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Molecules of Interest

Menthol: A simple monoterpene with remarkable biological properties

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ABSTRACT

Menthol is a cyclic monoterpene alcohol which possesses well-known cooling characteristics and a residual minty smell of the oil remnants from which it was obtained. Because of these attributes it is one of the most important flavouring additives besides vanilla and citrus. Due to this reason it is used in a variety of consumer products ranging from confections such as chocolate and chewing gum to oral-care products such as toothpaste as well as in over-the-counter medicinal products for its cooling and biological effects. Its cooling effects are not exclusive to medicinal use. Approximately one quarter of the cigarettes on the market contain menthol and small amounts of menthol are even included in non-mentholated cigarettes. Natural menthol is isolated exclusively from *Mentha canadensis*, but can also be synthesised on industrial scale through various processes. Although menthol exists in eight stereoisomeric forms, (−)-menthol from the natural source and synthesised menthol with the same structure is the most preferred isomer. The demand for menthol is high and it was previously estimated that the worldwide use of menthol was 30–32,000 metric tonnes per annum. Menthol is not a predominant compound of the essential oils as it can only be found as a constituent of a limited number of aromatic plants. These plants are known to exhibit biological activity *in vitro* and *in vivo* such as antibacterial, antifungal, antipruritic, anticancer and analgesic effects, and are also an effective fumigant. In addition, menthol is one of the most effective terpenes used to enhance the dermal penetration of pharmaceuticals. This review summarises the chemical and biological properties of menthol and highlights its cooling effects and toxicity.

1. Introduction

Menthol (also known as mint camphor) is a cyclic monoterpene alcohol which is found as a major constituent in the essential oils of *Mentha canadensis* L. (cornmint) and M. x piperita L. (peppermint). Menthol along with menthone, isomenthone and other compounds imparts the cooling minty taste and smell to plants, especially to members of the *Mentha* genus. Originally plants were the only source of menthol and have been cultivated for medicinal purposes in Japan for ages before the compound was isolated and characterised (Lawrence, 2013). It was the Dutch botanist, Gambius who first isolated this compound as a crystalline principle in 1771 (Read, 1930). When referring to menthol in general, it means that the L- or (−)-menthol is usually implied. Commercially, this compound is the most important natural isolate (Lawrence, 2006; Patel et al., 2007). It is estimated that between 30 and 32,000 metric tonnes of menthol is consumed annually. After vanilla and citrus, (−)-menthol is one of the most important flavouring substances and it is the prominent compound in many tobacco products, where it was first used as an additive in the 1920s (Ruskin et al., 2007; Etzold et al., 2009). Menthol is sometimes present at low levels even in non-mentholated cigarette brands and it is estimated that one quarter of cigarettes sold contains menthol (Ruskin et al., 2007). The "coolness" of the smoke of menthol is viewed as pleasurable to the smokers who prefer mentholated cigarettes particularly in the United States (Werley et al., 2007). Menthol (CAS No. 2216-51-5, EINECS No. 218-690-9, FEMA No. 2665) is also included as an ingredient in a variety of consumer products including pharmaceuticals, cosmetics and pesticides, candies, chewing gum, liqueurs, toothpastes, shampoos and soaps as a cooling and/or flavour enhancing ingredient (Fig. 1A–C) (Patel et al., 2007; Kolassa, 2013). Menthol is a major essential oil constituent of a very limited number of aromatic plants, known to exhibit various biological properties such as antimicrobial, anticancer and anti-inflammatory activities. These plants are also used as insect repellents or fumigants.

1.1. Chemical and physical properties of menthol

Menthol [5-methyl-2-(1-methylethyl)cyclohexanol; 2-isopropyl-5-methylcyclohexanol or *p*-methan-3-ol] with the molecular

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Fig. 1. Menthol is included in many different consumer products including (A) chocolate, (B) chewing gum and (C) toothpaste.

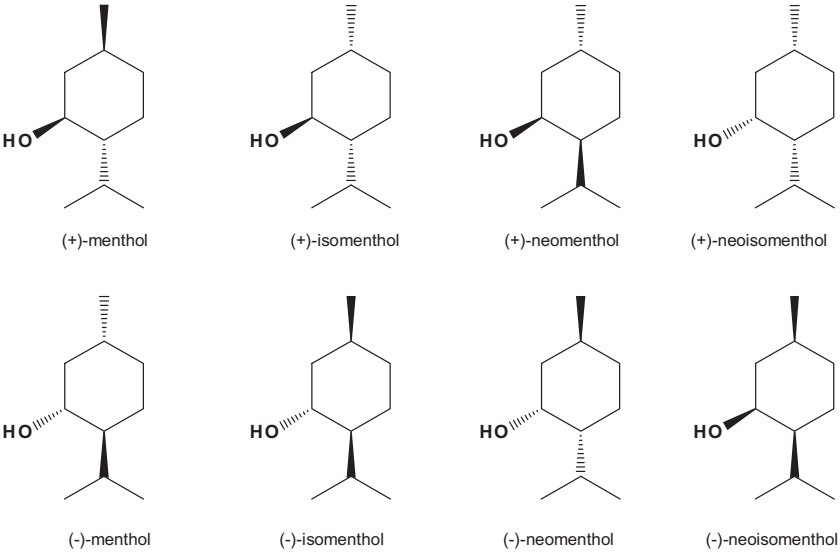

Fig. 2. The various stereoisomers of menthol.

formula $C_{10}H_{20}O$ (mol. wt. 156.27) is a natural compound with three asymmetric carbon atoms and, thus, occurs as four pairs of optical isomers namely (+)- and (−)-isomenthol, (+)- and (−)-menthol, (+)- and (−)-neomenthol, (+)- and (−)-neoisomenthol (Fig. 2). The principal form of menthol found in nature is (−)-menthol (L-menthol), with the following configuration; 1R,3R,4S. This form is commonly used because it possesses greater cooling properties than the other menthol isomers. Like other saturated alcohols, menthol reacts in many ways and can be oxidised to menthone. Menthol is a white or colourless, flaky, crystalline substance, solid at room temperature with a density of 0.890 kg/dm^3 (25 °C) and a melting point of 41–44 °C depending on its purity. Menthol is not entirely soluble in water (435.5 mg/L at 25 °C), but freely soluble in alcohol, diethyl ether or chloroform (Sell, 1999; Hopp and Lawrence, 2006). Menthol, like many other terpene alcohols such as citronellol, geraniol, linalool, myrcenol, nerol and nerolidol, does not absorb UV light well in the 290–320 nm range, but absorbs below 290 nm with the peak absorption at 220 nm (Belsito et al., 2008).

1.2. Origin of menthol

1.2.1. Natural origin and biosynthesis

Monoterpenes such as menthol are derived primarily from aromatic plants. They are chemical messengers with diverse functions together with other organic compounds of essential oils. Menthol is obtained from cornmint oil that is produced by steam distillation. Cornmint oil has a menthol content of 55–85% (Lawrence, 2006). Natural menthol is generally preferred because the scent of synthetic L-menthol is influenced by contaminants that arise during the crystallisation process (Sell, 1999).

