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Geraniol Uses and Beneficial effects on different systems

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Abstract: Geraniol is an acyclic isoprenoid monoterpene that is biosynthesised by a large number of aromatic plants. It is widely used in cosmetics, household products and pharmaceuticals, because of its low toxicity and environmentally-friendly profile. An increasing demand for the compound has encouraged research into alternative synthetic routes, and great efforts are still aimed to increase the compound yield using a variety of strategies. Geraniol is proven to exhibit various biological activities, including antitumor, anti-inflammatory, anti-oxidant, antimicrobial, hepatoprotective, cardioprotective and neuroprotective effects. This review discusses some of the most important uses of geraniol.

Keywords: *Essential oils; monoterpenes; geraniol; antioxidants; neuroinflammation*

Introduction

Introduction:

Essential Oils (EOs) are complex mixtures of volatile compounds derived from aromatic plants. They are extracted from various plant parts such as roots, leaves, stems, flowers and fruits **(Abate et al., 2021).** Owing to their characteristic fragrance, EOs are extensively used in many cosmetics and hygiene products. Due to their antibiotic, antiviral, anti-microbial, antioxidant and anti-inflammatory properties, they have been part of traditional therapies and herbal medicines **(Guzmán and Lucia, 2021).** Terpenes are secondary metabolites primarily found in plants as constituents of EOs. They are made up of building blocks called isoprene units (C_5H_8). So, terpenes are classified according to the number of isoprene units present in their molecular structure into hemiterpenes (one unit), monoterpenes (2 units), sesquiterpenes (3 units), diterpenes (4 units) and polyterpenes (> 4 units). They can be either cyclic or acyclic according to the number of rings in their molecular structure **(Tang et al., 2022).** Geraniol is an acyclic monoterpene alcohol used commercially as an ingredient of cosmetics, fragrances, personal care products and pharmaceuticals, as well as many other consumables. It is approved by the Food and Drug Administration (FDA) as an additive for flavouring foods, such as beverages, candies and ice cream because of its favorable safety profile **(Chen and Viljoen, 2022).** It is abundant in the essential oils of orange, lime, lemon, cardamom, nutmeg, ginger, lavender and rose and the principal component of orange flower and palmarosa oils **(Truzzi et al., 2021).**

Physical and Chemical Properties of Geraniol:

Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol) molecular formula is $C_{10}H_{18}O$ **(Fig. 1).** It is clear pale-yellow oil that is insoluble in water but soluble in organic solvents. It has a typical rose-like odor. Its taste is sweet at a concentration of 10 ppm **(Kandeepan et al., 2021).** Geraniol has molecular weight of 154.25 g/mol, boiling point is 230°c, water solubility is 255.8 mg/L and specific gravity is 0.878 **(Api et al., 2022).** Lethal dose 50 (LD50) of geraniol is about 2100 mg/kg **(Ebrahimi et al., 2020).**

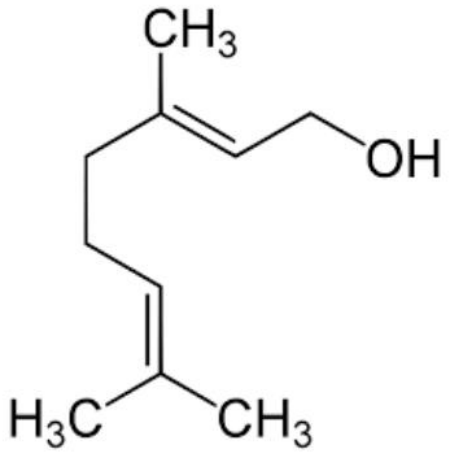

Figure (1): Chemical structure of geraniol **(Pavan et al., 2018).**

Biosynthesis of Geraniol:

Geraniol was mainly obtained through distillation from plant biomass. However, because of low yields, high costs and difficult purification steps, production from plant biomass restricts the wide production of geraniol. In addition, seasonal variations and environmental conditions influence essential oil yield and composition so that a consistent supply of geraniol from natural resources can't be guaranteed **(Gerke et al., 2020).** Chemical synthesis is an option to increase production. However, the complex reactions are associated with high cost and the risk of environmental pollution. Recently, there has been growing interest in commercial production of geraniol by using micro-organisms, which could provide an alternative eco-friendly and potentially cost-effective route. Several micro-organisms, such as Escherichia coli, serve as "microbial cell factories" for the industrial production of geraniol. Yeasts have also proven to be appropriate alternative to E. coli. Such metabolic engineering strategies are developed by researchers to meet the high global demand for geraniol **(Chen and Viljoen, 2022).**

Pharmacokinetics of Geraniol:

Half-life of geraniol is very short, around 12 min., due to fast metabolic and excretion processes and wide distribution in the body compartments. It has remarkable bioavailability reaching 92% that is accompanied with a high rate of elimination from the circulation. It was found that oral geraniol reaches the cerebrospinal fluid (CSF) within 30 min. with a fast decline in its concentration over time similar to that of blood i.e. no geraniol in the CSF was detected after 60 min. **(Pavan et al., 2018).**

Absorption: Following oral exposure, geraniol has high tendency to permeate across the intestinal barrier. Additionally, it can be actively transported from the intestinal lumen into the circulation **(Mączka et al., 2020).** Following inhalation, intranasal administration improves the bioavailability due to bypassing the effect of the 1st pass metabolism in the liver. Besides, bypassing the hepatic metabolism and circumventing the brain barriers, provides better option for targeting directly to the brain **(Soliman et al., 2020).**

Metabolism: Geraniol is readily absorbed after oral administration through the lumen of the gastrointestinal tract (GIT) into the portal vein to the liver where it undergoes 1st pass metabolism **(Soliman et al., 2020).** In

the liver, phase I (oxidation, reduction and hydrolysis) and phase II (conjugation) reactions assume the role of the enzymatic pathways mainly involved in geraniol metabolism. Geraniol is stepwise oxidized to (di)hydroxylated metabolites and (di)carboxylic acids. Hildebrandt acid is a terminal metabolite of several oxidation pathways of geraniol and is the most abundant metabolite **(Jäger et al., 2020).** Members of the cytochrome P450 (CYP) take part in the metabolism of geraniol with CYP2B6 being dominant in the liver while CYP1A1 and CYP3A5 are responsible for the majority of geraniol metabolism in the skin **(Kandeepan et al., 2021).**

Excretion: Conjugated or free geraniol metabolites were identified in urine after oral administration. The most prominent acidic compounds were Hildebrandt acid followed by geranic acid, 3-hydroxycitronellic acid and 8-carboxy geraniol, while the neutral metabolites identified were geraniol itself and 8-hydroxygeraniol **(Pavan et al., 2018).**

Mechanism of Action of Geraniol:

Antioxidant properties: Reactive oxygen species (ROS) is produced from different oxidation-reduction reactions in the healthy cells, such as the production and clearance of hydroxyl radical (OH^-) in a dynamic equilibrium state. When endogenous or exogenous harmful stimuli challenge the system, oxidative stress can result from an increased ROS production. In a normal physiological environment, the body has an enzymatic antioxidant system that protects against the harmful effects of ROS, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) **(Lin et al., 2021).** According to **Younis et al. (2021a),** the antioxidant features of geraniol include free radical scavenging besides boosting the activity of several antioxidant enzymes e.g. glutathione peroxidase, glutathione reductase, catalase and SOD by stimulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway that promotes gene expression of antioxidant enzymes. The anti-oxidant effects of geraniol in the central nervous system (CNS) include: inhibiting inducible nitric oxide synthase (iNOS) activity and reducing the level of nitric oxide (NO) by lowering Ca^{2+} levels in different regions of the brain; reducing neuropathic pain and functional impairment in spinal cord injury; increasing the number of NeuN positive cells, and reducing the expression of glial fibrillary acidic protein (GFAP), caspase-3 activity, malondialdehyde (MDA), and iNOS expression in the damaged area; promoting the protein expression of Nrf2 and HO-1 **(Chen and Viljoen, 2022).**

