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Bioactive components of peppermint (*Mentha piperita* L.), their pharmacological and ameliorative potential and ethnomedicinal benefits: A review

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Abstract
Peppermint is a medicinal herb, cultivated globally and is known for its distinct flavour and aromatic fragrance. Peppermint is used in different industrial purposes, also consumed as tisane Peppermint is used as traditional medicine from time immemorial. Peppermint possesses flavonoids, volatile oils, lutolin, hesperidins etc. The major components of the volatile oil are methanol and methone. Peppermint has some efficacy as an antineoplastic, anti-microbial, anti-viral, anti-radiation, anti-oxidant as well as anti-inflammatory. Peppermint leaf is used mainly to treat Upper G.I tract diseases, respiratory tract problems, irritable bowel syndrome (IBS), nausea, hepatotoxicity, diabetes etc. Anti-microbial effect of peppermint mainly in corona virus (Covid-19) has been found also, peppermint helps to prevent the interaction between corona virus (Covid-19) and the host body by inhibiting the formation of receptor complex of viral spike protein and ACE2 receptors of the host body. Furthermore it may act directly on virus or may pierce the viral membrane or may inactivates essential viral enzymes. Its effectivity has also been seen during post-covid phase. The consumption of peppermint is generally safe for all age –groups, but intake of large volume can cause heart burn and gastroesophageal reflux disease (GERD). This article holistically reviews the therapeutic roles of peppermint in various physiological and disease conditions.

Keywords: menthol, hesperidins, volatile oil, hepato-toxicity, anti- microbial, anti-radiation, anti-inflammatory, carcinogenic effect. irritable bowel syndrome, therapeutic approaches

1. Introduction
In this era almost 10% herbs have been identified to have medicinal impacts among all the herbs present in the world [1]. The medicinal herbs are those which have the ability to prevent different types of diseases. Mainly the phytochemicals of these herbs are responsible for the therapeutic approaches of these herbs to treat different types of diseases [2]. One of the popular type of medicinal herb is peppermint (*Mentha piperita* L.) , which is known as pudina in India [3]. This is mainly grown in hilly areas and mainly in cold climatic regions. It is widely known to the world for its cooling and calming effects. It is mentioned in Ayurveda as it is used to maintain the balance of '*vata dosha'* whereas is used to decrease the '*pitta*' and '*kapha doshas'* [4]. Peppermint (*Mentha piperita.* L.) is actually a crossed-hybrid mint of watermint (*M. aquatica* L.) and spearmint (*M. spicata* L.) It belongs to the family of '*Lamiaceae*' [5]. In Sanskrit it is known as '*rochani*', which means taste perception improver [6] There are found many significant uses of peppermint in various industrial purposes, as well as it is used to prepare tisane. Leaves of this plant are mainly used to made tisane. Peppermint (*Mentha piperita* L.) is among the renowned mainly single component herbal teas [7]. India stands at the topmost producer and exporter country of mint oil among all over the world, which is produced from the leaves of it after extraction [8]. Mint oil and its constituents and derivatives can be used in different types of industrial purposes including food, pharmaceutical, perfumery and flavouring industry. In the manufacturing process of lozenges, toothpastes, pain balms, cold balms, and others, 'menthol' the prime constituent of peppermint, is used widely as well [9]. It is a real bonus in medical therapy as it helps to get rid of biliary colic disease, menstrual pain, ulcer, gastritis, intestinal colitis, convulsion of the bile duct and different types of gastrointestinal diseases [11]. Anti-microbial and anti-allergic effects of peppermint have high impact on even prevention and curation of corona virus (Covid-19) infections.

1.1 Therapeutic phytochemical compounds present in peppermint

Peppermint has a number of bioactive phytochemicals that have well defined and proven chemical structures and possess significant physiological roles. Some of these components have been listed along with their IUPAC name in the table no. 1 [11].

