International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Chemical conversions of essential oil components and their properties – A review

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Abstract

Essential oils, scented constituents, aromatic compounds or ethereal oils are natural secondary metabolites of plants that are highly volatile and lipophilic in nature. Essential oils constitute various bioactive components that can be extracted from different parts of plants through hydro-distillation, steam-distillation and supercritical fluid extraction. Essential oils obtained from different plants are known to contain different chemical constituents that make them useful in traditional and advanced system of medicines due to their excellent therapeutic potentials and strong bioactivities. Although natural chemical compounds obtained from essential oils can be directly used as a medicinal component but their structural modifications via different synthetic pathways increase their therapeutic potentials, medicinal importance, commercial applications and industrial uses. The basic purpose of this review article is to compile the scattered available information about different groups of compounds in oils of aromatic plants such as alcohols, ethers, aldehydes and esters that include some important bioactive compounds to be converted into their corresponding derivatives. Alcohols include borneol, eugenol and menthol, ethers include methyl chavicol, aldehyde include citral while esters include linalyl acetate that have camphor, methyl eugenol, menthone, trans-anethole, citronellal, geraniol, epoxycitral, linalool, geranyl acetate and terpinyl acetate as structurally modified derivatized products. Their wide ranging applications and bioactivities are discussed in detail.

Key words: Essential oil, borneol, eugenol, menthol, methyl chavicol, citral, linalyl acetate

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1. Introduction

Essential oils are mainly composed of lipophilic components and volatile secondary metabolites of plants that can have approximate molecular mass of about 300 which can be separated from membranous tissues or plant components using physical methods. The term "essential oil" as defined by ISO (International Organization for Standardization) is commonly used for the products obtained from vegetable's raw material either by distillation with water or through steam. Essential oils can also be obtained from epicarp of various citrus fruits through direct mechanical pressing that is also known as dry distillation [1]. Most of the essential oils that are available in market are obtained by hydro-distillation. There is a need to comply with national or international pharmacopoeia to use essential oils for medical purposes. Essential oils are usually considered safe by their dietary intake and also their intended use by the U.S. Food and Drug Administration (FDA). These are widely used as flavoring material and also represent a green alternative in many fields like nutritional, pharmaceutical and agriculture due to their anti-microbial, insecticidal, anti-fungal, anti-viral and nematicidal and anti-oxidant potential [2].

The conversion of various essential oil components into each other by oxidation, isomerization, cyclization or dehydrogenation reactions is possible because they have structural relationship within the same chemical group and these reactions are triggered either chemically or enzymatically [3]. It should be kept in mind that plant health, growth stage, edaphic factors and also harvest time may be influenced by variation of chemical composition in the starting material. Masotti and coworkers studied the structural pattern as a function of harvest time and they work throughout the year and found that there is a decrease in concentration of hydrocarbon monoterpene in essential oils along with increase in amount of oxidized metabolic intermediate successors. Consequently, there is a need to give special emphasis on quality evaluation because plant volatiles show natural fluctuations in their composition. Depending on their structure, "terpenoids" are easily

oxidized or hydrolyzed because they show both volatile and thermolabile properties. Factors that most likely effect the chemical composition of essential oils are processing and storage of plant material upon which distillation occur and also handling of oil itself. If constituents of essential oils have un-protective compartmentalization they will show oxidative damage, chemical transformations or polymerization reactions [4].

In addition to viscosity changes and organoleptic alterations, some aged essential oils as well as oxidative terpenoids have skin sensitizing capacities that lead to hypersensitivity that is quite similar to allergic contact dermatitis. In order to ensure elicit cutaneous and subcutaneous inflammations, chemical constituents must be able to deeply penetrate in epidermis layers that requires adequate lipophilicity and strong protein binding capacities which is supposed to occur via nucleophilic-electrophilic reactions if system exhibit radical interactions and electrophilic functional groups. The potential of allergic reactions in flavoring agents could be mainly attributed to terpenoid hydroperoxides that are built up as intermediates upon autoxidation while their non-oxidized counterparts along with many other degradation products are non-irritating in nature [5]. Degradation of monoterpenes at high temperature converts them into cyclic isomers like limonene, terpinenes and p-cymene by oxidation, polymerization and disproportionation and cyclization reactions [1].

2. History

The use of aromatic herbs and essential oils was introduced by Egyptians in 4500 B.C.E and there are various types of aromatic or scented oils that have been traditionally used in many cultures of different countries all over the world. Essential oils have wide spread applications starting from healing purposes to religious applications [6]. Egyptians prepared herbal medicinal product containing sixteen active ingredients including "Kyphi" that was also used in perfumes. They used perfumed oils, species, scented barks, resins and aromatic vinegar in daily routine. The preparation of medicinal cakes, suppositories, ointments, pills and powders is done by the using essential oil and other plant extracts. These aromatic scented oils have found number of fruitful applications in higher authorities of several countries as well. Aromatic gums were extensively used in embalming such as cedar and myrrh but extraction of essential oils in not possible from these aromatic gums. First time, the applications of essential oils in Chinese were recorded during 2697 to 2597 B.C.E in reign of Huang Ti who was a legendary yellow emperor in his book named "The Yellow Emperor's Book of International Medicine" [7].

In Indian culture about 3000 years ago, Ayurveda medicines have been used that are actually made of essential oils. Essential oils are not only used for medicinal purposes but also used as an essential part of prayers in some regions of India. Greeks got comprehensive knowledge through Egyptians about essential oils in between 400 B.C.E to 500 B.C.E and used them in medicines and thus known as the "Father of Medicine". They worked hard to prepare valuable medicines for therapeutic applications of essential oils for mankind. Essential oils were commonly used for bathing soaps and massage oils for maintenance of body health. Romans prepared massage oils and soaps from use of essential oils in perfumes and cosmetics. On the importance of essential oils and there uses along with extraction methods, Ali-ibn sena wrote a comprehensive book. However, recently number of books has been written on aromatherapy and lots of work is done by number of researchers in Europe related to aromatic oils and the system of treatment via aromatic oils [8].

3. Alcohol

Chemical constituents of essential oils like alcohols are ecologically safe, less toxic and environment friendly that are known to have strong antibiotic potentials including anti-bacterial, anti-septic and anti-viral activities against several human diseases. Alcohols chemically combine with other chemical groups like esters and terpenes or are found sole. Linalool and geraniol are the major chemical compounds of lavender and ylang-ylang, these compounds are found in citronellol and geranium while palmarosa is found in rose, lemon and eucalyptus. Some major types of alcohols abundantly present in essential oils are menthol, nerol and benzyl alcohol [9].

3.1 Borneol

Borneol is a constituent of essential oils which is colorless, crystalline monoterpene and have anti-bacterial, anti-fungal, tranquilizing, anti-spasmodic and choleretic effects [10].

3.1.1 Plant Source of Borneol

Borneol as a single enantiomer and as a racemic mixture is present abundantly in nature. Two enantiomers of borneol are (+)-borneol present in rosemary, lavender, olibanum and dryobalanops species and (-)-borneol is found particularly in pinus, abies and citronella oils [10].

3.1.2 Chemical Composition of Borneol

Enantiomers of borneol were reported in different essential oils having different properties as (-)-borneol has camphor like or woody odor and contains upto 40% iso-borneol while (+)-borneol has slightly sharp camphoraceous odor different from (-) form of borneol [10].

3.1.3 Commercial Applications of Borneol

Borneol is a commercially beneficial product which is used as a fragrant ingredient in cosmetics, shampoos, fine fragrances, toilet soaps and other none-cosmetic products like household cleaners and detergents. The worldwide use of borneol is about 10-100 metric tonnes annually in different regions all over the world. The maximum skin level in the formulation that go into the fine fragrances has been reported to be about 0.3% assuming use of the fragrance oil at levels upto 20% in final product.

Approximately 97.5% use level in formulae to be use in cosmetics in general has been reported to be almost 0.16% which would result in a maximum daily exposure on the skin of 0.0041 mg/kg for high end users of these products [11].

