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Peppermint and Its Functionality: A Review

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Abstract

Peppermint (*Mentha piperita* L.), is a medicinal plant that has received more attention from both food and pharmaceutical industries because of its health benefits for human society. Herein, the chemical structure of peppermint compounds evaluated using theoretical studies. Indeed, the health benefits of peppermint were reviewed. Our molecular docking showed that among peppermaint compounds, cineol and menthyl acetate apparently bound to the active site of arylamine N-acetyltransferase enzyme. This type of interaction indicates the inhibitory effects of these compounds against this enzyme. Quantum studies revealed that menthol (E_{gap}=16.9 eV) and pulegone (E_{gap}=12.6 eV) are stable and unstable compounds in this plant. Finally, our theoretical results are similar to experimental investigations that reported before. Summing up, this plant is a good target for research and further studies should be focus on evaluating of peppermint in prevention of human diseases.

Keywords: Peppermint; Human diseases; Peppermint oil; Quantum chemistry; Molecular docking

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Abbreviations

PO: Peppermint oil; WHO: World Health Organization; HOMO: The highest occupied molecule orbital LUMO: The lowest un-occupied molecular orbital; MEP: Molecular electrostatic potentials; NAT: Arylamine N- acetyltransferase; SD: Standard deviation; IBS: Irritable bowel syndrome; HSV=Herpes simplex virus (DNA virus); VACV=Vaccinia virus

Introduction

Medicinal plants have received more attention because of their health benefits, such as anti-infectious properties, since ancient times [1-6]. The term of medical plants is referred to the natural remedies that have used for treatment of human diseases [4,7-10]. These medicinal plants can be considered as a valuable source of ingredients which can be used in drug development [5,11-13]. On the other hand, medical plants significantly affected the human life across the entire world [5,7,14,15]. The use of herbal medicine is leading modality, followed in Middle East, Europe and certain other advance countries, in order to treat of catastrophic human diseases [16]. Based on the WHO reports, the advanced countries have used medicinal plant for both clinical therapy and food industries significantly [16,17].

Medicinal plants have significant potentials for human societies and consumed by people across the entire world. Although most of their health benefits have not investigated yet, their medical activities can be considered in the treatment of present or future diseases [7]. Currently, more than 80% of the world population use the traditional medicine and medicinal plants (especially plant extracts and essential oils) for their primary health needs [18]. Peppermint or mint (*Mentha piperita* L.), a perennial aromatic herb belonging to the *Lamiaceae* (*Labiatae*) family, is a natural hybrid between spearmint (*Mentha spicata* L.) and water mint (*Mentha aquatic* L.) [19, 20]. Although it is a native genus of the Mediterranean regions, it cultivated all over the world for its use in flavor, fragrance, medicinal, and pharmaceutical applications [21]. Members of the mint genus are characterized by their volatile oils which are of great economic importance, being used by the flavor, fragrance, and pharmaceutical industries [22].

This plant is widely used in folk remedies and traditional medicine for treatment of digestive disorders and nervous system actions because of its antitumor and antimicrobial properties, chemo-preventive potential, its renal actions, antiallergenic effects, and also for lessening cramping, digestive complaints, anorexia,

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nausea and diarrhea [23,24]. Preparations of peppermint include leafs, leaf extracts and water, however, the plant is cultivated mainly for its essential oil, which is obtained by distillation from freshly grounded leaves [25-28]. PO is composed of menthol and menthone together with several other minor constituents, including pulegone, menthofuran and limonene, and its chemical composition may vary with plant maturity, geographical region and processing conditions [28-30].

Menthol occurs naturally as a colorless crystal or powder [31]. It is greatly responsible for the spasmolytic nature of peppermint [32]. Menthol has reported to stimulate bile flow [33], reducing the tone in the esophageal sphincter [34], facilitating belching [35], as well as having antibacterial properties [36]. In addition, peppermint is also a rich source of polyphenolic compounds and hence the strong antioxidant properties [8,22,26,28,37]. Among all countries in the world, India is the largest producer, exporter [38] and consumer of mint oil [39]. Currently China is a major importer of peppermint [39].

HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) orbitals are very important parameters used in quantum chemistry [40-42]. Based on their characteristics, it can be specified how a molecule would interact with other molecules [40]. The HOMO orbitals can be considered as an electron donor group, while the LUMO orbitals as free sites able to accept them [40,43-46]. Energy of the HOMO orbitals can be directly linked to the ionization potential, whereas the LUMO orbital energy can be associated with the electron affinity [40,44]. The difference between the orbital energies of HOMO and LUMO is referred to as energy gap (ΔE) which is an important parameter that can determine the reactivity or stability of molecules [40,44-46]. Since quantum chemistry and molecular docking studies have not been reported, the present study aims at determining the optimized molecular geometry, HOMO-LUMO energies of peppermint main compounds, using Hartree-Fock, 3-21G basic set and also indicates the binding mode of these compounds into a selected receptor. Also, the most abundant medicinal benefits of peppermint have reviewed.

Methods

Herein the therapeutic application of volatile oil of peppermint is discussed and also chemical descriptors are calculated to determine the electron parameters of peppermint active constituents to search for biological activities of these compounds.

Molecular quantum studies

All computational calculations were performed at the Hartree-Fock model on a Pentium IV/2.8 GHz personal computer using Spartan 10 software Wavefunction, Inc. [47]. The geometry of the peppermint active constituents in the ground state is fully optimized.

Molecular docking

The 3D structure of NAT enzyme (PDB ID: 2IJA) was obtained from PDB database (http://www.rcsb.org/pdb/home/home.do) and selected as receptor against peppermint chemical compounds. The molecular docking (blind docking) was done by Molegro virtual Docker 4.2.0 version. Visualization of docking results was performed by MOE software (https://www.chemcomp.com/MOE-Molecular_Operating_Environment.htm).