Table 1: Chemical Components of Peppermint

Polyphenols	Rosmaric acid, eriocitrin, cinnamic acid, caffeic acid etc.
Flavonoids	glycosides –Narirutin, luteolin-7-o-rutinoside, isorhoifolin, hesperidin etc
Limonene	1-methyl-4-(1-methylethenyl)-cyclohexene
Cineole –	1,3,3 -Trimethyl-2-oxabicyclo [2.2,2] octane
Methone	(2S,5R)-2-isopropyl-5-methylcyclohexanone
Menthofuran	3,6-Dimethyl-4,5,6,7-tetrahydro-1-benzofuran
Isomenthone	(2R,5R)-5-methyl-2-propan-2-ylcyclohexan-1-one
Carvone	2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one,
Pulegeone	p-Menth-4(8)-en-3-one
Menthyl - acetate	Acetic acid [(1R,2S,5R) -2-isopropyl-5-methylcyclohexyl]ester

2. Role of peppermint

2.1 Pharmacological effect

2.1.1 Antineoplastic activity: A study (Ohara and Matsuhisa 2002) has claimed that almost 120 medicinal plants have shown anti-tumoric activity. These were found to supress the okadaic acid and other tumor promoter genes, which are responsible for tumorigenic activities **[12].** Peppermint is one of those and is a most commonly edible plant which has a strong anti-tumor activity by inhibiting okadaic acid, as mentioned **[13].** A study has shown that menthol, the primary constituent of peppermint, has an effect on the enzyme of N-terminal Acetyl-Transferases (NATs), an enzyme, which is mainly involved in xenobiotic metabolism by transferring the acetyl group from acetyl-CoA to its xenobiotic acceptor substrates [14]. Thus it prevents tumor formation specifically by inactivating the tumor lining cells in the liver. Another study has shown, the tumor inhibitory activity of NATs is directly proportional to the amount of menthol consumption [15].

2.1.2 Anti-bacterial action: A study of Iscan *et al*. (2002) has tested the effects of peppermint oil and its constituent menthol in almost 21 types of pathogens and they have found the inhibitory activities of menthol in these human and animal pathogens including *Staphylococcus aureus, Listeria monocytogenes* and also against some plant pathogens like *Xanthomonas* and *Pseudomonas* stains [16]. Another study which was conducted by Pattnaik *et al*. (1996), had also found 20 types of gram-negative and gram-positive bacterial stains in which peppermint oil showed inhibitory effects. Other bacterial stains on which it showed its effects included gram-negative rods and gram-positive cocci [17]. Tassou *et al*. (2000) suggested that, peppermint oil has beneficial effect on reducing count of the colony forming unit (CFU) of *Staphylococcus aureus, Salmonella enteritidis* and has resistant effect on S. aureus and *Enterococcus faecium* [18].

2.1.3 Anti-inflammatory and anti-allergenic effects

Arakawa *et al*., (1992) had examined *in-vivo*, they had administered peppermint oil, containing menthol and cineole orally on guinea-pigs and was found to supress homologous cutaneous anaphylaxis which is mediated by IgE antibodies [19]. This study suggests that peppermint is significant to prevent inflammation.

In-vivo studies of Kamei *et al*., (2000); Inoue *et al*., (2001), they had examined on rat having nasal allergies by administering the ethanol – peppermint (*M. piperita*) extract at a particular nasal dosage of 300 mg and 1000mg respectively and had shown to beneficially reduce the snezeeing [20, 21]. Further Inoue *et al*., (2002) had examined with the flavonoids mainly luteolin7-O-rutinoside of peppermint (*M. piperita*), was found the inhibitory effect of this to antigen-mediated nasal allergies [22].

2.1.4 Anti-fungal activity

Pattnaik *et al*. (1996**)** found almost 11 to 12 types of fungus (including *Candida albicans, Trichophyton mentagrophytes, Aspergillus fumigatus* etc**.)** against which peppermint oil has shown significant inhibitory activity [23] According to Nilo *et al*. (2017) the extract of peppermint leaves has fungicidal effect against the aggrandizement of some fungus including *Fusarium moniliforme, Aspergillus niger* and *Aspergillus fumigatus* [24].