3.1.4 Activity against Cardiovascular Disease

Borneol is preferably extracted from *Cinnamomum camphora* L. and various other plants that is a cyclic monoterpene alcohol in nature. Borneol promotes the relaxation of aortic rings that were pre-contracted with KCl or phenylephrine in an endothelium-independent and concentration dependent manner. Borneol interferes with intracellular calcium mobilization and also pre-incubation with K^+ channel blockers that attenuated the borneol-induced vasorelaxation. Borneol rich extract at a concentration of 1mg/ml promotes relaxation with the total relaxation obtained at 10mg/ml. Suxiao Jiuxin Pill was able to promote vasorelaxation by both dependent and independent-endothelium mechanisms. Borneol had neuro-protective properties against ischemic stroke as was evident in an in-vivo study that was conducted to determine these properties along with anti-inflammatory potentials [12].

3.2 Conversion of Borneol to Camphor

In the presence of sodium bromide, oxone can potentially oxidize borneol to camphor based on the work done by Koo and co-workers. Among all the aliphatic secondary alcohols, borneol can be oxidized easily by taking 2 equivalent of NaBr and 1 equivalent of oxone which gave satisfactory results within 2h using aqueous methanol as the solvent and this process is quite promising for use in the teaching laboratory. When waste and hazardous disposal was considered, it was noted that NaBr is a poisonous substance and collection of aqueous waste might be required. A more efficient procedure was discovered by Giannis and co-workers who with the help of oxone and catalytic quantity of sodium chloride (NaCl), oxidized variety of secondary alcohols to the corresponding ketones. The use of catalytic halide is usually preferred over the 2-equivalent of sodium bromide as used in previous research because bromide ion is not fruitful to be used in catalytic quantities. In addition, due to less toxicity and simpler waste disposal, sodium chloride is quite obviously a safer alternative [13].

Conversion of borneol to camphor in optimized conditions and the testing in the teaching laboratories is a straight forward, clean and environment friendly reaction as this conversion is completed by using 0.3 equivalent of sodium chloride and 0.6 equivalent of oxone (1.2 equivalent of the active oxidizing agent $KHSO_5$) to give >95% conversion to the product in good isolated yields (60-80%) as shown in figure 1. The reaction is completed at room temperature in one hour, at 90°C by refluxing hydrogen peroxide that is amenable to purification by sublimation to yield camphor product that is of high purity [14].

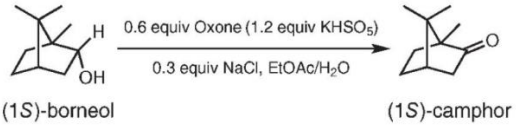


Fig 1 Conversion of borneol to camphor

3.2.1 Physical Properties and Sources of Camphor

Camphor is a waxy, transparent or white solid with a strong aromatic odour which melts at 180°C and sublimates at room temperature. Practically, it is soluble in alcohol, chloroform, ether and other organic solvents, but insoluble in water. It is a terpenoid with a chemical formula of $C_{10}H_{16}O$ and exists in two enantiomeric forms (1R)-(+)-camphor and (1S)-(-)-camphor. Nevertheless, stereochemical impacts on the biological activities of these two enantiomers are still unknown, but both have similar camphoraceous odour [15]. Natural camphor such as (+)-camphor is acquired through distillation of the wood from the camphor laurel tree (*Cinnamomum camphora)* especially found in Borneo and Taiwan; East African camphorwood tree (*Ocotea usambarensis*) and the borneo camphor tree (*Dryobalanops aromatica*) while synthetic camphor is mainly synthesized from α-pinene obtained from turpentine oil. Major sources of camphor in Asia are camphor basil (*Ocimum kilimandscharicum*). Camphor is present in many aromatic plant species as a major essential oil component [16].

3.2.2 Chemical Composition of Camphor

Essential oil composition from the aerial parts of sweet wormwood (*Artemisia annua*) includes germacrene D (16%), camphor (44%), trans-pinocarveol (11%), β-caryophyllene (9%), β-selinene (9%) and artemisia ketone (3%) [17].

3.2.3 Anti-Bacterial and Anti-Fungal Activities of Camphor

Camphor as a single compound exhibited weak anti-microbial activities. According to the Greek sage, *Salvia fruticosa* essential oil contains significant quantities of camphor as it is a major component and was tested against different bacterial strains such as *Escherichia coli, Salmonella typhimurium, Pseudomonas aeruginosa, Rhizobium leguminosarum, Staphylococcus aureus and Bacillus subtilis*. The results of anti-bacterial activity were found to be negative. The anti-microbial activity of rosemary essential oil was investigated by Santoyo and coworkers which obtained this scented oil via supercritical fluid extraction and molecules including camphor were tested against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans* and *Aspergillus niger* L. by the broth dilution and disc diffusion methods. Test samples were found active against all the test organisms with more sensitive organism being *Staphylococcus aureus* and less sensitive *Aspergillus niger* L. The basic anti-microbial activity tested against all microorganisms was in following order of effectiveness: borneol>camphor>verbenone. A narrow variety of (*Achillea*

sintenisii) was also found effective which contain camphor (14.8) as its main component. The essential oil was further fractionated to determine anti-fungal and anti-bacterial activities against a variety of micro-organisms [18].

Data analysis showed that camphor to be the more effective compound together with 1,8-cineole, as it showed remarkable activity against *Candida krusei* and *Candida albicans*. The fractions revealed the same or higher activity than pure essential oil in the majority of cases. Mevy and coworkers confirmed that camphor, elemol, p-cymene and 1,8-cineole can be considered as the basic anti-microbial components of tea bush (*Lippia chevalieri*) essential oil. Ouattara and coworkers investigated anti-microbial activity of rosemary (*Rosmarinus officinalis*) and many other oils against organisms involved in meat spoilage. Rosemary (*Rosmarinus officinalis*) essential oil in a 1/100 dilution containing mainly camphor was one of the most efficient anti-bacterial agent against four potential gram-positive (*Brochothrix thermosphacta, Carnobacterium piscicola, Lactobacillus curvatus and Lactobacillus sake*) and two major gram-negative (*Pseudomonas fluorescens and Serratia liquefaciens*) bacteria [19].

3.2.4 Anti-Viral Activity of Camphor

Worldwide viral diseases are increasing health concern and there has been demanding search for more effective but less toxic anti-viral agents than those currently used. Aromatic plants mainly their essential oils are known to exhibit strong anti-viral properties. Anti-microbial, anti-viral and cytotoxic activities of Greek sage (*Salvia fruticosa*) essential oil were investigated by Sivropoulou and coworkers. The results illustrate that the essential oil of Greek sage (*Salvia fruticosa*) and its four major components (1,8-cineole, α- and β-thujone and camphor) displayed high levels of virucidal activity against herpes simplex virus-1 and also this positive effect was accompanied by cytotoxic activity to cure African Green Monkey kidney (Vero) cells. Essential oil of lavender cotton (*Santolina insularis*) which is abundant in camphor contents also exhibited deactivated herpes type-2 (HSV-2) and type-1 (HSV-1) in vitro activity using plaque reduction assays with 0.7 μg/ml for HSV-2 and IC50 value of 0.88 μg/ml for HSV-1. Decline of plaque formation assays showed inhibition of cell to cell transmission of both HSV-2 and HSV-1 [20].

3.2.5 Cardiovascular Effects of Camphor

Camphor has been used for stimulation of heart and peripheral circulation for centuries. Cardiac failure and collapsed conditions were reported by Osborne characterized by a feeble pulse, cold skin and failing heart, the surface of the skin to become flushed, improved the whole circulation and dilated peripheral blood vessels by the subcutaneous injection of camphor in sterile oil. The results of controlled scientific studies on cardiovascular effects of (+)-camphor have been published in recent years. Effects of (+)-camphor (extracted from fresh *Crataegus berries*) in orthostatic hypotension using independent, randomized, double blind and placebo-controlled studies were estimated. It was noticed that (+)-camphor as well as the extract from natural hawthorn (*Crataegus*) berries contributed to pressoric effects with (+)-camphor inducing the initial quick effect and the extract is accountable for the long-lasting effects [21].

