miss garlic when they leave Egypt: “we remember the fish we did eat in Egypt, the cucumbers, the melons, leeks, onions and garlic.” An ancient Islamic myth states that when Satan left the Garden of Eden, garlic sprouted from his left footprint and onion from his right (Block 2010). According to the Bowers Manuscript, in ancient India, garlic is believed to have originated in the blood of a demon (Block 2010). In Greece, midwives used garlic when delivering babies to protect them against evil eye and often advised mothers to sew it into their clothing to protect them (Block 2010). Although some of these tales have negative connotations, these references all indicate garlic as a very powerful substance.

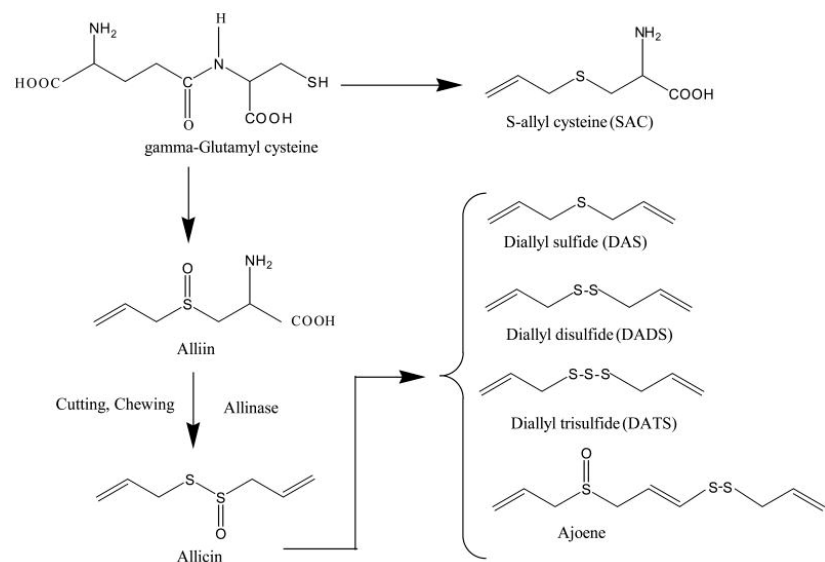


Figure 5. Chemical structures of organosulfur compounds involved in reactions with allicin. (Image source: Powolny and Singh 2008)

Chemistry and Pharmacology

Sulfur compounds are the main chemical constituents responsible for *Allium sativum*'s taste, smell, and likely for its biological effects. When a garlic clove is intact, glutamyl cysteins are the primary sulfur components (Powolny and Singh 2008). These are hydrolyzed to form alliin. When garlic is crushed by chewing, chopping, etc., the alliin promptly reacts with the enzyme alliinase to form allicin; after 30 seconds the reaction is 97% complete (Block 2010). Allicin is a diallyl thiosulfinate that accounts for 70-80% of the thiosulfates present in *Allium sativum* (Harunobu et al. 2001). Allicin is also highly unstable and quickly decomposes to yield sulfur compounds when oxidized such as diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide

(DATS), ajoene, and hydrogen sulfide (Banerjee and Maulik 2002; Harunobu et al. 2001; Mukherjee et al. 2009, Powolny and Singh 2008). The pathways of this reaction can be seen in **Figure 5**. DAS, DADS, DATS and ajoene are all oil soluble (Miroddi et al. 2011).

Chemical Manipulation

When garlic is manipulated to produce alternate forms, the unstable sulfur compounds react and hence alter active chemical constituents. It is important to note that these changes in chemistry can alter the bioavailability of the compounds. Unfortunately, many studies do not specify the actions taken, which could possibly account for inconsistencies in reported data. Traditionally used in its raw form, garlic is now often heated, dehydrated, and aged. Only freshly crushed garlic has hydrogen sulfide, which is suspected to have significant cardioprotective effects as a vasodilator (Mukherjee et al. 2009).

Garlic powder can be made through dehydrating the plant with heat, but when high temperatures are applied to garlic, alliinase is deactivated and hence cannot react with alliin to form allicin (Tsai et al. 2011). This explains why cooked garlic has a mellower flavor than raw garlic. Powder can retain some allicin content if the cloves are frozen before being pulverized; acetone removes the water and alliin and alliinase remain separate yet intact until water is added, at which point allicin is formed (Block 2010). While dehydration during the powdering process does not destroy alliinase like heat does, more than half of the alliin is lost (Banerjee and Maulik 2002; Harunobu et al. 2001). While levels are lower than with raw garlic, dried garlic does contain alliin and alliinase, as explained above. Alliinase is deactivated by the acidic environment of the stomach (Touloupakis and Ghanotakis

2011). Freeman and Kodera (1995) also came to this conclusion by exposing dehydrated garlic powder to simulations of the gastrointestinal fluids; allicin production decreased by 99%, presumably due to the lack of allinase. This suggests that it could be beneficial to further research the affects of dehydrated garlic powder when taken in a capsule with an enteric coating to protect it from stomach acid. These studies also show that manipulating garlic's form leads to changes in the active constituents and could lead to data inconsistencies in studies.

Garlic can also be aged by soaking it in aqueous ethanol and then extracting and concentrating essential compounds. When allicin is dissolved in oils, the major compound in the final product is S-Allylcystein (SAC) while ajoene, the most stable component of garlic, is also present (Rahman 2002). Kodera et al. (2002) suggest that SAC could pass through the gastrointestinal tract without decomposing and successfully be absorbed. Kodera et al. (2002) also suggest that SAC might be stable in blood, whereas allicin is unstable in blood and cannot reach target organs via circulation (Harunobu et al. 2001).

Biological Activity

Cardiovascular Activity

In a review of *in vitro* and clinical studies, Rahman and Lowe (2006) found an inverse correlation between garlic consumption and the progression of cardiovascular disease with the most significant effects being the inhibition of platelet aggregation, reduction of blood cholesterol, reduction of blood pressure and increase of antioxidant status.

Banerjee and Maulik (2002) found similar results regarding the cardioprotective effects of garlic. This was attributed to

suppressed low-density lipoprotein oxidation, which reduces lipid content in arterial walls, leading to protection against atherosclerosis, also known as hardening of the arteries. This anti-aggregatory response is attributed to the presence of allicin and thiosulfinates (Cavagnaro et al. 2007).

In a study of rats, Ali et al. (2000) fed all subjects a diet with increased serum cholesterol. Those who also had a garlic powder supplement experienced a reduction in serum cholesterol and in systolic blood pressure. Diallyl sulfide (DAS), Diallyl disulfide (DADS), and diallyl trisulfide (DATS) are the oil-soluble sulfur compounds responsible for reducing cholesterol (Harunobu et al. 2001). DAT's presence in garlic oil has also been attributed to anticoagulation in rats. Chan et al. (2006) found that DATS inactivated thrombin when given in a dose of 5mg per kg of body weight. Ajoene, a component of aged garlic extract, stops blood from clotting, acting as an antithrombotic (Block 2010).

Mukherjee et al. (2009) conducted a study comparing the effects of freshly crushed and processed garlic in rats. While both exhibited cardioprotective effects, the freshly crushed garlic's effects were more significant, likely due to the presence of hydrogen sulfide (H₂S), which is absent in processed garlic. Red blood cells convert diallyl disulfide and diallyl trisulfide to hydrogen sulfide, which then acts as a vasodilator and reduces blood pressure.

Anti-cancer Activity

In looking at multiple studies, Powolny and Singh (2008) conclude that organosulfur compounds such as DAS, DADS, and DATS act by arresting the cell cycle of cancerous cells. Data from Miroddi et al. (2011) and Omar and Al-Wabel (2009) support this, showing that these allyl derivatives act as

antioxidants and arrest the cell cycle. DATS was found to have the most significant role by Powolny and Singh (2008), and is even a potential skin cancer fighting compound (Wang et al. 2010). More specifically, garlic acts as anti-inflammatory agent by altering cytokines and inhibiting NF-kB activity in surrounding tissues (Keiss et al. 2003). In a study using human promyeloleukemic cells, Dirsch et al. (1998) found that ajoene prompted apoptosis in cancerous cells but not healthy ones; this might be due to peroxide production. In an in-vitro study involving rats, Jastrzebsk et al. (2007) found that raw garlic had the strongest antioxidant activity. Tsai et al. (2011) reviewed animal and cell studies and found an inverse correlation between consumption of garlic and presence of cancerous cells, suggesting it has anticancer effects. Eleischur and Arab (2001) conducted a review of in vitro studies, and while multiple reports concluded that garlic prevents cancer of the stomach, colon and rectum, the analyses were not thorough and did not adjust for potential cofounders and hence are not definitive.

Anti-Microbial Activity

While *Allium sativum* only has about 1% of the antibacterial activity of penicillin, it is able to act upon both gram-positive and gram-negative organisms (Ankri and Mirelman 1999). While it does act as a bactericidal agent, *A. sativum* is primarily a bacteriostatic agent that destroys sulfhydryl groups necessary for bacterial growth (Block 2010). Feldberg et al. (1988) found that allicin affects RNA synthesis and inhibits DNA protein synthesis in *Salmonella typhimuriam*. Allicin can also act as an antibiotic by reacting with thiol-containing enzymes such as L-cysteine to form S-allylmercaptocysteine, which inhibits cysteine proteinases (Ankri and Mirelman 1999). As an anti-fungal, garlic inhibits mycotoxin formation,

presumably through thiol enzymes, however this mechanism of action is not fully known (Ankri and Mirelman 1999). In an in-vitro study, the effectiveness of ajoene at its minimal inhibitory concentration, 15 µg/ml, was tested against *Candida albicans*. Ajoene inhibited 98.2% of fungal growth (Carrero et al. 2009). Ajoene is also known to have more antiviral properties than allicin (Ankri and Mirelman 1999). In another study involving *C. albicans*, allicin was not found to have any antifungal effects on its own, but enhanced the effects of the common treatment Amphotericin B both in vivo and in vitro (An et al. 2009). The wide-spectrum antimicrobial effects of garlic are due to the presence of allicin and ajoene, which are suspected to inhibit multiple thiol-dependent enzymatic systems (Ankri and Mirelman 1999). Allicin is effective against microbial cells that do not have an intracellular thiol content that can offset its thiol oxidation (Harris et al. 2001).

Other Activity

Eidi et al. (2006) conducted a study on both normal and diabetic rats, comparing the treatment effects of Glibenclamide, a known antidiabetic drug, and garlic. They found that garlic increases serum insulin. Liu et al. (2005) also found that garlic oil and DATS increase insulin sensitivity and secretion, hence improving glycemic control. Both studies suggest the need for further investigation into *A. sativum*'s antidiabetic role.

Ankri and Mirelman (1999) suggest that the short reactive time of allicin is an evolutionary adaptation. A larger production of allicin could be toxic for the entire plant, so the actions of allicin in a confined area prevent any self-damage. Allicin is not bioavailable and cannot reach target organs by circulating through the blood (Harunobu et al. 2001).

However, it is able to penetrate biological membranes. Shortly after injection into the bloodstream it is no longer in circulation (Block 2010). This has made it difficult to study alliin's antibiotic effects outside of *in vitro* applications. Many studies focusing on the role of garlic as an antibacterial, antiviral, and antifungal are only clear *in vitro*, perhaps due to alliin's short presence in the blood stream.

Clinical Studies

Some clinical studies report data that differs from data collected through *in vivo* and *in vitro* studies. These differences might be accounted for by the synergistic effects of compounds in *Allium sativum*, as the concentration of these compounds and their effects *in vivo* and *in vitro* may not determine effectiveness without considering their roles in relation to one another (Harunobo et al. 2001). The different forms of garlic must be considered in clinical studies, as this affects the bioavailability of various compounds. It is also important to note that blinded trials are difficult to conduct when using raw garlic due to its strong and recognizable scent and flavor.

Cardiovascular Clinical Studies

In a review of clinical studies, Banerjee and Maulik (2002) note reports of both positive and negative results in relation to the hypolipidemic role of garlic, possibly due to different levels of sulfur compounds in the forms of garlic used. Most studies involving the effects of garlic on hyperlipidemic patients use garlic powder rather than raw garlic. Powdered garlic has less alliin available than raw garlic. As far as cardiovascular studies are concerned, results on hypolipidemic patients are the least conclusive.

Steiner et al. (1996) conducted a double-blind study in hypercholesterolemic men in which aged garlic was used. It was found that aged garlic led to a significant total serum cholesterol reduction, low-density lipoprotein (LDL) cholesterol reduction, and systolic blood pressure reduction. Aged garlic has strong levels of SAC, which could account for these results (Rahman 2002). Ali and Thomson (1995) found that after consuming a single clove of fresh garlic daily for 26 weeks serum cholesterol levels dropped 20% and serum thromboxane levels dropped 80%. However, Gardner et al. (2007) compared treatments for adults with moderate hypercholesterolemia using raw garlic, powdered garlic, and aged garlic (each the equivalent of an average-sized clove six days per week for six months) but no significant effects on LDL levels were found. In a meta-analysis comparing the effects of garlic on serum lipid profiles, Zeng et al. (2012) note that garlic powder and aged garlic were more effective in the reduction of serum total cholesterol levels whereas garlic oil was more effective in the reduction of triglyceride levels. These are only a few examples of conflicting results presented by clinical studies. However, the majority of studies conclude that fresh garlic can slow atherosclerosis development and moderately reduce blood pressure, which is caused by the production of hydrogen sulfide (Mukherjee et al. 2009)

Bordia et al. (1996) note that while garlic components leave the body quickly, active ingredients may build up slowly. This was concluded because a single high dose of garlic did not affectively inhibit platelet aggregation, but long-term administration of low doses was found to be affective. This suggests that including garlic in the diet regularly could have more beneficial effects than consuming it only during times of compromised health.

Cancer Activity Clinical Studies

Most studies involving *A. sativum* and cancer are carried out in animal models because there is not enough information to advise a proper dose for a clinical trial (Thomson and Ali 2003). Ahmend et al. (2001) did find that ajoene enhanced the activation of two chemotherapeutic drugs, Cytarabine and Fludarabine, both used in leukemia treatments. Lamm and Riggs (2000) suggest that regular consumption of aged garlic extract may reduce the risk of stomach cancer. Thomson and Ali (2003) also note that aged garlic extract exhibits radical scavenging activity; these antioxidant properties are thought to inhibit tumor growth. While there are not many studies testing the clinical effects of *A. sativum* on cancer, research suggests that eating garlic as a regular part of the diet serves as a form of preventative medicine. More research is also suggested to investigate the effects of garlic on enhancing modern drugs.

Other Clinical Studies

Historically, *A. sativum* was used to treat the common cold. Lissiman et al. (2009) analyzed previous studies and clinical trials and found that garlic might prevent occurrences but the evidence is not conclusive; this also warrants future studies.

Borhan-Mojabi et al. (2012) tested the effect of garlic on salivary microbial populations and found it significantly decreased colony counts. This suggests the potential for use of garlic in a mouthwash, however most participants complained about taste and resulting breath, implying that the product would not be successful commercially.

Ledezma et al. (2000) compared the effects of ajoene (0.6% and 1.0%) against the topical drug Terbinafine (1%) in the treatment of *Tinea pedis*, more commonly known as athlete's



Figure 6. Burn wounds from the topical application of *A. sativum*. (Image source: Friedman, T., Shalom, A., and Westreich, M. (2006). Self-inflicted garlic burns: our experience and literature review, *Int J Dermatol* 45, 1161-1163.)

foot. They found that ajoene (1%) was more effective than Terbinafine (1.0%), which was only slightly more effective than the 0.6% ajoene.

Contraindications

A common side effect of garlic consumption is halitosis, more commonly known as bad breath. Allyl methyl sulfide (AMS) is a component of garlic that cannot be digested and is hence absorbed into the blood where it travels to the lungs and skin, causing consumers to emit “garlic breath” and “garlic sweat” (Tatteman 2005). An overconsumption of garlic can cause gastrointestinal upset, heartburn, diarrhea and flatulence. Because garlic inhibits platelet aggregation and acts as a vasodilator, garlic consumption should be avoided two weeks



Figure 7. One example of the many garlic supplements available for purchase. (Image source: <http://www.aragonproducts.com/theproducts.cfm?master=7434>)

before scheduled surgery and before childbirth due to risk of bleeding (Stanger et al. 2012). For the same reasons, excessive garlic should not be used in combination with anticoagulants and antiplatelets such as Aspirin and Warfarin (Chen et al. 2011). Garlic decreases the effectiveness of some non-nucleoside reverse transcriptase inhibitors used for the treatment of HIV/AIDS such as Ritonavir and Saquinavir (Chen et al. 2011; Berginc et al. 2010). It is also thought to increase the break down of estrogen present in many oral contraceptives and might decrease their effectiveness, although much more research is needed (Pinto and Rivil 2001). Dietz et al. (2004) and Friedman et al. (2006) investigated the effects of garlic burns. They both cited patients who applied crushed garlic topically. If there is too much pressure from wound wrapping, diallyl disulfide can cause severe local inflammation that can develop into

chemical burns. Some cases included applications to treat headaches, *T. pedis*, and self-mutilate. An example of garlic burns can be seen in **Figure 6**.

Because garlic is more commonly recognized as a food than as a medicine, it is not often acknowledged that it can interact with prescription drugs. *Allium sativum* and its commercial products might not be regarded as a drug, but merely as a form of functional food, which could lead consumers to not share their use with their physicians. Elmer et al. (2007) conducted a study evaluating medication use among the elderly and found that of 393 participants combining medications, 379 of these involved a risk of bleeding due to ginkgo, garlic, or ginseng use and its effect on prescription medications. This further indicates the need to educate people that natural products are not necessarily safe.

Current Use in Allopathic and CAM Therapies

While *Allium sativum* is generally recognized as safe and continues to be used as a food across the globe, many studies on garlic supplements are inconclusive, yet these are also commonly used for medicinal purposes. There are no prescription drugs derived from garlic, but herbal supplements are available over the counter. An example of a product can be seen in **Figure 7**. When the supplements are formed, the manipulation from heating, dehydrating and aging alters the active constituents. Studies use so many different variations of garlic, making the effects of each specific form not easily accessible to potential consumers. Garlic-derived products have a lot of variation among them and can be confusing to consumers. Harunobu et al. (2001) advise careful reading of products because garlic oil does not contain allicin and amounts of garlic essential oils are often minimal because customers do not like the smell. Something else to consider is

whether or not garlic supplements in pill form have an enteric coating. Without an enteric coating, all compounds will dissolve in the stomach and will not be present in the gastrointestinal tract (Kannar et al. 2001). Tattleman (2005) recommends the consumption of one to two cloves of raw garlic per day for adults. While their effects are not entirely confirmed, many use supplements for presumed cardiovascular, antioxidant, and anti-microbial effects.

Discussion

Allium sativum has long been recognized for its traditional ethnobotanical and ethnomedical uses. Many traditional uses have given rise to its modern uses as a functional food. *A. sativum* has been recognized for its role in maintaining normal blood cholesterol levels and blood pressure along with supporting immune function. While there is an extensive amount of research on garlic's potential role in many diseases, there is an absence of conclusive and reliable results, specifically involving the use of garlic supplements. Garlic has a high potential for continuing research because it is suspected to have effects on very relevant medical conditions, specifically cardiovascular disease and cancer. As populations are becoming resistant to western medicines, the development of new remedies or discovery of traditional ones is necessary. Many also express the desire to rely on natural medicine. Nonetheless, it is important to recognize that not all natural products are safe. There is a need for studies that consider the different forms of garlic; this specificity will allow for better understanding of the mechanisms of action of each component and better application of these, leading to an improving continuum of research.

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Aloe vera (L.) Burm. F., Xanthorrhoeaceae

Michele Bennett Paine

Introduction

Aloe vera (L.) Burm. F. belongs to the *Aloe* genus, which contains about 500 species of flowering succulent plants, the most well-known and common being *Aloe vera*. *Aloe* has many different common names even within countries, but it is most commonly *Aloe* in English speaking areas. It is known as *Sabila* in Central and South America and *Ghikumar* in India. Known under many families over the years, *Aloe vera* is currently listed under the Xanthorrhoeaceae family, and also under the subfamily Asphodeloideae. In the past, it has been categorized under the Liliaceae family and was also recognized by the scientific name *Aloe barbadensis* until it was discovered that the name *Aloe vera* given by Burman pre-dated the name *Aloe barbadensis*. The first record of *Aloe vera* is dated to Pedanius Dioscorides' *De Materia Medica*. Dioscorides was an authority on herbal plants around 60 AD (S. Carter, 2011). *Aloe* has been used for thousands of years to topically treat burns and other skin abrasions, as well as for its laxative properties when taken orally; it is also used to treat diabetes, asthma, epilepsy, and osteoarthritis, among other conditions (Medicine, 2011). The latex, or inner leaf, of the aloe plant contains strong laxative compounds such as aloin, aloemodin, and barbaloin, and the gel from inside the leaf may help to heal burns and abrasions, though more research is needed to verify these claims (Medicine, 2011).

Botanical Description

The origin of *Aloe vera* (**Figure 1**) is unknown, but it is native to North Africa, the Mediterranean region of southern Europe, and



Figure 1. *Aloe vera* leaves and flowers. (Image source: <http://www.tropicos.org/Name/18403421>)

to the Canary Islands (S. Carter, 2011). Now, however, it is found to be cultivated throughout the West Indies, tropical America, and in the tropics in general (Ross, 1999). The *A. vera* plant is a short-stemmed or entirely stem-less succulent plant with leaves that bunch together to form large groups of up to 20 leaves (Ross, 1999). The leaves are thick and fleshy, grayish-green with a brownish tinge in color, have spots when they are young and can grow to be 20-60 centimeters long and 6-7 centimeters wide at the base (S. Carter, 2011). The leaves are also 1 to 2.5 centimeters thick and have spiny edges (S. Carter, 2011). *A. vera* produces yellow flowers that grow on central stalks that can be up to 100 centimeters tall (Ross, 1999). The yellow outer part of the flower is divided into 6 different lobes with 6 stamens and a three-celled ovary in each flower (Ross, 1999). The fruit is a capsule that flowers then fruits from July through January (Gowda, 2004).

Traditional Uses

According to the National Center for Complementary and Alternative Medicine (NCCAM), *Aloe vera* has been traditionally used as a topical treatment for burns, wounds, and various other skin conditions, and has also been used orally as a laxative. Typically, the leaf extract is treated in hot water and then used for the treatment of burns, sores and other wounds (Ross, 1999). In Argentina, however, the hot water extracts from the leaves is taken orally to both alleviate painful menstruation and to induce abortion (Ross, 1999). It is also used as an abortifacient in Switzerland and in India (Ross, 1999). *A. vera* is used extensively in India: it is often taken orally to treat inflammation and pain (Ross, 1999). The leaves are also applied externally to treat wounds and guinea worm infection sites (Ross, 1999). In the Cook Islands in the South Pacific Ocean, fresh latex from the leaves is also taken orally, on a regular basis, to prevent high blood pressure, cancer, and diabetes (Ross, 1999). It is also used as a diabetes prevention method in Haiti, Mexico, Saudi Arabia, and Tunisia (Ross, 1999). Most peoples that use *A. vera* agree that it should be avoided during pregnancy, as it does appear to have possible abortifacient effects. For a more extensive list of traditional uses around the world, see **Table 1**.

Chemistry and Pharmacology

Aloe vera contains numerous chemical constituents that are shown to have significant activity. Alanine, for example, is found in the leaf in amounts of about 15,769 parts per million (Duke, 1996). Alanine is an amino acid and is known for displaying antioxidant and cancer-preventive activity (Duke, 1996). There are also significant levels of Aloctutin-A, which is an analgesic and cancer-agglutinator (Duke, 1996). Aloesin has purgative and sunscreen effects, and small amounts (about 20 parts per million) of aluminum and amylase (an enzyme) have antimicrobial and

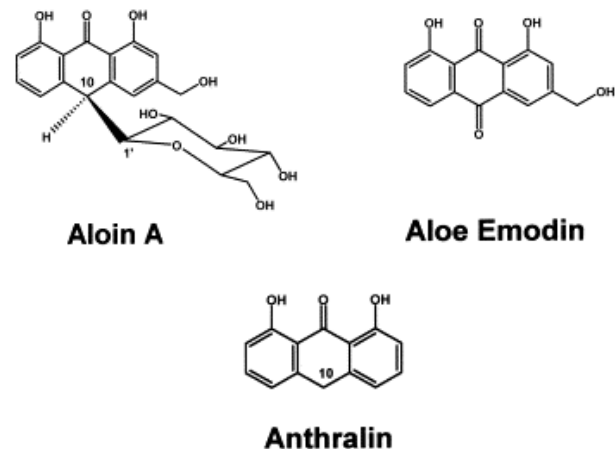


Figure 2: Chemical structures of the anthraquinones Aloin A, Aloe emodin and Anthralin (Wamer et al., 2003).

sedative effects, respectively (Duke, 1996). Another major group of chemical constituents in aloe include the anthraquinones, which are aromatic organic compounds that have antiitthic, carcinogenic, and laxative effects (Duke, 1996). Aloe emodin, anthralin and aloin A are the better-known anthroquinone constituents, and have significant antimicrobial activity as well as laxative, cathartic, anti-leukemic, antiseptic, cytotoxic, estrogenic, fungicide, pesticide, genotoxic, mutagenic, and tuberculstatic effects (Duke, 1996). To see the structures of the above anthraquinones, see **Figure 2**.

Biological Activity

In vitro

Antioxidant properties

Although the leaves are traditionally used, there are also possible beneficial compounds in the flowers of *Aloe vera*. A high polyphenolic content is associated with significant antioxidant

Argentina	Hot water extract of leaves is taken orally to induce abortion and to facilitate menstruation.
Bomini	Leaf juice is used externally for skin irritations, cuts, boils, and sunburn.
Bolivia	Fresh leaf juice is used as an analgesic topically for burns and wounds. Orally, the juice is used as a laxative.
Brazil	Fresh leaf juice is taken orally as an anthelmintic and febrifuge. Infusion of dried root is taken orally to treat colic.
Canary Islands	Fresh fruit juice (unripe) is taken orally as an antiasthmatic and purgative.
China	Infusion of fresh leaf juice is taken orally as a laxative, for dental caries, and as a teniafuge.
Cook Island	Hot water extract of leaf juice is taken orally as an emmenagogue.
Cuba	Fresh sap in water is taken orally, regularly, to prevent high blood pressure, cancer and diabetes. Externally it is used to treat burns and cuts.
Egypt	Water extract of leaf pulp is taken as an emmenagogue.
England	Fresh leaf juice administered intravaginally is used as a contraceptive before or after coitus. Data was obtained as a result of questioning 1200 puerperal women about their knowledge of birth control methods. 52.3% practiced a method, and 47.6% of these depend on indigenous methods and/or prolonged lactation.
Guatemala	Hot water extract of dried leaves with a mixture of <i>Zingiber officinale</i> , <i>Mentha pulegium</i> (essential oil), <i>Ipomoea purga</i> , <i>Glycyrrhiza glabra</i> and <i>Canella alba</i> is taken orally for amenorrhea.
Haiti	Hot water extract of dried leaves is used externally for wounds, ulcers, bruises and sores, skin eruptions, erysipelas, dermatitis, inflammations, burns, abscesses, and furuncles, and scrofula.
India	Hot water extract of dried leaves is taken orally both as a purgative and against diabetes and worms
Malaysia	Decoction of dried leaves is taken orally to induce abortion, for sexual vitality, and the dried leaf juice is taken as an emmenagogue
Mexico	Decoction of root is taken orally for venereal disease and externally it is used to treat wounds. Fresh fruit juice (unripe) is taken orally as a laxative, cathartic, and for fever. Fresh leaves are crushed and applied locally for guinea worms. Hot water extract of dried entire plant is taken orally as an emmenagogue, purgative, anthelmintic, stomachic, for liver enlargement, spleen enlargement, and piles. Hot water extract of fresh plant juice is taken orally for inflammation and amenorrhea. The pulp of the plant is mixed together with salt and fermented sugar cane juice and taken orally to treat pain and inflammation of the body. Hot water extract of leaf juice is taken orally as a cathartic; it should not be used by pregnant women. Leaf pulp is taken orally regularly for 10 days by women to prevent conception. Leaf juice is taken orally to treat viral jaundice. The juice is taken twice daily for three days.
Nepal	Hot water extract of leaf juice is taken orally as a cholagogue and emmenagogue. Hot water extract of leaves is taken orally as an emmenagogue
Panama	Fresh stem juice is taken orally for diabetes. Infusion of dried leaves is taken orally to treat ulcers.
Peru	Fresh leaf pulp is taken orally to relieve amenorrhea. 10–15 gm of leaf pulp is given with sugar or honey once a day.
Puerto Rico	Hot water extract of dried entire plant is taken orally as a purgative and to terminate pregnancy.
Saudi Arabia	Fresh leaves crushed with egg white is taken orally as a laxative and demulcent. Sap is taken orally for stomach ulcers and externally for erysipelas and to treat swellings caused by injuries.
South Korea	Hot water extract of fresh leaves is taken orally for asthma, as a purgative, and antivenin. Externally, the extract is used as an antiseptic for washing wounds.
Switzerland	Drink made from fresh leaf pulp plus fruit pulp of <i>Genipa americana</i> is a popular remedy for colds.
Taiwan	Hot water extract of dried aerial parts is taken orally for liver complaints, piles, as an emetic, antipyretic, against tumors, for enlarged spleen, as a cooling agent, purgative, for diabetes, skin diseases and asthma. Hot water extract of dried leaves is taken orally for functional sterility, amenorrhea, piles, thermal burns, constipation, flatulence, intestinal worms, diabetes, to treat functional sterility, amenorrhea, to treat constipation, and piles. Externally used for burns.
Thailand	Hot water extract of whole dried plant is taken orally as a contraceptive, an abortifacient, and emmenagogue. Use is contraindicated during pregnancy.
Tunisia	Hot water extract of dried leaves is taken orally as an abortifacient.
USA	Decoction of dried leaves is taken orally to treat hepatitis.
	Fresh leaf juice is used on burns. Hot water extract of dried resin is taken orally as a cathartic.
	Hot water extract of dried leaves is taken orally for diabetes and to treat problems of venous circulation. Externally, the extract is used for eczema.
	Fresh leaf juice is taken orally for stomach ulcers and used externally to heal wounds. Fluid extract of leaf juice is taken orally as an emmenagogue. Hot water extract of dried leaves is taken orally as a cathartic. Hot water extract of gum is taken orally as an emmenagogue to promote and stimulate menstruation. Water extract of leaves is used externally for insect bites, myopathies, arthritis, topical ulcers, and other skin conditions. Hot water extract is taken orally to increase menstrual flow; should be avoided during pregnancy.

Table 1. Comprehensive list of the traditional uses of *Aloe vera*. Adapted from (Ross, 1999)

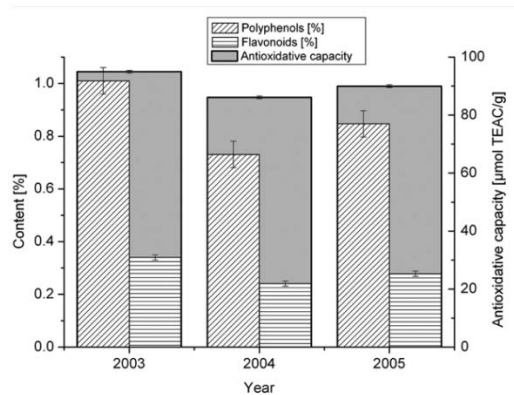


Fig. 1 Polyphenol and flavonoid contents in Aloe vera flowers of three batches and their antioxidative capacity.

Figure 3. Results of a study examining the correlation between polyphenol and flavonoid content in *A. vera* flowers and the antioxidant activity (Keyhanian & Stahl-Biskup, 2007).

activity (Keyhanian & Stahl-Biskup, 2007). Aloin A and B, anthraquinones associated with the laxative properties of aloe, were not found in the dried flowers, but the antioxidant activity measured correlated positively with the amount of flavonoid and polyphenol content (Keyhanian & Stahl-Biskup, 2007)(**Figure 3**).

Photobiological properties

Aloe emodin and aloin A are two important anthraquinones in aloe. Since aloe is now often included in topically applied cosmetics because of its moisturizing properties, it is important that any adverse effects are identified. A recent study indicated that the constituent aloe emodin may make the skin more sensitive to UV light, so a follow-up study was conducted to examine the events that follow photoexcitation of both aloin A and aloe emodin (Wamer, Vath, & Falvey, 2003). Human skin fibroblasts that were treated with aloe emodin then irradiated with UV light showed diminished survival, while cell survival was

not effected by aloe emodin alone (Wamer et al., 2003). The oxidative damage to both RNA and DNA occurred even at low levels of photocytotoxicity (Wamer et al., 2003).

Anticancer activity

Aloe emodin may also exhibit antineuroectodermal tumor activity. Researchers at the Universities of Padova and Genova in Italy devoted their attention to natural compounds in plants that have been used traditionally to treat numerous diseases for hundreds of years and focused on aloe emodin (Pecere et al., 2000). Neuroblastoma cells that were grown in a complete medium and treated with aloe emodin displayed cytotoxicity; the growth of the cells was inhibited and cells showed signs of having undergone apoptotic cell death, as identified by cell shrinkage, membrane blebbing, and nuclear fragmentation (Pecere et al., 2000). It was also determined that, unlike other cancer drugs that are toxic at the necessary therapeutic levels, the aloe emodin did not inhibit the proliferation of hematopoietic progenitors; that is, it displayed selective toxicity where necessary (Pecere et al., 2000). To further address this topic, the same researchers conducted follow-up studies in 2003; aloe emodin induced apoptosis in p53 mutant cells, p53 being a tumor suppressor gene (Pecere et al., 2003).

In vivo

Abortifacient effects

In one study, aloe that was extracted with water was given to pregnant rats during the first nine days of gestation ("Final report on the safety assessment of AloeAndongensis Extract, Aloe Andongensis Leaf Juice,aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadosensis Flower Extract, Aloe Barbadosensis Leaf, Aloe

Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice, aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract," 2007). It was found to be an abortifacient and produced significant skeletal abnormalities in the fetal rats ("Final report on the safety assessment of Aloe Andongensis Extract, Aloe Andongensis Leaf Juice, aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice, aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract," 2007).

Immunostimulatory effects

A study was conducted on industrial broiler chickens to test the effects of *A. vera* against coccidiosis, a parasitic infection. Results showed that pulp from the leaves stimulated both humoral and cellular immune responses in the chickens (Akhtar et al., 2011). Higher antibody activity can hinder the development of the parasites in the intestines, and it is stipulated that the anthraquinones, saponins, and sterols of the plant may have inhibited the multiplication of the parasites as well (Akhtar et al., 2011). It has potential to be used as a low cost alternative to allopathic medicines to control coccidiosis.

Hepatoprotective effects

In investigating how to remedy the improper handling of petroleum products that leads to possible hepatotoxicity and carcinogenic effects, researchers found that mice treated with *A. vera* gel exhibited reduced γ -glutamyl transferase (γ GT)

levels, indicating hepatoprotective qualities (Gbadegesin, Odunola, Akinwumi, & Osifeso, 2009).

Hypoglycemic and hypolipidemic effects

In a study by researchers at ShamYook University in Seoul, South Korea, a mouse model was used to test the effects of processed *Aloe vera* gel (PAG) on diet-induced non-insulin-dependent diabetes mellitus (NIDDM). This is especially relevant to humans because of the dramatic increase in rates of NIDDM and the associated complications of the disease (Kim et al., 2009). Processing the *A. vera* gel involves incubating the gel with cellulase (the enzyme that catalyzes the hydrolysis of cellulose) followed by passing the gel through a charcoal column in order to remove the anthraquinones, responsible for the laxative effects of aloe (Kim et al., 2009). To induce the NIDDM state in the mice, they were fed a high fat diet for 21 weeks, followed by the treatment of different doses of PAG for 8 weeks whilst continuing the high fat diet (Kim et al., 2009). After 2 weeks, the hypoglycemic effects were apparent: the fasting blood glucose levels of the diet-induced obesity (DIO) mice were not significantly different from those of regular diet-fed mice (Kim et al., 2009). In addition to a decrease in blood glucose and insulin levels, improved blood glucose homeostasis was observed; that is, when given high doses of glucose, the mice that had been treated with PAG showed high tolerance and a faster return to homeostasis than the control mice (Kim et al., 2009). While there have been other reports that indicate that aloe may actually increase plasma glucose levels, it is speculated that this may be due to the parts of the plant used, as well as the difference in animal models – the mouse model reasonably models NIDDM in humans (Kim et al., 2009).

Another study was conducted to determine the constituents of *A. vera* that normalize hyperglycemia in a mouse that has been induced into the NIDDM state. Fresh *Aloe vera* gel was divided into five separate extracts and administered separately to the mice (Tanaka et al., 2006). Only one of the five extracts, T1, significantly reduced blood glucose levels of the mice, and was further divided into fractions until five phytosterols were isolated via chromatography and detailed C-NMR spectroscopy, which allows for the identification and elucidation of chemical structures (Tanaka et al., 2006). Phytosterols are structurally similar to cholesterol, and in the 1950s it was recognized that plant sterols lower the serum concentrations of cholesterol (Tanaka et al., 2006). Mice that were treated with the five phytosterols showed decreases in both fasting blood glucose levels and random blood glucose samples (Tanaka et al., 2006).

Burn care

While aloe is generally regarded as beneficial in the treatment of minor burns, a study in 2008 found that the application of *Aloe vera* to the burn wound of a large white juvenile pig was no more beneficial than the control group in terms of re-epithelialisation, cosmetic appearance or histology of the scar (Cuttle et al., 2008). The aloe did, however, decrease the subdermal temperature of the wound, indicating possible cooling and soothing purposes, which cannot be overlooked (Cuttle et al., 2008).

Immunomodulatory activity

To test the immunomodulatory activity of processed *Aloe vera* gel (PAG) in a diabetic mouse model, the mice were infected with *Candida albicans*, to which the kidney is particularly

susceptible (Im et al., 2010). The mice that were given PAG had significantly reduced renal strain, though the mechanisms could not be indentified (Im et al., 2010).

Clinical Studies

Periodontal Effects

In a study conducted by the Jaipur Dental College in India, 15 subjects were evaluated for periodontitis and treated by applying *Aloe vera* gel to periodontal pockets (Bhat, Kudva, & Dodwad, 2011). After three months, subjects showed a significant reduction in pocket depths as compared to the control group, as well as a reduction in gingival index, which is attributed to the anti-inflammatory and antibacterial effects of *A. vera* (Bhat et al., 2011). Improved healing was attributed to increased oxygenation because of the *A. vera*, as well as the presence of vitamins A, C, E, B₁₂ and folic acid (Bhat et al., 2011). Vitamin C especially dilates blood vessels, thus increasing oxygen concentration. No adverse effects were found, though a longer study time and larger sample size is necessary (Bhat et al., 2011). These promising results, as well as the ease of application and low cost of *Aloe vera* show the potential for its use as a means to improve periodontal conditions.

Anti-hyperglycemic/Anti-hypercholesterolemic effects (Anti-diabetic)

In a randomized double-blind placebo-controlled clinical trial at the Research Institute of Medicinal Plants in Karaj, Iran, aloe leaf gel powder was prepared was evaluated for efficacy in the treatment of patients with type II diabetes. Just as in the mouse model trial described above, the aloe gel was treated to remove aloin and other anthraquinones, known to have laxative effects (Huseini, Kianbakht, Hajiaghaee, & Dabaghian, 2012). The gel was then freeze-dried and made into 300 mg capsules (Huseini et al.,

2012). One variant from the mouse model is that the patients were recommended to decrease their intake of carbohydrates and fatty foods, while the mice continued to eat a high-fat diet. The results of this study showed that the aloe gel improved glycemic control and lowered both total cholesterol and low-density lipoproteins, but did not effect any other blood lipid levels and did not seem to have any adverse effects (Huseini et al., 2012). The only bioactive compound that was indentified in this trial was the mucopolysaccharide acemannan, but the mechanisms involved in these hypoglycemic and hypocholesterolemic effects were not investigated in this study (Huseini et al., 2012).

Burn care

Aloe vera is generally considered safe for topical use (Maenthaisong, Chaiyakunapruk, Niruntraporn, & Kongkaew, 2007). In some studies aloe has been shown to reduce healing time for burns and other wounds, while other studies have been inconclusive or show that aloe has no great effect on healing (Maenthaisong et al., 2007). Some studies indicate that the aloe may simply be used for its cooling and soothing effects, but it is generally agreed upon that 100% aloe is most effective at treating topical wounds, and anything less than 50% has no effect (Korac & Khambholja, 2011). One study found that application of *A. vera* increased the production of collagen, thus increasing the rate of epithelialization (Korac & Khambholja, 2011). In directing the care of outpatient burns, the application of aloe to the affected area was noted to be successful in treating the pain associated with superficial wounds or burns (Lloyd, Rodgers, Michener, & Williams, 2012).

Ulcerative colitis

Since *Aloe vera* is known for its anti-inflammatory activity, a double blind, randomized trial was used to examine the effectiveness of aloe in the treatment of mild to moderate ulcerative colitis. Subjects took 100mL of *A. vera* gel orally twice daily for four weeks and the control group were given a placebo (Ke, Yadav, & Ju, 2012). Subjects who had been taking the *A. Vera* gel were nearly four times as likely to show response, improvement, or complete clinical remission as compared to those taking the placebo (Ke et al., 2012).

Contraindications

Aloe vera is known to contain compounds that have been documented to be cytotoxic. In a study by Patna University in India, researchers found that while there was not an increase in structural abnormalities of the chromosomes in the bone marrow of mice injected with the crude leaf extract of aloe, there was a significant increase in chromosome number anomalies and in the mitotic index, or proliferation status, of the cells (Verma, Gupta, Kumar, & Khan, 2012). There have also been reports of hepatotoxicity induced by aloe. Patients who had been taking aloe preparations and had been diagnosed with acute hepatitis showed the return of liver enzymes to normal levels after the aloe use had been discontinued (Yang et al., 2010). Although still unclear, there are also some findings that indicate that the compound aloe-emodin induces apoptosis in human kidney-2 (HK-2) cells, though these possible toxic effects are unclear and need further research (Zhu et al., 2011). There was clear evidence of carcinogenic activity in rats from oral consumption of the whole leaf of the aloe plant, but once again, more research is needed (Medicine, 2011). Also with the oral use of aloe, especially as a stimulant laxative, there have been reports of abdominal cramps and diarrhea, which can further lead to a

decrease in the ability of other drugs to be absorbed (Medicine, 2011). Since some compounds in *A. vera* are known to lower blood-glucose levels, people with diabetes are warned to be cautious, as they are generally already prescribed an alternate glucose-lowering medication (Medicine, 2011).

Current Use in Allopathic and CAM Therapies

Aloe vera supplements are not FDA approved, and thus are used at the patient's own risk. There are many people who do choose to supplement biomedicine with an herbal supplement such as aloe, but drug-herb interactions may be overlooked and can lead to serious, sometimes fatal consequences. There is anecdotal evidence of older patients taking aloe preparations for months and developing acute hepatitis that returned to normal after discontinuing the use of the oral aloe (Yang et al., 2010). This is discordant with the *in vivo* study mentioned above that indicates hepatoprotective properties in aloe, and it is clear that more clinical trials need to be conducted before people continue to use *A. vera* in complementary and alternative medicine without consulting a healthcare professional. There is further risk of using aloe as complementary medicine if it is used in combination with antiretroviral drugs for the treatment of HIV, as the pharmacokinetic interactions between the antiretrovirals and herbal medicine is unknown; only antiretrovirals have proven efficacy in treating HIV (Lamorde, Byakika-Kibwika, & Merry, 2012). There were several studies conducted on complementary and alternative medicine usage in Nigeria. In hypertensive patients who visited a tertiary care center, 4.5% used *Aloe vera* in addition to conventional medical treatments (Amira & Okubadejo, 2007). At a multi-specialist hospital in Nigeria, aloe was also found to be used by 28% of patients with osteoarthritis (Obalum & Ogo, 2011). In Germany, 7.3% of children with type I diabetes mellitus are given an aloe supplement as part of a complementary

medicine regimen, with 77.8% of parents stating that they assumed aloe had fewer potential side effects (Dannemann et al., 2008). It generally accepted that aloe gel is generally regarded as safe for the treatment of minor burns – there are many topical aloe gel treatments available on the market, but anything less than 100% *Aloe vera* gel is thought to have little to no efficacy in treating burns, so one might be best served by having the plant itself for usage.

Discussion

Aloe vera has been used for its medicinal properties all over the world. The gel inside the leaf has been used to treat burns and other minor wounds topically, and it can also be ingested orally; the anthraquinones make it a very effective laxative. Aloe has also been employed traditionally for its possible abortifacient effects, hypoglycemic and hypolipidemic effects, and hepatoprotective activity. Though many studies have been conducted to determine the efficacy of *A. vera* in regards to these potential beneficial effects, there are enough discrepancies that the results are generally inconclusive, and it is clear that further studies are required, especially since determining the exact mechanism of action could help to identify how the chemical constituents in aloe help or inhibit certain qualities. Since aloe can be cultivated in a wide range of areas it is not in danger of being overharvested, so more studies can be conducted in the future without fear of extinction of the species. *Aloe vera* has the potential to have many advantageous medicinal properties, even anticancer activity, and further research will help to solidify findings now that support aloe in the treatment of diabetes mellitus, among other diseases. Since rates of obesity have increased, rates of diabetes have followed, and finding new, effective treatments that have no adverse effects may prove to be where *Aloe vera* is needed.

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Ananas comosus (L.) Merr., Bromeliaceae

Anum Dhukani

Introduction

Ananas comosus, otherwise known as the pineapple, belongs to the family Bromeliaceae. It is also known as the *piña* by the Spanish, *abacaxi* by the Portuguese, *ananas* by the Dutch and French, as well as *nanas* in Southern Asia and the East Indies (Morton, 1987). While the family Bromeliaceae includes approximately 2,000 species, the genus *Ananas* consists of 2 species: *A. macrodontes* and *A. comosus*. Of these 2 species, the more common species is *A. comosus* (Sanewski 2011) (Figure 1). It is native to Central and South America but is grown in other areas such as Hawaii, South Africa, China, India, Kenya, Thailand, Malaysia, and the Philippines (Tochi et al. 2008). Bromelain is a proteolytic enzyme obtained from the stem of the pineapple that exhibits therapeutic properties such as preventing malignant cell growth and platelet aggregation, thrombus formation, anti-inflammatory and wound-healing action, and increased permeability of drugs (Maurer 2001). Other constituents besides stem bromelain include fruit bromelain, ananain, and comosain (Rowan, Buttle, and Barrett 1990).

Botanical Description

Pineapple is indigenous to the tropical and subtropical regions, especially southern Brazil and Paraguay. It is essential for the pineapple to grow in these regions due to the favorable temperatures ranging from 65°F to 95°F; low temperatures can potentially delay growth as well as cause the fruit to taste acidic. In addition, high elevations can also induce acidity. The



Figure 1. The 5 most common pre-Columbian cultivars: 'Perola' (A), 'Queen' (B), 'Manzana' (C), 'Red Spanish' (D), and 'Cayenne' (E). (Source: Sanewski 2011).

Volatile compound	Aroma
4-hydroxy-2,5-dimethyl-3(2H)-furanone	Sweet, caramel, fruity, burnt. Strawberry and pineapple at low conc
4-methoxy-2,5-dimethyl-3(2H)-furanone	Sweet, caramel, fruity, musty, savoury
Ethyl 2-methyl butanoate	Green, apple, fruity
Methyl 2-methyl butanoate	Fruity, apple
Methyl butanoate	Fruity, apple
Ethyl 3-(methyl thio) propanoate	Pineapple
Methyl 3-(methyl thio) propanoate	Sulfurous, pineapple
Ethyl 2-methyl propanoate	Sweet, fruity
Methyl 3-propanoate	Fruity, pineapple
Methyl propanoate	Fruity, rum-like, apple, banana, strawberry
octalactone	Creamy, coconut
decalactone	Sweet, coconut, peachy
hexalactone	Sweet, creamy, coconut, herbaceous
vanillin	Vanilla
1-(E,Z)-3,5-undecatriene	Fresh, green, pineapple
octanol	Citrus
Methyl hexanoate	Fruity, pineapple
Ethyl hexanoate	Fruity, pineapple
3-methylbutyl acetate	Fresh, fruity. Banana and pear at low conc

Table 1. Major compounds in pineapple aroma. This is a list of the compounds that give the pineapple its sense of aroma and flavor (Source: Sanewski 2011).

plant can be grown on small plots or steep slopes, but since the pineapple's roots are shallow, the land must be prepared on the surface to avoid damage (Morton 1987). The Bromeliaceae family consists of two branches: terrestrial and epiphytes. While the terrestrial plants are rooted in soil, the

epiphytes grow on other plants and objects. The pineapple belongs to the terrestrial branch (Okihiro 2009, 76).

The pineapple plant is an herbaceous perennial ranging from 2.5 to 5 ft high with a short stem of pointy, waxy green leaves that are 20 to 72 in. long (Pineapple 1996). The stem begins to elongate near the apex during blooming time and small purple or red flowers appear. Known as the "crown" of the pineapple, this clump of firm, short leaves grows after the stem develops. Developing from the flowers is the cone shaped fruit that is 12 or more in. in height (Morton 1987).

The pineapple fruit is composed of many small fruitlets, which determine the pineapple's size. In general, fruit size can be as little as 100 g to as much as 7 kg. Most pineapples range from yellow to orange skin; however, there are also cream, pink, and red skinned pineapples. The yellow, green, and red skin color is due to carotenoids, remaining chlorophyll, and anthocyanins, respectively. The yellow flesh color is also a result of carotenoids similar to the skin. The sweet flavor of the pineapple is because of the sucrose content. However, it is important to note that the smaller the fruit, the sweeter it is. Flesh and skin volatile compounds establish the pineapple's distinctive aroma (Sanewski 2011). **Table 1** lists some of the major compounds that contribute to the pineapple's aroma and flavor.

The primary pollinator of the pineapple plant is the hummingbird. Hard seeds can be present in the fruit if the flowers are pollinated; however, if they are not, few seeds will be present (Morton 1987). There are several pests and diseases that can infect the pineapple including mealy bugs and rats. Bud rot, fruit core rot, and heart rot are diseases that are also common. Bud rot is rotting of the stem and the eventual death of the plant while fruit core rot is seen in fruits that turn brown in the inside and are smaller in size. Heart rot

is when the leaves begin to redden and the edges become brown and wilt. To avoid bud rot, the plant should not be cut in a way as to allow fungus to infect it. Controlling mealy bug invasion and removing the crown in the rainy season can prevent fruit core rot. In addition, proper drainage and elevation of the plant can ensure safety from heart rot (Pineapple: Pests and Diseases 2011).

Five common pineapple cultivars include the 'Perola', 'Queen', 'Manzana', 'Red Spanish', and 'Cayenne' illustrated in **Figure 1** (Sanewski 2011). The 'Perola' is a yellow, large, and cylindrical pineapple with no spines and is popular in Venezuela and Columbia. The 'Queen' is prevalent in South Africa, Queensland, and the Philippines. It is cone-shaped, golden-yellow with more fragrance and flavor than other cultivars. However, it matures early, requires thinning, and has a low yield. A minor cultivar in Columbia is the 'Manzana.' In addition to these is the popular cultivar in Florida, the West Indies, Venezuela, and Mexico known as the 'Red Spanish.' Resistant to rotting, it ranges from having orange to red skin and represents 85% of commercial planting in Puerto Rico. Due to its cone-shaped form, orange skin, mildly acidic flavor, and canning properties, the 'Cayenne' is known worldwide despite its lack of ability to withstand disease (Morton 1987).

Traditional Uses

Traditional medicinal uses

The pineapple has been used traditionally for a variety of ailments particularly in Central and South America (Tausig and Batkin 1988). The juice was not only consumed as a diuretic but also gargled for sore throats and to prevent seasickness. Because unripe pineapples are poisonous, it was traditionally taken for abortion and removal of intestinal

worms. The pineapple root in the form of dried powder was used to heal edema in Africa while the rind was topically applied to fractures and hemorrhoids. Even today, compounds in the pineapple are commonly used to treat edema as well as to reduce pain and inflammation. In Panama, the leaf juice was used to promote menstruation, remove worms, and cleanse the intestine (Morton 1987).

Food uses

Pineapples are also commonly used in food. The flesh of the fruit can be eaten alone, in desserts, salads, pies, cakes, puddings, or made into sauces. Malaysians add the pineapple in their curries while the Filipinos use extracted pulp in a dessert called *nata de piña*. The pineapple cannot be frozen because the flavors are subsequently extinguished. Because pineapples contain a proteolytic enzyme called bromelain, either the pineapple or the enzyme is commonly used as a meat tenderizer to break down protein. The canning of pineapples has significantly increased its demand and made it one of the leading fruits worldwide. Hawaii alone supplied 70% of the world's canned pineapple for about a decade starting in 1970 until the company, Dole, transferred its operation to the Philippines due to increased production costs (Morton 1987).

Ethnobotanical uses

Native Americans cultivated the pineapple in Mexico and the West Indies before the arrival of Christopher Columbus. Columbus and his crewmembers saw the pineapple for the first time in 1493 in Guadeloupe. Inhabitants of the Caribbean set pineapples outside their homes to represent friendship and hospitality. As a result, Europeans in Spain and England



Figure 2. Decorative fruits. The pineapple's flowers were commonly used as a source for flower arrangements (Source: Sanewski 2011).

illustrated the fruit in carvings on doorways (Morton 1987). Pineapple ware such as pots, mugs, cups, and bowls were even sold in colonial America (Okihiro 2009, 164).

In addition to its medicinal value, the pineapple was used for many other applications. The juice was used as a cleanser for knife blades and scrubbing boat decks (Morton 1987). The flowers of the plant could be used as an ornamental or flower arrangement illustrated in **Figure 2**. The fruit itself was also used as a means to decorate the home. For example, George and Martha Washington adorned their wall lamp with a pineapple on top illustrated in **Figure 3** (Okihiro 2009, 166). In the Philippines, the natives extract fiber from the leaves in order to make fabric (Pineapple: Pests and Pesticides, 2011).

Harvesting

Pineapple harvesting requires an enormous amount of experience; in addition to size and color, other factors must be



Figure 3. The pineapple as a common ornamental. A pineapple sits as an ornamental on top of a wall lamp in George and Martha Washington's home. (Source: Okihiro 2009).

taken into account. Before the pineapple reaches maturity, starch is converted into sugars in a span of a few days. During the summer, crop is harvested when the skin shows a light green color because sugar content and volatile flavors begin to develop. However, the winter crop takes approximately one month longer to reach maturity; therefore, fruits are harvested when the base is covered with a light yellow pigment. In spite of this, winter pineapple is more acidic and has lower sugar content than summer pineapple. In addition, if the fruit is overripe, it is not as flavorful and is more likely to perish. Usually after the stem is cut, a 3% solution of benzoic acid is applied to the stem in order to protect the fruit from rain and dew. Pineapples should not be stored for more than six weeks although storage life can be extended by immersing the fruit in a wax solution with fungicide (Morton 1987).

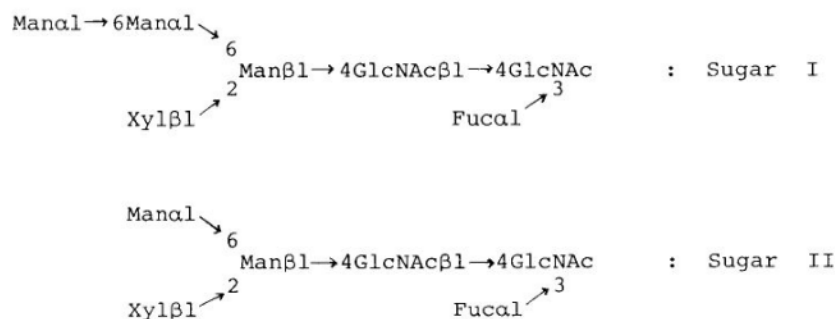


Figure 4. Structure of bromelain. This illustrates the complete structure of the 2 oligosaccharides in bromelain. (Source: Ishihara et al. 1979)

Chemistry and Pharmacology

One of the main constituents in the pineapple is a cysteine protease known as stem bromelain (**Figure 4**). It is an aqueous extract from the stem and sometimes fruit of pineapples that is prepared by centrifugation, ultrafiltration, and lyophilization. This complex process yields a yellow powder. However, when in an aqueous solution, bromelain can degenerate due to self-digestion; therefore, α_2 -macroglobulin, a plasma protein, is added to prevent deterioration (Maurer 2001). The majority of research has been conducted on bromelain and many of the therapeutic effects are attributed to it. However, there are also other cysteine proteases such as fruit bromelain also known as bromelin, ananain, and comosain. Ananain and comosain are found in the stem along with stem bromelain. Bromelain is a proteolytic enzyme comprised of a mixture of components including peroxidase, acid phosphatase, protease inhibitors, and organically bound calcium (Orsini 2006). Used as complementary medication to glucocorticoids, antirheumatics, and immunomodulatory agents, proteolytic enzymes' low toxicity provides the capability for the treatment of

inflammatory conditions. They consist of a broad range of therapeutic effects such as antiedematous, anti-inflammatory, antithrombotic, and fibrinolytic activities. These proteolytic enzymes also help regulate immune cells and cytokine production as well as functions of adhesion molecules on blood and endothelial cells (Maurer 2001). **Table 2** lists the components found in *Ananas comosus*.

Biological Activity

In vitro

Pineapple's main therapeutic component, bromelain, has been studied in many *in vitro* and *in vivo* studies. *In vitro* studies have found that not only is bromelain degraded in blood plasma by protease inhibitors, but oral administration may facilitate bromelain in preserving its proteolytic activity (Orsini 2006).

Researchers stimulated mouse ileum to induce contractions and then administered bromelain, resulting in the inhibition of contractions. This suggests bromelain inhibits intestinal motility. This discovery could help bromelain become a leading drug in regulating intestinal motility in intestinal inflammation as well as diabetes (Borrelli et al. 2011). Bromelain also hinders tumor growth by 90% in Lewis lung carcinoma, YC-lymphoma, and MCA-1 ascitic tumor even after destruction of the proteolytic activity by heat. This indicates that another factor is responsible for the anticancer effect observed in pineapple (Taussig and Batkin 1988). Bromelain also reduces platelet adhesion to endothelial cells as well as platelet aggregation. In addition, it has the ability to stimulate plasminogen to produce plasmin, which can then cleave fibrin and decrease fibrin levels (Maurer 2001).

Components of *Ananas comosus*

Plant	
2,5-dimethyl-4-hydroxy-3(2H)-furanone (1.2 ppm)	Ethyl propionate
5-hydroxytryptamine	Gaba
acrylic acid	Gamma-butyrolactone
ananasic acid	Gamma-caprolactone (.12 ppm)
beta-methyl-thiopropionic-acid-ethyl-ester	Gamma-octalactone (.3 ppm)
beta-methyl-thiopropionic-acid-methyl-ester	Hexosans (1000-1500 ppm)
ergosterol peroxide	Indole acetic acid oxidase
ferulic acid (200-760 ppm)	Isobutanol
p-coumaric acid (330-730 ppm)	Isobutyl acetate
stigmast-5-ene-3-beta-7-alpha-diol	Isobutyl formate
tetrahydro-alpha-alpha-5-trimethyl-5-vinylfurfuryl-alc	Isocaproic acid
	Isopropyl isobutyrate
	L-malic acid
	Malid acid (1000-4700 ppm)
	Methanol
	Methyl acetate
	Methyl-beta-acetoxyhexanoate
	Methyl-beta-hydroxybutyrate
	Methyl-beta-hydroxyhexanoate
	Methyl-beta-methylthiopropionate
	Methyl butyrate
	Methyl caproate
	Methyl caprylate (.75 ppm)
	Methyl-cis-4-octenoate (.001 ppm)
	Methyl isobutyrate
	Methyl isocaproate (1.4 ppm)
	Methyl isovalerate (.6 ppm)
	Methyl-n-propyl ketone
	N-valerianic acid
	Nitrate (1200 ppm)
	Oxalic acid (50-58 ppm)
	P-aminobenzoic acid (1 ppm)
	P-coumaric acid (330-730 ppm)
	Pentanol
	Pentosans (3300-4300 ppm)
	Phosphatase
	Phytosterols (60-444 ppm)
	Propanol
	Propyl acetate
	Propyl formate
	Serotonin (19-60 ppm)
	Vanillin
	Vit-b-6 (.9-6 ppm)
Fruit	
Acetic acid (.49 ppm)	
Acetoxyacetone	
Alpha-linolenic acid (620-4592 ppm)	
Amyl caproate	
Asparagine (1251 ppm)	
Biacetyl	
Bromelain	
Bromelin	
Butyl formate	
Chavicol (.27 ppm)	
Delta octalactone (.3 ppm)	
Dimethyl malonate (.06 ppm)	
Esters (1-250 ppm)	
Ethyl acetate (3-120 ppm)	
Ethyl acrylate (.77 ppm)	
Ethyl alcohol (60 ppm)	
Ethyl-beta-acetoxyhexanoate	
Ethyl-beta-hydroxyhexanoate	
Ethyl-beta-methylthiopropionate	
Ethyl butyrate	
Ethyl caproate (.77 ppm)	
Ethyl caprylate	
Ethyl formate	
Ethyl isobutyrate	
Ethyl isovalerate (.39 ppm)	
Ethyl lactate	

Table 2. Components in *Ananas comosus* (Duke 2010).

Bromelain also has an antisecretory effect. Diarrhea is caused by the activation of the cAMP, cGMP, or calcium-dependent signaling pathways in the large intestine. Using rabbit ileum, researchers found that bromelain prevents changes in these pathways (Mynott et al. 1997).

In vivo

A common question is whether bromelain is absorbed after oral ingestion; researchers found that 40% of labeled bromelain is absorbed from the intestine (Maurer 2001). Bromelain's anticancer effect was tested *in vivo* as well in mice subjected to ultraviolet radiation. Those fed bromelain showed retardation of the growth of lesions (Goldstein et al. 1975). Baez et al. also studied a number of tumor lines *in vivo* including P-388 leukemia, sarcoma (S-37), Ehrlich ascitic tumor, Lewis lung carcinoma, MB-F10 melanoma, and ADC-755 mammary adenocarcinoma. All were administered bromelain intraperitoneally and all had an increase in survival rate besides MB-F10 melanoma (Baez et al. 2007).

Bromelain also has the capability of reducing existing edemas as well as preventing the formation of new edemas (Maurer 2001). Oral bromelain not only reduces swelling and pain but also reduces the time it takes to heal by half. Experiments explored the anti-inflammatory effect of bromelain on edemas in rats along with eight other drugs, including aspirin, and found that bromelain was the most effective in terms of a reduction in inflammation (Taussig and Batkin 1988). Further experiments found similar results of bromelain's potency in comparison to other drugs even when applied intraperitoneally (Smyth, Brennan, and Martin 1962).

Topical bromelain is used for debridement of third degree burns without removing unburned tissue; a study was done on rats with experimental burns in which topical bromelain helped remove damaged tissue with no side effects (Klaue, Aman, and Romen 1979). Bromelain is especially beneficial because it prevents bacterial growth, contamination, and infection to the healthy tissue by removing the burnt tissue (Rosenberg et al. 2004).

Mechanism of action

Bromelain has a number of therapeutic uses implicating that it must have multiple mechanisms (Taussig and Batkin 1988). The anti-platelet and anti-inflammatory effects are related to bromelain's proteolytic activity. However, the anticancer and burn debridement properties are due to some other unknown factor in bromelain. A possible mechanism of action has been proposed for the anticancer property of bromelain which stimulates differentiation of leukemic cells possibly leading to apoptosis of tumor cells (Maurer 2001).

Bromelain's mechanism of action is partially due to the activity of two types of prostaglandins: pro-inflammatory prostaglandins and anti-inflammatory prostaglandins. Pro-inflammatory prostaglandins stimulate inflammation, platelet aggregation, and vasoconstriction. Anti-inflammatory prostaglandins have the opposite effect. Bromelain is a pro-inflammatory prostaglandin inhibitor that is similar to aspirin but weaker so it does not promote bleeding. Bromelain activates plasminogen, which induces plasmin production. Plasmin subsequently cleaves fibrin, which inhibits pro-inflammatory prostaglandins. Consequently the ratio between pro-inflammatory and anti-inflammatory prostaglandins shifts in favor of anti-inflammatory prostaglandins. This leads to the activation of adenylyl cyclase and the production of c-

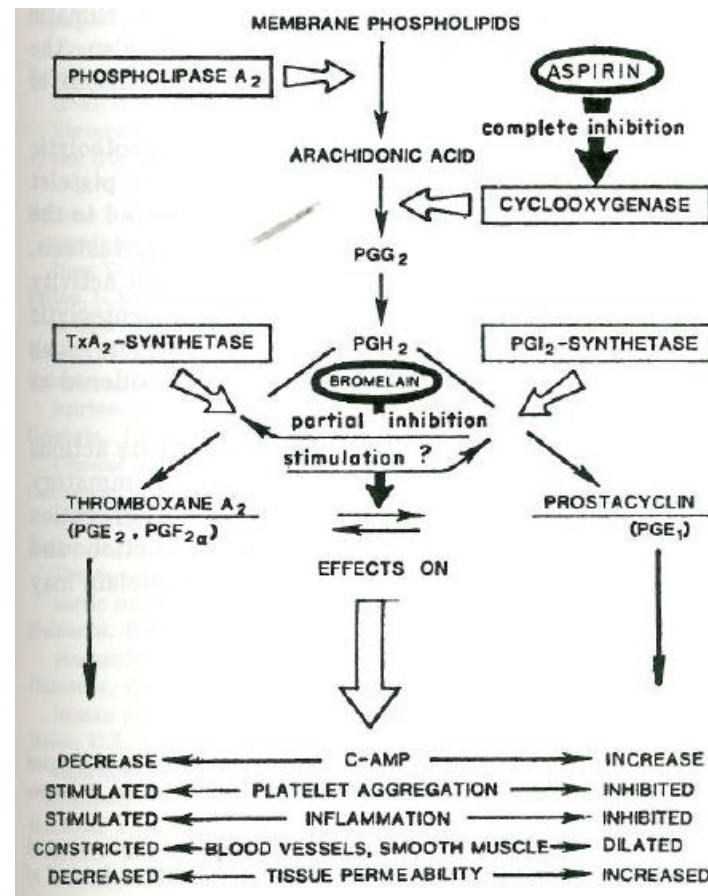


Figure 5. Biosynthesis of prostaglandins and bromelain effect. This diagram illustrates how bromelain and aspirin affect prostaglandins (Source: Taussig and Batkin 1988).

AMP. Anti-inflammatory prostaglandins generally lead to increased c-AMP production, inhibited platelet aggregation, inhibited inflammation, dilated blood vessels and smooth muscles, and increased tissue permeability; this mechanism is illustrated in **Figure 5** (Taussig and Batkin 1988).

Clinical Studies

Pain and Inflammation

Bromelain demonstrates both analgesic and anti-inflammatory properties (Brien et al. 2004). Patients given bromelain felt less pain linked to mediolateral epistomy (Zatuchni and Colombi 1967) and bradykinin (Bodi 1966). Furthermore, bromelain reduces mild knee pain and helps improve general well-being in patients given 200 or 400 mg of oral bromelain (Walker et al. 2002). It has been widely used for inflammation ever since its discovery and is commonly used for rheumatoid arthritis, thrombophlebitis, hematomas, oral inflammations, diabetic ulcers, rectal and perirectal inflammations, oral and plastic surgery (Taussig and Batkin 1988). Researchers found that patients suffering from arthritis with joint swelling when administered bromelain report reduction in swelling, pain, and soreness (Walker et al. 2002). Previous studies have indicated that bromelain may serve as an alternative treatment to NSAIDs for patients suffering from osteoarthritis (Brien et al. 2004). However, the required dosage is unclear; while one study used between 60 and 160 mg of oral bromelain per day (Cohen and Goldman 1964), another study administered 1890 mg of oral bromelain (Tilwe et al. 2001) per day both of which reported reduced pain and swelling. Adverse reactions must also be taken into consideration when assigning dosage. While one study using 945 mg of oral bromelain per day reported gastrointestinal problems and subsequent drop-outs (Singer, Singer, and Oberleitner 2001), the previously mentioned study administering 1890 mg of oral bromelain per day reported no drop-outs or safety issues (Tilwe et al. 2001). Bromelain's use in the treatment of osteoarthritis is promising; however, more studies must be conducted in order to identify an optimum dosage.

Cancer

Bromelain is shown to have an anticancer effect; however, studies verifying this have primarily been *in vivo*. Nevertheless, its activity was tested in a few clinical studies. Twelve patients with different tumors were treated with oral bromelain and were found to have a decrease in ovarian carcinoma, breast cancer, and metastases. Another study found tumor regressions in patients administered high doses of bromelain simultaneously with chemotherapeutic agents such as vincristine. Both studies found that at least 2.4 g per day of bromelain was necessary and dosages less than 1000 mg were insufficient (Taussig and Batkin 1988).

Antibiotics

It has been shown that bromelain can enhance the absorption of antibiotic drugs. It increases tissue permeability yielding enhanced diffusion of the antibiotic after subcutaneous or intramuscular application (Maurer 2001). Researchers found that patients treated with bromelain and antibiotics had an increase in serum and tissue levels of amoxicillin (Tinozzi and Venegoni 1978). Twenty-three patients with pneumonia, bronchitis, staphylococcus infections, thrombophlebitis, as well as other conditions were administered bromelain with antibiotic therapy. These patients previously did not react to antibiotic therapy but after simultaneous bromelain treatment, 22 of the patients responded (Neubauer 1961).

Burn debridement

One of bromelain's few topical treatments is its effectiveness in the debridement of third degree burns. Patients with second and third degree burns were treated with Debridase, a multienzyme combination containing bromelain. Debridement

of the eschar was achieved after only one to two applications (Rosenberg et al. 2004). Eschar is burnt and traumatized tissue that can prevent proper assessment of the burn's depth and lead to bacterial growth, contamination, and infection. Surgical removal is not only painful and results in significant bleeding but it also requires frequent doses of anesthesia (Tochi et al. 2008). Bromelain can achieve the same end result with no blood loss and few side effects (Rosenberg et al. 2004).

Circulation

By inhibiting platelet aggregation, bromelain can serve as an important treatment in cardiac medicine. Patients with a high platelet count or history of heart attack and stroke were treated with oral bromelain leading to a decrease in platelet aggregation (Heinecke, Waal, and Yokoyama 1972). Researchers suggest the activity is due to the activation of plasminogen followed by an increase in fibrinolytic activity, therefore blocking fibrin production (Orsini 2006). Bromelain also inhibits thrombus formation due to its inhibition of platelet aggregation and decreased fibrin production (Tochi et al. 2008).

Contraindications

According to the U.S. Federal Drug Administration, bromelain is generally recognized as safe (Orsini 2006). It has low toxicity and few side effects associated with it (Maurer 2001). Possible adverse effects of bromelain include gastrointestinal problems, headache, fatigue, dry mouth, skin rash, and allergic reactions (Orsini 2006). However, these effects are uncommon in the general population; a study found a 1.8% prevalence of side effects after bromelain administration

(Maurer 2001). It is important to note that higher doses of bromelain will lead to a greater likelihood of exhibiting side effects (Orsini 2006). Since unripe pineapples were used as an abortifacient in the past, pregnant women should limit intake unless used for that purpose (Morton 1987). Consumption of pineapples can also cause allergic reactions in which symptoms include itching, rashes, abdominal pain, vomiting, and diarrhea (Kabir, Speelman, and Islam 1993). The blood glucose response in diabetic patients after pineapple consumption is significantly higher than other fruits such as mango and chico. Due to the increased glucose response and pineapple's identification as a fruit with a high glycemic index (GI), it is suggested that diabetic patients limit intake to moderate amounts (Guevarra and Panlasigui 2000).

Bromelain can potentially increase bleeding when taken with aspirin and warfarin due to its anticoagulant properties. In addition, there is very little research conducted on the drug safety of bromelain in children; most clinical studies focus on adults. Therefore, children should not be given bromelain supplements due to the lack of studies in children. There is also little information on bromelain's effects at high doses, taken long term, or taken in combination with other medication (Orsini 2006). More research is needed for bromelain's use as an established compound for medicinal purposes.

Current Use in Allopathic and CAM Therapies

Bromelain is an extract that yields a yellow powder (Maurer 2001) available in the form of a powder, tablet, cream, or capsule (Orsini 2006). Bromelain is also available in multienzyme combinations in Debridase, Phlogenzym, Wobenzym, and Traumanase (Orsini 2006) (**Figure 6**). Other trade names include Ananase, Bromelain, Resolvit, Extranase,



Figure 6. Examples of bromelain multienzyme herbal supplements. (Source: <http://www.apomio.de>).

and Inflanen (Sittig 2007). The German Commission E recommends 80-320 mg of bromelain two to three times per day. However, if used for arthritis, 500-2000 mg per day should be consumed; for injuries, 500 mg should be consumed four times per day. In order to use bromelain for its anticancer activity, at least 2.4 g per day must be consumed (Taussig and Batkin 1988). Bromelain is a popular supplement in European countries such as Germany; the German Commission E approved bromelain to be used simultaneously with other therapeutic agents in the treatment of inflammations of the nose and sinuses due to surgery (American Cancer Society 2011). It is also recommended to consume the bromelain herbal supplements on an empty stomach to reduce reactions with other foods (University of Maryland Medical Center 2011).

Discussion

Ananas comosus is an important plant with many ethnobotanical and even more medicinal uses. Its primary

constituent, bromelain, is not only an anti-tumor agent, but prevents platelet aggregation and hence thrombus formation. It is an analgesic as well as an anti-inflammatory agent used in a number of conditions such as rheumatoid arthritis, oral inflammations, ulcers, and plastic surgery. Although it can promote antibiotic drug absorption, one of the most important capabilities of bromelain is its use in burn debridement of second and third degree burns. Bromelain is generally recognized as safe and there are very few if any side effects due to it, which can possibly occur at very high doses. However, research is limited in bromelain's use in children as well as the required dosage to view its effects. With more research, *A. comosus* can serve as an important plant for the treatment of dermatological disorders, inflammatory conditions, as well as cancer treatments in the future.

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Arctostaphylos uva-ursi (L.) Spreng., Ericaceae

Marston Jones

Introduction

Arctostaphylos uva-ursi (L.) Spreng. is a well-known plant in the Ericaceae family. It goes by many names due to its thorough distribution across the northern hemisphere, and because it has been widely used from North America and Canada, through Europe, and into Russia. Kinnikinnick, or bearberry, as it is most often referred to in the English language, grows in North America from northern California stretching up into Alaska, across Canada and the northern U.S., and even to New England and Newfoundland. On the western portion of the states, it follows the Rocky Mountains down into New Mexico, and can be found throughout the Appalachian mountains, even as far south as Georgia (Crane, 1991). The berries are a well known food source for bears, grouse, and deer (Kuhlein and Turner, 1991). This may be due to the fact that the fruit spoils slowly, so it is available throughout winter and into spring, which means it can be a constant food source when others are no longer available. It can withstand low summer moisture, salt-spray, and can grow slowly in semi-shady conditions. In some places it may also be a good indicator of areas that are moisture deficient, and grows rapidly in areas following moderate disturbances (Crane, 1991).

It was first reported for medicinal use in the thirteenth century, and throughout time has made its way into many pharmacopeias because of its wide range of uses. In 1601, it had reported use as a hemostatic, and by the time Western medicine began to flourish, beginning with Spanish and Italian physicians, bearberry found use for calculus complaints,



Figure 1. *Arctostaphylos uva-ursi* flowers. (Source: http://calphotos.berkeley.edu/cgi/img_query?enlarge=0000+0000+0506+1197)

bladder and kidney disorders, and urogenital disorders, though since then many more uses have been recorded (Kay, 1996; Radulovic et al., 2010).

Botanical Description

Arctostaphylos uva-ursi is a prostrate, evergreen shrub with dark green, leathery leaves and twisted trunks. The leaves are

obovate and smooth edged while the bark is thin and reddish brown. The plant flowers with white-pink urn shaped clusters, and is followed by red berries (**Figures 1 & 2**). The berries themselves are noted to be very dry and mealy when eaten. The plant can be found at altitudes from 3000 to 9000 feet, and often in open, rocky slopes and sandy areas. (Kuhnlein and Turner, 1991; Kay, 1996; Crane, 1991) Bearberry can be confused with both cowberry (*Vaccinium vitis-idaea* L., Ericaceae) and box (*Buxus sempervirens* L., Buxaceae), but while box does not share the same pharmacological constituents as bearberry, cowberry could potentially be used as a suitable substitution in certain cases (Radulovic, 2010).

Traditional Uses

Bearberry has been used over time for many different reasons. Much of the information available pertains to its use by Native Americans of North America, though its use is certainly not limited to one group of indigenous people or a single area. It's been noted to have appeared in the thirteenth century pharmacopoeia of the Welsh, "Physicians of Myddfai", in addition to being mentioned by Gerhard in Berlin around 1763 (McKenna et al., 2002). Its use continued to be recorded in many different locations for a variety of applications. One of the most widely mentioned uses of *A. uva-ursi* comes from its leaves. The leaves of the plant were used in smoking mixtures, either to be mixed in with tobacco to lessen the harsh taste, or to be toasted in an oven to be smoked alone (Kuhlein and Turner, 1991; Crane, 1991, Duke, 1985). Another name by which bearberry is known, Kinnikinnick, means smoking mixture, but the leaves of *A. uva-ursi* are generally used in conjunction with other plants and not just smoked by themselves (Willard, 1992). The smoke from the



Figure 2. *A. uva-ursi* fruits. (Source: http://calphotos.berkeley.edu/cgi/img_query?enlarge=9189+3301+3549+0113)

leaves was also used by some tribes to attract game and to treat earache (Pennachio et al, 2010). Some of its earlier uses were based on its astringent properties, and it was used as a wash for sores, to treat kidney pain, and as a tea for cold, chest, and lung conditions (Kay, 1996).

The fact that the berries of the plant are edible gave way to another simple use: food. In some instances it could be used as an "emergency food" because of its nature of lasting through winter, but it was also eaten in general by many North American tribes. The berries can be eaten raw, but because of their dry mealy texture, many recorded instances involve individuals roasting and cooking the berries, and even mixing them with animal grease (Kuhlein and Turner, 1991; Duke, 1985). There are many more advantages of the plant, such as using the leaves for tanning in Sweden and Russia, and using different methods for the treatment of backache,

bladder ailments, bronchitis, diabetes, diarrhea, dysentery, dysurea, fever, hemorrhoids, hepatitis, nephritis, pancreatitis, rheumatism, ulcers, urinary disorders and many other issues (Duke, 1985; McKenna et al. 2002).

Bearberry's long history of use as an anti-inflammatory and antiseptic has led to specific application that helps aid in strengthening the tone of urinary passages in response to inflammatory diseases. Many different Native American tribes would prepare an infusion for the urinary tract and also for venereal disease, with some even using the leaves as a poultice to for swelling and sprains (McKenna et al., 2002). Its use has continued up through the 19th and 20th centuries, being used widely now in homeopathic remedies for many of the aforementioned maladies (Duke, 1985).

Chemistry and Pharmacology

Bearberry contains phenols, tanning agents and flavonoids. The flavonoids can be used to chemically differentiate the taxa within the genus, and are may be different depending on the geographical origin of the plant (McKenna et al., 2002) Its main phenolic constituent is arbutin, its most notable compound (**Figure 3**), with a content level of about 5-18%. Its main flavonoid is quercetin-3-0-galactoside. *A. uva-ursi* also contains 6-40% tannin, methyl arbutin, ericinol, ericolin, allantoin, isoquercetin, gallic acid, malic acid, quinic acid, ursolic acid, ursone, ellagic acid, uvaol, hyperin, myricetin, myricitrin, corilagin, and pyroside, to name a few (Kay, 1996; Kenndler, 1990; Duke, 1985)

Biological Activity

For the current uses of bearberry, arbutin is the chemically active compound of importance. It has antimicrobial activities

Arbutin

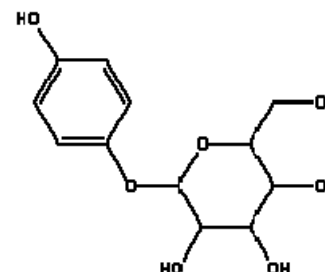


Figure 3. Structure of arbutin. (Source: <http://ntp.niehs.nih.gov/files/Arbutin.pdf>)

which is why, nowadays, the plant is used primarily as a treatment for urogenital diseases, or at least marketed as such. Many different things can be natural antioxidants: phenolic compounds such as flavonoids, phenolic acids, and tannins, nitrogen containing compounds such as alkaoids, chlorophyll derivatives, amino acids, peptides, and also carotendoids, tocopherols or ascorbic acid and its derviatves. Epidemiological evidence shows that eating items containing a large number of these antioxidant phytonutrients is very healthy (Amarowicz et al. 2004). Bearberry contains several compounds that fall under these categories, but another pharmacologically active compound of medical importance in this plant is hydroquinone, which is the result of *in vivo* glucoside cleavage of arbutin (Kenndler, 1990). The antimicrobial activity of the plant is dependent on arbutin being hydrolysed by β -glucosidase to yield hydroquinone which is an antiseptic and an astringent (Heinrich et al., 2004).

In a study performed by Radulovic et al. (2010) using GC and GC/MS analyses, 243 different constituents were identified in *Arctostaphylos uva-ursi* oils. Within the *A. uva-ursi*, α -

terpineol, linalool, hexdeconic acid, and (E)-geranyl acetone were predominant. There were high levels of terpenoids, in addition to fatty acid derived compounds, and fatty acid ester and carotenoid derived compounds also made up a large portion of the oils. The study stressed that the essential oils contained in this plant are vital to the contribution of any medicinal properties, even though they may be found in very small amounts.

A study performed by Dykes et al. (2003) looked at the biological effects of antioxidants extracted from *A. uva-ursi* on food-related bacteria. The antioxidant activity in extracts is beneficial to human cells, and will hopefully have the potential to serve as a natural replacement to synthetic antioxidants for foodstuffs. Dykes et al notes that ethanolic extracts have already been found to have “potent antioxidant activity” in model and meat systems, and while this plant has been used traditionally as antiseptics in European countries, the use as an antioxidant in foods will be a new non-medical use for the plant. The study showed that the extract used affected the hydrophobicity of a very wide variety of bacteria, and hydrophobicity can be associated with increased pathogenicity and ability to invade human cells. While some bacteria actually increased in hydrophobicity, others, such as *S. aureus*, saw a substantial decrease. The authors caution against use of plant extracts as nutraceuticals, but support that bearberry does show antibiotic effects against various strains of bacteria.

Clinical Studies

In a clinical study performed by Larsson et al (2003), women who had been through multiple bouts of cystitis (at least three) before the study were treated with UVA-E or a placebo for a month. UVA-E contained a hydroalcoholic extract from

the leaves of *Arctostaphylos uva-ursi* as well an extract from *Taraxacum officinale*, which provided mild diuretic effects. After being given three pills a day for a month of either UVA-E or the placebo, there was a significant effect on the recurrence of cystitis between the two groups. None of the women in the UVA-E group experienced a recurrence, whereas 5 of the women in the placebo group did. The researchers concluded that UVA-E had a significant prophylactic effect on recurrent cystitis, but also noted that it may only act on the most common microorganisms to be isolated in cases of urinary tract infections.

While there are not many clinical studies directly relating to the use of *A. uva-ursi*, there are studies looking at potential effects that arbutin, one of bearberry’s primary constituents has on the human body, and the ways that the two interact. In a study by Blaut et al (2006), hydroquinone, a mutagenic and carcinogenic substance that is an aglycone of arbutin, was shown to be present in fecal slurries from several human subjects. The release of this aglycone due to glycosylation by intestinal species was determined to pose a potential risk, even though a large majority of arbutin (65-75%) is excreted in urine. Any potential dangers would also be directly related to large consumption of foods containing arbutin as well.

Contraindications

If making a tea from the leaves of *Arctostaphylos uva-ursi*, one should be careful not to extract using hot water to minimize the tannin content and avoid upsetting the stomach. Prolonged use is also cautioned against because of the high tannin content and the hydroquinones which can damage the liver in high doses (Kay, 1996). Very large doses containing hydroquinone are oxytoxic and can lead to collapse, convulsion, delirium, nausea, tinnitus and possibly death

(Duke, 1985). For the compounds to have antiseptic properties on the urinary tract, urine must be alkaline, so acidic foods should not be consumed during treatment (Heinrich et al., 2004).

Current Use in Allopathic and CAM therapies

Bearberry is recommended in homeopathy for cystitis, dysuria, hematuria, incontinence, pyelitis, urethritis, and urogenital disorders. Because arbutin shows antiseptic affects on the urinary mucous membrane, it is also used for cervical ulcerations, cystitis, blennorrhoea, enuresis, gallstones, gonorrhoea, gout, and nephritis (Duke, 1985). Willard (1992) even suggests soaking feet in a strong decoction of the plant for one hour the night before a long hike or walk to “toughen up the feet” and to avoid blisters. Other than its advantages in treating urinary tract infections, many of the uses of *A. uva-ursi* are yet to be fully investigated scientifically (McKenna et al. 2002). There are plenty of available products that contain bearberry ranging from simple supplement and vitamin items to skin care products (Figure 4).

Discussion

For a small shrub, *Arctostaphylos uva-ursi* has been utilized in an incredibly large variety of ways for centuries. This is due in part to its abundance in the northern hemisphere, and as a result of record keeping of its use throughout history. Its many different names are evidence of its widespread influence and use, as well as its efficacy. Other than research showing its ability to aid against urogenital problems, few studies have been done to verify the many different ways that the plant has been utilized in the past, but the fact that so many uses exist stands as a testament to the versatility of this plant. It



Figure 4. Uva ursi products. (Source: <http://www.herbalremedies.com/uva-ursi-standardized.html> ; <http://www.herbalremedies.com/17600.html> ; <http://www.johnmasters.com/osc.htm>)

continues to be used in homeopathic remedies, and can still be easily found in many of the regions where it has grown for years. Some characteristics about the plant, such as its astringent, anti-inflammatory, and antiseptic properties have been well studied, but there is still much to learn, and ways to make sure its use either as a strictly homeopathic or maybe even allopathic remedy are safe and viable.

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Armoracia rusticana G. Gaertn., B. Mey. & Scherb., Brassicaceae

Andrew Mongue

Introduction

Armoracia rusticana, more commonly known as horseradish, is a member of the Brassicaceae family which includes broccoli, turnips, and mustard (Sampliner & Miller, 2009). The name *Armoracia* comes from Celtic and roughly means “near the sea.” Another old name, searadish, furthers the idea that this plant was traditionally found near the coast. The German for searadish was ‘meerettich’ and it has been proposed that the name horseradish resulted as a mistranslation confusing ‘meer’ (sea) for ‘mare’ (a female horse) (Courter & Rhodes, 1969). However the common name came to be, it is rather ironic because horseradish is toxic to horses, pigs, and cattle. Despite the widespread occurrence of *A. rusticana* in the United States however, reports of livestock poisoning are rare, perhaps do to the pungent taste of the plant (DiTomaso).

This plant derives its famous smell and taste from a class of compounds known as isothiocyanates, which are also responsible for much of its biological activity and therefore important in its medicinal uses (Nedorostova et al., 2011). These chemicals are natural antibiotics with broad ranging applications from the treatment of sinus infections to the preservation of food.

The other major class of chemicals is the peroxidase enzyme family found in horseradish. These compounds have a range of uses in both laboratory and industrial settings. They can be used in everything from waste treatment to chemotherapy (Govere et al., 2005; Greco, Folkes, Wardman, Tozer, & Dachs, 2000).



Figure 1. Whole view of a horseradish plant. Image source: http://www.finecooking.com/assets/uploads/posts/5645/ING-horseradish-2_sql.jpg

For centuries *A. rusticana* has been recognized as a source of food and medicine, though its uses have changed through time. During its history of use the plant we know today was created through directed selection (commonly known as

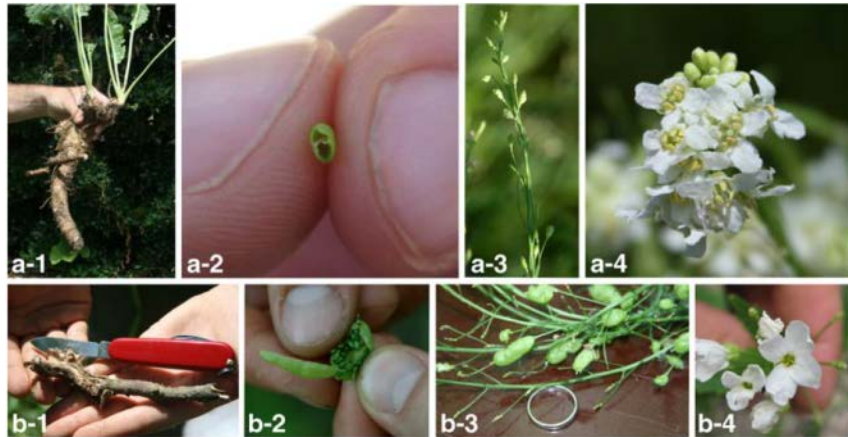


Figure 2. Features of *A. rusticana* (a) compared to the closely related *A. macrocarpa* (b). Note the lack of seeds in a-2 compared to b-2 and the increased root size in a-1 compared to b-1. Image adapted from Sampliner & Miller, 2009.

domestication); however its status is now in doubt because of its apparent inability to produce seeds (Courter & Rhodes, 1969). As discussed below, despite the continued apparent success of horseradish as a crop, the method of its cultivation could lead to problems in the future. This cannot be allowed given all of the applications botanists are just now discovering for this versatile plant.

Botanical Description

Though *Armoracia rusticana* is now grown on several continents worldwide, it is believed that horseradish most likely originated in Europe. Wild populations in America began to grow in Boston in 1840 and were likely the result of previously cultivated plants being abandoned and left to

propagate on their own (Courter & Rhodes, 1969). Outside of cultivation it grows best in wet, disturbed areas such as fields and along roadsides.

A. rusticana, like all members of the *Armoracia* genus, is a perennial herb. Horseradish has smaller flowers than other members of its genus, but like all *Armoracia* species, its flowers are four-merous and white in color. Its hairless, crenulated leaves are arranged in a rosette and grow basally (**Figure 2**). Despite continued fruit production, it is unclear whether this species has retained its non-vegetative reproductive ability. Since its domestication it has been propagated almost exclusively from root cuttings and many *A. rusticana* fruits in domestication lack seeds entirely (Sampliner & Miller, 2009). One suggested reason for this apparent sterility is the possibility that domestic horseradish is an interspecific hybrid of two true species. The observation that chromosome count varies between individuals and even within an individual plant (leading to partial chromosomal pairing) supports the hybrid theory (Courter & Rhodes, 1969).

Alternatively, some researchers now believe that horseradish as we know it, *A. rusticana*, is nothing more than a domesticated form of other wild *Armoracia* species. Evidence for this is mostly negative, that is to say, despite surveying efforts no *A. rusticana* specimens have been recorded in the wild. They can be found only in areas associated with current or previous human cultivation. Some possible positive evidence is the relative root size of horseradish in comparison to other *Armoracia* species. *A. rusticana* roots are much larger than those of related herbs, suggesting that this trait may have been cultivated by human rather than natural selection (Sampliner & Miller, 2009).

The sterility phenomenon was examined by experiments conducted on seed production in various American cultivars

of horseradish. Plants from various backgrounds (i.e. commercial farming and untended “wild” locations) were collected and allowed to flower. In the overwhelming majority of cases the plants could not produce functional pollen grains. In those that did, no more than 50% of pollen was viable, and those plants were effectively incapable of producing viable seeds through self-fertilizing. Outcrossing between the two varieties collected (Bohemian and common) had the greatest success in securing seed but even then only one to two seeds were obtained per fruit. When planted, these seeds successfully germinated and grew, suggesting that there is hope for restoration of sexual reproduction (Weber, 1949).

Traditional Uses

References to *Armoracia rusticana* by Dioscorides place its first confirmed use to roughly two thousand years ago. While Europe has a long history of using this plant, cultivation in America can only be traced back to 1806. The now robust agricultural production of horseradish can be specifically linked to the Sell and Sass families who immigrated from Germany to Chicago in the 1850’s (Courter & Rhodes, 1969). To this day, the plant is a successful commercial crop and is still grown throughout Illinois (Walters & Wahle, 2010). Typically, only the taproot is sold commercially while the smaller offshoot roots are used as propagates for next year’s crop (Courter & Rhodes, 1969).

The now gigantic condiment business started by Henry Heinz also has its roots with *A. rusticana*. The would-be condiment king grew up in Pennsylvania, which by this time was recognized as a fertile ground for horseradish. At the beginning of his career in the mid-eighteen hundreds, foods like horseradish were either grown by individuals or by small vendors who then bottled and sold preserves locally in green

or brown glass jars. Anecdotal reports of other plants and even wood chips used to pad out the contents of these jars speak to a general lack of quality in the condiment market at the time.

The key then to Heinz’s success was in the way he preserved the condiment. By boiling the preserves in clear glass jars in salt water after packing he could boast a superior quality that customers could clearly see. Additionally, this sterilizing process meant he could ship goods to more distant markets and eventually become a national and then international name brand. Though Heinz today is synonymous with tomatoes and ketchup it is important to note that it all started with horseradish (Koehn, 1999).

In cooking, horseradish has been used as a flavoring condiment on everything from meats to salads. German recipes including *A. rusticana* can be found as early as the 1500’s (Courter & Rhodes, 1969). The root can be grated directly onto food or mixed with ketchup, vinegar, or oil to form a sauce. In some cases the root is boiled, squeezed, washed, and mixed with salt and sugar to remove some of the isothiocyanates which cause its pungent taste.

Leaves and roots of *A. rusticana* are used in the process of pickling other vegetables, which allows them to be stored for much longer periods of time. In some places it is still the preferred method of generating a stock of food for the winter. The plant is also fermented to produce a Romanian brandy called Tuica (Sampliner & Miller, 2009).

Horseradish has a long tradition of ritualistic use as well. It is one of the traditional plants eaten during Jewish Passover.

English herbalist John Gerard studied horseradish in the sixteenth century. His medical uses included treatment of colic and sciatica. It was also reported as a diuretic and an

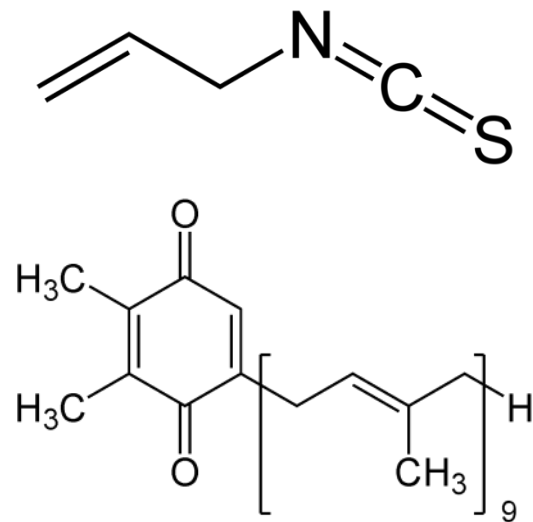


Figure 1. Structure of allyl isothiocyanate (top) and plastiquinone-9 (bottom). Images source:

<http://upload.wikimedia.org/wikipedia/commons/9/98/Allyl-isothiocyanate-2D-skeletal.png> and <http://upload.wikimedia.org/wikipedia/commons/3/3b/Plastoquinone.png>

aphrodisiac. *A. rusticana* was also used to kill parasitic worms in children and promote the expulsion of afterbirth (Courter & Rhodes, 1969). While its agricultural uses have remained largely unchanged, today's medical uses are quite different from those described above.

Chemistry and Pharmacology

The essential oils of *Armoracia rusticana* consist almost entirely (i.e. nearly 98%) of allyl isothiocyanate (Chen, Akinkurolere, & Zhang, 2011). This compound, along with butyl isothiocyanate and phenylethyl isothiocyanate are

responsible for the distinct aroma of the plant (Courter & Rhodes, 1969; Nedorostova et al., 2011).

The peroxidase enzymes found naturally in *A. rusticana* can be used to screen for the presence of phenolic compounds in water samples (Gonzalez-Sanchez, Laurenti, Rubio-Retama, Valero, & Lopez-Cabarcos, 2011). Additionally peroxidase has been proposed as part of the treatment for bladder, breast, and nasoesophageal cancer (Greco et al., 2001).

Three more compounds from horseradish (plastoquinone-9, see **Figure 3**; 1,2-dilinolenoly-3-galactosylglycerol; and 6-O-acyl-β-D-glucosyl-β-sitosterol) have been implicated in cancer inhibition (M. J. Weil, Y. Zhang, & M. G. Nair, 2005).

Biological Activity

Enzymes in the peroxidase family have a range of applications as oxidizing agents and can be efficiently recovered (up to 72% yield) from relatively simple extraction and purification methods applied to *Armoracia rusticana* roots (Lavery et al., 2010). There have also been studies showing that certain genetically modified moth larva can be made to produce peroxidase, thus providing an alternative source with similarly high yields (Romero, Targovnik, Wolman, Cascone, & Miranda, 2011).

One example of horseradish peroxidase use is in the farm industry. Here it has been proven effective as a deodorant when added to livestock manure. It removes malodorous phenolics for up to three days per application (Govere et al., 2005).

Allyl isothiocyanate (**Figure 3**), an essential oil of *A. rusticana*, has shown promise as a natural fumigant that is lethal to at least two common crop pests, weevils and meal moths. It has been proposed that this gaseous compound suffocates insects

by blocking their spiracles and thus preventing oxygen from reaching their internal tissues. This hypothesis is supported by the observation that allyl isothiocyanate is effective against adult weevils but not to their pupae, which are less permeable to gases due to their structure (Chen et al., 2011).

Essential oils from *A. rusticana*, composed of allyl isothiocyanate along with the related phenylethyl isothiocyanate, were tested as gaseous antibiotics in an *in vitro* study alongside extracts from several other plants, including garlic. Researchers found the isothiocyanates to be the most effective oils tested (as determined by the minimum inhibitory concentration), effective against even MRSA *Staphylococcus aureus*. As such, it could have applications as a nontoxic disinfectant spray pending clinical trials (Nedorostova et al., 2011).

Finally with regard to isothiocyanates, there is some evidence that these phytochemicals may have applications as a preservative. One study found that adding no more than 300 parts per million of isothiocyanates, distilled from *A. rusticana* root, to commercial grade tofu was enough to significantly decrease bacterial growth and increase shelf life of the product (Shin et al., 2010). This idea is particularly appealing since isothiocyanates are organic and nontoxic to humans at such concentrations.

Laboratory studies suggest that the roots of *A. rusticana* are quite effective at removing harmful substances from the soil. By adding phosphate to soil containing uranium, the roots were able to absorb 98% of the heavy metal and even without the phosphate assistance the plants removed more than 80% of the uranium (Soudek, Petrova, Benesova, & Vanek, 2011). In another experiment, horseradish root completely depleted soil concentrations of the pharmaceutical acetaminophen, making it a good candidate for use in phytoremediation, the

use of plants to deal with environmental contamination (Kotyza, Soudek, Kafka, & Vanek, 2010).

The aforementioned anti-cancer potential of horseradish comes from two different mechanisms. First are the inhibitory effects of plastoquinone, sitosterol, and galactosylglycerol on the cyclooxygenase-1 (COX-1) enzyme in cancer cells. When purified, these compounds showed 50 to 75% inhibition of the COX-1 enzyme and growth inhibition in both lung and colon cancer cell lines (Marvin J. Weil, Yanjun Zhang, & Muraleedharan G. Nair, 2005).

The second approach to cancer treatment uses the nascent technique of gene therapy. Researchers found that by inserting the gene for the already discussed peroxidase enzyme, also known as horseradish peroxidase (HRP), into bladder cancer cells, these cells became susceptible to the otherwise harmless plant hormone indole-3-acetic acid (IAA). Cancer cell DNA became condensed and fragmented, ultimately leading to cell death (Greco, Dachs, Tozer, & Kanthou, 2002). This treatment shows promise because IAA is a long lasting chemical that can cross cell membranes, but it is not inherently toxic. Thus it would not produce the deleterious side effects of many chemotherapies (Greco et al., 2000).

A follow up study expanded the treatment using HRP to treat two other cancer cell lines, with more promising results. This study also noted that successful treatment could be obtained through proportionally low successful integration of the target gene. Even when only 5% of cells expressed HRP, up to 90% of cancer cells were killed by IAA treatment. Additionally, researchers found that by modifying IAA slightly, they could achieve better results, indicating great potential for this treatment. Like most gene therapies however, HRP therapy is

not yet in clinical trials and has to undergo more testing before reaching public use (Greco et al., 2001).

Clinical Studies

A double blind study in Germany examined the use of *Armoracia rusticana* as an ingredient in an herbal treatment for urinary tract infections. Participants took two doses a day for a three month period. At the end of the study it was found that patients on the *A. rusticana* derived treatment, marketed as Anti-Infekt N, had a significantly lower recurrence of urinary tract infections with no adverse side effects thus making it a safe and effective treatment option (Albrecht, Goos, & Schneider, 2007).

Another study using the same drug, Anti-Infekt N, and a much larger pool of participants also found it to be as safe and effective in treating sinusitis and bronchitis as traditional antibiotic regimens. That is, both treatment groups saw comparable reductions in symptoms (around 80% in both treatments) at the end of the study (Goos, Albrecht, & Schneider, 2006). It is worth noting that both the respiratory and urinary tract infection treatments are traditional applications as well, demonstrating that traditional knowledge has much to offer modern medicine.

Contraindications

While the human trials above showed no harmful side effects, in vitro studies involving rats suggest that consuming more than eight milligrams per kilogram of the isothiocyanates found in *Amoracia rusticana* on a regular basis can cause bladder lesions (Hasumura et al., 2011).

Since Hasumura et al.'s study found no other side effects and the dosages were much higher than the dosages in Albrecht et al.'s study, the results of the Hasumura study should not be seen as evidence against the therapeutic use of *A. rusticana* taken at typical or traditional quantities.

Of note for the cancer inhibition research, the same scientists who found cancer inhibiting effects also found that another horseradish compound, desulfosinigrin, actually promoted proliferation of colon and lung cancer cells (Weil, Zhang, & Nair, 2004). As mentioned in their later study with COX-1 inhibitory enzymes, *A. rusticana* possesses cancer inhibiting chemicals as well. The authors suggest that in typical culinary use these two effects balance each other out and result in no effect on cancer risks (M. J. Weil et al., 2005).

Finally, as a culinary and supplement note, like most members of the Brassicaceae family, horseradish has been classified as a goitrogen. Consumption of raw goitrogens leads to decreased thyroid function which can cause goiters over a period of time (Robbins, 2007). The chemical culprits here are the abundant isothiocyanates which are part of a broader class of known goitrogens: thiocyanates (Keshteli, Hashemipour, Siavash, & Amini, 2010). Additionally as discussed with relation to the origin of the common name, horseradish is toxic to some domestic animals and should thus be separated from livestock if grown in their presence (DiTomaso).

Current Uses in Allopathic and CAM Therapies

Armoracia rusticana has both internal and external historical use as a remedy and continues to be used as such in some European countries. For rheumatic pain and headache, grated horseradish roots or leaves are wrapped in cloth and applied to the skin at the site of pain. The same preparation is used in

treating sinusitis with the cloth being placed on the throat. For internal use it is often mixed with other ingredients like honey or vinegar and sugar and ingested to treat cough or high blood pressure, respectively. In some countries, like Romania, it is common to eat a teaspoon of *A. rusticana* daily prophylactically (Sampliner & Miller, 2009).

As a western dietary supplement, horseradish is sometimes sold as a powder or pill, made by grinding up roots which can sell for over seventy dollars per pound. It is marketed in much the same ways it has been historically used. It is purported to be beneficial to the lungs and sinuses as well as kidneys and bladder. In addition, *A. rusticana* supplements are said to increase blood flow to extremities. Warnings attached to this product include specific mention that individuals with thyroid problems should not take horseradish supplements (Plus, 2011). As a liquid extract horseradish root is dissolved in water and alcohol; it can sell for seven dollars per ounce and is marketed as a treatment for urinary and respiratory tract infections. Additional claims include relief from gout, indigestion, rheumatism, and influenza (Creek).

Discussion

Human domestication of plants like *Armoracia rusticana* has significantly altered them, both phenotypically and genotypically. Most immediately obvious is the increase in size of consumable plant parts like flowers, fruits, leaves, or roots depending on the plant (compare the roots of the now predominantly if not exclusively domestic *A. rusticana* with the still wild *A. macrocarpa* in **Figure 2**), but domestication also has the effect of bottlenecking the gene pool for the targeted species. Domesticated crops show a decrease in genetic diversity compared to wild plants (Doebley, Gaut, & Smith, 2006).

As mentioned above, the apparent decrease in fecundity in *Armoracia rusticana* may be a result of a drastic loss of genetic diversity. In cultivation, this problem is circumvented by root propagation with great success (Sampliner & Miller, 2009); however, it should be noted that this method essentially creates clones of the main plant and can only ideally preserve or more realistically decrease, but not increase, genetic diversity. From an evolutionary point of view, this implies that as an agricultural crop horseradish is highly vulnerable to disease since any disease able to infect one plant would necessarily be adapted to infect all the plants propagated from that plant. Indeed there are reports that this is the case; some estimates claim effectively 100% of one *A. rusticana* variety is susceptible to mosaic viruses. It follows that increased efforts to use sexually produced plants (i.e. those from seeds rather than root cuttings) would lead to greater disease resistance and benefit the farming industry (Weber, 1949), but given the current state of the species, this method of farming would not be profitable for some time.

With less variation now it may be harder to select for preferable medicinal or culinary traits. Luckily, the plant in its current state already has a wide range of applications from food preparation to pain relief. Up until now, horseradish has been grown largely for food and minor remedies. However recent research shows that it has great untapped potential.

The essential oils in *A. rusticana* may become another useful tool in the arsenal used to fight drug resistant bacteria and insects. This idea is particularly appealing because the extract of *A. rusticana* is topically nontoxic, making it well suited for use in situations where it could come into contact with people. Isothiocyanate sprays could be used as hospital disinfectants and organic pesticides on food crops in the field. After harvest, perishables could be treated with isothiocyanates to increase their shelf life, leading to greater distribution possibilities and

potentially less wasted food. The issue of thyroid suppression linked to thiocyanates means that the isothiocyanate products would have to be regulated and monitored but their potential should not be left unexplored.

The live plant itself has proven to be a versatile clean-up tool, absorbing heavy metals and pharmaceuticals from the soil. Given this, horseradish could be introduced in industrial accident sites to help dispose of contaminants. In addition, it could be planted downstream from medical facilities to limit the spread of antibiotics and therefore antibiotic resistance to the surrounding ecosystem. The odor blocking activity of the peroxidases combined with the antibiotic properties of the isothiocyanates make *A. rusticana* a good choice for managing animal waste in farm settings. While it is true that horseradish is toxic to some farm animals, using it in a cleaning capacity would be safe as long as the animals were kept away from the waste treatment, which they should be anyway.

There is no doubt that horseradish will continue to enjoy popularity as a condiment; see, for instance, the twenty five year history of the International Horseradish Festival (Davis). Additionally, as mentioned above, it has yet unexploited uses that could benefit a variety of fields, both medicinally and agriculturally. For both of these reasons it is important that this plant is maintained as a viable species, with enough genetic variation to reproduce on its own and survive attacks from disease and changing environmental conditions.

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Artemisia absinthium L., Asteraceae

Michael Clanahan

Introduction

Artemisia absinthium L., commonly known as wormwood, green ginger, or wermot, has been used for thousands of years in a variety of fashions. Although most famous for its role in the production of the alcoholic drink Absinthe, wormwood has played a major part in traditional medical practices in multiple cultures. A few main components of the plant that have been isolated include thujone, absinthin, caffeoylquinic acids, phenols, and select flavonoids, all of which have different physiological effects and in some cases, beneficial health properties.

Traditionally, this plant has been used to treat many different ailments from diabetes to stomachaches to tuberculosis. Used all over the world, this powerful plant has faded in and out of popularity, but continues to have significant medicinal value in many areas.

Botanical Description

Morphologically, wormwood is very similar to other plants in the Asteraceae family. This herb has a perennial root system, and has characteristic firm, branched stems that are woody at the base (Grieve, 2011). Typically, the plant reaches no more than two to three feet, as it is found mainly in arid climates (Arnold, 1989). The leaves of the plant are whitish on both sides, but also contain silvery gray sheen due to short, fine hairs on the indented outside. This sheen can be seen in **Figure 1**. Wormwood is a flowering plant, identifiable by its small globular flower bundles of greenish-yellow tint, mainly



Figure 1. Characteristics sheen of *Artemisia absinthium* L. leaves. (Source: <http://www.flowertropes.com/index/tag/kevin-kline>)

between the months of July and October. (Grieve, 2011). Unlike many other plants of the Asteraceae family, the small wormwood fruits do not contain a crown of hairs, also called “pappus” (Grieve, 2011). Although the leaves and flowers of the plant taste very bitter, the roots have a characteristic aromatic taste. The flowers smell of thujone, an important compound with medicinal values will be discussed. (Grieve, 2011).

Closely related plants include Roman wormwood (*Artemisia pontica*), *A. judaica*, Sea Wormwood (*A. maritima*), as well as

the herb Tarragon (*A. dracunculus*) which is also known commonly as dragon's-wort (Grieve, 2011). Tarragon is found in many spice gardens, and Southernwood (*A. abrotanum*) is found primarily in border habitats between fields. The entire family is characterized not just by physical likeness, but most importantly the intense bitterness contained in all parts of the plant (Grieve, 2011).

Traditional Uses

Wormwood is one of the oldest known herbs to be used in traditional medicine, with evidence tracing its usage back to ancient Egyptians. Wormwood's appearance in the Ebers Papyrus dating from 1550 B.C. support this claim and indicate not only medicinal value, but also religious significance (Arnold, 1989). Another important historical medical document, *Historia Naturalis*, written by Pliny in the first century A.D. mentions wormwood in a medical context that shines light on the common name of the plant. The encyclopedia describes wormwood extract as having powerful effects on gastrointestinal worms, often ridding the human of a large part of the parasitic load (Arnold, 1989). Dioscorides' *De Materia Medica*, completed around 65 A.D., also mentioned wormwood's anthelmintic properties, but included many more applications. These include applications such as a natural insect repellent and a natural antidote to poisoning by hemlock and toadstools (Grieve, 2011). The leaves were commonly dried and stored with garments and furs to protect them from moths (Arnold, 1989). *De Materia Medica's* authority for over 1500 years is illustrated by the fact that John Gerard, a highly revered Elizabethan herbalist in the 1500s, mentions in his book *Herball* that "wormewood voideth away the wormes of the guts" (Mann, 2009).

Wormwood was utilized by other cultures, such as traditional practices in modern day Turkey. In the Kirklareli Province, wormwood is known locally by many names, including pelinotu and pelin. People in this particular area would use almost all of the parts of the plant to treat different ailments. For example, the aerial parts, when prepared as an infusion could be used as an abortifacient, a cure for stomach ache, and appetizer, or a blood depurative. However, when prepared as a decoction and consumed 1-2 times a day for 7-8 days, it could be used to treat diabetes, uterine cysts, and tuberculosis. Also, by cutting the shoots into small pieces and eaten two times a day for 8 days, it is believed to treat malaria (Kültür, 2007). In traditional Caribbean medicine, the plant is used primarily for women's health. This includes treatment for menstrual cramps and vaginitis (Lans, 2007). Wormwood even plays a part in traditional Chinese medicine (TCM) as a treatment for bacillary dysentery (Zhang, 2005).

Wormwood is traditionally most famous for its role in the production of the alcoholic beverage, absinthe. Although used medicinally all over the world for centuries, its narcotic effects did not become significant until around 1790 in Switzerland. Pierre Ordinaire, a French refugee and physician, created an extract of wormwood for use as a stomach tonic. Due to its characteristic green tint and reported hallucinogenic properties, the drink quickly became known as *La Fée Verte*, or The Green Fairy (Lainer, 1995). Early in the 19th century, the drink recipe was acquired by a Frenchman named Major Dubied and his son-in-law, Henry-Louis Pernod. Pernod would eventually take over the company, and his name became historically attached to absinthe (Lainer, 1995). At this point, the drink became associated more with social functions than the medical world. Because of its high price originally, only those in certain circles could afford it, and this included the world of the artists (Lainer, 1995). A few artists known to

have partaken in the consumption of absinthe were Baudelaire, Rimbaud, Picasso, and most famously, Vincent Van Gogh (Ashcraft, 2011). Van Gogh may have been addicted to absinthe in his lifetime. Evidence also suggests that this addiction aggravated his psychosis and that the hallucinations he witnessed stemming from thujone may have caused him to commit suicide (Arnold, 1989). Other artists couldn't get enough. Oscar Wilde once wrote, "What difference is there between a glass of absinthe and a sunset?" (Ashcraft, 2011).

As the drink became more accessible, the general public began to take part. The French public consumed an estimated 700,000 liters of absinthe in 1874. However, due to increased popularity and a severely decreased wine-grape harvest (phylloxera infestation), by 1900, the number of liters consumed surpassed 36 million (Ashcraft, 2011).

Absinthism emerged as a serious disease around this time due to excessive public consumption. Characterized by dazed victims, as well as incredibly vivid hallucinations, absinthism became a serious problem towards the end of the 19th century, and also became a point of attack for those opposing the absinthe business (Arnold, 1989). Some suggested raising the taxes on absinthe to reduce addictions within the population. When this proposal failed, another bill was brought forward and ultimately passed in 1908 that increased the amount of alcohol in absinthe. The explanation for this was that absinthe with a higher degree of alcohol was healthier and that the requirement for higher alcohol content would eliminate those producers who used artificial essences with lower standards of purity," as this was thought to be the reason for some of the addictions (Lanier, 1995). It would not be for another 6 years until the sale absinthe was banned on August 16th, 1914. This was done as an "emergency measure" to stem alcoholism, but absinthe continued to circulate in the public. In January 1915, a presidential decree was issued, explicitly banning absinthe

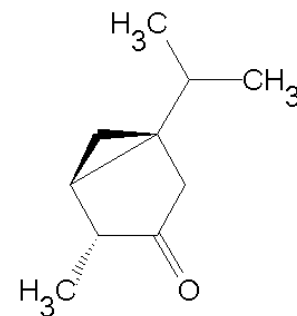


Figure 2. Chemical structure of thujone. (Source: http://www.rdchemicals.com/chemicals.php?mode=details&mol_id=8286)

(Lanier, 1995). Although the fear of alcoholism and absinthism was greatest in France, several countries banned absinthe before France, including Switzerland in 1908, The United States in 1912, and Italy in 1913 (Lanier, 1995).

In 2007, the effective ban was lifted when the Alcohol and Tobacco Tax and Trade Bureau (TTB) redefined the restrictions on the drink. Today, one can buy absinthe in liquor stores, but with one major difference: it is thujone-free. The FDA requires that all thujone be filtered out of the final product before distribution to the public. In order for absinthe to be "thujone-free," it must test for lower than 10ppm (CFR, 2007).

Chemistry and Pharmacology

Wormwood has a rich variety of present compounds. The major constituent is thujone (absinthol), a terpene, which is toxic if ingested in sufficient quantities. Thujone, characterized by its menthol-like odor, is commonly credited with causing the convulsion episodes anecdotally reported to be associated with Absinthe consumption. The structure of thujone can be seen in **Figure 2**.

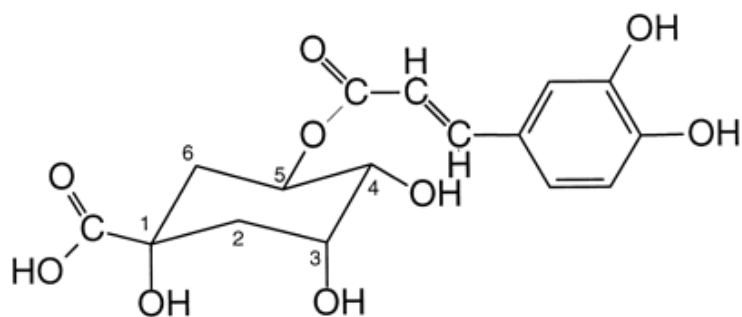


Figure 3. Chemical Structure of 5-caffeoylquinic acid.

(Source: <http://www.39kf.com/cooperate/qk/American-Society-for-Nutrition/037804/2008-12-28-551072.shtml>)

Wormwood's overpowering bitter taste can be directly attributed to its absinthin content. This sesquiterpene lactone has a bitterness threshold of one part per 70,000. In other words, a single ounce can be detected in 524 gallons of water (Arnold, 1989). Interestingly, the King James Bible mentions the bitterness of wormwood a few times. This occurs a few times in the Old Testament, most notably in the book of Proverbs: "But her end is bitter as wormwood, sharp as a two-edged sword" (AV Prov.5:4). Wormwood is again specifically mentioned by name in The Book of Revelations as part of the rapture: "And the third angel sounded, and there fell a great star from heaven, burning as it were a lamp, and it fell upon the third part of the rivers, and upon the fountains of waters; And the name of the star is called Wormwood: and the third part of the waters became wormwood; and many men died of the waters, because they were made bitter" (AV Apoc. 8:10-11). Although the biblical source is accurate in depicting wormwood's intrinsic bitterness, there is no evidence to support its lethality.

Wormwood also contains important compounds called phenols, which have been linked to antioxidant activities. According to Mahmoudi group, wormwood contains 194.9 ± 9.7 mg gallic acid equivalent/g of extract. Polyphenols, or more specifically flavonoids, have also been shown to exhibit antioxidant activities. Total flavonoid levels in *A. absinthium* are 12.4 ± 0.6 mg quercetin equivalent/g of extract, a promising value (Mahmoudi, 2009). It is thought that the antioxidant properties of many phenols and flavonoids may decrease incidence of certain human diseases when the consumption of foods rich in these compounds is increased (Mahmoudi, 2009).

Caffeoylquinic acids contained within wormwood are a relatively new discovery in the scientific community. 5-caffeoylquinic acid is one of the most abundant within *A. absinthium*, and also goes by the name of chlorogenic acid (Fiamegos, 2011). **Figure 3** depicts the structure of 5-caffeoylquinic acid. Studies suggest 5-caffeoylquinic acid is a potent antimicrobial compound, as well as an effective biofilm reducer (Fiamegos, 2011).

Biological Activity

Thujone may be the most important, as well as controversial compound contained within wormwood. Its method of action is thought to be a reduction of GABAA receptor activity, thereby reducing serotonergic responses (Deiml, 2004). Because thujone reduces GABAA receptor activity, neuron-firing inhibition is reduced, allowing neurons to fire more frequently. This is thought to cause the convulsions anecdotally and scientifically reported (Höld, 2000). As stated before, wormwood was traditionally used as an anathematic. Thujone is the compound responsible for this anti-parasitic activity. Although thujone is a toxic substance, and can be

lethal as high doses, ethanol appears to protect against lethal effects of thujone, which may have implications for thujone content in the popular drink, Absinthe (Höld, 2000).

As discussed before, the phenolic and flavonoidic contents of *A. absinthium* exhibit important antioxidant properties. Oxidizing compounds, such as H₂O₂ (hydrogen peroxide) and NO (nitric oxide), can cause severe damage within the human body due to the propagation of free radicals. Although not fully understood, flavonoids exhibited strong reducing potential. When compared to a known reducing (antioxidant) compound, in this case Vitamin C, a methanolic extraction of wormwood flavonoids showed no significant difference in absorbance levels (Mahmoudi, 2009).

Phenolics, including quercetin, may have a direct effect on H₂O₂ scavenging, thereby resulting in the termination of the free radical chain reaction (Mahmoudi, 2009). The structure of quercetin, a polyphenolic, is shown in **Figure 4**. Quercetin showed high antioxidant activity, or high H₂O₂ scavenging activity, as its IC₅₀ was 17.01 ± 0.03 µg/ml. Hydrogen peroxide as a compound does not have a high rate of activity, but can sometimes create hydroxyl radicals within the body (Mahmoudi, 2009). Wormwood phenolics were also extremely effective in chelating Fe²⁺, a transition metal capable of free radical generation from peroxides, with an IC₅₀ value of 419 ± 20.95 µg/ml (Mahmoudi, 2009).

A study from the Ahmad group showed that methanolic wormwood extractions exhibited strong analgesic properties using the tail immersion method in mouse model. Analgesic properties were detectable in all three tested dose levels (300, 500, and 1000 mg/kg), of which the results were dose dependent (Ahmad, 1992). When compared to the standard acetylsalicylic dose of 300 mg/kg, the wormwood extract showed a significantly faster onset of analgesic effects, but

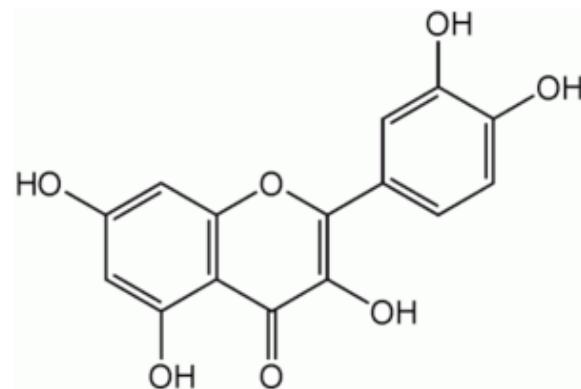


Figure 4. Chemical structure of quercetin. (Source: <http://www.worldofmolecules.com/antioxidants/quercetin.htm>)

ultimately this analgesia was less potent overall (Ahmad, 1992). This same group then studied anti-inflammatory effects of the methanolic extract to conclude that it was effective, but also dosage-dependent. The 1000 mg/kg dose was tested using the hind paw edema method in a mouse model, and again exhibited significant activity. Results showed a peak activity at 3 hours after administration, and a resulting 41% inhibition in increased paw volume (Ahmad, 1992). Again, however, this activity was much less intense and lasted a shorter period of time, as well as a delayed response in anti-inflammation (Ahmad, 1992). Although these effects were exhibited, the exact compounds responsible for the medicinal actions are unknown.

A method of action is unknown for the methanolic wormwood extraction resulting in antidepressant effects in the mouse model. For this experiment, a forced swimming test (FST) was used. The results showed a remarkable decrease in duration of immobility, and were dose dependent (Mahmoudi, 2009). These results can be seen in **Table 1**. The results for the 1000 mg/kg wormwood extraction dose are very similar to the 5

Table 1. Effect of methanol extract of *Artemisia absinthium* L. on the duration of immobility during forced swimming test and tail suspension test.

Group	Dose (mg/kg)	Duration of immobility (s), FST	Duration of immobility (s), TST
Control	-	150.2 ± 8.9	159.6 ± 12
<i>Artemisia</i>	125	130.8 ± 8.2*	93.4 ± 1.2*
<i>Artemisia</i>	250	111.6 ± 5.1*	83.2 ± 1.4*
<i>Artemisia</i>	500	49.2 ± 2.3*	71.2 ± 2.4*
<i>Artemisia</i>	1000	21.0 ± 0.9*	-----
Imipramine	5	21.6 ± 0.7*	-----
Imipramine	10	14.4 ± 0.5*	73.8 ± 4.2*

*ANOVA followed by Newman-Keuls multiple comparisons test shows that all test groups are significantly different from control group ($P < 0.001$). Values are mean ± SD (n = 10).

Table 1. Effect of methanol extract of *Artemisia absinthium* L. on the duration of immobility during forced swimming test and tail suspension test (Mahmoudi, 2009).

mg/kg dose of the antidepressant imipramine, a known serotonin (HT-5) and norepinephrin reuptake inhibitor (Mahmoudi, 2009).

As mentioned before, *A. absinthium* extracts contain a significant amount of 5-caffeoylquinic acid (5-CQA). Recent developments in antimicrobial studies have pointed towards bacterial efflux pumps. Efflux pump inhibitors (EPIs) effectively stop bacteria from expelling antibiotics taken up from the surroundings, therefore effectively allowing the antibiotics to kill the bacteria. Although the effective compounds from *A. absinthium* extracts have not been completely identified, 5-CQA plays a key part in the antimicrobial actions as an EPI by docking with the efflux pump and changing its conformation, effectively cutting off any flow (Fiamegos, 2011).

Clinical Studies

One of the most interesting clinical studies conducted on wormwood involves its usage in treating Crohn's Disease. This disease, characterized by intense abdominal pain and frequent diarrhea, is thought to be an autoimmune disorder, but there is existing evidence pointing towards a viral cause (Smith, 1993). Wormwood extracts contain caffeoyl and dicaffeoylquinic acids that have been shown *in vitro* to inhibit HIV-1 integrase. HIV-1 integrase is responsible for the integration of reversibly transcribed viral DNA into the host genome (Fiamegos, 2011). Another study conducted by Karim et al. (1996), produced evidence suggesting that aqueous extracts of *A. absinthium* are capable of protecting cells against herpes virus (Karim, 1996). The Omer group (2007) conducted a study administering wormwood capsules to Crohn's Disease patients being regularly treated with 5-aminosalicylates and select steroids. For standardization, the wormwood capsules contained 250mg wormwood powder, and a filler consisting of 100mg rose, 40mg cardamom, and 10mg mastic resin, whereas the placebo capsule only contained the filler (Omer, 2007). The results showed that at week 10, 65% of the test group exhibited little to no symptoms of the disease. Even more interesting is that these patients did not need to restart steroid treatment, as there is no remission of the disease (Omer, 2007). Another interesting point is that those patients that benefited from the treatment also experienced a higher quality of life and better mood than those who didn't, according to Hamilton's Depression Scale (Omer, 2007).

