Future Developments

TLC of polymers is more complex than that of small molecules for the following reasons: the size of sorbent pores and that of macromolecules are similar and co-operative effects exist which are characteristic of macromolecules as multicentred formations. For the same reasons, TLC of polymers is a very useful technique to investigate chromatographic mechanisms. The open sorbent layer in TLC makes it much easier to detect and investigate chromatographic artefacts than by column chromatography. The versatility of this method, the absence of restrictions with respect to solvents, and high sensitivity to functional groups (ATLC) make it possible to analyse effectively the compositional and structural heterogeneity of polymers.

Further development of this method involves investigations of mechanisms of adsorption and chromatography of macromolecules, more extensive use of chemically modified sorbents, more extensive application of quantitative methods of analysis and such promising methods as overpressured-layer chromatography (OPLC). The investigation of macromolecules with complex architecture and of reaction mixtures is not possible without perfecting complex methods of investigation. The combination of ATLC and column chromatography in different regimes and the combination of TLC with spectroscopic methods, especially with MALDI-TOF-MS are very promising.

See also: **II/Chromatography:** Size Exclusion Chromatography of Polymers. **III/Polymers:** Field Flow Fractionation; Supercritical Fluid Extraction.

Further Reading

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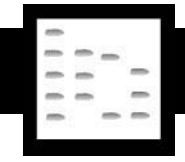
TERPENOIDS: LIQUID CHROMATOGRAPHY



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Introduction

Essential oils are secondary metabolites of plant origin and are complex mixtures of fragrance and flavour substances. They originate in roughly one-third of known plant families and are isolated from plant bodies by extraction or distillation procedures. The composition of the constituents are dependent on the isolation method used, the part of the plant body from which they are isolated and also on their thermal, pH and intrinsic chemical stability. Most essential oils are currently separated from nonvolatile materials by steam distillation. As for other classes of natural products, a fully satisfactory definition of essential oils is difficult to put into words. Although they are volatile plant materials, they do not leave a grease stain on paper.

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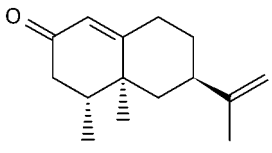
Terpenoids in Essential Oils

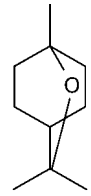
The majority of the essential oils of commercial interest are mixtures of mono- and sesquiterpenoids, containing only minor amounts of compounds belonging to other classes. The second largest group of essential oils consists of aromatic compounds including phenolic ones. The terpenoid components occur admixed with the corresponding terpene hydrocarbons, which generally contribute less to the aroma component. Among the popular essential oils are bergamot, grapefruit, lemon, lime, mandarin, orange, petitgrain and neroli oils belonging to the citrus class of oils. These oils contain varying proportions of different types of monoterpenoids, e.g. linalyl acetate, linalool, citrals (geranial and neral), corresponding acetates, and nootkatone. Lime oil, one of the most important distilled citrus oils contains 1,4- and 1,8-cineole, terpinen-4-ol and α-terpineol, along with aromatic p-cymene, which is probably derived from limonene by oxidation. Another important class of essential oils is cedar oils, which are characterized by the sesquiterpenoids cedrol, cedryl acetate, cedrene, thujone, thujopsene, *trans*-α-atlantone and the monoterpenoids pinenes and delta-3-carene along with 2-*trans*-4-*cis*-decadienyl isovalerate. A major class of essential oils derived from the plant class *Eucalyptus* has about 500 species. Monoterpenoids such as citronellal, citronellol, isopulegol, piperitone and β-phellandrene are the important constituents apart from geraniol and nerol. See [I]–[VII] for structures of some of these components of essential oils.

Other important essential oils are grass oils, e.g. lemon grass oil containing citral, geraniol, etc. Vetiver oil has high sesquiterpene content of α and β vetivone.



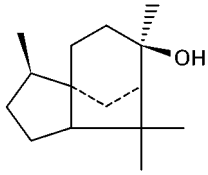
(+)-nootkatone

Structure [I]



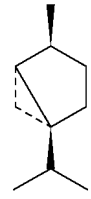
1,8-cineole

Structure [II]



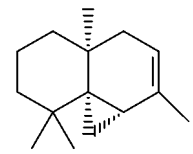
(+)-cedrol

Structure [III]



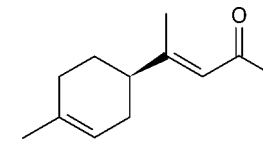
(–)-thujone

Structure [IV]



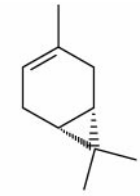
thujopsene

Structure [V]



trans-α-atlantone

Structure [VI]



Δ-carene

Structure [VII]

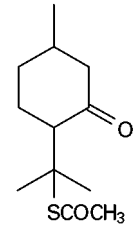
Lavandula oils contain linalool and linalyl acetate in the lavender oil variety whereas lavandin oil contains camphor and 1,8-cineole. Essential oils of the mentha variety are characterized by the presence of menthol, menthone and menthyl acetate. Spearmint oil of the mentha variety contains carvone, dihydrocarveol, menthone and limonene. Pulegone is also found in the mentha variety of oils. Balsam and wood terpentine oils contain bornyl acetate along with pinenes, limonene, p-menthadienes, whereas the Sage oils class of essential oils contain sclareol and α- and β-thujones.

