Chapter

Safety Profile of Essential Oils

Oliviu Vostinaru, Simona Codruta Heghes and Lorena Filip

Abstract

Essential oils are complex mixtures of terpenes and phenylpropanoid compounds, present in multiple species of aromatic plants. They are extensively used in food and cosmetic industries in order to give flavor to food and drinks or as natural fragrances. Moreover, several compounds present in essential oils are important for the pharmaceutical industry due to their antioxidant, antimicrobial, anxiolytic or spasmolytic effects. Although many essential oils are generally recognized as safe, a series of adverse reactions have been reported after their use either by internal or external routes. The aim of this chapter is to increase the awareness of healthcare professionals concerning possible safety issues of essential oils. Common adverse effects of essential oils like sensitization and dermatitis but also more severe phenomena like neurotoxicity will be presented in detail, concerning their epidemiology, mechanism and clinical significance. A thorough understanding of the safety profile of essential oils is necessary for healthcare and food industry professionals in order to maximize their beneficial effects while minimizing the risk for the users.

Keywords: essential oils, terpenes, sensitization, neurological toxicity, endocrine disrupting potential

1. Introduction

Essential oils (EOs) are complex mixtures of aromatic terpenes (monoterpenes and sesquiterpenes) and other aromatic or aliphatic compounds, formed as secondary metabolites in specialized secretory tissues of aromatic plants [1]. Various parts of the aromatic plants (leaves, flowers, fruits, roots, bark) could be used for essential oil extraction by multiple techniques including steam distillation, solvent extraction or supercritical fluid extraction [2]. A verified botanical origin (chemical composition) and protection against contamination and oxidative degradation provided by adequate recipients are key factors influencing essential oils quality. Essential oils from peppermint, lavender, jasmine or ylang-ylang have been used from Antiquity in European and Asian traditional medicine for the prevention and treatment of several diseases but also for food flavoring. Nowadays, over 3000 compounds have been identified in EOs and more than 300 essential oils are commercially available [3] (**Table 1**).

Essential oils are extensively used as food flavors, as fragrances in cosmetic industry but also, a para-medicinal use like aromatherapy has become increasingly popular in the last decades (**Figure 1**). Moreover, due to a complex chemical composition, they are capable to interact with multiple pharmacological targets (receptors, ion channels or enzymes), being studied with promising results for the development of new drug candidates. Some essential oils like peppermint oil are already used in clinical settings for the treatment of functional dyspepsia or irritable bowel

No.	Plant species	Common name of EO
1.	*Boswellia carterii*	Frankincense
2.	*Cananga odorata*	Ylang-Ylang
3.	*Carum carvi*	Caraway
4.	*Cinnamomum zeylanicum*	Cinnamon
5.	*Citrus aurantium* var. *Amara*	Neroli
6.	*Cupressus sempervirens*	Cypress
7.	*Cymbopogon citratus*	Lemongrass
8.	*Eletaria cardamomum*	Cardamom
9.	*Foeniculum vulgare*	Fennel
10.	*Gaultheria fragrantissima*	Wintergreen
11.	*Juniperus communis*	Juniper
12.	*Melaleuca alternifolia*	Tea tree
13.	*Melaleuca viridiflora*	Niaouli
14.	*Mentha x piperita*	Peppermint
15.	*Rosmarinus officinalis*	Rosemary
16.	*Thymus vulgaris*	Thyme
17.	*Zingiber officinale*	Ginger

Table 1.
A selection of commercially available essential oils and their botanical origin (in alphabetical order) [1, 2].