Contraindications

As stated before, because thujone reduces GABAA receptor activity, neuron-firing inhibition is reduced, allowing neurons

to fire more frequently. This is thought to cause the convulsions anecdotally and scientifically reported (Höld, 2000). These convulsions were also reported in other sources, along with a possible connection to kidney failure (Ashcraft, 2005). Another source reported thujone as hepatotoxic, as well as damaging to the brain. Other reported side effects include anxiety and sleeplessness (Naser, 2005). Thujone's interactions with other drugs has not been well documented.

Current Use in Allopathic and CAM Therapies

Artemisia absinthium is not used currently in allopathic medicine the United States. However, it is commonly used in CAM therapies as a tea or tincture, and there are claims that it aids in many common ailments, including appetite promotion, anti-anxiety, as well as hastening the child birthing process. Wormwood has even been reported as an effective agent in treating dropsy, as it is believed to be a powerful diuretic (Grieve, 2011). However, because of the negative aura surrounding wormwood from previous centuries, natural supplements and use is relatively low.

Discussion

Artemisia absinthium is an incredibly important historic herb, used for thousands of years for its medical benefits, abused for its hallucinogenic and euphoric properties, and in modern times, studied for its beneficial compounds that aid in fighting disease. Although in past centuries it was abused and consequently received negative light, current applications of incredibly important compounds contained within wormwood (phenols, flavonoids, caffeoylquinic acids, etc.) show a promising future for the plant.

Currently, wormwood's promise in treating Crohn's Disease and other viral diseases is attracting the attention of the scientific community. As stated previously, *A. absinthium* contains large amounts of 5-caffeoylquinic acid (5-CQA), which is being investigated as a compliment to antibiotics. This may have larger implications in the medical community's struggle to keep up with antibiotic-resistant strains of bacteria. If 5-CQA is investigated further in its mechanism and effectiveness against bacteria, it may grant the medical community more time to develop stronger antibiotics.

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Atropa belladonna L., Solanaceae

Kristen Cross

Introduction

Atropa belladonna, commonly known as deadly nightshade, belladonna, devil's cherries or death cherries, belongs to the Solanaceae family, which is also home to other well-known plants such as tobacco and potatoes (*Nicotiana* and *Solanum*, respectively). As implied by its common names, the toxicology of this plant is well known and it has been used as a poison as well as a cosmetic and anesthetic throughout its extended and interesting tale with the human culture. This 'femme fatale' has been incorporated into human history since before the Middle Ages, making a name for itself as a temptress due to the neurological and muscarinic effects as conveyed by its tropane alkaloids scopolamine and atropine. These drugs are still used today as an antidote for cholinergic crises and have been implicated in helping those with mental illnesses such as depression and bipolar disorder. These constituents are also responsible for the plant's notorious use as a recreational drug in order to induce hallucinogenic episodes. The fascination with this plant stems from its alluring appearance as well as the mystery and taboo surrounding it.

Botanical Description

Atropa belladonna is native to Western Europe and North Africa, where it commonly grows in disturbed woodlands as a result of it being a somewhat shade-intolerant species. The herbaceous perennial is often found cultivating the soil on rocky hillsides and other regions where the soil contains an adequate amount of calcium carbonate. *A. belladonna* is



Figure 1. *Atropa belladonna* in natural habitat. Source: www.plants.usda.gov

nitrophilous and requires a sufficient amount of nitrogen present in the soil in order to grow. Due to the plant's importance as an anticholinergic, studies were conducted to

find the ideal growing conditions that produce the highest concentrations of these alkaloids. They found that an increase in nitrogen in the soil would increase the concentrations of atropine and scopolamine, especially if water is limiting (Baricevic et al. 1999). This factor could be a large contributor to the fact that *A.belladonna* is rarely found growing in grass communities, but rather in largely open and uncultivated areas.

It appears as an erect, weed-like plant, standing 50-200 cm high depending on the amount of sunlight available (**Figure 1**). The stem is densely covered in fine, short hairs while the broad, ovular leaves branch out in unequal pairs starting about 25cm from the ground. These leaves are green, smooth and often asymmetric. A single purple flower droops from each leaf-axil and in the fall season a smooth, dark purple berry is produced (Butcher 1947). It is important to note that all parts of the plants are poisonous upon ingestion, as the alkaloids are ubiquitous throughout.

The plant was initially confused with mandrake (*Mandragora*), as they are closely related members of the Solanaceae family, but belladonna conveys a higher toxicity than the former. Dioscorides was the first to recognize that *Atropa* was a distinct genus and should not be used in place of mandrake for medicinal purposes (Lee 2007).

Traditional Uses

Atropa belladonna gets its namesake from Atropos, the Fate responsible for cutting the thread of life. This christening was based on the plant's dark tie to 11th century black magic, especially related to its use in love potions and enhancing the appearance of female allure via dilation of the pupils (Müller 1998). Witches and wizards of the olden days incorporated it

into their pharmacopeia as a flying ointment known as 'sorcerers pomade'. This ointment included nightshade, henbane, mandrake and hemlock mixed together and pounded with bear grease. The ointment was then applied all over the skin and the users claimed to experience hallucinations and sensations of flying. Divination practices also included the consumption of nightshade in small amounts in order to experience visions that may foretell events to come (Lee 2007). Many superstitions surround this mystic plant, including the placement of cuttings of the belladonna plant in the household in order to ward off evil spirits. Conversely, the witches and wizards took a liking to the plant because they believed that it was a favorite of the Devil himself.

The practice of using plant extracts (particularly those from the Solanaceae family) to dilate the eye in order to enhance physical appeal was first recorded by Matthioli in 1565 (Matthioli, Feinsod 2000). This activity was recognized as being generally dangerous, but as the doses were relatively small, few fatalities were recorded. It was this practice of Venetian women that led to the discovery of the mydriatic effects of atropine, as well as what led Linnaeus to give the plant its species name, *belladonna*. This translates to "beautiful lady" in Italian, referring to the enhanced appearance of the women after their pupils were dilated by drops extracted from the plant.

Pre-dating these medieval witches, *A. belladonna* was included in tinctures during the Bacchanalian festivals celebrated by the Greeks and Romans (Lee 2007). In larger doses, the plant was indicated as a deadly poison and is thought to have made an appearance in *The Odyssey* as the poison administered to the sailors by the lovely yet malicious Circe (Campbell 2007, Lee 2007). Tropane alkaloids have also been used to bolster beers of the ancient world in order to give them more potent effects upon consumption.

During the Roman and Byzantine empires, the drug began to lose its tie to religious and prophetic rites and instead became an important soporific used for medicinal purposes. (Ramoutsaki et al. 2002). From the mid-nineteenth century into the 1950s, *A. belladonna* was incorporated into plasters and liniments for the treatment of neuralgia, chronic rheumatism, lumbago, myalgia, pleurisy, pulmonary tuberculosis and acute mastitis. These plasters were taken off the market when pharmacists realized that some of them contained extracts from monkshood (*Aconitum napellus*), which produces an alkaloid called aconitine. This alkaloid was implicated in respiratory and cardiac failures and could be used in combination with atropine to poison people (Lee 2007).

Based on this long history of the plants use for recreational purposes, herbalists and apothecaries began to examine the mechanisms behind its - in some cases deadly - effects on the body and they found that in lower doses it was useful for medicinal purposes. Andrew Duncan of the Edinburgh Dispensary recommended it as a treatment for the plague as well as nervous disorders such as epilepsy and mania (Duncan 1803). He also recorded the first use of mydriatic drugs in ocular surgery by Professor Reimarus, an eye specialist in the 1800s. The professor used an infusion of nightshade to dilate the pupil while he removed cataracts.

A. belladonna has had a dark and fascinating tie to European culture ever since its first recorded use in cosmetic applications in the 1500s (Matthiolus). It has even worked its way into modern media in Tim Burton's movie *A Nightmare Before Christmas*. The movie featured the dried flowers implicated in a potion used for its soporific effects. The intrigue induced by this plant stems from its use in taboo, sexual practices as well as the fear of its lethal properties. Though it is dangerous to handle without proper care, this

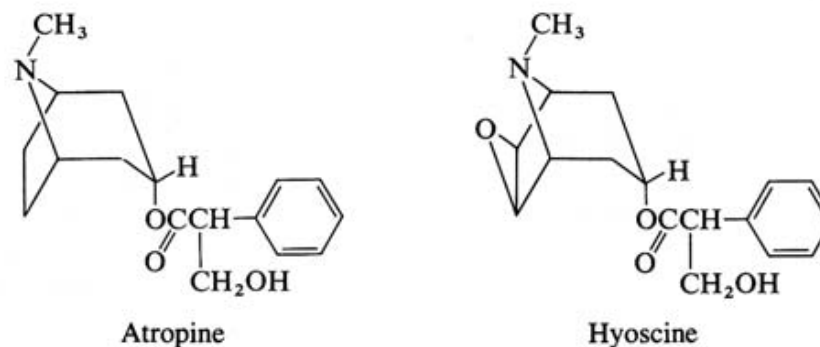


Figure 2. Structures of atropine and hyoscine (scopolamine). Source: Lee 2007

mystic past is what led to the investigation of it for medicinal practices.

Chemistry and Pharmacology

The main chemical constituents of this plant include atropine and scopolamine (**Figure 2**). Atropine, a tropane alkaloid, was first isolated from *Atropa belladonna* in 1831 by German pharmacist Mein (Sneader 1985). The compound exists as l-hyoscyamine in the plant and is the only active isomer, but it isomerizes upon extraction into the dextro compound. The racemic mixture of these two isomers is called dl-hyoscyamine or, more commonly, atropine. Its unique tertiary-amine structure allows penetration of the central nervous system (CNS). It is the important characteristic of its structure that makes it so potent as an antidote, or in cases of overdose, a lethal poison.

Hyoscine (also called scopolamine) is another tropane alkaloid that has been isolated from *A. belladonna*.

Chemical	Part	Lo PPM	High PPM
Atropine	Root		
Hyoscyamine	Root	2000	8712
Scopolamine	Root	40	88

Table 1. Average concentrations of chemicals in *Atropa belladonna*. Source: <http://www.ars-grin.gov/duke/>

Scopolamine is 10 times more potent than atropine, but it works in the same pathway. The only difference in the structure of the two alkaloids is in incorporation of an oxygen atom into one of the 6-membered rings. Like atropine, scopolamine is able to penetrate the central nervous system (CNS) and act on the muscarinic receptors. It is interesting to note, however, that these two compounds act only on the muscarinic receptors and not nicotinic receptors.

The average concentrations of the two compounds found in *A. belladonna* are reported in **Table 1**.

Biological Activity

Atropine has significant effects on the central nervous system. Its properties as a stereotypical anti-muscarinic xenobiotic are well-known and given in the right dosages, it can be a vital antidote following exposure to muscarinic agonists, such as pilocarpine and physostigmine (Wills 1963, Greenblatt and Shader 1973). In the 1970s, atropine was recognized as having the ability to reverse the effects of the cholinergic crisis as it competes with muscarinic agonists and acetylcholinesterase inhibitors at both central and peripheral muscarinic receptors. This activity was extremely beneficial for military personnel, as it could mitigate the cardiac effects

of exposure to physostigmine as well as prevent the effects if given preemptively, of up to two to three times the lethal dose (Greenblatt and Shader 1973).

The isolation of l-atropine from *A. belladonna* in the 1830s also marked an important venture into the study of neurotransmitters in mammals, specifically the in activity of acetylcholine and its effects in the body. It was used to map this pathway because it allowed for a better understanding of what effects particular neurotransmitters have on the body (Lee 2007).

Laboratory studies on mice showed that atropine extracted from *Atropa belladonna* has immuno- and gastroprotective effects in the event of stress-induced alterations on behavior. Although the mechanism of action was not elucidated in this study, the authors attribute the behavioral inhibition to the “anxiolytic-like effects” of *A. belladonna* (Cromwell 1943).

Studies of the effects of atropine extracted from *A. belladonna* as applied to the eyes of rabbits confirmed the mechanism by which atropine is absorbed in the iris and results in dilation of the pupils. This is achieved by blocking the innervation to the sphincter pupillae and ciliary (North and Kelly 1987). Reversal of the mydriasis can take up to 10 days in humans and can also lead to blindness and other complications when dosed inappropriately (Salazar et al. 1976). The effect is responsible for the plant’s use in the Middle Ages in order to dilate the pupils for cosmetic appeal. In humans, the drug works on the M₃ muscarinic receptor on the iris sphincter muscle. The effect is almost immediate and it extremely powerful, lasting for 7 to 10 days depending on the administered dose. This is due to the ease by which it is absorbed into the body, showing a systematic absorption of up to 65% in some cases (Howland 2011).

A review of the general effects of atropine was conducted using 250 laboratory mice. Each of the subjects was injected with 10µg of atropine and the resulting behaviors were then observed. The authors noted that there was an increase in respiration, a relaxing of the tail and the ears flattened against the head. Increased sensitivity to touch and sound was also noted, though the animals were fatigued for 2-3 hours after the injection. After 24 hours, all of the symptoms had ceased (Haley and McCormick 1957). This study was conducted as a general survey of the effects of atropine in order to potentially expound upon previous findings and perhaps better understand the mechanism of action. The results of this study have been used to further investigate the mechanisms of action behind the atropine-induced behavioral changes.

Hyoscine has an anesthetic effect and unlike atropine, it does not have negative effects on the electrical activity of the brain. This was used to calm patients with mental illnesses and it was later found useful in the treatment of major depressive disorder and anxiety disorders. These were observed in mice initially as a having the ability to increase “engagement” and awareness of seemingly disinterested mice. Animal studies such as these have been effective in the past in determining which drugs may act on the receptors of neurotransmitters in such a way as to regulate mood and behavior. Hyoscine is currently undergoing clinical trials in humans with promising results (Katz and Hersh 1981, Drevets and Furey 2010).

The primary uses of atropine and scopolamine involve its potent effects as an anticholinergic. Its ability to work on neurotransmitters has led to recent studies, which are looking into its ability to alleviate the symptoms of depression as well as inhibition of short-term memory recall (Aigner and Mishkin 1986, Drevets and Furey 2010). Its use in modern medicine has been decreased due to the infamous cases of poisoning by

some doctors who misused their access to the drug, but it is still an important component in ophthalmic therapies.

Clinical Studies

The most common symptoms of *A. belladonna* poisoning are tachycardia and mydriasis, as indicated by the anticholinergic effects of the drug. Other observed symptoms include increase in body temperature, flushing of the face, repressed salivation, bizarre mental state described as manic and paralysis of the detrusor muscle of the bladder, resulting in urine retention (Lee 2007).

Most studies of the effects of *A. belladonna* on humans come from toxicology reports wherein the plant was accidentally ingested and the symptoms were severe enough to warrant medical attention. The amount ingested from eating the berries, which are sometime mistaken for blackberries, was not enough to kill any of the 23 children in the reported cases. Common symptoms of belladonna intoxication include meaningless speech, tachycardia, mydriasis, and flushing. In some cases the anticholinergic effects were so severe that physostigmine had to be administered to restore homeostasis (Çaksen et al. 2003).

Scopolamine was administered transdermally to 16 patients with nausea induced by calorization of the ear in a randomized, double blind study. Nausea was reduced significantly compared to the effects of the placebo and it was also noted that introduction of scopolamine into the body 6 to 8 hours before exposure to a known motion sickness-inducing stimulus will prevent the onset of symptoms. Side effects were negligible (Pyykkö et al. 1985).

One of the most important uses of atropine came about during the 1930s and 40s when OP insecticides that were later

developed into nerve agents in chemical warfare due to their ability to inhibit acetylcholinesterase. Upon exposure to these agents, one would experience increased levels of acetylcholine, as the enzyme to metabolize it was no longer functioning due to inhibition. Atropine was then administered due to its muscarinic antagonist effects and it worked effectively and in small enough doses to be safe (Howland 2011).

Few clinical studies have been conducted using these drugs due to the well-known cases of poisoning and the generally infamy the plant has earned throughout its long, dark history. The most recent interest with these muscarinic antagonists comes in the field of mental health, where a new theory is circulating that Alzheimer's and dementia may be related to the cholinergic system. Scopolamine has been used to induce short-term memory inhibition in order to help elucidate the mechanism by which dementia develops. (Aigner and Mishkin 1986). This new field has shown some promising results and may potentially provide just retribution for atropine and scopolamine and import and effective treatments in western medicine.

Contraindications

Allergic reactions to topical application of atropine have been described as causing swelling of the eyelids, followed by itchy and stinging sensations. In patients who are prone to developing narrow angle glaucoma, application of the drug can lead to an acute attack, but this risk has been evaluated as minuscule.

'Hot as a hare, blind as a bat, dry as a bone, red as beet and mad as a hen' was an aphorism widely used to describe the symptoms of belladonna poisoning. These symptoms are fairly

unique to the effects of this particular plant, but can sometimes be confused with other plant poisons in the Solanaceae family, such as henbane (*Hyoscyamus niger*). Dilation of the eyes, as induced by atropine, results in photophobia until the pupils return to their normal circumference, which is usually no longer than a few hours. Dryness of the skin, mouth and throat can occur due to decreased secretion from the mucous membranes. Restlessness, irritability or delirium can also occur, as atropine stimulates the central nervous system. Use of atropine for any condition in elderly patients is not recommended, as it can cause confusion and may cause brain damage. Fatalities, though rare, can occur upon ingestion of this drug due to depression of circulatory and respiratory functions. This is more dangerous in children than adults, as the fatal dose in children is 10mg versus 100mg (North and Kelly 1987). 90-130 mg is considered to be a toxic dose (Lee 2007). Death is rare in the modern age because the symptoms are so well known and a cleansing of the stomach as well as use of artificial ventilation and diazepam can control convulsions and reduce the risk of mortality. In most cases, atropine is eliminated from the body in 72 to 96 hours without lasting effects on the patient.

When atropine was first isolated and brought to the medical market the medicinal knowledge about the drug's effects was incomplete. The plasters and eye drops could be incorrectly prepared and as a result, many accidental deaths occurred (Lee 2007, **Figure 3**). These treatments have since been banned from the market. Atropine can also be absorbed through the GI tract, so if an animal consumes the berries and the meat from said animal is ingested by a human, it can cause unusual and sometimes toxic symptoms (Polson et al. 1983).

One of the most notorious incidences of atropine poisoning was the attempted murder of Mrs. Agutter by her husband in



Figure 3. Plaster containing atropine that used to be sold in drug stores. Source: Lee 2007.

1994. By the 1990s, atropine was only available for the use of physicians and nurses, so it was relatively easy for him to acquire as he worked in a hospital. Dr. Agutter served his wife a gin and tonic laced with atropine, as the quinine in the tonic water disguised the bitter taste. Within five minutes she felt an agonizing pain in her throat and she started to experience hallucinations. It was later found that she had only consumed 50mg of atropine before the symptoms hit and she stopped drinking. Due to her husband's miscalculations, she survived and he was found guilty of attempted murder and spent the next twelve years in prison (Lee 2007).

Current Use in Allopathic and CAM Therapies

Atropine sulfate drops are one the main therapies prescribed for the treatment of amblyopia, a condition of the eye that can lead to vision impairment. A clinical study evaluating the efficacy of the atropine drops over a 6-month and two year period showing 49% improvement in the condition of the

affected eye (Repka et al. 2005). Atropine can be administered via oral, inhalation and intramuscular routes and it can last for 24 hours within the body depending on the dose. When given a 2mg dose via autoinjector, heart rate increased to maximal level in 16 minutes. These autoinjectors are used as an immediate response for terrorist attacks, especially when they involve exposure to nerve gas. The atropine stops muscle spasms and allows heart rate to return to normal (Howland 2011).

Atropa belladonna is commonly used to combat local inflammation that, if untreated, can lead to sepsis and death. A study on the various homeopathic remedies that used *A. belladonna* outlines the major drug used in homeopathic treatment of infection. These include *Belladonna—Injeel®*, *Belladonna—Injeel Forte®* and *Belladonna Homaccord®*. Preparations containing *A. belladonna* constituents were effective in regulating what types of cells migrate during the inflammatory process. This activity helps lower the presence of proteolytic enzymes, free radicals and chemical mediators that may infer with the immune processes (Pedalino et al. 2004). Another medicinal use of atropine is to lower blood pressure via competition for the norepinephrine receptor, thus mitigating the effects of hypertension (Abraham et al. 1981).

Hyoscine is currently undergoing clinical trials as a treatment for major depressive disorder. Its efficacy in relieving symptoms of depression relative to the effect of placebo is promising and the efficacy improves with continuous dosing. The mechanism of action is currently unknown, but the late onset of the antidepressant effects (past the time of the anticholinergic effects) suggest that the drug may work on transcription of later onset genes as opposed to working on the muscarinic receptors (Drevets and Furey 2010). This alkaloid has also been found to alleviate motion sickness

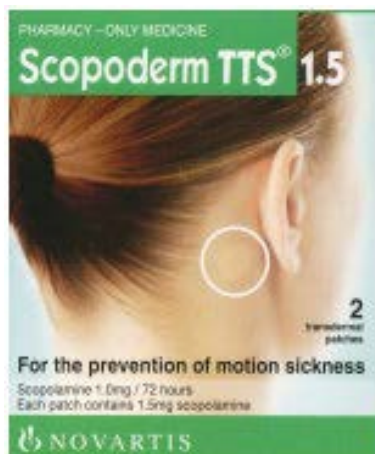


Figure 4. Scopolamine patches used to prevent the onset of motion sickness. Source: pharmacydiscounter.com

through transdermal administration (Price et al. 1981). Current uses of scopolamine also include its use in anti-vertigo drugs, as well as a preventive against motion sickness (Pyykkö et al. 1985), **Figure 4**. Major adverse effects of this drug include dryness of the mouth and throat, both common symptoms of taking anti-nauseates.

Discussion

Atropa belladonna has fascinated and intrigued people for centuries with its mystical yet deadly allure. From a notorious past as the plant of the devil to its vital role in modern medicinal practices, it has become irrevocably entwined in human culture. Although atropine is considered too dangerous to be incorporated into modern medicinal practices, its ability to act on muscarinic receptors has led to important discoveries about human physiology and it is still critical as an antidote for cholinergic crises. Hyoscine, another important alkaloid extracted from belladonna, has aided in the

mitigation of mental illnesses and helped to enhance our understanding of depression and its causes. Ultimately, the powerful and potent biological activity of *Atropa belladonna*, initially only recognized by its ability to poison people or induce hallucinogenic stupors, is what makes it such a powerful tool to the future of drug discovery. We have known about some of the effects of belladonna for centuries, and we are just now discovering some of its new applications. The story of deadly nightshade is an important tale, as it clearly illustrates the mercurial temperament of western medicine and how important it is to understand that we do not yet know all there is to know about the effect of these compounds on the human body.

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Avena sativa L., Poaceae

Kylee Martens

Introduction

Avena sativa L., commonly known as oat, is a part of the Poaceae family of grasses. *A. sativa* is also called avoine in French, hafer in German, avena in Spanish, and javi or jai in Hindi (Butt et al., 2008). *A. sativa* was first discovered in ancient Egyptian ruins that date back 4,000 years and the first documented medicinal use of oats was recorded by Dioscorides in *de Materia Medica*. Though oat is believed to be Asiatic in origin, it is now predominately grown in moist, temperate regions in the United States, Canada, Russia, and Europe. Oats rank sixth in world cereal production, following wheat, maize, rice, barley and sorghum (Stevens et al., 2000). Oats contain high nitrate content largely due to the presence of phenolic compounds known as avenanthramides, which are unique to oats. They also contain soluble dietary fiber, in the form of β -glucans. Both avenanthramides and β -glucans are responsible for most of the biological and pharmacological activity of oats. Though oats were first used as food for animals and scorned for their bland taste, they are now a valued source of antioxidants and contain anti-inflammatory, antipruritic, emollient, and anxiolytic properties. The study of the medicinal value of *A. sativa* is gaining popularity as more health benefits of this functional food are being discovered.

Botanical Description

Avena sativa L. grows in cool, moist regions throughout the United States, Canada, Russia, and in the Mediterranean countries in Europe (Heywood, 1982). As mentioned above, *A. sativa* is in the Poaceae family and is an annual grass that



Figure 1. *Avena sativa*, commonly known as oat.

(Source: <http://ddr.nal.usda.gov/bitstream/10113/3559/1/IND43886716.pdf>)

typically grows and matures rapidly during the spring and summer. Oats are hardy crops that can generally withstand the cold (Vavilov, 1992). There are three main cultivated forms of oats that differ based on the number of chromosomes, including diploid *strigosa-brevis*, tetraploid *abyssinica*, and hexaploid *sativa-byzantina-nuda* (Heywood,

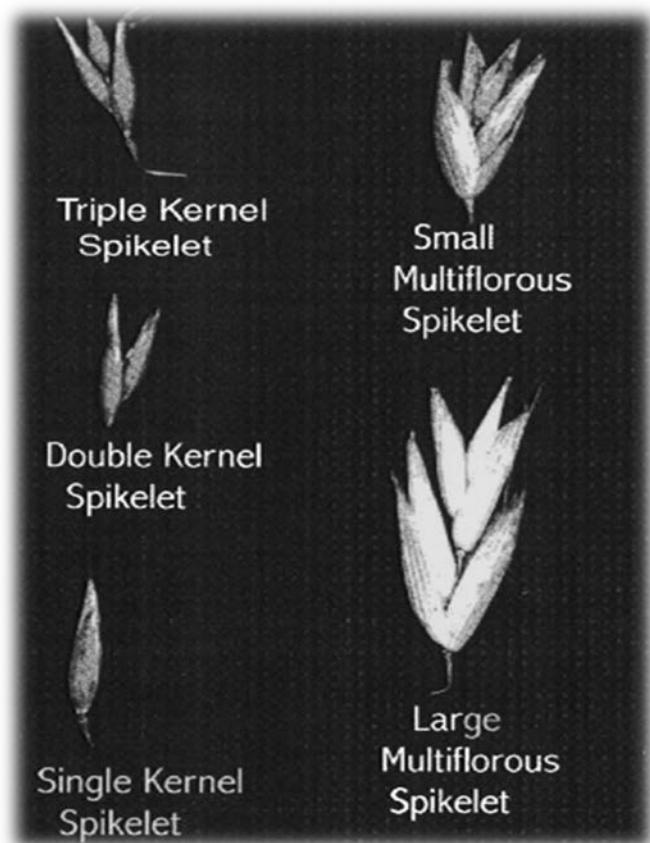


Figure 2. Spikelets of varieties of oats, which contain the oat groat. (Source:

<http://books.google.com/books?hl=en&lr=&id=h7coAAAAAYAAJ&oi=fnd&pg=PA1&dq=history+of+oat&ots=4rjyPduEf1&sig=D1i10Ut1F1VuVPqJNnPbsM7kilg#v=onepage&q=history%20of%20oat&f=false>)

1982). The hexaploid form is the most common type of subspecies.

A. sativa (Figure 1) consists of leaves and up to thirty tillers, or lateral shoots, projecting from each stem. The main stem

and tillers can reach a height of up to two or more feet (Butt et al., 2008). Each tiller terminates in a panicle that bears spikelets (Figure 2), which contain one to two kernels, also known as groats, which are small and spindle shaped. When oat plants mature into a yellow color, the groats are ready to be harvested and processed to the desired consistency. The groats are heated and dehulled and can then be processed further (Sides et al., 2001). Some of the varieties of processed oats are rolled oats, flaked oats, or steel-cut oats, often heated and eaten with water in the form of oatmeal. Colloidal oatmeal, a recognized natural skin product, is prepared through a fine-mill process, which produces a powder of oats with concentrated starch and protein (Cerio et al., 2010).

Oats in general have a rather bland taste and a tendency to spoil (Butt et al., 2008). This occurs because the grinding process activates a lipolytic enzyme system in oats, which causes rancid properties (Sides et al., 2001). Ideally, the heating process stabilizes the oat from spoiling, but doesn't affect its antioxidant content. The typical nutty, "oaty" flavor associated with *A. sativa* often presents itself after the oats have been heated.

Oats use self-pollination, in which pollen grains settle on the stigma of the same floret (Thapa, 2007). Pollen advance occurs from the uppermost floret towards the basal spikelets in about 10 to 11 days (Rajala & Peltonen-Sainio, 2011). Pollen is most often distributed by wind, but oats also benefit from insect pollination (Thapa, 2007).

Traditional Uses

Use as fodder

The origins of *Avena sativa* L. are mostly unclear, but this species is believed to have originated in Asia and may have

spread throughout Europe with barley and wheat and been mistaken as a weed (Vavilov, 1992). *Avena* most likely comes from the Latin word, *Aveo*, which means to desire (Coffman, 1977). Before oat was desired as a food source for humans, it was first used as fodder for animals in central Europe and west Asia (Pieroni, 2009). Oats are not indigenous to North America, but were instead introduced by the Spanish to the southern part of North America in the 16th century as food for their horses (Coffman, 1977). The first oats introduced in northern North America were planted by English colonists in Jamestown in the early 1600s, primarily as fodder.

Use as food

A. sativa eventually evolved into a food source for people, mainly in Ireland and Scotland beginning in the sixteenth century. English author Samuel Johnson defined oats as “eaten by people in Scotland but fit only for horses in England” to which James Boswell responded, “that’s why England has such good horses and Scotland has such fine men” (Maunsell, 2011). Due to their bland taste, oats were not highly reputed and mainly eaten only in Scotland and Ireland. Oats were even thought to be a diseased form of wheat. Today, oats have evolved from a food for animals to a desired and important food for humans throughout the world. Processed oats are now found in many different kinds of foods including oatmeal, different varieties of cereal and granola, breads, and oat flour. Oats are often combined with other food condiments to enhance their bland taste.

Traditional ethnomedicinal uses

Not only were oats used for fodder and for food, but they also have a long history of use for skin treatment, especially by the

ancient Greeks and Romans. Medical texts written by Pliny suggest the topical application of oatmeal for the treatment of a variety of dermatologic conditions (Sur et al., 2008). The topical application of oats was used in facial masks and baths to relieve itching and irritation, as well as eczema (Aburjai & Natsheh, 2003). Ayurvedic practitioners also used a tincture of oats to cure the opium addiction, and oats were also reputed to reduce nicotine cravings (Lewis & Elvin-Lewis, 2003). Oats were most likely selected for this use because of their sedative properties and ability to act as a depressant on the central nervous system. *A. sativa* has also traditionally been used by the ancient Greeks and Romans to treat nervous anxiety, stress, and excitation as well as to promote mental health and cognitive function (Abascal & Yarnell, 2004).

The ancient traditional uses of *A. sativa* for skin disorders have largely remained the same, and much of the knowledge of the ethnomedicinal uses of oats have come from ancient medical texts like *de Materia Medica*. While whole or rolled oats were traditionally used in baths for their soothing properties, oats are used today in the form of finely ground colloidal oatmeal (Kurtz & Wallo, 2007). Colloidal oatmeal is more effective than whole or rolled oats because it is more easily dispersed in bath water, and thereby applied more thoroughly.

Other uses

The Spanish settlers in the 16th century combined *A. sativa* with other materials to make adobe brick buildings (Coffman, 1977). Oats have not only been used as fodder, but also traditionally used as bedding for animals. Oats also were distilled for the production of alcohol, which is still a method used today (Pereira, 1855).

Chemistry and Pharmacology

Avena sativa contains about 65-85% starch and soluble polysaccharides, 15-20% proteins, 3-11% lipids, and 5% fiber (**Table 1**) (Sur et al., 2008). Polyphenols, saponin glycosides, flavonoids, and vitamin E represent the remaining compounds found in oats (Heinrich, 2004). The major medicinal chemical components of *A. sativa* are discussed below.

β-glucans

The dietary fiber in oats mainly consists of the compound *β*-glucan (**Figure 3**). *β*-glucan is a linear-nonbranched polysaccharide with high viscosity, which is responsible for its exceptional nutritional value. Its high viscosity contributes to many of oat's medicinal properties, including its low glycemic response and its emollient properties. Oat groats contain about 2.3 to 8.5% *β*-glucan content, mainly present in the outer layers of the groat (Butt et al., 2008).

Phenolic Compounds

Oats contain many different forms of phenolic compounds, such as vanillin, sinapic, ferulic, and caffeic acids (Bratt et al., 2003). Perhaps the most important phenolic components unique to oats and responsible for their flavor are the low molecular weight, soluble polyphenolic compounds known as avenanthramides (Meydani, 2009). Oats contain over twenty avenanthramides produced by the oat plant in response to pathogens. They are present in oats at about 300 parts per million, or 0.03%, and are available in three major forms: A, B, and C (Sur, et al., 2008).

Major Compounds	Percent Composition in <i>A. sativa</i>
Starch	65-85%
Proteins <ul style="list-style-type: none">• Avenin• Albumen	15-20%
Lipids	3-11%
Fiber <ul style="list-style-type: none">• <i>β</i>-glucan	5%
Polyphenols <ul style="list-style-type: none">• Avenanthramides A, B, C• Vanillin acid• Sinapic acid• Ferulic acid• Caffeic acid	0.03%
Flavonoids <ul style="list-style-type: none">• Apigenin• Luteolin• Tricin	0.05%

Table 1. Major chemical compounds found in *A. sativa*.
(Source: Sur et al., 2008)

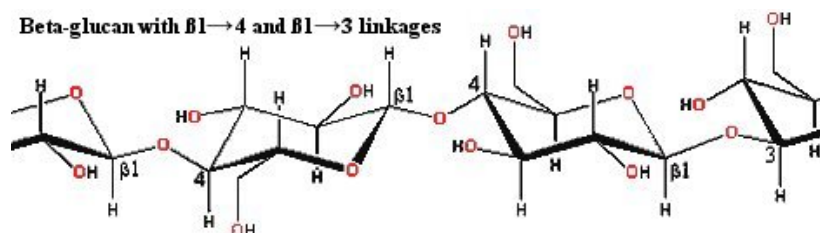


Figure 3. Structure of *β*-glucan, main component of soluble fiber in *A. sativa*

(Source:
http://www.oatsandhealth.org/index.php?option=com_content&view=article&id=14&Itemid=38)

Flavonoids

Three major flavonoids have been identified in oats, apigenin, luteolin, and tricetin, which also are responsible for *A. sativa*'s antioxidant properties and its resistance to the generation of reactive oxidative species (Cai et al., 2012). Though avenanthramides have been shown to have greater antioxidant activity than flavonoids, flavonoids are still an important medicinal component to oats.

Biological Activity

Results of *in vitro* and *in vivo* studies have demonstrated that *Avena sativa* has antioxidant, anti-inflammatory, antipruritic, emollient, and anxiolytic properties.

Antioxidant

The antioxidant activity of *A. sativa* was studied by analyzing the concentrations of phenolic compounds of oat fractions *in vitro*. The total phenolic content of the pearling fractions, which contain a greater percentage of the outer layers of the oat groat, was almost double the total phenolic content in other oat fractions (Emmons et al., 1999). This suggests that the outer layers of the groat, as opposed to the inner content, contain more phenolic compounds, which have been linked to increased antioxidant activity. Antioxidant activity was evaluated by β -carotene bleaching, which showed that the cinnamic acids, like ferulic acid and caffeic acid, inhibit low-density lipoprotein (LDL) oxidation (Emmons et al., 1999). Avenanthramides have also been analyzed for their antioxidant activity and have been found to have 10-30 times the antioxidant activity of the other phenolic compounds found in oats (Emmons et al., 1999). Though there are many different kinds of phenolic compounds present in oats,

avenanthramides appear to be the most medicinally beneficial, present in highest amounts in the outer layers of oats.

An *in vitro* study using two different tests to determine antioxidant activity, β -carotene bleaching and DPPH assay, confirmed that avenanthramides have antioxidant properties (Peterson et al., 2002). *In vivo*, the antioxidant activity of avenanthramides was also analyzed by feeding rats an avenanthramide-enriched diet of 0.1g/kg for 50 days (Li Ji et al., 2003). The results of this study concluded that the rats that were fed this diet had decreased reductive-oxidative species (ROS). Specifically, it was found that avenanthramides increased the level of superoxide dismutase (SOD) and glutathione peroxidase (GPX). Both SOD and GPX are tissue antioxidant enzyme systems.

Anti-inflammatory and anti-irritant

Avenanthramides have also been shown to have anti-inflammatory properties. It was found in an *in vitro* study that avenanthramides inhibit NF- κ B signaling in cells treated with these polyphenols (Sur et al., 2008). NF- κ B is an important regulator of expression of pro-inflammatory proteins. By inhibiting this signaling, avenanthramides inhibited the production of interleukin-8 and thus prevented inflammation in cells.

The anti-irritant properties of oats have also been studied and attributed to the effects of avenanthramides. Specifically, these phytochemicals have been shown to decrease the ionophore-stimulated liberation of arachidonic acid and can inhibit prostaglandin biosynthesis (Sur et al., 2008). By

inhibiting these processes, oats can naturally relieve skin irritation through this topical application of *A. sativa*.

Antipruritic

The antipruritic property of avenanthramides was also evaluated in an *in vivo* study in mice. Avenanthramide-treated mice scratched 40.7% less than the control mice when injected with pro-itch compound 48/80 (Sur et al., 2008). Because avenanthramides can inhibit the production of interleukin-8, they can thereby inhibit the release of inflammatory cytokines shown to be elevated in pruritic skin disorders. Avenanthramides may also inhibit histamine signaling, which suggests another mechanism for the role of these compounds in the treatment of chicken pox and other pruritic skin diseases (Sur et al., 2008).

Emollient

In vitro studies on the effects of β -glucan on the skin have concluded that this dietary soluble fiber is able to penetrate the dermis layer of the skin. Pillai et al. concluded that β -glucans interact directly with macrophages to produce interleukin-1 (IL-1), which promotes the production of procollagen (2005). The conversion of procollagen to collagen explains oat's emollient properties, as well as its cosmetic uses for the reduction of wrinkles in the skin. β -glucan's high viscosity also contributes to oat's emollient and moisturizing properties.

Anxiolytic Properties

Oats have also been proven to act as a mild sedative to alleviate anxiety, stress, and excitation (Abascal & Yarnell,

2004). A recent *in vivo* study was performed on rats to assess the effects of oats on behavioral responses in situations that would produce anxiety (Schellekens et al., 2009). Rats given oat extract showed friendly social behavior and less aggressive behavior in agonistic interactions, supporting the claim that oats provide anti-anxiety and calming effects. The oat extract showed inhibition of the neurotransmitter metabolizing enzyme monoaminoxidase B and of the cAMP degrading phosphodiesterase 4. These enzymes play a role in anxiety and depression, so this inhibition may account for the anxiolytic properties of *A. sativa*.

Clinical Studies

Various clinical studies have been conducted to study the medicinal benefits of *A. sativa* in the prevention and treatment of heart disease, diabetes, skin disorders, gastrointestinal disorders, and libido.

Heart Disease

Avena sativa has been linked to cholesterol-lowering effects, which reduce the chance for developing coronary heart disease. In a study conducted to analyze this property of oats, it was shown that there was an 8.7% reduction in low-density lipoprotein (LDL) cholesterol levels in subjects who ate two oat-bran muffins a day for a month (Gold & Davidson, 1988). Another study demonstrated that there was a similar reduction of total and LDL cholesterol levels in patients with an increased coronary heart disease risk (Berg et al., 2002). Soluble fibers, like β -glucan, are able to bind to bile acids and cholesterol, which increases bile acid excretion (Berg et al., 2002). This excretion increases lipid excretion and upregulates the amount of hepatic cholesterol receptors,



Figure 4. Aveeno skin lotion contains 1% colloidal oatmeal

(Source: <http://www.aveeno.com/skincare/products/daily-moisturizing-lotion>)

which help to clear cholesterol from the blood. In 1997, the FDA issued a statement that declared that diets low in saturated fat and cholesterol that include soluble fiber from whole oats may reduce the risk of developing heart disease (Wood, 2006). This statement recognized the beneficial effects of soluble fiber from β -glucans in *A. sativa* in the prevention of heart disease. There are also a few studies that support the blood-pressure lowering effect of β -glucans. Specifically, Maki et al. studied the effects of a β -glucan diet in obese patients (2007). The blood pressures of these patients dropped

significantly when they followed this diet, suggesting a strong correlation between β -glucan and lowered blood pressure in overweight patients. This correlation may be related to insulin responses, which may have indirectly lowered blood pressure in these patients, but additional research is necessary to define the mechanism of lowered blood pressure in response to the intake of *A. sativa*.

Hyperglycemia

Oats have been associated with the prevention of diabetes by lowering blood-glucose levels, which prevents the development of insulin insensitivity. Specifically, β -glucans in oats have been studied for their blood-glucose-lowering capabilities. In one study, blood-glucose levels of both healthy and type 2 diabetic subjects were reduced after consuming oat bran as compared to the blood-glucose levels of subjects in the control group who received no oat products (Wood, 2006). The primary factor responsible for oat's low glycemic response and reduced blood glucose levels is β -glucan's high viscosity.

Skin Disorders

A. sativa has been used to treat eczema and repair UVA/UVB damaged skin (Aburjai & Natsheh, 2003). Oats have even been evaluated for their efficacy in the reduction of wrinkles. In one study by Pillai et al., 27 subjects used gel formulations of β -glucan twice daily for 8 weeks, applying the gel to the face (2005). A significant reduction of wrinkles was observed on the faces of the subjects, and it was also concluded that β -glucan penetrates the dermis layer of the skin and is able to stimulate the production of collagen.

Using the sodium lauryl sulfate irritation model, Vie et al. studied the anti-inflammatory effects of oat extract on the upper arms 12 healthy subjects (2002). The oat extract was able to significantly counteract the inflammation caused by this irritation model, suggesting the use of oat products in the reduction of skin irritation and inflammation. Avenanthramides were shown to have these anti-inflammatory and anti-irritant effects, which explains the use of oats in the treatment of dermatitis and eczema.

Celiac Disease

Celiac Disease is an autoimmune disease that generates intolerance to gluten. Oats have been studied in patients with Celiac disease to determine if they can be tolerated (Butt et al., 2008). Oats do not contain the intolerable protein gliadin that is found in wheat, but instead contain the protein avenin. Oats are safe to eat by those with Celiac disease, but they must be pure because often, processed oats contain some gluten from other grains. Pure oats provide an alternative food source for celiac patients who follow a gluten-free diet.

Gastrointestinal Disorders and Colon Cancer

Soluble dietary fiber in oats, found in the form of β -glucans, has also been shown to have numerous beneficial effects on the gastrointestinal system. The high viscosity of β -glucans have been shown to increase fecal wet-weight, and thereby relieve constipation (Malkki & Virtanen, 2001). There may also be a correlation between the soluble fiber in oats and the prevention of colon cancer. This is mainly due to the fermentation of the fiber in the intestine, which stimulates cell proliferation in normal epithelium, but prevents the growth of

carcinoma cells (Malkki & Virtanen, 2001). This potential anti-cancer effect is still being reviewed and researched.

Libido and impotence

The phrase, “sowing ones wild oats,” was coined in the 16th century to describe destructive sexual liaisons. The correlation between sex and oats has been widely marketed in the past few years, and oats have been suggested as a treatment for male erectile dysfunction. However, a few studies have confirmed its effectiveness in treating erectile dysfunction and promoting libido (Moyad et al., 2004). Though oat is a well-known aphrodisiac, more research must be conducted to determine its effectiveness in treating impotence.

Contraindications

Avena sativa has no known contraindications, adverse effects, or interactions (Abascal & Yarnell, 2004). It is generally regarded as safe (GRAS). Colloidal oatmeal is one of the few natural products that has been recognized and approved by the FDA in the treatment for dermatologic conditions (Cerio et al, 2010). In 1997, the FDA also recognized that oats rich in soluble fiber may reduce the risk of heart disease (Wood, 2006).

Current Use in Allopathic and CAM Therapies

Avena sativa ranks sixth in world cereal production and has gained much popularity since they were first used solely as fodder. Not only are they eaten, but they are also widely used for their emollient properties. Oats have long been used to provide antipruritic relief, skin hydration and smoothness. In

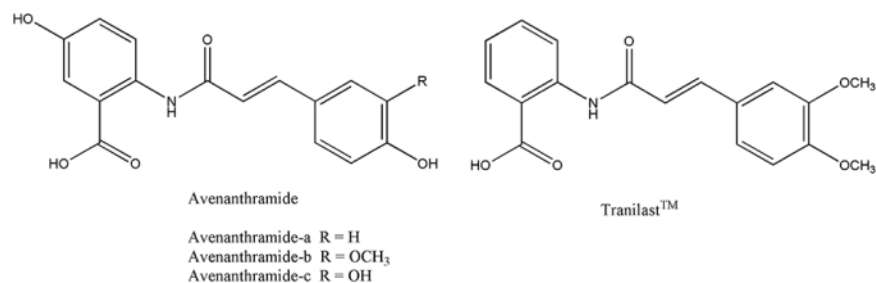


Figure 5. Structure of drug Tranilast compared to an avenanthramide, polyphenol compound unique to *A. sativa*.

(Source: <http://onlinelibrary.wiley.com/doi/10.1111/j.1753-4887.2009.00256.x/full>)

1945, colloidal oatmeal became available by finely grinding the oat and extracting the colloidal material (Kurtz & Wallo, 2007). Today, colloidal oatmeal is included in shampoos, bath powders, and in moisturizing creams like Aveeno (**Figure 4**). The use of oats in skin products for cosmetic purposes provides a cheaper and safer alternative to cosmetic procedures. In 2003, the FDA approved colloidal oatmeal as a safe and effective skin protectant based on its moisturizing and anti-irritant properties (Aburjai & Natsheh, 2003). Colloidal oatmeal is also commonly used to treat the itching and irritating symptoms of chicken pox, due to its soothing and antipruritic effects. It is also currently used to topically treat diseases like dermatitis and psoriasis (Cerio et. al, 2010).

Currently in Japan, the synthetic drug Tranilast, with a structure similar to an avenanthramide, is used as an antihistamine (Meydani, 2009). Both avenanthramides and Tranilast (**Figure 5**) were discovered to have anti-proliferative effects on vascular smooth muscle cells, which could explain the mechanism by which oats reduce the risk of colon cancer. Avenanthramides may also inhibit histamine

signaling and play a similar role as the drug Tranilast, which could also explain the antipruritic effects of avenanthramides (Sur et al., 2008).

A. sativa is currently sold as a supplement and is marketed as an aphrodisiac to improve sexual libido. There are few studies that confirm these properties of oats, and these herbal supplements have not yet been proven to be effective. Some oat extract supplements also claim to improve nervous system health, though this claim also needs to be further studied.

Discussion

Avena sativa L. has evolved throughout the centuries, since it was first used in ancient Egypt almost 4,000 years ago. Because of its rich content of avenanthramides and β -glucans, oat is a rich source of antioxidants and it contains anti-inflammatory, anti-irritant, antipruritic, emollient, and anxiolytic properties. The traditional medicinal knowledge of oats for the skin, discovered over 2,000 years ago by the ancient Greeks and Romans, is still valued today, and continued research of oats has helped to discover both CAM and biomedical treatments for heart disease, diabetes, gastrointestinal ailments, and impotence. *A. sativa* provides a natural prevention to many of the prevalent diseases that humans are succumbing to throughout the world. Oat is a cheap and healthy plant that is easily accessible and can be added to the diet with no known contraindications. For these reasons, the medicinal future of *A. sativa* appears promising as this plant gains more popularity as a healthful food source, and continued research leads to the discovery of more of the medicinal benefits of this plant.

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***Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton, Malpighiaceae**

David Nardo

Introduction

The term ayahuasca refers to a hallucinogenic brew used in many of the healing practices and religious rituals of the natives of the Amazon Basin region. The word stems from Quechua and means “vine of the souls” (aya = spirit or ghost, huasca = vine or rope). The hallucinogenic brew is composed of a myriad of plants and varies in recipe from person to person, the only constant being the use of *Banisteriopsis caapi*. *B. caapi* is known colloquially by many names, among them are ayahuasca, yaje (also yage), caapi, and huasca (Dobkin de Rios, 1971; Rivier & Lindgren, 1972). *Banisteriopsis caapi* (**Figure 1**), of the Malpighiaceae family, is a vine that has been the source of several political arguments over the last few decades as it has made its way from the heart of the Amazon into ‘civilized’ areas and has been exploited by thrill seekers under the pretext of achieving a higher state of mind and a more personal relationship with god.

Although little is known about the origins of its use, the role of the plant in indigenous cultures dates back to ancient times. There is an abundant body of archeological evidence affirming its use as early as 1500, although much of this archeological evidence seems to attest more to the use of other plants, like tobacco and coca, rather than ayahuasca (Dennis J, 2004). Knowledge of the plant and its use have been passed down through generations, from shaman to shaman, and continues to take part in many of the practices today. Non-natives that also use the brew in their religious practices are the UDV, Barquinia and Santo Daime sects in Brazil. These, although not part of native tribes, have partaken in many of the customs



Figure 1. Botanical drawing of *Banisteriopsis caapi* (Image source: <http://jornadasdamente.blogspot.com/p/ayahuasca.html>)

and religious practices of the native, including the consumption of ayahuasca. It is also because of these groups that the plants used to concoct ayahuasca have made it into mainstream culture. Despite the cultural roots of the beverage, however, it seems likely that the use of ayahuasca will fade from society, namely because of people who use the cover of religion to partake in the use of ayahuasca. As more and more people join religious communities, like the Santo Daime, for the sole purpose of using the drug, the public opinion will over time become worse and most likely, the plants that are used in making ayahuasca will be banned from every country.



Figure 2. *B. caapi* vine. (Image source: <http://interactivetimeline.com/824/timeline-of-entheogen-use/57.php?w=580>)

Botanical Description

Banisteriopsis caapi (**Figure 2**) is endemic to the entire Amazon basin area and can be found anywhere from Brazil, to Peru, to Ecuador (Tupper, 2008). The plant grows naturally in the moist climate of South America but can also be cultivated through the cuttings: the cuttings are allowed to sit in water until they develop roots, at which point they can be transplanted to soil (Luna, 1984). It should be noted, however, that most of the plants used in making the ayahuasca brew are taken from the wild and not cultivated (De Alvarez De Toledo, 1960; Dobkin de Rios, 1971; Flores & Lewis, 1978; Kjellgren, Eriksson, & Norlander, 2009).

The ayahuasca plant takes the shape of a large vine and grows only in moist tropical climates. In its early stages, the plant stems are green and the leaves are small (**Figure 3**). However,



Figure 3. Young leaves of *B. caapi*. (Image source: <http://en.wikipedia.org/wiki/File:Caapi.jpg>)

as it reaches maturity, the vine becomes long and woody and branches significantly. The woody stems of the vine can reach several inches in diameter, giving the appearance of thin trees or tree branches. In adult vines, the leaves are green and appear only on the smaller branches. The leaves have an oblong shape that points at the ends and can reach about 7 inches in length. On the more distal branches grow the inflorescence holding the flowers, which are white or pale pink and reach about a half inch in length (**Figure 4**). Pollinators include bees and other forest insects that help carry pollen (Dennis J, 2004; Rättsch, 2005). The seeds, due to their “helicopter shape” (see **Figure 5**) are able to travel great distances being carried by the wind.

With pertinence to the plant’s use in making the ayahuasca brew it should be noted that two varieties that have been distinguished, *B. caapi* var. *caupari* and var. *tukonaka*. The latter of these two is the better known one, which has a



Figure 4. Flowers of *B. caapi*. (Image source: <http://upload.wikimedia.org/wikipedia/commons/f/f6/Banisteriopsis-caapi-flowers-lg.jpg>)

smooth stem. The former, said to be more potent, has knotty stems (Gates, 1982; Kjellgren et al., 2009; Rättsch, 2005). Aside from the differences in stem shapes and in chemical concentrations, there seem to be no other notable differences in the varieties.

Traditional uses

Although the plant leaves are sometimes smoked, caapi is most commonly consumed in a brew. The shamans believe that, while other plants are responsible for visions, it is *B. caapi* that allows them to connect to the spirit world and to escape their corporeal forms. They consider the plant to be a connector to the realm of the spirits where they can communicate with the dead, or with the spirits of the forest, from whom they can derive knowledge on healing, etc



Figure 5. “Helicopter-shape” seeds of *B. caapi*. (Image source: <http://www.shamanic-extracts.com/xcart/shamanic-products/banisteriopsis-caapi-seeds.html>)

(Dobkin de Rios, 1971; Flores & Lewis, 1978; Kjellgren et al., 2009; Luna, 1984; Reichel-Dolmatoff, 1987). The plant is used for spiritual, rather than physical healing. Although it does not produce physical healing, *B. caapi* is believed to confer a sense of completeness and a connection with the spiritual. It is used by shamans as a guide when they are trying to find answers to problems, and it is used by laymen in trying to resolve conflicts.

In preparing the ayahuasca brew, the stems, bark and leaves of the vine can be employed, although the stems are used in most cases (**Figures 6 and 7**) (De Alvarez De Toledo, 1960). The stems of the plant are taken and crushed and placed in a vessel and other plants, such as *P. viridis*. The vessel is filled with water and the mixture is boiled for at least one hour, after which the brew can be strained and allowed to cool (Rivier & Lindgren, 1972).

On her treatise of the plant, Dr. de Alvarez de Toledo mentions that the plant is used by Peruvian natives ‘when a person is in love and the family knows that the other person is bad for them and they take them to a healer’. It is believed that the plant can help a person find out another person who has wronged you and can also work to make you confess to



Figure 6. Ayahuasca vine. (Image source: <http://upload.wikimedia.org/wikipedia/commons/5/51/Banisteriopsis-caapi-vine2.jpg>)

wrongdoing. The natives also mentioned that, while under the influence of ayahuasca, a healer can also make a person commit crimes. Upon taking the beverage, the first symptoms felt are usually nausea and vomiting. Once these started, it was only necessary to open one's eyes and see, by focusing the mind, what it was that one wanted to see, whether it was those who wished us ill, or a dead person's spirit. The overall experience described by de Alvarez de Toledo, however, is extremely disappointing since, according to her, the experience was not at all what the natives described and



Figure 7. Preparation of Ayahuasca. (Image source: <http://fbgamestipsandtricks.com/wp-includes/Text/ayawaska-buy>)

rather she perceived but mild pseudohallucinations. Finally, she adds that the natives of the High Amazon use the plant in the treatment of mental illnesses, although she was unable, herself, to presence any of these (De Alvarez De Toledo, 1960).

Chemistry (pharmacology and toxicology)

Despite what one might assume, none of the chemicals in *B. caapi* are responsible for causing hallucinations in humans. Instead, *B. caapi* contains high amounts of β -carboline MAOIs (uses discussed later), namely banisteriopside A and B, harmine, tetrahydroharmine, harmaline, harmol and harmamol (also called h-carbolines) (Riba et al., 2003). The stems of the plant contain up to .83 percent of these alkaloids,

Plant Part	Yield, ^a %	Compounds Quantified (Content, %)								
		1	2	3	4	5	6	7	8	9
Fresh leaves	0.49	0.002	0.0004	0.0004	0.000	0.004	0.0001	0.002	0.021	0.002
Fresh leaves ^b	5.28	0.072	0.015	0.011	0.003	0.114	0.002	0.042	0.333	0.090
Dried leaves	10.06	0.166	0.027	0.005	0.005	0.101	0.004	0.031	0.070	0.030
Fresh young stem	0.85	0.009	0.002	0.0004	0.0003	0.005	0.0003	0.001	0.002	0.002
Fresh young stem ^b	11.70	0.129	0.032	0.007	0.005	0.055	0.005	0.020	0.070	0.070
Dried matured stem	12.74	0.270	0.572	0.004	0.003	0.148	0.042	0.233	0.166	0.624
Dried matured stem ^b	9.27	0.075	0.046	0.002	0.003	0.030	0.005	0.007	0.195	0.185
Fresh bark of matured stem	2.16	0.085	0.198	0.005	0.004	0.012	0.005	0.089	0.151	0.093
Dried bark of matured stem	14.29	0.314	0.809	0.019	0.014	0.041	0.017	0.280	0.672	0.486
Fresh debarked young stem	2.67	0.087	0.058	0.001	0.002	0.107	0.015	0.063	0.112	0.096
Dried debarked young stem	9.76	0.267	0.188	0.007	0.002	0.340	0.058	0.226	0.527	0.703
Fresh leaves	0.60	0.005	0.001	0.001	0.0002	0.010	----	0.003	0.014	0.005
Fresh young stem	0.80	0.005	0.002	0.002	0.001	0.006	----	0.002	0.011	0.002
Fresh bark of large branch ^d	3.0	0.117	0.322	0.003	0.007	0.020	0.004	0.098	0.051	0.018
Dried bark of large branch ^d	18.1	0.711	1.926	0.018	0.040	0.103	0.029	0.672	0.434	0.163
Fresh debarked large branch ^d	5.2	0.120	0.279	0.002	0.010	0.089	0.018	0.177	0.062	0.036
Dried debarked large branch ^d	7.6	0.154	0.378	0.002	0.010	0.103	0.020	0.229	0.205	0.114
Fresh leaves	3.71	0.080	0.049	0.007	0.003	0.126	0.007	0.062	0.063	0.056
Fresh young stem	2.50	0.027	0.041	0.005	0.001	0.016	0.004	0.040	0.008	0.010
Dried young stem	8.20	0.158	0.125	0.003	0.007	0.157	0.030	0.103	0.098	0.148
Fresh leaves	2.17	0.018	0.007	0.004	0.002	0.039	----	0.011	0.254	0.156
Dried leaves	8.33	0.107	0.021	0.008	0.006	0.147	----	0.025	0.017	0.025
Fresh matured stem	2.9	0.062	0.103	0.002	0.003	0.050	0.010	0.075	0.078	0.099
Dried matured stem	9.56	0.210	0.382	0.004	0.008	0.207	0.046	0.350	0.057	0.115
Dried matured stem (BCEx-1)	15.43	0.150	0.074	0.002	0.006	0.103	0.017	0.043	0.046	0.031
Dried matured stem (BCEx-4)	9.80	0.170	0.153	0.002	0.008	0.159	0.024	0.133	0.245	0.382

^aYield of the aqueous plant extract measured by weight.

^bExtracted with water by automated ASE-200 extractor.

^cPlants from this collection are 3 years old.

^dLarge branches: diameter: 3-8 cm. NT = Not tested. NA = No antioxidant activity up to 31.25 µg/mL.

Table 1. Quantification of markers banistenoside A (1), banistenoside B (2), harmol (3), THNH (4), THH (5), harmaline (6), harmine (7), epicatechin (8) and procyanidin B2 (9) of various extracts of *B. caapi*. Adapted from: <http://ukpmc.ac.uk/articles/PMC2878139?table=T1/>.

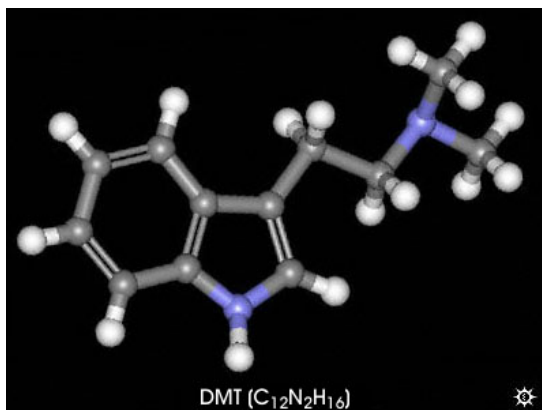


Figure 8. DMT, found in Ayahuasca brew (derived from other species – not *B. caapi*). (Image source: http://www.erowid.org/chemicals/dmt/dmt_chemistry.shtml)

while the branches contain up to .37, the leaves up to .70 and the roots contain up to 1.95 percent (**Table 1**) (Riba, Anderer, Jane, Saletu, & Barbanoj, 2004; Riba & Barbanoj, 2005; Riba et al., 2003; Rivier & Lindgren, 1972; Wang et al., 2010; Winkelman, 2005). Interestingly, in dried plant material, the concentration of these chemicals does not seem to diminish, but rather increases, indicating that they are not lost due to evaporation.

In addition to the great variety and quantity of β -carboline MAOIs found in *B. caapi*, there are also two proanthocyanidins, epicatechin and procyanidin 2B, which exhibit a great deal of antioxidant activity. There are also several other compounds in the plants that have yet to be classified, but exist in very small amounts (Wang et al., 2010). It should be noted that several sources indicate that DMT (discussed later) is present in *B. caapi*. According to all the literature cited here, this is not the case. While DMT (**Figure 8**) is present in the ayahuasca brew, it does not come from *B. caapi*, but rather from other sources.

Biological activity

The procyanidins mentioned in the previous section, epicatechin and procyanidin 2B, belong to the flavonoid class of compounds. Flavonoids have the distinct ability that they are able to rid the body of reactive oxygen species (ROS). ROS are oxygen containing compounds that can be found in the body as a response to pathogens, as a result of oxidative phosphorylation, or simply due to intake in certain foods. These compounds contain unpaired electrons with extremely high levels of energy that cause them to react with nearby molecules, resulting in damage to tissues and potentially causing cancer. Flavonoids, as do other antioxidants, interact with these ROSs and absorb the damage, thus preventing any harm to the body. Because of the composition of these compounds, they are able to deal with the stress created by ROS much better than say, DNA or cell phospholipids. Drinking ayahuasca has also been linked with improved immunity and several of the β -carbolines have shown effectiveness in getting rid of protozoal, bacterial and helminthic pathogens (Dennis J, 2004).

For the making of the brew, however, it is the β -carboline MAOIs that prove useful. One key aspect of digestion is the ability to break down nitrogen containing compounds. One class of nitrogen containing compounds are monoamines, compounds containing a single nitrogen atom. Via a process called monoamine oxidation, spearheaded by molecules called monoamine oxidases (MAOs), single-nitrogen containing molecules are broken down by the body. This results in the formation of a complex carbohydrate and an ammonia molecule, which is then expelled along with other wastes. The β -carbolines found in *B. caapi*, such as harmaline, act as monoamine oxidase inhibitors (MAOIs). By performing this duty, MAOIs are able to prevent the breakdown of single-nitrogen containing molecules (MB & PF, 2004).

One of the uses of MAOIs has been in the treatment of depression. Depression is caused by a low level of serotonin in the brain. Serotonin is normally released from one neuron to the next and is reabsorbed from the neuronal synapse. As a monoamine, however, serotonin is sometimes broken down by MAO and the resulting drop in serotonin levels eventually leads to depression. Later studies also found that in patients with Parkinson's disease, who are also afflicted by low levels of serotonin, MAOIs have a significantly positive effect, which has led to research on the use of MAOIs for this condition (MB & PF, 2004). MAOIs also affect the concentrations of epinephrine and norepinephrine in the body. Like serotonin, these two molecules are monoamines and can be up-regulated by administering MAOIs. This can help regulate several conditions that are dependent of these neurotransmitters (Dennis J, 2004).

Indeed the happy feeling of those who take ayahuasca is likely due to the effects of MAOIs in the brew (Dennis J, 2004). However, what makes *B. caapi* so interesting is the interaction that it has with another chemical present in the brew. The compound in the ayahuasca brew that produces hallucinations N,N-Dimethyltryptamine (DMT), a monoamine that is not actually found in *B. caapi*, but in *Psychotria viridis*, *Diplopteryx cabrerana* and the other plants used in the ayahuasca brew.

Upon oral ingestion, a drug has to go through the stomach where it is broken down and eventually absorbed in the intestine, this is also true of DMT. However, upon reaching the stomach DMT is broken down by monoamine oxidases and it is unable to reach the brain, where it causes its hallucinogenic effects. DMT acts by interacting with serotonin and dopamine receptors in the brain, which lead to the euphoric and hallucinogenic properties of the chemical. When inhaled or injected, DMT can act on the body to induce these properties and its abilities have been properly documented by researchers

in the field. However, when taken orally, DMT is broken down and procures no reaction (de Araujo et al., 2011).

By combining *B. caapi* with other plants that contain DMT the stomach is unable to break down DMT and it can be absorbed into the bloodstream and make its way to the brain. What makes ayahuasca so interesting is that it provides such a finely balanced mixture of chemicals, coming from a people who haven't the slightest knowledge of chemical. The ayahuasca brew exemplifies the complexity and the knowledge of the natives of South America (Morton, 1931; Riba et al., 2004; Riba et al., 2003; Rivier & Lindgren, 1972; Wang et al., 2010).

Contraindications

B. caapi alone seems to confer the MAOI effect in the brew. When an extract of the vine is used alone, it produces mood-enhancing and sedative properties, however, the β -carbolines in the plant can induce nausea and vomiting (Dobkin de Rios, 1971; Luna, 1984; Rivier & Lindgren, 1972). Aside from the nauseating feelings caused by ayahuasca consumption, the brew also seems to have other side effects. Among the more significant ones is an increase of diastolic pressure. According to several studies, however, this might actually be caused by DMT and not by any of the chemicals found in *B. caapi* itself (Riba et al., 2003).

Several studies seeking to test the potentially adverse effects of the plants showed no adverse side effects in pregnant women, or their children (dos Santos, 2010; Labate, 2011). There is also no evidence to suggest that consumption of the plant has negative effects on teenagers (Doering-Silveira et al., 2005). Frequent use of the plant seems to have a higher rate of illicit drug use, although ayahuasca itself does not seem to

have any particularly harmful or addictive properties (Fábregas et al., 2010).

In interesting case mentioned by McKenna is that the β -carbolines in *B. caapi* can induce epileptic form seizures in rat and in chickens homozygous for the epileptic gene. In addition, rats fed with *B. caapi* extract showed decreased fertility (Dennis J, 2004).

Current Uses in Allopathic and CAM Therapies

Most studies performed on *B. caapi* focus on trying to determine whether the plant is safe to use, or not. Some research has been done regarding its potential use in treating substance abuse, alcoholism, serotonin deficiency, as well as immunity enhancing, but these studies have been uncertain and have had difficulty progressing, often because of legal issues with the plant (Dennis J, 2004).

Today, *B. caapi* is still used by South American natives in pretty much the same manner that it has always been used. In addition, several groups throughout the world use the plant in their so called religious practices. Among these are the UDV, Barquinia and Santo Daime sects in Brazil, who use the plant in religious rituals in trying to become enlightened, but have been in part responsible for bringing the attention of authorities to the plant (Dennis J, 2004).

Another important aspect of ayahuasca use is the artistic visions it produces. Several artists, like Peruvian native Pablo Amaringo and New Yorker Robert Venosa, have helped popularize ayahuasca through awing portrayals of their visions (**Figure 9**). These paintings range from simplistic geometric patterns to very complex symbolist imagery of the spiritual ideas associated with ayahuasca. Vines and serpents



Figure 9. Ayahuasca vision art. (Image source: <http://inyectamemas.blogspot.com/>)

are often seen in the paintings as well as other images that are imbedded in the psyche of the drinker (Shanon, 2010).

Legal Status

During the twentieth century, media and government attention was brought to ayahuasca. This was due in part to the previously mentioned religious groups, many of which have a negative light in the public's eye. These religious groups, like Santo Daime are based on syncretic beliefs, taking from African, Native American and European Judeo-Christian cultures. Their goal in using ayahuasca is to achieve a connection with God. As these groups have made their way out of Brazil into Europe and the United States, they have

gained popularity among those who wish to “achieve enlightenment”. In addition to those who seek enlightenment, there are many who have learned to use ayahuasca as a recreational drug. This has brought the plants used in the brew, *B. caapi* included, to be questioned by politicians and mass media (Kjellgren et al., 2009; Winkelman, 2005).

In the United States and in most other countries, DMT is a Schedule I drug. However, the right to use plants containing DMT varies from country to country and there are no international laws prohibiting the growth and sale of these plants by the public (Bullis, 2008; Dennis J, 2004; Winkelman, 2005). This means that those who wish to purchase *B. caapi* or *P. viridis* can do so freely in most countries and they can do with these plants as they desire.

In the United States, those who believe the plant is harmful and those who use it in their spiritual practices are debating the use of plants containing DMT. The law currently allows for the importation of many of the plants used to make ayahuasca for the purpose of religious ceremonies. Brazil has had similar issues since the 1980s; they have concluded that so long as the plant is being used for religious purposes, then the consumption of the plants is allowed. However, the Brazilian government bans the use of ayahuasca for recreational purposes. The legal status in the Netherlands is a bit more permissive, as people are allowed to buy the plants needed for the brew as they please (Bullis, 2008; Dennis J, 2004).

Conversely, in France and the UK the law forbids the sale and use of any plant containing DMT. Several public articles online explain how a French supreme court ruling in 2005 allowed the use of ayahuasca plants so long as no extractions were performed on these to obtain pure DMT. This decision was overturned four months later because of another case that

made all of the ingredients in ayahuasca illegal to use or possess.

Discussion

Ayahuasca’s healing properties exist for those who believe in them. The natives continue to use the plant for healing rituals that focus on healing the soul and the mind. In those cases where they use the plant to search for lost causes to illnesses, the healer, or the “patient”, interprets the hallucinations created by the plant to discover a cause or cure. Again this requires a great deal of belief in the spiritual something that is not found in many “civilized cultures.” As far as Western medicine is concerned, ayahuasca conveys no actual medicinal purpose and like many other plants used by indigenous people, its useful for nothing other than sooth saying and spiritual psychobabble. What little evidence is reported on the potential use of the plant in treating diseases is unconvincing and the current legal issues regarding the plant make it barely worth the effort.

While the Native Americans who use ayahuasca do so in order to heal, whether the mind or some physical state through spiritual means, the newer groups that have spread ayahuasca to the rest of the world propagate it as purely religious plant. In the religious ceremonies of groups like Santo Daime, ayahuasca takes the brew to connect with God. This has led thrill seekers to join these religions for the sheer purpose of “getting high”. What is worse, people have started to use it for recreational purposes. Since the spread of Santo Daime, drug tourism has caused a negative light to be shed on ayahuasca (Bullis, 2008).

In reality, the brew seems to convey little harm to those who take it, yet many countries, like France, have chosen to ban the

plants used to make ayahuasca. Because of the exploitation of the plant by tourists and by those who have close constant with natives, as well as by natives themselves, who choose to sell their knowledge for monetary gain, the banning of the ayahuasca plants from public opinion is imminent. Looking at the history of plants like cannabis, it seems inevitable that ayahuasca will eventually become one of the many plants that are controlled by government regulations globally.

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Camellia sinensis (L.) Kuntze, Theaceae

Nina Patel

Introduction

The scientific name for tea is *Camellia sinensis*, and it belongs to the Theaceae family ("Tropicos," 2012). It is one of the oldest drinks in the world, and only water surpasses it in consumption (Chow & Hakim, 2011). Other common names of tea used by different cultures include thee, cha, chai, shai, and O cha (Saberri, 2010). Archaeological evidence suggests that the origins of tea date back to China over 5,000 years ago, and from there it diffused into India, Japan, Thailand, Korea, and Sri Lanka (Meltzer, Monk, & Tewari, 2009). Tea was native to the ancient kingdoms of Shu, which was located in the "four rivers" and the neighboring kingdom of Ba in China. The Chinese book *Chajin* by Daoist Lu Yü, is the first book written that discusses tea, and it dates back to 780 CE (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009). The medicinal use of tea was also discussed in the ancient Chinese pharmacopoeia "Ben Cao Gang Mo" (Lin, Tsai, Tsay, & Lin, 2003).

There are three main types of tea originating from the same plant: green, oolong, and black (Ferrara, Montesano, & Senatore, 2001). Green tea is consumed mostly in China, Japan, India, some North African and Middle Eastern countries whereas black tea is consumed mostly in Asian and Western countries (Cooper, Morre, & Morre, 2005). Green tea is prepared from fresh leaves and buds that are heated by pan frying or steaming to inactivate the enzymes and stabilize the monomeric catechins, and then these leaves are dried (Ferrara et al., 2001); (Hara, 2011). To produce oolong tea, fresh leaves

are wilted in the sun, bruised a bit, and then finally fermented. However, if the wilted leaves are fermented, black tea is produced instead (Ferrara et al., 2001).

Tea is composed of three main constituents: caffeine, catechins, and theanine (Saberri, 2010). Tea also contains other compounds, such as volatile oils, vitamins, and minerals. The active compounds in tea are the polyphenols, mainly epigallocatechin, gallic acid, and bioflavonoids. These catechins may help to fight various types of cancers, such as skin, esophageal, stomach and colon cancer. Tea can also be used as a topical agent to help control bleeding that has resulted from cuts and scrapes. *C. sinensis* can also be used to relieve insect bites and help control blood sugar and insulin levels (Ferrara et al., 2001). Overall, tea has many medicinal uses.

Apart from its medicinal uses, it is also a historically, economically, and culturally significant plant. For example, one of the reasons that the colonization of India occurred was to control the tea trade (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009). *C. sinensis* is an important botanical plant that still continues to have relevance 5,000 years after it was first discovered.

Botanical Description

Camellia sinensis is grown in thirty countries (Cooper et al., 2005). It is grown 1,000-7,000 feet above sea level, in temperatures between 50-85°F, and in areas with annual



Figure 1. *Camellia sinensis*. Source (Hamilton, 2010)

rainfall between 80 to 90 inches (Saber, 2010). It is grown best in humid climates (Cooper et al., 2005). The ideal geographical area for tea to be grown ranges from Java in the south to Japan in the east and the north and India to the west. This area also includes Formosa, China, Sumatra and outer neighboring countries. It is grown best on terraced hillsides and open fields (Shalleck, 1972). It can be grown as a tree or a shrub (Mahmood, Akhtar, & Khan, 2010). It is an evergreen, perennial plant (Mondal, Bhattacharya, Laxmikumar, & Singh Ahuja, 2004).

For tea growth, warm weather with an even distribution of rainfall throughout growing season is needed. The leaves will grow more if the weather is wetter and the rainy season is longer. The colder the weather, the slower the growth of the tea bushes, which will result in fine tea with small supple leaves. However, frost will blacken the leaves thereby marring the tea (Shalleck, 1972).

Tea can reach a height of 10-15 meters when grown in the wild, and 0.6-1.5 meters when cultivated. The leaves are green, short stalked, coriaceous, alternate, lanceolate, serrate margin, glabrous or pubescent beneath, and vary in length from 5-30 cm and are 4 cm in width. Mature tea leaves are bright green, smooth, and leathery whereas the young tea leaves are pubescent. The flowers are white fragrant and range from 2.5-4 cm in diameter. The flowers either occur by themselves, or they can occur in clusters of two or four. They have stamens with yellow anthers, and they make brownish red capsules. The fruit is a flattened, smooth, round trigonous three celled capsule, and there are seeds the size of a small nut in each fruit (Mahmood et al., 2010). The seeds ripen on the plant, and then they germinate in damp sand pits. When the seed shell opens, the seeds are planted in either nurseries or in fields. Proper shading is crucial for tea bushes. The tea plants are prevented from developing into trees by pruning and hand-picking (Shalleck, 1972). A picture of the plant can be seen in **Figure 1**. Tea is a self-sterile and cross-pollinating crop (Abrol & Abrol, 2012).

There are four varieties of plants: the Assam (Indian) plant; the Chinese plant (Bohea); a relative of the Indian plant which is grown in Ceylon, Java, and Sumatra; and a relative of the Chinese plant which is cultivated in Formosa and Japan (Saber, 2010). These types are mainly distinguished by their leaves (Mondal et al., 2004). Bohea is a small and stunted bush that is compactly branched containing small stiff leaves and purple leaf buds (Saber, 2010). The relative of Bohea is similar in appearance, but it is larger and contains bigger leaves. Assam tea can reach up to a tree height of thirty feet when grown in its wild state. This Indian tea plant contains huge leaves and few flowers. The relative of Assam is similar, but it is composed of smaller, thicker, and more precisely serrated flowers (Shalleck, 1972). The Chinese plant can live

for hundreds of years whereas the Assam variety can live for about 40 years (Saber, 2010).

Traditional Uses

Traditional Medicinal Applications

Tea has been used as an ethnomedical remedy for centuries. For example, in the Chinese book *Kissa Yojoki* (ca 1191), tea was described as a medicine to help control bleeding, heal wounds, regulate blood sugar, help with digestion, and regulate body temperature (Meltzer et al., 2009). During the Zhou dynasty in China, tea was used as a stimulant to promote positive moods. Tea was consumed to calm and clear the mind, sharpen mental acuity, and relax smooth muscles. It was also used as a diuretic, antitoxin, mild disinfectant, and as an efficacious rinse to soothe strained, tired eyes and to alleviate skin ailments (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009). The remedy used to treat many of these discussed problems was drunk as a bitter medicinal drink. This drink was prepared by infusing tea leaves in hot water. Salt was often added (Saber, 2010). When rinsed in the mouth, tea cleansed the palate and since it contains trace minerals like fluoride, it promoted dental health and aided digestion (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009). In the ancient world, tea was thought to increase blood flow, act as an immunostimulant, speed up metabolism, help with anemia, fight the effects of summer heat, and increase the number of years a person lived (Blufeld, 1985).

For the Daoists, tea was thought to promote health and increase life span. It was prescribed as a tonic and remedy by

apothecaries and Daoist healers. These healers worked with chefs of noble houses to infuse tea into healthy recipes and tasty dishes. It was a bitter herb that was used in cooking and took on many forms: fresh leaves, pulp, pastes, and gels in season, dried loose leaves or “bricks” of compressed leaves, and “wafers” and “cake” of dried paste (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009)

Many of these ancient uses still have relevance in modern CAM applications as well as modern day traditional medicines. Powerful infusions of tea are used often for bathing the feet and to treat fungoid infections. Tea (in the drinking form) can be used as cleanser for the face to help get rid of pimples and skin rashes. In rural China, strong tea is used as a mild disinfectant for new skin lacerations. Hair can become soft and glossy when washed with tea. It is also used for halitosis in the leaf form by placing the leaves in the mouth. In North China, individuals rinse their mouths with green tea after eating. Toothaches can be relieved by chewing tea leaves (Blufeld, 1985). Green tea is consumed between meals or after meals in Japan and Asian countries (Lee et al., 1997). In Japan, tea can be found in foods, such as *kanten* (tea jelly) and a green tea ice cream called *matcha*. It is also found in *O-chazuke*, which is a rice dish (Saber, 2010)

Oolong tea has hypocholesteromic properties that become active after a fatty meal, and this can help with hypertension and arterial disease by being an anti-clot agent. Black tea has a high content of tannins, which can help with diarrhea and headaches. Damp black tea bags can help with tired, red eyes as well and relieve itching and redness caused by insect bites (Ferrara et al., 2001). Many of the ancient day uses of tea still apply today.

Tea Drinking

Around the world, many forms of drinking tea occur, and this is intricately tied into the cultures of many societies. In Central Asia and Tibet, the oldest form of tea drinking still remains. This ancient practice consists of boiled tea that is made with compressed tea, which is either shaved off a brick or broken off a cake. Then, it is boiled with water and usually other ingredients. Indian chai is made in a similar manner. During the Song Dynasty (960-1279), whisked tea arose in China and diffused into Japan, where it was integrated into ceremonial practices. Whisked tea is made from leaves that are grounded into a fine powder, and then whipped with bamboo sticks and hot water in separate bowls. Steeped tea, in which tea leaves are steeped in the tea pot, became a common practice during the Ming dynasty in China (1368-1644). It was steeped tea that maritime traders introduced into Europe (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009).

Tea drinking is intricately tied into the Japanese culture as it has influenced the fine arts, including garden design, flower arrangement, architecture, calligraphy, painting, lacquer, and ceramic arts. The tea ceremony in Japan is called *chado*, 'The Way of Tea,' and it was originally a Buddhist ritual. This tea ceremony still continues on today in Japan (Saber, 2010).

In Korea, consumption of tea is tied with the *Panyaro Seon* (Zen) of tea. Tea ceremonies are seen as a spiritual activity that results in inner awakening and even total enlightenment. Temples in Korea also serve tea to visitors (Saber, 2010).

In England in the 1850s, tea began to become the focus of social visits. It was served with sandwiches, biscuits, cakes, and pastries. Fancy silver or fine bone china tea-ware arose to accommodate this important social event. Afternoon tea became a unique event. It became common among the high,

middle, and lower classes in Great Britain. Although today this tradition has declined, tearooms can be found across Great Britain, and they are very popular places (Saber, 2010).

The Economics and History of Tea

Camellia sinensis is a historically important plant and is closely interlaced with the histories and economies of China, India, and Britain. China used to dominate the international tea trade till the mid-nineteenth century. China lost control because Great Britain started to compete with them, as they were eager to make their own tea. To do this, Britain turned to other regions. For example, the colonialization of India started in 1757 in part because the British wanted to make their own tea, and India presented the perfect opportunity with its huge population of peasant cultivators. As in other British islands, the indenture system was eventually established in India. This system recruited and constrained laborers to tea plantations under a penal system. Indian indentured laborers also supported the British plantation economy in other places besides India, such as Fiji and East Africa and the lives of these laborers were like those of the African slaves. This indenture system eventually caused Indian tea to surpass Chinese tea in the global market (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009).

The history of tea is also closely interlaced with the history of sugar because sweetened tea was a common beverage. Both tea and sugar entered the British market as rare and expensive items during the mid-seventeenth century that only the elite could afford. Two hundred years later, sweet tea replaced both beer and malt liquor as the top beverage. The United Kingdom drank 40 percent of the tea worldwide by 1900. This was due to industrialization—it helped the new

industrial workers meet their caloric needs and helped to keep them awake by acting as a stimulant—and the growth of the British Empire. In the British Caribbean colonies, over a million African slaves worked under arduous conditions to produce sugar. These workers were overworked, malnourished, and disease ridden and their death rate far exceeded their birth rate. This cheap land and labor increased the demand for tea by making it cheap and readily accessible to the lower classes in Britain (*Steeped in history : the art of tea / Beatrice Hohenegger, editor ; with essays by Terese Tse Bartholomew ... [et al.]*, 2009).

Tea has a rich history that was tied to the exploitation of native populations. It has changed the world, and it still is relevant today. As a highly consumed beverage, tea is still an economically significant commodity. For example, in the United Kingdom, around 165 million cups of tea are consumed daily (Saber, 2010). Also, 2/3rd of the world population consumes tea daily as a morning drink, and about 2.2 millions tones of it are produced annually (Mondal et al., 2004).

Chemistry and Pharmacology

The constituents of tea possess biological properties that are beneficial for one's health as they have been shown to be possess antiallergenic, antioxidant, antimutagenic, anticancer, antiatherosclerotic, and antibacterial properties (Ferrara et al., 2001). Many of these biological activities can be traced back to the three main components of tea: caffeine, catechins, and theanine. Catechins are polyphenolic flavonoids (tannins), and they are responsible for the briskness and astringent flavor of tea. Caffeine, a mild stimulant, also brings about the bitter flavor of tea. In contrast to caffeine, theanine is an amino acid that is responsible for the sweetness of tea, and it

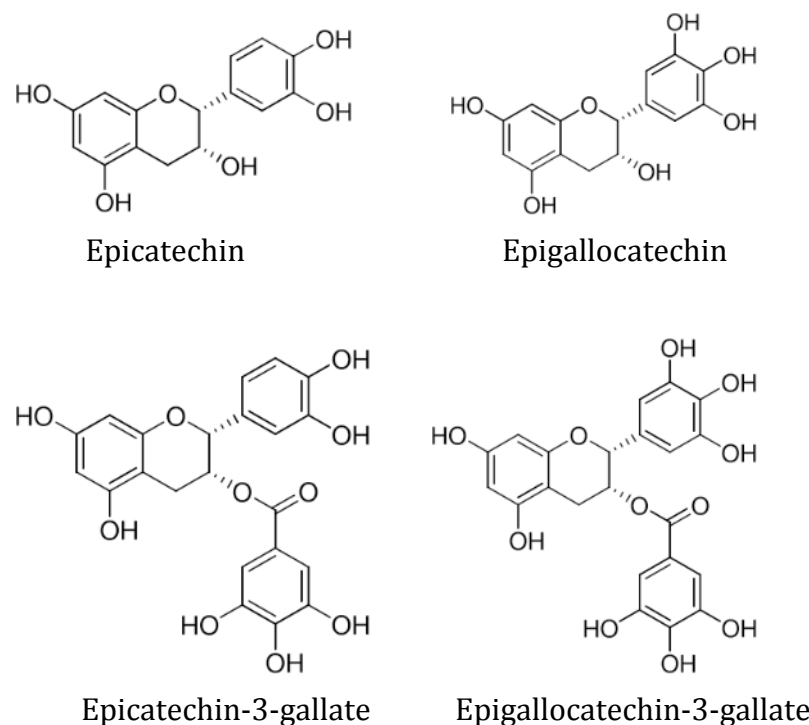


Figure 2. Chemical structures of the four major catechins found in *Camellia sinensis*. These catechins are EC (epicatechin), EGC (epigallocatechin), ECG (epicatechin-3-gallate), and EGCG (epigallocatechin-3-gallate). Source (Kim et al., 2010)

acts to suppress the stimulant activity of caffeine (Saber, 2010).

Catechins are made by the tea plant/shrub during the day and stored in cell vacuoles in the shoot of the plant. As the temperature gets higher, the rate of production of these catechins increases. These catechins may be useful secondary metabolites that may serve to protect leaves from bacteria, viruses, fungi, and vermin bites. Catechin oxidation forms

Active Ingredient	Content (g/kg dry leaves)
Caffeine	36
Catechins	
Epicatechingallate	15.2
Epigallocatechin	46.0
Epigallocatechin gallate	129
Epicatechin	0.9
Major catechins	191
Flavonols	
Myricetin	0.8
Quercetin	1.8
Kaempferol	2.6

Table 1. Major constituents of green tea by g/kg of weight.
Source (Perva-Uzunalic et al., 2006)

dimers and polymers named theaflavins and thearubigins, which retain many of the properties of catechins. Catechin oxidation is the main chemical reaction involved in the synthesis of black tea (Shalleck, 1972).

Catechins comprise 30% of the dry weight of tea leaves (Chyu et al., 2004). They can be categorized as either free catechins or galloyl catechins. The free catechins include (+)-catechin (+C), (+) galocatechin (+GC), (-) epicatechin (EC) and (-) epigallocatechin (EGC). Galloyl catechins include (-) epicatechin gallate (ECG), (-)-epigallocatechin gallate (EGCG), and (-)-galocatechin gallate (GCG) (Hara, 2011). EGCG is also the main antioxidant catechin found in tea, and is responsible for many of the attributed health effects of tea (Chyu et al., 2004). The structures of some of these major catechins are shown in **Figure 2**. They consist of polyphenolic aromatic rings that contain hydroxyl groups (Hara, 2011).

In a cup of tea, the following percentages of compounds are found: caffeine constitutes 2-4% tea; amino acid constitute 4% of tea; lignins constitute 6.5%; organic acids constitute 1.5%

Components	Green Tea	Black Tea
Catechins	30-42	3-10
Ravanols	5-10	6-8
Other flavonoids	2-4	-
Theogallin	2-3	-
Ascorbic acid	1-2	-
Gallic acid	0.5	-
Quinic acid	2	-
Other organic acids	4-5	-
Theanine	4-6	-
Other amino acids	4-6	13-15
Methyxanthines	7-9	8-11
Carbohydrates	10-15	15
Minerals	6-8	10
Volatiles	0.02	<0.1
Theaflavins	-	3-6
Thearubigins	-	12-18
Caffeine	3-4	3-4

Table 2. Major constituents of green and black tea by weight % of extract solids. Source (Chow & Hakim, 2011).

of tea; proteins constitute 15% of tea; chlorophyll constitutes 0.5% of tea; the polyphenols, such as EGCG and EGC constitute 25-35% of tea. A cup of green tea can contain anywhere from 300-400 mg of polyphenols or 10-30 mg of EGCG. The polyphenolic compounds present in tea are essentially colorless (Meltzer et al., 2009). **Table 1** shows the percent composition of the constituents of tea as present in green and black tea.

Table 2 shows the content by weight of active ingredients in dry tea leaves. Caffeine weighs 36g/kg; the major catechins weigh 191 g/kg; the flavonols weight 5.2 g/kg (Perva-Uzunalic et al., 2006).

Among the three different types of tea, there is also a difference in chemical content as they undergo different

levels of fermentation. Green tea has the most antioxidant content due to a higher EGCG content with black tea having the least EGCG content (Cheng, 2006). Black tea has the most caffeine content, and green tea has the least (Lin et al., 2003).

Biological Activity

Many of the health benefits of tea can be attributed to its EGCG content. EGCG has strong antioxidant properties, and it also accounts for more than 65% of the catechin content of tea and more than 10% of the extract dry weight of tea (Kaedei et al., 2012).

In Vivo

Atherosclerosis

Many of the potential protective effects of catechins found in *Camellia sinensis* may not work once a disease or illness is well established. For example, many of the human clinical trials that administer antioxidants may fail because the therapy begins long after atherosclerosis is already established in the patients. In contrast, the positive results seen in laboratory animals may occur because the early initiation of antioxidant therapy occurs when atherosclerosis is still developing.

This study investigated the preventive potential of tea catechins in hypercholesterolemia apolipoprotein E-null mice. Mice with either evolving or established atherosclerotic lesions were injected daily with either intraperitoneal injections of EGCG (10 mg/kg) or PBS. These lesions were produced by periadventitial cuff injury to carotid arteries. Results were taken after 21 and 42 days of treatment. It was found that this therapy decreased evolving atherosclerosis plaque sizes at 21 days by 55% and 42 days by 73% compared

with PBS treatment ($P < 0.05$). Also, the sizes of the plaques were the same in both day 42 and day 21 treated mice that had been administered EGCG. This suggests that treatment may halt the development of these lesions. EGCG treatment did not reduce established lesions in the aortic sinuses or the rest of the aorta. EGCG injections may have reduced evolving lesions because it increased antioxidant capacity in local vascular tissue as well as systemic circulation. It also decreased vascular smooth muscle cell proliferation and redox sensitive gene activation (Chyu et al., 2004).

Diabetes

Hyperglycemia can lead to diabetic complications, such as neuropathy, retinopathy and nephropathy in diabetes mellitus. This study investigated the effect of oral administration of green tea (GT) on kidney tubules of diabetic rats, and it found that diabetic rats treated with green tea showed a reduction in serum levels of glucose, glycosylated proteins, creatinine, and blood urea nitrogen levels in comparison to untreated diabetic rats. Glucose, protein, urea nitrogen and creatinine excreted in the urine of GT treated diabetic rats also decreased. A decreased number of glycogen-filled proximal tubules were also seen in diabetic rats treated with GT, which means that GT has a positive effect on renal histochemical parameters. Overall, GT was found to improve serum levels and urine excretions as well as reduce glycogen levels in the kidneys (Renno, Abdeen, Alkhalaf, & Asfar, 2008).

In Vitro

EGCG and motility of Sperm In Vitro

Catechins can inhibit some of the effects of ROS (reactive oxygen species), hydrogen peroxide, hydroxyl radicals, and

nitric oxide. They have also been shown to have higher antioxidant properties than both vitamin C and E (Kaedei et al., 2012; Zhao, Li, He, Cheng, & Xin, 1989).

For motility, sperm require the production of ATP. The synthesis of ATP in the mitochondria results in the formation of ROS, which can decrease the motility of sperm. In this study, it was found that the motility and penetrability of boar spermatozoa improved with co-incubation of 50 and 100 μ M of EGCG. EGCG could potentially protect spermatozoa from oxidative stress and improve energy production, which would result in improved sperm movement (Kaedei et al., 2012).

Breast Cancer

A long-term exposure to low doses of environmental carcinogens may cause most human cancers. For example, short term exposure to low doses of NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and B[a]P (benzo[a]pyrene) results in higher levels of ROS (reactive oxygen species). NNK is a potent lung carcinogen in tobacco products and B[a]P is an environmental, dietary, and tobacco carcinogen. This study looked at the preventive aspects of catechins found in *Camellia sinensis* in preventing breast cancer.

Immortalized, non-cancerous human breast epithelial MCF10A cells in culture were exposed to 100pmol/l of NNK and B[a]P. This exposure resulted in carcinogenesis of human breast epithelial cells due to an increase in ROS levels, which activated the Raf-independent extracellular signal-regulated kinase (ERK) pathway and led to successive cell growth and DNA damage.

Green tea catechins (GTCs) stopped ROS elevation, ERK activation, cell growth, and DNA damage in non-cancerous

breast cells. EC, ECG, EGC, and EGCG are some of the main catechins found in green tea. It was shown that EC decreased cell proliferation and apoptosis at 100 μ g/mol. ECG, EGC, and EGCG decreased cell viability and proliferation and increased cell apoptosis. EGCG was more toxic than EGC, which was more toxic than ECG, which was more toxic than EC. GTCs have preventive activity as they were shown to suppress chronic cellular carcinogenesis from exposure to environmental carcinogens (Rathore, Choudhary, Odoi, & Wang, 2012).

Melanoma

This study tested whether a physiological concentration of EGCG at .1-1 μ M inhibited human metastatic melanoma cell lines, 1205Lu and HS294Y, and they found that it did in a dose dependent manner. The research group showed that EGCG depresses NF-kB activation in a dose dependent manner. IL-1beta signaling led to activation of NF-kB. The secretion of IL-1 beta also decreased because NLRP1 (a part of the inflammasomes) was suppressed and this led to subsequent capase-1 activation depression. They also found that turning off NLPR1, an inflammasome that may be involved in tumor inhibition, reversed these results (Ellis et al., 2011).

Mechanism of Action

EGCG is involved in several cellular pathways (**Figures 3 and 4**) that result in inhibition of apoptosis, cell cycle arrest, growth inhibition, inflammation, antiangiogenesis, and inhibition of metastasis. EGCG inhibits receptor tyrosine kinases, such as epidermal growth factor receptors (EGFRs), insulin-like growth factor-I receptor and vascular endothelial growth factor (VEGF) receptor (VEGFR), and some of their

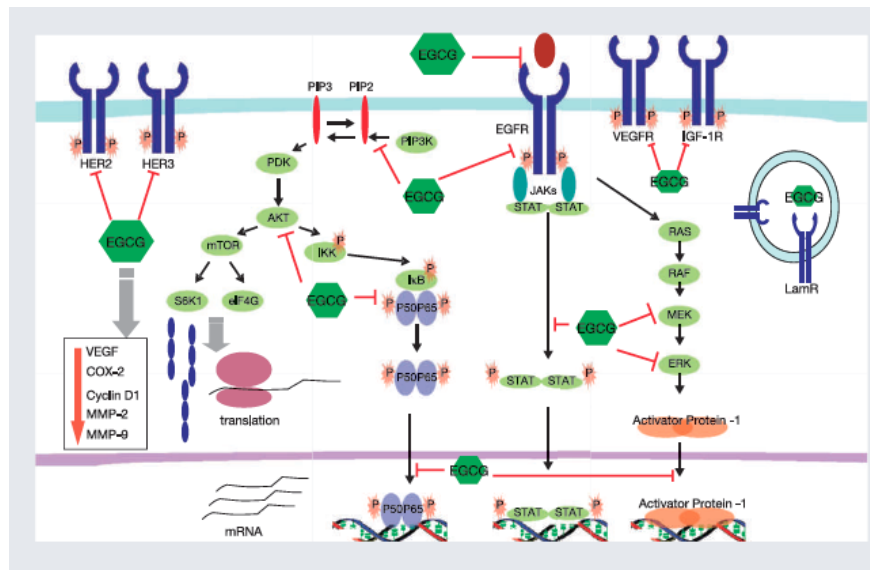


Figure 3. Some of the cellular pathways that EGCG targets.

Source (Kim et al., 2010)

downstream effectors, such as pAkt and pERK by preventing ligand binding and phosphorylation/activation of the receptor tyrosine kinases. It also inhibits cytoplasmic signaling molecules, such as Akt, extracellular signal-related kinase (ERK) $\frac{1}{2}$, and mitogen-activated protein kinase or ERK kinase (MEK). EGCG inhibits intracellular signaling pathways, such as phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (mTOR), Janus-activated kinase (JAK)/signal transducer and activator of transcription (STAT), RAF/mitogen activated protein kinase or ERK kinase (MEK)/ERK/AP-1, and Akt/NF- κ B. NF- κ B is involved in DNA transcription of genes, and these genes are involved in inflammation, immunity, and carcinogenesis. EGCG also activates p53 and its downstream targets p21, p57, and Bax, which results in cell death and G₀-G₁ arrest. It also inhibits the binding of effector transcription factors—NF- κ B, AP-1, and the

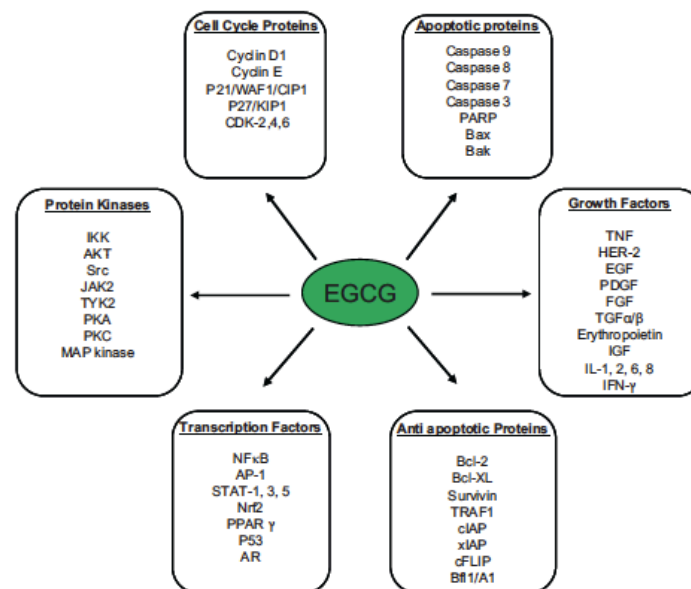


Figure 4. Some of the cellular pathways that EGCG targets.

Source (Singh, Shankar, & Srivastava, 2011)

signal transducer and activator of transcription 3 (Kim, Amin, & Shin, 2010).

In the atherosclerosis study already mentioned, in vitro studies showed that treatment with EGCG 30 μ mol/L reduced the activation of redox-sensitive transcription factor AP-1 and TNF- α induced iNOS expression. iNOS is a source of reactive oxygen species and is a part of the tissue proliferative repair process (Chyu et al., 2004).

Clinical Studies

Obesity

In this clinical study, AR25, which is a green tea extract, was found to inhibit lipases and at the same time stimulate thermogenesis and fat oxidation. AR25 is an 80% ethanolic

dry extract that is standardized at 25% EGCG catechins. This study involved seventy patients aged between 20 to 69 years that were given an AR25 extract. During the course of the study, a decrease of 4.6% in mean body weight and a reduction of waist circumference by 4.48% was observed. After three months of treatment, no significant decreases in plasma cholesterol levels or reduction in blood pressure was seen. The increased thermogenesis and fat oxidation was not linked to a heart rate increase. This is promising since obese patients tend to have underlying cardiovascular problems and hypertension. This extract can influence both body weight and composition by influencing body energy expenditure and the utilization of various substrates in the body (Chantre & Lairon, 2002).

Cancers

Recent research shows that 30% of men with high-grade prostate intraepithelial neoplasia (HG-PIN) develop prostate cancer (CaP) within a year after repeated biopsy. Several epidemiological studies have shown that Asian countries where green tea is a popular beverage have a lower incidence of CaP, and that when these Asian immigrants migrate to the United States and adopt new dietary habits, the prevalence of CaP increases. The green tea catechins capsules used in this clinical trial consisted of 5.5% (--)epigallocatechin, 12.24% (-)-epicatechin, 51.88% epigallocatechin-3-gallate, and 6.12% (--)epicatechin-3-gallate. Less than 1% caffeine was used. Sixty male volunteers with HG-PN underwent this double blind, placebo-controlled trial, and they were given three daily green tea catechin (GTCs) capsules, 200 mg each for one year. The incidence rate of tumors among the 30 GTCs-treated men was 3% (1 person developed a tumor), and it was 30% (9 individuals developed tumors) among the 30 placebo treated

individuals. There were no significant side effects. This study shows that GTCs are both safe and effective as a preventive therapy for the development of CaP. These capsules also reduced lower urinary tract symptoms associated with benign prostate hyperplasia (Bettuzzi et al., 2006).

A study examined the chemopreventive effects of green tea among cigarette smokers of 52 healthy male aged 20-51 years of age. Smoking increases the frequency of sister-chromatid exchange (SCE) in mitogen stimulated peripheral lymphocytes by 35%. This increase may be due to smoking-induced DNA damage. It was found that the frequency of SCE in smokers who consumed green tea (3 cups a day for 6 months) was similar to that of non-smokers suggesting that consumption of green tea may help to prevent lung cancer (Lee et al., 1997).

Contradictions

Camellia sinensis should be avoided if on anticoagulants, such as Warfarin as it decreases the anticoagulant effect through an antagonism mechanism. Warfarin inhibits the production of vitamin-K dependent clotting factors. Green tea contains vitamin K, and therefore acts in opposition to the drug (Izzo, Di Carlo, Borrelli, & Ernst, 2005).

Products containing green tea have been found to be hepatotoxic. A study examining this found that no chronic liver damage occurred. All of the patients recovered within 4 months after stopping to use supplements containing *C. sinensis* (Bonkovsky, 2006).

Tea herbal supplements should also be checked for their caffeine content. Caffeine levels can reach a high level in these products and may cause thermogenic, cardiovascular, and other health effects in humans (Seeram et al., 2006). Too much

consumption of tea may also result in insomnia, and this may be due to the caffeine content of tea (Izzo et al., 2005).

Since EGCG and polyphenols in green tea may be proteasome inhibitors, they should not be taken with other proteasome inhibitors, such as boronic acid-based inhibitors or Bortezomib. If taken in conjunction with these drugs, then tumor cell death may not occur thereby preventing these drugs from working (Shord, Shah, & Lukose, 2009).

The catechins in *Camellia sinensis* are metabolized by catechol-O-methyltransferase, and therefore should not be taken in conjunction with monoamine oxidase inhibitors or dopaminergic drugs due to a potential adverse interaction (Shord et al., 2009).

Current Use in Allopathic and CAM Therapies

Allopathic Medicine

The green tea sinecatechin, Polyphenon E (*Veregen*) ointment is the first FDA approved botanical drug. Polyphenol E is administered for the treatment of anogenital warts because of its antiviral, immunostimulatory, and antioxidant properties (Meltzer et al., 2009). It is sold as a 15% ointment. Each gram of ointment is composed of 150 mg of sinecatechins ("Veregen: a botanical for treatment of genital warts," 2008). Over 85% of this drug consists of catechins that are derived from a partially purified fraction of water extract of green tea leaves from *Camellia sinensis* (Meltzer et al., 2009). The tea leaves are extracted with water followed by ethyl acetate. The resulting product undergoes column chromatography using water/alcohol to elute the catechins. The resulting catechin powder has the following composition: EGCG>65%, EC<10%, EGC<10% and other trace catechin derivatives (Hara, 2011). Gallic acid, caffeine, and theobromine compose another 2.5 %

of the drug ("Veregen: a botanical for treatment of genital warts," 2008).

A 0.5 cm strand of *Veregen* ointment should be dabbed on each wart, covering it with a complete layer, 3 times each day. Treatment should continue until the warts completely disappear, but should not last longer than 16 weeks ("Veregen: a botanical for treatment of genital warts," 2008).

CAM Therapies/ Modern Day Products

Camellia sinensis is found in many herbal supplements on the market (Seeram et al., 2006). For example, EXOLISE® is a capsule containing 375mg of green tea extract AR25, and it has been found to have anti-obesity properties (Chantre & Lairon, 2002). Many of these other supplements are available in capsule form with a recommended dosage of 100mg to 150mg a day (Shord et al., 2009).

C. sinensis is also available in iced and brewed teas, and no more than 2.25g of tea per 6 ounces of water is recommended per serving (Shord et al., 2009). Many skin care products sold by corporations, such as Avon Products Inc, Estee Lauder Inc, Elizabeth Arden, L'Oreal, Carter-Wallace Inc, Aubrey Organics, and Schwartzkopf & Dep Corp. contain green tea. These merchandises include toothpastes, shampoos, depilatory creams, facial cleansing lotions, moisturizing creams, moisturizing lotions, scented sprays, body lotions, and bath and shower gels. Due to the presence of catechins, these products may have anticarcinogenic, antioxidant, and anti-inflammatory activity. Clinical trials should be conducted to investigate these potential biological activities (Katiyar, Ahmad, & Mukhtar, 2000).

Apart from being used in supplements and skin care products, *C. sinensis* has been found to be incorporated into the

treatments of patients suffering from illnesses and chronic diseases. For example, a study conducted in Jordan found that 20.5% percent of diabetes patients used some form of *C. sinensis* in their treatment. Most of these patients used this plant to relieve the symptoms (Wazaify, Afifi, El-Khateeb, & Ajlouni, 2011). In another study, it was found that some cancer patients undergoing radiation therapy for various neoplasms at rural cancer centers used green tea. Of the 153 patients surveyed at these rural centers, 23 people or roughly 15% reported using green tea (Rausch et al., 2011).

Discussion

The origins of *Camellia sinensis* began in China, but today it has diffused into all regions of the world. It is a culturally, historically, and economically relevant botanical plant. For example, the plant is used in food, cosmetics, tea ceremonies, and traditional and allopathic medicinal therapies. Many of the biological and clinical studies discussed in this paper focused on the preventive aspects of tea in preventing cancer, diabetes, obesity, and atherosclerosis. Many of these activities are due to the major catechin found in tea, which is EGCG. EGCG has numerous cellular targets, and therefore may be an effective product to consume to prevent diseases and illnesses. EGCG is also a rich source of antioxidants. The first FDA approved botanical drug was also derived from tea catechins. Due to its relevance in many diverse areas, *C. sinensis* will continue to play an important role in human history.

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Capsicum annuum L., Solanaceae

Ezinne Nwankwo

Introduction

Capsicum annuum L. is also known by a variety of names. The numerous subspecies include bell peppers, chili peppers, paprika, and banana peppers to name a few. It is a member of the nightshade family, Solanaceae (Andrews, 1995). These peppers are native to Central and South America but have been cultivated worldwide and are essential members of many cultural cuisines. Other members of this family are the tomato and *Atropa belladonna*, or deadly nightshade (Andrews, 1995).

The fruit of this plant is rich in vitamins A, B complex C, E, and P. Additionally; it serves as a source of polyphenols. The chemical constituent, capsaicin, gives the fruit its well-known pungent characteristic (Andrews, 1995) and confers many of its medicinal properties. Capsaicin is anti-carcinogenic and anti-inflammatory (Surh, 2002), (Reddy, Ravinder, Prasad, & Kanjilal, 2011). Peppers have been used to combat diseases as diverse as inflammation, diabetes, and evil eye (Aggarwal, Surh, & Shishodia, 2007), (Ishtiaq, Hanif, Khan, Ashraf, & Butt, 2007). *C. annuum* varieties have other uses also. They have been used as a coloring agent for processed food, drugs, and cosmetics.

Botanical Description

Capsicum annuum is herbaceous when young and woodier with age. The woodiness only occurs in areas that do not freeze when grown as a perennial. There is dichotomous branching, with the main stem ending in a flower with several



a.



b.

Figure 1 a and b. Flowering *C. annuum*

(Source: <http://www.g6csy.net/chile/var-ann.html>)

leaves branching off of the same main stem. There are also two or three more stems branching off of the first, main stem



Figure 2. *C. annuum* fruits

(Source:

<http://www.beautifulbotany.com/STOCK%20C/Capsicum%20annuum%20'Garda%20Tricolor'.jpg>)

that also end in flowers. The height of the plant varies with the variety. It can be tall and erect, compact, or prostrate. The leaves vary in shape and texture. They can be smooth or wrinkled. The colors of the leaves range from green to purple to white. The roots can be deep or shallow depending on the variety.

The corolla of the plant (all of the petals of the flower) tapers to a point. This means that they are acuminate. On average the corolla is five lobed but this number can also change. There are three veins in each lobe. The color of the corolla can be anything from cream to purple to greenish white (**Figure 1a and 1b**). There are also some varieties with greenish yellow spots. The pistil can be longer than the stamens, which is characteristic of more primitive plants, or shorter than the stamens. The shorter variety is more favorable for self-fertilization. Sexual reproducing plants are frequented by

honey bees, who are attracted to the scentless nectar. The nectar is secreted and accumulates at the base of the lobes of the corolla and eventually presents at the surface of the petals. Other insects such as aphids, butterflies, and ants also transfer pollen (Andrews, 1995).

The fruit formation depends on genetic factors (size and shape) as well as environmental factors (growth). The apex of the fruit can be sunken and lobed with a depression, as in the boxy bell peppers. In other varieties it can be pointed or blunt. The base of the pod, the attachment point to the peduncle or stalk, may bulge or be nonbulged. In domesticated versions, a hard to detach stem is present. This feature was selected on the basis of ease of storage. Wild versions have a deciduous or easily detachable stem. Many cultivators prefer this version to use with machine harvesting and to decrease the amount of waste generated. The pericarp, or fruit wall, ranges in thickness from thin to thick. This has an impact on preservation technique. The fruit with a thin pericarp can be dried readily but those with thicker pericarps must be pickled, canned, or smoked. The placenta and vein of the plant are also included in the pericarp and contain the active ingredient, capsaicin. The color of the fruits is usually green when unripe but is known to be yellow-green, yellow, orange, bright or deep purple (**Figure 2**). When the fruits reach maturity, the colors range from yellow, orange, and red or brownish red. Red, however, is the most common color. (Andrews, 1995)

Traditional Uses

Traditional Medical Uses

West Indians use a mixture of ground bird peppers combined with onions, cucumber, lemon juice and Madiera as a stomachic, or stomach strengthener (Andrews, 1995). The

people of the Samahni valley in Pakistan use *Capsicum annuum* as a rubefacient as well as sore throat, dyspepsia, yellow fever and snake bites. It is treated by moving three, five, or seven chilies over the head. These same chilies are then burned in a fire. Chili smoke is also used as a ghost repellent in the treatment of giant. Giant is a cultural disease in the middle east (Ishtiaq et al., 2007).

The Mayans used chilies for similar ailments that include sore throats, asthma, cough and respiratory disorders. They also used the peppers topically to heal infected gums. Swedes use a salve made from Chiltepine peppers to sooth sore muscles. In Germany, the peppers are an ingredient in a warming bandage used for muscle pain (Andrews, 1995).

Many cultures use peppers for other medicinal purposes. *C. annuum* has been used as an aphrodisiac, carminative, central nervous system stimulant, and a tonic. Interestingly, it has been used to treat gonorrhoea (Dr. Duke Ethnobotanical Uses).

Food Uses

The use of *Capsicum annuum* as a condiment and spice is spread worldwide. It is a constituent of Indian curry powder and Texan chili powder. The dried, crushed peppers of the red and cayenne varieties are used in America and Turkey. The ground form of cayenne pepper is grown and used in Africa, India, Japan, and Louisiana as a flavoring. Red peppers are grown in the southern and western regions of the United States as well as Turkey. Other pepper varieties are used in the whole form, either dried or fresh. This form is popular in Central and South America as well as southern North America. (Andrews, 1995)

Paprika is a ground mixture of many capsicum varieties. It has a characteristic red coloring and can be mild or more pungent. Sweet paprika contains mostly fruit wall with the seeds removed. The hotter versions contain more of the placenta, seeds and stalks. Interestingly, there is a Hungarian version that is very pungent and uses the long, dried pods. Conversely, the Spanish version contains a more tomato shaped pepper. Morocco and Bulgaria are two other countries that have their own versions of paprika. Many Balkan growers brought paprika seeds to South Carolina after World War II and California is one of the leading producers of paprika. This increase in the United States industry may be due to the decline of the Soviet Union, which caused a decrease in the European paprika industry. (Andrews, 1995)

Pepper sauce is another way that *C. annuum* is consumed. The peppers are either pickled whole in brine or vinegar or mashed to make the sauce. The sauce is then used to flavor other foods. Chili peppers are the variety used in this method. Peppers can also be canned or processed to make dips and sauces. (Andrews, 1995)

Use as a Coloring Agent

The peppers have been used by Central and Southern Americans to enhance the color of a bland diet. They are also used to replace red coloring lost in food preparation. Carotenoids from the peppers are also used to color drugs and cosmetics (Andrews, 1995).

C. annuum has been used extensively in the food industry. Foods from sausages to salad dressings to gelatin are colored with the extractable colors of capsicums. The waste from pimento pepper processing is used to influence the color of egg yolks. The capsanthin present in the pimento waste gets

deposited in the egg yolk and gives it a dark reddish yellow color. The color of the chicken itself is also influenced, with the addition of pimento assuring a yellow skin color in the body of the chicken. An unintentional influence is that the hatched chicks are stronger and offspring of pimento fed chicken have a higher rate of hatchability. This “improved” color is also manifested in faded pink flamingos and trout that are fed pimento waste. (Andrews, 1995)

Other Uses

Italians in the high Molise region of central-southern Italy use a pungent variety of *Capsicum annuum* to protect food products from parasites (Guarrera, Lucchese, & Medori, 2008).

Chemistry and Pharmacology

Capsicum annuum contains a large variety of chemicals that have a huge impact on its pharmacology. It is to be noted that there are multiple varieties of this species that differ in their chemical makeup. The major difference in these varieties is the amount of capsaicin. More pungent varieties such as the red chili pepper have more capsaicin content than less pungent varieties like bell peppers which have a minimum amount of capsaicin (Andrews, 1995).

Capsaicin or CAPS is the major pungent ingredient in *C. annuum*. CAPS is a homovanillic acid derivative (see **Figure 3**) (Aggarwal et al., 2007). It has effects on many organ systems in humans. For example, it causes peristalsis in the stomach stimulating the mucous membranes. This movement aids in digestion. Stomach acid secretions are increased with *C. annuum* consumption. These increased secretions also increase appetite along with aiding digestion. The increased

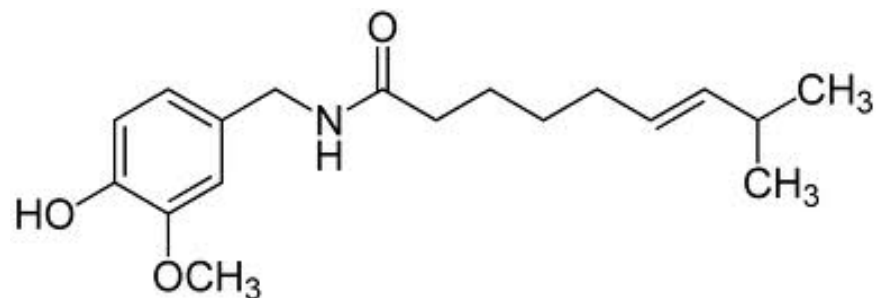


Figure 3. Capsaicin structure

mucous production in the mouth from ingestion protects stomach ulcers from harsh stomach acids (Andrews, 1995).

Mammals are unique in that they have a specific capsaicin receptor on their sensory neurons called the vanilloid receptor-1 (VR1) or the transient receptor potential of vanilloid 1 (TRPV1). Administration of CAPS to peripheral nerve endings results in an initial reaction of pain and neurogenic inflammation. However, desensitization occurs with repeated application of CAPS to the same nerve endings may have indications for its use as an analgesic for many painful neuralgic conditions. The nerve desensitization from CAPS is most likely from the effect on the neuropeptide Substance P. Substance P is involved in pain transmission to the brain and is inhibited by CAPS. The inhibition with increased, repeated exposure to CAPS has the effect of moderating pain (Aggarwal et al., 2007).

As shown above, *C. annuum* has effects on the nervous system. Similar to other members of the Solanaceae family, more pungent varieties of *C. annuum* can alter the conscious state, albeit momentarily. The effect of *C. annuum* differs from other members of the Solanaceae family in that it is nonhallucinogenic and nonaddictive. It is also generally safe for consumption

although. *annuum* has stimulant activities that can activate the vagal reflex and cause vomiting (Andrews, 1995).

In hot climates, *C. annum* can cause psychological gustatory sweating. This is a form of thermoregulation that is confined to the face and scalp. Evaporation of this sweat can facilitate a cooling effect. Cooling the body can relieve this gustatory sweating from consuming the peppers (Andrews, 1995).

Other chemicals in *C. annum* include many nutrients, including Vitamins A (beta-carotene) and C (ascorbic acid). They also contain capsanthin and many capsianosides. Carotenoids and phenolic acid compounds are also found in these peppers. Minerals, amino acids and sugars occur in abundance in *C. annum* fruits (Dr. Duke Phytochemical and Ethnobotanical Database).

Biological Activity

In vitro

It has been found that the CaBtf3 NAC subunit in *Capsicum annum* is involved in the hypersensitive response of plants to viral infection (Huh, Kim, & Paek, 2012). The hypersensitive response facilitates plant cell death after viral infection. Plants use it as a strategy for preventing viral movement and gaining systemic acquired resistance against further viral infection (Huh et al., 2012). It is not known whether this is a transcription factor but knowledge of its involvement in the plant viral response could have implications for potential therapies. In 2011, researchers isolated 28 polyphenols from three *C. annum* bell pepper varieties and determined that these compounds had both anticancer and antioxidant effects in vitro (Jeong et al., 2011). Many studies conducted confirmed that the polyphenols found in *C. annum* do exhibit

antioxidant activity in vitro (Lee et al., 2009), (Materska & Perucka, 2005).

A study was conducted on effect of Indian spices on esophageal squamous carcinoma cells. In the study, an aqueous chili pepper extract induced a 88% apoptotic cell demise and cell death within 24 hours of exposure (Dwivedi, Shrivastava, Hussain, Ganguly, & Bharadwaj, 2011).

In a similar vein, a study was done on human umbilical vein endothelial cells in which extracts from *Capsicum* species and capsaicin were assessed for cytotoxicity to the endothelial cells and protection from lipopolysaccharide (LPS) induced cellular apoptosis (Chularojmontri, Suwatronnakorn, & Wattanapitayakul, 2010). It was shown that the extracts and capsaicin improved endothelial cell function and conferred protection against the LPS induced apoptosis. It was also shown that the extracts were not cytotoxic to the endothelial cells. This protection indicates that consumption of the fruits of *Capsicum annum* species could promote endothelial health (Chularojmontri et al., 2010).

In addition to promotion of cellular health, *C. annum* may be a potential antibacterial agent. A Japanese study showed that a methanol extract of capsaicin inhibited cholera toxin production in *Vibrio cholera*. (Chatterjee et al., 2010) This discovery may have implications for the use of natural compounds to combat increasingly antibiotic resistant bacterial pathogens (Chatterjee et al., 2010).

In Vivo

Many rat and mice studies have been conducted on the effects of capsaicin on pain reduction, weight reduction, and cancer treatment and prevention along with a host of other topics. In one study it was shown that capsaicin may confer protection

from autoimmune diabetes. This study was conducted by researchers at the University of Connecticut School of Medicine. The vanilloid receptor 1 or VR1 is present on sensory neurons as well as immune cells (Nevius, Srivastava, & Basu, 2012). This receptor can regulate gut events in response to its ligand, capsaicin. In mice, when capsaicin is administered orally it stops the growth and activation of autoreactive T cells, which attack the cells of the body. This attenuation is specific to lymph nodes in the pancreas, which is the area of insulin production. The attenuation is how the protection from type 1 diabetes is conferred (Nevius et al., 2012) because capsaicin prevents the autoreactive T cells from attacking the insulin producing cells. The researchers also found that the binding of capsaicin to the VR1 receptor activates pancreatic macrophages that express anti-inflammatory factors (Nevius et al., 2012). The influencing of nutrient-immune interactions by VR1 through inhibiting the autoreactive T cells and activating anti-inflammatory macrophages could have implications on gut-mediated immune tolerance (Nevius et al., 2012).

Capsaicin has been implicated as an anti-carcinogenic. Female mice treated topically with capsaicin exhibited lowered multiplicity of VC-induced skin tumors (Aggarwal et al., 2007). When CAPS was applied prior to induced mutagenesis there was less skin tumor formation in the treated mice (Aggarwal et al., 2007). Several studies conducted showed that capsaicin inhibited metabolic activation of carcinogens via various mechanisms. One such mechanism was the modulation of CYP-dependent monooxygenase activities (Aggarwal et al., 2007). Specifically, a rat study showed that capsaicin inhibited the activity of epidermal arylhydrocarbon hydroxylase. This inhibition blocked the activation and binding of the carcinogen benzopyrene to DNA which prevented it from mutagenizing the DNA (Aggarwal et al., 2007).

As stated above, capsaicin can decrease sensation of sensory neurons. One study measured the effects of capsaicin mediation denervation on bone metabolism in adult rats (Ding, Arai, Kondo, & Togari, 2010). It was shown that high doses of capsaicin decreased trabecular bone volume because of increased bone resorption. This increase in bone resorption led to weaker bones in the rats. The study concluded that sensory innervation of bone helps to maintain trabecular bone volume by inhibiting bone resorption (Ding et al., 2010). There was no indication of whether the amount of capsaicin administered to the rats was comparable to levels commonly consumed by humans.

Several *in vivo* studies have shown that capsaicin has an effect on weight. One such study focused on rabbits (Yu et al., 2012). It was shown that the capsaicin specific receptor, TRPV1, was expressed in many organs. The organs were the brain, kidneys, spleen and adrenal gland. The rabbit TRPV1 receptor amino acid sequence was more similar to humans than to rats, which makes the rabbit a great model system for the effects of capsaicin on humans. In the study, two groups of rabbits were fed a high fat diet. One group's high fat diet also included 1% hot pepper. This group had a significantly lower body weight than the high fat control group. This study concluded that capsaicin could potentially decrease diet-induced obesity (Yu et al., 2012).

Another study fed a spice cocktail including ginger, curcumin, piperine and capsaicin to high fat rats to measure the influence on bile secretion and fat digestion (absorption of dietary fat) in the rats (Prakash & Srinivasan, 2011). This study found that fat digestion was enhanced by the spice cocktail because of increased secretion of bile salts and stimulation of other pancreatic enzymes. It was also found that the spice cocktail increased energy expenditure in the rats, which prevented the accumulation of the digested fats

(Prakash & Srinivasan, 2011). This study differs from the first in that it shows a mechanism of action for the capsaicin induced weight loss.

Clinical Studies

Many of the *in vivo* studies about energy expenditure and weight control effects of *Capsicum annuum* focused on capsaicin. A clinical study showed that capsinoids, which are non-pungent capsaicin analogs, activate brown adipose tissue in humans. This activation increases energy expenditure, which could have implications in the use of capsaicin as a weight loss aid (Yoneshiro, Aita, Kawai, Iwanaga, & Saito, 2012). In this same study, participants ingested an oral dose of the capsinoids under warm conditions. The energy expenditure was measured under both warm and cold conditions. The subjects in the negative control and placebo group did not show the same amount of energy expenditure (Yoneshiro et al., 2012).

Capsaicin has demonstrated anti-carcinogenic activity in both *in vitro* and *in vivo* studies. One study completed in 2002 showed that the vanilloid compounds that make up capsaicin induce oxidative stress and contributes to the death of tumor cells from human cutaneous squamous cell carcinoma, which is a form of skin cancer (Surh, 2002).

A crossover placebo controlled study was conducted that included nineteen health male athletes with experience (Opheim & Rankin, 2012). The purpose of the study was to assess the influence of capsaicin on inflammation and exercise performance. The same group was used for two trials, a placebo study and a capsaicin study. After each supplementation period, the subjects completed repeated sprint tests. Additionally, blood was drawn before

supplementation, 45 minutes before the repeated sprint test and immediately after the repeated sprint test. Several perceived symptoms were also recorded which included perceive exertion, gastrointestinal distress, and muscle soreness. This data was collected one minute before the test, during the test, and one minute after the test. Muscle soreness was also measured three days after the test. The capsaicin increased the amount of gastrointestinal symptoms 6-fold. It did not influence performance on the sprint test. The study concluded that capsaicin should not be recommended for athletes involved in repeated sprints (Opheim & Rankin, 2012).

Another recent study tested the tolerability of a capsaicin patch on human patients for treatment of neuropathic pain. In this case, three other topical anesthetics were used as a pretreatment in the patients. It was generally safe and well tolerated in the patients (Webster et al., 2011). Two clinical trials also conducted in 2011 compared Qutenza, a new high potency capsaicin patch, to existing capsaicin patches (Jones, Moore, & Peterson, 2011). It was found that the Qutenza patch reduced the numeric pain rating scale (NPRS) score at higher rates than the control capsaicin patch (Jones et al., 2011). However, the Qutenza must be administered under a doctor's care and comes with a risk of application site pain and erythema (Jones et al., 2011).

Contraindications

The contraindications found in *Capsicum annuum* other than the risks of application site pain and erythema associated with the Qutenza pain patch (Jones et al., 2011). *C. annuum* is also an emetic (Andrews, 1995). Further research into this area may prove otherwise.



Figure 4. Capsaicin Pain Cream

(Source: <http://drugster.info/drug/medicament/4073/>)

Current Use in Allopathic and CAM Therapies

Topical capsaicin in complementary and alternative medicine is used in the treatment of various ailments like rheumatoid arthritis (Richards, Whittle, & Buchbinder, 2012) and peripheral neuralgia (Webster, Peppin, Murphy, Tobias, & Vanhove, 2012). It can come in a cream form or as a patch (**Figure 4**) and is also used in allopathic medicine (Jones et al., 2011).

Discussion

Capsicum annuum L. is a very diverse species. There are many varieties under the *C. annuum* umbrella that have many unique properties in terms of the botanical description, capsaicin content and traditional uses. Additionally, there are not a lot of scientific studies that describe the ethnobotanical uses of *C. annuum* as it relates to specific cultures and uses. The peppers included under this umbrella are widely used as a food and flavoring source worldwide, even though they are native to South America. There is evidence that *C. annuum*, like

many members of the Solanaceae family as well as other brightly colored fruits contain polyphenols, which have antioxidant properties. The fruits have a rich plant chemistry that contributed a promising drug in capsaicin. Interestingly, this fruit has been used for similar reasons in different cultures across the globe. This is a nod to the knowledge of indigenous peoples that embrace the natural world. Though it is consumed primarily as a food source, there may be other traditional medical uses for it. For example, my mother and many other West Africans use a pepper soup as a normal food as well as a treatment for colds and respiratory ailments. This plant is very influential worldwide and deserves to be the subject of more ethnobotanical research.