There are other varieties of essential oil containing terpenoids, e.g. ambrette seed oil; amyris oil containing sesquiterpenoids, e.g. elemol, eudesmols and α-agarofurans. Buchu leaf oils contain menthone, isomenthone, pulgeone and bifunctional diosphenols also known as 'buchu camphors' and some sulfur-containing terpenoids, e.g. p-menthane-8-thiol-3-one and its thioacetate. The plethora of essential oils containing mono- and sesquiterpenoids occurring in nature is extremely large and a description of the principal constituents in them is beyond the scope of this chapter. Among the oils having importance in the perfumery industry, rose oil contains damascenone, *cis*-rose oxide and verbenone in various species; sandalwood oil contains the santalols; rosemary oil contains verbenone; patchouli oil has patchoulol and norpatchoulenol; orris root oil contains neoiso-α-irone; jasmin oil contains *cis*-jasmone and methyl jasmonate; guaiac wood oil contains guaiol; and costus root oil contains costol and dehydrocostuslactone.

Among the essential oils used as food flavouring, ginger oil contains the zingiberenes, *ar*- curcumene and β-sesquiphellandrol, copaiba (balsam) oil con-

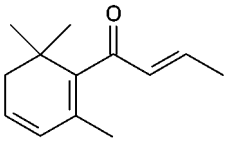
tains caryophyllene, celery seed oil contains β-selinene, cardamom oil has 1,8-cineole and α-terpinyl acetate. Some tea aroma components are presumed to be derived partly from the ionone series of compounds (probably derived from carotene besides other terpenoids such as methyl jasmonates, which give the sweet taste to Oolong tea leaves.

Essential oils also have therapeutic significance, e.g. in antiseptics and antibacterials, analgesics (clove, peppermint, lavender, birch oils), anti-fungals (tea tree, thyme), anti-inflammatories (German chamomile, lavender), anti-toxics (chamomile oil), anti-virals (*Melissa officinalis*, *Eucaliptus smithii*, *Ravensara aromatica*, *Niaouli*), diuretics (juniper oil), balancers, deodorants, digestives (anise, caraway, peppermint, lavender), spasmolytics (basil, majoram, German chamomile, cypres, laurel), mucolytics and expectorants (*Eucalyptus globulus*, pine, anise, thyme). They are also used as insecticides and insect repellents (citronella, cinnamon, geranium). See structures [VIII]–[XXIV] for some components of therapeutic essential oils.



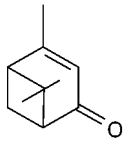
p-menthene-3-one-8-thiolacetate

Structure [XIV]



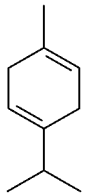
β-damascenone

Structure [XV]



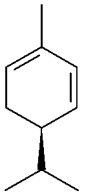
verbenone

Structure [XVI]



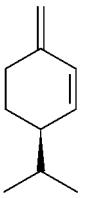
1,4-*p*-menthadiene

Structure [XVII]



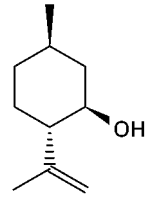
1,5-*p*-menthadiene

Structure [XVIII]



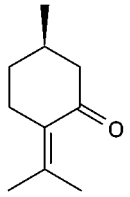
1(7),2-*p*-menthadiene

Structure [XIX]



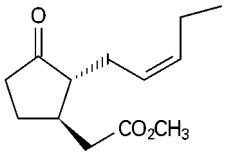
(–)-isopulegol

Structure [VIII]



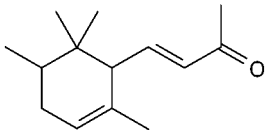
(+)-pulegone

Structure [IX]



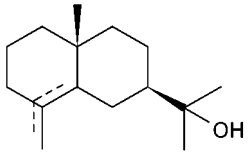
methyl jasmonate

Structure [X]



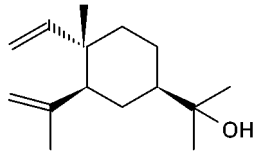
neoiso-α-irone

Structure [XI]



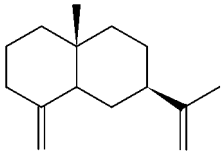
(+)-β- or (+)-γ-eudesmol

Structure [XX]



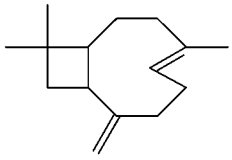
(–)-elemol

Structure [XXI]



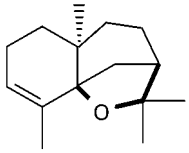
(+)-β-selinene

Structure [XII]