Menthol is biosynthesised in plants in an 8-step pathway from primary metabolism. The biosynthesis was described eloquently in great detail by Croteau et al. (2005) including the anatomic structures where synthesis takes place as well as the enzymes involved. A simplified version of this biotransformation is illustrated in Fig. 3. The universal monoterpene precursor geranyl diphosphate is formed by the condensation of isopentenyl diphosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) which in turn is converted to (−)-limonene through cyclisation. (−)-Limonene is converted to (−)-*trans*-isopiperitenol through NADPH- and oxygen-dependent hydroxylation. (−)-Isopiperitenone is formed by allylic oxidation followed by NADPH-dependent reduction to form (+)-*cis*-isopulegone. Isomerisation of (+)-*cis*-isopulegone leads to the formation of (+)-pulegone (Croteau et al., 2005) which is the precursor of (+)-menthofuran (Lawrence, 1978), (−)-menthone and (+)-isomenthone. Reduction of these ketones yield (−)-menthol, (+)-neomenthol, (+)-isomenthol and (+)-neoisomenthol (Croteau et al., 2005).

1.2.2. World production of menthol and chemical synthesis

The main supply of menthol is obtained naturally and in 2007, the world production of (−)-menthol was approximately 19,000 tonnes (Clark, 2007) principally obtained from *M. canadensis*. Only approximately 6300 tonnes were produced synthetically (Etzold et al., 2009) by companies such as Symrise, (Germany), Takasago (Japan) and to a lesser extent Camphor & Allied (India) (Sell, 1999). More recently, BASF has commenced production of synthetic menthol (Lawrence, 2013). Various routes have been

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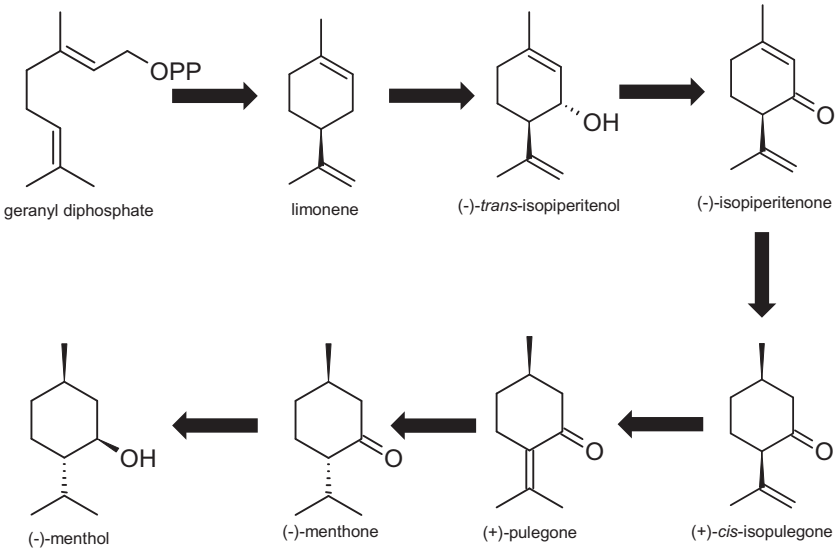

Fig. 3. The 8-step pathway of menthol biosynthesis (adapted from Croteau et al., 2005).

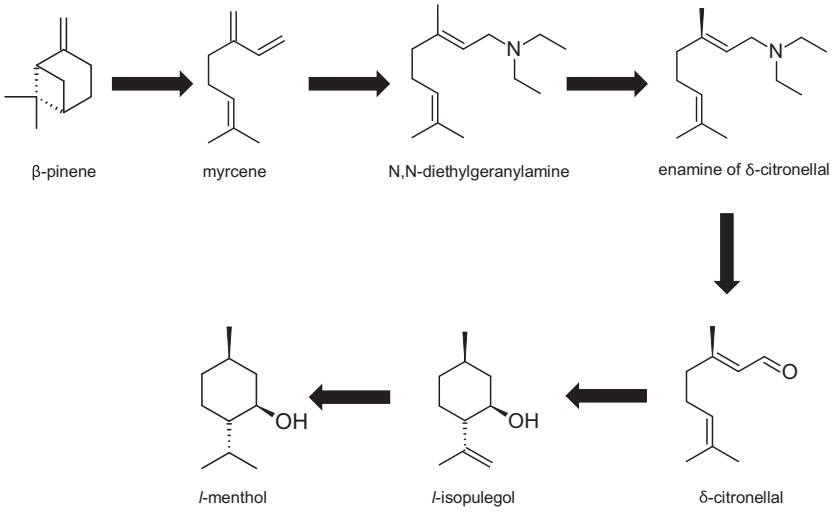

Fig. 4. The chemical synthesis method of L-menthol used by Takasago (Japan) developed by chemistry nobel laureate Prof Noyori (adapted from Sell, 2006).

described for the industrial synthesis of (−)-menthol. These include synthesis from (−)-β-pinene, (+)-limonene, (+)-citronellal, (+)-pulegone, (−)-piperitone, thymol, β-phellandrene, δ-3-carene, citral, or *m*-cresol as precursors. The synthetic pathways are described in detail by several authors (Sell, 1999; Hopp and Lawrence, 2006). The Japanese company Takasago produces more than 2000 tonnes of synthetic L-menthol annually using β-pinene as a starting material. The Nobel Prize for chemistry was awarded to Professor Noyori in 2001 for this work. Myrcene is formed through pyrolysis of β-pinene. Diethylamine is then added in the presence of a catalytic amount of strong base to form N,N-diethylgeranylamine. The enamine of δ-citronellal is produced through isomerisation with rhodium BINAP complex followed by hydrolysis to δ-citronellal. δ-Citronellal is cyclised into isopulegol and pure L-isopulegol is produced due to the chirality of citronellal. Finally, L-isopulegol is hydrogenated to L-menthol. A simplified version of the chemical synthesis using this method is illustrated in Fig. 4 (Sell, 2006).

2. The cooling effects of menthol and its effect on body temperature

2.1. The cooling effects of menthol

Menthol is well known for its cooling effect or sensation when it is inhaled, chewed, consumed or applied to the skin due to its ability to chemically activate the cold-sensitive transient receptor potential cation channel (TRPM8) (Yosipovitch et al., 1996). Studies have shown that menthol acts upon TRPM8 receptors by speedily increasing intracellular calcium and mobilising calcium flux through the channels to induce cold response signals at the application site (Farco and Grundmann, 2013). A study by Yosipovitch et al. (1996) determined that the cooling effect of menthol could last for 70 min or more in 65% of the human subjects investigated. Almeida et al. (2006) demonstrated that low levels of menthol administered intravenously caused rats to search for warmer ambient temperatures. However, enhancement of warmth

intensity was observed in one human subject. At a temperature above 37 °C, solutions containing 0.02% menthol is warmer than water that does not contain menthol (Green, 1985). Furthermore, it was noted that after application of 40% menthol to human subjects, 10% reported sudden sensations of warmth (Hatem et al., 2006).

