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COMPONENTS OF PEPPERMINT AND ITS APPLICATIONS

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Abstract: Peppermint (*Mentha x piperita L.)* is a globally cultivated hybrid mint known for its essential oil, which is rich in volatile organic compounds, particularly menthol. This essential oil is widely utilized across various industries, including food, cosmetics, and medicine, owing to its therapeutic properties such as analgesic, antispasmodic, and antimicrobial effects. The flavor profile of peppermint enhances numerous culinary applications, while its medicinal benefits have made it a staple in traditional and modern herbal remedies. However, the presence of volatile components raises concerns regarding potential allergens, necessitating caution in its use, especially among sensitive individuals. Understanding both the benefits and risks associated with peppermint is crucial for safe and effective applications in consumer products and therapeutic settings. This abstract highlights the significance of peppermint in diverse fields while addressing the need for awareness regarding its allergenic potential.
Keywords: Peppermint; Essential oil; Benefits and risks

1 INTRODUCTION

Mints, of the genus *Mentha*, are plants which have been historically cultivated as an agriculturally important product, due to their purpose as an aromatic product that has medicinal properties and provides additive flavorings to food and beverages [1]. Deriving from the taxonomic family *Lamiaceae*, the genus *Mentha* includes up to fourty-two separate species and fifteen hybrids of the fragrant medicinal herb, differentiated based on their morphological, cytological and genetic characteristics [2]. However, these classifications can be up to debate, due to its widespread hybridization over the years, involving the complication by polymorphism, cultivation, polyploidy and vegetative propagation [3,4]. Common species of *Mentha* include M. *aquatica* L, M. *piperita* 'Lavendula', M. *arvensis* L., M. *canadensis* L., M. *longifolia* L., M. *piperita* L., M. *piperita f.* citrate, M. *pulegium*, M. *spicata* L. and M. *suaveolens* [5]. Due to its wide range of viable environmental conditions for growth, the herb genus has a wide global distribution across Eurasia, Australia, South Africa and North America [6]. Applications of the mint's essential oil include but are not limited to cuisine, cosmetics, pharmaceutical, dental, perfumery and aromatherapy [7–9]. Its widespread applications have allowed for *Mentha* cultivation a thriving industry, where in 2022, the global market sales of synthetic and natural menthol -a natural mint essential oils (EO) product - has reached $713.6 million, projected to reach $1161 million by 2030, with a compound annual growth rate (CAGR) of 7.2% [10]. A major user of *Mentha* EO is the tobacco industry, it consumes 40% of the total oil production for *Mentha,* leading the consumption share of *Mentha* EO greater than both the pharmaceutical and confectionary industries [11]. Currently, the global annual consumption of L-menthol exceeds 40,000 tons, primarily sourced from natural peppermint extraction.
Peppermint, or *Mentha x piperita L*., is a common hybrid mint species cultivated around the world, including countries such as China, India, Brazil, United States for its EO [12]. Products in the commercial market that have mint flavorings include but are not limited to toothpaste, mouthwash, chewing gum, chocolate, ice cream, candies, teas, alcoholic beverages, and more [11]. The peppermint ingredient is often used to provide a coolant scent, and is the result from the volatile organic compounds (VOCs), which are secondary metabolites that are found in the plant's EO [12,13]. Common peppermint VOC components include menthol, menthone, and menthyl acetate, which their percentage composition can vary dependent on the peppermint's origin or cultivation methods [13]. From a therapeutic perspective, It has historically been utilized as a remedy against digestive and diuretic issues, as well as for coughs and colds [14]. Based on traditional Chinese medicinal knowledge recordings in the "Compendium of Materia Medica" or Bencao gangmu, published from the 16th century, the herb is beneficial for "the throat, mouth, and various ailments. Treats scrofula, sores, itchiness, wind-induced itching rash"[15] . Modern day uses in traditional Chinese medicine (TCM) for peppermint is said to disperse wind-heat, clearing heat from applied surfaces, reducing swelling, soothing the throat, and alleviating pain [3]. Recently, constituents of peppermint have been reported to provide antibacterial, antiviral, antioxidant, antifungal, insecticide properties, as well as having anti-inflammatory, antispasmodic, anti-carcinogenic, and radioprotective properties [7,16-19]. Although peppermint widely used for varying applications, the VOCs found in the plant also have considerations and concerns such as allergens, specifically when applied to skin and dermal contact [20]. Overall, peppermint is a popular flavoring component with lots of

potential other than flavoring, with many functional applications and synergistic possibilities that are awaiting to be researched and evaluated. This review aims to discuss the chemical composition of *M.piperta*, including the current methods of analysis and evaluation, description of functions, applications of the herb in different industries, and a discussion of innovative potential of the plant.