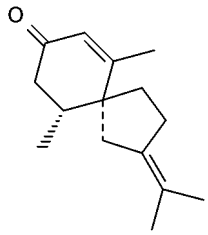
Caryophyllene

Structure [XIII]



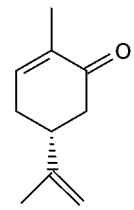
(+)-α-agarofuran

Structure [XXII]



β-vetivone

Structure [XXIII]



(–)-carvone

Structure [XXIV]

Analysis of Essential Oils

The economic importance resulting from their fragrance and aroma which is used extensively in the perfume and food flavour industries as well as the therapeutic applications requires that reliable analytical methods are available for qualitative and quantitative analysis of the individual ingredients as well as methods for their preparative separation from the complex mixtures they exist in. In fact, most varieties of essential oils are so complicated that resolution and analysis of any single component of interest is a formidable task. Although liquid and gas chromatographic separations on analytical and preparative scales have been used, such techniques are plagued with the problems of weak UV absorbance, volatility and thermal instability of many of the ingredients. Most of the essential oils contain only very minor amounts of the active principles and large amounts of undesired components that obscure the separation and reduce the sensitivity. The important developments that have taken place in liquid chromatographic analysis of essential oils over the years are discussed later. Before attempting any liquid chromatography (LC) or gas chromatography (GC) analysis, the terpene hydrocarbons are usually removed by distillation because of their considerably lower odour and aroma values. Furthermore, these olefins polymerize and are poorly soluble in lotions.

Thin-Layer Chromatography

Thin-layer chromatography (TLC) is an inexpensive technique and was the earliest LC method used to provide information on the complexity of essential oils. TLC studies of thymus essential oil on SiO_2 plates using various developing solvent systems and detection by spray reagents, e.g. H_2SO_4 charring, could identify thymol and carvacrol as the essential components by comparison with standard substances. This TLC method has been further employed to quantify these components by scanning densitometry. Additionally, quantification of geraniol, citral, terpinen-4-ol, cineole and gamaterpiniol have been carried out on thymus essential oil. Coscia described various reagents used to quantify mono-, sesqui- and other terpenoids (also polyphenols) such as carotenoids, tocopherols, retinoids, etc. in analysis of essential oils by TLC.

HPLC Analysis of Essential Oils

Almost 90% of the components present in essential oils that are responsible for fragrance and flavour are in the boiling range of 150–300°C and possess ideal vapour pressure to be successfully analysed by gas chromatography. The molecular weights of these

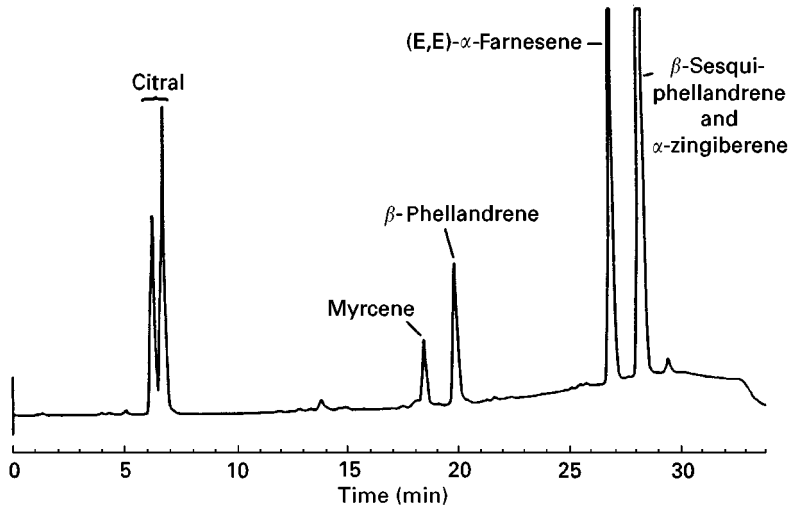


Figure 1 Typical analytical HPLC separation of citrus essential oil mixture. Analytical HPLC of a citral-type ginger oil. Experimental conditions: 15 × 0.46 cm. Column filled with Microsorb 5 μm C-18 silica gel, solvent MeCN; $H_2O = 6:1$ to MeCN: $H_2O = 95:5$ in 30 min, 1 mL min^{-1}, detection 236 nm. (Courtesy Springer-Verlag GmbH & Co.)