3.2.6 Toxicity of Camphor

Camphor has been well documented toxic compound and ingestion of 3.5g of camphor can cause death. Even 2.0g can cause toxic effects in adults leading to congestion of gastro-intestinal tract, brain and kidney. The instantaneous collapse of an infant has been reported after the application of a small dose via nostrils. In humans, typical symptoms of camphor poisoning after ingestion are nausea, headache, vomiting, dizziness, muscular sensation causing tremor and twitching, delirium and convulsions depending on dosage. In a stern, overdose status epilepticus persisting for few hours occurs, eventually causing coma and death by asphyxia or exhaustion. Inhalation of camphor may cause irritation of mucous membranes above 2 ppm and respiratory depression and apnea may occur. Camphor may also cause eye and skin irritation on contact. Skin exposure or inhalation may result in intensive poisoning depending on the dose with above described symptoms. Camphor poisoning is treated symptomatically however there is no known antidote available to cure poisoning [17].

3.2.7 Commercial Benefits of Product

Additional dimensions to the experiment involved collection of product synthesized for use in an active research program by the students. In this conversion, the starting material (1S)-borneol is commercially inexpensive ($ 0.372/g), whereas the final product (1S)-camphor is relatively more expensive ($ 7.60/g) however it has extremely good therapeutic potentials in homoeopathic system of medicines [13].

3.3 Eugenol

Eugenol is a phenolic photochemical which can be extracted from certain essential oils particularly from nutmeg, clove oil, cinnamon, basil and bay leaf. It also possesses anti-cancer and anti-microbials activities. Its name is eugenol as it is extracted from leaves and buds of *Eugenia caryophyllata* (clove). For the first scale and industrial scale, this eugenol was prepared by allylation of guaiacol with the allyl chloride having a functional property of similar type. It got much attention by the researchers because it is the main component in the extracts of various medicinal herbs, it opened up vast area of research in applying it as a medicine to cure various diseases. Eugenol is also well-known to have several pharmacological properties, anti-oxidant, anesthetic, anti-helmintic and anti-microbial, anti-inflammatory, anti-fumigant, anti-carcinogenic and anti-repellent properties. It can also be used as a traditional remedy for toothache and also for culinary purposes. This versatile molecule is a major ingredient in cosmetics, perfumes and flavoring agents. Food and Agriculture Organization (FAO) and also

World Health Organization (WHO) have allowed the daily intake of eugenol of 2.5 mg/kg body weight for human. Eugenol proclaimed as a safe and also considered non-mutagenic and non-carcinogenic by the U.S Food and Drug Administration (FDA) [22]. Studies on eugenol and clove products still remains a research priority due to its anti-inflammatory and chemo-preventive activity, as well as it has superior anti-oxidant activity [23].

3.3.1 Physical and Chemical Properties of Eugenol

Eugenol belongs to phenylpropanoids ($C_{10}H_{12}O_2$) class of compounds. The IUPAC name of eugenol is 4-allyl-2-methoxyphenol and its structural formula is shown in figure 2. It have molecular mass 164.2g/mol with pKa=10.19 at 25°C temperature. It has two isoforms (i) eugenol and (ii) isoeugenol. It is also known as allyl guaiacol, 2-methoxy-4-(2-propenyl) phenol, caryophyllic acid and 4-allylcatechol-2-methyl ether. Presence of phenolic group in chemical structure of eugenol confers the anti-oxidant property of it. Its color ranges from clear to pale yellow. The metabolism of eugenol results the formation of conjugates with glucuronic acid (major), sulphate and glutathione studied in vitro with 1mM concentration [24].

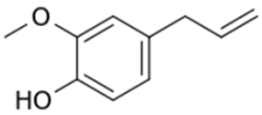


Fig 2 Chemical structure of eugenol

3.3.2 Plant Source of Eugenol

Extraction of eugenol is done from many aromatic plants. Eugenol beside the *Eugenia caryophyllata* is also isolated by *Zygium aromaticum*, *Ocimum grattisimum*, *Myristica fragrans*, *Ocimum tenuiflorum*, *Cinnamomum tamala* and *Pimenta racemosa*. Clove essential oil is a major source of eugenol which contains 45-90% eugenol among all of its' constituent [25].

3.3.3 Isolation of Eugenol from Plants

In 1929 first time eugenol was isolated and its commercial production started in United States in the 1940s. However, eugenol is mainly prepared from natural oil sources by mixing the essential oil with potassium hydroxide solution or an excess of aqueous sodium (3%) followed by shaking that leads to the formation of phenolic alkali salt. The non-phenolic insoluble portion is then extracted via steam distillation or with a solvent. The alkali solution acidified at low temperatures results in undissolved portion that removes and liberates eugenol purified by thin layer chromatography, fractional distillation and high-pressure liquid chromatography. FTIR, NMR and MS were used to check the purity of the compound [26].

3.3.4 Anti-Fungal Activity of Eugenol

Essential oil of clove (*Eugenia caryophyllata*) containing eugenol as a main constituent was evaluated against 53 human pathogenic yeasts using a disc paper diffusion method and the anti-fungal effects were also assessed. Among all synthesized eugenol derivatives, 4-morpholin-4-ium chloride and 4-allyl-2-methoxy-6-(morpholin-4-ylmethyl) phenyl benzoate was found to be the most efficient anti-fungal compound when compared with fluconazole. Eugenol treatment significantly reduced the loyalty metabolic activity of biofilms of *Candida albicans* which was isolated from oral cavity of HIV infected patients. Uncovered candida cells to eugenol resulted in decrease of ergosterol biosynthesis followed by apoptosis. Eugenol has a capacity to alter the morphogenesis of *Candida albicans*. Certain combinations of thymol and eugenol led to a synergistic effect which is appealing in view of potentiating their inhibition of *Candida albicans* infectivity and colonization [27].

3.3.5 Anti-Bacterial Activity of Eugenol

Eugenol exhibited effective anti-bacterial activity against various strains of gram-positive (*Bacillus cereus; Staphylococcus aureus, Bacillus subtilis; Staphylococcus epidermidis, Streptococcus pneumonia, Enterococcus faecalis, Streptococcus pyogenes* and *Listeria monocytogenes*) and gram-negative (*Escherichia coli; Salmonella typhi; Salmonella choleraesuis; Helicobacter pylori, Pseudomonas aeruginosa, Yersinia enterocolitica* and *Proteus vulgaris*) bacteria. Eugenol brought about cell lysis of gram-negative and gram-positive bacteria by damaging the cell wall and membrane caused leakage of lipid and protein contents. Eugenol has strong inhibitory and eradicative effects that were revealed after in-vitro and in-vivo studies on biofilms [28].

Eugenol showed synergistic interaction with gentamicin, vancomycin and β-lactam anti-biotics leading to greater anti-microbial effects. Eugenol also showed synergic interactions with cinnamate, thymol, cinnamaldehyde and carvacrol thereby resulting in higher anti-bacterial activities. The few drawbacks of eugenol include its liability to sublimation, low solubility and strong odor. It can be overcome by conversion of glycosylation to eugenol α-D-glucopyranoside (α-EG), which is much effective than that of pure eugenol as tested with *Staphylococcus aureus* and *Escherichia coli* [29].

3.3.6 Anti-Cancer Activity of Eugenol

The treatment of cancer lies in prohibiting the cells growth that can destroy malignant cells. For their anti-cancer properties, eugenol and its derivatives were investigated. In vitro studies exhibit that eugenol and its monomeric forms did not inhibit the cells growth but biphenyl forms of eugenol had some effects. Eugenol related biphenyl (S)-6,6' dibromo-de-hydro-di-eugenol draw out specific anti-proliferative activity on neuroectodermal tumor cells by partly speeding up the apoptosis. The eugenol epoxide form is potentially a drug candidate that plays a significant role for inducing apoptosis in human breast cancer cells. ROS plays an important role in eugenol and eugenol loaded nano emulsion induced apoptosis in HTB_{37} and HB_{8065} cells. Hydro distillation of bark and roots of *Uvariodendron angustifolium* contains 68.3% and 85.3% of

methyl eugenol respectively that give volatile extracts and exhibits appealing cytotoxic properties on human breast cancer cells MCF-7. Eugenol at low dose (2 μM) has particular toxicity against different breast cancer cells [30].