Nomenclature, botany and cultivation

Peppermint has more than 101 local names in different countries **(Table 1)** [48-51]. The principle of naming of mint is considered based on local culture and customs.

In botany, *Mentha piperita* L. is the common name for genus of peppermint [19]. The genus *Mentha* includes 25 to 30 species [52] which is a perennial herb and native to Europe, naturalized in the northern USA and Canada, and cultivated in many part of the world [53,54].

The mint is a sterile hybrid of spearmint (*Mentha spicata*) and water mint (*Mentha aquatica*) from the *Lamiaceae* family **(Figure 1)** [20,27].

The most relevant of mint species with commercial or medicinal usage are listed in **(Table 2)**.

Peppermint grows particularly well in lands with high water-holding capacity soil [55-70]. All commercial mint varieties are seed sterile and are propagated using the underground stolons (runners or rootstock) produced by existing plants [71]. The stolons can't be stored for more than a few days since they deteriorate rapidly due to heat or dehydration [71]. In general, mints tolerate a wide range of conditions, and can also be grown in full sun [72].

Chemical properties

Many studies showed that peppermint essential oil is composed of various secondary metabolites [27,28,31,33,34,38,53,54,73,74]. The mint main chemical compounds consist of limonene, cineole, menthone, menthofuran, isomenthone, menthyl

Table 1 The most abundant local names of mint around the world.

Country	Local name
Iran	Nanafelfeli
Brazil	Nortela pimento
USA	Lab Mint, mint
Norway	Peppermynte
Poland	Pepparmunta
Spain	Mentainglesa
Portugal	Hortelana pimentosa
Swedish	Pepparmynt
China	Po Ho
India	Urdu, mint, Pudina, Pudyana, Puthina
Turkey	Nana
Russia	Myata perechnaya
Uruguay	Menta
French	Menthe
Iraq	Nana
Bogota	Yerba Beuna
Denmark	Pebermynte
Germany	Peppermint
England	Brandy Mint
Mexico	Menta piperita

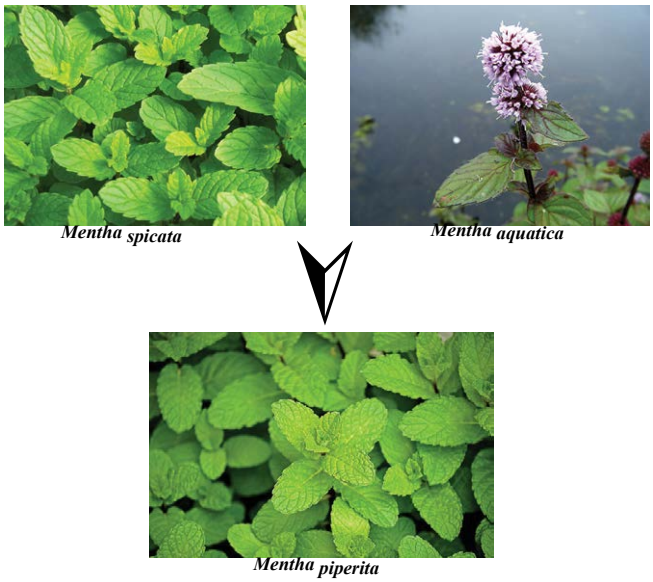

Figure 1 A schematic illustration of peppermint hybrid.

Table 2 The list of the most abundant mint species and their functions.

Species	Usage	References
Mentha spicata L.	Medicine	[55]
Mentha suaveolens	Ornamental Consumption	[56]
Mentha requienii Benth.	Ornamental Consumption	[57]
Mentha pulegium L.	Medicine	[58]
Mentha piperita L.	Medicine, Ornamental consumption, commercial	[59-61]
Mentha citrata Ehrh	Medicine	[62]
Mentha longifolia L	Medicine, Commercial	[63,64]
Mentha cardiaca	Medicine	[65]
Mentha arvensis	Medicine	[66]
Mentha canadensis	Weed	[67]
Mentha flavouring	Ornamental consumption, Medicine	[68,69]

acetate, isopulegol, menthol, pulegone and carvone **(Figure 2 and Table 3)** [38,74].

Other constituents include flavonoid glycoside (eg. Narirutin, Luteolin-7-o-rutinoside, Isorhoifolin and Hesperidin etc) [75] polyphenols (e.g Rosmaric acid, Eriocitrin, Cinamic acid, Caffeic acid and Narigenin-7-oglucoside); luteolin-diglucoronide and eriodictyol glucopyranosyl-rhamnopyranoside were also purified from aerial parts of mint [75-79].

The amount of peppermint compounds is different in various species [80]. Various factors including physiological variations, environmental conditions, geographic differences and genetic factors cause differences in chemical composition of these plants [80].

The most abundant chemical compounds that isolated form peppermint are largely classified into monoterpenes [81]. Currently, peppermint is the best model system for the study of monoterpene metabolism [82]. The pathway of monoterpene biosynthesis in peppermint has been well characterized by *in vivo* and systems biology studies **(Figure 3)** [83-85]. and all of the enzymes involved have been described [81,84]. According to the traditional view [86,87] monoterpenes are amongst the major constituents of essential oils and common secondary metabolites of plant metabolism, and as such they generally have been regarded as metabolic deadlock [83,84,87]. As shown in figure 3, the peppermint monoterpene-derived compounds separate from primary metabolism by conversion of isopentenyl diphosphate and dimethylallyl diphosphate, via the action of the prenyltransferase geranyl diphosphate synthase (EC 2.5.1.29), to geranyl diphosphate, which undergoes subsequent cyclization by limonene synthase (EC 4.2.3.16) to (4S)-(-)-limonene [84,88]. In peppermint a microsomal cytochrome (*Cyt*) P450 limonene-3-hydroxylase (EC 1.14.13.47) adds an oxygen molecule in an allylic location to produce (-)-trans-isopiperitenol and thereby establishes the oxygenation pattern of all subsequent derivatives [81,88,89].