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Catharanthus roseus (L.) G.Don, Apocynaceae

MyKeya Henderson

Introduction

Catharanthus roseus, whose common name is Madagascar periwinkle or just periwinkle, belongs to the Apocynaceae. Although *C. roseus* is the accepted scientific name, this plant was once referred to as *Vinca rosea* in the West Indies from its association with folk medicine (Lewis and Elvin-Lewis 2003). Probably one of the most important pharmacological properties of *C.roseus* is its production of vinca alkaloids or bisindole alkaloids (Shams, et al. 2009). This is a native plant of the Island of Madagascar, hence the common name “Madagascar.” This plant has been widely cultivated and used in traditional medicine for thousands of years. Not only was this an important plant in Europe for medicinal purposes such as treatment of diabetes, but it has also been used in several other countries such as China and the Caribbean for a variety of health conditions and diseases ranging from cough suppressants and eye infections to Hodgkin’s disease and even cancer (Quave 2011). Aside from its medicinal use, Madagascar Periwinkle is also grown for its beautiful botanical appearance as an ornamental plant.

Description

If you have ever seen any vivid beds of flowers or visited a botanical garden, you have probably seen the plant *Catharanthus roseus*, as shown in **Figure 1**. *C. roseus* is an annual evergreen perennial shrub. It usually has five petals. The flowers are typically rose pink in color, but sometimes red, purple, white, and pink. The flowers are tubular in shape



Figure 2. *Catharanthus roseus*, commonly known as Madagascar Periwinkle. (Source: http://digilander.libero.it/felrig/photos/catharanthus_roseus.htm).

and have a corolla tube that is a 1 inch long. This slender tube can expand to be 1 ½ inches wide. The leaves are not glossy and are about 2 to 3 inches wide with rigid-like stems. The plant is typically small and grows to be anywhere from 2 to 3 feet tall. The fruit are classified as follicles and are anywhere from 2 to 4 centimeters long. Madagascar periwinkle grows best in frost-free environments. Although this plant is native to Madagascar, it grows world-wide, but mostly in the tropics, subtropics, and the southern parts of the United States. It is

also grown in Australia, Africa, India, and southern Europe for commercial use (Afolayan and Sunmonu 2010). Even with its pharmaceutical interest, this plant can be found often times in the wild. The type of conditions that Madagascar periwinkle grows best in is one with full sunlight exposure or partial shade with well-drained soil. Growth is inhibited when the soil is too fertile or moist. A unique characteristic about this perennial is that the flowers fall off after blooming and the plant reseeds itself under favorable conditions. Madagascar periwinkle can even withstand hot conditions, unlike other periwinkle plants. This plant also produces “milky latex” like sap from its stem (Floridata 2010). Madagascar periwinkle is closely related to the class of true periwinkles, *Vinca*, which also belongs to the family Apocynaceae. The difference in the two is that Madagascar periwinkles can endure hot conditions, but true periwinkles cannot; the leaves of true periwinkles tend to curl until the temperature returns to normal (Floridata 2010).

Traditional Uses

As mentioned before, Madagascar periwinkle is found often as an ornamental plant in flower pots or bedding of flowers; however, it also has a variety of other uses. The usage is specific to the area and culture in which it is cultivated.

European Usage

In Europe, the primary pharmaceutical interest is for the treatment of diabetes. They sometimes used the plant to treat headaches too. Herbalists would use the juice from the leaves as a household remedy. In India, about 7 flowers or leaves were used each time, but in other countries such as the West Indies who used the roots along with whiskey, and the Cook

Islands who used 18 leaves boiled in a pot of water, different variations were practiced (Nammi, et al. 2003). The extracts were also used in India for treatment of wasp stings. During the medieval period, Europeans also believed that this plant could ward off evil spirits” and thought of it as a “magical plant,” while the French believed it to be “the violet of sorcerers” (Lewis and Elvin-Lewis 2003).

Chinese Usage

The Chinese, on the other hand, used Madagascar periwinkle as an astringent and cough remedy, as well as for its diuretic properties (Lewis and Elvin-Lewis 2003). These forms of treatment were made using extracts from the plant.

Caribbean Usage

The traditional use for this plant in the Caribbean was for eye infections and diabetes (Lewis and Elvin-Lewis 2003). However, using extracts of the whole plant, the plant was used for treating asthma and flatulence in the Bahamas. Among the other islands such as Cuba, Puerto Rico, and Jamaica, the flower of the plant was used as general eye wash (Mishra 2009). Although there is very limited research; Madagascar periwinkle has also been used to treat “unspecific male problems” such as those related to reproduction issues in Trinidad and Tobago (Lans 2007).

Other Usage

Recently, the pharmaceutical properties of Madagascar periwinkle have drawn interest for the treatment of cancers such as lung or leukemia (Ueda, et al. 2002). There are several other usages for this plant such as for the treatment of Malaria

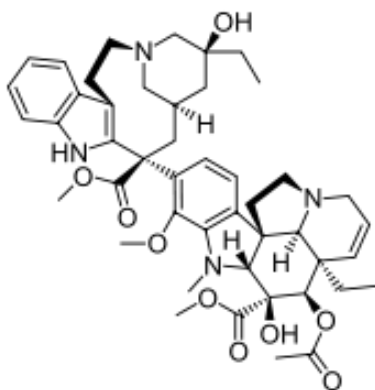


Figure 3. Chemical structure of vinblastine (Source: <http://www.thefullwiki.org/Alkaloid>).

in Vietnam, a remedy for sore throat in South America, for controlling hypertension in Curacao in Bermuda, controlling bleeding in patients in Hawaii, for treatment of dyspepsia and indigestion in Mauritius and for treatment of dysmenorrhea in Indo-Chinese (Mishra 2009). Other indications of the plant's usefulness in medicine include treatment of hypertension and tuberculosis and for regulation of menstruation. (Nazif, et al. 2009) Because of the wide-variety of medicinal purposes that Madagascar periwinkle has, it has become one of the most interesting plants in the pharmaceutical industry.

Chemistry and Pharmacology

For several years, *Catharanthus roseus* had been studied for its anti-diabetic properties, which was influenced by folk medicine. The discovery of vinca alkaloids was by Robert Laing Noble (Wright 2002). Noble had obtained some leaves of the Madagascar periwinkle plant from his brother, Clark Noble, who is best known for his studies on insulin. Robert Noble then tested leaf extracts and discovered that there were little effects on blood glucose levels. However, the extracts did

cause a noticeable effect on bone marrow and the white blood cell count. About 2 years later, Robert Noble and an organic chemist joined forces and began to isolate and characterize vinca alkaloids. These alkaloids soon became one of the most important drugs to cancer chemotherapy (Wright 2002).

C. roseus is the source of two important chemical compounds that are also classified as anticancer agents. The compounds vinblastine and vincristine, whose chemical structure is shown in **Figure 2**, are well known vinca alkaloids that are derived from this plant (Roepke, et al. 2010). Vinblastine, which is marketed as by Eli Lilly, is used to treat lymphoma, advanced breast and testicular cancer, Hodgkin's disease, and Kaposi's sarcoma. Likewise, vincristine is marketed as Oncovin and is used to treat acute leukemia, Hodgkin's disease, as well as other types of lymphomas (Lewis and Elvin-Lewis 2003).

The fractions and percentages of the alkaloids are shown in **Table 1**. Although vinblastine and vincristine are the primary alkaloids, a study by The Phytochemistry Department in Europe showed another alkaloid, catharanthine, to be present (Shams, et al. 2009). These alkaloids were discovered over a course of five different methods.

Biological Activity

Vinca alkaloids of the plant *Catharanthus roseus* are some of the most widely studied anti-mitotic drugs because of their biological activity as it relates to treating certain forms of cancer. The alkaloids act by disrupting the microtubules in cells. First, they bind to tubulin monomers. At low concentrations of the alkaloids, the formation of microtubules is inhibited. If the concentration of the alkaloids is high enough, they can cause the protofilaments of the microtubule

Method	Frations	* % of alkaloidal fractions	*HPLC % of Vb & Vc rich fractions	
			Vb	Vc
I	Vindoline rich fraction (A)	0.748	-	-
	Vinblastine rich fraction (B)	0.00274	0.00399	0.00012
	Vincristin rich fraction (C)	0.0075	0.00014	0.00772
II	vinblastine rich fraction (D)	0.002	0.00253	0.0007
	Vincristin rich fraction (E)	0.0015	0.0009	0.00184
III	vinblastine rich fraction (F)	0.1153	0.1417	0.00017
IV	Vindoline and catharanthine rich fraction(G)	0.0087	-	-
	Vinblastine rich fraction (H)	0.0035	0.0041	0.0004
V	Vinblastine & Vincristin rich fraction (I)	0.1033	0.0950	0.0110

Table 1. Alkaloids and the percentage present in *Catharanthus roseus*.

walls to peel. If the microtubules fail to form, the assembly of the mitotic spindle cannot take place, which therefore blocks mitosis (Jordan, Himes and Wilson 1985). Once mitosis is blocked, the affected cells begin to die.

Over the past few years, there have been lots of studies regarding the biological activity of *C. roseus*. One study explored the chemical composition and activity that occurs through the leaf. The results showed indications of the leaf secreting varying amounts of catharanthine (Roepke, et al. 2010). This is an important feature because catharanthine has antifungal and antiseptic properties, among others. In fact, the complexity of the leaf is so dynamic that the monoterpenoid indole alkaloids (MIAs) regulate the transport mechanism and the rate of biosynthesis within the plant (Roepke, et al. 2010).

Another study explored the vast gene-to-metabolite networks that are inhibited by the alkaloids. The results showed the varying branches and metabolic pathways within the planet. According to the review, the purpose of the networks is to “identify a select number of genes and metabolite likely to be

involved in the biosynthesis of terpenoid indole alkaloids” (Rishcer, et al. 2006). The results are important for understanding the metabolic rate and mechanism within the plant.

There have been several innovating studies conducted concerning *Catharanthus roseus* and its medicinal contribution. In a study by the Department of Pharmaceutical Sciences at the Andhra University, results indicated there are notable juices produced by the plant the exhibits hypoglycemic activity. These juices showed a significant decrease in blood glucose of normal and diabetic rabbits (Nammi, et al. 2003). These results thus support the belief of traditional herbalists who used the plant a remedy for diabetes.

Another study showed the healing power of *C. roseus*. This experiment was conducted on lab rats, rather than rabbits as in the previously mentioned study. Results showed that extracts from the plant “increased the wound breaking strength in the incision wound model” (Nayak and Pinto

Pereira 2006). This study, too, supports the beliefs incorporated from traditional medicine that *C. roseus* can be used as an antiseptic.

One other study focused on the biochemical specialization of the plant. The plant is composed of several classes of metabolites. Among that was about different types of cells as well as numerous genes and gene networks (Murata, et al. 2008). All of these components contribute to the plants ability to multifunction for different medicinal purposes.

Clinical Studies

Aside from the *in vivo* studies, there have also been clinical studies conducted. One study focused on the treatment of Hodgkin's lymphoma with BEACOPP. BEACOPP is a regimen composed of the vinca alkaloid, vincristine, and a host of other drugs such as bleomycin, etoposide, doxorubicin, cyclophosphamide, procarbazine, and prednisone. A random selection of patients that had untreated Hodgkin's lymphoma were given BEACOPP, while another group were given ABVD. ABVD is composed of a vinblastine, doxorubicin, bleomycin and dacarbazine. The study showed that patients with the regimen that included vincristine (BEACOPP) showed a greater progression than the patients who received ABVD (Simonetta, et al. 2011).

One of the newest vinca alkaloids is vinflunine. It was developed through the process of fluorination. The alkaloid is most studied for its anticancer properties as well. Studies have shown that like most vinca alkaloids, vinflunine has "mitotic-arresting and tubulin-interacting properties" (Kruczynski 2001). However, this alkaloid is easily distinguishable from other vinca alkaloids because it "induced smaller spirals with a shorter relaxation time" (Kruczynski 2001). In clinical

studies, vinflunine is most noted for its antitumor activity (Kruczynski 2001).

In addition to the ongoing clinical trials has begun approval of some vinca alkaloids and their derivatives. For instance, vincristine has been approved and is available as an injection by prescription only (Drugs.com n.d.). Something interesting to note about this drug is that although it has received approval, the mechanism of action is still under investigation.

Contraindications

As with any medicinal plant or drug, there are always cautions associated with the usage. *Catharanthus roseus* has displayed toxic effects when exposed to cattle (Lewis and Elvin-Lewis 2003). For humans, it should not be taken by mouth because the vinca alkaloids present can be highly poisonous. Some common side effects associated with consumption include nausea and vomiting, the loss of hearing, as well as liver damage and death (Lewis and Elvin-Lewis 2003).

Current Use in Allopathic & CAM Therapies

Currently, there are several studies being conducted to verify the safe usage of the drug as an anticancer agent. However, several semi-synthetic derivatives of the drug are available for clinical usage. Aside from Velbe and Oncovin, as mentioned before, *Catharanthus roseus* is also marketed as Eldisine to treat leukemia and lung cancer and as Navelbine to treat ovarian cancer (Lewis and Elvin-Lewis 2003).

Discussion

Catharanthus roseus is a complex plant that has a wide variety of medicinal uses. Because of the vinca alkaloids that are produced, cancers such as leukemia and lymphomas can be treated (Lewis and Elvin-Lewis 2003). Minor health conditions such as the common cough can also be treated by this plant. *C. roseus* is so dynamic that is cultivated in countries across the world to treat anywhere from everyday wasp stings to more serious conditions such as diabetes. Extracts of this plant has linkages to traditional medicine dating all the way back to folk medicine in the West Indies. Even today, *C. roseus* still proved to be an important plant in the pharmaceutical industry.

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Cimicifuga racemosa (L.) Nutt., Ranunculaceae

Aerhealle Hampton

Introduction

Native to North America, *Cimicifuga racemosa* (syn. *Actaea racemosa*) has long been a plant of many debated names. Its common names include black cohosh, black snakeroot, bugwort, bugbane, rattleweed, and squawroot, though the latter is also used to refer to the unrelated blue cohosh (*Caulophyllum thalictroides*). Of the Ranunculaceae family and originally recognized by Linnaeus as belonging to the genus “*Actaea*,” in 1818, Nuttall re-classified the plant’s genus as being that of “*Cimicifuga*.” This was largely accepted until recent years in which taxonomists have called for the return to its original genus classification (Compton 1998). To reduce conflicts with cited literature, however, *C. racemosa* will here be used as the recognized scientific name.

Black cohosh has traditionally been used as an herbal remedy in women’s health as it was believed to ease childbirth and stimulate menstruation. It continues to be marketed toward women and sold as a reliever of menopausal symptoms. The exact method of action is still unknown, but many important compounds have been isolated from *C. racemosa* including triterpene glycosides and phenolic acids. Antioxidant, anti-inflammatory, and anti-HIV properties have also been documented in black cohosh.

Description

Cimicifuga racemosa is a perennial herbaceous plant that is harvested from the wild, almost exclusively (Thomas et al 2007). It thrives in sunny woodland pastures, as well as



Figure 1. Racemes of *C. racemosa* displaying showy, white flowers. Source: treefrogfarm.com

shaded, wooded hillsides that stretch across the mountainous regions of the midwest to eastern United States and Canada (Li et al 2002). These wooded areas provide the well drained soils that allow black cohosh to be an understory plant in deciduous forests (Thomas et al 2007). Since it is an herbaceous plant, the leaves and stems of black cohosh die down at the end of each growing period. During the next growing period, however, new flowering stalks 1-2.5 meters

in length grow and produce a crown of large, green, tri-ternate leaves. Smaller, ovoid leaflets (about 5-8 centimeters wide) are also produced with doubly serrate edges. Presumably the “black” in *C. racemosa*’s common names has its origins in the dark brown to black coloring of its rhizome, from which the flowering stalks sprout (Lloyd and Lloyd 1884).

C. racemosa begins to bloom in late June and continues throughout August. It is during this time that the large flowering racemes are produced, containing between fifteen to twenty flowers (Lloyd and Lloyd 1884). The showy flowers themselves, shown in **Figure 1**, are comprised of a small pistil surrounded by multiple stamens, creamy white in color. The clustered flowers lack noticeable petals and produce abundant pollen as well as a strong, unpleasant odor that attracts pollinators (Wood 2000). The fruiting bodies of *C. racemosa*, which brought about one of the major conflicts in the designation of an appropriate genus for the plant, are a little over six millimeters in length, long, dry, oval in nature, and covered with thick, leathery sides. When the pod, containing 8-10 brown and angular seeds, dies, it remains on its stalk throughout the winter and produces a rattling sound when struck by coming winds, providing insight as to why this plant is sometimes called “rattleweed” and “rattlesnake root” (Lloyd and Lloyd 1884). In the following warm season (following a warm-cold-warm seasonal pattern of temperate regions), the seeds reach ripen and reach maturity (Wood 2000).

Traditional Uses

Traditionally, black cohosh was used as a very important and popular remedy in Native American cultures. In the instance of snakebite, the chewed root was thought to be a sure cure for the onset of the poison when applied directly to the wound. For other ailments, a decoction of the root was rubbed

onto affected areas, as in a common treatment for rheumatism. Especially important was the use of *Cimicifuga racemosa* in Native American women’s health. The use of this plant by Native American women was so prevalent that pioneers designated it with yet another nickname: “squawroot,” using the Algonquian word for “woman”. The females of these native cultures used black cohosh for ailments such as painful childbirth and to stimulate menstruation (Sattler 1884).

In the 1800s, many doctors began to include *C. racemosa* in their own reports and materia medica. Benjamin S. Barton (1801) heralded the astringent properties of the root. He noted that the gargling of a strong decoction made from the rhizome of black cohosh was useful as a treatment for an ailment known as “putrid sore throat,” as well as a cure for “the itch.” T.S. Garden later reported in *The American Medical Recorder* (1823) that he self-medicated with *C. racemosa* to treat what he referred to as “Phthisis pulmonalis.” Though he was most likely suffering from what would now be recognized as a case of bronchitis, Garden still reported that doses of an extract from this plant lessened his night sweats, improved his coughing, and lowered his pulse. In addition to this, he claimed that the black cohosh extract also calmed him with its sedative properties and may have even possessed possible vasodilatory properties. Described under the name of *Botrophis serpentine*, C. R. Rafinesque also referred to the use of *C. racemosa* as an inducer of both sweat and menstruation, a treatment for joint pains, as well as a remedy in the treatment of hysteria. Rafinesque also mentions veterinary uses of the plant in which he suggests that the consumption of black cohosh by cattle purged them of worms. Chapman, in *Elements of Therapeutics and Materia Medica* (1831), classified *C. racemosa* as an expectorant and sited uses of it being used as a narcotic (in the sense of it being a sedative and analgesic),

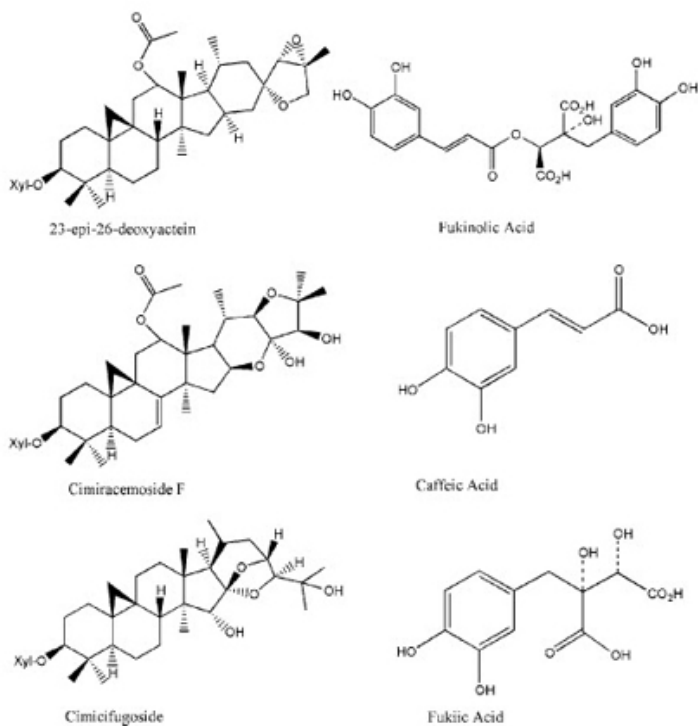


Fig. 1 Triterpenes and phenolics of biological interest.

Figure 2. Major compounds found in *Cimicifuga racemosa*.

Source : <http://nutrition.perfectskillset.com/main/dietary-supplements/supplements-a-c/700-black-cohosh-cimicifuga-racemosa.html>

an antispasmodic, a diaphoretic, and also an emetic when taken in large enough doses. Around this time, *C. racemosa* was also a popular treatment for pulmonary ailments, including asthma and what we now know to be tuberculosis, as it relieved cough, and reduced fever and heart rate (Sattler 1884). *C. racemosa* was also documented as being a useful treatment for St. Vitus Dance chorea, a disease believed to cause sporadic movement and twitching of the limbs, loss of

appetite, and possibly permanent decrease in brain function in a matter of months (Young 1832).

Chemistry and Pharmacology

Cimicifuga racemosa contains an abundant number of secondary metabolites and compounds, varying in composition during the lifecycle of the plant and dependant of from where a sample is taken. That being said, many of these compounds remain undiscovered. Due to this heterogeneity, and lack of uniform results in research, the active components in black cohosh also remain unknown. An example of two secondary metabolites that vary greatly throughout the plant and season are the terpenoids 23-epi-26-deoxyactein and cimracemoside A. It was found that about ten times the amount of 23-epi-26-deoxyactein was found in inflorescence tissues than the amount found in the rhizome of black cohosh. The drying of this matter, however, lowers this amount to a mere fourth of that found in the rhizome (Thomas et al 2007).

A large number of the main major constituents that have been identified in *C. racemosa* are its triterpene glycosides. Of the cyclolanostane triterpenes found in *C. racemosa*, the largest group contains cimigenol as an aglycone (Zhou et al 2008). Cimicifugosides, cimracemosides, and actein are also important compounds in the chemical makeup of this plant. Though a uniform standard for purity markers have not been created for black cohosh, these compounds have been found in varying levels in liquid extract, powdered extract, and milled plant material. Phenolic compounds, such as ferulic acid, isoferulic acid, and caffeic acid, as well as the alkaloid cimipronidine have also been found in *C. racemosa* (Li et al 2002). Structures of some of these compounds can be seen in **Figure 2**.

Biological Activity

Though extensive testing has been performed, the method of action for *Cimicifuga racemosa* is still unknown (Li et al 2002). A common misconception posited for many years that black cohosh acted as a phytoestrogen, mimicking the effects of estrogen in the body. However, contrary to popular belief, when tested alongside 7 other extracts from botanical sources *in vitro* for estrogenic activity, *C. racemosa* exhibited did not exhibit any estrogenic activity (Liu et al 2001). In 2003, Burdette et al tested rhizome extracts from *C. racemosa* to try to determine the mechanism of action for the alleviation of hot flashes using ovariectomized Sprague- Dawley rats. The rats were given a 40% propanol extract of black cohosh for two weeks with and without the presence of the compound estradiol. These researchers looked for clues of estrogenic and antiestrogenic properties by observing the uterine weight of the rats as well as recording their vaginal cellular makeup. This team's results also showed that *C. racemosa* does not possess any antiestrogenic nor estrogenic properties. Instead, the results of their experiment indicated that the mechanism responsible for the decrease in hot flashes may actually involve the 5-HT₇ serotonin receptor pathway, which is involved in thermoregulation, through possible serotonin receptor ligands (Burdette et al 2003).

In 2008, Powell et al performed *in vitro* experiments to uncover more about this possible mechanism of action by testing for receptor binding activity and cyclic AMP production. They found that, like many serotonin selective reuptake inhibitors (SSRIs), *N_ω*-methylserotonin may be the compound responsible for relieving hot flashes by working through the serotonin transporter (SERT) by binding to the 5-HT₇ serotonin receptor and blocking serotonin re-uptake (Powell et al 2008). In an experiment to determine possible hepatotoxicity, 300mg/kg of dry root extract of *C. racemosa*

was given to male Wistar rats each day for thirty days. Their liver morphology and other hepatic functions were closely watched and samples were taken and examined for damage and abnormal cells. It was concluded that there was no correlation between *C. racemosa* and liver damage because an absence of affected liver enzymes were found (Mazzanti et al 2008). Possible uses of *C. racemosa* in the treatment of HIV have also been pursued *in vitro*. The compound actein was tested alongside twelve saponins has been tested for anti-HIV activity. By inhibiting the replication of H9 lymphocytes, this triterpenoid displayed great effectiveness and anti-HIV in experiments (Sakura et al 2003).

Clinical Studies

In a randomized controlled study comparing the effect of exercise in changes on bone mineral density and 10 year risk for coronary heart disease, *Cimicifuga racemosa* was tested to see if it could aid in bone mineral retention. Over one hundred women were assigned to three different groups and subjected to different exercise routines involving high intensity resistance and high impact workouts with low intensity programs interspersed. Overall the study showed a positive correlation between exercise and decreased risk of coronary heart disease, but the addition of black cohosh showed no added benefits when paired with this exercise (Bebenek et al 2010). Phase III double-blind and randomized trials were performed between 2003 and 2004 in which the experimental group of postmenopausal women who had either completed or were undergoing breast cancer treatment. Given a single capsule of 20 mg black cohosh, the women were to report their incidence of hot flashes in the form of a diary. The results of this study showed a mean decrease of 20% in hot flashes in comparison to the placebo-controlled group (Pojak et al

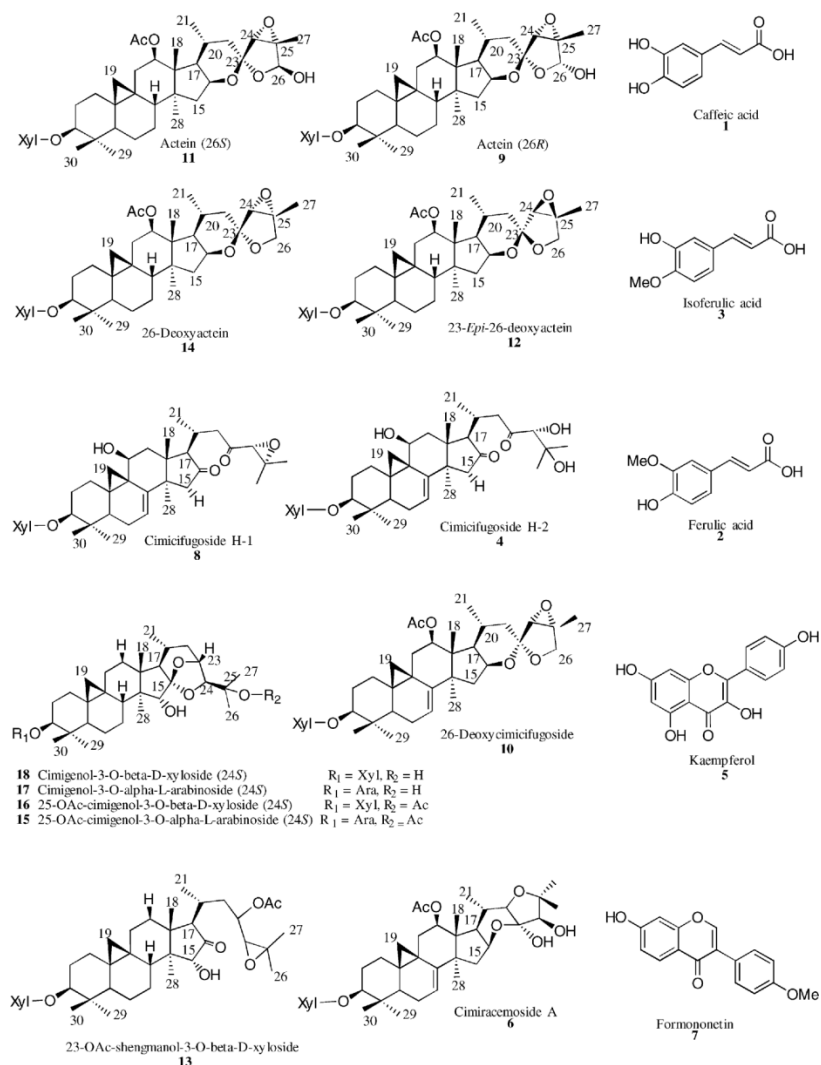


Figure 3. Marker compounds used for *Cimicifuga racemosa*.

2006). In a 2009 longitudinal clinical trial, no evidence was found to support hepatotoxic effects acting on

postmenopausal women who continued use of *C. racemosa* for twelve months (Nasr and Nafeh 2009).

Contraindications

Though *Cimicifuga racemosa* is seen as relatively safe, there was an instance of forty-two possible cases of hepatotoxic effects being reported and investigated by the European Medicines Agency (Mazzanti 2008). A follow-up was conducted on four of the patients with the highest possibility of *C. racemosa* related hepatotoxicity. The results of this follow-up indicated no causality between the liver disease present in the patients and the continued usage of supplements from this plant (Teschke and Schwarzenboek 2009). Gastrointestinal upset and rash have also been reported. A possible association between *C. racemosa* extract performed in ethanol and hepatic mitochondrial toxicity (*in vivo* and *in vitro*) has been indicated, but this possible relationship is thought to be clinically irrelevant unless the patient taking supplements has underlying risk factors for liver disease (Lude et al 2007).

Current Use in Allopathic and CAM Therapies

Since the method of action is still unknown, marketed products that advertise *Cimicifuga racemosa* content typically consist of the powdered dried root or powdered root extract of this plant with no uniform composition across product lines. No single compound is recognized as a tell-tale sign of purity in the commercial black cohosh products, and as the supplements fall under the DSHEA act of 1994, they are not subject to quality assurance standards. Of the products that have made attempts at quality control, many limit still their focus on triterpene glycoside content. However, with this

limited basis of standardization, the large number of unknown and undocumented compounds being ignored in the process may be lacking and nowhere near the original content levels of the plant, itself (Zhou et al 2008). Though the search for the active compound of *C. racemosa* continues, steps are being taken to bring about some sort of standardization of products using 16-18 of the most common constituents of *C. racemosa* listed in **Figure 3** (Li et al 2002). Despite the lack of certainty in quality, sales of *C. racemosa* amounting to \$79 million were reported in 2003 (Pojak et al 2006).

With many of the active compounds in black cohosh remaining a mystery, correct dosing for various ailments remain tricky as well. Experiments conducted by Powell et al in 2008, however, suggest that a 120 mg daily dose of *C. racemosa* could contain a therapeutic amount of *N*_ω-methylserotonin (3.7μg), sufficient enough to battle hot flashes and increase serotonin in postmenopausal women (Powell et al 2008).

Discussion

Though the scientific information on black cohosh is steadily developing, the long history that it has maintained as a helpful aid in women's health as well as other illnesses is sure to be a guide in future discoveries for the uses of this plant. Much more research is necessary to discover the definite method of action as well as a certainty of active chemical constituents, but the growing demand for black cohosh as a modern supplement for menopausal women as well as possible anti-HIV treatments and cures will also surely spearhead more investigative studies. Safety and purity also remain a concern, but with more research will come more knowledgeable and responsible uses of *Cimicifuga racemosa* supplements and products.

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Cinnamomum verum J. Presl, Lauraceae

Leah Demakovsky

Introduction

The recognizably spicy flavor of ethnic foods is often attributed to *Cinnamomum verum*, one of the major spices of the ancient world and one that is still commonly used today. There are several synonyms; *Cinnamomum zeylancium*, *Camphora mauritiana*, and *Laurus cinnamomum* are all recognized scientific names (Tropicos.org). In English the most common colloquial name for *Cinnamomum verum* is cinnamon, although it is also referred to as true cinnamon or Ceylon cinnamon, where the latter describes cinnamon grown specifically in Sri Lanka (Ravindra 2009). Cinnamon is a member of the Lauraceae family, or the laurel family (Tropicos.org). It has been used both in culinary practices and medicinally for centuries due to its cinnamaldehyde-containing volatile essential oils. It is a perennial tree that was first recorded by Redgrove in the 1200's (Ravindran, 2004). Cinnamon is invasive in many areas of the world, but because owning a cinnamon tree is a source of pride in places like the Union of the Comoros, many people are happy to have it grow (Vos, 2004). The spice is derived from the inner bark of the tree, and the oils are distilled from both the leaves and bark (Parthasarathy, 2008).

Botanical Description

The *Cinnamomum verum* plant, shown in **Figure 1**, is an evergreen tree with green, oval shaped leaves, purple berry fruit and flowers, which are usually found in clusters (Parthasarathy, 2008). The bark is made up of quills, which



Figure 1. The *Cinnamomum verum* tree.

Source: (Yake, 2009)

are the source of the traditional ground spice. It is 0.2 -0.8mm thick and is darker on the inside of the bark than on outside. The leaves have a leathery texture and grow in an opposite pattern on the stem. They are typically 3.8-7.5 cm long and



Figure 2. The buds and flower of *Cinnamomum verum*.

Source: (Ambepitiyage, 2009)

7.5-20 cm wide and have more shine on the top than underneath the leaf. The flowers are silky in texture and yellow in color, as seen in **Figure 2**. The perianths can grow up to 5-6 mm and are longer than the inner tube of the flower, which only grow to about 2.5 mm in length. Even smaller are the fruit, which are only 1.3-1.7 cm in length and contain a single seed inside. They are both enclosed in an 8 mm purple bell shaped perianth (Cepae, 1999).

When ground, cinnamon is reddish brown in color. Cinnamon sticks are somewhat lighter than the ground plant, and are derived from peelings of the inner bark, which curl when dried. This utilization of the cinnamon plant is the common form seen in culinary arts (Cepae, 1999).

Cinnamon is indigenous to Sri Lanka and parts of India but was introduced to Seychelles and Madagascar by the Dutch and British (Ravindra, 2009). However, the plant is invasive

in other areas of the tropics, and can survive in areas that are more greatly affected by human disturbances (Vos, 2004). It has been especially invasive in the Comboni in Mayotte and on the Mohéli mountains, as well as some humid forests (Vos, 2004).

In Sri Lanka, locals have developed subclasses of the Ceylon cinnamon based on specific plant properties. *Pani kurundu* describes sweet, *pani miris kurundu* describes sweet and hot, *rasa kurundu* describes tasty, *suwanda kurundu* describes fragrant, and *tita kurundu* describes bitter cinnamon. Although they are all scientifically classified as the same *Cinnamomum verum*, differences in the soil and environment of Sri Lanka gives the cinnamon that is grown there a unique flavor (Ravindra 2009). Currently, cinnamon imports are primarily from Sri Lanka, but the plant is also grown in Africa, India, Indonesia, the Seychelles, South America and the West Indies (Cepae, 1999).

Traditional Uses

Medicinal Uses

Cinnamomum verum has been used extensively as a traditional medicine throughout the world. It was used as an anti-diuretic, a digestive aid, and as a treatment for eye infections, menstrual symptoms, inflammation of the kidney and intestines, stomachaches, and as a topical for stings and bites throughout Asia and Europe (Ravindran, 2004). The extracts of cinnamon have been used in India for the treatment of diabetes (Subash, 2007). It was a common part of Traditional Chinese Medicine, with uses in treating fever and diarrhea (Heinrich, 2004). Sho-seiryu-to, or Xian Qing Long Tang, is a mixture of several plant species including cinnamon bark that was used in the treatment of perennial allergic rhinitis, asthma, and other upper respiratory infections. Sairei, another

concoction used for the treatment of these illnesses, also contained cinnamon bark (Preedy, 2008).

Cinnamomum verum had a wide use in Ayyurvedic medicine. In "The Indian Materia Medica" it is referenced as a treatment for flatulence and stomachic and was used as an antispasmodic, stimulant, astringent, antiseptic and antimicrobial. Each specific grouping of cinnamon has a different use; the names of the characteristics of cinnamon are similar to the Ceylon groupings. *Tikarasm* increases appetite and produces dry mouth, *ushnaveeryam* raises body temperature, increases circulation, increases appetite and increases digestion and *laghu* increases digestion. Each class was used in the treatment of a variety of ailments including anorexia, cardiac diseases, bowel dysfunctions, and helminthic infections (Thampuran, 2003).

Cinnamomum verum is also used in "folk" medicine for impotence, frigidity, dyspnea, eye inflammation, leucorrhoea, vaginitis, rheumatism, neuralgia, wounds and toothaches, although there are no studies to show that it is effective for any of these ailments (Ravindran, 2004).

Culinary Uses

Cinnamomum verum has been used as a spice in cooking for centuries. The oils extracted from the bark and leaves are used to flavor numerous foods, drinks, sauces, baked goods, and tobacco products (Flavours and Fragrances of Plant Origin, 2012). In Latin America, as well as many other places in the world, the quills are boiled in water and are drunk as a tea. In the United States it is used as a flavoring in the home as well as in the food industry (Ravindra, 2009). Cinnamon is commonly used in soaps, toothpastes, dentifrices and liquor flavoring, and is also used in the synthetic production of

vanillin (Parthasarathy, 2008). It is an integral part of Indian curry and other traditional ethnic foods. Due to its antioxidant properties, cinnamon was a common food preservative before refrigeration was available (Parthasarathy, 2008).

Other Traditional Uses

Cinnamomum verum was extensively used as a fragrance by the ancient Egyptians in their embalming rituals (Heinrich, 2004). Cinnamon oils were commonly found in the perfumes worn by Egyptian men, and was also added to oils used as light to prevent harmful or bad smelling vapors. The spice was so highly prized by the Egyptians that Nero, the Emperor of Egypt in 66AD, was said to have burned a year's supply of cinnamon at his wife's funeral as a demonstration of his grief and sorrow (Ravindran, 2004).

Cinnamomum verum is mentioned several times in the bible and is one of the plants used in the holy anointing oil. It is also described in Rev. xviii. 13, "cinnamon, and odours, and ointments, and frankincense" (Grindon, 1883), giving light to some of the uses of cinnamon during the time period.

Traditional Importance

Cinnamomum verum has been traded extensively for centuries; there are records of its trade history during the Roman era. It was passed to the Arabs who tried to keep its original location a secret from other traders, causing European explorers to search for the plant during the 1400s (Ravindra, 2009). Herodotus, the "father of history", described the cinnamon dilemma, and stated that the Arabs did not know of its origins. The secrecy caused it to be one of the first plants which oriental traders searched extensively (Grindon, 1883). When it was found in Sri Lanka, the country was

eventually taken over by the Portuguese, Dutch and British who propagated cinnamon cultivation (Ravindra, 2009).

Chemistry and Pharmacology

While *Cinnamomum verum* has over one hundred chemical components, cinnamaldehyde is the chemical responsible for the strong smell and distinct flavor. Cinnamaldehyde, shown in **Figure 3** alongside eugenol, is an alkaloid with an aromatic ring that acts as a strong antioxidant by inhibiting amino acid decarboxylase activity (Gupta et. al., 2008). Eugenol is a phenylpropene that is found in cinnamon leaves, giving them a less appealing odor than the bark which contains much higher concentrations of cinnamaldehyde (Flavours and Fragrances of Plant Origin, 2012).

The bark contains 6,000-30,000 parts per million of cinnamaldehyde (Duke, 1996), which is its primary constituent. Mucilage is another constituent in high amounts; there are 20,000-37,000 parts per million found in the bark (Duke, 1996). Volatile components are found in every part of the plant and consist of monoterpenes, sesquiterpenes and phenylpropenes (Parthasarathy, 2008). More specifically, these volatile oils include B-caryophyllene, linalool, safrole, cinnamic aldehyde, cinnamyl acetate, cinnamyl alcohol and benzyl benzoate (Ravindran, 2004). The primary constituents of the extracted volatile oils are cinnamaldehyde and eugenol, which make up 65-80 % and 10% of the oil, respectively (Cepae, 1999).

In the United States, the Fragrance Materials Association (FMA) monograph uses percent eugenol solubility in potassium hydroxide to regulate the standard of cinnamon; it must be 80-88% soluble (FMA, 1992).

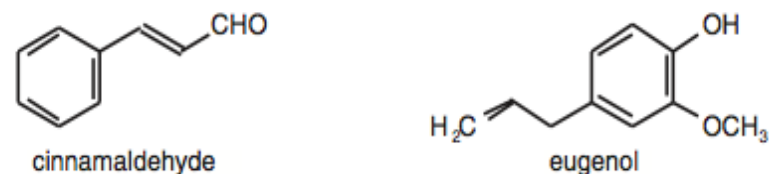


Figure 3. The chemical structure of cinnamaldehyde, the primary constituent of *Cinnamomum Verum* and Eugenol, one of the main chemical components of cinnamon oils.

Source: (Cepae, 1999).

A recent study used matrix-assisted laser desorption/ionization tandem time-of-flight mass spectrometry to determine the proanthocyanidins in cinnamon in order to better understand the chemical components, which yield cinnamon's medicinal properties. It was found that the proanthocyanidins contain (epi)catechin, (epi)catechingallate, (epi)gallocatechin, and (epi)afzelechin (Mateos-Martin, 2012).

The chemical components of *Cinnamomum verum* (**Table 1**) can aid with the identification of the plant when compared to other species of *Cinnamomum*. *Cinnamomum verum* contains less than 2% foreign organic matter, less than 6% ash, with less than 4% of this ash being insoluble in acidic solutions. There also must be less than 6% sulfated ash due to government regulations on the treatment of plant products with sulfides. Lastly, *Cinnamomum verum* extracts have a 14-16% solubility rate in 90% alcohol solutions (Cepae, 1999). Other species of *Cinnamomum* have different percentages of these components, which may affect their different chemical properties.

Chemical Constituent in Bark	Amount	Chemical Constituent in Bark	Amount	Chemical Constituent in Bark	Amount
1,8 Cineole	165- 800ppm	Fiber	270,000 ppm	Trans-Linalol-Oxide	5-20 ppm
2-Vinylphenol	3-12 ppm	Furfural	3-12 ppm	Zinc	11.4-20 ppm
3-Phenyl-Propyl-Acetate	13-52 ppm	Gamma- Terpinene	3-12 ppm		
Acetoeugenol	16-64 ppm	Geraniol	6-24 ppm	Chemical Constituents in Leaf	Amount
Alpha-Pinene	20-236 ppm	Humulene	20- 124 ppm	Chromium	14.4 ppm
Alpha-Terpineol	40-264 ppm	Hydrocinnamaldehyde	40-160 ppm	Cobalt	1.1ppm
Alpha-Ylangene	31-124 ppm	Iodine	3 ppm	Copper	10.9 ppm
Ascorbic-Acid	309 ppm	Iron	60- 421 ppm	Manganese	101.6 ppm
Barium	60 ppm	Isoeugenol	2-8 ppm	Nickel	4.2 ppm
Beta-Carotene	1-2 ppm	Limonene	46- 184 ppm	Zinc	34 ppm
Beta- Pinene	14-76 ppm	Linalol	230- 956 ppm		
Borneol	2-8 ppm	Manganese	66-140 ppm	Chemical Constituents in Plant	Amount
Bornyl-Acetate	10-20 ppm	Mucilage	20,000- 37,000 ppm	2-Phenylacetaldehyde	
Boron	7-15 ppm	Myrcene	5-20 ppm	Alpha-Terpinene	42-168 ppm
Bromine	10 ppm	Niacin	8 ppm	Benzaldehyde	26-104 ppm
Calcium	5,329-6,000 ppm	Nickel	1.1 ppm	Peperitone	7-28 ppm
Camphene	18-72 ppm	P-Cymene	55-448 ppm		
Caryophyllene	135-1,316 ppm	Phellandrene	63-252 ppm		
Chlorine	300 ppm	Phenyl-Ethyl-Alcohol	41- 164 ppm		
Chromium	2-10 ppm	Phenylethyl-Acetate	7-28 ppm		
Cinnamaldehyde	6,000-30,000 ppm	Phosphorus	674- 1,100 ppm		
Cinnamyl-Acetate	510- 2,040 ppm	Potassium	5,525-6,000 ppm		
Cinnamyl- Alcohol	26- 104 ppm	Protein	35,000- 43,000 ppm		
Cis-Ocimene	3-12 ppm	Riboflavin	1 ppm		
Cobalt	0.6ppm	Rubidium	20 ppm		
Copper	4.9-9 ppm	Sabinene	2-8 ppm		
Cumene	66-264 ppm	Sodium	287 ppm		
Cuminaldehyde	4-100 ppm	Strontium	80 ppm		
Delta-3-Carene	3-12 ppm	Sulfur	1,900 ppm		
Eo	40,000 ppm	Terpinen-4-Ol	36-144 ppm		
Eugenol	220-3,520 ppm	Terpinolene	11-44 ppm		
Farnesol	3-12 ppm	Thiamin	1 ppm		
Fat	14,000 ppm	Titanium	40 ppm		

Table 1. The most abundant chemical components of *Cinnamomum verum* bark, plant, and leaves. Source: (Mathew, 2006; Parthasarathy, 2008)

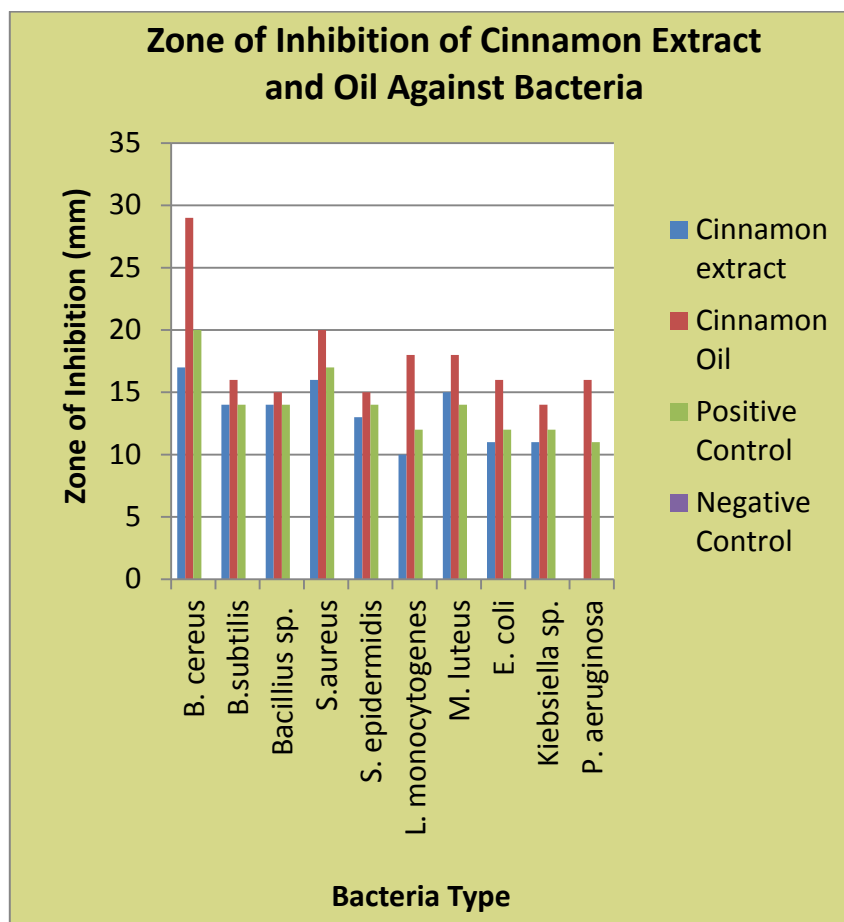


Figure 4. A study examining the antimicrobial activity of *Cinnamomum verum* against common food borne bacteria demonstrated cinnamon’s effectiveness across a broad range of bacteria. The essential oils were found to be particularly effective against *Bacillus cereus*, as shown above. Adapted from Gupta et al., 2008.

Biological Activity

Cinnamaldehyde, the primary constituent in *Cinnamomum*

verum, has been found to have antiallergenic, antiulcerogenic, antipyretic, antimicrobial, anesthetic and antimutagenic properties (Mathew, 2006). There are also numerous antibiotic uses; the essential oils have been found to act as an antibacterial *in vitro* against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Ravindran, 2004). The oil has also been found to act as an antifungal *in vitro* against *Aspergillus* spp., *Cladosporium werneckii*, *Geotrichum candidum*, *Kloeckera apiculata*, *Candida lipolytica* and *C. albicans* (Ravindran, 2004). Additionally, a study examining the effects of cinnamon oil and extracts found both to increase the zone of inhibition of several food born bacteria. Cinnamon had the greatest effect against *Bacillus cereus*, as shown in **Figure 4** (Gupta et al., 2008).

With the increasing problem of antibiotic resistance causing a need for new therapies, cinnamon has been studied for its antibacterial effects on resistant species of bacteria. The essential oils of cinnamon were found to decrease the minimal inhibitory concentration of amikacin needed to kill resistance species in the *Acinetobacter* genus (Guerra, 2011).

Many of the biological activities seen when utilizing cinnamon have been attributed to cinnamaldehyde, methoxycinnamaldehyde, and other compounds found in high concentrations in the bark and oil (Ravindran, 2004). Cinnamaldehyde’s phenolic compounds act as an electron donor and catalyzes the reaction of hydrogen peroxide to water (Gupta et al., 2008). Other studies have attributed many of the beneficial properties of cinnamon to the phenolic proanthocyanidins also found in the essential oil (Cabello, 2009). The cinnamic aldehyde found in the essential oil contains phenolic proanthocyanidins, which have been found to inhibit growth of melanoma *in vitro* and *in vivo* (Cabello, 2009).

Cinnamaldehyde also acts as an antispasmodic and has been found to decrease histamine and barium induced smooth muscle contractions in guinea pig trachea and ileum (Reiter 1985).

The methanolic extracts of cinnamon have been shown to have antioxidant properties and act as a hydroxyl radical scavenger, act as a reducing agent, and have demonstrated metal ion chelating activity. The cinnamon extracts act as a transition metal stabilizer which prevents the perpetuation of the formation of new free radicals in the body (Mathew, 2006). The phenolic compounds can act as electron donors to catalyze the reaction of H₂O₂, a toxic substance, to H₂O (Mathew, 2006).

Clinical Studies

Several species of *Cinnamomum* have been used as medicine throughout history. Cinnamon and its active ingredients are generally regarded as safe by the 'Flavor and Extract Manufacturers' Association (FEMA no. 2286, 2201) (Cabello, 2009). Although many studies fail to distinguish which subspecies within the *Cinnamomum* genus were used, there are numerous studies indicating *Cinnamomum verum* can have health benefits. Similarly, there have been many clinical studies involving the efficacy of using cinnamon as a treatment for several diseases, especially type 2 diabetes and metabolic syndrome. Unfortunately, there are no current studies examining just *C. verum* in humans.

Sairei, the traditional Chinese remedy containing cinnamon bark used to treat upper respiratory infections has been found to inhibit basophil growth and histamine content *in vivo* (Preedy, 2008), however, there is some uncertainty regarding the species of *Cinnamomum* used and if the results can be

directly attributed to the components of the cinnamon rather than the other ingredients added. This finding explains the results that people have been using for centuries, and although it is not a human clinical trial, has indications for use in humans.

A study conducted in India found that cinnamaldehyde reduces blood glucose levels in streptozotocin induced diabetic rats and thus has hypoglycemic and hypolipidemic effects (Subash, 2007). This study was important for diabetes research because it identified cinnamaldehyde as the component of cinnamon that decreased plasma glucose levels, or acted as an antidiabetic.

Although this study did not directly involve humans, the rat model is a fairly accurate indicator. Studies similar in nature have been conducted with humans. However, these studies often do not specify the type of species used, or more commonly or use a mixture of more than one species. Over all, the lack of causal evidence indicates that more clinical studies are needed to determine the specific effects of *C. verum* in humans.

Contraindications

Although *Cinnamomum verum* has numerous health benefits, Italy and Germany blocked some importation of cinnamon from Sri Lanka due to high sulfur content. Cinnamon does not have a high sulfur content naturally, but is often fumigated with sulfur dioxide during processing as a preservative which coats the cinnamon in a sulfur residue. The acceptable maximum amount of sulfur is now regulated under the Codex Alimentarius Commission (CAC). Until 2006 the CAC did not have a standard maximum residue limit, and the level acceptable in Sri Lanka was more than the level acceptable in

the European countries, leading to the block of importation in certain parts of Europe (Ravindra, 2009). Although there are limits in place currently, it is not known how the sulfur fumigation affects the medicinal properties of the plant.

Few cases of fever of unknown origin, pregnancy, stomach ulcers, and duodenal ulcers have been indirectly associated with the use of cinnamon (Bisset, 1994; Ravindran, 2004). Reactions to cinnamon have occurred in individuals who have allergies to active ingredients in cinnamon or Peru balsam (Ravindran, 2004). The "Indian Materia Medica" states cinnamon can cause irritation and can be poisonous in large quantities (Thampuran, 2003). When used in food as a flavor additive, the daily intake should not exceed 700 µg per kg of body weight per the World Health Organization and Food and Drug Administration guidelines (Thampuran, 2003). Occasionally the cinnamaldehyde can cause skin or mucus membrane irritation when used as a perfume, or in toothpastes. Oral lesions after chewing cinnamon gum are rare but have been reported in those with sensitivity to cinnamaldehyde or cinnamon (Thampuran, 2003).

The use of cinnamon in children has not been extensively studied. There are no studies indicating that *C. verum* is unsafe for use during pregnancy, nursing, or with certain other drugs. However, studies have indicated other species of *Cinnamomum* do have associated risks (Ravindran, 2004). Since *C. verum* has unique chemical properties, it does not mean that all *Cinnamomum* has these risks, although one study did find cinnamaldehyde to be teratogenic in chick embryos (Keller 1999).

Current Use in Allopathic and CAM Therapies

The use of *Cinnamomum verum* as a complementary and

alternative medicine (CAM) therapy may be its most well known medicinal use. There are few drugs on the market involving cinnamon or the active ingredients in cinnamon in the United States however clinical trials are investigating the indigenous use of cinnamon to treat diabetes as well as a variety of other diseases (Ravindran, 2004). Currently, there is an herbal treatment for inflammation of the eye called *Ophthacare* which contains 0.5% cinnamon. When tested in rabbits, it was found to be effective (Thampuran, 2003). The bark and oil are included in drug cocktails as a carminative or flavoring in several countries including India, Britain, China, Australia, Belgium, Europe, France, Germany, Hungary, Japan, the Netherlands, Portugal and Switzerland (Thampuran, 2003).

Several studies have identified cinnamon as a CAM therapy throughout the world. One study in Australia surveyed diabetics and found that one-fourth of individuals with diabetes mellitus who used CAM therapy used cinnamon. However their sample size was small providing the need for a larger study to confirm results. There were no significant correlations between gender, age, income and severity of diabetes and using cinnamon as a CAM treatment. (Manya, 2012). Although the study uses the scientific name *C. verum* in its report, the common name cinnamon was used on the questionnaire, meaning there was no way to know exactly what species of cinnamon was used. There was also no question regarding the amount of cinnamon taken or the frequency. It is assumed that the powdered (ground) form of cinnamon was used as the supplement.

A larger study found that thirty percent of individuals in Bahrain with diabetes mellitus who used CAM therapies used cinnamon for the treatment of their diabetes (Khalaf, 2010). This study also did not have a way to identify the species of cinnamon used or the amount taken by the patients, but its

results were similar to studies previously done on several world populations including the United States. Another even larger study conducted in Israel found 10.8% of diabetics used cinnamon as a CAM remedy, but most individuals were from refugee camps (Ali-Shtayeh, 2012). A study using a random sample is needed to confirm results.

The World Health Organization estimates the average daily dose of cinnamon taken by those who use cinnamon for medicinal purposes is about 2- 4 grams per day when used ground, or 0.05-0.2 grams when the volatile oil is used (Ravindran, 2004).

Throughout Africa and other developing countries, the lack of legal, safe and affordable abortion or birth control services lead to the development of systemic abortifacients. Boiled wine, raisins and cinnamon is drunk as an oral abortifacient, but is not considered to be safe and the efficacy has not been studied (Warriner, 2006).

Discussion

Cinnamomum verum has a vast variety of uses and the potential for even more applications. There is an immense cultural value associated with the plant due to its significance in earlier centuries and its importance in many ethnic foods around the globe. Originating in Sri Lanka, the plant has become invasive in many areas as it can outcompete other species in a variety of climates. Cinnamaldehyde, the primary chemical constituent in cinnamon, has shown great promise in the treatment of diabetes and other chronic illnesses. There is, however, some controversy regarding the use of cinnamon. In ancient writings the exact species of cinnamon was not always stated, so the traditional benefits derived from the use of the plant may have been caused by the chemicals unique to other

species of *Cinnamomum*. Even today, there are numerous studies that fail to properly ensure that the substance they are using is *C. verum* and not a cheaper species labeled as such. Studies also fail to mention which species of *Cinnamomum* they used and simply refer to the plant as “cinnamon” despite the numerous differences in chemical constituents.

Further, due to the many methods of extracting the oils of the bark and leaves, there is a high chance that one sample of oil may not match another sample chemically. Though they will still contain the same basic constituents, the varied concentrations of such can yield entirely different effects. Also, since the plant is grown in regions of the world with differences in environment, the concentration of chemicals may also vary from region to region (Flavours and Fragrances of Plant Origin, 2012). These differences are roadblocks in research involving cinnamon, but one that can be overcome as technology advances.

Currently, scientists are attempting to cultivate cinnamon with increased concentrations of cinnamaldehyde and eugenol in order to use cinnamon more widely in the treatment of disease. The major problem with cinnamon is that it is widely available but 68% of patients in the Israeli diabetes study did not report using cinnamon to their doctor, although this is far too common in many CAM remedies (Ali-Shtayeh, 2012). This has the potential for unknown medical complications. More research will be necessary before these plants can be utilized, but the future for cinnamon looks promising (Flavours and Fragrances of Plant Origin, 2012). Until then, it will be grown and used as the spice the world has come to love.

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Coffea arabica L., Rubiaceae

Alison Yarp

Introduction

Coffea arabica L., known to most of the world as coffee, is a member of the Rubiaceae family. It is also known as the “coffee shrub of Arabia” (Weinberg & Bealer, 2001), café, and multiple other regional names (I. A. Ross, 2005). *C. arabica* is the oldest known cultivated species of coffee (Weinberg & Bealer, 2001). Originally from the Ethiopian mountains, it is now cultivated in the subtropics and high altitude tropics and now grows naturally in many of these environments. There are 25 to 100 species in the genus *Coffea*, but *C. arabica* is one of the two main species currently being used in coffee production – the other being *C. canephora* (Rieger, 2006). However, *C. arabica* makes up about 75% of the worldwide coffee consumption (Weinberg & Bealer, 2001). One of the main derivatives, caffeine, is a potent stimulant, and is responsible for most of the effects, which includes central nervous system stimulation, as well as stimulation of other body systems (Kraft & Hobbs, 2004).

Botanical Description

Coffea arabica is a small evergreen tree and can grow up to 30 feet in the wild, but is generally maintained at 6 to 8 feet (Rieger, 2006) for easier harvesting (Weinberg & Bealer, 2001). It is cultivated primarily in tropical and subtropical countries including Brazil, Colombia, Mexico, and Guatemala (Khan & Abourashed, 2010). They are considered an “upland” species, so the ideal places for growth are at 5000 to 7000 feet at the equator. In the subtropics, it grows well at sea level



Figure 1. *Coffea arabica*. Source: <http://www.gutenberg.org/files/28500/28500-h/28500-h.htm>

(Roecklein & Leung, 1987). *C. arabica* growth can be hindered above 77°F, and frosts can kill the leaves and fruits (Francis). However, for a tropical plant, *C. arabica* is still resilient at lower temperatures (Weinberg & Bealer, 2001). The appropriate amount of rainfall is about forty to sixty inches throughout the year (Weinberg & Bealer, 2001).

For a picture of *Coffea arabica*, see **Figure 1**. *C. arabica* can grow as a single shoot, but it will often branch off into multiple

stems towards the bottom (Francis). The bark of the tree is an ash white (*PDR for herbal medicines*, 1998). The leaves are dark green with an oval shape (Francis). They are about half a foot long and 1 to 2 inches wide (*PDR for herbal medicines*, 1998). They grow in pairs opposite each other on the stems. The dorsal sides have a “smooth and shiny” appearance with obvious veins (Francis) and resemble leather (*PDR for herbal medicines*, 1998). These leaves can live about 2 to 3 years.

The flowers on *C. arabica* are white and fragrant (Francis), with 5 petals coming out of a slender tube shaped base (Rieger, 2006). Up to 20 flowers will grow on an axil, and they each contain two ovules, allowing for possibly two seeds to form (Rieger, 2006). Flowers that open when it is dry and sunny generally produce more fruit than those that open on a wet day because of the increased pollination by wind and insects (Weinberg & Bealer, 2001). *C. arabica* is self pollinating and can even pollinate itself when the flowers are closed (Rieger, 2006). However, it also benefits from cross pollination by bees (Klein, Steffan-Dewenter, & Tschardtke, 2003).

The fruit, also known as berries or drupes, of *C. arabica* is elliptical and is flat when observed by cross section. They are about 12 to 18 mm long and 12 to 15 mm wide. They are green until they become ripe, at which point they are yellow and dark red (*PDR for herbal medicines*, 1998). Because of the color of the berries after they mature, farmers and processors commonly refer them to as cherries. Under the skin is a sweet and moist fleshy pulp, which is commonly eaten (Weinberg & Bealer, 2001). The fruits generally contain two seeds, or beans, which are between 8 and 12 mm long. They have one rounded and flattened end and have a groove on one of the sides (Francis). Depending on the individual characteristics and the climate conditions, a single tree can yield from one to

twelve pounds of dried beans in a year (Weinberg & Bealer, 2001).

Traditional Uses

Medicinal

Depending on the region, *Coffea arabica* has many uses. As seen by **Table 1**, these uses range from inducing labor to treating headaches (I. A. Ross, 2005). In Brazil, the seed is decocted and taken orally to treat influenza. In Cuba, a hot water extract of the seed is taken orally as an aphrodisiac for males (I. A. Ross, 2005). Haitians have multiple uses of the plant: grilled decoction of the fruit and leaf is taken orally for anemia, fruit is eaten for hepatitis and liver troubles, soaked fruit is applied externally for nervous shock, and the leaf is decocted and taken orally or applied externally for headache (I. A. Ross, 2005). In Mexico, the leaf is made into a poultice and applied externally for fever, and the hot water extract of a roasted seed is taken to increase milk production in nursing mothers. Nicaraguans also have many ways of using coffee. They use the leaf externally to treat headache and orally as a hot water extract to help with stomach pain. They also use the decoction of the seed orally for fever and externally for cuts and hemorrhage (I. A. Ross, 2005). In Uganda, a decoction of the leaves is used to treat aerophagia and a cough (Lacroix et al., 2011). In Peru, a hot water extract of dried fruit is used orally for sleepiness and drunkenness, while the leaf is used to induce labor or as an antitussive in flu and lung sicknesses. The Thai use the hot water extract of the dried seed orally as a cardiogenic or neurotonic. Lastly, in the West Indies, the hot water extract of the seed is used orally for asthma, and juice from the root is taken orally for scorpion stings (I. A. Ross, 2005).

While not necessarily just used to treat ailments, coffee has also been used by many cultures as a general stimulant, to

Country	Plant Part	Preparation	Route	Use
Brazil	Seed	Decoction	Oral	Influenza
Cuba	Seed	Hot water extract	Oral	Aphrodisiac (males)
Haiti	Fruit and leaf	Grilled Decoction	Oral	Anemia, edema, asthenia, rage
Haiti	Fruit	-	Oral	Hepatitis, liver trouble
Haiti	Fruit	Soaked	External	Nervous shock
Haiti	Leaf	Decoction	Oral, External	Headache
Mexico	Leaf	Poultice	External	Fever
Mexico	Seed	Roasted Hot water extract	Oral	Increase milk production in nursing mothers
Nicaragua	Leaf	-	External	Headache
Nicaragua	Leaf	Hot water extract	Oral	Stomach Pain
Nicaragua	Seed	Decoction	Oral	Fever
Nicaragua	Seed	Decoction	External	Cuts, Hemorrhage
Peru	Fruit	Dried Hot water extract	Oral	Sleepiness, drunkenness
Peru	Leaf	Infusion	Oral	Induce labor
Peru	Leaf	Hot water extract	Oral	Antitussive in flu and lung ailments
Thailand	Seed	Dried Hot water extract	Oral	Cardiotonic, neurotonic
West Indies	Seed	Hot water extract	Oral	Asthma
West Indies	Root	Juice	Oral	Scorpion sting

Table 1: Traditional Medicinal Uses of *Coffea arabica*

Source: (I. A. Ross, 2005)

increase alertness and improve productivity (Chevallier, 1996). For example, the average daily consumption of a coffee drinker in the United States is 3.1 cups (Bisht & Sisodia, 2010).

Food

Coffee has been consumed as a beverage for about 1000 years (Chevallier, 1996), and it has become the most consumed functional food around the world (Bisht & Sisodia, 2010). In the United States, 68% of people over the age of 10 consume coffee, and in 1969, 2.8 billion pounds of coffee, which equals approximately 150 billion cups (Lewis & Elvin-Lewis, 2003). The main importers of coffee are the United States, Germany, and France (Roeklein & Leung, 1987), while the main producers are Brazil and Columbia (Bisht & Sisodia, 2010).

C. arabica has become a competitive crop in Costa Rica and is important to the nation's livelihood. To maintain this, they have to produce enough of it in a reasonable amount of time. Small farm owners did this traditionally, but today this is moving towards large plantations (Weinberg & Bealer, 2001).

Gourmet coffees are generally high quality varieties of *C. arabica* without the harsh or hard taste. They mainly come from Latin America, except Brazil (Weinberg & Bealer, 2001). However, they can also come from Kenya, Tanzania, Ethiopia, Cameroon, and Yemen. Fine coffee used to come exclusively from Yemen and would be shipped globally through the port of Mocha. After World War I, the wells in Mocha dried up, so the coffee cultivation there was almost completely abandoned. Small amounts of coffee still come from Yemen through the port of Hodeida, but it is still referred to as Mocha, as this name is still engrained in people's minds as the best coffee

beans (Weinberg & Bealer, 2001). Regarding Brazil, most coffees coming from this country are *Coffea arabica*, but they

are known to have a less refined flavor and aroma than the milder forms (Weinberg & Bealer, 2001).

Other

Other uses have included various parts of the tree. The bark can be made into parchment, mulch, manure, and pulp, which is occasionally fed to cattle in India (Roecklein & Leung, 1987).

Chemistry and Pharmacology

A list of the chemical constituents of *Coffea arabica* can be seen in **Table 2** (Duke). However, the more important ones out of the list are the purine (or also known as xanthine) alkaloids, theobromine, theophylline, caffeic and ferulic acid esters of quinic acids, no-diterpine glycoside esters, trigonellines, and diterpenes (Kraft & Hobbs, 2004). Among these, the notable ones are caffeine, chlorogenic acid, theobromine, and theophylline, especially for their medicinal and physiological effects. Caffeine, a purine alkaloid, can be seen in **Figure 2** and can range in concentration from 600 to 32000 parts per million (ppm) (Duke). In an even greater concentration is chlorogenic acid, with a range of 50000 to 80000 ppm (Duke). Because of the high concentration of chlorogenic acid, estimates have been made that state that the intake of chlorogenic acid is many times higher for people who consume coffee on a regular basis, especially when compared to non coffee consumers (Bisht & Sisodia, 2010). Theobromine and theophylline are present as well in 35 to 40 and 7 to 23 milligrams per kilogram, respectively (Weinberg & Bealer, 2001). Regarding how some of the other constituents affect *C. arabica*, 2-furfurylthiol, 4-vinylguaiacol, alkyl pyrazines, furanones, acetaldehyde, propanol, methylpropanol,

Chemical Constituents in <i>Coffea arabica</i>	
Plant Cyanidin, P-coumaric Acid, Sinapic Acid	Cholestanol, Cholesterol, Choline, Citric Acid, Citrostadienol, Caffeoil-3-Quinic Acid, Caffetannic Acid, Cahweol, Calcium, Campestanol, Campesterol, Caprinic Acid, Carbohydrates, Carnaubic Acid, Cellulose, Chlorogenic Acid, Cholestanol, Cholesterol, Choline, Citric Acid, CitrostadienolCoffeasterol, Cycloeucaenol, Cysteine, Cystine, Daturic Acid, Dextrins, Dihydrolanasterol, Dihydrositosterol, EO, Eugenol, Fat, Fiber, Fufuryl Alcohol, Furfuraldehyde, Galactan, Galactomannan, Gamma-sitosterol, Gamma-tocopherol, Glucogalactomannan, Glutamic Acid, Guaiacol, Guanosine, Hemicellulose, Homocellulose, Hydrogen Sulfide, Hypoxanthine, Iron, Isochlorogenic Acid, Isoeugenol, Kahweol, Lanosterol, Lignoceric Acid, Linoleic Acid, Linolenic Acid, M-Cresol, Mannan, Mannose, Methionine, Myristic Acid, N-Nonacosane, Niacin, Nitrogen, O-Cresol, O-Xylenol, Obtusifoliol, Oleic Acid, P-Cresol, P-Xylenol, Palmitic Acid, Pectin, Pentosane, Pentosans, Phosphorus, Phytate, Phytosterols, Polyamines, Protein, Putrescine, Raffinose, Rhamnose, Riboflavin, Saccharose, Salicylates, Scopoletin, Spermidine, Spermine, Squalene, Stachyose, Stearic Acid, Stigmasterol, Sugar, Tannic Acid, Tannin, Tetracosic Acid, Theobromine, Theophylline, Thiamin, Trigonelline, Water, Xanthine, Xylan
Fruit Caffeic Acid, L-Asparagine, L-Aspartic Acid, Oxalic Acid	
Leaf Allantoic Acid, Allantoin, Beta-Carotene, Caffeic Acid, Calcium, Carbohydrates, Fat, Fiber, Iron, Niacin, Phosphorus, Protein, Riboflavin, Theobromine, Theophylline	
Seed 2,3,5-trimethylphenol, 2-ethylphenol, 2-methoxy-4-ethylphenol, 24-methylene-cycloartenol, 24-methylenephenol, 3,4-dicaffeoyl-quinic-acid, 3,5-dicaffeoyl-quinic-acid, 4,5-dicaffeoyl-quinic-acid, 4-ethylphenol, 4-methoxy-4-vinylphenol, 5-avenasterol, 7-stigmasterol, Acetaldehyde, Adenine, Alpha-tocopherol, Arabinogalactose, Arabinose, Arachidic Acid, Ash, Asparagine, Aspartic Acid, Attractyligenin, Beta-sitosterol, Beta-tocopherol, Cafesterol, Cafestol, Caffeine, Caffeol, Caffeoil-3-Quinic Acid, Caffetannic Acid, Cahweol, Calcium, Campestanol, Campesterol, Caprinic Acid, Carbohydrates, Carnaubic Acid, Cellulose, Chlorogenic Acid,	

Table 2. Chemical Constituents in *Coffea arabica*
Source: (Duke)

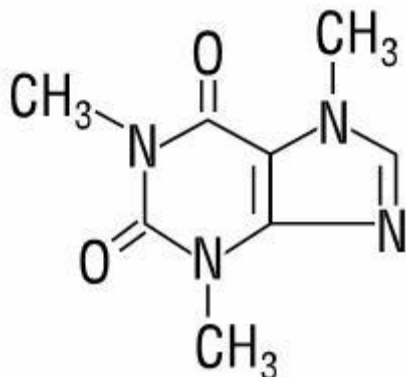


Figure 2 Structure of Caffeine. Source: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16514>

2-methylbutanol, 3-methylbutanol have greatest impact on coffee flavor (Czerny, Mayer, & Grosch, 1999). Also, caffeine is actually a defense mechanism for *C. arabica*. It has the capability of destroying harmful bacteria and fungi and sterilizing certain dangerous insects. If it has inhabited an area for a long period of time, it could possibly inhibit weed growth as well (Weinberg & Bealer, 2001).

Biological Activity

Most of the biological activity in *Coffea arabica* stems from the presence of caffeine (Khan & Abourashed, 2010). Its stimulant properties are responsible for stimulating the central nervous system, respiratory system, skeletal muscles, and performing cardiac stimulation, arterial dilation, smooth muscle relaxation, and acting as a diuretic (Khan & Abourashed, 2010). Also, it has been observed that within 1 hour of having 250 mg of caffeine, non-coffee drinkers tend to have an

average increase of 10 mmHg in systolic blood pressure (Kraft & Hobbs, 2004).

Caffeine works by binding to adenosine receptors and blocking phosphodiesterase (Wyk & Wink, 2004). As stated previously, it can affect many parts of the human body. In the cardiovascular system, it has a positive inotropic effect on the heart and a positive chronotropic effect on the sinoatrial node, which causes increased heart rate, contraction force, and a greater cardiac output (Walter & Maheswari, 2006). It can also cause vasoconstriction in the cerebral vasculature, which decreases the blood flow and the oxygen tension of the brain (Walter & Maheswari, 2006). For some patients, this could provide relief from headache pain (Walter & Maheswari, 2006). In the gastrointestinal system, caffeine initiates the secretion of pepsin and gastric acid from the parietal cells

(Walter & Maheswari, 2006). In the renal system, caffeine causes an increase in renal blood flow and the glomerular filtration rate, while decreasing the reabsorption of sodium and water by the proximal tubules. This can create mild diuresis (Walter & Maheswari, 2006). Caffeine also impedes uterine contractions and transiently increases plasma glucose with stimulation of glycogenolysis and lipolysis (Walter & Maheswari, 2006).

Studies have shown that the methylxanthines in coffee can help with respiratory issues. Theophylline, an example of a xanthine, is present in *C. arabica* at about 7 to 23 milligrams per kilogram, and has been used as a prescription medication for the treatment of asthma (Bisht & Sisodia, 2010).

In vitro & *ex vivo*

One study performed on *Coffea arabica* was done both in vitro and ex vivo and was looking at the antioxidant and protective

properties of green and roasted coffee. For the in vitro part of the study, the model system was β -carotene-linoleic acid (Daglia, Papetti, Gregotti, Berte, & Gazzani, 2000). According to the study, the green coffee had a higher antioxidant activity than the roasted (Daglia et al., 2000). However, when looking at the protective activity against rat liver cell microsome lipid peroxidation, the roasted coffee performed better than the green coffee (Daglia et al., 2000).

Clinical Studies

Blood Pressure

A clinical study observing the amount of coffee consumed and increase in blood pressure was performed on 522 subjects. The average amount of coffee consumed per day over a median period of 56 days. After linear regression analysis, a positive relationship between amount of coffee consumed and systolic blood pressure appeared (Jee, He, Whelton, Suh, & Klag, 1999).

Caffeine and Asthma

The methylxanthines in coffee have the capability of functioning as bronchodilators. This idea was tested by looking at data from the Second National Health and Nutrition Examination Survey (NHANES II), which was taken from a sample representing the civilian United States population. The possibility of relationships between normal coffee and tea intake to asthma and wheezing symptoms was determined. After comparison to non-coffee drinkers, the results showed that people who consumed coffee regularly saw a 29% decrease in the odds of presenting with current asthma symptoms. An inverse relationship appeared between the cups of coffee consumed per day and the occurrence of

asthma, while tea consumption did not have a significant relationship to asthma prevalence (Schwartz & Weiss, 1992).

Caffeine and Analgesics

Over the last twenty years, thirty clinical studies with over 10,000 patients have been performed, and the data from these was studied to see if caffeine was useful as an analgesic adjuvant. Most of the studies involved patients with postpartum uterine cramping or episiotomy pain, but some had patients with pain from a headache or oral surgery. The results showed that to get the same response from an analgesic without caffeine, one would have to take about 40% more than one with caffeine (Laska et al., 1984). Based on this study, it was determined that a reasonable conclusion would be to add 65 milligrams of caffeine to an analgesic tablet to create a more effective analgesic. According to the study, the analgesic with caffeine has the capabilities of being an important option for therapy and management of a patient's pain (Laska et al., 1984).

Caffeine Consumption and Spontaneous Abortion

A population based study of early spontaneous abortion was performed with 562 Swedish women who had a spontaneous abortion, or miscarriage, between six and twelve weeks gestation and 953 Swedish women who did not have an abortion. The goal of the study was to see if caffeine consumption could increase the risk of an early spontaneous abortion in non-smoking women carrying fetuses with normal karyotypes. Among the non-smoking women, there were an increased number of occurrences of spontaneous abortions in the women who consumed at least 100 milligrams of caffeine per day than in women who ingested less than that. With the

smoking women, no association between caffeine ingestion and increased risk of spontaneous abortion was found. The conclusion was made that consumption of a moderate to high amount of caffeine correlated with an increased risk of spontaneous abortion when the fetus had a normal or unknown karyotype (I. A. Ross, 2005).

Mental Workload and Caffeine

Many studies have been performed and shown that caffeine is associated with the excretion of catecholamines and their metabolites. They have also shown that urinary levels of norepinephrine and epinephrine increase after the consumption of caffeine. This was seen in the levels of adrenaline and noradrenaline, as well, along with a dose dependent effect of caffeine (Papadelis et al., 2003). The possibilities of correlations between caffeine and cognitive performance, blood pressure, and catecholamines were observed under resting conditions and with a mental workload. The research subjects took the test after consuming one cup of coffee and then three cups of coffee. Blood pressure was taken at the beginning and end of each step of the experiment, and the root mean square error was watched continuously. After the three stages - at rest, under mental stress, after one dose of caffeine under stress, and after a triple dose of caffeine under stress - catecholamines were collected and measured (Papadelis et al., 2003). The only group that showed a statistically significant difference was the smokers and coffee drinkers. The study saw an increase in the urine adrenaline after consumption of one cup of coffee and a significant increase of noradrenaline in the urine. After an intake of three cups of coffee, both catecholamines significantly increased. They also increased with a mental

workload. In the end, the conclusion was made of causation between caffeine and catecholamines (Papadelis et al., 2003).

Coffee and Parkinson Disease

Affecting about 3% of the population over 65 years of age, Parkinson disease is a large source of morbidity in the United States, and this statistic is expected to grow doubly over the next 30 to 40 years. One study began looking at the possible association of coffee and caffeine consumption and the incidence of Parkinson disease. The subject population consisted of 8004 Japanese-American men between the ages of 45 and 68 who were a part of the Honolulu Heart Program from 1965 to 1968. The incidence of Parkinson disease, amount of coffee consumption, and total dietary caffeine intake were measured. The coffee consumption was measured at the time of enrollment and at a 6-year follow-up, while the caffeine intake was observed at enrollment. The results showed the incidence of Parkinson disease significantly decreased with the increase of coffee and caffeine consumption. The conclusion of the study was that caffeine intake was related to the decline of risk of Parkinson disease and not the other nutrients in coffee (G. W. Ross et al., 2000).

Contraindications

When consumed in large doses, the caffeine in *Coffea arabica* can be harmful. One gram or more can cause "headache, nausea, insomnia, restlessness, excitement, mild delirium, muscle tremors, tachycardia, and extrasystoles" (Khan & Abourashed, 2010). These symptoms have also been observed in people who consume more than 1.5 grams of caffeine a day for a long period of time or with 300 to 500 mg per day for individuals with more sensitivity (Kraft & Hobbs, 2004).

Consumption of over six cups of coffee per day can lead to a negative fluid balance, due to the increased urine production caused by caffeine (Dorea & Costa, 2005). Also, for susceptible groups like the elderly, drinking more than six cups of coffee is one of the factors related to short sleep (Dorea & Costa, 2005).

Some side effects coming from the chlorogenic acid concentration in *C. arabica* are an increase in gastric acid, gastric irritation, diarrhea, and a depressed appetite (Kraft & Hobbs, 2004). Two signs of poisoning are vomiting and cramps in the abdomen (Kraft & Hobbs, 2004).

Nursing mothers should not ingest caffeine because it can cause the infant to have a sleeping disorder (*PDR for herbal medicines*, 1998). Pregnant women should also avoid caffeine, and if they consume it, they should not have more than 300 mg per day (*PDR for herbal medicines*, 1998).

The regular intake of caffeine can actually lead to “caffeinism,” the psychic and physical dependency to caffeine. Withdrawal from this can present itself with headache and sleeping disorders (*PDR for herbal medicines*, 1998).

Current Use in Allopathic and CAM Therapies

“Coffee charcoal” or *Coffea carbo* is created from carbonized, or roasted, seeds of *Coffea arabica* (Wyk & Wink, 2004). This is generated through roasting the outer part, or exocarp, of green and dried fruit. After they become almost black, they are ground up. *Coffea carbo* is used for two main things: diarrhea and inflammation in the mouth and pharynx (*PDR for herbal medicines*, 1998). It is a powder that can be taken orally or applied topically. One dose of *Coffea carbo* is generally about 3 grams, and the daily dose is about 9 grams (for internal use) (*PDR for herbal medicines*, 1998).

Caffeine is also used by the United States Pharmacopeia in several different pharmaceuticals. These include “internal analgesics, cold and allergy products, weight control formulations (appetite depressants), and others” (Khan & Abourashed, 2010).

In traditional Ayurvedic therapies, the unripen beans of *C. arabica* are known to be used for headaches, while the ripened and roasted beans are used for diarrhea (Chevallier, 1996).

Discussion

Coffea arabica has had many uses over the years, which range from food to medicine. Because of its beneficial effects, it has become the second largest commodity in the world after crude oil (Meletis, 2006). This originally Ethiopian plant is now cultivated in many places around the world, and exported to the others. Many people have become dependent on the effects that its main functional derivative, caffeine, gives them. While a lot of people use it for the stimulation of the central nervous system, it also can affect the renal system, gastrointestinal system, and musculoskeletal system. Before being one of the top products in the world, it was used traditionally by many cultures, and this has led to it being used in many different pharmaceuticals, including analgesics, cold remedies, stimulants, and diuretics. Unfortunately, caffeine does have its negative effects, including the possibility of addiction, but research is being done to see what else it affects. So far, this has included the possibility of helping asthma, pain, neurologic conditions, and more. Overall, *C. arabica* has provided the world with a stimulant that is used daily, not only for general stimulation but also medicinal purposes.

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Cola nitida (Vent.) Schoot & Endl, Malvaceae

Ijeoma Okafor

Introduction

Cola nitida, also referred to as the Kola Nut, is a well-known fruit in the Malvaceae (formerly in Sterculiaceae) family and one of Africa's most valuable plants. Originally given the name *Sterculia nitida* by the French, it was later decided by the Germans that it belonged in the *Cola* family. Depending on its global location, it may also be referred to as gbanja kola, bitter kola, bese, goro, bissy or biche, kolatier, or colatero. With over sixteen different species in the *Cola* genus, the two most common edible types are the *C. nitida* and *C. acuminata*. Both *C. nitida* and *C. acuminata* are essential to African countries for their usage and commercial value, but the more prevalent and valuable of the two is the *C. nitida*. The kola nut coined the phrase "the kola of the caravan trade", as it is used for a variety of functions (Lovejoy, 1980). Having been transmigrated by the slave trade, the kola nut is quite versatile and has been used as a mild stimulant, antidote for specific diseases, a hunger-suppressant, gift to royalty, a token of peace or war, and even as a dye for decorating cloth (Abaka, 2005). Used in conjunction with herbal plants such as ma huang and in well-known commodities like Coca-Cola soda, the kola nut has become a major cash crop for its native African countries. Although *C. nitida* has medicinal and recreational uses, the kola nut is commonly recognized as a part of the stimulant substance group. Known for its astringent taste and high caffeine content, the kola nut produces a mild stimulating and sustaining effect once consumed (Brooks, 1980).



Figure 1. *Cola nitida* carpel and flowers: The kola nut can be found inside the carpels, which are the seeds. Image source: http://english.xtbg.cas.cn/rs/ma/201112/t20111206_79718.html

Botanical Description

Cola nitida is an understory, evergreen tree that produces the kola nut fruit. The tree can reach up to 40-60 feet tall, 1.5 meters in diameter, and is capable of producing light brown carpels that can contain anywhere from one to fifteen seeds; allowing a single tree to produce well over a thousand nuts per year (Brooks, 1980). The carpels are accompanied by flowers that are normally greenish-yellow or white with



Figure 2. Kola Nuts ranging in colors: The variety of color between kola nuts can be found in every fruit. Image source: <http://www.shamanaustralis.com/forum/index.php?showtopic=2747>

purple tracing along the edges of the petal (**Figure 1**). The kola nut, which is not a true nut but a seed from a follicular fruit, is roughly the size of a Brazil nut or a chestnut ranging approximately from 1 to 2 inches in size. The kola nut can also be found in a wide range of colors varying from a cream/white when found fresh to a dark reddish brown when dried (**Figure 2**). The red kola nut is the likely choice for trade because of its long-lasting qualities, while the white and pink kola nuts are generally more valued (Abaka, 2005).

The genus *Cola* is mainly located in the African tropics. More specifically, *C. nitida* is primarily indigenous to the Western Africa regions (**Figure 3**). Originally a tropical rainforest tree,



Figure 3. Western African Tropics: The location for indigenous *C. nitida*. Image source: http://www.mnzo.com/animals/animals_dwarfCroc.asp

C. nitida can be found in hot and humid climates located in places such as Cote d'Ivoire, Ghana, Liberia, Nigeria, Sierra Leone, and the confluences of the Niger and Benue rivers. However, due to the frequent traveling by man and the rising of trade routes, the kola nut can now be found in locations such as the West and East Indies, Brazil, Jamaica, Mali, Zimbabwe, Sudan, Ethiopia, Guinea, Somalia, Chad, Congo, and several other countries (Abaka, 2005). Low elevations, well-drained soil, and moderate rainfall are needed for the successful growth of *C. nitida*, which cannot withstand flooding (Abaka, 2005). Because most African countries experience a dry season (December to March), it is important to grow *C. nitida* in areas where soil retains sufficient moisture during this season. However, *C. nitida* has even been found in altitudes over 300 meters high, where there is rich soil due to heavy rainfall (Lovejoy, 1980).

Within six to seven years after planting, *C. nitida* is able to bear fruit that can be harvested seasonally between October and February. After 5 days of fermentation, the ripe fruits are

harvested before the follicles are able to split open. The kola nuts that are chosen for cultivation are left to fully mature and ripen. *C. nitida* can then be spread by cuttings or aerial layering. However, the most important pollinators for *C. nitida* are insects. One method used to obtain the maximum yield of kola nuts, is to cultivate it along with other crops. One crop, *Theobroma cacao* can grow in the same climate conditions. Both species can actually be grown together, with *C. nitida* acting as an intercrop by providing top shade for *T. cacao*. Both *C. nitida* and *T. cacao* are close relatives to one another. Both species are a part of the Sterculiaceae (now Malvaceae) family, which contain flowering plants and is also known as the cacao family. The moderate leaching and acidity of the environment, in addition to 45-65 inches of rainfall, provides this climate with enough fertile soil to maintain the growth of both the *C. nitida* and *T. cacao* (Abaka, 2005).

Traditional Uses

Traditional Medicinal Uses

For centuries no other African commodity has been held to such a high importance in West Africa than the kola nut. Around the twelfth century, the Arabian doctor El-Ghafeky first discovered the importance of *C. nitida* as a drug. He reported that the use of powdered kola nut had the ability to relieve colic and stomachaches, while possessing “warming properties” (Abaka, 2005). During the same century, the kola nut was documented to help ease the pains of childbirth and as a treatment for rheumatism and dyspnea. In the fifteenth century, a report stating the existence of an African kola trade was documented in Pacheco Pereira’s *Esmeraldo de Situ Orbis* (Abaka, 2005). For Muslims, kola nut was, and still is, a high demanding masticatory product because it is one of the only stimulants Islam condones. What was once a commodity for

the elites gradually became available to the masses. Upon learning of its additional medicinal properties, the Islamic world further expanded the use and marketing of the kola nut. Traditionally, traders venturing on long journeys would chew the kola nut raw to reduce the effects of fatigue, hunger, and thirst, while maintaining alertness. In 1688, the historian Hans Sloane examined the effects of kola nut samples taken from Jamaica. He discovered the kola nut could be used as a diuretic and was great for treating water retention caused by diseases such as edema or dropsy (Mitchell, 2001). The kola was also known to provide cures for headaches and male sexual impotency (Lovejoy, 1980). It was believed that by submerging a minced kola nut in wine and taking it as a tonic daily would help stimulate a man’s desire and sexuality (Brooks, 1980).

Ethnobotanical Uses

Even before the discovery of *C. nitida*’s medicinal uses, many African tribes were aware of its stimulant properties and integrated the masticatory process as a part of everyday life (Seeds, 2012). Now, many African societies see the kola nut as a high, valued commodity that is used in various ways in different cultures. In these societies, the social aspect encompassing the kola nut holds great importance as well. The kola nut can be offered to friend the same way tobacco products are shared in Western societies, it can either be chewed individually or in a group setting (Abaka, 2005). In certain Nigerian cultures, to be given a kola nut is a great honor. There are special occasions and ceremonies that encompass the use of or the giving of the kola nut. During wedding ceremonies, the breaking and sharing of kola nuts is considered a vital component during the wedding reception. The kola nut is also used as a way to accept or decline a

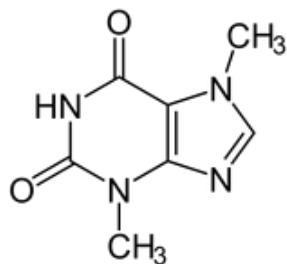


Figure 4. Caffeine. Image source: <http://chemistry.about.com/od/factsstructures/a/theobromine-chemistry.htm>

marriage proposal (returning a white kola means yes while a red kola means no), or could even be used to pay off part of a dowry. The color of the kola nut also plays a significant role in social and cultural communication. In many African societies, a white kola nut symbolizes friendship and could be used as ratifying treaties, while a red kola nut symbolized enmity and challenge to warfare. During a christening, a red kola represents life and the white kola purity. Also, the breaking of a kola nut is said to be a valued expression of hospitality. In Western societies the kola nut, due to its high caffeine content, was a major ingredient in the production of the Coca-Cola products. Invented by John Pemberton, the original Coca-Cola drink was made by combining coca and kola extracts with the hopes of concocting a remedy for headaches and hangovers (Burdock, 2009).

Food Source

The seeds of the *C. nitida* can be pounded into a powder and boiled in water to prepare as a tea. Due to the kola nut's strong bitter taste followed by a sweet aftertaste, it has also been used as a sweetener to get rid of bad tastes (Lovejoy, 1980). In addition to being implemented in soft drinks like Coca-Cola,

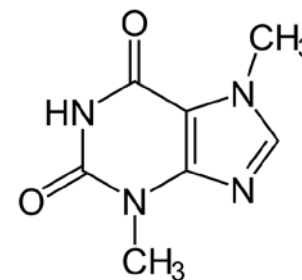


Figure 5. Theobromine. Image source: <http://chemistry.about.com/od/factsstructures/ig/Chemical-Structures---T/Theobromine.htm>

the kola nut can also be combined with the coca leaves and incorporated into tonic wines, brands of cocoa, and other beverages. In Nigeria, kola nut is simply a common snack favored among the elderly (Adebola, 2011).

Other Uses

The kola nut is said to have multifarious uses. *C. nitida* can act as a water purifier in addition to dyeing clothing and as a candle. The bark is strong enough to be used for timber. It has been used for making furniture, house and boat buildings, domestic utensils, musical instruments, and wooden games and toys. The pod husk of the kola has been integrated into the production of liquid soap, and the most recent and remarkable advancement is that the kola pod husk has replaced up to 60% of maize for poultry feed formulations (Lim, 2011).

Chemistry and Pharmacology

The two active constituents present in *C. nitida* are the alkaloids, caffeine and theobromine (**Figures 4 & 5**). Both stimulate the central nervous system and the amounts of each

Stimulant	Caffeine (%)	Theobromine (%)
Kola	1.0 – 4.0	.02 - .09
Coffee	.7 – 2.3	None
Tea	1.0 – 4.7	None
Cocoa	.08 - .23	.8 – 2.3

Table 1. Caffeine and theobromine content in mild stimulants.

constituent in a kola nut fluctuate from one kola to the next. While caffeine has the stronger presence in a kola nut, theobromine has the greater responsibility in stimulating the skeletal muscles. However, there are only traces of theobromine present in *C. nitida*, while caffeine can make up anywhere from one to four percent of the kola nut. In addition to the two alkaloids, a glucoside heart stimulant, kolatin, is also present (Lovejoy, 1980). The combination of these three constituents makes the kola nut a highly effective stimulant in relations to other stimulants (**Table 1**). It is estimated that *C. nitida* has as much caffeine as 100 grams of coffee and as much theobromine as 100 grams of tea (Brooks, 1980). Because of this, one average sized kola nut is equivalent to approximately three cups of American coffee, but these effects can vary from person to person. Other chemicals found in *C. nitida* are strychnine, catechin, flavonoids, anthocyanins, quinine, theine, and tannin (Abaka, 2005).

Biological Activity

Biological activity is not only present in the kola nut, but parts

of the whole tree have been reported to have significant medicinal uses. The cotyledon can be used to help treat herpes while the bark can be used for dystocia. The twigs can be taken and made into a chewing stick, which acts like a toothbrush by being able to clean the teeth and gums. A tonic can be prepared using the leaves, twigs, flowers, fruit follicles, and the bark to concoct a remedy for dysentery, coughs, diarrhea, vomiting, and chest complaints. There have also been reports about the extracts from the stem bark of *C. nitida*. It may have the potential to regulate natural fertility (Adebola, 2011).

Elastase Reduction Activity

Inflammatory diseases like asthma or cystic fibrosis are characterized by excess uninhibited neutrophil elastase, which contributes to tissue destruction. α 1PI is one major inhibitor of elastase, and its presence or deficiency can also cause physiological disorders such as emphysema. A study shows that kola nut extract, depending on its concentration, can protect α 1PI from HOCL inactivation by suppressing the MPO-H₂O₂ system. The suppression is caused the phenolic content in the extract scavenging oxygen species like H₂O₂ (Daels, 2003).

Aphrodisiac

During the eighteenth and twentieth century kola consumption in the Hausaland was promoted by the belief that a society's interest in sex and sexuality could be heightened (Brooks, 1980). Another study was performed on adult male rats. The study substituted drinking water with three different kola beverages for three months. At the end of the study the kola intake increased both oestradiol and

testosterone levels, suggesting that there is an additional mechanism of action beyond the effects of caffeine (Schliep, 2012).

Antimicrobial

An *in vitro* study examines four human pathogenic bacteria against *C. nitida*. The results show that the presence of secondary metabolites partially enhances the chemotaxonomic characterization of *C. nitida*. The presence of antimicrobial activity allows for the *C. nitida* extract to inhibit growth of certain bacteria and fungi. *C. nitida* showed inhibitory activity against *Aspergillus niger* and *Candida albicans* (Sonibare, 2009).

Antioxidant

The high levels of phenolic compounds found in kola nuts allow the extract to exhibit antioxidant capacities. The IC₅₀ values range from 1.70-2.83 in hypoxanthine/xanthine oxidase and 2.75-4.08 mg/ml in 2-deoxyguanosine HPLC-based assays. Of the secondary metabolites found in kola nut extracts, caffeine has the most antioxidant capacity proving to be an effective cancer chemopreventive metabolite (Sunday, 2007).

Cardiovascular and CNS Activity

Kola nut is reported to enhance alertness, physical energy, elevate moods, increase tactile sensitivity, and suppress the appetite. Various doses of kola nut extract were giving to male mice. The results showed that at medium doses locomotors activity increased while low doses showed no effect and high doses resulted in a depressive effect of locomotors activity

(Ajarem, 1990). A later study explained the locomotors activity due to the caffeine content while kolanin is responsible for stimulating the heart (Lim, 2011).

Ocular Activity

Thirty grams of *C. nitida* was tested on visually acute and healthy volunteers to determine ocular effects. Results showed no effect on the pupil diameter of visual acuity but improvement in the near point of convergence by 43%. The amplitude of accommodation was increased by 11% while existing heterophorias were ameliorated. The kola nut extracts allows near work to done without stress. The extract could also aid the elder by relieving somnolence and ocular muscle imbalance (Lim, 2011).

Antibacterial Activity

The methanol extract that can be extracted from the root bark of *C. nitida* is shown to affect *Mycobacterium bovis* and strains of *Mycobacterium vaccae*. The aqueous and alcoholic extracts also found in the bark were show to inhibit growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, β -haemolytic streptococci, *Escherichia coli*, and *Neisseria gonorrhoeae* (Lim, 2011).

Clinical Studies

In 1888-1889, several tests were performed to examine whether the kola nut could be beneficial to soldiers in the battlefield. Ten pounds of kola nut varying in size were supplied R.H. Firth to test for four properties of a kola nut: whether a person could undergo long periods of fasting and fatigue without exhaustion, adjuvant to sustain the body

during exertion without food, restore a person in the drunken state to practical sobriety, and as a remedial agent allowing those to recover from lengthened sicknesses. The first experiment tested two patients who had venereal disease. They were administered a hot infusion of powdered kola and boiling water with their diet unchanged and urine examined twice a day. The results showed that the men's weight, pulse and respiratory capacities were unchanged, but their daily total excretion and urine increased in watery content. Those were the only physical results, however, both men stated that they had "less appetite and felt less want of food." The second test examined three soldiers performing physical activities without having eaten in 60 hours, but could be administered an infusion of 200 grams of kola powder, milk, and sugar during this timeframe. The experiment was also performed by Firth himself, and the three subjects concluded that the sense of hunger and exhaustion was less prominent. The third case used 50 men to show that the kola nut could sustain the body against fatigue and hunger. They were only allowed to chew the kola nut bit by bit for the next two days. Only 26 of the soldiers followed the rules properly and gave an accurate account of the experience. The majority stated that for the first 16 hours they felt hungry and tired, but for the remainder of the time they did not show signs of hunger or tiredness. The last experiment tested the ingestion of kola nut on a drunken person. The kola nut taken as a hot infusion was said to relieve the head of "the sense of heaviness peculiar to alcoholic excess of the previous night" (Abaka, 2005).

Branching off of the study previously mentioned, Firth was also able to determine the kola nut's direct relationship to the central nervous system. After the conclusion of the study involving the twenty-five soldiers that had eaten in two days, the majority of the men were craving fat and butter, allowing Firth to conclude that the body resorted to using fat reserves

for recuperation. Therefore, the action of chewing a kola nut in addition to the absence of food is an artificial stimulant to the central nervous system (Abaka, 2005).

A clinical study was performed to show the effects of kola nut extract on the heart. The concentration of kola nut extract is directly related to the rate of metabolism and rhythmic heart activity. At low doses, the kola nut extract caused the rate of the heartbeat and the force of contraction to increase. When person consumed higher doses of the extract it resulted in the spike of metabolic rates (increasing approximately 118.76%) (Chukwu, 2006).

Contraindications

The FDA and FEMA have labeled the kola nut extract GRAS for the usage of a flavoring ingredient. However, in 1996, the FDA reported that the kola-mahuang combination for hallucinogenic effects is a deadly pair, and this brought attention to issue that more experiments involving the kola nut and kola nut combinations needs to be further explored. One study shows a linkage between the consumption of kola nut and malaria morbidity. The results revealed that eating the kola nut increases the expression of malaria symptoms by favoring parasite multiplication. *C. nitida* also contains hydrocyanic acid which, if consumed in high doses for a short period of time, is known to cause harm to the nervous, respiratory and cardiovascular systems. Also, if exposed to hydrocyanic acid for longer durations, irritation of the eyes, appetite loss, headaches, dizziness, and damages to the nervous system and thyroid gland could be potential results (Alaribe, 2003). There are also side effects to taking in too much caffeine. Problems that could arise are nausea, insomnia, headaches, and tachycardia. If caffeine is ingested in significantly large doses then muscle tumor and tinnitus could



Figure 6. Herbal supplement of kola nut: The kola nuts are crushed into a powder and encapsulated and can now be found in certain drugstores. Image source: <http://www.swansonvitamins.com/SW1122/ItemDetail>

be potential results. Peptic ulcer patients are advised not to kola nut since caffeine, along with theobromine, are known to stimulate gastric acid secretion. However, caffeine is still considered a GRAS but is regulated by FDA for the use in cola beverages, with .02% being the maximum concentration allowed. The FDA also regulates the use of caffeine, alone, as an OTC stimulant drug. Even with these precautions there is always the rare chance of a person becoming hypersensitivity to the active substances in *C. nitida* (Burdock, 2009).

Current Use in Allopathic and CAM Therapies

Many of the traditional uses of the kola nut are still used today. Recently in Western societies, the kola nut has been reintroduced as a flavoring for drinks. Also, the CoE, FDA and FEMA have approved the use of kola nut extract for foods (Burdock, 2009). The kola nut can also be used as a base for

certain chocolates and wine. Due to its high pectin content, there is possibility that kola nut can be included in jams or jelly. The kola nut also contains high protein content that could be a useful ingredient in making fertilizers. The nuts can also be used in tinctures or made into teas. Powdered kola is now available in capsule form; however, in comparison to naturally chewing the kola nut, the strength and its effectiveness is much lower since the caffeine content is not as high (**Figure 6**) (Burdock, 2009).

Discussion

Despite its economic importance in Western and Central Africa, much still unknown about *C. nitida*. Having been exported to all parts of the world, *C. nitida* is centuries old and will most likely remain a vital resource in many cultures for centuries to come. The kola nut was already accepted amongst African societies when only the stimulant effects were known. Now that there is a worldwide awareness of the kola nut's medicinal and recreational uses, the plants significance has only gotten greater. With uses ranging from social and cultural interactions to fighting off fatigue to a component in beverages, as we begin to learn more about *C. nitida* and its diversifying effects, its demand in the world will become more prevalent. With that being said, the kola nut will continue to play a significant role as an important economic crop for internal, regional, and foreign trade (Adebola, 2011).

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Commiphora molmol (Engl.) Engl. ex Tschirch, Burseraceae

Elizabeth Giffen

Introduction

Commiphora molmol (Engl.) Engl. ex Tschirch, Burseraceae, also known as *Commiphora myrrha* var. *molmol* Engl. and commonly as the myrrh tree, ("Tropicos.Org," 2011) is an arid tree or shrub from Somalia and Ethiopia (**Figure 1**). Its main utilization is as a gum, resin or essential oil (Nomicos, 2007) and has been in perfumes and incenses since ancient times. It has religious significance in Judeo-Christian traditions and is often used ritually. Myrrh has also seen use as a wine preservative and in embalming fluids in ancient Egypt (Groom 1981). In medicine, myrrh has been traditionally used from northern Africa east through India to treat a huge range of ailments, as an anti-inflammatory, analgesic, emmenagogue, antibacterial, and for oral maladies (Groom, 1981, Walter H. Lewis, 2003). The plant produces an oleogum resin that is 2-8% essential oil (El-Shahat, et al., 2011) 23-40% resin, 40-60% gum and 10-25% bitter principles (Su, et al., 2011). Some active constituents of myrrh include the sesquiterpenes furanodiene-6-one and methoxyfuranoguaia-9-ene-8-one, which have antibacterial, antifungal and local anesthetic activities, (Dolara, et al., 2000) and furanoeudesma-1,3-diene and curzarene, which have potent analgesic effects (Dolara, et al., 1996). The furanosesquiterpenoids lindestrene and its analogues make up 19% of the essential oil and are responsible for the famous scent associated with myrrh (Jensen). Other important constituents are terpenoids, steroids, flavonoids, lignans, carbohydrates, and long chain aliphatic alcohol derivatives; these various metabolites give myrrh its manifold biological activities (Su, et al., 2011).



Figure 1. Myrrh. (Source: http://www.plantsasmedicine.com/~cleanen2/index.php?title=Commiphora_myrrha)

Botanical Description

The myrrh plant is a small, thick-stemmed tree or shrub with a succulent trunk and spine-like twigs. It grows in arid and alpine habitats in Djibouti, Ethiopia, Somalia, Kenya, Oman and Yemen (USDA). The leaves are small and sparse, generally single and grey-green, and quite variable in size and shape,

but usually oval-shaped and trifoliate (Nomicos, 2007). The leaves become yellow in autumn before falling off (Cactuspedia). The bark is silver, papery and peeling, with green bark underneath. Myrrh tree fruits are tiny and brown, with a smooth, oval shape (Nomicos, 2007). Puncturing the stems or trunk produces a pale yellow, oily myrrh resin with a bitter taste but a warm, smoky scent, which turns reddish and dusty upon hardening (Michie and Cooper, 1991).

Myrrh resin is harvested by making incisions roughly 2 inches long into the bark of the tree. The sap hardens when exposed to air and forms into pearls which are easily harvested around two weeks after the incision is made, and new incisions, or “taps” can be made over old ones after removing the resin; these usually only require an additional scratch. Tapping is done at certain times of year and specific duration depending on the region (Dharmananda 2003).

Traditional Uses

Traditions involving myrrh are well known in Western and Christian-dominated cultures primarily because of the legend of the Magi bringing the Christ-child gifts of gold, frankincense and myrrh to the nativity (Matthew 2.11). In fact, myrrh is a prominent plant throughout Biblical literature, being mentioned frequently in the Song of Solomon. It was also the last gift offered to Jesus before the crucifixion (presumably as an analgesic): “Then they offered him wine mixed with myrrh, but he did not take it,” (Mark 15.23). Nicodemus is also said to have brought myrrh and aloes for the embalming of his body after his death (John 19.39). Jewish tradition utilized myrrh as a main component of anointing oil for the priests, tabernacle, ark and altar (Groom, 1981). Myrrh was once as valuable as gold and ivory, and its use as a plant-based traditional remedy

is one of the oldest therapies on record (Michie and Cooper, 1991).

In a temple near Thebes, we see some of the first evidence of the myrrh trade in frescoes detailing the voyage of a fleet of Egyptians sent by Queen Hatshepsut to the land of Punt, from which they brought back, among many items, quantities of incense (*'ntyw* is believed to be myrrh, although there is some debate that it may be frankincense (Lucas and Harris, 1999)) and incense-bearing trees. Texts from centuries earlier indicate the ritual use of incense, however, and still earlier texts detail previous expeditions to Punt, although no indication of incense is made (Groom, 1981).

Medicinally, it has been said that the Greek soldiers would not go into battle without myrrh to treat wounds (Hanus, et al., 2005). The Ebers Papyrus, which dates back to c. 1550 BC, details its use as both incense and medicinal remedy (Chisholm, 1910). It is listed as being used in funerals, mummifications and cremations, but also in the treatment of wounds and skin sores (Michie and Cooper, 1991). Mesopotamian texts in Assyrian cuneiform script dating from the 10th to 6th century BC record myrrh being used medicinally, and Pliny, Theophrastus and Dioscorides have all made mention of it in various ancient texts, including the famous *De Materia Medica* (Groom, 1981).

De Materia Medica (c. 65 A.D.) in particular mentions myrrh several times as an ingredient in concoctions as an abortifacient, antiseptic ointment and a diuretic, and to treat asthma, “female ailments,” dandruff, varicose veins, sleeplessness, cleaning boils, glaucoma, purging ulcers, and softening various somatic scleroses. *Stacte*, the substance made from myrrh gum resin, has an entry in *De Materia Medica*, which describes it as a precious ointment with a very sweet smell and a great deal of strength in small doses. In the

main entry on *Smyrna* (myrrh), Dioscorides even explains a method of counterfeiting myrrh by soaking gum in myrrh-infused water. When one is buying it, he recommends myrrh that is fragrant, brittle, light, and monochromatic, smooth and small when broken, and sharply bitter in taste. It is constantly referred to as 'warming' in nature, and is also drying, astringent, and retaining. As a salve it is used to soothe and open the closed vulva, as an emmenagogue, and to expedite birth. In pill form, myrrh would be taken to help a chronic cough or asthma, side and chest pains, loose bowels and dysentery, kill worms, and to calm feverish chills. It was held under the tongue like a cough drop to treat atherosclerosis and hoarseness, or chewed to treat bad breath. Myrrh could also be used in a mouthwash with wine to strengthen teeth and gums. It was used to heal broken ears, exposed bones, armpit sores, pus and inflammation in the ears, impetigo, alopecia, and smoothing rough skin (Dioscorides, 50-70).

Additionally, myrrh is mentioned in the anonymous Syriac book of medicine and the works of Avicenna (Michie and Cooper, 1991) and by Hippocrates in the 4th century BCE (Nomicos, 2007). Theophrastus says that myrrh would be added to wine to add astringency because of its bitter character. Athenaeus says that Aristotle wrote that myrrh could be boiled in water and the liquid could then be added to wine to "diminish drunkenness" (Groom, 1981).

Celsus, who lived from 25 BC to 50 AD, wrote extensively about its use to treat a huge variety of ailments: a form of malaria, dropsy, intestinal pain, as a poison antidote, to agglutinate wounds, and heal burns, for colic, throat ulcers and to treat abscesses and scabies. He also lists it among the erodents and caustics, includes it as part of ointments for liver, chest and side pain, tuberculosis infection of the lymph nodes in the neck, neuralgia, as a plaster for "broken heads," treatment of inflammation in the uvula and "for the genitals

when foul," and when there is difficulty with urination, as well as to treat anal fissures, canker sores and kidney stones. As an example, to induce menstruation, the prescription is for pounded garlic with myrrh and lily ointment. Celsus writes that it is also useful for treating eye and ear afflictions, tooth pain (although it should be applied on the shoulder), swollen tonsils, and ulcerations of the mouth (Celsus, 25).

Myrrh is used in Ayurveda, although it does not come from *Commiphora myrrha* but *Commiphora mukul* (Hook ex Stocks) Engl. (*C. wightii* (Arnott.) Bhanol.), and is called guggul or false myrrh. Guggul has been used to adulterate myrrh, ("Efloras," 2008) and has some similar properties to *C. myrrha* but also contains many very different active compounds, such as guggulsterone (Hanus, et al., 2005).

Myrrh is first seen in traditional Chinese medicine (TCM) in Kaibao Bencao, 973 CE, under the name *mo yao*. It is still in use as an aid in promoting circulation, treating traumatic injury, and as an anti-inflammatory (Dharmananda, 2003). Myrrh has neutral, bitter properties, usually dosed at 3-10 grams in decoction (Sionneau, 1997), and is almost always used together with frankincense (Jiao, 2003). In TCM, myrrh is sometimes soaked in rice vinegar and then stir-fried or baked (Dharmananda, 2003).

Chemistry and Pharmacology

The main constituents of the myrrh oleo-gum resin are 2-8% volatile oil (El-Shahat, et al., 2011) 23-40% resin, and 40-60% gum (Su, et al., 2011). The gum is water-soluble and contains polysaccharides, proteoglycans and proteins, as well as the compounds D-galactose, L-arabinose, and 4-methyl D-glucuronic acid. The volatile oil is made of steroids, sterols and terpenes (Hanus, et al., 2005) including the

furanosquiterpenoids lindestrene and its analogues, which account for 19% of the essential oil's character and its aromatic properties (Jensen). Close to 20 furanosquiterpenoids have been isolated from myrrh essential oil (Su, et al., 2011), including furanodiene-6-one (0.4%) and methoxyfuranoguaia-9-ene-8-one (0.1%), (Dolara, et al., 2000) furanoedesma-1,3-diene (15%), and curzerene (40.1%) (Dolara, et al., 1996). The essential oil can be extracted from the resin by steam distillation (Walsh, et al., 2010). The resin contains isolinalyl acetate, 3-epi-lupenyl acetate, lupeone, 3-epi- α -amirin, α -amirone, acetyl β -eudesmol, and a sesquiterpene lactone (Hanus, et al., 2005). Other metabolites of myrrh are terpenoids, flavonoids, lignans, carbohydrates, and long chain aliphatic alcohol derivatives (Su, et al., 2011). Marker standards for myrrh are shown in **Figure 2**.

Biological Activity

In an anti-inflammatory test, both an ethanol and a petroleum ether extraction of *Commiphora myrrha* significantly inhibited formalin-induced paw swelling and acetic acid-induced writhing in mice. Because no attenuation in temperature-dependent nociception was shown in this study, the authors noted that this suggests that myrrh extracts with analgesic properties act on the peripheral and not central nociceptive pathway.

A hexane (nonpolar) extraction of myrrh for analgesic activity identified furanoedesma-1,3-diene and curzarene as having analgesic activity when injected intracerebroventricularly in mice at 1.25 mg per kg. Both significantly increased latency to pain reaction (paw licking when placed on a hot plate). Furanoesdesma-1,3-diene given 50 mg per kg orally was also effective in reducing the number of acetic acid-induced

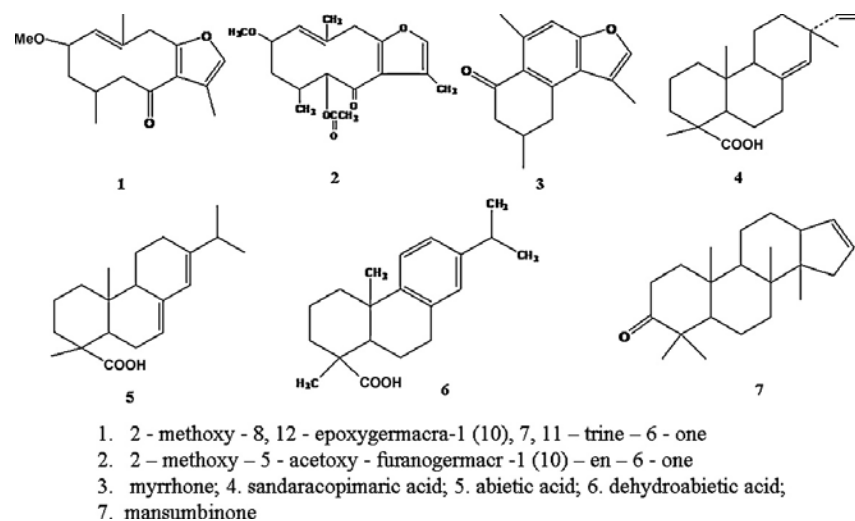


Figure 2. Marker compounds used in myrrh (Su, et al., 2011).

writhes (completely rescued by naxolone and morphine) and again increased latency to temperature-dependent pain reaction. The authors conclude that this suggests an interaction with opioid mechanisms in the central nervous system (Dolara, et al., 1996).

Clinical Studies

A survey done in Ezbet El-Bakly, Egypt, assessed the efficacy of myrrh extract, Mirazid, in the treatment of fascioliasis, a helminthic disease. Those with fascioliasis were given two capsules of Mirazid (600 mg) every day an hour prior to breakfast for six days. The cure rate was 88.2% and 94.1% two and three months after treatment, respectively (Abomadyan, et al., 2004). The same drug was assessed on a population of schistosomal infections in the same region and found to have similarly miraculous results, with the same



Figure 3. *In vitro* antimicrobial activity of myrrh (Moussaieff, et al., 2005).

regimen showing a cure rate of 97.4% and 96.2% two and three months afterward (Abo-Madyan, et al., 2004). Unfortunately, neither of these figures stands up to rigorous repetition. Multiple experimental and clinical studies show myrrh has no significant efficacy in reducing parasite loads (Abdul-Ghani, et al., 2009). However, the anthelmintic mode of action of myrrh is still unknown. Some have postulated that myrrh causes the worms to lose muscle mass, which makes them move into the liver where they are destroyed (Abdul-Ghani, et al., 2009).

An unrelated study in India examined the efficacy of an herbal toothpaste containing myrrh compared with conventional toothpaste for the control of plaque and gingivitis. The researchers found the herbal toothpaste to be just as effective as conventional toothpaste, without any additional benefit (George, et al., 2009). Additionally, a Chinese study examined the efficacy of a number of TCM herbs for the treatment of reflex sympathetic dystrophy (RSD). It found that traditional

remedies decreased both pain and swelling significantly more than placebo (Xu, et al., 2009).

Myrrh ethanolic extract in combination with aloe, mastic and olibanum (the ingredients of the historic Jerusalem Balsam, wildly popular in the early 1700s) has been shown to be strongly antiseptic. **Figure 3** shows the *in vitro* effect of Jerusalem Balsam on *Staphylococcus aureus*; disc 1 is treated with 20 μ l balsam, disc 2 with 20 μ l ethanol, (used to make the extraction) and disc 3 with 20 μ l chlorhexidine 0.2%, (a known antiseptic). Disc 1, similar to disc 3, has almost no colonies on it; compare with the ethanol-treated disc 2 (Moussaieff, et al., 2005).

Contraindications

Myrrh is approved by the US FDA as a safe, natural flavoring substance (Abdul-Ghani, et al., 2009). However, it should not be used by pregnant women as it is an abortifacient and emmenagogue (Brinker, 2001). People with sensitive skin should avoid topical applications containing myrrh, as it has been known to cause contact dermatitis (Lee and Lam, 1993). Raw myrrh can be taken internally in very small quantities, but too much will upset the stomach, thus myrrh in the raw form is generally used externally (Dharmananda 2003). The LD₅₀ value of Mirazid solution, a myrrh extract, is 3,139mg/kg in mice (Abdul-Ghani, et al., 2009) and the LD₅₀ value of myrrh oil is 1650mg/kg in rats (MSDS, 2005).

Current Use in Allopathic and CAM Therapies

The People's Republic of China is currently the leading consumer of myrrh medicinal products in the world (Nomicos, 2007). It does see use elsewhere, however; a cross-sectional study looked at how diabetics in Jeddah, Saudi Arabia treat

foot disorders (open wound, chronic ulcer, skin cracks). 52.9% of respondents said they had used CAM products, among which 37.4% said they used myrrh (Bakhotmah and Alzahrani, 2010). Although there are a plethora of products containing myrrh on the market today, most of them are fragrance products. Tom's of Maine produces a toothpaste containing myrrh, which is marketed as a fluoride-free option that, along with propolis, "promote[s] a naturally clean, healthy-mouth feeling" (Bonapace, et al., 2002). Frankincense & Myrrh offers a line of homeopathic treatments for neuropathy, fibromyalgia, cold and flu prevention and sinus relief. All of them contain myrrh oil as an "inactive ingredient," and the sinus and cold & flu treatments contain "myrrha" as an active ingredient, cited as an antibacterial/anti-inflammatory. The sinus rubbing oil is dosed at 10-30 drops rubbed onto chest and throat, up to three times a day. The cold and flu prevention rubbing oil ("a topical immunity booster") is dosed at 10-30 drops massaged onto feet and ankles before bed or after waking, every day ("Frankincense & Myrrh," 2007).

Discussion

Myrrh has been an exceptionally useful plant to humans for a very, very long time. We are leaning more and more about the various mechanisms of action it can have and the benefits it confers. It is highly likely in the future that we will see it increasingly used in both CAM and allopathic treatments. It is generally safe despite some warnings, and is already beloved as a fragrance and religious symbol throughout the world. However, before we can begin to once more use myrrh as widely as someone like Celsus would have had us do, more research needs to be done into the activities of specific compounds in the resin, oil and gum components of myrrh. For example, the myrrh extract Mirazid has shown both

extreme promise and equal measures of disappointment in clinical and experimental treatments of helminthic diseases like schistosomiasis. More thorough, strictly controlled evidence is needed to determine whether or not this product shows real results, but it certainly seems to have promise.

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Croton lechleri Müll.-Arg., Euphorbiaceae

Latavia Carroll

Introduction

Croton lechleri Müll.-Arg. is a member of the Euphorbiaceae family, consisting of plants that are known for the dark resins they produce. *Croton* has red latex that is released from its bark when slashed (**Figure 1**). This species is mostly found growing in Mexico, Venezuela, Ecuador, Peru, Colombia, Bolivia, and Brazil (Gupta, 2008; Jones, 2003). This species has many different uses including treatment of diarrhea, wound healing, treatment of tuberculosis, bone cancer, to treat insect bites, stomach ulcers, and it is used to promote healing after an abortion or used as a vaginal douche after childbirth (Castner, page 46). It also has other therapeutic uses as an antimicrobial, antiviral, anti-inflammatory, and



Figure 1. *Croton lechleri* tree. (Taken by Ricarda Riina, 2009. <http://cms.herbalgram.org>).

antioxidant (Gupta, 2008). Some common names of this species include: Sangre de grado, sangre de drago, sangre de dragon, dragon's blood, drago, sangue de drago, and sangue de agua. In Belize it is called kush-uh-che; in Mexico: shonashe; in Honduras: pela nariz, and in Cameroon it is called ebine, enok, ndouon, or nouogui (Quattrocchi, 2000). There are more than 750 species within the genus, *Croton*, that are found all over the world (Duke, page 411). The phytochemistry of dragon's blood consists of alkaloids: sinoacutine, found in the leaves, and taspine, found in the sap; as well as proanthocyanidins, diterpenes, steroids, and lignans. All of these different chemical constituents provide the synergy that makes dragon's blood bioactive.

Botanical description

As mentioned previously *Croton lechleri* grows in the Amazon rainforest of Peru, Colombia, Bolivia, and Ecuador where the climate is very wet and humid. This species is a tree that grows at a fast rate of 10-15 meters in three years and is usually found at elevations of 100-600 meters (Jones, 2003). It can grow between 10-20 meters high and usually has a diameter of 30 cm (**Figure 2**). *C. lechleri* is also known as a pioneer species because it is usually one of the first plants to appear in areas that have been cleared and along roadsides (Ubillas et al., 1994). The dark green leaves of this tree are heart-shaped and are characterized by a long narrow drip-tip at the end of the leaves (**Figure 3 & 4**). The leaves tend to grow in clusters towards the ends of the branches, and can range in size from 13-30 cm long by 15-30 cm wide. There are

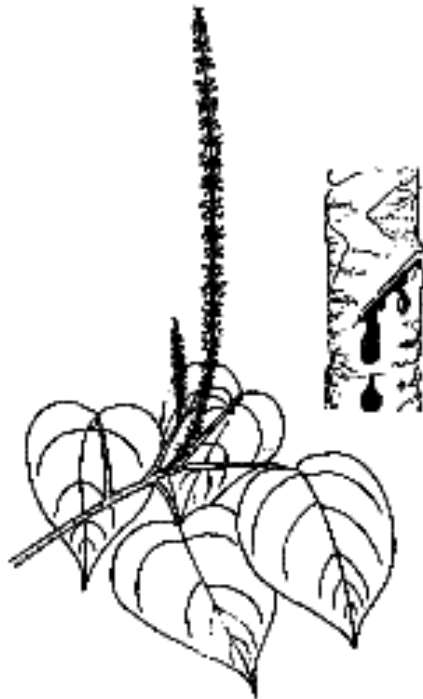


Figure 2. *Croton lechleri* Müll. Arg. (Source: <http://www.rain-tree.com/Plant-Images/sangre-pic.htm>).

three main veins that palmate from the leaf base, as well as 6-8 obvious parallel secondary veins that diverge diagonally from the mid-vein. The larger veins and petiole are covered with tiny bumps or hairs that rub off, and the smaller veins have a dotted appearance (Castner, page 46). The greenish-white flowers bloom on a tall slender upright stalks that can be from 30-50cm long (**Figure 4**). The fruits of this tree are brown, three-parted capsules (**Figure 5**).

Traditional uses

The name “dragon’s blood” dates back to the 1st century AD when a Greek sailor wrote in a shipping manual called the



Figure 3. A volunteer holding a bundle of *C. lechleri* leaves, 2008. (Source: <http://cms.herbalgram.org>).

“Perilous of the Eritrean Sea” about a tree that yielded drops of cinnabar on the island of Discordia (Gupta, 2008). Spanish naturalist and explorer P. Bernabe Cobo observed and recorded that *Croton lechleri* was widely used throughout the indigenous tribes of Mexico, Peru, and Ecuador in the 1600s. This information can be found in the Mateo’s: Biblioteca de Autores Espanoles Series of 1956 in volumes 91 and 92 (Gupta, 2008).

Sangre de grado is used in traditional Ecuadorian and Peruvian medicine to treat diverse illnesses in adults, children, and infants (Jones, 2003). Its internal ethnomedical uses were for treatment of diarrhea, dysentery, cholera, coughs, flu, lung problems, stomach ulcers, and hives. Hives were treated by



Figure 4. Close-up picture of the flowers and leaves of *C. lechleri*. (Source: Photo taken by Leslie Taylor, 2000. <http://www.rain-tree.com/Plant-Images/sangre-pic.htm>).

orally taking the sap in pineapple juice at a dosage of 20 drops per 200 mL (Jones, 2003). In the upper Amazon, the sap is taken diluted in hot water to speed internal healing after an abortion, and used as a vaginal douche after childbirth (Jones,



Figure 5. Fruits of *C. lechleri*. (Source: Photo by: Brian A. Smith, 2006. http://www.discoverlife.org/mp/20p?see=I_GEO374).

2003). The sap is also used to treat tuberculosis and bone cancer, and is used externally to treat insect bites, stings, and for wound healing (Jones, 2003). The sap is also used in the healing of open sores in the mouth or on the body, as well as for herpes infection. The Quijos Quichua of eastern Ecuador soak a piece of cotton in the sap form dragon's blood and apply it to alleviate the pain of tooth extractions and cavities. The traditional internal dosage of the sap in Ecuador and Peru is generally 5–10 drops, once to twice per day for 5 days, but often the treatment is repeated for as long as 3 weeks. The sap is taken in water (cold or warm), milk, or alcohol (Jones, 2003). The yield of latex from *C. lechleri* is traditionally dependent on the age of the tree. The sap is usually harvested by slashing from a tree up to 6 years old with a diameter of about 25 cm. Felling the tree and scoring the bark produces about 5–6 L of sap, which is why is the preferred method for industrial scale production (Ubillas et al., 1994).

C. lechleri is also used in African-American folk magic or voodoo where the resin is used in mojo hands for money-drawing or love-drawing; it is used as an incense to cleanse negative entities or influences. In neopagan witchcraft, it is used to increase the potency of spells for protection, love, banishing and sexuality (Gupta, 2008).

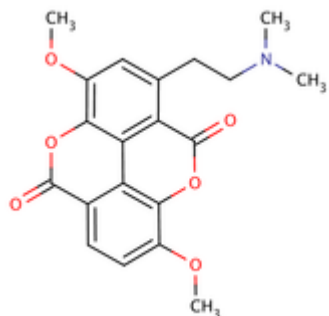


Figure 6. Taspine. (Source: <http://en.wikipedia.org/wiki/>).

