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THE ROLE OF PEPPERMINT AND ITS ESSENTIAL OIL ON THE HUMAN IMMUNE SYSTEM ENHANCEMENT AND PREVENTING COVID-19 VIRUS

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ABSTRACT

Considering the spread of the COVID-19 virus in most countries of the world, it is necessary to pay attention to good and healthy food that enhance the defenses of the immune system in general against this virus. Maintaining the health of the immune system is the key to reduce the infection; in order to support and strengthen the immune system, the body is required nutrients that are rich in medical compounds, vitamins and nutrients that help the body to confront the emerging corona virus, COVID-19 Such as medicinal and aromatic plants that specialized in this aspect, which can be used fresh or dried herb or a capsule of volatile oils and has many medicinal uses, Peppermint is one of the plants that is characterized by rich composition of medicinal compounds, which is an effective treatment for many diseases as well as being a preventive factor for many of them, especially respiratory diseases.

Therefore, we will discuss in detail about the most important medical benefits of *Mentha piperita* and the influential role in strengthening the human immune system and preventing respiratory viruses, especially COVID-19.

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دور النعناع الفلفلي وزيته الطيار في تعزيز الجهاز المناعي للإنسان والوقاية من فايروس

COVID-19

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الخلاصة

في ظل تفاصي انتشار فايروس COVID-19 في معظم دول العالم وجب الاهتمام بالغذاء الجيد والصحي الذي يساعد على تعزيز دفاعات الجهاز المناعي بشكل عام حتى يتمكن من مقاومة هذا الفيروس، وان الحفاظ على صحة الجهاز المناعي يعتبر المفتاح

الأساسي لتقليل الإصابة بهذا الفايروس، ومن أجل دعم وقوية الجهاز المناعي فإن الجسم يحتاج مواد غذائية تتميز بgunها بالمركبات الطبية والفيتامينات والعناصر التي تساعد الجسم على مواجهة فيروس كورونا المستجد COVID-19. مثل النباتات الطبية والمعطرية المتخصصة في هذا الجانب، والتي يمكن ان تستخدم بشكل طازج أو مجفف أو بشكل كبسولات من الزبوت الطيارة والتي لها العديد من الاستخدامات الطبية، يعد النعناع الفلفلي من النباتات التي تتميز بتركيبتها الغنية بالمركبات الطبية والتي تعد علاجاً فعالاً للعديد من الامراض فضلاً عن كونها عالماً وقائياً للعديد منها لاسيما امراض الجهاز التنفس لذا سنتعرف بشكل مفصل عن أهم الفوائد الطبية للنعناع الفلفلي ودوره المؤثر في تقوية الجهاز المناعي للإنسان والوقاية من فايروسيات الجهاز التنفسي خصوصاً COVID-19.

كلمات مفتاحية: فيروس كورونا، زيت عطري، نزلة برد، نباتات طبية، النعناع الفلفلي.

INTRODUCTION

1.1 What is the immune system?

The immune system is specialized in defending the body against intrusive agents, or invaders, therefore, we must identify the factors that belongs to the body (internal) and what does not belong to the body (external). If the immune system did not recognize whether the problem is internal or external, it may attack the body's own tissues, causing an autoimmune disorder. Disorders of the immune system occur when the body generates an immune response against itself (the immune system attacks the body's own tissues), or because the body may not be able to generate an appropriate immune response against invading microorganisms (immunodeficiency), or the body may generate an excessive immune response to harmless strange antigens and damage the normal body tissues (Horváth and Kamilla, 2015; Kim et al, 2021).

1.2 Peppermint (*Mentha piperita*. L)

A perennial herbaceous plant that belongs to the Lamiaceae family, the stem is erect, with a red-violet color. The leaves are simple, opposite, oval, consisted with glands that filled with an aromatic oil with a distinctive aroma. The leaves can be used after drying or by using their volatile oils. Peppermint is a hybrid between *M. spicata* and *M. aquatica* (Hakim, 1992; Mckay and Blumberg, 2006; Mieso and Abdela, 2020)

