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Geraniol — A review of a commercially important fragrance material

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Abstract

Geraniol is a commercially important terpene alcohol occurring in the essential oils of several aromatic plants. It is one of the most important molecules in the flavour and fragrance industries and is a common ingredient in consumer products produced by these industries. In addition to its pleasant odour, geraniol is known to exhibit insecticidal and repellent properties and used as a natural pest control agent exhibiting low toxicity. Geraniol has been suggested to represent a new class of chemoprevention agents for cancer. Other biological activities such as antimicrobial, anti-oxidant, anti-inflammatory and some vascular effects have also been investigated. The effect of geraniol as a penetration enhancer for transdermal drug delivery has also attracted the attention of researchers and formulation scientists. This review aims to coherently discuss some of the most important applications of geraniol and unites the results obtained from several studies reporting the biological properties of this molecule.

Keywords: Bioactivity; Biosynthesis; Geraniol; Nerol; Repellency

1. Introduction

Geraniol (3,7-dimethylocta-trans-2,6-dien-1-ol) is an acyclic monoterpene alcohol with the chemical formula $C_{10}H_{18}O$. The product referred to as "geraniol" is a mixture of the two *cis-trans* isomers (Fig. 1) properly named geraniol (*trans*) and nerol (*cis*). Geraniol was isolated from Palmarosa oil while nerol was obtained from the oil of neroli (Bedoukian, 1986; Clark, 1998). It is a common constituent of several essential oils and occurs in *Monarda fistulosa* (>95%) (Simon et al., 1986), ninde oil (66.0%) (Başer et al., 2005), rose oil (44.4%) (Baydar and Baydar, 2005), palmarosa oil (53.5%) (Dubey and Luthra, 2001) and citronella oil (24.8%) (Rajeswara Rao et al., 2004). Geraniol appears as a clear to pale-yellow oil which is insoluble in water, but soluble in most organic solvents. It is emitted from the flowers of many species and it is present in vegetative tissues of many herbs and often co-exists with geranial and neral, which are the oxidation products of geraniol (Regev and Cone, 1976). Pharate females (*Tetranychus urticae*) also emit geraniol (Regev and Cone, 1976).

Geraniol has characteristic rose-like odour and the taste (at 10 ppm) is described as sweet floral rose-like, citrus with fruity, waxy nuances (Burdock, 2010). This monoterpene alcohol is a widely used fragrance material. A survey of consumer products revealed that it is present in 76% of investigated deodorants on the European market, included in 41% of domestic and household products and in 33% of cosmetic formulations based on natural ingredients and its production exceeds 1000 metric tons per annum (Rastogi et al., 1996, 1998, 2001). In addition, geraniol exhibits various biochemical and pharmacological properties. Researchers have shown geraniol to be an effective plant-based insect repellent (Barnard and Xue, 2004) and its potential as an antimicrobial agent has been highlighted in several studies (e.g. Bard et al., 1988). Geraniol exerts *in vitro* and *in vivo* antitumour activity against murine leukemia, hepatoma and melanoma cells (Burke et al., 1997; Yu et al., 1995a,b).

The purpose of this paper is to provide an overview of the published data on the biosynthesis and some of the biological properties of geraniol.

2. Biosynthesis and transformation

2.1. Biosynthesis of geraniol

Geraniol is known to be derived from geranyl diphosphate (GPP) by related synthases based on a common ionization-

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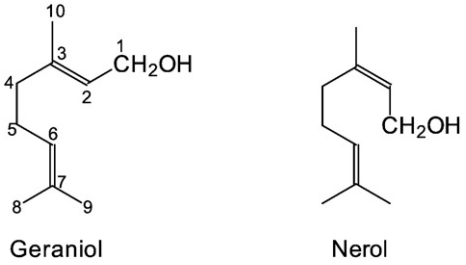

Fig. 1. Chemical structure of geraniol and nerol.