Combination therapy is the most useful treatment strategy in cancer to control drug toxicity and drug induced resistance. Eugenol blend with 5-fluorouracil showed more cytotoxicity against the cervical cancer cells (HeLa). Combination of eugenol and 5-fluorouracil raised the number of cells in the G2/M and S phases indicated by flow cytometry results when compared to treatment with the individual compounds alone. This indicated that eugenol have different cell cycle targets and induced apoptosis in the cancer cells. Eugenol and its chemically synthesized derivatives have proven its activity against skin tumors, melanoma, prostate cancer, gastric cancer and leukemia via oncogene regulation and caspase dependent pathway which is widely reviewed by many scientists [31].

3.4 Conversion of Eugenol to Methyl Eugenol

Eugenol belongs to alcohol which forms an alkoxide salt when react with a base as this salt reacted with an alkylating agent like as dimethyl sulphate. This process proceeds through the mechanism of nucleophilic substitution reaction to the reactant ion eugenolat dimethyl sulphate. By utilizing the clove oil that contains much amount of eugenol this process of methyl eugenol synthesis can be ensured by reacting eugenol compound with dimethyl sulfate inside water with strong base of NaOH as shown in equation 1 [32].

$$C_{10}H_{12}O_2 \xrightarrow[2.(CH_3)_2SO_4]{1.H_2O,OH,\Delta} C_{11}H_{14}O_2$$

Equation 1 Conversion of eugenol to methyl eugenol

The result of this synthesis is a clear yellow-brown solution with softer scent then eugenol. One of the phenomena that occur when methyl eugenol compound is formed is that fruit flies' insects (male) get on together and they regard smell comes from (female) fruit fly. However, it should be making sure through a repeated laboratory tests to characterize the sample. The synthesis results by gas chromatography analysis are 79 by percent yield with purity gained of about 90.73%. For the confirmation of methyl eugenol production, several different analyses should be carried out for determination of the structure through FTIR and NMR spectroscopies [31].

3.4.1 Physical and Chemical Properties of Methyl Eugenol

Methyl eugenol is a colorless to pale yellow, oily liquid which have an odor of cloves and carnations and structurally resembles with safrole. It is soluble in ethanol, chloroform, ethyl ether and many other organic solvents and insoluble in glycol, water and propylene glycol. Ethyl eugenol readily evaporates at room temperature because it is unstable at room temperature; when exposed to air it darkens and thickens. Chemical and physical properties of methyl eugenol are listed in table 1 as shown below.

Table 1 Physical and Chemical Properties of Methyl Eugenol

Property	Information
Molecular Weight	178.2
Specific Gravity	1.0396 at 20°C/4°C
Melting Point	-4°C
Boiling Point	254.7°C at 760 mm Hg
Log K_{ow}	3.03
Water Solubility	0.500 g/L at 25°C
Vapor Pressure	1 mm Hg at 85.0°C

3.4.2 Plant Source and Composition of Methyl Eugenol

The general population may be uncovered to methyl eugenol through eating foods or inhalation of fragrances containing that compound. Methyl eugenol is found in many essential oils as it is a naturally occurring substance including the oils of rose, basil, hyacinth, pimento, citronella, mace, cinnamon leaves, anise, nutmeg, pixie seeds and laurel fruits and leaves. It is also present in blackberry essence, black pepper, bananas and bilberries. Methyl eugenol is used as a flavorant at concentrations of 5 to 52 ppm and in fragrances at concentrations of 0.002% to 0.3% in commercial products. The highest concentration of methyl eugenol was 390 pg/g and the average concentration was 24 pg/g. The WHO estimated the daily per-capita consumption of methyl eugenol in food was to be 0.073 mg and more recently, 0.26 mg/kg of body weight [32].

Methyl eugenol is present in various natural substances however there are no quantitative studies found that evaluate environmental exposure to methyl eugenol. Methyl eugenol exists in air as a vapor and it reacts with air photochemically thereby producing hydroxyl free radicals that degrades with an estimated half-life of about 5 hours. Methyl eugenol is a wastewater effluent from a paper mill. Methyl eugenol may have occupational exposure through dermal contact, ingestion and inhalation. The National Occupational Exposure Survey (conducted from 1981 to 1983) predicted that 12,682 workers, including 9,413 women were potentially exposed to methyl eugenol [33].

3.4.3 Cancer Studies in Experimental Animals

Methyl eugenol caused tumors into rodent species and also at several different tissue sites due to oral exposure. Methyl eugenol through stomach tube caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice and rats of both sexes. Methyl eugenol caused tumors in rats like malignant or benign stomach tumors (neuroendocrine tumors) in both sexes. The tumor of kidney (renal-tubule adenoma), mammary gland (fibro adenoma) and skin (fibroma or fibrosarcoma) in males was also evident. Methyl eugenol and two structurally related allyl-benzenes such as estragole and safrole caused liver tumors in mice through intra-peritoneal injection. Safrole is listed as a carcinogen and reasonably to be a human carcinogen by the International Agency for Research on cancer by intra-peritoneal injection [33].

3.4.4 Uses of Methyl Eugenol

Methyl eugenol is used in fragrances and also as a flavoring agent in jellies, chewing gum, backed goods, candy, pudding, relish, nonalcoholic beverages and ice creams. It is used in combination with insecticides as an insect attractant and also used as an aesthetic in rodents [33].

3.5 Menthol

Menthol is a cyclic monoterpene alcohol which is found as a main component in the essential oils of *Mentha canadensis* L. (corn mint) and *Mentha piperita* L. (peppermint). Menthol along with menthone and isomenthone transmit the cooling minty taste and smell to plants, especially to the members of genus mentha. Menthol has been cultivated for medicinal purposes in Japan for long time before it was isolated and characterized and plants were the only source of menthol. Gambius a Dutch botanist was the first who isolated this compound as a crystalline principle in 1771. This compound is very useful commercial natural isolate. The estimated consumption of menthol is between 30 and 32,000 metric tonnes annually. The (-)-menthol is one of the most important after vanilla and citrus flavoring substance and it is the most important compound in many tobacco products. Menthol is usually present at low levels even in non-mentholated cigarette brands and it is supposed that one quarter of cigarettes sold contains menthol. Menthol is included in many of consumer products including pharmaceuticals, candies, chewing gum, cosmetics and pesticides, liqueurs, shampoos, toothpastes and soaps as a cooling and/or flavor enhancing ingredient. Menthol exhibits various biological properties such as anti-cancer, anti-microbial and anti-inflammatory activities [34].

3.5.1 Chemical and Physical Properties of Menthol

Molecular formula of menthol is $C_{10}H_{20}O$ (mol. wt. 156.27) is a natural compound and have three asymmetric carbon atoms that occurs as four pairs of optical isomers namely (+)-isomenthol, (-)-isomenthol, (+)-menthol, (-)-menthol, (+)-neomenthol, (-)-neomenthol, (+)-neo-isomenthol, (-)-neo-isomenthol and various other chemical structures are shown in figure 3. The basic form of menthol that is found in nature is (-)-menthol (L-menthol). It possesses greater cooling properties than other menthol isomers therefore this form is commonly used. Menthol reacts in many ways as other saturated compounds are readily oxidized to menthone. Menthol does not absorb UV radiations in the range of 290–320 nm, like other terpene alcohols such as citronellol, linalool, geraniol, myrcenol, nerol and nerolidol but it absorbs below 290 nm with the high absorption peak at 220 nm [35].

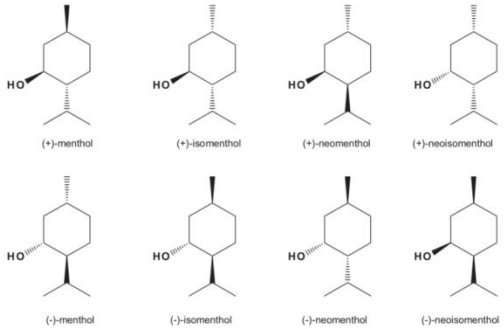


Fig 3 Some important stereoisomers of menthol

3.5.2 Origin of Menthol

Monoterpenes such as menthol are derived initially from aromatic plants. Menthol is extracted from corn mint oil that is produced by steam distillation. Menthol content in corn mint oil is 55-85%. Natural menthol is usually preferred because the scent of synthetic L-menthol is impacted by contaminants that arise during crystallization process [36].