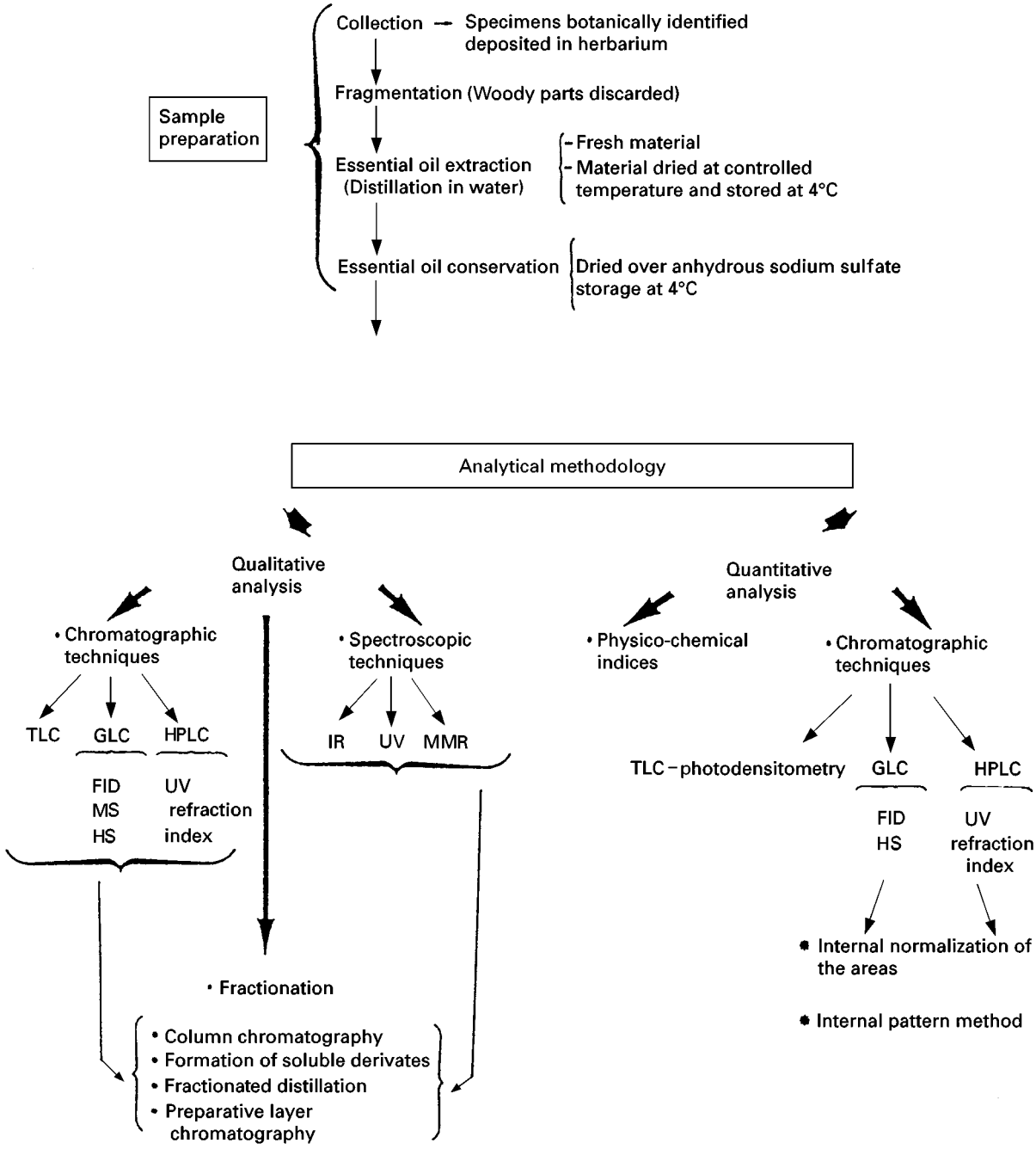


Figure 2 General protocol recommended for the identification and quantification of essential oil components. (Courtesy, Springer-Verlag GmbH and Co.)

compounds are mainly in the range up to 300 amu, thus making GC-MS an ideal technique for analysis and identification. However HPLC is being used increasingly to analyse essential oils (**Figures 1–4**) and in fact HPLC shows certain significant advantages over currently used open tubular column GC methods, such as minimal exposure to air, the avoidance of high temperature degradation, ease of separation of nonvolatile components and higher sample recovery. Furthermore, although as mentioned earlier, a majority of the terpenoids are weakly absorbing in the ultraviolet (UV) region due to the lack of a chromophore, the availability of highly sensitive online ultraviolet-visible (UV/Vis) detectors has expanded the utility of high performance liquid chromatography (HPLC) applications in essential oil

