Genus Mentha

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Mint (*Mentha* species) exhibits multiple health beneficial properties, such as prevention from cancer development and anti-obesity, antimicrobial, anti-inflammatory, anti-diabetic, and cardioprotective effects, as a result of its antioxidant potential, combined with low toxicity and high efficacy. *Mentha* species are widely used in savory dishes, food, beverages, and confectionary products. Phytochemicals derived from mint also showed anticancer activity against different types of human cancers such as cervix, lung, breast and many others. Mint essential oils show a great cytotoxicity potential, by modulating MAPK and PI3k/Akt pathways; they also induce apoptosis, suppress invasion and migration potential of cancer cells lines along with cell cycle arrest, upregulation of Bax and p53 genes, modulation of TNF, IL-6, IFN-γ, IL-8, and induction of senescence phenotype. Essential oils from mint have also been found to exert antibacterial activities against *Bacillus subtilis*, *Streptococcus aureus*, *Pseudomonas aeruginosa*, and many others.

mint Mentha phytochemicals essential oils anticancer antimicrobial

1. Introduction

Medicinal plants and their derived compounds (phytochemicals) have been considered of pharmacological significance since ancient times. The use of plants in medicine dates back to 60,000 years ago, before the birth of civilization [1]. Today, more than 30% of all medicinal drugs (and their derivatives and analogs) derive from plants, and natural products will continue to possess considerable impact in human medicine. Most synthetic bioactive drugs are structurally similar to the phytochemicals of plants from which they were firstly isolated [2][3]. In many developing countries, plant materials have an important role in primary care or disease treatment. In addition, due to contraindications in the usage of chemical drugs, there is a growing interest in the utilization of the plant-derived medicinal products [4], since compared to synthetic drugs some of these natural products have lower toxicity and higher efficacy [5]. Anticancer drugs, antibiotics, anti-inflammatory drugs, immunomodulators are among the most important drugs having herbal origin [6][7][8]. Moreover, some of the aforementioned plant-derived compounds have pleasant taste and odor and can be used in kitchen as flavorings, spices and food [9]. Among the plants with global economic and culinary importance, mint is used worldwide for perfuming sweet and savoury dishes and flavouring tea, in addition to its pharmacological importance.

2. Phytochemical Composition of *Mentha*

Mentha species are rich in polyphenols [10] and, moreover, contain caffeic acid and its derivatives caftaric acid, cinnamic acid, ferulic acid, and oleanolic acid [11][12][13]. Flavonoids including luteolin and its derivatives apigenin,

acacetin, diosmin, salvigenin and thymonin, have also been detected in these plants, accounting for some 10–70 compounds out of the total phenolics, and also flavanols such as catechin, epicatechin and coumarins, including esculetin and scopoletin [14][15][16][17]. With regard to mint compositions, the essential oils represent a major focus. They are colorless, pale yellow or greenish yellow [18] and alcohols, ketones, esters, ethers and oxides are their main components in *Mentha* species [19][20]. Menthol, menthone, isomenthone, menthyl acetate, linalool, linalyl acetate, lippione, pulegone, carvone, piperitenone oxide and *cis*-piperitone epoxide are the main constituents of essential oils prepared from different mint species [19][21][22][23]. Table 1 lists the main compounds isolated from different species of this genus.

Table 1. Main chemical compounds isolated from different *Mentha* species.