dependent reaction mechanism (Bohlmann et al., 1998). GPP is synthesized via head to tail condensation of isopentenyl diphosphate (IPP) with dimethylallyl diphosphate (DMAPP). IPP is in turn synthesized from cytoplasmic acetate-mevalonate or the recently discovered plastidic non-mevalonate (pyruvate/triose-phosphate) pathway (Mahmoud and Croteau, 2002). In general, geraniol biosynthesis is via the mevalonate route, but in some plants geraniol is known to be synthesized via the non-mevalonate pathway (Luan and Wüst, 2002). Iijima et al. (2004) first purified and characterized geraniol synthase (GES) from the peltate glands of sweet basil. This geraniol synthase was highly specific and produced only geraniol. Subsequently, Yang et al. (2005) reported the isolation of cDNA clone functionally expressed in *Escherichia coli* and identified as a geraniol synthase from *Cinnamomum tenuipilum*.

The ratios of geraniol and geranyl acetate of lemongrass (*Cymbopogon flexuosus*) fluctuated during leaf development. The level of geranyl acetate decreased from ~59 to ~3% whereas the level of geraniol increased from ~33 to ~91% during the leaf growth period. These fluctuations clearly indicated the role of an esterase involved in the conversion of geranyl acetate to geraniol during leaf development (Fig. 2) (Ganjewala and Luthra, 2009). These results are congruent with a previous study by Dubey and Luthra (2001).

The biocatalytic production of high-value chemicals from abundant, cheap and renewable feedstocks is an area of great interest. The ability of the abundant triene β-myrcene from hops to produce geraniol in the presence of the soil microbe, *Rhodococcus erythropolis* was investigated by Thompson et al. (2010). Pre-incubation of cells with the cytochrome P450 inhibitors metyrapone or 1-aminobenzotriazole reduced geraniol production by 23% and 73% respectively.

2.2. Biotransformation of geraniol

In recent years there has been an increasing tendency to produce aroma molecules from monoterpenes by biotechnological conversion. Some research has focused on the adoption of a plant cell or tissue culture process for the production of various aroma compounds (Faria et al., 2009; Nunes et al., 2009). Many micro-organisms have shown the ability to metabolize geraniol into various derivatives (Demyttenaere and De Pooter, 1996; Demyttenaere et al., 2000; Garcia Moruno et al., 2002; Rama Devi and Bhattacharyya, 1978; Wood, 1969). Geraniol can be a starting material to prepare (R)-(+)-citronellol in enantiomerically pure form by microbiological (*Saccharomyces cerevisiae*) reduction (Gramatica et al., 1982). Luan et al. (2005) also found that geraniol can be stereoselectively reduced to (S)-citronellol, E/Z-isomerization to nerol, oxidation to neral/geranial (Fig. 3) and glycosylation of the corresponding monoterpene alcohols in grape mesocarp of *Vitis vinifera* by *in vivo*-feeding experiments. Spores of *Penicillium digitatum* were able to convert geraniol NAD^+-dependently into citral by citrol dehydrogenase. The citral formed was subsequently deacetylated by citral lyase to yield methylheptenone (Wolken and Van Der Werf, 2001).

The biotransformation of geraniol by the common cutworm (*Spodoptera litura*) larvae was investigated. Geraniol was preferentially oxidized at the allylic methyl group and primary alcohol by *S. litura* larvae and transformed to 8-hydroxygeraniol, 9-hydroxygeraniol, (2E,6E)-8-hydroxy-3,7-dimethyl-2,6-octadienoic acid, (2E,6E)-3,7-dimethyl-2,6-octadiene-1,8-dioic acid and (2E,6Z)-3,7-dimethyl-2,6-octadiene-1,9-dioic acid (Takechi and Miyazawa, 2006).