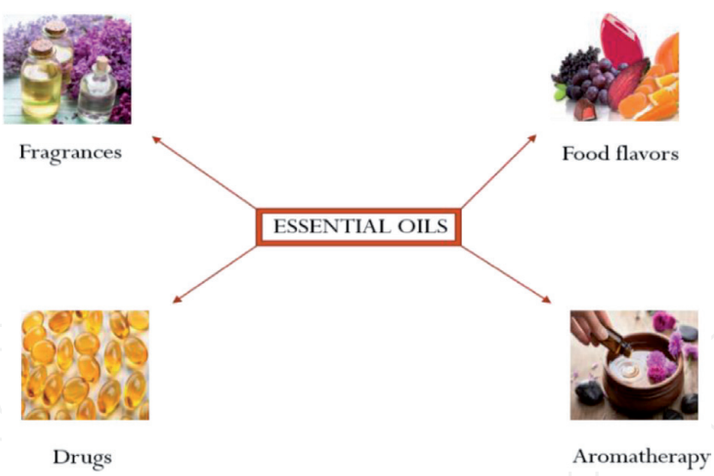

Figure 1.
Main uses of essential oils.

syndrome. Numerous *in vitro* and *in vivo* experiments have proved significant antioxidant, antimicrobial, anxiolytic, spasmolytic or anti-inflammatory effects for several essential oils, which could be also translated in human medicine [4, 5].

Despite their extensive use, key information concerning the safety profile of essential oils are not known to the general public or practitioners of aromatherapy. A significant proportion of the general public mistakenly believes that all essential oils are completely safe for human use, being hailed as "natural and risk-free medicines." Therefore, the aim of this chapter is to increase the awareness of healthcare and food industry professionals, but also general public, concerning possible safety issues of essential oils. Common adverse effects of essential oils like sensitization

and dermatitis but also more severe phenomena like neurotoxicity will be presented in detail, concerning their epidemiology, mechanism and clinical significance. A thorough understanding of the safety profile of essential oils is necessary in order to maximize their beneficial effects while minimizing the risk for the users.

2. Primary routes of systemic absorption of essential oils

Essential oils have a significant lipophilicity due to a high content of monoterpenes, being capable of easily passing through several biological barriers. Thus, a systemic absorption of specific chemical constituents is possible after oral, cutaneous or pulmonary administration of essential oils with beneficial therapeutic effects but also with toxicological implications [6].

After an oral administration of EOs, the systemic absorption of several molecules present in their chemical composition could be significant. A study in rats showed that after oral administration of radio-labeled trans-anethole, over 90% of the substance was absorbed from the digestive tract into the bloodstream, being subsequently metabolized and excreted in feces and urine [7]. Recently, a study from 2018 showed that an immediate release formulation with geraniol orally administered in Sprague-Dawley rats showed an absolute bioavailability of 92%, thus showing an increased systemic absorption [8]. In humans, the absorption of 1,8-cineole from the digestive tract was clearly demonstrated in a study which used enteric coated capsules with a mixture of three terpenoids: limonene, 1,8-cineole and α-pinene [9].

The contact of essential oils with the skin, frequently encountered in aromatherapy massage, could also lead to a systemic absorption of the chemical constituents, depending on the contact time, size of exposed skin surface and concentration of the compound. Essential oils and their volatile constituents can penetrate the skin barrier and facilitate the absorption of other topically applied drugs by inducing a conformational modification of intercellular proteins in the corneal layer and by increasing the drug partitioning [10]. Transdermal absorption was demonstrated for several monoterpenes like α-pinene, camphor or limonene, other structurally related compounds being also capable of passing the skin barrier and generating systemic effects [6].

The volatility of essential oils makes them ideal for pulmonary administration, suitable in the treatment of respiratory diseases. Nevertheless, a fraction of the inhaled compounds could be rapidly absorbed at alveolar level and through airway mucosa, with the apparition of plasmatic concentrations and possible systemic effects. The pulmonary absorption was confirmed for α-pinene, camphor and menthol, the rate of absorption depending on the nature and concentration of inhaled volatile substances and local physiological factors like breathing mechanics [6].

3. General aspects of essential oil toxicity

Essential oils are easily available in pharmacies, supermarkets or online, being used by large segments of the general public. A recent study found that 11% of Australians have used essential oils in 2016, for medicinal purposes, usually self-prescribed [11]. Despite their popularity and extensive use, the safety profile of essential oils has not been fully determined to date. Chemical complexity of essential oils is challenging when investigating which individual components are responsible for certain unwanted effects. Nevertheless, some necessary steps have already been undertaken.

