Mini Review
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A mini-review on the safety profile of essential oils

Abstract

Essential oils (EOs) are defined as secondary metabolites of plants that are volatile in nature and synthesized by various parts of plants such as buds, trichomes, bark, leaves, flowers, twigs, etc. They are generally extracted through steam and hydro distillation processes. The chemistry of these essential oils is very complex and mainly consists of terpenes and their oxygenated derivatives. The color, aroma, volatility, lipophilicity are some of the salient features of these essential oils. Primarily, they are used for flavoring purposes, but with the advancement in science and scientific tools, many properties such as antioxidant, antimicrobial, and anti-inflammatory were explored by the scientific community. Their role as natural food preservatives has evolved in recent years, like biofilms and nano encapsulation in the active packaging of food products. The pharmaceutical industries also look at these essential oils as one of the potent candidates in ameliorating various ailments. The significant components of many essential oils such as piperine of pepper family, eugenol, thymoquinone, curcuminoids were found to have promising therapeutic effects and provide wider research scope for pharmaceutical industries. Besides all these applications, the safety profiling of these EOs is a matter of concern. This mini-review documented the updated published data related to the various aspects related to toxicity and safety issues of EOs.

Keywords: essential oils, terpenes, safety, toxicity

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Introduction

In European and Asian traditional medicine literature, the use of essential oils (EOs) for the prevention and treatment of several diseases was well documented. More than 3000 EOs are known to date, among which approximately 300 are commercially exploited by the food, beverages, and pharmaceutical markets. Some commonly known commercially available EOs are Caraway *(Carum carvi),*Cinnamon *(Cinnamomum zeylanicum)*, Neroli *(Citrus aurantium* var. *Amara),* Lemongrass *(Cymbopogon citrate),* Cardamom *(Elettaria cardamomum)*, Fennel (*Foeniculum vulgare)*, Ginger (*Zingiber officinale),* Juniper *(Juniperus communis)*, Thyme *(Thymus vulgaris)*, Tea tree *(Melaleuca alternifolia)*, Peppermint (*Mentha x piperita)*, and Rosemary *(Rosmarinus officinalis).*[1] The bioactive components present in these EOs are responsible for the antioxidant, anti-inflammatory, anticarcinogenic, anti-diabetic, antimutagenic, and antiproliferative properties,[2] which are exploited in the flavor, fragrance, and pharma sectors. Especially in pharmaceutical sectors, the bioactive components present in EOs have an ability to interact with several pharmacological targets such as enzymes, receptors and help in the development of potent drug options for the industry. In recent years, piperine, curcumin, and thymoquinone are also considered bio-enhancers used in drug delivery systems to enhance the availability of drugsin the body.[3]

The chemistry of EOs is very complex, and the bioactive components found in EOs range from 20 to 60 in number.[4,5] The chemical profile of EOs showed the presence of more than 300 polar and non-polar fractions of components at variable percentages.[4,5] Major components contribute more than 85% in the chemical profile of EOs, while other components are present in trace amounts.[6] However, based on chemical moieties, these components of EOs are classified into terpenes/ terpenoids (oxygenated derivative of terpenes) and phenylpropanoids. The basic unit of terpenes comprises isoprene units $(C_5H_8)n$. These groups are synthesized through separate metabolic pathways.[7] The complexity of the EOs composition is due to different geographical conditions, harvesting time, and extraction techniques. The notion that being natural is always safe and risk-free also gets wells with usage EOs. But in recent years, there have been many reports regarding the toxicity and safety issues related to the exposure of these EOs. There is a strong need for proper awareness among the people regarding the usage of these EOs. This mini-review accounts for the published data available with toxicity-related issues associated with the use of EOs.