3. Biological activities

3.1. Insecticide and repellent effects

Essential oils and their major components are emerging as potential pest control agents due to their insecticidal, repellent and/or antifeedant properties (Barnard and Xue, 2004; Papachristos et al., 2004). Their low mammalian toxicity and biodegradability favour their development. Using an impregnated fabric disc bioassay Jeon et al. (2009) studied the acaricidal activities of geraniol from the oil of *Pelargonium graveolens* against the storage food mite, *Tyrophagus putrescentiae*, and compared the activity to the commercial acaricide, benzyl benzoate. The results

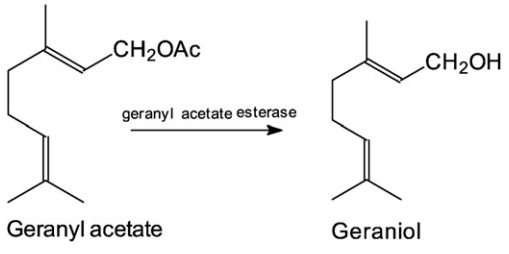

Fig. 2. The transformation of geranyl acetate into geraniol according to Dubey and Luthra (2001).

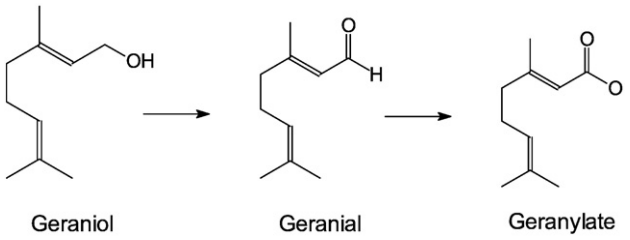

Fig. 3. The oxidation of geraniol to geranic acid according to Seubert and Fass (1964).

revealed that geraniol was more effective than benzyl benzoate with the 50% lethal dose value being 1.95 μg/cm^3 and 1.27 μg/cm^3, respectively. Another study showed that among four monoterpenes (α-pinene, geraniol, limonene and *p*-cymene), geraniol, in a 5% dilution displayed the strongest acaricidal activity against *Otodectes cynotis* by direct contact with the mites (Traina et al., 2005). Geraniol (1%) showed a reduction in the mean number of ticks per animal of 98.4%, 97.3% and 91.3% at days 7, 14 and 21, respectively (Khallaayoune et al., 2009).

The mechanism of the insecticidal property ascribed to geraniol was investigated by testing its neurophysiological effect in *Periplaneta americana* (the American cockroach) and *Blaberus discoidalis* (discoids). Geraniol suppressed spontaneous and stimulus-evoked impulses recorded extracellularly in the abdominal nerve cord, but increased spontaneous firing at lower doses (threshold 2.5×10^{-4} M). Geraniol produced dose-related biphasic effects on dorsal unpaired median neurons. Low doses of geraniol (threshold ca. 10^{-4} M) reversibly increased the frequency of spontaneous foregut contractions and abolished these at 2×10^{-3} M (together with response to electrical stimulation) (Price and Berry, 2006).

Mosquitoes pose a potential health risk, because they are vectors of several serious diseases. Geraniol proved to be effective in repelling mosquitoes (Omolo et al., 2004). Geraniol-based products are available commercially in several countries as natural repellents. Geraniol candles were found to be more effective than citronella and linalool candles in protecting a person from being bitten indoors by mosquitoes and sand flies (Müller et al., 2008). In a comparative study between three botanical natural repellents, a lemongrass extract in combination with 25% geraniol oil exhibited the longest protection time against mosquitoes (Qualls and Xue, 2009). Müller et al. (2009) determined the degree of personal protection provided by commercial citronella, linalool and geraniol candles or diffusers. Indoors, the repellency rate of geraniol candles was 50%, while the diffusers provided a repellency rate of 97%. Outdoors, geraniol diffusers placed 6 m from mosquito traps repelled female mosquitoes by 75%. Geraniol had significantly more repellent activity than citronella or linalool in both indoor and outdoor settings. Hao et al. (2008) evaluated the changes of the host-seeking and blood-feeding behavior of *Aedes albopictus* surviving in a space containing vapors of geraniol, eugenol, citral, anisaldehyde, or citronellal by using an arm-in-cage test and a bioassay of blood meals on a shaved mouse. After 48 h of exposure to 0.250 μg/ml geraniol, almost 100% of the mosquitoes lost their host-seeking ability. Geraniol also significantly affected the activation and orientation stages of the blood-feeding behavior.