2 METHODS

In this review, we employed a curated set of keywords for our search, used in different combinations and order: ([peppermint] OR [*Mentha x piperita L.*]) OR [*Mentha*]). We conducted an exhaustive search within the databases of PubMed, Web of Science, and Scopus to address the following pivotal research questions: What are the applications and associated science of peppermint? The search would focus on the application of peppermint, specifically variations of the compounds. Initially, we identified and saved 237 full-text articles in Endnote, limited to 10 years, during the search process that was reviewed in April 2025. Ultimately, our review incorporated 98 articles that met our criteria and scope.

3 CHEMICAL COMPOSITION OF PEPPERMINT

As previously discussed, genetic diversity within the genus, species and hybrids of *Mentha* EO, along with cultivation process, environment, weather and harvest timings can offer differential chemical composition, denoting the plant's difficulties to characterize its chemical composition in a general sense [3]. Common peppermint chemical composition of its EO includes 1-menthone, isomenthone, menthol and menthyl-acetate, but this extraction of the volatile EO only yields between 0.1 – 1.0% from peppermint leaves [21–23]. Gas chromatography-mass spectroscopy analysis of peppermint EO samples from the United States, as denoted in Table 1, found the herb's most abundant chemicals to be menthol (38.45%), menthone (21.8%), 1,8-cineole (5.62%), neo-menthol (4.19%), and menthyl acetate (3.9%) [24]. The EO of *Mentha* is extractable from various different methods after the drying, grounding and sieving steps, where common extraction steps for the EO include steam distillation, hydrogenation distillation, microwave-assisted extraction, microwave-assisted hydro-distillation, Soxhlet extraction, and supercritical fluid extraction [25]. Major components extracted for its "cooling" properties for taste and sensation, termed as cooling agents, are its menthol, menthone and menthyl acetate[26]. The cooling property of these cooling agents as shown in Table 1 is largely a result of its role as an agonist for the transient receptor potential melastatin-8 channels (TRPM8) [27]. The cyclic monoterpene alcohol menthol is the major component found in most *Mentha* EO extracts, varying between 30 to 55% of the active compounds of the *Mentha spp.*, and is a major proponent for the cooling sensation and *minty* flavoring of peppermint products [28,29]. As a result of its larger proportion of *Mentha* extract composition, it is also the most studied compound from the *Mentha* VOCs. Among different stereoisomers of menthol, (-)-menthol possess the most intense cooling property and cleanest mint odor, and in terms of cooling threshold ranked by taste dilution, (-)-menthol requires the smallest amount to elicit a cooling sensation (0.8 ppm), followed by (+)-neomenthol (2.5 ppm), (+)-menthol (3.0 ppm), (-)-neoisomenthol (6.0 ppm), (+)-isomenthol (7.0 ppm), (-)-neomenthol (25.0 ppm), (+)-neoisomenthol (>25.0 ppm) and (-)-isomenthol (30.0 ppm) [30]. In contrast, menthone makes up approximately 14-32% of the bioactive components found in peppermint EO [31]. Lastly, menthyl acetate is found to make up between 0.7%-23% of the monoterpenes in peppermint EO, and as a result of it usually observed in smaller amounts, limited information is known regarding this molecule and its effects on the human body [32].

Phenolic compounds identified in European peppermint leaf samples through high-performance liquid chromatography – electrospray ionization – quadrupole time of flight – tandem mass spectroscopy (HPLC-ESI-QTOR-MS/MS) observed caffeic acid, eriocitrin, luteolin-7-I-rutinoside, eriodicytol-7-O-glucoside, luteolin-7-glucuronide, isorhoifolin, and rosmarinic acid [33]. Compositional differences between leaf samples and products could be compared through usage of high-performance liquid chromatography-photodiode array/ mass spectrometry detection and headspace solid-phase microextraction–gas chromatography–flame ionization/MS detection, where differing ranges of flavonoids and volatile content percentages are observable across different samples, proving as useful tools for quality control and product standardization for the future [33].