2.2. The effect of menthol on body temperature and the pharmacokinetics of nicotine

Nicotine is the main active constituent of tobacco but menthol is commonly added to cigarettes. It was expected that interactions such as augmentation will take place and increased intake of nicotine and inhibition of nicotine metabolism has been noted. It has also been shown that menthol has a modulating effect on nicotinic acetylcholine and other ionotropic neurotransmitter receptors. Hypothermia is a known effect of the activation of central nicotinic receptors and menthol is a known antagonist of the TRPM8, which is a cold sensor (Ruskin et al., 2007). Ruskin et al. (2007) investigated the effect of menthol and nicotine on body temperature of rats. Subcutaneous injection of (−)-menthol (200 or 400 mg/kg) and (−)-nicotine (0.5 mg/kg) was followed by body temperature monitoring. Independent and opposite effects of the combination of nicotine and menthol on body temperature was noted. Mild hyperthermia of 0.4–0.8 °C, not due to locomotor activation, was caused by menthol alone while nicotine caused robust hypothermia (−1.6 °C). It was concluded that the central nicotinic receptors known to regulate body temperature was not affected by subcutaneous menthol injection and its mechanism for causing hyperthermia is therefore still unclear. The presence of menthol in cigarettes is unlikely to cause an increase in body temperature in smokers as studies have confirmed (Ruskin et al., 2007).

3. Biological properties of menthol

Peppermint tea and peppermint essential oil containing high concentrations of menthol and menthone are used in traditional medicine to treat various conditions including infections and also as insect repellant. Various *in vitro* and *in vivo* studies have documented the biological properties of menthol such as its analgesic, antibacterial, antifungal, anaesthetic and penetration-enhancing effects as well as chemopreventive and immunomodulating actions.

3.1. Analgesic effect

Hyperalgesia is the enhancement in sensitivity to pain caused by nociceptors or peripheral nerves. The analgesic effect of menthol was investigated by monitoring thirteen quasistatic tester (QST) parameters in 12 healthy male volunteers. Menthol was applied to the right hand at a concentration of 400 mg and the results were compared to baseline measurements. Cold- and heat-hyperalgesia was recorded over 180 min and decrease of cold-pain (6.93 ± 6.5 °C/20.23 ± 6.8 °C) and heat-pain (45.5 ± 2.1 °C/44.1 ± 1.5 °C) was noted. At 225 min, however, cold-pain was not statistically significant (9.5 ± 7.9 °C), whereas heat-pain decreased significantly (Stengel et al., 2007). In another study, high menthol concentrations (>30%) were found to induce cold pain. The thresholds for cold-pain and warm-pain detection were evaluated using two groups; the capsaicin group composed of regular chilli-eaters (n = 11) and the control group (n = 11). The effect of menthol was evaluated by requesting that all 22 participants suck a lozenge containing 0.52% menthol for 5 min. Cold detection and warm detection increased by 3.7 and 4.1 °C, respectively after treatment with menthol (Kalantzis et al., 2007). The most prominent characteristic of neuropathic pain is cold hyperalgesia. The effect of menthol on cold hyperalgesia was investigated on 12 healthy volunteers after topical application of 40% (−)-menthol on hairy skin. It was observed that menthol decreased the cold pain and mechanical pain thresholds and increased the mechanical pain sensitivity in all subjects, displaying cold and mechanical pinprick hyperalgesia (Binder et al., 2011).

Some studies have shown that the stereochemistry of a compound could have a profound effect on its biological activity. The structural relationships of menthol was investigated by Galeotti et al. (2002) who highlighted the analgesic properties of (+)- and (−)-menthol using thermal (hot-plate) and chemical (abdominal constriction) stimuli on albino mice. (−)-Menthol was able to amplify the pain threshold, while (+)-menthol did not exhibit any analgesic effects (Galeotti et al., 2002). It is important to note that the effect of menthol may vary greatly depending on the concentration used, the duration of application and the area of application as shown in some studies (Green, 1986; Cliff and Green, 1996). Yosipovitch et al. (1996) showed that 10% menthol in ethanol applied to the skin of the forearm resulted in unchanged pain thermal sensory thresholds, whereas increasing the menthol concentration to 40% caused cold allodynia.

Scientific investigations have shown that voltage-gated Na^+ channels are critical for experiencing pain sensation (Gaudioso et al., 2012). A study conducted to determine whether menthol can block voltage-gated Na^+ channels in dorsal root ganglion neurons revealed that menthol inhibited Na^+ channels in a concentration-voltage-and frequency-dependent manner. Menthol was found to promote rapid and slow inactivation states thus causing use-dependent depression of Na^+ channel activity (Gaudioso et al., 2012). The cooling effects of menthol are due to the stimulation of 'cold' receptors by inhibition of Ca^{2+} currents of neuronal membranes. In a study conducted on the skin of 16 human volunteers, the analgesic effects of tetracaine gel containing menthol and active control analgesia cream (EMLA®) were investigated. No reactions were recorded in any of the 16 subjects investigated. However, 5% menthol penetration-enhanced tetracaine gel showed a strong analgesic effect which was significantly higher than with tetracaine gel alone. Moreover, the analgesic effect of 5% menthol tetracaine gel was even better than the commercially available topical EMLA® anaesthetic cream (Liu et al., 2005). The *in vivo* (rabbit) and *in vitro* (rat) anaesthetic effects of menthol were examined using the conjunctival reflex test and a phrenic nerve hemidiaphragm preparation, respectively. The effects were dose-dependent and both (+)-menthol and (−)-menthol significantly reduced contractions in the *in vitro* rat test and significantly increased the number of stimuli needed to produce a reflex in the *in vivo* rabbit test, thereby confirming a local anaesthetic effect (Galeotti et al., 2001).

3.2. Antifungal activity

Several authors have investigated the inhibitory potential of menthol against fungi (Moleyar and Narasimham, 1986; Kishore et al., 1993; Edris and Farrag, 2003). Menthol was tested against *Fusarium verticillioides* using the semisolid agar susceptibility technique. The growth of *F. verticillioides* was reduced by 75% when 200 ppm menthol was used (Dambolena et al., 2008). Using the shake culture method it was shown that menthol (MIC value: 400 μg/mL) was lethal to the spores of *Rhizopus stolonifer* after a 48 h treatment (Moleyar and Narasimham, 1986). In a follow up study Moleyar and Narasimham (1986) tested 15 essential oil components on five fungi namely *Aspergillus niger*, *F. oxysporum*, *Penicillium digitatum*, *R. stolonifer* and *Mucor* spp. Menthol showed high activity against *R. stolonifer* and *Mucor* spp. (MIC value of 200 μg/mL), while other components such as citral, cinnamic aldehyde,

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citronellal and geraniol were most active against *A. niger*, *F. oxysporum* and *P. digitatum* (MIC value: 100 μg/mL). In another experiment, the vapour of peppermint oil and two of its main components (menthol and menthone) were evaluated against two fungi (*Sclerotinia sclerotiorum* and *Mucor* spp.) in a closed system. The results indicated that menthol alone was found to be the compound responsible for the antifungal properties of peppermint oil, whereas menthone alone did not show any effect at all the concentrations tested (Edris and Farrag, 2003).

