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Review

The chemistry, pharmacology and clinical properties of *Sambucus ebulus*: A review

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***Sambucus ebulus* is known as dwarf elder or elderberry. *S. ebulus* extracts are an important area in drug development with numerous pharmacological functions in the Middle East. However, their pharmacological functions have not been clearly studied. For a long time, *S. ebulus* has been prescribed in traditional medicines for the treatment of inflammatory reactions, such as hemorrhoid, bites and sore-throat. In addition, *S. ebulus* has recently been shown to have anti-inflammatory, anti-nociceptive, anti-cancer, anti-angiogenic and anti-oxidative activities. Ebulitin, ebulin 1, flavonoid, athocyanin and other components have been isolated from *S. ebulus* and identified as active ingredients of biological and pharmacological activities. Due to the easy collection of the plant and remarkable biological activities, this plant has become both food and medicine in the coastal area of Iran. This review presents comprehensive analyzed information on the botanical, chemical, toxico-pharmacological and clinical aspects of *S. ebulus*.**

Key words: *Sambucus ebulus*, Adoxaceae, RIPs, anti-inflammatory, anti-nociceptive, anti-cancer, anti-oxidative.

INTRODUCTION

Sambucus ebulus whose common name is dwarf elder, elderberry or danewort, is a native perennial herb of the Adoxaceae family in the order of the Dipsacales, that contains about 190 species and 4 genera and is mainly distributed across southern and central Europe, northwest Africa and Southwest Asia (esp. northern Iran) (Westwood, 1985). Much of the debate over the taxonomy of plants in Dipsacales has been settled. Two of the most familiar members of Dipsacales, the elderberry (Sambucus) and the viburnum, formerly in Caprifoliaceae, have been moved into Adoxaceae, along with some other genera (Vernon, 1987). The Sambucus genus contains between 5 to 30 species (http://en.wikipedia.org; Medve and Medve, 1990; Zakay-Rones et al., 1995). The main species are *S. ebulus*, *Sambucus nigra, Sambucus racemosa*, *Sambucus africana* and *Sambucus palmensis*.

S. ebulus has been known as 'Palam' and 'Aghtti' in Iran and distributed in moist grasslands or forest margins on Northern coast of Caspian Sea, Iran (Azadbakht, 1999). *S. ebulus* grows about 60 - 200 cm high (Figure 1A), with erect, usually unbranched stems growing in large groups from an extensive perennial underground rhizome (Figure 1B). The leaves are opposite, pinnate, 15 - 30 cm long, with 5 - 9 finely-toothed and lobed leaflets with a foetid smell (Figure 1C). The stems terminate in a corymb 10 - 15 cm diameter with numerous white (occasionally pink) flowers (Figure 1D). The fruit is a small glossy black berry that is 5 - 6 mm in diameter (Figure 1E) (Westwood, 1985). *S. ebulus* flowers from July to August and its seeds ripen from August to September and die down in winter. It however, spreads by vigorous underground rhizomes to form large colonies. The scented flowers are self-fertile and hermaphrodite (having both male and female organs) and are pollinated by bees, flies and beetles. The plant prefers light (sandy), medium (loamy) and heavy (clay) soils, but it can grow in semi-shade (light woodland) or no shade situation and heavy clay soil. Also, *S. ebulus* prefers acid, neutral and basic (alkaline) soils to grow. The plant can tolerate atmospheric pollution and strong wind, but not maritime