Potential toxic effects of some essential oils and their components were tested on laboratory animals, usually rodents. Acute toxicity was evaluated by LD_{50} test (median lethal dose) in rats, which revealed that most essential oils have a LD_{50} of 1–20 g/kg, indicating a low toxicity. In humans, some essential oils like lemon oil have an LD_{50} of above 5 g/kg. Thus, the lethal dose would be 350 g for an adult of 70 kg, difficult to reach in normal circumstances [12, 13].

A few notable exceptions are EOs from *Boldo* leaf, *Chenopodium*, *Mentha pulegium* (pennyroyal), *Satureja hortensis* (savory) and *Thuja* who presented an LD_{50} between 0.1 and 1 g/kg in rats, signaling a significant toxicity which recommends necessary precautions for their use [12].

Essential oils are susceptible to oxidative degradation, some of the resulting molecules like oxidation products of limonene being potential skin sensitizers [14]. Therefore, a proper storage of essential oils is necessary to conserve their effectiveness and reduce the risk of adverse reactions. Essential oils should be stored in a refrigerator or in a cool, dark place in tightly sealed recipients (brown bottles).

Although most essential oils received the GRAS (generally recognized as safe) status, granted by Flavor and Extract Manufacturers Association (FEMA), it should be pointed out that they were evaluated as flavors with a very low concentration in the tested products. For a concentrated essential oil, certain toxic effects, local or systemic, could develop in specific circumstances [12].

4. Acute intoxication with essential oils

Acute intoxication (poisoning) with essential oils almost invariably results from an oral ingestion of large quantities of undiluted oil, usually accidental. The intoxicated person may present polypnea, convulsions, nausea and vomiting or even death in rare cases. Tea tree oil and the oils of wintergreen, clove, cinnamon and eucalyptus are responsible for most cases, although acute intoxication with other essential oils is possible [13].

In the US, 966 intoxication cases due to tea tree oil ingestion were recorded in 2006, most subjects being represented by children up to 6 years old [13]. In Australia, a recent study identified 1387 cases of essential oil poisoning between 2014 and 2018 [15]. The exposures were accidental or due to a confusion between liquid cough medicines and essential oils. In young children, oral ingestion of 0.6–5 mL of pure eucalyptus oil is sufficient to cause severe symptoms, a fatal case being reported after the ingestion of 30 mL of the oil by an 8-month-old infant [16]. In acute intoxication, infants and young children are particularly at risk due to their reduced body weight combined with the immaturity of enzymatic systems capable of metabolizing essential oils.

Essential oil poisoning was reported also in dogs and cats treated topically with tea tree oil used in large doses for dermatological conditions. The animals presented depression, weakness, motor incoordination and tremors but they recovered after supportive treatment was given [17].

In order to reduce acute intoxication risk, it is recommended that essential oils are kept in child proof recipients, with droppers, separated from oral medication, to avoid confusion.

5. Dermatological toxicity of essential oils

In aromatherapy, essential oils, usually diluted in a carrier oil, are applied directly to the skin. The most important dermatological adverse reactions that may occur include irritation, sensitization and photosensitization [18, 19].

The severity of a dermatological reaction is variable, according to factors like applied substance (aldehydes, phenols), used vehicle, quality/adulteration of the essential oil, method of application, dilution, anatomical site of exposure, integrity of the skin and age of the subject. Environmental conditions could play also an important role. The presence of ultraviolet (UV) light is the decisive factor in photosensitization. Also, ambient temperature and humidity can influence general sensitivity, warm and humid conditions being more favorable for increased severity of adverse reactions [18, 19].

5.1 Skin irritation

Cutaneous irritation is the biological response of the skin to a variety of external stimuli that can induce skin inflammation. The main pathological mechanisms of irritancy include skin barrier disruption, induction of a cytokine cascade and involvement of the oxidative stress network [20]. Primary irritation (contact dermatitis) occurs rapidly the first time an essential oil is used, manifesting as a red wheal or burn and is more likely to occur when essential oils contain large amounts of compounds like phenol, carvacrol and thymol (oregano, savory or thyme), phenolic ethers like eugenol and anethole (clove) or aromatic aldehydes like cinnamaldehyde (cinnamon) (**Figure 2**). Skin reaction is usually limited to the area where the essential oil is applied [21].