General use of EOs

EOs are one of the constituents in the products related to perfumery, cosmetics, sprayers, deodorants, food products, beverages, soaps, fumigants, and detergents.[8,9] EOs of tea tree is effective in controlling the growth of pathogens because of which they are widely used in hand washes and antiseptics liquids.[10] Eucalyptus, thyme, and menthol are generally used in mouthwashes for providing refreshing fragrance as well as antiseptic properties.[8,11,12] EOs derived from Species of *Ocimum*, Eucalyptus, Cymbopogon are widely used as mosquito repellants.[13] There are many patents regarding these repellants containing EOs around the world. Chemical moieties mainly responsible for the repellant properties are monoterpenes and sesquiterpenes.[14] *Cinnamomum camphora*, *Syzygium aromaticum* L., *Lavandula angustifolia*, *Cinnamomum zeylanicum* are also known for their mosquito repellency properties.[14] Synergism among different constituents also plays an influential role in the properties of Eos.[15] Camphor, vanillin, limonene, thymol, citronellol, and alpha-pinene are some of the major components of EOs having insecticidal properties.[8] These EOs derived repellants have no side effects and are eco-friendly options of mosquito repellants.[15]

Different routes for EOs systemic absorption

Due to their lipophilic nature, EOs can easily pass through the biological barriers, permitting a possibility of systemic absorption of the chemical components present in them, which allows their administration easier through oral, pulmonary, or cutaneous pathways but comes with toxicological implications and complications.[1,16] In one of the works reported, it was observed that more than 90% of

trans-anethole was absorbed from the digestive tract into the blood of rats and being metabolized and excreted with fecal waste and urine.[1,17] Orally administered geraniol showed a systemic absorption of about 92% in Sprague-Dawley rats.[1,18] In aromatherapy, EOs are one of the significant components, and there is a possibility of systemic absorption because the skin is in direct contact with EOs. Components like limonene, camphor, and α–pinene were systemically absorbed transdermally, crossing the skin barriers.[1,16] One of the studies reported inhaling ingredients of EOs such as menthol, camphor, and α-pineneduring pulmonary administration for treating respiratory diseases. Inhalation occurs due to the volatility property of EOs, which makes them readily available to get absorbed at the alveolar level.[1,16]

Toxicity related to EOs

EOs in the form of natural preservatives are generally recognized as safe (GRAS) as recommended by the FDA and allowed their permitted use.[19] Figure 1 demonstrates some of the components of EOs with toxicity.[1,8] Since these EOs are required to use in higher concentrations, the issues related to their toxicity cannot be ignored. Presently applied toxicity and safety evaluations are available with different variables for EOs. One of the most used methods for evaluating EOs safety and toxicity is the acute oral test in which LD_{50} or Median Lethal Dose value is determined.[20] In various reported works done in animal models, the acceptable range of EOs and their chemical components with LD_{50} is 1-20 g/kg body weight.[8,19] These evaluations are needed because of the side effects reported in recent years such as oestrogenic, carcinogenic, and abortifacient effects.[21] EOs derived from *Salvia lavandifula*, *Mentha pulegium*, *Satureja hortensis*, *Chenopodium*, and *Thuja* were found to have significant toxic effects with LD_{50} value ranges between 0.1-1 g/kg in the animal model (rats) and requires prescribed precautions before their use.[8,21]

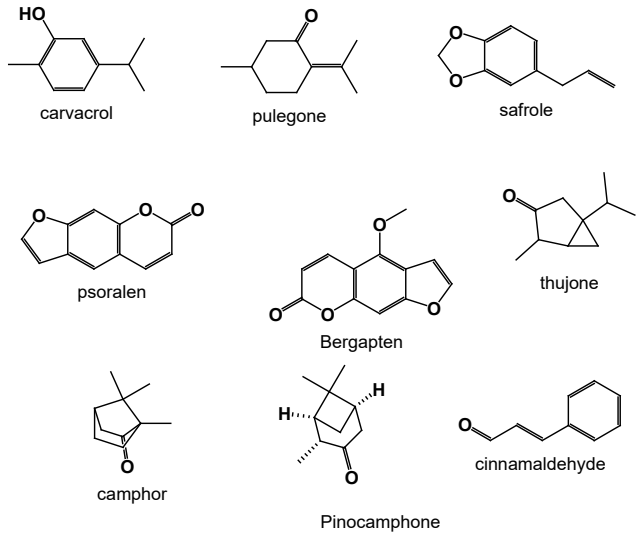

Figure 1 Some of the components present in EOs are reported to be toxic in nature.