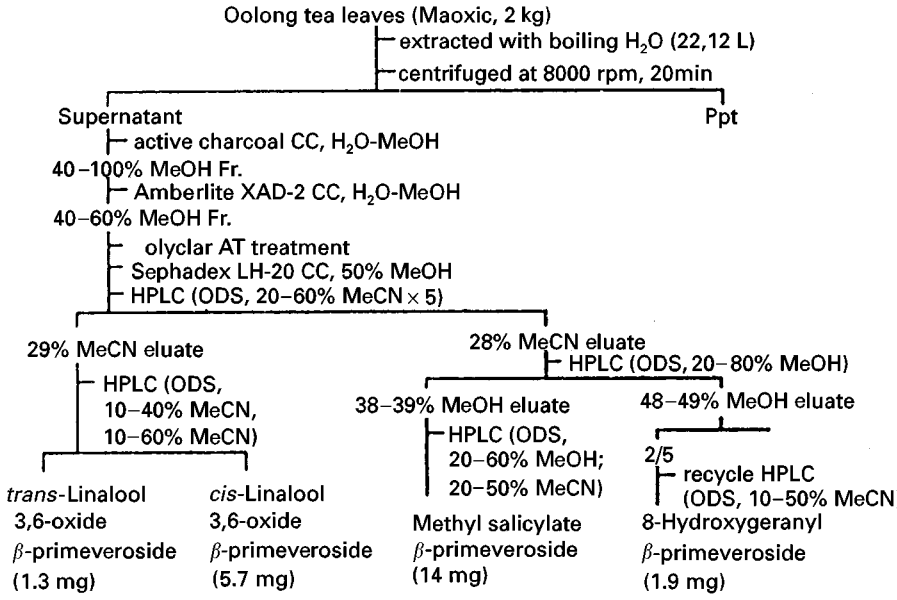


Figure 3 Isolation procedure of aroma constituents from Oolong tea.

analysis. The problem of UV detection on normal phase columns using eluents that are strongly UV absorbing has been largely alleviated by using reversed-phase columns which permit the use of solvents like methanol and acetonitrile, and detection by end absorption, i.e. between 200–220 nm. Although differential refractive index (RI) and polarimetric detectors have been used, they suffer from poor sensitivity. Polarimetric detection is however claimed to have better selectivity. Pulsed electrochemical detectors have been used for flavour-active alcohols by Le Fur. Primary terpenols are detectable at ppb level with others at ppm level. Primary and secondary alcohols can be quantified with good repeatability and sensitivity.

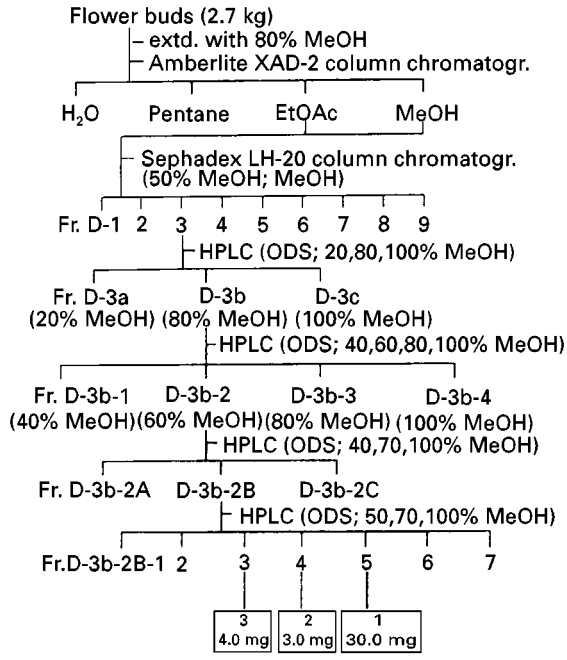


Figure 4 Isolation procedure of linalyl β-vicianoside, bornyl β-primeveroside, and 2′-phenylephenylthyl β-primeveroside from *Gardenia jasminoides*. (Figures 3 and 4 – Reproduced from *The International Congress of Flavours, Fragrances and Essential Oils*.)

Since essential oils are highly complex mixtures; HPLC is of great assistance for both the separation of the components into classes and of such a class into its components. Such pre-fractionation is followed by subsequent high-resolution GC (HRGC) analysis of the fractions. Multiple LC separations have been frequently carried out in tandem in order to obtain adequate pre-fractionation before subjecting each fraction to GC analysis. Thus the labile sesquiterpene germacrene B has been isolated by Clark from lime peel oil as an important flavour impact component. Various types of HPLC columns have been used, e.g. normal phase, diol-bonded silica and reversed phase, e.g. C2, C4, C8 and C18. In one example strawberry jam was previously gel filtered through Sephadex LH-20 to remove fatty acids. The resulting material was subjected to gradient HPLC using a diol-bonded silica column and gradient elution using pentane-diethyl ether resulting in two major fractions, the first containing hydrocarbons, esters, aldehydes and ketones and the second fraction consisting of polar

compounds such as alcohols, hydroxy esters and lactones. GC-MS analysis of these fractions identified 150 compounds as compared to only 60 in the absence of HPLC pre-fractionation. Computer-controlled online HPLC-HRGC has thus emerged as a powerful method for essential oil analysis. Munari used a fully automated HPLC-GC instrument for HPLC pre-separation of citrus oil into four major fractions – hydrocarbons, aldehydes, esters and alcohols – using gradient elution, and the fractions were automatically transferred to the GC. HPLC pre-separation with multiple GC transfer from a single HPLC injection combined with other identification techniques, e.g. mass spectrometry (MS), Fourier transform infrared (FT-IR) spectrometry gives additional advantage of online identification. The most widely used among such techniques is high performance liquid chromatography-gas chromatography-mass spectrometry (HPLC-GC-MS). This technique has been used in a fully automated form by Mondello for the analysis of several essential oils: bergmot, lemon, clementine, sweet orange, bitter orange, grapefruit and Mexican lime. The information was more accurate than that obtained by only GC-MS analysis of the essential oil. Using chiral GC columns Giovanni determined the enantiomeric distribution of the monoterpene alcohols in citrus essential oils. In the same vein it can be envisaged that such multidimensional techniques as microbore HPLC-electrospray ionization/MS-MS holds great potential in essential oil analysis since in addition to improved column efficiency, the second mass analyser permits mixture analysis by interpretation of the collision activated dissociation (CAD) spectrum obtained.

