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” There is only one thing in long run more expensive than education – no education “- J.F. Kennedy

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1. Abstract

Essential oils are volatile complex mixtures extracted from different plant material. These natural products have become an important part in consumer products due to their variety of benefits. When used in lower concentration, they are considered as safe and nontoxic and as such they are widely incorporated in cosmetic products, perfumes, and household products and as a flavoring agent in food. Their composition may vary depending on the quality of plant material from which they were obtained and the extraction method by which the essential oil was produced. These factors are also important for the safe use of essential oils in personal care products. As they contain compounds that easily change their chemical structure and their effects when exposed to air, which is what happens when applied to the skin, skin sensitivity and irritations can follow and other symptoms may arise. Since essential oils and fragrances are considered to have a strong allergy potential, a lot of scientific studies have been performed to determinate the toxicity of essential oils and their compounds in personal care products.

This paper focuses on side effects and allergy contact dermatitis caused by essential oils and their single compounds in cosmetic products. The scientific literature was summarized with the focus on research studies performed between 2012 and 2017.

1. Zusammenfassung

Ätherische Öle sind flüchtige komplexe Gemische, die aus verschiedenen Pflanzenmaterialien extrahiert werden können. Diese natürlichen Produkte sind aufgrund ihrer vielfältig einsatzbaren Vorteile zu einem wichtigen Bestandteil von Konsumgütern geworden. Bei Verwendung in niedrigeren Konzentrationen gelten sie als sicher und sind daher häufig in kosmetischen Produkten, Parfums und Haushaltsprodukten sowie als Aromastoff in Lebensmitteln zu finden. Die Zusammensetzung der ätherischen Ölen kann in Abhängigkeit von der Qualität des Pflanzenmaterials, aus dem die Bestandteile gewonnen wurden, und der Extraktionsmethode, mit der das ätherische Öl hergestellt wurde, variieren. Diese Faktoren sind auch wichtig für die sichere Anwendung von ätherischen Ölen in Körperpflegeprodukten, da sie Verbindungen enthalten, die an der Luft leicht ihre chemische Struktur und ihre Wirkung verändern, was beim Auftragen auf die Haut zu Hautempfindlichkeiten und -reizungen führen kann. Zudem weisen ätherische Öle und Duftstoffe ein starkes Allergiepotential auf, worauf zahlreiche wissenschaftliche Studien durchgeführt wurden, um die Toxizität der Öle und deren Verbindungen in Körperpflegeprodukten zu untersuchen.

Diese Diplomarbeit befasst sich mit den Nebenwirkungen und allergischer Kontaktdermatitis, die durch ätherische Öle und deren Einzelverbindungen in kosmetischen Produkten verursacht wurden. Die erforderliche wissenschaftliche Literatur wurde mit dem Schwerpunkt auf, zwischen 2012 und 2017 durchgeführten, Forschungsstudien zusammengefasst.

This diploma thesis served as a draft version of "Essential oils in and Their Single Compounds in Cosmetics – A critical Review " [1].

2. Introduction

2.1 Essential oils

2.1.1 Composition and characteristics of essential oils

Essential oils are liquid, flammable, lipophilic complex mixtures that are mostly obtained from plant material via steam distillation [2]. Exceptions are citrus oils derived from the peels of citrus species such as grapefruit, lemon, mandarin, orange, or tangerine that are obtained by cold pressing [3]. Essential oils are mainly colorless, except for clove essential oil, which is reddish brown, and chamomile oil that is blue. This bluish color depends on the content of chamazulene.

Essential oils are composed of numerous individual substances which, depending on their concentration, can be divided into main components (20 to 95%), secondary components (1-20%) and trace components (less than 1%) [4]. These constituents must have a small molecular mass and should not be bound to sugar by glycosidic bond. Monoterpenes, sesquiterpene and phenylpropane derivatives are the main constituents of essential oils [5]. Essential oils are soluble in all lipoid solvents such as fatty oils, petroleum ether, chloroform, benzene, ether and in high percentage alcohols (over 90%) [2]. The chemical composition of essential oils derived from one plant species can vary depending on the time of harvest as well as the location of the crop [6]. One of the main characteristic is an intense and characteristic aroma. This resembles the fragrance of the plant from which the oil was obtained and as a rule that aroma is mostly less pleasant than the plant itself. The taste of an essential oil is usually peppery, stinging or burning. Following the dilution of the oil, its taste becomes more pleasant. Most essential oils are lighter than water and when mixed, they appear on the water surface. Exceptions are cinnamon oil and clove oil whose specific weight is heavier than water. At room temperature, essential oils are liquids and do not leave a persistent greasy trace on paper with the exception of sandalwood oil. This characteristic can be used to distinguish between essential oils and fatty oils [3].

2.1.2 Origin of essential oil – availability

Asteraceae, Lamiaceae, Apiaceae, Cupressaceae, Pinaceae, Myrtraceae, Lauraceae, Ruataceae and Zingiberaceae are the most important families when it comes to essential oils [7]. Essential oils are produced in the oil glands of plants and can be found in plant tissues. They are located in the flower, leaf, stem, bark, and seed or in the tree [8]. Some species can excrete essential oils from different parts of the plant. These essential oils may differ in their composition [9]. Essential oils are very useful for the plant as they serve as protection from microorganisms but are also used to attract insects that are important for pollination [10].

2.1.3 Production of essential oils

The quality production of essential oils is dependent upon several factors which include: growing methods (preferably organically grown, bio-dynamically grown, or ethically wild crafted), geography, weather and territory conditions. The plant material for the production of essential oils can grow in various countries and on more than one continent. A cultivated plant benefits from warm and sunny climate with enough rain and water supply. If the plant uses the oil as insect repellent, higher amount of oil will be produced if there is a higher concentration of insects surrounding the plant. Essential oils can generally be extracted from every part of a plant via steam distillation or by cold pressing of the rind or peel as it is the case with citrus fruits. Furthermore, suiting predistillation plant material preparation influences the quality of production of essential oil [11].

2.1.3.1 Steam distillation

For steam distillation, an inorganic solvent such as water or water vapor is needed. The boiling point for most components in essential oils ranges from 150º C to 300º C. These temperatures are close to the decomposition temperatures of certain substances and this can lead to destruction of these substances or to polymerization of substances forming a plastic mass which is no longer usable. For this reason, steam distillation is preferred as an extraction method. The principle of steam distillation is that water or steam is added to the distillation apparatus and heated. Vapor runs through the plant material in the course of distillation. The hot vapor breaks down cells

of the plant and transfers the essential oil to a cooling chamber where the hydrosol and the essential oil then separate. The quantity of an essential oil gained by distillation is dependent upon the plant [12].

2.1.3.2 Extraction by cold pressing

Cold pressing of the rind or peel produces citrus essential oils of highest quality. The oil of sweet orange, lemon, bergamot, lime, bitter orange, mandarin, and grapefruit is located in the epicarp fruit layer. This method is often called scarification. Steam distillation of citrus oils is impossible since they contain components which are sensitive to high temperatures [11].

2.1.3.3 Extraction by dry distillation

This method is a sort of distillation without adding water or steam. Essential oils produced from certain wood, barks, roots, or gums are dry distillated using a phenolic chemical solvent which is then responsible for extraction of the oil out of plant material.
An example of dry-distilled essential oil is birch tar oil, which was used in perfumery but due to its high toxicity level, it is no longer in use [11].

2.1.4 Quality control and counterfeiting of essential oil

Essential oils belong to a substance group that is most often exposed to counterfeiting. They are used as a strong marketing advantage in sale and promotion of numerous beauty products as well as personal care products but the prices of natural oils are always higher than those of synthetic oils. The oils sold on the internet are often labeled as “pure”, “natural” or ‘‘100% natural”. The International Organization for Standardization (ISO) defines an essential oil as products manufactured by either water- or vapor distillation or by mechanical processing of citrus rinds or by dry distillation of natural ingredients [13]. Therefore, essential oils must be generally natural and pure so such labels are unnecessary and do not guarantee good quality of the oil. Adulteration, contamination, incorrect oil production, and aging are consequences of low quality oils [14].