The fungitoxicity of sixteen essential oils were investigated against two dermatophytes, *Trichophyton rubrum* and *Microsporum gypseum*. The essential oils of *Artemisia nelagrica*, *Caesulia axillaris*, *Chenopodium ambrosioides*, *Cymbopogon citratus* and *M. canadensis* (with menthol as the major compound) showed strong activity (Kishore et al., 1993). Ointment formulations containing the five oils were also able to cure experimental fungal infection (ringworm) on the skin of guinea pigs within 7–12 days (Kishore et al., 1993). Ramsewak et al. (2003) examined the efficacy of some terpenes such as camphor, menthol and thymol, against the dermatophytes *T. rubrum*, *T. mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum* and *Epidermophyton stockdale*, using the disc diffusion assay. Camphor, menthol and thymol were among the individual oil components exhibiting good activity against the tested organisms.

The efficacy of a unique peppermint oil and its vapours against yeasts causing food spoilage in fruit juice was investigated. The organisms included in the study were *Saccharomyces cerevisiae*, *Zycosaccharomyces bailii*, *Aureobasidium pullulans*, *Candida diversa*, *Pichia fermentans*, *Pichia kluyveri*, *Pichia anomala* and *Hansenula polymorpha*. The composition of the oil was determined using GC–MS and the major compounds identified were isomenthone (27.4%), menthol (24.3%), menthone (9.2%), limonene (5.8%), 1,8-cineole (5.6%), menthofuran (4.4%) and isomenthol (3.2%). The disc diffusion method revealed good zones of inhibition (9–40 mm) but complete growth inhibition was not seen at the maximum concentration of 30 μL. Exposure to peppermint oil vapours resulted in significantly larger zones of inhibition of up to 85 mm. MIC and MFC values varied from 0.28 to 2.25 mg/mL and 0.56–0.45 mg/mL, respectively, in the micro broth dilution method. The appropriate sensory evaluation was also carried out and the menthol odour persisted for 8 days longer in the testing group (Tyagi et al., 2013). (−)-Menthol (by contact) also inhibited the postharvest fungi *Botrytis cinerea* and *Monilinia fructicola* (Tsao and Zhou, 2000).

Napkin dermatitis with or without associated candidal infection is a common occurrence in infants and neonates and the essential oil of *M. piperita* has been shown to have inhibitory effects on *Candida albicans*. In 2004–2006, a study was performed on 84 neonates randomly assigned to two classes of 42 each. The treatment group received topical application of drops consisting of menthol 5%, ethanol 25% and polyethylene glycol 400 75% while the same formulation without the menthol component was included as a control group. Generic clotrimazole 2% cream was applied 10 min after drop application. It was noted that complete healing occurred faster in the menthol group and erythema and pustules were significantly relieved. In addition, the total rash score was statistically and clinically significantly different between the groups as assessed on the 3rd, 5th and 7th day of therapy (Sabzghabaee et al., 2006).

Structural functional group relationships play an important role in the biological activity of certain molecules. Five menthol stereoisomers investigated for antifungal activity by radial growth showed varying levels of activity against *Fusarium verticillioides*. (+)-Menthol and (−)-menthol were observed to be the most active with an MIC value of 1.50 mM, followed by (+)-neomenthol at 2.00 mM (Dambolena et al., 2010). The chirality of the biomembrane components plays an essential role in the organisation and biological functions of the cellular membrane (Bombelli et al., 2008). It has been demonstrated that slight structural differences in some chemical compounds are enough to alter the physical or chemical characteristics, and therefore modify the antifungal activity. Furthermore, the lipophilic compounds may also affect the capacity of certain compounds to accumulate inside the membrane and thus trigger changes in the physico-chemical characteristics of certain molecules. Some authors have reported that when monoterpenes become less soluble in water, they can easily interact with the root membrane and disturb the integrity, and therefore cause a fast depolarisation (Maffei et al., 2001).

The antifungal activity of 14 essential oil components singularly and in combination was investigated against aflatoxigenic fungus *Aspergillus flavus* LHPA9 and *Asparagus racemosus* herbal raw materials. The results clearly demonstrated that thymol, eugenol, menthol, and their combinations were active against the pathogens tested with their minimum inhibitory concentration value of fungal growth and aflatoxin B1 secretion lower than 1.0 μL/mL (Mishra et al., 2013).

3.3. Antibacterial activity

Essential oils have been used since ancient times to treat infections. Although there are a number of papers reporting the antimicrobial activity of essential oils, very few have focused on the activity of a single molecule. The antibacterial activity of 20 monoterpenes commonly found in aromatic plants (e.g. menthol, camphor, carvone, 1,8-cineole, terpinen-4-ol, α-terpineol, isomenthol and linalool) were investigated using the *in vitro* disc diffusion method against several bacterial strains. Menthol and all the other monoterpenes except camphor and 1,8-cineole exhibited variable degrees of antibacterial activity by inhibiting the growth of bacterial strains with inhibition zones ranging from 7 to 11 mm in diameter. However, this activity was lower compared to the comparator antibiotic penicillin (Kotan et al., 2007). Many other studies have confirmed the antimicrobial activity of menthol (Pattnaik et al., 1997; Osawa et al., 1999; Trombetta et al., 2005).

The *in vitro* antimicrobial properties of *M. piperita* oil, menthone and menthol were investigated against human and plant pathogenic micro-organisms by micro-dilution, agar diffusion, and bioautographic methods. Peppermint oil and two of its constituents were found to inhibit plant pathogenic micro-organisms, while human pathogenic micro-organisms showed moderate activity. Using the bio-autographic assay, menthol was identified as the compound accountable for the antimicrobial activity of *M. piperita* oil (Işcan et al., 2002). Sung-Hee and Seung-Won (2007) also found that *M. piperita* essential oil and its main component menthol exhibited the strongest inhibitory activity against two antibiotic-susceptible and two antibiotic-resistant strains of *Streptococcus pneumoniae*. Moreover, the combination of menthol with known antibiotics such as oxacillin, norfloxacin or erythromycin, resulted in synergistic antibacterial effects.