According to Hussain *et al*. (2010), peppermint oil was found to show an inhibitory effect on *Aspergillus niger, Aspergillus flavus, Rhizopus solani and Fusarium solani* [25]. Sandasi *et al*. (2011) suggested that the peppermint oil was found to inhibit the growth of *Candida albicans* and *Candida albicans* [26].

There are many relevant significant literature about peppermint and it's fungicidal effect against different types of fungus and these have proved mechanism of action. Peppermint has been suggested for a number of antifungal treatments in human beings [27, 28, 29].

2.1.5 Anti-hepatotoxicity effects

Most of the chemical reactions take place in liver for that many toxic substances [carbon tetrachloride (CCl4),uric acid, creatinine], oxygen radicals etc. are produced, which are responsible for liver damage; additionally some viruses, medicines etc can also be significant causes for liver damage or hepatotoxicity.

A study of Khalil *et al*., (2015) had examined, *in-vivo*, on rat model with orally peppermint oil dose of 0.5 ml/kg and demonstrated that peppermint leaves are effective to give protection against some toxic chemicals , produced in liver including carbon tetrachloride (CCl_4). It was believed that CCl_4 could promote hepatotoxicity by decreasing the level of alanine transferase, aspartate aminotransferase, alkaline phosphatase (ALP), urea, Uric acid, creatinine, bilirubin and some peroxidases like glutathione peroxidase (GPX) , these induce hepatotoxicity [30].

Maliakal and Wanwimolruk (2001) suggested that aqueous peppermint extract can act as a modulator of drug-metabolism enzymes at a different phase. As it contain phenolic compounds and carotenoids, these are able to absorb free radicals.[31] Other studies have figured out that the anthocyanin of herbs extract can able to protect the liver against carbon tetrachloride-induced lipoperoxidation [32].

Another study of Ogaly, *et al*. (2018) confirmed by their in-vivo model experiment that peppermint leaves have significant anti-hepatotoxicity effect by improving lipid peroxidation, transforming growth factor -β1 (TGF-β1) and was found to suppress desmin [33].

2.1.6 Anti-oxidant activity

Mekinic *et al*. (2014) examined with ethanol/water extract in a particular ratio of 80:20 of peppermint leaves and

demonstrated that peppermint extract has the highest ability to prevent the unwanted bleaching of β-carotene [34]. Li *et al*. (2017) claimed by their experiment that ethanol extract of peppermint has significantly shown the inhibitory effect on DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical [35]. Another study of Farnad *et al*. (2014) confirmed with their test and demonstrated that ethanol extract of peppermint leaves (*M.piperita*) inhibited radicals scavenging activities of DPPH (2,2-diphenyl-1-picrylhydrazyl) and nitric oxide [36] . Mallick *et al*. (2016) investigated in-vitro antioxidant activity of menthol of peppermint extract and was found significant scavenging activity on DPPH radicals [37]. In a study of Mimica-Dukic *et al*. (2003) it was shown that peppermint(*M.piperita*) has the highest capability to inhibit DPPH ((2,2-diphenyl-1-picrylhydrazyl) radical by reducing the generation of the OH radical [38] .

Gurdip *et al*., (1998) claimed peppermint oil has shown the greater antioxidant effect on peroxidation of sunflower oil than butylated hydroxytoluene (BHT) [39].

2.1.7 Anti-viral activity

According to Herrmann and Kucera (1967), the aqueous extract of peppermint leaves has significant efficacy to inhibit different types of virus including *'Influenza A'*, *'Herpes simplex virus* (*HSV*)' and '*Vaccinia virus'* and many more, which are present mainly in egg and the system of cell-culture [40]. The aqueous extract of peppermint (*M. piperita*) was found to have potential efficacy of anti-human immunodeficiency virus-1 (anti-HIV)-1 [41].

Similarly Minami *et al*. (2003) claimed by their experiment that peppermint oil (1%) has significant effect against HSV-1 infected cells, which inhibit HSV to replicate further [42]. Another study Yucharoen *et al*. (2012) demonstrated that peppermint extract (containing mainly dichloromethane and methanol) has great inhibitory effect against the HSV-1 as well as also against HSV-2[43]. Another study of Nolkemper *et al*. (2006) also claimed that peppermint has shown highest (85%) protective effect against both HSV-1 and HSV-2 [44].