3.2. Anthelmintic activities

Human infection with parasites can cause zoonotic diseases such as anisakiasis. Some monoterpenes have shown a significant anti-helminthic activity *in vitro* and *in vivo* (Hierro et al., 2006; Navarro et al., 2008). Leela et al. (1992) investigated the nematicidal activity of essential oil of *P. graveolens* and its major constituents (citronellol, geraniol and linalool) against the root-knot nematode (*Meloidogyne incognita*). Geraniol was found to be the most effective constituent. Another study tested the anthelmintic activity of the essential oil of *Cymbopogon martinii* (palmrosa) and its main constituent geraniol *in vitro* employing the nematode, *Caenorhabditis elegans*. The ED_{50} of geraniol was found to be 66.7 μg/ml, suggesting geraniol as the putative anthelmintic principle of palmrosa oil (Kumaran et al., 2003). Geraniol was also found to exhibit larvicidal activity against the genus of roundworms *Contracaecum* (Barros et al., 2009) and against marine nematodes *Anisakis simplex* (Hierro et al., 2004).

3.3. Antimicrobial effects

Essential oils are known to exhibit antimicrobial activity against a wide range of bacteria and fungi. The antimicrobial activity of essential oils is due to their solubility in the phospholipid bilayer of cell membranes (Knobloch et al., 1989). It was also reported that the antibacterial activities of monoterpene alcohols (including linalool, nerol, citronellol and geraniol) are more effective than their antifungal activity (Suppakul et al., 2003). Friedman et al. (2002) evaluated the bactericidal activity levels of 96 essential oils and 23 oil compounds against *Campylobacter jejuni*, *E. coli*, *Listeria monocytogenes* and *Salmonella enterica* obtained from food and clinical sources by using a microtiter plate assay. Geraniol was most active against *E. coli* (with a bactericidal activity value of BA_{50} 0.15), against *L. monocytogenes* (BA_{50} 0.28) and *S. enterica* (BA_{50} 0.15). Among the 66 essential oils/compounds tested, geraniol inhibited the growth of both human and animal pathogens, *Salmonella typhimurium* and *E. coli* (Si et al., 2006). According to Inouye et al. (2001), geraniol in the gaseous state exhibited antibacterial activity against respiratory tract pathogens, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *S. pyogenes* and *Staphylococcus aureus*. The *in vitro* antimicrobial activity of geraniol towards seven strains of *Erwinia amylovora*, the causal agent of 'fire blight' of rosaceous plants, was assessed in tube cultures by Scortichini and Rossi (2008). All of the strains tested at 1×10^5 cfu/ml were inhibited for 24 h by geraniol in the range 600–1500 μg/ml. Geraniol reduced the germ count by 64% when vaporized with an air washer (Sato et al., 2007). The antitubercular activity of citronellol, nerol and geraniol against *Mycobacterium tuberculosis* was evaluated *in vitro* and exhibited MIC values between 64 and 128 μg/ml (Cantrell et al., 2001).