A soluble NADP-dependent dehydrogenase (EC 1.3.1.82) oxidizes

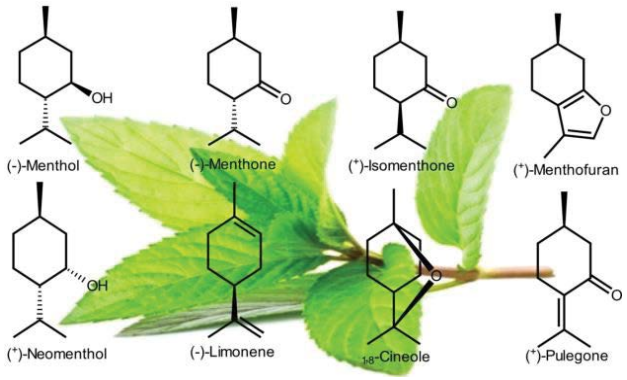

Figure 2 Representation of the most abundant chemical compounds of PO.

Table 3 The most abundant active compounds of *Mentha spp.*

Compounds	IUPAC name	Percentage (%)	References
Limonene	1-Methyl-4-(1-methylethenyl)-cyclohexene	1 to 5	[38]
Cineole	1,3,3-Trimethyl-2-oxabicyclo[2,2,2]octane	3.5 to 14	[23,76]
Menthone	(2S,5R)-2-Isopropyl-5-methylcyclohexanone	14 to 32	[31]
Menthofuran	3,6-Dimethyl-4,5,6,7-tetrahydro-1-benzofuran	1 to 9	[23,28]
Isomenthone	(2R,5R)-5-methyl-2-propan-2-ylcyclohexan-1-one	1.5 to 10	[27]
Menthyl acetate	Acetic acid [(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl] ester	2.8 to 10	[77]
Isopulegol	5-methyl-2-prop-1-en-2-ylcyclohexan-1-ol	0.2	[73]
Menthol	(1R,2S,5R)-2-Isopropyl-5-methylcyclohexanol	30 to 55	[23,31,33, 38,49,53,77]
Pulegone	p-Menth-4(8)-en-3-one	4	[78]
Carvone	2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one	1	[79]

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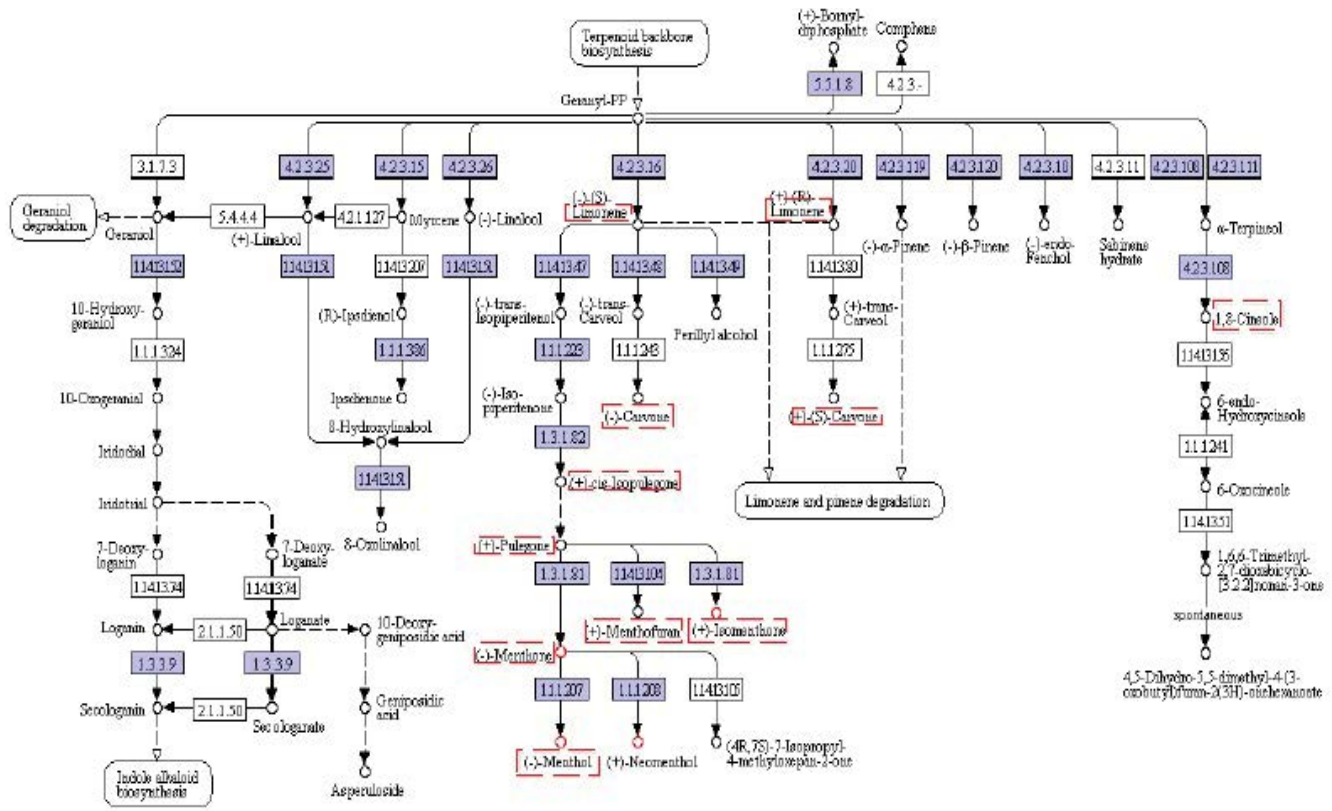