2.1.8 Anti-radiation activity

The peppermint (*M. piperita*) extract was found to show a prophylactic effect against radiological-chromosomal damages [45]. Samarth *et al*. (2001) examined *in vivo* experiment on mice in which mice were orally administered aqueous extract of peppermint doses of 1 g/kg body weight and were found to increase spleen colonies, leukocyte count, haemoglobin level, erythrocytes count. [46] In an another study of Samarth *et al*., (2004) reported by their *in vivo* experiment on mice that the anti-radiation properties of the essential oil derived from peppermint has induced the alternation in haematological alternation in blood and had observed that only 17% mice, those which were treated with peppermint oil (menthol oil), died succumbed to radiation damage in the test group whereas 100% was the mortality rate in control group due to the radiological effects [47]. In addition, Samarth & Samarth, (2009) tested on mice with oral doses of *M. piperita* leaf extract for 30 days and found significant reduction in lipid peroxidation [48] .

2.1.9 Anti-nociceptive effect

The anti-nociceptive effect of peppermint was found, actually it significantly lowers writhing by about 38 –44% as compared to control group. This was observed with an oral administration of peppermint oil at a doses of 200 or 400 mg/kg daily [49].

2.2. Medicinal effects

2.2.1. Peppermint in diabetes

Hemalakshmi *et al*. (2012) described diabetes as a disorder of metabolism, in which serum glucose level is high due to either lack of the glucose-anabolic enzyme, namely insulin or inactivation of insulin which this further manifests to different abnormalities in lipid, protein and carbohydrate metabolism, resulting in imbalance of homeostasis and leads to a rise in various physiological problems [50].

Figueroa-Pérez *et al*., (2018) examined, *in-vivo*, that with oral administration of 2 mM infusion extract of peppermint - salicylic acid on diabetic rats for 4 weeks there was a decrease in the blood and urine glucose level as well as the albumin, urea and uric acid levels in urine [51]. According to Barbalho *et al*. (2011), the extract of peppermint leaves has significant effect on the reduction of blood glucose level and simultaneously increase insulin level in blood, in this study orally administered at a dose of 0.29 g/kg (100 g/L) to non-diabetogenic and glucosamine-nitrosourea compound (streptozotocin)-injected diabetogenic rats [52]. Though the exact mechanism of exactly how peppermint reduced blood glucose level was not understood in its entirety.

But in addition Badal *et al*. (2011) had confirmed by their experiment on fructose-fed male Sprague dawley rats at a dosage of 100 and 250 mg/kg per day of peppermint oil, that peppermint has the ability to reduce serum glucose levels, along with triglyceride, very low density lipoprotein(VLDL), low density lipoprotein (LDL) and cholesterol levels in blood [53].

2.2.2 Neuro-psychiatric effects of peppermint

According to some scientists, peppermint is famously known as one of the central nervous system stimulants. They performed some researches on the benefits of fragrances on cognitive performance, perceived stressful physical work, and pain responses were conducted, depending on possible changes of brain's activity [54].

2.2.3 Cardiovascular properties of peppermint

It generally has a vasodilating property in some animals and thus is related to lowering of blood pressure, especially systolic and reduction in heart rate as well. Reduced arterial smooth muscle tonicity may also be a possible cause of these cardiovascular effects of peppermint oil [55].

2.2.4 Fever reducing activities of peppermint

Some indirect effects of peppermint, especially when used in tea as a herbal nfusion, includes healing of fever fever. This may be due to the presence of menthol which has a cooling effect on the body naturally. The excess fluids also undergo detoxification so body can exclude the reasons of cough, cold, flu and fever. Simultaneously the menthol works internally to decreasing fever. Additionally, Menthol is a natural muscle soother and can thus reduce the aches and pains that are associated with high temperature [56].