The antifungal action of palmarosa oil (*Cymbopogon martinii*) is mainly attributed to its geraniol content (Prashar et al., 2003). The antimicrobial action of palmarosa oil against *S. cerevisiae* takes place via a two-step process. The first step involves the passive entry of the oil into the plasma membrane in order to initiate membrane disruption. The second stage was the accumulation in the plasma membrane resulting in the inhibition of cell growth. The antifungal activity can be ascribed to the combined membrane effects such as increased bilayer disorder and ion leakage. These effects disturbed the osmotic balance of the cell through loss of ions, making its membrane associated proteins inefficient due to increased membrane disorder eventually leading to inhibition of cell growth or cell

death. This result was further confirmed by Dalleau et al. (2008). Essential oils are known to not only be active again in the planktonic forms of microbes but also exert an inhibitory effect on the more resistant biofilms. Among 10 tested terpenes, carvacrol, geraniol and thymol were able to significantly reduce biofilm development of a *Candida albicans* strain and induced >80% inhibition of the biofilm when assayed at concentrations of 0.06%. Therefore, carvacrol, geraniol and thymol can be used as potential antibiofilm agents. Van Zyl et al. (2006) tested 20 nature identical essential oil constituents for antimalarial, antimicrobial and anti-oxidant properties. Geraniol displayed strong activity against *C. albicans* (MIC value 19.5 mM). Palmarosa oil and geraniol were both found to inhibit *Cryptococcus neoformans*, a fungus causing infection during the last stages of AIDS (Viollon and Chaumont, 1994). Geraniol exhibited significant antifungal activities toward *Colletorichum camelliae*, with an MIC value of 440 μg/ml (Zhang et al., 2006). When combined with vaginal washing, geraniol (25 μg/ml) significantly decreased the viable cell number of *Candida albicans*, and possibly offered protection from vaginal inflammation (Maruyama et al., 2008).

Several plant extracts have exhibited synergistic activity against micro-organisms. The essential oil of *P. graveolens* and its main components (geraniol and citronellol) exhibited strong synergism with ketoconazole against *Trichophyton schoenleinii* and *T. soudanense*, with FIC indices in the range of 0.18–0.38 (Shin and Lim, 2004). In another combination study undertaken by Rosato et al. (2007) on Norfloxacin and *P. graveolens* essential oil, a synergistic effect was obtained against *Bacillus cereus*, *S. aureus* and *S. aureus* 29213 with a FIC index of 0.50, 0.37 and 0.38, respectively. When Norfloxacin was administered with geraniol, the antibacterial effects were also shown to increase to a lesser extent. The essential oil of *Helichrysum italicum* (2.5%) can significantly reduce the multidrug resistance of Gram-negative bacteria, *Enterobacter aerogenes*, *E. coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* to the antibiotic chloramphenicol. Combinations of this essential oil with phenylalanine arginine β-naphthylamide yielded synergistic activity. Geraniol, an active constituent of *H. italicum*, significantly increased the efficacy of β-lactams, quinolones, and chloramphenicol by targeting efflux mechanism (Lorenzi et al., 2009).

3.4. Anti-oxidant effects

Free radicals cause oxidation of biomolecules and ultimately produce molecular alterations related to aging, arteriosclerosis, cancer, Alzheimer's disease, diabetes and asthma (Edris, 2007). Recently researchers have focused on essential oils as anti-oxidants or free radical scavengers. Choi et al. (2000) investigated 34 citrus essential oils and their components for radical-scavenging activities using the *in vitro* 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay and comparing the activity with a standard anti-oxidant, Trolox. Geraniol (a citrus volatile) showed marked scavenging activities against the DPPH radical (87.7%, 235.9 mg of Trolox equiv/ml). Tiwari and Kakkar (2009) also reported the anti-oxidant potential of geraniol using tsigniertiary-butyl hydroper-oxide stressed rat alveolar macrophages. Geraniol increased the cell viability significantly and showed 45% increase in superoxide dismutase activity, 120% increase in glutathione content and restored the mitochondrial membrane potential. Geraniol was found to significantly decrease lipid peroxidation, inhibit NO release (64.61%) and ROS generation in the pre-treated cells as compared to stressed cells. Geraniol also showed significant protection against ROS. These results indicated the pharmacological potential of geraniol in lung inflammatory diseases where oxidative stress was a critical control point.