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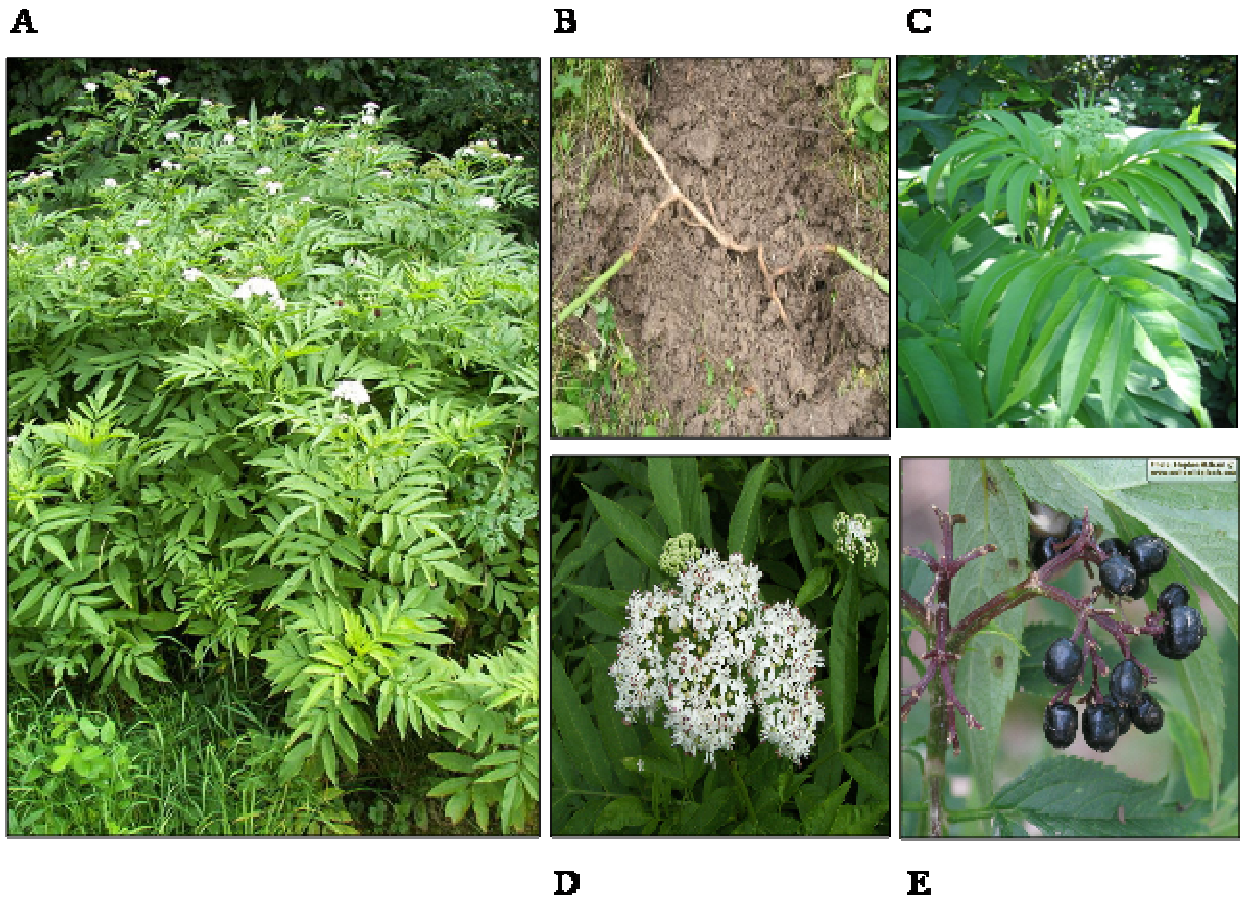

Figure 1. *Sambucus ebulus* (dwarf elder, elderberry or danewort) is characterized by small glossy black ies, white (occasionally pink) flowers, and opposite and pinnate leaves with 5-9 lobes and a finely toothed margin. A = *Sambucus ebulus*; B = rhizome; C = leaves; D = flower; E = berry.

exposure (Rechinger, 1963; Tutin, 1980).

For a long time, *S. ebulus* has been used as a folklore medicine for treatment of various diseases which are thought to be inflammatory in nature e.g. rheumatism, fever, infections, edemas or related inflammatory diseases. In ancient oriental medicine, its leaves, rhizomes and roots were administered to patients to treat bee and nettle bites, arthritis and sore-throat (Saravi et al., 2009b; Ebrahimzadeh et al., 2007; Tuzlaci, 2000; Guarrera, 1999; Yesilada et al., 1999; Petkov, 1986; Mirhaydar, 1984; Zargari, 1981; Samsamshariat et al., 1981; Ognyanov et al., 1979). This plant also has other uses. For instance, a blue dye and ink can be obtained from the fruit. Also, the root juice is used to dye hair and the leaves are said to repel mice and moles (Duke et al., 2002; Davis, 1988; Rechinger, 1963; Tutin, 1980).

On the other hand, raw berries are poisonous and all parts of the plant may be toxic if consumed in excess. The leaves and stems of some, if not all, members of Sambucus genus are poisonous. Even the leaves may cause contact dermatitis. The fruit of this species has been known to cause stomach upsets to some people. However, any toxin the fruit might contain is liable to be of very low toxicity and is destroyed when the fruit is cooked (Nova Scotia Museum Website).