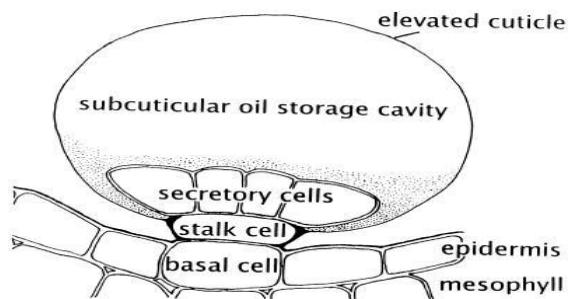
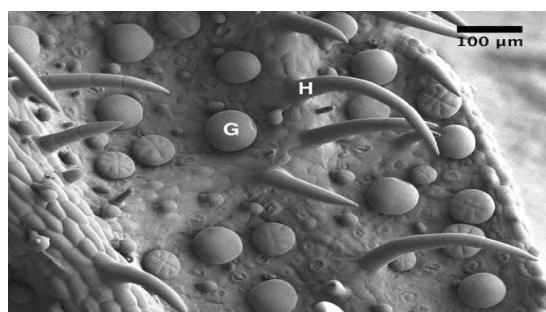
It is cultivated in different regions of the world and has many species (Table 1). The mint and its volatile oil have been widely used in Iraq and it is considered as one of the most important natural herbs that are very useful for treating many diseases, health and aesthetic problems because it contains many pharmaceutically active substances isolated from its leaves such as Isomenthone, Carvone, Pulegone, 1,8-cineole, Piperitenone oxide, 1,8-cineole, limonene, Terpenen, Menthol, Phelleudrene, Pinene and p-cymene (Abo-Elgawad and Elsayed, 1995; Al-Bayati, 2009).

Table (1): Some species of mint (Ahmad et al, 2020).

	Species	Binomial name
1.	Peppermint	(<i>Mentha piperita</i> L.)
2.	Spearmint	(<i>Mentha spicata</i> L.)
3.	Japanese mint	(<i>Mentha arvensis</i> L.)
4.	Pennyroyal	<i>Mentha pulegium</i>
5.	Longifolia	<i>Mentha longifolia</i>
6.	Wild mint	<i>Mentha arvensis</i>
7.	Water mint	<i>Mentha aquatic</i>

2. Essential and peppermint oils

Oils are lipophilic substances, a mixture of volatile components and chemical compounds that are produced from secretory ducts, cavities or specialized glandular hairs found in the leaves called glandular trichomes responsible for the production and storage of essential oils (figure 1). The spread of oil glands on the leaf is irregular and their number varies according to the leaves age, and the older it is, the less its content of menthol and isomers. Studies on mint leaves indicated that lasted 33 hours, between Turner et al (2000) the secretory activity required to fill the glands with essential oil takes 30-20 hours. These oils are concentrated in order to make 15 ml of peppermint oil it takes 450 g of fresh mint leaves (Turner et al, 2000; Glenn et al, 2002; Rigoberto et al, 2008).



The figure (1) show the oil glands in leaf surface (Oz et al, 2017)

3. The chemical components

The oil extracted from the peppermint plant *Mentha piperita* contains many active compounds, the most important of which are Menthol 35-45%, Menthone 20-15%, Menthyl acetate 5-3%, Neomenthol 3.5-2.5%, Pulegone, and iso-menthone 3-2%, menthofurane 7- 2%, limonene, Alpha - beta Pinene, Rosmaric acid, and flavonoids (glycosides, apigenine, diosmetin). Monoterpene are the main components in the volatile oil of all species of peppermint (PDR for herbal medicines, 1998; Schmidt et al, 2009; Moghtader et al, 2013).

The nutritional value of the mint plant is represented by the minerals content such as Fe, Cu, Mg, Na, K and vitamins such as A and C (Nair, 2001; Keifer et al, 2007). Table 2 reveals the oil chemical components of two types of Spearmint (*Mentha spicata* L.) and *Mentha piperita* L.

Table (2) Result of MS essential oil analysis by gas chromatography-mass spectrometry (Motamed and Naghibi, 2010; Shahbazi, 2015).