Most common ways of counterfeiting essential oils are [15]:

a. Adding of single raw materials

In order to make essential oils cheaper, some producers will alter the oils by diluting them with fatty oils such as almond oil, coconut oil etc., or by adding alcohol, surfactants and emulsifiers. If an essential oil is stretched with fatty oil, it is detectable since it leaves a greasy trace on the skin. A pure essential oil will normally not leave any greasy feeling on the skin. Another way to check its quality is to put some essential oil on paper. Since pure essential oil will not leave an oily mark when dried, a simple way to spot emulsifiers in essential oil is by adding a drop in water. Pure essential oil will appear on the surface whereas emulsified mixtures will dissolve in water and produce milky or opaque solutions. Diluents added to cause adulteration are benzyl alcohol, benzyl benzoate, dipropylene glycol, carbitol, isopropyl myristate, triacetin. They can be detected by aqueous alcohol solubility tests and by using different GC columns and operation conditions or by derivatization.

b. Adding cheaper essential oils of the same plant but from another country - adjuncts

Mixing with cheaper oils to decrease the price of the oil to make extra profit is a common practice present in the trade of essential oils. The usual adulteration practices for numerous essential oils are:

- **Bergamot oil** – Adding of lemon oil, rectified ho oil, sweet orange oil and terpenes etc.
- **Lavender oil** – Adding of cheaper lavandin oil varieties / spike lavender oil / rectified ho oil
- **Lemon oil** – Adding of orange terpenes / lemon terpenes
- **Peppermint oil piperita** – Adding of peppermint oil arvensis / L-menthol

c. The adding of cheap synthetic compounds (identical to natural) isolated from other oils – Adding of synthetical substances which are already existent in the oils. Some examples include:

- **Bergamot oil** – Adding of linalool and linalyl acetate
- **Lavender oil** – Adding of eucalyptus and white camphor oil fractions

- **Lemon grass oil** – Adding of citral
- **Spearmint oil** – Adding of (-)-carvone
- **Rosemary oil** – Adding of camphor, eucalyptus oil, isobornyl acetate etc

d. Adding of individual synthetic substances to oils and aromatic raw ingredients

e. Labeling one essential oil as another - These are the examples of this type of practice:

- *Mentha arvensis* oil as *Mentha piperita* oil
- *Litsea cubeba* oil as melissa oil
- Clove leaf oil as clove bud oil
- Synthetic anethole as star anise oil
- *Cinnamomum camphora* fractions as *Eucalyptus globulus* oil
- Orange oil Brazil as sweet orange oil Florida
- Wild thyme as thyme (*Thymus vulgaris*)

f. Blending with less expensive essential oils of the same plant but taken from a different part of the plant.

These examples include: Clove bud with clove leaf oil, cinnamon bark with cinnamon leaf and angelica root with angelica leaf oil.

Standard profiles for quality assurance for essential oils

As essential oils are often mixed with other substances, many tests are needed. For all analyses of essential oils and their mixtures the observance of the standard profile for essential oils is of high importance. Table 1 contains the whole program of analyses [16].

2.1.5 Storage and packing of essential oils

The requirements of the European Pharmacopoeia state that essential oils need to be protected from light in a tightly closed and fully filled container [17]. The relative instability of the components of essential oils should be taken into account and care should be taken to ensure quality

during storage. Photoisomerization, photocyclization, oxidation, peroxidation and decomposition of alcohols and ketone hydrolysis are consequences of inappropriate storage conditions. Safety of essential oils can be altered through degradation. In order to avoid such consequences of degradation, the ISO/TS standard 210 prescribes general rules for packaging, conditioning and storage of essential oils that need to be followed. Accordingly, essential oils need to be stored in a clean, dry container that is glazed with aluminium, stainless steel or anti-actinic tinted glass and which is almost fully filled and sealed tightly. The air space in the container may possibly be filled with nitrogen or some other inert gas. Storage instructions have to state that the container must be protected from heat and light. During storage of a cosmetic product that contains an essential oil, these precautions measures should be taken into account. Furthermore, severe incompatibilities may occur with some types of plastic packaging and this should be also considered. Sometimes, a suitable antioxidant may be mixed with an essential oil. In this case, the added substance needs to be mentioned to the customer at the time of sale or use of that particular essential oil [18].

2.1.6 Effect of essential oils

It is known that essential oils pose various biological activities, such as analgesic, antiseptic, antimicrobial, carminative, diuretic, spasmolytic, hyperemic and stimulatory. When used in adequate concentrations, most essential oils exert antimicrobial and antifungal effects. For this reason, cosmetic preparations (creams, gels, ointments) which are exposed to the risk of being contaminated with germs or bacteria do not require an additional chemical preservative if they contain an essential oil as active substance (e.g. rosemary oil, eucalyptus oil) [19].

2.1.7 Side effects of essential oils

Essential oils and drugs containing essential oils including cosmetics and spices have a significant role in causing allergic reactions. Externally, they may cause contact dermatitis, and when taken oral, they may cause food allergies [20].

Table 1: Analyses program for quality assurance of essential oils [1]

Profile	The parameters to be determined
Organoleptic Evaluation	• Appearance • Color • Odor
Physical Analysis	• Specific gravity at 30^0C • Refractive Index at 25^0C • Optical rotation with 100mm cuvette • Melting or congealing point
Chemical Analysis	• Acid value • Ester content • Saponification value • Acetyl value • Free alcohol content (as free single substance like geraniol) • Combianed alcohol (e.g citronellol, geraniol, nerol) • Total alcohol content • HLB value (stearoptene, paraffine)
Values of Toxicological Relevant Substances	• Phenol value • Peroxide value
Contents	• Different GC/MS • HPLC/MS,Ion Chromatography • C-13 Analytic, Enantiomer-Analytik

3. Allergy contact dermatitis

Allergic contact dermatitis, also called contact allergy, is a form of contact dermatitis developed due to an allergic response to an allergen after it came in contact with the skin. It is a hypersensitivity reaction which occurs 48–72 hours after exposure to the allergen. CD^{4+} T-lymphocytes recognize an antigen on the skin surface and release cytokines which then activate the immune system. As immune response, dermatitis is developed. Most common symptoms of contact dermatitis are inflammation of the skin, skin redness and itchy blistered as well as dry and thickened skin. These symptoms can affect any area of the body but most commonly hands and face. Contact dermatitis can be developed by jewellery due to nickel contact allergy or due to fragrance contents in cosmetics and household products but also due to acrylates used in hair extensions and nail cosmetics. Sometimes contact allergy occurs after a certain chemical has been applied to the skin and then exposed to sunlight. This is called photo-contact dermatitis [21].

Two case reports described patients which developed phototoxic skin reactions within 48 to 72 hours after they came in contact with bergamot aromatherapy oil and then were exposed to ultraviolet radiation: A 54-year-old Austrian woman developed facial phototoxic reaction followed by red and oedematous lesions after having applied bergamot aromatherapy oil for few days and later being exposed to sunlight. Using high-performance liquid chromatography (HPLC) the bergamot aromatherapy oil preparation was identified to contain a higher concentration of bergapten (5-MOP) than allowed in cosmetics and tanning agents (0.1 ppm) in Austria. Another 41-year-old patient was treated with bergamot aromatherapy oil in a sauna. When visiting a tanning salon, the patient was exposed to ultraviolet radiation which caused a photocontact dermatitis [22].

The cause of allergy contact dermatitis is commonly determined by using patch test (contact delayed hypersensitivity allergy test). Small patches containing small amounts of potential allergens are applied to the patient's skin. After 48 h, they are removed to observe the skin for allergic reactions. If a patient is allergic to any of the test substances, a red, itchy bump will appear on the skin. The patch test is repeated but then interpreted 72 to 96 h after application [23].

4. Cosmetics

Cosmetics and personal care products became an integral part of everyday life. There is a variety of cosmetics and personal care products on the market for the purpose of cleaning,

nourishing, beautifying and perfuming of the human body in order to protect, retain improved condition of the body and to promote its attractiveness.

EU Cosmetics Regulation (Regulation (EC) No. 1223/2009) defines cosmetics as „any substance or mixture intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours" [24].

Cosmetics and personal care products can be categorized in seven groups – oral care, skin care, sun care, hair care, decorative cosmetics, body care and perfumes [25].

4.1 Cosmetics and essential oils

Essential oils are very often used in cosmetic products as they offer various benefits. One of the main reasons why they are used together with fragrance substance is to give a pleasant aroma to cosmetic products. Fatty acids, fatty oils, surfactant and plant extracts are often used during the production of cosmetic products. Since these ingredients have an unpleasant odor, an effective perfume mixture is added to a cosmetic product in order to mask it. If a cosmetic product is not labelled as "fragrance-free", "contains no perfume" or "scented –free" it can be assumed that the product contains fragrance chemicals [26].

As essential oils and fragrances can be sources of potential allergens, experts gathered at the IFRA (International Fragrance Association) defined which essential oils and which components of them represent a potential allergy risk. They have also determined the maximum concentration of them in order to produce safe cosmetic products [27].