3.5. Anticancer activities

Geraniol has demonstrated anticancer activity *in vitro* and *in vivo* in a number of models of human cancer. It exhibited chemotherapeutic activity towards pancreatic and other cancers (Burke et al., 1997). Geraniol (100 μM) significantly inhibited the anchorage-independent growth of human MIA PaCa2 pancreatic tumor cells, and Syrian Golden hamsters fed geraniol at 20 g/kg diet exhibited complete inhibition of PC-1 pancreatic tumour growth *in vivo*. Burke et al. (2002) further investigated the mechanism of action of geraniol against pancreatic tumors. They reported that geraniol can induce apoptosis and increase expression of the proapoptotic protein Bak in cultured pancreatic tumor cells. Wiseman et al. (2007) demonstrated that geraniol caused arrest in the G_0/G_1 phase of the cell cycle through induction of cyclin kinase inhibitors $p21^{Cip1}$ and $p27^{Kip1}$, resulting in a reduction of Cdk2 activity and decreasing expression of downstream cell cycle-related proteins in human pancreatic adenocarcinoma cells. Geraniol showed chemopreventive activities on hepatocarcinogenesis during the initial phases of the RH model by inhibition of cell proliferation, DNA damage and increasing hepatic placental glutathione S-transferase positive preneoplastic lesions (PNLs) apoptosis (Ong et al., 2006). Yu et al. (1995b) also reported that female Sprague–Dawley rats treated with geraniol for 2 weeks prior to initiation with 7,12-dimethylbenz[α]anthracene and 22 weeks afterwards presented inhibition of mammary tumour multiplicity.

Geraniol has antiproliferative effects on hepatoma and melanoma cell growth (Polo and De Bravo, 2006). The antiproliferative effects of geraniol on human colon cancer cells were related to its ability to reduce DNA synthesis leading to a blockade of the cells in the S phase of the cell cycle (Carnesecchi et al., 2001). 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzed the formation of mevalonate, a precursor of cholesterol that was also required for cell proliferation. Inhibition of mevalonate synthesis may be a useful strategy to impair the growth of malignant cells (Goldstein and Brown, 1990; Jakobisiak and Golab, 2003). Geraniol suppressed HMG-CoA reductase synthesis in mammalian cells by decreasing the translation efficiency of HMG-CoA reductase transcripts (Peffley and Gayen, 2003). Pattanayak et al. (2009) found that geraniol can interact with HMG-CoA reductase. Duncan et al. (2004) reported that geraniol can inhibit proliferation, cell cycle progression, and

cyclin-dependent kinase 2 activity in MCF-7 breast cancer cells independent of effects on HMG-CoA reductase activity. This finding indicated that understanding the growth and cell cycle inhibitory effects of plant isoprenoids would require further investigation of mevalonate-independent mechanisms.

Geraniol (150 μM) has been identified to reduce thymidylate synthase and thymidine kinase expression in colon cancer cells. In nude mice, the combined administration of 5-fluorouracil (20 mg/kg) and geraniol (150 mg/kg) caused a 53% reduction of the tumor volume, whereas a 26% reduction was obtained with geraniol alone (Carnesecchi et al., 2004). Mans et al. (1999) found that thymidylate synthase and thymidine kinase were involved in 5-fluorouracil (5-FU) toxicity and decreasing in these enzymes was related to enhanced 5-FU cytotoxicity. Carnesecchi et al. (2002a, b) also reported that geraniol can lower the resistance of cancer cells to 5-FU and increase the survival time of nude mice grafted with the human colorectal tumor cells TC118 by increasing cell membrane permeability which leaded to enhanced uptake of 5-FU by colon cancer cells and causing a significant change in the resting potential and cell membrane polarization and further may trigger modifications of membrane bound protein activity and alterations in intracellular signaling pathways.