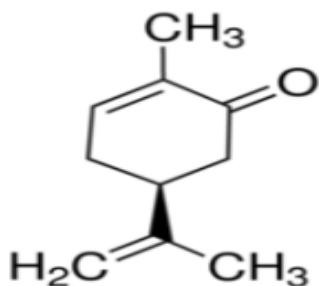
Spearmint (<i>Mentha spicata</i> L)		<i>Mentha piperita</i> L.	
Compound	Percentage (%)	Compound	Percentage (%)
β - myrcene	0.25	α-Pinene	0.65
Limonene	11.50	Sabinene	2.23
Γ-terpinene	0.16	β-Pinene	1.22
Menthone	1.01	Myrcene	0.76
Menthol	1.00	3-Octanol	0.12
Terpinen-4-ol	0.99	α-Terpinene	0.54
Cl-terpinol	0.31	P-Cymene	0.17
Dihydrocarveol	0.22	Limonene	5.33
Cis-dihydrocarveol	1.43	1,8-Cineole	3.27
Dihydrocarvone	0.43	(E)-β-Ocimene	0.59
Trans-carveol	0.30	γ-Terpinene	0.45
Carvone	78.76	Terpinolene	0.21
Dihydrocarvyl Acetate	0.57	Iso-menthone	2.87

L-carveol	0.32	Linalool	0.36
β – bourbonene	1.23	Menthone	21.45
Trans-caryophyllene	1.04	Menthyl acetate	12.49
γ – amorphene	0.21	Menthol	38.33
α -amorphene	0.16	α -Terpineol	0.57
Other compounds	0.11	Pulegone	1.34
Total	100.00	Piperitone	0.68
		β -Caryophyllene	1.23
		Germacrene D	0.58
		γ -Cadinene	0.81
		Total	96.25

4. The most important chemical compounds found in peppermint are:

4.1 Carvone

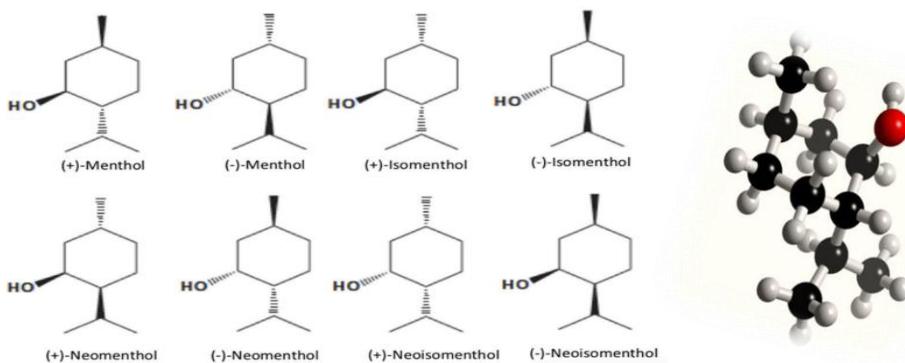
Carvone is considered as one of the natural compounds consisted of one ring, (molecular formula: $C_{10}H_{14}O$) (figure 2), it belongs to the ketones group, that is naturally present in many essential oils, but it is found in abundance in mint and caraway. There are two analogues of this compound (positive and negative): R(-)-carvone is extracted from peppermint oil and has anti-inflammatory and antibacterial properties and high antioxidant activity (De Carvalho and Da Fonseca, 2007; Elmastaş et al, 2006; Kee et al, 2017).



The figure (2) show the chemical structure of carvone (Bouyahya et al, 2021)

4.2 Menthol

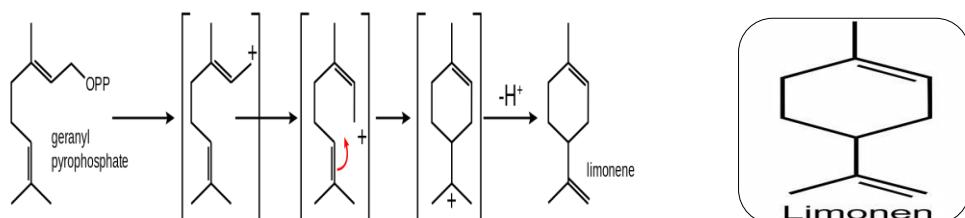
Menthol is one of the natural compounds found in mint leaves and oil (molecular formula: $C_{10}H_{20}O$) (figure 3), It is characterized by its antioxidant characteristics and viral infections; it can also be used to treat a variety of respiratory diseases. Clinical trials have revealed that the use of menthol in low concentrations significantly reduces shortness of breath, antitussive and bronchodilator, and improves lung function (Mimica-Dukic et al, 2003; Motamed and Naghibi, 2010; Can Baser and Buchbauer, 2010).