Inouye et al. (2001) investigated the effects of menthol and their major constituents against pathogens affecting the respiratory tract (*Staphylococcus aureus*, *S. pneumonia*, *Streptococcus pyogenes*, *Haemohphilus influenza*) by gaseous contact. The results showed that menthol exhibited moderate activity with the minimal inhibitory dose ranging from 6.3 to 50 mg/L air (Inouye et al., 2001). A rare *Mentha longifolia* subsp. *longifolia* oil, which was found to contain menthol (19.4–32.5%) and menthone (20–28%) as major constituents, exhibited good activity against some human bacterial pathogens with MIC values ranging from 0.195 to 3.12×10^3 μg/mL (Hajlaoui et al., 2008).

Although menthol and peppermint oil have shown antibacterial activity, the mechanism of action is not clearly elucidated. The toxic effects on the membrane are often used to elucidate the

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antimicrobial activity of the oil. Trombetta et al. (2005) who investigated the mechanism of action of three monoterpenes, speculated that the antimicrobial effect of monoterpenes such as (+)-menthol, thymol and linalyl acetate, is partially due to the disruption of the lipid fraction of the plasma membrane, resulting in altered permeability and leakage of intracellular materials.

Twenty-eight essential oil constituents were investigated for their activity against growth, virulence attributes, and biofilms of *C. albicans* and planktonic pathogens. Menthol, linalool, nerol, isopulegol, carvone, α-thujone, and a farnesol isomer were found to inhibit yeast to hyphal dimorphism at low concentrations and also inhibit biofilm formation (Raut et al., 2013).

3.4. Antipruritic activity: sensitisation/desensitisation

Menthol is widely used in a number of products which are applied topically to the skin for its antipruritic, analgesic, antiseptic and cooling effects. Bromm et al. (1995) showed that cooling the skin by 2–4 °C will reduce the intensity of histamine-induced itch, while the topical application of 1% menthol yielded a similar reduction of pruritus. In contrast, Yosipovitch et al. (1996) demonstrated that application of menthol did not reduce histamine-induced itch degree or its duration. However, transepidermal water loss at the site treated with alcohol or control was low in comparison to the site treated with menthol ($p < 0.05$). This implies that menthol demonstrated a higher skin irritating effect and modified the stratum corneum water permeability. The antipruritic effects of L-menthol (0.3%, 1%, 3%) dissolved in 75% polyethylene glycol aqueous solution were investigated by applying the solution to the backs of mice in which pruritis was induced through serotonin or substance P (100, 300 nmol) intradermal injection. The pruritic effect was significantly inhibited for serotonin (100 nmol) and substance P (300 nmol) inhibited scratching behaviour represented as a 6-min count. The comparator, cyproheptadine (0.3, 3%) exhibited inhibition of the pruritic effect caused by serotonin but not substance P (Koga et al., 2009).

Studies have demonstrated the capability of menthol to produce desensitisation to sensory irritation in the oral cavity (Cliff and Green, 1996). The irritant property of menthol was examined psychophysically in human subjects by applying 0.3% L-menthol to one side of the tongue after every minute (30 s inter-stimulus intervals) ten times. A decrease in the intensity of irritation was obtained (desensitisation) across trials. An additional study was performed by repeatedly applying menthol to one side of the tongue at 20 s intervals (5 s inter-stimulus) which revealed a quick increase in the irritant sensation over the initial trials (sensitisation) followed by a progressive decrease in irritation (desensitisation) (Dessirier et al., 2001). Ishihara et al. (1986) also observed no sensitisation effects when 10% L-menthol was topically applied in guinea pigs using a maximisation test. Takenaka et al. (1986) applied 0.05–0.5% menthol in a base cream or 99% ethanol on the back or forearm of 133 subjects for 24–48 h. The patch was removed after 30 min and only two subjects showed slight erythema thirty minutes after patch removal.

Due to the presence of menthol in almost all commercial cigarette brands, Willis et al. (2011) used plethysmography to investigate possible positive effects of menthol on respiratory irritation which occurs in mice on exposure to acrolein, acetic acid and cyclohexanone. At a concentration of 16 ppm enough menthol was absorbed in the respiratory tract to activate TRP receptors. Although this concentration is lower than that found in menthol cigarettes, the irritant response to acrolein (TRPA1 agonist) was halted and the responses to acetic acid and cyclohexanone (TRPV1 agonist) assuaged. Menthol may therefore have numerous effects: it acts as a counter-irritant to constituents of smoke; may ease the inhalation of smoke; increase nicotine addiction; and most importantly, due to the suppression of the respiratory irritation usually caused by smoking, morbidities related to smoking may be increased (Willis et al., 2011).

3.5. Menthol as anticancer agent or cancer promoter and the possible mechanism of action

Approximately 10–20% of people develop hypercalcaemia (high level of Ca^{2+} in the blood) due to the leak caused by cancer cells into the bloodstream from the bones which increase the Ca^{2+} concentration. Ca^{2+} is implicated in two cellular processes: cell proliferation and cell death. The Ca^{2+}-permeable channel TRPM8 is believed to play a crucial role in the pathophysiology of prostate cancer, thus, Ca^{2+} transport has emerged as a novel therapeutic target for cancers (Monteith et al., 2007). Kim et al. (2012) reported that menthol activates the TRPM8 Ca^{2+}-permeable channel. However, despite the increased Ca^{2+} concentration in human prostate cancer cells (PC3), the supramillimolar concentrations inducing cell death was not induced by Ca^{2+} influx pathways. More recently, Wang et al. (2012) reported that menthol caused cell cycle arrest at the G0/G1 phase and inhibited the movement of DU145 cells expressing TRPM8. They concluded that menthol may be useful in the treatment of androgen-independent prostate cancer. It was shown that menthol also induces G2/M arrest through the down-regulation and inhibition of downstream signalling of polo-like kinase 1 (PLK1) in PC3 cells (Kim et al., 2012).

In another study, the chemopreventive effects of monoterpenes was investigated using a 7,12-dimethylbenz[α]-anthracene (DMBA)-induced rat mammary carcinogenesis model. Dietary additions of (−)-menthol and other monoterpenes such as, D-limonene, 1,8-cineole, DL-α-pinene, DL-linalool and myrcene resulted in a significant inhibition of mammary carcinogenesis (Russin et al., 1989). A multiple mechanism of action for monoterpenes was suggested including the induction of Phase II carcinogen-metabolising enzymes, and the induction of apoptosis or tumour redifferentiation (Crowell, 1997). The anticancer activity of menthol against various cancer cell lines is via the transient receptor potential melastatin 8 (TRPM8)-dependent or TRPM8-independent pathway. The effects of menthol on the human bladder cancer cell lines T24 were investigated and the results indicated that menthol exhibited anticancer activity. Further investigation showed that menthol could induce cell death through TRPM8 in T24 cells, rather than programmed cell death (apoptosis) and could also induce mitochondrial membrane depolarisation in T24 cells (Li et al., 2009).