The plants whose essential oils are potentially irritant to the skin are listed in **Table 2**. Considering all these aspects, it is recommended that a patch test should be performed before using these oils.

5.2 Skin sensitization

In contrast to irritation, skin sensitization is a response of the adaptive immune system to certain chemical substances called sensitizers or haptens, which can modify skin proteins and induce a delayed T-cell-mediated allergic response [23]. Some of the ingredients which may trigger allergic reactions are listed in the seventh amendment of directive 76/768 CEE (directive 2003/15/CE) and include benzyl alcohol, cinnamyl alcohol, citral, eugenol, hydroxycitronellal, isoeugenol, benzyl salicylate, cinnamaldehyde, coumarin, geraniol, anisyl alcohol, benzyl cinnamate, farnesol, linalool, benzyl benzoate, citronellol, or limonene [24, 25]. Skin sensitization occurs on first exposure to a substance, with only a slight (or absent) effect on the skin. Subsequent exposure to the same compound/compounds will produce a severe inflammatory reaction caused by T-lymphocytes.

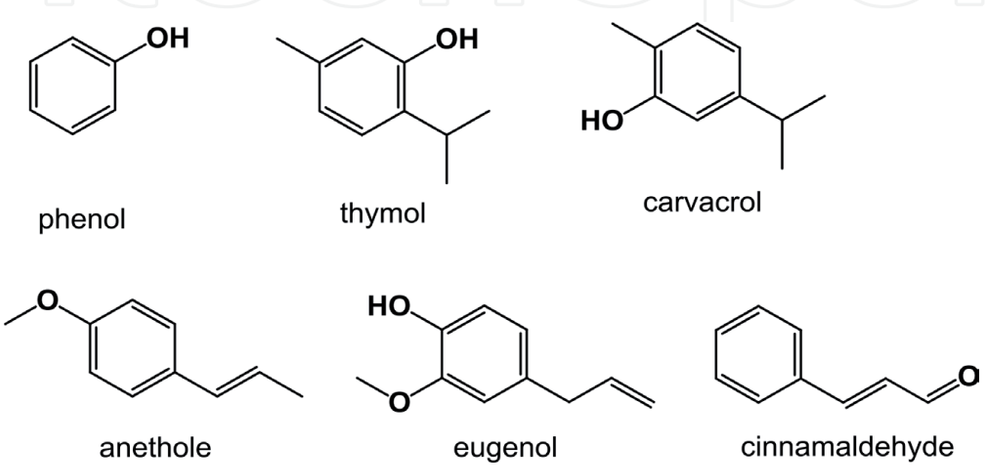

Figure 2.
Chemical structures of the main skin irritant compounds.

Latin name (botanical family)/common name	Part used in EO extraction
Cuminum cyminum (*Apiaceae*)/Cumin	Fruits
Tagetes minuta (*Asteraceae*)/Marigold	Leaves
Origanum vulgare (*Lamiaceae*)/Oregano	Aerial parts
Satureja hortensis (*Lamiaceae*)/Summer savory	Leaves
Satureja montana (*Lamiaceae*)/Winter savory	Leaves
Thymus capitatus ct. carvacrol or thymol (*Lamiaceae*)/Spanish oregano	Aerial parts
Thymus serpyllum (*Lamiaceae*)/Wild thyme	Aerial parts
Thymus vulgaris ct. phenol (*Lamiaceae*)/Red thyme	Aerial parts
Cinnamomum cassia (*Lauraceae*)/Chinese cinnamon	Barks
Cinnamomum zeylanicum (*Lauraceae*)/True cinnamon	Leaves, barks
Pimenta racemosa (*Myrtaceae*)/Bay rum tree	Fruits, leaves
Syzygium aromaticum (*Myrtaceae*)/Clove	Buds, leaves, stems
Cymbopogon citratus (*Poaceae*)/Citronella	Aerial parts
Cymbopogon nardus (*Poaceae*)/Lemongrass	Aerial parts
Lippia citriodora (*Verbenaceae*)/Lemon verbena	Leaves

Table 2.
Essential oils potentially irritant to the skin (in alphabetical order of the botanical family) [22].