Table 1 Chemical composition of the non-polar constituents (peak area %) from United States peppermint essential oils (EO) detected through gas chromatography-mass spectroscopy (GC-MS). Data extracted from study performed by Wu et al., 2019 [24].

Compounds	Retention Time, min	Peppermint EO, %	TRPM8 Channel Modulation (Cooling Properties)
alpha-Pinene	14.03	0.56	
1-Octen-3-ol	15.8	0.11	

Sabinene	15.91	0.43	
beta-Pinene	16.16	0.81	
3-Octanol	16.82	0.26	
beta-Myrcene	16.87	0.2	
alpha-Terpinene	18.41	0.35	
para-Cymene	18.6	0.32	
1,8-Cineole	19.07	5.62	
Limonene	19.31	1.58	
cis-beta-Ocimene	19.53	0.34	
gamma-Terpinene	20.91	0.56	
trans-Sabinene Hydrate	21.15	0.86	
alpha-Terpinolene	22.81	0.18	
cis-Sabinene Hydrate	23.04	0.11	
Linalool	23.21	0.37	✓[26,34]
Amyl Isovalerate	23.83	0.15	
3-Octanol Acetate	24.84	0.05	
Menthone	26.33	21.8	✓ [26]
Isomenthone	26.91	3.75	✓
Menthofuran	27.41	2.08	
neo-Menthol	27.56	4.19	✓
Menthol	28.59	38.45	✓[26]
iso-Menthol	28.78	0.71	✓
neoiso-Menthol/alpha-Terpineol	29.21	0.41	✓
Pulegone	31.83	0.91	✓[34]
Piperitone	32.86	0.65	
neo-Menthyl Acetate	34.96	0.22	✓

Thymol	35.66	0.1	✓[34]
Menthyl Acetate	36.05	3.9	✓[26]
iso-Menthyl Acetate	37.03	0.19	✓
Eugenol	39.33	0.05	✓[35,36]
cis-Jasmone	41.71	0.03	
beta-Bourbonene	42.73	0.43	
beta-Elemene	43.05	0.23	
beta-Caryophyllene	44.8	2.87	
beta-Copaene	45.37	0.07	
trans-beta-Farnesene	46.88	0.49	
Germacrene D	48.47	3.24	
Bicyclogermacrene	49.33	0.53	
delta-Cadinene	50.78	0.16	
Viridiflorol	54.51	0.8	

As the demand of peppermint EO, and menthol increases over the years, Synthetic menthol has become a comparable alternative to the natural product, as it can become more economically viable to synthesize at a large scale, compared to natural menthol dependent on cultivation conditions and environments[3]. Presently, there are three main processes for synthesizing L-menthol [37]. The first utilizes thymol/caravel phenol and is often referred to as the "Symrise process," developed initially by the German company Symrise [37]. The Symrise process is the hydrogenation of thymol to racemic dl-menthol, where the final (-)-menthol product is selectively crystalized[30]. The second process involves using myrcene or isoprene as the raw material, and asymmetric catalytic synthesis via chiral rhodium (S)-NINAP complex, produces (-)-menthol [30]. The process was developed by scientists including Yoshito Kishi at Nagoya University, earning him the Nobel Prize in Chemistry in 2001. The first company to apply this asymmetric synthesis catalysis technology to produce L-menthol was Takasago in Japan, hence known as the "Takasago process" [3]. The third process involves an asymmetric catalytic synthesis using citral as the raw material, developed by BASF in Germany, hence termed the "BASF process" [37]. These are all processes with high efficiency, used to make up for the increasing demand for menthol as supply from natural menthol production is increasingly insufficient [3,37].