Anti-inflammatory properties: According to **Araruna et al. (2020),** terpenoids inhibit the nuclear factor- κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. According to **Horváth et al. (2021),** geraniol reduces the expression of inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor- α (TNF-α), by modulating the NF-κB signaling pathway. Geraniol has the ability to positively influence the Nrf2/HO-1 signaling pathway. Nrf2 and HO-1 can directly inhibit NF-κB signaling and pro-inflammatory cytokines and activate the anti-inflammatory cytokines, thereby regulating the inflammatory cascade **(Younis et al., 2021a).**

Protective and Therapeutic Effects of Geraniol:

Geraniol is classified by the FDA as generally-recognized-as-safe (GRAS). So, the potential therapeutic effects of geraniol have major clinical implications **(Miró et al., 2022).**

Effects on the central nervous system: Geraniol has the ability to permeate directly from the circulation to the CNS following oral administration, reaching detectable amounts in the CSF **(Pavan et al., 2018). El Azab and Abdulmalek (2022)** displayed the efficacy of dietary geraniol supplementation in modifying age-related neuroinflammation and oxidative stress and triggering off the use of geraniol as a noninvasive natural compound for controlling age- and diet-associated neuronal impairments and toxicity. **Wu et al. (2022)** reported that geraniol provides protection against cerebral injury following ischemic stroke by suppression of endoplasmic reticulum (ER) stress. It inhibited expression of ER stress proteins and pro-apoptotic Bax while increased expression of antiapoptotic Bcl-2, thus reducing apoptosis. **Soliman et al. (2020)** demonstrated the efficacy of geraniol in the form of nanostructured mixed micelles, offering increased solubility and bioavailability of geraniol, as prophylaxis in cases of cerebral ischemia/reperfusion (I/R) injury. Intranasal administration of the drug had rapid brain access and better effect through bypassing hepatic breakdown of

oral geraniol. **Farokhcheh et al. (2021)** reported that geraniol could improve learning and memory deficit induced by zinc oxide (ZnO) NPs. Geraniol decreased necrosis and gliosis, resulting in an increase in the number of neurons in the cerebral cortex and the hippocampus. It increased anti-oxidant markers and decreased the levels of the oxidative stress marker, MDA, and Zn bioaccumulation.

Effects on the cardiovascular system: According to **Younis et al. (2021b),** geraniol ameliorated doxorubicin-induced cardiac damage via its strong antioxidant, anti-inflammatory and anti-apoptotic properties. Geraniol restored the myocardial mitochondrial antioxidant response by activation of Nrf2/HO-1 pathway. It abolished doxorubicin-induced inflammation by suppression of NF-κB signaling pathway. Anti-apoptotic effect of geraniol was evidenced by reduced Bax and caspase-3 and caspase-9 in heart tissue. **Ben Ammar et al. (2022)** tested the efficacy of geraniol against atherosclerosis. Oxidative stress and inflammation of the vascular endothelium are fundamental factors in the development of atherosclerosis. Geraniol managed to decrease the production of pro-inflammatory cytokines including TNF-α, IL-6 and IL-1β. It also blocked the activation of ROS-mediated inflammation of the vascular endothelial cells. **Demirel (2022)** reported that geraniol caused vasodilatation of precontracted isolated thoracic aorta in experimental animals, suggesting its efficacy in treatment of hypertension. Similar results were obtained by **El-Bassossy et al. (2016)** who partially attributed this vasodilatory effect to endothelium-independent pathway involving calcium channel blocking effect through inhibition of the entry of Ca^{2+} via voltage dependent Ca^{2+} channels and receptor-operated calcium channels. The NAPDH oxidases (NOXs) are primary source of ROS in the vasculature. The development of hypertension and atherosclerosis is preceded by endothelial oxidative stress via activation of NOX-2. Geraniol could improve endothelial function by inhibiting NOX-2 derived ROS generation which may partly underlie its antihypertensive effect **(Wang et al., 2016).**