The figure (3) show the chemical structure of menthol (Oz et al, 2017)

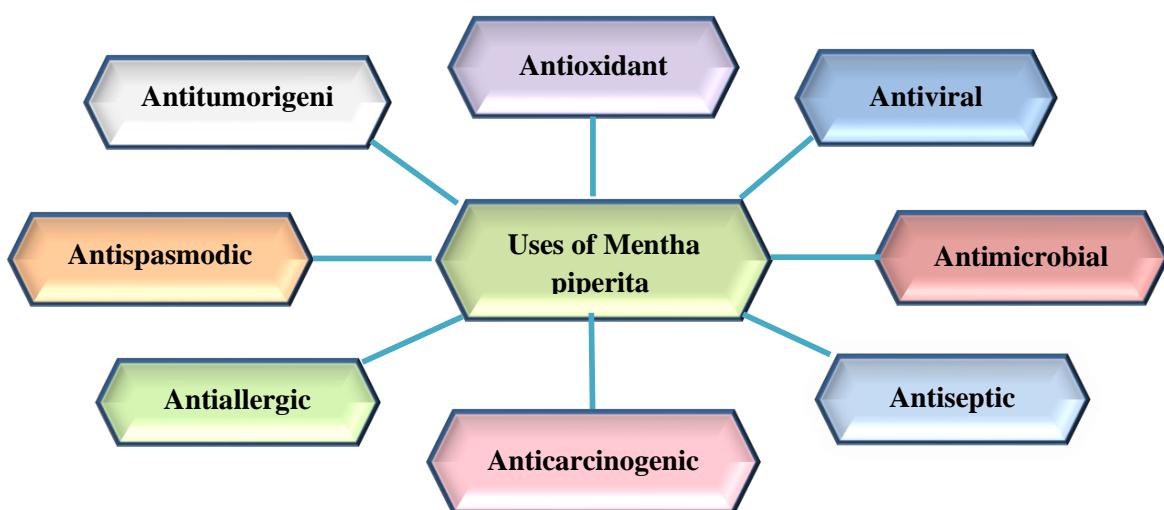
4.3 Limonene

Limonene is a pure transparent hydrocarbon liquid classified as a monocyclic terpene (molecular formula: $C_{10}H_{16}$) (figure 4) It is considered as a relatively stable terpene and can be distilled without disintegration; it also may break down at high temperatures to convert to isopropene. Limonene is easily oxidized in moist air, producing carvion, carvone and limonene oxide. Limonene exists in three forms, d-limonene, the most common of which is found in the peel of oranges, lemons, and crepes, and l-limonene and dl-limonene, the latter found in peppermint oil, have the same physical characteristics as the previous two compounds (Pakdel et al, 2001).



5. Peppermint Benefits

The mint plant has many medicinal and therapeutic benefits shown in the following figure (5).



6. The Medical Benefits of Mint And Its Oil and Their Role in Treating Cold Flu

Mint has been used since antiquity in the treatment of many diseases, it was known as the water nymph in the myths of Greece for its many benefits, while it is called the magical plant in Germany. It is still used so far, especially to treat coughs and respiratory problems, the most important of which is infection with the cold flu, which attacks the body due to the weakness of its immune system. Mint treats colds, persistent sneezing, runny nose, and cleans the nose, throat, and lungs from congestion. It also expands the bronchus and relieves their irritation, thus relieves coughing, which contributes to the natural breathing. Therefore, most cough medicines contain mint (Wang and Weller, 2006; Gulluce et al, 2007; Khalil et al, 2015).

The volatile oil is also characterized by many medicinal benefits because it has biological activity against many viruses, fungi and bacteria, especially antibiotic resistance, which is why it's considered as a natural antidote for the treatment of congestion and infections of the mucous membranes in the mouth, pharynx, bronchitis, and respiratory tract. As well as the mouthwash use of the extracts (Al-Bayati, 2009) due to its richness in the compound Carvone, which is characterized by the antibacterial and antiviral properties, which helps in the prevention the corona virus. It also contains the phenolic acids, flavonoids, and ascorbic acid in the leaves (Dorman et al, 2003; Scherer et al,2013).