Annex II and Annex III of the EU Cosmetics Regulation settle the use of essential oils and their single compounds in cosmetic products. It states that potential allergen substances must be declared on the packaging. Twenty-six possible allergenic fragrances have been defined, 18 of which can be found as ingredients of essential oil (Table 2). For this reason, they must be declared on the packaging or in the information leaflet if the concentration of these allergenic fragrances is higher than the permissible concentration of 0.01% in shower gels and baths (rinse- off products) and higher than 0.001% in body oils, massage oils and creams (leave on products) [28]. The

Cosmetic Directive also requires that a product containing other fragrances, these must also be labeled as aroma, fragrance, or perfume.

In a recent study Bennike and co-workers investigated the exposure of the general population to these 26 fragrances contact allergens. The study was conducted on 5.588 cosmetic products. A new non-profit smartphone application was used to identify the compounds. It was designed to provide users with information about the chemical substances of their cosmetic products. 85.5% of the tested products contained one of these 26 fragrance allergens, 73.9% of the products contained at least two or three of them. Among all investigated products linalool (49.5%) and limonene (48.5%) were most often labelled. 5.9% of investigated products had one or more of the 26 allergens labelled, but did not mention "perfume/fragrance/aroma" on the label. Additionally, hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lycral®) was found in 13.5% of the tested deodorants [29].

A retrospective study based on data from the Department of Dermatology and Allergology, Copenhagen University Hospital Gentofte, investigated the frequency of sensitization to these 26 individual fragrances. 1508 eczema patients were patch tested and 115 (7.6%) patients developed a positive reaction to at least one of these ingredients. 60.9% patients reacted positive to one substance when patch tested while 39.1% of patients had a positive reaction to more than one allergen. In a total of 196 patients (13.0%) a sensitization to a fragrance ingredient was determined when all of the fragrance screening markers (Lycral®, Fragrance Mix I, Fragrance Mix II, and *Myroxylon pereirae*- balm of Peru) were included [30].

The obligatory labelling of the 26 allergens on cosmetic products is highly important as it helps to optimize the diagnosis of contact allergy to fragrance ingredients. For a patient with diagnosed contact allergy to one of these 26 fragrances, it is of great importance to be informed whether the desirable product contains the allergenic fragrance since it could lead to reoccurrence of allergy symptoms [31].

Table 2: List of 26 fragrances in accordance with EU Directive

Fragrances
Amylcinnamal
Amylcinnamyl alcohol
Anisyl alcohol
Benzyl alcohol
Benzyl benzoate
Benzyl cinnamate
Benzyl salicylate
Cinnamyl alcohol
Cinnamal
Citral
Citronellol
Coumarin
Eugenol
Farnesol
Geraniol
Hexyl cinnamicaldehyd
Hydroxy-citronellal
Hydroxy-methylpentylcyclohexenecarboxaldehyde
Isoeugenol
D-Limonene
Linalool
Methyl heptin carbonate
3-Methyl-4-(2,6,6-tri-methyl-2-cyclohexen-1-yl)-3-buten-2-one
Oak moss and treemoss extract
Treemoss extract
2-(4-tert-Butylbenzyl) propionaldehyde

5. Essential oil vs. other plant extracts

According to ISO an essential oil is a product manufactured by either water- or vapor distillation or by mechanical processing of citrus rinds or by dry distillation of natural ingredients. In practice, in addition to natural oils of herbal origin, synthetic essential oils are becoming more and more important. Synthetic oils can be identical to natural oils and in this case, they are called "natural identical essential oils" or they can be synthetic oils. Essential oils used for medical purposes are natural essential oils whose composition meets the Pharmacopoeias standards for quality. Natural identical essential oils are only approved by Pharmacopoeia when it comes to mono substances, as it is the case with vanillin, thymol or camphor. Pure synthetic oils are most often used in the perfume industry.

Pharmaceutical products whose composition is almost the same as the composition of cosmetics, such as bath salt and bath oil, are allowed to contain natural or synthetic essential oils [32].

In scientific literature the term essential oil can often be found incorrectly used for numerous of products extended from plant material by methods other than distillation or cold pressing.

Absolutes, aromatic waters and concentrates are some of those products which are produced from plant material but are no essential oil. These products are often used either as part of a cosmetic product or as cosmetic product like aromatic water. These hydrolates are aqueous solution of the essential oil that remains after steam distillation of the plant material (e.g.”rose water”).

Concretes are products extracted from fresh plant material with solvents such as hexane or supercritical fluids such as CO_2, which are then partly or totally removed. Steam distillation is considered not to be suitable for some products obtained from flowers and other plant materials since they contain compounds which are sensitive to high a temperature which is the case with jasmine, narcissus, and violet leaves. Concretes are also used for the production of absolutes. Absolutes are products obtained mainly from concretes, resinoids, supercritical fluid extracts, or pomades by using ethanol as solvent. These products contain all fragrance compounds and also some fatty compounds. Absolutes are widely used in the fragrance industry. Most important are jasmine and violet leaf absolutes [33].

6. Essential oils in cosmetics

The present review provides an update on side effects and allergy contact dermatitis caused by selected essential oils and their compounds that are often added to cosmetic- as well as household-products and therefore appear in our everyday lives.

6.1 Helichrysum italicum oil – Immortelle

Helichrysum italicum essential oil is a pale yellow to red, oily liquid with a strong, honey-like aroma. The flower of *Helicrysum italicum* (Roth) G. Don does not wither and the lively color stays even if the flower is collected and dried. Therefore, it is called "Immortelle"- immortal. In Europe, the oil has mostly been used as an infusion or as tea to treat respiratory tract infections such as asthma and chronic bronchitis and it has also been applied against headache, migraine, skin burns and allergies. Nowadays, immortelle is one of the most popular essential oils in cosmetics as it stimulates the blood circulation in the skin, strongly regenerates the skin and helps to reduce the appearance of fine lines and wrinkles. Due to its scent, immortelle essential oil is used as a fragrance in soaps, cosmetics and perfumes [34]. Several studies on composition of *H. italicum* essential oil can be found which varies according to geographical regions: *H. italicum* oil collected in Montenegro was characterized by a high number of oxygenated monoterpenes (43.9%) and sesquiterpene hydrocarbons (41.2%). GC/MS analysis identified neryl acetate (28.2%) and γ-curcumene (18.8%) as the main compounds while neryl propionate (9.1%) and ar-curcumene (8.3%) existed in significantly lower concentrations [35]. Oil extracted from *H. italicum* collected in Greece contained high amount of geraniol and geranyl acetate [36]. Furthermore, three different chemotypes for the essential oils of *H. italicum* were described: one was rich in nerol, another contained the majority of α- and β-selinene and the third chemotype was characterized with high concentration of γ-curcumene [37].

Despite this large diversity of its chemical contents, several studies have shown that immortelle oil has an antimicrobial and antifungal activity [38]. It has been effective against bacteria and fungi that can cause skin irritations, infections and delay wound healing. A very strong hematoma-dissolving effect makes immortelle oil one of the best effective oils in treatment of hematomas [39]. In one study a contact toxicity test was performed with six essential oils (*Achillea*

millefolium, Myrtus communis, Rosmarinus officinalis, Helichrysum italicum, Foeniculum vulgare and *Lavandula angustifolia*) against the stored food insect *Sitophilus zeamais* Motsch. Essential oils of *A. millefolium*, *L. angustifolia* and *F. vulgare* showed highest toxicity at any concentration while *H. italicum* essential oil showed low toxicity rate up to a dosage of 0.5 mL per insect [40].

6.2 Lavender essential oil

Lavender essential oil is a clear, colorless to pale yellow liquid with a characteristic odor which is extracted by steam distillation from the flowering tops of *Lavandula angustifolia* Mill. According to ISO standard, the oil should contain linalyl acetate (25-47%), linalool (max. 45%), terpinen-4-ol (max. 8%), camphor (max. 1.5%), limonene (max.1%) and 1,8-cineole (max. 3%) [41].

There are two varieties of lavender essential oil:

- **Lavender essential oil**, the classic lavender, is distilled from the flowers of *L. angustifolia.* It has a sweet floral aroma and contains a high percentage of esters, mostly linalyl acetate. It does not contain camphor which distinguishes it from other lavender varieties. The oil is often used for its anti-inflammatory, calming, headache relieving, sedative and skin healing properties. One of the rarely known effects and qualities of *L. angustifolia* oil is its ability to relieve menstrual pain. One research study used a 2% dilution of lavender essential oil which was massaged on the abdominal area [42]. In another investigation lavender oil was inhaled [43]. Both clinical trials stated statistically significant differences in the lavender test groups regarding lavender oil's effect on menstrual cramps.