3.6. Anti-inflammatory activities

Ji et al. (2002) investigated geraniol's immunosuppressive properties by using *in vitro* lymphocyte proliferation assays and *in vivo* rat cardiac allograft transplant model. The results revealed that geraniol can prevent acute allograft rejection. In 2003, Abe and his co-workers assessed the anti-inflammatory activity of some essential oils on neutrophil activation by measuring tumor necrosis factor-alpha (TNF-α)-induced adherence reaction of human peripheral neutrophils *in vitro*. They found that lemongrass, geranium, spearmint oils and their major constituent terpenoids (citral, geraniol, citronellol and carvone) clearly suppressed TNF-α-induced neutrophil adherence at 0.0125% concentration.

3.7. Other effects

Geraniol enhanced the anti-herpetic activity of antisense phosphorothioate oligonucleotide (SON) with less cytotoxicity in a sequence specific manner (Shoji et al., 1998). At high concentration, geraniol appeared to have the potential to interact with estrogen receptors by using recombinant yeast cells expressing the human estrogen receptor (Howes et al., 2002).

Human CYP2B6 had been regarded as a minor hepatic drug-metabolizing enzyme, and it was important in the metabolism of drugs such as bupropion, cyclophosphamide, efavirenz, sibutramine, and tamoxifen. Geraniol showed potent inhibition of human CYP2B6 activity, with Ki values of 6.7 μM, which was higher than the Ki (1.8 μM) of the well-known CYP2B6-selective inhibitor thio-TEPA (Seo et al., 2008).

Azarmi et al. (2009) investigated the vascular effect of geraniol by using isolated rat aorta. Geraniol in a dose dependent manner reduced the contractile response to noradrenalin and relaxed of KCl induced active tone in rat aorta. Relaxant effects of geraniol on the KCl induced contraction was not modified by the NO synthase inhibitor N-nitro-L-arginine methyl ester, methylene blue and indomethacin.

3.8. Absorption and transdermal enhancement effects of geraniol and possible mechanism of action

The percutaneous absorption of geraniol from an oil-in-water emulsion was studied by Doan et al. (2010). *In vivo* absorption of geraniol 24 h after dermal application was 15.1 ± 1.8% of the applied dose. *In vitro* absorption of geraniol over 24 h was 45.9 ± 3.2% of the applied dose in receptor fluid by using flow-through diffusion cells (0.64 cm^2). The difference between *in vivo* and *in vitro* dermal absorption values for geraniol may be due to the rapid evaporation of geraniol from the skin.

Transdermal drug delivery systems represent a novel and beneficial therapeutic approach to the delivery of pharmaceuticals. Terpenes have been used as penetration enhancers for improved transdermal drug delivery (Aqil et al., 2007), because they are reported to have good toxicological profiles, high percutaneous enhancement abilities, and negligible cutaneous irritancy at low concentration (1–5%) (Nokhodchi et al., 2007). The acyclic monoterpene geraniol has also been investigated as a percutaneous enhancer. Eleven monoterpenes were investigated for their effect on percutaneous absorption of three different model drugs with varying lipophilicities. Geraniol gave a 16-fold increase in the permeation of caffeine (Godwin and Michniak, 1999). Arellano et al. (1996) studied the effect of 1% concentration of several terpenes in a carbopol gel formulation containing propylene glycol on the excised abdominal rat skin penetration of diclofenac sodium. The most effective terpene was geraniol. Another study revealed that addition of tetrahydrogeraniol in a gel containing 5-fluorouracil markedly enhanced the 5-fluorouracil permeability. The maximum flux was obtained at a concentration of 8% tetrahydrogeraniol (Hanif, 1998). In 2009, Kigasawa et al. examined *in vivo* availability and safety of ion-exchange iontophoresis combined with geraniol in the transdermal delivery of anionic diclofenac to rat dorsal skin. The results revealed that geraniol combined with iontophoresis increased the plasma concentration of diclofenac sodium over 20-fold, and suppression of inflammation was achieved. The enhancing effect of geraniol was attributed to increased penetration of the drug into the stratum corneum as well as enhanced transport across the anion-exchange membrane. Recently, geraniol was found to increase permeation flux of the antimicrobial agent, silver sulphadiazine, through third-degree burn eschar with enhancement ratio of 5.5. The main mechanism of geraniol increasing permeation of silver sulphadiazine was ascribed to increased partitioning of this drug into the eschar (Moghimi et al., 2009).