The respiratory system in humans is divided into two parts: the upper respiratory system (UR) and the lower respiratory system (LR), and according to data from the World Health Organization (WHO), lower respiratory tract infections (LRTI) are responsible for 5% of deaths worldwide. The infection of the respiratory system with viruses is usually associated with cold flu which results in throat inflammation, bronchitis or bronchitis, fever, and suffocation, which may pose a great danger to human life (Horváth and Kamilla, 2015; Forbes et al, 2007). Studies of the German Committee (E monographs) showed that peppermint oil and leaves can be used as a treatment for respiratory infections and the oral mucous membranes infections. The experiment conducted by Kim et al (2021) that lasted for 24 days on a group of 5-week-old mice suffering from asthma, the mice were placed in special rooms containing nebulizers to inject the experimental parameters, 0.1 v/v% of peppermint oil was infused for 5 minutes During the day; the results showed that inhaling peppermint oil can significantly suppress inflammation by reducing the levels of IL-6 (a type of cytokine whose increase is harmful to the immune system) and controlling its synthesis and secretion with a decrease in inflammatory cytokines (their increase causes an immune storm); the study also showed that inhalation of peppermint oil is effective in regulating the air canals through its inhibitory activity to produce pro-inflammatory cytokines mediated by JAK2/STAT3 in response to increased IL-6, which contributes to reduce asthma in treated mice and improve overall lung function.

Grupp et al (2013) and Vatansever and Becer (2020) confirmed that there is a huge relationship between infection with COVID-19 virus and IL-6 (Interleukin 6). When a viral infection occurs, viruses enhance and stimulate IL-6 transcription from the cells, causing a fatal immune response to overactive cells. therefore, controlling IL-6 synthesis and secretion is important as a therapeutic target for inhibiting cytokine storm and organ damage associated with cytokine storm.

Lu et al (2020) found that people infected with SARS-CoV-2 had high levels of IL-6, which was associated with patient symptoms including pneumonia and systemic lung damage. Another study reported that IL-6 levels were higher in severe COVID-19 patients, and this can be used as one of the bases for predicting the transition from mild to severe infection (Wan et al, 2020). Therefore, these studies confirm the role of peppermint and its oil in controlling IL-6 levels in the body and preventing its harmful effect.

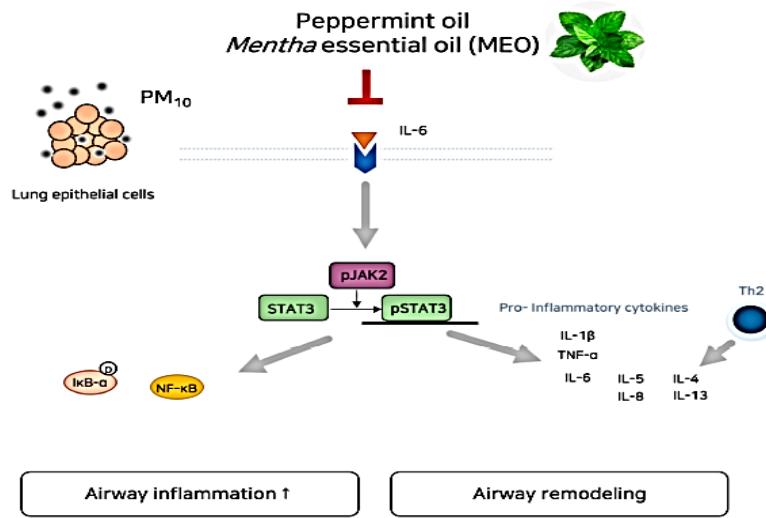


Figure (6): the work mechanism of peppermint oil by inhibiting the IL-6 pathway (Kim et al, 2021)

7. Peppermint Role in the Immune System

Mint is of great importance in strengthening the human immune as it consisted of effective compounds and vitamins which is important antioxidant. Rad et al (2011) indicated that the application of peppermint oil to the broilers provender has strengthen the immune system by the effect of flavonoids and chemical compounds in mint that have important biological roles that contribute to enhance the immunity by increasing lymphocytes, which reduce the risk of diseases; also, its content of Menthone and limonene has supported the bird's immune system. Lavina et al (2009) confirmed the positive role of mint when mixed with the provender in raising the efficiency of the bird's immune system as an antioxidant, which leads to the reduction of free radicals and the good content of volatile oils, flavonoids, carotenoids, and vitamin C.