Menthol inspired synthetic coolants specifically able to modulate TRPM8 have also been considered as alternatives to menthol, where natural and commercially synthesized menthol esters are alternatively utilized for its similar functions in odor, taste and sensation, although perhaps at a lower intensity, including compounds such as (-)-menthyl lactate, menthyl acetate, monomenthyl succinate and menthyl-3-hydroxybutyrate for food, cosmetic and perfume products, with up to [26]. Nonvolatile cooling agents such as the menthane carboxamides and other compounds of the Wilkinson Sword (WS) series such as WS-1, WS-3, WS-5, WS-12, WS-14, WS-23 and WS-30 are also prepared and commercially used over menthol depending on the design nature of the products, providing different strength levels and duration of cooling sensation, taste, odor and cost considerations [26,38,39]. SS Bharate and SB Bharate compiled a list of 161 cooling agents that have modulation effect either as agonists or antagonists for TRPM8, and denoted that derivatives of menthol with a hexacyclic ring structure such as WS-5, WS-12, CPS-125, CPS-368, and CPS-369 are most selective for activating TRPM8 with a greater potency and lower EC50 than menthol [26].

3.1 Associated Functions of Peppermint Components

3.1.1 Effects of cooling sensation

When ingested or applied, a cooling effect is sensed as a result of the compound through different sensation pathways of the body, varying from inhalations, consumption, or direct topical application to the skin [28]. Specifically, the cooling effect from digesting menthol and other cool substances like menthone and menthyl acetate is the binding result of activated transient receptor potential melastatin-8 (TRPM8) channels, a type of transient receptor (TRP) channel ubiquitously present in highly cold sensitive tissues to obtain external information as a stimulatory response [27,40,41]. It was found that the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP2) is essential for TRPM8 to function, such that primed TRPM8 channels provides a favorable electrostatic environment for the stimuli binding to engage in the ion gated channel's opening [42]. Menthol stimulates TRPM8 channels at concentrations between 10 μM to 1 mM, and has been shown in HEK293 and CHO cells with overexpressing TRPM8 channels to increase intracellular Ca2+ levels in a concentration dependent manner [43]. This modulation of the TRPM8 channel allows for phospholipase C (PLC) enzymatic hydrolysis of PIP2, producing inositol 1,4,5 triphosphate (IP3) and diacylglycerol[44]. It should be noted that, external environment can also inhibit TRPM8 responses, specifically ethanol can also inhibit TRPM8 through disrupting PIP2-TRPM8 binding interaction, resulting in reduced binding sensitivity to PIP2 [45]. The G -protein subunit $G\alpha_q$ is also able to induce inhibition or reduced sensitivity of TRPM8 to its cooling agents, prohibiting the depletion of PIP2 and the modulation of TRPM8, but the inhibition is independent of the PLC-PIP2-IP3 pathway, a pathway that regulates the influx of calcium ion concentrations [46].

TRPM8 channel function is also summarized by Liu et al., to have the following functional roles as a result of its cooling sensory capabilities: immunomodulatory effects, pigment production activity of skin, regulating superior laryngeal nerve activity, facilitating swallow reflex, controlling tear flow of the cornea, respiratory pathway control, mechanical nociception of the colon, bladder contractility, ion and cell secretion, regulating cell proliferation/apoptosis, and maintain homeostasis [47]. From impacting sensory afferents and impacting the meninges, TRPM8 activation seems to also impact migraine like behaviors, which could be blocked in the presence of TRPM8 antagonists [48]. Presently, both TRPM8 agonists and antagonists have been utilized as potential treatment methods, depending on the type of migraine triggered by individual patients [49].

3.1.2 Effects on digestive, respiratory and circulatory systems

Oral ingestion of peppermint leaves is a product licensed as a treatment product in medicinal tea form in Germany to treat dyspepsia, uneasiness of the digestive tract, as well as for discomfort for the GI tract, gall bladder, and bile ducts [50]. Menthol specifically, observed a concentration dependent decrease between 0.1mM to 30mM, in the amplitude but not the frequency of spontaneous mechanical activity for circular smooth muscle experimented using a vertical organ bath [51]. Observations of calcium levels in the presence of varying amounts of menthol in human colonic circular muscle strips confirmed that the menthol decreased smooth muscle contractions in a TRPM8 independent manner but through blocking Ca2+ influx through voltage dependent L-type sarcolemma channels, as the TRPM8 receptor antagonist 5-BT failed to affect menthol effects, but nifedipine, a voltage activated L-type Ca2+ channel blocker observed the same effect patterns as menthol addition [51]. Lastly, peppermint EO was found to have superior results as Irritable bowel syndrome treatment in trials with 482 patients versus placebo across 5 different trials [52]. But, it should be noted that there was high heterogeneity across the different studies [53].