Since cyanogenic glycoside from *S. ebulus*, named sambunigrin and ester iridoid glucoside, named ebuloside were isolated and the structure determined (Buhrmester et al., 2000; Campa et al., 2000; Gross et al., 2004), a number of chemical constituents such as flavonoids, steroids, tannins, glycosides, cardiac glycosides, caffeic acid derivatives, ebulitins, ebulin 1 and volatile substances have been isolated from this plant (Saeedi Saravi and Shokrzadeh, 2009b; Ebrahimzadeh et al., 2006 and 2007; Ahmadiani et al., 1998; Yesilada, 1992; Ghannadi and Ghassemi-Dehkordi, 1997; De Benito et al., 1995; Pribela et al., 1992) (Figure 3).

From current pharmaceutical studies, additional pharmaceutical applications of *S. ebulus* have revealed anti-inflammatory, anti-rheumatoidal, anti-nociceptive, anti-hemorrhoidal, anti *Helicobacter pylori* effects among others. Also, effects of this plant in the treatment of burns, infectious wounds, edema, eczema, urticaria and cold are reported (Saravi and Shokrzadeh, 2009b;

Ebrahimzadeh et al., 2006, 2007; Tuzlaci and Tolon, 2000; Yesilada et al., 1999; Guarrera, 1999).

The usage of the plant has been recently extended into the medicinal plant due to the advent of new functional and biological active material. However, review and systemic analysis of chemistry, pharmacology and clinical properties of *S. ebulus* have not been reported. This review intended to provide the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant.

The aim of this present review is to introduce *S. ebulus* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

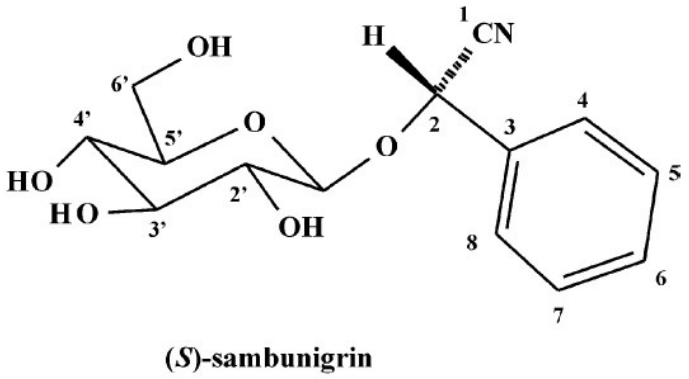

Figure 2. Structure of (*S*)-sambunigrin ((S)-O-β-D-Glucopyranosyl mandelonitril) from *Sambucus ebulus* (Buhrmester et al., 2000).

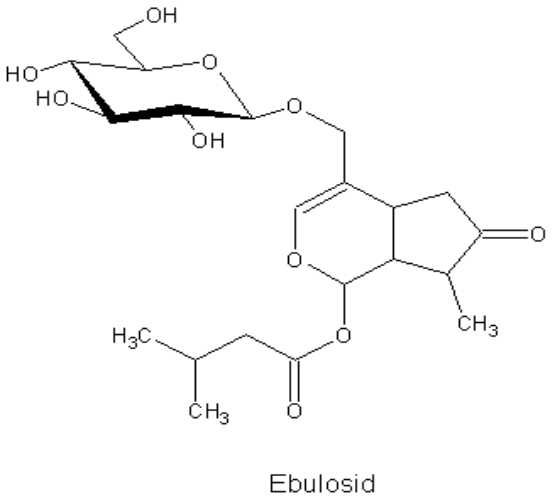

Figure 3. Structure of ebulosid (7-Oxo-8-desoxyvalerosidatum), an iridoid glycoside, from *Sambucus ebulus* (www.giftpflanzen.com/sambucus_ebulus.html).