Acute and oral toxicity related with EOs

The data relating to EOs toxicity in mammals are relatively low compared to animal models. The dose of Eucalyptus EO (2772 mg/kg b.wt) is toxic in one of the investigations, and the administration of EO causes reduced growth with damage in the liver and kidney of rats.[8,22] A dose of 400 mg/kg of *Syzygium aromaticum* significantly reduces the body weight in rats. The LD_{50} value for oral dose was found to be 4500 mg/kg approximately.[8,23] Commonly known EOs derived from lemongrass, marjoram, eucalyptus, clove, chamomile, anise have oral LD_{50} values ranging from 2000 to 5000 mg/kg body weight in rats.[8,13] EOs of *Eupatorium cannabinum* L. containing germacrene D and neryl acetate as one of the major components have an oral dose of LD_{50} value equal to 16.3–22.0 µg/mL.[8] Fourteen days toxicity study was conducted in Wistar rats using *Ocimum basilicum, Ocimum gratissimum, Cymbopogon citratus* EOs, which showed dose dependent (>1500 mg/kg body weight) adverse effects and caused damage in stomach and liver.[8,24] Recently, in the US and Australia, acute intoxication cases were reported with symptoms such as vomiting, convulsions, polypnea, and nausea.[1] Clove, Tea tree oil, eucalyptus cinnamon, and wintergreen oils are responsible for these acute intoxication cases.[25] Oral consumption of 0.6–5 mL of pure eucalyptus EO is found to cause severe symptoms in young children, even a fatal case being reported in an infant of an 8-month-old.[26]

Dermatological toxicity related to EOs

In recent years, aromatherapy with some EOs and their components is known to cause allergic dermatitis infrequent use, due to their lipophilic nature and capacity to penetrate the skin. Especially in aromatherapy, EOs are diluted with carrier oils and applied directly to the skin. Skin irritation, sensitization, and photosensitization are some of the adverse effects with topical administration of these EOs. Factors such as method of application, adulteration in EOs, exposure area, environmental condition play an essential role in developing the various adverse reactions on the skin.

Skin irritation

EOs derived from *Cuminum cyminum, Origanum vulgare, Cinnamomum zeylanicum, Syzygium aromaticum, Thymus vulgaris, Tagetes minuta* are some of the common skin irritant oils.[1] Components like carvacrol, thymol, eugenol, anethole, and cinnamaldehyde are some of the constituents causing skin irritation. Mode of action involves the disruption of the skin barrier, causing destruction at cellular levels involving the oxidative stress factor. EOs of *Cananga odourata, Melaleuca* species, *Lavandula spica*, and *Mentha* species were found to show severe adverse effects while applied in aromatherapy.[8,27,28]

Skin sensitization

Skin sensitization is a cumulative response of the immune system to certain foreign particles or chemicals that come in contact with the skin in the form of an allergic response. The use of EOs can cause modification in proteins of the skin and induce a delayed response of the T-cell mediated system.Components such as citral, cinnamaldehyde, geraniol, eugenol, coumarin, linalool, citronellol, limonene, benzyl cinnamate, farnesol, anisyl alcohol, cinnamyl alcohol, and hydroxycitronellal are responsible for allergic reactions.[1,29,30]

Photosensitization or phototoxicity

Some chemical moieties absorb light which causes changes in structural level and causing toxic effects. This phenomenon is known as photosensitization. In the case of EOs, the chemical components present in EOs absorb light and cause skin irritation. This interaction will be either phototoxic or photoallergic in nature. Psoralens or Furanocoumarins are a class of phototoxic compounds, mainly present in EOs derived from citrus species, parsley leaf, cumin, and marigold.[1,8,31] The most common compounds are bergapten and psoralen, producing phototoxicity.[1,8,31]

Other physiological toxicities related with EOs

Some EOs are found to be abortifacients and can induce miscarriages orabortion during pregnancy. EOs derived from *Mentha pulegium, Petroselinum sativum, Salvia lavandulifolia, Juniperus sabina*, containing pulegone, apiole and sabinyl acetate as major component respectively is generally avoided in pregnancy. Some works also reported toxicity issues such as damage to kidney and liver to conceiving mother.[1,21,32] The lipophilic nature of EOs make them able to cross the placenta and even disturbs the fetal circulation system.[1,25,32] It was recommended that EOs containing components such as (E)-anethole, β-eudesmol, thujone, apiole, methyl salicylate, and thuja should be avoided during pregnancy and breastfeeding.[1,21,32]