Symptoms include a bright red rash, which may be painful to some individuals and sometimes a pigmentation of the skin, more frequently in Asians [21, 24]. In order to prevent sensitization, it is recommended to avoid known dermal sensitizers and avoid application of the same essential oil every day for a long period of time.

Table 3 lists some of the oils considered to be dermal sensitizers, but the sensitization process can occur for any essential oil [22, 25].

Essential oils obtained from different species of *Pinus* and *Abies* should only be used when the level of peroxides is kept to the lowest practical level, preferably by adding anti-oxidants at the time of production [19].

Skin sensitization reactions are idiosyncratic, identification of the causative allergen(s) and their subsequent withdrawal generally leading to a resolution of the problem. Some standard mixtures (fragrance mixture) can be used in a patch test to screen for allergic reactions in susceptible individuals, but not all the allergies can be predicted by this method [26, 27].

5.3 Photosensitization

Photosensitization is a reaction between a phototoxin from an essential oil that is applied to the skin in the presence of sunlight or ultraviolet A (UVA) light. The interaction with the light may be either phototoxic or photoallergic.

Photoallergy is an immune-mediated skin reaction, while phototoxicity may lead to photocarcinogenesis. Furanocoumarins (psoralens) appear to be primarily responsible for phytophototoxic reactions in humans. Reactions can vary from pigmentation, blistering, to severe full-thickness burns. Furanocoumarins occur mainly in expressed citrus peel oils (*C. bergamia*, *C. aurantium, C. limon*, *C. aurantifolia*) although they are also found in angelica root (*Angelica archangelica*), rue (*Ruta graveolens*), cumin (*Cuminum cyminum*) parsley leaf (*Petroselinum crispum*), and marigold (*Tagetes minuta*) essential oils [19, 28].

The most common compounds are bergapten and psoralen (**Figure 3**). They are not found in distilled citrus peel oils [21].

Latin name (botanical family)/common name	Part used in EO extraction
Cananga odorata (*Annonaceae*)/Ylang ylang	Flowers
Inula helenium (*Annonaceae*)/Elecampane	Flowers, leaves
Saussurea costus (*Asteraceae*)/Costus	Roots
Commiphora erythraea (*Burseraceae*)/Opoponax	Resin
Myroxylon pereirae (*Fabaceae*)/Peru balsam	Resin
Liquidambar styraciflua (*Hamamelidaceae*)/Styrax	Resin
Cinnamomum cassia (*Lauraceae*)/Chinese cinnamon	Barks
Cinnamomum zeylanicum (*Lauraceae*)/True cinnamon	Leaves, barks
Melissa officinalis (*Lamiaceae*)/Lemon balm	Leaves
Backhousia citriodora (*Myrtaceae*)/Lemon myrtle	Leaves
Melaleuca alternifolia (*Myrtaceae*)/Tea tree	Leaves
Pimenta racemosa (*Myrtaceae*)/Bay rum tree	Fruits, leaves
Syzygium aromaticum (*Myrtaceae*)/Clove	Buds, leaves, stems
Pinus spp. (*Pinaceae*)/Turpentine	Leaves
Cymbopogon nardus (*Poaceae*)/Lemongrass	Aerial parts
Lippia citriodora (*Verbenaceae*)/Lemon verbena	Leaves

Table 3.
Essential oils considered to be dermal sensitizers (in alphabetical order of the botanical family) [21, 22].

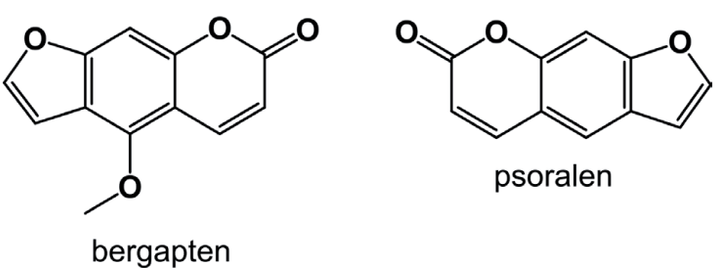

Figure 3.
Chemical structure of the most common furanocoumarins involved in photosensitization.