Figure 3 A schematic illustration of metabolic pathway for biosynthesis of peppermint chemical compounds (The pathway is taken from KEGG database: http://www.genome.jp/kegg/).

the alcohol to a ketone, (-)-isopiperitenone, thereby activating the adjacent double bond for reduction by a soluble, NADPH-dependent, regiospecific reductase to afford (+)-cis-isopulegone. An isomerase next moves the remaining double bond into conjugation with the carbonyl group, yielding (+)-pulegone. A NADPH-dependent reductase then converts (+)-pulegone to (+)-isomenthone and (-)- menthone, which predominates [89].

Finally, two stereo-selective NADPH-dependent reductases convert (-)-menthone and (+)-isomenthone to (-)-menthol and (+)-neoisomenthol, respectively, and (-)-menthone and (+)-isomenthone to (+)-neomenthol and (+)-isomenthol, respectively [81,88,89]. In these pathways, (-)-limonene is the first committed intermediate for biosynthesis of other compounds in the peppermint species. However, production of monoterpenes in peppermint id restricted to developing oil glands of young leaves [88,90,91], and the correlation between in vitro activity for the several enzymatic steps of menthol biosynthesis and the rate of biosynthesis measured in vivo suggests that monoterpene production is controlled by the coordinately regulated activity of relevant biosynthetic enzymes [82,90,92]. As mentioned above, (-)-Menthol greatly important among the menthol isomers (often exceeding 50% of the essential oil) and is primarily responsible for the characteristic flavor and cooling sensation of peppermint [31,89,93,94].

HOMO and LUMO orbitals analysis

The HOMO and LUMO orbitals are very important in quantum chemistry calculations [95,96]. The HOMO energy determines the electron donating ability while the LUMO designates the electron accepting ability and the HOMO–LUMO energy gap (ΔE_{Gap}) ($E_{LUMO} - E_{HOMO}$) [97,98] is an important value for stability index [96,99]. A large ΔE_{Gap} implies a good thermodynamic stability of the compound, in the sense of its lower reactivity in chemical reactions [100,101]. However, the magnitude of the HOMO-LUMO gap has very important chemical implications, even if qualitatively evaluated [102]. To determine stability and reactivity of peppermint main chemical compounds according to Hartree-Fock model 3-21G basis set calculation for water solution, the gap energies were measured **(Table 4)**.

Based on table 4 data, menthol, cineole and isopulegol have higher stability than other compounds. The increase of stability that showed by ΔE_{Gap} promotes the low reactivity of these compounds in a chemical reaction. The relationship between ΔE_{Gap} energy, stability and reactivity is well known described in many studies [103-105]. According to Hartree-Fock, 3-21G basic set calculation, the highest and lowest gap energies is related to menthol (16.9 eV), pulegone (12.6 eV) and carvone (12.6 eV) respectively. Our result about stability of menthol is similar to result that reported by Harlod and coworkers [106]. Froehlich et al. reported that in the aqueous ethanolic solutions, pulegone was unstable and it can be degraded to other products [107]. This case confirmed our molecular orbitals analysis for pulegone. Also, surfaces for the frontier orbitals were drawn to understand the bonding scheme of present compounds. The features of these molecular orbitals can be seen in **(Figure 4)**.

Table 4 HOMO and LUMO orbitals energy values for peppermint main chemical compounds in water, calculated with Spartan 10 V1.1.0, software, Hartree-Fock, 3-21G basic set.

Compounds	HOMO (eV)	LUMO (eV)	ΔE_{Gap} (eV)
Limonene	-9.1	5.0	14.1
Cineole	-10.1	6.3	16.4
Menthone	-10.6	4.2	14.8
Menthofuran	-8.4	4.8	13.2
Isomenthone	-10.3	4.4	14.7
Menthyl acetate	-11	5.0	16.0
Isopulegol	-9.7	5.0	14.7
Menthol	-10.9	6.0	16.9
Pulegone	-9.3	3.3	12.6
Carvone	-9.6	3.0	12.6

MEP analysis

The electrostatic potential of a molecule is an established tool in medicinal chemistry, modeling, and computational chemistry [108,109]. The MEP employed abundantly for predicting potentials have been and interpreting the reactive behavior of a wide range of chemical system in both electrophilic and nucleophilic reactions, the study of biological recognition processes and hydrogen bonding interactions [109-111]. To predict reactive sites for electrophilic and nucleophilic attack for the peppermint chemical compounds, MEP was calculated at Hartree-Fock, 3-21G basic set optimized geometries. In the most of the MEP, while the maximum negative site which preferred region for electrophilic attack indications as red color, the maximum positive region which preferred site for nucleophilic attack symptoms as blue color [112,113]. In the present study, 3D plot of molecular electrostatic potential of studied compounds has been drawn in **(Figure 5)**. In this plot the different values of electrostatic potential at surface are represented by different colors. Potential increase in order red<orange<yellow green<blue [113].

As shown in **(Figure 5)**, the regions having the negative potential are over the electronegative atom oxygen, respectively. Thus, it would be predicted that an electrophile would preferentially attack peppermint compounds at the oxygen positions. In addition, we found the positive regions over hydrogen atoms of methyl group of peppermint compounds and indicating that these sites can be the most probably involved in nucleophilic processes. Red and blue colors in peppermint compounds map refer to the regions of negative and positive potentials and correspond to electron rich and electron-poor regions, respectively, whereas the green regions signify the neutral electrostatic potential. The MEP surface map of peppermint compounds provides necessary information about reactive sites. These results can be used for design and development of the stable peppermint-derived drugs. The importance and application of MEP map in drug development is discussed in many studies [114-117].