Chemistry and Pharmacology

A list of chemical constituents of *C. lechleri* were taken from the text of Jones, 2003 and typed into table format (**Table 1**). Taspine, 3', 4-O-dimethylcedrusin, and proanthocyanidins make up about 90% of the weight of dried dragon's blood (Cai et al., 1991). These chemical compounds are also responsible for the wound healing properties of dragon's blood. An *in vivo* study on female Wistar rats was conducted by Pieters et al. 1995 to determine the wound healing activity of dragon's blood. The study concluded that the proanthocyanidins stimulated contraction of wounds cut into the rats' back and formation of crust; 3', 4-O-dimethylcedrusin stimulated formation of new collagen, and regeneration of the epithelial or top-skin layer (Pieters et al., 1995).

Antimicrobial activity of chemical compounds 2,4,6-trimethoxyphenol and 1,3,5-trimethoxybenzene at amounts of 0.0003 µg showed high potent activity against the bacteria, *Bacillus subtilis*, which at this small amount was thirty times more active than chloramphenicol and penicillin (Chen et al., 1994). Crolechinic acid was also active against *B. subtilis* and *E. coli* at administered amounts of 0.2 µg and 1.0 µg,

Alkaloids	Ligans	Proanthocyanidins and Flavonols	Steroids	Diterpenes
Sinoacutine	3', 4-O-dimethylcedrusin	(+/-)-galloepicatechin	β-sitosterol-	Bincatriol
Taspine		(-)-epicatechin	β-D-glucopyranoside	Crolechinol
Magnoflorine		(+)-catechin	β-sitosterol	Crolechinic acid
Isoboldine				Hardwickiic acid
Norisoboldine				Koberins A and B
Glaucine				
thaliporphine				

Table 1. Some of the chemical constituents found in *Croton lechleri*.

respectively. And Korberins A and B at administered amounts of 0.04 µg and 0.05 µg also showed activity against *B. subtilis* (Chen et al., 1994).

According to an *in vitro* study conducted by Chen et al., 1994, taspine, a major chemical constituent in dragon's blood (**Figure 6**), was determined to have potent cytotoxicity against KB cells (human oral epidermoid carcinoma). Taspine was able to inhibit KB tumor cell growth by 50% at a concentration of 0.39 µg/mL (Itokwa et al., 1991). The mechanism of action is not known, but it is believed to be the result of immunostimulation that cytotoxicity (Chen et al., 1994).

Biological Activity

In vitro studies

Pereira et al. 2010 conducted an *in vitro* study on the effects of de grado on cutaneous neurogenic inflammation (CNI). The procedure for how the plant extract was prepared was not mentioned, but concentrations of 1%, 0.1%, 0.01%, and 0.001% were made. These different concentrations of extract were applied to cell cultures made up of porcine or swine skin

cells and a co-culture of dorsal root ganglion neurons and keratinocytes, to examine sangre de grado's ability to reduce substance release of cutaneous neurogenic inflammation. The results yielded that there was a dose-dependent decrease in substance P release after ten minutes of incubation at concentrations of 1% with an average of 32% and at 0.1% with an average of 26%. This suggests that sangre de grado does inhibit cutaneous neurogenic inflammation. The second part of the study looked at sangre de grado's effect on substance P release when induced by capsaicin. The results yielded that after a one-hour incubation, substance P was strongly inhibited and after a 72-hour incubation, substance P was completely stopped. The study concluded "that sangre de grado is a potent inhibitor of CNI through direct inhibition of neuropeptide release by sensory afferent nerves," but more studies need to be conducted to determine which compounds in the plant were responsible for the activity (Pereira, 2010).

An *in vitro* study of SP-303 showed antiviral activity against Herpes simplex viruses (HSV-1 and HSV-2), when applied topically to infected guinea pigs. The inhibition of the thymidine kinase mutants of the viruses by SP-303 is probably done at the plasma membrane level where penetration and/or absorption are interrupted during the early stage of viral activity (Barnard et al., 1993; Ubillas et al., 1994).

An *in vitro* study conducted by Rossi et al., 2003 examined the mutagenic, antimutagenic, and antiproliferative potential properties of sangre de drago. Sangre de drago was determined to have antiproliferative effects on the human myelogenous leukemia K562 cells. The mutagenic and antimutagenic activity of *C. lechleri* sap was evaluated by means of the Ames/Salmonella test. There was no mutagenic activity found on neither of the Salmonella typhimurium strains T98 and T100. On the other hand, the sap showed an inhibitory effect against the mutagenic activity of mutagen 2-

Aminoanthracene in the presence of S9. And a moderate protective activity was shown against mutagens Sodium Azide and 2-Nitrofluorene. Therefore it was suggested that *C. lechleri* sap interacts with the enzymes of the S9 mix, thereby inhibiting the transformation of 2-Aminoanthracene into its active forms (Rossi et al., 2003).

In vivo studies

Froldi et al. 2009 conducted a study on the activity of sap from *C. lechleri* on rat vascular and gastric smooth muscles. The sap was collected in a traditional way by cutting it from a tree growing in Napo river region of Ecuador. The voucher code No: sangre de grado 005 for the crude drug was sent to the Department of Pharmaceutical Sciences of Padua University. The study revealed "*Croton lechleri* increased contractile tension in a concentration-dependent way for both the vascular and gastric smooth muscles of rats" (Froldi, 2009). The purpose of the study was to look at how the sap increased contractile tension by observing if regulation of certain receptors and ion channels by pharmacological drugs could stimulate the activity of sangre de grado. The drugs used were atropine, a competitive muscarinic antagonist; prazosin, a selective antagonist of α_1 -adrenergic receptors; ritanserin, a 5-HT_{2a} selective antagonist. All of these drugs had no effect on the vasoconstriction of sangre de grado, so therefore were not responsible for its activity.

Clinical Studies

Dragon's blood has many different traditional uses that have been shown to be beneficial through scientific studies conducted. But one particular illness that has been explored more in the potential development of drugs is diarrhea.

Diarrhea is a big problem, especially in underdeveloped areas where access to conventional medicines is limited. But another important issue that Daniel DiCesare et al. 1998 explored was traveler's diarrhea, particularly people that traveled to Jamaica and Mexico. He and his colleagues conducted a clinical trial in which 184 people from the United States with diarrhea from traveling to Jamaica and Mexico participated in a double-blind, placebo-controlled study of SP-303 or Provir, a plant-derived from *C. lechleri* with antisecretory properties. The purpose of the study was to determine the effectiveness of three doses of SP-303 given to patients four times a day for 2 days in treating and reducing acute diarrhea. Provir is a large heterogeneous natural polymer that breaks down in the presence of gastric or stomach acid and the mechanism of action of this drug is inhibition of intestinal chloride channels. The study concluded that Provir shortened the duration of diarrhea by 21% and the optimal dosage was determined to be between 125-250mg given 4 times a day for 2 days. The drug was also well tolerated with no side effects which are probably due to the fact that it is minimally absorbed by the body (DiCesare, 1998).

Another developed drug, Crofelemer, is currently in the clinical trial phase for treatment of secretory diarrheas associated with acute infections like cholera, chronic diarrhea related to HIV/AIDS, and diarrhea-predominant irritable bowel syndrome. Crofelemer is a dark reddish-brown powder that consists of proanthocyanidin oligomer extracts from the latex of *C. lechleri* (Figure 7). According to Lukmanee et al. 2009, Crofelemer gets its antisecretory and antidiarrheal properties by inhibition of two major apical membrane transport processes involved in intestinal fluid transport. These two apical membrane Cl⁻ channels are

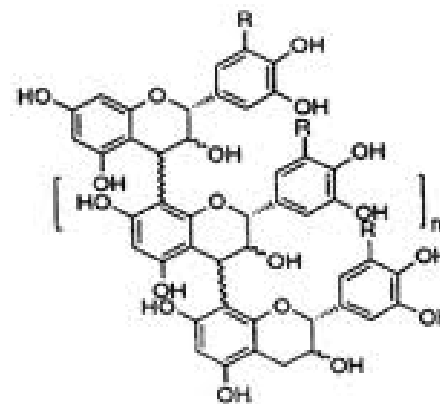


Figure 7. Chemical structure of Crofelemer. (Source: <http://www.theannals.com/content/44/5/878.abstract>).

cAMP-stimulated cystic fibrosis transmembrane regulator (CFTR) and calcium-stimulated (CaCC). The mechanism of action of Crofelemer in net reduction of Cl⁻ secretion is probably the result of inhibition of one or more transporters involved in transcellular Cl⁻ secretion such as basolateral Na⁺/K⁺ pump, NKCC symporter, or K⁺ channels.

Contraindications

Given the cytotoxicity of taspine, it is recommended that sangre de drago saps containing a high content of the alkaloid should not be used for wound-healing or for internal use (Chen et al., 1994). The latex on the other hand is considered non-toxic and is well-tolerated in clinical studies. According to Ubillas et al., 1994, there are no report side effects in traditional medicine of taking the sap of dragon's blood internally.

A study conducted by Bussmann et al., 2011 used a brine-shrimp assay to test the toxicity of medicinal plants used in

traditional medicine in Northern Peru. The results concluded that *Croton lechleri* was not toxic when prepared traditionally as an aqueous extract for oral or topical use, but it was very toxic when an extract was prepared with ethanol.

According to the scientific literature, *C. lechleri* is considered to be non-toxic and well tolerated, but there is no research concerning its effect on pregnant or lactating mothers.

Current us in Allopathic and CAM therapies

Published in 2010, a survey was conducted by Kazhila and Marius on plants used to manage HIV/AIDS opportunistic infections in Katima Mulilo, Caprivi region, Namibia. The purpose of the article was to collect and record knowledge of plants traditional healers used to treat illnesses related to HIV/AIDS. *Croton lechleri* was one of the 72 species used that was listed in Table 1 of article. The common name for *C. lechleri* was tassel berry, but the local name was mukena. Traditional healers use the bark of mukena to form a drink that treated diarrhea, lack of appetite, and anemia. The procedure for how the drink was prepared was not mentioned and neither was the mechanism of action. However, the article did mention that most plants used to treat AIDS-related opportunistic infections contained flavonoids, which have anti-oxidant properties that inhibit free radical production and tissue damage associated with the onset of AIDS (Chinsembu, 2010). This survey is important because it is the basis for identifying plants with anti-HIV active compounds, which could led to the development and usage of new drugs in allopathic therapies.

A study conducted by Miller et al., 2001, examined the potential soothing effect of a 1% sangre de drago balm (Zangrado Bug Bite Balm, Rainforest phytocecuticals) on

itching and pain caused by insect bites. The study involved ten workers from the Terminex Pest Control Company in New Orleans, LA who applied the balm topically to insect bites of fire ants over a period of three months. The results showed that the workers experienced relief less than two minutes after applying the balm. This result provided evidence that sangre de drago inhibits sensory nerve afferent activity, but the mechanism is unknown (Miller et al., 2001).

Shaman pharmaceuticals was a company that based its development of natural products from the knowledge of traditional healers. Shaman is the creator of Provir, which at first was identified as a potential treatment for respiratory syncytial virus, but after Shaman scientists witnessed use of *C. lechleri* for a cholera outbreak in Peru of 1993, its target was switched to diarrhea treatment. As mentioned previously, Provir works by slowing down loss of water in secretory diarrhea and allows the body to get rid of toxins and bacteria at a gradual pace. Shaman is also the creator of Virend, a topical formulation of the polyphenol found in Provir, SP-303. Unfortunately this drug died in Phase III trials for herpes and Shaman did not have enough money to support its trials and had to file for bankruptcy. On August 18, 2005 Shaman pharmaceutical was no more, but it was later bought by Napo pharmaceuticals.

Discussion

Croton lechleri is an amazing plant that as many different uses in South America and the United States. Most of its uses such for wound healing, pain relief of insect bites, treatment of herpes, treatment of diarrhea, and other uses have been demonstrated in lab settings, where these properties have been shown to be effective. This plant has been important in the past to traditional cultures and it has now become

important in more developed nations where the need for new effective drugs is of constant need. As time goes on and more is learned about this plant and the compounds responsible for its activity, there will be great advancements in treatments and medicines available to humanity.

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Curcuma longa L., Zingiberaceae

Ashvi Mittal

Introduction

Plants have been used medicinally throughout history by various regions, cultures, and societies in the world. One such plant with deep historical roots is *Curcuma longa*, commonly known as Turmeric (**Figure 1**). The plant belongs to the Zingiberaceae family. The name 'turmeric' is derived from the ancient Medieval Latin name *terramerita*. This transformed into *terre merite* in French, meaning meritorious Earth (P.N. Ravindran, 2007). This was the original name that powdered turmeric was referred to in commercial practices. A few modern common names associated with the plant today include Haldi (Hindi), Saffron de India (French), acafrao de india (Portuguese), Ukon or Gajyutsu (Japanese), kurkuma (German), Daruhaldi (Arabic), Chiang husang (Chinese) Kha min chan (Thai) and Ulgeum or Gangwhang (Korean) (Aggarwal, Sundaram, Malani, & Ichikawa, 2007a; Jansen, 2005),(P.N. Ravindran, 2007).

C. longa is believed to have originated in South Asia, primarily India. Researchers believe that turmeric was introduced to India through ancient tribal groups during their migration from present day China (P.N. Ravindran, 2007). It has been used in Asian medicines since the second millennium BC. It is mainly used in South and East Asia as part of Traditional Chinese Medicine and Ayurveda (Aggarwal et al., 2007a). Turmeric is significantly known for its anti-inflammatory effects in treating muscle sprains, swelling, arthritis, and rheumatism. It also provides protection against high cholesterol levels, angina, irritable bowel syndrome, liver



Figure 1. Photograph of the rhizomes and powder of *Curcuma longa* (Image source: <http://www.natural-healing-with-foods.com/turmeric.html>)

diseases, and bacterial infections (Goel, Kunnumakkara, & Aggarwal, 2008; Society, 2008) Moreover, some researchers believe that turmeric has the potential to treat certain types of cancers including breast, skin, and stomach cancers (Society, 2008).

The majority of these diverse properties of the plant are due to the main compound in turmeric known as curcumin. The phytochemicals in curcumin are responsible for the yellow color of the plant (Goel et al., 2008). The compound displays a

wide array of properties such as antifungal, antiviral, anti-inflammatory, antioxidant, and anticancer activities. It is also effective against health conditions such as diabetes and arthritis (Pari L, 2008). In addition to acting as a medicine, *C. longa* is used as a spice in culinary practices, herb in religious rituals, and a coloring agent for dyeing clothes (Muhammed Majeed, 1996).

Botanical Description

Curcuma longa is well known to be a perennial herb which grows about 3-5 feet high. The plant is cultivated primarily in tropical areas of Asia, namely China and India (Stewart & Costerton, 2001). Its pointed, oblong leaves are about two feet long with a consistent green color surrounded by yellow-tinted funnel shaped flowers (Stewart & Costerton, 2001). The plant has tuberous roots like bulbs that produce rhizomes which are used medicinally. In its fresh condition, the roots emit a spicy and aromatic odor (Jansen, 2005). The rhizomes are commonly transformed into a yellow powder by boiling, cleaning, and drying (**Figure 2**) (Stewart & Costerton, 2001). *C. longa* generally thrives in warm and moist environmental habitats. It is usually grown in the tropical regions with about 640-4200 mm of rainfall (P.N. Ravindran, 2007). The plant is grown well in soil that is well drained, fertile, loamy, or alluvial as it cannot tolerate alkaline soil conditions (P.N. Ravindran, 2007). For the efficient growth of rhizomes, stony and bumpy areas are not preferred. The optimum temperature for the sprouting of rhizomes is 25 to 35° Celsius. The plant is capable of growing in shaded areas; however, an exposure to the sun can enhance its growth. The flowers blossom about five months after planting and approximately 7-10 months after the rhizomes have matured, the yellow coloration of leaves begins to appear (Jansen, 2005)



A B C D

Figure 2. Illustrations of *Curcuma longa* in various forms

Turmeric as a botanical illustration (**A**) and as a full grown plant with green leaves and tinted yellow flowers (**B**). The tuberous roots of the plants produce rhizomes (**C**). These are further boiled, cleaned, and dried to produce a powdered form (**D**). (Image sources: <http://www.philographikon.com/botanicalsregault.html>- **A**; http://database.prota.org/dbtwwpd/exec/dbtwwpub.dll?ac=qbe_query&bu=http://database.prota.org/se_arch.htm&tn=protab~1&qb0=and&qf0=Species+Code&qf1=Curcuma+longa&rf=Webdisplay -**B**; <http://www.marxfoods.com/Fresh-Turmeric-Rhizomes> -**C**; <http://organicindia.mercola.com/herbal-supplements/turmeric.aspx> -**D**)

Turmeric is also prone to certain herbivorous invaders. One such feeder is *Taphrina malucans* which is responsible for a disease called leaf spots on the plant (Jansen, 2005). The leaves of the contaminated plant are dried up by the rhizome rot, causing the rhizomes to turn brown. The best way to control this phenomenon is to burn infected plants, and sometimes, it is recommended to sanitize the soil using a fungicide (Jansen, 2005). Examples of fungicide used to treat



Figure 3. *Udaspes folus*, commonly known as the grass demon, feeds on the leaves of *Curcuma longa*.

(Image Source: <http://www.butterflycircle.com/checklist%20V2/CI/index.php/start-page/startpage/showbutterfly/283>)

the soil include mancozeb and metalaxyl. In several Asian countries such as India, caterpillars such as *Udaspes folus*, commonly known as the grass demon, is the main insect that feeds on the plant (**Figure 3**). In several countries of Africa, a sucking insect named *Aspidiella harti* nourishes on the plant's rhizomes (Jansen, 2005).

Traditional Uses

The history of *Curcuma longa* in Asian medicine dates back to the second millennium BC (R.A. Sharma, 2005). Turmeric was initially cited in the *Atharvaveda* wherein it was prescribed to cure jaundice (P.N. Ravindran, 2007). It was introduced in China before the 7th century and to Africa in the 13th century. The spice was first brought to the West, essentially to Europe by Arab Sailors (Aggarwal et al., 2007a). The plant was also listed as a coloring agent in the writings of Marco Polo



Figure 4. Movement of *Curcuma longa*.

Turmeric is believed to originate in Asia, primarily in India and later spread to the West via the spice trade.

(Image source: <http://ancientstandard.com/2011/02/11/how-cooking-changed-the-face-of-the-earth-the-spice-trade/>)

regarding his 1280 AD journey to China and India (Aggarwal et al., 2007a). Turmeric was exposed to North America during the British colonial rule over America (**Figure 4**). It was then that turmeric combined with a variety of other spices and remained curry power in the West (Aggarwal et al., 2007a). Today, *C. longa* is primarily grown in South and East Asia and some home gardens in parts of Africa. It is used not only as medicine, but also as a beauty care agent, spice, religious herb, and a coloring agent (P.N. Ravindran, 2007). The spice is widely used as a culinary enhancement to enrich foods with its vivid yellow color and flavor. In the West, it is also used in mustard and to give color to milk products such as cheese ("Turmeric", 2011).

Medicinal

C. longa has been traditionally used to treat a wide variety of ailments across Asia and Africa such as skin, pulmonary, gastrointestinal diseases, aches, wounds, and liver disorders (Aggarwal, Sundaram, Malani, & Ichikawa, 2007b). India is considered to be the central hub of the cultivation and application of turmeric. The spice has been used as part of Ayurvedic medicine (Ayurveda) for more than 6000 years. It was applied as a blood purifier, used internally as a tonic for stomach infections, and employed externally for skin diseases. About half to one gram of powder was taken for relieving dyspepsia and flatulence (Muhammed Majeed, 1996). In order to cure nasal mucus, the fumes of burning *C. longa* were inhaled which led to a discharge of the mucus relieving blockage. In addition, turmeric was often boiled with sugar and milk as an ancient remedy for the common cold (Muhammed Majeed, 1996). The fresh rhizomes were used to make medicinal juices to heal skin infections, wounds, sprains, and inflammations. The powder made from these rhizomes was often mixed with olive oil to enhance and soften the skin.

In rural villages in the Northern part of India, it is common to get eye diseases (Pandeya, 2005). This is due to a lack of availability of health practitioners and antibiotic ointments to cure such diseases. In these cases, the native people use turmeric which they refer to as haldi, as a means of treatment and prevention (Pandeya, 2005). In the villages it has become a folklore that if people do not include turmeric in their daily diet then they will be infected with diseases which may kill them (Pandeya, 2005). Turmeric paste is applied to the infected regions surrounding the eye. Generally, one ounce of turmeric is added to twenty ounces of water to form a mixture. This mixture is then used as a cooling eyewash to heal an infection known as 'country sore eye.' In addition, after the neonatal period, women make a paste of turmeric

with powdered ginger and mix in a hot glass of milk as a tonic drink to stay healthy. It is also believed that applying turmeric poultice is beneficial in the healing of lacerations of the birth canal (Pandeya, 2005). In addition, neem leaves and turmeric powder was used as an anti-septic to treat chickenpox and smallpox. Turmeric was applied to the body and a bath was taken in boiling water with neem leaves. The ash of the rhizomes was also believed to cure the eruptions caused by the infection (P.N. Ravindran, 2007).

In many African countries such as Ethiopia and Madagascar, turmeric is grown in many residential home gardens. The rhizomes of turmeric are considered to be highly aromatic and contain antibacterial properties (R.A. Sharma, 2005). The locals commonly use the rhizomes as an ailment for bronchitis, cold and, asthma (Pari L, 2008). The juices formed from rhizomes are believed to be an effective remedy for several skin and eye infections (Jansen, 2005).

Rituals/Beliefs

Hindus believe turmeric to be sacred and auspicious. In a few tribal communities in the southern states of India such as Tamil Nadu, a piece of turmeric is tied to a string which is believed to be a sacred nuptial string (P.N. Ravindran, 2007). This practice is still prominent in many areas of South India today. In addition, a piece of turmeric is tied on the hand along with an amulet as a way to fight evil spirits (P.N. Ravindran, 2007). The upper class societies use a natural yellow rhizome in the form of a gold chain, whereas, the lower class and poor rely on turmeric alone.

Traditionally, *C. longa* was used to give yellow coloration to clothing during religious festivals. The villagers believed that the yellow color was associated with Lord Krishna who only



Figure 5. Indian yellow rice prepared with turmeric

(Image Source:

<http://www.lifesambrosia.com/category/recipes/cuisine/indian/>)

wore yellow attires. In addition, in many rural and urban communities, turmeric is used during marriage preparations and ceremonies. Before marriage, turmeric and oil are applied on the bride and their groom by their relatives (P.N. Ravindran, 2007). In the state of Punjab in Northern India, the elders of the community place rice and an areca nut between the joined hands of the couple. Their hands are tied with dyed turmeric seven times. The couples' parents pour turmeric water from a leaf seven times over their hands to conclude the marriage ceremony.

In East Asia, *C. longa* has been an essential component of Traditional Chinese Medicine throughout history. In Indonesia, the yellow color derived from the spice is used in cooking yellow rice called nasi kuning (Aggarwal et al., 2007a). The nasi kuning has religious significance and is believed to be a sacred dish as it is sacrificed to the Gods (Aggarwal et al., 2007a).

Culinary

Turmeric remains a primary ingredient in culinary practices today. It is frequently used to give rice and Indian curry their yellow hue (**Figure 5**). It is added as a relish in authentic dishes and gives food its necessary spice and color ("Turmeric", 2011). In the South East Asia region, the native people prefer turmeric dry. In Thailand, fresh rhizomes are used to embellish curry dishes and to make yellow curry paste (Aggarwal et al., 2007a).

Coloring Agent

In India, turmeric was believed to be used as a coloring dye by the British. They used the plant as a coloring agent for commercial purposes and monetary gain. In the city of Calcutta, the dyers make a bright yellow hue called *basanti rang* by mixing it with lemon and the carbonate of sodas (P.N. Ravindran, 2007). The plant was also used to make shades of green and indigo. First, the cloth was dyed with indigo and then exposed to a mixture of turmeric. In addition, the Indian Calico printers mixed turmeric with alum and pomegranate to make a dye (P.N. Ravindran, 2007). The mixture was later used to color silk and wool to produce different shades such as browns and olives. Currently, *C. longa* is not applied as a commercial coloring agent.

In West Africa, rhizomes of the plant are used as yellow coloring dyes for products such as cotton clothing, thread, palm fibers, and tanned leather (Jansen, 2005). In Nigeria, a paste is made from the rhizomes with water and rubbed into tanned leather hides. This is a technique which is used to color leather. In Ethiopia, the cloth for coloring is placed into a boiling decoction of turmeric paste. This method is commonly used in many regions of Ethiopia to dye clothes (Aggarwal et

al., 2007a). In addition, in many Asian nations, turmeric is used to form different color combinations of yellow in cotton and silk clothing which is subsequently sold for household earnings (Jansen, 2005).

In European nations, the ground rhizome of turmeric is employed in the food industry as well as a coloring agent in several processed foods. In addition, turmeric is considered a cheaper substitute for saffron as it is utilized in pharmaceutical companies and textile industries (Jansen, 2005). Some European countries use turmeric in dyeing wool to make various shades of yellow and gold (Jansen, 2005). In North America, the oils of *C. longa* have been labeled as Generally Recognized as Safe (GRAS) (Jansen, 2005)

Chemistry and Pharmacology

Curcuma longa comprises of a wide range of compounds (Table 1). The plant contains essential macronutrients such as minerals (3.5%), fats (5.1%), protein (6.3%), moisture (13.1), and carbohydrates (69.4%) (Ishita Chattopadhyay, 2004). The leaves are rich in various types of acids such as o-coumaric acid, protocatechuic acid, astringic acid, and vanillic acid (Duke, 2012). The essential oils consist primarily of monoterpenes and sesquiterpenes. The root of the plant contains bisabolene and boron. The rhizomes contain the largest variety of chemical constituents which include polyphenols, monoterpenes, flavonoids, curcuminoids, carotenes, alkaloids, minerals, fiber, and water (Araújo & Leon, 2001; Duke, 2012). The primary compound of *C. longa* found in the rhizomes is curcumin (Figure 6). The compound is a polyphenol, responsible for the yellow color of turmeric and comprises approximately 2-5 percent of the spice (Aggarwal et al., 2007a). The phytochemical has hydrophobic properties and is soluble in several substances ranging from oils, ethanol,

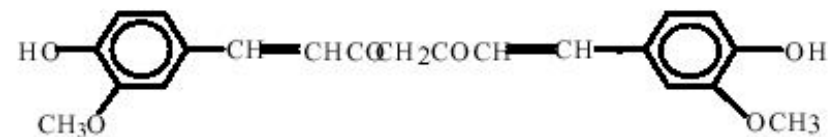


Figure 6. Chemical structure of curcumin (main compound in *C. longa*) (Image source: <http://www.scielo.br/img/fbpe/mioc/v96n5/html/404001.html>)

to acetone (R.A. Sharma, 2005). When curcumin is taken orally, it is broken apart into curcumin glucuronide and curcumin sulfonate. However, upon systematical administration it is metabolized into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol (Aggarwal et al., 2007a). Curcumin acts by down regulating iNOS enzymes and COX-2 and suppressing the NFκB pathway (Appleton, 2011). It also inhibits the scavenging free radicals and proliferation of inflammatory cytokines (Appleton, 2011).

Biological Activity

Antioxidant Effects

Turmeric is known for its high antioxidant effects. This is due to curcumin behaving as a scavenger of oxygen free radicals (Ishita Chattopadhyay, 2004). In various *in vitro* studies, curcumin was found to inhibit the generation of reactive oxygen species by stimulating macrophages. These species include ROS, H₂O₂, and nitrate radicals. In transgenic mice with Alzheimer's disease, curcumin can decrease the oxidized proteins in amyloid pathology. In addition, it can reduce lipid peroxidation in rat brain homogenates, liver microsomes, and erythrocyte membranes (Ishita Chattopadhyay, 2004). Numerous studies have been conducted to examine

Plant Part	Active Constituents
Rhizomes	1-8 Cineole, 2-Hydroxy-Methyl-Anthraquinone, 4-Hydroxy-Cinnamoyl-Methane, Alpha-Atlantone, Alpha-Terpineol, Ar-Turmerone, Arabinose, Ascorbic Acid, Ash, Azulene, Beta-Carotene, Beta-Sesquiphellandrene, Bis Methane, Bis-Desmethoxycurcumin, Borneol, Caffeic-Acid, Carbohydrates, Chromium, Cinnamic-Acid, Cobalt, Copper, Cuminy-Alcohol, Curcumin, Curzone, Curzerenone, Cyclo-Isoprenemyrcene, D-Alpha-Phellandrene, D-Camphene, D-Camphor, D-Sabinene, Dehydroturmerone, Desmethoxycurcumin, Di-Coumaroyl-Methane, Didesmethoxycurcumin, Diferuloyl-Methane, Dihydrocurcumin, Eo, Fat, Fiber, Fructose, Gamma-Atlantone, Glucose, Guicacol, Iron, L-Alpha-Curcumene, L-Beta-Curcumene, Manganese, Monodesmethoxycurcumin, Niacin, Nickel, P-coumaric acid, P-Cymene, P-Tolymethyl Carbinol, Phosphorous, Potassium, Resin, Riboflavin, Sodium, Thiamin, Turmerone, Ukonan, Water, Zinc, Zingiberene
Leaf	O-Coumaric Acid, Protocatechuic Acid, Syringic Acid, Vanillic Acid
Essential Oils	Alph-Pinene, Beta-Pinene, Caryophyllene, Curcumene, Curcumenol, Curdione, Curzerenone-C, Eugenol, Limonene, Linalol, Terpinene, Terpineol,
Plant	2-Bornanol
Roots	Bisabolene, Boron,

Table 1. The chemical constituents of *C. longa* according to corresponding parts of the plant

(Source: Information obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases <http://www.ars-grin.gov/cgi-bin/duke/farmacy2.pl>)

curcumin's effect on lipid peroxidation (Araújo & Leon, 2001). It was consistently found that curcumin remains an effective antioxidant and restrains lipid peroxidation in rat livers (Pulla Reddy & Lokesh 1994). This lipid peroxidation plays an essential part in cardiovascular effects, inflammatory effects, and cancer (Araújo & Leon, 2001). Some extracts of *Curcuma longa* are fat and water soluble. These extracts along with curcumin exhibit strong antioxidant activities, comparable to vitamins C and E. One particular study of cardiac ischemia showed that a pretreatment with curcumin reduced ischemic injury (Thorne Research, 2002a).

In addition, curcumin's effects on endothelial heme oxygenase-1 were examined in a *vitro* study using bovine aortic endothelial cells. As a result of a seemingly incessant incubation of approximately eighteen hours with curcumin, an increase in the cellular inhibition to oxidative damage was detected. (Thorne Research, 2002a).

Hepatoprotective Effects

Several animal studies have been conducted to determine turmeric's hepatoprotective effects. This ability to prevent

liver damage is due to the anti-hepatotoxic compounds in the plant, which include carbon tetrachloride, galactosamine, acetaminophen, and aspergillus aflatoxin (Thorne Research, 2002b). These compounds decrease the formation of inflammatory cytokines (Thorne Research, 2002a).

In addition, an interesting study done on ducklings infected with fungus *Aspergillus parasiticus*, showed that turmeric extract reduced the production of fungal aflatoxin by ninety percent (Thorne Research, 2002a). Moreover, research suggests that curcumin may also be used to treat cholelithiasis, commonly known as gallstones. (Thorne Research, 2002a).

Anti-inflammatory Effects

Curcumin acts by inhibiting the NF-kB activation and decreasing the TNF-a-induced expression of the gene in endothelial cells (Ishita Chattopadhyay, 2004). The anti-inflammatory effects of turmeric are stimulated by the down regulation of cyclooxygenase-2 and inducible nitric oxide synthetase through repressing the NF-kB pathway (Ishita Chattopadhyay, 2004).

The volatile oils of turmeric along with curcumin produce anti-inflammatory effects. A study using rats with arthritis was performed in which curcumin was given orally. This caused a great reduction in the inflammatory swelling compared to the controls (Thorne Research, 2002a). Another study conducted on monkeys illustrated inhibition of neutrophil aggregation which is related to inflammation (Thorne Research, 2002a). In studies on mice with diabetes, curcumin has found to enhance the wound healing and the damage caused by H₂O₂ in human fibroblasts (Ishita Chattopadhyay, 2004). Curcumin can also be administered

topically to counter inflammation and irritation related to skin allergies (Thorne Research, 2002a).

Anti-carcinogenic/ Anti-tumor Effects

In vivo studies on rats and mice, have exhibited the ability of curcumin to inhibit carcinogenesis at three different stages: during tumor promotion, angiogenesis, and tumor growth (Thorne Research, 2002a). Studies examining colon and prostate cancer show that curcumin suppressed cell division and tumor growth (Thorne Research, 2002a). Several *in vitro* studies using human cell lines have indicated that turmeric has the capacity to restrain mutagenic and carcinogenic presence in various types of cells. This anti-carcinogenic effect of the plant is because of its antioxidant effects and the ability to help in hepatic detoxification of those carcinogens resulting in reduced nitrosamine production (Thorne Research, 2002a).

A study was conducted by Huang et al. (1988) examining the effects of ferulic acid, caffeic acid, chlorogenic acid, and curcumin on tumor growth in mice. It was discovered that curcumin was the most efficient in hindering the epidermal metabolism of arachidonic acid through the cyclooxygenase and lipoxygenase passages (Araújo & Leon, 2001).

Antimicrobial/ Anti-bacterial Effects

Essential oils of *C. longa* and its extracts are known to inhibit the proliferation of many types of bacteria, parasites, and fungi (Thorne Research, 2002a). An *in vivo* study conducted on chicks that had caecal parasite *Eimera* showed that the diets which were enhanced with one percent turmeric caused a decrease in small intestinal lesion scores and enhanced weight gain (Thorne Research, 2002a). In addition, a study performed on guinea pigs infected with pathogenic molds or

yeast showed that turmeric oil applied topically aided in the reduction of pathogenic fungi, however the curcumin did not have an effect on the yeast. The guinea pigs infected with fungi showed signs of improvements in the lesions. A week after the turmeric was applied to the animals, no lesions were detected (Thorne Research, 2002a).

In 1979, Murthy and Bhavani Shankar performed an *in vitro* study of turmeric fractions applied to intestinal bacteria. The results showed the inhibition of *Lactobacilli* growth when the bacterium was exposed to turmeric (Araújo & Leon, 2001). When examining the alcoholic extract, there were signs of inhibition but they were not as effective as the application of the whole fraction of turmeric (Araújo & Leon, 2001).

Cardiovascular Effects

Turmeric is also known to have positive effects on our cardiovascular system (Thorne Research, 2002a). These effects include lowering of triglyceride levels, cholesterol, and reducing vulnerability of low density lipoprotein to lipid peroxidation (Thorne Research, 2002a). It also aids in inhibiting platelet accumulation (Thorne Research, 2002b). An *in vivo* study performed on rabbits that were exposed to a low dose of turmeric extract showed a decrease in susceptibility of LDL to lipid peroxidation and reduced triglyceride levels. When the rabbits were exposed to a higher level of turmeric extract, the result indicated no decrease in lipid peroxidation of LDL, however there was a reduction in triglyceride and cholesterol levels. This occurred due to the decreased cholesterol uptake in the intestines and increase in exchange of cholesterol to bile acids found inside the liver (Thorne Research, 2002a). In addition, curcumin protects the harm caused by myocardial infarction by reducing the level of severity of pathological changes. It increases the chances of

pharmacological interventions to repair the calcium ²⁺ homeostasis in the cardiac muscle by improving the Ca ²⁺ transport (Ishita Chattopadhyay, 2004).

Gastrointestinal Effects

Several compounds in turmeric serve as effective protective agents of the gastrointestinal tract (Thorne Research, 2002a). *C. longa* is demonstrated to restrain the presence of ulcers due to factors such as stress, alcohol, indo methacin, pyloric ligation, and reserprine (Thorne Research, 2002a). A study done on rats who suffered with these gastrointestinal problems were found to have increased gastric wall mucus production when exposed to the plant (Thorne Research, 2002a).

Clinical Studies

There have been clinical studies performed which apply turmeric power in patients with respiratory ailments (Ammon & Wahl 1991). It was discovered that the patients felt relief of symptoms such as cough, dyspea, and sputum production. Other studies accounted improvement in eighteen patients with rheumatoid arthritis upon administration of the drug orally on a daily bases (Araújo & Leon, 2001)

Studies examining curcumin have occurred over the last fifty years. The compound is known for its anti-carcinogenic properties as it suppresses the growth of tumor cells (Anushree Kumar, 2003). Human clinical trials performed showed no-dose limiting toxicity when given at doses up to ten grams per day (Anushree Kumar, 2003). These studies indicated that curcumin had the ability to prevent and treat various types of cancers such as breast and colon cancer (Anushree Kumar, 2003).

Another study was performed testing curcumin in cancer treatment at initial stages (Society, 2008). Fifteen patients with colorectal cancer were examined to observe their intake of curcumin safely. It was found that the patients could take 3.6 grams of curcumin without any side effects (Society, 2008). Some curcumin and its compounds were detected in the blood at this level of high dose. The lower doses may be beneficial for the intestine and stomach (Society, 2008). Although, it does not absorb effectively in the body, curcumin is able to absorb into the cancerous tissues of the colon. It was recommended from the study that a high dose of curcumin should be used when examining effects outside of the intestine. Further research indicated that individuals were able to ingest ten grams of curcumin per day for a few weeks without observing any side effects (Society, 2008). Currently, researchers are focusing on combining curcumin with other compounds in order to increase the absorption rate in the body (Society, 2008).

An interesting study was conducted on women in Southern India who use turmeric in order to prevent acne and reduce growth of hair (Jasmine H Shaffrathul, 2007). Seventy three individuals including female nurses, visitors, and workers of a hospital were surveyed concerning the period and reason for their turmeric use. The individuals were inspected for signs of acne. Thirty five of the 75 subjects used turmeric daily, while the remaining did not apply turmeric. The results of the study indicated no statistical significance in the *p* value between the individuals with acne who utilized turmeric and ones who did not employ the herb (Jasmine H Shaffrathul, 2007). In addition, the subjects who used turmeric did not indicate a reduction in the growth of hair when compared to the individuals who did not use turmeric.

A recent clinical study examined the use of a distinctive extract of *C. longa* on patients with osteoarthritis. In Italy, a

team of scientists chose fifty patients with osteoarthritis in the knee in order to test a special formulation of turmeric known as Meriva ("Special Turmeric Extract Benefits Osteoarthritis Patients," 2010). After separating the individuals into two groups, the first group was exposed to the standard medical treatment by physicians, while the individuals in the second group were treated with curcumin extract in addition to the typical medical therapy. After a ninety day period, the individuals exposed to the extract had a 58 percent increase in their overall health and functionality when compared to the control group. Moreover, the Social and Emotional Index score for the Meriva patients increased by 300 percent, followed by a 16 fold decline of inflammation levels ("Special Turmeric Extract Benefits Osteoarthritis Patients," 2010). The most astonishing finding of the study was that patients treated with the turmeric extract reduced their use of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) by 63 percent when compared to the patients with the standard medical treatment ("Special Turmeric Extract Benefits Osteoarthritis Patients," 2010).

Contraindications

Turmeric is generally considered to be a low toxicity plant, especially when used as a spice in foods. However, there needs to be more research conducted to examine the side effects of using turmeric as a herbal remedy. It is believed that ingesting large amounts of the spice orally can lead to stomach pains, indigestions, and nausea. Long term exposure to the plant can further be a cause of stomach ulcers and skin rashes. Individuals who have allergic reactions to ginger products or food colorings are likely be allergic to turmeric. Furthermore, women who are pregnant or breastfeeding and individuals



Figure 7. The different forms of turmeric which are marketed: Capsules (A), Tinctures (B), and ground powder (C) (Images Sources: <http://www.nutritionexpress.com/natures+way/natures+way+turmeric+extract+500+mg+120+tablets.aspx> -A; <http://www.dinnervine.com/2012/01/turmeric-and-tinctures-and-rhizomes-oh-my/> -B; <http://www.masterfoods.com.au/products/productdetail/tabid/83/productid/1574/turmeric-ground.aspx> -C)

with bleeding disorders or a record of ulcers should avoid the use of turmeric (Society, 2008).

A study conducted in humans indicated that curcumin has the ability to make changes in the metabolism of oxalate. According to the results, the researchers cautioned individuals in using curcumin with conditions which can lead to kidney stones. In addition, people taking blood thinners should avoid the use of turmeric as a spice because it can cause detrimental herbal drug interactions (Society, 2008).

In various *in vivo* studies, it was found that turmeric can reduce the effectiveness of many anti-cancer drugs (Society, 2008). This is due to the antioxidant supplements which can intervene with the efficacy of cancer treatments such as radiation therapy and chemotherapy. It is often advised that people should not solely depend on turmeric to cure cancer as overuse of the plant can have side effects (Society, 2008).

Therefore, it is vital to inform our health care practitioners about any herbal supplements we taking. According to the National Center for Complementary and Alternative Medicine, turmeric is a safe plant for most adults. However, long term exposure or high doses of the spice can be a cause of indigestion and diarrhea. Many studies in animals have shown that intake of high doses may lead to liver illnesses. Moreover, individuals who have gallbladder infections should avoid the use of turmeric as a dietary supplement (NCCAM, 2007).

Current Use in Allopathic and CAM therapies

Curcuma longa persists as an essential part of Ayurveda and Chinese Medicine today. Auyrvedic medicine remains one of the oldest medical systems worldwide. Ayurveda is comprised in the subcategory of CAM: whole medical system (NCCAM, 2005). This category includes practices that have evolved over time. Ayurvedic therapies consist of herbs, massages, and specialized diets (NCCAM, 2005). Studies have exhibited that practice involves using herbal therapies which include curcuminoids. This is believed to aid in cardiovascular diseases. In addition, botanicals such as ginger, turmeric, and boswellia are used in NCCAM as a treatment for inflammatory illnesses such as arthritis and asthma (NCCAM, 2005) Turmeric is also used to cure dental related issues (Chaturvedi, 2009). The process for treatment can include rinsing the mouth with turmeric water for relief, massaging the paining tooth with ground turmeric to eliminate any swelling, employing turmeric powder with weed seeds to clean the gums, and applying turmeric paste (½ teaspoon salt, ½ teaspoon mustard oil) to prevent gingivitis and periodontitis (Chaturvedi, 2009).

Currently, there are not any drugs derived from this plant. However, the roots of turmeric are on the approved list of

Form of turmeric applied	Dose recommendation for adults
Cut root	1.5-3 g per day
Dried, powdered root	1-3 g per day
Standardized powder (curcumin)	400-600 mg, 3 times per day
Fluid extract (1:1)	30-90 drops per day
Tincture (1:2)	15-30 drops, 4 times per day

Table 2. The amount of dose recommended for adults according to the form of turmeric used.

(Source: <http://www.umm.edu/altmed/articles/turmeric-000277.htm>)

Supplement Facts

Capsules per bottle: 200

Amount Per 1 Capsule	%RDA
Turmeric Extract (Curcumin 95%) 500 mg	**

**Daily value has not been established.

Figure 8. Turmeric supplement marketed as containing ninety five percent curcumin. (Image Source: <http://www.turmeric-curcumin.com/>)

herbs which are accessible as a spice in local grocery shops (Society, 2008). The average turmeric consumed commonly by Asians ranges from .5-1.5 g/day/person producing no toxic symptoms or side effects (Ishita Chattopadhyay, 2004). *C. longa* is available in the form of a capsule, tincture, and ground powder (Figure 7). Extracts of pineapple called bromalein are

frequently combined with the products of turmeric as it has the ability to enhance the anti-inflammatory effects of curcumin ("Turmeric ", 2011). The supplements of turmeric have not been studied extensively in children; therefore there are no known recommended doses for children. However, there are suggestions of doses for adults (Table 2). Several sellers who market supplements of turmeric today argue that their products comprise of 95 percent curcumin compounds (Figure 8) (Society, 2008).

Discussion

The extensive use of *Curcuma longa* throughout history in Ayurvedic and Traditional Chinese Medicine is truly remarkable. Its wide array of uses as a spice, herb, medicine, dye, and various other applications enable the plant to cure and prevent numerous ailments. Moreover, the use of *C. longa* as a spice to give authentic foods its flavor and color remains an essential component of culinary practices today. Turmeric is beneficial for patients suffering from liver disorders, heart disease, diabetes, inflammations, osteoarthritis, and many other illnesses. Currently, turmeric is being studied to prevent aging, Alzheimer's disease, and most essentially cancer. There are numerous studies examining the ability of curcumin, the main compound in *C. longa*, in the treatment of cancer by inhibiting the proliferation of tumor cells. Despite widespread research on the possible medicinal applications of turmeric, there have not been any studies examining drug development of the plant. Today, curcumin is accessible in its pure form comprising of various biological activities. In the future, this could enable researchers to develop new drugs from curcumin by observing the pharmacological effects and mechanism of action of the compound. Curcumin may be employed as a

novel drug in the coming decades, which could prevent and treat a wide range of illnesses.

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Digitalis purpurea L., Plantaginaceae

Ian McCullough

Introduction

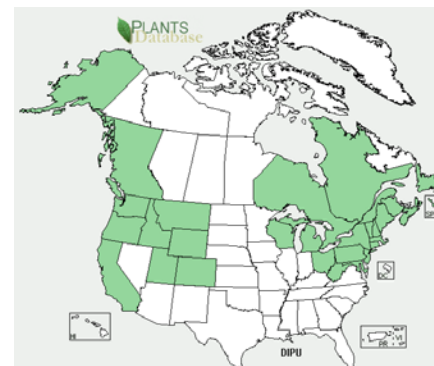
Commonly referred to as purple foxglove, *Digitalis purpurea* is a flowering plant in the Plantaginaceae family (USDA, 2012). *D. purpurea* is native to North Africa, Europe, as well as central and western Asia (Lin, Yang, Phua, Deng, & Lu, 2010). It was first mentioned in a Welsh Pharmacopeia published in the early 12th century AD, and was described as having blossoms which resembled a glove by Fuchsius in his 'De Historia Stirpium Commentarii Insignes,' published in 1542 (Rietbrock & Woodcock, 1985; Withering, 1785). Although *D. purpurea* has been used medically for over 700 years, the medicinal properties of *D. purpurea* were categorized by Withering in 1785 as a treatment for dropsy, which is now referred to as cardiac insufficiency or congestive heart failure resulting in edema (Whitfield, 1985; Withering, 1785). The medicinal value of *D. purpurea* results from high concentrations of potent cardiac glycosides it contains (Norn & Kruse, 2004). Two of these cardiac glycosides, digoxin, and digitoxin, have since become the most potent inotropic agents yet identified, as well as some of the most widely prescribed inotropic agents in the world (Rietbrock & Woodcock, 1985).

Botanical Description

Digitalis purpurea, also known as common foxglove or purple foxglove, is a flowering plant that is native to North Africa, Europe, as well as Asia (Lin et al., 2010). However, purple foxglove was extensively imported to North America following the publication of Withering's book in the late 1700's, and it is



A)



B)

Figure 1. Habitat of *Digitalis purpurea* in western Europe (A), and North America (B).

Source A:

<http://pbio209.pbworks.com/w/page/11342445/Snyder.%20K%20-%20Digitalis%20purpurea>

Source B:

http://plants.usda.gov/java/profile?symbol=DIPU&photoID=dipu_008_ahp.tif



Figure 2. *Digitalis purpurea* (Purple foxglove).

Source:

http://plants.usda.gov/java/largeImage?imageID=dipu_007_avp.tif

now commonly found in the wild (**Figure 1**) throughout much of New England, the Mid-Atlantic States, the Pacific Northwest, as well as Canada (Rietbrock & Woodcock, 1985; USDA, 2012).

Withering describes purple foxglove (**Figure 2**) as a biennial common to dry gravelly soil and flowering from late spring to early summer (Withering, 1785). It is a herbaceous plant with dark green foliage as well as a conspicuous purple flowers from which *D. purpurea* originally derived its name (USDA, 2012; Withering, 1785). The scientific name *Digitalis purpurea* directly translated to ‘purple fingers’ and was given to purple foxglove by Leonard Fuchs in 1542 (Rietbrock & Woodcock, 1985). These purple flowers grow in elongated clusters around the stem of *D. purpurea* and resemble fingers of a glove (Rietbrock & Woodcock, 1985). The plant tends to be between one and two meters tall at maturity and produces only foliage during its first growing season then typically flowers, produces seed, and dies in the subsequent growing season (Rietbrock & Woodcock, 1985; USDA, 2012; Withering, 1785).

Nearly all of the bioactive constituents derived from *D. purpurea* can be classified as cardiac glycosides (Doherty, 1973; Doherty & Kane, 1975). Although quantities of these glycosides can vary depending on growing conditions, the concentration typically found in as few as one or two leaves is nearly always toxic and potentially even lethal (Ramlakhan & Fletcher, 2007). That said, its bitter taste is generally sufficient to deter ingestion by herbivores (Rietbrock & Woodcock, 1985).

Traditional Uses

Historical accounts indicate that *Digitalis purpurea* has been used medically for over 700 years as part of traditional English folk medicine for treating dropsy, and written records of *D. purpurea* being prescribed medically date to as early as 1250 AD by Welsh physicians (Norn & Kruse, 2004). However, its medicinal use was inconsistent until the late 18th century

(Norn & Kruse, 2004). An English physician named William Withering became interested in *D. purpurea* in 1775 when he observed a patient's recovery from dropsy, now referred to as congestive heart failure, following her consumption of herbal tea for several months (Rietbrock & Woodcock, 1985; Withering, 1785). Withering identified the active ingredient of this herbal tea as *D. purpurea*, and began conducting research into its effectiveness (Breckenridge, 2006). By 1785 he had treated 163 patients suffering from dropsy with *D. purpurea* and published his findings in 'An Account of the Foxglove and Some of its Medical Uses' (Whitfield, 1985). Withering drew upon the treatment outcomes of his own patients to objectively demonstrate the efficacy of using *D. purpurea* in treating dropsy, the edematous bodily swelling that typically accompanied heart failure (Withering, 1785). Withering, as well as medical practitioners in subsequent decades employed *D. purpurea* therapeutically by boiling its leaves into a herbal tea (Rietbrock & Woodcock, 1985). This process of boiling served to extract some of the more water soluble cardiac glycosides into the aqueous solution, including gitaloxin, which will be discussed later (Rietbrock & Woodcock, 1985).

Purple foxglove was widely cultivated throughout England and subsequently in North America following its introduction in the late 1700's (Rietbrock & Woodcock, 1985; USDA, 2012). Prior to identification of its medicinal properties *Digitalis purpurea* was predominantly grown for its ornamental flowers (Foster, 2000). *D. purpurea* proliferated widely in the United States following the discovery of its therapeutic properties. However, now that homemade *D. purpurea* preparations are no longer commonly made for the treatment of congestive heart failure *D. purpurea* is once again cultivated for its aesthetically pleasing flowers (Foster, 2000).

Chemistry & Pharmacology

The active components found in *Digitalis purpurea* include a number of cardiac glycosides, however, it is most widely known for containing the cardiac glycoside digitoxin (Rietbrock & Woodcock, 1985; Walter Lewis, 2003). The direct inotropic effects of the cardiac glycosides found in *D. purpurea* result from their inhibition of the activity of the sodium/potassium ATPase, also known as the sodium potassium exchanger, in the myocardium (Eric J. Eichhorn & Mihai Gheorghide, 2002). The predominant method of expelling calcium from myocardial cell between contractions is the action of the membrane bound sodium potassium antiporter protein (Khatter, Agbanyo, Navaratnam, Nero, & Hoeschen, 1989). This protein uses the energy produced from moving sodium ions down their concentration gradient into the cell from the extracellular environment to pump calcium ions out of the cell against their concentration gradient (Khatter et al., 1989). By inhibiting the active transport of sodium ions out of the cell, *D. purpurea* derived cardiac glycosides bring the intracellular and extracellular sodium concentrations closer to equilibrium (Khatter et al., 1989). Because the sodium/calcium antiporter is powered by the movement of sodium down its concentration gradient into the cell, the reduction of the sodium gradient decreases the activity of the sodium/calcium antiporter and results in increased levels of intracellular calcium ions (Eric J. Eichhorn & Mihai Gheorghide, 2002). Increasing the concentration of intracellular calcium ions directly results in more interaction between the actin and myosin contractile proteins within the cells of the myocardium (Hauptman & Kelly, 1999). The increase in interaction between actin and myosin contractile proteins increase the contractile force generated by each cardiac myocyte (Doherty, 1973). The increase in contractility results in a stronger heart beat as well as an increased ejection

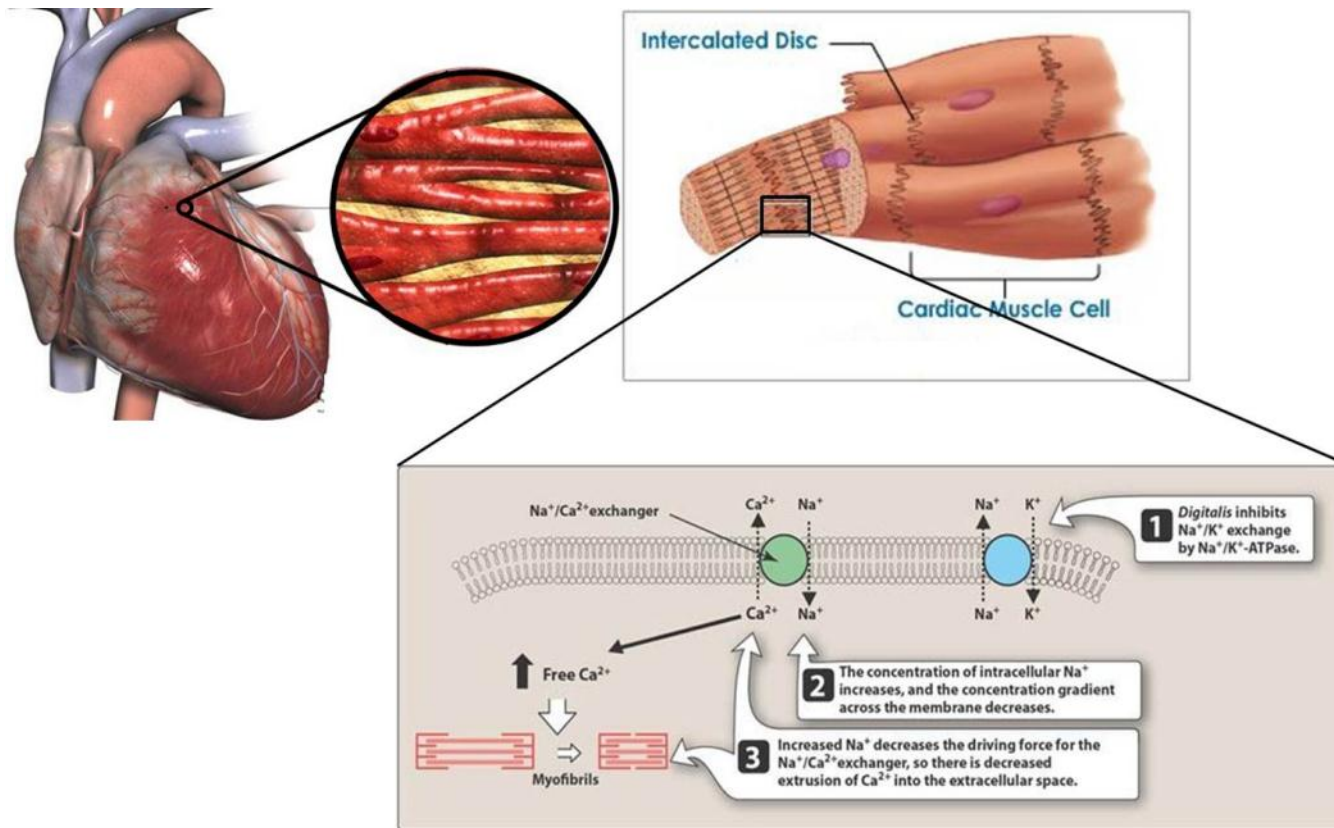


Figure 3. Mechanism of action of cardiac glycosides. Source <http://e-learning.perubatan.org/index.php?topic=738.0>

fraction (Eric J. Eichhorn & Mihai Gheorghide, 2002). *D. purpurea* derived cardiac glycosides also exert an effect on the cardiac conduction system via inhibition of the sodium potassium exchanger (Doherty & Kane, 1975), **Figure 3**.

Multiple factors can and do influence the concentration of cardiac glycosides present in *D. purpurea* preparations such as the time of the year when the leaves are gathered, the climate and the soil conditions where the plant is cultivated (Goldman, 2001; Rietbrock & Woodcock, 1985). Withering noted that

foxglove leaf preparations were efficacious in small, non-toxic doses and that their action varied according to the plant's stage of bloom (Rietbrock & Woodcock, 1985; Withering, 1785).

Major *D. purpurea* derived cardiac glycosides

Of the 38 cardiac glycosides found in *D. purpurea*, the two which have, or are currently used therapeutically are

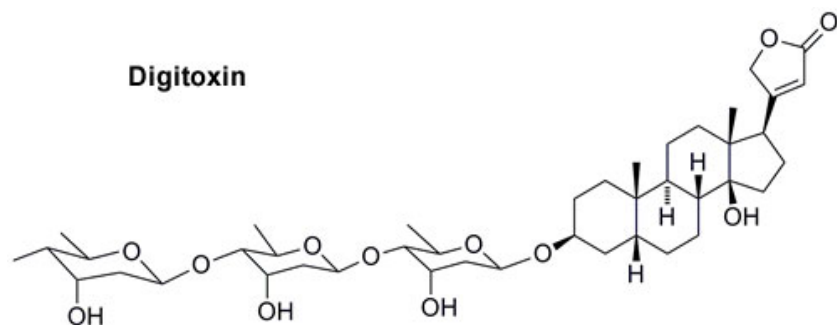


Figure 4. Chemical structure of Digitoxin

Source: <http://www.soci.org/News/Hort-newsletter-jun-10>

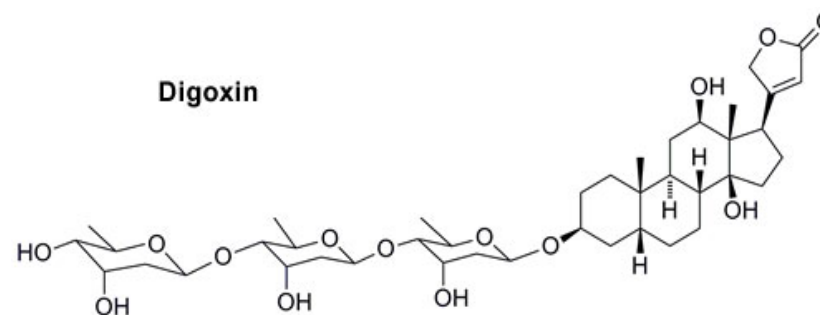


Figure 6. Chemical Structure of Digoxin

Source <http://www.soci.org/News/Hort-newsletter-jun-10>

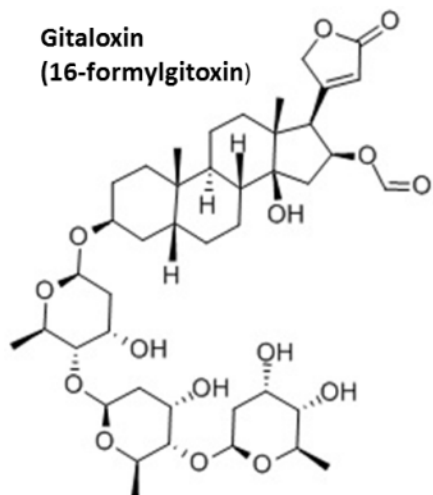


Figure 5. Chemical structure of Gitaloxin

Source:

http://www.chemicalbook.com/ProductChemicalPropertiesCB6877110_EN.htm

digitoxin (**Figure 4**), and gitaloxin (**Figure 5**) (Rietbrock & Woodcock, 1985). Gitaloxin is the only cardiac glycoside that can be collected from the leaves of *D. purpurea* in appreciable quantities by boiling (Rietbrock & Woodcock, 1985). Since

traditional foxglove teas were made by boiling *D. purpurea* leaves in water, it is highly likely that gitaloxin was the cardiac glycoside responsible for the diuretic effects observed by Withering and other traditional practitioners of foxglove therapy (Rietbrock & Woodcock, 1985). The most commonly used cardiac glycosides employed pharmacologically today are digoxin (**Figure 6**) and digitoxin (Beermann, 1974; Doherty, 1973).

Dosing considerations

The cardiac glycosides derived from *Digitalis purpurea* have a relatively narrow therapeutic window with therapeutic dosages which can be as high as seventy percent of the dose required for toxicity (Walter Lewis, 2003). Moreover, the therapeutic dose varies widely from patient to patient. Withering, like physicians today, had to tailor the dose of *D. purpurea* preparations specifically for each patient individually as a dose which would be sub therapeutic on one patient may result in toxicity in another patient (Doherty, 1973; Doherty & Kane, 1975).

Causes, presentation, & management of overdose

The majority of cases involving *D. purpurea* toxicity result from an unintentional overdose on pharmacological agents derived from the plant (Antman, Wenger, Butler, Haber, & Smith, 1990). However, cases of toxicity resulting from intentional overdoses as well as from unintentional exposures to the plant occur occasionally as well (Church, Schamroth, Schwartz, & Marriott, 1962). Accidental toxicity can result from ingestion of water with *D. purpurea* growing in it or nearby (Ramlakhan & Fletcher, 2007). Toxicity may also result from inhalation of smoke produced by burning *D. purpurea* (Ramlakhan & Fletcher, 2007). Toxicity resulting from accidental ingestion by wild food gatherers who mistake *D. purpurea* for comfrey is one of the most common causes for toxicity not related to allopathic treatment with cardiac glycosides (Lin et al., 2010; Ramlakhan & Fletcher, 2007).

Symptoms of overdose from cardiac glycosides will vary from patient to patient, however, the most common indicators of toxicity include fatigue, anorexia, nausea, loss of visual acuity, as well as cardiac rhythm abnormalities which can be either tachycardic or bradycardic in nature (Doherty & Kane, 1975; Fisch & Knoebel, 1985; Ramlakhan & Fletcher, 2007). Symptomatic bradycardias induced by *D. purpurea* typically result from decreased conduction through the Atrioventricular node, and symptomatic tachycardias result from spontaneous depolarization of autorhythmic cells located in the ventricles (Fisch, 1962; Rodensky & Wasserman, 1962). First and second degree Atrioventricular blocks, as well as junctional rhythms also occur frequently following *D. purpurea* toxicity (Doherty & Kane, 1975; Fisch, 1962). However, the most reliable indicator of *D. purpurea* toxicity observed on an electrocardiogram prior to such symptomatic arrhythmias is depression of the ST segment with a concave upward slope (**Figure 7**) (Ramlakhan &

Fletcher, 2007). If untreated, cardiac glycoside toxicity may result in death from ventricular fibrillation (Doherty, 1973; Walter Lewis, 2003).

The three primary objectives when treating a patient suffering from *D. purpurea* toxicity are supporting the heart and preventing the occurrence of arrhythmias, preventing further absorption of cardiac glycosides from the gastrointestinal tract, and reducing the concentration of serum glycosides as rapidly as possible (Antman et al., 1990). Various medications are used to protect the heart from arrhythmias. Atropine can be administered to counter the increased parasympathetic tone caused by the *D. purpurea* derived glycosides, short acting beta blockers may be administered to suppress tachycardias, and lidocaine may be administered in the case of persistent ventricular ectopy (Khatter et al., 1989; Ramlakhan & Fletcher, 2007). Synchronized cardioversion is indicated in cases of symptomatic tachycardias which are unresponsive to pharmacological interventions (Bourel & Gouffault, 1962; Ramlakhan & Fletcher, 2007). Symptomatic bradycardias should be electrically paced if they are unresponsive to pharmacological interventions (Ramlakhan & Fletcher, 2007). Activated charcoal is commonly administered orally to prevent further absorption of glycosides from the gastrointestinal tract (Rodensky & Wasserman, 1962). Most importantly, the concentration of circulating cardiac glycosides should be rapidly reduced via intravenous administration of anti-digoxin antibodies (Antman et al., 1990). Antibodies to digoxin were first created in 1967, but were only later employed as standard therapy for digoxin toxicity (Doherty, 1973; Ramlakhan & Fletcher, 2007). These antibodies to digoxin are currently marketed under the brand name Digibind and have also been effective in cases of digitoxin toxicity, although to lesser extent (Antman et al., 1990; Ramlakhan & Fletcher, 2007).

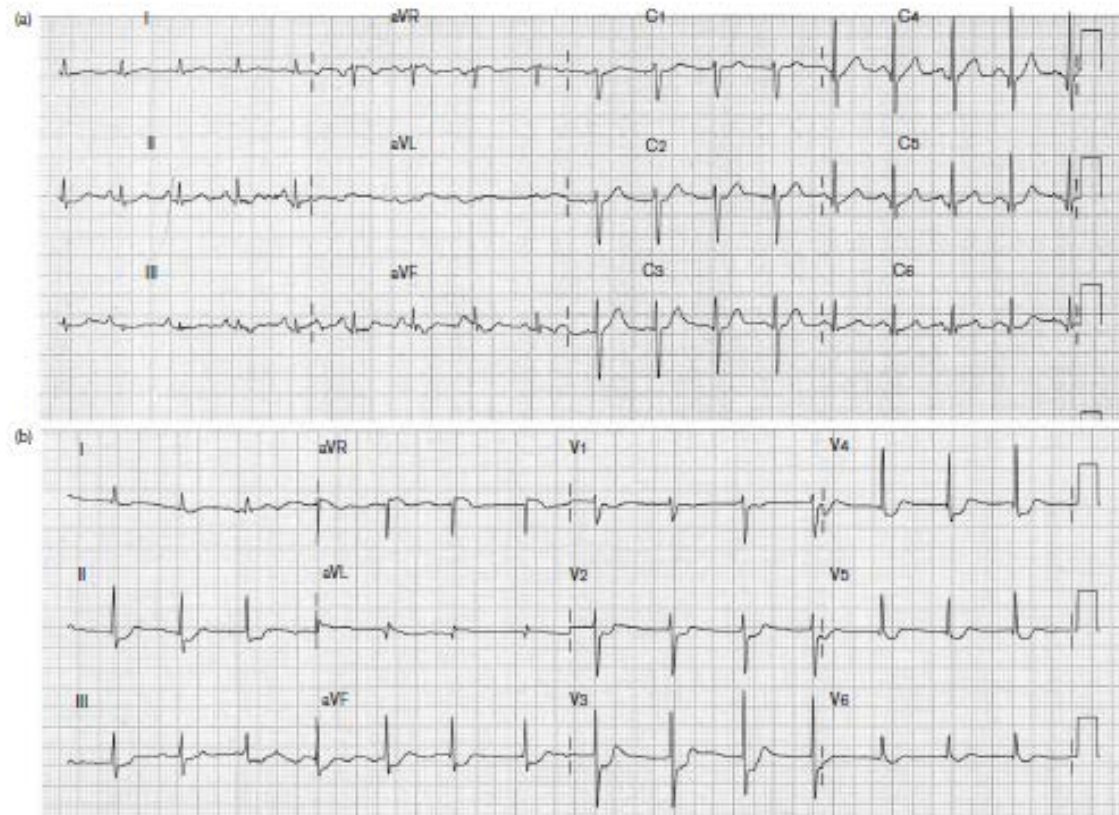


Figure 7. Electrocardiogram displaying the effects of *D. purpurea* toxicity. (a) depicts a normal ECG. Note the concave upwardly sloping ST segment depression in (b). Source (Ramlakhan & Fletcher, 2007)

Biological Activity

Withering and others describe the diuretic effect of *Digitalis purpurea* extracts; however, this effect is the indirect result of three direct effects of the cardiac glycosides found in *D. purpurea* on the heart (Beermann, 1974; Doherty, 1973; Doherty & Kane, 1975). The first of these three direct effects is an increase in myocardial contractility (Doherty & Kane, 1975). The second is an increase in parasympathetic tone

which results in decreased heart rate which allows more time for the ventricles to fill between each beat (Eric J. Eichhorn & Mihai Gheorghide, 2002). Finally, the third direct effect of *D. purpurea* derived glycosides is a slowing of the electrical impulses through the cardiac conduction system (Krantz & Ling, 1960). Such effects on the cardiac conduction system are confined to the atria, notably decreasing spontaneous depolarization in the Sinoatrial node and intermodal tracts, and slowing conduction through the Atrioventricular node

(Eric J. Eichhorn & Mihai Gheorghide, 2002; Ramlakhan & Fletcher, 2007). Together these three effects increase contractility as well as decreased heart rate is in an increase in ejection fraction which increases the volume of blood pumped from the heart with each contraction (Doherty & Kane, 1975; Soffer, 1962). This increase in ejection fraction results in increased systemic perfusion. Specifically, renal perfusion is increased which enhancing the production and excretion of urine thereby eliminating excess fluid form the body (Doherty & Kane, 1975; Rietbrock & Woodcock, 1985).

Clinical Studies

Empirical evidence for the clinical effectiveness of *Digitalis purpurea* dates to the time of Withering, formal clinical trials of various *D. purpurea* preparations began at least as early as 1915 (Simson, 1962). Since then numerous studies of *D. purpurea* have demonstrated the positive inotropic effect of its cardiac glycosides on the myocardium (Cattell & Goodell, 1937). These studies have been conducted in animals such as frogs, cats and dogs to determine the mechanisms of action for the various cardiac glycosides extracted from *D. purpurea* (van Dyke & Li, 1935). Moreover, these animals were also to develop standardized concentrations for administration of digoxin and digitoxin which are two more recently identified cardiac glycosides (Doherty, 1973; van Dyke & Li, 1935)

Following the development of agreed upon standard for dosing were developed in the early to mid 1900's, studies into the effectiveness of the various glycosides were conducted (van Dyke & Li, 1935). In a 300 patient multicenter trial digoxin reduced hospitalization for congestive heart failure as well as increasing left ventricular ejection fraction (Eric J. Eichhorn & Mihai Gheorghide, 2002). The Digitalis Investigation Group (DIG) trial was another example of the

effect of digoxin verses alternative medicinal therapies for congestive heart failure. Over several months *D. purpurea* derived cardiac glycosides were shown to reduce hospitalization for congestive heart failure by twenty five percent (Gheorghide & Pitt, 1997). Moreover, *D. purpurea* derived cardiac glycosides is the only currently marketed oral inotropic agents which do not result in increased mortality when administered to patients suffering from congestive heart failure (Eric J. Eichhorn & Mihai Gheorghide, 2002).

Lastly, studies have indicated that concurrent use of aldosterone antagonists with the *D. purpurea* derived cardiac glycoside digoxin may reduce the occurrence of toxicity associated with their use (Eric J. Eichhorn & Mihai Gheorghide, 2002). Aldosterone is a compound secreted by the adrenal cortex in response to activation of the rennin-angiotensin-aldosterone-cascade which is not only up regulated in response to hypotension, but also in response to administration of digoxin (Eric J. Eichhorn & Mihai Gheorghide, 2002). Because aldosterone has been observed to alter serum concentrations of potassium and potentially result in arrhythmias and potentiate the effects of digoxin toxicity, concurrently blocking the secretion aldosterone may increase the safety of *D. purpurea* based glycosides used for the management of congestive heart failure (Eric J. Eichhorn & Mihai Gheorghide, 2002).

Contraindications

The two most commonly prescribe cardiac glycosides derived from *Digitalis purpurea* are digoxin and digitoxin. Digoxin is excreted from the body via the kidneys and extreme care should be taken when administering the drug to patients in renal failure their lack of renal clearance can result in the increase of serum cardiac glycoside concentration to toxic

levels (Hauptman & Kelly, 1999). However, digitoxin clearance is independent of renal function and is widely considered the safer of the two cardiac glycosides for administration to patients suffering from renal failure (Genazzani, 1977).

There are no medications which are completely incompatible with cardiac glycosides derived from *Digitalis purpurea*; however, diuretics which act by altering serum electrolyte concentrations, specifically potassium concentrations, such as furosemide, should be administered with care, as such medications can significantly increase the likelihood of developing arrhythmias (Ramirez-Ortega et al., 2007).

Current Use in Allopathic and CAM Therapies

The most widely prescribed *Digitalis purpurea* extract prescribed today is digoxin however, digitoxin is also occasionally prescribed as both are cardiac glycosides isolated in the early 1900's and both have relatively similar effects on the body (Rietbrock & Woodcock, 1985; Walter Lewis, 2003). These cardiac glycosides have become the most widely proscribed inotropic agents in the United States (Doherty, 1973). In fact, the *D. purpurea* derived cardiac glycosides are employed so widely in modern medicine that the term 'digitalis' is commonly used in place of 'cardiac glycosides' (Hauptman & Kelly, 1999).

No herbal supplements derived from *D. purpurea* are currently marketed however; it may still be grown and used by some practitioner's in England for the treatment of congestive heart failure (Rietbrock & Woodcock, 1985). It is worth noting that correct identification of plant species is essential for practitioners of CAM. As previously mentioned, several instances of severe toxicity have resulted from the misidentification of *D. purpurea* as *Symphytum officinale*,

commonly referred to as comfrey (Lin et al., 2010). Leaves of *S. officinale* resemble those of *D. purpurea*, and during times of the year when *D. purpurea* lacks its distinctive purple flowers misidentification of the two plants becomes possible (Lin et al., 2010).

Discussion

The cardiac glycosides found within purple foxglove both increase contractility and reduces heart rate (Michael Heinrich, 2004). This increase in inotropy and reduction in chronotropy result in a slower but stronger heart beat and can increase cardiac output by as much as thirty percent (Walter Lewis, 2003).

As in the time of Withering, therapeutic administration of modern cardiac glycosides is often problematic for three reasons. First, its therapeutic window is very narrow, with the dosage required to achieve a physiological effect often approaching seventy percent of the dose necessary to produce toxicity (Breckenridge, 2006). In addition to this narrow therapeutic window, cardiac glycosides extracted from *D. purpurea* have relatively long half-lives, 36 to 48 hours in the case of digoxin, and approximately 10 days in the case of digitoxin (Doherty, de Soyza, Kane, Bissett, & Murphy, 1978). Repetitive dosing over time can, and often does progressively increase serum cardiac glycoside concentration eventually resulting in toxicity (E. J. Eichhorn & M. Gheorghade, 2002; Pruitt, 1962). Finally, therapeutic doses of *D. purpurea* extracts vary widely from patient to patient (Pruitt, 1962). For example, the dosage required to achieve a therapeutic effect in one patient may be significantly greater than the dosage required for toxicity in another (Breckenridge, 2006; Pruitt, 1962). In fact, even the plasma concentrations of digoxin required to achieve a therapeutic effect can vary widely

between individuals (Breckenridge, 2006; Ramlakhan & Fletcher, 2007).

Interestingly, approximately twenty percent of patients receiving *D. purpurea* derived cardiac glycoside therapy today report experiencing adverse side effects, whereas the therapeutic success rate observed by Withering in the late 1700's was slightly higher, with only eighteen percent of his patients reporting side effects (Rietbrock & Woodcock, 1985). Moreover, Withering achieved this success rate while administering these glycosides in the form of teas brewed from foxglove, as opposed to modern practitioners who administer digoxin or digitoxin which are highly standardized and regulated *D. purpurea* derived cardiac glycoside, suggesting that herbal treatment administered by early practitioners such as Withering was no less successful, and no more likely to result in toxicity than modern synthetically derived *D. purpurea* therapy (Rietbrock & Woodcock, 1985).

Despite the potential for toxicity, *D. purpurea* derived cardiac glycosides have been a fixture in the treatment of congestive heart failure for over two centuries (Rietbrock & Woodcock, 1985). The use of *D. purpurea* derived cardiac glycosides will likely continue long into the future as they are the most potent inotropic agents yet identified and no suitable replacements have been identified (Rietbrock & Woodcock, 1985; Rodensky & Wasserman, 1962; Simson, 1962).

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Echinacea purpurea (L.) Moench, Asteraceae

Charity Coleman

Introduction

Echinacea purpurea (L.) Moench is 1 of the 477 genera in the Asteraceae family and 1 of 9 species in the *Echinacea* genus (USDA 2011). It is most commonly known as the purple coneflower. Other common names include eastern purple



Figure 1. Photograph of *Echinacea purpurea* and a female Pipevine Swallowtail butterfly (*Battus philenor*). (Source: Photograph by Rhonda Stewart. <http://www.fs.fed.us/wildflowers/pollinators/butterflies.shtml>)

coneflower, snakeroot, Kansas snakeroot, broad-leaved purple coneflower, scurvy root, Indian head, comb flower, black susans, hedgehog and American coneflower (MDidea 2010). *Echinacea* is one of the most popular, top-selling, and most studied herbal treatments in today's society. Traditionally, *Echinacea* has been used to prevent and/or treat colds, flu and other upper respiratory infections. It is believed that *Echinacea* is capable of stimulating the immune system in order to help fight off infections. Also, *Echinacea* has been used to treat wounds and skin problems such as acne and boils, although these uses of *Echinacea* are less common (NCCAM 2005-2010). *Echinacea* is generally sold as a preparation derived from 3 of the 9 species including *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida*. The most commonly used preparation in the United States is a liquid extract made from the root of *Echinacea purpurea* (Kligler 2003). The active component of the plant has not been identified; however, the main components believed to be responsible for its immune-stimulating effects are the high-molecular-weight polysaccharides: heteroxylan and arabino-galactan (Kligler 2003).

Description

Echinacea purpurea is an herb that is native to the eastern and mid-western regions of North American and the southern regions of Canada. Although it does not grow naturally anywhere else, it is cultivated worldwide because of its great use as an herbal medicine. Its habitat is mainly that of rocky areas, open woods, thickets, prairies, and roadsides. It is a

single stem, erect, perennial with an active growth period in the spring and summer. Its mature height is approximately 1.2 feet but can reach heights of up to 4 feet (Upton 1997). The flower is purple in color, with elliptical petals radiating from the spiny seed head (cone), which is responsible for the plant's name (*echinos*: Greek word-root for "hedgehog") (Upton 1997). Foliage color is green and the fruit and seed color is black (FNA 2011). The seeds are produced in the cone and are small, 4 sided achenes. The stems are rough and have small hairs along their entire length with alternate, simple and ovate leaves coming from them. The roots occur in a mass of thin, beige-brown rootlets that are approximately 12 inches in length. The taste of the stem has been described as a sweet but acrid flavor (Upton 1997). The growth rate is moderate, but regrowth rate after harvesting is quite slow (FNA 2011). Preferential growth requires full sun with low tolerance to drought. The optimum pH is between 6.5 and 7.2 for growth. Echinacea does not compete well with other plants (USDA 2011). When in bloom, the flowers of *Echinacea purpurea* attract pollinators such as insets and butterflies. Also, song birds such as Goldfinches are fond of the seeds during the fall. **Figure 1** is a photo of *Echinacea purpurea* along with one of its pollinators, the female Pipevine Swallowtail butterfly. There are no known pests of potential problems associated with *E. purpurea*. However, because it is such a popular herbal remedy, it is becoming increasingly rare in its natural habitat due to over harvesting.

Traditional Uses

Echinacea has been used for hundreds of years among Native Americans, North Americans and Europeans. Archaeological digs in the Lakota Sioux village sites uncovered evidence of Echinacea plants dating back to the 1600's. The use of

Echinacea as an herbal medicine was introduced to Europe in the late 1800's by H.C.F. Meyer (MDidea 2010). It has been used in Europe extensively since the 1930s and is used by millions of Europeans today as their primary therapy for colds, flus and other upper respiratory infections (URIs) (MDidea 2010). As in European use, Echinacea is commonly used in the North America to treat/prevent colds, flus, upper respiratory infections, and also for general immune-boosting effects. It is also used, less commonly, for the treatment of urinary tract infections, treatment of wounds, and skin conditions such as acne, boils, psoriasis, and eczema (MDidea 2010). *E. purpurea* has also been used in Canada to treat abscesses in livestock (Lans, Turner, Khan, Brauer and Boepple 2007). Studies have shown activity against bacterial and viral infections and some of the chemical compounds extracted from Echinacea have shown inhibitory effects against certain forms of cancer (USDA 2011). Echinacea was introduced into the 1887 *Materia Medica* but was eventually removed due to lack of efficacy from clinical studies (MDidea 2010 and Upton 1997).

Traditional Medicinal Uses by Native Americans

Echinacea is said to have been the most commonly used medicinal plant by Native American tribes, being used for more illnesses than any other plant (Upton 1997). The most common uses of Echinacea by Native Americans were to treat toothaches, sore throats, coughs, infections, burns, venereal diseases, and even snake bites and other venomous bites, stings, and poisonings. The most common method for treating coughs was to chew the root and swallow the juices (Moerman 2011). Use of Echinacea extended through many tribes including the Blackfoot, Cheyenne, Choctaw, Comanche, Crow, Dakota, Delaware, Kiowa, Lakota, Omaha, Pawnee, Ponca,

Sioux, and more (Upton 1997). Use has also been reported by the Montana and Winnebago tribes (Borchers, Keen, Stern and Gershwin 2000). When using Echinacea to treat snakebites, most of the tribes employed the same preparations and applications. The root was used internally by chewing the fresh root, and externally by making a fresh poultice and applying it to the bite to draw out the poison (Upton 1997). Another common application throughout the tribes was to suck on the root to treat toothaches, sore throats, coughs, and infections. Other tribes applied juice, from the roots, to burns, wounds, ulcers and other skin conditions (MDidea 2010).

Specific Traditional Medicinal Uses by Tribe

The Blackfoot chewed the root to reduce pains from toothaches. The Sioux used freshly scraped root to make a poultice to treat hydrophobia caused by bites of rabid animals. The Dakotas also used freshly scraped root to treat hydrophobia, snakebites, and wounds that had putrefied (MDidea 2010). The Delaware tribe used *E. purpurea* to treat venereal disease by combining the roots with staghorn sumac roots. For more advanced cases of venereal disease, they would use an infusion of roots. The Delaware also reported high effectiveness with the use of *E. purpurea* in the treatment of gonorrhea (Moerman 2011). The Lakota tribe used Echinacea as a painkiller for toothache, tonsillitis, stomachache, pain in the bowels, and also when they were thirsty or perspiring by eating the roots and green fruits of the plant. The Omaha tribe used some parts of the plant for sore eyes. The Kiowa and Cheyenne chewed pieces of the root and let saliva run down their throats in order to treat colds and sore throats. The Cheyenne also made tea from the leaves of Echinacea to treat sore mouths and gums, toothaches due to large cavities, rheumatism, arthritis, mumps and measles. This

same liquid was also applied to necks to relieve sore neck pain. Salves were also made by the Cheyenne to treat the same ailments externally. Echinacea root was also mixed with *Mentzelia laevicaulis* (blazing star) and boiled to make a tea for treating smallpox (MDidea 2010 and Upton 1997). The Choctaw tribe is reported to have used *E. purpurea* as a cough medicine by chewing the root and swallowing saliva containing the juice. They also prepared a tincture which they used for coughs as well. The Choctaw also used *E. purpurea* as a gastrointestinal aid to help with dyspepsia. They used the same methods of preparation as with the cough medicine (Moerman 2011). This information was also reported in the *American Journal of Clinical Nutrition* (Borchers, Keen, Stern and Gershwin 2000).

Non-medicinal Traditional Uses

Echinacea had traditions not only in medicinal uses, but decorative, ceremonial and other uses as well. Echinacea, due to its beautiful flowers, is grown as a decorative flower in many gardens and can be found in many homes. Native American tribes would use Echinacea in many religious ceremonies to show supernatural abilities. They would use the numbing qualities of Echinacea by mashing the fresh root and rubbing the juice on their hands with tallow to enable them to handle fire painlessly. Also, others would chew the root to numb the mouth in order to hold a hot coal in their mouths for religious ceremonies as well as for medicinal practices (Upton 1997). Winnebago medicine men would do this in order to create confidence in their ability to heal (MDidea 2010). Children of the Pawnee tribe used Echinacea in a game in which the stems were twirled around each other. Many tribes have also been known to use the spiny seed cone as a hair comb (Upton 1997).

Plant Part	Active Constituents
Flower	Cichoric-Acid (12,000-31,000 ppm), Cyanadin-3-O-(6-O-Malonyl-Beta-D-Glycopyranoside), Cyanadin-3-O-(Beta-D-Glycopyranoside), EO (600-6,000 ppm)
Fruit	Alpha-Pinene, Beta-Farnesene, Beta-Pinene, Epishiobunol, Limonene, Myrcene
Leaf	2,3-O-Diferuloyltartaric-Acid, 2-O-Caffeoyl-3-O-Feruloyltartaric-Acid, 2-O-Caffeoyltartaric-Acid, 2-O-Feruloyltartaric-Acid, Apigenin, Ascorbic-Acid (2,140 ppm), EO (100-6,000 ppm), Flavanoids (3,800-4,800 ppm), Isorhamnetin-3-Rutinoside, Kaempferol, Kaempferol-3-O-Glucoside, Kaempferol-3-O-Rutinoside, Luteolin, Luteolin-7-Glucoside, Quercetagenin-7-Glucoside, Quercetin, Quercetin-3'-Glucoside, Quercetin-3-O-Galactoside, Quercetin-3-O-Xyloside, Quercetin-3-Robinoside, Quercetin-3-Xylosylgalactoside, Rutin, Rutoside, Selenium, Silicate (15,340 ppm), Silicon (301 ppm), Sodium (90 ppm)
Plant	(+)-Tartaric -Acid, (E)-10-Hydroxy-4,10-Dimethyl-4,11-Dodecadien-2-One, 2-Methyltetradeca-5,12-Diene, 2-Methyltetradeca-6,12-Diene, 2-O-Caffeoyl-3-(5-(Alpha-Carboxy-Beta-(3,4-Dihydroxyphenyl...)), 3,5-Dicaffeoyl-Quinic Acid, 4,5-O-Dicaffeoylquinic-Acid, Borneol, Bornyl-Acetate, Caffeic-Acid, Ferulic-Acid, Isotussilagine, Vanillin
Root	6-O-Caffeoylechinacoside, Alkylamides (40-1,510 ppm), Aluminum (786-12,900 ppm), Arabinogalactan, Ascorbic-Acid (843 ppm), Ash (80,000 ppm), Behenic-Acid-Ethyl-Ester, Beta-Carotene, Betaine, Calcium (3,290-7,760 ppm), Carbonate (7,100 ppm), Caryophyllene (42 ppm), Caryophyllene-Epoxyde (26 ppm), Chloride (760 ppm), Chromium (19 ppm), Cichoric-Acid (6,000-21,000 ppm), Cichoric-Acid-Methyl-Ester (6,000-21,000 ppm), Cobalt (148 ppm), Cynarin, Deca-(2E,4E,6E)-Trienoic-Acid-Isobutylamide, Des-Rhamnosylverbascoside, Dodeca-(2E,4E)-Dienoic-Acid-Isobutylamide, Dodeca-(2E,6Z,8E,10E)-Tetraenoic-Acid-Isobutylamide, Dodeca-2,4-Dien-1-yl-Isovalerate, Echinacein (10-100 ppm), Echinacin, Echinacoside (3,000-17,000 ppm), Echinolone, EO (50-40,000 ppm), Fat (13,000 ppm), Fiber (111,000 ppm), Germacrene-Alcohol, Germacrene-D, Heptadeca-(8Z,11Z)-Diene-2-one, Heteroxylan (800 ppm), Humulene (8-12 ppm), Inulin (59,000-200,000 ppm), Iron (700-4,800 ppm), Kilocalories (2,800/kg), L-Pentadecene (400 ppm), Magnesium (1,170-1,860 ppm), Manganese (101 ppm), Niacin, Palmitic-Acid, Penta-(1,8Z)-Diene (400 ppm), Pentadeca-(8Z)-en-11,13-diy-2-one, Pentadeca-(8Z)-en-2-one (4,000 ppm), Pentadeca-(8Z,11Z)-diene-2-one, Pentadeca-(8Z,13Z)-diene-11-yn-2-one, Pentadeca-8-en-2-one, Phosphorus (790 ppm), Polyacetylenes (20 ppm), Polysaccharides, Ponticaepoxide, Potassium (3,140-8,090 ppm), Protein (92,000, ppm), Rhamnoarabinogalactan, Sulfate (2,450 ppm), Tetradeca-(8Z)-en-11,13-diy-2-one, Thiamin (2.6 ppm), Tin (17 ppm), Trideca-1-en-3,5,7,9,10-Pentayne, Tussilagine, Verbascoside, Water (749,000 ppm), Zinc (51 ppm)
Shoot	12-Hydroxyoctadeca-(9Z,11E,15Z)-Trienoic Acid, 2-O-Caffeoyl-3-O-Cumaroyltartaric-acid, Beta-Sitosterol, Chlorogenic-Acid, Isochlorogenic-Acid, N-Triacontanol, Sitosterol-3-Beta-O-Glucoside, Stigmasterol

Table 1. Chemical composition of *Echinacea purpurea*. (Source: Information obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases. <http://www.ars-grin.gov/cgi-bin/duke/farmacy2.pl>)

Chemistry and Pharmacology

Due to the heterogeneity of the products used in the majority of studies of *Echinacea*, the main active component of *Echinacea purpurea* is not known. Most studies examine combinations of *Echinacea* species and others study *Echinacea* combined with other herbs (Kligler 2003). However, the chemical composition of *E. purpurea* has been well documented and is categorized based on plant parts in **Table 1**. The main constituents thought to be responsible for the immune-stimulating effects are heteroxylan and

arabinogalactan (Kligler 2003). Other classes of compounds considered to contribute to the activity of *Echinacea* are alkaloids, polysaccharides, and polypropenoids, in particular, caffeic acid derivatives echinacoside and cichoric acid (MDidea 2010). Echinacoside is present in the roots at approximately 7,000-13,000 ppm and cichoric acid is present in the flower at levels of 12,000-31,000 ppm and in the root at levels of 6,000-21,000 ppm (Duke 2011). Also, inulin is found at very high concentrations ranging from 59,000-200,000 ppm in the roots. **Figure 2** shows the chemical structures of some

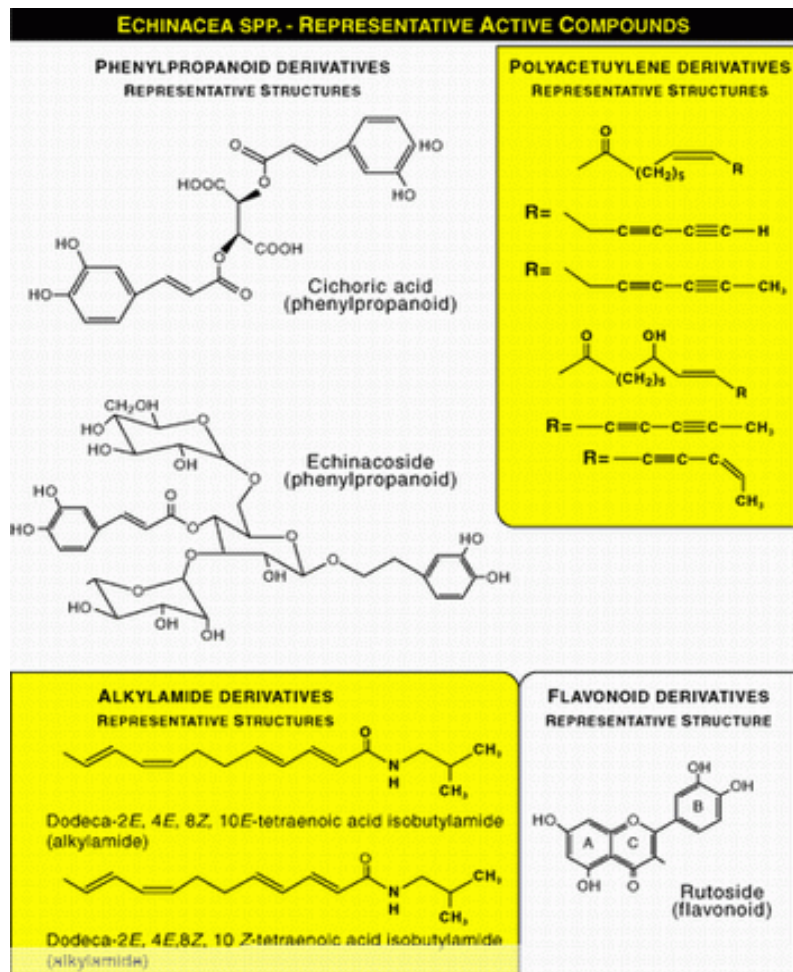


Figure 2. Chemical compounds found in *Echinacea purpurea*. (Source: Mdidea Exportind Division Extract Professionals. <http://www.mdidea.com/products/herbextract/echinacea/data05.html>)

of the main chemical compounds found in *E. purpurea*.

Biological Activity

There have been many *in vitro* and *in vivo* studies done to evaluate the efficacy and to try and determine the main active components of *Echinacea purpurea*. Due to the vastness of chemical constituents and the different compounds present in different parts of the plants and in different species, the main active ingredients are not known. Therefore, when sold, Echinacea extracts are generally a mixture of *E. angustifolia*, *E. pallida*, and *E. purpurea* as many herbalists believe that the effects of Echinacea are due to a complex interaction among the constituents (Fiebert and Kemper 1999).

Immunostimulant

One study incubated mouse serum with polysaccharides (thought to be one of the main active components for immune-stimulation) from *Echinacea purpurea* roots. They found that this stimulated proliferation of bone marrow cells and promoted phagocytosis by macrophages. Also, another study in rats showed that, in isolated, perfused rat livers, Echinacea extracts enhanced phagocytosis. A study performed in immunosuppressed mice showed a reduction in renal *Candida* load by 80% when the mice were injected with Echinacea polysaccharides prior to infection with *Candida albicans*. Bacterial counts in both the liver and spleen were also reduced by 95% in mice treated with Echinacea prior to infection with a lethal dose of *Listeria monocytogenes* (Fiebert and Kemper 1999). A study in undefined murine animals (mice or related rodents) sought to define the effects of *E. purpurea* root and leaf extracts in dendritic cells. These cells are responsible for the generation of innate and adaptive immune responses. This study concluded that *E. purpurea* can function as an immunostimulant, immunosuppressive, and/or an anti-inflammatory agent. The achieved affects are

determined by the portion of the plant used as well as the method of extraction applied (Benson, Pokorny, Rhule, Wenner, Kandhi, Cech and Shepherd 2010). Aly and Mohamed performed a study to investigate the immunostimulant effects of *E. purpurea* and garlic in Nile tilapia. They found that fish supplemented with *E. purpurea* and garlic showed an improvement in body weight gain, increased survival rates and increased resistance against challenged infections (Aly and Mohamed 2010).

Antimicrobial: Antiviral

In a study of cultured mouse cells, treatment with aqueous extracts of *Echinacea purpurea* caused a 50-80% resistance to infection of Influenza and Herpes viruses when treated four to six hours prior to exposure. The resistance lasted for 24 hours after exposure, but after 48 hours the cells were sensitive to infection (Fiebert and Kemper 1999).

Antifungal

An *in vitro* study of human granulocytes and monocytes treated with *Echinacea purpurea* extracts showed enhanced mobility. Also, there was an increase in phagocytosis of *Candida albicans* by 30-45%. Also *in vitro*, inhibition of *Candida albicans* growth was seen with use of purified polysaccharides from *E. purpurea* (Fiebert and Kemper 1999). A study on light-mediated antifungal activity of *E. purpurea* showed that extracts of *Echinacea* have phototoxic antimicrobial activity against fungi. Under near UV irradiation, growth inhibition was shown against yeast strains of *Saccharomyces cerevisiae*, *Candida shehata*, *C. kefyr*, *C. albicans*, *C. steatolytica* and *C. tropicalis*. These effects were contributed to the ketoalkenes and ketoalkynes found in roots of *E.*

purpurea (Binns, Purgina, Bergeron, Smith, Ball, Baum and Arnason 2000).

Complementary immune support

In an *in vitro* study, a cytotoxic response of macrophages against tumor targets was seen with use of purified polysaccharides from *Echinacea purpurea*. One study with mice showed an increase in the number of white blood cells, compared to controls, after receiving intravenous *E. purpurea* polysaccharides prior to injection of cyclophosphamide. A study in rats that received dietary supplements of *E. purpurea* showed enhanced mobilization of vitamin E mediated oxidation/reduction pathways. This suggests that there is a protectant effect against radiation damage (Fiebert and Kemper 1999).

Mechanism of Action

Since the exact active components of *Echinacea purpurea* have not been identified, the exact mechanism of action is not known. However, the mechanisms are known for many of the constituents found in *Echinacea*. Several studies show that *Echinacea* provides an increase in immunological activity by increasing levels of interferon and increasing phagocytosis, cellular respiratory activity, and lymphocyte activation. This is achieved through the release of tumor necrosis factor, interleukin-1, and interferon beta-2 (Kligler 2003). *Echinacea* promotes T-cell activation, natural killer-cell activity, lymphatic function and antibody binding. It also increases the reticulo-endothelial layer which increases antibodies by increasing the production of alpha, beta, and gamma globulin (Valentino and Yance 1999). *Echinacea* is thought to assist in wound healing, a cortisone-like activity, by inhibiting

hyaluronidase enzyme that is associated with swelling and inflammation (Valentino and Yance 1999). This activity is accomplished by Echinacea's ability to maintain the structure and integrity of the collagen matrix in connective tissue (MDidea 2010). Echinacea is most properly termed an immunomodulator as it stimulates in the immune system in some conditions and suppresses it in others (MDidea 2010).

There has been much debate about the length of use of Echinacea and its long term effectiveness. Some sources say that it is only efficient for a seven to ten day period. However, one source indicates that this is a misconception and that it came from the mistranslation of a few German graphs from an oral double blind study with *E. purpurea* vs. a placebo (MDidea 2010).

Clinical Studies

Many clinical studies have been performed to determine the efficacy of Echinacea in treating human conditions with many mixed results reported. A double-blind, placebo-controlled randomized trial by Melchart, Walther, Linde, Brandmaier and Lersch on the prevention of upper respiratory tract infections found that no prophylactic effects of Echinacea extracts could be shown. The placebo group showed 36.7% infection while the group treated with *E. purpurea* only showed 29.3% infection, however these results were not conclusive enough to confirm efficacy. They did conclude however, based on their research and 2 other studies, that there could be speculation of a 10-20% risk reduction with treatment of Echinacea products (Melchart, Walther, Linde, Brandmaier, and Lersch 1998). Another randomized controlled trial on the effectiveness of *E. purpurea* in treatment of URIs found there was no difference in duration or severity of symptoms between patients treated with *E. purpurea* and those receiving

a placebo (Taylor, Weber, Standish, Quinn, Goesling, McGann, and Calabrese 2003).

On the other hand, a study by Brinkeborn, Shah and Degenring (1999) concluded that preparations from *E. purpurea*, including Echinacea concentrate and Echinaforce, were low-risk, effective alternatives to standard symptomatic medicines in the treatment of the common cold. Also, according to the University of Maryland Medical Center, a study of 95 people with early symptoms of the flu who drank tea made from Echinacea felt better sooner than those who drank a placebo tea. They also reported that a review of 14 clinical trials revealed a 58% reduction in the odds of developing a cold when using Echinacea (UMMC 2011).

Contraindications

According to the National Center for Complementary and Alternative Medicine, when taken by mouth, Echinacea does not generally cause side effects. Generally uncommon and minor side effects include abdominal upset, nausea and dizziness (Kligler 2003). Although rare, some people have experienced allergic reactions such as rashes, increased asthma, and anaphylaxis (NCCAM 2010). People more likely to experience allergic reactions to Echinacea include those who are allergic to related plants in the daisy family such as ragweed, chrysanthemums, marigolds and daisies, as well as individuals with asthma (NCCAM 2010).

There have been no significant herb-drug interactions reported with the use of Echinacea. Although, theoretically the immune-stimulating properties of Echinacea could possibly interfere with immunosuppressive medications taken by individuals with autoimmune disease, such an effect has not been documented in humans or animals. Also, *in vitro* studies

of Echinacea have shown that there may be a mild inhibition of the cytochrome P450 3A4 enzyme complex system which causes an increase in levels of drugs metabolized by the system. Drugs affected are itraconazole (Sporanox), fexofenadine (Allegra), and lovastatin (Mevacor). None of these interactions have been reported in humans but caution should be taken when using Echinacea along with these medications (Kligler 2003).

Current Use in Allopathic & CAM Therapies

There are literally hundreds of products containing Echinacea species currently on the market (Echinacea 2011). The most common uses of Echinacea today are for the treatment/prevention of colds, flus, upper respiratory tract infections, and general enhancement of the immune system. Echinacea is generally sold as a combination of *E. angustifolia*, *E. pallida*, and *E. purpurea* and can be purchased as extracts, tinctures, tablets, capsules, ointments, and in teas. It is also sold in capsule forms combined with other immune boosting herbs, vitamins, and minerals (UMMC 2011).

When purchasing Echinacea products, do take caution to make sure you are purchasing from a reputable, established company that distributes through trustworthy and knowledgeable establishments. According to the University of Maryland Medical Center, a study performed by ConsumerLab.com found that only 4 out of 11 brands of Echinacea purchased for testing contained what was stated on their labels. Moreover, approximately 10% of them had no Echinacea in them at all! Also, half of them were mislabeled as to which species of *Echinacea* they contained and the standardized preparations did not match the label (UMMC 2011).

The UMMC recommends the following dosages of Echinacea for general immune stimulating effects, during colds, flus, URIs or bladder infections: 1-2 grams of dried root or herb as a tea, 2-3 mL of standardized tincture extract, 6-9 mL of expressed juice (succus), 300 mg of standardized, powdered extract containing 4% phenolics, tincture (1:5): 1-3 mL (20-90 drops) or stabilized fresh extract: 0.75 mL (15-23 drops). It is recommended to choose one of these dosages and take it 3 times a day for 7-10 days (UMMC 2011).

Discussion

Echinacea purpurea has played an extremely important role in natural medicine for hundreds of years, dating back to the 1600s. It was the most widely used medicinal plant by the Native Americans in the past and is still one of the most widely used herbal medicines today. The vastness of use of this plant is extraordinary, ranging from treatment of the common cold to its tumor fighting properties and hundreds of preparations containing Echinacea are already on the market. Although the efficacy of Echinacea has not yet been truly confirmed, it is used by millions of people worldwide with personal opinions of success. With its use traversing hundreds of years, there are obviously some benefits. I believe that this plant will continue to be highly regarded as a beneficial herbal supplement and that future studies will find and confirm its efficacy.

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Ephedra sinica Stapf., Ephedraceae

Samuel C. Turner

Introduction

Ephedraceae is a family of herbs that have been exploited for their stimulating properties for nearly 5,000 years. Ephedraceae contains only one genus, *Ephedra*. *Ephedra* is composed of about 40 species. *Ephedra sinica* is the most potent in the genus *Ephedra*. *E. sinica*, known originally as Ma Huang, has had many epithets, including; Chinese Ephedra, Ephedra, upitonia, ephedrine (referring to its active ingredient), desert tea, desert herb (referring to its ecology), whorehouse tea and any number of other names (asiarecipe.com).

The Chinese have used *E. sinica* for thousands of years as a treatment of asthma, hay fevers, sweating and the common cold. Although *Ephedra* is one of the earliest recorded medicines; its active ingredients, ephedrine and pseudophedrine, have only been isolated in recent history (1887) (Frank, 2009). Ephedrine is an alkaloid that stimulates the central nervous system, constricts the blood vessels and opens lungs. Since its isolation it has used as a treatment for asthma, weight loss and athletic performance enhancer, as well as an antihistamine and decongestant (Thomas, 2010). Its abuses have led to increased scrutiny on its dosage, usage and availability.

Description

Ephedra sinica is a small, shrub-like plant that grows to a maximum of three feet and is prevalent eastern China and Mongolia. Since its mass production, it has been planted in



Figure 1. *Ephedra sinica*. (Source: http://www.herbie_sherbs.com/pages/herbpictures/ephedra2386L.jpg)

other, similar habitats in the Mediterranean, India, Persia and South America. *Ephedra* is dioecious and a gymnosperm. Its ideal habitat includes dry regions of sandy or rocky deserts. This habitat provides the well-drained soil needed for growth,

but may not be conducive to the copious amounts of water needed to provide the best conditions (Yang, 2004).

Ephedra is a green, erect species, with a plethora of branches, each individual branch contains roughly two opposing scale-like leaves, or a 'whorl' of three (**Figure 1**). During propagation, the dioecious (rarely, some are found to be monoecious) males produce egg-shaped seeds, which it stores. During autumn or spring, the smooth, mature male gametes are seeded into the female's mature, fleshy bract. Up to three seeds are inserted per bract. *Ephedra* can also propagate through root division, but this is a rare occurrence (Yang, 2004). Characteristics of *E. sinica* include; dark, reddish-brown seeds; bitter taste when brewed into coffee; and no particular smell (although decomposition can cause a distracting odor.)

Traditional Uses

Although *Ephedra sinica* has been used for many thousands of years, its history can be viewed as bleak. Its first use was noted around 3,000 B.C., where it was considered somewhat of a miracle drug. Physicians would prescribe *Ephedra*, or more commonly known at the time as, Ma Huang, to treat a number of conditions, including; the common cold, asthma, arthritis, hay fever, hypotension and other conditions.

Ma Huang was listed in the first chapter of a classical Chinese herbalism text, written by Sheng Nong in the first century A.D. Its many manipulations have allowed for a broad range of treatments. Although, *E. sinica* is limited to Asia, other *Ephedra* species have been used in the Middle East for asthma and other similar conditions (Frank, 2009).

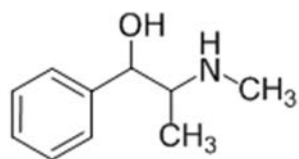
Traditionally, Ma Huang has been prepared and administered as a tea, by adding two grams of the most concentrated

portions of the Ma Huang into eight ounces of water, and boiling for ten minutes. This produces a 15 - 30 mg serving of Ephedrine (Crazyforte.com, 2007). Presently, synthetic Ephedrine has been administered in several ways, most often as dietary pills, which range in concentrations of 10 - 80 mg (Herb Research Foundation, 1995).

Ephedra's traditional use has been limited to its physiological properties. Its physical properties as a shrub, do not lend it to more artistic uses, such as clothing or dye. But, its stimulant properties have led to more creative uses. Much like coffee, it has been brewed to make a recreational tea. Made by Mormon settlers in the 1800's to replace tea (considered taboo by their religion), Mormon settlers brewed to the herb to produce "Mormon tea" (Larsen, 2009). After the synthesis of ephedrine, use of *E. sinica* and its derivatives skyrocketed. Along with its prescribed use, ephedrine become synonymous with weight loss, athletic enhancement and substance abuse. In particular, weight loss products contained considerably higher doses than traditional use. These can be dangerous concentrations and prompted criticism over *Ephedra's* potential harm. Its abuse as an over-the-counter medication has resulted in several deaths, especially in teenagers (Nertheim, 2003).

Chemistry & Pharmacology

The chemical composition of *E. sinica* includes: Ephedrine alkaloids 0.481-2.47% (l-ephedrine, d-pseudoephedrine, l-norephedrine, d-norpseudoephedrine, l-methylephedrine, d-methylpseudoephedrine), 2,3,5,6-tetramethyl-pyrazine 2,3,4-trimethyl-5-phenyloxazolidine-benzylmethylamine, ephedroxane, essential oil 0.25% (1- α -terpineol) (Chen, 2004). Although the amount of constituents is rather abundant, the active ingredients comprise only a relatively small amount.



ephedrine - an indirectly acting sympathomimetic amine, a bronchodilator and vasoconstrictor

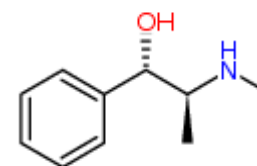


Figure 3. Structure of pseudoephedrine. (Source: <http://isomer design.com /Cdsa/C/dl375.png>)

Figure 2. The structure of ephedrine. (Source: <http://www.thekanjifoundrypress.com/sketch%20files/e%20GIF/ephedrine.gif>)

The active components of *E. sinica* are alkaloids. Of the total makeup, alkaloids compose about .5 - 2.5% of the entire chemical composition. Of this .5 - 2.5%, ephedrine and pseudophedrine account for up to 90% (Haller, 2010).

Ephedrine (**Figure 2**) and pseudophedrine (**Figure 3**) work by increasing the amount of epinephrine and norepinephrine, which are sympathetic nervous system neurotransmitters. As well, ephedrine stimulates receptors found in the central nervous system and circulatory system (Edward, 2009).

Biological Activity

Ephedrine, the most abundant and potent alkaloid in *Ephedra sinica*, works by increasing the amount of norepinephrine reuptake. This is accomplished by increasing the amount of norepinephrine released from its terminal storage vesicles, into the synaptic cleft. More neurotransmitters allow for more activated terminal receptors. In turn, these receptors initiate a cascade of enzymatic reactions. Receptor stimulation increases production of adenylate cyclase, which prompts an

increase in the enzyme kinase. This acts like a amino-acid based hormone and stimulates cyclic AMP levels, which increases lipid metabolism (Edward, 2009).

This mechanism (**Figure 4**) contains potential for medical miracles and recreational exploitation. The ability to manipulate the sympathetic nervous system allows for the systematic utilization of its benefits, such as increased metabolism. Conversely, this provides an amped or excited state popular among athletes. This explains the controversy and numerous conflicting studies over its potentially harmful effects.

Clinical Studies

In one study, the researchers investigated 37 cases of cardiovascular disease that were directly related to the use of Ma Huang. The results indicated that Ma Huang was temporarily related to stroke and death, even if there was no underlying medical problems and dosage requirements were followed (Samenuk, 2002). Another study was conducted over its effects as a dietary supplement. This study reported that its benefit/ detriment ratio that was well within acceptable limits. Stating that after an eight week trial, patients that used an *E. sinica*/caffeine combination lost over

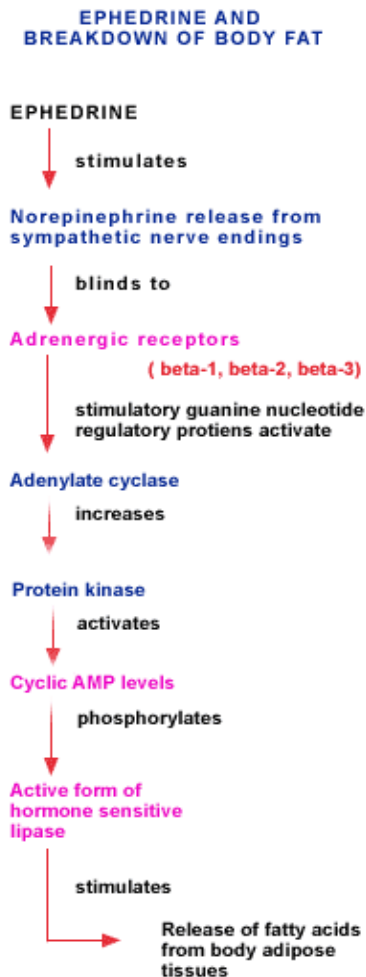


Figure 4. Catabolism of ephedrine in the body.

two pounds (lbs) more, per month, than the placebo-control group. However, the study also found that there was a definite increase in gastrointestinal and psychiatric symptoms, as well as an increased number of heart palpitations (Pittler, 2004). There is a plethora of conflicting research over

E. sinica. The results can be construed to fit your needs, but the overall consensus tends to be positive, if used under appropriate conditions.

Contraindications

The dangers associated with this plant stem from its stimulant activity. Patients should avoid *E. sinica* if they have a history of cardiovascular disease, angina, hypertension, thyroid disease, enlarged prostate, Insulin resistant diabetes, anxiety, history of substance abuse and other similar conditions. Adverse reactions can consist of nervousness, anxiety, insomnia, anorexia, hypertension, tachycardia, arrhythmias. Prolonged use can lead to addiction, eating disorders and its use has been linked to psychoses, strokes, heart attacks and abrupt deaths (Thomas, 2010).

Furthermore, care should be taken to avoid potentially harmful drug interactions. Combination of Ephedra with other stimulants can magnify the aforementioned adverse reactions. As well, Beta blockers and monoamine oxidase (MAO) inhibitors in conjunction with Ephedra can lead to lethal hypertension. Phenothiazines can counter the effects of Ephedra, causing an unsafe drop in blood pressure, known as hypotension. Theophylline can increase the risk of CNS and GI problems. Other examples of drug interactions that should be watch for, include; oxytocin, antidepressants, digoxin, guanadrel, guanethidine, mecamylamine, methyldop, thyroid therapies, diabetes medications, dexamethasone, diuretics, ACE inhibitors, ergot alkaloids, anesthetic drugs, Morphine, gout medications and St. John's Wort. In short, any patient debating on using this medication regularly should seek a physician's advice (Thomas, 2010).

Current use in Allopathic and CAM therapies

Ephedra is a hybrid of sorts, graying the lines between Allopathic and CAM therapies. Because of its properties of a bronchodilator, it is used to treat asthma, bronchitis, nasal congestion, the common cold and sinusitis. These are both traditional practices and common allopathic uses (although, there are several more westernized medicines commonly used to treat these as well) (Thomas, 2010). Its effects as a stimulus have been used to treat hypotension, weight management and more notably among the alternative side, it has been used to treat attention deficient disorder in children (Myatt, 1990).

Discussion

Ephedra sinica is a unique and powerful medicine, that has transcended generations and its use today is no less significant than its use 5,000 years ago. The ability of a single medicine to treat an array of conditions is unparalleled. Through its sympathetic-stimulating mechanism, *E. sinica* has been able to treat conditions from hypotension to the common cold. This dynamic herb has had no humble beginning, earning a rare spot among the world's earliest medicines. Thus, Ma huang remains ageless and will only become more relevant in the next 5,000 years.

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Ficus insipida Willd., Moraceae

Jennifer C. Howell

Introduction

Ficus insipida Willd. also known by its other scientific names, *Ficus glabrata* H.B.K. and *Ficus anthelmintica* Martius and common names such as wild fig, ojé, posen, higueron, and glabrate fig belongs to the Moraceae family, also known as the fig family (Smithsonian; Tropicos; University of Hawaii; Hansson et al., 2005; de Armorin et al., 1999). It is a large buttressed tree that produces relatively small fruits (figs) and grows in the tropical regions of Central and South America, including the Amazon basin (Smithsonian; Tropicos). The latex of this tree has been copiously used throughout Amazonian villages, particularly in Peru, where it is applied traditionally as a vermifuge in both children and adults. The latex is used to treat helminthiasis, anemia, diarrhea, malnutrition, immune deficiency, and other such effects resulting from these physiological compromises (Quave 2000; de Amorin et al., 1999; Jernigan 2011; Phillips 1990).

Very few studies have specifically investigated the biological activity of latex derived from *F. insipida*. Of the studies conducted, the efficacy as an anthelmintic as well as the toxicity of the latex was proven, both at low and high doses (de Amorin et al., 1999; Hansson et al., 2005). The active constituent found to digest and get rid of the parasites, causing helminthiasis, was ficin. Ficin is a class of papain-like cysteine proteases (Gonzalez-Rabade et al., 2011). The use of this tree's latex is still in practice today as an alternative to allopathic medicine and/or as the primary source of treatment (Hansson et al., 1986; Natural Remedies Haven Ltd.).



Figure 1. *Ficus insipida* tree (Smithsonian).

Botanical Description

Ficus insipida can be found in forest areas in places such as Mexico, Central America (mainly in Panama, Costa Rica, and Peru), South America (stretching as far as Brazil), and in the Amazonian regions (Tropicos). This plant is a free-growing, non-flowering tree reaching approximately 40 m tall with a grayish-tinted smooth bark and large buttressed roots protruding from the ground (**Figure 1**). Additionally, a milky latex sap can be found in the tree, which gives the tree one of its defining characteristics. The leaves of the tree are characterized by their long stretched oval shape, ranging from 10-40 cm long and 5-16 cm wide depending on the maturity of



Figure 2. *Ficus insipida* leaves (Smithsonian).

the leaf; the veins occur in 15-30 pairs angled slightly up and out from the center and base (**Figure 2**). The fig, *F. insipida*'s fruit, at maturity displays a yellowish-green color with lighter yellowish-green spots. These figs only reach about 5-15 cm long when fully matured (**Figure 3**). In order for the tree to grow, the seedlings require a sufficient amount of light, meaning many of these trees are found in “younger” or newly formed areas of forests (Smithsonian). The sustainability of these trees includes guidelines that only allow for a particular tree to be tapped after the tree has reached at least seven years of maturity, leaving a gap of twelve months between each tapping, and not allowing a cut of more than 1 cm in the tree to ensure tree viability (Phillips 1990).

Because of its similarity to other species in Costa Rica and Panama, this particular species of fig tree has been confused

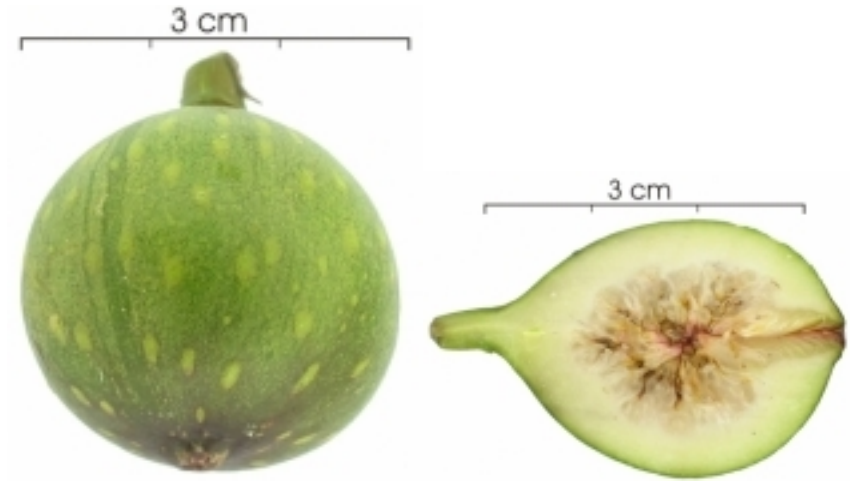


Figure 3. *Ficus insipida* fruit (Smithsonian).

(by untrained eyes) with species *Ficus crassiuscula* Warb. One of the main tell tale signs that these species are not *F. insipida* is that *F. insipida* only proliferates at elevations below 500 m whereas the other species occur at elevations above 1,000 m. Also, *F. insipida* has a different pollinator from the other two species (Smithsonian). Each *Ficus* species has a species-specific wasp that contributes to the pollination process. One of the known pollinators of *F. insipida* is the agaonid wasp. These wasps, like many of the other fig wasps, use the syconium, a fleshy hollow enclosure inside the surface of the fig fruit, as a mating receptacle. When these wasps retreat from the fruit, seeds are carried along and dropped along the wasps' path, thus spreading the seeds of the fig tree and prolonging the existence of *F. insipida* (Smith and Bronstein, 1996). While studying *F. insipida* at the Le Selva Biological Station in Costa Rica, bats and fish were also found to be pollinators of the tree (Banack et al., 2002).

Traditional Uses

The latex from this species has been used traditionally as an anthelmintic in Central and South America (de Amorin et al., 1999). Based on current knowledge sought out by Hansson et al. (2005), indigenous populations living in the upper Napo River region of Peru that have used or currently use *Ficus insipida* to treat parasitic-related illnesses, mainly in children, did/do not relate the parasites to the illnesses (ex. anemia and diarrhea). Rather, they felt that since one was born with such parasites, they were merely treating the symptoms, such as diarrhea, respiratory complications, and pale complexion, and not the eradication of the parasites. Another reason for the disconnection between the parasites and illness is due to the fact that the transmission of these parasites to the child is accomplished via non-boiled or unsanitized drinking water and/or via the soil.

Preparation of the remedy involves collecting the latex in a jar the day before treatment, to ensure freshness. The latex is then mixed with the juice of oranges, cocona, or sugar cane and given orally in small doses (spoonfuls). The latex is sometimes mixed with sugarcane brandy to prevent decomposition and fungal growth, in order to prolong storage (Hansson et al., 2005). This is done in the early morning, before sunrise. Accompanying the latex mixture is a period of fasting in which only sanitized water is drunk throughout the day. At night a light meal of plantains and manioc is commonly eaten; foods such as peppers, salt, and meat are avoided several days before and after the use of this remedy. To treat anemia, diarrhea, and abdominal distension, this remedy is taken for 2 consecutive days once every 4 months, to avoid overdose. The remedy is considered successful when visible symptoms have disappeared (Quave 2000).

Among the peoples of the Peruvian Amazon that speak Iquito, the approach to healing involves not only dietary restrictions and limiting physical activity but also the use of plants associated with specific plant spirits, to avoid exacerbating illnesses. According to a study conducted by Jernigan (2011), the Iquito speaking people believe that diarrhea comes from temperature, dirty water, and bad food, parasites result from walking barefoot and eating bad, and anemia comes from having bad blood, lack of blood, and bad hygiene. Spirits associated with certain plants are integral into the type of diet and illness treated. Unlike the peoples living in the Napo River region, this group believes *F. insipida* has a plant spirit that helps in treating only parasites. *F. insipida* remedies are accompanied by strict diet guidelines because it is believed, by the Iquito, to be a “jealous” spirit. Another group that uses the latex mixture are the Ese-Eja Indians, who tap the tree for latex in the early morning when it is most viscous and distribute dosages according to the season (Phillips 1990).

Chemistry and Pharmacology

In a recent study, the chemical constituents of *Ficus insipida* were measured from the reserves at La Selva Biological Reserve in Costa Rica via the leaves collected from the tree. The leaves were dried and subsequently doused in 70% acetone to extract constituents. All constituents found can be seen in **Table 1** (Ardon and Pringle, 2009).

The active constituent that gives this tree its anthelminic properties is the proteolytic enzyme ficin, also known as ficain (de Amorin et al., 1999). Ficin is a general term for the cysteine proteases, in the papain family, found within the *Ficus* genus (Azarkan et al., 2011). Ficin contains 2 L-cysteine thiol groups; these thiol groups act as catalytic sites (Malthouse and Brocklehurst, 1976). It is at these sites that

Known Constituents	% Mass
Condensed Tannins	0.5
Total Phenolics	11.8
Hydrolysable Tannins	2.7
Lignins	8.3
Cellulose	19.1
Hemicelluloses	14.7

Table 1. Known constituents of *Ficus insipida* expressed as a percent mass of the plant.

ficin is able to digest the parasitic invaders without harming the human host. Peak activity of ficin was found to be at pH 7.0 and found to be related to the solvents added, such as sucrose, trehalose, and xylitol (Devaraj et al., 2008). Cysteine proteases are used by the plant in insect resistance, protein degradation, maturation, to regulate the folding of proteins, and in some cases involved in proteolysis. They also are involved in the assembly of storage proteins for seed utilization. For insect resistance, it was found that the hydrolytic enzymes are involved in the inhibition of larvae growth (Gonzalez-Rabade et al., 2011).

Biological Activity

In a study conducted by de Amorin et al. (1999), mice infected with helminthes (*Syphacia obvelata*, *Aspicularis tetraptera*, and *Vampirolepis nana*) and treated with *F. insipida*-derived latex at 3 ml/kg/day for 3 consecutive days showed significant elimination of *A. tetraptera* and *V. nana* but not *S. obvelata*. During necropsy of the animals they found hemorrhagic effects in the mucosa of the gastrointestinal tract. When a high dose of 10 ml/kg/day was applied for 3 consecutive days, the authors found a lethality of 60%, thus, demonstrating the toxicity of this latex at both high and low doses.

Clinical Studies

A clinical study consisting of 181 persons from three Amazonian villages sought to determine the safe and effective dosage of latex taken systemically. The persons involved held a 92% prevalence of helminthiasis: *Ascaris* 68%, *Strongyloides* 42%, *Trichuris* 41%, *Ancylostoma/Necator* 26%, and *Taenia* 1%. Biological activity was measured using a milk coagulation test. Pharmacological efficacy was determined using live *Ascaris*, *in vitro*, in which concentrations of latex (in physiological saline solution) as low as 0.05% was sufficient for the suppression and digestion of *Ascaris* (Hansson et al., 1986).

The anthelmintic activity of *Ficus insipida* was studied retrospectively over a 12-year period by Hansson et al. (2005) in Pucallpa, Peru. This area was of great interest due to the 39 reported cases, involving mostly children, of *F. insipida*-related symptoms due to toxicity. Of the 39 cases, the majority were due to overdoses (small >1.5 cm³/kg, large >4 cm³/kg). One fatality occurred among the hospitalized patients, while two fatalities were reported to have occurred outside the confines of the hospital. In severe cases of toxicity cerebral edema was reported, for which the treatment was mannitol.

Additionally, in less severe overdoses adults were reported as having primarily cardiovascular and respiratory complications and children were reported as having more musculoskeletal complications, while both adults and children were reported as having gastrointestinal issues. The treatment for the less severe cases involved various kinds of drugs including antacids, pyridoxine, atropine, and dexamethasone, depending on the symptoms present.

Contraindications

It has been reported in both adults and children that gastrointestinal complications, cerebral edema, and death have occurred. However, only large overdoses ($>4 \text{ cm}^3/\text{kg}$) have been reported to cause the cerebral edema and fatalities (Hansson et al., 2005).

Current Use in Allopathic and CAM Therapies

There are no current uses of *Ficus insipida* latex in allopathic medicine; however, it is still used in today among Amazonian villagers and among those who live near those areas where *F. insipida* flourishes. In Peru, bottles of latex mixtures are sold by independent vendors in many of the main markets. Although the sale of the latex mixtures is still lucrative, it is not as prominent as it once was, due to the accessibility to allopathic medicine. According to the vendors, the recommended dose is approximately $2 \text{ cm}^3/\text{kg}$, which can be taken over the course of three days, and should be taken in the early morning on an empty stomach, following a conservative diet for the rest of the day. This regimen should be applied once or twice a year, as needed (Hansson et al., 2005). This slightly contradicts the recommended dose found to be safe through clinical trials: 1 cm^3 of latex mixture/kg for 3 days every 3 months (Hansson et al., 1986).