8. The Mechanism of Antioxidants in the Body Protection

The exposure on body cells to oxidation by means of unstable and destructive oxygen-based molecules (free radicals), which divide and destroy cell molecules and the fatty acids present in the cell, which makes the body vulnerable to many infections and viruses. Therefore, antioxidants act as the basic lines of defense for the cell, as they help the cell membrane to maintain the protein, and through these antioxidants, food is allowed to enter the cell and send waste abroad and prevent the entry of toxins and viruses through, including COVID 19, as the mint is characterized by its antioxidant properties, Mairapetyan et al (2016) and Mallick et al (2016). Scherer et al (2013) indicated that mint can become an alternative to industrial antioxidants, which has an important role in reducing infections, including respiratory infections, and strengthening the immune system. Studies revealed that peppermint oil has a strong effect in reducing muscle pain, swelling, and contributes to accelerate the healing process of broken bones by improving blood circulation, the tissues damage repair of damaged, reducing swelling, inflammation, and pain; also, it is considered an antispasmodic, (Bove, 1996; Blumenthal, 1998). It also has an effective role in calming the muscles of the digestive system by reducing the flow of calcium ions into the jejunum and large intestine, as it increases the secretion and activity of salivary glands and digestive enzymes, which helps the digestive system in the process of digestion and treats the indigestion cases; also, it also can be used as a treatment for Irritable Bowel Syndrome (IBS), and carminative (Nissen, 2016; Sadraei et al, 2016; Shabbir et al, 2020). also the peppermint relieves headaches, nerve pain, arthritis, and

general body aches. In a study he conducted by Mimica-Dukic et al (2003) to find out the effectantimicrobial activity of three type of essential oil is *Mentha aquatica* L., *Mentha longifolia* L., and *Mentha piperita* L for free radical scavenging capacity (RSC) of essential oils from, the result show All essential oils have exhibited very strong antibacterial activity, in particular against *Escherichia coli* strains but The most powerful was *M. piperita* essential oil, especially towards multiresistant strain of *Shigella sonei* and *Micrococcus flavus* ATTC 10,240, also all examined essential oils (*Mentha aquatica* L., *Mentha longifolia* L., and *Mentha piperita* L) were able to reduce DPPH radicals into the neutral DPPH-H form, and this activity was dose-dependent. However, only the *M. piperita* oil reduced DPPH to 50 % (IC50 = 2.53 microg/mL).

The menthol in mint creates a cooling sensation while applied to the skin, which may relieve pain and itching. Additionally, it promotes oral health, freshens the breath, and fights the bacteria responsible for tooth decay, it also has an important role in reducing toothache, which is why it is used in toothpastes and mouthwashes (Nam et al, 2018).

9. How to Use

Mint has a various application in cooking, as it used as a flavor, with lemon juice, fresh or dried mint can be used in tea bags, or mint extract or its volatile oil etc. Mint can also be taken in capsule form; for the highest benefits, it is recommended to consume it in the medicinal forms. Peppermint oil is generally considered safe, unless it taken in very large doses; accordingly, the FDA recommends the use of peppermint essential oils, considering that these oils are diluted properly before use.

10. Dosage

The therapeutic dose for adults is 0.4-0.2 ml per day of peppermint oil, which is equivalent to 8-4 drops, for children over the age of 8 years, the dose ranges between 0.2 - 0.1 ml, while children whose weight is less than 45 kg, it is more appropriate to give them a dose not exceeding 0.1 ml. also, 4-3 drops of peppermint oil can be placed in hot water and inhaled. In order to prepare a cup of peppermint tea, it takes 150 ml of hot water with 1 tbsp of mint and leave it for 10 minutes (Malekmohammad et al, 2019; Ahmad et al, 2020; Shabbir et al, 2020).

11. Precautions of Use

1. The essential oil of peppermint may combine with an analogue of the cytochrome P450 enzyme in the human liver microsome, causing a real damage.
2. Peppermint oil is not recommended in cases of gallstones, kidney stones and bile duct obstruction.
3. volatile oil is not recommended for the faces of infants, and children, especially near the nose and mouth.
4. Applying concentrated peppermint oil to the skin may cause irritation or rashes.
5. Avoid using peppermint extract or oil with people who suffer from G6PD enzyme deficiency.
6. Inhalation of pure Menthol can cause apnea and laryngeal stenosis for the susceptible people.
7. Not recommended even in the authorized doses the pregnant ladies .

(Turner et al, 1999; Kligler and Chaudhary, 2007; Ahmad et al, 2020).

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