Antiviral Activity

Nowadays, the development of phytotherapies aiming at the inhibition of viral diseases [118], in combination with classical anti-viral therapies, is among the most intensively studied approaches for the treatment of pathogenic viruses [119]. Infectious viral diseases remain an important worldwide problem, since many viruses have resisted prophylaxis or therapy longer than other microorganisms [120]. At the moment, only few effective antiviral drugs are available for the treatment of viral diseases [121]. There is need to find new compounds with not only intracellular but also extracellular antiviral properties [122]. There are several reports showed that various peppermint extracts has significant antiviral activities [123-126]. It seems, peppermint helps to immune system and protect the body from viruses [127-137]. **Table 5** presents a comprehensive list of antivirus effect of peppermint extracts.

Antibacterial Properties

Medicinal plants have been broadly used in common medicine and therefore, plant secondary metabolites are increasingly of interest as antimicrobial agents today [138,139]. Currently, biologically active compounds from peppermint sources have always been a great interest for scientists working on infectious diseases [140]. PO and extracts showed a good antimicrobial activity against: 1) *Escherichia coli,* 2) *Salmonella pullorum,* 3) *Comamonas terrigena,* 4) *Streptococcus faecalis,* 5) *Acinatobacter* sp, 6) *Streptococcus thermophiles,* 7) *Lactobacillus bulgaricus,* 8) *Staphylococcus pyogenes,* 9) *Staphylococcus aureus,* 10) *Streptococcus pyogenes,* 11) *Serratia marcescens*, 12) *Mycobacterium avium, Salmonella typhi,* 13) *Salmonella paratyphi A/B,* 14) *Proteus vulgaris,* 15) *Enterobacter aerogenes,* 16) *Yersinia enterocolitica* and 17) *Shigella dysenteriae* [131,141-143]. Studies showed that the antibacterial activity of peppermint leaves extract against Gram negative bacilli was higher than of its stem extract [131]. A number of studies demonstrated that essential oil from leaves of peppermint exhibited the highest antibacterial activity with 11.58 to 17.24 mm ± 0.87 SD, zone of inhibition [1,62,125,133], while the effect of extract obtained from the stem of peppermint is an average zone of inhibition 15.82 mm ± 3.56 SD, respectively [131]. On the other hand, PO has strongly effects against *Enterococcus faecium* ATCC10541, *Salmonella choleraesuis, Staphylococcus* aureus and *Bacillus subtilis* [140- 144]. There are differences in the chemical composition of peppermint essential oil from different parts of its structure [131]. As mentioned above, this differences can be effect on antibacterial activity of peppermint species [133]. Generally, mint oil and menthol have moderate antibacterial effects against both Gram-positive/negative bacteria [131]. It seems peppermint can become a novel target for synthesis of plant-derived drugs against a large spectrum of multidrug resistance bacteria.

Antifungal Activity

In-vitro data suggested that PO and extracts are good fungicidal against *Candida albicans, Aspergillus albus* and dermatophytic fungi [145]. The leave oils of *Mentha spicata* exhibited moderate activity against *Aspergillus fumigatus* (with 16 mm ± 0.5 SD, zone of inhibition) and *A. niger* (with 14 mm ± 0.5 SD) [146].

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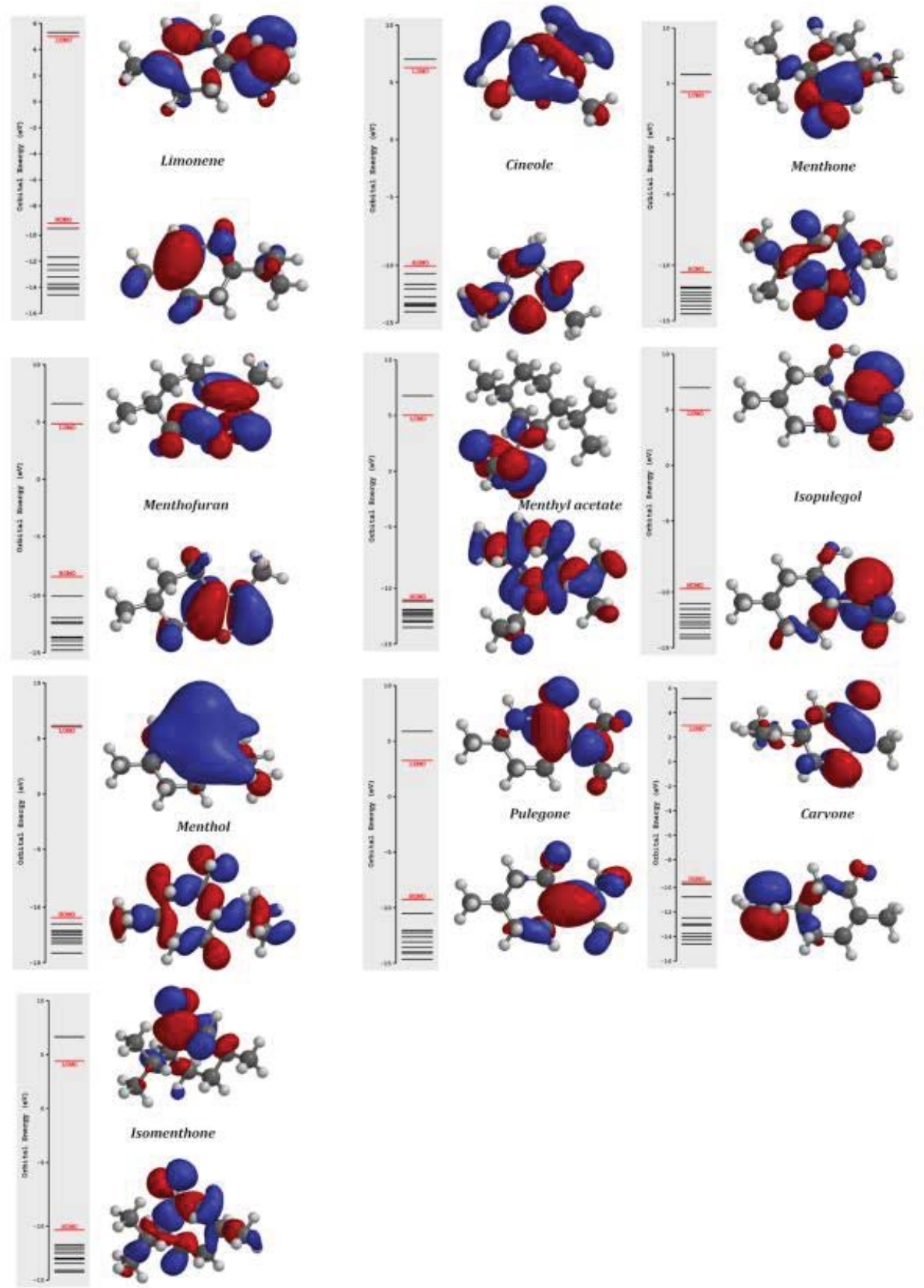