Peppermint oil capsules mainly composed of menthol, when ingested, observed significant reduction in heart rate from 25 to 50 mins in healthy adult humans, presumably from the increase of cardiac parasympathetic efferent activity [54]. Menthone supplementation can also inhibited allergic inflammatory conditions in asthma conditioned mice with impaired respiratory systems; regulatory hallmarks of inflammation were improved by regulation of decreased protein and chemokine production, gene expression inhibition, increase, mass cell degranulation, Th1/Th2 immune balance, and monocyte/macrophage restoration [55].

3.1.3 Effects on immune system and anti-cancer characteristics

Functionally, menthol has been a molecule that has been researched for its anti-cancer capabilities. A review from Zhao et al., (2023), summarizes that menthol has influence over several anti-cancer strategies including but not limited to induction of cancer cell apoptosis, cell cycle arrest, tubulin polymerization, Ca2+ mediated endocytosis, tumor invasion inhibition, preventing tumor angiogenesis, and limiting tumor angiogenesis [21]. However, these applications have not been thoroughly evaluated, especially on a human model, requiring further research and in-depth studies on menthol specific treatments. The molecule menthone has also been demonstrated to inhibit pro-inflammatory cytokine release in mice, specifically TNF-α, IL-1β, and IL-6 in collagen II-induced arthritis mice, suggesting possible treatment against rheumatoid arthritis with local relief [56]. A docking experiment between peppermint compounds and arylamine N-acetyltransferase enzymes showed that menthyl acetate has affinity to the His107 active site of the enzyme [29]. The enzyme is known as both a drug and carcinogen metabolizing enzyme, and has historically been studied due to having interfering reactions with drug treatments [57,58].

Peppermint is also a potential target of inflammation suppression, where it may alleviate the inflammation effects by AMP-activated protein kinase/unc-51 like kinase 1/nuclear factor-E2 associated factor 2 (AMPK/ULK1/Nrf-2) autophagy

pathway, and also downregulating the signal-regulated kinase nuclear factor-kappa B signaling pathways, overall acting as natural anti-inflammatory agents that can improve inflammatory conditions [59].

3.1.4 Other pharmacological effects of M.piperita constituents

The applications and functions of *M.piperita* are not all thoroughly specified to individual components, and multiple components can provide similar functionality within the human body. In regard to antibacterial function, *M. x piperita* has been proved to strongly inhibits the growth against bacteria such as *E.coli, B. subtilis and C. albicans* [60]. Moreover, a nano-emulsified PO formulation's antimicrobial properties were evaluated against *Listeria monocytogenes* Scott A and *Staphylococcus aureus* ATCC 25923[61]. These antimicrobial properties show potential of EOs to be used as methods to increase shelf life of aqueous food or beverage products [61].

Other than the VOCs discussed previously, peppermint extracts contain phenolic acids, flavonoids and anthocyanins, which contribute to the extract's phenolic content, and antioxidant properties [7]. The antioxidant properties of peppermint is attributed to its phenol compounds, often measurable through denoting the total phenol and flavonoids contents of the mixtures, where phenols are highly effective free radical scavengers[62]. These phenolic acids include chlorogenic acid, rutin, caffeic acid, 4-Hydroxy benzoic acid, 1-Naphtol, ferulic acid, ascorbic acid and vanillic acid [7]. Antioxidant properties of peppermint phenol content increases when extracted with methanol as a mixture compared to peppermint ethanol mixtures, and also has greater superoxide radical scavenging activity [7]. Peppermint ethanol mixtures, however, contain greater diphenyl picryl hydrazyl and hydroxyl (DPPH) radical and nitric oxide radical scavenging activity compared to methanol and methanol/ethanol mixtures [7]. Components such as Eugenol, caffeic acid, rosmarinic acid and α-tocopherol were attributed for anti-oxidant properties, while Caffeic acid, rosmarinic acid, eriocitrin, luteolin-7-O-glucoside are acknowledged as components that provide the primary radical scavengers function [19].