- **Spike lavender essential oil** is obtained from flowers of *L. latifolia* Medik. This species of lavender contains high percentage of 1,8-cineol and camphor and therefore has a strong camphoraceous odour. Due to these components, spike lavender oil is recommended for skin damages (cuts, burns, stings), as a pain reliever, for headache treatments and for its antimicrobial properties [45]. It has anti-bacterial, antiviral, antimycotic, anti-inflammatory and nourishing properties and is one of most common used and best investigated oil in aromatherapy. It is used for relaxing and stress relief, for nose and throat

infections, for skin care, in wound treatments and for stomach problems. It has a pleasant aroma. Lavender oil is also commonly used in pharmaceutical products and as a fragrance ingredient in soaps, cosmetics and perfumes [44].

In Japan, a study was conducted over nine years to estimate the tolerability of lavender oil. Contact dermatitis was diagnosed with patch tests. The results were positive to lavender oil in 13.9% patients [45]. One case described photoallergic contact dermatitis caused by lavender oil in topical ketoprofen, administered in Fastum® gel. A 45-year-old patient suffered from erythematous and itching plaque which started on patient's left foot and then spread onto the left leg. The patient was patch positive to 2% lavender oil and to Fastum® gel which indicated that lavender oil caused photoallergic contact dermatitis and ketoprofen caused contact dermatitis [46]. One review article summarized 19 publications on allergic contact dermatitis caused by lavender oil. In some of these case reports, patients allergic to lavender oil also showed positive patch test results to linalool [47].

As aforementioned, main components of lavender oil are linalool and linalyl acetate, which are easily oxidized when exposed to oxygen as it happens when the oil is applied onto skin. The oxidized fragrance increases the irritancy on the skin. One study using 6% oxidized lavender oil investigated the frequency of contact allergy caused by oxidized lavender oil. 2.8% of the patients had positive reactions to oxidized lavender which indicated that oxidized compounds of lavender oil are a common cause of contact allergy [48].

6.3 Matricaria recutita oil – German chamomile oil

Essential oil of German chamomile is one of the most used essential oil in cosmetics. The blue chamomile oil is steam distillated from the flowers and flower heads of *Chamomilla recutita* L. (Syn. *Chamomilla recutica*, *Matricaria recutica*) [49]. During steam distillation process, colorless proazulene forms matricin, matricarin, guajazulen and chamazulene, which is responsible for the blue color of the essential oil [50]. The oil has a sweet herbaceous odor and bitter aromatic flavor. When exposed to air, the light oil changes its color to brown. It contains a high percentage of sesquiterpene and a low amount of monoterpenes. Important components are β-farnesene, farnesol, chamazulene, α-bisabolol oxides A and B which are responsible for anti-inflammatory, antiphlogistic, spasmolytic and antiseptic properties of the oil. Chamomile oil is often adulterated

with cheap pure bisabolol extracted from *Vanillosmopsis erythropappa* (DC.) Sch.Bip., which can be detected by IRMS and GC-IRMS [51].

The oil can be used for the treatment of different health problems such as migraine, nerve problems and digestive problems. It is often used external in skin-creams, skin oils and added to bath as it is considered to be effective in the treatment of skin inflammation. It can also be found in mouthwash-products, toothpastes, decorative cosmetics and shampoos [52].

Lee and coworkers determined the antipruritic effects of chamomile essential oil in relieving atopic dermatitis symptoms. Patients in essential oil group experienced a lower scratching frequency compared to patients in control group [53]. Perisomal skin problems can cause numerous of unpleasant symptoms such as skin discoloration, pain, full-thickness wounds and itching. Patients are often treated with topical corticosteroid preparations whose long-term-use can cause serious side effects. One study was conducted to compare the effects of a German chamomile extract and 1% topical hydrocortisone ointment in colostomy patients diagnosed with perisomal skin lesion. The results implicated that German chamomile oil can be recommended in treatment of peristomal skin lesions as it showed anti-inflammatory and antipruritic effects [54].

A randomized controlled clinical trial exerted that topical application of chamomile oil to patients diagnosed with knee osteoarthritis was effective as patients used less of acetaminophen, a known pain reliever. In this study, no adverse reaction to essential oil of *M. recutita* was reported [55]. Despite the fact that German chamomile oil is most commonly used in cosmetics and personal care products, barely any reports of contact allergy or allergic contact dermatitis have been described in the scientific literature [56].

6.4 Neroli essential oil

Neroli essential oil is extracted from the flower of *Citrus aurantium* var. *amara* L., also known as bitter orange. It is an extremely expensive essential oil since for the production of 1kg of oil, 850 kg of bitter orange flowers are necessary [57]. The citrus tree produces three different kinds of essential oils. Neroli essential oil is steam-distilled from the flower, petitgrain oil is produced from the leaves and orange oil comes from the orange peel [58]. Neroli is a pale yellow to coffee brown essential oil with a sweet, fresh and floral odour. Due to its very fine fragrance, it is one of the most important oil in perfume and soap industry. The oil has antidepressant, antiseptic, carminative, antispasmodic and sedative properties. Ammar and coworkers reported that this oil

had strong antimicrobial properties, especially against *Pseudomonas aeruginosa*, and also strong antifungal properties, when compared to antibiotic Nystatin [59]. In cosmetics products, it is used to refresh the look of a tired skin, for sensitive skin but also for oily skin [60].

A comprehensive two-dimensional GC-TOF-MS identified terpenoid compounds, such as linalool, β-pinene, α-terpineol, (+)-limonene, sabinene, nerol, nerolidol, linalyl acetate and α-pinene as main chemical compounds of neroli essential oil [61].

In one study, 83 patients with hypertension or prehypertension inhaled either an aromatherapy mixture of neroli, ylang-ylang, marjoram and lavender essential oils or a placebo. Results showed that the patients exposed to aromatherapy experienced a significant decrease in blood pressure compared to patients in the placebo group [62].

Neroli essential oil is generally recognized as nonirritant, non-sensitizing and non-phototoxic oil, but it does contain known allergens [63]. However, occupational contact dermatitis was reported due to use of essential oils including neroli essential oil [64]. From May 2001 to June 2002, Belgian Contact & Environmental Dermatitis Group investigated 20 patients suspected of developing dermatitis caused by Fastum® gel with open patch and photo-patch tests. Fastum® gel base contains 5% of lavender oil and 5% of neroli oil in alcohol and 2% lavender oil and 2% neroli oil in in white petrolatum. The results showed that three patients out of 17 had positive photo-patch test and two patients had positive patch test to 5% neroli oil in alcohol. Out of 20 only one patient showed positive photo-patch test to 2% neroli oil in white petrolatum [65].

6.5 Peppermint oil

Peppermint essential oil is extracted from *Mentha piperita* L., a cross between watermint (*Mentha aquatic* L.) and spearmint (*Mentha spicata* L.) [66]. The main active ingredients of peppermint oil are (-)-menthol (33-55 %) and (-)-menthone (14-33%). Other chemical compounds are 1,8-cineole, methyl acetate, methofuran, isomenthone, limonene, β-pinene, α-pinene, germacrene, *trans*-sabinene hydrate and pulegone [67]. Peppermint oil is commonly used as a fragrance in soaps, cosmetics and as spice since it possesses a fresh, minty and cooling effect due to menthol. Added to bitter tasting capsules, peppermint is able to mask the bitterness when orally applied [68]. Due to this flavoring property, peppermint is often found in chewing gums, toothpastes and mouthwashes. For medical use, peppermint oil can be taken orally as dietary supplements for gastrointestinal complications such as irritable bowel syndrome [69].

One case report described four patients with allergic contact cheilitis (inflammation of the lip) after being exposed to peppermint oil contained in a lip balm product. The patients' lips and the skin around the lips were inflamed. The lip balm product which they were using contained potential allergens such as lanolin, propolis, coconut oil, almond oil, vitamin E and peppermint oil. The patch-test results were positive to peppermint oil and indicated that peppermint oil was the most likely cause of allergic reactions in these patients [70]. Another case report noted allergic contact cheilitis caused by menthol in a toothpaste and throat medication [71]. In the period of 2000-2009, positive patch test reactions or positive usage tests to the patients' own cosmetic products were investigated. In this nine-year period one patient had positive reactions to peppermint oil which was contained in his cosmetic product [72]. Furthermore, there was one report on allergic contact dermatitis due to use of a product for depilation which contained peppermint oil [73].