Figure 4 The atomic orbital composition of the molecular orbital of peppermint-derived compounds. For interpretation of the references to color in this figure, the reader is referred to the web version of this article.

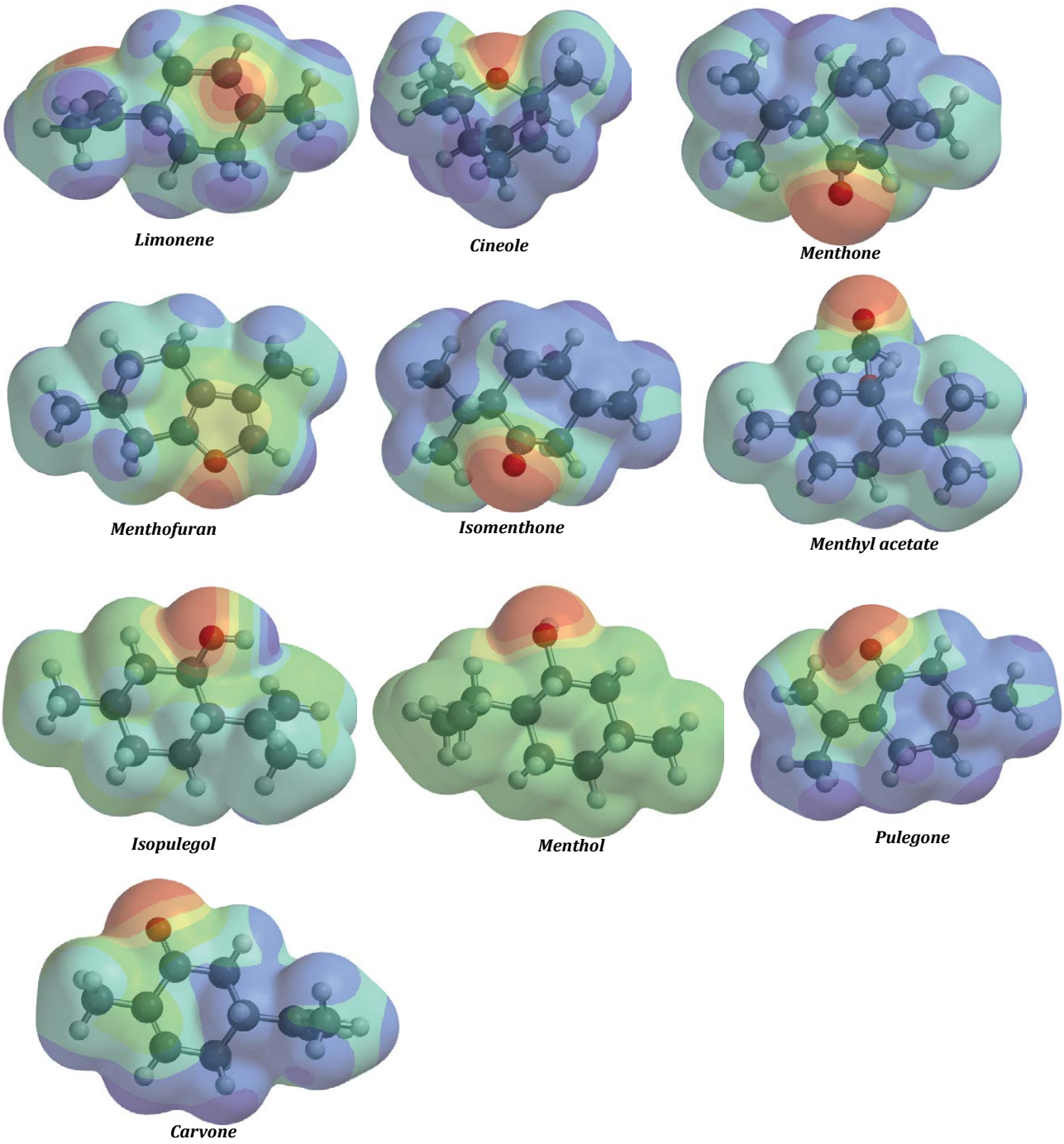

Figure 5 Molecular electrostatic potential surface of peppermint active compounds. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

Allelopathic Effects

Allelopathy is one kind of stress that plays a significant role in agro-ecosystems, and affects the growth, quality and quantity of the crops [147,148]. It was reported that water extract of peppermint (at concentration 10% v/v) is able to inhibits the growth of the tomato seedlings [149]. Skrzypek and Coworkers [150], demonstrated that aqueous extracts of peppermint (at concentration 15% v/v) decreases non-photochemical and photochemical quenching and vitality index of photosystem II in sunflower.