The possible carcinogenic effects of racemic-menthol was evaluated through administration in feed to rats (Fischer 344) and mice (B6C3F1). In general, no tumours were formed in dosed groups at incidences that were significantly different from those of corresponding control groups and it was concluded that DL-menthol was not carcinogenic in these rats or mice (NCI (national Cancer Institute), 1979). A study performed in the United States aimed to determine whether menthol cigarette smokers may be less exposed to lung cancer in comparison to non-menthol cigarette smokers. The results of the study showed people smoking menthol brands tended to consume fewer cigarettes per day compared to non-menthol brand smokers indicating a lower risk of lung cancer incidence. This suggested that menthol cigarettes are no more, and perhaps less damaging than non-mentholated cigarettes (Blot et al., 2011).

3.6. Anti-inflammatory activity

Inflammation is a complex biological response which occurs when the body is exposed to infective agents or to physical or chemical changes (Baylac and Racine, 2003). Some essential oils or essential oil components are used in aromatherapy for their

therapeutic properties such as anti-inflammatory activity. The efficacy of L-menthol and peppermint oil as anti-inflammatory agent was investigated on healthy volunteers using the LPS-stimulated monocytes method. Arachidonic acid (key inflammatory intermediate) metabolism was examined by determining leukotriene (LTB-4) and prostaglandin E2 (PGE-2) levels as indicators for the lipoxygenase and cyclo-oxygenase pathways, respectively. Furthermore, the anti-inflammatory activity of L-menthol and peppermint oil tested on interleukin-IL-1-β (pro-inflammatory cytokines involved in immune defense against infection) was studied. The study revealed the preferable anti-inflammatory effects of L-menthol compared to peppermint oil. An *in vitro* study showed that L-menthol significantly suppressed the production of each of the three inflammation mediators by monocytes. At a concentration of 10 subset −7 mg/mL, L-menthol decreased LTB-4 by 64.4 ± 10%, PGE-2 by 56.6 ± 8%, and IL-1-β by 64.2 ± 7%, respectively (Juergens et al., 1998).

3.7. Antitussive effects of menthol

Many remedies used to counteract coughs generally contain menthol (Morice et al., 1994). The antitussive effects of three aromatic compounds (menthol, camphor and 1,8-cineole) were studied by investigating the action of aromatic vapours on the cough reflex in conscious guinea-pigs ($n = 13$) at concentrations of 3 and 10 μg/lL. Menthol was the most active compound producing a significant reduction in cough frequency by 28% and 56%, respectively (Laude et al., 1994). Kenia et al. (2008) also found a reduction in cough count in paediatric patients after menthol inhalation in comparison to the baseline. However, the difference was not significant when compared to placebo. A structural change in the form of nitrogen insertion to form the lactam of menthol which was aerosolised increased cough latency and decreased cough frequency. In addition, pre-exposure decreased the initial cough response as well as the latency period (Kumar et al., 2012).

3.8. Antiviral activity of menthol-rich oils

Essential oils have been used for centuries in traditional medicine to treat viral infections. This prompted research to determine the antiviral activity of certain common essential oils. The inhibitory capacity of *M. piperita* oil which contained menthol (42.8%), menthone (14.6%) and isomenthone (5.9%) as the major constituents, was evaluated *in vitro* on RC-37 cells against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), using a plaque reduction assay and viral suspension test. Peppermint oil showed a time-dependent activity 3 h after incubation. The concentration required to inhibit 50% of herpes simplex virus plaque formation was found to be 0.002% and 0.0008% for HSV-1 and HSV-2, respectively (Schuhmacher et al., 2003).

3.9. Fumigant and insecticidal activities

Chemical and biological treatments are generally used for insect control. However, in the past years, awareness on the toxicity of chemical treatments (use of pesticides), pest resurgence and resistance, and environmental pollution has prompted research towards green, safe and non-toxic applications in pest control. Some essential oils or their constituents have been suggested by many contributors as a source of alternative fumigants and insect repellents (Papachristos et al., 2004). The use of peppermint oil as fumigant was evaluated against the red flour beetle (*Tribolium castaneum*) and the results indicated that the oil exhibited activity with LC_{50} values of 0.8, 11.8 and 20.4 μL/100 cc volume against the second, third and fifth larvae, respectively (Mishra and Krumar, 1983). In addition, the LC_{50} values for adults after 24 and 48 h exposure were 3.0 and 3.2 μL/100 cc volume, respectively. Harwood et al. (1990) evaluated the effect of the monoterpenes; pulegone, menthol and menthone against the larvae variegated cutworm *Peridroma saucia*. Menthol was found to inhibit the pupation at doses similar to its content in peppermint oil. The repellency of various essential oil constituents including menthol was investigated against adults of the fungus gnat, *Bradysia* sp. nr. *coprophila* (Lintner). The results clearly indicated that menthol exhibited repellency activity with the mean percentage of fungus gnat adults recovered from the menthol petri dish of 10.4 ± 2.6% which was statistically lower than those in the petri dish containing distilled water (60.9 ± 7.4%) used as negative control (Cloyd et al., 2011).

The fumigant and repellent properties of various essential oils and individual compounds (e.g. (−)-menthol, pulegone, (+)-menthol, benzyl alcohol, 1,8-cineole, citronellol and menthone) were evaluated against the human head louse (permethrin-resistant *Pediculus humanus capitis*) collected from the hair of 2450 lice-infested children. The fumigant activity was determined by direct exposure to vapours while the repellency was measured in a test arena composed of two zones. (+)-Menthol and (−)-menthol exhibited poor fumigant activity (knockdown time $KT_{50} > 60$ min), while benzyl alcohol followed by (−)-menthol with repellency index RI: 58 and 54, respectively compared to piperonal used as positive control (RI: 72) exhibited the highest repellency ability (Toloza et al., 2006). In a similar study, selected monoterpenoids (citral, thymol, carvacrol, α-terpineol, pulegone, D-limonene and menthol) were investigated as fumigants against *Acarapis woodi* (honey bee tracheal mite) and their bee hosts (*Apis mellifera*). Menthol and thymol were the most toxic constituents to honey bees, while menthol was nearly 20 times more toxic to *A. woodi* than their hosts (Ellis and Baxendale, 1997).

Eight individual essential oil components (anethole, carvacrol, 1,8-cineole, *p*-cymene, menthol, γ-terpinene, terpinen-4-ol and thymol) were studied against females and eggs of the carmine spider mite (*Tetranychus cinnabarinus*), females of the cotton aphid (*Aphis gossypii*) and second instar larvae of the western flower thrips (*Frankliniella occidentalis*). All the oil constituents exhibited fumigant activity at varying levels. However, this activity was also dependent on time of exposure (Erler and Tunç, 2005). In a study involving carvacrol, 1,8-cineole, menthol, γ-terpinene, terpinen-4-ol and thymol, against adults and eggs of the confused flour beetle (*Tribolium confusum*) and larvae and eggs of the Mediterranean flour moth (*Ephestia kuehniella*), at a dose ranging between 5.8 and 184.8 mg/L air and exposure periods of 24–96 h, menthol and 1,8-cineole achieved nearly 100% mortality against any insect tested, while carvacrol achieved more than 90% mortality at 46.2 mg/L of air and an exposure of 24–96 h (Erler, 2005).