Separation of Enantiomeric Components

The terpenoids present in essential oils are chiral molecules occuring in enantiomerically pure form. HPLC analysis using chiral columns and co-elution with authentic optically pure compounds furnish information on the chirality of the constituents. HPLC separation of enantiomeric mixture of α-pinene, β-pinene, camphene and limonene were carried out by Moeder on a C4 column with UV detection at 210 nm and a mobile phase containing 5–20 mM of α-cyclodextrin, or 0.01–0.8 mM of β-cyclodextrin (90 : 10 mixture of MeOH and 0.1% phosphoric acid). Equations were derived for the apparent formation constants of the diastereoisomeric complexes of the solute with cyclodextrin and their stoichiometry estimated. It was observed that efficient separation was achieved with only α-cyclodextrin for these bicyclic terpenes. Chiral discrimination of enantiomeric derivatives of α-pinene has been achieved using amylose *tris*(3,5-dimethylphenyl)carbamate as the chromatographic stationary phase. The major contributing factor to achieve such separation is H-bonding of the analytes with the carbamated amylose.

Supercritical Fluid Chromatography

Supercritical fluid chromatography (SFC) has also been used for the separation of terpenoid compo-

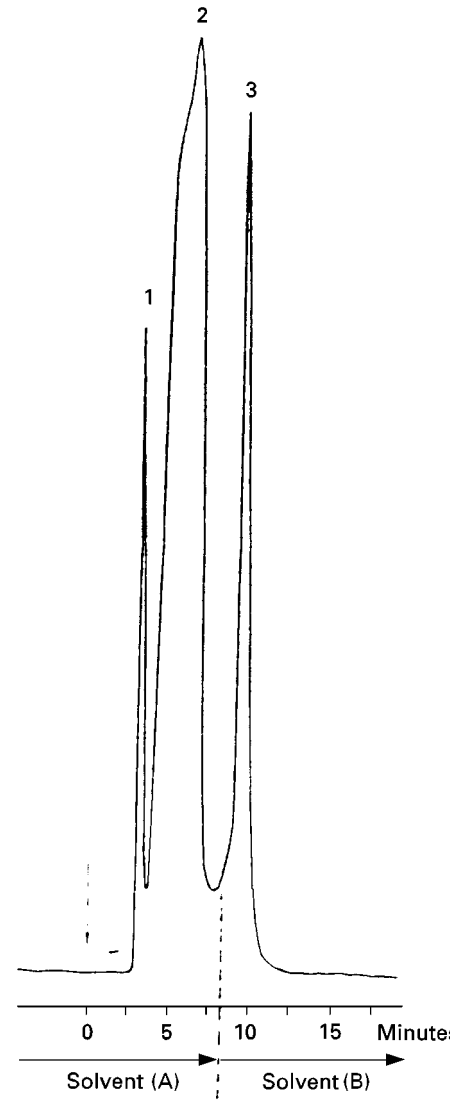


Figure 5 Enrichment of essential oil fractions by semi-preparative HPLC. HPLC fractionation of an essential oil at a flow rate of 8 mL min^{-1}. Conditions: column, 24 cm × 10 mm i.d. LiChroprep RP 18 (40 μm), mobile phases. (A) methanol–water 82.5 : 17.5 (v/v), (B) methanol, flow rate 8 mL min^{-1}, detector, UV 220 nm. 1 = oxygen-containing compounds, 2 = monoterpene hydrocarbons, 3 = sesquiterpene hydrocarbons. (Courtesy Kluwer Academic Publishers, The Netherlands.)

nents. The advantage of SFC lies in the fact that it has features of both GC and LC. Both GC and LC columns can be used and various detectors like flame ionization detector (FID), UV and MS can be used making it a nearly universal technique. To illustrate the application of SFC 2-*Z*- and 3-*E*-nerolidols, R/S-geranyliol, α-bisabolol and 2E,6E-fernesol were separated in 10 min on a column packed with 5 μm Zorbax Z215 silica equipped with a guard column of the same material operated at 40°C with CO_2 containing 0.5% MeOH as the mobile phase and monitoring the components at 220 nm. In another example eight terpenoid components of cinnamon oil were separated on a delta-bond SiO_2 column at 125°C using a gradient elution of 100% CO_2 to 7% EtOH in CO_2. The detection limits were typically 1.0 $\mu g\,mL^{-1}$ for the terpenes with a linear response over four decades.