Medicinal Uses

Currently, PO has become most considered agent as treatment for a large body of human diseases [38]. The major health benefits of PO are shown in (Figure 6). In addition to medicinal uses, its extract is broadly used as flavoring in food industries [151]. As mentioned in pervious sections, among all chemical compounds

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Table 5 Antiviral activity of different peppermint extracts.

Extracts	Virus	References
Aqueous	HSV-1/2	[128,129]
	HIV-1	[130]
	Influenza A virus	[131]
	Newcastle disease virus	[132]
	VACV in egg	[132]
	Semliki Forest	[133]
	West Nile viruses	[133]
Alcohol	Influenza A virus	[134]
	HSV	[135]
Essential oil	HSV-1	[122,136,137]
	HSV-2	[122,137]

that purified from PO [31], menthol is common ingredient and widely is used for respiratory congestion [152,153], headache [154], and skeletal muscle pain [155]. The best dosage of PO for consumption in adult was reported 0.2 to 0.4 mL of oil three times daily in enteric-coated capsules [156].

Anti-angiogenic/Inflammatory effects

Angiogenesis, the formation of new arterioles from pre-existing vessels, is a multistep event involving degradation and remodeling of the underlying basement membrane and the surrounding extracellular matrix with subsequent proliferation and migration of vascular endothelial cells into the tissue to be vascularized [157-159]. Inflammation is regarded as an important baseline reaction responsible for manifestations of various chronic diseases such as cancer, septic shock, diabetes, atherosclerosis and obesity [18,160]. Recent data have expanded the concept that inflammation is a critical component of tumor progression [143]. There are several reports that peppermint compounds have crucial roles in prevention of inflammation and angiogenesis [161-163]. Methanol extract of peppermint has cytotoxic effect on L1210 cancer cells [164]. Lin and colleagues [165] showed that apparently menthol, in higher doses, effects on NAT activity in the human liver tumor cell line J5 [166]. The NAT is responsible for the biotransformation of numerous arylamine drugs and carcinogens [141]. This enzyme has three critical residues consist of Cys^{68}, His^{107} and Asp^{122} [167]. These residues corresponding to active site of NAT enzyme [142]. Herein, we performed a molecular docking to find the binding mode of peppermint compounds into NAT enzyme as receptor **(Figure 7)**.

Docking results showed that cineole and menthyl acetate interact with His^{107} residue and therefore, they are able to inhibit NAT enzyme activity **(Figure 7A and 7C)**. The docking energies for cineole, menthol, menthyl acetate, isopulegol, menthone and carvone were -11.2, -13.4, -11.91, -9.82, -7.83 and -10.11 kcal/mol, respectively. The His^{107} is one of critical residues in the active site of NAT enzyme and it is important for its activity [168]. Lin and Co-workers [165] reported that menthol a possible uncompetitive inhibitor to NAT activity in cytosols. Our docking result showed that menthol is able to interact with two residues (Tyr^{94} and Thr^{96}) from NAT enzyme with a great probability **(Figure 7B)**. In other hand, menthon was also able to interact with these two residues from NAT enzyme **(Figure 7E)**. Other docked compounds (i.e. isopulegol and carvone) interact with different residues of receptor **(Figure 7D and 7F)**.

Antispasmodic effects

PO relaxes gastrointestinal smooth muscle [169] by reducing calcium influx in both large intestine and jejunum [170]. PO and menthol are inhibitor for calcium channel activity in rats and

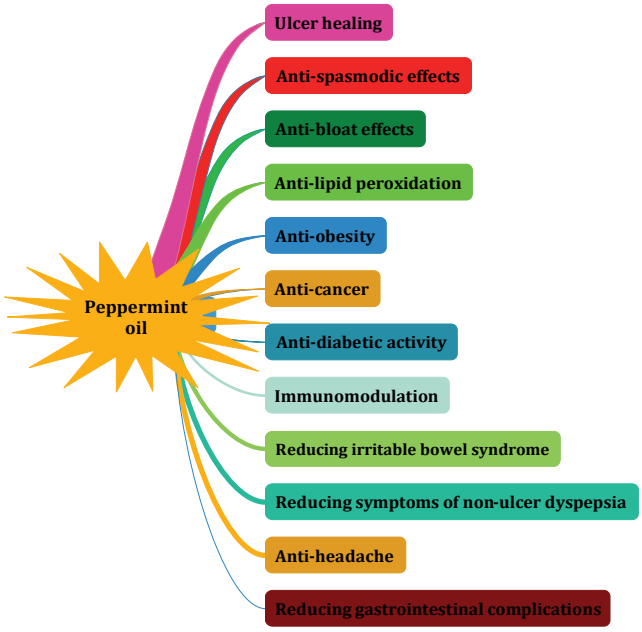

Figure 6 The major health benefits of PO.