3.5.3 Anti-Fungal Activity of Menthol

The inhibitory potential of menthol against various fungal strains has been investigated by several authors. Menthol was tested by using the semisolid agar susceptibility technique against *Fusarium verticillioides*. The growth of *Fusarium verticillioides* was decreased by 75% when 200 ppm menthol was used. Using shake culture method, it was noticed that menthol (MIC value: 400 l g/mL) was deadly to the spores of *Rhizopus stolonifer* after a 48h treatment. In the follow up study, fifteen essential oil constituents on five fungi namely *Fusarium oxysporum*, *Aspergillus niger*, *Penicillium digitatum*, *Rhizopus stolonifer* and *Mucor* spp. Menthol showed high activity against *Rhizopus stolonifer* and *Mucor* spp. (MIC value of 200 lg/mL), while other constituents such as citral, citronellal, cinnamic aldehyde and geraniol were found most effective against *Aspergillus niger*, *Fusarium oxysporum* and *Penicillium digitatum* (MIC value: 100 lg/mL). The results showed that menthol alone was found to be the compound responsible for the anti-fungal properties of peppermint oil, whereas the menthone alone did not exhibit any effect at all the concentrations tested [37].

3.5.4 Anti-Tussive Effects of Menthol

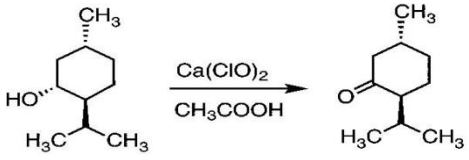
Many remedies that are used to prevent coughs usually contain menthol. Three aromatic compounds (such as menthol, camphor and 1,8-cineole) were tested for their anti-tussive effects by investigating the activity of aromatic vapors on the cough reflex in conscious guinea-pigs (n=13) at the concentrations of 3 and 10 lg/1L. Menthol was most active compound producing a meaningful decrease in cough frequency by 28% and 56%, respectively also found a decrease in cough count in the pediatric patients after menthol inhalation in comparison to the baseline [38].

3.5.5 Menthol as a Vehicle for Transdermal Drug Delivery

The percutaneous way of drug delivery has many benefits over other modes of delivery such as intravenous and oral administration as the architecture of the stratum corneum provides a horrible barrier to topical and transdermal administration of some therapeutic agents. Menthol permeates epidermis which in turn could comfort the approachability of other drugs. Limonene and menthol have been considered as the most productive transdermal penetration enhancers that considerably increases the transdermal delivery of certain drugs such as caffeine, imipramine hydrochloride and hydrocortisone that has shown quite similar effects to 1,8-cineole used for transdermal delivery of imipramine hydrochloride. The essential oil rich in menthol promotes the transdermal permeation of L-tetrahydropalmatine in in-vitro approaches. Various studies have shown that L-menthol (1% or 5%) considerably increased the flux of tetracaine gel (an aesthetic agent) and methyl salicylate in mouse skin compared to the negative control. Miscellaneous strategies have been developed to attain better transdermal delivery of certain compounds, such as nicardipine (used to treat high blood pressure and angina), propanolol (used to treat hypertension and angina) as well as ketoprofen and indomethacin that is known to have anti-inflammatory and analgesic properties [39].

3.6 Conversion of Menthol to Menthone

A two-week experiment is stated that require calcium hypochlorite oxidation of menthol to menthone. The oxidation reaction of (+)-menthol and (-)-menthol is well documented in the article but generally apply expensive or toxic reagents such as Dess−Martin periodinane or chromic acid. A laboratory experiment was grown that employs calcium hypochlorite, $Ca(ClO)_2$, is more environmentally friendly and inexpensive oxidizing reagent with enough strength to produce high yields of product show in figure 4.



(-)-Menthol (-)-Menthone

Fig 4 Conversion of Menthol to Menthone

$Ca(ClO)_2$ is familiar chemical usually found in swimming pool products. This chemical reaction is quite easy to handle as a solid can be used to make solutions of much higher hypochlorite concentration than household bleaches [40].

3.6.1 Reaction Hazards

We should take care when working with calcium hypochlorite as any hypochlorite source can bleach clothing and upon skin contact it should be washed immediately. All the hypochlorite reactions have the capacity to expel chlorine gas. This is unusual under weakly acidic conditions used in this experiment. To ensure safety, all the reactions should be performed in a ventilation hood. When neutralizing the remaining hypochlorite solution, care should be taken. The reaction is exothermic and produces HCl and this could ease the expulsion of chlorine gas, this step should be done in ice-water bath to avoid any formation of chlorine gas. Any diethyl ether waste should be correctly disposed in appropriate waste container. Extraction of diethyl ether should be done in ventilation hood and also inhalation should be avoided. Sodium hydroxide is corrosive and causes burns to any area it come in contact with [19].

3.6.2 Menthone Physical Properties and Source

Menthone occurs naturally in a number of essential oils and is a monoterpene with minty flavor. The l-menthone or (2S,5R-trans-2-isopropyl-5-methylcyclohexanone) is most plentiful in nature and found in four possible stereo isomeric forms. It has structural resemblance to menthol, which has a secondary alcohol in place of the carbonyl. Menthone is used in flavoring, perfume and cosmetics for its distinctive aromatic and minty odor. Menthone is a component of essential oils of *Mentha arvensis*, peppermint, geraniums and others. Menthone was firstly synthesized by oxidation of menthol in 1881 before it was found in essential oils in 1891 [41].

3.6.3 Menthone In-vitro Skin Permeation Studies

The inactive diffusion (without enhancer) of valsartan through rat skin produced a flux of 39.3 mg/cm^2/h. All the investigated terpenes used in the study provided a meaningful (p50.01) increase in the flux at a concentration of 1% w/v. The efficiency of terpenes at 1% concentration was in the following order: anethole>menthone>eugenol. The flux value immersed when the terpene concentration was increased to 3% w/v in case of all enhancers. When concentration was increased by 5% w/v, valsartan flux value further decreased. This shows that 1% w/v is the optimized concentration for anethole, eugenol and menthone which produced 4.4±1.7-, 4.0±1.1-, and 3.0±0.6-fold enhancement ratio over control properly [42].

3.6.4 Menthone in DSC Studies

Skin treated in DSC study was investigated with terpenes and it was noticed that both T_1 and T_3 endotherms totally disappeared or shifted to lower melting points in thermogram of stratum corneum treated with terpenes (anethole, menthone and eugenol). When the treatment was made with anethole and eugenol they decrease the protein endotherm T_4 to lower melting points. However, in case of menthone treatment, there was no ample change in T_4. The treatment of stratum corneum with anethole shifted T_4 down to 106°C with broadening of the peak. There was no miracle that anethole produced highest flux value of valsartan through rat skin as compared to other two terpenes [42].

4. Ethers

Ethers are important cyclic mono-terpenoid aroma compounds that are abundantly found in flavors and essential oils. Most essential oils have high odorous contents hence contribute essentially to the particular odor impression of the individual food articles. In flavor

chemistry of cyclic mono-terpenoid ethers being defined in some outstanding reviews covering their natural occurrence, synthesis and structure-odor relationships with an importance on constitutional isomers. However, chiral discrimination has been acknowledged as one of the most important principles in odor perception as chiral odorants show different qualitative and quantitative activities. Concerning the biogenesis of cyclic mono-terpenoid ethers and the isolation and characterization of their precursors, much of work has been done yet. Poly-hydroxylated monoterpenes are direct precursors of mono-terpenoid ethers.

4.1 Methyl Chavicol

Plants contain thousands of different semi-volatile and volatile organic compounds and community of atmospheric chemistry has historically focused on a small subset of these. With ongoing improvements in analytical instrumentation in recent years, a vast suite of biogenic volatile organic compounds (BVOCs) have been measured in the atmosphere. Methyl chavicol (1-methoxy-4(2-propenyl)-benzene) also known as estragole or 4-allylanisole is an oxygenated aromatic BVOC with a chemical formula of ($C_{10}H_{12}O$) is not actually a terpenoid compound although it has 10 carbon atoms. Plants from which it is synthesize smells like licorice from the amino acid phenylalanine via the shikimate pathway [43].