Species Name	Essential Oil Components	Other Polyphenol Compounds	References
M. aquatica L.	epi-bicyclosesquiphellandrene, 1,8-cineole, menthofuran, β-caryophyllene, limonene, *p*-menthone, β-pinene, germacrene D, α-pinene, α-humulene, δ-cadinene, caryophyllene oxide, viridiflorol, viridiflorol epoxide II, α-cadinol, β-bisabolenol, α-trans-bergamotene, *p*-cymene, borneol, sabinene, β-myrcene, terpinyl acetate, eucalyptol	Rosmarinic acid, lavandulifolioside, rutin-*O*-glc, eriodictyol-*O*-rut, quercetin-3-*O*-soph, verbascoside, caffeic acid	[24][25][26][27][28][29]
M. arvensis L.	3-Octanol, fenchone, endo-fenchol, *p*-menthone, iso-menthone, neo-menthol, menthol, epi-bicyclosesquiphellandrene, isopulegone, 1-α-terpineol, pulegone, eugenol, *cis*-jasmone, β-bisabolene, *cis*-3-hexenyl phenyl acetate, β-eudesmol, oxygenated monoterpenes, 1,8-cineole, β-caryophyllene oxide, linalyl acetate, α-phellandrene, terpinolene, limonene, pulegone	Monogalactosyl diglycerides, digalactosyldiglycerides, decyl anhydride, 1-decanol	[30][28][29]
M. canadensis	Oxygenated monoterpenes, 1-menthol, isomenthone, 1-limonene, menthone,	3,4-Dihydro-3,6,7-trihydroxy-2(1*H*)-quinolinone, (*E*)-2-methoxy-2-	[30][28][31]

Species Name	Essential Oil Components	Other Polyphenol Compounds	References
L.	neomenthol, isopulegone, pulegone, linalyl acetate, piperitone	oxethyl-3-(4-hydroxyphenyl) acrylate, syringic acid, *p*-coumaric acid, esculetin, methyl rosmarinate, nepetoidin B, syringaresinol, methyl ester of caffeoyl glycollic acid, 2″,3″-diacetyl- martynoside and bracteanolide A, *cis*-3-[2-[1-(3,4-dihydroxyphenyl)-1-hydroxymethyl]-1,3-benzodioxol-5-yl]-(*E*)-2-propenoic acid	
M. longifolia L.	τ-Cadinol, γ-cadinene, γ-gurjunene, 1-limonene, piperitone oxide, piperitenone oxide, piperitenone, menthone, borneol, pulegone, verbenone, β-caryophyllene, linalool, 3-tripinolenone, dihydrocarvon, 1,8-cineol, germacrene D, citronellal	Prasterone acetate, sclareol	[32][33]
M. mozaffarian L.	Piperitone, 1,8-cineol, linalool, α-terpineol	Piperitenone, pulegone, piperitenone oxide, menthone, *cis*-piperitone epoxide	[32][33][34]
M. piperita L.	Oxygenated monoterpenes, menthol, methyl petroselinate, menthyl acetate, isopulegol, pulegone, carvone, menthone, cineole, menthofuran, isomenthone, limonene, β-pinene, β-myrcene, α-pinene, α-thujene, linalool	Riboflavin, *cis*-carvone oxide, caffeic acid, *p*-cumaric acid, ferulic acid, rosmarinic acid, caftaric acid, chlorogenic acid, *m*-coumaric acid, *o*-coumaric acid,	[28][35][36][37][38][39]
M. pulegium L.	Piperitone, piperitenone, 4-terpineol, menthone, limonene, naringenin, pulegone, iso-methone	Rosmarinic acid, ellagic acid, caffeic acid, caftaric acid, chlorogenic acid, *m*-coumaric acid, *o*-coumaric acid, *p*-coumaric acid, cryptochlorogenic	[28][40][41]