4. Toxicity and allergenicity

Toxicity of geraniol has been investigated in various organisms. Rat studies have shown that neither 10 000 ppm geraniol in the diet fed for 16 weeks nor 1000 ppm in the diet

fed for 28 weeks produced any adverse effects (Hagan et al., 1967). In clinical sensitization testing, 6% geraniol in petrolatum was tested in 25 volunteers and produced no positive reactions (Greif, 1967). No mutagenic effects were observed in an Ames test conducted on *S. typhimurium* with 0.5 mg geraniol in DMSO with and without S9 activation (Ishidate et al., 1984).

Geraniol is not an electrophile and should consequently not show any sensitizing capacity, but there are some reports of allergic contact dermatitis resulting from sensitivity to geraniol (Cardullo et al., 1989). In addition, geraniol is listed on the European Union's 26 fragrance allergens that must be identified on cosmetic and detergent product labels (Buckley, 2007). Contact sensitization is caused by low molecular weight compounds which penetrate the skin and bind to proteins. Hagvall et al. (2007, 2008) reported that geraniol had the potential to autoxidize on air exposure or by CYP-mediated metabolic activation in the skin, and formed highly allergenic compounds. The autoxidation of geraniol followed two paths, originating from allylic hydrogen abstraction near the two double bonds. Hydrogen peroxide was primarily formed together with aldehydes geranial and neral from a hydroxyhydroperoxide, and small amounts of a hydroperoxide was formed. The hydroperoxide formed was believed to be the major contributor to allergenic activity, together with the aldehydes geranial and neral (Hagvall et al., 2007). Geraniol could also be metabolically activated to geranial, neral, 2,3-epoxygeraniol, 6,7-epoxygeraniol and 6,7-epoxygeranial by a skin-like CYP cocktail consisting of cutaneous CYP isoenzymes. Geranial, neral and 6,7-epoxygeraniol were shown to be moderate sensitizers, and 6,7-epoxygeranial a strong sensitizer (Hagvall et al., 2008). In 2008, Lapczynski et al. comprehensively summarized safety data relevant to the risk assessment of the use of geraniol. They listed studies on oral, dermal, intramuscular, subcutaneous, inhalation acute toxicity; skin irritation and sensitization; mucous membrane (eye) irritation of geraniol. The scientific evaluation focused on dermal exposure because skin was considered to be the primary exposure route for this fragrance material. Phototoxicity and photoallergy, repeated dose toxicity, mutagenicity and genotoxicity of geraniol were also described.

5. Conclusions

Geraniol is abundant and occurs in a large number of plants. This molecule is widely used as a fragrance chemical in both cosmetic and household products. Several studies have confirmed the pharmacological properties of this acyclic monoterpene alcohol. Conclusive research has shown geraniol to be an effective plant-based mosquito repellent, insecticide for controlling pests with low mammalian toxicity and biodegradability. Geraniol is employed as natural enhancer to improve the skin penetration of 5-fluorouracil, diclofenac sodium and silver sulphadiazine. The good chemopreventive activity of geraniol may present a new class of cancer therapeutic agent and renders a great opportunity for further investigation. The several biological properties of geraniol including antimicrobial, anti-oxidant and anti-inflammatory activities, together with negligible toxicity, warrant further studies to explore the feasibly of formulating geraniol-containing consumer products with health promoting properties.

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