2.2.5 Nausea preventing activities of peppermint

The anti-spasmodic properties of peppermint tea treat nausea and prevent puking. The aroma of peppermint can increase feelings of nausea while organic compounds in the mint help to relax stomach muscles which contract and lead to retching. It is equally helpful to cure motion sickness or sea sickness if it is drunk before boarding a flight, boat or while onboard a ship [30].

2.3. Covid-19 and peppermint: Essential Oils of peppermint contain several bioactive compounds like menthone and menthanol , which are able to inhibit the replication of some viruses even including covid-19 virus and help to improve consumer's respiratory system by dialating the bronchioles and as well as help in the lysis of mucus [57]. Various mechanisms were found by which phytochemicals of peppermint (*Mentha piperita* L.) inhibit infectious ability of viruses like SARS CoV . Some of these mechanisms included piercing of the viral membrane, direct inhibitory effect on virus, preventing the replication and inactivating the various enzymes of the virus [58, 69]. Mainly by forming the complex of 'S1(region of the spike protein of covid-19 virus)– ACE2 receptor(of host body)' infections are spread out thoughout the host body, a silico study of Kulkarni *et al*. (2020) was found that phytochemicals of essential oils of various medicinal herbs including 'pulegeone', 'menthone' of peppermint inhibit the action ability of the spike protein of covid virus by inactivating the receptor binding region (S-1) of spike protein, in which the ACE-2 – receptor of the host body usually binds. Thus peppermint prevents the interaction of covid-19 virus with host body [60]. Covid-19 virus infections has high impact on respiratory organs , researchers have found that menthol of peppermint is highly potent to prevent chronic obstructive pulmonary disease (COPD) by forming 'Cold-Menthol-Receptor-complexes,'[61]. As well as vapour of peppermint , hot peppermint tea and other peppermint-containing products give relief from various nasal problems as described earlier. In fact peppermint is effective in post-covid condition as well, as has been shown in some research studies as well. It improves taste perception, which is a major complication during this viral attack, since peppermint has the property of acting as a taste improver [62].

3. Toxicology

Though peppermint consumption is safe but there are many studies which have confirmed by their *in vivo* as well as *in vitro* experiments that peppermint consumption is safe .

Small amounts of acute toxicological effects were found if doses are exceeded compared to normal consumption limits. But no death reports were found due to peppermint chronic toxicity. A study of Spindler & Madsen, 1992 investigated in ethanol-peppermint- aqueous- extract -fed mice at the dosage of 3,700 and 4,800 mg/kg body weight has given similar results but there was not found any mortality report due to its toxicological effects [63]. Another study of Thorup *et al*.,1983 had examined for 90 days on four groups of rat at a dose but no encephalopathy symptoms , biochemical , cellular changes were found except only histopathological changes were observed. Some of these are cyst-like spaces which could spread throughout the white matter of the cerebellum and hyaline droplets scattered in the proximal convoluted tubules of the kidney were also observed [64]. As peppermint contain 'pulegeone' – a carcinogenic substance, which, if exceeds more than 1%, may prove to be harmful. Skin rashes, irritation, allergic reaction may result sometimes due to the excess intake of peppermint as a result of the presence of 'menthol'. Heart burn may be reported also due to the excess intake of peppermint tea [65]. Although some data is available but chronic toxicity reports of peppermint were not found significantly and thus the toxic effects of peppermint intake is not of prime concern.

4. Conclusion and future perspectives

In this paper detailed findings of the effects of peppermint have been presented. Peppermint is effective against different types of non-communicable diseases like nausea, diabetes, fever, etc. as well as pharmacological effects like anti-inflammatory, anti-allergenic, anti-oxidants, fungicidal, anti-viral, anti-radiation and anti-toxic effects. In some cases it has shown anti-nocidetive effects also and even possesses anti-pesticide effects.

There are several studies in which the bioactive compounds of peppermint have been described in details but much more work is needed to identify clearly the exact components and their roles as agents of prophylaxis and treatment. Nevertheless it can be concluded without any doubt that peppermint, in its numerous combinations with tea, oils etc can not only act as a potent healer but is most definitely a natural gift for mankind.

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