In recent years some EOs have been reported to cause genotoxicity and carcinogenicity.[8] In an experiment conducted on rodents, estragole containing EOs of *Ocimum basilicum* and *Artemisia dracunculus* were carcinogenic in nature.[8,33,34] Pulegone and safrole components showed carcinogenicity after getting activated in metabolic channels.[8,35] Estrogen-related cancer can be induced by EOs of *Salvia sclarea* and *Melaleuca quinquenervia*, which can stimulate estrogen production.[8] In rodents, methyl eugenol and D-limonene in EOs of *Laura nobilis* and citrus plants, respectively, have been reported as carcinogenic in nature.[36,37] Eugenolis one of the major components of clove EOs is found to be genotoxic and causes aberration at the chromosomal level in cells.[38] In higher doses EOs of peppermint *Pinus densiflora* and *Anethum graveolens* have been reported to be cytotoxic and genotoxic in lymphocytes of humans.[39]

In recent years, there have been enough pieces of evidence suggesting that some EOs can disrupt the endocrine system. Topical administration of tea tree and lavender EOs causes prepubertal gynecomastia in patients.[1,40] They are found to be involved in activating estrogenicreceptors (ER).

During systemic absorption of EOs, they can quickly reach to the central nervous system. In one of the experimental studies done on rats, EOs of *Hyssopus officinalis* and *Salvia officinalis* at the doses of 0.5 g/kg and 0.13 g/kg given intraperitoneally is found to involve developing convulsions.[1,41] Studies on human done with EOs of *Mentha pulegium*, *Thuja plicata, Eucalyptus* spp, *Salvia officinalis,* and *Anethum graveolens* induces seizures, especially in children.[42,43] Standard convulsant evoking components of EOs are pulegone, camphor, pinocamphone, and thujone.[1,42] One of the studies reported some EOs with pentylentetrazole having convulsive effect.[44] The usage of EOs affects the mechanism related to GABA and brings modification in the action of Na/K ions at neuron levels.

Conclusion

In recent years there has been an increased awareness among the consumers' approach towards the product of natural origin. EOs comes as a potential candidate for perfumery, cosmetics, fragrance, and pharmaceutical sectors. Advancement in extraction techniques to separate bioactive components present in EOs has opened new horizons for many sectors. The widespread applications such as antioxidant, anti-diabetic, antiproliferative, antimutagenic, anticarcinogenic were experimentally investigated in *vitro* and *in vi*vo models. Even though various agencies recommend the EOs as safe additive, their toxicological and safety issues cannot be ignored. Investigation on the toxicological assessment is limited to the animal model, which should be expanded more and more. In vivo evidences are very scarce in the literature. These toxicological assessments are also needed and helpful in exploring the therapeutic potentials of EOs.

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Conflicts of interest

The authors declared no have conflict interest for the study.