Methyl chavicol is produced by variety of plants and also a major essential oil component of many common herbs such as tarragon (up to 86%), basil (up to 70%) and fennel (up to 65%). It is also a main component in the oils of culturally-significant plants found worldwide, including a Turkish herb (up to 90%), a Latin American herb (up to 97%), an Indian herb (up to 93%) and a Mexican avocado (up to 95%). It has been identified in the resin of pines *(Pinus spp.)* such as Caribbean, scots, slash, black, longleaf, loblolly, lodge-pole and ponderosa. After studies of ponderosa pine oil, methyl chavicol accounts for 3–40% of total needle oil which is comparable or higher than the monoterpene 3-carene [44].

4.1.1 Barkeley GC-MS Analytical Technique of Methyl Chavicol

The gas chromatograph with quadrupole mass spectrometer (GC-MS) is an instrument which was optimized to quantify C_{10}–C_{15} biogenic compounds with the reconstruct of the inlet system. Methyl chavicol was never dependably observed at Blodgett Forest during the 10 years of sampling until these modifications were made. To lower the sample loss due to condensation process, all the tubing and fittings prior to the GC oven which were heated to 50°C and also the sub-zero water trap was eliminated. The hydrocarbon preconcentration trap packed with Tenax TA due to ambient water vapor in the sample and remained at ambient temperature during sample collection. All the fittings and tubing were changed from PTFE to the silcosteel because the metal tubing permit for even heat dispersal and the internally passivated surface reduces wall reactions and subsequent losses. Chemically-effective ozone trapping material was changed from impregnated glass wool to a 1μm pore size Pall A/E glass fiber filter to minimize the chance of sample adsorption. This filter was also used to remove unrefined matter from the sample. The ozone filter was changed at least once per day, to assure its effectiveness [44].

The GC oven temperature was set up at 43°C for 4.25 min and increasing to 160°C at the rate of 5°C min^{-1} then to 220°C at the rate of 10°C min^{-1} and held at this temperature for 11.75 min. Methyl chavicol was quantified with mass to charge ratio m/z 148 and mass spectrometer (HP 5971) was conducted in single ion mode. Methyl chavicol is a semi-volatile compound and it is not easily available as a gas phase standard produced a gas phase methyl chavicol make standard by volatilizing diluted pure liquid standards in a Tedlarbag. In this research activity, methyl chavicol was adjusted in the Berkeley GC-MS by manually injecting liquid standards (Sigma-Aldrich) diluted in cyclohexane (Sigma-Aldrich) into a 100–200 $mLmin^{-1}$ flow of nitrogen gas where the injector port was heated to 100°C. At least once a day, the Berkeley GC-MS system was calibrated and measurement uncertainty for monoterpene and methyl chavicol was 18% and 27% respectively [45].

4.2 Conversion of Methyl Chavicol to Trans Anethole

Trans-anethole has a demand in the world market due to its large applications in various products and its demand is still increasing rapidly since last few years. To overcome these shortages and to decrease the dependence upon a natural crop, different economic routes for the synthesis of trans-anethole have been developed. Presently, anethole (which is a mixture of cis and trans isomers) was extracted from anethole-rich natural essential oils like anise oil, anise seeds, fennel oil, star anise oil and pine oil along with anisole and methyl chavicol (1-methoxy-4-(2-propen-1-yl) benzene). Multi step synthesis of anisole is not favorable from industrial viewpoint nevertheless single step synthesis through double bond isomerization in the presence of base catalysts is highly valuable from both industrial and academic viewpoint.

4.2.1 Physiochemical Properties of Anethole

Anethole exists as both cis- and trans-isomers, involving double bond outside the ring. Trans or E isomer of anethole is more abundant and preferably used. Anethole is a colorless and clear to amber liquid with a sweet anise-like flavor, slightly soluble in water but shows high solubility in ethanol. This difference induces certain anise-flavored liqueurs to become opaque when diluted with water due to spontaneous formation of a micro-emulsion. Anethole is clearly sweet ans even thirteen times sweeter than sugar and used in many alcoholic drinks. It flavors Middle Eastern arak, French spirits absinthe, anisette and pastis, Colombian aguardiente, Greek ouzo, German Jagermeister, Italian

sambuca, Bulgarian and Macedonian mastika, Dutch Brokmopke, Portuguese, Peruvian and Spanish anisado, Herbs de Majorca, Mexican Xtabentun and Turkish rakı. Anethole can cover nasty odors, so it is largely used as a masking agent in commodities, such as toothpaste, toilet soap and mouth wash. The chemical structure of anethole is shown in the figure 5 as given below [46].

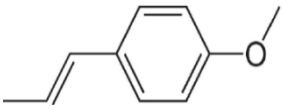


Fig 5 Chemical structure of anethole

4.2.2 Occurrence of Anethole in Nature

Anethole is an aromatic compound that is naturally present in essential oils. It contributes to the unique flavors of anise and fennel (both in the botanical family Apiaceae), *anise myrtle* (Myrtaceae), liquorice (Fabaceae), *magnolia blossoms*, camphor, *star anise* (Illiciaceae) and many other plants. Anise oil has a high concentration of natural anethole upto 80-90%, star anise oil upto over 90% and fennel oil upto 80%. Essential oil has two functions in plants: protection and communication. It manages the host plant protection from pathogenic micro-organisms, such as viruses, bacteria and fungi and/or deters herbivorous animals from consuming the plant [46].

4.2.3 Anti-Oxidant Activity of Anethole

Fennel oil demonstrated strong anti-oxidant abilities as calculated by two lipid model systems: an altered thiobarbituric acid reactive species assay and a spectrophotometric detection of hydroperoxydienes from linoleic acid in a micellar system which is related to that of the reference antioxidants such as tocopherol and butylated hydroxytoluene. Ethanol and water extracts of fennel seeds exhibit 99.1% and 77.5% inhibition of peroxidation in linoleic acid system that is higher than same dose of standard compound tocopherol that showed 36.1% [47].

4.2.4 Anti-Microbial, Anti-Fungal, Anti-Helmintic and Insecticidal Activity

Anethole has effective anti-microbial properties against bacteria, yeast and fungi. Star anise essential oil and all isolated compounds show anti-HSV-1 activity by direct inactivation of free virus particles in viral suspension assays. Star anise oil decreased viral infectivity by >99%. An acetone extract of aniseed barred the growth of a range of bacteria including *Escherichia coli* and *Staphylococcus aureus* and also showed anti-fungal activity against *Candida albicans* and other organisms. Anise oil (0.2%) alone exhibited in-vitro activity against *Salmonella enteritidis*. Aniseed essential oil barred the growth of *Escherichia coli* (minimal inhibitory concentration (MIC):0.5%), *Salmonella typhimurium* (MIC:2.0%), *Staphylococcus aureus* (MIC:0.25%) and *Candida albicans* (MIC:0.5%) using the agar dilution method [48].

4.2.5. Gastro-Protective Activity

The gastro-protective effects of *Foeniculum vulgare* essential oil and anethole at doses 50 and 100 mg/kg were investigated in ulcerogenesis caused by ethanol (90% 1 ml) in rats. Fennel oil and anethole showed an important gastroprotective activity against the erosive damage caused by ethanol. Their similar anti-ulcer activity could be attributed, to maintenance of an acceptable blood supply in the gastric mucosa through their anti-platelet and vasorelaxant effects. Actually, they could prohibit the disturbance in the gastric circulation generated by ethanol which was induced by a local vasocongestion with vascular stasis and mucosal damage associated to overproduction of oxygen-derived free radicals. The pretreatment with anethole at the rate of 30 and 300 mg/kg increased the mucus production by gastric mucosa in the ethanol-induced ulcer model. Oral treatment with anethole at the dose rate of 30, 100 and 300 mg/kg induced the gastro-protection activity against ethanol and indomethacin-induced gastric damage. Ethanol caused histopathological lesions in the stomach wall, characterized by mucosal hemorrhages and edema that was reversed by FVS [49].

4.2.6 Safety and Toxicity of Anethole

Anethole is associated with an insignificant increase in liver cancer in rats, although the evidence is meager and usually regarded as evidence that anethole is not a carcinogen. An assessment of anethole by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) found its remarkable pharmacologic properties to be reduction in motor activity, lowering of body temperature and hypnotic, analgesic and anti-convulsant effects. Anethole has no safety concern at current levels of intake when used as a flavoring agent, according to JECFA. In large quantities, anethole is somewhat toxic and may act as an irritant. The council of Europe (1970) listed trans-anethole giving a sufficient daily intake of 1.5 mg/kg. Oral LD50 values per kg were determined for the essential oil as 2.7 g in rats and for trans-anethole as 1.8-5.0 g in mice; 2.1-3.2 g in rats and 2.16 g in guinea pigs. Also, mice were fed up to 240 mg trans-anethole/kg/day with diet for 90 days. Anethole has a moderate enzyme-inducing effect on mouse liver (cytochrome P450 and P448). The increased liver weight was considered to be an adjusting physiological response associated with enzyme induction properties of trans-anethole inspite of negative effect.