CHEMICAL COMPOSITION

The commonly known phytochemical compounds from *S. ebulus* are flavonoids, steroids, tannins, glycosides, cardiac glycosides, caffeic acid derivatives, ebulitins, ebulin 1 and volatile substances (Saeedi Saravi and Shokrzadeh, 2009b; Ebrahimzadeh et al., 2006, 2007; Ahmadiani et al., 1998; Ghannadi and Ghassemi-Dehkordi, 1997; De Benito et al., 1995; Yesilada, 1995; Pribela et al., 1992). Traces of a cyanogenic glucoside, sambunigrin and the triterpenes alpha- and beta-amyrin were isolated from leaves, roots and fruits. Both (*S*)-sambunigrin (2) and (*R*)-prunasin, as well as the meta-substituted compounds (*R*)-holocalin and (*S*)-zierin are other active compounds of *S. ebulus* (Buhrmester et al., 2000; Jensen and Nielsen, 1973). Cyanogenic glucosides, such as (*S*)-sambunigrin ((*S*)-O-β-D-Glucopyranosyl mandelonitril) were isolated from fruits of this plant; but, leaves and stems contain more sambunigrin (Figure 2). *S. ebulus* flowers contain 0.03 to 0.3% of an essential oil (approximately 0.01% of the berries is essential oil) that contains free fatty acids (particularly palmitic acid) and a large number of compounds called alkanes. They also contain at least 0.8% flavonoids. Also, caffeic acid and derivatives, including chlorogenic acid and *p*-coumaric acid, have been identified. Chlorogenic acid, an ester of caffeic acid with quinic acid, is found in many plants and recognized as an antioxidant (Rhee et al., 2009; Bonita et al., 2007; Bouayed et al., 2007; Medina et al., 2007). Ebulosid (7-Oxo-8-desoxyvalerosidatum), an iridoid glycoside with formula $C_{21}H_{32}O_{10}$, was isolated from *S. ebulus*. In addition, other active compounds, such as ebulitin and ebulin 1 were found in leaves and berries (Saeedi Saravi and Shokrzadeh, 2009; Shokrzadeh et al., 2009). Ebulitin, a single chain (type 1) ribosome-inactivating protein (RIPs), has been found in mature leaves of *S. ebulus L.* that contains a non-toxic two chain (type 2) RIP named ebulin 1 in its leaves. Ebulitins are basic proteins of Mr 32,000, 29,000 and 29,000 for ebulitins α, β and γ, respectively. Therefore, to compare the ebulitins with each other, amino acid composition of each is presented in Table 1 and Figure 4. On the other hand, Ebulin 1 is composed of two subunits, a catalytic A subunit (Mr 26,000) and a D-galactose-binding lectin B subunit (Mr 30,000). Ribosome-inactivating proteins (RIPs) are plant toxins with N-glycosidase activity on the large rRNA of mammalian, fungal, plant, and bacterial ribosomes that irreversibly impair protein synthesis (Barbieri et al., 1993; Citores et al., 1993; Girbes et al., 1993; Stirpe et al., 1992; Endo and Tsurugi, 1987). The action of RIPs on ribosomes abolishes ribosomal ability to interact with elongation factors 2 or G and thus irreversibly arrests polypeptide chain elongation (Girbes et al., 1993; Stirpe et al., 1992). The molecular action of RIPs involves the

Figure 4. Amino acid sequences of A and B chains of ebulin 1, isolated from *S. ebulus* (Girbes et al., 1993).

Table 1. Amino acid compositions of ebulitins (De Benito et al., 1995).

Amino acid	α-Ebulitin	β-Ebulitin	γ-Ebulitin
Cysteine	0	6	6
Aspartic acid	35	36	31
Threonine	27	31	33
Serine	21	15	16
Glutamic acid	36	21	22
Proline	14	15	15
Glycine	24	17	18
Alanine	21	21	22
Valine	23	12	9
Methionine	5	2	4
Isoleucine	14	15	18
Leucine	28	19	18
Tyrosine	7	9	7
Phenyl alanine	10	6	8
Lysine	9	9	6
Histidine	4	8	9
Arginine	16	19	20
Tryptophan*	-	-	-

Composition is expressed as the rounded-off number of residues per mol of protein based on an M_r of 32,000, 29,000 and 29,000 for α, β and γ,-ebulitin, respectively.
*Trp not determined.

depurination of the largest rRNA which upon treatment with acid aniline releases the diagnostic RNA fragment (Girbes et al., 1993; Hartley et al., 1991; Stirpe et al., 1988; Endo and Tsurugi, 1987). RIPs consisting of a unique enzymic polypeptide chain have been classified as type 1, while those consisting of one or two dimers of two different polypeptide chains linked by a disulfide bridge, one being the enzymic chain and the other a lectin able to recognize membrane sugars, mostly galactose residues have been classified as type 2 (Girbes et al., 1993; Barbieri et al., 1993; Olsnes and Pihl, 1982).

POTENTIAL OF *S. EBULUS* IN PHYTOTHERAPIES

S. ebulus is used in traditional Iranian medicine to treat various diseases, such as rheumatoid arthritis, fever, infections, edemas or related inflammatory diseases (Saeedi Saravi et al., 2009b; Ebrahimzadeh et al., 2007; Tuzlaci and Tolon, 2000; Guarrera, 1999; Yesilada et al., 1999; Petkov, 1986; Mirhaydar, 1984; Zargari, 1981; Samsamshariat et al., 1981; Ognyanov et al., 1979). Although the anti-inflammatory and anti-rheumatoidal effects of *S. ebulus* berry and rhizome extracts have been well documented and are potential non-steroidal anti-inflammatory herbal drug in the Middle East, so far the therapeutic potential has not been exploited by the Western countries (Ahmadiani et al., 1998; Ebrahimzadeh et al., 2006, 2007). In recent years, accumulating evidence indicated that not only is *S. ebulus* important in treating inflammation and rheumatoid arthritis, but that it also contains antibacterial, antivirus and anti-cancer effects (Yesilada et al., 1999; Saravi and Shokrzadeh, 2009b; Shokrzadeh et al., 2009).