The phenolic components of peppermint oil also has radiation protective activity, such that mice pre-administered orally with M. piperita extract prior to γ radiation exposure in mice has been shown to observed bone marrow cells protection, with reduced aberrant cells, and reduced chromosomal damage in terms of chromatid and chromosome breaks compared to the control irradiated group [63]. Similar protective properties were observed against radiation induced hematopoietic damage of bone marrow, testes and intestinal mucosa after preemptive treatment with leaf extract treatment of Swiss albino mice [64–66].

4 APPLICATIONS OF MENTHA COMPONENTS

4.1 Applications in Food/Beverages

Peppermint is mainly used for its flavoring, aroma, sensory manipulation and relaxation purposes by food and beverage manufacturers, acting as the third most demanded flavor in the food market, such as in cooling beverages, chewing gum, tobacco and alcoholic beverages [6]. A common trend of peppermint products is to utilize it as an synergistic additive to add health value to food and beverage products, varying from white tea to cheese [67-69]. Addition of peppermint to 0.5 and 1.0 v/v% before alcohol fermentation observed an 72.80% increase in total antioxidant content, and 72.05% increase in total polyphenol, resulting in beverage products rich in polyphenol and antioxidants [70].

Menthol additives are also added to tobacco products, as it can be mask the harshness of inhaling cigarette aerosol, such as suppressing cough and reducing airway irritation, making the action more attractive in beginner smokers or younger people with a refreshing effect [71]. However, the Tobacco Products Directive (2014/40/EU) on 20th May 2020 in Europe has begun the movement to ban menthol additions to cigarette products, introducing regulatory action against flavored tobacco products that make it harder to quit the action of smoking [71].

4.2 Applications in Cosmetics/Topical Treatment

Topical application peppermint EO based creams or lotions has been widely known to be used as a traditional medicinal treatment against dermal disorders such as wounds, skin infections, insect bites, eczema, hives, and psoriasis [72]. Peppermint EO's cooling agents and their effect on TRPM8 also encourages its development in analgesic and anti-irritation applications both as activators and inhibitors for TRPM8, as studies have shown that TRPM8's activation/inhibition has both shown evidence of being analgesic and nociceptive, but mechanical hyperalgesia is best treated with TRPM9 antagonists [73,74]. Proudfoot et al. reported that Group II/III metabotropic glutamate receptors can mediate TRPM8 activation, eliciting analgesia in neuropathic and chronic pain rat models [74,75]. Experiments from Pan et al.'s group, suggests that menthol has analgesic action because of blocking Na+ and Ca2+ channels present at dorsal horn neurons, but did not have evidence showing that it is through blocking TRPM8 [76]. In contrast, the sensation of cold detected from TRPM8 as a temperature is known to shorten itch duration and intensity, but Palkar's et al. also found menthol to be effective in mimicking cold stimulation's effect in inhibiting both histaminergic and non-histaminergic itches dependent on intact and functional TRPM8 containing neurons, but possibly lacks selectivity for the effect compared to potent TRPM8 activators [77,78].

Property wise, menthol can also be used to increase the skin permeability of specific compounds in gel formats through the skin as vehicles, compared to formulations without menthol [79]. Evidence suggests that the property of menthol encourages permeability through cutaneous skin is a result of calcium-dependent cadherin modulated cell to cell cohesiveness decreased as a result of TRPM8 modulations [80]. Another study with rat and Göttingen minipig skin using a 1-menthol-indomethacin solid nanoparticle gel formulation alludes to the inclusion of 1-menthol promotes energy dependent endocytosis of the formulations after adsorption, and is transported through the stratum corneum, overall improving the transdermal penetration effect[81]. There also is potential for peppermint EO's wound healing and skin lesion treatment applications, where research has been placed on electrospun fibers aided with anti-microbial features of EO to be used for healing, although its combination with poly(ε-caprolactone) fibers did not increase cell viability [82,83]. Moreover, Peppermint EO's application in chitosan polymeric nanogels were effective against *Streptococcus mutans* biofilms, demonstrating its potential as a biofilm inhibiter when used in toothpaste and mouth wash products [84].
Peppermint EO is also known to have a high SPF value amongst different volatile oils of 6.7, providing a great fragrance inducing component for manufacturers to use to develop sunscreen products for the protection against ultra violet rays from the sun as skin care products [85]. Also, topical application has shown that peppermint oil can induce growth of thick and long hair in C57BL/6 mice, with characteristically greater follicle numbers, depth as well as dermal thickness [86]. These effects were accompanied by alkaline phosphatase and insulin like growth factor, both biomarkers associated with hair growth enhancement. Lastly, Peppermint EO component piperitone oxide is also added to mosquito repellents, found to be highly repellent to adult *An. Stephensi* [87].