5. Aldehydes

Aldehydes are found in large amount in lemon scented oils including lemon verbena, citronella, Melissa, neral and citral. These chemical compounds are also known to have tranquilizing potentials and anti-septic properties. Benzaldehyde, peril aldehyde and cinnamic aldehyde are important aldehydes of essential oils. Aldehydes are used for the treatment of inflammations, viral infections and more specifically candidum diseases [1].

5.1 Citral

Citral is largely used in the flavor and fragrance industry and its application range from meat products to hard candy. The amounts used in the products differ

incredibly and amounting to as little as 0.20 ppm in cheese and as many as 429.8 ppm in chewing gum. Citral has a solid, lemon-like odor and a typical bittersweet taste. It was found in lemon grass accounting upto 75% of the oil and its chemical structure shown in figure 6. Commercial citral is obtained by chemical synthesis from *α*-pinene or isoprene.

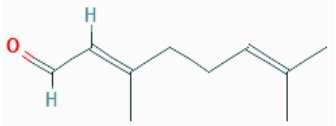


Fig 6 Chemical structure of citral

5.1.1 Anti-Fungal Activity of Citral

Using the disk diffusion method, the anti-fungal activity of the lemon grass oil and citral against yeasts was determined. There were eight strains of Candida species used: *Candida albicans* ATCC 10231, *Candida albicans* CI-I (clinical isolate), *Candida albicans* ATCC 18804, *Candida albicans* CI-II, *Candida glabrata* ATCC 2001, *Candida krusei* ATCC 6258, *Candida tropicalis* ATCC 750 and *Candida parapsilosis* ATCC 22019 [50].

5.1.2 Anti-Microbial Activity of Citral

The essential oil of *Cymbopogon citratus* has shown considerable activity against bacteria especially gram-positive organisms. The major anti-bacterial components (~75%) of the oil (LGO) were separated and identified as α-citral and β-citral. A full calculation of the anti-microbial activity of citral becomes essential in order to complement its already common use in the food, perfumery and soap industries. This study will therefore judge the activity of citral against, typed and wild strains of bacteria and fungi using minimum inhibitory concentration (MIC) and also minimum bactericidal concentration (MBC) conclusion including the effects of nutrient composition, inoculum size and pH as well as its effects on bacterial growth and viability.

5.1.3 Activity of Citral against Cardiovascular Disease

Citral is a mixture of isomeric aldehyde's geranial and neral which exist in plants and citrus fruits that used aortic rings to explore the vasorelaxant proprieties of this monoterpene. The authors showed that this compound using an endothelium-independent mechanism was promoted vasodilation in phenylephrine pre-contracted rings. The results recommended that citral developed relaxation by changing calcium dynamics, which is an effect that occurs once citral-prohibited contractions by both high K^+ and phenylephrine manifest, this study did not investigate the effects of citral on calcium receptors [51].

5.2 Conversion of Citral to Valuable Products

Citral, geraniol, citronellal and nerol are fragrant natural products found in a many essential oils, including those of lemongrass, geranium, citronella and rose. Even more irresistible from a pedagogical view is the potential for illustrating chemo-selectivity in the conversions of citral into citronellal, geraniol, nerol or epoxycitral as shown in figure 7. The products have unique fragrances and are useful as insect repellants and perfumes. Epoxy citral may be less familiar than others but it is mite pheromone with important anti-cancer effect [52].

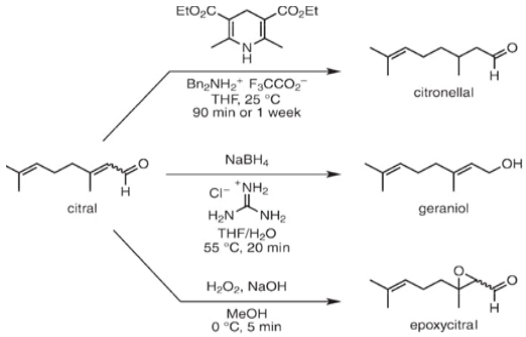


Fig 7 Conversion of citral into valuable market products

5.2.1 Hazards of Chemical Reaction

Citral, dichloromethane, dibenzyl amine, citronellal, geraniol, guanidinium chloride, nerol and 4-methoxybenzaldehyde produce irritation and are corrosive in nature. Some other compounds such as trifluoroacetic acid, sodium hydroxide and sulfuric acid also fall in this category. Acetic acid is corrosive and flammable. Tetrahydrofuran and diethyl ether are irritants, flammable and may form explosive peroxides. Sodium borohydride and methanol are flammable and toxic by contact with skin, inhalation or ingestion. Ethanol is also flammable. Deuterated chloroform is a cancer distrust agent and strong mutagen. Gloves and protective eyewear must be worn during this experiment. Attention should be exercised when smelling the concentrated perfumes (waft vapors with a hand toward the nose rather than placing nostrils directly above a flask in many cases, the fragrances are strong enough to be detected even when the vessels are capped) [53].

5.2.2 Physical Properties and Sources of Geraniol

Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol) is an acyclic monoterpene alcohol with chemical formula $C_{10}H_{18}O$. The chemical structure of geraniol is shown in figure 8. Geraniol is a mixture of two cis-trans isomers properly named nerol (cis) and geraniol (trans). Geraniol was obtained from Palmarosa oil while nerol was isolated from oil of neroli. It is a major constituent of several essential oils and present in *Monarda fistulosa* (upto 95%), rose oil (upto 44.4%), ninde oil (upto 66.0%), palmarosa oil (upto 53.5%) and citronella oil (upto 24.8%). Geraniol is a clear to pale-yellow oil which is insoluble in water but soluble in organic solvents [54].

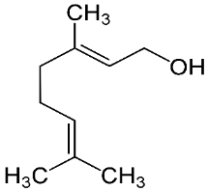


Fig 8 Chemical structure of geraniol

5.2.3 Insecticide and Repellent Effects of Geraniol

Essential oils and their main constituents are emerging as potential pest control agents due to their

insecticidal, repellent and/or anti-feedant properties. The results showed that geraniol was more impressive than benzyl benzoate with the 50% deadly dose value being 1.95 μg/cm^3 and 1.27 μg/cm^3 respectively. Geraniol in 5% dilution showed the strongest acaricidal activity against *Otodectes cynotis* by direct contact with mite, among the four monoterpenes (α-pinene, geraniol, limonene and p-cymene). Geraniol (1%) showed a decline in the mean number of ticks per animal of 98.4%, 97.3% and 91.3% at days 7, 14 and 21 respectively [55].

5.2.4 Anti-Cancer Activities of Geraniol

Geraniol has been exhibited anti-cancer activity in vitro and in vivo, in a number of models of human cancer. It showed chemotherapeutic activity towards pancreatic and other cancers, further explored the mechanism of activity of geraniol against pancreatic tumors. They reported that geraniol can cause apoptosis and increase expression of the pro-apoptotic protein back in cultured pancreatic tumor cells. Geraniol has also anti-proliferative effects on hepatoma and melanoma cell growth [56].

5.2.5 Commercial Benefits of Geraniol

Geraniol has its own commercial importance and it is an important terpene alcohol found in the essential oils of several aromatic plants. It is one of the most useful molecules in the flavor and fragrance industries and is a main ingredient in consumer products produced by these industries. In addition to its pleasing odour, geraniol is known to show insecticidal and repellent properties and used as a natural pest control agent exhibiting low toxicity. Geraniol has been representing a new class of chemo-prevention agents for cancer. Geraniol has attracted the attention of researchers due to its effect as a penetration enhancer for transdermal drug delivery [57].