Species Name	Essential Oil Components	Other Polyphenol Compounds	References
		acid, isochlorogenic acid, neochlorogenic acid, protocatechuic acid	
M. rotundifolia L.	Menthol, menthone, menthyl acetate, menthofuran, piperitone oxide, linalyl acetate, neomenthol, piperitone, isomenthone, 1,8-cineole, linalool, geraniol, myrcene, geranyl acetate, germacrene D, carveol, limonene, rotundifolone, *p*-menthane-1,2,3-triol, D-limonene, piperitol, diosphenol, β-caryophyllene,, germacrene D, calamenene, *trans*-piperitone epoxide, piperitenone oxide, *cis*-piperitone oxide, cyclohexanol, *trans*-sabinene hydrate	Hypericin, apigenin, quercetin, *trans*-cinamaldehyde acid, rosmarinic acid, quercetin3-*O*-galactoside, hydroxybenzoic acid, procyanidin B2	[42][43][44] [45][46]
M. spicata L.	Carvone, piperitenone oxide, pulegone, 1,8-cineole, limonene, *cis*-piperitone oxide, piperitone, piperitenone, menthofuran, caryophyllene	Rosmarinic acid, salvianolic acids, hydroxybenzoic acids, caffeoylquinic acids, hydroxycinnamic acids, flavanones, and flavones	[47][48][49]
M. suaveolens Ehrh L.	Piperitenone oxide, pulegone, trans-caryophyllene, germacrene D, nepetalactone, piperitenone, *cis*-piperitone, limonene, menthone, terpinen-4-ol, *p*-cymen-8-ol, E-hydrate sabinene	4-Hydroxybenzoic acid, vanillic acid, chlorogenic acid, syringic acid, *o*-coumaric acid, *p*-coumaric acid	[50][51][52]

chemical

Pharmacological Properties	Chemical Compounds Responsible for Pharmacological Properties	References
Antioxidant	Ascorbic acid, rosmarinic acid, δ-terpinene, α-terpinene, *p*-cymene, 1,8-cineole, *cis*-carveol, carvone, rosmarinic acid, cynaroside, cryptochlorogenic acid, naringin	[53][59] [60]
Antibacterial	Luteolin, rosmarinic acid, caffeic acid, gallocatechin, epigallocatechin gallate, catechins, menthone, isomenthone, hexadecanoic acid, *cis*-carveol, carvone,	[4][59][60]

Pharmacological Properties	Chemical Compounds Responsible for Pharmacological Properties	References
	limonene	
Antifungal and Antiyeast	Limonene, piperitenone oxide, menthol, menthone, carvone, *cis*-carveol and carvone, piperitone, citronellal, caffeic acid, naringin, cryptochlorogenic acid, rosmarinic acid	[4][59][61]
Antiviral	Menthol, eriocitrin, rosmarinic acid, luteolin 7-*O*-rutinoside, hesperidin, phytol	[4][62]
Anticancer	Eugenol, caryophyllene, t-cadinol, menthone, menthol crotonate, naringin, cryptochlorogenic acid, rosmarinic acid	[63][64][65]

nery and cosmetic industries. In traditional Iranian medicine, it is reported that *Mentha* species have cooling sensation properties, strengthen the stomach and are effective to relieve digestive symptoms, respiratory tract problems and hemorrhoids [66]. It has been shown that *Mentha spicata* essential oil can reduce pain caused by Caesarean section [67][68]. Recent investigations have suggested that the transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8) and transient receptor potential cation channel, subfamily A, member 1 (TRPA1) are implicated in pain relief (analgesia) and sensation of cooling [67][69]. In Ayurvedic medicine, some *Mentha* species were used to mitigate skin problems and headaches [70]. In vitro studies showed that peppermint essential oil and menthol acted as smooth muscle relaxants via blocking Ca^{2+} influx through L-type Ca^{2+} channels [71][72]. Also peppermint juice led to reduction in total cholesterol levels, triglycerides and could increase HDL levels in the blood of university students [73] (Figure 1).

