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Mentha spicata L. essential oil, phytochemistry and its effectiveness in flatulence

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ABSTRACT

Flatulence as the continuous feeling of abdominal distension is equal to "Nafkh" in Iranian Traditional Medicine. Nafkh is believed to derive from the amount of stomach temperature, humidity of food or abnormal humidity in digestive tract and their interactions. *Mentha spicata* as cool and spicy plant with astringent and digestive property is recommended for treatment of flatulence. The information was extracted from accessible international databases, traditional books, electronic resources, and unpublished data. *M. spicata* essential oil with main component of carvone has potency for treatment of flatulence related to indigestion, cesarean section and dysmenorrhea. Also, it can reduce the pain severity during the colonoscopy or dysmenorrheal conditions. No hazardous effects were reported for *M. spicata* essential oil, if it is used in proper dosages. *M. spicata* essential oil can be applied for other intestinal complaints with pain and flatulence such as Irritable Bowel Syndrome (IBS) that needs more deep clinical trials for demonstrating its potential.

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1. Introduction

Flatulence is a prevalent problem of human's intestinal systems. No identified organic reason has been known for flatulence, thus, it is introduced as functional ones. There was an incorrect view about functional flatulence and it was believed that the origin of functional flatulence was psychological diseases or inorganic origin, while, functional flatulence is a combination of social psychological, physiological (intestinal movement, changing the bacterial flora), genetic agents and environmental conditions.[1] The impact on quality of life and imposing high costs on community are the consequences of flatulence.

Flatulence is the continuous feeling of abdominal distension and can be associated with many ailments such as irritable bowel syndrome (IBS), functional constipation and so on. Flatulence is the second most common symptom in IBS patients and is associated with abdominal pain in IBS patients.[2] Some researchers know flatulence as the subgroup of IBS, but others know it as independent disease and divide it to some groups with considerable pain or less pain. Regardless of disease type, the most important point is high prevalence of flatulence among 30% of population.[3] Regard to the prevalence of flatulence in the society, and tendency to use the natural treatments, in this review, we considered the definition of flatulence from the Iranian traditional aspect and then introduced *Mentha spicata* essential oil as the best known anti-flatulence in the traditional and novel medicines.

2. Definition of flatulence in Iranian Traditional Medicine

According to traditional believes, flatulence is as the result of indigestion in stomach. Gas production in the abdominal cavity derives from the amount of stomach temperature, humidity of food or abnormal humidity in digestive tract and the interaction of these elements together. Flatulence is equal to "Nafkh", "Nafkhah" or "Rih" in Iranian Traditional Medicine.[4] The symptoms are distention and feeling of heaviness in abdominal cavity. Ibn-Sina (Iranian Scientist) discussed in his book "The Canone of Medicine" about "Rih" or gas with cold, dense smoky smell that caused flatulence in the abdomen. Iranian Traditional Practitioners knew some psychological states for flatulence[5] and believed that flatulence may happen in different anatomic sites of the body, for instance in stomach, spleen, liver, intestine, bowel and they named as Nafkh-e-Mede, Nafkh-e-Tahali, Nafkhe-Kabedi, Nafkhe-e-Batn, qaraqer,

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josha and Bagh-baghe. Traditional practitioners believed that some diseases such as various headaches, stretching pain, trembling and pains in the back and joints are as the result of flatulence.[6–8] Ibn-Sina believed gas production occurred in the case of heat deficiency and was the result of nutritional factors, dietary habits, life style, gastric diseases, and other factors such as obesity, medications, liver diseases and etc.[4] In Iranian Traditional Medicine, Za'af-ol-Hazm (imperfect digestion), Su-Ol-Hazm (indigestion) are two main reason for producing the flatulence.[4] Accumulation of improper humors such as black bile or phlegm in digestive system can cause the flatulence.[4,9–11]

Ibn-Sina recommended many efficient medicinal plants for treatment of flatulence the plants such as Clover dodder (*Cuscuta epithymum* L), anise (*Pimpinella anisum* L.), Bishop's weed fruit (*Trachyspermum ammi* (L)), celery (*Apium graveolens* L), and spearmint (*M. spicata* L).[4] *M. spicata* is called "Na'Na Bostani" or "Na'Na Dashti" in Iranian traditional documents[12] and is a heat producing plant with astringent and digestive property.[4]