Anti-inflammatory and anti-nociceptive effect

Although a number of steroidal or non-steroidal anti-inflammatory drugs have been developed, researchers are changing their focus to natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs (Hyun and Kim, 2009). As a result, the search for other alternatives seems necessary and beneficial. This leaves an open door for new and better compounds (Elisabetsky et al., 1995; Ebrahimzadeh et al., 2006, 2007). Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-α, interleukin (IL)-1β and granulocyte/ macrophage colony-stimulating factor (GMCSF)] and inflammatory mediators [for example, reactive oxygen species (ROS) and nitric oxide (NO)] (Rhee et al., 2009; Lundberg, 2003; Walsh, 2003). The leaves of *S. ebulus* has been functionally used as a traditional crude drug for the treatment of various inflammations (for example, contact dermatitis, bee and nettle bites, eczema) and there are several reports describing the influence of *S. ebulus* extracts on inflammation (Ahmadiani et al., 1998; Ebrahimzadeh et al., 2006, 2007; Saeedi Saravi et al., 2009a, b). In animal models, the methanol and n-hexane extract from *S. ebulus* fruits has shown similar anti-inflammatory effects to diclofenac, a well-known non-steroidal anti-inflammatory drug (NSAID), via the inhibition of carageenan-induced paw edema in rats (Ebrahimzadeh et al., 2006, 2007). The methanol extract from *S. ebulus* rhizome caused the inhibition of formalin-

induced edema in rats, compared with sodium salicylate (Ahmadiani et al., 1998). The study showed that administration of methanol rhizome extract produce anti-inflammatory activity in both acute and chronic inflammatory tests. During inflammation, the activated interleukin-1 (IL-1) and tumor necrosis factor (TNF) up-regulate the proinflammatory, type II phospholipase (PL) A2, cyclooxygenase (COX)-2 and induce nitric oxide (NO) synthesis, resulting in increased prostaglandins (PGs: synthesized by COX) and NO synthesis. More relevant to pain and inflammation is the increase in PG-E2 mediated by IL-1 or/and TNF (Hyun and Kim, 2009; Charles and Dinarello, 2000). Therefore, the inhibition of COX has been targeted by anti-inflammatory drugs to reduce pain and inflammation. In fact, diclofenac or sodium salicylate exhibits this anti-inflammatory property by inhibiting COX activity (Hyun and Kim, 2009; Vane and Botting, 2003). The mechanisms underlying the anti-inflammatory action, like the exogenous effect of steroids or endogenous release of glucocorticods, interaction with prostaglandin biosynthesis, interaction with tachykinin, or other inflammatory mediators are probable (Ahmadiani et al., 1998). Also, the anti-inflammatory effect related to the active compounds might be the flavonoids and steroid. On the other hand, differential effect of the ethyl acetate extract of *S. ebulus* fruits was observed that indicated the toxic effects of this fraction.

In anti-nociceptive studies, the methanol and n-hexane extract from *S. ebulus* fruits has shown similar anti-nociceptive activity via hot plate test in mice (Ahmadiani et al., 1998). Also, the methanol extract from *S. ebulus* rhizome caused the inhibition of formalin-induced pain in rats and showed anti-nociceptive effect in rats which were studied via tail flick test. The study showed that administration of methanol rhizome extract produce clear dose dependent anti-nociceptive effects on tail flick and also on both phases of formalin test. These findings suggested that the central mechanisms are involved in the anti-nociceptive activity of the extract. The underlying mechanisms of anti-nociceptive actions of *S. ebulus* extract are proposed in the endogenous release of glucocorticods or exogenous effect of steroids, interaction with α-2 adrenoceptor or serotonergic system, L-arginine derived from nitric oxide or nitric oxide-related pathway, and interaction with tachykinin pathway (Ahmadiani et al., 1998).

Anti-oxidative effect

An antioxidant is defined as 'any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate' (Rhee et al., 2009; Halliwell et al., 1995; Wiseman et al., 1997; Mates et al., 1999). Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damage induced by reactive free radicals generated in cancer, atherosclerosis, and aging (Halliwell et al., 1995; Mates et al., 1999). There are many reports that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-cancer, hypolipidemic, antiaging and anti-inflammatory activity (Rhee et al., 2009; Halliwell et al., 1995; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006).