Natural Remedies Haven Ltd. currently markets, online, *F. insipida* latex as an alternative supplement, in the form of ojé latex sold in 25 ml bottles, to current pharmaceuticals (**Figure 4**). The ojé latex is mixed with either water or fermented with sugar. The company markets this to treat worms, bacteria, anemia, and rheumatic inflammations. As for the dosage, they recommend mixing one tablespoon of the latex mixture with



Figure 4. The 25 ml bottle of *F. insipida* latex marketed by Natural Remedies Haven Ltd. (Source: http://www.weight-care.com/herb_Ojelatex.htm)

one liter of water, and to drink this mixture every other day until the problems subside (Natural Remedies Haven Ltd.).

Discussion

The latex derived from *Ficus insipida* Willd. has been used traditionally for generations among the peoples of the Amazonian region for the treatment of helminthiasis and its resulting symptoms. Because of this tree's distinct characteristics and the vast exposure Amazonians have experienced with this tree, it is not confused with other species from the *Ficus* genus. The traditional preparation of the latex is still in practice today. The maximum biological activity is achieved when the latex is mixed with sugar (sucrose), which reflects its traditional preparation. This latex mixture is sold locally in markets and internationally (on a very small scale) via the internet. Quality of the latex being

sold, at least among the local markets, is of little concern because of the abundance of the tree and the knowledge the vendors carry about the preparation and use of the latex. The toxicity experienced from those taking *F. insipida* mixtures is not due to taking the improper latex from other *Ficus* species, but rather taking an overdose of the *F. insipida* latex.

Furthermore, the use of this latex has yet to become a dominant remedy globally due to the limited availability of the tree worldwide and to the ability to access either allopathic or safer, alternative CAM therapies. Another reason these latex or pharmacologically-derived latex remedies are not found in allopathic medicine is that the associated risks and possible side effects far outweigh the benefits that come with the use of the latex compared allopathic remedies, which are often much safer and more readily available. Additionally, the active component, ficin, is currently not isolated from this tree, for reasons unknown, even though ficin has been found to be involved in several diseases and cell signaling pathways. However, because of the relatively easy access to this particular species and the growing importance of the cysteine proteases found within this plant, future pharmaceuticals will probably include some form of these cysteine proteases, whether it be synthetically derived forms or pure forms.

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Ginkgo biloba L., Ginkgoaceae

Benjamin Kramer-Roach

Introduction

Ginkgo biloba L. (**Figure 1**) is the sole surviving member of the Ginkgoaceae family, a family of “living fossils” that has its roots in the Mesozoic era (Taylor, 1993). In more recent times *G. biloba* is thought to only grow natively in a certain region of Southeast but it is now common to find them in many countries throughout the world. Botanist Engelbert Kaempfer introduced the ginkgo tree to Europe in 1690 and gave it the name “duck foot tree” due to the signature shape of its leaves (Bilia, 2002). The name “ginkgo” is derived from the Chinese word for silver apricot, and this name was given to the tree because of the size and coloring of the fruit (Mahadevan, 2008). Other common names of *G. biloba* include silver apricot, yajiao (duck foot), gong sun shu (grandfather tree), maidenhair tree, temple tree, noyer du Japon, Kew tree, and Ginkgobaum (Hori, 1997). The leaves and nuts of this tree have been used in traditional Chinese medicine (TCM) for millennia to treat a variety of ailments involving the brain, heart, and lungs. In modern medicine ginkgo extract is primarily known for cognitive enhancement and treatment of cardiovascular problems, but the standardized extract (EGb 761) has shown promise as a cancer-preventative as well. As with every plant-based medicine, it is challenging to attribute the medicinal effects of *G. biloba* to a single chemical or pathway because of the synergistic tendencies of the chemicals. Ginkgo leaves have been shown to contain terpene lactones, biflavones, and flavonoid glycosides, which act on a variety of pathway and receptors (Spinella, 2001). These chemicals provide it with ample resistance to infections and



Figure 1. *Ginkgo biloba* tree.

Source: David Stang, Tropicos.org

insect invasions, which has led to its proliferation in cities and gardens and has made it extremely popular in global markets for its perceived cerebral enhancing properties. In addition, it

is annually a top-selling herbal supplement sold around the world for its effects in boosting memory (van Dongen, 2000).

Botanical Description

Approximately 180 million years ago, the Ginkgoaceae family extended to nearly every continent, from sub-polar regions like Canada to the tropics. *Ginkgo biloba*, though, the last remaining species, is now thought to only grow in the wild in the Zhejiang Province in China, specifically on the Tian Mu Mountain (Shen, 2005). However, mystery still shrouds the origins of this population, and there is debate over whether the trees are truly wild or are merely semi-wild descendants of trees cultivated in Buddhist temples (Del Tredici, 1992).

Ginkgo trees grows best in cool, wet climates and in deep soil with good water retention, but in recent decades it has been able to adapt to a variety of habitats around the world due to their high resistance to disease, insects, and air pollution (Andrews, 1947). Ginkgo trees are dioecious, meaning that each tree produces either all male or all female flowers. The trees themselves can grow to be around 100 feet (30 meters) high and have been known to live thousands of years. They do not start producing seeds for up to 25 years, but can remain fertile for as long as they live (Taylor, 1993). Flowers appear in spring from stubby appendages on the branches, called short roots, in small clusters as catkins. The plum-sized fruit ripens throughout the fall to a golden color and covers the seed in a plump outer covering and a woody shell. Fertilization occurs via motile, multi-flagellated sperm from the pollen (Dallimore, 1948). Due to the butyric acid content of the fruit, when the ripe fruit falls and splits open during autumn, it emits a powerful odor, akin to rancid butter, despite the edible nut inside (Andrews, 1947). Male trees, which do not bear fruit, tend to be more common in



Figure 2. Leaves and fruit of *Ginkgo biloba*.

Source: W. H. Hodge from Tropicos.org

ornamental areas like cities and gardens to avoid the odoriferous fruit.

The leaves of *Ginkgo biloba* are flat and fan-shaped and exhibit two lobes divided by a cleft of varying sizes, a trait to which *G. biloba* owes its name (**Figure 2**). Sprouting in clusters of 4 - 8 from the short roots, the leaves emerge light green in the spring and fade through dark green to a golden color in late autumn. The veins on the leaves are unique from other shade trees in that rather than having a mesh-like structure, ginkgo leaves have a branching venous pattern that protrudes from the stem and branches continuously to fill out the leaf (Andrews, 1947).

Traditional Uses

Ethnomedicinal uses

Ginkgo biloba has a long history of use in traditional Chinese medicine (TCM) with a host of uses. The seeds or nuts, removed from the outer fruit, were used to treat certain pulmonary disorders, like asthma, bronchitis, cough, and

enuresis, in addition to bladder inflammation, kidney ailments, and leucorrhoea (Mahadevan, 2008; Bilia, 2002; Smith and Luo, 2004). The seeds have been used extensively in TCM for millennia. In contrast, leaves of *G. biloba* were only used marginally in the past and were first recorded to have medicinal properties in a book by Lan Mao, published in 1436 C.E., when they were recorded to have effects on treating skin disorders such as head sores. A little later, in 1505, C.E Liu Wan-Tai wrote about the first internal use of ginkgo leaves, which was for the treatment of diarrhoea (Bilia, 2002). The leaves, though, have grown to be seen as being beneficial to the heart, brain, and lungs (Mahadevan, 2008; Bilia, 2002).

Uses in cuisine

The seeds, often called Pak-Ko (meaning white fruit), are a popular snack and considered a delicacy in many East-Asian countries, including Japan, Korea, and China. They can be cooked into sweet desserts, like the dish Cheng Tengm, or roasted and eaten as an appetizer (Porterfield, 1951; Goh, 2002). Ginkgo seeds, shown in **Figure 3**, are in season during winter months after the fruit has matured (Goh, 2002). The extraction of the seed begins by harvesting the plum-sized fruits from the tree and allowing them to ferment in water for several days. (This process causes a highly unpleasant aroma.) If the fruit itself is eaten, it has a bitter taste and is therefore typically fermented or cooked (Mahadevan, 2008). Once soaked in water, the flesh of the fruit can be easily removed from the edible seed within. The seeds must be roasted or cooked because raw seeds are toxic and consumption of them often results in serious food poisoning (Bilia, 2002). Traditional Chinese foods like chawan-mushi, a custard-like dish, and nabe-ryori incorporate ginkgo nuts as a main ingredient (Bilia, 2002).



Figure 3. *Ginkgo biloba* seeds and nuts.

Source: Oregon State University, 1999-2012.

Cultural uses

Taoist beliefs incorporate the balances of yin and yang and are often represented by certain plants and animals. Ginkgo is used to exemplify this concept, with one temple serving a dish called ginkgo chicken, with ginkgo representing yin and rooster symbolizing yang. It is believed that when eaten as a whole, the dish replenishes vitality (Shermann, 1985).

Due to its beauty and hardiness against disease, insects, and air pollution, *G. biloba* has been a popular ornamental tree for thousands of years (Briskin, 2000). It appears in Buddhist temples in both China and Japan, but its popularity has grown and can now be found in many countries all across the world, particularly in urban centers (Bilia, 2002). The unique elegance of the leaf has also led to its incorporation in various forms of art and sculpture.

Chemistry and Pharmacology

Ginkgo biloba has a multitude of phytochemicals, including terpene trilactones, flavanol glycosides, biflavones,

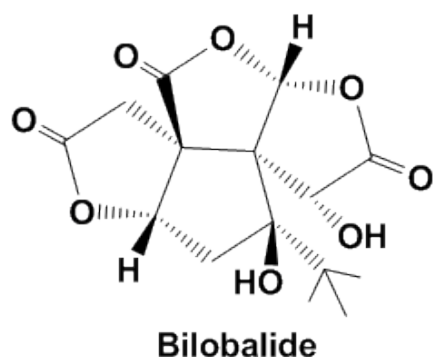


Figure 4. Structure of bilobalide. Source: <http://www.pipitech.com/newproduct/bilobalide/bilobalideLS.htm>

proanthocyanidins, alkylphenols, polyprenols, and 4-O-methylpyridoxine (van Beek, 2002). The unique, primary constituents found in *Ginkgo biloba* are terpene lactones, biflavones, and flavonoid glycosides. The terpene trilactones include bilobalide (technically a sesquiterpene trilactone), shown in **Figure 4**, and five types of ginkgolides (A, B, C, J, and M), which are twenty-carbon terpenes manufactured in the roots and leaves of the tree (Mahadevan, 2008; Smith, 2004; Spinella, 2001). The flavonol glycosides include compounds such as quercetin, rutin, kaempferol, and isorhamnetin (van Beek, 2002; Mahadevan, 2008). Other chemicals such as Isoginkgetin, ginkgetin, bilobetin and sciadopitysin are all biflavones (van Beek, 2002).

A standardized extract was developed by German and French pharmaceutical companies called EGb 761, which is the main extract used in experiments. The chemicals are extracted through either a water-ethanol or water-acetone process from green leaves harvested and dried in the summer (Mahadevan, 2008; Bilia, 2002). The chemical constituency of the leaves varies depending on the season, with greater flavanoid

Class	Major Constituents	Approximate % in EGb 761
Flavanol glycosides	Quercetin, kaempferol and isorhamnetin	24
Carboxylic acids	Phenolic and non-phenolic acids	13
Proanthocyanidins	-	7
Terpene trilactones	Sesquiterpene trilactones (bilobalide) Ginkgolides A, B, C, J, and M	6
Alkylphenols	Ginkgolic acids, ginkgols and bilobols	5 - 10 ppm
Biflavones	Bilobetin, ginkgetin, isoginkgetin and sciadopitysin	0
Polyprenols	-	0
-	B6 4-O-methylpyridoxine	0

Table 1. Chemical constituents of *G. biloba*. (Information derived from van Beek, 2002)

concentration in the fall than in the spring, and therefore the leaves must be analyzed during the multi-step extraction process for chemical levels and presence of heavy metals before being made into the extract (Mahadevan, 2008; Chan, 2007). The creation of this extract involves many procedures, some of which are undisclosed, and condenses leaves to extract in the ratio of 50 to 1. This concentration also removes unwanted components like biflavones, catechins, and polyprenols, which can have negative health effects (Chan, 2007; van Beek, 2002). Consuming ginkgo leaves, as in a tea for example, instead of extract has minimal health effects because of the extremely low concentration of active chemical compounds (Chan, 2007). The standardized *Ginkgo biloba* extract contains approximately 6% terpene lactones, 24% flavonoid glycosides and less than 5 ppm Ginkgolic acid (Van Beek, 2009; Goh, 2002). The chemical constituents of *G. biloba*

are listed in **Table 1** with their associated concentrations in the extract.

Proanthocyanidins, also found in wine, are partly responsible for the antioxidant properties of the extract and contribute to ginkgo extract's medicinal effects (van Beek, 2002). B6 4-O-methylpyridoxine, a chemical found in primarily in the seeds, is toxic to humans and is removed in the creation of the extract (van Beek, 2002).

Biological Activity

In Vivo

Numerous studies have been conducted to test the benefits of standardized *Ginkgo biloba* extract (EGb 761), particularly for its memory enhancement capabilities and its efficacy in protecting against neurodegeneration.

A study by Winter (1997) tested the memory effects of EGb 761 extract on rats. The rats were first acclimated to a multi-armed maze and the number of false starts made by the rats was recorded. The research found that rats that had been orally administered EGb 761 via consumption of sweetened, condensed milk showed improved memory, as judged by fewer false starts. Moreover, rats that consumed EGb 761 lived significantly longer than those that had not (Winter, 1997). A study by Anna Walesiuk et al. (2005) found that rats subject to either stress or drug-induced memory loss regained memory function with the addition of EGb 761 into their diet. In an experiment by Yohitake (2010), aged rats improved their spatial cognition after doses of *Ginkgo biloba* extract were administered. In addition, the extract was effective against Alzheimer's and Parkinson's disease in animals tested (Yohitake, 2010). Extracts have also been shown to

improve memory function and spatial learning in young and old rats as well as short-term memory in mice (Perry, 2011).

By acting on the hippocampus in animals, which is involved with the creation of new memories, EGb 761 was shown to boost memory retention and acquisition in other vivo studies as well (Smith and Luo, 2004). EGb 761 was found to be beneficially involved with the following processes in rats: free radical scavenging, age-related brain losses, ischaemic neuronal death, hippocampal function, hippocampal uptake of high-affinity choline, regulation of hippocampal glucocorticoid receptors, plasticity of neurons, and stress-related cognitive deficits (Smith and Luo, 2004).

Smith and Luo (2004) found that *Caenorhabditis elegans*, a nematode, demonstrated increased resistance to both thermal and oxidative stress when fed EGb 761. Similarly, rats treated with moderate amounts of ginkgo extract through their drinking water showed reduced oxidative damage to mitochondrial DNA in the liver and brain (Chan, 2007). This emphasizes the importance of antioxidants as a component of ginkgo extract (Smith and Luo, 2004).

To highlight another pathway that ginkgo extract effects, mice fed EGb 761 for four weeks in one study showed a dramatic up-regulation in ten genes that have neuroprotective roles (Smith and Luo, 2004). Other studies along the same theme point towards the capability of ginkgo extract to regulate transcription of certain genes pertaining to adaptive response of organisms thereby increasing tolerance to oxidative stress (Smith and Luo, 2004). The stress-reducing activities of ginkgo extract suggest effects on receptors in the dopaminergic system (Yohitake, 2010).

Rats fed EGb 761, one study showed, had substantially decreased levels of stress, which researchers attributed to the effects of the ginkgolides on the expression of the peripheral

benzodiazepine receptor in the adrenal cortex (Smith, 2004; DeFeudis, 2000). This reduction helps to control levels of circulating glucocorticoids, which has extensive favorable consequences such as decreased immunosuppression, neurotoxicity, and neuroendangerment (Amri et al., 1996).

Certain flavanols, like kaempferol, have been tested for cancer prevention and some studies have found a positive effect on colon and prostate cancers (DeFeudis et al., 2003). Monte et al. (2004) found that in mice, EGb 761 inhibited lymphocyte-induced angiogenesis, a process essential to cancer growth. Similarly, DeFeudis et al. (2003) found that mice given ginkgo extract showed decreased expression of peripheral benzodiazepine receptor (PBR) and therefore suppressed proliferation of breast cancer cells. Feng, et al. (2009) found that the flavanoids in ginkgo extract exhibited anticancer properties. When the extract was administered to mice with leukemia, many of the treated mice showed signs of tumor suppression and reduction after a week and a half of treatment (Feng, 2009).

In Vitro

The neuroprotective qualities of EGb 761 are derived from its reaction with many cellular pathways simultaneously and synergistically (Smith and Luo, 2004). In vitro EGb 761 was observed to have multiple methods of action for its neuroprotective characteristics such as up-regulating certain proteins and maintaining membrane potential in mitochondria. (Smith and Luo, 2004). Likewise EGb 761 has been shown to improve cardiac conditions by altering ion concentrations across membranes, thus altering action potentials that results in vasorelaxation and vasodilation in aortic smooth muscles (Satoh, 2004).

Both the proanthocyanidins and flavonol glycosides have antioxidant properties, such as free-radical scavenging, which can reduce oxidative stress (Chan, 2007). This is also responsible for some of the relaxation of blood vessels, and thus the increased blood-flow, effects of the extract (Kleijnen and Knipschild, 2002).

An altered version of EGb 761, called IPS200, was administered to human breast cells in an in vivo study conducted by DeFeudis et al. (2003). The study found that the altered version had regulatory effects on a number of genes involved with cell proliferation and apoptosis, suggesting anti-cancer properties.

Clinical Studies

There have been many clinical trials of *Ginkgo biloba* leaf extract, particularly EGb 761, for its cognitive enhancing abilities on both mentally impaired and healthy people, the treatment of other conditions involving cardiovascular deficiencies and neurodegenerative disorders, its antioxidant and anxiolytic effects, and its efficacy in treating antidepressant-induced sexual dysfunction. Many of these found ginkgo extract to have an overall beneficial effect.

There is a wealth of studies demonstrating the beneficial characteristics of EGb 761 on a number of ailments, but there are also many studies that found no substantial evidence supporting the use of EGb 761 for treating many of them. One study highlighted this schism in the literature by first positing that while they found mild cognitive improvement in patients treated with ginkgo extract, the trials with overwhelming success might have been due to other factors, and then in the same study, admitting that *G. biloba* is one of the plants most effective against dementia and other cognitive ailments like

premenstrual tension and tinnitus (Perry, 2010). The few studies showing no effect are lost among the flood of studies detailing the successes of ginkgo extract. In a series of clinical trials conducted by a research team, extract of *G. biloba* was found to be effective against a variety of conditions such as “early-stage Alzheimer’s disease, vascular dementia, peripheral claudication, vertigo, heart disease, eye diseases, chronic cerebral insufficiency, accidents involving brain trauma, dementia, and tinnitus of vascular origin” (Cxavusxog̃ lu, 2011; Napryeyenko, 2007).

In two trials testing the effects of ginkgo extract on healthy volunteers aged 18-40 and 22-59, at the dosage of 120 mg/day for thirty days and fourteen days respectively, both found that exposure to extract from the leaves increased the working memory of volunteers, but did not effect long-term memory (Hartley, 2003). Numerous other studies echo similar results in finding that healthy volunteers who had ginkgo extract of a comparable dosage showed an improved working memory, particularly in older subjects, while not exhibiting any changes in other types of memory like reaction time, attention, or word recall (Hartley, 2003). From this information it can be deduced that certain sections of the brain, most likely the frontal lobe (responsible for working memory), and certain age groups (primarily the elderly) are most affected by *G. biloba* extract (Hartley, 2003).

Most studies agree that *Ginkgo biloba* is effective in the treatment of Alzheimer’s disease and mental deterioration. This effectiveness can be attributed to several characteristics of chemicals found in the leaves. The extract inhibits the creation of the protein A β from its precursor β -amyloid, which is an essential step in Alzheimers disease pathogenesis. Aggregation of this proteolytic fragment exacerbates and promotes early onset and autosomal dominant versions of Alzheimer’s disease, which can be suppressed by EGb 761.

The reduction in A β also leads to decreased apoptosis of neurons: a counter to the cause of many neurodegenerative diseases (Mahadevan, 2008; Smith, 2004). Le Bars, et al. (1997) also found in a double-blind, placebo-controlled experiment that EGb 761 improved cognitive functioning in elderly patients with dementia or Alzheimer’s disease. Kleijnen and Knipschild (1992) found that when ginkgo extract (120-160 mg daily for a period of more than four weeks) was given to forty patients with cerebral insufficiencies, most experienced beneficial outcomes. The cerebral insufficiencies encompassed a range of symptoms from tiredness to confusion.

The alkaloids in the extract were found to be powerful antagonists of platelet-activating factors (PAF) in several studies. Since PAF are inflammatory autacoids and are important to the pathologies of inflammatory conditions like ischemia, asthma, CNS disorders, and shock, ginkgolides are a valuable natural defense against these diseases (Braquet and Hosford, 1991). Along the same lines, ginkgolides reduce aggregation, increase blood circulation, and can be used to increase blood flow to the brain after an ischemic incident (Smith and Luo, 2004). The sesquiterpene trilactone bilobalide has shown promise in reducing volume of cortical infarct following a stroke or cerebral ischemia by amplifying flow of glucose and oxygen to the brain (Smith and Luo, 2004).

There have also been several studies that found there was statistically significant data to support the use of EGb 761 to increase standards of living and mental well being in terms of decreased depression, anger, and fatigue (Cieza A et al.; Kennedy, 2007). Ginkgo extract was also found to be anxiolytic in humans and to reduce depression (Smith, 2004; DeFeudis, 2000; Evans, 2009).

The antioxidant properties in EGb 761 have also been found to be useful in treating sexual dysfunction. The antioxidants have the effect of protecting nitric oxide from degradation, which in turn activates the enzyme guanylate cyclase. This effect leads to producing smooth muscle relaxation in the penis, thus allowing an inflow of blood much like Viagra (Chan, 2007). This explains the results of a similar study, in which ginkgo extract was found to be highly effective in increasing sexual potency and minimizing the effects of antidepressant-induced sexual dysfunction (Cohen, 1998).

Contraindications

Ginkgo biloba leaf extract has been shown to have vasodilatory properties, which has given rise to worries about possible interactions with drugs that have anti-platelet forming or blood-thinning effects. One study even found an increased risk of hemorrhage when ginkgo extract was used in combination with more potent anticoagulants and blood thinners due to its effects on the platelet-activating factor (Perry, 2010). However, similar to the debate over whether ginkgo extract has cerebral enhancing properties, there are conflicting studies involving the negative side effects of ginkgo extract consumption. Specifically, one study focused on testing case studies that suggested negative synergistic reactions between *G. biloba* extract and drugs such as warfarin, aspirin, and ibuprofen (Izzo, 2009). Despite past claims that patients suffered from spontaneous hyphaemas or intracerebral haemorrhages due to drug reactions with ginkgo extract, this study found that there was no evidence for links between ginkgo extract and changes in blood coagulation parameters (Izzo, 2009).

On the other hand, there have been several instances of seizures, though not statistically significant, among people

taking high doses of *G. biloba* extract or consuming large amounts of the seeds (Spinella, 2001). In Germany, where much of the supply of EGb 761 is manufactured, companies are required to include on the label symptoms such as “headaches, dizziness, palpitations, gastrointestinal disturbances and allergic skin reactions” that can result from overdoses (Chan, 2007). Though these side effects must be included on the labels, a study by Kleijnen and Knipschild (1992) showed that there were no negative side effects to taking EGb 761 over a period of three months (Chan, 2007).

If the seeds are consumed raw they can produce symptoms of food poisoning and gastrointestinal problems due to the presence of the toxic 4-O-methylpyridoxine (van Beek, 2002).

Current Use in Allopathic and CAM Therapies

Ginkgo biloba extract is one of the most popular drugs and herbal supplements in Europe and the rest of the world, and it is part of a billion-dollar industry, primarily for its perceived value in increasing cognitive function (van Dongen, 2000). In 2008 in the U.S., *Ginkgo biloba*, as a dietary supplement and prescription drug, was the top-selling herbal medicinal product with a retail value of over \$150 million, even outselling popular herbal supplements such as echinacea, garlic, and ginseng (Smith and Luo, 2004). It is sold under a variety of trade names in America including “Ginkgobene, Ginkgold, Ginkoba, Vasan” and many others (Spinella 2001). Popular prescription and over-the-counter ginkgo-based drugs in Germany and France include brands like “Tebonin, Kaveri, rōkan, and Tanakan” (van Dongen, 2000).

As a dietary supplement ginkgo extract is typically taken by people looking to increase mental alertness, memory, and

attention, which makes it especially popular among the elderly. In addition, ginkgo extract is a powerful antioxidant and has appeal for its ability to fight aging and age-related mental disorders (Goh, 2002; Bilia, 2002).

Discussion

Ginkgo biloba is exceptional in many characteristics that make it extremely valuable socially, medically, historically, and economically. Its unique chemical constituents have helped the tree remain largely unchanged for millions of years, and give it resistance to infection, insects, and air pollution. This tree is found in nearly every country around the globe in urban centers and in temples in Japan and China. Traditional Chinese medicine has used ginkgo seeds for thousands of years and incorporates them into many foods and delicacies. The standardized extract, EGb 761, has been shown to increase memory in rats as well as to help prevent Alzheimer's disease and dementia, and the antioxidants also show promise in having anti-cancer and anti-aging properties. In humans it has also proven effective in promoting cerebral enhancement in healthy volunteers, increasing brain function after ischemic events, and helping with cardiovascular disorders. There have been no conclusive studies proving any side effects of usage and most studies have found ginkgo extract to be safe. It is sold as an herbal supplement, in 120 mg tablets, for its memory enhancement effects including increased sharpness and energy. As an herbal supplement its popularity has skyrocketed and is now part of a billion-dollar industry, despite not being approved by the FDA in America. This beautiful and noble tree will no doubt continue to appear in gardens and cities all over the world and will provide many cures for cerebral insufficiencies and hopefully several forms of cancer as well.

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Glycyrrhiza glabra L., Fabaceae

Elsa Lake

Introduction

Glycyrrhiza glabra L. belongs to the Fabaceae family. The extract obtained from the roots is called licorice, and this is the part of the plant that people use in foods and medicine. The scientific name of the plant comes from the Greek word *glukurrhiza*, which means “sweet root” (Edwards, 2000, p. 119). Common names for *G. glabra* include European licorice, Spanish juice licorice root, liquorice, sweet wood, sweet licorice, lacrisse (German), réglisse (French), and regolizia (Italian) (Sena, 2010, p. 256; Lakshmi, 2011). The plant is native to the lands around the Mediterranean, and it is alleged that in the 1560’s it was brought to Britain by Dominican monks (Edwards, 2000, p. 119). There are two closely related species which originate in different parts of the world: *G. uralensis*, which is known as Chinese licorice, and *G. lepidota*, known as American licorice (Sena, 2010, 256). The main active constituent of all three species of licorice is Glycyrrhizin, which has a sweet taste (Li et al, 2011). For this reason, licorice is commonly used to mask bitter tastes in medicinal preparations (“*Glycyrrhiza glabra*”, 2005). The plant has also been used as a mild laxative, anti-arthritis, anti-inflammatory, anti-biotic, anti-viral, anti-ulcer, memory stimulant (being an MAOinhibitor), anti-tussive, aphrodisiac, anti-mycotic, estrogenic, antioxidant, anti-caries agent, anti-neoplastic, anti-cholinergic, anti-diuretic, and hypolipidemic agent (Lakshmi, 2011). The many different chemicals in licorice continue to be studied for these and more medicinal properties.



Figure 1. Drawing of *Glycyrrhiza glabra*. (Source: Koehler’s *Medicinal-Plants*

http://upload.wikimedia.org/wikipedia/commons/a/a4/Glycyrrhiza_glabra_-_K%C3%B6hler%E2%80%93s_Medizinal-Pflanzen-207.jpg)

Botanical Description

Glycyrrhiza glabra is a halophytic perennial shrub that grows to a height of four or five feet (**Figure 1**) (Li et al, 2011; “*Glycyrrhiza glabra*”, 2005). Every year, new stems are produced, which are sturdy, erect, rough at the top, and branched either from the base or from further up. The foliage leaves are 10 to 20 cm long, alternate, and odd pinnate. The leaflets are in three to eight pairs, and the stipules are very small and drooping (Lakshmi et al, 2011). The plant has pale, white to purplish flowers that resemble lilacs (Sena, 2010, 256). The axillary inflorescences resemble spikes, are 10-15 cm long, and are upright. Each flower is 1 to 1.5 cm long and short-pedicled. The petals are narrow. The carina petals are not fused, or beaked, but are pointed. The calyx is short, shaped like a bell, and glandular-haired. The tips of the calyx are pointed lanceolate and are longer than the tube. The fruit is a pod which is 1.5 to 2.5 cm long and 4 to 6 mm wide. It is flat with thick sutures, erect and splayed, glabrous, somewhat reticulate-pitted, and usually has three to five brown, reniform (kidney-shaped) seeds (Lakshmi et al, 2011).

G. glabra and *G. uralensis* look very similar in many respects, but they can be distinguished in that *G. glabra* has straight pods and linear-oblong shaped leaves, while *G. uralensis* has falcated pods and ovate shaped leaves (**Figure 2**) (Hayashi et al, 2003). There have also been plants documented in Kazakhstan that have fruit and leaves with an appearance in between that of the two species; these plants are thought to be hybrids (Hayashi et al, 2003).

There is an extensive root system that is subdivided into three to five subsidiary roots that are 1.25 m in length. The main taproot is 15 cm long. There are also several horizontal woody stolons that can reach eight meters (Lakshmi et al, 2011). The main taproot, which is harvested every third or fourth year for



Figure 2. A Comparison of Fruits of *G. uralensis* (left), the Intermediate Plant (middle), and *G. glabra* (right) from Kazakhstan. (Source: Hayashi et al, 2003)

medicinal use, is soft, fibrous, and has a bright yellow interior (Loftin, 1953; “*Glycyrrhiza glabra*”, 2005).

In symbiosis with rhizobia, *Glycyrrhiza* spp. fix nitrogen from the atmosphere. *G. glabra* provides nutrients and shelter to rhizobia (Li et al, 2011).

G. glabra thrives best in fertile, sandy or clay soil near a river or stream or under cultivation where it can be irrigated (Lakshmi et al, 2011). It tends to grow on the riverbanks and in the flooded fields of Mediterranean countries, which are subtropical (Loftin, 1953; “*Glycyrrhiza glabra*”, 2005). *G. glabra* can currently be found in Spain, Italy, Turkey, the Caucasus, Central Asia and the western part of China (Hayashi et al, 2003).

Traditional Uses

Preparation of Licorice Extract

Dried roots of *Glycyrrhiza glabra* are collected in autumn, and the powdered and finely cut roots are used to prepare dry and fluid extracts (Barceloux, 2008, p. 538). A simple aqueous extract is prepared by boiling the root and then allowing most of the water to evaporate (Sena, 2010, p. 256). From this extract commercial forms of licorice can be made. The three main ones are licorice powder, licorice paste and ammoniated glycyrrhizin crystals.

Ethnomedical Uses

Stores of *G. glabra* roots were found in the tombs of Egyptian pharaohs such as the 3000-year-old tomb of King Tutankhamen (Loftin, 1953). These roots were placed there for the pharaohs to make a sweet beverage called *mai sus* in the afterlife. This ceremonial drink, still used today in modern Egypt, is used to honor the pharaohs (Sena, 2010, 259-60).

The Greek botanist Theophrastus, who lived in the fourth century BC, stated that licorice could be used to quench thirst and treat asthma, dry cough, and other respiratory diseases (Barceloux, 2008, p. 537). He also said it could be used to heal wounds when mixed with honey. The armies of Alexander the Great and later the Roman armies carried licorice root with them to quench soldiers' thirst during long marches (Sena, 2010, p. 260). In the first century BC, the Roman naturalist Pliny the Elder wrote in his work *Naturalis Historia* about the usage of licorice for reducing hunger and thirst and for treating asthma and sterility in women (Sena, 2010, p. 260; Barceloux, 2008, p. 537). He also wrote that licorice could be used in lozenges to clear the throat and as a remedy for

dropsy, ulcerous sores of the mouth and genitals, and bladder and kidney ailments (Sena, 2010, p. 260).

During the Middle Ages, the knowledge of licorice was kept alive in southern European monasteries (Loftin, 1953). It was used at that time to treat hypotension (Barceloux, 2008, p. 537).

Licorice also plays a large part in traditional Chinese medicine; the *Shen Nong Ben Cao Jing* contains references to it (Barceloux, 2008, p. 537). The Chinese make frequent use of the species *G. uralensis*, but this species does share major active constituents with *G. glabra* (Kondo, 2007).

Usage in Food, Beverages, and Tobacco

Licorice candies consist of three main ingredients: licorice extract, sugar, and a binder (Sena, 2010, p. 258). The licorice extract is in the form of a spray dried powder or 'block juice'. The powder has a mild licorice aroma and bitter-sweet taste (Edwards, 2000, p. 119). Contrary to common beliefs, licorice powder is actually a light brown color. Artificial black coloring is frequently "added to licorice candy just to humor the consumers' preconceptions of what licorice should look like" (Loftin, 1953). Block juice is a solid block resembling coal and has an overpowering licorice flavor and bitter-sweet taste (Edwards, 2000, p. 119). Not all candies labeled "licorice" actually contain licorice extract; "red licorice" is actually made with cherry, strawberry, or raspberry flavorings, and many "black licorice" candies are actually flavored with anise seed oil, synthetic anisole, or anethole (Sena, 2010, p. 259).

Licorice is used to flavor and sweeten soft drinks, herbal teas and various liqueurs, among other beverages. For example, glycyrrhizin crystals are used as a sweetening and foaming

Root	Plant
18-ALPHA-GLYCYRRHETINIC-ACID	GLYCYRRHIZIC-ACID
18-BETA-GLYCYRRHETINIC-ACID	
ASPARAGINE	Leaf
GLABRIDIN	LICOFLAVANONE
GLYCYRRHETINIC-ACID	NICOTINIC-ACID
GLYCYRRHIZIN	
GLYCYRRHETINIC-ACID-MONOGLUCURONIDE	Rhizome Essential Oil
ISOLIQIRITIGENIN	ALPHA-TERPINEOL
LIGNIN	BENZALDEHYDE
O-ACETYL-SALICYLIC-ACID	OCTANOIC-ACID
SUGAR	PAEONOL
Shoot	Rhizome
GLABRANIN	GLABRIDIN
PINOCEMBRIN	
URALENIC-ACID	
URALOZIDE-ACID	

Table 1. Non-ubiquitous chemicals in *G. glabra* that have a concentration over 1,000 ppm. (Source: Duke 2012).

agent for beverages like root beer and birch beer” (Loftin, 1953).

In Italy and Spain, the root of *G. glabra* is chewed for use as a mouth freshener. Licorice is also a conditioning and flavoring agent in many tobacco products (Sena, 2010, p. 259).

Miscellaneous Uses

G. glabra was cultivated in Uzbekistan for a period of four years in water-logged saline soils to keep the water table

below the critical level. The plant decreased the soil and water salinity and increased the productivity of wheat and cotton crops (Li et al, 2011).

After licorice is extracted from the roots of the *G. glabra*, the root fiber itself has a variety of uses. It can be boiled with caustic soda to make a stabilizer used in fire-fighting foam, and it can be used to make a very effective insulation board. Pulp made from the leftover roots can be used to make a superior boxboard. The leftover roots can also be fortified with chemicals and composted for about a month, and the resulting fibers can be used as groundwork on which to grow mushrooms (Loftin, 1953).

Chemistry and Pharmacology

Some major chemical constituents in *Glycyrrhiza glabra* are listed in **Table 1** (Duke, 2012). Glycyrrhizin, also called glycyrrhizic acid, is the main compound in *G. glabra* root extract (**Figure 3**). It is a triterpenoid saponin glycoside, and licorice root contains around 2-15 % triterpenoid saponins (Sena, 2010, p. 256). Glycyrrhizin, when isolated as the pure compound, is an odorless, crystalline solid that is partially soluble in cold water and very soluble in both hot water and alcohol (Sena, 2010, p. 258). Glycyrrhizin tastes much sweeter than sucrose; Sena (2010, p. 258) reports that it is 30-50 times sweeter, while Barceloux (2008, p. 539) reports that it is around 100-200 times sweeter. The sweet flavor is recognized more slowly and lasts longer than sucrose (Sena, 2010, p. 258).

Glycyrrhizin is found in *G. glabra*, *G. uralensis*, and *G. inflata*. Other compounds common to all three species include liquiritin, liquiritin apioside, isoliquiritin, isoliquiritin apioside, and liquiritigenin (Kondo, 2007). Glabridin, a

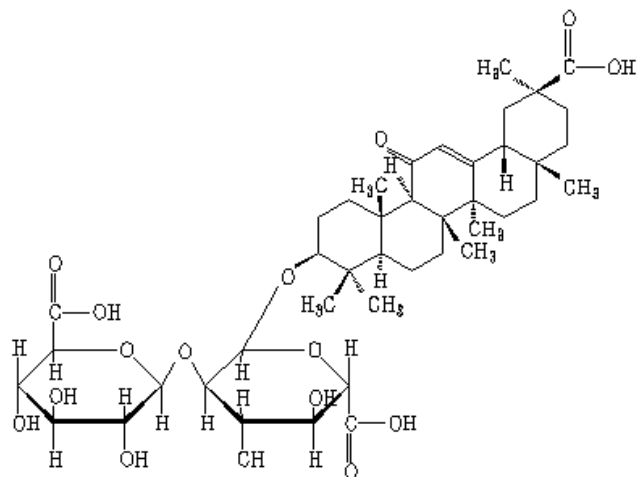


Figure 3. The Chemical Structure of Glycyrrhizin. (Source: http://riodb01.ibase.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi).

polyphenolic flavonoid, is a major compound specific to the species *G. glabra* (Hayashi et al, 2003). When licorice is used for medicinal purposes, the species does need to be taken into consideration because of the difference in constituents. Kondo (2007) advises that “in the assessment of the six kinds of main constituent contents, *G. glabra* and *G. inflata* can be used equally as medicine, but *G. uralensis* might be not able to use similarly with *G. glabra* or *G. inflata*.”

Percentages of constituents also vary depending on the geographic location of the plant. Rutin was the major flavonol glycoside found in the leaves in Kazakhstan, but isoquercitrin was the major leaf flavonoid glycoside in specimens collected in Turkey, Italy, and Spain (Hayashi et al, 2003).

Biological Activity

Antiviral activity

Glycyrrhizin and glycyrrhizic acid have been shown to inhibit growth and cytopathology of numerous RNA and DNA viruses. *In vitro* research with a human hepatoma cell line has shown that glycyrrhizin completely suppresses the expression of the hepatitis A virus' antigen. Glycyrrhizin was proved to be 10 times more potent at reducing the infectivity of the virus. It was also more cell-selective by five-fold, meaning that it was less cytotoxic to the hepatoma cells. Glycyrrhizin has been shown to irreversibly inactivate the *Herpes simplex* virus, and it has been shown to inhibit viral replication and the infectivity of HIV, herpes zoster, *Varicella zoster*, and CMV (“*Glycyrrhiza glabra*”, 2005).

Steroid-like anti-inflammatory activity

This activity is due to the inhibition of phospholipase A2 activity. *In vitro* research has also shown that glycyrrhizic acid inhibits cyclooxygenase activity and prostaglandin formation, as well as indirectly inhibiting platelet aggregation (“*Glycyrrhiza glabra*”, 2005).

Antioxidant and hepatoprotective properties

Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species by neutrophils at the site of an inflammation. *In vitro* studies have demonstrated that the licorice isoflavones hispaglabridin A and B inhibit Fe³⁺-induced mitochondrial lipid peroxidation in rat liver cells (“*Glycyrrhiza glabra*”, 2005).

Anticarcinogenic properties

Research has found that glycyrrhizin and other licorice components inhibit abnormal cell proliferation, tumor formation, and growth in breast, liver, and skin cancers (“*Glycyrrhiza glabra*”, 2005). The licochalcones have been found to have radical scavenging properties, which may be due to the regulation of (per)oxidizing enzymes.

Antibacterial activity

Nand, Drabu, and Gupta (2011) found that methanolic extracts of licorice have broad-spectrum antibacterial activity. An *in vitro* study showed that licorice flavonoids show activity against clarithromycin and amoxicillin-resistant strains of *Helicobacter pylori*. Deglycyrrhizinated licorice (DGL) preparations may be effective against *H. pylori* infection since the flavonoids seem to be what is behind the antimicrobial property (“*Glycyrrhiza glabra*”, 2005). Licorice root extract also showed significant antibacterial activity against the gram positive *Bacillus subtilis* and *Staphylococcus aureus* and the gram negative *Escherichia coli* and *Pseudomonas aeruginosa* (Lakshmi et al, 2011).

Antifungal activity

The compounds licochalcone A and glabridin are effective antifungal agents (Messier & Grenier, 2011). *G. glabra* extracts with 80% methanol (oil-based extract of licorice; OEL) were effective against filamentous fungi and some thermo-resistant bacilli. It also lessened contamination in polyethyleneterephthalate bottled tea based beverages, indicating potential application in the prevention of beverage and food spoilage due to microorganisms (Lakshmi et al, 2011).

Memory enhancement

Maze and passive avoidance testing in mice indicate that aqueous extracts of licorice may have memory-enhancing properties by reversing chemically-induced amnesia.

Clinical Studies

Herpes simplex virus

In one case report, a two-percent topical glycyrrhizic acid cream (carbenoxolone sodium) was applied six times daily to 12 patients with acute oral herpetic infections, and the result was that pain and dysphagia were resolved within 24-48 hours of the beginning of treatment. Ulceration and lymphadenopathy gradually healed within 24-72 hours (Lakshmi et al, 2011).

Stronger Neo Minophagen C (SNMC) is comprised of 0.2 % glycyrrhizin, 0.1% cysteine, and 2.0% glycine (Coon & Ernst, 2004). Oral and IV preparations of SNMC were given to infants with CMV (*Cytomegalovirus*, a genus of herpes virus). Liver dysfunction and weight gain improved in nearly all cases as compared to groups without treatment (Lakshmi et al, 2011).

HIV

A clinical study consisted of three HIV patients with hemophilia who were administered glycyrrhizin by IV at 400-1600 mg on six occasions over a one month period. The HIV p24 antigen, which was detected in all patients at the beginning of treatment, had either decreased significantly or become negative by the end of one month. P24 antigen levels immediately elevated when the glycyrrhizin dose was tapered off (“*Glycyrrhiza glabra*”, 2005).

Ulcers

In a double-blind study, 70 patients with endoscopically confirmed gastric or duodenal ulcers were given either 300 mg of carbenoxolone sodium or a placebo daily for seven days, then 150 mg daily for the next 3-5 weeks. In the experimental group, there was an increase in pH of the stomach antrum from 1.1 to 6.0 and a reduction in basal and histamine-induced gastric acid secretion at pH 3 and 5. 70 percent of ulcers in the experimental group healed within 3-5 weeks, while 36 percent of ulcers in the placebo group healed within that time frame (Glycyrrhiza glabra", 2005).

In one study on aphthous ulcers, twenty patients used a DGL mouthwash four times a day, and in fifteen there was 50-75 percent clinical improvement after just one day, and after three days, the canker sores completely healed. A double-blind trial was completed where 24 patients with recurrent aphthous ulcers were randomly allocated to consume either oral licorice mouthwash or a placebo three times a day after meals for four weeks. The mouthwash consisted of 2 g glycyrrhizin (carbenoxolone sodium) in 30 mL of warm water. The use of the mouthwash significantly reduced the average number of ulcers per day, pain sores, and the development of new ulcers compared to the placebo (Glycyrrhiza glabra", 2005).

Clinical trials using DGL formulations, however, do not all show clear evidence of effectiveness in treatment of ulcers. In a placebo-controlled, randomized clinical trial of 96 patients with gastric ulcers, the group given DGL showed no differences in healing than the placebo group over a period of 4 weeks (Barceloux, 2008, p. 538).

Weight Loss

Fifteen normal-weight subjects (seven males, eight females, ages 22-26) were given 3.5 mg of a commercial licorice preparation every day for two months. Plasma rennin activity and aldosterone were suppressed and there was a decrease in body fat mass, but there were no changes in body mass index. The results indicate that licorice and its components may be able to reduce body fat by inhibiting 11-R-hydroxysteroid dehydrogenase in fat cells ("Glycyrrhiza glabra", 2005).

Contraindications

Side Effects and Toxicity

In the United States, the US Food and Drug Administration (FDA) regulated licorice as a food supplement. As a flavoring agent in food products, the FDA regards licorice as GRAS (generally recognized as safe) (Barceloux, 2008, p. 538). When taken in higher concentrations as a supplement, however, a common side effect of licorice consumption is a condition known as pseudoaldosteronism. Glycyrrhizin's structure is very similar to the hormones secreted by the adrenal cortex, so glycyrrhizin is capable of potentiating aldosterone action while binding to mineralocorticoid receptors in the kidneys. This can cause high blood pressure, hypokalemia (potassium loss), high blood pressure, and sodium retention, which results in edema ("Glycyrrhiza glabra", 2005).

The high concentration of glycyrrhizin in the root of *G. glabra* is also evidenced to be toxic when chronically ingested in moderate to excessive amounts. An example of an "excessive" amount would be the ingestion of two to four licorice twists daily for a month, which can increase glycyrrhizin levels to over 400 ng/mL. Symptoms are usually related to abnormalities in cortisol metabolism and include edema,

weight loss, weakness, hypertension, confusion, and hypokalemia. The toxic effects of high levels of glycyrrhizin in the body usually fade away by themselves once the consumption of licorice is halted (McLawhon, 2010, p. 438)

Drug Interactions

There are reported licorice-drug interactions with hydrocortisone, prednisolone, and oral contraceptives (Sena, 2010, p. 268). Use of diuretics and licorice simultaneously may cause hypokalemia in patients with essential benign hypertension. When licorice is used in conjunction with digoxin, there is an increased likelihood of cardiac arrhythmias, especially in people with ischemic heart disease (“*Glycyrrhiza glabra*”, 2005).

Current Use in Allopathic and CAM Therapies

Powdered preparations of licorice root usually contain 4-9 percent glycyrrhizin, and oral doses of 1-4 g per day divided into three to four doses have been used. Licorice extract is also available in liquid form, which contains 10-20 percent glycyrrhizin, and oral doses of 2 – 4 mL per day are used (Sena, 2010, p. 259). Individuals vary widely in how much licorice is safe to consume, but at daily oral intake, the 1-10 mg of glycyrrhizin (1-5 g of licorice, which contains 2% glycyrrhizin) is an estimated safe dose for most healthy adults. In studies of DGL for peptic ulcers, the dosages ranged from 760 to 2,280 mg daily (“*Glycyrrhiza glabra*”, 2005).

The German Commission E approved daily doses of 200 – 600 mg glycyrrhizic acid for the treatment of peptic ulcers. However, treatment is limited to five weeks, and patients with cardiovascular or renal disease are discouraged from using licorice unless closely supervised by a physician (Barceloux,

2008, p. 538). Licorice extract is also available as the above mentioned deglycyrrhizinated licorice (DGL) for treatment of ulcers (“*Glycyrrhiza glabra*”, 2005). Glycyrrhizin has been removed from these extracts, and thus the metabolic side effects caused by glycyrrhizin do not appear to occur with use. DGL comes in tablet form and in studies on peptic ulcer treatment, DGL was used in dosages ranging from 760- 2,280 mg daily (Sena, 2010, p. 259; “*Glycyrrhiza glabra*”, 2005). DGL formulations use a different mechanism than many other medications for ulcers. Others act by suppressing gastric acid release, but DGL formulations increase mucous production and blood supply to the damaged stomach mucosa, which aids in mucosal healing (“*Glycyrrhiza glabra*”, 2005).

Several preparations specific to other countries include constituents from *G. glabra*. Stronger Neo Minophagen C (SNMC), mentioned above, has been used by the Japanese for over 40 years in the treatment of Hepatitis C (Kumada, 2002). It is an intravenous drug containing glycyrrhizin, glycine, and L-cysteine (Miyake et al., 2002). Ankaferd Blood Stopper (**Figure 4**) is used in Turkey for the management of external hemorrhage and dental surgery bleedings. It is a standardized mixture of *G. glabra*, *Thymus vulgaris*, *Vitis vinifera*, *Alpinia officinarum* and *Urtica dioica* (Goker et al., 2008).

Licorice is also used in hand, skin, and body lotions, and as an ingredient in anti-aging creams (Sena, 2010, p. 259). Glycyrrhizin crystals are also used to mask disagreeable flavors and as a base for many drugs (Loftin, 1953)



Figure 4. Ankaferd Blood Stopper (Source: <http://www.pakimarket.com/wp-content/uploads/classipress/ankaferd-blood-stop-592027747.jpg>).

Discussion

Glycyrrhiza glabra has been used, documented, and recommended by a variety of prominent figures throughout history for many different ailments such as ulcers, bacterial and viral infections, and inflammation. Constituents of the plant, especially glycyrrhizin, have been and continue to be extensively studied for medicinal properties. However, conclusive evidence regarding the effectiveness of standard licorice preparations for many conditions still has not been established. The extent to which licorice has been used in traditional medicine, however, does suggest strong medicinal properties, and more research will likely lead to development of powerful new drugs in the future. Overall, *G. glabra* has very useful components that will certainly continue to benefit

human health. One must keep in mind, however, that just like many other medicinal plants, licorice is a flavoring in small amounts, a medicine in average amounts, and in large amounts, it can be a deadly poison.

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Hypericum perforatum L., Hypericaceae

Yinan Yang

Introduction

The genus of *Hypericum* contains about 370 species; within this large group, *Hypericum perforatum* or St. John's wort is known to be a highly variable tetraploid that propagates asexually. *Hypericum* is derived from its Greek name, hyperikon, meaning above (hyper) and image (eikon) (Radun 2007). The common name, St. John's wort, is named after John the Baptist in Christian tradition. The herb *H. perforatum* is usually harvested on June 23rd, the eve of the festival that celebrates St. John the Baptist, and it was used to ward off evil spirits, purify the surroundings and promote the harvest. Wort also comes from the Anglo-Saxon origin meaning medicine (Kim et al. 1999).

The use of *H. perforatum* can be traced back to ancient times and is currently widely cultivated around certain continents of the world like Asia and Europe. It is traditionally used as an herbal tea and antiseptic or as a topical medicine for burns and wounds but recently most commonly for its antidepressant activities. St. John's wort can also be used for treating skin irritation, asthma, inflammation and ulcers. Although the main components of St. John's wort extract are hyperforin, hypericin and pseudohypericin, the 2 latter ones are not yet linked with mechanisms for reducing depression. Other compounds in St. John's wort include tannins, flavonoids, proanthocyanidins and xanthenes. St. John's wort is one of the top 15 best selling herbs in the world (Radun 2007). *H. perforatum* is a perennial herb but is also invasive; it was first introduced to the US in 1700s for ornamental purposes but has been overtaken some the native species (De



Figure 1. Illustration of *Hypericum perforatum*.

Smet et al. 1996). In terms of medicine, St. John's wort is one of the top 15 best selling herbs in the world (Radun 2007).

Description

Until recently, the origin of St. John's wort was thought to be in Africa that later spread to Asia, Australia and America. However, recent evidence tells us that it actually originated in the Mediterranean in Europe and later grew all over Europe, except in the coldest of places (Radun 2007). Today, St. John's wort can be located in most parts of Europe, North America, Australia and Asia, in the temperate climates and also in the tropics. St. John's wort grows in the shrub habit and also in tree-like habit in the tropics. Its habitat also includes the prairie, woodland, forest and rangeland (Radun 2007). While St. John's wort doesn't have very strict conditions for growth, its growth is optimally in the full sunlight with plenty of moisture. Lean or gravel soil is also a good condition to grow in as it reduces growths of other plants (Radun 2007).

St. John's wort grows upright and ranges from 30-100cm in height (Radun 2007). Its stems have 2 distinct ridges and branches off in bundles at the upper part of the plant (**Figure 1**). The leaves of St. John's wort are narrow and oval, ranging from 1.5-3cm in length and 1.5-5mm in width; they also have perforated holes spread throughout the leaves that produces essential oil (Radun 2007). In the summer, St. John's wort produces bundles of small yellow flowers with black dots; they are very abundant, often produced in clusters of 25-100 per stem. The fruits of St. John's wort look like capsules that store around 50 seeds per plant. Each plant produces up to 34,000 seeds per season and the seeds are around 5mm in length and black in color (Radun 2007).

H. perforatum is an invasive species that is capable of self-pollination and therefore, does not depend on pollination by insects. In many instances, *H. perforatum* is introduced to a new habitat along with an alien insect species that feeds on it. Alien insect species are more likely to feed on the plant they are familiar with than those that are not and *H. perforatum* is an example of an invasive weed species that has been biologically controlled by specialist insect herbivores (De Smet et al. 1996).

Traditional Uses

Uses of St. John's wort have been thought to exist from prehistory. St. John's wort is documented to be used mostly as medicine as other uses such decoration and food has not been found. Uses of St. John's wort as a medicine have had a long history whether as a topical medicine or an oral medicine. The uses of St. John's wort are many and are described as follow, however, in current times, St. John's wort is mainly used as an antidepressant. For example, in historical Britain, doctors used St. John's wort as a tranquilizer and to ward off evil spirits (Radun 2007). In Herzegovina (Southern region of Bosnia), the documented use of St. John's wort has been traced back to the 13th century (Radun 2007). The perforation of the leaves of St. John's wort was thought to be useful in covering deep wounds as it had antimicrobial properties (De Smet and Nolen 1996). Many notable Greek figures such as Hippocrates, Dioscorides, Theophrastus and Galen have been documented in using St. John's wort for treating menstrual problems, neurological disorders, treating wounds and as a diuretic. The Greeks also used it to ward off evil spirits in religious rituals and valued the plant greatly; this practice was carried on in Britain until recently (Zobayed, Murch, Rupasinghe and Saxena 2003). Paracelsus is also documented to use St. John's

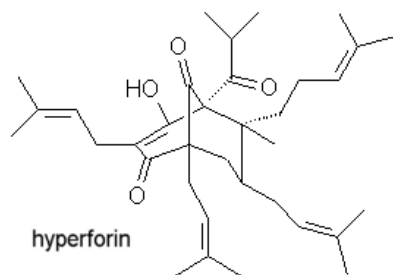


Figure 2. Structure of hyperforin (Source: biologie.uni-hamburg.de).

wort for treating wounds in the 1500s (Radun 2007). Traditionally among the ordinary citizens, St. John's wort has been used in Europe for treating anxiety, depression, wounds, inflammation and burns (Radun 2007). St. John's wort is also used as herbal tea and it is widespread in many countries such as Turkey, Bosnia, Pakistan, Britain, Germany and China as well as by Native Americans. The tea is used to treat ulcers, asthma, and bronchitis. An oil extract can also be used for skin irritation and bruises (Radun 2007). St. John's wort has also been used as liquid extracts, powdered herbs and tinctures, and is applied orally or topically in historical Europe (De Smet et al. 1996). Many of these methods to using St. John's wort is still being used today like oral capsules.

Chemistry and Pharmacology

Many kinds of chemicals are naturally found in St. John's wort: they are tannins and proanthocyanidins (catechin, epicatechin, leucocyanidin) (6.5-15%), flavonoids (hyperoside, rutin, quercitrin, isoquercitrin, quercetin and kaempferol) (2-5%), biflavonoids, phloroglucinol derivatives (including 4% hyperforin), phenolic acids, volatiles oil (up to 1%), higher alkanes, sterols, naphthodian-thrones (including

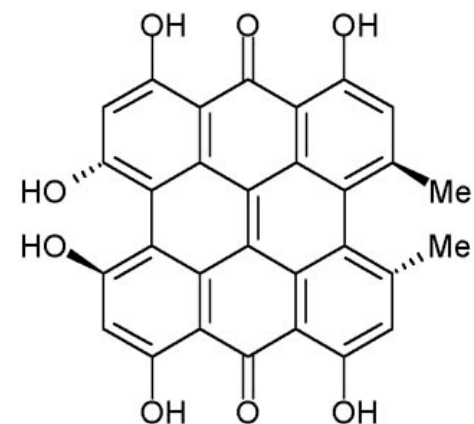


Figure 3. Structure of hypericin (Source: biopsychiatry.com).

hypericin and pseudo-hypericin), vitamin C and A and xanthoes (10ppm) (Radun 2007).

The most notable compounds are hyperforin (**Figure 2**), hypericins (**Figure 3**) and pseudohypericin (**Figure 4**). Capsules of St. John's wort have a standard dose around 300mg (0.3% hypericin) standardized around hypericin and pseudohypericin (Kopleman, Augsburg, NguyenPho, Zito and Muller 2001). Hyperforin is a compound that is naturally present in humans, and this is the compound responsible for inducing metabolism of St. John's wort. Among some popular brands that are sold in stores, the content of hyperforin ranged from 0.01-1.89%. Normally 1-6% of hyperforin is required in treating mild depression (De Los Reyes and Koda 2002). The content of hypericin and pseudohypericin in commonly sold drugs can be highly variable and in a study by De Los Reyes and Koda (2002), these compounds ranged from 0.03-1.29% in weight: this is approximately 56.6-130% of what all of the labels claimed to have in the amount of hypericin and pseudohypericin (0.15, 0.2 or 0.3%).

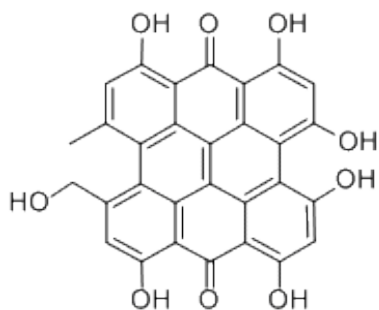


Figure 4. Structure of pseudohypericin (Source: chemicalbook.com).

Biological Activity

Flavonoids (rutin, hyperoside, isoquercitrin, quercitrin and quercetin) are thought to be responsible for the antidepressant activity of St. John's wort as well as some antioxidant activities (which are thought to increase the amount of extraction by preventing degradation of other chemicals). The naphodianthrones (hypericin and pseudohypericin) are used as standards in pharmacy, and was until recently also thought to contribute to antidepressant activity (Lewis and Elvin-Lewis 2003).

St. John's wort is an inhibitor of the reuptake of serotonin at the presynaptic axons and it also seem to alter neurotransmitters at the postsynaptic axons. Norepinephrine is also inhibited during reuptake but to a lesser extent. *In vitro* studies revealed that the β -adrenoceptor is down-regulated in a dose-dependent manner in similar fashion to other anti-depressants, however, the activity could not be traced back to hypericin nor hyperforin and therefore, the identity of this active chemical is still currently unknown. Still in other studies like by Muller et al. (2001) it was found that St. John's wort extract was able to inhibit not only serotonin and norepinephrine, but also dopamine, GABA and L-

glutamate. It is hypothesized that another mechanism using sodium ion channels is responsible for the mechanism. So far, hypericin is the only compound known to be a preclinical antidepressant with a completely new mechanism (Lewis and Elvin-Lewis 2003).

Clinical Studies

In clinical studies, extract of St. John's wort has proven to be significantly more effective than placebo in treating mild to moderate depression. The efficacy is not significantly different as that of tricyclic antidepressants, but it seems that St. John's wort causes fewer side effects than those other antidepressants. These conclusions are based on a meta-analysis of 23 randomized trials with over 1700 patients (Lewis and Elvin-Lewis 2003). Several clinical trials have been used in testing St. John's wort: one study compared the efficacy of 800mg of St. John's wort with 20mg of Prozac, and found that these had equal efficacy.

Other recent clinical studies and meta-analysis have found that the use of St. John's wort is twice as less likely in causing side effects as the tricyclic antidepressants. There were also less drop outs observed in using St. John's wort than tricyclic antidepressants in those trials: both of these are important factors for the patients since many treatments are abandoned due to onset of side effects causing patients to drop out (Kim, Streltzer and Goebert 1999).

Many of the clinical trials, however, have design problems with methods and sample sizes so a definitive conclusion that St. John's wort is effective cannot be drawn (Kim, Streltzer and Goebert 1999). For example, some of these studies used only subjective standards or older diagnostic criteria to measure the presence of depression (Kim, Streltzer and Goebert 1999).

Certain studies also lack certain information that are critical to the study like the patient's history of depression, family history of depression, and the duration of depression which all cause the studies to lack strong support and structured diagnosis (Kim, Streltzer and Goebert 1999).

Another questionable point in many of the clinical studies involving St. John's wort and depression is that many of these trials last only 4-6 weeks often with no follow up and so do not address any long term effect of St. John's wort. Currently there haven't been any study involved in using St. John's wort over the long-term efficacy, side effects, relapse...etc. for depression and other ailments.

Finally, many of these clinical trials and diagnosis were done by generalized primary care physicians instead of specialized psychiatrists. This raises the question of the accuracy in treating and diagnosing patients as primary physician have been known to mistreat and misdiagnose depression 50% of time (Kim, Streltzer and Goebert 1999), and so this further weakens the conclusions gotten by these clinical studies (Kim, Streltzer and Goebert 1999).

Contraindications

So far, St. John's wort has had no indication of any significant severe adverse effect that has been observed (Jobst, McIntyre, St. George and Whitelegg 2000). St. John's wort is currently used in clinical setting in Germany and has so far produced no record of any severe implications, overdose or toxicity (De Smet and Nolen 1996). St. John's wort is currently used in Germany for mild to moderate depression, anxiety, psychogenic disturbances and nervousness (De Smet and Nolen 1996). Some common mild side effects have been reported which include gastrointestinal problems, allergic

reactions and fatigue, but all of these complaints combined constituted less than 2% of all clinical uses. On the other hand, St. John's wort is poisonous to livestock especially in the tropical regions or Southern regions of the US due to photosensitization of the chemicals (Lewis and Elvin-Lewis 2003).

Another point to consider is the amount of variation in the active ingredients found in different brands of St. John's wort that are sold. As mentioned before, hypericin and pseudohypericin are used to measure the standard dose, but research done by Liu *et al.* found that there were significant variations in other compounds within the different products that are sold (De Los Reyes and Koda 2002). Since hyperforin is considered to be the main ingredient in treating depression, and that it is not standardized (since it is difficult to standardize), different brands of St. John's wort may cause different degrees of effectiveness.

Research has not yet shown that the effect of St. John's wort is linked to hypericin and having variable amounts of other ingredients may cause deleterious effects, especially when combined with other drugs. It is still currently generally unknown that combination with any other drug may lead to dangerous effects and more research is needed.

Current Use in Allopathic & CAM Therapies

Currently, the only nation in the world that allows its doctors to prescribe St. John's wort as anti-depressant is Germany. In fact, in 1994, German doctors prescribed 66 million doses of medicine containing hypericum each day (De Smet and Nolen 1996). There are currently 20 times more St. John's wort prescriptions in Germany than Prozac that are used to treat depression (Kim, Streltzer and Goebert 1999). The German

healthcare system favors individualized and subjective standards for evaluating depression as opposed to a more objective system, and this may be another reason why they use St. John's wort in mainstream medicine (Kim, Streltzer and Goebert 1999).

Despite these promising data, the use of St. John's wort toward major depression, especially long-term trials, lack sufficient number of study and therefore, is not proven to be yet effective in treating them. Furthermore, relapse of depression and late side effects haven't been adequately studied (De Smet and Nolen 1996). In order for the extracts to be used for major depression, further research is needed and it must also meet the same regulations that govern other antidepressants. The extracts of St. John's wort also need 2 to 4 weeks to affect the mood.

There are currently many herbal supplements in the US and can often be seen sold in bottles over the counter as oral capsules. In the US, they are simply marked as capsules containing St. John's wort branded under certain names like Nature's Way, Sundown and Now Foods. The standard dose of hypericin and pseudohypericin in these capsules are around 300mg.

The use of St. John's wort is also growing in North America and it has also been used in aromatherapy and is currently under investigation for using it against HIV. The traditional uses of St. John's wort for curing wounds, bruises, ulcers and inflammation still remain (Radun 2007).

Discussion

St. John's wort is a commonly known herb that almost everyone in North America has heard of its existence. The popularity of this well known herb can be partly due to its

widespread use across the world that dates back to ancient times. Although allopathic medicine continues to grow, the reality is that a large portion of the population in the world depends on traditional methods like medicinal plants to support their well being and cure diseases. This is especially true for rural areas around the world where there is no access to allopathic medicine. Plants like St. John's wort are also used to for food, flavoring, liquors, perfumes, cleaning products and essential oil.

Many clinical trials have obtained significant result for St. John's wort versus placebo, however, lack of an organized and standardized procedure and diagnosis for clinical trials confounds the promising results obtained: further studies are seriously needed in long-term trials that objectively assess the follow up of patients to definitely conclude that St. John's wort is effective in treating depression.

The use of St. John's wort is not recommended as a stand-alone treatment for depression and any use should be consulted by a doctor. The fact that St. John's wort produces fewer side effects than conventional anti-depressants opens a door for doctors to consider using it for patients that have side effects with conventional antidepressants (Kim, Streltzer and Goebert 1999). However, this can only be said for mild to moderate depression, and major depression and other severe psychiatric disorders require more attention.

It is interesting to note that St. John's wort is widely prescribed in Germany by doctors even though the effects of St. John's wort are not totally conclusive. As mentioned before, this is probably due to the more subjective treatments practices utilized.

One point that needs to be researched is whether hypericin and pseudohypericin have any effect against treating depression through an alternative mechanism yet to be

discovered. The difficulty in storing hyperforin (the main ingredient acting against depression) prevents it from being used as the standard in conventional drugs. There is also the possibility that some other compounds may be responsible.

The traditional use of St. John's wort around Europe for treating wounds and inflammation still exists today after thousands of years. Due to its multitude of uses, *Hypericum perforatum* will probably never cease to be used by people around the world, at least not in the foreseeable future.

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Ilex paraguariensis A. St.-Hil., Aquifoliaceae

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Introduction

Ilex paraguariensis A. St.-Hil is a member of Aquifoliaceae or the holly family (Tropicos 2012). Classified by Auguste Francois César Prouvencal de Saint-Hilare, its common names include “té del Paraguay” in Paraguay, “erva mate” and “chimarrão” in Brazil, and “maté” in Uruguay and Argentina (**Figure 1**). These refer to its hot tea form. But when it is prepared as a cold beverage, it is called “tereré” (Cordoba et al. 2011). However, it is also universally known throughout most of the world as yerba maté. Yerba comes from the word ‘herb’ in the Quichua language, and maté is the name of the gourd from which it is traditionally consumed (Stern 2000).

Grown naturally as well as cultivated throughout South America, this plant has remained an integral part of the culture of Argentina, Brazil, Paraguay, and Uruguay since the time of the Guaraní Indians, who employed this tea as a form of social ritual (Joyce 1934). Now, it is universally consumed throughout South America as well as around the world within everything from candy to beer to soft drinks to creams and even energy drinks (Andrade et al. 2012). However, the most common method of consumption of *I. paraguariensis* is in the form of tea (**Figure 2**) also known as “maté cebado” (Conforti et al. 2012).

Recently, *I. paraguariensis* has become available in the form of supplements and pills. Mainly consumed as a tonic and a stimulant, it is used in the treatment of cardiovascular, hepatic, digestive, and inflammatory disorders. People commonly ingest yerba maté for its elevated caffeine content to combat fatigue and to promote weight loss. Important



Figure 1. *Ilex paraguariensis* plant (leaves, flowers, and berries).

Source: <http://www.nhm.ac.uk/nature-online/species-of-the-day/biodiversity/economic-impact/ilex-paraguariensis/index.html>

purine alkaloids, phenolic compounds, saponins, tannins, and flavonoids provide *I. paraguariensis* with anti-oxidant, anti-viral as well as anti-inflammatory effects, which in turn give



Figure 2. Traditional yerba maté tea contained in a gourd with a 'bombilla'. Source: <http://guayaki.com/product/61/Pre-Columbian-Gourd-Gift-Pack.html>

this plant much of its medicinal properties (Bastos et al. 2007).

Botanical Description

Native to South America, *Ilex paraguariensis* mainly occupies the subtropical region of the continent (Rakocevic et al. 2011). While this shrub tree grows in Bolivia, Colombia, and Ecuador, it flourishes specifically in northeastern Argentina, southern Brazil, eastern Paraguay, as well as throughout Uruguay (Service, U. N. R. C.; Gorzalczany et al. 2001). *I. paraguariensis* prefers the full, direct sunlight and extreme humid conditions of this subtropical region, enjoying temperatures averaging around 21 degrees Celsius (Giberti 1998). As a member of

Aquifoliaceae, otherwise known as the holly family, yerba maté expresses “monopodial and rhythmic” proliferation, occurring in biannual growth spurts in the spring and autumn seasons (Giberti 1998; Rakocevic et al. 2011). It can even live up to one hundred years. The pollination that it undergoes is entomophilous or via insects such as bees and flies; birds then scatter the seeds within the fruit of *I. paraguariensis* (Gauer & Cavalli-Molina 1999).

The characteristics of this perennial, dioecious plant depend on how it is grown—whether it is grown naturally or cultivated. Naturally, wild yerba maté resides in the South American forests as an understory evergreen tree, preferring the sandy and clay soils present on the banks of local waterways. Here, this small to medium sized tree grows upwards of eighteen meters tall. It is, however, cultivated throughout South America as a part of their agroforestry programs, seeking to combine the benefits of both agriculture and forestry in order to produce a flourishing crop population (Giberti 1998).

In addition to agroforestry, yerba maté farmers cultivate this plant as the sole crop on plantations due to the increasing demand for the leaves of this plant (Rakocevic et al. 2011). Compared to the wild versions, cultivated *I. paraguariensis* remains smaller, about two to three meters total in height (Shua & Prada 2003). By comparing the picture of cultivated yerba maté in **Figure 3** to the wild version of the plant in **Figure 4**, the height differences remain quite noticeable.

There are also distinct leaf differences in addition to the asymmetry in stature between the wild and cultivated yerba maté. The leaves of *I. paraguariensis*, which are the part of the plant most commonly used, average twenty centimeters in size in the wild (Giberti 1998; Stern 2000; Shua & Prada 2003). The cultivated leaves are much smaller, only about five



Figure 3. *Ilex paraguariensis* cultivated through monoculture on plantations.

Source: <http://www.nhm.ac.uk/nature-online/species-of-the-day/biodiversity/economic-impact/ilex-paraguariensis/biology/index.html>

centimeters. (Shua & Prada 2003). The tea from cultivated leaves also tastes less bitter (Rakocevic et al. 2008).

Despite how they are grown, the leaves are eye-shaped with tooth-like edges. These shiny, deep green colored leaves have a leathery, fleshy quality. The leaves are attached via deep red petioles. **Figure 1** displays the specific leaf, fruit and flower structures. The tree's flat and somewhat smooth bark alternates in color between brown, gray, and green. The white colored flowers of *I. paraguariensis* give rise to spherical shaped fruits—magenta tinted berries—in the autumn months (Giberti 1998).

Due to *I. paraguariensis*' significant and ever present role in South American society as well as their economy, the plant population has suffered. No longer can the naturally grown tree stripped of its leaves produce enough supply for its



Figure 4. Wild *Ilex paraguariensis* grown in the forests of South America.

Source: <http://www.nativayerbamate.com/12.jpg>

increasing demand. This abuse directly influenced the *I. paraguariensis* population, causing a significant decrease in numbers. Even through cultivation, specifically the use of plantations to grow this crop, the population continues to deteriorate until a balance is created between supply and demand (Giberti 1998).

Traditional Uses

Since ancient times, *Ilex paraguariensis* has been richly steeped in South American culture. Recently, this plant's cultural role remains severely intertwined with its economical importance. However, for hundreds of years, *I. paraguariensis* has continued to occupy an integral part of South American society. Not only did the ancient South Americans recognize the important medicinal implications held by this plant, but they also utilized this tea within social settings. Dating back hundreds of years, the Guaraní Indians, dwelling in the regions of Brazil and Paraguay, consumed this plant known to them as 'caamini' or 'caaguazú' (Gorzalczany et al. 2001; Joyce 1934). Its tea was deemed a social and ritual drink, one that promoted "trust and communion" between people and facilitated meaningful conversations. It was also involved in relaxation rituals (Gorzalczany et al. 2001).

Legend has it that yerba maté was given to the Guaraní Indians by the Goddess of the Moon. Yasí, the moon goddess, and her sister Araí, the cloud goddess, left Heaven one night to travel to Earth. Unable to defend themselves against a jaguar attack, they were rescued by an elderly Guaraní Indian who shot the jaguar with a bow and arrow and saved the goddesses' lives. Out of thanks, the Goddess of the Moon gave this Guaraní yerba maté, along with directions on its preparation. This drink was then shared with the rest of the Guaraní tribe (Shua & Prada 2003).

The traditional method of drinking the yerba maté tea can be seen in **Figure 2**. The leaves are gathered, dried over the fire, pulverized, and then steeped in water to produce a brewed tea. The gourd that the tea is commonly contained in is known as a maté, and a metal 'bombilla' strains the dried leaf particles as it is being consumed (Conforti et al. 2012). Amazed at the tea's caffeinated effects, the Spanish Jesuits

who were missionaries to the Guaraní then proceeded to cultivate the plant for the first time on plantations. The Guaraní Indians also chewed the leaves to extract the caffeine (Butler 1900).

In addition, this tea was used historically for its medicinal properties, which have provided relief from a wide variety of ailments for hundreds of years. These include, but are not limited to, digestive disorders, inflammatory processes, weakness of the body and mind, cardiovascular problems, as well as joint issues (Andrade et al. 2012). The plant is mainly ingested via tonics. However, cataplasms, moist compresses with pulverized plant parts, were also placed on inflamed and ulcerated skin lesions in order to soothe as well as treat. The plant was first documented in South America for its remedial effects within *Examen de los Simples Medicinales* in 1617 (Joyce 1934). Due to these yerba maté botanical remedies, studies have resulted in order to not only isolate the active compounds, but also to potentially find treatments or cures for specific illnesses.

Chemistry and Pharmacology

The active constituents within *Ilex paraguariensis* are responsible for not only increased plant survival, but also the plant's medicinal properties. Amongst the plant's most prominent constituents are alkaloids, phenols, flavonoids, saponins, tannins, as well as a host of vitamins and minerals (Bastos et al. 2007). **Table 1** lists these major constituents within *I. paraguariensis*.

The three most active alkaloids, specifically purine alkaloids, within yerba maté are caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine), and theophylline (1,3-dimethylxanthine). **Figure 5** shows the structural differences

Compound	Class of Compound
Caffeine	Purine alkaloid
Theobromine	Purine alkaloid
Theophylline	Purine alkaloid
Caffeic acid	Phenol
Ferulic acid	Phenol
Sinapic acid	Phenol
p-coumaric acid	Phenol
5-O-caffeoylquinic acid	Phenol
caffeoylshikimic acid	Phenol
dicafeoylshikimic acid	Phenol
caffeoyl glucose	Phenol
Matesaponin	Saponin
Ursolic acid	Saponin
Oleanolic acid	Saponin
Quercetin	Flavonoid
Rutin	Flavonoid
A	Vitamin
B complex	Vitamin
C	Vitamin
E	Vitamin

Table 1: Major Constituents within *Ilex paraguariensis* A. St.-Hil.

Source: Bastos et al. 2007

between these three types of xanthines. While some scientists still debate the presence of theophylline within the plant, caffeine and theobromine are present in high doses, with caffeine being the highest. This provides the plant with a means of preventing predation as well as fighting off competing plants in its surrounding area. The differences in the caffeine concentrations among plants of *I. paraguariensis*

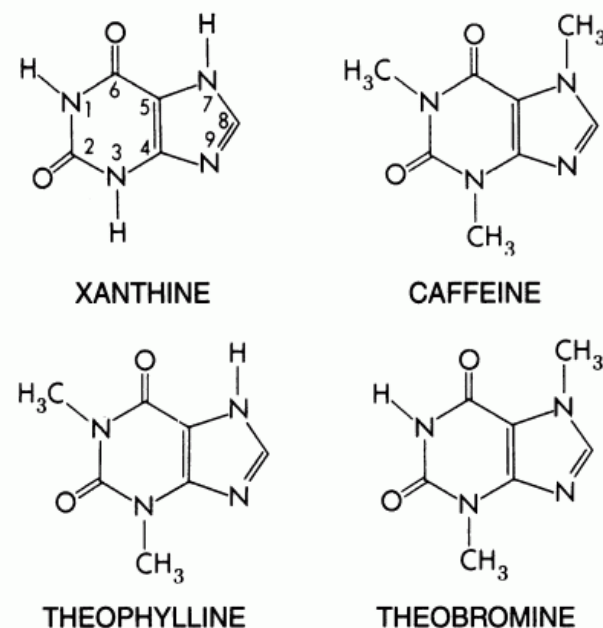


Figure 5. The chemical structures of the major alkaloid constituents within *Ilex paraguariensis*, which are caffeine, theophylline, and theobromine (the three most prevalent xanthines).

Source: <http://www.benbest.com/health/xanthines.gif>

may be due to the time of year as well as the location that the plant is growing. The winter and autumn months result in a decreased concentration of caffeine. “Light intensity and temperature, stress conditions, presence of predators, kind and frequency of trimming” may also influence the amounts present. Also, studies differ on whether or not the concentrations of these purine alkaloids are elevated post-drying of the leaves (Bastos et al. 2007).

In addition to alkaloids, phenolic compounds are present within the leaves of *I. paraguariensis*, making up roughly thirty percent of the plant constituents (Matsumoto et al. 2009). These mainly occur in the form of esters as chlorogenic acids or CGAs and include caffeic (3,4-dihydroxycinnamic), ferulic (3-methoxy, 4-hydroxy), sinapic (3,5-dimethoxy, 4-hydroxy) and p-coumaric (4-hydroxy) acids. Amongst these acids, the characteristic chlorogenic acid within yerba maté is 5-O-caffeoylquinic acid or 5-CQA. Other extracts of the dried leaves revealed caffeoylshikimic acid and dicaffeoylshikimic acid. Caffeoyl glucose remains another present polyphenol within the plant. The anti-oxidant properties owe themselves mainly to the phenolic compounds present in yerba maté. However, there is debate over the methodology responsible for the anti-oxidant properties. This oxidation prevention occurs either due to the donation of excess electrons to “free radical scavengers” or the “chelating [action] of transition metal ions” (Bastos et al. 2007).

Similarly, saponins are prevalent throughout the *I. paraguariensis* plant. The majority of these glycosides are triterpenoid, but there are “monodesmosidic and bidesmosidic saponins found in the aerial parts of the plants” (Bastos et al. 2007). In 1989, research of yerba maté yielded the “isolation and elucidation of a new saponin” known as matesaponin, a “three sugar residue bidesmoside” (Bastos et al. 2007). Since then, research observed matesaponin 1 through 5 within the plant. Ursolic acid and its isomer oleanolic acid are minor saponins occupying the leaves of the plant. In all, 29 different saponins have been identified within *I. paraguariensis* (Bastos et al. 2007).

The rest of the important constituents are flavonoids and tannins, as well as some vitamins. Quercetin and rutin are two common flavonoids present in yerba maté. The tannin content is partly responsible for the bitter nature of the tea. Vitamins

A, B complex, C, and E are present; however, their amounts are highly influenced by how the tea is produced as well as where it is grown (Bracesco et al. 2011).

Biological Activity

Over the past few decades, many researchers have studied the effects and mechanisms of action of *Ilex paraguariensis* in hopes of gaining new and more in depth medical insight. Because this plant has been used for years in medical treatments, researchers are determined to uncover the medicinal basis of yerba maté. In order to do so, biological assays are performed *in vitro* as well as *in vivo* in reference to a variety of different health issues and diseases.

Herpes

Due to the rapid increase in drug resistance, researchers are desperately searching for new modes of action in the treatment of infections due to the herpes simplex virus. Because certain constituents of the plant have anti-viral effects, yerba maté was examined for its potential anti-herpes properties. Extracts from *I. paraguariensis* were tested against HSV-1, KOS strain, and HSV-2. Through the laboratory study, all plant samples used were positive for anti-herpes effects. Furthermore, it showed “reduced HSV-1 and HSV-2 infectivity to concentrations ranging from one to three times below their original infectivity concentration value.” This information may propose microbicidal properties, which may “inactivate the herpes virus and interfere with virion envelope structures or mask viral structures necessary for absorption or entry into host cells.” The studied fraction decreased the spread of the virus into adjacent cells and the number of virions transferred to unaffected cells. The saponins found in yerba maté were

specifically believed to be responsible for its anti-herpes effects (Lückemeyer et al. 2011).

Weight Loss

I. paraguariensis has long been associated with weight reduction. Therefore, studies were performed to assess the accuracy behind this association. One particular *in vivo* study sought to examine the effects of yerba maté on mice obesity. These mice were fed high fat diets and then were randomly assigned either water or yerba maté extracts. The results proved that the extracts in fact led to a considerable reduction in body mass of those mice, which consumed the extract. The evaluation of the mice showed a minimization in “serum levels of cholesterol, triglycerides, LDL cholesterol, and glucose.” In addition, the expression of many genes and proteins that were increased due to the high fat diet experienced a reduction. Chlorogenic acid, a phenolic compound, is believed to be associated with the metabolism of glucose via the enzymatic activity of glucose-6-phosphatase. It also plays a role in the prevention of cardiovascular disease by the anti-oxidation of cholesterol. The purine alkaloids and saponins potentially work with the phenolic compounds to produce these effects visible in the mice (Arcari et al. 2009).

Bile Flow

Because *I. paraguariensis* was historically utilized to treat digestive and hepatic disorders, this *in vivo* study examines the effects of yerba maté on bile flow and peristalsis of the digestive tract. While under anesthesia, the rats underwent surgery to measure their bile output in order to calculate bile flow. They then received either saline or *I. paraguariensis* extract intravenously or intraduodenally. To measure the

intestinal propulsion via peristalsis, mice were fed charcoal and killed approximately twenty minutes later. The distance that the charcoal traveled down the small intestine was measured. A considerable increase of bile flow resulted from the 250 milligram per kilogram dose. *I. paraguariensis* failed to show any effects on peristalsis. However, it does increase the output of bile from the liver, thereby restating the hepatoprotective effects (Gorzalczany et al. 2001).

Clinical Studies

Bone Mineral Density

Ilex paraguariensis has been involved in a multitude of clinical studies to further test the notions of health benefits associated with this plant. One such study sought to investigate bone mineral density associated with osteoporosis in postmenopausal women. This study examined 146 women who drank an average of one liter per day of yerba maté tea and 146 women who never ingested the tea as the control group. Bone mineral density or BMD was measured for each woman’s lumbar spinal region and hip joint via a dual-energy X-ray absorptiometry. Women who regularly consumed yerba maté tea showed considerably higher bone mineral density in both of the regions. This amounted to an increase of 9.7% for the lumbar spine and 6.2% for the femoral neck of the hip joint. Therefore, *I. paraguariensis* shows protective activity against osteoporosis in postmenopausal women (Conforti et al. 2012).

Diabetes

Another clinical study set to investigate the correlation between *I. paraguariensis* and diabetes, specifically patients who are type II diabetic and pre-diabetic. Because research

has proved that this plant decreases blood sugar in some animals as well as decreases cholesterol levels in humans, this study wanted to test the notion that yerba maté may be of benefit to these people. There were three treatment groups—yerba maté tea, dietary counseling, and yerba maté tea in conjunction with dietary counseling. 29 individuals with diabetes mellitus and 29 pre-diabetic individuals were utilized in this study. The yerba maté tea reduced “levels of fasting glucose, glycated hemoglobin, and low density lipoprotein cholesterol.” The clinical study found that yerba maté regulated blood sugar levels and decreased cholesterol in these diabetic and pre-diabetic individuals. This may point to yerba maté containing preventative means against coronary artery disease (Klein et al. 2011).

UADT Cancers

Because the incidence of upper aerodigestive tract cancers is significantly greater in South America, a clinical study was performed to test the hypothesis that the increased consumption of yerba maté may influence these rates. Upper aerodigestive tract cancers include cancers of the oral cavity, oropharynx, hypopharynx, larynx, and esophagus. 1,168 individuals as well as 1,026 control individuals were involved in this clinical study. This study was indicative of a positive correlation between esophageal cancer and excessive consumption of yerba maté tea. If an individual drank the tea consistently for roughly twenty years, he/she was 3.5 times more likely to acquire this type of cancer than someone who had never drank the tea. For forty years of consumption, the likelihood increases to five times. There has been controversy regarding previous studies, which believe that this association is due to the temperature of the tea. A high temperature could induce thermal damage to the head and neck regions.

However, this particular study found that the increased risk was greater for those who drank the tea either cold or warm than those who drank it hot or very hot. This proposes that yerba maté may in fact have carcinogenic effects especially in the UADT (Szymańska et al. 2010).

Contraindications

Ilex paraguariensis ingested in any form is considered GRAS or generally recognized as safe. However, despite the fact that it is described as nontoxic whether in the form of tea, pills, supplements, etc., there remain contraindications as well as positive associations with certain diseases and cancers. Due to these dangerous interactions, *I. paraguariensis* should potentially be avoided by certain people whose health issues may be exacerbated by the active constituents within the plant.

An *in vivo* study with rats and rabbits tested toxicity levels immediately following consumption as well as after continued intake for up to three months. Not only did the study show no forms of toxicity for a single dosage, it was also found to be safe for chronic consumption. Other studies have confirmed that there is no toxicity associated with the liver, the kidneys, or the bladder. *I. paraguariensis* even shows a potential protection against DNA strand damage in an *ex vivo* study. The constituents prevented the DNA strands from damage due to peroxide content, and they enhanced the mending of DNA within liver cells (Andrade et al. 2012).

Because *I. paraguariensis* contains caffeine and other xanthines, people that consume any form of this plant should avoid it if they have allergies to either compound. In addition, women who are either pregnant or breastfeeding should refrain from ingesting yerba maté. The caffeine within the

plant reduces fatigue and increases alertness; therefore, it may cause problems with sleep if ingested around bedtime. It also should be avoided when taken in conjunction with sleeping medications due to drug interference. Yerba maté also has diuretic effects and should not be consumed if diuretic effects are to be avoided especially with urinary tract obstruction. People suffering from cardiovascular diseases such as hypertension and arrhythmia should avoid yerba maté. Those who show signs of hyperthyroidism and gastric and duodenal ulcers should refrain from consumption. In addition, use with monoamine oxidase inhibitor drugs or MAO-inhibitors should not occur. These drugs are used in the treatment of depression. *I. paraguariensis* decreases the sedative and anti-anxiety processes within these drugs and therefore, exacerbate the side effects associated with sympathomimetic drugs (Products, C. o. H. M. 2010). Unfortunately, there has been a positive correlation with head and neck cancers, especially oropharyngeal and esophageal cancers (Szymańska et al. 2010). However, due to the antioxidant effects of yerba maté, some of the constituents have anti-carcinogenic effects. While people with specific health conditions should avoid *I. paraguariensis*, the plant remains GRAS and is established as nontoxic.

Current Use in Allopathic and CAM Therapies

Today, *Ilex paraguariensis* still remains a leading medicinal plant. Based on the knowledge that native South American Indians possessed of its curative properties, yerba maté continues to be used to treat a multitude of ailments. Use of this plant within traditional medical practices propagated its use in the current world of complementary and alternative medical therapies. This has instigated the creation, production, and use of *I. paraguariensis* in many forms,

including capsules, tablets, and pills. The majority of these medicinal remedies remain in the form of supplements. Mainly, yerba maté is utilized as a stimulant to increase alertness and decrease fatigue (Gorzalczany et al. 2001). These supplements on many occasions are used in conjunction with guarana, kola nut, and green tea to enhance the effects (Bastos et al. 2007). 29 different dietary supplements of yerba maté from the years 1963 to 2006 gained international patents with a significant influx in supplements after the turn of the century. These included but were not limited to supplements to facilitate weight loss, promote sexual arousal, enhance hair thickness, and decrease levels of cholesterol. Other uses for yerba maté aim to treat the underlying issues of “arthritis, headache, constipation, rheumatism, hemorrhoids, obesity, fatigue, fluid retention, hypertension, slow digestion, and hepatic disorders” (Gorzalczany et al. 2001).

Albeit no prescription or over the counter drugs are either on the market or have been approved by the FDA, many studies are attempting to gather more information regarding *I. paraguariensis* in the hopes of isolating the mechanisms of action for its active constituents. While studies have produced positive results concerning the treatment for hypercholesterolemia as well as osteoporosis, more research needs to be done in order for a FDA-approved drug. Until more information is known, yerba maté will continue to be a commonly used supplement and CAM therapy.

Discussion

Hundreds of years ago, the Guaraní Indians of South America recognized the importance as well as the medicinal potential of *Ilex paraguariensis*. Today, researchers are beginning to recognize this same thing. For the Guaraní, this highly

regarded tea remained an integral part of their culture, from social rituals to traditional medicinal practices. Over the years, it has been associated with the treatment of a variety of different ailments. This yerba maté decoction treats everything from weakness of the body and mind, digestive disorders, inflammatory processes, cardiovascular problems, as well as joint issues.

Recently, researchers have gone further to investigate these treatments, looking at the constituents of *I. paraguariensis* as well as their mechanisms of action. These constituents include purine alkaloids, phenolic compounds, saponins, tannins, and flavonoids, providing anti-inflammatory, anti-viral, and antioxidant effects. Within *in vitro* and *in vivo* studies, *I. paraguariensis* showed anti-herpes activity, weight loss as well as a reduction in LDL cholesterol and an increase in bile flow. In regards to clinical studies, while it increased BMD and lowered LDL in diabetic patients, it did show a carcinogenic effect. Knowing which problems yerba maté has been known to treat through traditional medicine, researchers may be able to learn more about *I. paraguariensis* and its potential for the future. However, to be able to utilize this plant for generations to come, we must protect it from environmental abuse and overharvesting.

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Lavandula angustifolia Mill., Lamiaceae

Cimma Sefat

Introduction

Lavandula angustifolia, also known as true lavender, is a member of the Lamiaceae family (**Figure 1**). It is commonly known as English lavender or xun yi cao in Chinese ("Lavandula angustifolia Mill.," 2012). *L. angustifolia* is the most common species of lavender, and other species include *L. burnamii*, *L. dentate*, *L. dhofarensis*, *L. latifolia*, and *L. stoechas* (Basch et al., 2004). This plant is native to the western Mediterranean region, and its hybrid lavandin is widely cultivated in Australia, Europe, and the United States. *L. angustifolia* has been known for its cosmetic and medicinal uses throughout history (Basch et al., 2004). Advertised as a calming agent, *L. angustifolia* is said to ease restless minds. Its aromatic essential oils are highly prized and used for aromatherapy, candles, cooking, laundry detergent, massage oils, perfume, and soap (Basch et al., 2004). Being a member of the Lamiaceae or mint family, lavender leaves also serve a culinary purpose and are commonly used in salads, stews, tea, honey, jam, and jelly (Craig, 2006).

Botanical Description

Lavender is an evergreen subshrub plant that grows approximately two to three feet tall and produces small, slender blue-violet flower spikes on the stalks and narrow silver green foliage. This detail can be noted in **Figure 2**. The *angustifolia* species is a stockier plant with fuller flowers unlike other the lavender species ("Lavender," 2007). Native to low mountains and altitudes of 1,970-3,940 feet, *L.*



Figure 1. Lavender field in Provence, France. (Source: <http://gourmetcyclingtravel.com/wp-content/uploads/Lavender-Field-800X2752.jpg>).

angustifolia originated in the Mediterranean basin and is cultivated in Albania, Argentina, Australia, Bulgaria, China, France, Hungary, Italy, Moldova, Montenegro, the Netherlands, Russia, Serbia, Spain, the United Kingdom, and the United States (Craig, 2006). *L. angustifolia* is capable of surviving in temperatures as low as -15°C (Bourne, 2004). This plant prefers full sun and can also survive in a wide range of soils but these soils must be well drained since the plant cannot tolerate sitting in very wet soils (Fowler, 2004). *L. angustifolia* flourishes on hard pruning, and if pruned every year, it can survive for approximately 20 years (Bourne, 2004). Lavender is a popular and reliable drought-tolerant perennial for gardens and hedges, requires little fertilizer, and is bothered by few pests (Anonymous, 2011).

The hybrid lavandin is much more widely cultivated and exceeds *L. angustifolia* in essential oil production; however, the finest oil used in cosmetics, perfume, and aromatherapy



Figure 2. Close up of *L. angustifolia* (Source: <http://sciencera.com/biology/lavender-a-fragrant-plant-of-the-family-lamiaceae/>).

come from *L. angustifolia* (Bourne, 2004). Since lavender has been cultivated for so long, most lavender found in gardens are hybrids and identification can be difficult (Craig, 2006). Dried lavender flowers contain less than 13 ml/kg of essential oil that is obtained by steam distillation from the flowering parts (Basch et al., 2004).

Traditional Uses

Lavender is derived from the Latin word *lavare*, which means to wash. The Grecians, Persians, and Romans used lavender flowers as a perfume in the baths and for laundry (Craig, 2006). As a part of mummification, ancient Egyptians soaked wrapping linen in lavender oil containing asphalt as a method

of casting. The bodies would be wrapped in these linens and dried in the sun until the casts hardened (Craig, 2006). Lavender is known as a “healing agent” in India and Tibet, and can also be used medicinally to treat insanity and psychoses in Tibetan Buddhism (Basch et al., 2004). It has been reported that in fourteenth century France, Charles VI’s court used cushions stuffed with lavender which provided not only a pleasant aroma but also helped repel insects (Craig, 2006). During the twelfth century in Grasse, located in southeast France, lavender oil was the main component of commercial perfumes. Many thought the scent of lavender surpassed all other scents due to its delicate and unique aroma (Craig, 2006). In Iranian folk medicine, lavender leaves are used to treat various inflammatory diseases (Hajhashemi, Ghannadi, & Sharif, 2003). Infusions of the plant have been used as a carminative, diuretic, anti-epileptic, anti-rheumatic, and pain reliever especially for headache and migraine pain. Associated with cleanliness, lavender maintains great popularity as fresh or dried flowers, potpourri, gifts, crafts, and more (Anonymous, 2011).

Chemistry and Pharmacology

Lavender is known for its rich content of volatile oils, and for centuries it has been used for both fragrance and medicine. Aromatherapy is thought to be effective due to the effect of odor and the physiological effect of inhaling volatile compounds like the oil of *L. angustifolia*. Lavender is composed of several hundred constituents which include flavonoids, cineole, coumarins, triterpenes, tannins, limonene, camphor, linalyl acetate (**Figure 3**), perillyl alcohol, and linalool (**Figure 4**) (Basch et al., 2004). The highest concentration of naturally occurring compounds in lavender oil include linalool, linalyl acetate, 1,8-cineole, beta-ocimene,

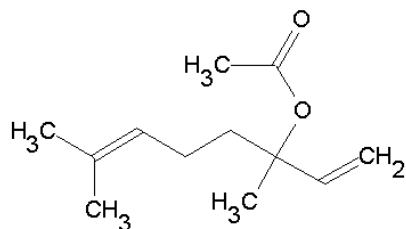


Figure 3. Linalyl acetate (Source: http://www.rdchemicals.com/chemicals.php?mode=details&mol_id=8000).

terpinen-4-ol, and camphor (Oliff, 2003). Linalool and linalyl acetate are rapidly drawn into the skin when massaged and believed to cause central nervous system depression. Linalyl acetate has narcotic actions while linalool acts as a sedative (Basch et al., 2004). Due to the calming actions of these constituents, they may be the origin of the use of lavender pillows to induce sleep (Oliff, 2003). Lavender leaves yield a pale-yellowish essential oil with a fresh and pleasant odor (Hajhashemi et al., 2003). Twenty-one components were characterized which represent 99.1% of the total oil components detected, listed in **Table 1**.

Biological Activity

In Vitro

Oil of *L. angustifolia* is active against several bacterial and fungal species, and it has been suggested that lavender oil may be useful in treating bacterial infections resistant of antibiotics (Lodhia, Bhatt, & Thaker, 2009). In a study by Hui et al., *L. angustifolia* oil was studied for antimicrobial activity for

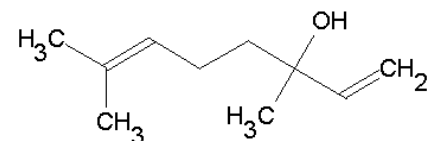


Figure 4. Linalool (Source: http://www.rdchemicals.com/chemicals.php?mode=details&mol_id=7998).

Table 1. Gas chromatographic composition of the essential oil (%; uncorrected values)

Constituents	<i>Lavandula angustifolia</i>
α -Pinene	0.14
Camphene	0.10
β -Pinene	0.11
Myrcene	0.64
Limonene	0.20
1,8-Cineol	1.06
γ -Terpinene	traces
<i>p</i> -Cimene	9.05
Camphor	1.19
Linalool	27.34
Linalyl acetate	32.10
Terpinen-4-ol	3.63
Lavandulyl acetate	1.05
Bornyl acetate	traces
β -Caryophyllene	2.68
Lavandulool	0.86
Borneol	0.30
α -Terpineol	0.29
Neryl acetate	0.18
Geranyl acetate	0.40
Geraniol	0.38

Table 1. List of essential oils in *L. angustifolia* (Source: Hajhashemi et al., 2003).

	8.5 mg/ml	17 mg/ml	34 g/ml	51 mg/ml
<i>Staphylococcus aureus</i>	+	+	+	-
<i>Micrococcus ascoformans</i>	+	+	+	-
<i>Proteus vulgaris</i>	+	+	+	-
<i>Escherichia coli</i>	+	+	+	-

Table 2. Anti-bacterial activities of lavender essential oil
(Source: Lu Hui, 2010).

potential treatment for rhinitis patients. It was found to be active against all tested strains of bacteria seen in **Table 2**. The oil's activity is dependent on concentration. At 51 mg/ml, none of the tested bacteria survived. The study believes that the *L. angustifolia's* essential oil is capable of disrupting the cell membrane, and the cell loses chemiosmotic control (Lu Hui, 2010). Antimicrobial activity of lavender oil may not be related to the main constituents in the oil and there is little known about the possible relationship. Many of the lavender antimicrobial studies do not have standardization so directly comparing studies is impossible (Oliff, 2003).

Another study published in 2007 studies essential oils in plants like *L. angustifolia* as an acaricide, or a substance poisonous to mites or ticks. There is a long tradition that aromatic herbs such as lavender are used to repel insects. In folklore, essential oils are held in high regard because of their use as an insecticide and repellent. It is known that different essential oil components render different species of insect susceptible. The study performed by Perruci et. al has shown that when the mites *Psoroptes cuniculi* (mange mite of the rabbit) is exposed to linalool, the parasite loses mobility (5). It is suggested that inhalation and direct contact to linalool causes loss of mobility. The experiment placed the mites (10-15/sample) on a 6 cm petri dish covered with a filter. Then that petri dish is placed in a 9 cm petri dish containing the *L. angustifolia* oil. The experiment was done at room

temperature (22 °C). The mites were exposed to a series of doses. To verify that linalool was the only effective constituent responsible for acaricidal activity, an artificial mixture of 27% linalool (the percentage found in the essential oil) and 73% saline (1mL/plate) with 2% vaseline oil (1mL/plate) was tested the same way. The controls used were plates containing just the physiological saline and plates containing solely vaseline oil. Motionless mites were observed with a stereoscopic microscope after a 24-hour period, and then transferred to a fresh petri dish and observed again for another 24 hours. The mites were stimulated with a needle, and any lack of reaction or continued immobility indicated death. However, further studies on the toxicity and mode of action and in vivo activity are necessary to confirm whether lavender essential oil and linalool can be used as an alternative acaricide.

In Vivo

There also was a study on anti-inflammatory and analgesic properties of leaf extracts and essential oil of *L. angustifolia* published in 2003. The study evaluates the analgesic and anti-inflammatory activities of the hydroalcoholic extract, polyphenolic fraction and essential oil of plant leaves in mice and rats. The leaves of *L. angustifolia* were collected near Isfahan, Iran. The leaves were then air dried and powdered, and the essential oil was isolated by hydro distillation. The hydroalcoholic extract was made by taking the powdered *L. angustifolia* leaves (100 g) and macerating with EtOH-H₂O (500 g) for 48 hours. The extract was shaken, filtered, and evaporated until dry. The polyphenolic fraction of the plant (100 g) was made in 2 steps. The fraction was extracted with EtOH:H₂O (9:1) then again with a 1:1 ration of the same solution. The mixture was left for 12 hours. Then the two

extracts were combined and evaporated to 1/3 its original volume. The remaining aqueous solution was extracted with chloroform and evaporated until dry, which left semi-solid masses of both the hydroalcoholic extract and polyphenolic fraction (yield 42.0% and 12.2%, respectively). Analgesic activity was tested with two tests: a formalin test and an acetic acid-induced writhing test. For the first test, mice were injected with 20 μ l of 2.5% formalin (in 0.9% saline) in their right hind paw. The hydroalcoholic extract, polyphenolic fraction and essential oil were given orally prior to the formalin injection.

For the acetic acid-induced writhing test, 6 mice received different oral doses of hydroalcoholic extract, polyphenolic fraction, and essential oil one hour prior to the intraperitoneal injection of 1% acetic acid (volume 10 ml/kg). Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test in the rat. The rats were anaesthetized with ether and injected with 0.1 ml of 1% suspension of carrageenan in isotonic saline. The left hind paw was injected with 0.1 ml saline as a control. The extract and essential oil mixture was diluted and administered 1 hour before the carrageenan injection.

While the hydroalcoholic extract failed to produce any significant analgesic effects in the first phase, when given in doses of 400, 800, and 1600 mg/kg, paw licking time was reduced 69, 72, and 93%, respectively. The polyphenolic fraction and essential oil suppressed paw licking in both phases of formalin test. For the acetic-induced writhing test, hydroalcoholic extract did not apply a significant decline of abdominal twitches, while the polyphenolic fractions (doses of 400 and 800 mg/kg) and essential oil (100 and 200 mg/kg) significantly reduced writhing. The results were not dose-dependent since the increased dose did not alter the response. For the carrageenan test, the neither the hydroalcoholic nor

the polyphenolic fraction in high doses (such as 4000 mg/kg) did not exhibit a considerable anti-inflammatory effect. At a dose of 200 mg/kg, the essential oil showed a 48% inhibition of carrageenan-induced paw edema (S. Perrucci, 1996).

A study by the Cline group investigates the anxiolytic effects of the compound linalool and the GABA_A receptors in rats. Forty-four rats were given a 1 mL total volume intraperitoneal injection of positive control, midazolam, linalool, or a linalool and flumazenil mixture. Then, they were put on an elevated maze and had their corticosterone levels measured. The data suggests that linalool does not produce anxiolytic effects by regulating GABA_A receptors but it may modulate motor movements in the rats. The rats were placed on an open arm of the elevated plus maze (EPM) for a 5-minute evaluation of behavioral response to anxiety. The EPM was networked with MotorMonitor software to track the number of times the rats would enter either type of arm (open or closed), time spent in the arms, and basic motor movement. After the 5-minute test on the EPM, the rats were humanely killed by guillotine and their blood was collected for corticosterone and catecholamine (epinephrine and norepinephrine) analysis. There was no significant analysis of the ratio of open arm time versus total time in the EPM between the linalool and the flumazenil plus linalool group. There was significant difference in the open arm, a measurement of behavioral changes with anxiety, between the midazolam and the control groups. As for fine motor movements, analysis showed a significant decrease in movement in both the midazolam group and flumazenil plus linalool group compared to the control. The behavioral measurements comparing time spent in different arms on the EPM does not suggest that linalool produces anxiolysis. There was no difference between the mixture group therefore suggesting that linalool does not regulate the benzodiazepine receptor site. The results do not

support that linalool modulates the GABA_A receptor. The neurohormonal data did not demonstrate a significant difference amongst the groups. Motor movement exhibited that midazolam and the flumazenil and linalool combination significantly decreased both basic and fine motor movements. The study is unsure how to interpret these results but it is speculated that another neurotransmitter site is being modulated. It is suggested that linalool modulates receptors at the neuromuscular junction thus decreasing acetylcholine release and limiting motor activity. Although the data does not support anxiolytic effects of linalool in rats, there is evidence to suggest linalool regulates the central nervous system by producing unconsciousness and deterioration of motor movements (Cline, Taylor, Flores, & Bracken, 2006).

Clinical Studies

The chemical composition and pharmacological study and evaluation of *L. angustifolia* have been the subject of several studies for years. Most of these studies focus on extracts and essential oils of lavender. In pharmacological studies, the extracts and essential oils are believed to have CNS-depressant, anti-convulsive, sedative, spasmolytic, local anesthetic, antioxidant, anti-bacterial, and mast cell degranulation effects (Hajhashemi et al., 2003).

A cross-over randomized study conducted at nursing homes in Hong Kong studied pharmacological intervention of *L. angustifolia* for agitated behaviors among people with dementia. Seventy participants diagnosed with dementia with significant agitation were recruited, and participants taking psychotropic medication to control their aggression (51.4%) continued to take their medication. Participants were assigned to group A or B but both groups received both treatments. Either treatment A or treatment B was

administered for 3 weeks with a wash out period (2 weeks) in between treatments. Then, the other treatment was given. Treatment A was *L. angustifolia* inhalation, and treatment B was sunflower inhalation (placebo). Aroma diffusers were placed at each side of the participants' bed during sleep at night for 1 hour. No adverse effects were reported from either staff or patients during the study period. Caregivers noted a significant decrease in agitated behavior in patients receiving Treatment A. Agitation scores decreased from 6.49 to 5.63. Irritability decreased from 4.81 to 4.53. The aromatherapy treatment was well tolerated and resulted in a significant decrease in agitation of patients with dementia (Wan-ki Lin, Wai-chi, Fung-leung Ng, & Chiu-wa Lam, 2007).

Support of lavender as an anxiolytic is still weak but some evidence does suggest an effect in the plant's ability to relieve anxiety (Basch et al., 2004). In one study, nurses used aromatherapy on 20 hospitalized children with HIV to relieve them of physical pain. They used a variety of essential oils known for their "analgesic and nervine" properties including *L. angustifolia* oil. Nurses noted that the children responded well to the essential oils, which helped reduce the need for analgesic drugs. Chronic chest pain, intermittent muscle spasm, and peripheral neuropathy were alleviated almost completely. This is a descriptive study and no statistical data was analyzed (Buckle, 1999, p. 44).

Another study suggests that there is some scientific evidence regarding the use of lavender oil baths for relieving postpartum perineal pain. The effect of lavender oil baths was examined on 635 postpartum women in a randomized trial. The women were divided into three groups. One group added a natural lavender oil extract, the second group added synthetic lavender oil, and the third group added a GRAS substance. Neither the midwives nor the mothers know what kind of oil was administered. Daily baths were routine for the

mother's care after delivery, and each day the midwife added six drops of the oil from which the mother's name was placed on the bottle. Thirty minutes after the bath, the mothers were asked to record the degree of discomfort experienced, and the midwives assessed the mother's perineum as part of the normal daily examination of the mother. Daily visits helped reinforce the procedure for the mother, and assessment continued until the 10th day. Mood scores were analyzed over a 10-day period. The mean discomfort scores showed a steady reduction. There was missing data from this study possibly due to the fact that those whose pain improved were more likely to stop recording the amount of discomfort experienced. The women in the pure lavender oil group showed the lowest mean discomfort scores after the first 5 days of childbirth. No side effects by the mothers or midwives were reported during the trial (Dale & Cornwell, 1994).

Contraindications

There have been few reports of sensitization after topical use of lavender. The lavender species is considered "likely safe" or GRAS (generally recognized as safe) for internal and external use. Generally, lavender is well tolerated with mild side effects. People with known allergy or hypersensitivity to lavender should exercise caution when using this plant. People with lavender allergy may experience mild local skin reactions after topical use of lavender oil. Lavender is believed to the potential of heightening effects of barbiturates and other depressants to the central nervous system. It is said to exhibit narcotic like effects on both humans and animals. In theory, lavender may intensify the effects of other sedative or hypnotic agents. Since lavender contains varying amounts of coumarins, it theoretically can increase the effect of anticoagulant medications. There is no reported lethal dose of

L. angustifolia but nausea, vomiting, and anorexia were reported after consuming large doses of lavender (>0.5 g/day). Lavender has still not been proven safe for consumption for pregnant women or children, and more research is necessary to understand the medicinal action of lavender (Basch et al., 2004). Those should avoid the plant if they allergies to members of the Lamiaceae family. People with sensitivity to plants with volatile oils or sensitivity to strong smells are advised to avoid contact with *L. angustifolia*.

Current Use in Allopathic and CAM Therapies

Throughout the United States and Europe, lavender oil has been used in aromatherapy, balneotherapy (treatment of disease by bath), and massage therapy. In Germany, lavender tea is used to promote sleep and ease stomach illness and nervous conditions. Lavender is used as an anti-depressant in Ayurvedic medicine in India while Tibet includes the plant in psychiatric treatment. Also, lavender oil is used externally to medicate burns, sunburn, wounds, insect bites, and muscle pain (Craig, 2006).

Aromatherapy is acknowledged as complementary therapy for "increased comfort, relief of pain, relaxation, improved coping, reduction or moderation of stress, and an increased sense of well-being" (Buckle, 1998, p. 56). Because many essential oils like lavender have calming and soothing properties aromatherapy has gained popularity in the general population and specifically among nurses who want to incorporate a holistic approach to their care (Buckle, 1998, p. 54). This kind of aromatherapy is known as clinical aromatherapy. Unlike recreational aromatherapy, clinical aromatherapy heavily relies on understanding the different species of the plant, not just their common name. For example, *L. angustifolia* is a relaxant, *L. latifolia* is a stimulant, and *L. stoechas* may exhibit

neurotoxic properties but is effective in treating pseudomonads or gram-negative bacteria (Buckle, 1998, p. 59).

In nursing, aromatherapy often times is used with topical applications such as compresses, therapeutic baths, or gentle massage. For each method, 1 to 5 drops of essential oil is diluted; essential oils are highly concentrated and should not be directly applied to skin if undiluted. The essential oil can be diluted in cold-pressed vegetable oil, cream, gel, or water. For baths, the essential oils should be diluted in a small amount of milk before being added to the tub since these oils are insoluble in water and will merely float on the surface of the water and provide uneven treatment (Buckle, 1998, p. 57). One example of clinical aromatherapy that utilizes lavender is to mimic the effect of diazepam (valium). Diazepam reduces the effect of external emotional stimuli by increasing inhibitory neurons in the amygdala, which governs emotional response in the brain. *L. angustifolia* is thought to have a similar effect and produce a sedative effect on patients (Buckle, 1998, p. 56).

Discussion

There is a lack of consistent data and reporting on the true effects of lavender and its therapeutic importance (Oliff, 2003). Although research is still needed, the potential contribution lavender has on human health can be noteworthy. Its use in clinical aromatherapy offers a more sensitive, holistic care especially for critical care patients. Also, there can be future research opportunities to explore the efficacy of linalool as a complement with anesthesia or the interactions with anesthesia medication. Many of the studies, especially concerning the research done by Buckle, show that *L. angustifolia* oil can help with pain management. According to Buckle, the United States spends over \$70 million on

chronic pain therefore utilizing *L. angustifolia* oil can be a holistic and cost-effective approach to pain management. Lavender is an extremely diverse plant in terms of its uses from cosmetic to culinary to medicinal. One cannot deny the historical significance of *L. angustifolia* as well as its fantastic and pleasant scent.

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Linum usitatissimum L., Linaceae

Alexa Kahn

Introduction

Linum usitatissimum L., commonly referred to as Flax, is a member of the Linaceae family. Another common name is linseed (Linnaeus 1857). Flaxseeds are known to be rich in α -linolenic acid and when used in the diet, it can be a therapy for reducing serum cholesterol and triglyceride levels, and ultimately used as a supplement to reduce platelet aggregation. Some data on antiplatelet effects are inconclusive, and more research needs to be conducted to better define flax as a functional food in reducing diseases such as cardiovascular disease. Secoisolariciresinol diglucoside (SDG) is another main constituent of flax and is the primary lignan found in the crop that is responsible for its therapeutic benefits. Flaxseeds have been studied for their benefits in treating conditions such as arteriosclerosis and high cholesterol (Lewis and Elvin-Lewis 2003). Flax is available in multiple forms such as, raw seeds, powder and oil. All forms are beneficial for both industry as well as in the human and animal diet and nutrition.

Botanical Description

Linum usitatissimum is among the oldest crop plant that is cultivated for obtaining fiber and oil. In Linnaeus' book "Species Plantarum" he gave the botanical name for flaxseed: *Linum usitatissimum* (Linnaeus 1857). There are currently 200 species of flaxseed known. It has a shallow root system and is known to be an annual herbaceous plant. The shallow system allows the plant to better survive on sandy or rocky terrain.



Figure 1. *Linum usitatissimum* (Flax capsules)

Source: <http://en.wikipedia.org/wiki/Flax>

The plant is short in height and has secondary branches and seed balls (**Figure 1**) (Jhala & Hall, 2010). Flax is a blue flowering crop that can produce small seeds that are flat, ranging in golden yellow to a reddish brown in color (**Figure 2**). In stores, flaxseeds sold in stores are normally available in ground seed (powder-like), whole seeds, and also in an oil form. The varieties of flax used for fiber come from plants with



Figure 2. *Linum usitatissimum* (flower and seeds).

Source. <http://www.colourbox.com/preview/2288281-427644-flax-seeds-with-flower.jpg>

longer stems, 80-120 cm tall, containing fewer branches and seeds. The oil forms come from shorter plants approximately 60-80 cm tall, and has stems dense with branches. The flax used to extract oil, also generally has a greater number of seed capsules and larger seeds itself (Shahidi 2005). Due to the versatility of flax, many universities and laboratories around the United States are showing an increased interest in studying the plant to solidify and learn more about its medicinal properties.

The flaxseed is home to warm and cool climates, and has been cultivated for many centuries across the world, primarily for its stem fiber, seed and linen cloth. Another common name used is linseed (Carter 1993). In India and the United Kingdom, the crop is called linseed, whereas throughout the United States and Canada the crop is termed flaxseed. In Canada, flax has a dark brown seed coat. In the United States, flaxseeds are available with yellow seed coats. The differences



Figure 3. Golden Flax

Source: <http://en.wikipedia.org/wiki/Flax>



Figure 4. Brown Flax

Source: <http://en.wikipedia.org/wiki/Flax>

in color are generally aesthetic (**Figures 3 and 4**) (Shahidi 2005) and not significant medicinally.

During a ten-year period, the total average yearly production of flax was 2.52 million metric tons. This ranked higher than



Figure 5. Graph of the major world producers of flaxseed during a ten year period (Shahidi, 2005).

sunflower, yet slightly lower than the soybean. Canada is shown to be the highest growing region for flax (**Figure 5**). In the northern latitudes, higher production of oil from the seeds is seen with high levels of polyunsaturated fatty acids contained in the oil. In the United States, North Dakota is the flaxseed production leader with over 95% of the region growing with flax (Shahidi 2005).

Traditional Uses

Flax has been used in food cooking throughout Europe and Asia since 5000-8000 BCE. Specially, the fiber contained in the flax stem has been utilized for linen cloth (Bloedon & Szapary, 2004). Originally, the stem fiber was brought to North America for its use in making linen and parchment paper. Over the past 100 years, flaxseed has been used throughout the Northern Great Plains region of the United States and

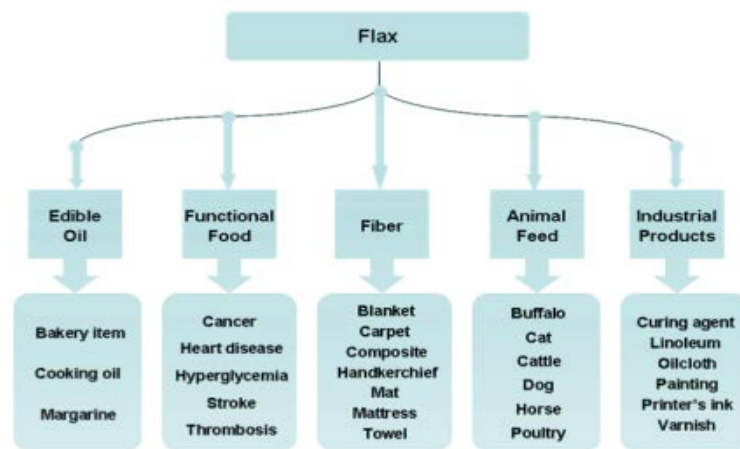


Figure 6. Schematic diagram of flax uses (Jhala & Hall, 2010).

Canada, as a commercial oilseed crop sold in many “health foods” stores as a dietary supplement (Carter 1993). Flax is grown in a wide range of countries and is known for its adaptability and product diversity (Jhala & Hall 2010)

Flax has many uses (**Figure 6**) and has stemmed back to ancient cultures in China, Greece, Egypt and India. In the flax growing region of the People’s Republic of China, many of the villages used flaxseed oil for low temperature stir-frying in many of their home cooked food dishes. (Carter 1993). In ancient Greek and Egyptian cultures, flax was utilized as a natural laxative and food source by many of the villagers.

In India, flax was mainly grown for its oil, as a baking and cooking item. However, flax was additionally used as a fiber source to make blankets, mattresses, linen clothes, and parchment paper (Vajpeyi, Abhishek, Shukla & Srivastava, 2008). As a result, the fiber obtained from flax was a main contributor to the textile industry of India. In Egypt, the art of

<i>Linum usitatissimum</i> , the whole flaxseed	
% Fat	41
% Protein	21
% Dietary Fiber	28

Table 1. The percentage components of one whole flaxseed (Bloedon & Szapary, 2004).

woven flax fiber to linen became important for the making of clothes for the upper class figures, such as Pharaohs in their society (Jhala & Hall 2010). Additionally, they used linseed oil as the main ingredient of the “finishing oil” for their woven and wooden furniture. The linseed oil is added to paints to create a more fluid and transparent liquid that can then be applied to hard surfaces, specifically wood. This leaves a nice, shiny appearance before it is then sold in markets in their villages.

It was measured that Europe generally has taller flax compared to the United States, which can be a reason why Europeans still use flax for linen cloth. The United States uses the fiber from flax less for linen and clothing since the discovery of cotton has been made (Carter 1993). While today flax is less used for its properties useful for parchment making or clothing for a community of people, we still do use flax as a cooking item. Today many people add flax in the form of seeds or even powder to their cooking to meet their daily fiber requirements.

Chemistry and Pharmacology

Linum usitatissimum, the whole flaxseed, is composed of 41% fat, 21% protein, and 28% dietary fiber, along with other minerals and vitamins (**Table 1**). The oil in flaxseed on the other hand, is unique in that it is concentrated in 73%

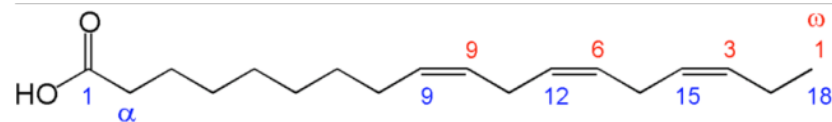


Figure 7. alpha-Linolenic acid molecule

Source: http://en.wikipedia.org/wiki/Alpha-Linolenic_acid

polyunsaturated fatty acids, 18% monounsaturated fatty acids, and only 9% saturated fatty acids. This lends itself to be considered a low-saturated fat food. The richest source of omega-3 fatty acid comes from flaxseed oil, which comprises approximately 55% of the total fatty acids (Bloedon & Szapary, 2004).

Flax is known for its higher fiber content, both an insoluble and a soluble source of fiber. They are rich in α -Linolenic acids (**Figure 7**) as well as phytoestrogens, or lignans. Lignans are phenolic compounds. The richest source lignans are, seciosolariciresino diglucosides (SDG) (**Figure 8**) (Bloedon & Szapary, 2004).

Flaxseed is known to contain approximately 35-45% oil, 25% protein with 10% moisture. The flaxseed has high constituents of oil, but extracting this oil is difficult to do and often requires double pressing to do so. Prior to crushing the seeds, clean ones are needed in order to ensure moisture levels of 9.5-10%. Ultimately, this will minimize the formation of fine particles when the seeds are cracked and will then maximize the removal of oil from them. Next, the moisturized seeds pass through a set of corrugated and smooth rolls to be cracked and then flaked. Consequently, the production of flax oil is differentiated from that of Solin or Linola oil. In order for flaxseed to be consumed by humans, it is necessary for it to be cold-pressed. The process of cold-pressing entails the temperature of oil coming from extruder to not exceed 35 °C,

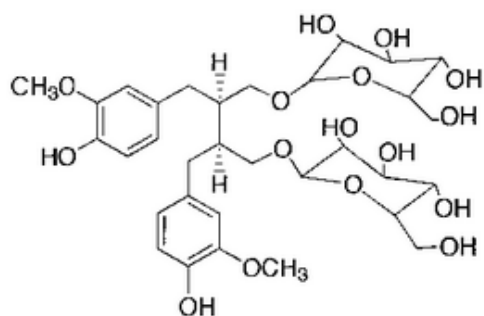


Figure 8. Seciosolariciresino diglucosides (SDG)

Source:

<http://www.biopurify.com/admin/editor/UploadFile/20071018141427125.gif>

(Carter 1993) and the pressing is done under a blanket of nitrogen in order to protect it from oxygen. Expellers can be used to cool parts of the press that are in contact with the seeds and the oil in hopes of controlling the temperature during the extensive processing technique (Vassel & Nesbitt 1945).

Flax may be used as a protective agent against cardiovascular disease through a number of different mechanisms of action. Flax is capable of reducing serum cholesterol, inflammatory marks, and platelet aggregations. Furthermore it acts as an antioxidant. The high soluble fiber content of flax allows for enhanced gastric emptying, which interferes with the bulk phase diffusion of fat, while also increasing the excretion of bile acids. The viscous fiber component of flax has been associated with increase glucose tolerance (Bloedon & Szapary, 2004).

Some evidence suggests that SDG is correlated with lower serum cholesterol levels. Lignans are potentially capable of lowering serum cholesterol through the modeling of enzymes,

specifically, 7α -hydroxylase and acyl CoA cholesterol transferase, which are both involved in cholesterol metabolism. The lignans in flax have been shown to reduce oxidative stress, and SDG, has been shown to act as an antioxidant and further as an antagonist of platelet activating factor (Lewis and Elvin-Lewis 2003).

Biological Activity

Many studies have been conducted to assess the biological activity of flax. Both *in vivo* and *in vitro* studies have been conducted to determine the mechanism of action of flaxseeds to ultimately better understand the biological activity in animals as well as humans

In vivo

Animal studies have been conducted to question the capability of flaxseed products improving serum lipids. The rats fed 20% and 40% flaxseed for 90 days has substantially lower serum total cholesterol and LDL level than those rats that had a diet absent of flax. The results found that SDG found in flax reduced hypercholesterolemic atherosclerosis by 73% suggesting the effect was associated with lower serum levels (Prasad 1997). Additionally, the antioxidant activity of flaxseed lignans in rabbits was evaluated *in vivo*. Results showed that a 7.5 g/kg regular flaxseed added to an antioxidant free diet, along with the addition of 1% cholesterol, decreased atherosclerosis in the aorta by nearly 46% and lowered the number of inflammatory polymorphonuclear leukocytes as compared to the same diet in the absence of flax. The study projects that dietary flaxseed supplementation could be used to minimized heart attacks and strokes (Prasad 1999).

Overall, purified SDG from flax seed have been evaluated in mammary, colon, prostate, and thyroid cancers as well as diabetes, liver and heart disease in animal rat models. On the whole, results suggest beneficial effects of lignans. Some caution should be taken in relation to the dose of lignan and time of administration during reproductive stages in females (Westcott & Muir, 2003). Although the mechanism of action is not completely understood, researchers suggest that it may involve influence of hormonal or anti-oxidant activity.

Skin and hair conditions were studied in animals that consumed flaxseed or flaxseed oil. In Capuchin monkeys, it was reported that severe skin lesions were healed after consumption of flaxseed. Although the scientists have not yet confirmed and documented the effects of flax in human skin conditions, current research suggests possible improvements of a variety of skin disorders after assessing the improvements of psoriasis in humans who had sufficient consumption of flaxseed (Sinclair, Fiennes, & Crawford, 1973). Additionally, a study with Swiss mice showed that α -linolenic acid inhibited progression of skin cancer development (Ramesh & Das, 1993).

In vitro

The outcome of linseed oil fed to New Zealand white rabbits were compared to the outcomes of a diet that consisted of soy oil and safflower oil. An *in vitro* study looked at peripheral blood lymphocytes that were cultured with T-cells mitogens. The blood lymphocytes were noticeably higher in the group of rabbits that were fed linseed oil as compared to the group that was given either soy or safflower oil. Lymphocytes are a type of white blood cell that is in the immune system of vertebrates. The immune system of the rats that were fed linseed oil appeared more responsive compared to the rabbits

that were given the other two types of oil. The results suggests that the increase in immunoresponsiveness in the linseed oil fed rabbits may be useful in fighting infections in the body (Kelley, Nelson, Senator, Schmidt & Branch, 1988). Based on the results of this study, researchers hope to investigate the effects of a linseed oil based diet in immunocompromised humans as well as healthy individuals for comparison.

Clinical Studies

In a North Dakota State University clinical study, the effects of flaxseed supplementation were examined in overweight patients who had hypertension and a family history of diabetes. The study determined that flaxseed consumption decreased insulin resistance, in other words, decreased glucose concentration in patients after use of flaxseed supplementation. The bioactive component of flaxseed, lignan, is responsible for do decreasing insulin resistance as well as inflammation (Rhee & Brunt 2011). Another study looked at the relationship between flax consumption and treatment of diabetes. 6 patients were monitored as they fasted overnight, and in the morning were randomly given a meal that consisted of 50g carbohydrate bread that was either made from white flour (control) or flax flour (experimental). The researchers concluded that the blood glucose levels were 28% in those subjects that were given the flax bread (Shahidi 2005).