The factors influencing risk of photosensitization include the amount of essential oil applied topically and the area of exposure. It is considered there is no risk of photosensitization if the skin is covered to prevent exposure to UVA light for at least 2 h [28].

6. Neurological toxicity of essential oils

Essential oils could easily pass the blood-brain barrier, reaching the central nervous system after a systemic absorption. In an experimental setting, essential oils from *Salvia officinalis* and *Hyssopus officinalis* evoked convulsions after intraperitoneal administration in rats at doses of 0.5 g/kg and 0.13 g/kg, respectively [29].

In humans, essential oils from *Salvia officinalis*, *Thuja plicata*, *Cedrus* spp., *Hyssopus officinalis*, *Eucalyptus* spp., *Mentha pulegium*, *Cinnamonum camphora* and *Anethum graveolens* produced tonic-clonic convulsions, particularly in children and especially in those with a history of epileptic syndromes, according to several reports [30, 31].

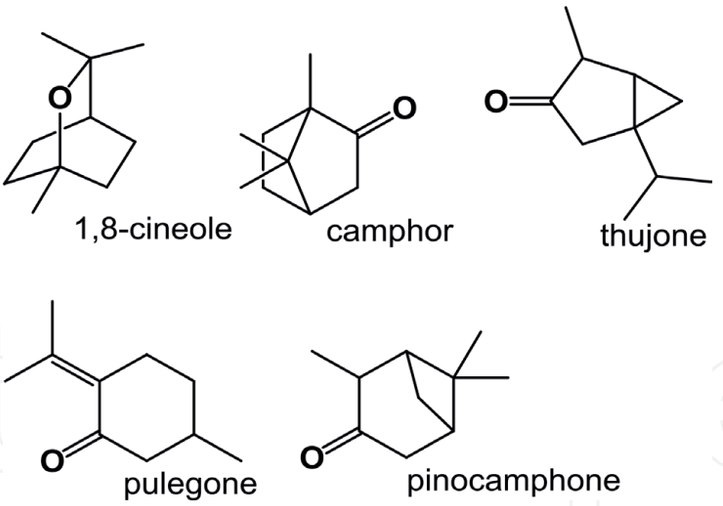

Figure 4.
Chemical structure of terpenes with epileptogenic potential.

The identified chemical constituents responsible for convulsions were usually 1,8-cineole, camphor, thujone, pulegone and pinocamphone (**Figure 4**) [29, 30].

Molecular mechanisms of the convulsant effect of essential oils and their constituents were investigated in laboratory animals. According to a study, some essential oils resemble pentylentetrazole, a powerful convulsive agent, modifying tissue gradients of Na and K and leading to increased cellular excitability in the brain [32]. In another experimental study, thujone one of the frequently incriminated pro-convulsant terpenes, suppressed GABA-induced peak currents in rat dorsal root ganglion neurons, with the subsequent apparition of convulsions, terminated by diazepam or phenobarbital [33]. On the contrary, other research proved that different terpenes could have an anticonvulsant effect. Menthol, another terpene derivative found in the chemical composition of some essential oils enhanced electric currents induced by low concentrations of GABA and directly activated $GABA_A$ receptors in laboratory animals [34].

In the context of potential neurological toxicity of essential oils, European Medicines Agency (EMA) reviewed the safety of suppositories containing terpenes used in seven European countries (France, Belgium, Portugal, Spain, Italy, Luxembourg and Finland) for the treatment of respiratory diseases. The report concluded that terpenes could induce convulsions in children less than 30 months, recommending they should be contraindicated in this particular segment of patients [35].

7. Endocrine disrupting potential of essential oils

In the last decade, there has been an accumulation of evidence suggesting a possible endocrine disrupting effect of some essential oils. Initially, a report signaled the apparition of idiopathic male prepubertal gynecomastia in patients with topically applied lavender oil or tea tree oil [36]. The experimental data showed that both lavender oil and tea tree oil effects are produced by the activation of estrogenic receptors (ER), with a potency of 50% of estradiol, being attenuated in the presence of fulvestrant, a pure antagonist of ER receptors.