An insecticidal investigation using *M. piperita* oil revealed that the presence of menthol was responsible for its effect against mosquitoes. Derivative synthesis and subsequent testing revealed good activity of various analogues including menthyl cinnamate and menthyl choloracetate etc. against *Culex quinquefasciatus*, *Aedes aegypti* and *Anopheles tessellatus* mosquitoes. Structure activity studies showed that minor variation in the chemical structure or functional group changes may significantly enhance mosquitocidal activity (Samarasekera et al., 2008).

3.10. Other biological activities

Alzheimer's disease is the most common form of dementia and no treatment to curb the progression of the disease is currently available. Alzheimer's disease patients have decreased brain levels of acetylcholine and the inhibition of the acetylcholinesterase enzyme favours the accumulation of acetylcholine. Therefore research carried out to evaluate potential treatments for this disease

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is based on the inhibition of the acetylcholinesterase and butyrylcholinesterase enzymes. The inhibitory activity of the two enzymes by nineteen essential oils obtained from various aromatic plants including *M. piperita* and *Mentha spicata* were investigated. In addition, the effects of individual essential oil components such as menthol and thymol were also studied. High inhibitory activity (over 80%) was obtained against both enzymes by different essential oils, while the single components were not as active as the essential oils (Orhan et al., 2008). This may suggest that the inhibitory activity of the enzymes could be as a result of the combination of several compounds in the oil rather than a single component. Bhadani et al. (2012) reported significant improvement in the learning and memory of young and aged mice when treated with menthol possibly due to maintenance of glutamate concentration as it has been shown that decreased hippocampal glutamate may cause deterioration in the learning and memory process. Gamma aminobutyric acid (GABA) is an amino acid located in the central nervous system and this amino acid acts as an inhibitory neurotransmitter. The stereo-selectivity of menthol on the $GABA_A$ receptor was investigated and only (+)-menthol, among the five stereoisomers studied was active, stimulating in a dose-dependent manner the binding of an allosteric $GABA_A$ receptor ligand (Corvalán et al., 2008).

4. Menthol as a vehicle for transdermal drug delivery

Although the percutaneous route of drug delivery has many advantages over other modes of delivery such as intravenous and oral administration, the architecture of the stratum corneum provides a formidable barrier to the topical and transdermal administration of some therapeutic agents (Kalia et al., 2004). To increase the permeability of the stratum corneum, permeation enhancers are often used. Being mostly non-irritant and non-toxic to the skin, they are commonly used to enhance the transdermal permeation of drugs such as 5-fluorouracil (Williams and Barry, 1989), propranolol hydrochloride (Zhao and Singh, 1999), lipophilic indomethacin and ketoprofen (Akithoshi et al., 1988) as well as estradiol (Moghimi et al., 1996). Some studies have shown that menthol as penetration enhancer is more effective than other monoterpenes such as α-terpineol, menthone, pulegone and carvone. Menthol permeates the epidermis which in turn could ease the accessibility of other drugs (Patel et al., 2007). Menthol and limonene have been considered to be the most effective transdermal penetration enhancers, significantly increasing the transdermal delivery of certain drugs such as caffeine, hydrocortisone and imipramine hydrochloride and has shown similar effects to 1,8-cineole used for the transdermal delivery of imipramine hydrochloride (Aqil et al., 2007). Qian et al. (2011) showed that oil rich in menthol promotes the transdermal permeation of L-tethrahydropalmatine *in vitro*. Studies have also shown that L-menthol (1% or 5%) significantly increased the flux of tetracaine gel (anaesthetic agent) and methyl salicylate in mouse skin compared to the negative control (Liu et al., 2005; Yano et al., 1991). Various strategies have been developed to achieve better transdermal delivery of certain compounds such as nicardipine (used to treat high blood pressure and angina), propanolol (used to treat hypertension and angina), as well as ketoprofen and indomethacin (anti-inflammatory and analgesic properties) (Ho et al., 1998; Zahir et al., 1998; Wu et al., 2001).

Excised guinea pig skin was used to investigate the skin-penetration enhancing effect of menthol by assessing the depth to which Rhodamine B (active principle) penetrated the skin in the presence of 50% menthol. Penetration enhancement was defined as detection of Rhodamine B in the corium or subcutis and histological examination of the epithelium, hair follicles, corium and subcutis was performed. After 2 h, Rhodamine B was detected only in the epithelium indicating that menthol did not enhance skin penetration (Meyer, 1965). However, contrasting results were obtained with other drugs. The effect of 0–12% menthol on indomethacin penetration through nude mouse skin using different co-solvent systems (water, alcohol and propylene glycol) was investigated. Menthol not only improved the drug solubility for the three solvents, but also enhanced indomethacin penetration. The effect of menthol was more significant compared to that of the co-solvent systems and the extent of the influence was concentration dependent (Ho et al., 1998). Franz diffusion cells were used to investigate the transdermal delivery of buspirone hydrochloride across hairless mouse skin in combination with iontophoresis. Iontophoresis alone increased the flux 15-fold while in combination with menthol, it increased 200-fold. In another study, different concentrations of monoterpenes (1%, 5%, 10%) were investigated for their permeation enhancement effects across mouse skin using propranolol hydrochloride. (−)-Menthol at a concentration of 1% w/w had a higher skin permeation and shorter lag time compared to (+)-limonene, (±)-linalool and carvacrol (Al-Khalili et al., 2002).

Yucatan micropig skin was used to test the permeation enhancing effects of L-menthol and *p*-menthane-3,8-diol (ametabolite of L-menthol) using antipyrine (hydrophilic) and indomethacin (lipophilic) as model drugs. These compounds showed a similar effect on the skin permeation of indomethacin, while p-menthane-3,8-diol exhibited a lesser effect on the permeation of antipyrine (Fujii et al., 2003). Menthol was investigated as a permeability enhancer of dexamethasone disodium phosphate in the cornea and sclera of rabbits' eyes through topical drop application and subconjunctival injection of dexamethasone disodium phosphate (DDP) in the presence or absence of menthol. Menthol at a concentration of 0.05% was found to significantly increase the penetration of DDP in the cornea, but did not affect the DDP penetration in sclera. A high concentration of menthol (0.1%) in topical drops resulted in a significantly increased concentration of DDP in the cornea and aqueous humour tissues. Evidently, menthol improves the ocular penetration of DDP in transcorneal and transscleral drug delivery systems (Xu et al., 2011).

Zidovudine (AZT) is widely used in the treatment of AIDS and AIDS-related complex, either singularly or in combination with other antiviral agents. Monoterpenes containing oxygen (1,8-cineole, menthol, α-terpineol, menthone, pulegone and carvone) were evaluated to determine whether these compounds may improve the transdermal delivery of AZT *ex vivo* across rat skin. The results showed a significant increase in the transdermal flux of AZT in comparison to the vehicle (water) ($p < 0.05$) in the presence of the monoterpenes. The enhancement activity of the individual monoterpenes were as follows: 1,8-cineole > menthol > menthone ≈ pulegone ≈ α-terpineol > carvone > vehicle water (Narishetty and Panchagnula, 2004).