In order to compare the anti-oxidative capacities of methanol and aqueous fractions of *S. ebulus* fruits, the antioxidant activity of each extract of the plant was determined by using DPPH radical-scavenging activity assay, nitric oxide-scavenging activity assay, metal chelating activity assay, scavenging of hydrogen peroxide, reducing power determination and FTC Method. Also, total phenolic compounds and flavonoid contents of the extracts were determined (Ebrahimzadeh et al., 2009a). In DPPH radical-scavenging activity assay, the anti-oxidative activity of methanol fraction of *S. ebulus* flowers showed that the radical-scavenging activity of the extract increased with increasing concentration (Ebrahimzadeh et al., 2009b). The IC_{50} value for DPPH radical-scavenging activity was 228 ± 12 µg ml^{-1}. On the other hand, in nitric oxide assay, the radical scavenging activity of the fraction (IC50 value = 309 ± 14 µg/ml) was much weaker than that of quercetin (IC50 value = 17 µg/ml). In addition to reactive oxygen species, nitric oxide is also implicated in inflammation, cancer and other pathological conditions. Methanol extract of *S. ebulus* flowers also showed anti-oxidative activities by using Fe^{2+} chelating ability. Iron chelators mobilize tissue iron by forming soluble, stable complexes that are then excreted in the feces and/or urine (Ebrahimzadeh et al., 2009b). Chelation therapy reduces iron-related complications in human and thereby improves quality of life and overall survival in some diseases such as thalassemia major (Ebrahimzadeh et al., 2009b; Hebbel et al., 1990). In addition, brain iron dysregulation and its association with amyloid precursor protein plaque formation are implicated in Alzheimer's disease (AD) pathology and so, iron chelation could be considered as a rational therapeutic strategy for AD (Ebrahimzadeh et al., 2009b; Reznichenko et al., 2006). The transition metal, iron, is capable of generating free radicals from peroxides by Fenton reactions and may be implicated in human cardiovascular disease (Ebrahimzadeh et al., 2009b; Halliwell and Gutteridge, 1990). Because Fe^{2+} causes the production of oxyradicals and lipid peroxidation, minimizing its concentration affords protection against oxidative damage. It was reported that chelating agents are effective as secondary antioxidants, because they reduce the redox potential, thereby stabilizing the oxidized form of the metal ion (Gordon et al., 1990). The extract had very weak activity in iron chelating (IC_{50} = 1.3 ± 0.07 mg mL^{-1}). The ability of the extract to effectively scavenge hydrogen peroxide, has been determined (Nabavi et al., 2008a), where it was

compared with that of quercetin and ascorbic acid as standards. The extract was highly capable of scavenging hydrogen peroxide in a concentration-dependent manner (IC_{50} value = 59.5 ± 3.3 µg ml^{-1}). Although hydrogen peroxide itself is not very reactive, it can sometimes cause cytotoxicity by giving rise to hydroxyl radicals in the cell. Thus, removing H_2O_2 is very important in food systems (Nabavi et al., 2008b). The peroxidation inhibition (antioxidant activity) of the extract exhibited 86% (at 48 h), in FTC test. At the other incubation times (24 and 72 h), extract showed below 50% inhibition (Ebrahimzadeh et al., 2009b).

Also, methanol and aqueous fractions of *S. ebulus* fruits showed similar anti-oxidative property (Ebrahimzadeh et al., 2009a). The DPPH radical scavenging activity (IC_{50} value = 202.50 ± 1.38 µg mL^{-1}) of the methanol fraction was much more effective than the aqueous fraction (IC_{50} = 723.62 ± 3.36 µg ml^{-1}), but less effective than ascorbic acid, quercetin and BHA. In the nitrite scavenging assay, aqueous fractions were found to be more effective than methanol fraction. Therefore, some ingredients in the aqueous fraction of *S. ebulus* fruits seem to play an important role in the anti-oxidative capacity. On the other hand, the anti-oxidative effect of methanol and aqueous extract of fruits of *S. eulus* showed weak Fe^{2+} chelating ability. The methanol and aqueous fractions showed 48 and 21% inhibition, respectively (Ebrahimzadeh et al., 2009a).