Recently, another study published in 2019, confirmed the mentioned data, showing that a continuous exposure to lavender-fragranced products induced a

premature thelarche in four patients [37]. The chemical constituents from the essential oils were individually tested concerning their capacity of stimulating ERα estrogen response element (ERE)-mediated activity. The most active compounds with estrogenic activity were α-terpineol, 4-terpineol and linalool. Further research on a more statistically significant population is needed to confirm the relevance of these findings [37].

8. Essential oils in pregnancy and lactation

The main concerns of the use of essential oils during pregnancy is related to the risk of chemical compounds crossing the placental barrier with direct effects on the product of conception, but also to the direct abortive effect. The use of essential oils during pregnancy is a controversial topic and one that is yet to be fully understood.

Some essential oils are abortifacients, being capable of inducing miscarriage/abortion. Essential oils like persil oil (*Petroselinum sativum*) rich in apiole, pennyroyal oil (*Mentha pulegium*) rich in pulegone, plectranthus oil (*Plectranthus amboinicus*), Spanish sage oil (*Salvia lavandulifolia*) or savin oil (*Juniperus sabina*) rich in sabinyl acetate should be avoided during pregnancy (**Figure 5**). The amounts required to induce an abortion may also pose toxicity risks to the mother, including kidney and liver damage (could be the reason of pregnancy termination in pennyroyal oil case) or even death [12, 38].

Due to their chemical properties (low molecular weight, lipophilicity), it is likely that certain essential oil components could cross the placental barrier, reaching fetal circulation. Following a possible biotransformation into polar molecules, they can accumulate in the fetus due to a reduced glomerular filtration rate and low content of plasma proteins capable of binding xenobiotics [13, 38].

Essential oils should not be used in pregnancy (or breastfeeding) if they contain large amounts of the following components: (E)-anethole (aniseed-*Pimpinella anisum*, star anise-*Illicium verum*, fennel-*Foeniculum vulgare,* dill-*Anethum graveolens*), apiole (persil-*Petroselinum sativum*), β-eudesmol (cypress-*Cupressus sempervirens*), camphor (Spanish lavender-*Lavandula stoechas*), methyl salicylate (sweet birch-*Betula lenta*), pinocamphone (hyssop-*Hyssopus officinalis*), or thujone (mugworth-*Arthemisia vulgaris,* savin-*Juniperus sabina,* thuja-*Thuja occidentalis*) [12, 38].

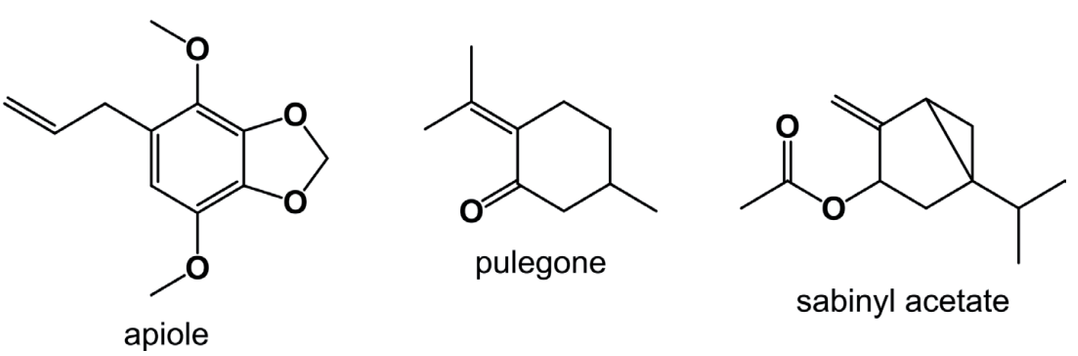

Figure 5.
Chemical compounds responsible for the abortifacient effect.

9. Conclusions

Essential oils have gained an increased attention in the last decades, being used as flavors, fragrances, medicines or in aromatherapy. Although generally considered as "natural and safe," some essential oils could cause significant adverse effects like skin sensitization and contact dermatitis, neurological toxicity or endocrine dysregulations.

An increased awareness of healthcare professionals and general public concerning the safety profile of essential oils is needed in order to correctly exploit their diverse biological effects.

Conflict of interest

The authors declare no conflict of interest.

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