Preparative Liquid Chromatography

Isolation of individual essential oils is a formidable task because of their complexity. Open column chromatography, droplet countercurrent chromatography (DCCC), rotation locular countercurrent chromatography (RLCCC) and gel permeation chromatography are some of the techniques which have found considerable use. However each of these techniques has its weaknesses. Multiple separations on either normal- or reversed-phase packing materials (40–70 μM) using low to medium pressure (10–40 bar) accomplishes substantial enrichment of the components in terms of their functional group type and/or polarity. Using step or gradient elution techniques the complex mixtures of terpenoid hydrocarbons, carbonyl compounds, alcohols, esters, etc. can be cut into fractions. Online UV detection and automatic fraction cutting considerably enhances the utility of such medium pressure liquid chromatography–low pressure liquid chromatography (MPLC-LPLC) techniques. The fractions can then be subjected to preparative HPLC using columns of inner diameter >10 mm to furnish the semipure components. Even preparative HPLC may have to be repeated several times before adequate resolution is achieved. The pooled fractions are then subjected to semi-preparative HPLC (column i.d. <10 mm) followed by peak collection from analytical columns to yield the pure terpenoids. The level of purity desired depends on the use for which the component materials are required. Some representative HPLC traces for the separation of essential oil components are shown in **Figures 5–7**. In several cases where the terpenoids exist as glycosides or some such deriva-

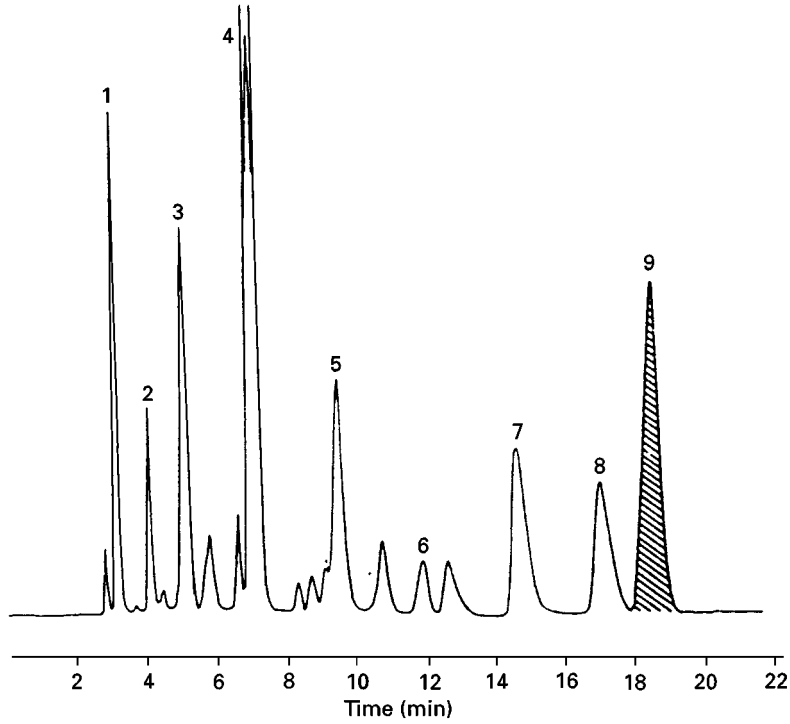


Figure 6 HPLC separation of sesquiterpene hydrocarbons. Conditions: 300 × 4 mm i.d. Lichroprep Si 60 (7 μm) column with 48% water. Eluent: n-pentane. 1 = α-copaene, 2 = δ-elemene, 3 = β-elemene. 4 = β-caryophyllene, 5 = α-bergamotene. 6 = β-bisabolene, 7 = α-humulene. 8 = δ-cadinene, 9 = standard. (Courtesy Kluwer Academic Publishers, The Netherlands.)

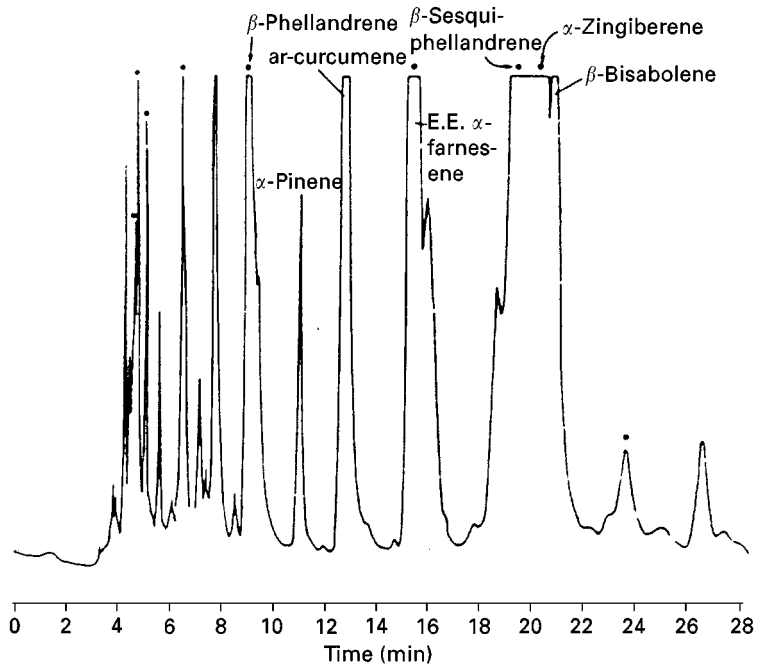


Figure 7 Semi-preparative HPLC of ginger oil. Experimental conditions: load 4 mL oil dissolved in 4 μL EtOH, column 25 $\times$ 1 cm. Filled with Microsorb 5 u C-18 silica gel, solvent MeCN–H_2O = 9 : 1. 4 mL min^{-1}, detection UV 215 nm. (Courtesy Springer-Verlag, GmbH and Co.) • indicates UV absorption at 245 nm.