Anti-*Helicobacter pylori* activity

The role of *Helicobacter pylori* in the pathogenesis of peptic ulcer has been well-established and combined treatments of proton pump inhibitors (that is, omeprazol) with antibiotics (that is, ampicillin, amoxicillin, ofloxacin or tetracycline) have shown to be successful in some of the patients suffering from this complaint, with cure rates up to 90% (Yesilada et al., 1999; Korman et al., 1997). Since antibiotic resistance reported in some of the treated patients is considered to be a major drawback of this therapy, anti-*Helicobacter pylori* activity of *S. ebulus* with shown anti-ulcerogenic effect was investigated, in order to find new active agents which could be used as an alternative to the existing ones. In order to determine anti-*Helicobacter pylori* activity, MIC values were measured by the method described by Imamura et al. (1995) and Fabry et al. (1996) with the slight modifications. MIC values were determined by the agar dilution method. The MIC was defined as the minimum concentration of the test sample (antibacterial agent) in a given culture medium above which bacteria are not able to form colonies. Studies showed that the chloroform ($CHCl_3$) fraction inhibited 37% of the *H. pylori* strains tested (3:8) against the standard strain, with MIC = 31.2 µg/ml. On the other hand, aqueous and methanol extracts and n-Butanol fraction of herbaceous parts of *S. ebulus* showed no inhibitory activity against the microorganism (Yesilada et al., 1999).

Cytotoxic and anti-angiogenic effects

Isolation and identification of some potent anti-tumor compounds, such as colchicine, vinca alkaloids, taxol as natural anticancer compounds, has encouraged scientists to screen different parts of plant species against cancer cell lines (Shokrzadeh et al., 2009; Jafarian-Dehkordi et al., 2004; Prasain et al., 2001; Van Uden et al., 1992; Huang et al., 1986). Tumour development is characterised by the establishment of a fine vascular network, which supplies tumour mass with oxygen and nutrients. The induction of such a network is dependent on pro-angiogenic factors released by tumour cells (Benitez et al., 2005; Hanahan and Folkman, 2006; Folkman, 1995). The growth of cancer cells inside the tumour creates a positive pressure that hinders entry of anti-cancer medicaments thus leading to the reduction of their effectiveness in the therapeutic potential of the conventional chemotherapy (Benitez et al., 2005; Jain, 1990). In order to study the cytotoxic effects of *S. ebulus*, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was performed to determine the IC_{50} of the ethyl acetate extract of fruits and cell viability of hepatocarcinoma (HepG2) and colon carcinoma (CT26) cells after exposure to the extract. The results demonstrated that IC_{50} values of the extract on HepG2 and CT26 cancer cell lines were much lower than that on fibroblast and ovary (CHO) normal cells. Also, the lowest and highest IC_{50} values of the extract was evaluated on HepG2 (97.03 ± 1.52 µg/ml) and CHO (346.2 ± 3.02 µg/ml) cell lines (Shokrzadeh et al., 2009).

On the other hand, since one blood vessel supports hundreds of cancer cells, suppressing vessel proliferation will prevent the growth of a large number of cancer cells. This enables the reduction in the concentration of the anticancer drug required to reach its therapeutic level, thereby reducing the harmful effects of the highly aggressive anticancer agents. A relatively large number of anti-angiogenic compounds have been found and some of them are already in clinical trials (Benitez et al., 2005; Novak, 2002). Another approach to act on the tumour vasculature is the anti-vascular therapy targeted on the tumour neovasculature carried out with immunoconjugates and immunotoxins (Benitez et al., 2005; Tabata et al., 1999). Immunotoxins contain the antibody and a toxin (Benitez et al., 2005; Girbes et al., 2003; Von Mehren et al., 2003; Kreitman, 2000; Thorpe and Burrows, 1995). The most common toxins used in the construction of immunotoxins have been the plant ribosome-inactivating proteins (RIPs). Therefore, the anti-tumour potential of RIPs (ebulin 1) has been demonstrated in clinical trials with immunotoxins. The immunotoxin displays cytotoxicity with nanomolar IC_{50} values on human CD105+ cells like the mouse fibroblasts L929 cells transfected with the short form of human CD105 and the rat myoblasts L6E9

transfected with the long form of human CD105. This work presents evidence which indicated that the non-toxic type 2 RIP (ebulin 1) is suitable for the construction of immunotoxins, in particular an immunotoxin directed towards human CD105. Targeting CD105 could help to destroy large tumour masses (Benitez et al., 2005; Maio et al., 2001; Fonsatti et al., 2003; Matsuno et al., 1999; Seon et al., 1997).