6.6 Rosemary essential oil

Rosmarinus officinalis L., also known as rosemary, is an aromatic plant which belongs to Lamiaceae family and is native to Mediterranean region. Rosemary essential oil is produced by steam distillation from the flowering tips of the plant yielding a colorless to pale yellow liquid with a strong, warm, woody, balsamic aroma. The main chemical compounds in rosemary essential oil are eucalyptol (19.4%) and α-pinene (14.7%). Camphor (9.5%), bornyl acetate (9.1%), camphene (6.9%), β-pinene (6.7%), β-myrcene (5.8%), (+)-limonene (5.2%), and borneol (5.0%) are also found in the oil [74]. Due to its stimulating effects, it is widely used in aromatherapy. Rosemary forms three different chemotypes depending on their location, climate and environment: α-pinene chemotype, camphor chemotype and 1,8-cineole chemotype. As such, they have different chemical and physical properties. The composition of 1,8-cineole chemotype was analysed with GC/MS and three main compounds were identified: α-pinene (37-40%), camphor (41.7-53.8%) and 1,8-cineole (58.7-63.7%). The camphor chemotype contains 41-53% of camphor while α-pinene chemotype contains 37-40% of α-pinene [75].

Rosemary essential oil is often an ingredient in bath salts, bath oils, liniments, gels and ointments. It can also be found in cosmetic products such as lavender water, cologne water and as fragrance in soaps [76]. The essential oil of rosemary is widely used for hair care as it nourishes the hair, promotes hair growth and helps against dandruff. It is also recommended in hair-loss

treatment as it is believed that it has similar function to Minoxidil, an antihypertensive vasodilator medication, which revitalizes hair follicles that are damaged. Rosemary oil widens blood vessels and opens them and makes blood and nutrients more available to the follicles which are then stimulated into producing new hair. In 2015, one study conducted on patients with pattern hair loss (androgenic alopecia) compared the effectiveness of rosemary oil vs. 2% Minoxidil in the treatment of androgenic alopecia. It was discovered that rosemary oil was as effective as 2% Minoxidil and that patients in the rosemary group experienced less side effects compared to patients in the Minoxidil group [77].

Allergic contact dermatitis due to rosemary oil has been reported in a few publications. Three of them were related to the essential oil from rosemary. An aromatherapist, a physiotherapist and a masseur were diagnosed with occupational contact dermatitis due to exposure to rosemary oil [78].

6.7 Rose oil

Rose oil is extracted from the flowers of the *Rosa* x. *damascena* Mill., also known as damask rose as the flower was initially brought to Europe from Damascus. The literature often mentioned different variety of rose flower essential oil extracted from different rose species such as *R. canina*, *R. centifolia*, *R. galica*, *R. moschata* and *R. rugosa*. However, most of commercial rose oil is produced from *R. damascene* including rose oil produced in Bulgaria and Turkey which are world's biggest producers of rose essential oil. Rose oil is widely used as a fragrance in different types of cosmetic products (soaps, body lotions, face creams etc.) and also as flavoring agent in food products such as jam, ice cream, pudding and yogurt [79].

Next to rose oil, rose absolute, rose water and rose concrete are important basic materials in cosmetic industries. For the production of 1 kg of rose oil 3500 - 4000 kilograms of rose flowers are necessary. Due to its expensive industrial production and also to high importance in cosmetic industry, rose oil is often called "liquid gold" [80]. The most common chemical compounds present in essential rose oil obtained from *R. damascena* are citronellol, geraniol, nerol, farnesol and rose oxide, which is a fragrance attributed to rose [81-82].

Mohamadi and co-workers investigated the effect of storage on essential oil content and composition of *R. damascena* under different conditions. The authors concluded that it was better to use fresh petals for essential oil production. As the petals collected in large amount cannot be

steam distilled all together at the same time, some parts of the petals can undergo various fermentation processes until distillation which influences the rose oil composition. Therefore, it is important to store petals until the time of distillation and to freeze them without water, which has been proven to be the best storage method [83].

The pharmacological properties of *R. damascena* are numerous including hypnotic, analgesic, and anticonvulsant, antidiabetic, antimicrobial, anti-HIV, anti-inflammatory and antioxidant effects. Furthermore, in Persian traditional medicine essential oil of *R. damascena* has been used for treatment of male sexual dysfunction as also for libido stimulation. It is considered that lipophilic constituents of *R. damascena* was responsible for most of these effects [84]. Due to its antibacterial properties, it is very effective in moisturizing dry skin and it is often recommended for acne treatment. Rose oil cleanses the skin from bacteria that causes acnes and then hydrates the skin.

Four cases of allergic contact dermatitis to essential oils occurred in three aromatherapists and in one chemist with a particular interest in aromatherapy. Patch tests in all four cases were positive to 2% Bulgarian rose oil, which makes it the only oil to which all four patients were positive [85]. In general, patch positive reactions were reported in persons working with the essential oil. Geraniol and citronellol are considered to be most relevant allergens [86].

6.8 Tea tree oil

Tee tree oil, also known as melaleuca oil, is the essential oil obtained by distillation from leaves and terminal branchlets of *Melaleuca alternifolia* (Maiden et Betche) Cheel (narrow-leaf tea tree), *M. linariifolia* Smith (flax-leaf tea tree) or *M. dissitiflora* F.Muell (creek tea tree).

M. alternifolia, Australian tea tree, is either a tall shrub or small tree which belongs to the Myrtaceae family and is native in the coast of New South Wales and Queensland, Australia [87]. It has been used by the Aborigines in traditional medicine. They crushed tea tree leaves in order to extract the oil, which was then inhaled for treatment of coughs and colds or applied directly onto the skin for healing. It has antiseptic, antifungal and anti-inflammatory properties and its dilution is used as topical antiseptic for the treatment of acnes [88].

Tea tree oil is a clear, colorless to pale yellow, volatile liquid and has a characteristic, intensive aromatic fresh camphoraceous odour. α-Pinene, β-pinene, sabinene, myrcene, α-phellandrene, α-terpinene, limonene, 1,8-cineole, p-cymene, linalool, terpinen-4-ol and α-terpineol

are the most common chemical compounds found in tea tree oil [89]. In order to be defined as "tea tree oil", it must contain the following 15 components in specified levels, according to the ISO standard given in Table 3 [90].

In the presence of oxygen, high temperature, light and humidity the composition of tea tree oil changes and antioxidant compounds α-terpinene, ɣ-terpinene and terpinolene are converted to p-cymene. As it is sensitive to oxidation, European Cosmetics Association recommended that presence of tea tree oil in cosmetic products should not exceed the concentration of 1% and that it should be specially packed to secure minimal light exposure. Tea tree oil targets Gram-positive and Gram-negative bacteria such as *Staphylococcus, Streptococcus* and *Pseudomonas aeruginosa*. It is also effective against *Candida albicans, Dermatophytosis* and *Herpes simplex* virus. Applying 5% tea tree gel to acne lesions was more than threefold as effective in reducing the number of lesions than a placebo [91].

Tea tree oil is also used in the treatment of fungal nail infections. It can be used as a chemical-free mouthwash since it helps to fight bad breath and dental plaque. Several studies suggest that tea tree oil might be effective against germs that cause tooth decay and bad breath [92-93]. If administered orally, tea tree oil is toxic. One case report noted that an 18-month-old boy suffered serious injuries after accidentally swallowing tea tree oil [94]. One study compared the effects of different treatments for contact dermatitis and tea tree oil. Tea tree oil reduced symptoms by 40% was more effective than standard medications used on the skin. Surprisingly, there have been many case reports of allergic contact dermatitis, the conditions that tea tree oil may help to treat, reported as a cause of using tea tree oil [95]. One case report noted that five patients developed allergic contact dermatitis due to topical application of tea tree oil [96]. A review article which summarized chemical compounds but also case reports and case series of contact allergy to tea tree oil, stated that of all essential oils, tea tree oil has caused the most allergic reactions with the first case reported in 1991 [97]. It is worth mentioning that the use of tea tree oil in pets may be unsafe: more than 400 dogs and cats developed tremors and other problems of the nervous system after administration of 0.1–85 mL of tea tree oil orally or onto the skin [98].

Tabel 3. ISO 4730 (2004) – Tea tree oil composition

Component	Concentration
Terpinen-4-ol	30–48%
γ-Terpinene	10–28%
1,8-Cineole	traces-15%
α-Terpinene	5–13%
α-Terpineol	1.5-8%
p-Cymene	0.5–8%
α-Pinene	1-6%
Terpinolene	1.5-5%
Sabinene	traces-3.5%
Aromadendrene	traces-3%
δ-Cadinene	traces-3%
Viridiflorene	traces-3%
Limonene	0.5-1.5%
Globulol	traces-1%
Viridiflorol	traces-1%

7. Individual fragrances

7.1 Anethole

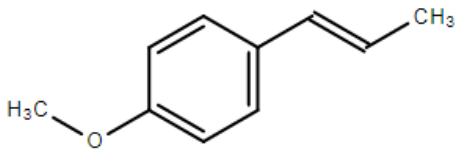


Figure 2: Chemical structure of *trans*-anethole

Anethole is a phenylpropane derivative and the main aromatic component of anise, anise myrtile and fennel oil. It can also be synthetically obtained. Anethole exists as *cis* and *trans* isomers, but the *trans* isomer is used more often. Anethole can have form of white crystals or a liquid. It has a sweet taste and pleasant odor of anise oil [99]. Anethole has antibacterial, antifungal, antispasmodic and mucokinetic properties and is often used as an expectorant and carminativum. Since it is thirteen-fold sweeter than sugar, it is widely used as the flavoring agent in alcohol drinks, ouzo and raki and in cosmetic products for oral care. It is also used as fragrance in soaps and as flavoring agent in pharmaceutical products. In some perfumes, the fennel fragrance can often be found while star anise fragrance is used in detergents [100].