The mechanism by which terpenes enhance drug permeation through the skin is not well elucidated, but three modes of actions are generally reported. These include: the disruption of the highly ordered lipid structure of the stratum corneum; the increase in drug diffusivity in the stratum corneum or increased drug partitioning into the stratum; and the increase in electrical conductivity of tissues thereby opening polar pathways within the stratum (Vaddi et al., 2002; Godwin and Michniak, 1999; Zhao and Singh, 1998). The evidence suggests that menthol is one of the most useful monoterpenes to achieve skin penetration enhancement.

5. Toxicity and metabolism of menthol

Terpenes are regarded as a very safe and effective class of natural compounds. Menthol is classified by the Food and Drug

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Administration (FDA) as safe (Vaddi et al., 2002) and effective as a topical over-the-counter (OTC) product. The FDA has approved concentrations of menthol of up to 16% for OTC external use, their safety profile has been demonstrated by *in vitro* and *in vivo* studies and most investigations reveal a low potential for toxicity in humans (NCI (national Cancer Institute), 1993, RIFM, 2003). Topical use of formulae containing fragrance oil of up to 20% of the final product results in a maximum skin level of 0.52% according to the International Fragrance Association. However, for cosmetics, the conservative maximum daily exposure was determined to be 0.0074 mg/kg if included in a concentration of up to 0.29% (Bhatia et al., 2008). During a 103-week chronic toxicity study, 9-week old Fischer 344 rats (50/sex/dose) were exposed to DL-menthol, equivalent to 375 mg/kg bodyweight/day, in corn oil as part of their diet. The rats were observed daily for any signs of toxicity and their mean food consumption and body weight recorded every 2 weeks for 3 months and monthly thereafter until the study was concluded. Microscopic examination of the major organs and tissues revealed no clinical effects, signs of toxicity, histopathological changes or increased incidences of tumours compared to controls (NCI (national Cancer Institute), 1979).

Most of findings in literature have reported no genotoxic or mutagenic effects for menthol. L-Menthol in ethanol or in dimethyl sulfoxide (30–300 μg/mL in DMSO) with and without activation did not augment chromosome aberrations in Chinese hamster V79 cells after 24 and 48-h exposure periods. Similar results were obtained when D-menthol was used (Matsuoka et al., 1998; Murthy et al., 1991). DL-Menthol (isomer unspecified) showed no genotoxic effects on Chinese hamster ovary K5 cells (CHO K5 cells) at various concentrations ranging from 6.25 to 100 lg/mL in dimethyl sulfoxide. Hartmann and Speit (1997) investigated the mutagenicity of D-menthol using the Comet assay (alkaline single cell gel electrophoresis) on human blood leukocytes and V79 Chinese hamster cells at different concentrations (0.5, 1.5 and 2 mM). No genotoxic effects of D-menthol were noted at a concentration of up to 2 mM. In contrast, a decrease in cell viability and death was observed at all concentrations. The mutagenicity of (±)-camphor, 1,8-cineole, citral, citronellal and (−)-menthol on *Salmonella* was investigated using the plate incorporation method. At a concentration range of 100–800 μL/mL, no mutagenic effects were recorded for (±) camphor, citral, citronellal, 1,8-cineole, and (−)-menthol (Gomes-Carneiro et al., 1998). However, Yoo (1986) recorded a positive response for L-menthol at a high concentration of 10,000 μg/disk against *Bacillus subtilis* M45, H17 with more than 12 mm difference in circle diameter comparing to the control using the Rec assay (spore plate assay).

Menthol is efficiently metabolised to menthol glucuronide as well as hydroxylated metabolites (Belsito et al., 2008). An *in vivo* study in rats showed the major metabolites to be p-menthane-3,8-diol and 3,8-dihydroxy-p-menthane-7-carboxylic acid after oral menthol administration of 800 mg/kg/day for 20 days. Several analytical techniques including thin layer chromatography, gas chromatography and proton NMR were used to identify these compounds in the urine of the test animals (Madyastha and Srivatsan, 1988). Studies conducted in order to evaluate the effects of menthol in cigarettes showed that L-menthol was metabolised to diols in rat and monkey liver microsomes. Repeated ingestion of the same dose of L-menthol for seven days resulted in the increase of liver microsomal P-450 content and NADPH-cytochrome C reductase activity by approximately 80% after three days compared to the control (MacDougall et al., 2003). *In vitro* studies using human liver microsomes revealed that the menthol enantiomers, (+)-menthol and (−)-menthol, are oxidised in the liver principally by the CYP2A6 enzyme to (+)-*trans*-p-menthane-3,8-diol and (−)-*trans*-p-menthane-3,8-diol (Miyazawa et al., 2011).

6. Concluding comments

Menthol is an important essential oil component of oils of the *Mentha* genus, and has been used since antiquity in traditional medicine to treat several ailments. Menthol has found application in diverse fields ranging from the pharmaceutical and cosmetic industries to the tobacco and food industry where it is used as a flavour enhancer, preservative and for its cooling characteristics. Numerous biological properties have been ascribed to menthol and the mint oils rich in menthol including antibacterial and analgesic effects amongst others. One of the major effects of menthol is the sensation of coolness produced when it is chewed, inhaled or applied to the skin. Additionally, it may also enhance the skin penetration of a variety of drugs. Therefore, a topical formulation which includes menthol due to its cooling effect as well as its penetration enhancing effect in combination with an anti-inflammatory analgesic such as indomethacin may result in synergistic effects. Taking into account the low toxicity of this compound, it is not surprising it has been a popular topic for research and has enjoyed tremendous commercial interest.

Although the research is promising, there is a lack of information regarding other aspects of menthol. The mechanism by which this compound exerts its activity *in vitro* or *in vivo* is still poorly understood. Furthermore, since menthol exist in various forms, the structure–activity relationships needs to be further investigated. Essential oils in general and individual molecules in particular, have been popularly used as fumigants and insect repellents. Various gaps still exist in the scientific literature and it would be of interest to investigate extensively the effect of menthol on the causative vector of malaria (*Anopheles* mosquitoes) as well as the potential effect against *Plasmodium falciparum* causing malaria, one of the main killer diseases in many developing countries. It is evident that menthol, for which there are copious documented uses already, has unlimited potential to be developed into medicinal compounds either as such or as a blueprint for synthetically modified drugs. Medicinal products however, are not the only market as mentioned earlier. Many tonnes of menthol are produced annually and it is clear that interest in this compound is not waning if one is to judge on the number of patents filed of products containing menthol or menthol synthesis methods, etc. On one such a patent site, freepatentsonline.com, a search on menthol produced 49 738 results. The future of this molecule used as a medicine in Japan 2000 years ago, remains bright as new uses are discovered frequently.

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