Biochemical and pathological effects

There are a variety of plant substances being used as protective herbal liver drugs such as phenols, coumarins, lignans, essential oils, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthenes (Hyun and Kim, 2009; Sharma et al., 2002). On the other hand, some of the plant genera show toxic effects on liver and kidneys. Pharmacological (anti-inflammatory and anti-nociceptive effects) study of methanol, n-hexane and ethyl acetate extracts from *S. ebulus* showed that the ethyl acetate extract have hepatotoxic and nephrotoxic effects in mice, which were administered in this fraction. Pathological assessment from mice liver and kidney tissue samples by light microscopy showed considerable alteration in tissue samples remarkably seen in group which were contaminated with the extract (Saeedi Saravi and Shokrzadeh, 2008, 2009a, b). Main alteration in kidney tissue samples after contamination with the extract include fatty changes of renal tubular epithelium, tubular epithelium is necrotic in areas and preserved epithelial lining of the tubules. Also, basic alteration in hepatic tissue samples, such as apoptotic cell, necrotic hepatic parenchyma cells, central vein dilation and kuppfer cells hypertrophy were demonstrated. The study showed that the hepatic disorders were dose-dependent.

Otherwise, nephro-pathological tests showed tubular necrosis and interstitial inflammation which showed no significant differences between dose groups together. Exposure to the ethyl acetate extract led to significant increase in serum BUN and creatinine levels in the tested mice. Also, vitamins C and E at specific concentrations significantly prevented the extract-induced nephro- and hepatotoxicity. Combination of the vitamins showed more protective response, compared with single therapy of the vitamins (Saravi and Shokrzadeh, 2008, 2009a and b).

Additional benefits of *S. ebulus*

The *S. ebulus* (Dwarf elder) has more drastic therapeutic action and it is the leaves, flowers or very occasionally the berries that are used medicinally. For instance, *S. ebulus* can be used as expectorant, diuretic, diaphoretic, purgative agents (Rechinger, 1963; Tutin, 1980). The leaves are probably more used in herbal practice than those of other Sambucus species and are ingredients in medicines for inflammation of both the kidney and liver. The drug is said to be very efficacious in dropsy. Dwarf elder tea, which has been considered as one of the best remedies for dropsy, is prepared from the dried roots, cut up fine or ground to powder. The drug was much used by Kneipp (Rechinger, 1963; Tutin, 1980). The herbal tea made with elderberry leaves (which contain cyanide inducing glycosides) should be treated with high caution. However, ripe berries (pulp and skin) are safe to eat (Nova Scotia Museum Website). The root, which is white and fleshy, has a nauseous, bitter taste and a decoction from it is drastic purgative. It has been shown that the decoction cures the bites of mad dogs and adders. The root-juice has been employed to dye hair. The leaves have a healing effect on bruises, boils and scalds. In France, the leaves are boiled in wine and made into a poultice to resolve swellings and relieve contusions. A rob made from the berries is actively purgative. Also, oil extracted from the seeds has been used as an application to painful joints. Mice and moles are said not to come near the leaves and in Silesia there is a belief that it prevents some of the diseases of swine, being strewn in sties (Duke et al., 2002; Davis, 1988; Rechinger, 1963; Tutin, 1980).

In addition, in a placebo-controlled, double-blind study, elderberry was shown to be effective in treating Influenza B (Zakay-Rones et al., 1995). People using the elderberry extract recovered much faster than those only on placebo. This is partially due to the fact that elderberry inhibits neuraminidase, the enzyme used by the virus to spread infection to host cells (Zakay-Rones et al., 2004).

It's likely that antioxidants called flavonoids—which are contained in the extract—stimulate the immune system. Also, other compounds in elderberry, called anthocyanins, have an anti-inflammatory effect. This could explain the anti-inflammatory and anti-nociceptive effects on aches, pains and fever (Howard, 1987).

Conclusion

In spite of the tremendous strides in modern medicine, numerous natural products from traditional medicinal plants have been introduced in the development of theoretical drugs. In addition, many products containing herbal extracts are sold in the Asian market as substitutes or supplements of modern medicine. The objective of this review has been to show the recent advances in the exploration of *S. ebulus* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *S. ebulus* has pharmacological functions including anti-inflammatory, anti-nociceptive, anti-cancer and anti-angiogenic, anti-oxidative effects, among others. Also, cytotoxic studies allow us to conclude that extract of fruits of *S. ebulus* is a good candidate for further studies of activity-monitored fractionation to identify their active components. As the current information shows, it is also possible that anthocyanins might be useful in the development of new drugs

to treat inflammatory diseases including rheumatoid arthritis and hemorrhoid. However, the present results suggest a possibility that this fraction can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *S. ebulus*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this review emphasizes the potential of *S. ebulus* to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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