There have been a few reports of allergy contact dermatitis reactions. A 63-year-old woman suffered from a six-year history of persistent cheilitis. The symptoms were pain, persistent itch and blistering lips. The patient did not use any lipsticks but she was using lip balms and toothpastes produced in China. The ingredients were not listed on the package of the toothpaste. Patch test showed a positive reaction to anethole, which was found in the toothpaste [101]. Another 55-year-old female patient experienced cheilitis for three months. The patient complained about crust on her lips, intra-oral burning sensation, dry mouth and loss of taste. She was patch tested to cosmetics, dental products, fragrances and bakery product series and to her own toothpaste. The patch test was positive to anethole and *trans*-anethole. On all of her dental care products, “aroma” was listed as an ingredient. The producers of oral products she used revealed that almost all of them contained anethole [102]. Recently a similar case report indicated a 15-year-old girl with perioral dermatitis

due to usage of toothpaste. Patch test reaction was positive to anethole. On the toothpaste, “flavour“ was listed as only ingredient, which was later confirmed to be anethole by the manufacturer [103].

7.2 Bisabolol

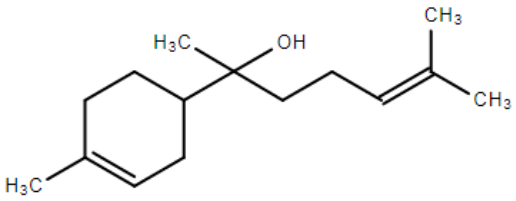


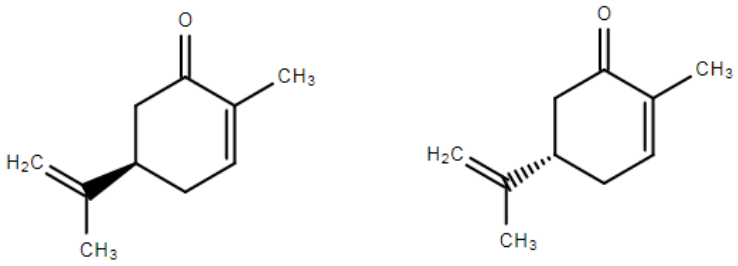
Figure 3: Chemical structure of α-bisabolol

α-(−)-Bisabolol, also called levomenol, is a monocyclic sesquiterpene alcohol which is one of the main active compounds found in essential oil from German chamomile (*Matricaria recutita*) [104]. It is a clear, pale yellow liquid which is slightly soluble in water and glycerin but well soluble in ethanol. α-(+)-Bisabolol is an enantiomer which is very rare in nature. Bisabolol can also be produced synthetically as racemic mixture. Due to its pleasant sweet floral odor, it is used in fragrances and in personal care and cosmetic products. Bisabolol has anti-inflammatory, healing, soothing, and anti-microbial properties and it is often a component in moisturizers, sun creams, face creams, cleansers and lipsticks [105].

One case report described seven paediatric patients with a history of intolerance to moisturizers that contained bisabolol. Atopic dermatitis was reported by six patients, while in 14 patients a patch test was performed with 0.5 % and 1% bisabolol (three patients) and with 1% and 5% bisabolol in petrolatum. The patients were also patch tested for other moisturizer components. Results showed that four patients were patch positive to 1% and 5% bisabolol. Bisabolol positive patients reacted also positive to Compositae Mix. The rest of the 16 patients with intolerance to the same moisturizer had no positive reaction to patch testing with 1% and 5 % bisabolol [106]. In another report, a 14-year-old girl suffered from acute cheilitis over a period of two months. She complained about her red and very dry lips after she had been using a lip care stick a few times per day for two months. Patch tests were performed on patient with the European baseline series and

with the patient's own cosmetics. Patch test reactions were positive to the girl's lipstick and to Fragrance Mix I as well as nickel. A patch test was also performed with the ten ingredients of the stick released by the manufacturer. Two ingredients were patch positive: Bisabolol 5% pet. and Parsol® SL [107].

7.3 Carvone



R-(-)-carvone (spearmint) *S*-(+)-carvone (caraway)

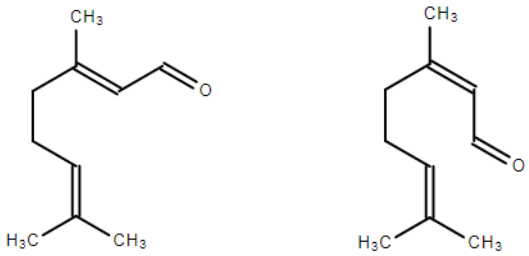
Figure 4: Chemical structure of both carvone enantiomers

Carvone is a volatile monocyclic terpenoid which can be found in many essential oils but it is mostly concentrated in caraway, spearmint and dill [108]. Carvone forms two enantiomers with different biological properties: (*S*)-(+)-carvone (= d-carvone) is found in caraway seeds and has a caraway odor. Its enantiomer (*R*)-(-)-carvone (= l-carvone), is found in mint leaves and is responsible for mint odor [109]. For thousands of years, both carvones have been used in spices and as flavoring agents in food products. (*R*)-(-)-carvone is a pale yellow to colorless, pleasant smelling liquid which is often added to liqueurs, toothpastes, chewing gums as well as to soaps and perfumes to improve their aromas. It is also widely used in aromatherapy and in complementary medicine [110].

Carvon is considered as a potential allergen since there have been several case reports of hypersensitivity of skin and allergy contact dermatitis due to (*R*)-(-)- carvone [111-113]. It is not obligatory to be labelled on cosmetic products according to European Cosmetics Regulation. A recent study performed in Sweden analysed a total of 66 toothpastes available on the Swedish market with straight-phase HPLC. The products containing limonene were also chosen since (*R*)-(-)-carvone can be produced from D-limonene by various methods. The results showed that (*R*)-(-)- carvone was found in 64 of 66 toothpastes with the concentration of 0.00005-0.35%. In ten toothpastes on which limonene was labelled, the concentration of (*R*)-(-)-carvone was higher than

0.1% [114]. One control study investigated whether contact allergies due to potential allergens were causing oral lichen lesions in patients exposed to variety of dental material. This study included 83 patients with oral lichen lesions and a control group of patients with dermatitis. Patients in both groups were patch tested and examined intraorally. The results indicated that patients with oral lichen lesions had developed contact dermatitis to mercury and carvone more often compared to patients with dermatitis, while the number of contact allergy to nickel and colophony was higher in the group with dermatitis patients. Therefore, carvone is suspected to be one of the main causes of oral lichen lesions. Hypersensitive patients with oral lichen lesions should be advised to avoid carvone-containing products for oral use [115].

7.4 Citral



Geranial (citral A) Neral (citral B)

Figure 5: Chemical structure of geranial and neral

Citral is a pale yellow liquid and can be obtained from lemongrass oil which contains 70 - 80% of this monoterpene. It is also found in other essential oils such as verbena oil, citronella oil, orange oil and lemon oil [116]. Citral can be synthetically produced from myrcene, ionone and methylionone. It is an isomeric mixture of two aldehydes, neral and geranial. Neral (citral B) is the (*Z*)-isomer, while geranial (citral A) is the (*E*)-isomer. Due to its pleasant lemon odor, it is widely used in perfumes and as a flavoring agent [117].

Several single cases of allergic contact dermatitis in masseuses working in the same health spa were reported by De Mozzi and Johnston. These nine massage therapist were directly exposed to the essential oil as they were massaging their clients. In all of nine masseurs which suffered from hand dermatitis, patch tests with British baseline series were performed. Six persons who had

positive patch test reactions were later diagnosed with allergic contact dermatitis. One person gave a positive reaction to Fragrance Mix I, five of the nine masseurs were positive to Fragrance Mix II and all nine had positive reactions to citral [118].

As a compound of Fragrance Mix II, citral is often patch tested and as such it is considered to be a potential allergen. Due to EU Cosmetic Regulation it has to be labelled on consumers products (Table 2).