4.3 Other Applications

A double blinded randomized placebo study on aromatherapy massage with peppermint EO also suggests that EO effectively decreased joint and muscled discomfort, sweat problems, sleep disturbances and cardiac issues during menopause and post menopause stages, and also relieving urogenital or sexual issues [88]. Peppermint-lemon based inhalation aromatherapy also observed changes in nausea, vomiting and retching scores in children undergoing chemotherapy, where the therapy provided improvements of the quality of life scores of those leukemia patients during chemotherapy cycle enduring from chemotherapy caused nausea and vomiting [89].
Oral administration of peppermint powder as aquatic feed has been found to enhance the development of *Rutilus caspicus,* specifically the fishes' growth hormone and insulin-like growth factor gene expression was the greatest at 4g/kg, promoting growth and hematological parameters such as hematocrit, hemoglobin, red blood cell and white blood cell count [90]. Similar results were found against *Rutilus frisii kutum,* along with increasing protein concentration, alkaline phosphatase and bactericidal effects of the mucosal layer for its skin [91].

4.4 Toxicity and Side Effects of Peppermint

Peppermint is a generally recognized as safe (GRAS) food by the United States Food and Drug Administration, as is menthol and menthyl acetate [92]. A report also states that peppermint oil, extract, leaves and leaf water are all safe to be used in cosmetics when the ingredients do not exceed over 1% [93]. Components that can introduce allergic effects from its Eos include menthol, caryophyllene, limonene, alpha-pinene, piperitone and pulegone [94]. Side effects of peppermint oil are considered to be mostly mild, but oral ingestion can be near fatal at a near toxic dose [95]. Symptoms resulted from intaking large doses include heartburn, nausea, vomiting and headaches. The lethal dose of peppermint oil in mice is known to be 4411 mg/kg in Wistar rats and 2426 mg/kg at 24 and 48 hours respectively, although the dosage likely can differ dependent on the chemical composition of the peppermint oil [96]. The LD50 of ethanolic and aqueous extracts of *M.piperita* were 3700 and 4800 mg/kg body weight in Wistar rats [97].

5 CONCLUSIONS AND FUTURE DIRECTIONS

Due to the complexity of the plant, with it varying chemical compositions depending on its hybrid subtype, cultivation methods, cultivation environments and other impacting factors, the usage of mint could be seen as not elucidated enough, including its impact on the human body and differing metabolic pathways that alter its chemical composition. Specifically, other constituents of *mentha*, such as menthone and menthyl acetate are lacking in terms of dedicated studies due to its generally lower concentration and availability in peppermint compared to menthol. Menthol has been found to have various applications, but further studies could be done for the other EO components, especially as menthol supply does not meet the increasing demands for menthol. Long term studies on the impact it has on diabetes and cardiovascular diseases could also be further explored, either of direct consumption of peppermint, or synergistic additives to health products, all have great potentials due to its large range of potential health benefits [6]. Impact of peppermint and *Mentha* EO on the gut microbiota is also a promising topic to explore, although a recent study of children with abdominal pain did not find that peppermint oil altered the abundance or diversity of the gut microbiome [98]. Overall, there is still a lot of application potential for peppermint and its associated EO products, mostly developed for its function in flavoring. But its therapeutic potential and

health additive effects as a previous traditional medicine solution, or innovative synergistic as new food and beverage products is worth paying attention to.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

DISCLAIMER

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