In Toronto, flaxseed was used as alternative to hormone replacement therapy, since it is rich in the phytoestrogen precursor, secoisolaricriesinol diglucoside (SDG) and α -linolenic acid. It was hypothesized that these factors may be protective against vascular disease. The study analyzed 35 women with vascular disease ranging from ages 54 to 70. These women were administered different strains of flax: Flanders (high in α -Linolenic acid and low in lignan), AC

Linors (a mixture of intermediate levels of lignan and α -Linolenic acid) as well as Linola 989 (low α -Linolenic acid and high lignan). Results showed that all three types of flax lowered blood pressuring during mental stress. The Flax phytoestrogens ameliorate specific responses to stress, which in turn can protect patients against atherosclerosis, thickening of the arteries (Spence, Thornton, Muir & Westcott, 1973).

A two year study was done with subjects having multiple cardiovascular risk factors, correlating the risk of ischemia heart disease and nutritional diets. Two groups were randomized, giving one group margarine rich in α -linolenic acid while the other group obtained margarine that was rich in linoleic acid. After the two year period, results suggest that individuals who had a rich source of α -linolenic acid, showed a higher total cholesterol to HDL cholesterol ratio than when the experiment first began. This improvement of cholesterol levels decreased estimated ischemia heart disease (Bemelmans, Broer, Feskens & Smit, 2002).

In another study in Toronto, seven elderly patients were give two flax muffins per day. The results of the study reported increased bowel movements and frequency of bowel movements per day (Cunnane, Ganguli, Liede, Hamadeh, Chen, Wolever & Jenkins, 1993). This increase of bowel movements suggests the laxative properties of flax.

A clinical trial in China examined the SDG-rich flaxseed extract to determine the possible effects of SDG on total cholesterol, HDL-cholesterol, LDL-cholesterol as well as glucose concentrations in a group of 35 men and 20 women over the course of 8 weeks. In order to be eligible, subjects needed to meet the requirements of LDL-cholesterol levels no lower than 1400 mg/l. Additionally, they could not be taking any drugs, herbal supplements, products containing flax, or any products used to lower cholesterol. Subjects were randomly

assignment to the 300mg SDG, 600mg SDG or the placebo group. Results showed that the dietary flaxseed lignan extract (SDG) did decrease plasma cholesterol and glucose concentrations significantly in hypercholesterolaemic subjects (Zhang, Wang, Lui & Tian, 2007).

Contraindications

There is minimal risk with the consumption of flaxseeds in humans. Food allergies to flax seem to be quite rare. Those who question a possible allergy to Flaxseed should consult their physician for permission of use prior to incorporating it into their daily diet. Those individuals with allergies to nuts should be cautious. It's also important to realize that flaxseed is rich in α -linolenic acid, which is has been a major component of the Mediterranean diet for many years. In a 5-year prevention trial, a high content α -linolenic acid Mediterranean proved to be more efficient than present day diets in preventing coronary diagnosis and deaths (Bemelmans, Broer, Feskens & Smit, 2002). Its wide use for many years with no major side effects allows it to be viewed as safe.

However, one concern lies in the consumption of uncooked flaxseed due to cyanogenic glycosides (HCN) content, which in high quantities can be toxic to animals as well as humans. No cases have been reported of acute or chronic cyanide toxicity from flaxseed consumption. It is important to note that baking flaxseed is capable of removing any potential risks from HCN (Bloedon & Szapary, 2004). By cooking the raw flaxseeds (in baking products or hot cereals; some oatmeal's contain flaxseed) this seems to eliminate the potentially toxic cyanogenic glycosides (Cunnane et al, 1993). Furthermore, those who experience harmful side effects from cyanogenic glycosides generally have a poor quality diet as well. For the

most part, populations in North America have well-balanced diets and receive proper nutrients that allow the body to eliminate the potentially harmful, HCN, which is found flax (Shahidi, 2005).

Current Uses in Allopathic and CAM Therapies

The flaxseed has only recently been introduced in North America. Some known benefits of flaxseed in human and animal nutrition include, its high component of alpha linolenic acid (also known as omega-3 fatty acid) content pertinent to humans, its high percentage of insoluble and soluble dietary fiber, and lastly, it has the highest content of plant “lignans”. Lignans are important because they are known for their anti-carcinogenic properties (Shahidi, 2005).

The use of flax in industry and food is continuing to grow and develop. Around 200 new food and health care products were introduced and marketed in the United States in 2005 (Jhala & Hall, 2010). Today, ground or whole flaxseed can be easily added to almost any baking recipe. Ground flax in a powder form is often used in liquid foods such as yogurt and soup to hide the taste, whereas whole flaxseed can be used in bread, pancakes, waffles to add a nutty flavor. Whole flaxseeds are a great food additive in recipes to add a crunch (Shahidi, 2005). Many U.S. companies are manufacturing fiber bars for those who don't receive adequate amounts of daily fiber that contain high quantities of flax. Additionally, there are few side effects of flaxseed making it a more widely used product among many Americans.

The National Cancer Institute is now considering flax a “designer” food. The term “designer” means the product consists of more than one ingredient that contributes to the overall beneficial qualities. Flax contains nutrients for good

health but also is known to be protective against cancer and cardiovascular disease (Carter, 1993).

Another fairly new and current use of flax is in the form of flaxseed gum, or mucilage (Mazza, 1989). The gum is reported to be extracted using hot and cold water. Then it can be mixed with ethanol, eventually dehydrated and then freeze-dried. The acid hydrolysis of gum then produces polysaccharides. In experimental study, it was found that flaxseed gum is a similar alternative to gum arabic, which is a mixture of complex polysaccharides, which is used as a food stabilizer. In fact, it was noted that flaxseed mucilage has great emulsifying properties compared to gum arabic, enabling it to be more efficient. It was estimated about 7-10 lbs of gum could be yielded from about 100 lbs of flaxseed. Today, the usefulness of flaxseed gum is in improving loaf volume of bread while also keeping the quality fresh (Mazza, 1992).

Today, the Food and Drug Administration and several universities are conducting extensive research in feeding flaxseed to animals as well as humans to further discover health benefits of flax. Although flaxseed and cold-pressed linseed oil don't already have the Generally Recognized as Safe status, there is a “no objection” status, that seems to be adequate while flax undergoes more testing in the laboratory (Carter,1993).

Discussion

Linum usitatissimum is a crop grown in various countries and climates for different purposes, and has been around for over 6,000 years. Flax is known for its adaptability and diversity as a product traditionally, as well as in current allopathic and CAM therapies. Its prime use today is in dietary supplements and cooking. North Dakota is currently the leading state for

flax production. With the high content of α -linolenic acid and SDG in flax, both *in vivo* and *in vitro* studies as well as numerous clinical trials have examined its effects in controlling diabetes, as a laxative, managing cardiovascular disease as well as a tool to enhance the immune system. Some *in vivo* studies also looked at flax in monkeys and its effects on fur condition. From this research in monkeys, scientists predict that flax can be a source of improving skin conditions such as psoriasis. Since the flax is available in the form of oil, the scientist suggests topical use of flaxseed oil can be beneficial to numerous skin diseases in individuals. However, more clinical trials are underway to confirm these hypotheses.

Many Americans are first becoming aware of flax and its health benefits. Flax is an easy food supplement to any current diet and has a high nutritional component with a great source of fiber. The high fiber contents are not only beneficial for food intake but also in the linen and parchment paper industry. Although flax has been used for many years now, further clinical studies can be done to better understand the mechanism of action of flax itself as well its main components such as omega-3 fatty acids, α -Linolenic acid, and SDG.

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Melaleuca alternifolia Cheel, Myrtaceae

Elizabeth M. Cappello

Introduction

Melaleuca alternifolia Cheel is an angiosperm in the Myrtaceae family. The common names of *Melaleuca alternifolia* are tea tree and paperbark tree. *M. alternifolia* has many different uses, both traditional and modern, including flavoring, antiseptic, antibiotic, antiviral, anti-inflammatory, antifungal and topically for skin abrasions (Brophy et al., 1989; Carson et al. 2002; Hammer et al., 2004). *M. alternifolia* has been used as a natural preservative in both pharmaceutical and cosmetic products (Cox et al., 2000). Halberstein noted that *M. alternifolia* has been prescribed as an antibiotic and is similar to Elecampane flower (2005). The main constituents are terpinen-4-ol, 1,8-cineole and α -terpineol (Carson et al., 2002). The essential oil extracted from *M. alternifolia* has become popular within the last century and is an economically significant essential oil (Homer et al., 2000).

Botanical Description

The Myrtaceae family is known for its popular genus, Eucalyptus, and also includes *Psidium guajava* L. (common guava) and *Syzygium aromaticum* L. (clove). *M. alternifolia* (**Figure 1**) is a small evergreen tree found in New South Wales and Queensland and is native to Australia, found in the low and swampy areas near the Clarence and Richmond rivers (Butcher et al., 1994; Carson and Riley., 1993). A correlation has been observed between the composition of tea tree oil (TTO), the essential oil of *M. alternifolia*, and the geographic location of the tree in Australia; high levels of terpinen-4-ol



Figure 1. *Melaleuca alternifolia* (Source: http://toptropicals.com/catalog/uid/melaleuca_alternifolia.htm)

were seen mostly in northern New South Wales, low levels of terpinen-4-ol (high levels of 1,8-cineole) were seen near Grafton and terpinolene was seen in abundance in *M. alternifolia* populations in Queensland (Homer et al., 2000). It has been hypothesized that this chemical distribution

according to geographic location is because of genetic rather than environmental pressures; the close proximity of these trees may have caused a type of “inbreeding” effect allowing for a more “pure breed” within each geographic area (Homer et al., 2000). *M. alternifolia* has very small white flowers and a papery, black bark with narrow leaves, growing up to 22 meters in length. The evergreen grows to about 5 meters in height (Carson and Riley, 1993). The essential oil of *M. alternifolia*, famous for its biological activity, is pale, yellow, viscous oil with a pungent odor (Carson and Riley, 1993).

Traditional Uses

The use of *M. alternifolia* has been a part of the Australian Aboriginal tradition, particularly the Bundjalung Aborigines (Budhiraja et al., 1999; Hammer et al., 2003). When traditionally used by Aborigines, the leaves and branches were crushed or decayed leaves were placed in water (Carson and Riley, 1993). The collection of *M. alternifolia* was originally done by coppicing process, a method of cutting down the plant to its tree stump and allowing it to grow back (this make take up to 10 years) (Carson et al., 2006). The use of the essential oil, tea tree oil, became popular within the 20th century. Prior to the scientific discoveries of the benefits of TTO from *M. alternifolia* in the 1920s and 1930s, the raw materials of *M. alternifolia* were used (Carson et al., 2006). A steam distillation is preformed of the leaves to extract the essential oil, which is now in demand today (Carson and Riley, 1993). In a more crude process of extracting the essential oil, people would simply break off the leaves and terminal branches and do a very simple steam distillation over a temporary wood fire (Carson et al., 2006).

The Aborigines used *M. alternifolia* for skin infections, bruises, insect bites and cuts by sprinkling the crushed leaves over

wounds (Carson et al., 2006). *M. alternifolia* has also been used for cleansing and dressing wounds (Carson and Riley, 1993). Medicinally in Aboriginal culture, the crushed leaves were inhaled for coughs and colds while an infusion of the leaves were used for treatments of sore throats (Carson et al., 1993; 2006). The Aborigines also noted sacred healing rivers in which leaves of the *M. alternifolia* fell in the river, creating a simple infusion; these rivers were used for healing (Carson et al., 1993; 2006). It is unlikely that the Aborigines used extractions of *M. alternifolia* for its essential oil, but they were aware of the plant’s medicinal benefits (Carson et al., 1993).

There was no documentation of medicinal uses of *M. alternifolia* prior to colonization of Australia as the Aborigines had an oral tradition (Carson and Riley, 1993). Due to this oral tradition, there are no ancient texts documenting the medicinal uses of *M. alternifolia*. The oral tradition of the Aborigines influenced modern physicians to look more closely at *M. alternifolia* that led to the increase of scientific knowledge of the tea tree in the past century.

The use of *M. alternifolia* has changed over time. The raw materials were originally used, but now the focus is on the essential oil that is extracted through steam distillation. It is now harvested for its oil (Butcher et al., 1994). The traditional uses of *M. alternifolia* are still relevant today. These uses provide scientists and physicians with an idea of what it could be used to treat. Since the Aboriginal culture has relied on *M. alternifolia* for so long, this indicates that there must have been some efficacy associated with its medicinal use.

Chemistry and Pharmacology

The essential oil of *M. alternifolia*, tea tree oil (TTO), is the focus of research and is extracted by steam distillation from

the evergreen's leaves (Brophy et al., 1989). This essential oil is similar to nutmeg oil and contains terpinen-4-ol (**Figure 2A**), 1,8-cineole (**Figure 2B**) and α -terpineol (**Figure 2C**) (Brophy et al., 1989; Carson et al., 2002). Tea tree oil from *M. alternifolia* is insoluble in water (Carson and Riley, 1993).

There are actually three different varieties of *M. alternifolia* according to the concentration of cineole; low, medium and high, with low being the most sought after for medication (Brophy et al., 1989). The essential oil of *M. alternifolia* is composed of monoterpenes, terpinen-4-ol, cineole and various hydrocarbons (Carson and Riley, 1993). Of the monoterpenes, 50% are oxygenated and 50% are hydrocarbons (Cox et al., 2000). The International Standard of *M. alternifolia* oil is a minimum of 30% terpinen-4-ol and a maximum of 15% 1,8-cineole (Homer et al., 2000). The composition of the oil of *M. alternifolia* may change if not stored properly (the proper storing requires a cool, dry, dark setting in a container with as little air as possible) (Carson et al., 2006).

Biological Activity

The essential oil of *M. alternifolia* known as tea tree oil (TTO) is the main constituent that contributes to the biological activity of *M. alternifolia*. While there is still speculation regarding how TTO is able to disrupt the cell membrane functions, it is hypothesized that there is not one single mechanism of action due to its heterogeneous composition and structure (Carson et al., 2002). The essential oil of *M. alternifolia* is able to disrupt cell membrane function by increasing permeability, disrupting homeostasis and inhibiting cell respiration (Carson et al., 2006). TTO and other terpenes have been shown to affect cell respiration, leading to the hypothesis that it has an adverse effect on the mitochondria organelles within cells (Hammer et al., 2004).

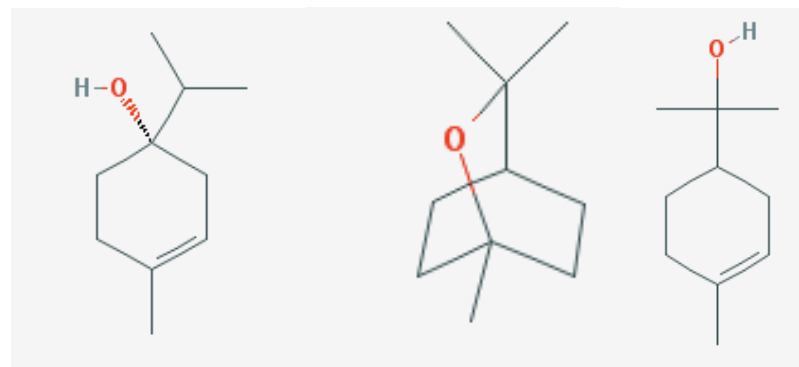


Figure 2. Chemical structures of (A) Terpinen-4-ol, (B) 1,8-cineole, and (C) α -terpineol – all main constituents of *Melaleuca alternifolia* oil. (Source: http://pubchem.ncbi.nlm.nih.gov.proxy.library.emory.edu/summary/summary.cgi?cid=2724161&loc=ec_rcs)

These effects from TTO lead to cell death (Cox et al., 2000). TTO has also been observed to increase potassium ion leakage from cells (Cox et al., 2000). TTO can permeate skin very easily, but this also dependent on how it is applied to the skin (an ointment will permeate the skin more than a cream for example) (Reichling et al., 2006).

TTO has demonstrated a variety of uses ranging from antibacterial and antifungal to antiviral and anti-inflammatory (Carson et al., 2002; 2006). *M. alternifolia* is even used for flavoring and an antiseptic for mouthwashes (Brophy et al., 1989). *M. alternifolia* has been shown to be great for treating oral infections, such as oral candidiasis, but is not very useful as a preventative measure (Hammer et al., 2003). While TTO has demonstrated a variety of uses, there have not been many investigations displaying these uses *in vitro* (Carson et al., 2006).

M. alternifolia has demonstrated to be effective against furunculosis, wood-destroying fungi, vaginitis, oral vaginitis,

dermal infections, ulcers and cuts (Brophy et al., 1989; Budhiraja et al., 1999). TTO can penetrate body tissues and shows high biological activity with low irritation effects (Budhiraja et al., 1999). White blood cells were activated after interacting with TTO (Budhiraja et al., 1999).

As an antibacterial, TTO was shown to kill *Staphylococcus aureus* during its stationary phase within the host (Carson et al., 2002). During one investigation of antiviral uses of the essential oil of *M. alternifolia*, TTO was tested on tobacco plants with tobacco mosaic virus (Carson et al., 2006). Tobacco plants treated with TTO did show a decrease in lesions in comparison to controls (Carson et al., 2006). Tea tree oil was also studied for antiprotozoal activity, showing a 50% decrease in growth primarily due to terpinen-4-ol found in TTO (Carson et al., 2006). *M. alternifolia* is best when attacking “free” viruses that have not yet infected a cell (Carson et al., 2006). *In vitro* studies of TTO have shown both antimicrobial and anti-inflammatory activity (Carson et al., 2006). TTO has been difficult to evaluate for antimicrobial activity because it is not soluble in water (Carson et al., 2006).

While investigating the antibacterial use of TTO on *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*, it was concluded that TTO was able to inhibit cell respiration and increased the permeability of the bacterial cytoplasm and yeast cell membrane through the increased uptake of propidium iodide, which is normally impermeable to the cell (Cox et al., 2000). Potassium ion leakage of *E. coli* and *S. aureus* cells was observed when exposed to TTO (Cox et al., 2000).

One *in vitro* study of TTO investigated the effect on bacterial vaginosis, which is a growth of fungus within the vagina, not to be confused with a yeast infection (Kessel et al., 2003). A capsule composed of a few drops of TTO and gelatin inserted into the vagina overnight for six days was able to control the

infection by inhibiting both aerobic and anaerobic respiration (Kessel et al., 2003). This treatment was also estimated to be of low cost to the patient (\$2.00 - \$20.00 per day) (Kessel et al., 2003).

M. alternifolia is an effective treatment of fungal infections such as dandruff or oral candidiasis, a yeast infection that allows for fungal growth on the mucous membranes of the mouth typically the tongue (Hammer et al., 2004). In an *in vivo* study of *M. alternifolia* against *Candida albicans*, terpinen-4-ol of TTO was showed to be the main contributor to treatment of the fungal infection and eliminating the fungus within three weeks (Mondello et al., 2006). The use of *M. alternifolia* for treatment of *C. albicans* would be cost effective because the only active compound is terpinen-4-ol, allowing for faster production and lower costs to patients (Mondello et al., 2006).

TTO showed antioxidant activity during an investigation by Kim et al. (2004) using two assays to determine the activity: 2,2-diphenyl-1-picrylhydrazyl and hexanal/hexanoic acid. The assays confirmed antioxidant activity due to α -terpinene, α -terpinolene and γ -terpinene, rather than the expected terpinen-4-ol (Kim et al., 2004). The antioxidant activity of *M. alternifolia* oil is similar to butylated hydroxytoluene (BHT), a synthetic antioxidant used as an additive to food and cosmetic products; this suggests that TTO may be a good, natural alternative to butylated hydroxytoluene (Kim et al., 2004).

M. alternifolia is used topically for infections of the skin (Carson et al., 2006). Several investigations have been conducted to observe the effect of tea tree oil on mild acne. Oil was extracted from *M. alternifolia* and made into a gel (Magin et al., 2006). This was compared to 5% benzoyl peroxide, a typical compound used in skin care products (Magin et al., 2006). While 5% benzoyl peroxide was better at controlling inflammatory lesions, *M. alternifolia* oil was able to reduce

non-inflammatory lesions and provides less side effects such as itching, redness and stinging, etc. (Carson and Riley, 1993; Magin et al., 2006).

Hammer et al. investigated resistance of *Staphylococcus aureus*, *S. epidermidis* and *Enterococcus faecalis* (all Gram-positives) to TTO and rifampicin (an antibiotic) (2008). Low resistance of *S. aureus*, *S. epidermidis* and *E. faecalis* to TTO was observed ($<10^{-9}$), indicating that single-step mutants of these bacteria have low resistance to TTO (Hammer et al., 2008). Recently, Hammer et al. investigated resistance of *S. aureus* and *Escherichia coli* to TTO (2011). In this study, multi-step mutants were evaluated and Hammer et al. concluded that TTO has little effect on the development of resistance of *S. aureus* and *E. coli* (2011).

TTO has been seen to be effective against cancerous melanoma cells (Buzzoto et al., 2011). One reason that melanoma is so deadly is because it is resistant to chemotherapy and radiation treatment (Buzzot et al., 2011). TTO has been observed to inhibit the growth of melanoma cells by overcoming their resistance of apoptosis (Buzzoto et al. 2011). This data shows how TTO is a possible alternative to chemotherapy and radiation to treatment of melanoma.

Clinical Studies

Barker and Altman investigated the efficacy of TTO, lavender oil, suffocation product and pyrethrin products against head lice (2010). Lavender oil and TTO was almost four times more effective than products containing pyrethrin in killing lice after one day of treatment (Barker and Altman, 2010). These results show that not only could TTO be used in place of pyrethrin-containing products for individuals that would have an adverse effect to pyrethrin, but also that TTO is more

effective (Barker and Altman, 2010).

TTO has also been used in a clinical study to evaluate double-blind testing (clinical trials where both the investigator and research volunteers are unaware of receiving the control or treatment) (Carson et al., 2008). TTO is difficult to use in clinical trials due to its distinctive odor (Carson et al., 2008). Carson et al. investigated the use of deception by looking at TTO as an effective treatment of recurrent herpes labialis (cold sores) (2008). Carson et al. concluded that double-blinding is not ineffective (only 50% of volunteers in each test group were able to correctly identify if they received a placebo product or TTO product) (2008).

Contraindications

The long history of use of *M. alternifolia* and its essential oil has led to a general consensus that it is safe and because of this, there is very little scientific documentation of its safety with the exception of case studies (Carson et al., 2006). While the essential oil of *M. alternifolia* was shown not to be mutagenic by the Ames test, there are still cases of toxicity (Carson and Riley, 1993). That being said, ingestion of the essential oil, especially orally, can result in toxicity but there have yet to be any human deaths due to the oil of *M. alternifolia* as of yet (Carson et al., 2006). There are dangers of toxicity when TTO is ingested orally as it has been shown that even a modest intake of *M. alternifolia* has resulted in toxicity symptoms (Budhiraja et al., 1999; Carson and Riley, 1993; Jacobs and Hornfeldt, 1994). Toxicity due to TTO ingestion was observed in a 23-month-old after found with an empty bottle of T36-C7, which is made up of entirely tea tree oil (Jacobs and Hornfeldt, 1994). The child was described to have decrease motor coordination and was disoriented. Physicians were able to treat the patient and release him from the

hospital relatively quickly, but this case did show that a small amount (the bottle was 10ml) of oil extracted from *M. alternifolia* could be toxic when ingested orally (Jacobs and Hornfeldt, 1994). This has raised concern because of the prevalence of tea tree oil in soaps, lotions, creams, cleaning products and toothpaste (Jacobs and Hornfeldt, 1994).

Any skin irritation due to using TTO topically is mostly due to its improper storage and production rather than the constituents themselves (Carson et al., 2006). It is difficult to store TTO because plastics absorb the oil quite readily (Carson et al., 2006).

Current Use in Allopathic and CAM Therapies

You can currently purchase an array of products with TTO as a constituent. You can also find tea tree oil in soap, shampoos, skin care products, etc. (Jacobs and Hornfeldt, 1994). One commercial product of tea tree oil is Melasol (Carson and Riley, 1993). The production of Melasol was so important during World War II that those employed to collect *M. alternifolia* were not required to enter the service (Carson and Riley, 1993).

M. alternifolia is marketed as “tea tree oil.” It may be purchased as just the oil, but is also part of many skin care and hair care products. The Body Shop has a complete “Tea Tree” line including facial washes, concealers and exfoliants. The tea tree oil used in these products is *M. alternifolia* that is cultivated in Africa. Typically tea tree oil is marketed as 100% pure essential oil and is advertised to be part of first aid kit to be used on cuts and abrasions. Other companies, including Desert Essence market tea tree oil skin ointments and creams, but the products are not entirely composed of the essential oil from *M. alternifolia* and are instead a mixture of oils from

several plants.

Some more obscure current uses of *M. alternifolia* include its use for ceasing cannibalism among chickens (Carson and Riley, 1993). Not only did *M. alternifolia* heal the wounds of chickens, but also the constituents within the plant created an irritant to chickens causing them to stop eating other chickens because of taste (Carson and Riley, 1993).

Discussion

Melaleuca alternifolia is an economically important plant that has a variety of medicinal uses. *M. alternifolia* has been a central part of Australian Aborigine medicine and is now a sought after plant for its essential oil. TTO has shown to be beneficial for a variety of treatments and as more clinical investigations are conducted, we will have a greater understanding of TTO’s power to be used medicinally.

TTO is used as an antibacterial, antimicrobial, antifungal and antiviral. It also is useful for skin abrasions, mild acne and cuts. Further research should be done of how the Aboriginal culture used *M. alternifolia* and see how those traditions and methods can still be applied to medicine today. The many studies discussed here show how *M. alternifolia* and more specifically, TTO, can be beneficial for human health, providing more cost effective treatments than those currently used.

From its use as an antibiotic to another therapy in battling melanoma, TTO has great potential. Tea tree oil is more than just an essential oil to be purchased at a health food store, but instead an oil that has a wealth of opportunities to help human health.

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Momordica charantia L., Cucurbitaceae

Soraya Chanyasubkit

Introduction

Many plants serve a dual role as food and medicine. With a majority of the world's healthcare system based in traditional medicine, up to 80% dependency in some regions according to the World Health Organization, plants are critical in health promotion and disease prevention. The term "functional food" refers to a modified food or specific food ingredient that can provide a health benefit beyond basic nutrition (Hasler, 2002) and can be applied to the many herbs and plants used in traditional healing. *Momordica charantia* is such an exemplary plant that is widely consumed in the tropics of Asia, the Caribbean, Africa, and the Amazon (**Figure 1**). It is in the Cucurbitaceae family, which also includes melons, squashes, and gourds. The plant's defining characteristic is its bitter taste, hence its common names like bitter melon, bitter gourd, balsam apple, balsam pear, sorosi, karela (Hindi), and ampalaya (Tagalog) (Kumar *et al.*, 2010; Grover and Yadav, 2004).

Aside from its culinary use, *M. charantia* is also employed in traditional medicine due to its hypoglycemic, antibacterial, antioxidant, wound-healing, and other therapeutic properties. It is typically prepared as a tea or bath by soaking the leaves, stem, and fruit in water or directly eating the juice or the fruit itself (Behera *et al.*, 2010). The key anti-diabetic compounds are charantin and momordicin, but bitter melon is known as a health-promoting vegetable due to the presence of many kinds of chemical compounds such as phenolic acids, saponins, triterpenes, and proteins (Kumar *et al.*, 2010). It has been incorporated into many cultures for over 3,000 years and



Figure 1. *Momordica charantia* as the fruit and the plant.

(Image source: <http://kookiecurious03.files.wordpress.com/2010/10/ampalaya.jpg>)

continues to be an integral part of diet, ceremonies, and health worldwide (Behera *et al.*, 2010; Taylor, 2002).

Botanical Description

The most well-known part of *Momordica charantia* is its edible fruit which has an oblong shape, similar to a large cucumber, but with a rough surface full of ridges and warts. Unripe, it has varying shades of green but matures into a brilliant yellow-orange fruit that bursts to reveal the vibrant red seeds within. In a cross section of the fruit, the flesh is crisp and full of water and has a mostly hollow cavity similar to a bell pepper. In this cavity, a mesh, white pith suspends its flat seeds (**Figure 2**).

The fruit of *M. charantia* can be categorized into three groups which are described in **Table 1**. Depending on the phenotype, the fruit can range from a smoother, pale green (Chinese) to an incredibly warty and spiky surface of deep green (Indian). The size of the fruit can range from 9-12cm to 30-60cm, again depending on variety. However, a more recent categorization for Indian and Southeast Asian bitter melons is by diameter: *M. charantia* var. *minima* (< 5cm) and *M. charantia* var. *maxima* (> 5cm) (Behera *et al.*, 2010).

This herbaceous, tendril-bearing vine has leaves with jagged edges hence the genus name *Momordica* which means “to bite” in Latin. The plant itself can grow to a height of 2-4 meters. *M. charantia* is monoecious and its flowers have five petals and are typically yellow. Bees are the primary pollinators. All parts of *Momordica charantia* are bitter (Taylor, 2002).

M. charantia can tolerate a variety of environments from tropical to subtropical climates but it grows best in hot, humid areas. The cultivation of bitter melon is similar across countries except for the spacing between plants. Frost can kill the plants, and cooler weather can slow development. Ideally, it is grown in a sunny, warm area with well-drained sandy soil at pH 6.0 – 6.7 (Behera *et al.*, 2010).

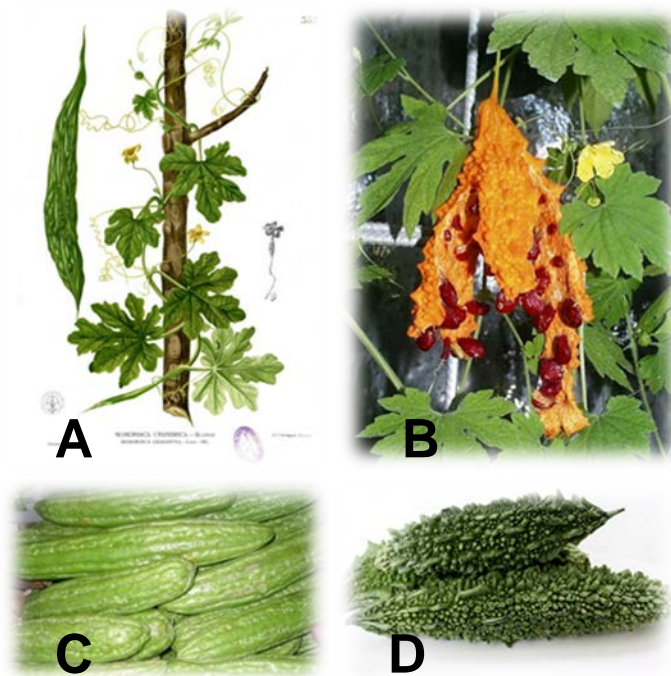


Figure 2. The growth and phenotypes of *M. charantia*. Bitter melon is a tendril-bearing vine with jagged leaves and yellow flowers (**A**). At maturation, the fruit is a brilliant yellow-orange and bursts to expose the seeds (**B**). The phenotypes of Chinese and Indian bitter melons are easily distinguishable (**C and D**).

(Image sources: **A** - http://www.herbal-supplement-resource.com/images/bitter_melon_herb_img.jpg; **B** - http://www.whitetigernaturalmedicine.com/wp-content/uploads/2010/10/Herb_0109.jpg; **C** - <http://yourhomegardenblog.com/wordpress/wp-content/uploads/2009/03/chinese-bitter-melon.jpg>; **D** - http://farm4.static.flickr.com/3318/3475604705_27b918fed6.jpg)

	Small fruit type (var. <i>charantia</i> - Indian)	Long fruit type (var. <i>charantia</i> - Chinese)	Triangular fruit type (var. <i>muricata</i>)
Size	10-20 cm in length/ 5-8 cm in width	30-60 cm in length/ 3.5-6.0 cm in width	15-25 cm in length/ 9-12 cm in width
Weight	0.1-0.3 kg	0.2-0.6 kg	0.3-0.6 kg
Color	Dark green	Light green	Light-dark green
Bitterness	Extremely bitter	Slightly bitter	Medium-strongly bitter

Table 1. Categories of *Momordica charantia*. The phenotypes of *M. charantia* can be classified due to the distinct appearances of each type. The most commercial is the Chinese bitter melon due to its more suave bitter flavor.

Traditional Uses

The origin of *M. charantia* is unknown, though the domestication of the plant is thought to be in Asia, namely China or India. The first mention of the bitter melon is in Ayurvedic texts dating back 2000-200 BCE by Indo-Aryans in India. The ancient Chinese medicinal book Pen Ts'ao (or Ben Cao in pin-yin) referenced the bitter vegetable later in 1370 AD (Walter and Decker-Walters, 1988; Yang and Walter, 1992). The use of *M. charantia* moved westward through the African continent toward the New World into the Americas via the slave trade as one of many domesticates introduced from the Old World as early as the 16th century (Figure 3). The melon is a versatile vegetable used in soups and curries, stir-

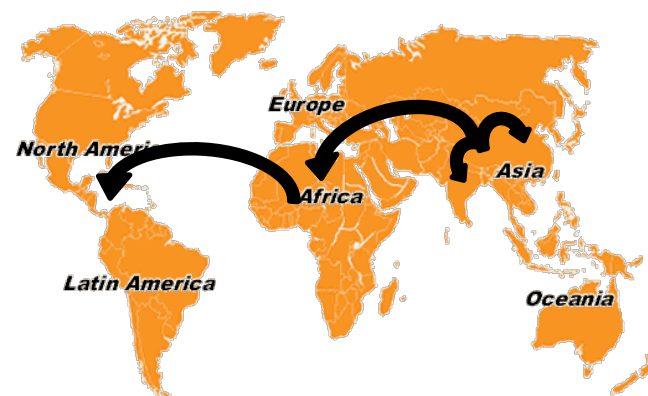


Figure 3. Origin and movement of *M. charantia*. Bitter melon is believed to originate in Asia near China and India, and its domestication spread to Africa and later the New World via the transatlantic slave trade.

fries, or is stuffed or pickled. Before culinary use, the bitter melon is typically boiled, blanched, or soaked in salt water to attenuate the bitter flavor (Behera *et al.*, 2010).

Historically, the plant has been used all over the world as an edible plant product to treating a variety of ailments from gastrointestinal to veterinary to, most famously and universally, diabetes. Though its use has been primarily medicinal, the exact applications differ from region to region. Preparation across cultures typically involves extracting juice from the unripe fruit and leaves or soaking and boiling the plant in water to create tea or a bath (Basch, 2003).

Africa

M. charantia has a variety of uses to both traditional healers and the general population. According to Beloin *et al.* (2004), in Togo, bitter melon is used primarily not only to combat

gastrointestinal diseases and childhood viral infections like chicken pox, but also to treat infections and skin afflictions. The groups soaked the vine in water for several hours and the resulting liquid was drunk or bathed in, sometimes using vines as a sponge if necessary. The seed is applied locally in gynecological circumstances. It is notable that traditional healers and the villagers used the plant to treat the same diseases, except for diabetes where none of the general population uses the plant as a treatment and 33% of healers do. Healers use all parts of the plant except for seeds which 47% of healers agree that they are toxic. It is also notable that many healers hold university degrees and a few even have medical degrees and still rely heavily on plant-derived remedies and therapy.

Bitter melon also has strong spiritual and ritual properties in Togo. It is used to provide protection against evil spirits, diseases, malignant intentions, and madness. It is viewed as a purifying plant and used in ceremonies involving sacred objects. The vine itself is worn as jewelry or a crown during traditional rituals. This custom is likely derived from the mid-1600s when the Guin tribe moved to current Togo due to warfare and the slave trade and wore the vines to protect themselves from enemies and ensure a safe journey (Beloin *et al.*, 2004).

In the Democratic Republic of Congo, whole plant decoction is used to treat many gastrointestinal afflictions such as intestinal worms, colic, diarrhea, dysentery, constipation and for general ailments like, diabetes, cold, hypertension, malaria, fever, anemia, psoriasis, and jaundice. It can also be used as a laxative and an aphrodisiac (Mesia *et al.*, 2008).

M. charantia is also one of the more frequently used plants in the treatment of measles in Nigeria and Cucurbitaceae is the most widely mentioned family according to interviews

conducted by Sonibare *et al.* (2009). The primary methods of extraction are juicing the leaves or boiling the leaves and ingesting or bathing in the juice. According to recipes gathered from Nigerian herbalists, fresh leaves of *M. charantia* (local name: ejinrin) are washed and squeezed to extract juice. Two tablespoonfuls of this liquid is taken orally three times a day and in bathing morning and evening. In another recipe the leaves of ejinrin are boiled with the leaves of *Newbouldia laevis* Seem. (Bignoniaceae), *Vernonia amygdalina* Chevallier (Asteraceae) and *Ocimum gratissimum* (Lamiaceae) and the resulting concoction is drunk three times daily as well.

The Americas

Generally, across the Americas and the Amazon, locals and indigenous peoples grow bitter melon in their gardens as a source of food and medicine. Some applications are similar in use and purpose and other remedies are more highly emphasized depending on the region. In Mexico, the most common afflictions are diabetes and dysentery. Peruvian shamans use the plant mainly to treat different types of inflammation (Taylor, 2002).

However in Brazilian herbal medicine, the whole plant or various parts are used to combat many skin infirmities such as scabies, eczema, and leprosy, in addition to tumors, inflammation, allergies helminthiasis, rheumatism, diarrhea, dandruff, and wounds (de Albuquerque *et al.*, 2007; Taylor, 2002). In Colombia, it is taken as an oral infusion to treat intestinal parasites, fever, and pruritic ailments (Gomez-Estrada *et al.*, 2011). Various Amazonian Bolivian indigenous groups also use the mashed leaves for skin infirmities and considers *M. charantia* a valuable medicinal plant (Boudary *et al.*, 2000; Thomas *et al.*, 2010).

In eastern Nicaragua, bitter melon is used extensively in fertility health and childbirth among the Rama midwives. Taken orally or applied topically, *M. charantia* can relieve abdominal and back pain, post-partum abdominal pain, menstrual hemorrhage and pain, fever, vaginal infections, weakness and anemia and promote contraception and induce abortions (Coe, 2008).

The Caribbean

Trinidadian hunters use botanical and zoological methods to stimulate their hunting dogs, typically foxhounds, or to enhance their sense of smell to ensure more successful hunting trips. Lans et al (2001) interviewed a hunter who uses *M. charantia* to help his dogs acclimate to hunting for larger game, specifically wild hogs. First, he bathes the dog in congo lala (*Eclipta prostrata* L., Asteraceae) and the dog will begin hunting the small matte lizard. Next, the dogs are bathed in *M. charantia* (caraaili in Trinidadian Creole) and barbadine leaf (*Passiflora quadrangularis* L., Passifloraceae) and they will hunt for bigger game. Finally, the dog is bathed with unspecified plants that promotes hunt for wild hogs (Lans, et al., 2001).

M. charantia usage is also based on the doctrine of signatures which dictates that a specific plant trait resembles the desired outcome; thus after application of this plant, the foxhound would want to hunt for the particular animal the plant corresponds to (**Figure 4**). In this case, there is an association between caraaili and agouti, a type of rodent similar to the guinea pig (Lans, et al., 2001).

Another use of caraaili by Trinidadian hunters for dogs is for medical treatment rather than improved hunting. Crushed leaves and vines of *M. charantia* are steeped in bathwater for



Figure 4. Doctrine of Signature. Comparison of the agouti rodent and *M. charantia* which Trinidadians use in hunting (Image source: <http://plantecology.files.wordpress.com/2010/05/agouti.jpg>; http://upload.wikimedia.org/wikipedia/commons/5/54/Momordica_charantia_003.JPG)

dogs infected with mange, or parasitic mites, and then a poultice of other plant species can be applied to the affected areas. Aside from veterinary use, the vine is steeped in water to create a “cooling” tea for individuals who have too much “heat” or impurities in their system e.g. blood. In the Caribbean as a whole, *M. charantia* is used as an abortifacient, to treat diabetes, and to lower high-blood pressure (Lans, 2006).

China

Traditional Chinese Medicine is one of the oldest whole medical systems beneath the umbrella of complementary and alternative medicine founded on the principle of balance between *yin* and *yang*. If they are out of balance, this leads to disease. In the case of diabetes, a *yin* deficiency results in dryness in the body that can be remedied by eliminating the heat and promoting fluid (Li *et al.*, 2004). This can be achieved by the incorporation of a common traditional Chinese plant into the diet of the patient. *M. charantia* is one of 13 plants listed in Liu *et al.* (2004) study and has been used to treat diabetes in China for thousands of years through oral administration of the extract or fruit juice.

In addition, many plants in the Cucurbitaceae family are mentioned in ancient Chinese texts including *M. charantia*. Even in modern-day China, use of bitter melon is still highly prevalent to treat rheumatism, gout, dysentery, and toothaches (Yang and Walters, 1992). In tea form, it is also used to stimulate appetite and treat gastrointestinal infections (Kumar *et al.*, 2010).

India

As one of the countries with the longest tradition of *M. charantia* use, India has extensive applications for the plant. This exhaustive list includes but is not limited to “antidiabetic, abortifacient, anthelmintic, contraceptive, antimalarial and laxative and is used for treatment of dysmenorrheal, eczema, emmenagogue, galactagogue, gout, jaundice, kidney (stone), leprosy, leucorrhoea, piles, pneumonia, psoriasis, rheumatism, and scabies” (Grover and Yadav, 2004).

In specific regions of India, use of the *M. charantia* (local name: karela) is more specialized. For example, in the

Moradabad district of northern India, it serves an ethnoveterinary role (Ali, 1999). The fruit is mixed with onion (*Allium cepa* L., Amaryllidaceae) and vinegar and the resulting paste is applied to the forehead, horns, and legs of cattle with ephemeral fever. Boiled in equal quantities with *Boerhavia diffusa* L. (Nyctaginaceae), *Luffa acutangula* L. (Cucurbitaceae), onion, and sugarcane, it is an oral remedy for stomach disorders and fever.

In the northwestern state of Rajasthan, karela treats a variety of afflictions. The whole plant is combined with cinnamon, long pepper, rice and *Hydnocarpus wightiana* Blume, (Achariaceae) oil for topical application of scabies and other skin disorders. The leaf juice is externally applied around the eyes for night blindness. The paste of its roots is also used topically over piles. Of course, ingestion of one spoonful of fruit paste in water can reduce blood sugar (Namsa *et al.*, 2011).

Other miscellaneous applications of karela across India include a topical snakebite antidote when mixed with olive oil (Samy *et al.*, 2008), topical paste when mixed with lime for skin diseases like dhobis itch and ringworm (Mahishi *et al.*, 2005), and as a blood purifier for diabetes and eye infections (Jain *et al.*, 2005)

Chemistry and Pharmacology

Momordica charantia has a variety of phytochemicals dispersed throughout the plant anatomy, totaling to 228 known compounds. The leaves are rich in alkaloids, flavonoids, hecogenins, steroidalglycoside, saponins, and tannins. Many minerals like iron, calcium, copper, and zinc are present in the roots (Bakare, 2006). The essential oil from the

seeds is comprised mostly of trans-nerolidol (61.6%) and apiole (8.9%) and many trace compounds (Braca *et al.*, 2007).

The fruit, the most used part of the plant, contains glycosides, saponins, alkaloids, triterpenes, proteins, and phenolic compounds and steroids, which contribute to the range of medicinal uses. Namely, charantin (a steroidal saponin), momordicin (an alkaloid), and protein P-insulin demonstrate anti-diabetic activity (**Figure 5**). Phenolic compounds have an antioxidant, anticarcinogenic, and anti-inflammatory effects. The protein MAP-30 shows potential anti-HIV properties. The plant in general is rich in vitamin A, vitamin B, and vitamin C (Kumar *et al.*, 2010, Singh *et al.*, 2011). A more exhaustive list of known chemical constituents in *M. charantia* can be found in **Table 2**.

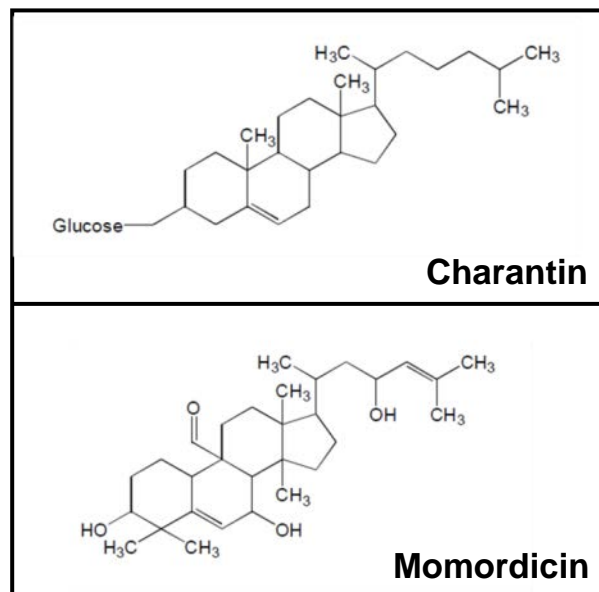


Figure 5. Structures of Charantin and Momordicin.

Plant Part	Chemical Constituents
Fruits	Momordicoside K, L, two acylglycosylsterols-3-O-[6%-O-palmitoyl-b-D-glucosyl] stigmast-5,25(27)-diene and 3-O-[6%-O-stearyl-b-D-glucosyl]stigmasta-5,25(27)-diene, benzyl alcohol, myrtenol, <i>cis</i> -3-hexenol, <i>trans</i> -2-hexenal, 1-penten-3-ol, <i>cis</i> -2-penten-1-ol, charantin, stigmast-5,25-diene-3b-O-glucoside
Leaves	Octacosane, 1-triacontanol, 7-stigmasten-3b-ol, 7,25-stigmastadien-3b-ol, 5,25-stigmastadien-3b-ol glucoside, phytosphingosine, momordicine I, II, III
Tendrils	Benzyl alcohol, myrtenol, <i>cis</i> -3-hexenol, <i>trans</i> -2-hexenal, 1-penten-3-ol, <i>cis</i> -2-penten-1-ol b-sitosterol-b-D-glucoside, stearic acid, two lectins, two new triterpene glycosides – momordicosides A and B, characterized as 3-O-b-gentiobioside and 3-O-b-D-xylopyranosyl (1.4)-[b-D-glucopyranosyl (1.6)]-b-D-glucopyranoside, respectively, of cucurbit-5-en-3b,22(S),23(R),24(R),25pentaol; momordicosides C, D and E characterized as 3-O-b-gentiobiosides of cucurbit-5-en-3b,23,24,25-tetraol, cucurbit-5,24-dien-3b,22,23-triol and 3b-hydroxy-23.24,25,26,27-pentanol-20(j) cucurbit-5-en-22-al, respectively; two cytokinins – zeatin and zeatin riboside –; two proteins a and b momorcharins, p-cymene, hexadecanol, menthol, nerolidol, pentadecanol, and squalene, 10a-cucurbit-5,24-dien-3b-ol, 24-methylencycloartanol, taraxerol, b-amyrin, campesterol, cycloeucaleanol, 24b-ethyl- 5a-cholesta-7-trans-22-dien-3b-ol, 24b-ethyl-5a-cholesta-7-trans-22,25(27)-trien-3b-ol, lophenol, 4a-methylzymosterol, obtusifoliol, spinasterol, stigmasterol, stigmasta-7,25-dienol and stigmasta- 7,22,25-trienol, momordica anti-protein (MAP 30), ribosome-inactivating-proteins (RIPs)
Seeds	Momordicosides G, F1, characterized as 3-O-b-D-allopyranoside and 3-O-b-D-glucopyranoside, respectively, of 5,19-epoxy-25-methoxy-5b-cucurbita-6,23-dien-3b-ol, momordicosides F2, I characterized as 3-O-b-D-allopyranoside and 3-O-b-D-glucopyranoside of 5,19-epoxy-5b-cucurbita-6,23-dien-3b,25-diol, 3-O-[6%-O-palmitoyl-b-Dglucosyl]-stigmasta-5,25(27)-diene and stearyl derivative
Unripe fruits	

Table 2. Chemical constituents of *Momordica charantia* by plant part. Courtesy of Scartezzini and Speroni, *J of Ethnopharmacology* 71 (2000).

Biological Activity

Hypoglycemic activity

Since its initial documented use thousands of years ago, *Momordica charantia* has been associated with reducing blood sugar levels. The compounds involved in this process have come to light, though the exact mechanisms of action are still under debate. Charantin, a steroidal saponin, momordicin, an alkaloid and protein P-insulin all have structures similar to animal insulin, leading to the hypothesis that their makeup plays a hypoglycemic role. Unfortunately, there is a dramatic lack of standardization among the studies, and concrete conclusions are difficult to glean. There are discrepancies among concentrations, extraction procedures, experiment duration, and model organisms used; though for the most part, there is a consensus that *M. charantia* does reduce plasma glucose levels (Basch *et al.* 2003).

Some proposed methods include stimulation of pancreatic insulin secretion, attenuation of hepatic gluconeogenesis, or rise in hepatic glucagon synthesis. Application of *M. charantia* fruit juice increased the number of functional beta cells which produce insulin in the pancreas though not to the normal amount. Other literature suggests an extra-pancreatic mechanism of action, resulting in increased glucose breakdown in the liver, inhibition of glucose-6-phosphatase, or enhanced GLUT4 transporter protein in muscles (Kumar *et al.*, 2010, Singh *et al.*, 2011).

Fernandes *et al.* (2007) attempts to provide experimental evidence for hypoglycemic activity by using a well-standardized *M. charantia* extract in alloxanic diabetic rats compared to glibenclamide, a current anti-diabetic drug. The sample was obtained through an ethanolic extract and received as 10% processed powder. Their results showed an increase in insulin serum, a decrease in plasma glucose, and a

less damaged pancreas compared to control untreated rats. Thus, the authors concluded “MCE [*Momordica charantia* extract] exhibited promising anti-diabetic activity in alloxan diabetic rats” (p 7). In this study, the researchers suggested that the extract increased pancreatic beta cells insulin stimulation.

New literature proposes that *M. charantia* extract possesses 11 β -hydroxysteroid dehydrogenase type 1 inhibitor (11 β -HSD1) which is involved in the etiology of obesity and thus type 2 diabetes. 11 β -HSD1 has been implicated in regulating obesity: 11 β -HSD1-deficient mice have better lipid and glucose profiles and overexpressed-11 β -HSD1 mice are obese and have diabetes. Blum *et al.* (2011) suggests that the presence of this inhibitor contributes to *M. charantia*'s anti-diabetic activity and opens another avenue for future research.

Antioxidant/Anticarcinogenic activity

Aside from its strong hypoglycemic activity, *Momordica charantia* has also been implicated in having antioxidant and antitumor properties as well. Though there is no evidence to suggest that bitter melon can treat cancers, research suggests that it can retard or suppress tumor growth. Pitchakarn *et al.* (2010) observed bitter melon leaf extract reduced cell growth, invasion, and migration in rat prostate cancer cell line PLS10 *in vitro*. The authors also observed reduced metastatic lesions in lung cancer, though not in incidence in rats. This study significantly showed the anti-metastatic activity of *M. charantia in vitro* and *in vivo*.

Crude extracts have also shown anticancer effects in leukemia, lymphoma, melanoma, breast cancer, and many other cancers. Methanol extract has demonstrated cytotoxicity in human

cancer cell lines. The mechanisms of action for this property include inhibition of guanylate cyclase, disruption of G2 and M phases of cell cycle, activation of NK cells, or instigation of apoptosis (Kumar *et al.*, 2010).

Antimicrobial/Antiviral activity

Another property of *M. charantia* that makes it a widely-used and beneficial plant is its ability to fight off nearly any type of infection. The leaf extracts of bitter melon have demonstrated a wide-range of antimicrobial effects including activity against *Escherichia coli*, *Salmonella paratyphi*, *Helicobacter pylori* and *Mycobacterium tuberculosis*. It also has demonstrated antihelminthic properties against *Ascaridia galli* worms, antiprotazoal properties against *Trypanosoma brucei brucei*, and antifungal properties against *Candida albicans* and *Cryptococcus neoformans* (Grover and Yadav, 2004). Such infections are common in the developing world and the value and benefit of bitter melon is immediately obvious in these circumstances.

Notably, protein MAP 30 has potential as antiviral drug, specifically in HIV treatment. This activity can be credited to inhibition of HIV-1 integrase and viral reverse transcriptase. *M. charantia* extract has also been shown to combat herpes and the polio virus, likely by inhibiting protein synthesis (Grover and Yadav, 2004).

Clinical Studies

Few clinical studies have been conducted to verify, quantify and explore the mechanism of action of glucose tolerance due to *Momordica charantia*. Leatherdale *et al.* (1981) conducted a study with nine non-insulin-dependent diabetic Asian

subjects. The human subjects underwent glucose tolerance tests (GTT) as a standard test and after consumption of 50 ml of bitter melon juice and eight to 11 weeks of consuming fried bitter melon. In both instances where the subjects ingested *M. charantia* regardless of modality, the blood sugar level declined. There appears to be a significant decrease in plasma glucose level between the standard and the consumption of the juice. However, it is not apparent if the authors conducted a statistical analysis between consumption of the fried vegetable and the standard or the juice. They conclude their study demonstrated *M. charantia*'s hypoglycemic properties.

Basch *et al.* (2003) compiled the literature of previous clinical studies in a review article including Leatherdale *et al.* (1981)'s study and noted the many shortcomings that were common in all the previous research conducted: not randomized and double-blind, lack of standardization and controls, poor experimental set-up, and establishment of patient history and proper baselines. The authors suggested that though the research has shown *M. charantia*'s antidiabetic activity, these are only preliminary studies.

A more recent study, however, provides more conclusive data and results. In Thailand, Fuangchan *et al.* (2011) conducted the first multi-week, randomized, large sample size, double-blind, active-control trial in four paralleled treatment groups to determine the minimum effective dose of *M. charantia* in newly diagnosed type 2 diabetes patients. Headache, dizziness, and increased appetite in the highest concentration group were noted as low-incident side effects and bitter melon was generally well tolerated. This study concluded that 2000 mg/day of bitter melon significantly lowered fructosamine levels and had a modest hypoglycemic effect.

Contraindications

Though *Momordica charantia* is widely eaten and incorporated into many diets around the world, it should be avoided in certain circumstances. Bitter melon has historically been used as an abortifacient and should not be ingested during pregnancy as it might result in premature birth or accidental abortion. In general, it has been shown to reduce fertility in females and sperm production in males. Thus, couples trying to get pregnant should avoid eating this vegetable (Basch *et al.*, 2003).

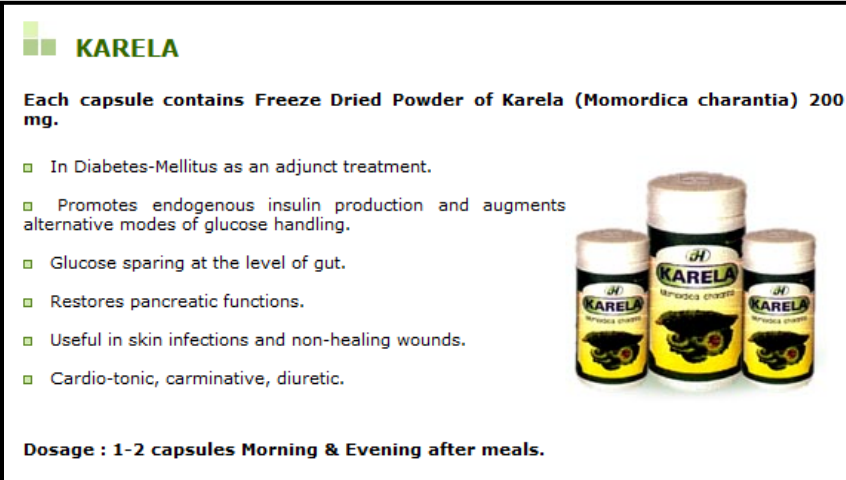
A large-scale study has not been conducted investigating the potential harmful effects of bitter melon, but rather isolated cases of strong side effects have been reported. Of course, any individuals with known allergies to the Cucurbitaceae family such as melon, pumpkin, or squash should avoid consumption of bitter melon (Basch *et al.*, 2003). Fruits in this family have been reported to be one of the most allergy-causing fruits in the United States (Figueredo *et al.*, 2000). Similarly, people of Mediterranean or Middle Eastern descent or that have a glucose-6-phosphate dehydrogenase deficiency should take caution in the ingestion of bitter melon seeds which has the compound vicine that can cause favism, or hemolytic anemia. The red arils enveloping the seeds are also toxic to children and can cause headaches (Basch *et al.*, 2003). All parts of the plant register low toxicity, but extracts administered intravenously or intraperitoneally in high doses can cause death in laboratory animals (Gover and Yadev, 2004).

Due to its hypoglycemic effects, it has had great success as a possible treatment for diabetes. However, this property can be exacerbated when used in conjunction with other anti-diabetic medication. Two incidences of hypoglycemic coma and convulsions have been reported in children after consumption of bitter melon tea. Also, additive-glucose

lowering effects have been reported when bitter melon was consumed while the patient was taking sulfonylureas, a class of antidiabetic drugs that stimulate insulin production (Basch *et al.*, 2003).

Current Use in Allopathic and CAM Therapies

Generally, the current market for *Momordica charantia* is directed to promoting healthy blood sugar levels, reducing hyperglycemia and stimulating the immune system (Figure 6). According to Birdee and Yeh (2010) in *Clinical Diabetes*, approximately a third of adults with diabetes use some type of



KARELA

Each capsule contains Freeze Dried Powder of Karela (*Momordica charantia*) 200 mg.

- In Diabetes-Mellitus as an adjunct treatment.
- Promotes endogenous insulin production and augments alternative modes of glucose handling.
- Glucose sparing at the level of gut.
- Restores pancreatic functions.
- Useful in skin infections and non-healing wounds.
- Cardio-tonic, carminative, diuretic.

Dosage : 1-2 capsules Morning & Evening after meals.

Figure 6. Example of how *M. charantia* is marketed today as an herbal supplement. Rather than the traditional method of eating the whole vegetable, pharmaceuticals have condensed the plant and marketed it as convenient, easy-to-swallow capsules. However, there is no mention of potential side effects or a consultation with a certified physician. Courtesy of <http://www.ayurvedatoday.org/karela.htm>

CAM therapy, which can include botanical sources, dietary supplements, and mind-body medicine. Many diabetes journals suggest *M. charantia* reduces blood glucose but also cautions its use due to lack of conclusive clinical studies (Birdie and Yeh, 2010; Yeh *et al.*, 2003; Krawinkel and Keding, 2006). Bitter melon can come in many forms. The encapsulated extract dosage is usually 100-200 mg 2-3 times daily or liquid form is 50-100 mL/d and the dry powder can range from 3-15g daily (Najm and Lie, 2010).

In Traditional Chinese Medicine, *M. charantia* is dried, powdered, and placed into capsules to make pills. This is the most common form that is available in the herbal remedy market (Covington, 2001). In local communities across the globe that have a long history with bitter melon, it is incorporated as a functional food rather than any direct treatment to an illness, and this is considered the safest method of ingestion because extract dosage has not been standardized nor extensively studied (Geil and Shane-McWhorter, 2008).

Discussion

The breadth of activity and illnesses that *Momordica charantia* encompasses and treats is truly far-reaching. History can witness the medicinal and therapeutic value this plant has had over many continents and throughout millennia. Though its current and traditional primary use is treatment of diabetes mellitus, many other applications have arisen that are integrated to everyday life such as gastrointestinal affliction, skin infirmities, human fertility, infections and many more.

This wide spectrum of treatment is due to the hundreds of chemical constituents that comprise the bitter melon. Research continues today to analyze and better identify the

components of this versatile plant. The one grave deficit in this vegetable's history is the lack of reliable, conclusive clinical trials in humans. The studies thus far have been poorly executed and thus have not effectively showed that the research conducted in mice, rats, and rabbits can be translated to human subjects.

Such conclusive research would be invaluable to current human health with the global increase in obesity, type 2 diabetes, and cancers. Incorporation of this vegetable into the daily diet, with certain restrictions of course, and purification of the active compounds into medication could produce more potent and efficacious resources in the future.

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Panax ginseng C.A. Mey., Araliaceae

Mengshi Dai

Introduction

Panax ginseng C.A. Mey, otherwise known as Asian ginseng or Chinese or Korean ginseng, is an important medicinal plant in the Araliaceae family (Duke, 2012). Asian ginseng is called 'ren shen' (man plant) in Chinese, due to the root's forked shape which resembles a man's body. The genus *Panax*, derived from the Greek word 'panakos' (panacea) meaning 'all healing', refers to the many inclusive curative properties attributed to this plant (Swerdlow, 2000). Not to be mistaken for its American counterpart (*Panax quinquefolius* L.) or Siberian ginseng, (*Eleutherococcus senticosus* (Rupr. ex Maxim.) Maxim.), which belong in the same family, Asian ginseng is solely native to China and Korea. However it is also cultivated in Japan, Russia, and parts of North America. Asian ginseng has been used for centuries in Asia, but was introduced to the West in the 1700s by Father Jartroux who advocated its use in the treatment of fatigue, pleurisy, and convalescence. Ginseng's primary constituents are ginsenosides and panaxans. Ginsenosides stimulate the cardiovascular and central nervous systems to enhance physical and mental performance. Panaxans are polysaccharides derived from ginseng extract which lower blood sugar, strengthen the immune system, and treat diabetes (Swerdlow, 2000). Ginseng also has antioxidant, antiaging, and appetite-stimulating properties. In addition, the Chinese and Koreans use this plant for almost every ailment ranging from sexual potency to colds and even to cancers in the forms of teas, tonics made from decoctions, and infusions of the roots or powdered extracts (Harriman, 1973).



Figure 1. *Panax ginseng*. (Source: <http://foodspeople.com/wp-content/uploads/2011/05/ginseng1.jpg>)

Botanical Description

Panax ginseng (Figure 1) grows on mountainous or hilly forest slopes in the Manchurian region of China, and North Korea. It thrives in small patches in climates with cold and dry air, especially in wooded regions where the shady forest



Figure 2. Stem, Leaves, and Flowers of *Panax ginseng*.

(Source: http://i01.i.aliimg.com/photo/v0/269775813/plant_extract_panax_ginseng_P_E_ginsenoside.jpg)

canopy offers protection from wind, rain, and sun. Asian ginseng grows among hardwoods rather than conifers, and often grows together with basswood (*Tilia tomentosa*) and royal paulownia (*Paulownia tomentosa*) (Harriman, 1973). In addition, Asian ginseng requires rich, moist soil and around five to seven years to mature fully (Swerdlow, 2000). These difficult growing requirements cause ginseng to remain quite



Figure 3. Fruit of *Panax ginseng*. (Source: <http://www.herbs.org/greenpapers/panaxq.jpg>)

rare and elusive, contributing to extremely high prices for roots of good quality. The plant is a perennial shrub, growing up to two and a half feet tall with an erect stem and a single cluster of greenish yellow or pink flowers in groups of 15 to 30 shooting up each spring. The leaves are thin and finely serrated, clustered in groups of three to five, which grow up to eight inches long (**Figure 2**). The fruits are scarlet, smooth, and glossy (**Figure 3**). The root is cream-colored or white, resembling a parsnip with rootlets branching in the form of a human body shown in **Figure 4** (hence the indigenous name 'ren shen', or man plant). Ginseng root extracts and tea have a distinctive sweet taste mixed with underlying bitter tones. There is little or no odor and the root is starchy with small amounts of resin, volatile oils, and the medicinally active compound, *panaquilon* (Harriman, 1973).



Figure 4. Root of *Panax ginseng*. (Sources: http://www.bouncingbearbotanicals.com/images/ginseng_root.jpg, <http://www.buzzle.com/img/articleImages/489358-262329-53.jpg>)

Traditional Uses

Increased sexual potency

Panax ginseng has been used in China for thousands of years. It was documented for its life-prolonging effects in one of the ancient medical texts, *Shen Nong Ben Cao Jing* (Shen Nong's Materia Medica) as early as 502-557 in the Liang Dynasty (Yun, 1996). Aside from its inherent medicinal properties, ginseng was used to increase potency. In Chinese medicine, health is holistic. The balance of yin (feminine attributes) and yang (masculine attributes) and humans with nature was essential to good physical, mental, and spiritual health. Ginseng was considered the most "yang" of all the herbs. As such, true believers wore a well-shaped ginseng root as a

sexual amulet to increase sexual potency. Folklore has it that an emperor once paid \$10,000 to buy a particularly shapely root. To be able to afford fine ginseng was sign of wealth and commanded respect because it was used by wealthy Oriental aristocrats to keep concubines satisfied. Even now, men take ginseng before and after intercourse to enhance performance and to replenish his sapped energy and sexual potency after a taxing encounter (Harriman, 1973). According to Jartroux, the man who introduced *Panax ginseng* to the West, ginseng was a necessity in all the prescriptions set by the Chinese physicians, and only the Emperor had the right to collect its roots (Swerdlow, 2000). Ginseng was, and still is, a scarce, expensive, and highly prized possession.

Religious Uses

During the 18th and 19th centuries, several reports of ginseng found their way back to America from missionaries and officials serving in Asia. They discovered that the Chinese and Koreans attributed stimulating and restorative properties to Asian ginseng, and that this plant has been held in high esteem for centuries. A report in 1900 from a president of one of the largest trading companies in the Orient said that the Chinese used ginseng for thousands of years for medicinal and religious purposes. He also elaborated that its use has been firmly established in their religion for generations. Due to its seemingly supernatural powers, it was also worshipped (Harriman, 1973). Owing to its long history of use, several folklores exist about ginseng. One tale from the 6th century attributes ginseng with human qualities. One day, a general coming back from war stopped to stay at a stranger's house to rest. That night, he heard the cries of a man coming from a close distance. The strange cries continued for several nights with the entire house searching for the source of the voice. At

last, the general followed the voice to a distance of about half a kilometer from behind the house, and there he found a single ginseng plant. He dug until the root was exposed, and was startled by its human-like appearance. In fact, it had been this root that had been calling out in a man's voice over the previous nights (Harriman, 1973). Stories where dreams or voices led to the discovery of wild patches of ginseng are common in China. The people believe that if someone finds wild ginseng, they will be blessed and luck and fortune will come their way (Harriman, 1973).

Medicine

Panax ginseng remains famous in the East and West for its numerous and ubiquitous health benefits, ranging from colds to cancers and everything in between. Even now, Chinese people believe in corresponding ginseng body parts to the actual limbs that are hurting. For example, taking medication derived from part of the root that looks like an arm will be beneficial to that individual's ailing arm (Harrison, 1973). The root was, and still is, often used as a tonic. One can chew a bit of root or take a spoonful of extract each morning on an empty stomach to help the body gain vigor and resilience. Preparation of ginseng tonic involves ginseng extract, which is produced by soaking the root in water and evaporating the solution. The extract is then kept in a tightly sealed container, and no metal except silver may come into contact with it (Harriman, 1973). Ginseng extract can be used alone or in conjunction with several other ingredients, which will enhance the individual healing properties of each drug. Most Chinese medicines are decoctions or infusions of various ingredients, and certain plants are frequently used with ginseng. These herbs are ginger, licorice, fou ling, cassia, and huang ch'i. Taken together, these decoctions are powerful

Tuberculosis	Dysentery
Fitful coughs	Enuresis
Nausea	Gout
Diabetes	Suppurating sores
Thirst accompanied by dry skin and flushed throat	Degeneration of the kidneys, characterized by continual thirst, polyuria, and pain in renal area
Indigestion	Rheumatism in lower limbs
Diarrhea	Sexual potency

Table 1. Conditions and diseases involving the use of Ginseng in traditionally prescribed remedies in China (Harriman, 1973).

tools against stomach and bowel pains as well as gas, coughs, and chest and lung problems (Harriman, 1973). Aside from *Shen Nong Ben Cao Jing*, ginseng medicinal recipes are found in additional ancient texts in China and Korea, such as *Ben Cao Kang Mu* and *Pang Yak Hap Pyung* (Harriman, 1973). These formulas serve as guides and healers adapted them to fit the specific cases of their patients. Some examples of these medicinal recipes include a tonic decoction using equal parts of several herbs, including ginseng; a tincture of ginseng using powdered ginseng root fermented with rice and yeast; date and ginseng pills made by pounding together fresh ginseng root with dates and others plants. One Cantonese ginseng tonic uses ginseng in combination with several other ingredients to treat loss of vitality, loss of appetite, fever, weakness of legs, jaundiced appearance, and laborious breathing. It is also used to strengthen the spleen and stomach and to increase yang forces. Since ancient times, ginseng has been used as a panacea, treating many serious illnesses. A list of conditions and diseases involving the use of ginseng in traditionally prescribed remedies in China is shown in **Table 1**, and in Korea is shown in **Table 2** (Harriman, 1973).

Chemicals/Molecules	ppm	Plant Part	Chemicals/Molecules	ppm	Plant Part	Chemicals/Molecules	ppm	Plant Part
Carbohydrates	834000	Root	Ginsenoside-RG-1	2000	Root	Chromium	11	Root
Fiber	72000	Root		15000	Leaf	Panthenic-acid	6.6	Root
ASH	50000	Root		2000	Flower	Riboflavin	1.8	Root
Fat	17700	Root		200	Fruit	Thiamin	1.7	Root
Calcium	2880-4140	Root	Ginsenoside F-1	4000	Leaf	Biotin	0.9	Root
Ginsenoside-RB-1	5000	Root	Ginsenoside-F2	2000	Leaf	Ascorbic Acid		Root
	2000	Bud	Ginsenoside-F3	2000	Leaf	Beta-Carotene		Root
	1000	Leaf	Carbon-disulfide	1500	Root	Beta-Flemene		Root
Ginsenoside-RB-2	2000	Root	Choline	1000-2000	Root	Beta-Sitosterol		Root
	4000	Leaf	Panaxynol		Root	Beta-Sitosterol Glucoside		Plant
	2000	Flower	Water	788000	Root	Camptesterol-6'-linolenylglucoside		Root
	200	Fruit	Protein	109000	Root	Camptesterol-6'-linolenylolglucoside	Root	
Ginsenoside-RB-3	50	Root	Disaccharides	33000	Root	Camptesterol-6'-oleylglucoside		Root
Ginsenoside-RC	3000	Root	EO	500	Root	Camptesterol-6'-palmitylglucoside		Root
	2000	Flower	Potassium	2430-10700	Root	Camptesterol-6'-stearylglucoside		Root
	2000	Leaf	Magnesium	481-1950	Root	Citric Acid		Root
	1000	Fruit	Iron	180	Root	D-Fructose		Root
Ginsenoside-RD	2000	Root	Heptadeca-1-EN-4,6-Dien-3,9-Diol	150	Root	D-Glucose		Root
	15000	Leaf	2-Glucoginoside-RF	50	Root	Fumaric Acid		Root
	2000	Flower	Zinc	27		Panaxene		Root
	1000	Fruit	Aluminum	22	Root	Panaxic Acid		Root
Ginsenoside-RE	2000	Root	Manganese	19-180	Root	Panaxin		Root
	15000	Leaf	Tin	16	Root			
	25000-60000	Fruit						
	28000	Flower						

Table 3. List of active chemicals and biological molecules in ppm in *Panax ginseng* (Duke 2012).

Another study was conducted on the immunological effects of ginseng on cells. Water-soluble ginseng oligosaccharides (WSGO) were obtained from extracts of ginseng roots and

separated into fractions. Preliminary immunological tests suggest that WSGO were potent T and B-cell stimulators and

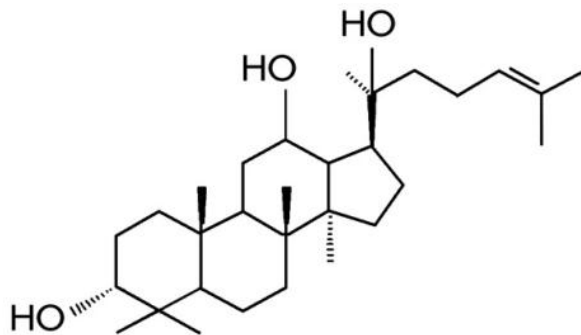


Figure 6. A Panaxoside in *Panax ginseng*. (Source: <http://actanaturae.ru/article.aspx?id=190>)

were effective towards lymphocyte proliferation (Wan et al., 2011).

In Vivo

Research has shown *Panax ginseng* extracts, specifically ginsenosides, have a positive effect on lowering hypertension in rats. The extract stimulated nongenomic Akt-mediated endothelial NO synthase (a regulator of systematic blood pressure) activation. It also enhanced NO production and vessel wall thickening, and alleviated hypertension in hypertensive rats (Hong et al., 2012). Ginseng is also proven to protect against influenza. One study shows that mice infected with the H1N1 virus that were treated with ginseng polysaccharides (GP) had higher survival rates than the control mice. Mice exposed to GP had lower levels of lung viral titers and inflammation (Yoo et al., 2012). Ginseng can also suppress asthma through the inhibition of lung inflammation by the ginsenoside RG-II (Jung et al., 2012).

One traditional use of ginseng was for the purpose of antiaging. In ancient China, people used to believe ginseng

could be taken to achieve immortality (Harriman, 1973). In a modern experiment, the effect of fermented *Panax ginseng* extract (GINST) on oxidative stress and antioxidant activities in major organs of aged rats was studied. Oxidative stress throughout life is the major cause of aging. The study found that administration GINST to aged rats resulted in increased activities of superoxide dismutase, catalase, and glutathione peroxidase as well as levels of ascorbic acid and α -tocopherol. Levels of malondialdehyde, aspartate aminotransferase, and urea were lowered, on the other hand. These findings indicate that ginseng extract can decrease oxidative stress and age-related disorders due to free radicals (Ramesh, 2012). Another research study also showed ginseng to possess antioxidant effects. The ginsenoside RG3 inhibited Cy-induced oxidative stress by increasing levels of catalase and superoxidase dismutase while lowering activities of xanthine oxidase and nitric oxide (Wei et al., 2012).

So far, there has been no research supporting issues of the development of drug resistance. Ginseng is mainly taken as a 'bu yao' and 'bu yin,' which are herbs or plants used to enhance and nourish the body (Guo, 1961). Even when ginseng extracts are used to target biological receptors in the body, they are not used to fight microbiological agents, which is why there have been no instances documenting drug resistance to ginseng.

Clinical Studies

Although *Panax ginseng* has been used for thousands of years for its obvious health benefits, not many controlled clinical studies have been carried out. One study, however, investigates experimental and epidemiological evidence of cancer-preventive effects of ginseng on humans. The relationship between ginseng consumption and cancer was

evaluated by interviewing 905 human pairs of case and control subjects matched by various factors, such as age, sex, and date of admission to the hospital. Ginseng extract and powder were more effective at fighting and reducing cancer than fresh sliced ginseng, ginseng juice, or ginseng tea (Yun et al., 1996).

A later experiment was carried out to further study the effects of types of ginseng products that have the most cancer-prevention. The study also investigated the duration of ginseng consumption, types of preventable cancers, and effect of ginseng on cancers related to smoking. Ginseng intake was found to decrease risk of cancer and there was an inverse relationship between cancer risk and frequency and duration of ginseng intake. The longer and more often an individual ingests ginseng, the lower risk of developing cancer. There was an effect on lung, lip, oral, and liver cancer, but no effect on breast, uterine cervix, or thyroid gland cancers. With regards to smokers, cancer of the lung, lip, and oral cavity decreased as opposed to smokers who did not intake ginseng extract. These findings show that ginseng intake can decrease cancer at various sites (Yun et al., 1996)

The mechanism for this anticancer effect is still not understood. However, it is hypothesized that saponins are the active components of ginseng, giving this plant its anticarcinogenic effects. Saponins have been shown to have antimutagenic activity, growth inhibition activity against several mouse tumor cells lines, growth inhibition of human ovarian cells, and immunomodulating activity in mice. Polysaccharides, another main active constituent in ginseng, have anticomplementary activity, reticuloendothelial system-potentiating activity, and alkaline phosphatase-inducing activity. Also, polyacetylenes extracted from ginseng have been shown to have cytotoxic activity. It is reasoned that the synergy of the combination of these different constituents is

what is reducing cancer risks. However, further studies need to be carried out to support this theory and to identify unknown constituents that may have anticarcinogenic effects (Yun et al., 1996).

Aside from reducing cancer, ginseng has also been shown to lower hypertension in humans. One study compared blood pressure from two groups of adults. One group took 200 mg daily extract of ginseng and the other group took 200 mg daily of the placebo. The study showed that taking ginseng extract reduced blood pressure by 5 mm Hg in two hours after ingestion (Caron et al., 2002). There are also studies of ginseng on diabetes. Although used traditionally to treat this disease, there are mixed results from experiments regarding its effect on diabetes. Some studies have found ginseng extract to reduce diabetes while others did not produce conclusive evidence. A study investigating the effect of red ginseng (heated *Panax ginseng*) on type 2 diabetes did not yield supporting data for the effectiveness of red ginseng on glucose control (Kim et al., 2011). Other studies investigating ginseng and cardiovascular illness also produced mixed conclusions. One experiment showed taking ginseng extracts did not lower deaths related to cardiovascular disease, but did decrease mortality overall (Yi et al., 2009). Although the results were not definite, this study supports the holistic practice of taking ginseng to enhance and nourish the body rather than to treat specific diseases (Guo 1961).

Like most medicinal plants, clinical evidence of ginseng efficacy in treating various diseases are contraindicating and sometimes produce no conclusive evidence in the benefits of ginseng intake. However, this problem is mostly due to the scarcity of well-designed, randomized, and controlled clinical trials rather than to any problems related to the plant (Karmazyn et al., 2011).

Contraindications

Harriman states in 1973 that no studies so far have shown any toxicity related to *Panax ginseng* intake. In fact, of all the research done on ginseng, not one has shown even the slightest deleterious side effect of this gentle “Queen of the herbs” (Harriman, 1973). Toxicology and carcinogenesis studies of ginseng were made in rats, mice, and other microbes. Genetic toxicology studies were performed in *Salmonella typhimurium*, *Escherichia coli*, and mouse peripheral blood erythrocytes, as well as on live mice and rat subjects. The mice and rats all survived in 2-week, 3-month, and 2-year studies. No increases in the incidences of neoplasms or nonneoplastic lesions were attributed to the administration of ginseng. Almost 30 years later, in modern studies contradictions exist in data regarding ginseng toxicity. In a genetic toxicity study, ginseng was not mutagenic in either of the two independent bacterial mutagenicity assays. Under the conditions of these 2-year studies, there was no evidence that ginseng was carcinogenic in male or female rats (National Toxicology Program, 2011).

However, another study found that Rg3, a ginsenoside, suppresses normal physiological responses *in vitro* and leads to vascular remodeling in rats, which is surprising concerning ginseng’s proven protective effects on vascular function (Karmazyn et al., 2011). Potential embryotoxic effects exist for mice embryos that were directly exposed to the Re ginsenoside, but no side effects were found in embryos exposed to the Rc ginsenoside (Chan et al., 2004). In general, ginseng has relatively few adverse effects although this could be due to low reporting instead of low incidences (Karmazyn et al., 2011). The other recorded side effects were provided mostly through case reports and were not conclusive data taken from controlled experiments. A female without cardiovascular risk factors reported developing long QT

syndrome (which can lead to arrhythmias) during periods when she was consuming large amounts of ginseng (Torbey et al., 2011). Another report of an elder man developing bradyarrhythmia after prolonged exposure to ginseng (Liao et al., 2011) also calls into question the potential toxicity of ginseng.

Current Use in Allopathic and CAM Therapies

The current uses of *Panax ginseng* have not changed much from the thousand-years-old traditions of the ancient people. Ginseng is one of the most important herbs used in traditional Chinese medicine. According to a study asking elderly Chinese patients in America to list their medications, ginseng was listed as a home remedy benefitting the lungs and spleen, used against weakness with chronic illnesses, vaginal bleeding, diabetes, and palpitations (Guo, 1961). Ginseng is still used by modern people to fight colds and chronic illnesses, amongst many other traditional uses. The preparations of decoctions and tonics have not changed since earlier times. The roots are still soaked in water then kept in an airtight container for later use. Ginseng roots are still being sought after, and prices on the market vary according to the quality. Fine ginseng costs many times more than rougher forms. Eastern people regard the root shape (how closely it resembles a man) as the defining factor in quality while Westerners look for ginsenoside content. **Table 4** shows the difference in prices of various grades of ginseng. Asian ginseng costs more than American or cultivated ginseng. Ginseng is a highly priced and popular root that has spread from Asia to the Western hemisphere. Even in the United States, all oriental drugstores carry the root or extracts of it. The harvesting and processing of Korean and Chinese ginseng is done entirely under supervision and the seal on packaged products ensures the

Grade	Price (per Catty)
Chinese Wild Imperial	\$5000.00
Korean and Chinese Red	\$26.50
Korean White	\$196.50
American Wild	\$133.30
Japanese and American Cultivated	\$36.60

Table 4. 1971 Hongkong wholesale prices of ginseng according to grades (Harriman, 1973).

identity of this herb. Whole roots are shipped to the US in boxes weighed in cattys, with one catty equal to 1.33 lbs. There have been many attempts (now successful ones) to cultivate this precious herb outside of its native Chinese and Korean forests, in America, Japan, and Russia. The popularity of this herb maintains the use of tonics and decoctions found in traditional Chinese medicine and herbal teas, and powdered forms can be taken as drugs in the form of capsules (Harriman, 1973).

Discussion

Panax ginseng has been an important plant in the treatment of a broad range of diseases and illnesses since ancient times. Today, it continues to be one of the leading herbs used in traditional Chinese medicine. Its active biological constituents include various ginsenosides and polysaccharides. Research has been done on this herb to classify its active constituents on biological pathways and diseases, with results showing antihypertensive, anti-inflammatory, and anti-carcinogenic effects. As with the use of all plants and herbs, well-controlled and effective studies are few in number. Further research still needs to be made in clinical trials, as well as continued *in vitro* and *in vivo* studies. The preventive and curative effects of

ginseng extract on cancer and tumor cells are especially exciting, with studies documenting favorable results supporting the anticancer properties of this herb. Research data is favorable in the use of ginseng as a possible herb against cancer, and future anticancer drugs containing ginseng is possible. However, the pathways in which ginseng suppress cancer still remain to be elucidated. The main theory involves the synergy created by the various components acting together although this hypothesis has not been proven yet.

Although new studies are emerging in the potential adverse effects of ginseng, these cases are few and far between. Ginseng has been used for over two thousand years as a medicinal plant, and traditional techniques in preparing ginseng decoctions remain almost unchanged to this day. Ginseng acts as a panacea, restores energy, and nourishes the body. In addition, its antihypertensive and anticarcinogenic properties are most exciting, as these can be utilized to treat chronic diseases for which Western medicine still lacks a cure. The potential for the active constituents to be made into drugs is high and favorable, as *in vivo*, *in vitro*, and clinical studies continue to support ginseng's various positive effects on health.

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Papaver somniferum L., Papaveraceae

Ben Jarvis

Introduction

Papaver somniferum L., commonly known as the opium poppy or the poppy plant, belongs to the family Papaveraceae. The opium poppy is one of the most well known plants because of its many uses. It has a long history throughout the world as being one of the most useful as well as one of the most abused plants. In fact, opium is perhaps one of the oldest narcotics known to man with evidence of its use found in limestone caves in Spain from about 55,000 years ago (Schultes 1995). The earliest writings of the opium poppy date back to about 4000 B.C., where the Sumerians refer to it as the “joy plant” (Lewis 2003). The opium poppy has a range of uses from the commonly used food ingredient, the poppy seed, to one of the most effective pain relievers, morphine. Other common drugs derived from the opium poppy include codeine, noscapine, thebaine, and papaverine. Because of the addictiveness and abuse caused by this plant’s effect on the central nervous system, there has been a lot of conflict and controversy over its growth and cultivation. In fact, the Opium Wars that took place between England and China in the nineteenth century were over this very plant. Even today, with the United States and other countries battling a war front in Afghanistan, Opium farming and its funding of the Taliban remains a key issue in the war. The opium poppy has many therapeutic uses in humans, but its addictive nature also brings about a great deal of controversy and concern.

The two most common food ingredients of the opium poppy are poppy seeds and poppy seed oil. They provide a unique flavor that can be found in many cuisines from cultures

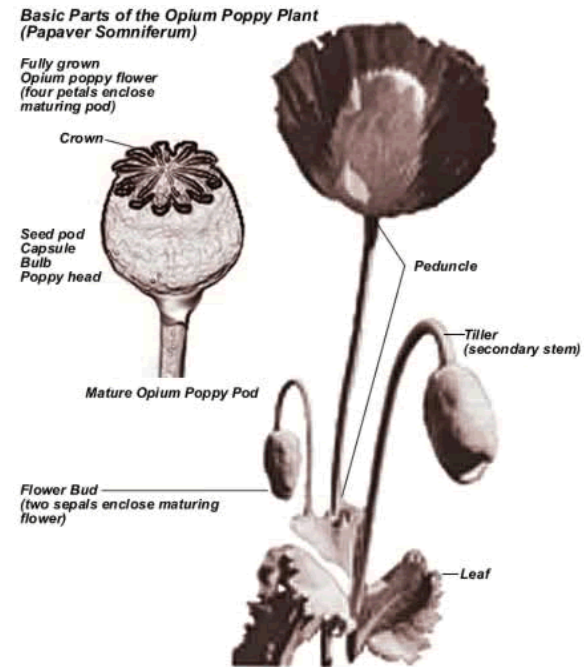


Figure 1. The basic parts of the opium poppy are shown above. The opium poppy consists mainly of a stem, leaves, flower and flower buds, peduncle, tiller, and typically three seed pods with a crown. (Image Source: poppies.org)

around the globe. The seeds and their oil contain very low levels of opiates and are considered to be safe ingredients for all ages.

P. somniferum also has many medicinal uses that have had a great impact on anesthesia and healthcare as a whole. There are over 25 alkaloids that come from the opium poppy, the

most common of which is morphine. Morphine, a benzyloquinoline alkaloid with two additional rings, is derived from the poppy's latex, or milky fluid commonly found in angiosperms, and is commonly sold under 125 different brand names worldwide.

Description

The plant species, *Papaver somniferum*, can be found in fields and flower gardens throughout the world. The opium poppy consists mainly of a stem, leaves, flower and flower buds, peduncle, tiller, and typically three seed pods with a crown (**Figures 1 and 2**). It is these seed pods which contain the valuable latex that is so commonly used in codeine, morphine salts, and other drugs derived from the plant. The plant secretes this thin latex as a response to mechanical damage, but it is still unclear why the opium poppy produces the latex in the first place. Most recent evidence shows that the metabolism of morphine to bismorphine serves as a defense mechanism in the opium poppy (Morimoto 2001). Morphine comes from two molecules of the amino acid L-tyrosine through a series of at least 17 enzymatic steps (Grothe 2001).

Perhaps the most commonly seen poppies are in the movie "The Wizard of Oz," where Dorothy and her friends travel through the poppy fields (**Figure 3**). It is in that movie that many people learn about the sedative effects of the opium poppy. The opium poppy is not only grown in fields. Many growers include the opium poppy as an ornamental flower in their gardens. The flowers of the opium poppy can be found in many different colors, but are most frequently seen as red, white or pink flowers. The flowers have two sepals that fall off as the flower blooms. The exact number varies, but the poppy flower can usually be seen with four to six petals. The seeds of the poppy plant are most commonly planted in the



Figure 2. The image above shows another view of the major parts of the opium poppy. Notice the different color flowers. (Image Source: botanical.com)

fall under a thin moist layer of soil. The opium poppy grows very quickly and a seedling can be seen within a week or two. The pods of the poppy plant contain the seeds and the latex that are commonly sought after.

P. somniferum also has over 75 close relatives which are grown as weeds or flowers. A few common relatives are the corn poppy, *Papaver rhoeas*, the Western poppy, *Papaver californicum*, and the Oriental poppy, *Papaver orientale*.



Figure 3. In this popular scene from the “Wizard of Oz,” Dorothy and her friends pass through the poppy fields on their journey. (Image Source: joewmccord.com)

Although less common, there have been medicinal uses found in these other species as well.

In *P. somniferum*, most of the flowers are planted by humans in controlled environments where they can keep a close watch on the plant. Because of the value obtained from the latex in the opium poppy, growers pay close attention to the growth and harvesting of the crop.

Traditional Uses

Papaver somniferum is used not only as one of the most common analgesics and narcotics, but it is also commonly used in food, gardening and recreational drug use. The majority of its influence, however, has been because of its drug effects.

Some of the earliest writings focused on the opium poppy show that it was used in anesthesia. In the Roman Empire, a sponge was soaked with the latex from the opium poppy and placed under the nose of the patient. The vapors that were released when the sponge was moistened would induce sleep. Mandrake wine and other concoctions containing morphine were also used to induce sleep, but it was quickly noted that high dosage could cause negative side effects and often lead to death (Carter 1996). William Shakespeare referred to the poppy’s sedative effects in two of his most common plays, in *Othello* and in *Romeo and Juliet*. It was from the opium poppy that the potion was made that put Juliet to sleep.

Throughout recorded history, there is evidence of the use of the opium poppy for anesthesia and for its sedative effects. The opium poppy has also been used to treat many other ailments and as an aphrodisiac. Papaverine, one of the alkaloids from the opium poppy, has been used as an antiviral to combat cytomegalovirus (CMV), measlesvirus, and human immunodeficiency virus (HIV) and has potential to help AIDS patients who also have CMV disease. Papaverine has also been used to treat conditions of the nervous system, peptic ulcers, painful menstruations, gastrointestinal complications and spasms among many other things. Cryptopine, a colorless alkaloid obtained from the opium poppy, has shown to control arrhythmias and slow myocardium tissues. Protopine, another alkaloid found in the opium poppy, has been shown to inhibit histamine inhibitors and show bradycardial action. A powder from the poppy seed has also been shown to relieve toothache (Lewis 2003). The most common use of alkaloids from *Papaver somniferum* has been to relieve pain. Codiene has been used in cough syrups as an antitussive. Amorphine, an emetic derived from morphine, has been used in the removal of poisons from the stomach and in aversion therapy.

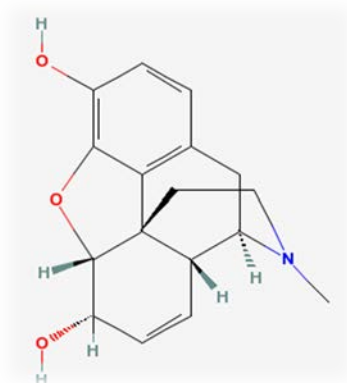


Figure 4. The chemical structure for morphine (C₁₇H₁₉NO₃). Notice the ring structure bearing nitrogen, which is a common characteristic of alkaloids. (Image Source: pubchem.ncbi.nlm.nih.gov)

Some of the common analgesics previously mentioned including morphine, codeine, noscapine, thebaine, and papaverine also have addictive tendencies associated with their use. Both mental and physical addictions are common with the abuse of these drugs. Overcoming the addiction, however, is not easy and can often require professional help. Withdrawal symptoms can be quite severe and include nausea, vomiting, and diarrhea among many other things (McClung 2006).

Perhaps one of the most addictive drugs, heroin, comes from the opium poppy. Heroin, or diacetylmorphine, is a semi synthetic drug created from morphine. In some countries, heroin is used to treat severe acute pain (van den Brink 2003). Unfortunately, the recreational use of heroin is much more popular than the medical uses. Heroin is a commonly sought after drug due to the induced euphoria effects. Tolerance forms quickly in heroin users and creates a need for more.

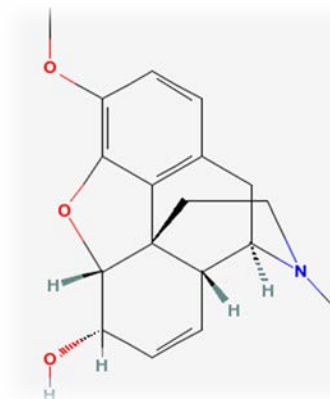


Figure 5. The chemical structure for codeine (C₁₈H₂₁NO₃). Like morphine, codeine is an alkaloid. (Image Source: pubchem.ncbi.nlm.nih.gov)

Many famous drug related deaths have been attributed to heroin.

A safer and very common use of the opium poppy includes the use of poppy seeds and poppy seed oil. Poppy seed and their oil are used to add flavor and texture to many foods. The seeds are commonly used in many baked goods, casserole dishes, and in several types of Indian curry.

Chemistry and Pharmacology

Alkaloids are commonly identified by their ring structure bearing nitrogen. Morphine (**Figure 4**) and codeine (**Figure 5**) are both alkaloids. Morphine has the chemical formula C₁₇H₁₉NO₃ and a molecular weight of 285.338 g/mol. The crystal structure of an anti-morphine antibody and its complex with morphine are shown in **Figure 6**. Codeine has the chemical formula C₁₈H₂₁NO₃ and a molecular weight of

Alkaloid	Chemical Formula	Molecular Weight
Noscapine	C ₂₂ H ₂₃ NO ₇	413.421 g/mol
Thebaine	C ₁₉ H ₂₁ NO ₃	311.375 g/mol
Papaverine	C ₂₀ H ₂₁ NO ₄	339.385 g/mol

Table 1. Chemical formulas and molecular weights of some common drugs derived from the opium poppy.

299.364 g/mol. The chemical formula and molecular weight of thebaine, noscapine, and papaverine are shown in **Table 1**.

Biological Activity

There has been a great deal of research surrounding the opium poppy and its uses. In 1988, an *in vitro* study showed how thebaine, an intermediate of morphine and codeine biosynthesis in the opium poppy, could be transformed to oripavine, codeine, and morphine by rat liver, kidney, and brain microsomes. (Kodaira 1988). In 1995, Lenz and Zenk showed the properties of codeinone reductase (NADPH), which catalyzes the production of codeine from codeinone, another step in the biosynthetic pathway shown in **Figure 7** (Lenz 1995).

Morphine and other opiate drugs greatly affect the central nervous system (CNS). There are four major receptive sites found in the brain and spinal cord of most vertebrates, known as the opioid receptors. The four opioid receptors are identified as MOP (μ), KOP(κ), DOP(δ) and the nociceptin receptor (NOP). Each of the four receptors has a different location in the brain and spinal cord and has a different function affecting the reception of pain (Dreborg 2008). A stimulation can activate these receptors, which will then

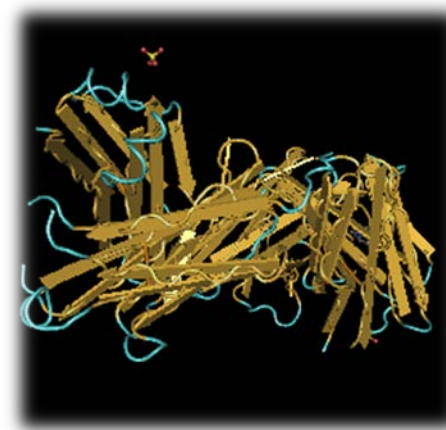


Figure 6. The crystal structure of an anti-morphine antibody and its complex with morphine are shown. (Image Source: pubchem.ncbi.nlm.nih.gov)

initiate a series of intracellular signals that affect many hormones and neurotransmitters throughout the body and can often cause respiration depression (Pattinson 2008). While the effects of many of the opiate drugs are well studied, the mechanisms of actions for many of them are still unclear. Although the mechanism of action for papaverine remains unclear, some researchers have found evidence that it is a strong inhibitor of cyclic-3',5'-nucleotide-phosphodiesterase (Kukovetz 1970).

Clinical Studies

New drugs, such as Kadian, are in clinical trials to determine the effectiveness of low dosage or sustained release morphine capsules. There are also clinical studies to determine more effective means of overcoming addictions to morphine and other narcotics. A current, ongoing study sponsored by the Norwegian University of Science and Technology is trying to

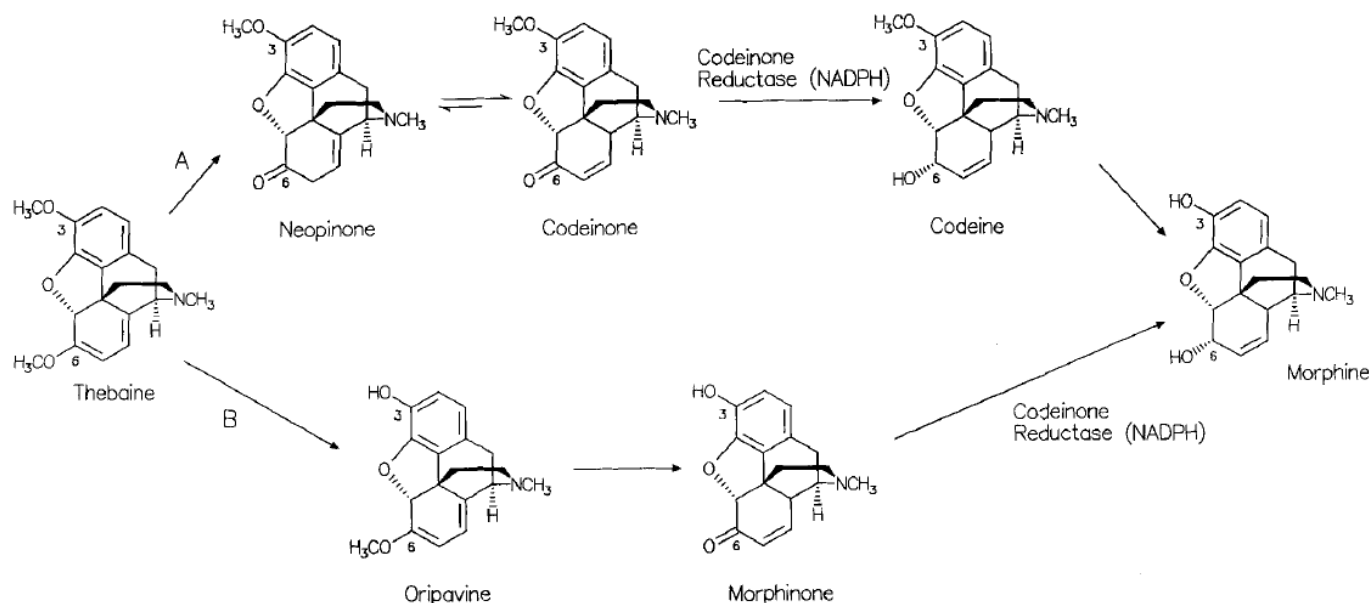


Figure 7. Codeinone reductase (NADPH), which catalyzes the production of codeine from codeinone is shown above. (Image Source: Lenz 1995)

determine if it is possible to switch from morphine treatments to methadone in patients with advanced cancer or short life expectancy.

Contraindications

There are many interactions to watch out for with the use of drugs from the opium poppy. Some of the more common interactions include alcohol, barbiturates, antidepressants, muscle relaxants, antihistamines, sleep medications, antipsychotics, and other narcotics. Morphine itself does not interact with grapefruit juice, but codeine, on the other hand, will cause an interaction. The two most common dangers associated with alkaloids from the opium poppy include

interactions and the addictive nature of the drugs. Pregnant women should be especially careful to avoid the abuse of morphine. Babies born from mothers addicted to morphine often have the physical addiction themselves (Becker 2005).

Current Use in Allopathic & CAM Therapies

Because of the addictive nature of the drugs and the widespread abuse, opiates are not commonly used in complementary and alternative medicine therapies. Codeine can be found in some combination preparations such as Tylenol with codeine and antitussives. There are many drugs derived from morphine, but in nearly every country, they are closely regulated by the government to prevent such abuse.

Morphine and other opiate drugs are often administered in hospitals and clinics to manage post-operative pain. Many doctors will choose to use NSAIDs instead of opiate analgesics because there is less risk involved, both in addiction and respiratory depression. NSAIDs are a good for mild to moderate pain, but it is recommended that practitioners “use opioid therapy for the short-term management of breakthrough pain that is not responsive to NSAIDs or acetaminophen” (Becker 2005).

Discussion

Papaver somniferum has generated many medicinal uses that have greatly impacted human health over the years. The controversy surrounding the opium poppy, however, has often overshadowed its positive effects. The highly addictive nature of heroin and other opiates can even be passed on through pregnancy. Over-dosage of opiates, like most narcotics, can often lead to death. Many lives have been improved and many lives have been lost over the opium poppy plant. With proper use and direction, morphine and codeine can help alleviate pain, spasms, coughs and many other conditions. Even when used correctly, one must be very careful to avoid addiction. While many drugs have been derived from the opium poppy, there is still a lot of research surrounding this plant.

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Passiflora incarnata L., Passifloraceae

Ronni Shalem

Introduction

Passiflora incarnata (**Figure 1**) is from the Passifloraceae family. It is most commonly known as the purple passionflower but alternate names include: apricot, ground ivy, Holy Trinity flower, mayapple, maypop, or mollie cockle (McGuire, 1999). *P. incarnata* is indigenous to warm temperate and tropical North America (Dhawan, Dhawan, & Sharma, 2004). It has a perennial vine (present at all seasons of the year) with white and blue or purple flowers, and an edible fruit. The fruits are berries and oval in shape (**Figure 2**). The main constituents include flavonoids, flavonoid glycosides, alkaloids, cyanogenic glycosides, carbohydrates, amino acids, benzopyrone derivatives and volatile constituents (Elsas, Rossi, Raber, White, Seelay, Gregory, Mohr, Pfankuch, & Soumyanath, 2001).

Passiflora has been used traditionally as a sedative, anxiolytic, antispasmodic, analgesic, anticonvulsant, and for the treatment of whooping cough, bronchitis, and asthma (Dhawan, Kumar, & Sharma, 2002). Topically, it has been used for hemorrhoids, burns, bruises, and inflammation. More recently, *P. incarnata* has been recommended for insomnia, neuralgia, seizures, menopause, and as an anti-diabetic (Tovar & Petzel, 2009; Tenney, 2007).

The pharmacological effects of *P. incarnata* include anticonvulsant, anti-asthmatic, antitussive, and anxiolytic activities (Grundmann, Wang, McGregor, & Butterweck, 2008). Although there is a vast use of *P. incarnata*, the pharmacological work on this plant has been insufficient and inconclusive in determining the mode of action of the plant as



Figure 1. *Passiflora incarnata* L. (Image source: http://www.wildflower.org/plants/result.php?id_plant=PAIN6)



Figure 2. Fruit of *Passiflora incarnata* L. (Image source: <http://www.duke.edu/~jspippen/plants/passiflora.htm>)



Figure 3. Juice with Passionflower

(Image source: <http://tastesfromaroundnz.co.nz/4-x-325ml-teza-peach-passionflower-juiced-teas.html>)

well as the phyto-constituents responsible for the anxiolytic and sedative effects of the plant (Soulimani, Younos, Jarmouni, Bousta, Misslin, & Mortier, 1997).

The passionflower fruit is widely eaten today and is used in juice drinks (**Figure 3**), beverages, baked goods, cereals, yogurt, ice cream, candy, jams, and jellies (Ngan & Conduit, 2011). It is currently used in complementary and/or alternative medicine for its treatment of anxiety, asthma, insomnia, nervousness, neuralgia and more (Tenney, 2007).

Botanical Description

Passiflora incarnata is an herbaceous perennial vine that climbs with the support of tendrils. Individual shoots are unclassified, grow up to ten meters long, and are usually branched. The plants often develop additional shoots from the underground roots and rhizomes. The shoots die in autumn,

and new shoots grow each spring from buds on rhizomes and roots that live over from one season to the next (McGuire 1999).

P. incarnata's wild growth, branching, and underground spreading can make it very difficult to manage in cultivation. The stems are not self-supporting, so plants must be bolstered in cultivation to protect the foliage and developing fruits from pests. The petioles, up to eight centimeters long, have two nectaries (gland that secretes nectar) attached at the base of the laminae (expanded part of a foliage leaf). Laminae of adult leaves are moderately to deeply three-lobed, and are 6-15 cm long along the mid vein. Two meristems (plant tissue that allow cells to differentiate and produce tissues and organs) in the axil of each leaf allows for the possible upper development into a branch, and the lower into a tendril, or a tendril and a flower (McGuire 1999).

Flowers are born individually on the stalks up to ten centimeters long. Three leaves, each bearing two nectaries, circle the base of the floral bud. Floral buds grow two to three centimeters long before opening. Open flowers are up to nine centimeters wide and have the complex floral structure typical of the *Passiflora* genus. The sepals and petals are white to pale lavender on their displayed surface. The prominent corona (crown) consists of five or six series of thin and flexible appendages. The outer two filaments are 10-20 mm long, colored white, pink, lavender, and/or purple, and variously banded. The remaining series of corona filaments are much shorter (two to four millimeters long) (McGuire 1999).

At maturity, fruits separate at the region of articulation on the peduncle, and the floral parts and a portion of the peduncle remain at the base of the separated fruit. The fruits are berries, oval in shape, and up to seven centimeters long. Immature fruits have smooth, green rings that at maturity

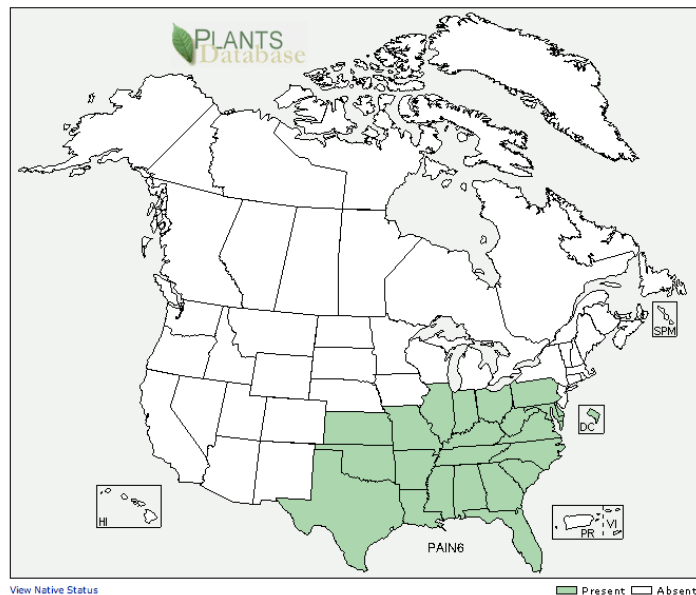


Figure 4. *Passiflora incarnata* is native to southeastern North America.

(Image source: <http://plants.usda.gov/java/profile?symbol=pain6>)

sometimes become wrinkled, yellow, and eventually brown. Some plants bear fruits with three longitudinal maroon stripes originating at the juncture of the peduncle and fruit and continuing down partially to the end of the fruit. Within the thin skin are three longitudinal parietal placentae, and the fruit interior contains up to 120 seeds, dark brown at maturity, four to five mm long, three to four mm wide, and individually enclosed. The arils (exterior covering) vary in size among fruits and contain an edible, aromatic, creamy yellow juice (McGuire, 1999).

P. incarnata can reproduce asexually from stem cuttings and root or rhizome fragments. Root or rhizome fragments four to eight cm long have nearly 100 percent germination when planted one cm deep, but shorter fragments have lower

germination percentages. Root or rhizome fragments lose their capability to grow, develop and even live very easily if they are not kept moist (McGuire, 1999).

There are four important aspects of *P. incarnata*'s reproductive biology that could affect fruit and seed set in cultivation. Firstly, *P. incarnata* is typically self-incompatible. Secondly, insect pollinators (generally *Xylocopa* spp.) are required to deposit compatible pollen on stigmas. Thirdly, flowers must have both male and female reproductive organs (hermaphrodites) to receive pollen, and plants vary hermaphroditic flower production in response to resource status. Finally, when pollinator visits are not frequent, seed set may cause a relatively long delay between flower opening and effect the way the plant bends (McGuire, 1999).

P. incarnata is a native of temperate and tropical North America (**Figure 4**). *P. incarnata* seeds occur in many human archaeological sites from the Late Archaic (3500- 800 B.C.E.) to Historic (1550-1800 C.E.) periods in the southeastern U.S., indicating that Native Americans were consuming the fruit. Moreover, seed abundance increases over time in the archaeological record. This suggests that human fruit consumption rose at this time. During the same time period, agriculture expanded in southeastern North America, and increased human consumption of *P. incarnata* fruits may indicate an increased cultivation of this plant. It is also possible that since *P. incarnata* prefers disturbed habitats, fruit consumption may have risen simply because the plant became more common, as it invaded the disturbed habitats associated with an expanding agriculture (McGuire, 1999).

Early European travelers in North America noted that Algonkian Indians in Virginia and Creek people in Florida ate *P. incarnata* fruit gathered from cultivated, semi-domesticated, or wild plants. The European settlers

themselves also consumed the fruit and praised its flavor (Dhawan, Dhawan, & Sharma, 2004). Since then, inhabitants of the U.S, as well as people globally, have continued to eat wild and cultivated *P. incarnata* fruits.

Traditional Uses

The discovery of seeds dating back to thousands of years from archaeological sites in North America provides evidence of the historic use of the fruit by the ancient Red Indians. Early European travels in North America (particularly Southeastern parts) documented the consumption of the fruit of *Passiflora* by the Algonkian Indians in Virginia and the Creek peoples in Florida. These fruits were eaten from cultivated as well as wild sources (Dhawan, Dhawan, & Sharma, 2004). The Native Americans also used passionflower as a tonic for bruises and injuries. The Aztecs used it as a sedative and for pain relief (Tenney, 2007).

The use of *Passiflora* as a medicine was documented for the first time in 1569 by Spanish researcher Monardus in Peru. The *Matrica Medica Americana*, published in Germany in 1787, mentions the use of *P. incarnata* to treat epilepsy for older people. An ancient report also describes its use in spasmodic disorders and insomnia in infants and the elderly (Dhawan, Dhawan, & Sharma, 2004).

P. incarnata is a popular traditional European remedy and a homoeopathic medicine for insomnia and anxiety. In North America, it has a history of use as a sedative tea. In America, it is used to treat diarrhea, dysmenorrhea, neuralgia, burns, hemorrhoids, and insomnia. In Brazil, *Passiflora* has been used as an analgesic, anti-spasmodic, anti-asthmatic, wormicidal, and sedative. In Iraq, it has been used as a sedative as well as a narcotic. In Turkey, *Passiflora* has been used to treat

dysmenorrhea, epilepsy, insomnia, neurosis, and neuralgia. It has been used to cure hysteria and neurasthenia in Poland. *P. incarnata* has also been used to treat morphine addiction in India (Dhawan, Dhawan, & Sharma, 2004).

The Houma, Cherokee and other Native American tribes used *P. incarnata* for food and medicinal purposes. In 1612, Captain Smith reported that Native Americans in Virginia planted the vines of *Passiflora* in order to produce the fruit of the plant. They were eaten raw, boiled to make syrup, and squeezed to make a drink from the juice. The roots were used in a tea infusion to treat boils, inflammation, and to cure liver problems. The plant was also used as a sedative to treat nervousness and hysteria (USDA).

The above ground (aerial) parts have been used as a sedative, anxiety reliever, pain reliever, as well as a convulsion preventative and reliever for epilepsy. Aqueous extract (extract prepared by evaporating a watery solution of the soluble properties to a semisolid or solid consistency) of *P. incarnata* roots has been used topically on ulcers and hemorrhoids. The whole plant has also been used in the treatment of insomnia, anxiety, and other central nervous system disorders (Dhawan, Kumar, & Sharma, 2001; Dhawan & Sharma, 2001). However, to date, there is little scientific validated evidence for the constituents of *P. incarnata* that are responsible for the sedative and anxiolytic effects (Ngan & Conduit, 2011).

P. incarnata is currently listed in the pharmacopoeias of Great Britain, United States, India, France, Germany, Switzerland and others. The active ingredients have not been conclusively defined. Most available data suggests flavonoids and indole alkaloids as possible active components (Elsas et al., 2010).

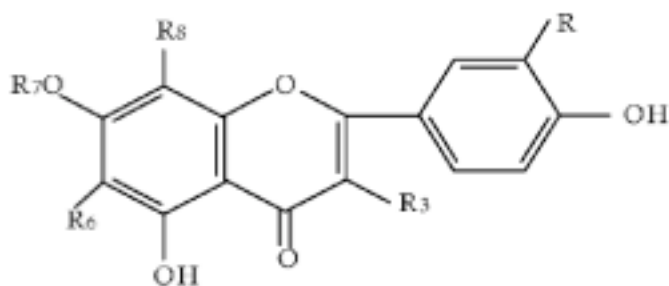


Figure 5. Flavonoid compound chemistry structure (Dhawan et al, 2004).

Passionflower fruit is widely eaten today and is used in juice drinks, beverages, baked goods, cereals, yogurt, ice cream, candy, jams, and jellies (Ngan & Conduit, 2011).

Chemistry and Pharmacology

The constituents of *Passiflora incarnata* include flavonoids, flavonoid glycosides, alkaloids, cyanogenic glycosides, carbohydrates, amino acids, benzopyrone derivatives and volatile constituents, as well as coumarins from the roots (Soulimani et al., 2007).

The main chemical constituents of *Passiflora incarnata* are flavonoids (0.25%). These include vitexin, isovitexin, orientin, isoorientin, apigenin, and kampferol, luteolin, quercetin, schaftoside, isoschaftoside (**Figure 5**). The greatest accumulation of flavonoids is found in the leaves (Dhawan, Dhawan, & Sharma, 2004). The simple indole alkaloids (0.1%) such as harman, harmin, harmalin, harmol, and harmalol are also active compounds (**Figure 6**). The medicinal extra of the plant has 10-20 ug/100 ml of harman and harmine. *P. incarnata* also contains the active compounds γ -benzo-pyrone

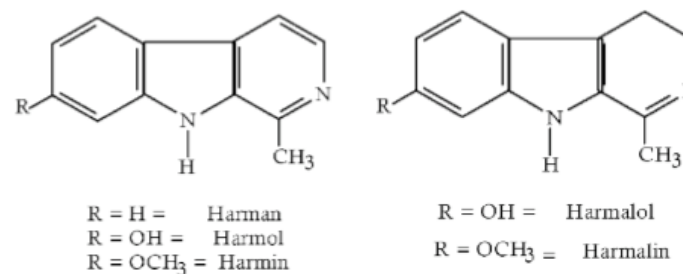


Figure 6. Indole alkaloids chemistry structure (Dhawan, 2004).

derivative maltol and ethyl-maltol (0.05%) (**Table 1**).

Other constituents include carbohydrates such as raffinose, sucrose, d-glucose, and d-fructose; essential oil with hexanol (1.4%), benzyl alcohol (4.1%), linalool (3.2%), 2-phenylethyl alcohol (1.2%), 2-hydroxy benzoic acid methyl ester (1.3%), carvone (8.1%), trans-anethol (2.6%), eugenol (1.8%), isoeugenol (1.6%), β -ionone (2.6%), α -bergamotol (1.7%) and phytol (1.9%). The constituents responsible for the odor are limonene, cumene, prezizaene, zizaene, amino acids; and cyanogenic glycoside gyanocardin (Dhawan, Dhawan, & Sharma, 2004).

The pharmacological effects of *P. incarnata* include anticonvulsant, anti-asthmatic, antitussive, and anxiolytic activities (Grundmann et al., 2008). Although there is a vast use of *P. incarnata*, the pharmacological work on this plant had been insufficient and inconclusive in determining the mode of action of the plant as well as the phyto-constituents responsible for the anxiolytic and sedative effects of the plant (Soulimani et al., 1997).

Researchers have proposed different theories on the bioactive chemicals of *P. incarnata*. However, there has been no

Active Compounds
Flavonoids (0.25%)
Vitexin
Isovitexin
Orientin
Isoorientin
Apigenin
Kampforel
Luteolin
Quercetin
Schaftoside
Isoschaftoside
Indole Alkaloids (0.1%)
Harman
Harmin
Harmalin
Harmol
Harmalol
Maltol and ethyl-maltol (0.05%)

Table 1. Constituents of *Passiflora incarnata*.

consensus regarding the exact mode of its pharmacology. Some researchers have highlighted the role of the flavonoid chrysin and even the b-pyrone derivative maltol to be responsible for the CNS effects of the plant (Movafegh, Alizadeh, Hajimohamadi, Esfehiani, & Nejatfar, 2008). The indole alkaloids and flavonoids have been speculated to be the main bioactive constituents of the plant. They are believed to be so due to their MAO enzyme inhibiting properties (Dhawan, Dhawan, & Sharma, 2004). Some findings have attributed the sedative and anxiolytic activities in *P. incarnata* to benzodiazepine and GABA receptors in the body. By increasing levels of GABA in the brain, lowering the activity of some brain cells, one feels more relaxed (Dhawan, Kumar, & Sharma 2001). Yet contrary to many of these reports, the

inclusive pharmacological studies on *P. incarnata* by Soulimani et al. (1997) ruled out the main phyto-constituents of flavonoids and indole alkaloids as the sources of psychotropic activity. Although the sedative and anxiolytic properties of the plant were shown in their studies, the mode of action of both the aqueous and hydroalcoholic extracts were not found.

Biological Activity

In vitro

Passionflower fruit, which is used to produce mark, jams, and juices, has shown to contain a considerable amount of lycopene. This finding shows that passionflower fruit products may serve as a good alternative for those people who do not or cannot eat tomatoes and tomato products (which is known to have a high amount of lycopene). Lycopene, a carotenoid antioxidant, has been shown to protect against oxidative damage in many epidemiological and experimental studies. In addition to its antioxidant activity, other metabolic effects of lycopene have also been demonstrated (Mourvaki, Gizzi, Rossi, & Rufini, 2005).

Dhawan, Kumar, and Sharma (2001) show that roots of *P. incarnata* do not have anxiolytic effects, but act as natural adulterants and should be separated from the aerial parts prior to any pharmacological, phytochemical and standardization studies on *P. incarnata*. The presence of flowers along with leaves and stems is also undesirable. Using the whole plant for pharmacological studies (both commercial and medicinal purposes) is not optimal for finding the CNS effects of *P. incarnata*. Although the separated leaves afford the best possible results, the selection of the entire aerial parts (except for the flowers) may prove to be the best approach for

identifying the bioactive parts of the *P. incarnata* plant.

In vivo

Studies in animal models show efficacy of *Passiflora incarnata* extracts and flavonoid fractions against pentylenetetrazol (PTZ) induced seizures. It is possible that *Passiflora* inhibits the benzodiazepine site antagonist Ro 15-1788, suggesting the involvement of GABAA receptors. Flavonoids bind to the benzodiazepine site of the GABAA receptor, but appear to alter GABAA and also GABAC receptor currents by a different mechanism than benzodiazepines (Elsas et al., 2010). This finding suggests that the anticonvulsant activity of the plant is attributed to the benzodiazepine and GABA receptors mediated biochemical processes in the body (Dhawa, Dhawa, & Sharma, 2004).

Soulimani et al. (1997) examined the potential anxiolytic and sedative effects of aqueous and hydroalcoholic extracts of *Passiflora* on mice. The aqueous extract appeared to induce sedative effects at 400 and 800 mg/kg. It reduced activity in the staircase and free exploratory tests. The hydroalcoholic extract did not have such sedative effects, rather, it appeared to enhance activity and have an anxiolytic effect at 400 mg/kg.

Singh, Singh, and Goel (2001) used hydroethanolic extracts of *Passiflora* to explore the anticonvulsant effects of the plant. Treatment with the extract significantly decreased seizure severity at 300 and 600 mg/kg. This finding suggests that the presence of flavonoids, which act by agonizing the GABA-benzodiazepine receptor may be responsible for the anticonvulsant activity. Since depression in the mice was induced by seizures, the anti-depressive effect can be due to the suppression of seizures.

In Grundmann et al. (2008), oral administration of an extract

prepared from the herb of *Passiflora incarnata* induced an anxiolytic-like effect in mice, since it increased the number of entries and the time spent in open arms in the EPM test at a dose of 375 mg/kg. Although the anxiolytic effects of various extracts from *Passiflora* have been demonstrated in animals and in humans, the mode of action and the identity of the active constituents of the different *Passiflora* species remained unclear.

In Dhawan and Sharma (2001), the methanol extract of the leaves of *P. incarnata* was shown to be significantly active in suppressing the SO₂-induced cough in mice. These results provide evidence for the folklore claims on the effectiveness of the plant in managing “tough” cough conditions. Moreover, this finding showed that *P. incarnata*, having no reports to possess an addictive quality, could be an optimal alternative to cough-suppressants opiates, which have several negative effects including CNS depression, dryness of the mouth, blurred vision, and severe gastrointestinal effects.

The ethanolic extract of *P. incarnata* showed anti-inflammatory properties at a dose of 125 to 500 mg/kg in rats when inflammation was induced by cotton pellets, dextran and carrageenin (Borrelli, Pinto, Izzo, Mascolo, Cappaso, Mercati, Toja, & Autore, 1996). This provides evidence for the plant’s anti-inflammatory properties.

Clinical Studies

Although the effects of *Passiflora incarnata* have been studied less in humans, Akhondzadeh, Naghavi, Vazirian, Shayeganpour, Rashidi, and Khani (2001) and Movafegh, Alizadeh, Hajimohamadi, Esfehiani, and Nejatfar (2008), are two clinical trials that have demonstrated *Passiflora*’s efficacy in the treatment of anxiety. The findings of the studies

attribute the effectiveness of the treatment to the anxiolytic and sedative actions of the passionflower extract (Ngan & Conduit, 2011). Akhondzadeh, Naghavi, Vazirian, Shayeganpour, Rashidi, and Khani (2001) also explored the use of the plant in the treatment of opiate withdrawal and attention-deficit hyperactivity disorder (ADHD).

Akhondzadeh et al. (2001) study on anxiety used the Hamilton anxiety rating scale to assess the anxiety levels of 36 outpatients diagnosed with generalized anxiety disorder. The anxiety scores indicated that passionflower (45 drops of *P. incarnata* extract per day) was just as effective as the positive control condition (30 mg of oxazepam per day) in reducing anxiety levels at the end of the 28-day treatment. In another study, Movafegh et al. (2008) used a numerical rating scale to assess the anxiety levels of 60 ambulatory surgery patients during the 90 minute period between premedication (placebo or 500 mg of passionflower tablets) and surgery. They found that the group that received passionflower had significantly lower anxiety ratings than the placebo group after premedication. These clinical findings indicated that *P. incarnata* may be effective in reducing short term as well as long term, heightened anxiety (Ngan & Conduit 2011).

Akhondzadeh et al. (2001) study on opiate withdrawal randomly assigned 65 opiate addicts to treatment of *Passiflora* extract and clonidine tablet or a placebo and clonidine tablet. Although both were effective in treating the physical symptoms of withdrawal, *Passiflora* in addition to clonidine had a significant increase in managing mental symptoms than clonidine on its own. These results suggest that *Passiflora* extract may be effective for the management of opiate withdrawal.

Contraindications

The FDA lists *Passiflora incarnata* as a safe herbal sedative. Since the mode of CNS depressant activity has not been conclusive, it is advised to take caution when taken with other CNS depressants or stimulants. The neuromuscular relaxing effects of the extract have synergetic effects with aminoglycoside antibiotics such as clindamycin (Dhawan, Dhawan, & Sharma, 2004).

The use of the plant up to one month is considered safe. However, negative affects associated with the plant include dizziness, confusion, sedation, and a lack of coordination (Tovar & Petzel, 2009).

There has been a report about a woman who developed severe nausea, vomiting, weakness, drowsiness, slower heart rate, and ventricular arrhythmia, after two days self-administration of an herbal remedy containing *P. incarnata* (Fisher, Purcell, & LeCouteur, 2000). A case of hypersensitivity with skin vasculitis (inflammation of blood vessels) and hives after ingestion of tablets containing *Passiflora* extract has been reported (Movafegh et al., 2008). Five patients have been reported to suffer altered consciousness after taking an herbal preparation from *P. incarnata* called Relaxir (Dhawan, Dhawan, & Sharma, 2004).

In an *in vivo* study, no acute toxicity was observed after an injection into the peritoneum of mice in doses larger than 900 mg/kg (Movafegh et al., 2008).

Passiflora may induce uterine contraction so its use is contraindicated during pregnancy (Movafegh et al., 2008). The use of *Passiflora* is also highly discouraged in lactating mothers. There is also a severe contraindication of the plant with the synthetic MAO inhibitor drug Phenelzine (NARDIL) (Dhawan, Dhawan, & Sharma, 2004).

Current Use in Allopathic and CAM Therapies

Passiflora incarnata is currently used primarily to treat alcoholism, asthma, insomnia, nervousness, anxiety, eye tension, headaches, menopausal symptoms, and neuralgia (acute pain). Its secondary applications include bronchitis, depression, muscle spasms, seizures, convulsions, diarrhea, epilepsy, pain (for example, menstrual) and restlessness (Tenney, 2007). It is available as a liquid extract, capsule, tea, and tincture (**Figure 7**). The recommended dose for anxiety is 45 drops (90mg) daily (Tovar & Petzel, 2009).

Gupta, Kumar, Chaudhary, Maithani, and Singh (2011) showed the anti-diabetic properties of the *Passiflora incarnata*. This study explored the hypolygemic and hypolipidemic effects of the methanolic extract of *P. incarnata* on induced diabetic mice. At a dose of 200 mg/kg, the mice had significantly increased tolerance in glucose. This depicts that the leaf can be a good alternative medicine for diabetes as it has significant anti-hyperglycemic activity in streptozocin-induced diabetic mice.

Frontier markets the herbal supplement to naturally promote relaxation. To make the tea, you boil 1-2 teaspoons of the herb, cover it, and let it seep for 5 to 10 minutes. Gaia markets the passionflower to support the nervous system, to promote calm and relaxation, and to support healthy sleep. Its recommended dose is 1 capsule, 2 times daily between meals. Gaia also makes an extract of the passionflower, and its suggested use is 40-60 drops in a small amount of water, three times daily between meals.