5.2.6 Activity of Citronellal against Cardiovascular Disease

The monoterpene citronellal is a main component of essential oils in different aromatic species such as *Cymbopogon winterianus Jowitt* (Java citronella), *Corymbia citriodora* (Hook.) K.D. Hill and *Cymbopogon nardus* L. Cardiovascular properties of citronellal were judged in a NO-inhibition model of experimental hypertension. Mean arterial pressure (MAP) was decreased by oral acute citronellal administration. Citronellal also caused vasorelaxation of the mesenteric arteries of rats using an endothelium-independent mechanism [58].

6. Esters

Esters are the vital chemical compounds of plants which are mostly formed by chemical reaction of acids with alcohols. Esters play an important role as smoothing and balancing agent and also have strong anti-microbial potentials. Esters are specialized for sedative potentials and anti-fungal actions. In order to maintain the balance in the nervous system they play an important role. Linalyl acetate, geranyl formate and lavender are major esters of bergamot and germanium [59].

6.1 Linalyl Acetate

Linalyl acetate is a fragrance material used in many fragrance compounds, it may also be found in fragrances used in cosmetics, shampoos, fine fragrances, toilet soaps and other toiletries as well as it is also used in non-cosmetic products such as household cleaners and detergents. Its general use is in the region of >1000 metric tons per annum. Determinant factors for fragrance exposure are quantities and frequency of cosmetic used and concentration of fragrance material in these products. Using these factors, it has been calculated that the total maximum exposure to linalool from 10 types of cosmetic products is most common. For consideration of promising results, sensitization exposure is calculated as a percent concentration used on the skin. The maximum skin level in formulae that go into elegant fragrances has been reported to be 4.3% assuming use of the fragrance oil at the levels upto 20% in the final product [60].

6.1.1 Physical Properties of Linalyl Acetate

Physical form of linalyl acetate is a clear, colorless liquid having vapor pressure of about 0.10 mmHg at 20°C with flash point 85°C; boiling point 220°C; refractive index 1.449–1.452 (at 20°C) and specific gravity 0.897–0.910 (at 20°C). Chemical structure of linalyl acetate is shown in figure 9 [61].

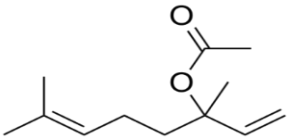


Fig 9 Chemical structure of linalyl acetate

6.1.2 Skin Sensitization of Human Studies of Linalyl Acetates

The samples of linalyl acetate that basically produces sensitization were re-tested or purified and again re-tested and produced no sensitization upon re-test. With the help of 20% linalyl acetate (sample 74-20-98 R 2) a maximum test was carried out in petrolatum on 25 healthy male and female volunteers. A multicenter study was conducted to conclude the creative allergens in cosmetic products. One hundred and nineteen (17 male and 102 female) cosmetic delicate patients were tested about 8–10 weeks after their basic diagnosis of cosmetic allergy. Patch tests were carried out with 3% linalyl acetate in petrolatum using Van der Bend patch chambers and acrylate tape. The patch was removed after 2 days and the reactions were read 20 min later and again 24 or 48 h later, one patient reacted reported the results of a multicenter study on patch tests with 48 fragrance materials. Linalyl acetate, 1 and 5% in petrolatum was tested in 100 patients where 36 male and 64 females were included. The material was used to the back for 2 days using Finn chambers 1 on Scanpor tape 1 and reactions were assessed per ICDRG guidelines on days 2 and 3 or on days 2 and 4. No effects were observed. There was no influence observed with 1% linalyl acetate in petrolatum when 70 contact dermatitis patients and 19

eyelid dermatitis patients were tested with a perfume series. Test materials were added to the upper back for 48–72 h with A1 test strips 1 or Finn chambers 1 and Scanpor tape 1 and reactions were scored according to ICDRG guidelines at patch removal and 48 or 72 h later.

6.1.3 Linalyl Acetate Activity against Cardiovascular Disease

Linalyl acetate is a monoterpene ester that mobilize intracellular calcium concentration ([Ca]i) in cultured vascular endothelial (EC) or in mouse vascular smooth muscle (MOVAS) cells in EC. LA caused a temporary increase followed by a sustained decrease in [Ca]i, whereas in MOVAS showed the increase that remained unchanged. LA surrounded the extracellular calcium influx in EC, but not in MOVAS. Therefore, LA differently influence the endothelium and smooth muscle cells and its influence on EC may explain its protective effects against endothelium dysfunction associated with cardiovascular diseases [62].

6.2 Conversion of Linalyl Acetate to Linalool and Other Products

The catalytic properties of zeolites and MCM-41 in linalyl acetate conversion were possible in order to avoid dehydration, as a result geranyl acetate as the isomerization product were obtained shown in figure 10. The OH group in linalyl acetate is surrounded, unlike in linalool. The data exhibited that under commensurable conditions, the rate of conversion and the condensation yields for linalyl acetate, conversion are higher than for linalool conversion, due to dehydration and cyclization selectivity being declined almost over all types of catalysts studied so far [63].

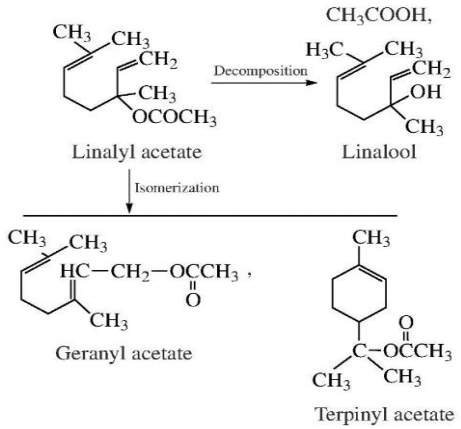


Fig 10 Conversion of linalyl acetate into products

6.2.1 Physical Properties of Linalool

Linalool is a colorless pale yellow liquid having vapor pressure (calculated) of about 0.05 mm Hg at 20°C; flash point of 71°C; boiling point about 198°C; refractive index ranging between 1.460–1.463 (at 20°C) and specific gravity around 0.860–0.864 (at 20°C). The chemical structure of linalool is shown in figure 11 [64].

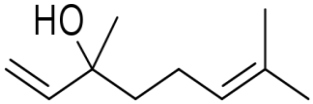


Fig 11 Chemical structure of linalool

6.2.2 Usage of Linalool

Linalool is a fragrance material used in many fragrance compounds, it may also be found in fragrances used in cosmetics, shampoos, fine fragrances, toilet soaps and other toiletries as well as it is also used in non-cosmetic products such as household cleaners and detergents. Its general use is in the region of >1000 metric tons per annum. Determinant factors for fragrance exposure are: quantities of cosmetic used, frequency of use and concentration of the fragrance material in these products. Using these factors, total maximum exposure to linalool has been calculated from 10 types of cosmetic products. For consideration of promising result or outcome, sensitization exposure is calculated as a percent concentration used on the skin. The maximum skin level in formulae that go into elegant fragrances has been reported to be 4.3% assuming use of the fragrance oil at the levels upto 20% in the final product [65].

6.2.3 Linalool Activity against Cardiovascular Disease

The monoterpene linalool (LO) is main constituent (87.7%) of rosewood oil (EOAR) which is known to cause hypotension and bradycardia in awakened animals that were abolished by pre-treatment with methyl atropine. Hyper-contraction of aortic segments induced by heavy metals such as arsenic and mercury was reduced by isolated LO and it also indicated additional participation of soluble guanylyl cyclase and K^+ channel on its vasorelaxant effects [66].

7. Conclusion

Evaluation of existent literature data on conversion of various essential oil functionalities revealed that oxidative changes and deterioration reactions, which may lead to both sensory as well as pharmacologically relevant alterations have scarcely been systematically addressed. The importance of extrinsic storage factors on the physicochemical stability of essential oils revealed that this issue still awaits profound scientific evaluation. For quality control purposes, the utility of HPLC to profiling genuine as well as oxidized essential oils appears promising, which may also be appropriate for the assignment of essential oil components in foods, cosmetics and pharmaceutical formulas. Besides POV assessment, conductivity and pH measurements should be part of the analytical toolbox to obtain a more complete picture on oxidative events that the respective essential oil may have undergone. Further research is required to underpin recent analytical approaches in order to gain an even deeper understanding of possible oxidation processes and strategies to avoid them. Also, the identification of oxidation products resulting from oxidative events appears to be a valuable future objective.

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