7.5 Eugenol

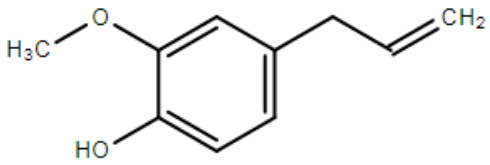


Figure 6: Chemical structure of eugenol

Eugenol is a pale yellow to colorless aromatic oily liquid. It is a cinnamate derivative of the shikamate pathway. It belongs to the chemical group of phenylpropanoides. Eugenol is the main component in clove essential oil (70-85%) and in allspice oil (60-90%). It can also be found in the essential oil of Ceylon cinnamon (10%) as well as in nutmeg, basil and pepper but in lower concentrations. As isoeugenol, eugenol is used for production of synthetic vanillin [119]. Eugenol is used in perfumes and also as a flavoring agent and in dentistry, due to its antiseptic and anesthetic properties. It can be mixed with zinc oxide and then used for temporary fillings [120].

A study was conducted to investigate antifungal activity of eugenol and essential oils containing eugenol (pimento oil, bay oil, clove oil, and cinnamon oil) against 38 clinical isolated strains of *Candida albicans*. The results led to the conclusion that antifungal effects of the investigated oils were strongly related with their concentration of eugenol [121].

Eugenol is hepatotoxic and can cause serious health issues when used in high concentrations. As a component in personal care and dentistry products, it can cause allergic reactions such as contact dermatitis and contact stomatitis. One case report described a 34-year-old woman who was diagnosed with occupational asthma and dermatitis due to eugenol in a cleaning product. She used a mop spray which contained chemical substances including eugenol.

After one month of using this spray, the woman developed maculopapular erythema on parts of her body which were exposed to the spray. Maculopapular erythema was also followed with other symptoms such as cough and dyspnea. After an antihistaminic treatment, the symptoms were reduced and after her holiday, all symptoms had vanished. A specific bronchial test was performed in a challenge chamber with 2 minutes inhalation of eugenol at the corresponding dilution. The patient showed positive spirometric reactions to eugenol and it was later considered as a main allergen [122]. Another case report noted a 53-year-old female patient who suffered painful oral mucosal lesions after she had received a new dental bridge. The patient was skin patched with the standard series recommended by the German Contact Allergy Group. The patient had no positive reaction to any of the tested substances at either 48 or 72 h after testing. Since it is often used in combination with zinc oxide in dentistry, eugenol as a single substance was tested and reaction was positive to eugenol after 72 h, a fact that revealed that eugenol caused delayed-type sensitization [123].

7.6 Farnesol

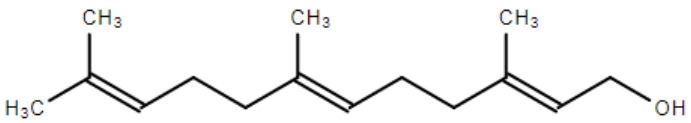


Figure 7: Chemical structure of farnesol

Farnesol is a sesquiterpene alcohol which is extracted from citronella oil, neroli oil, cyclamen oil and tuberose oil. It is a colorless to pale yellow liquid with flowery, weak-citrus odour and therefore it is used in aftershave lotions, cleansing products, colognes, deodorants, eye lotions, hair care products, moisturizers and skin care products. It is also used as co-solvent to regulate the volatility of the odorants, primarily in lilac perfumes. It can be also found in food as a flavoring agent, as an additive in cigarettes and due to its antibacterial properties in hygienic products [124].

Farnesol is a compound of Fragrance Mix II along with lyral, citral, citronellol, farnesol, coumarin and hexyl cinnamic aldehyde. Since farnesol has a strong allergen potential but is at the

same time a key ingredient in perfumes, EU Cosmetic Regulation requires that it has to be declared on personal care and cosmetic products (Table 2). A multicenter study that took place in Hungry investigated the contact hypersensitivity due to Fragrance Mix II and its compounds by patch testing a total of 565 patients. According to the results, 163 patients developed contact hypersensitivity due to one or more tested compounds of the mix. Patch tests were positive to Fragrance Mix II in 97 patients while contact hypersensitivity was noted to coumarin in 29 cases, to citral in 19 cases, to farnesol in 14 cases, and to citronellol in seven cases [125]. The published data indicate that farnesol has a sensitization potential but more data is required to determine whether farnesol alone is the main causative allergen in personal care and cosmetic products [126,127].

7.7 Geraniol

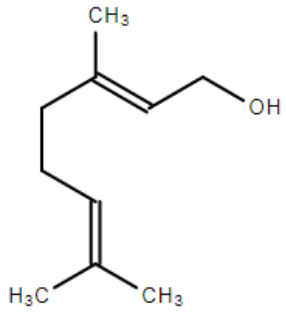


Figure 8: Chemical structure of geraniol

Geraniol is a monoterpenoid alcohol. It is a colorless to pale-yellow oily liquid that has a sweet rose, floral odour. It occurs naturally in rose oil, citronella oil and palmarosa oil but it can also be found in other essential oils like lemon, geranium, bergamot and lavender oil in lower concentrations. Due to its pleasant rose odour it is commonly used in perfumes, body lotions, creams, after shave lotions and hygiene products. Geraniol is also widely used as a flavoring agent to reproduce the flavor of fruits such as pineapple, raspberry, peach, grapefruit, plum, red apple, lime, watermelon, orange and lemon. As a flavoring agent it can be found in candies, ice creams and baked food products to improve the smell of the foods. Geraniol has antiseptic, antibacterial and anti-inflammatory properties [128].

As one of the 26 fragrances identified as a potential cause of allergy contact dermatitis by the EU Scientific Committee for Consumer Safety geraniol must be labelled on personal care products (Table 2).

Geranial and neral, two sensitizing compounds, are formed from geraniol by autoxidation and skin metabolism and they are considered as a possible cause of allergy reactions on the skin. Hagvall and co-workers tested the hypothesis that oxidized geraniol caused more cases of contact allergy dermatitis than pure geraniol. From January 2006 to August 2010, 2227 patients were patch tested with Swedish base line series. 14 out of 2227 patients were patch positive to one or more of the tested substances. From these 14 patients three were patch positive to geraniol, 11 reacted to oxidized geraniol, 11 to geranial, five to neral, and seven to citral [129]. In a follow-up study, they investigated the relationship between cross reactivity of citral and geraniol and allergic reaction to oxidized geraniol. The patients were tested for pure geraniol, citral mixture (66% geranial and 34% neral), geranial and neral. Patch test results showed that 19 of 655 tested persons reacted positive to one or more tested compounds. Out of these 19 patients, 13 reacted positive to geranial [130].

7.8 Limonene

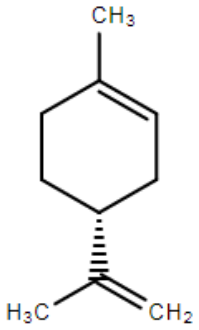


Figure 9: Chemical structure of (+)-Limonene

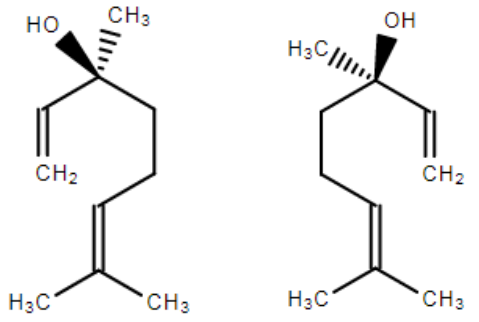
Limonene is a monoterpene and the component of the essential oil of oranges. At room temperature, it is a clear colorless liquid and it exists in two isomer forms: (*R*)-(+)-Limonene (= D-Limonene) and (*S*)-(-)-limonene (= L-Limonene). Limonene has a strong odour of orange and as such, it is widely used as a fragrance and flavoring agent in cosmetic products, pharmaceuticals,

perfumes and foods [131]. When exposed to air, it can be easily oxidized to carvone, carveole and limonene oxide, compounds that can cause skin irritation and dermal sensitization.

Several studies reported that the oxidation products of limonene were causes of allergy contact dermatitis [132]. In Spain 3639 patients were recently tested with three different concentrations of limonene, limonene hydroperoxides and linalool hydroperoxides. The results showed that 292 were patch positive to one or both hydroperoxides and out 187 of them (5.1%) developed positive patch reaction to limonene hydroperoxides [133].

Since hand cleansers and cleaning products often contain limonene, one study investigated allergy contact dermatitis caused by oxidized limonene in people who were often exposed to such products. From a total of 511 patients which were tested with oxidized limonene, 21 patients were patch positive to oxidized limonene. In 14 patients, occupational contact dermatitis caused by limonene was determined [134]. Additionally, in 2014 Christensson and co-workers summarized clinical data on 2900 patch tested patients with dermatitis in Australia, Denmark, United Kingdom, Singapore, Spain and Sweden. The results showed that 149 patients reacted positive to oxidized limonene [135].