The Passionflower fruit itself is eaten globally and is widely used in juice drinks, beverages, baked goods, cereals, yogurt, ice cream, candy, jams, and jellies (Ngan & Conduit, 2011).



Figure 7. Herb, extract, and capsule form of *Passiflora incarnata*. (Photo by Ronni Shalem).

Discussion

Passiflora incarnata was an important plant for the Native Americans in traditional medicine. It served many purposes including food and beverage as well as having medicinal properties. After being introduced to the Europeans, *P. incarnata* became a popular traditional European remedy and a homeopathic medicine for insomnia and anxiety. It is now used all over the world. This is evident by the fact that it is listed as an official plant drug in the British Herbal Pharmacopoeia (1983), Homeopathic Pharmacopoeia of India (1974), United States Homeopathic Pharmacopoeia (1981), Pharmacopoeia Helvetica (1987), as well as the pharmacopoeias of Egypt, France, Germany, and Switzerland (Dhawa, Dhawa, & Sharma, 2004).

The importance of the plant is exemplified in its use all over the globe. In Brazil, *Passiflora* has been used as an analgesic, anti-spasmodic, anti-asthmatic, wormicidal, and sedative. In Iraq, it has been used as a sedative as well as a narcotic. In Turkey, *Passiflora* has been used to treat dysmenorrhea, epilepsy, insomnia, neurosis, and neuralgia. It has been used to cure hysteria and neurasthenia in Poland. *P. incarnata* has also been used to treat morphine addiction in India (Dhawan, Dhawan, & Sharma, 2004).

Almost every component of the plant has shown to have some form of pharmacological activity. There have been many studies on the plant both in vivo and in vitro, although mostly *in vivo*, to explain the chemical activities of *P. incarnata*. Studies in animal models show efficacy of *Passiflora* extracts and flavonoid fractions against pentylentetrazol (PTZ) induced seizures. In Grundmann et al. (2008), *P. incarnata* extract induced an anxiolytic-like effect in mice when administered orally. In Dhawan and Sharma (2001), the methanol extract of the leaves of *P. incarnata* was shown to be significantly active in suppressing the SO₂ -induced cough in mice. Although the effects of *P. incarnata* have rarely been studied in humans, two clinical trials have demonstrated its efficacy in the treatment of anxiety. It has also been shown to be effective in opiate withdrawal. *P. incarnata*, serving so many medicinal purposes, has much to contribute to our world of medicine.

In the future of our medical sphere, as people continue to consider holistic lifestyles of alternative medicine, *P. incarnata* will be an important plant to turn to for its variety of medicinal applications. Its various uses to treat conditions from fevers to neuralgia and seizures to diarrhea, the multiplex applications of the plant are pretty remarkable. For someone who is not comfortable taking synthetic drugs or synthetically derived drugs to treat medical ailments such as

anxiety and insomnia, they can turn to *P. Incarnata* as a natural remedy. In addition, people can incorporate the passionflower fruit in their diets for its lycopene content, which is extremely notable for its antioxidant activity. To do so, the fruit can simply be blended into a juice.

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Persea americana Mill., Lauraceae

Corinne Grady

Introduction

Persea americana Mill. of the Lauraceae family is commonly known as the avocado tree. This edible fruit is also called the alligator pear, el aguacate in Spanish, and e li in Chinese ("Persea americana (Mill)"). The English name avocado is derived from the Spanish aguacate, which in turn comes from the Nahuatl, or Aztec, name ahuacatl (Popenoe, Zentmyer, & Schieber, 1997). As depicted in **Figure 1**, *P. americana* is a tall, green leafy tree with single seeded fruit. The plant originates from the tropical and subtropical climate regions of Central and South America, where indigenous people first cultivated it. For thousands of years, the fruit, leaves, and seeds of the avocado tree have been used as a food source and for medicinal purposes. The uses of *P. americana* range from emollients for the skin to treatments for hypertension. The main chemical constituents that lend to the activity of avocado are aliphatic acetogenins, flavonoids, terpenoid glycosides, and furan-ring derivatives (Yasir, Das, & Kharya, 2010). Today, the flesh of the fruit is cultivated and consumed worldwide and is generally recognized as safe as a food source (Morton, 1987).

Botanical Description

The genus *Persea* contains 8 species, which are all trees or shrubs ("Persea americana Mill, avocado,"). A polymorphic tree native to Central America, *Persea americana* has a variety of subspecies, which include the commercial varieties of avocado. The varieties of *P. americana* are *americana*, *drymifolia*, *floccosa*, *guatemalensis*, *nubigena*, *steyermarkii*,



Figure 1 *Persea americana* Mill (Source: <http://www.public.asu.edu/~camartin/plants/Plant%20html%20files/perseaspecies.html>)

tolimanensis, and *zentmyerii*. Each subspecies has distinct botanical features as described in **Table 1**. Three of these varieties (the West Indian, Mexican, and Guatemalan avocado) have been domesticated and are used commercially for their fruits, which all slightly differ in size, shape, and color. The necessary climate and soil type for each subspecies varies. For example, the Mexican variety is the hardiest and can survive in the coldest weather (25°F). The Guatemalan variety

Subspecies	Common name	Distinctive botanical features		
		Tree	Leaf	Fruit
<i>P. americana</i> var. <i>americana</i>	West Indian avocado	Small to large, low elevation	N/A	10-15cm long green mature fruit with flesh more than 1 cm thick
<i>P. americana</i> var. <i>drymifolia</i> (rare in Guatemala, common in Mexico)	Mexican avocado	Small to large	N/A	<5cm long purple-black mature fruit with little flesh, anise flavored
<i>P. americana</i> var. <i>guatemalensis</i>	Guatemalan avocado	N/A	N/A	Nearly round fruit >4cm diameter, 2-3 cm of flesh, rough to smooth exocarp, green to black
<i>P. americana</i> var. <i>floccosa</i>	N/A	Native to eastern Mexico	Young growth of floccose pubescent	Thick green to black exocarp, not much longer than broad
<i>P. americana</i> var. <i>nubigena</i>	N/A	N/A	Secondary veins 30-50° divergent, glaucous	Thick green to black exocarp, little flesh <4cm diameter
<i>P. americana</i> var. <i>steyermarkii</i> (rare)	N/A	N/A	Secondary veins 45-75° divergent, glabrous	Thick green to black exocarp, little flesh <4cm diameter
<i>P. americana</i> var. <i>tolimanensis</i>	N/A	Branching begins high on trunk	Dull foliage	Round to oblong fruit 6-8cm diameter, bitter taste, irregular rough green exocarp
<i>P. americana</i> var. <i>zentyerii</i> (very rare)	N/A	N/A	N/A	3.5-5cm diameter, little flesh, thick green to black exocarp covered with corky ridges

Table 1: Key features of the subspecies of *P. americana* (Whiley et al., 2002)

originated in the subtropical highlands of Central America and while not as hardy as the Mexican variety, it is tougher than the West Indian race, which only grows in tropical or near tropical climates like southern Florida and Puerto Rico.

Although the avocado tree needs a particularly humid and non-windy climate, it can grow in an assortment of different soil types. Some soil types include red clay, volcanic soil, sand, limestone, and slightly alkaline soils. The pH level preferred by *P. americana* is between 6 and 7, however avocados in southern Florida can grow on land with pH levels between 7.2 and 8.3. Good drainage is also essential for tree growth. The trees can grow up to 30 meters tall with leaves up to 20 centimeters long and 24 centimeters wide. The trees are almost evergreens, only losing their leaves briefly during dry

seasons. The leaves are glossy and dark green on top with a paler bottom surface. They vary from oval to oblong and rounded to obtuse in shape. The flowers of *P. americana* are small in comparison; only reaching from a few millimeters to a couple of centimeters long. They are small, yellow or pale green in color, and do not have petals. Instead, the flowers have sepals, whorls of perianth lobes and nine stamens (**Figure 2**). The female and male organs of the flower do not operate simultaneously. Unlike all other flowering plants, the avocado's flowers first function as only female – accepting



Figure 2. Avocado Flower (Source: <http://www.doyletics.com/images/avocflwr.jpg>)

pollen but not producing any from their stamen. This stage only lasts for two to three hours and is the only time in which sperm from another flower can fertilize the egg. Bees and sometimes other large insects are the pollinators for the avocado flower in addition to its self-pollination capabilities. Once the two to three hours have passed, the flower's sepals close for about twenty-four hours. When the flower reopens, it sheds pollen rather than receiving it until the flower closes again. This second closing is permanent and if fertilization is successful, an avocado will begin to grow. Cross pollination is able to occur because every plant has two different varieties of flower – the A type and the B type. Usually, the A type flowers open as female in the morning and are male the following afternoon while the B type do the opposite so that there is



Figure 3. A single fruit on a *P. americana* tree (Source: ("Persea americana Mill, avocado,"))

pollen to fertilize the female flowers during both parts of the day. When temperatures fall below 70°F, however, the flowers' cycles become irregular and the plant produces less fruit.

In general, *P. americana* produce fruit, called avocados (**Figure 3**). These single seeded berries range in size from 3.5 cm to 20 cm long, can have smooth to rough skin, and vary in color from green to purple-black. The fruit does not ripen until removed from the tree due to inhibition from the stem. Some related species include *Persea schiedeana* (Lauraceae) and *Beilschmiedia anay* (Lauraceae). These are both trees native to Central America. They can grow up to 20 meters high, which is slightly shorter than *P. americana*. Both produce fruit similar to varieties of the avocado, however, their flowers are very different. *P. schiedeana* produces yellow-green, downy flowers with stamens that redden over time. *B. anay* produces 5-inch long green flowers. The fruit of *P. schiedeana* is marketed locally while the fruit of *B. anay* is not (Bergh, 1973; Morton, 1987; Whiley, Schaffer, & Wolstenholme, 2002).

Traditional Uses

Food Uses

Avocados have been used as a food source in the Americas, particularly in Central America, for approximately 10,000 years. The three types of edible avocados consumed by the indigenous people are *Persea americana* var. *drymifolia*, *P. americana* var. *americana*, and *P. americana* var. *guatemalensis* (Williams, 1977). These three subspecies were selected and cultivated by indigenous populations of Mexico, the Pacific coast of Central America, and Guatemala respectively (Whiley et al., 2002). In addition, avocados were intentionally taken from their centers of origin to other places throughout Central and South America for cultivation purposes even before Europeans landed in the Americas. Evidence for the cultivation of avocado trees was discovered in excavations in Peru which revealed avocado remains dating back to 4000BC (Whiley et al., 2002). The Aztec people in

Central America used avocado, or ahuacatl, in the dish ahuacamulli, which is now known as guacamole. This term “mulli” means sauce or soft dish in the Nahuatl language. So the Aztec compound word for guacamole is a description of the dish, which is made by mashing up the avocado fruit into a soft paste and adding other ingredients. Ahuacachiualloti, meaning avocado oil, was also used by Aztec people thousands of years ago (Popenoe et al., 1997). Indigenous American peoples also eat avocados whole with salt and tortillas. Today, avocados are served with salads, in sandwiches, and are added to hot dishes just before serving. The avocado becomes very bitter when cooked due to a significant amount of tannins in the flesh so the fruit is normally served cold. In Brazil, New Zealand, Hawaii, and Java the avocado is treated more like a fruit than a vegetable like in the Americas. The fruits are used in milkshakes, ice creams, and fruit salads sweetened with sugar (Morton, 1987).

Ethnomedicinal Uses

P. americana has been, and continues to be, used for a variety of ailments as a traditional medicine. The leaves of *P. americana* are used in traditional medicine to treat hypertension in Trinidad and Tobago (Lans, 2006). In Togo, a decoction of *P. americana* leaves and *Theobroma cacao* leaves are taken orally as an antihypertensive agent. In addition, a combination of *Lippia multiflora* leaves, *Stachytarpheta angustifolia* leaves, *Allium sativum* bulbs and *P. americana* fruit are made into a powder and taken orally for the treatment of hypertension (Karou et al., 2011). In the Philippines, the seeds or a decoction of *P. americana* are used to relieve toothaches by applying them to tooth decay (Lewis & Elvin-Lewis, 2003). In the Dominican Republic, the seeds are fried and mashed along with several other plants to treat

lice (Lewis & Elvin-Lewis, 2003). Avocado are also used to treat snakebites through neutralizing the hemorrhagic effect of snake venom (Lewis & Elvin-Lewis, 2003).

Other Uses

Different parts of *P. americana* are utilized for nonfood and non-medicinal purposes. For example, the bark of *P. americana* is used to set the color of dyes in Guatemala. Wood from avocado trees is used in construction. During the time of the Spanish conquistadores, documents were written with the red-brown ink expelled from avocado seeds (Morton, 1987). In cosmetics, avocado oil is used as an emollient and sunscreen (Swisher, 1988).

Chemistry and Pharmacology

The main chemical components that have been identified in *Persea americana* include alkanols (or aliphatic acetogenins), flavonoids, terpenoid glycosides, furan-ring derivatives and a coumarin. These chemical groups all contain different functionality, which enable diverse biological activity (Yasir et al., 2010). There are over six hundred biological activities known for the compounds identified in *P. americana* (Duke, 2012). As described in **Table 2**, most of the known compounds in avocados have multiple activities ranging from antibacterial and antiviral to hypotensive and antidiabetic effects (Duke, 2012). Persin, **Figure 4**, is an alkanol constituent of avocado leaves that has been studied rather extensively. Persin was first studied due to its observed toxic effects on animals, especially among lactating mammals (Oelrichs et al., 1995). Later research found that persin has *in vitro* activity against breast cancer, as later described (Butt et al., 2006). Other major components of *P. americana* fruit are

lipids. With up to 864,000 ppm in the fruit, fat makes up a significant portion of avocado chemistry (Duke, 2012). The main form of glycolipids and phospholipids in *P. americana* are oleic and linolenic acids. There is a different composition of the lipids in the fruit and in the seed; the most significant difference being a higher oleic acid content in the fruit compared to the seed (Pacetti, Boselli, Lucci, & Frega, 2007). While many of the chemicals in *P. americana* are well understood and defined in terms of their biological activity, there are even more compounds with unknown activity and more studies are needed to elucidate a fuller picture of the avocado's chemical and biological effects within the human body.

Biological Activity

There is extensive biological activity among the constituents of *Persea americana*. Several studies have examined the effects of various extracts of different parts of *P. americana*, both *in vivo* and *in vitro*. These studies can be classified into several categories based on the type of activity found, including analgesic, anti-inflammatory, anticonvulsant, anticancer, antioxidant, and hypotensive activity, among others.

Analgesic and anti-inflammatory

Adeyemi et. al found in an *in vivo* study with mice, that an aqueous extraction of dried avocado leaves, which were processed through boiling, filtration, and drying, had significant analgesic and anti-inflammatory effects. For example, a 1600mg/kg dose of the extract inhibited acetic acid-induced pain (evaluated based on the writhes of the mice) equivalent to a 100mg/kg dose of acetylsalicylic acid. An 800mg/kg dose inhibited pain response to heat equivalent to

Plant Part	Antibacterial	Anticancer	Antioxidant	Colorant	Multiple activities ¹	Unknown
	Ascorbic-acid ² Proanthocyanidins ²	Alpha-carotene ² Alpha-tocopherol ² Folic acid ² Linoleic acid ² Lutein ² Oleic acid ² Serine	Alanine ² Histidine ² Lecithin ² Manganese ² Methionine ² P-coumaric acid ² Palmitic acid ² Riboflavin ² Tartaric acid ² Threonine ² Tryptophan ²	Alpha-cryptoxanthin ² Violaxanthin ²	Alpha-tocopherol, arginine, aspartic-acid, beta-carotene, biotin, boron, caffeic acid, calcium, carnitine, chlorogenic acid, copper, fiber, folacin, glutamic acid, glycine, glycerol, iron, isoleucine, lysine, magnesium, mufa, niacin, nonacosane, pantothenic acid, phyloquinone, phytosterols, potassium, propionic acid, pufa, pyridoxine, salicylates, serotonin, stearic acid, thiamin, tyramine, tyrosine, valeric acid, valine, zinc	1-acetoxy-2,4-dihydroxyheptadeca-16-ene, abscisic acid, ash, carbohydrates, d-erythro-d-galacto-octitol-d-erythro-l-gluco-nonulose, d-glycero-d-galacto-heptitol, d-glycero-d-galacto-heptose, d-glycero-d-galacto-octulose, d-glycero-d-manno-octulose, d-mannoketoheptose, d-taloheptulose, dopamine, fat, hentriacosane, heptacosane, isolutein, leucine, linolenic acid, myo-inositol, p-coumaryl-quinic acid, pentacosane, phenylalanine, phytate, proanthocyanidin-a-2, proline, sfa, triacosane avocadene, avocadenofuran, avocadenone-acetat, avocadineofuran, avocadyne, avocadynofuran, avocadynone-acetate, avocatin, d-arabitol, galactitol, isoavocadienofuran, perseitol N/A n-caffeoylputrescine N/A 24-methylene-cycloartenol Feruloyl-putresine
Fruit ³	N/A	4,8-biscatechin	N/A	N/A	N/A	
Seed ⁴	Pinene ²	N/A	Tannin ²	N/A	anethole, estragole, beta-sistosterol, methyl-chavicol, quercetin, N/A	
Leaf ⁵	N/A	N/A	N/A	N/A	N/A	
Flower	N/A	N/A	N/A	N/A	Anethole Estragole	
Bark	1,2,4-trihydroxyheptadeca-16-ene Cycloartenol	Catechol ²	Campesterol ² Cholesterol	Epsilon-carotene	Phosphorus Subaphyllin	

Table 2: Chemical composition of *Persea americana* Source: (Duke, 2012)

1. Compounds with 3 or more biochemical activities are listed here. The activities for an individual compound may include those listed in the table or any of the 630 known activities for *P. americana* compounds.
2. Compounds also have multiple biological activities, however they are listed under one of their significant activities.
3. Also contains: citrostadienol which is an antirheumatic; /cryptoxanthin which is antimutagenic; cystine which is antihomocystinuric; palmitoleic acid which makes soap; sodium; vit-B6; and vit-D.
4. Also contains volemitol, which is a sweetener.
5. Also contains paraffin, an emollient.

a 2mg/kg dose of morphine. Swelling and inflammation induced by carrageenan, a compound extracted from seaweed, was also inhibited by a previously administered dose of the extract (Adeyemi, Okpo, & Ogunti, 2002). In another study, polyhydroxylated fatty alcohols from avocados were found to suppress inflammatory response (Rosenblat et al., 2011).

Anticonvulsant

P. americana aqueous leaf extracts were tested on mice for the extract's ability to delay and reduce seizures induced by pentylenetetrazole, picrotoxin and bicuculline. In each type of induced seizure, the aqueous leaf extracts yielded positive results indicating that the extract has some effect on GABAergic action and/or neurotransmission involved with seizures (Ojewole & Amabeoku, 2006).

Anticancer

Extracts of avocado have been found to inhibit cancer growth and have some chemo-protective effects. In one study, a chloroform soluble extract of the avocado fruit flesh was found to have activity inhibiting oral cancer cell growth. The mechanism of action of two aliphatic acetogenin compounds isolated from this extract was found to involve the blocking of phosphorylation of protein kinases and growth factor

receptors in the EGFR/RAS/RAF/MED/ERK1/2 cancer pathway. The two compounds work together to produce this anticancer effect (D'Ambrosio, Han, Pan, Kinghorn, & Ding, 2011). Another study investigated the carotenoid content of avocado fruit and found that an acetone extract of the fruit inhibited prostate cancer cell growth *in vitro*. The main carotenoid in the extract was lutein, at 70%, but alone it did not have the anticancer effects that the extract possessed. A mechanism of action involving the monounsaturated fat content of avocado and the relationship with absorption of the phytochemicals into the bloodstream was proposed but has yet to be verified (Lu et al., 2005). Another chemo-protective effect was discovered with avocado fruit extracted using methanol. This effect works with regard to the anticancer drug cyclophosphamide, which may have genotoxic effects on healthy cells (Paul, Kulkarni, & Ganesh, 2011). A study on the effects of persin found that both *in vivo* and *in vitro* the compound is cytotoxic for mammary epithelium for mice and human breast cancer cells, respectively. Applications of persin to human breast cancer cells *in vitro* result in a halt of the cell cycle, preventing further division, and apoptosis due to interference with microtubules (Butt et al., 2006).

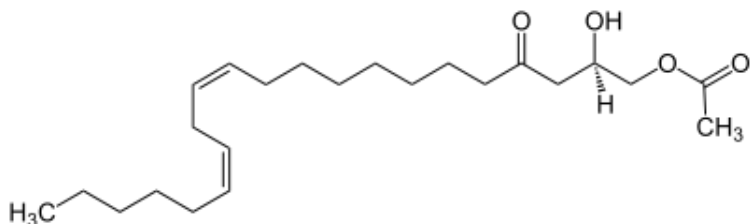


Figure 4 Chemical Structure of Persin. (Source: http://upload.wikimedia.org/wikipedia/commons/thumb/f/f6/Persin_Structural_Formulae_V.1.svg/400px-Persin_Structural_Formulae_V.1.svg.png)

Antioxidant

P. americana contains many chemical compounds that have antioxidant capabilities. Wang et al. investigated the antioxidant capacity of avocado along with its phenolic content and proyanidins. The seeds had the highest antioxidant capacity and proyanidins and phenolic content while the fruit flesh had the lowest antioxidant capacity (Wang, Bostic, & Gu, 2010). Another study found that the catechins, proyanidins and hydroxycinnamic acids in the peels and seeds were present in larger amounts and were more antioxidant *in vitro* compared to those constituents in the pulp (Rodríguez-Carpena, Morcuende, Andrade, Kylli, & Estévez, 2011). An *in vivo* study on rats found that a methanol extract of avocado probably has an antioxidant effect on intracellular defense mechanisms used to cope with increased oxidant stress. This mechanism supports the finding that the extract could protect against oxidative stress and paracetamol toxicity by increasing the activity of the particular defense enzymes during hepatic damage (Yasir et al., 2010).

Antiulcer

An *in vivo* study of albino rats, it was found that the rats treated with an aqueous leaf extract of *P. americana*

experienced a significant and dose-dependent antiulcer effect when ulcers were induced (Yasir et al., 2010).

Antiviral

An infusion and an ethanol extraction of *P. americana* were compared regarding their inhibitory effects on viral replication. The infusion had activity against the three viruses AD3, HSV-1, and ADV whereas the ethanol extract was only active against HSV-1 and ADV (Yasir et al., 2010).

Hypoglycemic

In one study, a reduction in blood glucose level was found to occur when aqueous leaf extract of avocado was administered to normal rats (Yasir et al., 2010).

Hypotensive

Dose-dependent hypotensive activity was discovered for intravenous doses of *P. americana* aqueous and methanol leaf extracts in normotensive rats. Doses used ranged from 6.25mg/kg to 50mg/kg with those above 12.5mg/kg having hypotensive activity when compared to the control group (Adeboye, Fajonyomi, Makinde, & Taiwo, 1999).

Vasorelaxant

There are several different mechanisms of action proposed for the vasorelaxant effects of aqueous *P. americana* extracts. In an *in vivo* study examining the aortas of rats, it was found that the vasorelaxation response occurs due to the administration of the extract and is concentration related (Yasir et al., 2010).

Wound healing

Normally, 17 days are required for an excision wound to heal in rats. However, in a study by Nayak et al. complete healing of an excision wound occurred in 14 days after oral or topical treatment with *P. americana* fruit extract at 300mg/kg/day (Nayak, Raju, & Chalapathi Rao, 2008).

Clinical Studies

Although there has been extensive research into the biological activity of *Persea americana*, few clinical studies have been done examining the avocado's effects in humans. There have been four clinical studies investigating the use of the non-soap-forming, or unsaponifiable, extract of *P. americana* combined with the unsaponifiable extract from soybeans, known as avocado/soybean unsaponifiables (ASUs), to treat osteoarthritis. These studies focused on osteoarthritis of the hip and/or knee. In two of the studies, 300mg of the extracts taken each day for three months resulted in lower use of non-steroidal anti-inflammatory drugs for pain and inflammation. There was no significant difference found between 300 and 600mg/day doses. In a 6-month study, a two month delayed onset of effects was observed and effects continued for two months past the end of treatment. No long-term effects on the prevention of joint narrowing were observed. The fourth study investigated effects of ASUs on hip osteoarthritis with two years of treatment. With a 300mg/day treatment, no statistically significant difference was found between the ASUs and placebo concerning levels of pain and NSAID usage after one year. Despite these negative results, ASUs may have symptom-relieving effects for the most severe hip

osteoarthritis. All of these findings require further study for confirmation, whether positive or negative, concerning ASUs ability to modify osteoarthritis symptoms (Ameye & Chee, 2006).

Research investigating the antidiabetic and cholesterol-lowering capabilities of *P. americana* has found positive results in clinical trials. For example, a study by Lerman-Garber et al found that a diet high in monounsaturated fatty acids from avocados and olive oil for patients with non-insulin-dependent diabetes patients resulted in minor decrease in cholesterol and a 20% decrease in plasma triglycerides (Lerman-Garber, Ichazo-Cerro, Zamora-González, Cardoso-Saldaña, & Posadas-Romero, 1994). Another study comparing an avocado enriched diet high in monounsaturated fatty acids and a high carbohydrate diet also found that the avocado enriched diet was more effective in lowering total cholesterol levels and low-density-lipoprotein (Colquhoun, Moores, Somerset, & Humphries, 1992). These clinical trial results coincide with the hypocholesterolemic activity of some of the chemical constituents in *P. americana* (Duke, 2012).

Contraindications

Although the fruit of *Persea americana* is widely cultivated and consumed safely as a food source, there are contraindications for the avocado. Avocado hypersensitivity, while rare, is one contraindication. Possible symptoms include anaphylaxis, angioedema, bronchial asthma, rhinoconjunctivitis, urticaria and vomiting (Blanco, Carrillo, Castillo, Quiralte, & Cuevas, 1994). In a study of avocado hypersensitivity, an allergic reaction usually occurred when the patient had a preexisting allergy to latex, chestnut, and/or other fruit, such as banana (Blanco et al., 1994). Interactions with Warafin, an anticoagulant, have been documented although the

mechanism through which avocado prevents the anticoagulant effects of Warafin is unknown (Blickstein, Shaklai, & Inbal, 1991). In addition, the leaves of *P. americana* contain a toxic compound, persin, which has been found to cause necrosis of lactating mammary glands and the myocardium in mice (Oelrichs et al., 1995). Instances of poisoning have been reported in rabbits, horse, cattle, goats, fish and canaries (Lewis & Elvin-Lewis, 2003). These poisonings are most likely due to the persin content present in the avocado plant (Yasir et al., 2010).

Current Use in Allopathic and CAM Therapies

The only major current use of *Persea americana* in allopathic medicine is as an osteoarthritis treatment in which the unsaponifiable portions of the fruit are added to soy bean unsaponifiables (Ameye & Chee, 2006). These ASUs (avocado-soybean unsaponifiables) are also used as dietary supplements in complementary and alternative medicine therapies for the treatment of arthritis and have support for effectiveness from positive results in clinical trials (Soeken, 2004). Another current use of avocado is the preparation of skin products with the oil due to the strong emollient properties of avocado oil. The oil is also a component of hair products. Some CAM treatments for skin disorders, like sclerosis, include the use of avocado oil (Khan & Abourashed, 2010). Although there are not many targeted medicinal uses of avocado being marketed at this time, the avocado is advertised as a health promoting food and is consumed internationally.

Discussion

Persea americana has been used for thousands of years as both food and medicine. The beneficial activity of avocado occurs due to its composition of bioactive compounds, which affect a myriad of pathways in the human body. Further studies are needed, especially clinical studies, to verify the efficacy of traditional uses of *P. americana*. The many biological activities found in laboratory studies also need to be investigated with clinical studies to determine the effectiveness of specific activities in humans. Since instances of cancer and diabetes have become more widespread threats to human health worldwide, the avocado's activity in preventing and treating these diseases needs to be further researched. In particular, the development of cancer treatments should be studied since *P. americana* has shown activity against so many different types of cancer. In addition, the many chemical components with unknown biological effects must be studied for complete understanding of the effects of *P. americana* in the human body (**Table 2**). As a widely consumed food, whose cultivation has spread globally in more recent years, the avocado will continue to remain an important food source that provides nutrition along with flavor (Whiley et al., 2002). With proper investigation and drug development, the avocado has the potential to provide much needed medicines for a wide range of ailments in the future.

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Rosmarinus officinalis L., Lamiaceae

Kedra Woodard

Introduction

Rosmarinus officinalis, commonly known as rosemary, is a perennial plant that belongs to the Lamiaceae family. It is also known in Chinese Pinyin as mi die xiang. The Lamiaceae family is a large group, rich in aromatic species and is used in many ways such as culinary herbs, part of folk medicine, and fragrance. Many of the species of this family are rich in essential oils. Studies have shown that species of the Lamiaceae family have antimicrobial, anticarcinogenic, antioxidant, cognitive-improving, and glucose level lowering properties due to the essential oils that are typically secreted by glandular trichomes (Okoh, Sadimenko, & Afolayan, 2011). Trichomes are present in most plants and are specialized epidermal cells. Glandular trichomes, found in most species in the Lamiaceae family, contain secretions produced by plants including volatile oils. There are typically two types of trichomes in the leaves and stems of plants, peltate and capitate. An illustration of both can be found in **Figure 1**. *R. officinalis* was first cultivated in the Mediterranean and was then transplanted in China. Today, *R. officinalis* is cultivated worldwide (Waggas & Balawi, 2008).

Botanical Description

Rosmarinus officinalis is an herb with ever-green needle-like leaves. It is indigenous to the Mediterranean where it grows wild. It can especially be found near the Mediterranean seashore in Spain, Portugal, Morocco and Tunisia where it can grow up to 6 feet high. Rosemary thrives best in warm, sunny



Figure 1. Picture on the left is of (A)peltate trichome and the picture on the right is of (B)capitate trichome. Source: <http://www.knottybits.com/jftrich/trichome.htm>

areas near seashores, which makes the Mediterranean seashore a perfect growing location. *R. officinalis* received its common name from where it can be found in abundance, near the sea. The term rosemary means “dew of the sea” (González-Trujano et al., 2007). Rosemary has been recorded in an Italian herbal, circa 1500 (Foley 1974). The picture from this document of *R. officinalis* can be seen in **Figure 2**. Rosemary can be identified by its dark green leaves, small blue, violet, or white flower, and minty odor.

The primary pollinators of rosemary are honeybees because rosemary is rich in highly concentrated nectar. Studies have shown that when compared to nine other plants of the Lamiaceae family, rosemary is one of the most preferred by honeybees (Zer & Fahn, 1992). One study discusses the



Figure 2. Rosemary illustration from an Italian herbal, circa 1500

Image Source: <http://en.wikipedia.org/wiki/Rosemary>

percentage of dry matter in the nectar of rosemary in varying locations in the summer. The amount found in Israel may be as high as 62-65% and about 44% in Jerusalem. The sucrose: glucose: fructose ration is about 2-83:1:1-85 however amino acid levels are pretty low (Dafni et al., 1988). Because honeybees pollinate based on the amount of nectar that can be found, rosemary in these areas are preferred.

There are several common cultivations of rosemary. Many of these cultivations, such as Albus, Arp, Salem, and Wilma's

Cultivars	Description
Albus	White flower
Arp	Leaves light green, lemon-scented
Aureus	Leaves speckled yellow
Benenden Blue	Leaves narrow, dark green
Blue Boy	Dwarf, small leaves
Golden Rain	Dark green leaves, with golden streaks
Gold Dust	Low and lax, trailing, intense blue flower
Irene	Procumbent selection from Tuscan Blue
Lockwood de Forest	Shrubby
Ken Taylor	Pink flowers
Majorica Pink	Distinctive tall fastigate form with wider leaves
Miss Jessop's Upright	Pink flower
Pinkie	Lower groundcover
Prostratus	Fastigate form, pale blue powers
Pyramidalis	Pink flowers
Roseus	Pale blue flowers, cold hardy similar to Arp
Salem	Spreading, low-growing, with arching branches; flowers deep violet
Severn Sea	Traditional robust upright form
Wilma's Gold	Yellow leaves

Table 1. Rosemary cultivars and descriptions (Mulas, Brigaglia, & Cani 1997).

Gold, are frequently sold in grocery stores and nurseries (Mulas, Brigaglia, & Cani 1997). **Table 1** is a chart illustrating more frequently sold cultivars and their varying descriptions.

Traditional Uses

Rosmarinus officinalis is used topically in Mexico to relieve rheumatic pain. The rosemary is prepared by maceration, which is the process of softening using an alcohol, in ethanol. This mixture is applied externally and directly to the skin

Chemical	Plant Part Present	Percent per million (ppm)
(+) Limonene	Plant	16-76
Acetic Acid	Esin, Exudate, Sap	
Alpha Terpineol	Plant	24-1555
Ascorbic Acid	Plant	612-673
Betulinic Acid	Leaf	
Cadalene	Plant	
Caffeic Acid	Plant	
Calcium	Plant	10919 - 16150
Camphor	Plant	60 - 5800
Carbohydrates	Plant	640,600 - 704660
Carnosic acid	Leaf, Plant	448.4- 5000
Chlorogenic Acid	Plant	
Copper	Plant	5 - 6
Ethanol	Plant	
Fenchone	Plant	250
Fiber	Plant	165420 - 206338
Glycolic Acid	Plant	
Iron	Plant	220 - 400
Lavandulol	Plant	7 - 34
Limonene	Plant	1,950
Methyl Ether	Plant	
Rosmaric Acid	Plant	3,000 - 3,500
Rosmarinic Acid	Leaf	3,500
	Plant	25,000
	Shoot	13,500
	Tissue Culture	38,957
Rosmarinol	Plant	
Safrole	Plant	32 - 95
Salicylates	Leaf	70 - 680
Sodium	Plant	462 - 592
Tannin	Plant	
Zinc	Plant	30 - 38
Zingiberene	Resin, Exudate, Sap	

Table 2. A few important constituents found in *Rosmarinus officinalis*.

(Ventura-Martínez, Rivero-Osorno et al., 2011). Rosemary is also used in ethnomedicine as a general stimulant, for

improvement of circulation, hyperglycemia and skin care (Hamedo, 2009). Rosemary tea, as a folk remedy, can be used for nervous headaches and healing colds. Some studies have reported its use as an effective diuretic and mood stabilizer (Haloui et al., 2000).

Rosemary was believed to strengthen memory in ancient Greece. Rosemary was consumed often in hopes to avoid forgetting. It was also very popular to see Greek students wearing rosemary leaves in their hair as they studied so they could remember reviewed information. Rosemary became a symbol of remembrance (Foley 1974).

Rosemary was cultivated in many of the ancient European countries, including France, Germany, Denmark, England, and parts of Scandinavia. It was too cultivated in ancient Central America, Venezuela, and the Phillippines. This plant has been associated with love and marriage as well as birth and death in many of these cultures. In Shakespeare's *Hamlet*, it is used as a symbol of love (al-Sereiti, Abu-Amer, & Sen, 1999).

Cosmetic Uses

Rosmarinus officinalis is commonly used as a fragrant additive in soaps and other cosmetic products. Rosemary is used in these products for treating cellulite, wrinkles, and normalizing excessive oil secretion from the skin (Hamedo & Abdelmigid, 2009). Rosemary can also be found in hair dyes and rinses to darken and retain color and in oils and shampoos to prevent premature balding.

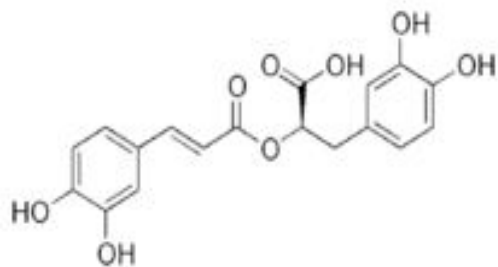


Figure 3. Chemical structure of rosmarinic acid.

Culinary Uses

Rosemary is an ancient spice. Because it is native to the Mediterranean, it is extremely common in Mediterranean cuisines. Extracts produced from the leaves of rosemary can also be used in food production to keep materials from spoiling due to its antioxidant properties. Its effectiveness in food preservation can be witnessed in many different types of foods including refrigerated beef and frozen pork patties (Lara, Gitierrez, Timón & Andrés, 2011).

Other Uses

When combined with other herbs, the chemical activity of *Rosmarinus officinale* can be increased. For example, a mixture of its leaves and juniper berries were burned in hospitals around France to kill germs during World War II (Foley 1974). Also, using rosemary leaves mixed with myrrh can be effective in treating bleeding gums.

Chemistry and Pharmacology

Rosmarinus officinalis has many important constituents with important biological activity. Some studies reported 1,8-

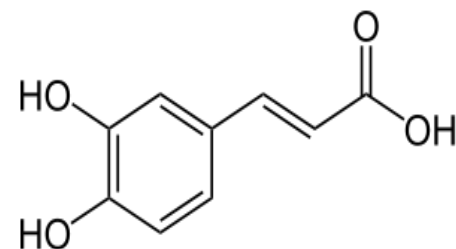


Figure 4: Chemical structure of caffeic acid.

cineole as a main component (Stojanović-Radić, Nešić, Čomić & Radulović, 2010) though, there are not many studies that discuss the role of this compound. **Table 2** displays several of the constituents found in rosemary, as well as its plant location, and abundance. The synergy of the constituents helps to produce the odor, appearance, and nutrients of rosemary. Rosemary extracts are effective in relaxing the smooth muscles of the trachea and intestine. It has choleric, hepatoprotective, and anticarcinogenic properties. Recently, scientists seem to be particularly interested in three of the acids found in rosemary: carnosic acid, caffeic acid and one of its derivatives, rosmarinic acid. All of these compounds have antioxidant effects (al-Sereiti, Abu-Amer, & Sen, 1999). **Figures 3** and **4** illustrate the structure of rosmarinic acid and caffeic acid, respectively.

Carnosic acid is a carbon dioxide solution found in many plant molecules. It can be found in abundance in rosemary. Carnosic acid has been found to promote weight loss. Ibarra et al. discovered this phenomenon while observing its effects in mice. In this study, standardized 20% carnosic acid rosemary leaf extract was used to identify its effects on weight gain, glucose level, and lipid homeostasis in mice (2011). Three groups were observed: mice given a high-fat diet, mice given a low-fat diet, and mice given a high-fat diet supplemented with 500mg of the standardized rosemary leaf extract since

juvenile. The mice were monitored for sixteen weeks. The rosemary extract reduced cholesterol level. This was visibly noted when the group given a high-fat diet and the extract were compared to those only given a high-fat diet. There was too, a direct correlation between fecal fat excretion and rosemary extract. This, however was not witnessed with decreased food intake (Ibarra et al. 2011). Though further studies are needed for this one to be conclusive, this study shows that perhaps rosemary rich in carnosic acid can be used for weight loss.

Caffeic acid is a naturally occurring compound that can be found in most plants. This compound may contribute to the prevention of cardiovascular disease (Olthof, Hollman, & Katan 2001). Margreet Olthof, Peter C. H. Hollman, and Martijn B. Katan conducted an experiment to determine the amount of caffeic acid absorbed in humans (2001). This was determined through a cross-over study using four healthy female and three healthy male subjects. The calculation used to determine the amount absorbed was the amount ingested minus the amount excreted. Eleven percent of the caffeic acid absorbed was excreted in urine (Olthof, Hollman, & Katan 2001). Accounting for human error, almost all of the caffeic acid intake will be absorbed by humans.

Rosmarinic acid, the ester of caffeic acid and 3,4-dihydroxyphenyllactic acid, is a compound commonly found in the Boraginaceae family but unique to rosemary in the Lamiaceae. In the plant, rosmarinic acid behaves as a defense compound (Petersen & Simmonds 2003). Rosmarinic acid is a phenolic compound; it has one phenolic ring from phenylalanine via caffeic acid and one phenolic ring from tyrosine via dihydroxyphenyl-lactic acid. Rosmarinic acid can be well absorbed through membranes such as the gastrointestinal tract and the skin. It is capable of increasing the PGE₂, prostaglandin E₂, and reducing the production of

leukotriene B₄, a fatty signaling molecule, and inhibits the complement system (al-Sereiti, Abu-Amer, & Sen, 1999). PGE₂ is important in childbirth labor because it softens the cervix and causes the uterine to contract; however if activated early can be an abortifacient. Many of the activities rosmarinic acid is involved with have therapeutic potential. For example, relaxing the bronchial and intestinal smooth muscles can treat bronchial asthma and be antispasmodic. Reduction of leukotrienes and the increase of PGE₂ production can also treat bronchial asthma, peptic ulcers, and inflammatory diseases.

The three constituents of rosemary discussed, caffeic acid, carnosic acid, and rosmarinic acid, are also found to have therapeutic potential in treatment. These constituents are able to inhibit lipid peroxidation which can then treat hepatotoxicity atherosclerosis and inflammatory diseases. They also prevent the formation of the carcinogen-DNA adduct which gives rosemary its anticarcinogenic property (al-Sereiti, Abu-Amer, & Sen, 1999).

Biological Activity

In vitro

Rosmarinus officinalis was tested in a study conducted by Vina Yang and Carol Clausen for its effectiveness in controlling mold growth on wood (2007). Moisture is the most critical component to consider when controlling mold growth, however when moisture cannot be controlled, one must consider what to do to control mold growth. In this experiment, seven plants, rich in essential oils were test for their antifungal effects including rosemary. Petri dish tests and tank test chamber gave similar results. Rosemary essential oil extract was among the group of essential oils

shown to have promising antifungal effects in this experiment (Yang and Clausen 2007).

In vivo

Fawzia A. Fahim and Amr Y. Esmat conducted an experiment to study the antimutagenic and hepatoprotective effects of the essential oil of *Rosmarinus officinalis* and ethanolic extract (1999). They used carbon tetrachloride as hepatotoxic and cyclophosphamide as mutagenic compounds. For three weeks, rats were administered rosemary ethanolic extract (0.15 g/100 g BW). This produced the better hepatoprotective results than when compared to silymarin. Mice were pretreated for seven days with rosemary essential oil (1.1mg/g BW) and later injected with cyclophosphamide. This significantly reduced the induced mitodepression of bone marrow cells in the mice. The presence of high percentages of phenolic compounds within the rosemary essential oil extract contributed to its antioxidant effects (Fahim & Esmat, 1999).

Hossein Hosseinzah and Mahnaz Nourbakhsh investigated the effects of aqueous and ethanol extracts of *R. officinalis* on morphine withdrawal syndrome in mice (2003). The aqueous and ethanol extraction of rosemary induced significant activity in the writhing test that showed a decline in sensitivity to painful stimuli and this activity was then inhibited by naloxone, an opioid antagonist drug, pretreatment. The mice developed dependence to morphine by being induced daily for three days using subcutaneous injections of morphine. Day four, the mice were injected two hours prior to the intraperitoneal injection of naloxone with morphine. The effects of the withdrawal syndrome was observed in the mice and were then measured by the number of jumps within the 30 minute period after the naloxone injection was administered. It was found that the number of jumps reduced

due to the aqueous and ethanol extracts of rosemary (Hosseinzah & Nourbakhsh 2003). This study introduced the possibility of using rosemary extractions to treat morphine withdrawal syndrome.

Clinical Studies

Moss and Cook conducted an experiment using human subjects to test the cognitive effects of *Rosmarinus officinalis* and lavender (Moss & Cook 2003). Many nontoxic herbal spices from Europe are traditionally used to treat cognitive deficiency. This experiment, however only tests two. Moss and Cook assessed the olfactory impact of the two plants on cognitive performance and mood. Rosemary was found to produce enhancement in secondary memory factors and terms of overall quality of memory. However, it was found to impair the speed component of memory (Moss & Cook 2003). This could be due to rosemary's essential oils; they produce a soothing effect.

Rosemary essential oils were found to moderately inhibit acetyl-cholinesterase (Orhan et al., 2008). The inhibition of acetyl-cholinesterase by rosemary essential oil can be explained by the synergy produced by the interaction between 1,8 cineole and 2-pinene. Inhibition of acetyl-cholinesterase is currently one of the treatment strategies against several neurologic disorders such as Alzheimer's and other dementias. Because rosemary was found to have this activity, it is now being further investigated to see how it can potentially treat these diseases (Orhan et al., 2008).

Contraindications

Rosmarinus officinalis is not known to be toxic. However, a large intake of the plant or its oils could pose a threat to

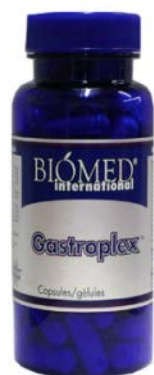


Figure 5. Gastroplex

Image source:

http://www.google.com/imgres?q=Gastroplex&um=1&hl=en&sa=N&biw=1441&bih=747&tbn=isch&tbnid=kRZczBPNBrnZrM:&imgrefurl=http://biomedicine.com/products-page/biomed-supplements/gastroplex%25E2%2584%25A2&docid=yr_hRbG4MT6qfM&imgurl=http://biomedicine.com/wp-content/uploads/2011/07/11080.jpg&w=600&h=480&ei=c91aT7baBsq9tweB_OSEDA&zoom=1

pregnant women (al-Sereiti, Abu-Amer, & Sen, 1999). A study was conducted on mice to see the dietary effects of rosemary on the fertility of adult rats. It was reported that sperm motility and density decreased. In addition, the number of aborted fetuses was increased. It was concluded that the increased amount of rosemary given caused infertility (Nusier et al. 2007). Because humans are much larger, it would take a lot more rosemary to cause this effect. The amount to cause such effects, however are not known due to lack of studies. There is no evidence that the intake of a moderate amount of rosemary could be harmful to breast-feeding women or their children. There is potential for the oil to act as an abortifacient, which is an agent that may induce abortion (al-Sereiti, Abu-Amer, & Sen, 1999). This is only due to its effects

on PGE2. Also, a frequent intake of rosemary can cause iron deficiency in susceptible individuals.

Current Uses in Allopathic and CAM Therapies

Extracts from *Rosmarinus officinalis* are presently used in herbal medicine today, such as in the drug Gastroplex. Gastroplex is used for the treatment of dysbiosis, the rapid overgrowth of yeast, parasites, and bacteria. Gastroplex is used to regain the proper function of the gastrointestinal tract and reclaim its health. This drug cannot be taken during pregnancy or lactation. A photograph of the drug can be found in **Figure 5**.

Because of the high concentration of volatile oils, rosemary is used in aromatherapy. It has also been effectively in use in massage therapy. Its scent has the effect of producing a relaxing sensation. Other uses of rosemary include its use as a diuretic. Teas with rosemary extract are used by the general public and are widely marketed and can be purchased with convenience.

Discussion

Rosmarinus officinalis is an amazing plant with many health benefits. It is anti-inflammatory, anticarcinogenic, antibacterial (Jarr et al., 2010), and an antioxidant. It is rich in phenols and tannins. It can be used medicinally and used in cuisines. Though originating in the Mediterranean, today this plant can be found in all parts of the world. This plant can even be grown in indoor pots inside the home. By simply incorporating *R. officinalis* into the diet, many bacterial infections can be avoided while gaining nutritious benefits.

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Sambucus nigra L., Adoxaceae

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Introduction

Sambucus nigra L., commonly known as Elderberry, belongs to the Adoxaceae family. Other common names include European Elder, Black Elderberry, Elder Flower, Elder, Flor de Novia (Peru) (Tropicos, 2001), Cinta de Novia (Peru) (Tropicos, 2001), Savuchə or Shtog (Arbëreshë) (Quave, 2009; Quave and Pieroni, 2005), Saúco (Spain) (Cavero et al., 2011), Savucu (Calabria) (Tagarelli et al., 2010), Sambuco (Italy), Sureau (France) and Sabugueiro (Brazil) (Charlebois, 2011). The origin of *Sambucus* is believed to be from the Greek word sambuca, which was a triangle-shaped instrument made from the bark. (Austin, 2004; Watts, 2007).

Elderberry is most commonly used today in Europe to treat colds and influenza (Anderson, 2007; Watts, 2007; Zakay-Rones et al, 2004). Other suggested uses include use as a laxative, for dropsy or for topical skin treatments of wounds, burns or insect bites (Picon et al, 2010; Quave and Pieroni, 2005; Uncini-Manganelli et al, 2005; Watts, 2007). Modern-day products of Elderberry extract include Sambucol and phytotherapeutic Brazilian tea. Studies have shown Elderberry extract to have antioxidant, antiviral and antibacterial activity and insulin-like properties (Gray et al, 2000; Heinrich et al, 2004; Roxas and Jurenka, 2007; Swanston-Flatt et al, 1991; Uncini-Manganelli et al, 2005; Wu et al, 2004). Its main constituents are comprised of cyanogenic glycoside, flavonoids, triterpenoids and anthocyanidins (Atkinson and Atkinson, 2002; Duke, 1992; Roxas and Jurenka, 2007). The Elderberry tree is referred to extensively in European folklore. (Anderson, 2007; Burne, 1914; Grimassi et al, 2011;



Figure 4: *Sambucus nigra*. (Image source: <http://irapl.altervista.org/nit/viewpics.php?title=Sambucus+nigra>)

Keightley, 1850; Morgenstern, 2000; *Notes and Queries*, 1907; Watts, 2007).

Botanical Description

Elderberry is a deciduous shrub that can range from 4m to 10m in height. The shrub initially grows straight and vertical from the base and has arching branches (Atkinson et al, 2002; Kabuce et al, 2006). The bark of the shrub is moderately acidic and is highly capable of holding water (Atkinson et al, 2002). The branches contain porous white pith. Individual leaves

grow up to 20cm in length and are oval shaped with a pointy tip. The flowers are a creamy white color and 5mm in diameter. The flowers commonly have 5 petals and have cream colored anthers (**Figure 1**). The fruits of this shrub are spherical black berries that grow in clusters and contain 3-5 seeds (Atkinson et al, 2002; Kabuce et al, 2006). They have a lifespan of up to 25 years (Atkinson et al, 2002).

Elderberries are believed to be native to continental Europe but are cultivated as far north as the Scandinavian countries, as far south as northern Morocco, Algeria and Tunisia, but it is also grown in North America, areas of Australia, New Zealand and east Asia (Atkinson et al, 2002). American elder (*Sambucus canadensis* or *S. nigra* subsp. *canadensis*), a close relative of *S. nigra*, is more commonly cultivated in North America and is sometimes confused with *S. nigra* (Charlebois et al, 2007).

Elderberry shrubs are commonly found in either naturally or unnaturally disturbed sites. These sites tend to have eutrophic soils or nutrient-rich soil (Atkinson et al, 2002). Disturbances can refer to woodland margins, hedgerows, neglected gardens, floodplain terraces, roadsides and building sites. The shrubs show stunted growth under shade, which suggest that they prefer sun-lit habitats (Atkinson et al, 2002; Kabuce et al, 2006).

The only pollinators known to impact elderberry are birds. They spread the seeds either by regurgitation or defecation after eating the berries (Atkinson et al, 2002; Charlebois et al, 2007; Kabuce et al, 2006).

Subspecies

In this monograph, *Sambucus nigra* subsp. *nigra* is being addressed, but another subspecies is *canadensis*. This

subspecies *canadensis* is known as American Black Elderberry and is predominately found in eastern United States (Austin, 2004; Charlebois et al, 2007; Tropicos, 2001). Another subspecies is *cerulea*, which is known as the Blue Elderberry in primarily found in western United States (Austin, 2004; Tropicos, 2001).

Traditional Uses

Medicinal/Ritual

Elderberry is mentioned in ancient texts and appreciated for its medicinal properties. Hippocrates is said to have called the elderberry a “medicine chest” in 400 BC. Additionally, Pedanius Dioscorides, author of *De Materia Medica* (50-70 AD), and Theophrastus used and wrote about elderberry as a medicinal plant (Krawitz et al, 2011).

The medicinal uses of elderberry are numerous and span across Europe. In general the flowers were used to heal sore or red eyes and gastrointestinal tract problems, and the fruit was used as a laxative (Uncini-Manganelli et al, 2005).

Primarily in the United Kingdom, tea was made from the leaves of *S. nigra* to treat diabetes (Gray et al, 2000; Swanston-Flatt et al, 1991). Elderberry tea was also used for the treatment of colds, coughs, fevers and influenza (Anderson, 2007; Watts, 2007). In medieval England, berry juice or tea was used for dropsy. In England, elderberry leaves were also used on wounds and lacerations, and were especially effective if picked in April (Uncini-Manganelli et al, 2005). Also, the leaves were used to heal insect bites (Watts, 2007). The inner bark was used to treat burns (Quave and Pieroni, 2005; Watts, 2007). It was common in England to use elder flower water, the inner bark or flower lotions to clear freckles and blemishes, whiten skin and heal sunburn (Watts, 2007).

Elderberry was also used in treating witchcraft that came in the form of wounds from animals or plants. One such remedy ritual involved placing the pus of the wound into a hole in the side of the elderberry tree and covering it with elderberry material (*Notes and Queries*, 1907).

In the Arbëreshë communities in Italy, there are numerous uses of elderberry to treat foot sores and blisters, toothache, sore throat, abscess and headache, and worked as an anti-inflammatory, anti-rheumatism and anti-pruritic. Flowers are used for sore throat, foot sores and blisters. For insect bites, wounds, inflammations, rheumatism and abscesses the leaves are used topically. The community also smokes the dried stems to relieve toothache (Quave, 2009). A cream made from elderberry bark, olive oil and bees-wax was used to treat '*cigli alla testa*', which is characterized by a headache on the top of the head. Part of the healing ritual for '*cigli alla testa*' includes a prayer being said under the elderberry (Quave, 2009; Quave and Pieroni, 2005). Another Arbëreshë ritual using Elderberry in conjunction with other plants (*Malva sylvestris*, *Matricaria recutita* and *Parietaria diffusa*) is used to treat '*mal vjnt*', or 'wind illness'. In this community '*mal vjnt*' is identified as a skin rash and the four plants are bundled together and brushed over the rash while a specific prayer is said (Pieroni et al., 2002).

In the region of Calabria (southern Italy), elderberry was traditionally used as an anti-rheumatic and purgative, to treat swollen breasts and legs, insect bites, toothache, colic and conjunctivitis. The plant materials used include the inflorescence, fruit, leaves, bark and dry flower heads (Tagarelli et al., 2010). Additionally, fresh leaf bunches were used to attract flies so could they kill them (Passalacqua et al., 2006).

In Spain, communities in the Middle Navarra had traditionally used elderberry for multiple purposes. Fourteen such uses were documented by Cavero et al. (2011). The inner bark and the inflorescence were used together or separately for the topical treatment of wounds, burns, blisters and animal bites. The plant material was roasted then mixed in either oil or wax, forming an ointment which was applied topically. The inflorescence had additional uses for toothaches, catarrhs, sore throat and as an expectorant. For the previously mentioned purposes the inflorescence was boiled and the smoke inhaled with the exception that a tea was made for sore throats. The researchers also noted that this community was aware that some medicinal usage knowledge about elderberry has already been lost (Cavero et al., 2011). Adjacent to the Navarra region is the Pyrenees area which separates Spain and France. In this area, elderberry was used for medicinal purposes as well (Akerreta et al., 2007). Another nearby region where the medical use of elderberry was prevalent was that of Catalonia. Here, elderberry was used to reduce blood thickness and as an anti-pneumonic (Agelet and Vallés, 2003).

In North America, the subspecies *canadensis* was used by the Native American tribes Cherokee, Menominee, Iroquois, Creek, Choctaw and Houma. The Cherokee and Seminoles prepared tea from the bark for stomach complaints. The Houma however, used bark tea for difficult childbirths, as analgesic and anti-inflammatory. The Iroquois also used elderberry as an anti-inflammatory. Among the Iroquois bark was used to treat headaches, cuts and measles. They used a mixture of roots and bark as poultice for newborn infant navels. Branches or bark could be used as a laxative and the pith from stems treated heart disease and gonorrhoea within Iroquois culture. Berry tea was used for rheumatism among the Cherokee and for fevers in Menominee and Cherokee. The Creeks treated swollen breasts with water soaked roots, the



Figure 5. Example of one type of elderberry wine. (Image Source: <http://heatherhillfarms.com/proddetail.php?prod=manischewitz-elderberry-wine>)

Choctaw mixed leaves with salt for headaches (Austin, 2004; Banks, 2004; Moerman, 1998).

The subspecies *cerulea* was commonly utilized by western Native American tribes including the Thompson and Kawaiisu and selectively used by eastern tribes Choctaw and Houma. The Kawaiisu used a mixed of leaves and flowers in a steam bath for headaches and colds. Additionally, leaf tea is used to wash blood poisoned appendage among Kawaiisu. The Thompson tribe treated arthritis with boiled bark, from a nonmetal pot otherwise will be poisonous. Bark was also used for toothaches and dried flowers treated syphilis in Thompson tribe. The Choctaw used leaves topically for swollen hands and internally as a purgative. The bark is used by the Choctaw to treat diarrhea and the Houma as an analgesic (Austin, 2004; Moerman, 1998).



Figure 6. Elder flower fritters. (Image source: <http://utmarketgarden.files.wordpress.com/2011/03/elder-flower.jpg>)

Culinary

Culturally, elderberry was most commonly used in the culinary arts. During the nineteenth and twentieth century elderberry was used to make soup, jam, wine and juice in the Polish countryside (Luczaj, 2010; Luczaj and Szymański, 2007). In traditional Europe and United States, elderflowers were used to make elderberry beer and the berries to make elderberry ale or Ebulon. The recipe for elderberry beer calls for fresh or dried elderflowers, water, sugar and yeast. Elderberry ale is made with elderberries, water, malt extract and yeast (Buhner, 1998). Elderberry wine was also a popular in England, possibly due to the belief that it was beneficial for sore throat, asthma, sciatica and longevity (**Figure 2**) (Watts, 2007). In Germany, a recipe called Hollerküchln, encompassed elderflowers deep fried and the leftover oil was used further for the treatment of ear infections (**Figure 3**) (Buhner, 2004).

This same recipe is used in the Calabria area of southern Italy too; there the flower fritters are called '*pitte cu majiu*' (Passalacqua et al., 2006).

The berries of both subspecies *cerulea* and *canadensis* were used in many tribes to make wine, pie, jelly and sauce and in one instance as a fish marinade (Moerman, 1998).

Folk-Lore

There is much folk-lore associated with the elderberry tree throughout Europe and America in traditional beliefs of Christianity, Wicca and others. In England, Germany, Scotland and Denmark it was considered bad luck to burn or cut an elderberry tree without asking permission (Burne, 1914; Keightley, 1850; Morgenstern, 2000; *Notes and Queries*, 1907; Watts, 2007). It was bad luck to burn the tree because by doing so the tree would release evil. Each culture had a different specific prayer or saying for the proper way to ask permission of the Elderberry, but all cultures had expressed a bargain to return wood to the elderberry (Keightley, 1850; *Notes and Queries*, 1907). In Germany and Denmark, if you did not ask permission before using the wood to make a cradle, the entity within the tree would torment the baby (Keightley, 1850; *Notes and Queries*, 1907; Watts, 2007). Additionally, in the areas near the Rollright Stones and Wales, people believed that the elderberry would bleed when cut (Blaine and Wallis, 2007; Burne, 1914; *Notes and Queries*, 1907; Watts, 2007). This stemmed from the belief that the entity within the tree was injured. The name of the entity was different in various countries: in England it was Old Lady, Old Girl or witch and in Denmark it was Hyldemoer, which translates to Elder-Mother (**Figure 4**) (Anderson, 2007; Blaine and Wallis, 2007; Burne, 1914; Grimassi, 2000; Keightley, 1850; Morgenstern, 2000; *Notes and Queries*, 1907; Watts, 2007).



Figure 4. Illustration of Hyldemoer (Elder-Mother Tree) from a Hans Christian Anderson story. (Image Source: <http://polarbearstale.blogspot.com/2010/06/sct-hans-and-elderflowers.html>)

One of the protective activities associated with the Elderberry was as a safeguard against lightning because it was never struck. In some Christianity sects, this was believed because Judas Iscariot hung himself from an Elderberry tree and the

Compound Class	
Flavonoids (<3%)	quercetin, rutin, isoquercitrin, kaempferol, astragalín, nicotiflorin and hyperoside
Triterpenes	Ca 1% α - and β - amyryn, occurring mainly as fatty acid esters; Triterpene acids: Ca 0.85% oleanolic and ursolic acids, 20 β -hydroxyursolic acid
Volatile Oil (.03-.14%)	65% of free fatty acids including palmitic acid and linoleic acid. 7% alkanes. Others include ethers, oxides, ketones, aldehydes, alcohols and esters.
Caffeic acid derivatives (3%)	chlorogenic acid
Sterols	β -sitosterol, stigmasterol, campesterol and cholesterol
Minerals	potassium
Other constituents	tanin, mucilage, plastocynin (protein), pectin and sugar

Table 1. Compounds and their percentages found in Elder flowers. (Image Source: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_HMPC_assessment_report/2009/12/WC500018238.pdf)

cross used during Jesus Christ's crucifixion was an elderberry tree (Morgenstern, 2000; *Notes and Queries*, 1907; Watts, 2007). Additionally, it became a common practice to place a stick of elderberry over a grave, because if it grew into a tree then the soul of the deceased was happy (Morgenstern, 2000; Watts, 2007). In Wicca, standing beneath the elderberry tree and inhaling the scent of its flowers was believed to reveal the fairies that live there (Grimassi, 2000; Watts, 2007). Elsewhere, a pregnant woman standing under the elderberry tree would have an abortion (*Notes and Queries*, 1907). In England, boys beaten with wood from elderberry were believed to have stunted growth (*Notes and Queries*, 1907; Watts, 2007).

Other

The flowers of *S. nigra* were used as a dark yellow dye for white doilies in the Latium area of Italy. The fruit juice was used as blackish ink and as a blackish dyeing agent for must (result of first step in wine making) in Latium, Abruzzo and Marche areas. These three areas are in the central portion of Italy adjacent to one another (Guarrera, 2006). The berries have been used as a dye to color wine since Greek and Roman times and their dyeing properties were utilized in other materials as well (Austin, 2004; Morgenstern, 2000; Watts, 2007).

The subspecies *canadensis* and *cerulea* were used by the North American Indian tribe Houma, to make blowguns. *Canadensis* specifically was used by the Menominee to make toy guns. The Kawaiisu used the subspecies *cerulea* to make a flute after removing the pith and making six holes in the wood (Moerman, 1998).

Chemistry and Pharmacology

The main constituents of elderberry are cyanogenic glycoside, flavonoids, triterpenoids and anthocyanidins (**Table 1**). Sambunigrin is the main cyanogenic glycoside and is found in the leaves (**Figure 5**). The common flavonoids found are rutin, which is found in the flower and berry, and quercetin, which is found in the berry and leaves (Atkinson and Atkinson, 2002; Duke, 1992; Roxas and Jurenka, 2007). There are numerous triterpenoids found in elderberry: ursolic acid, oleanolic acid, α -amyryn and β -sitosterin (Atkinson and Atkinson, 2002; Christensen et al, 2007; Duke, 1992). The latter is classified as a subtype called steroid alcohols (Heinrich et al, 2004). The two anthocyanidins present in the berries are cyanidin-3-sambubioside and cyanidin-3-sambubioside-5-glucoside

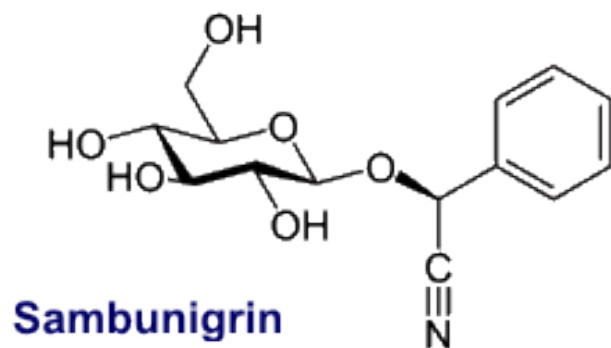


Figure 5. Sambunigrin is one of the chemical constituents of *Sambucus nigra*. (Image Source: http://www.awl.ch/heilpflanzen/sambucus_nigra/index.htm)

(Charlebois, 2007; Duke, 1992; Roxas and Jurenka, 2007). The berries also contain the sweetener compounds dextrose and levulose (Duke, 1992). The noteworthy fatty acids present in the flower are linoleic acid and α -linolenic for their activity on peroxisome proliferator-activated receptor (PPAR γ) (Christensen et al, 2007; Duke, 1992).

The elderberry's antioxidant capacity is due to the flavonoids and anthocyanidins, which are responsible for the color of the flower (Heinrich et al, 2004; Roxas and Jurenka, 2007; Wu et al, 2004). Cyanogenic glycosides are toxic and thus, thought to be a defense against herbivore. Triterpenoids contain steroid type compounds and are useful in mammals (Heinrich et al, 2004).

Biological Activity

There have been many studies addressing the biological activity of elderberry. In bacterial liquid culture standardized elderberry extract (Rubini) was effective in decreasing growth in Gram-positive bacteria such as, group C and G *Streptococci*

and *Streptococcus pyogenes*, and in Gram-negative bacteria including *Branhamella catarrhalis* and *Haemophilus influenza*. However, in the study using Rubini, the extract did not inhibit bacterial growth of *Staphylococcus aureus*, *Streptococcus mutans* and *Haemophilus parainfluenzae*. Rubini was also used in cell cultures where it decreased grow of avian type-A influenza virus (H5N1) and type B influenza virus (Krawitz et al, 2011).

Elderberry fruit extract was used in an *in vitro* study to determine the flavonoids effect on type-A influenza virus (H1N1). The extract was more effective in inhibiting H1N1 infection compared to when each flavonoid was used individually. The flavonoids used were a type of quercetin and dihydromyricetin because they were bound to the virus. It was suggested that either of these flavonoids bound to the domain of the virus responsible for binding to a host cell (Roschek et al, 2010). A different study used dried elderberry flower boiled in water in an *in vitro* for insulin-like properties. The compounds lectin, rutin and β -sitosterol were identified in the extract. The extract significantly increased glucose uptake, glucose metabolism and insulin secretion from pancreatic β -cells. The suggested mechanism of action was sulfonylureas receptor activity on β -cells, which depolarizes membrane and causes an influx of calcium ions. Diazoxide, which inhibits sulfonylureas activity, decreased insulin secretion by the extract (Gray et al, 2000). The effectiveness of elderberry extracts used for inhibition of H1N1 and insulin-like properties were dose-dependent (Gray et al, 2000; Roschek et al, 2010).

Additional antiviral properties were studied of elderberry bark with the feline immunodeficiency virus (FIV) *in vitro*. The boiled bark extract significantly inhibited syncytia formation (formed by virus) (Uncini-Manganelli et al, 2005).

The insecticidal activity of Elderberry is due to the plant protein type-2 ribosome-inactivating protein (RIP) of *Sambucus nigra* agglutinin I' (type-2 RIP SNA-I') found in the bark. In bioassays, tobacco plants (*Nicotiana tabacum*) were transformed with type-2 RIP SNA-I' and were found to be toxic for tobacco aphids (*Myzus nicotianae*) and pea aphids (*Acyrtosiphon pisum*) when ingested (Shahidi-Noghabi et al., 2008). In an additional study, transgenic tobacco plants (*Nicotiana tabacum*) with type-2 RIP SNA-I were harmful when ingested by tobacco aphids (*Myzus nicotianae*) and beet armyworm (*Spodoptera exigua*). The mechanism of action of RIP is proposed to inactivate eukaryotic ribosomes. The B-chain RIP binds to the cell surface receptors which allows the A-chain of the RIP to enter the cell where it inactivates ribosomes (Shahidi-Noghabi et al., 2009).

Clinical Studies

In a Norwegian clinical study, patients who took the elderberry product Sambucol syrup showed a faster recovery from influenza type A and B compared to placebo (**Figure 6**). The patients also reported no adverse effects after taking the syrup (Zakay-Rones et al, 2004).

In Brazil, a mixture of *Pimpinella anisum*, *Foeniculum vulgare*, *Cassia augustifolia* and *S. nigra* prepared as a tea is used to treat constipation. The efficacy of this mixture was supported. The patients had significant increases in evacuations per day (after day 2), and self-reported improvement of bowel functions. There were no reported adverse effects, but it was not recommended to be used with diuretics (Picon et al, 2010).

A clinical study addressed the before and after differences when obese people ingested a combination of psyllium, *S.*



Figure 6. A variety of Sambucol products. (Image Source: <http://www.nutranutra.com/nutraport/?cat=15&paged=3>)

nigra juice and berries and two sets of tablets, one made from *S. nigra* and the other *Asparagus officinalis*. This diet regiment consisted of 370mg flavonol, 150mg hydroxycinnamates and 1mg anthocyanin from *S. nigra* and 19mg saponins from *A. officinalis*. The participants had significantly decreased body weight and improvement of blood pressure, emotional and physical well-being (Chrubasik et al., 2008).

Contraindications

There are very few dangers associated with elderberry plant material use. The unripe berries can be toxic and might cause nausea, vomiting and severe diarrhea in the worst cases (Morgenstern, 2000). It is also recommended that elderberry extracts not be taken in conjunction with diuretics (Picon et al, 2010).



Figure 7. Example of laxative tea made with elderberry, not necessarily the same one from the study. (Image Source: http://oilnatural.com/product_info.php?cPath=42&products_id=31)

Current Use in Allopathic and CAM Therapies

Today there are some elderberry extract products used in CAM therapies but they are primarily used in Europe. One such product is Sambucol, a syrup used to alleviate and shorten duration of colds and influenza. In a clinical trial there were no side effects and it is advertised for both adults and children (Zakay-Rones et al, 2004). Another cold and influenza medicine is Rubini, but it has not been clinically supported for efficacy of treatment.

A phytotherapeutic tea of elderberry is used in Brazil to treat constipation (**Figure 7**). The tea contains one-third elderberry extract and the other two-thirds are comprised of Aniseed, Fennel and Senna. This tea also has no adverse side effects (Picon et al, 2010).

OptiBerry contains elderberry along with other berries including bilberry, blueberry, cranberry, raspberry and strawberry (Zafra-Stone et al, 2007).

Discussion

Elderberry has widespread traditional and modern-day uses and great treatment potential for colds, influenza and constipation. The modern-day uses are based on some of the traditional uses, but there are many more traditions that have yet to be explored. There are few clinical trials supporting the efficacy of extracts for colds and influenza and no clinical trials for laxative use. Additionally, a majority of the mechanisms of action of the elderberry extract's compounds have yet to be identified or replicated. While there is support for elderberry's antiviral and antibacterial activity, the same cannot be said for its laxative and insulin-like properties. Furthermore, its traditional use as a topical skin healing treatment has not been addressed. The alternative medicinal products mentioned previously are only available in Europe and Brazil, and are largely unknown to the America public. For the most part, Americans are unaware that its health benefits rival those of other berries, which is a shame because of all its wonderful medicinal properties and culinary uses.

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Silybum marianum (L.) Gaertn., Asteraceae

Annelies Carl

Introduction

Silybum marianum (L.) Gaertn, commonly known as Milk thistle, St. Mary's thistle, and Blessed Thistle, is a member of the Asteraceae family, commonly known as the daisy family (Abenavoli et al., 2010). Historically, milk thistle was administered to treat liver ailments, hemorrhoids, and used as a diuretic. Today this plant is still used in the same manner, and the isolated active compounds have a myriad of applications including anti-toxin properties and liver cleansing. This plant is also suggested as a panacea on many herbal Internet sources, reflecting milk thistle's popularity and frequency of usage. The main active ingredient in milk thistle is silymarin, which is found in the highest concentrations in the seeds of the plant but other parts of the plant like the leaves and fruit are also used. Milk thistle seeds or the isolated compound silymarin are sold in many products from biomedical pharmaceuticals to herbal supplements, which range in price. Although many clinical trials have been conducted that showed numerous positive effects of milk thistle components, many of the studies provide contradictory results because of unstandardized concentrations and preparations of milk thistle.

Botanical Description

Milk thistle is native to the Mediterranean basin but has spread throughout the world, and in some areas this plant is now considered to be a noxious and invasive weed that can often be found growing along roadsides, in waste ground, and



Figure 1. Milk thistle. Note the milky white veination patterns. (Source: <http://altmed.creighton.edu/MilkThistle/What%20Is%20It.htm>)

among cereal crops. Removing milk thistle can be a costly effort for those farmers who consider milk thistle to be a prickly annoyance, since the milk thistle is a very hardy plant. Milk thistles with well-developed root systems can be grown in light soils with periods of water deficiency. Milk thistle will also grow in heavier clay soils and will tolerate a wide variety of pH levels ranging from 5.5 to 7.6 (Karkanis et al., 2011). Although milk thistle is obvious highly adaptable, it prefers fertile soils. Also reflective of its adaptability, milk thistle can grow as an annual or biennial.

The stem of milk thistle can grow from 40cm to 200cm tall. The stem itself grows vertically and is slightly downy. Towards the upper part of the plant the stem becomes branched. When the stem branches, the lowermost leaves are large and alternate with spiny edges. These large leaves grow from 50cm to 60cm long and from 20cm to 30 cm wide (Karkanis et al., 2011). Milky white veins, a distinguishable characteristic, found on milk thistle leaves are what give the plant part of its name. Due to the white veins, tradition says that milk thistle was given the name 'marianum' based on the legend that the milk from the Virgin Mary landed on the plant when she was sheltering under a bower formed from milk thistle leaves, and this milk is what turned the veins of the milk thistle white (**Figure 1**).

The leaves on the stem are smaller than the leaves on the base. At the end of each stem, a flower head will form that is around 5cm in diameter with reddish–purple coloration. The seeds have a white pappus, are about 5 to 8 cm long, and range in color from brown to black. On average, each flower head produces about 190 seeds. While in the soil, the milk thistle seed can remain viable for nine years. It has not been observed that the seed needs dormancy (Karkanis et al., 2011) (**Figure 2**).

Many pests and diseases can threaten milk thistle. There have been reports of rust fungus (*Puccinia punctiformis* (F.Strauss) Rohl.) in the U.S, smut fungus (*Microbotryum silybum* Vanky & Berner) in Greece, and cucumber mosaic virus (CMV) in Spain. Milk thistle is also a host for the tomato spotted wilt virus. In addition, there are many insects that feed on milk thistle including the seed-head weevil in Egypt and aphids (*Dysaphis lappae cynarae* and *Aphis fabae cirsiacanthoidis*) in Iran and Greece (Karkanis et al., 2011).



Figure 2. Botanical drawing of *Silybum marianum*. (Source: Prof. Dr. Otto Wilhelm Thomé *Flora von Deutschland, Österreich und der Schweiz* 1885, Gera, Germany. Permission granted to use under GFDL by Kurt Stueber. www.biolib.de)

Traditional Use

The seeds of the milk thistle have been used for over 2,000 years in the treatment of liver ailments and gallbladder disorders including hepatitis, cirrhosis, and jaundice. Although other parts of the plant like the flowers are occasionally used, medicinally the seeds are most commonly used. Milk thistle was also used to protect the liver from damaging poisons from sources like snakebites, insect stings, mushroom poisoning, and alcohol (Abenavoli et al., 2010).

In the 4th century B.C. Theophrastus described milk thistle under the name *Pternix*. Milk thistle was later included in Dioscorides *De Materia Medica* in the 1st century A.D. All parts of this plant have been historically eaten as vegetables with no toxic side effects (Karkanis et al., 2011) and the root was also eaten as a nutritional supplement. Milk thistle was used in the Mediterranean and across Europe. Milk thistle was also used in Indian and Chinese medicine. In Traditional Chinese Medicine (TCM), milk thistle is thought to restore balance by fortifying *yin*, which is helpful in treating illness since illnesses that drain *yin*, the dark force that opposes yang (Bensky, 1986).

In Dr. Finley Elingwood's 1919 classic, *American Materia Medica, Therapeutics and Pharmacognosy*, milk thistle was used to improve the general bilious conditions like jaundice, hepatic pain, and swelling. In a study conducted in Mujib region of Jordan on the medicinal plants of the area, milk thistle was found to be an extremely important plant used for the treatment of liver diseases. The flowers and seeds were made into either decoctions or infusions (Hudaib et al., 2008). A different study conducted in the Calabria region (Southern Italy) found that milk thistle leaves are made into a decoction to treat hemorrhoids or make into an infusion as a diuretic (Passalacqua, Guarrera, and Fine, 2007).

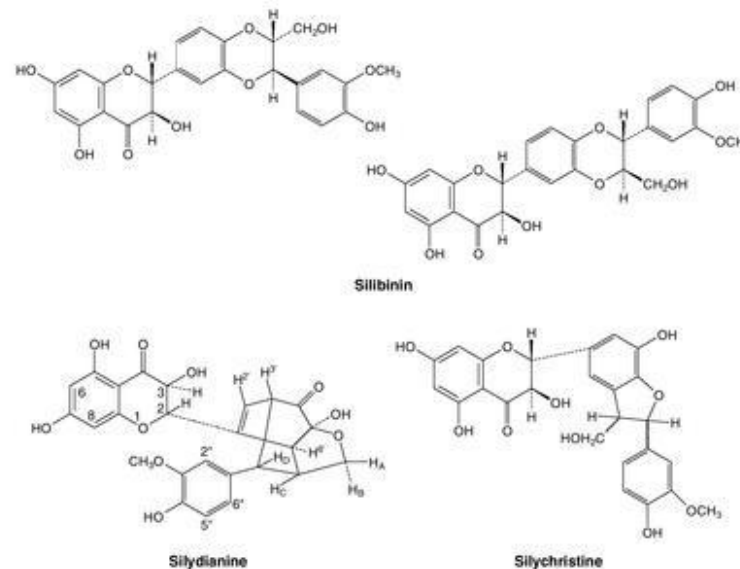


Figure 3. The components of silymarin: silibinin, silydianine, and silychristine. (Source: <http://www.medscape.com>)

Chemistry & Pharmacology

Most of the medicinal compounds found in milk thistle are present in high concentrations in the seeds. These compounds include silymarin, which is composed of three isomer flavonolignans: silybin, silydianin, and silychristin (Karkanis et al., 2011). Silymarin is 50 to 70% silybin. Silymarin has been shown to have the most biological activity and is a strong antioxidant. The seeds are about 20 to 35 % fatty acids and other polyphenolic compounds (Ramasamy and Agarwal, 2008). Seeds of milk thistle have also been discovered to contain other flavonolignans including isosilybin, dehydrosilybin, desoxysilychristin, silandrin, silybinome,

silyhermin, and neosilyhermin (Karkanis et al., 2011). Silymarin has very low toxicity, and silymarin is not water-soluble, so it is usually given in capsules that contain about 70 to 80% silymarin (Karkanis et al., 2011) (**Figure 3**).

Biological Activity

There are many hypotheses regarding the mechanism of action; the multitude of explanations concerning the mechanism of actions causes confusion and debate in the literature. Silymarin is absorbed orally and from there is distributed into the alimentary tract, which includes the liver, stomach, intestine, and pancreas (Karkanis et al., 2011). One theory is that silymarin's hepatoprotective action is due to its anti-free radical and anticarcinogenic ability, but its hepatoprotective action may also be due to other actions like its antioxidant, anti-lipid, peroxidative, antifibrotic, anti-inflammatory, immunomodulatory, and liver regenerating activity (Karkanis et al., 2011). Silymarin is a toxin-blocking agent, which inhibits how toxins bind to hepatocyte cell membrane receptors (Abenavoli et al., 2010). In addition, silymarin has shown anti-inflammatory and immunomodulation activity in various structures and pathways in the cell.

The anti-inflammatory properties of silymarin may be due to the way it regulates inflammatory mediators like the tumor necrosis factor (TNF), tumor necrosis factor-alpha, nitrous oxide, interleukin-6, and interleukin-1 receptors (Manna et al., 1999, Zi X et al., 1997, and Tager et al., 2001). This information suggests that silymarin may help to prevent and treat infectious disease.

With regards to the cytoprotective activity of milk thistle, several mechanisms have been observed. Milk thistle has been

shown to promote neuronal differentiation *in vitro* (Kittur et al., 2002). Another study suggested that silymarin inhibits leukotriene formation by Kupffer cells *in vitro* (Dehmlow et al., 1996). In addition, silymarin has been shown to increase the expression of growth factor beta-1 and c-myc in mice (He et al., 2002). Other *in vivo* studies have shown that silymarin may protect the pancreas from damage due to cyclosporine (von Schonfeld et al., 1997), protect the kidney from acetaminophen, cisplatin (Platinol), and vincristine (Oncovin) (Sonnenbichler et al., 1999), and protect the liver from damage due to carbon tetrachloride by reducing lipid peroxidation (Kravchenko et al., 2001). In baboons, silymarin was shown to slow the progression of alcohol-induced liver fibrosis (Lieber et al., 2003). Many other *in vitro* and *in vivo* studies suggest that milk thistle might have anti-cancer properties against cancers of the prostate, breast, skin, colon, tongue, and bladder (Tyagi et al., 2002, Zi et al., 1998, Kohno et al., 2002).

Clinical Studies

Most clinical trials have been done in patients with either hepatitis or cirrhosis, although other studies have been conducted concerning hyperlipidemia, diabetes, and *Amanita phalloides* (death-cap mushroom) poisoning. Overall, clinical trials have found lower bilirubin serum levels, which are a sign of an improved liver because high bilirubin levels are an indicator of liver inflammation, damage, and disease. One study on patients with hepatitis A and B found that silymarin helped lower levels of AST, ALT, and bilirubin in five days (Magliulo, Gagliardi, and Fiori, 1978). On the other hand, many clinical trials have shown that silymarin has no effect on liver disease or liver enzyme levels (Flisiak and Prokopowicz, 1997)

There is debate regarding whether or not silymarin has a direct effect on the hepatitis C virus, with contradictory evidence from various clinical trials. In a trial conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, users who were given silymarin reported fewer symptoms from their chronic liver disease and had a better quality of life than those who did not use the products containing silymarin. One report found that silymarin helped inhibit a tumor necrosis factor and increased peripheral blood mononuclear cells (Polyak et al., 2007). In addition, silymarin has also shown prophylactic and therapeutic effects against hepatitis C virus infection and helped increase the inhibitory ability of interferon-alpha against hepatitis C virus replication. This evidence shows that silymarin has both anti-inflammatory and antiviral properties for patients who suffer from hepatitis C.

Trials conducted on patients with chronic liver disease have also been promising. In a large study of over 2,500 patients with chronic liver disease, an eight week treatment of 560 mg/day of silymarin produced reductions of serum AST, ALT, and gamma-glutamyltranspeptidase (a sign of bile duct disease) and decreased the occurrence of palpable hepatomegaly (Albrecht et al., 1992).

Trials have discovered that silymarin may be useful in the treatment of cancer. In two case reports silymarin was used in individuals with cancer as a treatment and additional therapy. In one case a 34-year old woman with leukemia was given 800 mg of silymarin during maintenance therapy, which helped reduce the number of breaks in therapy due to abnormal liver enzyme levels (Invernizzi et al., 1993). In another case, a 52-year-old man with hepatocellular carcinoma was given 450 mg of silymarin per day and his tumor regressed although he had not started anticancer therapy (Grossmann, Hoermann, Weiss, et al., 1995). A report conducted on the use of silybin

claims that it is the only effective antidote for patients suffering from liver damage due to *Amanita phalloides* related poisoning (Enjalbert et al., 2002). In addition, a meta-analysis of herbal supplements on glycemic control, silymarin was shown to increase insulin resistance when used for eight weeks (Suksomboon et al., 2011).

Although milk thistle is arguably one of the most researched plants in the treatment of liver disease (Karkanis et al., 2011), studies done on silymarin and/or silybin are often controversial and are constantly reassessed (Kren and Walterova, 2005). Many studies have shown that constituents in various parts of milk thistle, most often the seeds, help the function of the liver but not all studies agree (Kren and Walterova, 2005). Studies concerning milk thistle also suffer from undefined mechanisms of action, undefined disease populations, different formulations of active components, and varying length of therapy (Kren and Walterova, 2005). Other studies are poorly designed. Overall, the undefined composition of silymarin preparations that are used in the studies is the most common cause of controversy (Kren and Walterova, 2005). This lack of standardization is because there is variation in the proportions of components in silymarin that depends on the source of the milk thistle seeds including the specific plant under cultivation and the conditions of cultivation (Kren and Walterova, 2005). In addition, silymarin extract and the pure compound of silymarin are often confused in the literature (**Table 1**).

Contraindications

In general, silymarin and silybin are thought to be safe with rare adverse effects. One study, Jacobs et al., 2002, reported three serious side effects. After being given a combination herbal formula which contained milk thistle one of the

Efficacy	Acute and chronic viral hepatitis, alcoholic liver disease: conflicting evidence. Cytoprotection: rigorous randomized controlled trials ongoing; limited evidence suggests benefit. Anticarcinogen: clinical trials ongoing Amanita phalloides poisoning: insufficient data
Adverse effects	Generally well tolerated; infrequent reports of gastrointestinal disturbances; rare reports of pruritus, eczema, rash, and anaphylaxis*CAUTION: do not use in patients with allergies to members of the aster family.
Interactions	No significant drug interactions
Dosage	Milk thistle seed extract, 150- to 175-mg capsule, standardized to 80 percent silymarin, three times daily. Ultrathistle (seed extract bound to phosphatidylcholine), 360-mg capsule, three times daily
Cost	\$15 to \$30 per month at 150 to 175 mg three times daily \$42 per month at 360 mg three times daily
Bottom line	Safe, no known drug interactions; insufficient data to recommend for treatment of liver disease; under investigation for anticarcinogenic and chemoprotective effects

*—Three nonfatal case reports, only one of which is sufficiently attributed to the herb

Table 1. Key points about milk thistle (Rainone, 2005).

patients in the study suffered from gastroenteritis symptoms. Jacobs et al. also reported anaphylactic reactions after drinking milk thistle tea. Other smaller reactions have been reported, the most common of which being gastrointestinal symptoms, dermatological effects, and headaches, but these symptoms were also reported in the placebo groups. Due to the low solubility of silybin, it is very difficult to reach toxic

concentrations *in vivo*. Although silybin and its related flavonolignans showed inhibition of the catalytic activities of cytochrome P450(CYP) isoenzymes *in vitro*, the concentrations required to achieve this are almost physiologically impossible (Kren and Walterova, 2005). These findings suggest that the likelihood of drug interactions involving silymarin and silybin are lower, although further studies are required to better determine the mechanisms of actions in order to better understand the adverse side effects (Kren and Walterova, 2005). On the other hand, other studies suggest that interactions between silymarin and other prescriptions may lead to serious clinical reactions. Milk thistle constituents may have negative reactions when taken with nifedipine, iriontecan, metronidazole, indinavir, pyrazinamide, digoxin, rosuvastatin, and ranitidine (Wu et al., 2009).

Current Use in Allopathic & CAM

Milk thistle is sold in many herbal products for the treatment of various ailments but mainly for liver problems. These products can be found online and in many stores from herbal specialty stores to supermarkets. Commonly, these products contain either the dried milk thistle seeds or extracted silymarin. Silymarin is sold under a wide variety of trade names including Legalon, Silipide, and Siliphos (**Figure 4**). These products can cost anywhere from three dollars to seventy dollars, but these costs can change dramatically depending on the supply of milk thistle that year.

In allopathic medicine, milk thistle, and the associated chemical silymarin, is mainly used in clinical settings for the treatment of hepatitis and cirrhosis (Post-White et al., 2007). The main constituent, silymarin, is given as a milk thistle seed extract, 150 mg to 175 mg per capsule with a standardization



Figure 4. Legalon – one of the tradenames that silymarin is marketed under. (Source: http://www.poisoncentre.be/article.php?id_article=223)

of 80 percent silymarin three times daily (Rainone, 2005). Milk thistle is also taken in other forms like liquid extracts and tinctures. This is taken to treat liver disease and used in conjunction with other treatments that may have liver damaging effects. Milk thistle may also be given to reduce damage from a variety of poisons.

Discussion

Milk thistle has been an important botanical throughout the world, especially in Europe and Asia, but also in the U.S in the growing herbal market for people interested in more natural alternatives to biomedicine. It is incorporated in many treatments, both allopathic and CAM, for liver ailments and other various health problems like diabetes, hemorrhoids, and liver damage from alcohol abuse. Like many other botanicals, there are many online sources that suggest milk thistle is a

panacea, but these claims should be used with care until more research can be completed. Although milk thistle may be as effective as herbal supplies describe, milk thistle is a relatively safe plant with low toxicity.

Currently, information on how milk thistle was traditionally prepared is rare in the scientific literature, perhaps because knowledge on the use of this botanical was spread by word of mouth. Studies that do include traditional uses of milk thistle lack detail, listing the part of the plant and the type of preparation made but not how that preparation is made. Historically, milk thistle was also reputed to help nursing mothers produce milk and eaten as a nutritional supplement, but these claims are not supported by the scientific literature although one study has suggested that milk thistle spouts may be a good source of nutrients and antioxidants (Vaknin, 2008). Milk thistle is used to improve liver function and often administered when certain diseases result in decreased liver function. There has been promising research that milk thistle might have many anti-cancer properties and also help relieve the liver damaging effects of many cancer treatments. Negative side effects of milk thistle are rare although there may be significant drug reactions, so consultation with a physician is important when combining milk thistle with biomedical drugs.

Future studies on milk thistle might clear up confusion regarding the effectiveness of milk thistle constituents. Milk thistle's most biologically active set of compounds found in silymarin may be found to have greater effects in the treatment of various liver diseases, cancers, and anti-toxin abilities. New treatments for these problems will become increasingly important as toxins build up in the environment, which will lead to increased cancer rates. As history has shown, cancer and chronic disease are on the rise due to many factors, some determined while others are unknown. The rise

in rates of liver disease and diabetes may be due to increased alcoholism and obesity, and there is potential for milk thistle to be used to combat the side effects from both diseases. Since milk thistle has a long historical use and numerous current applications, it should be tested further. Such studies may lead to new treatments for these health problems and many others.

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Solidago virgaurea L., Asteraceae

Alisha Morris

Introduction

Solidago virgaurea (European goldenrod) belongs to the Asteraceae family. The herbal substance consists of the dried, flowering parts of the plant. It has been used for treatment of different diseases such as arthritis and diabetes. Today, it is mostly used as an aquaretic agent. Studies have found that the active constituents help reduce inflammation, relieve muscle spasms, fight infections and cancer, lower blood pressure, and have antioxidant effects (UM Medical Center).

Description

European goldenrod is a perennial found along roadsides and in open fields. It has a single woody stem that grows to heights of 3 to 7 feet. It has yellow flowers, about 1/4 of a inch wide and come in large clusters. They appear mainly in August and September (**Figure 1**). The leaves alternate between toothed and smooth edges. The plant is native to Europe and the Asia mainland. Different species of the goldenrod can be found in many locations outside of Europe because of its ability to crossbreed with other plants. Its pollen grains are meant to be carried by insects because of their heaviness in comparison to plants with airborne pollens (UM Medical Center).

Traditional Uses

The goldenrod has been used to treat tuberculosis, diabetes, enlargement of the liver, gout, hemorrhoids, internal bleeding, asthma, and arthritis. Topically, it is used to treat inflammation of the mouth and throat as well as slow-healing



Figure 1. Picture of Golden rod, *Solidago virgaurea* (Source: Naturephoto-cz.eu).

wounds. It may be taken in a variety of forms, including the dried herb; for teas and capsules, tincture (a medicine consisting of an extract in an alcohol solution), or fluid extract (UM Medical Center). It also used frequently in Europe as a treatment for urinary tract infection and to prevent or treat kidney stones. It has been approved by the German Commission E as a diuretic, anti-inflammatory, and antispasmodic for the treatment of urinary tract disorders (Vitamin for life 2002). In the Appalachian Mountain region of the U.S., its leaves have been used to prepare tea, which is taken as a treatment to combat fatigue and physical exhaustion (Annussek 2001).

Chemistry & Pharmacology

European goldenrod contains about 1.5% flavonoids (quercetin, kaempferol, astragalin, and rutoside) and antocyanidins. Others constituents include about 2% of triterpene saponins, between 0.08% and 0.48% bisdesmosidic phenol glycosides leiocarposide and virgaureoside A, diterpenoid lactones of cis-clerodane type phenolic acids including caffeic acid and chlorogenic acid (0.2-0.4%), and small amounts of essential oils (**Figures 2**). The pharmacological effects of goldenrod have been described in several researches and reviews. A synergistic action of several components of the *S. virgaurea* are proposed. Therefore, the herbal substance or herbal preparations from goldenrod must be considered as the active ingredient (European Medicines Agency, 2008).

Biological Activity

Anti-inflammatory activity

Anti-inflammatory influence of goldenrod extracts from Phytodolor N on the activity of myeloperoxidase liberated by the activated granulocytes was estimated in *in vitro* experiments. Goldenrod extract did not inhibit myeloperoxidase activity at concentrations up to about 1%. It proved that its anti-inflammatory and anti-rheumatic properties were comparable to non-steroidal anti-inflammatories, but with little or no side effects (Von Kruedener et al. 1995). Extracts of *S. virgaurea* (aqueous/alcoholic) were tested individually for anti-inflammatory activity using carrageenan induced edema and adjuvant induced arthritis of the rat paw as well as Extracts of *Populus tremula* and *Fraxinus excelsior* were also tested. All of the extracts showed significantly reduction of the carrageen

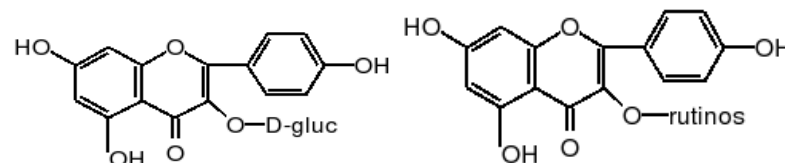


Figure 2. European goldenrod flavonoids (Dzyubak).

edema and the volume of the arthritic paw (El-Ghazaly et al. 1992). Phytodolor (composition of *S. virgaurea*, *Fraxinus excelsior* and *Populus tremula*) was tested for an anti-inflammatory, analgesic, and antipyretic activity in rats. Activity was similar to that of the reference substances salicylic alcohol and indomethacin. All of the extracts displayed considerable efficacy (Okpanyi et al. 1989).

Antibacterial activity

Nine clerodone diterpenes were isolated and characterised from ethanol-ethyl acetate extract of *S. virgaurea*. Many of these showed moderate antibacterial activity against *Staphylococcus aureus* (Starks et al. 2010). Antimicrobial activity of the extracts from *S. virgaurea* were tested *in vitro* by use of free-dried biomass from 4 week old callus cultures of the plant. The minimal bactericidal concentrations of the extracts estimated with the agar diffusion assay method showed moderate activity (Thiem and Goslinska 2002).

Antifungal activity

Triterpenoid glycosides obtained from *S. virgaurea* and *Beallia perennis* inhibited the growth of human pathogenic yeasts. The intensity of growth inhibition is influenced particularly by the carbohydrate chains of the glycosides. Monodesmosidic and bisdesmosidic glycosides of polygalacic acid exert

fungicidal effects (Bader 1990). Glycosides of polygalacic acid are isolated from the aerial parts of *S. virgaurea*. The glycosides were tested against human pathogenic strains of *Candida albicans*, *C. glabrata*, *C. krusei*, and *C. tropicalis* using a micro-dilution assay. The antifungal action can influence the variation of the etherglycosidically bonded carbohydrate units at C-3 and the acylglycosidically bonded oligosaccharide at C-28 of the aglycone (Bader et al 2000).

Antioxidant activity

Ethanollic extracts of *S. virgaurea*, *Potentilla anserina*, *Radix Rubiae tinctorum*, *Equisetum arvense*, *Oleum juniperi* and *Petroselinum sativi fructus* mixtures were used *in vitro* to estimate glucose consumption by rabbit brain slices. With an increase of glucose consumption and the aerobic formation of lactic acid, the swelling of the brain slices was significantly diminished (European Medicines Agency, 2008; Dittmann 1973). Extracts (aqueous/ethanollic) from *Fraxinus excelsior*, *Populus tremula* and *S. virgaurea*, all carriers of phytodolor, were tested *in vitro* for antioxidant activity. The activity of xanthine oxidase, diaphorase, lipoxygenase, riboflavin and rose bengal were studied. The results showed inhibition of production of reactive oxygen species that were mentioned above (Meyer et al. 1995).

Analgesic activity

The analgesic activity of *S. virgaurea* was tested *in vitro* for affinity to three neuropeptide receptors involved in the mediation of acute pain in mammals. The receptors were bradykinin (expressed in Chinese hamster ovary cells), neurokinin 1 (expressed in astrocytoma cells), and calcitonin gene related peptides. The results showed there was

significant inhibition of radioligand binding for bradykinin receptors (Sampson et al. 2000).

Spasmolytic activity

Extract of leaves from *S. virgaurea* inhibited muscarinic M2 and M3 receptor-mediated contraction of rat and human bladder muscle strips. 0.01% concentrations appeared to result from non-competitive muscarinic receptor antagonism. 0.1% concentrations might have a non-specific inhibitor effect. However, the relationship between *in vitro* concentrations and therapeutic doses remained unclear due to unknown bioavailability of the active ingredients of the extract (Borchert et al. 2004). According to Westendorf and Vahlenieck (1981), *S. virgaurea* ethanollic extract induced spasmolytic activity in the range of 14.7% of papaverin in an *in vitro* experiment on isolated smooth muscles of intestines of guinea pig (European Medicines Agency, 2008). According to Racz et al. (1980) and Duarte et al. (1993), the presence of flavonoids in goldenrod preparations may contribute to explain vascular smooth muscle relaxation. The vasodilatory action depends on the inhibition of protein kinase C, inhibition of cyclic nucleotide phosphodiesterase, or decrease of calcium uptake (European Medicines Agency, 2008). The phytotherapeutic product (Extr. Rad. Rubiae tinct. Spir., Extr. Sem. Ammeos visnagae spir., Extr. Herb. *S. virgaurea* spir., Extr. Rad. Taraxaci) and aescin exhibited spasmolytic activity *in vitro* in acetylcholine pretreated urinary bladder of the rat (European Medicines Agency, 2008, Westendorf and Wahlenieck 1983).

Anticancer activity

In a study using mice with an allogenic sarcoma-180 model and syngenic sarcoma model, significant tumor inhibitory action against Virgaurea saponin E was found (European Medicines Agency, 2008; Bader et al. 1996; 1998b). In another series of experiments the antitumor effects of polysaccharides were demonstrated. In an SCID mouse model antineoplastic activity of *S. virgaurea* on prostatic tumor cells was tested and cytotoxic activity on various tumor cell lines were demonstrated. The active fraction of the extract corresponding to a molecular weight of about 40,000 grams per mole, was administered intraperitoneal or subcutaneous every 3 days for 25 days in an experimental tumor model in mice. Tumor growth was inhibited at 5mg/kg (European Medicines Agency, 2008; Gross et al 2002).

Immunobiological activity

According to European Medicines Agency, Plohman *et. al* (1997,1999) stated that the immunomodulatory and antitumor activity of triterpene saponins were shown in *in vitro* experiments (Plohman et al. 1997, 1999). Choi et. al (2005) used *in vitro* mouse peritoneal macrophages to showed that two compounds from *S. virgaurea* exhibited stimulation macrophage function that suggested potential use in the treatment of infectious diseases and tumors (European Medicines Agency, 2008).

Diuretic activity

The diuretic properties are prevalence in studies performed on the European goldenrod. Leiocarposide was isolated from *S. virgaurea* var. *leiocarpa* (European Medicines Agency, 2008; Hiller et al. 1979) and was found in *Solidago virgaurea* L

(European Medicines Agency, 2008; Chodera et al. 1985a, 1985b; Budzianowski 1999). The compound exhibited diuretic activity in rats: only 75% lower than furosemide (European Medicines Agency, 2008; Chodera et al. 1985a). The diuretic action was delayed but, began 5 hours after administration and lasted up to 24 hours (European Medicines Agency, 2008; Chodera et al. 1985b). The flavonoid fraction of *S. virgaurea* was administered to rats and showed an increase of diuresis. Decrease of an overnight excretion of potassium and sodium and an increase of excretion of calcium ions was observed (European Medicines Agency, 2008; Chodera et al. 1991).

According to the European Medicines Agency (2008), Schilcher et. al (1989) demonstrated that leiocarposide diuretic activity was reduced by the presence of flavonoids and saponins. In contrary, some researchers suggest that diuretic activity of goldenrod is exerted by the mixture of flavonoids and saponins. Others demonstrated in animal studies that relative inactivity of the flavonoid mixture present. After 6 weeks of administration of leiocarposide, a significantly decreased of growth of the renal calculi was observed in experimentally induced renal calculi models in rats (European Medicines Agency, 2008; Chodera et al. 1988). After oral administration of an infusion of *S. virgaurea*, significant increase of diuresis in rats together with an increased elimination of sodium, potassium and chloride ions was observed. The lower dose was more efficient though (European Medicines Agency, 2008; Schilcher and Rau 1988). Active flavonoides of *S. virgaurea* inhibit NEP and the converting enzyme activity of angiotensin (European Medicines Agency, 2008; Schilcher and Rau 1988; Melzig et al. 2001a; Melzig and Major 2000; Major 2001). According to Melzig and Major (2000), the mechanism of beneficial renal and cardiovascular activity of *S. virgaurea* can depend on

modulation of neutral endopeptidase activity. By increasing water and sodium excretion and arterial and venous vasodilatation, *Solidago* treatment can regulate water and sodium balance and cardiovascular homeostasis by blocking the hydrolysis of the vasoactive peptides (European Medicines Agency, 2008).

Clinical Studies

An ethanolic extract made from fresh *S. virgaurea* was tested in an open post marketing crossover study with placebo in 22 healthy patients between the ages 17 and 61. The patients received 100 drops/day of the ethanolic extract for 2 days. In *Solidago* treated groups a significant increase of daily volume of urine was observed (European Medicines Agency, 2008; Klinisch-Experimentelle Studie Nr 23223. P 1. 1992). The ethanolic extract of *S. virgaurea* L., made from fresh plant, was tested in 53 patients in a year long open multicenter postmarketing study. The patients consisted of 45 females and 8 males between the ages 6 and 83 with symptoms of urinary tract inflammation, dysuria, pollakisuria, and tenesmus. Patients with renal stones, renal carcinoma, gonorrhoea, syphilis, AIDS and marked prostate hyperplasia were excluded, as well as patients with bacterial counts in urine over 10⁴. After treatment, 65.4% of treated patients showed significant clinical improvement with significant reduction of dysuria, pollakisuria and tenesmus (European Medicines Agency, 2008; Klinisch-Experimentelle Studie Nr. 23223.P2. 1992). In an open multicenter study, the efficacy of the dry extract of *S. virgaurea* was tested. It was performed by 289 physicians in 745 female patients between 12 and 94 years of age with dysuria of different origins. After 14 days of treatment with *Solidago* extract, 69.2% of patients' micturition frequency was decreased as the other symptoms

of cystitis (European Medicines Agency, 2008; Schmitt 1996). The efficacy of the *S. virgaurea* extract was estimated in a postmarketing study performed on 1487 patients with several urinary tract diseases. Patients were treated in average for 4 weeks. 79% of patients reached significance in global improvement when evaluated by physicians (European Medicines Agency, 2008; Laszig et al. 1999).

An open multicenter study was performed on 1,487 patients with chronic recurrent irritable bladder conditions. They were treated for five weeks. The patients received *S. virgaurea* dry extract. In result, 96% of the patients treated showed improvement registered in clinical global impressions scale, and in 80.1% of patient's estimation of effectiveness was good or very good. Side effects were not registered (European Medicines Agency, 2008; Melzig et al. 2001b; Pfannkuch and Stammwitz 2002). According to Laszig et al. (1999), there was a case report of patients treated with *S. virgaurea* dry extract for 4 weeks after extracorporeal shock wave lithotripsy resulted with spasmolytic effects, and lack of additional spasmolytic treatment needed (European Medicines Agency, 2008).

Contraindications

Solidago virgaurea is contraindicated for patients with the following conditions: hypertension, hypotension, and osteoporosis. This should not be taken if pregnant, breast feeding, or have heart or kidney disease. Goldenrod may increase the effects of diuretics, increasing the risk of dehydration. It could cause of lithium to build up in the blood, if taking lithium medication (UM Medical Center). Acute toxicity of leiocarpaside in rats was reported (European Medicines Agency, 2008; Chodera et al. 1985b).

Current Use in Allopathic & CAM

Solidago virgaurea is used in Pauri Garhwal and Uttarakhand for kidney trouble, asthma, and throat infection. It serves as an alternative to modern medical treatments available to the local inhabitants who have poor economic conditions (Pala et al. 2010). Phytodolor, an active constituent, is a reasonable alternative to NSAIDs and to cyclooxygenase-2-inhibitors such as rofecoxib (Gundermann and Muller 2007). In Europe, it is used as a supportive treatment for bladder infections, irritation of the urinary tract and for bladder/kidney stones. It increases the flow of urine, helping to wash out bacteria and kidney stones and it may also soothe inflamed tissues and calm muscle spasms in the urinary tract. Goldenrod is useful for the treatment of upper respiratory catarrh and it helps to thin mucus secretions and relieve congested mucus. This herb has been used in combination with other herbs in the treatment of influenza. It is beneficial when used for flatulent dyspepsia. It also promotes the healing of wounds. When gargled, it can relieve sore, throat, laryngitis and pharyngitis. When used as a wash or compress, it aids in wound healing, headaches, and rheumatism. As a douche, it can treat yeast infections. It can also be used as a poultice for bee stings, as a hair rinse for blond hair, and as a bath herb for facial steams (Viable Herbal Solutions).

Discussion

Research studies have shown diuretic, anti-inflammatory, antioxidant, analgesic, spasmolytic, antibacterial, antifungal, anticancer, and immunomodulatory activity of *S. virgaurea*. There is no single ingredient responsible for these activities but result from many of the constituents working together. However, the whole herbal preparation of goldenrod's flowering part must be considered as the area containing the

medicinal constituents. Acute toxicity of the leiocarposide in rats was reported (European Medicines Agency, 2008; Chodera et al. 1985b). European goldenrod is a reasonable alternative for treatment of diseases mentioned or can be used as supportive treatment in conjunction with antibiotics.

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Taxus brevifolia Nutt., Taxaceae

Wallace Wyeth

Introduction

The Pacific yew tree, *Taxus brevifolia*, is the source of a very important drug used in the treatment of cancer. The Pacific yew, also known as the western yew, is a member of the Taxaceae family (Lewis and Elvin-Lewis 2003). The discovery of *T. brevifolia* as a source of a biologically active phytochemical resulted from its collection in 1962 by botanists from the US Department of Agriculture (Kingston 2007). This collection was part of a large scale screening program then being conducted by the National Cancer Institute. The tree was among a group of 35,000 plants screened for bio-active metabolites (Vongpaseuth and Roberts 2007). The biologically active phytochemical found in this slow growing tree is paclitaxel, a diterpenoid that is extracted from the bark. The Pacific yew is so slow growing that it takes approximately 100 years for a tree to be large enough to harvest. Even then, the yield of anticancer diterpene is very low, in the range of about 0.01 to 0.02%. With such a low yield, it takes three 100 year old trees to produce 1 gram of paclitaxel. Each course of treatment requires 2 grams of the drug (Heinrich, et al. 2004), resulting in the need for a tremendous number of trees. Renneberg described the needed amount of paclitaxel in terms of how many trees would be required each year to treat the patients with ovarian cancer. 360,000 trees per year would be needed just to treat the US patients (Renneberg 2007). In order to protect *T. brevifolia* from being over utilized, a renewable source of paclitaxel would have to be found.



Figure 1. *Taxus brevifolia* in a forest in Canada. The brush in the foreground and the conifers in the background provide a sense of scale (Tigner 2008).



Figure 2. This photograph of the trunk displays the scaly nature of the bark and the multiple hues of purple described in the text (McDougall 2003).

Description

Taxus brevifolia Nutt. (Taxaceae) is described as a small tree, or a large evergreen shrub (**Figure 1**). The bark is thin, scaly, and is purplish in color (**Figure 2**). The tree may reach a height of 15 meters in areas conducive to maximum growth such as coastal areas or some low lying inland areas. Trees of this size are approximately 60 cm (about 2 feet) in diameter at chest height. When conditions are less favorable and at higher elevations, the Pacific yew will only reach a height of a few meters and will be proportionally smaller in diameter as well (Francis n.d.). Leaves are narrow and vary from 8 to 35 millimeters in length (up to 1 1/3 inch). The Pacific yew produces an ovoid seed 5 to 6 millimeters long that is enclosed in a fleshy cup shaped red aril (**Figure 3**). The range



Figure 3. Leaves and fruit of *Taxus brevifolia*. The leaves and seeds are toxic, but the red aril surrounding the seed is not (Pacific Yew *Taxus brevifolia* n.d.).

of the species is from southern Alaska to northern California. It is sometimes found as far inland as just east of the Oregon or Washington eastern borders. The largest examples of the species are found along the coast with those further inland generally diminishing in size. It is found from sea level to an elevation of 2,200 meters (Francis n.d.). *T. brevifolia* is usually the dominant understory plant, most commonly in coniferous forests. It sometimes grows exposed at higher elevations and also when exposed by logging of the overstory species. It is generally considered a hardy species (Francis n.d.), but is very vulnerable to fire, and controlled burns are not recommended in forests where the Pacific yew is found (Tirmenstein 1990). The same report stated that due to its thin bark, Pacific yew is always killed by even small ground fires. If the species is abundant in a given area its presence indicates a significant period with an absence of fire. It was observed that in one part of Idaho where the species was eliminated by fire, a

period of 6 years transpired before seedlings began to germinate (Tirmenstein 1990).

The Pacific yew can propagate both by seed and by vegetative means. Layering is the primary method of propagation in some areas (Tirmenstein 1990). Layering is a process where lower limbs that come into contact with the ground form roots and establish a new plant. Pacific yew is dioecious and male plants produce abundant 3 mm staminate cones. Ovulate cones are green and appear individually on the underside of branches. The fruit is red and berrylike as described above and is regularly consumed by several bird species (Tirmenstein 1990). It is common for birds to disperse the seeds of the Pacific yew. Seeds are known to exhibit dormant behavior. Passage through the avian gut may affect this dormancy in some way. It takes 250 to 350 years for a Pacific yew to reach maturity and individuals often survive for several centuries (Tirmenstein 1990).

Traditional Uses

Ethnomedical Uses

People of the Pacific Northwest made a tonic from the Pacific yew that was used medicinally (Tirmenstein 1990). Moerman (2004) lists a number of ethnomedical uses by the various tribes in that region. It was used either topically or taken internally as an infusion or decoction. The Chehalis people used *Taxus brevifolia* as a diaphoretic (Moerman 2004). An infusion was made from the crushed leaves that was then used as a wash to cause perspiration. These same people also used it as a panacea, a cure all, by making a similar infusion and using it as a wash to improve general health (Moerman 2004). The Bella Coola boiled the branches complete with leaves to make a decoction used as a pulmonary aid. The Cowlitz

people made a poultice from the ground leaves for use as a topical dermatological aid that was applied to wounds (Moerman 2004). Another group made a decoction of the wood and bark that was used both as a gastrointestinal aid to relieve stomach ache and also for other internal ailments. Several other tribes used products from the Pacific yew for similar treatments as well as using it as an analgesic to relieve pain, for the treatment of bloody urine, to treat internal injuries, to treat sunburn, and as a blood medicine to purify the blood (Moerman 2004). The Tsimshian people used it for internal ailments and to treat cancer, though the method of preparation for the cancer medication is not described (Moerman 2004).

Other Ethnobotanical Uses

In his book, *Native American Ethnobotany*, Moerman (2004) provides a list of the uses made by Native Americans of various plants. On the list of non food, non medical uses, *Taxus brevifolia* is second on the list with 84 uses, behind only *Thuja plicata* (Cupressaceae), the Western Red Cedar, with 121 uses (Moerman 2004).

The wood from *T. brevifolia* is fine grained and hard as well as being very strong and decay resistant. The sapwood is light yellow whereas the heartwood is orange or a rosy red. The wood finishes well and is sometimes used in cabinet making or to make tool handles or boat paddles. Despite this, the wood is not considered to be commercially important (Tirmenstein 1990). Native Americans also used the wood of the Pacific yew to make boat paddles, but additionally used it for making harpoons, spear handles, clubs and, most importantly, bows. Pacific yew is considered to be an excellent source of material for making

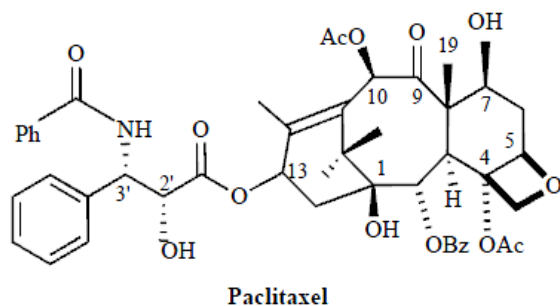


Figure 4. Structure of paclitaxel. Note the side molecule attached at carbon number 13 (Kingston 2007).

bows. The Salish people called it the bow plant (Tirmenstein 1990). Pacific yew is still used to make bows. These bows are very expensive because the wood from which they are made is usually cured for decades (Tirmenstein 1990). Though the Pacific yew is supposedly toxic to domestic livestock, it provides important browse for wildlife species including deer, elk and particularly moose. It is reported that moose depend on Pacific yew over the winter months and from it obtain approximately 40% of their nutritional requirements during this period. The claim that Pacific yew is toxic to livestock has not been substantiated. Some livestock owners claim it is not toxic when eaten as browse, but becomes dangerous if cut and allowed to decay. There are also claims that the fruit is toxic to some species, but songbirds and some mammals are known to feed on the fruit (Tirmenstein 1990). Native Americans also ate the fleshy portions of the fruit, but not the seeds which are poisonous. Native Americans used the foliage as a deodorant due to its fragrance and also used it as a cleaning agent. Some Native Americans associated the Pacific yew with death and bereavement (Tirmenstein 1990).

Chemistry and Pharmacology

The principle active molecule in *Taxus brevifolia* is paclitaxel. Originally known as taxol, paclitaxel is a very complex plant secondary metabolite (**Figure 4**). Because of this complexity, it took years to determine the molecule's structure and that it was the active constituent in *T. brevifolia*.

After its initial collection in 1962, plant extracts from the Pacific yew underwent testing in 1963. These tests confirmed the cytotoxicity of these extracts against human KB cells (Kingston 2007). This eventually led to a second bark collection in 1965 that was sent to the Research Triangle Institute (RTI) for further testing. Activity against mouse leukemia was confirmed in 1966, but nevertheless, the active constituent molecule was not isolated until 1969 (Kingston 2007). Taxol was identified as the isolated active constituent (Kingston 2007) but not until 1971 was it confirmed that taxol was the anti-tumor component of the *T. brevifolia* extracts (Vongpaseuth and Roberts 2007). This pattern of discovery and long lapses of time with little progress became the signature of the investigation of the extracts obtained from *T. brevifolia*.

Despite its activity against mouse leukemia that was discovered in 1966, and activity against other leukemia's and carcinosarcoma demonstrated later, other available compounds worked as well or better in these tests, so interest in the products from the Pacific yew remained low (Kingston 2007). There remained just enough interest in taxol, as it was still called then, that more testing was conducted in the early 1970's. These results led to even further testing and the eventual selection of paclitaxel as a development candidate in 1977. The end to the start and stop process of investigation did not come until the mechanism of action was discovered (Kingston 2007). It was the discovery of the unique tubulin

Year	Events
1963	Anti-tumor activity in the extract of <i>T. brevifolia</i> bark tissue was discovered during large-scale screening of 35,000 plants.
1971	Paclitaxel was identified as the active component of anti-tumor activity.
1974	First callus culture of <i>T. baccata</i> induced.
1979	Paclitaxel's unique mode of action, i.e., tubulin stabilization, was identified.
1983	NCI begins conducting clinical trials of paclitaxel's safety and its effectiveness against various types of cancer.
1989	Paclitaxel produced partial or complete responses in 30% of previously treated patients with advanced ovarian cancer.
1989	First reports of paclitaxel production from callus and cell suspension cultures.
1991	Bristol-Myers Squibb is selected by the NCI to be its commercial partner in developing TAXOL injection and signs a CRADA with the NCI.
1992	FDA approved the use of paclitaxel for refractory ovarian cancer. Clinical trials using paclitaxel demonstrated that the drug is effective against advanced breast cancer.
1993	Bristol-Myers Squibb ends <i>T. brevifolia</i> bark harvesting for the manufacture of TAXOL and begins to develop other renewable sources for the drug.
1994	FDA approved the use of paclitaxel for breast cancer that has recurred within 6 months of completion of initial chemotherapy and for metastatic breast cancer that is not responding to combination chemotherapy.
1994	Two separate groups independently report the total synthesis of paclitaxel. Unfortunately, efficiency is not high enough for industrial production.
1995	The semisynthetic form of paclitaxel receives clearance for marketing from the FDA.
1995	Phyton, Inc. announces that it has licensed its <i>Taxus</i> spp. cell culture technology to Bristol-Myers Squibb.
1997	FDA-approved semisynthetic TAXOL for the second-line treatment of AIDS-related Kaposi's sarcoma. Paclitaxel produced by plant cell culture was approved in Korea and was marketed as Genexol by Samyang Genex.
1998	FDA-approved semisynthetic TAXOL in combination with cisplatin for first-line treatment of advanced carcinoma of the ovary.
1999	FDA-approved semisynthetic TAXOL in combination with cisplatin for first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.
2001	Export of cell culture-based Genexol by Samyang Genex.
2004	Bristol-Myers Squibb receives a Presidential Green Chemistry Challenge Award for development of a green synthesis for TAXOL manufacture via plant cell fermentation and extraction.
2005	FDA approved abraxane, a drug that is composed of paclitaxel conjugated to albumin to increase efficiency of delivery. It is approved for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy.
2006	Studies examining the use of paclitaxel in Alzheimer's and heart disease treatments begin.

Table 1. History of paclitaxel (Vongpaseuth and Roberts 2007).

stabilization mode of action in 1979 (Vongpaseuth and Roberts 2007) that solidified interest in the molecule (**Table 1**).

Despite its halting nature, research of the chemical properties of the *T. brevifolia* extracts continued through the 1960's and 1970's. As earlier stated, Taxol was isolated in 1969. However, the yield of Taxol from the bark of the Pacific yew was only 0.01% and the concentration in other parts of the plant, such as the wood and needles, was even lower so little Taxol was available for experimentation. It was not until 1971 that the structure of paclitaxel was finally determined after the molecule was degraded by the cleavage of a side chain from the main molecule (Figure 5). The cleavage resulted in two molecules, 10-acetylbaccatin and β -phenylisoserine ester (Kingston 2007). There were a number of reasons why it was so difficult to determine the structure of paclitaxel. Magnetic imaging was not nearly as advanced at that time as it is now. The complex nature of the molecule was a contributing factor as was the extremely limited quantity of paclitaxel that was available for analysis (Wall and Wani 1995). Although a number of crystalline compounds were obtained prior to degradation of the main molecule, none of them were suitable for x-ray analysis which was necessary to help determine the structure of the molecule. After the cleavage of the side chain, the resulting smaller molecules were then crystallized and were suitable for x-ray analysis (Heinrich, et al. 2004). Determining the structure of the constituent molecules allowed the structure of the parent molecule to be determined (Wall and Wani 1995).

Biological Activity

Paclitaxel does exhibit biological activity. The extracts from the bark of *Taxus brevifolia* were first studied because of anti-

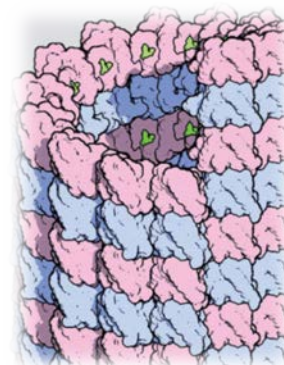


Figure 6. Paclitaxel (green) binding tubulin and stabilizing the microtubules (Renneberg 2007).

tumor activity discovered during screening using KB cytotoxicity assay (Kingston 2007). *In vivo* activity testing was done in 1966 that confirmed the bark extract was active against mouse leukemia. Other *in vivo* testing was done against other leukemia's and Walker 256 carcinosarcoma that showed only modest activity. Additional *in vivo* bio assays were developed in the early 1970's. The paclitaxel results in the B16 mouse melanoma assay led to growing support within the National Cancer Institute to pursue development. New tests were developed for testing mammary and colon xenografts in mice. Paclitaxel demonstrated good activity in these tests and was selected for development in 1977 (Kingston 2007).

Susan Horwitz discovered the mechanism of action of paclitaxel in 1979. Paclitaxel works by inhibiting mitosis. Other products discovered before paclitaxel such as vincristine and colchicine also inhibit mitosis. However, paclitaxel works completely opposite those other products. While vincristine for example inhibits mitosis by binding tubulin and preventing the formation of the microtubules required for mitosis, paclitaxel stabilizes microtubules and

prevents depolymerization (Heinrich, et al. 2004). Paclitaxel and its analogue docetaxel have their greatest effect on cells that divide rapidly such as cancer cells. It binds to the tubulin subunits of microtubules (**Figure 6**) and prevents disassembly. The interruption of the cell cycle leads to programmed cell death (Renneberg 2007). The novel method by which paclitaxel inhibited mitosis and initiated cell death contributed to the growing interest in the compound and led to clinical trials (Heinrich, et al. 2004).

Many patients do develop resistance to paclitaxel (Renneberg 2007). The mechanisms that result in resistance are complex and included many potentially contributing processes. Factors listed include rates of expression for cell membrane transporters with increased expression of efflux and decreased expression of influx transporters. Increased expression of resistance associated proteins was also reported. Other factors include over expression of enzymes that metabolize paclitaxel, tubulin mutations that reduce paclitaxel binding, and changes in the signaling pathways leading to microtubule formation (Kumar, et al. 2010).

Clinical Studies

Preclinical toxicology testing of paclitaxel was completed in 1982. Phase I clinical testing was started in 1984 and phase II trials followed in 1985. Serious side effects in the form of hypersensitivity reactions were encountered. Because of its low solubility, paclitaxel formulations include a surfactant (Cremophor EL). The side effects encountered during clinical trials were believed to be caused by Cremophor. Two deaths resulted from these unpredictable hypersensitivity reactions and clinical trials were almost ended (Kingston 2007). A 24 hour infusion protocol was developed that avoided the hypersensitivity reactions. Through these clinical trials,

melanoma response to paclitaxel was reported in 1987. Responses in ovarian cancer and breast cancer were reported in 1989 and 1991 respectively (Kingston 2007). Other clinical trials found paclitaxel also effective against advanced breast cancer (Vongpaseuth and Roberts 2007). Paclitaxel was approved for use in 1993 under the trade name Taxol (Heinrich, et al. 2004). The initial FDA approval was for use against refractory ovarian cancer. Additional FDA approvals follow over the next several years. Paclitaxel was approved for use against breast cancer in 1994, Kaposi's sarcoma in 1997, and for use against non-small cell lung cancer in 1999. The FDA approved the marketing of semi-synthetic paclitaxel in 1995 (Vongpaseuth and Roberts 2007).

Other more recent papers have reported clinical results as well. Many of these clinical trials compared the use of paclitaxel in combination with other medications. Platinum compounds are known to be active against ovarian cancer, so testing was done using paclitaxel in combination with cisplatin. Phase I trials provided information that the two drugs could be used safely in combination (Kumar, et al. 2010). Subsequent trials have compared cisplatin-paclitaxel combinations against combinations of other agents. For instance, one trial (GOG 111) compared the effectiveness of a combination of cyclophosphamide-cisplatin against the cisplatin-paclitaxel combination. The progression free survival period (PFS) was increased from 13 to 18 months by using the paclitaxel containing combination (Kumar, et al. 2010). This same trial reported a median survival increase from 24 to 38 months. A similar trial (OV-10) reported similar findings with the cisplatin-paclitaxel combination. These studies established this combination treatment as the first line therapy for ovarian cancer (Kumar, et al. 2010). Subsequent trials such as ICON3, reported in 2002, have not demonstrated the same clear superiority of this combination treatment as

reported by GOG 111. However, though not demonstrating a superior PFS and overall survival rate, the toxicity profile was superior and the cisplatin-paclitaxel combination remained the recommended first line therapy for ovarian cancer (Kumar, et al. 2010). Since these trials concluded, other work has resulted in the replacement of cisplatin by carboplatin. This is a better tolerated platinum compound that is proven equally effective. Most patients will respond to first line therapy, but unfortunately the majority of ovarian cancer patients also suffer recurrence (Kumar, et al. 2010). Work continues to better understand the complex interactions involved. New therapies continue to be tested for both platinum sensitive and platinum resistant cancer.

The combination of carboplatin-paclitaxel remains important for the treatment of ovarian cancer. Recently, clinical trials have been initiated to evaluate adding a third agent along with carboplatin-paclitaxel (Kumar, et al. 2010).

Contraindications

There are a number of toxic side effects related to use of paclitaxel. Neutropenia, an abnormally low number of neutrophils in the blood, is the most common toxic effect. Inflammation of the lining of the mouth and the lining of the gastrointestinal tract are also possible. Muscle pain is a common side effect. Cardiac rhythm disturbances have also been encountered (Georgatos and Theodoropoulos 2001).

Drug interactions with paclitaxel must also be considered. It is important that the dosing level of paclitaxel be relative to the metabolic capacity of the elimination pathway. If the dose exceeds this level, toxicity is increased. If the dose is below this level, efficacy is decreased. Any interactions that alter the rate at which paclitaxel is metabolized and eliminated can lead

to increased toxicity or a reduction in the cytotoxic antitumor activity (Kumar, et al. 2010). Paclitaxel is known to have interactions with several other cytotoxic drugs as well as some non-cytotoxic drugs. Even though cisplatin and paclitaxel have been demonstrated to be safe to use together, dosages have to be altered when doing so. Cisplatin administered prior to paclitaxel is known to increase neutropenia and reduce the antitumor activity of paclitaxel (Kumar, et al. 2010). Other cytotoxic drugs with known interactions include doxorubicin, etoposide, topotecan and trastuzumab. Interactions of trastuzumab with paclitaxel have resulted in increased incidence of congestive heart failure (Kumar, et al. 2010).