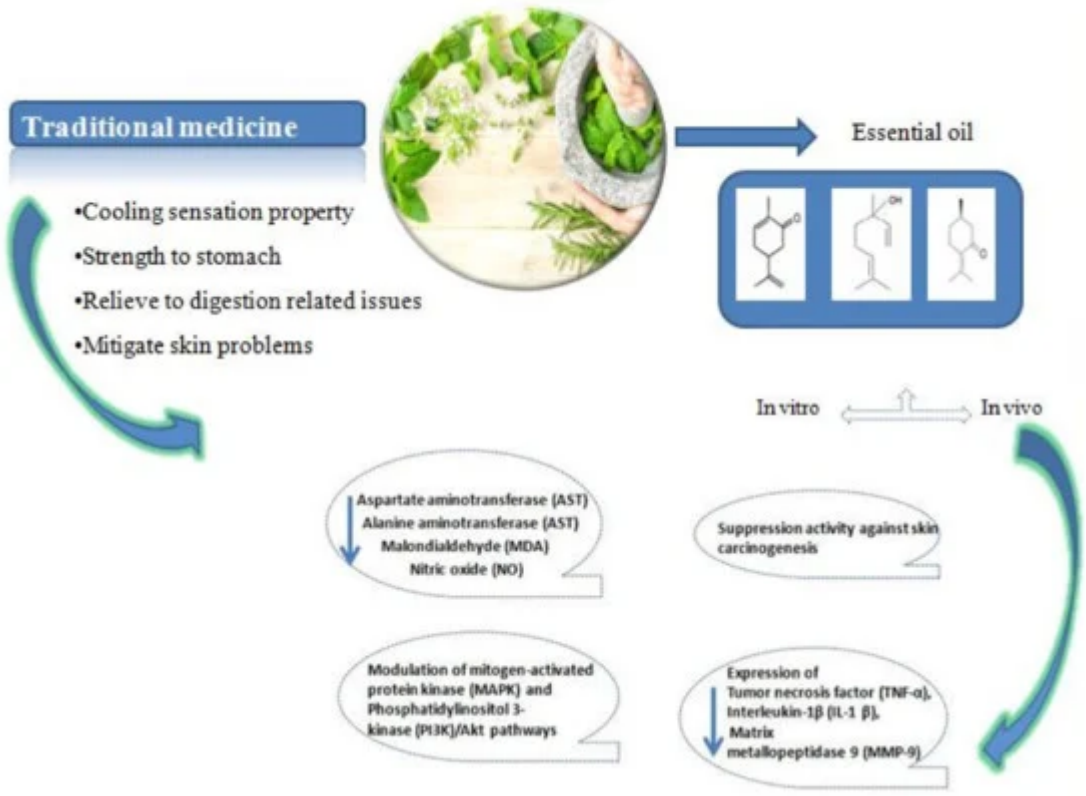

Figure 1. Summary of the main effects of *Mentha* species.

4. Clinical Trials

Limited data are available on clinical trials using *Mentha* species in humans [74], and indeed only two works reported the use of *Mentha* species in humans related to cancer. First a randomized, double-blind clinical trial was conducted in 200 patients to determine the efficacy of volatile oils of *Mentha piperita* or *Mentha spicata* in preventing chemotherapy-induced nausea and vomiting (CINV) in four groups, control, placebo, *M. piperita, M. spicata*. The results showed a significant reduction in the intensity and number of emetic events in the first 24 h with *M. spicata* and *M. piperita* in both treatment groups ($p < 0.05$) when compared with the control and no adverse effects were reported. The cost of treatment was also reduced when essential oils were used [75]. The second work is another randomized, double blind placebo clinical trial conducted in 60 patients to evaluate the effects of *Mentha piperita* (and *Matricaria recutita*) on oral mucositis (OM) in patients undergoing hematopoietic stem cell transplantation (HSCT) [76]. OM is one of the most common side effects of intensive chemotherapy in patients undergoing HSCT. Patients who received herbal mouthwash three times daily for 1 week before HSCT showed significant improvements in pain intensity ($p = 0.009$), dryness ($p = 0.04$) and dysphagia ($p = 0.009$), suggesting a therapeutic role for *M. piperita* in OM.