7.9 Linalool



(*S*)-(+)–Linalool (*R*)-(-)–Linalool

Figure 10: Both stereoisomer forms of linalool

Linalool is naturally a monoterpene alcohol which can be found in many essential oils, such as spearmint, rose, cypress, lemon and cinnamon. Licareol or (*R*)-(-)-linalool and (*S*)-(+)-linalool, known as coriandrol are two stereoisomers of linalool. Linalool is a colorless to pale yellow liquid with a sweet odour similar to odour of bergamot oil and French lavender. It is used as fragrance in

air care, cleaning and laundry products and also in personal care products as well as a flavoring agent and insecticide [136].

During 2010 to 2015, 6004 patients with dermatitis were patch tested with the 26 fragrances (Table 2). Results from this cross-sectional study showed that out of 6004 patients, 940 were patch positive to one of these fragrances. Among these 940 patients, most of them showed patch positive reactions to linalool-hydroperoxides [137]. A recent case report described a 45-year-old woman from Sweden who suffered from an eczematous reaction after she wore Footner® exfoliating socks' (Nordic Consumer Health, Nacka Strand, Sweden) on both feet for one hour as it was stated in the instructions. She had used this product three times before and had not experienced any side effects. She was then tested with the Swedish baseline series and reacted patch positive to nickel sulphate, palladium chloride but also to oxidized linalool which was considered as one of possible sensitizers [138].

7.10 Menthol

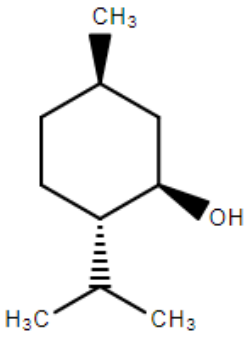


Figure 11: Chemical structure of (-)-menthol

(-)-Menthol, also known as levomenthol, is an organic compound extracted from peppermint or mint oils. In European pharmacopoeia, two menthol monographs can be found. One is naturally occurring (-)-menthol and the second is synthetically produced racemic menthol (*Menthol racemicum*). (-)-Menthol has sweet minty, cooling and fresh scent while (+)-menthol has a weak minty herbaceous scent. When applied topically, menthol expands blood vessels and has a refreshing cooling effect. As such, it relieves pain and symptoms of pruritus. (-)-Menthol reacts with TRPM8 thermoreceptors which are responsible for the cooling effect of menthol when it is

applied on the skin [139]. It has ten-fold stronger cooling effect on the human skin than (+)-menthol. Menthol is used as a flavoring agent in food and pharmaceutical products. In low concertation (0.1% -1%) as a part of topical preparations, menthol exerts antipruritic and anti-inflammatory properties is used for the treatment of pruritus and urticarial. In higher concentration (1.25% - 16%), it can cause skin-sensitizing and irritant properties [140].

Allergic contact cheilitis due to menthol content in toothpaste and throat medication has been reported. A 29-year-old male patient had eight-year history of erythematous, scaling and redness of the lips. Cheilitis started at both corners of the mouth and later spread to the upper and lower lip. The patient was treated with several medications but was never patch tested before. Patch test reaction was positive to menthol, peppermint oil and the menthol-containing throat spray. Semi patch test for his toothpaste which contained menthol was also positive [141].

Another 69-year-old patient developed anaphylactic reaction after he had consumed a peppermint candy. Symptoms were hard breathing, lip and tongue swelling, throat tightness and cough. A skin test was positive for menthol and peppermint oil and therefore considered as a cause of serious anaphylactic reactions. The patient was advised to avoid all products with traces of menthol and peppermint [142]. A case report of a two-month old infant that experienced an anaphylactic reaction after menthol containing-cologne was applied to his face was reported. The infant, which developed facial oedema, short breath and urticarial lesion, was treated with several medications but was never skin patch tested to menthol as the parents refused the further diagnostic. Parents were advised to avoid menthol containing products [143].

8. Perfume

8.1 Definition of Perfume

A perfume is a fragrant mixture which contains numerous ingredients such as essential oils which can be extracted from natural aromatic plants and/or synthetically produced aromatic compounds, fixatives and solvents. The main purpose of perfumes is to give a pleasant odour to the human body in order to increase attractiveness. They can be also found in foods and objects [144].

A perfume is a solution of perfume oil in 98 % ethanol and 2% water. Depending on the concentration of perfume oil in the solvent, there is a distinction between eau de toillete, eau de

perfume and eau de cologne. Eau de toillete and eau de perfume contain 7-10% of perfume oil dissolved in 80-90% ethanol with eau de toillete being less concentrated than eau de perfume. Eau de cologne contains up to 4% of perfume oil dissolved in 70-85% ethyl alcohol [145].

In perfumery, three fragrance notes have been described: top note, body note and end note. These three notes blend together to create a beautiful pleasant odour. Lemon, bergamot, grapefruit, lemongrass, geraniol and lavender are typical top notes while middle (body) notes include eugenol, jasmine and rose absolute. The end notes, as the final fragrances, often contain cedar wood, sandalwood, vanilla, amber and patchouli [146]. These odours are less volatile and as such they are responsible for a long-lasting appearance of perfume product.

8.2 Perfume Intolerance

Perfume or fragrance allergy can be defined as a sensation or an adverse reaction to chemicals in a perfume as also to fragrances contained in air fresheners, in personal care and in hygiene products, such as scented laundry products. Irritation due to strong scent can cause numerous side effects, especially in people with asthma or other respiratory illnesses [147].
Most common symptoms of perfume intolerance are:

- headache up to migraine attack
- skin irritation
- itching
- contact dermatitis
- allergic rhinitis
- inflammation of eyes

8.3 Antiperspirants and Deodorants

Antiperspirants are personal care products which contain compounds that control sweat and body odor effectively and are used as sprays, sticks, creams or roll-ons. When an antiperspirant is applied onto skin, its active compound aluminum salt dissolves in sweat, forms a gel on top of skin

pores which then reduce sweat liberation. At the same an antiperspirant has antimicrobial properties and as such, it reduces bacteria that cause unpleasant body odour.

Deodorants are hygiene products which contain only antimicrobial ingredients and therefore are only effective in preventing body odour but cannot reduce sweat. Since both products are used to prevent unpleasant body smell and to create fresh sense, they often contain perfumes and fragrances [148].

There have been several case reports of allergy contact dermatitis caused by antiperspirants and deodorants [149]. Heisterberg and co-workers investigated which cosmetic product caused most frequently fragrance allergy among eczema patients in Denmark. From January 2005 to June 2009 patients were examined by members of the Danish Contact Dermatitis Group. Patch tests were performed in all patients using baseline series. Baseline series included Fragrance Mix I and II, 5% hydroxyisohexyl-3-cyclohexene-carboxaldehyde (HICC) and 25% balsam of Peru in petrolatum. Patch tests were positive to one or more of the fragrance markers in 1790 tested patients. Out of these patients, 753 developed fragrance allergic contact dermatitis due to fragrance ingredients contained in cosmetic products. Furthermore, 966 different groups of cosmetic products were also tested. The results indicated that "leave on" products were almost three times more often (74.3%) responsible for allergic contact dermatitis when compared to "rinse-off" products (25.7%). Among all tested cosmetic products groups, deodorants were listed as products which caused fragrance allergic contact dermatitis most commonly [150].

9. Conclusions

Essential oils and their fragrance compounds are a very important part of perfume and cosmetic industry as they can serve as natural or natural-like chemical preservatives and, at the same time, offer various benefits for skin and body. Additionally, these chemicals increase the value of cosmetic products due to their pleasant odour. The cosmetic and perfume industry therefore are unimaginable without these precious substances. However, it should be taken into account that essential oils and their components could cause allergic reactions and symptoms. These reactions can be gleaned in the scientific literature. According to de Groot and Schmidt, 79 different essential oils have caused contact allergy or allergic contact dermatitis until 2015 [151]. Most of the reports described only single cases of allergy contact dermatitis caused by essential oils and many of the studies were performed on persons whose allergic potential was above average as well as on patients suffering from dermatitis or other dermal diseases. For these individuals, the application of cosmetic care products or perfumes containing potential allergens might be a risk. Therefore, the labelling of potential allergens is mandatory to enable persons with skin problems to avoid products containing critical substances. The demands for appropriate storage and handling of products containing fragrance compounds are also very important during all stages (industry, trade and consumer).

If the number of allergic reactions to essential oils and their compounds is compared to how widely these substances are applied, we can conclude that the use of essential oils in perfumes and cosmetic products could be considered as safe for the majority of the population.

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10.1 List of Tabels

10.2 List of Figures