Effects on the respiratory system: **Fu et al. (2022)** displayed the role of geraniol in treatment of pneumonia caused by Mycoplasma pneumoniae infection. They reported that geraniol restored oxidant status of lung tissue, decreased inflammatory cytokines and corrected the histopathological damage. This was mediated by modulation of the extracellular signal-regulated kinase (ERK1/2), NF-κB and Jun N-terminal kinase (JNK1/2) expressions. According to **Lin et al. (2021),** geraniol showed promising potential against pulmonary methicillin-resistant staphylococcus aureus (MRSA) infection. It significantly mitigated inflammatory changes in the lungs, decreased inflammatory mediators and oxidative stress biomarkers.

Hepato-renal effects: According to **Mohammed et al. (2020),** geraniol supplementation ameliorated cyclophosphamide-mediated liver injury in experimental animals thanks to its antioxidant and anti-inflammatory activities, as well as, modulation of MAPK and peroxisome proliferator-activated receptor-γ (PPAR-γ) signaling pathways. **AlAsmari et al. (2022)** revealed that geraniol pre-supplementation could protect against doxurubicin-induced kidney injury by lowering oxidative stress, inflammation, and apoptotic tissue damage via the modulation of the NF-κB, Bax/Bcl-2, and Nrf2/Ho-1pathways in a dose-dependent manner. Geraniol managed to alleviate renal damage sustained by exposure to two types of insecticides. Renal functions and markers of oxidative stress significantly improved as well as histopathological findings **(Marei, 2019).**

Effects on the GIT: According to **Ricci et al. (2022),** geraniol was tested in treatment of irritable bowel syndrome (IBS). Results showed relief of IBS symptoms, together with an improvement in the gut microbiota profile.

Metabolic effects: **Eskandari et al. (2022)** reported that geraniol administration to diabetic rats could regulate lipid profile, including serum total cholesterol (TC), triglycerides (TG), low density (LDL) and high density (HDL) lipoproteins. **Kamble et al. (2020)** reported that geraniol's antihyperglycemic activity was mediated by decreasing gluconeogenic enzymes and glucose transporter-2 (GLUT2). Meanwhile, **Valdes et al. (2019)** concluded that geraniol could suppress glucose absorption by repressing the α-glucosidase enzyme and sodium-glucose cotransporter (SGLT-1). Geraniol could also alleviate hyperglycemia by increasing activities of glucose 6-phosphatase and fructose 1, 6-bisphosphatase as well as reducing activities of hexokinase and glucose 6-phosphate dehydrogenase in streptozotocin induced diabetic rats **(Babukumar et al., 2017).**

Antibacterial effect: According to **Lin et al. (2021),** geraniol has a promising potential for the prevention of MRSA infection. It exhibited dose-dependent protective activities against MRSA similar to vancomycin. **Gu et al. (2022)** also highlighted the role of geraniol against MRSA infection. Geraniol inhibited bacterial biofilm formation via downregulation of the genes involved. In combination with vancomycin, it helped removing mature biofilms and decreasing bacterial adhesion to implants.

Anti-tumor effect: Geraniol may be useful as a chemoprevention agent. It is believed to be a competitive inhibitor of CYP2B6 enzyme which itself plays a role in activation of pro-carcinogens such as aflatoxin B1 and cyclophosphamide **(Mączka et al., 2020).**

Conclusions: Geraniol is a common component of many essential oils and it can be easily extracted from natural sources. It is not only widely used as a fragrance compound in cosmetic and household products, but it also exhibits a number of biological activities, such as antimicrobiological, antioxidant and anti-inflammatory.

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