Known interactions with anticonvulsant drugs such as phenytoin and phenobarbital result in reduced cytotoxic and antitumor activity of paclitaxel. Cytochrome P450 induction is involved in this interaction (Kumar, et al. 2010).

Current Use in Allopathic & CAM Therapies

Paclitaxel is currently marketed under the trade name Taxol by BristolMyersSquibb. Docetaxel is a semi-synthetically produced variant of paclitaxel that is also a taxane diterpene. Both paclitaxel and docetaxel were produced semi-synthetically from 10-acetylbaccatin III. Docetaxel has a modified side chain that is different than the side chain of paclitaxel (Heinrich, et al. 2004). Docetaxel is used for the treatment of breast and ovarian cancer and is marketed under the name Taxotere. Both of these medications are administered intravenously (Heinrich, et al. 2004). Paclitaxel is approved by the FDA for use against "...breast cancer, ovarian cancer, non-small cell lung cancer..." and is also used against Kaposi's sarcoma (Vongpaseuth and Roberts 2007, 219). It is also being studied for use against Alzheimer's and

as a follow up to angioplasty. It is hoped that paclitaxel can limit scar formation to prevent artery narrowing.

Discussion

The discovery of taxol in the Pacific yew was a very important discovery for the treatment of several forms of cancer. The discovery is also indicative of the potential importance of natural products. It is an often cited example of the random sampling method of discovery. The process by which this compound was researched and brought to market is a true example of persistence and tenacity. At several stages of the process, seemingly insurmountable obstacles were encountered. These included the complex nature of the molecule, the molecule's weak activity in early assays and most importantly the incredibly low yield of the host plant, the Pacific yew. Research scientists and pharmaceutical companies have derived a number of methods of producing the medication without overexploiting the original source, *Taxus brevifolia*. To prevent extinction of the species, a method was derived where the drug was produced semi-synthetically from 10-acetylbaccatin III harvested from the needles of *T. baccata*. Because this does not kill the tree, this is a sustainable process. Still not satisfied, as the process is sustainable but still not environmentally friendly, research continues to try and find better ways of producing this important medicine. Currently, Taxol is produced by plant cell fermentation (Vongpaseuth and Roberts 2007), a method implemented in 2004. Recently, a new process was announced based on an improved cell culture using *T. brevifolia* stem cells that will be even more environmentally friendly. This process involves culturing cambial meristematic cells and promises higher growth rates and paclitaxel production (Roberts and Kolewe 2010).

Despite this progress, more research is still needed to derive more analogues that can avoid the problems of dangerous side effects and acquired resistance.

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Theobroma cacao L., Malvaceae

Kira Ohmart

Introduction

Theobroma cacao, commonly known as cacao or cocoa, belongs to the Malvaceae family, or the mallow family, which includes marshmallow plants, kola nuts, okra, and cotton. *T. cacao* is one of the most significant perennial crops due to the massive manufacture of chocolate, which is how the plant is almost exclusively used (Almeida and Valle 2007). In 2006, the estimated world output of the cacao plant was 3.5 million tons. The plant has been cultivated and exploited for the seeds, which are used for the manufacture of chocolate (Almeida and Valle 2007). The main constituents of *T. cacao* include the methylxanthines theobromine, a similar compound to caffeine, and caffeine itself, both of which have stimulant properties. Other compounds in *T. cacao* include flavonoids, which exhibit antioxidative effects among other effects, lipids, sterols and, interestingly, trans-resveratrol, which may have significant effects on cancer (Colombo, Pinorini-Godly et al. 2012). The plant is native to tropical regions and can be found in neotropical rainforests, particularly the Amazon basin and Guyana Plateau (Colombo, Pinorini-Godly et al. 2012).

Botanical Description

Theobroma cacao is a small evergreen tree that is native to tropical and subtropical areas, and grows at elevations of 20 to 400 meters. The cacao tree requires a humid climate, with regular rainfall, and healthy soil to survive and produce fruit, tending to grow in areas with 1000-3000 millimeters of



Figure 1. Typical flower found on cacao tree. These grow in clusters directly on the trunk of the tree. Each flower has five fertile stamen and five infertile stamen. (Image source: panoramio.com)

rainfall each year and only within 10 degrees north or south of the equator (Colombo, Pinorini-Godly et al. 2012). The cacao tree is an understory tree, reaching 20 to 25 meters in height in its natural habitat, growing beneath the canopy of taller plants in the rainforest in shady areas indicating that it does not require lots of sunlight to survive (Almeida and Valle 2007). There are three different subvarieties of the species that are identified by their physical and genetic characteristics, and the geographical regions they are located in. These three subtypes are Criollo, Forastero, and Trinitario

(Almeida and Valle 2007). The cacao tree originates in the river valleys of Middle and South America. It was originally used by Central Native American groups including Maya, Aztecs, and Toltecs. Now that the *T. cacao* species is cultivated, however, it has been known to be grown not only in Central and South America, but also Asia and Africa (Almeida and Valle 2007).

The cacao plant has two different types of branches: those that grow vertically (orthotropic) and those that grow laterally (plagiotropic). In the *T. cacao* species the vertically growing branches are known as chupons, and the laterally growing ones are known as fan branches. The cacao tree is cauliflorous indicating that it produces flowers on older branches and the main trunk of the plant (Colombo, Pinorini-Godly et al. 2012), **Figure 1**. The leaves of the cacao tree are dark green and shiny with a leathery texture. The leaves are elliptically shaped and undivided blades. They grow to be about approximately 20 to 35 centimeters long and 7 to 8 centimeters wide (Colombo, Pinorini-Godly et al. 2012).

The flowers are tiny, usually just 1 to 2 centimeters in diameter, and contain a pink calyx. The flowers' color typically ranges from white with a yellowish tinge to a very pale pink. Unusual for the plants in the Malvaceae family, the flowers of the *T. cacao* plant grow throughout the entire year, producing, on average, between 50 thousand and 100 thousand flowers per year, and have no nectar or perceptible scent to them (Colombo, Pinorini-Godly et al. 2012). The flowers are produced in little clusters directly on the trunk and older branches (cauliflorous), and each has five petals, five fertile stamens, and five infertile stamens. The plant is pollinated by the *Forcipomyia midges* species, a tiny fly. Interestingly, when these flowers are pollinated, their morphology makes a drastic change from tiny to quite massive, becoming the large pods



Figure 2. Pod of *Theobroma cacao* tree. The husk or outer part is characterized by a yellow color. On the inside, the sweet white mucilage surrounds the seeds of the tree that give chocolate its typical flavor. (Source: EcoLibrary.org)

from where cocoa beans originate, the main ingredient of chocolate (Colombo, Pinorini-Godly et al. 2012).

The pods or berries, as they are sometimes referred to, are an ovular shape, ranging from about 15 to 30 centimeters long and 8 to 10 centimeters wide. These weigh around 500 grams, or a little over 1 pound. The color of the pods ranges between a yellowish to an orange color. Each pod typically contains 20 to 60 seeds, or what are commonly considered cocoa beans. These seeds are enveloped by sweet, white mucilage that is said to have a lemony taste or a taste similar to that of mango (**Figure 2**). Monkeys and other mammals break the pods open to eat this sweet mucilage, which is how the seeds of the plant

are dispersed. The seeds or beans have an extremely bitter taste to them (Colombo, Pinorini-Godly et al. 2012).

Present within the *T. cacao* species, there are fungal endophytes, particularly *Fusarium* species that grow within the plant tissues. These fungal endophytes do not necessarily have a harmful effect on the host unless the host is under environmental stress. Although they are not harmful, there have been no conclusive studies on the benefit of these organisms in the cacao tree (Colombo, Pinorini-Godly et al. 2012)

Traditional Uses

The *Theobroma cacao* species had several different uses in indigenous cultures, including culinary, medicinal, and even monetary uses. It had cultural significance within the Maya and Aztec cultures, among others. The first European encounter with the plant was in 1502, during one of Christopher Columbus's returns to the Americas. By this time, the cacao plant had already been cultivated for up to 2000 years. The indigenous peoples gave him the concoction that they usually create from the cocoa beans and his response was immediate and momentous. He claimed it a "divine drink which builds up resistance and fights fatigue. A cup of this precious drink permits a man to walk for a whole day without food" (Colombo, Pinorini-Godly et al. 2012). This reaction may have been due just to the very strong taste that accompanies the consumption of the bitter beans, or due to the small presence of the methylxanthines theobromine and caffeine.

The concoction that Columbus was given was a beverage drunk by the Mayan peoples. The beverage has an intricate preparation in these cultures. The fruits, or pods, are allowed to ripen throughout the course of a year, picked when ripe,

and the beans are removed and laid out on mats to dry. To create the beverage, the beans are roasted over a fire, and then ground between stones on a mortar, creating a paste. The paste is put into cups made from calabashes, similar to a gourd, produced from *Lagenaria seceraria*, mixed with water, sometimes spices were added, and then finally drunk (Colombo, Pinorini-Godly et al. 2012). The Maya groups consider *T. cacao* a significant ritual food due to the stimulant effect of the plant (Kufer, Grube et al. 2006).

Another traditional use of the *T. cacao* species is by the Choco Indians. These people originate in the Amazonian forest. They typically do not make chocolate beverages or even use the beans. This group is more interested in consuming the white pulp surrounding the beans as a snack between meals (Duke 1970).

A different indigenous group, the Cuna of Panama and Colombia, also consume *T. cacao*, in the form of a paste made from the beans. The Cuna people eat 25 grams of this paste per day as a snack. The Cuna also used *T. cacao* for medicinal purposes to treat malaria and fever (Duke 1975). The preparation for these treatments included burning the beans ceremonially with hot peppers. Additionally, the fruit pulp will be turned into a decoction, and taken by pregnant women to relieve their pregnancy symptoms. The Cuna people also use the leaves of the cacao tree to make an infusion for weary children. In addition, adolescent leaves are applied as antiseptics, while flowers are used to treat eye parasites (Duke 1975).

The Aztecs actually used cacao as a form of currency, and when consumed, it was as if one was "eating money". This made the cacao plant a luxury only ever drunk or eaten by the Aztec nobility because commoners simply could not afford to eat their money (Colombo, Pinorini-Godly et al. 2012).

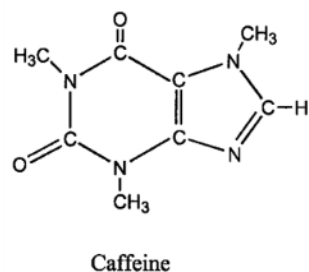


Figure 3. Chemical structure of caffeine, one of the purine alkaloids present in *Theobroma cacao*. Both caffeine and theobromine are considered methylxanthines. (Image source: med-chemist.com)

Filipinos have been known to use *T. cacao*, for specific ailments. For example, a decoction of the roots of the plant has been taken orally when menstruation has resulted in excessive and unceasing bleeding. Filipino people have also used scrapings of the skins of the pod placed around boils for two or three days to excrete and remove pus (Langenberger, Prigge et al. 2009).

In comparison to all of these seemingly advantageous uses for different parts of the cacao plant, the modern medicinal application for the plant is somewhat wanting. Because of the huge chocolate industry, the plant is primarily cultivated for chocolate production. However, chocolate has been marketed for its antioxidant properties, resulting in increased production value of the plant.

Chemistry and Pharmacology

Over the past fifteen years, there has been piqued interest in the potential of the products of the cacao plant, including the cocoa removed from the seeds and dark chocolate. There has

Component	Nib %	Shell %
Water	3.2	6.6
Fat (cocoa butter)	57	5.9
Cocoa powder	4.2	20.7
Nitrogen	2.5	3.2
Theobromine	1.3	0.9
Caffeine	0.7	0.3
Starch	9	5.2
Crude fiber	3.2	19.2

Table 1. Table of component percentages found in certain parts of the cacao plant. Nib refers to internal part of the plant, while shell refers to the external husk (Colombo, Pinorini-Godly et al. 2012).

been evidence to support the antioxidative properties and benefits of phytochemical-rich components of chocolate.

The constituents include a large variety of components that interact with each other. These are varieties of catechins, flavonoids, tannins, essential oils, alkaloids, polyphenols, proanthocyanidin glycosides, carboxylic acids, purine alkaloids, and fatty acids (Giorgetti, Negri et al. 2007).

Cacao is rich in methylxanthines, which are an alkaloid, particularly theobromine, theophylline, and caffeine (**Figure 3**). These can tend to have both negative and positive health effects, but primarily serve as stimulants. There are also flavonols and flavonoids present in the cacao plant, including flavan-3-ols, which exhibit antioxidative effects, protection from cardiovascular disease, and anticancer effects (Colombo, Pinorini-Godly et al. 2012). There are also a large variety of lipids present, especially in the seeds or beans of the pod. When ground into a paste, a cocoa butter results along with fine brown particles that are the main constituents of chocolate (**Table 1**). The cocoa butter makes up 50 to 57 percent of the dry weight of cocoa and contains a significant

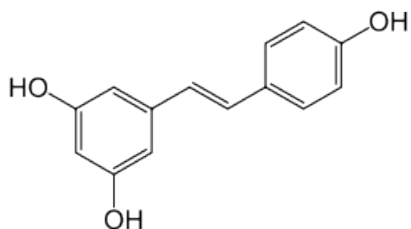


Figure 4. Chemical structure of trans-resveratrol, one of the most promising medicinal components found in *Theobroma cacao*. (Image source: mhhe.com)

amount of fat and fatty acids, including saturated stearic acids (35%), saturated palmitic acids (25%), monosaturated oleic acids (35%), and polyunsaturated linoleic acids (3%) (Colombo, Pinorini-Godly et al. 2012). There are also a number of sterols, and possibly most significantly, trans-resveratrol (**Figure 4**). Trans-resveratrols have exhibited a significant amount of anti-inflammatory effects, anticancer effects, and cardioprotective and estrogenic activities (Colombo, Pinorini-Godly et al. 2012).

Biological Activity

Several studies have been done involving the compounds found in *Theobroma cacao*. *In vitro* studies have provided evidence that suggest that the flavonols and procyanidins present in cocoa may possess immunoregulatory effects that may help modulate immune responses. Additionally, other studies have suggested that the removal of theobromine and caffeine from the cacao plant has actually enhanced the antioxidant effects of cocoa. This result provides evidence that these components may inhibit antioxidative activity thereby reducing the effectiveness of the plant as an antioxidant

(Colombo, Pinorini-Godly et al. 2012). However, this is not conclusive and needs more research.

Another *in vitro* study done has resulted in the discovery that flavonoids (including epicatechins and isoquercitrin) in cacao have affected transcription, resulting in enhanced expression in peripheral blood human mononuclear cells. There was also a decreased nitric oxide production along with cytokine secretion modulation reported when cocoa extracts were used rather than using the isolated chemical components suggesting that the synergism of all of the constituents present in cacao makes it more effective than isolating the compounds (Ramiro, Franch et al. 2005).

Some *in vivo* studies have indicated the antioxidant effects of epicatechin as well, enhancing oxidation scavenging activity in plasma. Antioxidant activities of this constituent have resulted in reduction of the concentration of free radicals, diminishing of oxidation of lipids, proteins, and nucleic acids. Additionally, other *in vivo* studies have provided support that caffeine and theobromine have resulted in reproductive toxicities in animals, particularly males, among other toxicities from the isolated compounds. However, the cacao plant does not have a high percentage of these methylxanthines, and, in fact, is known to have less caffeine than a cup of decaffeinated coffee (Colombo, Pinorini-Godly et al. 2012).

The mechanism of action involved in *T. cacao* constituents is still in debate, but a range of potential mechanisms of the flavanols in cocoa has been shown to improve cardiovascular health. Some of these possible mechanisms of action include nitric oxide activation, as seen in the above *in vivo* study. Additionally, there have been some anti-platelet effects that tend to improve endothelial function, blood pressure, and other heart conditions (Colombo, Pinorini-Godly et al. 2012). Flavonoids have also shown some bioactivity in the

modulation of cell signaling pathways that regulate several cell functions including survival and inflammatory responses (Giorgetti, Negri et al. 2007). In addition, the presence of

sterols also contributes to heart health because they contribute to an improvement of blood lipid profiles through the mechanism of competitive inhibition of cholesterol absorption through the gastrointestinal tract (Colombo, Pinorini-Godly et al. 2012). There is no known threat of drug resistance against the constituents in *T. cacao*.

In another *in vivo* study, the biological activity of cacao proteins were studied and identified. This supported the traditional uses of the plants against tumors and free radical scavenging, particularly inhibiting murine lymphoma L5178Y, a model cancer cell found in mice. It was found that the cacao albumin fraction (a certain protein isolated from the cacao plant) had a significant effect on tumor growth that differed from the other tested protein fractions, which tended not to be dose-dependent. The results suggested that antitumor activity was due to the amino acid profile that was present in the albumin fraction, which was rich in cysteine, leucine, arginine, and lysine. The presence and high percentage of these amino acids relates this protein to the trypsin inhibitor potential. There was also a significant correlation between radical scavenging capacity assays in cacao, and evidence shows that the cacao protein fractions can be considered a chain breaking antioxidant. This indicates that it halts the transfer of hydrogen atoms, creating a stable radical, rather than one that continues the chain reaction (Preza, Jaramillo et al. 2010).

Clinical studies

For the development of drugs using the constituents of the cacao plant, few clinical studies have been done, merely

because the primary use of cacao is for chocolate use. However, the few that have been done have suggested that the polyphenolic compounds present in the cacao have been useful in increasing blood flow and perfusion of the brain. Some clinical studies have discussed the use of flavanols to treat neurodegenerative diseases like Alzheimer's disease. Evidence has supported that flavanols may delay the onset of this type of disease (Colombo, Pinorini-Godly et al. 2012).

Current use in allopathic and CAM therapies

The current use of *Theobroma cacao* is commercial exploitation of the crop. The cacao plant has had a huge success in the marketing industry. *T. cacao* has not only been used for the manufacture of chocolate, but also derivatives and byproducts of the plant have been used for cosmetics, fine beverages, jellies, and juices (Almeida and Valle 2007).

The modern process of changing the cacao seeds into cocoa or chocolate has similarities to the ancient Mayan process. The cacao plant is allowed to ripen throughout the year, and once ripe, the pods are harvested. After this process, the cacao pods are cracked open and the seeds, or beans, are extracted from the pulp and pod. These are then fermented, dried, and finally roasted. These steps are what contribute to the typical chocolate flavor and color that most people are familiar with. The roasted seeds are then ground into a chocolate liquor, which contains 55 percent cocoa butter, and cocoa powder, which consists of nonfat, fine, brown particles of the beans. The cocoa powder is where the flavor of the chocolate primarily comes from and where the polyphenol antioxidants are located. This nonfat part of the cocoa liquor is what is actually used in the production of chocolate or the cocoa powder that is used for culinary and beverage purposes (Colombo, Pinorini-Godly et al. 2012).

It is important to note that chocolate and cacao are not interchangeable terms. Chocolate is actually a combination of the cocoa powder, cocoa butter, additional sugars, and other added chemicals that are made into a food. Different chocolates have different percentages of cacao, but usually range from 50 to 80 percent cacao.

Medicinally, one of the most important constituents in cacao is the trans-resveratrol. This is currently one of the phytochemicals in cacao with the greatest potential for use as a pharmacological drug. These are intended to prevent or reduce the risk of certain diseases (Colombo, Pinorini-Godly et al. 2012). Resveratrol is of significant interest because of its antioxidative, anti-platelet, anti-inflammatory, estrogenic, anticancer, anti-tumor, and antiviral activities. In one study, trans-resveratrol and its glycoside, trans-piceid, were found in dark chocolate extracts. Additionally, the same study discovered that presence of procyanidins increase the antioxidant activity of chocolate (Counet, Callemien et al. 2006).

Another study provides strong evidence to support that cacao husk lignin fractions prepared by acid precipitation and ethanol precipitation yielded an unexpected amount of anti-human immunodeficiency virus activity. These activities amount to almost as much anti-HIV effects as conventional treatments and popular anti-HIV chemical compounds. The husk lignin fractions have showed anti-flu virus activity as well. However, there was no reported antibacterial activity. This study also supports that there is stimulation in the generation of nitric oxide by macrophage-like cells, suggesting the possibility of an effective complementary alternative medicine (Sakagami, Satoh et al. 2008).

Discussion

Theobroma cacao is now primarily used for the economical benefit for the countries that cultivate and produce chocolate. The chocolate industry provides a powerful incentive for Mesoamerican and South American countries to distribute this cash crop widely. The commercial benefits of chocolate have a profound effect on these tropical and subtropical countries.

The cacao plant's traditional uses have guided researchers and ethnobotanists to compose research on the possible medicinal uses for cacao. These studies have resulted in a multitude of results that provide support for many different potential medicinal therapies. It can be used to effectively reduce oxidation, diminish tumor activity, and improve cardiovascular health. Some of the constituents found in *T. cacao* are also effective anti-inflammatory and estrogenic constituents including the trans-resveratrol. Stimulants, including but not limited to theobromine and caffeine, also contribute to the chemical compounds present in cacao plants.

As discussed previously, the economic value of the cacao tree has influenced the countries that grow and farm the plant to increase production and actually destroy native forests for the cultivation of cacao. This is problematic for the maintenance of forests and completely hinders the efforts to conserve native rainforests, which are already diminishing quickly with deforestation due to human expansion and other such reasons (Almeida and Valle 2007).

In the next ten years, it has been projected that the consumption of cacao will increase by nearly one million tons of cacao seeds. It is expected that there will be an increase in cacao production in West African countries. However, this would have an impact on the economy and resources of these countries. The chocolate industry actually foresees a challenge in the cacao supply in the future (Almeida and Valle 2007). In

fact, if cacao is not supplemented by another crop, this could actually be problematic for the chocolate industry and for individuals of certain indigenous groups (Hazlett 1986).

Besides this, there is also an ethical debate over the cacao plant and chocolate industry. In the United States, successful chocolate manufacturers, including Hershey's and Mars, were reported for using child labor on West African cocoa farms. Subsequent investigations revealed the conditions that children worked under as some of the most atrocious forms of child labor. Child labor probably produced a massive percentage of the chocolate products that Americans consider affordable luxuries (Mustapha 2010). The result of this discovery bears the presence of ethical concerns that were not previously considered or even detected by the huge chocolate industry. These threats make the cultivation of cacao into an entirely other issue, where the moral indications have to be considered.

Although there are some ethical concerns regarding the cultivation of the *T. cacao*, the plant is still a delectable treat, with a variety of different medicinal effects in humans. The traditional uses of cacao have permeated through today, in the social aspect of drinking the fine beverages. In addition, the stimulant effects of the plant make it a recharging treat.

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Thymus vulgaris L., Lamiaceae

Carly McCabe

Introduction

Thymus vulgaris is commonly known as Thyme, however, it goes by many other names such as common thyme, garden thyme, tomillo, thym, Ov'tos (by the Greeks) (Andrews, 1958) and many others (Basch, Ulbricht, Hammerness, Bevins, & Sollars, 2004). It is a member of the Lamiaceae family, which is the mint family, and so it is related to common plants like peppermint, rosemary, and oregano. It is native to the Mediterranean, however, it can be found in many regions of the world—these regions include Egypt, Iran, Israel, and the United States among others (Arraiza, Andres, Arrabal, & Lopez, 2009). Thyme has many applications and it is highly valued for its antibiotic, antispasmodic, antioxidant, antimicrobial and antifungal effects. Thyme has also been purported to possess analgesic, diuretic, carminative and stimulant properties. Additionally, it has been used in flavoring applications within the processed foods industry, as a soap, detergent and preservative (Arraiza, et al., 2009). Its medicinal activity comes from the diverse essential oil content—two main compounds within the extract are thymol and carvacrol (Lee, et al., 2005).

Botanical Description

Thyme is a small, shrubby, aromatic plant native to the Mediterranean (Robineau, 1997). It is a branched, woody plant with numerous stems and fibrous roots that usually grows to be eight to ten inches in height (Culpeper, 1955). At the base, the stems grow erect or along the ground without



Figure 1. Oblong-oval leaves of *T. vulgaris* (Modzelevich, 2008).

setting roots (Darlington, 1847). The leaves are small, quite short, broad, pointed, and dusky-green (Culpeper, 1955). They can either be an oblong oval shape or a narrow oval shape (**Figures 1 & 2**), curling on the edges, and bunching at their axils (Darlington, 1847). Its flower is commonly small and light blue or light purple. The calyx is hirsute, strongly ribbed, and studded with what appears to be tiny dots or holes, while parts of the lower lip subulate (Darlington, 1847). *T. vulgaris* is considered the garden thyme; wild thyme (*Thymus serpyllum*) and lemon thyme are others commonly encountered among the 100-plus varieties (**Figure 3**). The most suitable environment for thyme growth is one with poor, light and dry soil. When found in moist or rich environments,

2002). Bardeau proclaimed thyme as “an indispensable plant, which should be consumed to conserve health. Furthermore, if one could replace ones’ morning cup of coffee with an infusion of thyme, you would quickly appreciate its positive effects: animation of spirit, sensation, lightness in the stomach, absence of morning cough, and its euphoriant and tonic effect (Stahl-Biskup & Sáez, 2002).” Thyme earned itself a place in many ancient cultures, and it is referenced in many ancient texts for a variety of uses.

Medicinal Applications

The medicinal application of thyme and its essential oil are quite concordant when it comes to the many cultures that could take advantage of and had access to the plant. Nicholas Culpeper detailed the use of thyme in his herbal, originally published in 1652, for a sundry of applications, which find homology in other traditions. He listed it as a strengthener of the lungs, a remedy for the chin-cough (whooping cough) in children, it purges the body of phlegm, is a remedy for shortness of breath, and as cure for helminthiasis. He references it as ‘the notable herb of Venus’ such that it provokes the terms, gives a safe and speedy delivery to women in labor, and stimulates the afterbirth. When used as an ointment, it eases swelling and warts, helps sciatica and dullness of sight, and eases the pain and hardness of the spleen. It can be useful for gout and pains in the loins and hips. Additionally, when ingested it has beneficial effects on the stomach and expels wind (Culpeper, 1955). The essential oils have also been recognized for the treatment of respiratory conditions like bronchitis, whooping cough, as well as tooth ache (Porte & Godoy, 2008). In México, Thyme is commonly known as Tomillo and is popularly used for bronchial affectations, cough, cold, angina, inflammation,

stomachache, diarrhea, and parasitism (Navarro, Villarreal, Rojas, & Lozoya, 1996). Each of these prescriptions (especially ones for respiratory ailments) finds similarity in other cultures and other ancient texts that reference it.

Historical Texts

Cairo Genizah

A millennium ago, Old Cairo (Fustat) was one of the most important centers of social, economic and religious activity (Amar, 2008). The Perfumers’ Square in Fustat as well as in Alexandria were centers of the drug and perfume business (Amar, 2008). The Ben Ezra synagogue was a place of worship for the Palestinian Jews of Fustat. In this synagogue existed a “Genizah” or depository, in which sacred books were stored. Until recently, this treasure trove of historical and cultural knowledge was kept from the hands of researchers and scholars. However, the manuscripts were revealed to the world and later purchased by many institutions. These institutions have installed research efforts aimed at studying and understanding the texts and the information retained within them. The Cairo Genizah has its own *materia medica* in which it details the medicinal use of Mediterranean plants in and around Egypt (Amar, 2008). Thyme is mentioned in recipes for stomach ailments, colic, excessive lachrymation, eyelids growth, and as a tonic (Amar, 2008).

The Canon of Medicine

Avicenna recommends the use of thyme as a treatment for fresh wounds, abscesses, spleen swellings, chronic fevers, and scorpion stings, and as a diuretic, a purgative and menstrual stimulant (Amar, 2008).

al-Ghafiqi

An important scholar and physician in Andalusia, al-Ghafiqi describes thyme as a diuretic, menstrual stimulant, and as a cure for wounds, ulcers, bruises, and stings of poisonous insects (Amar, 2008).

Cooking

As mentioned, *Ov'tos* is the Greek name for thyme. However, the name was commonly applied to the species *Thymbra capitata*; many centuries ago this name was carried out of Greece by colonists and into southern Italy. From there, the Romans adopted the name in the form *thymum* and applied it to reference *Thymus vulgaris*, which grew all along the west side of the peninsula (Andrews, 1958). The use of thyme in ancient Greece is referenced with less frequency, however it is mentioned for its use in flavoring salt and grating it to flavor drinks (Andrews, 1958). Apicius cataloged the use of thyme by the Romans; he mentions thyme as an ingredient in sauces, whether that is boiled foods or meats, as well as with fish and vegetables. Today in Italy thyme is called *timo* and its dried or fresh versions are used to flavor soups, gravies, stews, sauces sausages and dressings (Andrews, 1958). These sources that reference thyme as a culinary supplement provide the appearance of thyme as a fine condiment used, quite secretively, by chefs.

Today

Thyme alone or in combination with other herbs such as sundew is one of the most commonly recommended herbs in use in Europe today; it is used for dry, spasmodic coughs, as well as whooping cough. It is prepared as a topical salve that consists of thyme, myrrh, and goldenseal to treat oral herpes.

Compound	Concentration (mg/g)
<i>Monoterpene hydrocarbons</i>	
α -Terpinene	0.005
γ -Terpinene	0.007
<i>p</i> -Cymene	0.013
<i>Oxygenated monoterpenes</i>	
1,8-Cineole	0.245
Camphor	0.148
3,7-Dimethyl-1,6-octadien-3-ol (linalool)	0.479
α -Terpineol	0.291
Borneol	0.244
<i>Sesquiterpene hydrocarbons</i>	
δ -Selinene	0.010
<i>Oxygenated sesquiterpenes</i>	
β -Eudesmol	0.014
<i>Aliphatic alcohols</i>	
(<i>Z</i>)-3-hexenol	0.017
<i>Aliphatic aldehydes</i>	
(<i>E,Z</i>)-2,4-heptadienal	0.004
<i>Aliphatic esters</i>	
Methyl 2-methylbutyrate	0.001
<i>Aliphatic ketones</i>	
Methyl jasmone	0.012
<i>Aliphatic acids</i>	
Octanoic acid	0.004
<i>Aromatic compounds</i>	
2-Isopropyl-5-methylphenol (thymol)*	8.554
2-Isopropyl-2-methylphenol (carvacrol)*	0.681

Table 1. Sampling of the compound in *Thymus vulgaris* essential oil. Notice the bolded compounds and their concentrations (Lee, Umamo, Shibamoto, & Lee, 2005).

It is also used to treat chronic candidiasis and halitosis (Taheri, Azimi, Rafieian, & Zanjani, 2011). As a result of its antibiotic, anti-fungal, and antimicrobial properties, the

essential oil of thyme is a very useful preservative in the food industry for stored food items and even for the preservation of stored fresh meat, specifically chicken (Kumar, et al., 2008), (Fратиanni et al., 2010).

Chemistry and Pharmacology

When inspecting the volatile oil profile and the antifungal, antibiotic, antimicrobial, and antioxidant activities of thyme (which exist a result of these oils), one will encounter many factors that influence results. Specifically, the level of volatile oil content differs depending on when the plant is harvested (month, season), from what part of the region it is collected, and the country from which it is being surveyed (Torras, Grau, López, & de las Heras, 2007). Another factor to note is the method in which the volatile oil is extracted; depending on which method is chosen, the quality and yield of the essential oil can be affected. Steam distillation is a common method used in the laboratory and in addition to being very efficient it typically yields high quality oil. The use of organic solvents for extraction, on the other hand, has a tendency to result in residual solvent in the extracts as well as insufficient solvent selectivity that allows other compounds to be dissolved in addition to the active substances (Grigore et al., 2010). Learning about the volatile oil in thyme is very important to understanding its various medicinal activities, for it is within the oil that the compounds responsible for these effects exist.

Volatile Oils

T. vulgaris possess many volatile compounds ranging from aromatics to monoterpenes (**Table 1**). Within this list of volatile compounds, there exists another list of compounds responsible for the characteristic aroma of thyme. A study

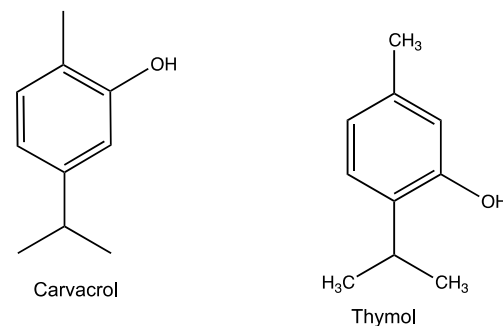


Figure 4. Structures of Carvacrol and Thymol (Carvalho et al., 2003).

used thyme that was purchased from a local market in Davis, California and identified 43 monoterpenes, 16 sesquiterpenes, 14 aromatic compounds, 7 alcohols, 3 aldehydes, 4 ketones and esters, and 3 acids (Lee, et al., 2005) as the aroma compounds. Within the entire list of volatile oils there are six compounds with the highest concentration: thymol (72%), carvacrol (5.7%), linalool (4.0%), α -terpineol (2.4%), 1,8-cineole (2.1%), and borneol (2.0%) (Lee, et al., 2005). Thymol and carvacrol are the most important compounds and collectively they comprise roughly three-quarters of measured volatile oils (**Figure 4**) (Lee, et al., 2005). Many studies have demonstrated that thymol and carvacrol are responsible for much of the medicinal activity of *T. vulgaris*.

Biological Activity

In vitro

In one study, various odiferous angiospermic essential oils were tested for antifungal activity against a toxic strain of *Aspergillus flavus*. *A. flavus* is a type of fungi or mold commonly found in food. The presence of said mold is particularly

troublesome when it occurs in the post harvest stage of food commodities (Kumar, et al., 2008). In developing countries, spoiled food is not only a loss of profit but also a loss of sustenance. This type of mold produces a particular class of mycotoxins (any toxic substance produced by a fungus) called aflatoxins, which are extremely poisonous and can cause liver damage and cancer. Nearly 4.5 billion people in underdeveloped countries are exposed to these toxins as a result of post harvest fungal infections of their cereals and pulses (Kumar, et al., 2008). This study's aim was to investigate possible compounds in various essential oils that could act as natural preservatives, since many industrial preservatives have their own slew of toxicities. The thyme used was collected from Banaras Hindu University, and the essential oil was collected using Clevenger's hydrodistillation apparatus. The culture was performed on potato dextrose agar (PDA). Dissolved oil was added aseptically to different pre-sterilized Petri dishes that had 9.5 ml of the PDA in order to obtain a concentration of 1.0 and 1.5 $\mu\text{l ml}^{-1}$. A fungal disk of the strain of *A. flavus* was inoculated aseptically to the center of the poured Petri plates. The plates were then incubated at 27 ± 2 °C for seven days, after which the diameter of fungal colonies was measured and the percentage of mycelial inhibition was calculated based on these diameters (Kumar, et al., 2008). *T. vulgaris* essential oil showed strong fungitoxicity and was further analyzed for its minimum inhibitory concentration (MIC) at which it showed absolute fungitoxicity. They performed this analysis by placing varying concentrations of the thyme oil on the PDA plates and incubating them with the fungal strain for another seven days at 27 ± 2 °C. They then investigated thyme oil's ability to arrest aflatoxin elaboration using the same conditions as above except they used SMKY medium (Sucrose, 200 g; MgSO₄ 7H₂O, 0.5 g; KNO₃, 0.3 g; Yeast extract, 7.0g; Distilled water,

1000 ml; pH, 5.6 ± 0.2) in Erlenmeyer flasks that were inoculated with 1 ml spore suspensions. These flasks were incubated for 10 days. After a variety of other steps, the researchers then evaluated the aflatoxin content.

The results indicated that the essential oil of *T. vulgaris* showed complete inhibition of inoculums of the toxigenic strain of the test fungus at 1.0 $\mu\text{l ml}^{-1}$ and an MIC of 0.7 $\mu\text{l ml}^{-1}$ (Kumar, et al., 2008). *T. vulgaris* showed better antifungicidal activity than most synthetic derivatives, mainly because of its MIC and its broad-spectrum fungitoxicant activity (which was also elucidated in this trial). The authors indicated that thyme would be an exceptional replacement for industrial preservatives mainly because it is a natural compound and it is quite stronger.

In vivo

In an *in vivo* study, scientists investigated the antispasmodic effect of *T. vulgaris* on guinea-pig ileum. This study aimed to evaluate the effectiveness of *T. vulgaris* and its hydroalcoholic extract on the motility properties of the ileum and to determine the mechanisms by which these motility effects are elicited (Babaei et al., 2008). After being excised and prepped, the ileum was placed in a Tyrode solution, which is an isotonic solution that contains: (mM) NaCl 136.9, KCl 2.7, CaCl₂ 1.8, MgCl₂ 1.0, NaHCO₃ 11.9, NaH₂PO₄ 0.4, and Glucose 5.0. Glucose acts as the energy source and bicarbonate acts as the buffer. The tissue bath was maintained at 37°C and whole segments of the tissue (roughly 3 cm long) were set up to record isometric contractions while in 50 mL of the Tyrode solution, which was gassed with 5% CO₂ and 95% O₂. Each strip of tissue was bound on one end to a glass holder and on the other connected by a silk thread to a strain-gauge transducer that allowed the scientists to monitor the

mechanical activity of the tissue. The tissue strip was loaded with a resting tension of 0.5g and after equilibration was ready for field stimulation with rectangular 1 ms pulses of supramaximal voltage delivered at 0.1 Hz through platinum electrode 10mm in length and 10mm apart. This electrical field stimulation of the ilea induced twitch contractions. After a control period, thyme extract was added to the bath in a volume of 0.5 mL at increasing concentrations. The responses of the tissue as a result of the addition of the varying concentrations of the extract were recorded for a five-minute period. Another experiment was performed that looked at the contractions of the ileum in the presence of Acetylcholine, Atropine, Granisetron, Morphine, and Naloxone. The leaves of *T. vulgaris* plant used in this experiment were collected from Iran and the extract was collected via a methanol extraction (Babaei, et al., 2008).

The effect of the extract and of the controls was determined by comparing the frequency and amplitude of the test and control materials. There were six different concentrations of the extract in which the tissue was tested (0.02mg to 6 mg mL⁻¹), which induced concentration-dependent depression of contraction that was evoked by the field stimulation. In comparison to the control substance, there was a significant, dose-dependent difference in the action of *T. vulgaris* on peristalsis. *T. vulgaris* extract displayed a 50% maximum effective concentration value of 1.7 mg mL⁻¹ as well as a maximum inhibition of 60.1±2.9%. This smooth muscle relaxant effect was determined while in the presence of Acetylcholine, which induces contractions of the isolated tissue. Acetylcholine can be blocked by Atropine and the extract can consequentially inhibit these types of contractions as well (Babaei, et al., 2008). These results and the successful dose-dependent decrease in contractions suggest that thyme essential oil is a potent inhibitor of the contractions in the

guinea-pig ileum. Therefore, these results also imply that *T. vulgaris* extract could be useful in the treatment of diarrhea predominant irritable bowel syndrome (Babaei, et al., 2008).

Mechanism of action

The constituents of thyme that confer biological activity and thereby usefulness in medicinal applications and everyday employment include its essential oils; specifically, the phenols of thymol and carvacrol, glycosides, flavonoids, *p*-cymene, borneol, linalool, alcohols, rosmarinic acid, saponins, tannins, and terpenoids (Basch, et al., 2004). Thyme's antimicrobial effects can be attributed to thymol, which expresses activity against strains of fungi and yeast including *Aspergiullus parasiticus*, *A. flavus* and *Candida albicans* via suppression of fungal growth and aflatoxin synthesis. Thyme's spasmolytic and antitussive activity is accredited to thymol and carvacrol, while flavonoids relax tracheal and ileal smooth muscles by inhibiting acetylcholine and histamine receptors and possibly through calcium channel antagonism. It has been shown *in vitro* that the extract of thyme and its volatile oil have relaxing effects by inhibiting phasic contractions. Thyme's antioxidant effects are due to a biphenyl compound and flavonoids, which inhibit superoxide anion production and protect red blood cells against oxidative damage. Finally, thyme's anti-inflammatory effects are due to thymol and carvacrol's inhibition of prostaglandin synthesis (Basch, et al., 2004).

Clinical Studies

Many studies have supported the efficacy of Listerine and one of its active components, thymol, in decreasing plaque formation and gingivitis. However, no evidence has been shown to implicate single therapies of thymol to be effective at



Figure 5. Bronchipret, a syrup comprised of *T. vulgaris* and *Primula* that treats acute bronchitis (Vitamin, 2012).

this same type of inhibition. A study was performed on a group of 110 school children in which they each received a combination product of 1% chlorohexidine and 1% thymol varnish. They were to receive this preparation for two years and the results would be compared to a control group. Analysis revealed that there were significant reductions in bacterial colonization levels and interdental plaque in the treated children (Basch, et al., 2004).

Another clinical trial was performed that compared a drug called Bronchipret to other pharmaceutical drugs that aim to treat acute bronchitis (**Figure 5**) (Ernst, et al., 1997). The use of antibiotics for acute bronchitis accounts for nearly 30% of all antibiotic prescriptions. This leads to the incurrence of large costs, which can be exacerbated when an antibiotic is pronounced ineffective or with absenteeism. Additionally, many traditional antibiotics have adverse side effects. One

clinical trial used Bronchipret to investigate whether herbal expectorant remedies were a viable replacement for the traditional antibiotics. Bronchipret contains 60mg of dried *Primula* extract and 160mg of dried *T. vulgaris* extract. The clinical study involved 771 German physicians who were asked to place their groups of patients into “lots” of five. They were then asked to prescribe one group the Bronchipret tablets and to prescribe the other group any other secretolytic drug that qualified for their condition. The groups were matched according to age, gender, and severity of disease. The researchers investigated two distinct age groups; those under the age of twelve and patients twelve years or older. Patients were seen initially by a physician and thoroughly examined; after which, they were either prescribed Bronchipret or another secretolytic drug. The patients returned ten days later and were examined in the same manner. Each patient was examined for a list of pre-determined criteria prior to taking the drug and after ten days of treatment. Odds ratios were calculated that related to each of these variables for the children and adult groups. The odd ratios depict the likelihood of therapeutic success such that if the odds ratio is low then the probability of a patient profiting from a control medication compared to Bronchipret is low. For example, in the adult group treated with a medication called Ambroxol, the odds ratio for the criteria coughing during the day was 0.51, which indicates a 49% higher chance for someone on Bronchipret to symptomatically improve compared to Ambroxol. Overall, in the adult and child group, for the three control drugs tested, the odds ratio was continually low, suggesting Bronchipret had an overall more effective therapeutic action in treating acute bronchitis. Additionally, the adverse drug reactions (ADRs) to Bronchipret were generally low, especially compared to the other drugs (Ernst, et al., 1997).

Contraindications

Toxicology

The suggested dose, taken orally, should not exceed 10g of the dried leaf with 0.03% phenol per day. Ensuring not to exceed this dose will most likely prevent toxicity, however, each individual will metabolize and respond to the compounds in thyme differently (see subsection Contraindications). Thyme oil, the essential oil and most active compound in thyme, is highly toxic. Symptoms of toxicity implicating exposure or over-exposure include nausea, tachypnea and hypotension (Basch, et al., 2004). The lethal dose (LD) of the essential oil is roughly 2.84g/kg of body weight (this is measured for rats), and in mice, oral doses of concentrated thyme extract equivalent to 4.3-26 g/kg of thyme decreased locomotor activity and respiratory activity (Basch, et al., 2004).

Typically, if one has a known allergy or sensitivity to members of the Lamiaceae (Mint) family or any aspect of thyme, the plant should be avoided. Many contact allergies have been reported, in cases recorded as long ago as the 1940s. Cases usually detail contact dermatitis, allergic alveolitis, and pruritic contact dermatitis provoked by the thyme plant and thymol. If one is allergic to other plants such as birch pollen, celery, or species in the mint family like oregano there is a chance for cross-reactions (Basch, et al., 2004).

Adverse Effects

Traditional and historical use of the thyme flower and leaves appears to generally be safe, especially when used in culinary pursuits. However, caution is advised when attempting to use the product for its medicinal properties. As mentioned in the toxicology subsection, thyme oil or thymol when concentrated is highly toxic and should be diluted if used for topical



Figure 6. Listerine with thymol (Johnson & Johnson Healthcare Products, 2012).

applications (Basch, et al., 2004). In regards to the neurologic and CNS, one may experience headache or dizziness with the ingestion of thyme, and in some cases the essential oil has caused seizure or coma. There have been reports of conjunctivitis in exposure to thyme dust as well as contact dermatologic reactions. Occupational asthma, as well as allergic alveolitis and rhinitis due to exposure to the dust has also been reported. Most side effects are related to an individual having some sort of established sensitivity to the plant and its constituents, however, a relative of *Thymus*



Figure 7. Typical herbal medicine preparations (Source: (Ltd)).

vulgaris, *Thymus serpyllum* has been shown to have more severe reactions such as those that interrupt TSH and prolactin in rats (Basch, et al., 2004).

Interactions

Some drug interactions include anti-thyrotrophic effects, estradiol and progesterone receptor-binding, and percutaneous absorption of topical thymol. Herbal supplements with estrogen or progesterone may interact with thyme's interaction with these receptors (Basch, et al., 2004).

Current use in Allopathic and CAM Therapies

A common drug or household item is mouthwash. Listerine (**Figure 6**) is the brand name of such oral cleansers, however, many use them without any idea of the true nature of their efficacy. Listerine is an antiseptic and contains a combination of essential oils like eucalyptol, menthol, thymol (found in *T. vulgaris*) and methyl salicylate. Studies have shown Listerine's

effectiveness as a broad-spectrum antibiotic against species like *Streptococcus mutans*, herpes simplex virus, and influenza A. It is also effective in the treatment of supragingival plaque and gingivitis (Basch, et al., 2004). Many parents also continually seek after Bronchipret as a natural remedy for their children with bronchitis. A typical CAM remedy for cough, the dried leaves can be used to make a tea; with one teaspoon of dried thyme per cup of water and consumed three times daily. The addition of honey, interestingly enough, increases the effectiveness of the tea (Thymes, 1998). These same proportions (1 teaspoon of dried thyme per cup of boiling water) can be used as a gargle to treat sore throat (Dworkin, 1998). Thyme can also be used to unplug clogged sinuses through steam inhalation. The preparation of such a steam bath includes pouring three cups of boiling water over two tablespoons of crushed thyme leaves in a medium bowl and placing one's face 10-12 inches above the fragrant water with a towel over the head to concentrate the vapors (Shinn, 2011).

In the herbal supplement market, products based on thyme and its extracts are typically those containing the essential oil, thymol. Most products display that the constituents come from Thyme and usually tote the fact that they contain the pure extract. (**Figure 7**) However, as mentioned, earlier, the use of the concentrated extract is quite dangerous and if it is to be used for topical application, it is highly recommended that the oil be diluted first.

Discussion

Upon first inspection, Thyme is a very mundane and common plant. However, upon further investigation one discovers the multifaceted and immense amount of applications that the plant can boast of. Centuries ago, the use of thyme developed a

homology between cultures, which lead to its popularity as a medicinal agent and has maintained its use in traditional medicine, allopathic and homeopathic medicine today. Thyme was commonly prescribed for respiratory ailments like bronchitis and whooping cough or for skin infections and inflammations. The continued use of thyme throughout history for these ailments and many others implicates a level of chemical activity that is biologically important. This turns out to be the case because thyme's chemical composition confirms its antimicrobial and antibiotic properties (as well as others). *T. vulgaris* undoubtedly offers new avenues of drug discovery, especially in this age of over use of antibiotics; exploring its inherent compounds (like thymol and carvacrol) as well as possible synthetic derivatives may allow for the expansion of the applications for which it is currently used. However, any uses that are investigated and potentially proposed for thyme and its derivatives should be carefully studied so as to ensure that its biological activity and application is taken advantage of in a way to prevent its decline into the same category of over-use as many antibiotics have today. It would be a shame to waste such a magnificent plant.

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Urtica dioica L., Urticaceae

Sarah Henkel

Introduction

Urtica dioica L., of the Urticaceae family, is commonly known as a stinging nettle (Lewis and Elvin-Lewis, 2003). Other common names include burn weed and burn nettle (Olsen, 1921). This plant is used as a treatment in a wide variety of ailments, both in traditional and modern medicine, such as bladder and kidney disorders, diabetes, various allergies, anemia, internal bleeding, osteoarthritis, and musculoskeletal aches. In some places, the plant is even eaten as food. Recent medical research has narrowed the use of the plant, making it more medicinally effective. The basic components of *U. dioica* are vitamin C, carotene, polysaccharides, beta-sitosterol, quercetin, rutin, and kaempferol (Rodriguez-Fragoso et al., 2008).

Description

Urtica dioica plants grow in a wide variety of areas and are spread throughout Europe, Asia, Denmark, America, and North Africa, in areas where moist soil is available. This green, leafy plant grows to be in between three and seven feet tall, with leaves reaching between one and six inches in length. These leaves are arranged on opposite sides of the wiry stalk and continue up the whole length of the plant.

Although the plant bears green leaves and numerous brown or green flowers, its extensive root system and rhizomes are a bright yellow color. The leaves and stems have visible hairs, which contain the chemicals responsible for the plant's characteristic sting. These hairs provide the plant protection and can grow to be more than one meter long. They are also



Figure 1. The leaves, flowers, and stem of *Urtica dioica*.
(Source: [http:// www.fitoterapia.net](http://www.fitoterapia.net))

capable of branching. The stings of this plant cause multiple, painful blisters. The stinging nettle is often found in areas of dense growth and is capable of cohabitating with other plants, due to its strong root system (Olsen, 1921). The plants are pollinated by a variety of different insects. In **Figure 1**, the green flowers and leaves of the plant can be seen. **Figure 2** shows the stinging hairs on the plant, while **Figure 3** shows the results of a sting on human skin.



Figure 2. The stinging hairs on the nettle stalk. (Source: <http://www.acupuncturebrooklyn.com/alternative-health/nettles>)

Traditional Uses

Medical Uses

Traditional medical uses of the stinging nettle are thought to have originated in Europe, especially in Germany. *Urtica dioica* is one of the plants mentioned in the 10th century book “Nine Herbs Charm.” Many forms of traditional medicine used *U. dioica* in a variety of ways to treat GI ailments, kidney disorders, musculo- skeletal aches, osteoarthritis, and rheumatoid arthritis. However, recent studies have provided scientific evidence to support the use of stinging nettle in only a few of these ailments which will be discussed later in this paper (Rodriguez-Fragoso et al., 2008).

The use of *U. dioica* has been recorded in Egypt over 2,000 years ago for the treatment of arthritis and lumbago pains. It was also one component used in a mixture of Passover herbs. The plant can still be found there today (Kavalali, 2003).



Figure 3. A rash resulting from contact with stinging nettles’ hairs. (Source: http://creationwiki.org/File:Nettle_sting.jpg)

U. dioica was also used by the ancient Greeks and Romans back in BCE times. Theophrastus, a student of Aristotle, describes the medical warming uses of the stinging nettle plant in his book *De historia et causis plantarum*. Pliny the Elder also recorded the medicinal uses of the stinging nettle in his *The Natural History of Pliny*. According to him, the plant should be eaten in order to prevent disease during the winter (Kavalali, 2003).

Food Uses

Records show that many cultures utilizing *U. dioica* for medical purposes also utilized the plant as a source of food, including the Native Americans. The leaves of the plant were first boiled in water to remove the stinging chemicals and then eaten as cooked greens. In some cultures, the water was saved and used for medical purposes, while in others it was

simply discarded (Rodriguez-Fragoso et al., 2008). Nettles have also been used to make nettle soup, nettle tea, and nettle ale (Kavalali, 2003).

Chemistry & Pharmacology

There are approximately fifty active chemical compounds in the *Urtica dioica* plant including sterines, coumarins, simple phenols, triterpenic acids, lignans, hydroxyl fatty acids, and ceramides (Kavalali, 2003). However, most of the medicinal uses of *U. dioica* come from chemicals located in the stinging hairs of the plant. Here, there is thought to be three significant chemicals responsible for the plant's smooth muscle stimulation: acetylcholine, histamine, and 5-hydroxytryptamine. The presence of 5-hydroxytryptamine was just recently accepted and is based on the result of six properties: the constriction of blood vessels in a rabbit's ear, the lowering of a rabbit's blood pressure, complete solubility in ether, simulation of a guinea-pig's and rabbit's small intestine and instability in the boiling of an alkaline solution (Collier and Chesher, 1956). The chemical structures of these three smooth muscle stimulators can be seen in **Figure 4**.

Biological Activity

Urtica dioica has many different biological activities. In an experiment by Gulcin *et al* (2003), scientists used water extract of nettle (WEN) to test the nettle's antioxidant, antimicrobial, and antiulcer biological activity.

Gulcin *et al* (2004) first tested the plant's antioxidant activity. The reason scientists are so interested in its antioxidant activity is because many common antioxidants have recently been shown to cause liver damage and cancer in some lab animals. Researchers are looking for more effective

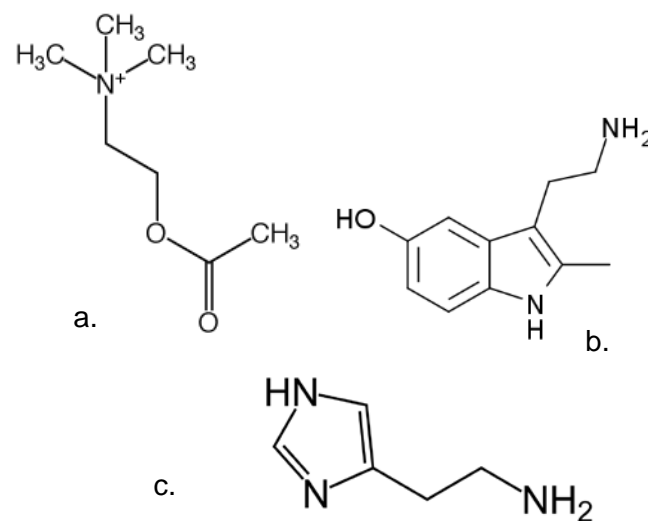


Figure 4. The chemical structures of three compounds present in the stinging nettle's hairs. (a) Acetylcholine, (b) 5-hydroxytryptamine, (c) Histamine.

and natural antioxidants. In this experiment, *U. dioica*'s antioxidant activity was measured by reducing power, superoxide anion scavenging activity, and metal chelating activity. These measurements showed that the higher the concentration of WEN, the higher its antioxidant properties. Also, the power of the stinging nettle's antioxidants was shown to be higher than that of the common ALPHA tocopherol. No *in vivo* experiments were done in this study.

In order to test the antimicrobial activity of *U. dioica*, agar with WEN was infected by ten different microbial agents: *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Micrococcus luteus*, *Staphylococcus epidermidis*, and *Candida albicans*. Then results were recorded by measuring zones of growth inhibition on the

agar plate. Each microbial agent was inhibited at least slightly, with the most significant inhibition being with *Staphylococcus epidermis* and *Miccrococcus luteus*. No *in vivo* experiments were done in this study.

Forty albino male rats were used for an *in vivo* study of the antiulcer activities of *Urtica dioica* in this study also. Using the ethanol-induced ulcer model, researchers injected the rats with 10 mg/kg WEN and then thirty minutes later with ethanol. One hour after the injection of ethanol the rats were killed and their stomachs examined. The larger amounts of WEN the rats, received, the fewer ulcers they had.

Clinical Studies

Numerous clinical studies on *Urtica dioica* have been conducted in the past and are still being conducted today. In this monograph, a focus is placed on three different conditions for which *U. dioica* has been tested as a treatment. First, *U. dioica* has been proven to treat lower urinary tract infections in several clinical trials (Lopatkin 2007, Lopatkin 2006, Safarinejad 2005). Sometimes *U. dioica* was used in combination with other chemicals or drugs, but in each of these three studies the administered drugs proved effective. Another ailment for which *U. dioica* has been used to treat is that of benign prostatic hyperplasia or benign prostatic syndrome. In several clinical trials, *U. dioica* has been proven to relieve irritative symptoms (Popa 2005, Schneider 2004). Other clinical trials studied the effect of *U. dioica* on gingivitis, but the plant did not offer any effective treatment (Van der Weijden, 1998).

Contraindications

So far, no negative interactions with other drugs have been recorded. However, it is recommended that pregnant women and breast-feeding women do not use any form of *Urtica dioica*. The plant and its drug derivatives are known to cause gastrointestinal issues, skin irritation, and sometimes diarrhea (Anderson, 2003). Also, one molecular contraindication is that the extract of the plant's leaf can reduce the amount of TNF-alpha and IL-1 beta in humans (Oberteis, 1996).

Current Use in Allopathic & CAM Therapies

Urtica dioica can be found in several drug therapies today. One drug marketed containing stinging nettle is known as Bazoton, which is taken in 300 milligram capsules, twice daily, for up to sixth months. One CAM therapy used today, for the treatment of allergic rhinitis, calls for the patient to take 600 milligrams of freeze dried nettles as soon as symptoms appear. Many nettle supplements exist, in which patients can buy a bottle of nettle capsules over the counter in pharmacies and online ("Nettle," 2010).

Discussion

The *Urtica dioica* plant has been utilized for both medical and food purposes throughout history. Today, modern science has found many of the key elements in the stinging nettle that make it useful as a medicine. For thousands of years, humans have utilized this plant and as science continues to narrow down the useful chemicals and possible dangers of the plant, its popularity as a drug is likely to grow.

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Vaccinium macrocarpon Aiton, Ericaceae

Sarah McMullin

Introduction

Vaccinium macrocarpon Aiton, or American Cranberry, is a member of the Ericaceae family. Sometimes the plant is placed in a genus its own, called, *Oxycoccus* (TWC staff, 2007). It is one of only three species of fruit native to North America, the other two being the blueberry and the bilberry, which are part of the same genus, *Vaccinium* (Lynch, 2004). It grew wild until 1816 when it was cultivated with difficulty by Henry Hall (History, 2011). Now US farmers grow over 40,000 acres of cranberries every year, primarily in Wisconsin, Massachusetts, and New Jersey (Wisconsin produces over 50% of the national total) (Keough, 2011). Cranberries are usually commercially harvested by flooding the bog where they grow, beating the berries off the bushes and then collecting the berries that float on top of the water (CCCCGA, 2011) (See **Figure 1**). In 2011 growers in the United States are projected to produce 7.5 million barrels of cranberries, and they received on average \$46.50 a barrel for their harvested cranberries in 2010 (Keough, 2011).

Cranberries were used as a food source and as part of traditional medicine by Native Americans before Europeans arrived in North America. It is even thought that cranberry sauce sweetened with maple sugar was part of the first Thanksgiving feast between the Native Americans and the Pilgrims. Cranberries continue to be very important in food, especially around the holiday season. They are seen on shelves in virtually all grocery stores near Thanksgiving and in the freezer aisle and as juice, all year-round. Cranberry



Figure 1. Workers harvesting cranberries from bog. (Photo courtesy of Wisconsin Farm Bureau Federation. < <http://www.history.org/foundation/journal/holiday06/cran.cfm>>)

production in the United States is projected to be up 10% from 2010 production this year (Keough, 2011).

While *V. macrocarpon* juice has been used under anecdotal evidence since before colonization as a prophylactic prevention for urinary tract infections, recently clinical trials have been adding hard scientific evidence its efficacy for this use (The Natural Standard Research Collaboration, 2011). The scientific community's interest in *V. macrocarpon* has even extended beyond this common treatment to explore other possible medicinal properties it might have, including possible compounds that treat heart disease and cancer.



Figure 2. *Vaccinium macrocarpon* sketch. (Source: Britton, N.L., and A. Brown. http://plants.usda.gov/java/profile?symbol=VAMA&photoID=oxma6_001_avd.tif)

Botanical Description

Cranberry plants are low growing perennial evergreen shrubs, less than 12 inches (30cm) high, that grow in moist bog-like acidic soil (pH 4.0 to 6.1) in partial shade. They are native to cool temperate boreal forests in the Northeastern United States and Southeastern Canada (TWC Staff, 2007). They are close relatives of the blueberry plant, which is also a member



Figure 3. *V. macrocarpon* in bloom. (Photo courtesy of Tom Harville. <http://www.ncwildflower.org/index.php/plants/details/Vaccinium-macrocarpon/>)

of the *Vaccinium* genus (Figure 2). The plants spread by rhizomes (TWC Staff, 2007), horizontal stems that grow new stems up to the surface from nodes. This allows the plants to spread very quickly but can make them difficult to transplant (Beaulieu, 2011). The leaves are very small, $\frac{1}{4}$ inch to $\frac{1}{2}$ inch (0.64cm to 1.28cm) long, leathery and oval shaped. They are shed in late summer every two years. The flowers have four petals and are white to pink in color. They hang inverted and flower for two to four weeks in late June to early July (Reiger, 1990). As the flower ages its petals curve back (Figure 3). Early settlers called the berries “cranberries”, because the early flowers’ (before they expanded) shape resembled a crane. The flower discourages self-pollination because the five

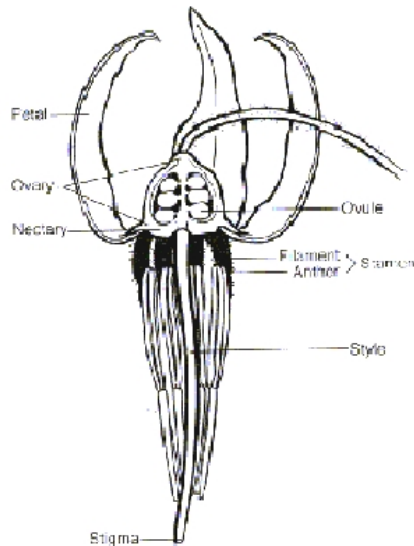


Figure 4. Reproductive parts of *V. macrocarpon* flower.
 (Photo courtesy of K.S. Delaplane & D.F. Mayer <http://ag.udel.edu/enwc/faculty/dmcaron/Pollination/cranberry.html>)

to eight stamens are exposed first, releasing their pollen before the single stigma is exposed. The pollen is heavy and not easily transported by wind, so insects, especially bees, are very important for pollination (Delaplane, 2011) (**Figure 4**). The flower takes on more of a pink color if it is not pollinated. The flowers produce some nectar, which is what attracts pollinators. The fruit is a small “false” berry (epigynous), which starts out green then changes to white and then bright to dark red as it matures. The berry matures in 60-120 days after fertilization, and is very tart to taste (Rieger, 1990) (**Figure 5**).

Traditional uses

Native Americans and Canadians called cranberries sassamanash and used them most often to treat bladder and



Figure 5. Ripe *V. macrocarpon* on bush. (Source: <http://www.justbio.ca/products/vacciniummacrocarpon>)

kidney problems (Block, 2011). They were also used for stomach problems, wounds, blood poisoning and appetite loss. Cranberries were used as a poultice to spread on the skin for wound healing and treating inflammation, and mixed with cornmeal to cure blood poisoning. An infusion of branches was made to treat pleurisy, chest pain caused by inflammation in the lining of the lungs and chest (Speck, 1917) (Dugdale, 2011). An infusion of the fruit could be made to treat nausea. (Smith, 1932). A decoction of the fruit could also be made to treat diarrhea (Lantis, 1959).

V. macrocarpon is high in vitamin C and therefore was very valuable to early explorers in preventing scurvy, a debilitating and often deadly disease caused by lack of vitamin C in the diet. The fruit could be sun or fire dried and kept over winter as a food source which was easily portable and could be taken on hunting expeditions (Waugh, 1916). Cranberries have also been used to treat type 2 diabetes (NIH, 2011), and have also

been used for infections, especially urinary tract infections, for hundreds of years, especially before the discovery of antibiotics (Lynch, 2004).

Native Americans made a sauce with the berries that was sweetened with maple syrup, and it is thought that this was likely part of the first Thanksgiving celebration. The berries were eaten either raw or cooked (Densmore, 1928), and were also used to make a special very high-energy food called pemmican which consists of dried meat or fish and berries pounded into a pulp, shaped into a cake and dried. It could then easily be stored and transported. It was taken along on canoe trips and became very important to the Métis people (Native people who intermarried with early French settlers in Canada). They often sold it as food to European traders along the French Fur Trade Route. (Block, 2011)

Traditional non-medical uses for cranberries include use of the juice for dyeing fabrics, such as blankets and rugs (Caruso, 2000), and the making of jewelry from firm ripe berries strung together (Leighton, 1985).

Chemistry and Pharmacology

The major active constituents of *Vaccinium macrocarpon* are members of the flavonoid group of compounds. Flavonoids are water-soluble polyphenols made by plants. They consist of two benzene rings connected by another three-carbon ring that often contains oxygen (Figure 6). These compounds are responsible for plant color (Top Cultures, 2011). *Vaccinium macrocarpon* has one of the highest phenolic contents in fruit. These include: phenolic acids, anthocyanins, flavonols, and flavan-3-ols, procyanidins and proanthocyanidins (Vvedenskaya, 2003). The most prevalent flavonol is quercetin. Most flavonoids, except flavanols (catechins and

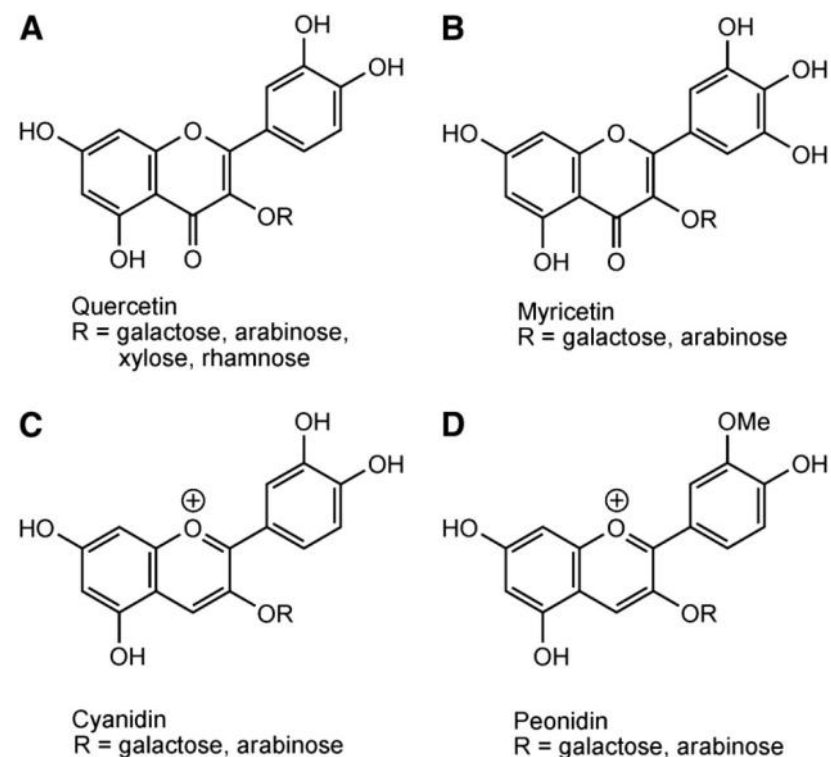


Figure 6. Compounds found in cranberry. (Courtesy of Catherine C. Netto. <<http://jn.nutrition.org/content/137/1/186S/F1.expansion.html>>)

protoanthocyanidins), are usually bound to a sugar, making a flavonoid glycoside (Higdon, 2005). The bioavailability of these compounds is strongly dependent on the structure of the bound sugar. These flavonols are strong free radical neutralizers. Free radicals are very dangerous and can kill cells, and damage DNA and proteins, which can cause cancer (University of Maryland, 2011). The stability of these flavonols caused by their aromaticity allows them to absorb the reactive extra electron into their rings, thereby stopping its ability to react with parts of the cell.

Biological Activity

Flavonoids are the main active chemical constituents of *Vaccinium macrocarpon*. They have been shown to have many positive effects against disease. Studies have shown that flavonoids are able to induce apoptosis, programmed cell death, in tumor cells. MacLean et al. (2011) showed that whole cranberry extract induced apoptosis in human prostate adenocarcinoma through caspase-8 activation. They found that it was the proanthocyanidin and flavonol-enriched fractions of the extract that increased caspase-8 and 9 activities, suggesting that it is these compounds that are involved in apoptosis activation. Caspase-8 cleaves the Bid protein, which causes release of cytochrome-c from the mitochondria. (MacLean et al., 2011) Cytochrome C initiates a cascade of events that destroy the cell from the inside out and package it into vesicles for disposal by macrophages (apoptosis). This is a very important mechanism in which cancer cells often have a defect. Normally if a cell senses a defect it will intrinsically initiate this apoptosis pathway. Cancer cells often over express BCL-2, which has been suggested to block cytochrome-c release (Yang, 1997). Kuida et al. also showed that mice lacking caspase 9 die early because of lack of apoptosis. (Kuida, 1998) Ferguson et al. showed that a fraction taken from cranberry presscake, the wet hulls left after juice is squeezed out, containing flavonoids was active against breast and prostate cancer. This fraction slowed proliferation and induced cell-cycle arrest and apoptosis in mouse tumors (Ferguson, 2004).

Another amazing property cranberries possess was shown in a 2011 study by Dohadwala et al. Extra-strength cranberry juice, provided by Ocean Spray, was given to patients with coronary artery disease, and was shown to provide an acute decrease in carotid femoral pulse wave velocity, which is directly related to arterial stiffness (Dohadwala et al., 2011),

and is associated with increased risk for cardiovascular events including heart attack. The mechanism that caused the decreased stiffness is still unknown, but future studies hope to discover this information.

A huge problem associated with bacterial infection is the colonization of many bacteria into biofilms. *Pseudomonas aeruginosa* is a type of bacteria that normally lives in soil, water or plants and causes many opportunist infections in humans with compromised immune systems (Todar, 2011). It uses flagellum-mediated swimming to move towards surfaces to attach itself and to swarm with other bacteria. They also use quorum sensing to move together as a group. O'May and Tukenjkji showed that proanthocyanidins from *V. macrocarpon* inhibit this swarming ability. This means that the bacteria were unable to form a colony on a surface. Cranberry extracts as low as 20 micrograms per milliliter almost completely blocked swarming. However, there was no effect on the growth rate of bacteria. These particular bacteria produce a biosurfactant, similar to a soap, to reduce surface tension so the bacteria can move across a liquid's surface. When surfactant, rhamnolipid, was added after cranberry treatment the bacteria regained some of its swarming ability. This suggests that the *V. macrocarpon* proanthocyanidins somehow interferes with the biosurfactant production. It is also possible that a compound in cranberries interferes with bacteria quorum sensing ability (O'May, 2011).

In 1991 Ofek et. al. presented their findings in the *New England Journal of Medicine* in which they stated that cranberry, and other members of the *Vaccinium* genus, blocked the colonizing ability of *E. coli* bacteria in the urinary tract. They showed that an isolate from cranberry juice inhibited adhesion of bacteria to the mucosal cells of mouse bladders, which prevented urinary tract infection. The isolate seemed to act on the adhesins on the pili which extend off the

surface of *Escherichia coli* cells (Ofek, 1991). Twenty years later Gupta et al. showed that it was the proanthocyanidin component of *V. macrocarpon* that produces this adhesion inhibition. An isolation that contained 10-50 micrograms per milliliter of proanthocyanidin inhibited 70% of adhesion in both sensitive and multidrug resistant *E. coli*. It is theorized that this inhibition is associated with the A-type linkages of proanthocyanidin, but the specific mechanism is not certain (Gupta, 2011).

Clinical Studies

Many clinical trials have been undertaken to examine whether *Vaccinium macrocarpon* can reduce the number of recurrent urinary tract infections in patients, and most have proved inconclusive. One study looked at women over the age of 45 who suffered from recurrent urinary tract infections. The most common treatment for people with recurrent UTIs is low-dose, long-term, antibiotic prophylaxis. Many clinical trials have shown this to be very effective, but there are significant side effects including fungal infections and a high risk for the development of antibiotic resistance. The study by McMurdo et al. compared the use of this prophylactic antibiotic treatment to daily treatment with 500mg of cranberry extract. The median time for UTI recurrence in the antibiotic group was 91 days, compared to 84.5 days in the cranberry group. The difference was not statistically significant and the women taking cranberry extract had fewer and less severe side effects and did not develop antibiotic resistant bacteria. It was concluded that women should talk to their doctors about possibly taking *Vaccinium macrocarpon* instead of antibiotics to prevent infection, because it is natural, much cheaper, has fewer side effects and works almost as well (McMurdo et al., 2008).

Another earlier clinical trial by Kontiokari et al. also showed the effectiveness of cranberry juice in preventing recurrent UTIs. It compared women who drank 50mL of cranberry-lingdonberry concentrate daily for six months to those who received no intervention. The recurrent rate in the cranberry group was 16% compared to 36% in the control group. This is statistically significant and shows that drinking cranberry juice has some effect on the likelihood of a urinary tract infection returning. (Kontiokari et al., 2001)

Another study using female children was also promising. Children who had suffered more than one urinary tract infection in the previous year were given either daily cranberry juice or one of two controls (*Lactobacillus* or no treatment). Only 18.5% of the children in the cranberry group suffered an infection during the trial, compared to 42.3% and 48.1% in the controls. There were no negative reactions except for a few children who did not like the taste of cranberry juice. (Ferrara et al., 2009)

Despite these studies showing promising results, a more recent study of 319 women between 18 and 40 years of age by Barbosa-Cesnik et al. was less positive. The participants in this study drank either 8oz of a low calorie 27% cranberry juice cocktail, or an 8oz of a placebo twice a day for six months. The placebo group had a recurrence rate of 16% while the cranberry group had a recurrence rate of 19%, indicating that cranberry juice gave no protection against recurrent UTIs (Barbosa-Cesnik et al., 2011). It is possible however, that the low concentration (27%) of cranberry juice in the cocktail did not contain enough of the active *V. macrocarpon* flavonoids to obtain good results. Most studies showing positive results used extra-strength cranberry juice, which has a higher percentage of active compounds, or cranberry extract pills, which are equivalent to several glasses of juice.

Contraindications

Vaccinium macrocarpon is generally regarded as safe and no significant drug interactions have been reported, but there is a lack of solid long-term safety information (Lynch, 2004). There is a possibility that cranberry may increase the amount of time Warfarin, a drug prescribed to slow blood clotting, remains in the body. This could lead to bruising or bleeding (NIH, 2011). Some very small studies have shown the possibility that cranberry juice can increase oxalate levels in the urine, which is the main cause of kidney stones. Large doses of cranberry can also lead to diarrhea (Burak, 2010). Diabetics should also be careful when they consume large quantities because its high sugar content could result in high blood sugar.

Current Use in Allopathic and CAM Therapies

Many cranberry supplements can be purchased in pharmacies. Most are in pill form and are advertised for improved urinary tract health and antioxidant benefits (Enzymatic Therapy, 2011). Urinary tract infections account for approximately 8 million outpatient and emergency room visits per year, and combined direct and indirect cost associated with UTIs in America is \$1.6 billion (Bowen, 2007). The recommended dosage of unsweetened cranberry juice for UTI prevention is 8oz, three times per day, or one 300-400mg tablet of concentrated cranberry extract (Lynch, 2004). One 64oz bottle of Ocean Spray Pure Cranberry Juice Costs approximately \$6 (Ocean Spray, 2011), and a thirty day supply of extract tablets costs between \$10-\$15 (Lynch, 2004). A 60 day supply of the most common antibiotic prescribed for prophylaxis, Trimethoprim (Regional Drug and Therapeutics Center, 2004), costs approximately \$33 at healthwarehouse.com (Health Warehouse, 2011); this is

slightly more than cranberry extract, but more importantly it puts patients at risk for many side effects, including antibiotic resistance. The National Institute of Health rates cranberry juice and supplements as “possibly effective” for preventing urinary tract infections, and it is often recommended first by physicians for prevention of, or to complement antibiotic treatment of, UTIs (NIH, 2011). The American Institute for Cancer Research also suggests eating cranberries to lower the risk of certain cancers, and there have been many news stories over the past few years promoting this (American Institute for Cancer Research, 2011). Since cranberry juice and cranberry extract pills do not require a prescription, it can be assumed that many people may take cranberry juice as a preventative measure for cancer and UTIs without consulting a doctor.

Discussion

Vaccinium macrocarpon has played an important role for centuries in food and complementary and alternative medicine, among Native Americans and then European settlers. It had been used under circumstantial evidence for treatment of urinary tract infections for years, especially before Alexander Flemming discovered antibiotics in 1928 (Bellis, 2011). While antibiotics are affective against the bacteria causing UTI's, the infection often recurs, which is where *V. macrocarpon* becomes important yet again. Studies have shown *V. macrocarpon* to be effective at significantly reducing the recurrence rate of these infections, while producing virtually no side effects. These promising studies have encouraged researchers to explore cranberries for many other disease fighting properties in the past few years, including the treatment and prevention of cancer and heart disease. Many papers have also been published this year exploring more unorthodox possible uses for this remarkable

berry such as, antifungal, wound healing, osteoclast inhibition in people with periodontitis, and blood pressure reduction properties. A few researchers are also looking deeper into the plant to learn more about its genetic makeup (Google Scholar, 2011).

It is exciting to imagine what new treatments might emerge in the next few years thanks to *V. macrocarpon*. Perhaps it will be the answer to some of the chronic diseases that seem to be only on the rise. Hopefully the positive results of clinical trials seen in this plant will encourage the study of more plants with traditional medicinal value.

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Vaccinium myrtillus L., Ericaceae

Tiffany Baerwaldt

Introduction

Vaccinium myrtillus L., commonly known as bilberry, is a member of the Ericaceae family. It is also known as whortleberry, European blueberry, huckleberry, black whortles, trackleberry, and bleaberry. The name Bilberry is derived from the Danish “bollebar,” meaning dark berry (Grieve, 1959). It belongs to a large genus (*Vaccinium*) of plants that also contains blueberry (*Vaccinium corymbosum*) and cranberry (*Vaccinium macrocarpon*). Bilberry is sometimes referred to as “blueberry” because both share many of the same characteristics and features, but the true blueberry is native to the United States (Benzie and Wachtel-Galor, 2011).

Bilberry is a perennial shrub whose fruit is purple or bluish black in color and is sweet tasting. It is native to northern Europe but can also be found in the mountainous regions of the northern hemisphere. Bilberry was used traditionally as food and also as medicine for ulcers, diarrhea, dysentery, diabetes, urinary infections, and vision, and its extracts were also used for bilberry’s anti-inflammatory properties. Dioscorides highly regarded the bilberry plant and its fruit, and bilberry fruit was also noted in Ayurvedic medicine as having use for oral infections and teeth cleaning. The leaves of the bilberry plant contain many active constituents including tannins, polyphenolics acids, flavanoids, arbutin, and quercetin. Its berries contain anthocyanoside flavanoids, as well as polyphenols and anthocyanins, which contribute to much of its pharmacological activities. Bilberry has antioxidant, vaso-protective, antimicrobial, and lipid-lowering

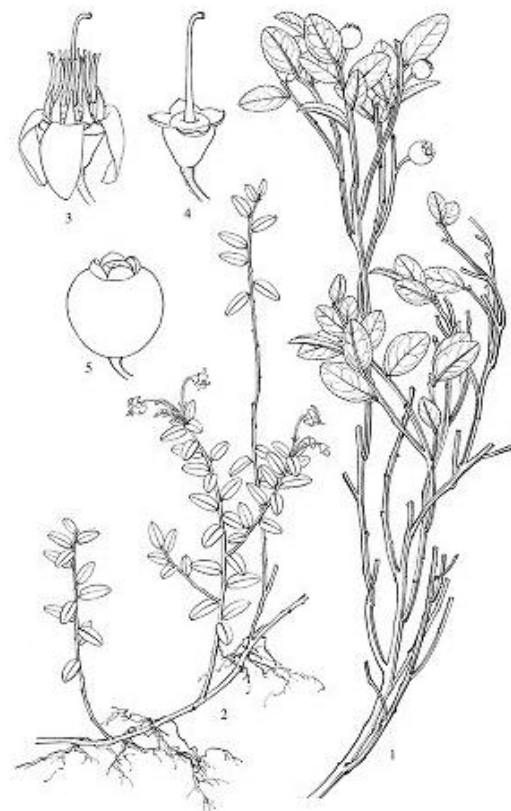


Figure 1. Line drawing of *Vaccinium myrtillus* L. (Source: Flora of China Illustrations vol. 14, fig. 688, 1 <http://tropicos.org/image/73875>)

properties, as demonstrated in many recent experiments. Bilberry also has a long history of use as for various eye conditions. It has corneal renewing effects, and is believed to



Figure 2. Photograph of *Vaccinium myrtillus* L. (Source: <http://www.zufglobus.com/xzcv/Page/index/135>).

improve human night vision and has promise for the treatment of cataracts and prevention of glaucoma. Bilberry is most commonly used for improvement of night vision and general eye health. Bilberry is generally considered as safe when used properly, and is currently used as an antioxidant in

the form of an extract, as a vitamin supplement for vision improvement, vascular problems, diabetes, and as a tea for vision health as well as antioxidant support for the whole body.

Botanical Description

Vaccinium myrtillus is a colony-forming, perennial, rhizomatous shrub ranging from 5-120 cm high. Its twigs and leaves are sharp-edged and green. It has alternating leaves that are broadly elliptical and approximately 19-27 by 7-11 mm in size. The leaves lack in rigor and firmness and are glandular beneath (**Figure 1**). The calyx is green and has a smooth surface without hairs or projections. The corolla, or part of the flower that consists of the petals, is thin, globose, and pink, cream, or greenish white in color (Vander Kloet and Dickinson, 1999, 242). The fruit of the bilberry plant are berries that are purple black or bluish black in color, and 7-9 mm in diameter. The berries grow in small clusters (**Figure 2**). The meat of the fruit is purple, unlike the American blueberry, which is usually cream or white (Thorne Research Inc, 2001, 500). The bilberry seedling takes approximately 6-10 weeks to develop its first leaves and shoot, and at 3 months the juvenile plant begins to show the features indicative of the adult plant (Ritchie, 1956, 297) (**Figure 3**).

V. myrtillus is native to northern Europe and is also abundant in the mountains and forests of the northern hemisphere, including northern and central Asia and in northern North America (Ritchie, 1956). Bilberry has been shown to have its highest vegetative and reproductive performance in woodlands, but it may also occur in mountainous heath soils, upland heaths, boggy communities, degraded meadows, open coniferous forests, pine forests, parklands, disturbed or open birchwoods, hummocky seepage slopes, podsol and

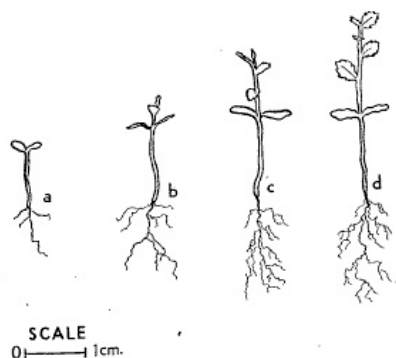


Fig. 3. Diagrams of seedlings to illustrate the early stages of development; (a) at 2 weeks, (b) at 7 weeks, (c) at 11 weeks and (d) at 16 weeks.

Figure 3. Diagrams of bilberry seedlings to illustrate the early stages of development. (Source: Ritchie, 1956)

moraines. Bilberry can flourish at altitudes from sea level to 2600 meters above sea level. The abundance of the bilberry plant as well as its size, shape, and color is determined by soil conditions such as the drainage factor and amount of organic matter in the soil. Climate conditions such as the presence of strong winds may also impact the morphological features of bilberry. One study determined that the tallest bilberry plants with the greatest density are usually found in mountain habitats, while populations in lowland forests are generally lower in height and grow in more erratic patches (Rolson et al. 2011, 238). However, results from previous studies demonstrated that the height of bilberry decreases with altitude, which could be the result of other environmental factors influencing the morphological features of the plant (Woodward, 1986).

Bilberry also interacts with various biotic factors that enhance its distribution and pollination. According to Ritchie (1956, 294), “When other more palatable plants are unavailable, sheep will graze bilberry, and areas in Derbyshire have been

examined where severe cutting back of the young green shoots was evident. Observation suggests that this has the effect of stimulating further growth and branching producing a densely busy habit.” It was also established that bilberry is pollinated by insects, birds, and through self-pollination by gravity.

Traditional Uses

Due to its rich, sweet and enjoyable flavor, as well as its nutritive value, bilberry has been used as food and as medicine for centuries. In addition to its use in tarts, pies, and preserves, bilberry was traditionally used in juices, jams, and wine as a colorant, and was also used to dye wool due to the presence of tannins in the fruit. In addition, according to “A Modern Herbal” written by Grieve in 1959, bilberry was used widely in the ancient world, and was highly regarded by Dioscorides. It was also noted that a decoction of the leaves or bark of the root was used as a local application to ulcers, and could also be applied to ulceration of the mouth and throat. The fruit’s astringent properties were used for diarrhea and dysentery in the form of syrup (Grieve, 1959). The fruit was also used for scurvy, tuberculosis, and urinary complaints (Grieve, 1959), and a tea made from the leaves was used as remedy for the treatment of diabetes (Cignarella et al. 1996, 311-312). Bilberry fruit was also used traditionally in Europe for discharges, as a lactation inhibitor (Grieve, 1959), in anti-inflammatory mixtures, and is commonly used as medicine for improving vision (Song et al. 2010, 520). Traditional herbal preparations are still used to enhance circulation and improve eye conditions, and dried berries are sold for the traditional treatment of mild diarrhea and inflammation of the mouth and throat (Grieve, 1959).

Bilberry fruit was also included in Ayurvedic medical practices. Deformities of the oral cavity, plaques, and infections were managed in ancient India, and it was noted that bilberry fruit and hawthorn berry stabilize collagen, strengthening the gum tissue (Singh and Purohit, 2011, 66).

Chemistry and Pharmacology

Bilberry leaves contain several active constituents including tannins, polyphenolic acids, flavanoids, arbutin, catechins, iridoids, and quercetin (Rolson et al. 2010, 238). In addition, bilberry berries contain anthocyanoside flavonoids, or anthocyanins, vitamins, sugars, and pectins (Thorne Research Inc, 2001, 500). Polyphenols and anthocyanins are the main components in bilberry, and many of the pharmacological activities of bilberry can be attributed to anthocyanins (Song et al. 2010, 520). Bilberry is one of the richest natural sources of anthocyanins (Benzie and Wachtel-Galor, 2011, 55). Anthocyanins are water soluble, glycosylated, nonacetylated polyphenolic compounds responsible for the red, blue, and purple pigments of fruits. These pigments are absorbed by the gastrointestinal tract after consumption, and have been shown to have tumor suppressive, anti-inflammatory, anti-viral, and anti-diabetic properties. Anthocyanins are also potent antioxidant and reactive oxygen species scavengers, and the anthocyanin concentration of fruit is highly correlated with the oxygen radical absorbance capacity (Bell and Gochenaur, 2006, 1164).

In a study conducted to evaluate the morphological and chemical variability of wild populations of bilberry in Poland, the content of phenols in bilberry leaves and fruits were determined. It was found that the content of tannins in bilberry leaves can reach 7.5-12%, and the content of anthocyanins in bilberry fruit can amount from 0.5 to 0.399%

$R_2 = H, R = R_1 = OH$: Cyanidin

$R = R_1 = R_2 = OH$: Delphinidin

$R_1 = OH, R = R_2 = OMe$: Malvidin

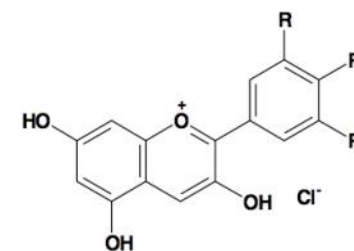


Figure 4. Chemical composition of bilberry fruit extract: Anthocyanins. (Source: National Toxicology Program, 1999. Bilberry Fruit Extract 84082-34-8 http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Bilberry.pdf)

(Rolson et al. 2010, 241). Polyphenols account for approximately 50-80% of the total polyphenol content in bilberries (Karlsen et al. 2009, 346). A concentration of 30mg/g of quercetin in bilberries has been reported (Erlund et al. 2003, 37). Another study determined and summarized the content of the major polyphenol classes found in bilberry, which include polyphenolic acids, tannins, arbutin, flavanoids, and anthocyanins (Karlsen et al. 2009, 352) The main anthocyanins in bilberry and their relative concentrations include delphinidins, cyanidins, petunidins, malvidins, and peonidins (Benzie and Wachtel-Galor, 2011, 57). The chemical composition of 25% bilberry extract, which is considered the standardized amount of anthocyanins in bilberry extract, contains a natural mixture of glycosides of aglycone anthocyanins, cyanidin, delphindin, and malydin (National Toxicology Program, 1999) (**Figure 4**).

Biological Activity

The anthocyanins present in bilberry are safe and proven antioxidants and chemoprotective agents. A variety of *in vitro*,

in vivo, and human studies have demonstrated that anthocyanins have antioxidant effects, promote healthy vision, urinary tract health, and skin health. Anthocyanins also exhibit cardiovascular, neuroprotective, anticarcinogenic potential, and antidiabetic properties and health benefits (Zafra-Stone et al. 2007).

A study that aimed at examining whether bilberry extract alleviates pruritus, or the sensation that causes the reflex to scratch, in mice with chronic allergic contact dermatitis concluded that anthocyanins from bilberry extract may be beneficial in the treatment of chronic pruritus. Chronic pruritus occurs in patients with anti-inflammatory skin diseases such as atopic dermatitis, which is the most common chronic inflammatory skin disorder and always induces pruritus. The daily intake of bilberry may provide a useful treatment and source of relief for pruritus in these patients (Yamaura et al. 2011).

In an *in vivo* study using type 2 diabetic mice, the effect of dietary bilberry extract on hyperglycemia and insulin sensitivity was examined. It was found that dietary bilberry extract significantly reduced the blood glucose concentration and enhanced insulin sensitivity. The upregulation of glucose transporter in white adipose tissue, skeletal muscle, and the liver of diabetic mice fed with bilberry extract was also shown. Acetyl-CoA carboxylase was also inactivated and PPAR α , acyl-CoA oxidase, and carnitine palmitoyltransferase-1A were upregulated in the liver. The result of these changes was improvement in hyperglycemia and insulin sensitivity in type 2 diabetes, which provides a biochemical basis for the use of bilberry fruits and implications for the prevention and treatment of type 2 diabetes (Takikawa et al. 2010).

Bell and Gochenaur (2006) recognized that plant pigment anthocyanins are especially potent oxygen radical scavengers,

and conducted an *in vitro* analysis of the direct vasoactive or vasoprotective properties of berry pigment extracts using coronary artery rings from mature female pigs. Their results suggest that such extracts could have significant beneficial effects in the treatment of vascular disease.

Huttunen et al. (2011) found that the antimicrobial activity of juice fractions including bilberries was notable against *Streptococcus pneumonia* binding to human bronchial cells, and that pneumococcal growth was completely inhibited at a concentration of ~86 mg/g. In summary, the results indicate that bilberry is a novel source for both antiadhesive and antimicrobial agents against pneumococci.

An *in vitro* study on the protective effect of bilberry extracts on cultured human limbal epithelial cells found that bilberry extract may be beneficial for the physiological renewal and homeostasis of corneal epithelial cells (Song et al. 2010, 520). Another study was conducted that generated a mouse model of endotoxin-induced uvetis that showed retinal inflammation and swelling of the middle layer of the eye. Mice that were pretreated with an anthocyanin-rich bilberry extract were analyzed, and the effect on the retina was documented. The anthocyanin-rich bilberry extract prevented the impairment of photoreceptor cell function, endotoxin-induced uvetis decreased, and the shortening of outer segments in photoreceptor cells were suppressed at the cellular level. The extract induced inflammation-related rhodopsin decrease, and the extract ameliorated the intracellular elevation of reactive oxygen in the inflamed retina. It was determined that anthocyanin-rich bilberry extract has a protective effect on visual function when the retina is inflamed (Miyake et al. 2011).

Cignarella et al. (1996) discovered that bilberry leaves have lipid-lowering properties by administering bilberry leaf

extract to streptozotocin-diabetic rats. Plasma glucose levels consistently dropped about 26% at two different stages of diabetes. The findings indicated that the active constituents of bilberry leaves, which include anthocyanins, might prove useful for the treatment of dyslipidaemia, or an abnormal amount of lipids in the blood.

Clinical Studies

Human data with respect to anthocyanins from bilberry are lacking, however dietary polyphenols present in bilberry fruit have been associated with the prevention and treatment of chronic inflammatory diseases, including cardiovascular disease (CVD). CVD has many risk factors including obesity, diabetes, hypertension, elevated lipid levels, and inflammation, and a novel treatment is therefore necessary. A clinical study on the effect of polyphenols in bilberry juice determined that a supplementation with bilberry juice resulted in significant decreases in plasma concentrations of C-reactive protein, interleukin, and monokine. Increases in plasma quercetin and *p*-coumaric acid were also observed in the bilberry group. These findings suggest that the supplementation with bilberry polyphenols may modulate the inflammation process (Karlsen et al. 2010, 345).

Quercetin, a polyphenolic flavanoid found in bilberry, exhibits antioxidative, anticarcinogenic, and enzyme-inhibiting activities. A study by Erlund et al. (2003) aimed to determine the impact of daily consumption of 100g of berries (black currants, lingonberries, and bilberries) on serum quercetin concentrations in healthy, middle-aged men, and found that in the berry group, the mean calculated intake of quercetin was significantly higher at the end of the 8 week study compared to the baseline group. Concentrations of quercetin were 32-51% higher in the berry group during the berry consumption

period. The results of this study recommend the increased intake of berries due to their bioavailable quercetin content in addition to the presence of other beneficial compounds.

The flavanoid anthocyanosides found in bilberry are potent antioxidants and have effects on the eye and vascular tissues. In a study of 50 patients with senile cataracts, a combination of bilberry extract with 25% anthocyanosides and vitamin E was given for four months. Taken twice daily, the extract stopped the progression of cataracts in 96% of the patients treated compared to 76% in the control group (Head, 2001). Consumption of bilberry extract may also have potential for protection against the development of glaucoma, or damage of the optic nerve. Eight patients with glaucoma were given a dose of 200mg *Vaccinium myrtillus* anthocyanosides and demonstrated improvement due to bilberry's collagen-enhancing and antioxidant properties (Thorne Research Inc, 2001).

Contraindications

Bilberry is classified as a Class 1 herb by the American Herbal Products Association, and is therefore considered safe when consumed appropriately. It has no reported mutagenic activity and there are no cited contraindications to its use (Benzie and Wachtel-Galor, 2011, 56). Dosages as high as 400 mg/kg body weight have been administered to rats without toxicity. Long-term oral administration in humans of doses equivalent to 180 mg/kg anthocyanosides per day for six months produced no toxic effects (Thorne Research Inc, 2001).

According to the University of Maryland Medical Center (UMMC), bilberry fruit and extract are generally considered as safe, and have no known side effects. However, as with any substance, bilberry leaf and extract should not be taken in

large excessive quantities for extended periods of time, especially because bilberries contain tannins, which may cause severe weight loss, muscle spasms, and possible death. The UMMC also notes that taking bilberry extract may change the way other remedies, medicines, and vitamins work and operate with one another. Using these products together may cause harmful effects and lead to dangerous consequences. The UMMC also acknowledges that the anticoagulant properties of anthocyanosides in bilberry may increase the risk of bleeding if taken with blood-thinning medication. The UMMC also proclaims that because bilberry may lower blood sugar, it could have synergistic effects with diabetes medication (UMMC, 2011).

Current Use in Allopathic and CAM Therapies

Currently, bilberry is used in products such as OptiBerry, a multiple-berry extract formulated for whole body antioxidant support. Its suggested uses include enhanced antioxidant protection, cardiovascular support, skin support, healthy cellular function, and healthy cognitive function. The recommended dose for the 50 mg capsules is 1-2 capsules per day, taken with a meal (Pure Encapsulations, 2011). OptiBerry has been demonstrated as being safer and more potent compared to the extracts of the individual berries used in the OptiBerry blend. OptiBerry also demonstrated superior bioavailability, antioxidative, antiangiogenic, antibacterial, anti-inflammatory, and antiatherosclerotic properties (Zafra-Stone et al. 2007, 675).

Bilberry leaf and berry is also sold as a liquid extract and as vitamin supplement for its antioxidant and vision-improving effects. Among many other supplement producers, Puritan's Pride sells bilberry as a supplement claiming to contain 1,000 mg bilberry extract. They suggest taking one soft gel once or

twice daily, preferably with a meal. Bilberry tea, prepared similarly to most packaged tea bags, is also available and promoted for vision health and support. Skin Actives Scientific, a skin care manufacturer, also markets bilberry for use as a face and body cream. Standardized for anthocyanins, which give this extract its color, the extract is said to have vasoprotective, anti-inflammatory, antioxidant and healing activity.

Discussion

Vaccinium myrtillus L. has been used for centuries in northern Europe as a functional food product as well as in jams, preserves, and baked goods such as pies and tarts. The use of bilberry across the northern hemisphere provides strong evidence for its efficacious medicinal properties. Bilberry is one of the richest natural sources of anthocyanins, which are responsible for bilberry's high antioxidant content, anti-inflammatory, antimicrobial, and lipid-lowering effects, and for the promotion of vision health and improvement. Therefore, bilberry has high potential in the treatment and prevention of conditions associated with diabetes, hyperglycemia, cardiovascular disease, inflammation, cancer, and eye conditions. However, human data with respect to anthocyanins from bilberry are lacking. The antioxidant effects of the anthocyanins present in bilberries give incentive for further clinical studies that aim to explore the additional health benefits from bilberry's antioxidant properties. The vasodilatory and anti-inflammatory effects of bilberry may also provide further therapies for age-related degenerative diseases. Due to its many biological activities, bilberry should be regarded as a functional food whose constituents hold the potential to provide therapies for a number of conditions whose current treatments are limited. More research on

bilberry and its constituents is necessary in order to fully recognize and benefit from the medicinal properties of the bilberry plant.

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Zingiber officinale Roscoe, Zingiberaceae

Sarah Mosby

Introduction

Zingiber officinale Roscoe, of the Zingiberaceae family, has played an integral part in human history, culture, and medicine, and it remains the most widely cultivated spice (Ravindran 2005, 7). The knotted rhizome (*Zingiberis rhizoma*) of the plant is commonly as ginger or ginger “root, though the latter is a misnomer. Ginger has been used in traditional healing remedies believed to affect nearly every human body system, and many of its medicinal uses have been verified as effective by *in vitro*, *in vivo*, and clinical studies. The use of ginger in complementary and alternative medicine (CAM) is growing and today includes use as a carminative, anti-emetic, anti-inflammation agent, and analgesic. It shows promise in biomedicine in treatments of arthritis, nausea and vomiting, and cancer.

Botanical Description

Zingiber officinale belongs to the tropical/sub-tropical family Zingiberaceae and the order Zingiberales. The specific origin of *Z. officinale* species is unknown, but it is most likely to have origins in tropical or sub-tropical India. Variants of the species are dependent on the environment and *Z. officinale* var. *cholmondeleyi* F. M. Bailey, *Z. officinale* var. *macrorhizonum* Makino, *Z. officinale* var. *rubens* Makino, *Z. officinale* var. *rubrum* Theilade, and *Z. officinale* var. *sichuanense* Z. Y. Zhu et al. (Tropicos 2011).

Z. officinale is a perennial herb, making it useful as an aesthetic plant, and can attain a stem length of 1.5 m. Branching out



Figure 1. The oblong flower of *Z. officinale*.

(Source: http://www.types-of-flowers.org/pictures/ginger_flower.jpeg)

from the stem are smooth, pale green, lanceolate leaves that can grow to 5-30 cm long, 8-20 cm wide, and up to 2 cm thick. A few shorter stems bear an ovate-oblong spiked flower: a purple anterior petaloid divided into three rounded lobes surrounds a tufted stigma and a fruit capsule with small arillate seeds (**Figure 1**). These branches extend horizontally from the stem of the plant, which projects vertically from the rhizome (WHO 2011).



Figure 2. The knotted rhizome known as ginger is used in food and medicine around the world. (Source: precision nutrition.com)

The dried rhizome of *Z. officinale* is scientifically referred to as *Zingiberis rhizoma* (Figure 2). The subterranean rhizomes are thickly lobed and tuberous with a yellowish-brown to pale buff external surface with few scales. When the skin is peeled, the aromatic rhizomes show fine longitudinal striations in the pale yellow to white-colored flesh (Pakrashi 2003, 16-18).

The optimal conditions for cultivation of ginger include an elevation of 300-900m and at least 1.98 meter of rainfall per year (Pakrashi 2003, 6). Today, ginger is cultivated in Asia, Africa, the Americas and Oceania. Propagated by planting of rootstalk cutting, cultivation of ginger ideally begins in April.

Country	Production (tons)	Country	Production (tons)
India	380100	Mauritius	616
China	331393	Dominican Republic	600
Indonesia	192500	Jamaica	459
Nepal	174268	Guyana	424
Thailand	170125	Kenya	245
Nigeria	152106	Dominica	169
Bangladesh	72608	Trinidad and Tobago	145
Japan	52000	Uganda	144
Philippines	27415	Reunion	107
Cameroon	12000	Puerto Rico	100
Malaysia	11200	Pakistan	94
Sri Lanka	10780	Ghana	81
Cote d'Ivoire	7680	Madagascar	29
Ethiopia	6834	Saint Lucia	14
Bhutan	3766	United Republic of Tanzania	10
Fiji	3041	Africa	179852
Republic of Korea	3000	Americas	3832
Costa Rica	1105	Asia	1429249
USA	816	World	1615974

Table 1. World production of ginger. India remains the earliest and largest producer of ginger (Source: FAO Statistics Division 2011.)

The rhizomes are harvested in stages dependent on their intended use. “Green ginger” is harvested before five months have passed since sowing, and “dry ginger” is harvested between 7-8 months after planting. Green ginger is used more often as a preservative, whereas dry ginger is more common in food preparation; both are commercially distributed (Pakrashi 2003, 8-10).

Though native to Asia, ginger is commercially grown and harvested in 34 countries spanning four continents. The majority of production and world trade still occurs in the Asian countries of India, China, Indonesia, Nepal, and Thailand, but Nigeria and Cameroon maintain significant levels of production as well. **Table 1** shows the most recent statistics of world production. India was the earliest producer of ginger and remains the largest producer today contributing to 30-40% of the world's production. India exports both dried rhizomes and extracted ginger oil, but only 10-15% of ginger produced in India is exported. China is the largest consumer of ginger, and contributes significantly to world ginger production (Ravindran 2005, 9-10). Like other species of the Zingiberaceae family—turmeric and cardamom—, ginger has a long history of consumption as a spice and food additive as well as a medicinal role.

Traditional Uses

Ginger has been used by humans since antiquity, and it remains the world's most widely cultivated spice. In its country of origin, ginger's use is prehistoric. It was renowned as *mahabheshaj*, *mahaoushadi*, meaning "the great cure, the great medicine," and was one of the most essential components of household folk medicines. Ginger's use in China dates back to at least 500 BC, as recorded by Confucius. The trade of ginger began with maritime circulation throughout India, China and Indochina, and by the 8th century AD, ginger was commonly traded throughout the Mediterranean. In second century Rome, ginger was one of the few items on which was imposed an import levy at Alexandria, evidence of its extensive trade (Ravindran 2005, 2-5). It was well known in Europe by the 11th century, where the Greeks

and Romans considered it a favorite spice, second to black pepper (Pakrashi 2003, 2).

Ginger is mentioned in the Koran, although not in the Christian Bible, and has long been incorporated into folklore, indicating its historical culinary and medicinal importance. Westerners are most likely familiar with the story of the Gingerbread man, a common child's folktale. Gingerbread became popular in Europe under Henry VIII's recommendation to consume ginger in preventive measures against the plague. In eastern Africa, ginger is associated with auspiciousness and is essential to the Savaras tribe for religious and marital ceremonies (Pakrashi 2003, 2; Ravindran 2005, 4). Another interesting example of ginger in culture is the Chinese Red Egg and Ginger party. It is traditional for parents or grandparents to welcome a newborn into the world with a celebration, and these celebrations often include "announcement packages" of red-dyed hard-boiled eggs and ginger root. This tradition is carried out today often with banquets or, in America, buffet-style lunches, when the baby is around one-hundred days old (Gong 2005, 164).

Culinary

The use of ginger as a cooking spice or condiment dates back 4,400 years to Asia, and it remains an integral part of Asian culinary use today. It has a distinctive, hot, pungent aroma and flavor that is essential to many modern and traditional Asian cuisines such as curry and chutney. The spice and flavor of ginger can be elicited from fresh or dried ginger root; the fleshy rhizome is first washed and peeled, then sliced, grated, or cooked whole. Ginger pickled in sweet vinegar is a common palette-cleanser in Asia, accompanying meals such as sushi, while crystallized or preserved ginger is consumed as a

confection. Ground ginger is a convenient kitchen spice that is available in most commercial grocery markets.

Ginger was one of the first spices of the orient to arrive in the West through trade. In Western food and culture, ginger is well-known as the spice of gingerbread, ginger beer, and ginger ale. The origins of gingerbread may date back to the ancient Greeks, who wrapped ginger in bread and consumed it after meals as a digestive aid (O'Hara 1998, 530). The spice is also incorporated into biscuits, cakes, puddings, soups, and pickles (Ravindran 2005, 12).

Medicinal

Many Zingiberaceous plants play a role in traditional medicine, especially in Asian medical systems such as Ayurvedic and Traditional Chinese Medicine. Across medical systems, ginger has been used medically as a carminative and a stimulant in the digestive tract (Tuntiwachwuttikul 1986, 191). The medicinal use of ginger dates back 2,500 years to ancient Chinese and Indian civilizations for treatments of many ailments including nausea, rheumatism, and headaches.

Ayurveda

In Ayurvedic medicine, *Zingiber officinale* is referred to by many Sanskrit names, most notably by Ardrak. Ardrak relieves the three dosha (energies of health), vata, kapha and pitta, and thus can help maintain balance of dosha in multiple systems of the body (Garodia et al. 2007, 2). Uses of Ardrak in Ayurvedic medicine are numerous and include external application as well as ingestion. Externally, ginger can be prepared as a paste with milk or water to reduce infantile cold and swelling. The ginger powder and oil are also used in massage therapy to alleviate chills, cold and stiffness, excessive swelling and

hypothermia (Gogte 2000). Ginger's balancing action against "cold" is appropriate for its characteristically "hot" aroma and flavor; and it is advised not to use ginger in the summer and autumn seasons.

Internally, ginger is believed to act upon the nervous system as a nerve-stimulant to improve impulse transmission and relieve pain. Prepared with castor oil, ginger powder is useful against rheumatoid arthritis. The stimulating and anti-inflammatory action extends to the heart and circulatory system, where it also acts as a blood-purifier. Consumption of ginger prepared with honey is an Ayurvedic remedy for asthmatic bronchitis, hiccups, coughs, and respiratory colds. In the reproductive system, ginger acts as an aphrodisiac and sex stimulant. Most importantly, however, are ginger's uses in the digestive system. Ginger improves appetite and digestion and is antifatulent, antihemorrhoidal, and antispasmodic. It is also used to treat anorexia, nausea, vomiting, abdominal pain, jaundice, and piles (Gogte 2000).

Traditional Chinese Medicine (TCM)

The use of ginger in TCM is comparable to that of Ayurveda. Ginger has traditionally been thought of as 'hot' and 'spicy,' both of which can treat coldness and weakness by mobilizing the body's reserves of *qi*. The Chinese distinguish between fresh, roasted, and dried ginger, attributing each with different healing properties. Fresh ginger is regarded as "mildly warm", dried ginger "warm," and roasted ginger "hot." All forms of ginger, however, have an "opening up" or "loosening" effect, enhancing the body's ability to integrate external stimuli. This assimilating property pertains to effects of certain foods and relates to ginger's perceived power in the digestive system (Pokert and Ullmann 1988, 218). Ginger is generally included in prescriptions for digestive ailments, appetite disorders, and

queasiness, and is useful in TCM because many of the remedies involve absorption through the GI tract. In addition, Chinese meals are extremely rich and are eaten late in the evening, thus the incorporation of ginger may be important in aiding digestion.

Western Medicine

Like ancient Asian peoples, Europeans took notice of ginger's activity on the digestive system (Alcock 2006). The laxative properties are described by the first century physician scholar Dioscorides, writer of *De Materia Medica* (Alcock 2006). Ginger is also described by author Charles Lamb to "make [millet] go down the more glibly" in his 18th-century works (Lamb 1994, 351). Henry VIII recommended the use of ginger in curing or preventing the plague, as by 1416, preserved ginger was a common import from China (Ravindran 2005, 279).

Chemistry and Pharmacology

The wealth and variety of chemicals present in rhizomes of *Zingiber officinale* are responsible for ginger's taste, aroma, and healing properties. Specific constituents of ginger extracts are dependent upon the origin of the variant and the condition of the rhizomes (fresh or dried). According to a phytochemical review of ginger, 63 compounds have been identified in fresh ginger compared to 115 compounds identified in dry ginger, and 45 of these compounds are shared by fresh and dry ginger. The compounds responsible for the pungency of fresh ginger, gingerols, become the dehydrated shogaols responsible for the pungency of dried ginger (Ali et al. 2008, 410).

The most medicinally active chemicals present in ginger rhizomes are components of the volatile oil and non-volatile pungent principles (gingerols and shogaols). Other components include fats, waxes, carbohydrates, vitamins such as Nicacin and Vitamin A, minerals, and zingibain, a proteolytic enzyme (Shukla and Singh 2006, 684; Murray 2004, 134).

Volatile Oil

There are over 50 components of ginger's volatile essential oil, which is present in amounts of 1-3% and is responsible for the aroma of fresh ginger (Dewick 2009, 168). Most of the components are monoterpenoids [β -phellandrene, (+)-camphene, cineole, geraniol, curcumene, citral, terpineol, borneol] and sesquiterpenoids [α -zingiberene (30–70%), β -sesquiphellandrene (15–20%), β -bisabolene (10–15%), (E-E)- α -farnesene, *ar*-curcumene, zingiberol] (Ali et al. 2008, 410).

Pungent Compounds

The non-volatile pungent principles are responsible for the hot taste sensation of ginger. These include the biologically active chemicals gingerols, shogaols, paradols, gingerdiols, and gingerones as well as derivatives.

Gingerols

The pungent taste of fresh ginger rhizomes is mainly due to the presence of homologous, phenolic ketones called gingerols (**Figure 3**). The gingerols are differentiated by the number of carbons in their C-5 side chains (Jolad et al. 2004). The compound [6]-gingerol is the most abundant at portions of 28-34%, followed by [10]-gingerol and [8]-gingerol. Gingerols

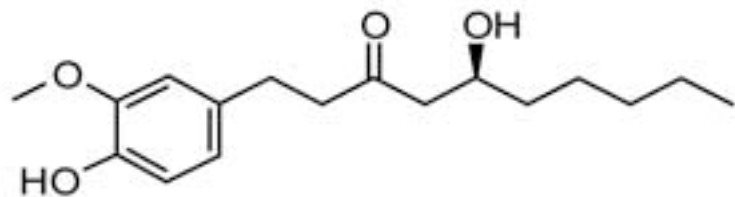


Figure 3. [6]-gingerol is the main pungent principle of fresh ginger. (Source: <http://www.dalton.com/images/prod/23513-14-6.jpg>)

degrade into shogaols or paradols under pH-specific conditions (for shogaols: when pH is between 2.5 and 7.2) upon the addition of heat. Studies on isolations of [6]-gingerol have suggested antipyretic, antioxidant, and anti-inflammatory effects (Young et al. 2005, 207).

Shogaols

Shogaols (**Figure 4**) are the products of dehydration of gingerols and are thus found in the dried rhizomes of *Zingiber officinale* and in non-fresh ginger powder. These compounds are analogous to gingerols and contribute to the pungency of dried ginger. The structural difference from gingerols is a double bond between C-4/C-5 and the absence of the hydroxide on the C-5 carbon (Jolad et al. 2004).

Biological Activity

Results of *in vitro* and *in vivo* studies on ginger root extract are often contradictory. One possible reason for discrepancies is the variability in chemical composition of the studied ginger, as it is dependent on whether the rhizome is fresh or dried. Besides the differences in composition of the ginger

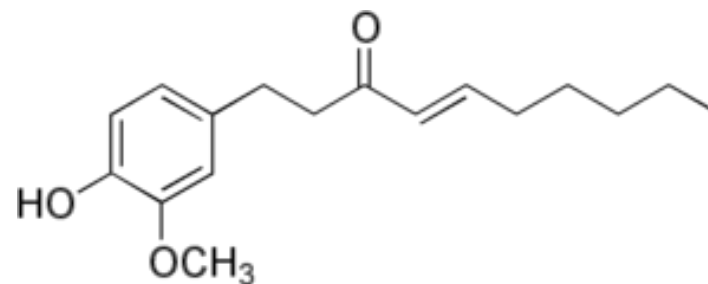


Figure 4. [6]-shogaol is the main pungent principle of dried ginger, it is the product of dehydration of [6]-gingerol. (Source: <http://upload.wikimedia.org/wikipedia/commons/thumb/0/05/Shogaol.png/300px-Shogaol.png>)

powders and extracts, another source of conflicting results could lie in the doses administered, the treatment duration, and the quality of the ginger products. As a result, standardization of ginger products is essential in researching its medicinal effects (Schwertner et al. 2006).

Anti-inflammatory and anti-pyretic

Anti-inflammatory action has been demonstrated *in vitro* and *in vivo* since the 1980s. Anti-inflammatory and soothing action from gingerols and shogaols may be the result of dual inhibition of both cyclooxygenase and lipoxygenase pathways that are involved in inflammatory processes (Yip and Tam 2008, 137; Jolad et al. 2004, 1937). Specific constituents such as gingerdiones and shogaols have properties mimicking dual-acting non-steroidal anti-inflammatory drugs *in vitro*, and the principle pungent ketones [6]-gingerol, [6]-paradol, and zerumbone have been shown to have strong anti-inflammatory activity (Shukla and Singh 2007, 687). *In vivo*, anti-inflammatory and analgesic activity of [6]-gingerol was shown by significantly reduced writhing of animals (Young 2005, 208, Chrubasik 2005, 691).

Other demonstrations of anti-inflammatory action include ginger's action against cytokines secreted at inflammation sites, ginger's modulation of some pathways activated in chronic inflammation, and ginger extract's suppression of pro-inflammatory cytokines and chemokine expression (Ali et al. 2008, 413-414).

Ginger plant extract has also been found to reduce swelling in a nearly identical fashion to aspirin. In a study of rats, dosages of 50 mg/kg of ginger extract reduced swelling in rats' paws by 22%, while an equal dose of acetylsalicylic acid reduced swelling by 23% (Mascolo et al. 1989). This study also demonstrated that anti-pyretic effects of ginger extract are similar to the effects of equal dosages of acetylsalicylic acid.

Anti-emetic

Both *in vivo* and *in vitro* studies suggest that ginger is an effective treatment for nausea and vomiting. The mechanism of action for the carminative and anti-emetic effects has not been identified. However, it has been suggested that [6]-gingerol may enhance gastrointestinal transport; that other ginger compounds have anti-hydroxytryptamine activity *in vivo*; that galanolactone, a constituent of ginger, is a competitive antagonist at ileal 5-HT₃ receptors; or that ginger affects emesis through the central nervous system (Ernst and Pittler 2000, 368). Current antiemetics act as ileal 5-HT₃ receptor antagonists. *In vivo*, ginger juice inhibited cisplatin (an anticancer drug) -induced emesis in rats and in dogs (Sharma 1998, 54; Sharma 1997, 95).

Hypoglycaemic

Mascolo et al. found ginger extract to exhibit potential hypoglycaemic activity *in vivo* (Mascolo et al. 1989).

Anti-fungal

Of three plant extracts (ginger, onion, and garlic), an ethanolic extraction of ginger was found to be the most effective in inhibiting fungal growth (Tagoe et al. 2011, 286). The isolated compound gingerenone A exhibited complete inhibition of hyphae invasion of *Pyricularia oryzae* and moderate inhibition of *Eimeria tenella* at concentrations of 10 ppm (Endo et al 1989, 798). Ginger oil and oleoresin show moderate to good inhibition of fungal growth in both food poison and inverted petri plate methods (Singh et al 2008, 3301). An antifungal protein was also identified from ginger extract, showing strong antifungal activity similar to the potency of *Asparagus officinalis* seeds (Wang et al. 2005, 103).

Anti-bacterial

Ginger extract has been shown to inhibit both Gram-positive and Gram-negative bacteria growth (Mascolo et al. 1989; Gao et al. 2010, 43). Essential oil and oleoresins of ginger exhibit inhibitory effects towards bacterial growth comparable to streptomycin and chloramphenicol. Oleoresins were shown to be less effective than the essential oil. This activity is most likely due to the phenolic compounds of the oil and oleoresin, and it is likely that the efficacy is synergistic of many of these phenolic constituents of ginger (eugenol, shogaols, zingerone, gingerdiols, gingerols) (Singh et al. 2008, 3300).

In one recent study, freeze-dried ginger was observed to have a significant effect on the relative radiation sensitivity of pork inoculated with *Escherichia coli*, providing supportive evidence of antibacterial properties of ginger (Yun et al. 2011). In a comparison of onion juice and ginger juice, however, ginger juice was found not to be effective against multi-drug resistant bacteria (Adeshina et al. 2011, 293).

Antioxidant

The antioxidant activity of ginger has been demonstrated in many *in vitro* and *in vivo* studies, and this activity may explain the protective actions of ginger against toxicity and radiation (Ali et al. 2008, 416). Bioactive components of ginger extract such as [6]-gingerol, zingerone, and dehydrozingerone have been shown to have potent antioxidant and tyrosinase inhibition activities, and zingerone may act as a scavenger of superoxide anions (Chrubasik 2005, 689; Shukla and Singh 2006, 686).

Cancer preventative effects

Cancer preventative effects of ginger have been found in studies relating to skin, gastrointestinal, colon, and breast cancer. Alcoholic extracts of ginger have been found to be cytotoxic to certain tumor cells *in vitro*. Both [6]-gingerol and [6]-paradol showed suppressive effects on proliferation of human cancer cells through the induction of apoptosis. Another chemical constituent, zerumbone, inhibits activation of NK- κ B-regulated gene expression that is induced by carcinogens. *In vivo*, ginger and specifically [6]-gingerol were shown to suppress promotion of skin carcinogenesis in laboratory mice. Animals treated with ginger extract also showed significantly lower tumor body burdens compared to controls (Shukla and Singh 2006, 686-688). The essential oil of ginger also showed antitumor activity (Chrubasik 2005, 689).

Clinical Studies

Nausea and Vomiting

In a review of the antiemetic effects of ginger, it was reported

that 1 g of ginger powder daily alleviated clinical nausea of diverse causes such as pregnancy-induced nausea, drug-induced nausea, and motion sickness (Ernst and Pittler 2000, 368). Ginger has been shown to be more effective in reducing severity of nausea in pregnant women than vitamin B6 or placebo (Ensiyeh 2009; Ozgoli et al. 2009, 245).

Rheumatism

Relief from rheumatism from ginger was shown to be comparable to that from ibuprofen (Haghighi et al. 2005). In osteoarthritis patients, reduction in knee pain on standing was superior for those taking ginger extract than placebo (Altman and Marcussen 2001).

Contraindications

Ginger root extract is generally recognized as safe (GRAS) by the FDA, but pregnant women are discouraged from use due to lack of relevant research. Some adverse effects have been reported by a study of pregnant rats including elevated birth rate of the fetal rat (Ali et al. 2004). However, the overall low toxicity of ginger and its chemical constituents have been confirmed by multiple studies (Weidner et al. 2000, Chang et al. 1995, Ali et al. 2004). Minor adverse effects observed in research include heartburn, mild diarrhea, and IGE-mediated allergy (Ali et al. 2004). Dangerously toxic effects have only been observed in extremely or unnaturally high dosages.

The potential interaction of ginger root extract with warfarin has been studied due to conflicting evidence of blood-thinning properties of gingerols, but no evidence suggests a significant effect of ginger on warfarin. Ginger root extract does have a synergistic interaction similar to aspirin with nifedipine on anti-platelet aggregation (Ali et al. 2008).

Current Use in Allopathic and CAM Therapies

Ginger extracts are commercially available around the world from multiple distributors in the form of capsules. However, the standardization of ginger root extract remains an unsolved problem. In a study of ten ginger dietary supplements, only five manufacturers listed a dosage recommendation. Of the recommendations, the serving size varied widely. Listing of expiration dates, ingredients, or methods of standardizations were not consistently present from all manufacturers. Finally, the composition of the ginger supplements was varied significantly (Schwertner et al. 2006). These results expose a problem characteristic not only to ginger supplements but also to much of the natural product market. The verification of the chemical constituents of ginger extracts is especially important due to the variability of chemical composition based on preparation methods.

Ginger is also used medicinally as a tea, where the fresh or dried rhizome is chopped and steeped in water. Ginger tea and ginger capsules are the most used natural product by pregnant women suffering from nausea, vomiting, and “morning sickness” symptoms (Hollyer 2002). Most women in this study who did not use CAM to alleviate nausea and vomiting reasoned that they wished to know more about the safety of ginger extract and other natural products. The safety of medicinal use of ginger in pregnant women has yet to be intensively studied.

Massage therapists and aromatherapists take advantage of the healing properties of ginger essential oil. Few of the ginger remedies using used in these manners have been clinically evaluated for safety in efficacy, though their uses are extensive. In one study, however, both ginger essential oil and ginger powder were shown to relieve pain when used in massage therapy (Yip and Tam 2008, 137).

Discussion

The use of ginger for multiple millennia serves as support to its efficacy and pertinence in human health. Because of ginger’s low cost and low toxicity, there are few, if any, deterrents to pursuing research on the chemical components of ginger and their roles in both biomedicine and CAM. Because ginger is not found growing wild, as long as cultivation promotes biological variation, there is little danger in continuing the large-scale cultivation and harvesting of ginger. The variability of the chemical makeup of ginger so dependent on its preparation is a prime example of a research area for ethnobotanists. Ethnobotanical approaches could potentially expose different methods of preparing and storing the rhizome and their applications to different treatments.

Especially of clinical interest is the role of ginger extract in cancer treatments. Because of the anti-emetic properties, ginger would be useful in relieving nausea induced by chemotherapy. Simultaneously, the antioxidant activity of ginger extract undoubtedly plays a role in reducing the oxidative stress that may accelerate tumor growth. Further research is necessary in this field as some studies have found conflicting evidence into carcinogenic properties of ginger’s chemical constituents. Ginger also shows promising results in clinical studies with osteoarthritis, and there is substantial support for ginger’s effectiveness as an antiemetic for diverse causes.

Until ginger rhizome extracts are standardized for maximum effectiveness, the biomedical future of ginger extract seems to be more promising than ginger’s use as a natural product. For one, the healing properties of gingerols are not found in ginger powder unless it is a fresh ginger preparation, therefore the use of dried ginger or ground ginger in the kitchen is not likely to provide benefits in consumption. As ethnobotany becomes

more closely tied to biomedical and pharmacological research, *Zingiber officinale* will remain a prime investigational target.

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INDEX OF CONTRIBUTORS

Baerwaldt, Tiffany	436	Henderson, MyKeya	121	Nardo, David	85
Berlin, Avery	259	Henkel, Sarah	421	Nelson, Katie	362
Cappello, Elizabeth M.	289	Howell, Jennifer	224	Nwankwo, Ezinne	111
Carl, Annalies	374	Jarvis, Ben	322	Ohmart, Kira	400
Carroll, Latavia	174	Jones, Marston	42	Okafor, Ijeoma	156
Chanyasubkit, Soraya	297	Kahn, Alexa	279	Paine, Michele	20
Clanahan, Michael	58	Kramer-Roach, Benjamin	231	Patel, Nina	97
Coleman, Charity	208	Lake, Elsa	242	Sefat, Cimma	270
Cross, Kristen	66	Martens, Kylee	75	Shalem, Ronni	330
Dai, Mengshi	310	McCabe, Carly	409	Turner, Samuel	218
Demakovsky, Leah	135	McCullough, Ian	196	Woodard, Kedra	353
Dhukani, Anum	30	McMullin, Sarah	426	Wyeth, Wallace	390
Giffen, Elizabeth	166	Mittal, Ashvi	183	Yang, Yinan	252
Grady, Corrine	341	Mongue, Andrew	48	Yarp, Alison	146
Hampton, Aerhealle	128	Morris, Alisha	383		
Healy, Shannan	6	Mosby, Sarah	445		

INDEX OF COMMON PLANT NAMES

Absinthe	58	Ephedra	218	Passionflower	330
Aloe	20	European Goldenrod	383	Pepper	111
American Coneflower	208	Flax	279	Pineapple	30
Avocado	341	Foxglove	196	Poppy	322
Ayahuasca Vine	85	Garlic	6	Purple Coneflower	208
Bearberry	42	Ginger	445	Purple Foxglove	196
Bell Pepper	111	Ginkgo	231	Purple Passionflower	330
Belladonna	66	Ginseng	310	Rosemary	353
Bilberry	436	Goldenrod	383	Sangre de Drago	174
Bitter Melon	297	Horseradish	48	Sangre de Grado	174
Black Cohosh	128	Kinnikinnick	42	St. John's Wort	252
Chile Pepper	111	Kola Nut	156	Stinging Nettle	421
Chocolate	400	Lavender	270	Tea	97
Cinnamon	135	Licorice	242	Tea Tree	289
Coffee	146	Madagascar Periwinkle	121	Thyme	409
Cranberry	426	Maté	259	Turmeric	183
Deadly Nightshade	66	Milk Thistle	374	Uva Ursi	42
Digitalis	196	Myrrh	166	Wormwood	58
Dragon's Blood	174	Oats	75	Yerba maté	259
Echinacea	208	Ojé	224		
Elderberry	362	Opium Poppy	322		
Elder tree	362	Pacific Yew	390		