tives, pre-purification using other forms of liquid chromatography like hydrophobic interaction chromatography on HP or XAD types of resins is done followed by separation of individual compounds on a reversed-phase HPLC column. Two such examples are the separation of linalyl β-vicianoside, bornyl β-primeveroside and 2-phenylethyl β-primeveroside from *Gardenia jasminoides*. Separation of *cis*-linalool 3,7-oxide-6-O-β-D-apiofuranosyl-β-D-glucopyranoside from oolong tea leaves was achieved using similar methodology.

Conclusion

In view of the importance of essential oils in the perfume, food and flavour industries as well as their therapeutic applications, it is imperative that research in their analysis and isolation continues. The crux of the problems associated with such endeavours lies basically in the fact that the constituents of essential oils most often occur in very minor amounts. Therefore the aim of further analytical research has to be directed to the achievement of the highest possible sensitivity and resolution. HPLC analysis using micro columns containing either normal- or reversed-phase silica as packing material coupled to detectors like the electrospray ionization mass spectrometer with ion-trap detectors permitting MS^n analysis holds good potential. Electroanalytical techniques like capillary electrophoresis can go a long way in both qualitative and quantitative analysis of essential oil constituents. Capillary electrophoresis interfaced with MS and/or a photodiode array detector is likely to solve the problems of separation complexity of essential oil components.

See also: **II/Chromatography:** Liquid Chromatography-Gas Chromatography. **III/Essential Oils:** Gas chromatography; Thin-Layer (Planar) Chromatography. **Medium-Pressure Liquid Chromatography. Natural Products:** Supercritical Fluid Chromatography.

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THERMALLY-COUPLED COLUMNS: DISTILLATION

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Introduction

A considerable amount of energy is used in distillation operations. Energy integration has proven to be successful in reducing energy costs for conventional distillation arrangements. However, the scope for energy integration of conventional distillation columns into an overall process is often limited. Also, practical constraints often prevent integration of distillation columns with the rest of the process.

If the column cannot be integrated with the rest of the process or, if the potential for heat integration is limited by the heat flows in the background process, then we must turn our attention back to the distillation operation itself and look at unconventional arrangements.

Figure 1 shows two conventional arrangements for the separation of a three-component mixture. The sequence shown in Figure 1A is the so-called direct sequence, in which the lightest component is taken overhead in each column. The indirect sequence shown in Figure 1B takes the heaviest component as bottom product in each column.

One of the most significant unconventional arrangements involves thermal coupling. **Figure 2** shows a number of unconventional arrangements that use thermal coupling. In thermal coupling part of the heat transfer necessary for the separation is provided by direct contact via material flows. Figure 2A shows a side-rectifier arrangement and Figure 2B a side-stripper arrangement. Arrangements similar to that in Figure 2B are widely used in petroleum refining. The fully thermally coupled arrangement in Figure 2C (sometimes known as the Petlyuk column) has been known for over 50 years. Various studies have shown that thermally coupled arrangements can save up to 30% of energy costs when compared with conventional arrangements.

Simple Versus Complex Columns

Consider first the design of distillation systems comprising only simple columns. These simple columns employ:

- one feed split into two products;
- key components which are adjacent in volatility;
- a reboiler and a condenser.

For a three-component mixture in which simple columns are employed, the decision is between the two sequences illustrated in Figure 1.

Consider the first characteristic of simple columns, which involves a single feed being split into two products. As a first option to two simple columns, the possibilities shown in **Figure 3** can be considered, in which three products are taken from one column. The designs can be both feasible and cost-effective when compared with simple arrangements, but only for certain conditions. If the feed is dominated by the middle product (typically more than 50% of the feed) and the heaviest product is present in small quantities (typically less than 5%) then the arrangement shown in Figure 3A can be an attractive option. If a pure middle product is required, then it is usually only possible if there is a large volatility difference between components B and C, with the middle product taken as a vapour to assist the separation. The heavy product must find its way down the column past the side-stream. Unless the heavy product has a small flow and the middle product a high flow, a reasonably pure middle product cannot be achieved.

If the feed is dominated by the middle product (typically more than 50%) and the lightest product is present in small quantities (typically less than 5%), then the arrangement shown in Figure 3B can be an attractive option. This time the light product must find its way up the column past the side-stream. If