References

1. Vostinaru Oliviu, Heghes Codruta Simona, Filip Lorena. Safety Profile of Essential Oils, Essential Oils - Bioactive Compounds, New Perspectives and Applications. In: Mozaniel Santana de Oliveira, Wanessa Almeida da Costa, Sebastião Gomes Silva, editors. *IntechOpen*. 2020. p. 01–200.
2. Pateiro M, Munekata PES, Sant'Ana AS, et al. Application of EOs as antimicrobial agents against spoilage and pathogenic microorganisms in meat products. *International Journal of Food Microbiology.* 2020;377:108966.
3. Singh S, Chaurasia PK, Bharati SL. Piperine: An Effective Bioenhancer for Drug Absorption. *Pharmaceut Drug Regul Affair J*. 2021; 4(1):000126.
4. Bhavaniramya S, Vishnupriya S, Al-Aboody MS, et al. Role of EOs in food safety: Antimicrobial and antioxidant applications. *Grain & Oil Science and Technology*. 2019;2(2):49–55.
5. Burt S. EOs: their antibacterial properties and potential applications in foods a review. *International Journal of Food Microbiology.* 2004*;*94:223–253.
6. Bauer K, Garbe D, Surburg H, et al. *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*. Wiley-VCH: Weinheim; 2001. p. 293.
7. Singh S, Chaurasia PK, Bharati SL. Extraction methods and Chemistry of volatile oils (EOs). In: Sunita Singh editors. *Volatile oils: Production, Composition and Uses.* 1st ed. Novascience publishers; 2021. p. 1–30.
8. Kuttan R, Liju VB. Safety evaluation of essential oils. 1st ed. In: Hashemi SMB, Khaneghah AM, de Sant'Ana AS, editors. *Essential oils in Food Processing: Chemistry, Safety and Applications.* UK. West Sussex: John Wiley & Sons; 2017. p. 339–358.
9. Rehman JU, Ali A, Khan IA. Plant based products: use and development as repellents against mosquitoes: A review. *Fitoterapia*. 2014;95:65–74.
10. Messager S, Hammer KA, Carson CF, et al. Effectiveness of hand cleansing formulations containing tea tree oil assessed ex vivo on human skin and in vivo with volunteers using European standard EN 1499. *Journal of Hospital Infection*. 2005;59(3):220–228.
11. Osso D, Kanani N. Antiseptic mouth rinses: An update on comparative effectiveness, risks and recommendations. *Journal of Dental Hygiene*. 2013;87(1):10–18.
12. Cavalca S, Cortelli F, Cavallini MF, et al. Clinical and microbiological effects of an essential-oil-containing mouth rinse applied in the one-stage full-mouth disinfection protocol—A randomized doubled-blinded preliminary study. *Clinical Oral Investigations*. 2009;13(2):189–194.
13. Regnault Roger C, Vincent C, Arnason JT, et al. Essential oils in insect control: low-risk products in a high-stakes world. *Annual Review of Entomology*. 2012;57:405–424.
14. Pohlit AM, Lopes NP, Gama RA, et al. Patent literature on mosquito repellent inventions which contain plant essential oils—A review. *Planta Medica*. 2011;77(6):598–617.
15. Nerio LS, Olivero Verbel J, Stashenko E. Repellent activity of essential oils: A review. *Bioresource Technology*. 2010;101(1):372–378.
16. Kohlert C, Van Rensen I, Marz R, et al. Bioavailability and pharmacokinetics of natural volatile terpenes in animals and humans. *Planta Medica*. 2000;66:495–505.

17. Bounds SV, Caldwell J. Pathways of metabolism of [1'14C]-trans-anethole in the rat and mouse. *Drug Metabolism and Disposition*. 1996;24:717–724.

18. Pavan B, Dalpiaz A, Marani L, et al. Geraniol pharmacokinetics, bioavailability and its multiple effects on liver antioxidant and xenobiotic metabolizing enzymes. *Frontiers in Pharmacology*. 2018;9:18.

19. Falleh H, Jemaa MB, Saada M, et al. Essential Oils: A Promising Eco-Friendly Food Preservative. *Food Chemistry.* 2020.

20. Nakavuma JL, Matasyoh JC, Wagara IN, et al. Toxicity Studies on Anti-fungal Essential Oils Extracted from Selected Aromatic Plants from Mabira and Kakamega Forests, East Africa. *European Journal of Medicinal Plants*. 2016;14(2):1–14.

21. Lis Balchin M. *Aromatherapy Science: A Guide for Healthcare Professionals*. 1st ed. London: Pharmaceutical Press; 2005. p. 528.

22. Hu Z, Feng R, Xiang F, et al. Acute and subchronic toxicity as well as evaluation of safety pharmacology of eucalyptus oil water emulsions. *Internation Journal of Clinical and Experimental Medicine*. 2014;7(12):4835–4845.

23. Liu BB, Luo L, Liu XL, et al. Essential oil of *Syzygium aromaticum* reverses the deficits of stress-induced behaviors and hippocampal p-ERK/p-CREB/brain-derived neurotrophic factor expression. *Planta Medica*. 2015;81(3):185–192.