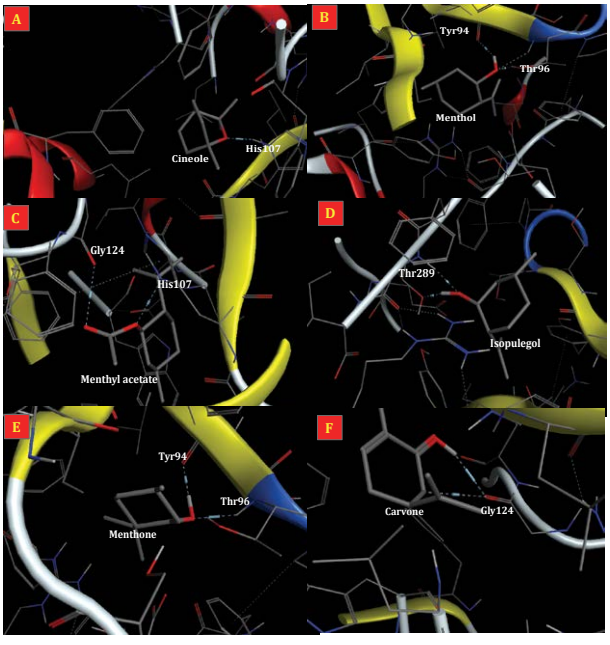

Figure 7 Representation of peppermint compounds docked with NAT enzyme as a receptor. (A) Cineole (B) Menthol (C) Menthyl acetate (D) Isopulegol (E) Menthone and (F) Carvone.

guinea pig atrial and papillary muscle, rat brain synaptosomes, and chick retinal neurons [171,172].

Treating Irritable Bowel Syndrome

IBS is defined as a chronic disorder of altered bowel function characterized by symptoms of diarrhea, constipation, or alternating bowel habits accompanied by pain or discomfort and may include a constellation of other symptoms, e.g., bloating, urgency, and incomplete evacuation [156,171,173-175]. This syndrome affects 9 to 23% of the population across the world [176]. It was reported that PO is a safe and effective short-term treatment for IBS [177,178]. Also, PO acts as inhibitor for calcium channel activity in the intestine and therefore it can able to reduce symptoms of IBS [31]. Other postulated mechanisms for PO in treatment of IBS include inhibition of potassium depolarization-induced and electrically stimulated responses in the ileum [179]. Also, it was reported that PO has crucial effects on histamine, serotonin, and cholinergic receptors in the gastrointestinal tract may also mediate some of its antiemetic effects [180]. Cappello et al. showed that a four weeks treatment with PO improved abdominal symptoms in patients with IBS [181]. The similar results also were reported in other studies [176,182-184]. Taken together, peppermint is the most encouraged plant for treatment of gastrointestinal disorders.

Anti-headache activity

Since ancient times, herbal therapy has been used as treatment for headache disorders [185]. Consumption of peppermint and derivatives is the best target for headache therapy [186]. Gobel et al. showed some benefit from peppermint and eucalyptus oil in combination in relieving patients' headache pain [186]. Also, similar result was reported by Levin [187].

Effect on hepatic enzymes

Maliakal and Wanwimolruk reported that aqueous extract of peppermint (at concentration 2% v/v) can modulate of phase I and phase II drug metabolizing enzymes [188]. In phase I, a variety of enzymes act to introduce reactive and polar groups into their substrates [189]. Phase II biotransformation reactions generally serve as a detoxifying step in drug metabolism [190]. Khodadust et al. showed that peppermint alcoholic extract ameliorated the adverse effects of CCl_4 on growth performance and liver function, therefore they indicated that it might be useful for the prevention of oxidative stress-induced hepatotoxicity in broilers [191].

Radioprotective Effects

The radioprotective activity of peppermint oil and aqueous extract has well been documented [192,193]. Kaushik et al. demonstrated the effectiveness of peppermint alcoholic extract against radiation induced morbidity and mortality using the optimum dose of 100 mg/kg for 3 consecutive days [192]. Samarth and Coworkers suggested the antioxidant and free radical scavenging activities of leaf extract of peppermint are directly related to its mechanism of radiation protection [193]. Several mechanisms such as antioxidant activity, immune response, and enhanced recovery of bone marrow have been suggested for chemoprevention and radioprotection of peppermint extracts [194].

Side Effects and Toxicity

Although peppermint is a considered medicinal plant for treatment of human diseases, it was reported that in rats, PO caused cyst-like changes in the white matter of the cerebellum and nephropathy at doses of 40-100 mg/kg per day for 28-90 days [195].

Adverse reactions to enteric coated PO capsules are rare [174], but may include hypersensitivity reaction, contact dermatitis, abdominal pain, heartburn, perianal burning, bradycardia and muscle tremor [175,196].

In patients with chronic cough, pre-inhalation of menthol reduces cough sensitivity to inhaled capsaicin and influences inspiratory flows [197]. In rats, doses of 80 and 160 mg of pulgeone for 28 days caused atonia, weight loss, decreased blood creatinine content, and histopathological changes in the liver and the white matter of the cerebellum [198]. Menthol causes hepatocellular changes in rats [195].

Marketing

The market for PO in the entire world is divided into local and international buyers. The local buyers included small buyers and companies from chemical and pharmaceutical, as well as food and flavoring industries. The international buyers are divided into flavor and fragrance houses, cosmetics and personal health care, aromatherapy and food manufacturers who buy in large quantities [199]. The peppermint industry is the largest commercial herb industry in the United States (more than 4000 tons per year). Keeping in view multiple benefits of peppermint, various dosage forms are available in market for treatment of various human lifestyle diseases **(Figure 8)**.

Conclusion Remarks

Regarding to health benefits of peppermint, it can be concluded that this plant has great potentials for treatment of human diseases and also it has strong future in the world marketing. Further studies are need to exploration of cellular and molecular mechanisms of peppermint and its compounds on human body. Although peppermint plant has great beneficial and economical role in human society, researches must be considered its minor side effects and toxicity. The future in vivo human studies are needed to determine the molecular mechanism of PO in human health. Currently PO is most frequently traded essential oil in the entire world and in many developed and developing countries it considered as a valuable target for both food and pharmaceutical studies.

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Figure 8 Different dosage forms of PO alone or in combination with other chemical ingredients are available in market.

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Conflicts of Interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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