5. Adverse Effects of *Mentha* Species

Although medicinal plants such as *Mentha* species are commonly believed to be safe, they are not devoid of side effects that can be severe in some cases. Furthermore, allergic reactions can occur with any natural or synthetic

compound in sensitive persons. No chronic toxicity studies in humans are available, therefore toxicity of *Mentha* species are scarcely reported. However, it seems that no adverse effects have been reported after consumption 0.24 mL of pure *M. spicata* essential oil daily for three continuous weeks in two different clinical studies [77][78]. Leaves of *Mentha spicata* are known for its contact allergy such as contact cheilitis caused by its essential oil use as toothpaste flavoring [79]. In addition, MPEO is also associated with adverse effects like vomiting, headaches, flushing, heartburn and nausea [80]. *Mentha piperita* and spearmint tea can deprive the human body of iron and cause anemia if consumed excessively, and carvone and limonene showed to be major allergens [79]. Gürbüz found that pulegone, contained in low concentrations in *Mentha piperita* oil extracts, is hepatotoxic, and Douros et al. also reported the likely liver injury caused by *M. piperita* [81][82]. Other research showed that menthol and pulegone could be toxic compounds; in particular, pulegone and its metabolite menthofuran have been suggested as the hepatotoxic compounds in *Mentha pulegium* and have been also found in smaller quantity in *Mentha piperita* [83]. Notably, inhalation of menthol can cause apnea and larygospasm in sensitive patients and indeed has been reported that mentholated preparation can be involved in nausea, anorexia, cardiac problems, ataxia and other CNS symptoms [84]. *Mentha spicata* extracts displayed toxicity to neuronal cells when applied at concentrations which are one order of magnitude higher than those effective for radical scavenging [85]. The positive correlation between the two aforementioned effects suggests that a higher desirable radical scavenging is associated with a higher undesirable toxicity.

Peppermint oil is contraindicated in obstruction of the bile ducts, gallbladder inflammation, and severe liver failure [83]. The American College of Gastroenterology has recommended reducing the peppermint intake as it is a risk factor for gastroesophageal reflux disease (GERD) and lifestyle changes [86][87]. Further, Zong et al. [88] reported that peppermint essential oil, not only stimulated bile fluid secretion, but might be involved in upregulating the bile acid synthesis-related gene, cholesterol 7α-hydroxylase (CYP7A1), and the nuclear bile acid receptor FXR (farnesoid X receptor) mRNA. In addition, peppermint oil could cause heartburn or perianal irritation, bradycardia and muscle tremor, a hypersensitivity reaction, contact dermatitis, abdominal pain and jaundice in newborn babies [89]. A study on a 58-year-old woman who smoked menthol cigarettes also established that she suffered from gastrointestinal upsets with occasional vomiting, hand tremor, mental confusion and depression which were all ascribed to menthol [90]. Similarly, in another case report, a 40-year-old woman with no history of asthma or any other forms of allergy has shown the symptoms of dyspnea, wheezing and nasal after using menthol containing candies and toothpaste, suggesting the development of classical symptoms of asthma [91]. Menthol administered for 28 days at a dose level (≤ 800 mg/kg) in rats caused hepatocellular changes and pulegone (≤ 160 mg/kg) has been reported as hepatotoxic and neurotoxic. Consequently, pulegone caused weight loss, atonia, decreased blood creatinine, histopathological changes in the liver and also in the white matter of the cerebellum [92]. Menthone (≤ 800 mg/kg orally) on the other hand, dose dependently decreased plasma creatinine, but increased alkaline phosphatase and bilirubin along with liver and spleen weight [93]. Menthone administered to rats at a high dose over 28 days did display some signs of hepatotoxicity and cerebellar histopathology [93]. In a later study examining peppermint constituents for their possible induction of encephalopathy, one-month treatment with limonene (≤ 1600 mg/kg) or 1,8-cineole (1000 mg/kg) produced an accumulation of protein droplets containing α-2μ-globulin in proximal tubular epithelial cells, but no encephalopathy in rats [94]. Peppermint and menthol have

both been shown to possess Ca^{2+} channel blocking properties, which might underlie their mechanism of efficacy against irritable bowel syndrome in the clinic [84]. However, in some patients, the use of peppermint is accompanied by oral symptoms like burning mouth syndrome and oral ulceration [87]. Also in this context, direct application of peppermint oil to the chest or nasal area of infants is not recommended due to the risk of apnea, bronchial and/or laryngeal spasms [95].

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