24. Fandohan P, Gnonlonfin B, Laleye A, et al. Toxicity and gastric tolerance of essential oils from *Cymbopogon citratu*s, *Ocimum gratissimum* and *Ocimum basilicum* in Wistar rats. *Food and Chemical Toxicology*. 2008;46(7):2493–2497.

25. Tisserand R, Young R. *Essential Oil Safety, A Guide for Health Care Professionals*. 2nd ed. London: Churchill Livingstone; 2014. p. 780.

26. Woolf A. Essential oil poisoning. *Clinical Toxicology*. 1999;37(6):721–727.

27. Posadzki P, Alotaibi A, Ernst E. Adverse effects of aromatherapy: a systematic review of case reports and case series. *The International Journal of Risk and Safety in Medicine*. 2012;24(3):147–161.

28. Stea S, Beraudi A, De Pasquale D. Essential oils for complementary treatment of surgical patients: state of the art. *Evidence-Based Complementary and Alternative Medicine*. 2014;72:6341.

29. Vigan M. Essential oils: Renewal of interest and toxicity. *European Journal of Dermatology*. 2010;20:685–692.

30. Heisterberg MV, Menné T, Johansen JD. Contact allergy to the specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. *Contact Dermatitis*. 2011;65:266–275.

31. Averbeck D, Averbeck S, Dubertret L, et al. Genotoxicity of bergapten and bergamot oil in Saccharomyces cerevisiae. *Journal of Photochemistry and Photobiology.* 1990;7:209–229.

32. Black JM. Essential oils and miscarriage. *Midwifery Today with International Midwife*. 2000;56:5–68.

33. Anthony A, Caldwell G, Hutt AG, et al. Metabolism of estragole in rat and mouse and influence of dose size on excretion of the proximate carcinogen 10 hydroxyestragole. *Food Chemical Toxicology*. 1987;25(11):799–806.

34. Miller EC, Swanson AB, Phillips DH, et al. Structure–activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Research*. 1983;43(3):1124–1134.

35. Zhou S, Koh HL, Gao Y, et al. Herbal bioactivation: the good, the bad and the ugly. *Life Science*. 2004;74(8):935–968.

36. Burkey JL, Sauer JM, McQueen CA, et al. Cytotoxicity and genotoxicity of methyleugenol and related congeners A mechanism of activation for methyleugenol. *Mutation Research*. 2000;453(1):25–33.

37. National Toxicology Program technical report series. NTP Toxicology and Carcinogenesis Studies of d-Limonene (CAS No. 5989-27-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies). *National Toxicology Program*. 1990;347:1–165.

38. Maralhas A, Monteiro A, Martins C, et al. Genotoxicity and endoreduplication inducing activity of the food flavouring eugenol. *Mutagenesis*. 2006;21(3):199–204.

39. Lazutka JR, Mierauskien J, Slap G, et al. Genotoxicity of dil (*Anethum graveolens* L.), peppermint (*Mentha piperita* L.) and pine (*Pinus sylvestris* L.) essential oils in human lymphocytes and Drosophila melanogaster. *Food Chemical Toxicology*. 2001;39(5):485–492.

40. Henley DV, Mueller S, Korach KS. Prepubertal gynecomastia linked to lavender and tea tree oils. *The New England Journal of Medicine*. 2007;356:479–485.

41. Millet Y, Jouglard J, Steinmetz M, et al. Toxicity of some essential plant oils. Clinical and experimental study. *Clinical Toxicology*. 1981;18:1485–1498.

42. Burkhard PR, Burkhardt K, Haenggeli CA, et al. Plant-induced seizures: Reappearance of an old problem. *Journal of Neurology*. 1999;246:667–670.

43. Halicioglu O, Astarcioglu G, Yaprak I, et al. Toxicity of *Salvia officinalis* in a newborn and a child: An alarming report. *Pediatric Neurology*. 2011;45:259–260.

44. Steinmetz M, Vial M, Millet Y. Actions de l'huile essentielle de romarin et de certains de ses constituents (eucalyptol et camphre) sur le cortex cerebrale de rat in vitro. *Journal de Toxicologie Clinique et Expérimentale*. 1987;**7**:259–271.