3. *M. spicata* L. in traditional medicines

Mentha (Labiatae family) with common name of mint or wild min has 6 perennial herbaceous plants in Iran.[13] *Mentha* sp. is used in folk medicine for treatment of bronchitis, nausea, flatulence, anorexia, liver complaints.[14] Among different species of *Mentha*, *M. spicata* was introduced before *Mentha piperita* and is the oldest ones of *Mentha* species. *M. spicata* (*Mentha viridis*) is known as spearmint or common mint in Iran.[13] *M. spicata* is used by humans from ancient times. *M. piperita* was introduced and hired by John Ray as anti-diarrheal agent in 1696 for the first time, while *M. spicata* and its variety *M. spicata* var. *longifolia* were used as appetizer and medicinal plants in Greco-Roman civilizations. The yield of *M. spicata* essential oil is lower than *M. piperita*. Carvone is the main components of *M. spicata* and *Mentha longlifolia*, while carvone is not present in *Mentha aquatic*, *Mentha arvensis*, *M. piperita* and *Mentha pulegium*. *Mentha* sp. and specially *M. spicata* essential oil and leaves has been therapeutic applications and its general property is carminative, tonic, stomach tonic, anti-cough, anti-seizure, astringent, analgesic and sedative.

Hippocrates and Dioscorides used *M. spicata* for treatment of different ailments in their documents and other scientists prescribed *M. spicata* for treatment of stomach diseases. *M. spicata* is believed to have carminative and analgesic effects. Roman soldiers distributed *M. spicata* throughout the Europe and gradually, *M. spicata* was cultivated in the church's ranches in ninths century. *M. spicata* is used for treatment of oral ulcers, rabies and reducing the pain of bee stings, in Median centuries. *M. spicata* was traditionally used for treatment of bloating, diarrhea, abdominal pain, indigestion, intestinal weakness, cold, sinusitis, and influenza, psychological problems in children, nose bleeding, headache and antidote.

The Iranian traditional practitioners believed that the temper of *M. spicata* is hot and dry, but its dryness is not high and a little humidity is present in it. The therapeutic property of *M. spicata* is higher than that of *Mentha puleguim*. The combination of *M. spicata* extract and honey is a cure for earache and putting the leaves on the tongue removed tongue coarsens. Chewing the *M. spicata* leaves reduced the toothache and drinking its extract stop bleeding, and is used to reduce the pain in chest. It is recommended to use for stomach weakness and neurological disorders.

In Iranian Traditional Medicine, there are three prescriptions for bloating, including: *M. spicata* decoctions, *M. spicata* tincture, *M. spicata* tablets that were used several times in a day.[15,16] Traditional practitioners recommended to insert *M. spicata* to the daily diets for preventing the flatulence. *M. spicata* is believed to clean improper humors from the stomach, strength the stomach, and also prevent the flatulence.[17] In one qualitative study on the medicinal plants that recommended for treatment of dyspepsia symptoms in Iranian Traditional medicines *M. spicata* leaf is one of the plant that is believed to strength the stomach and is effective in dyspepsia symptoms such as appetite, bloating, belching, digestion, nausea.[18]

M. spicata leaves, flowers and stems are currently used as flavor for beverages, food preparations, confectionery and chewing gum. *M. spicata* flowers are used to flavor sauces, ice cream, salads, soups, fruit drinks, desserts, dressings and vegetable dish or as garnish. PDR recommended the use of *M. spicata* leaves as carminative for digestive disorders and as a remedy for flatulence.[19]

In traditional Chinese medicine, *Mentha* sp. is believed to have pungent, spicy and cool properties. It is used to expel wind, heat, clear the head and eyes, clear up rashes, and remove liver qi stagnation.

In Ayurvedic medicine, *Mentha* sp. was used to help digestive conditions, skin problems, and headaches. The historical record shows that it was used extensively in ancient Greece. It was added to baths and used to treat sexually transmitted diseases, whiten teeth, and heal mouth sores.

For evaluating the efficacy of *M. spicata* essential oil in treatment of flatulence, we evaluate the chemical composition of its essential oil at first.

4. Chemical composition of *M. spicata* essential oil

Before evaluating the efficacy of *M. spicata* essential oil in treatment of flatulence, it is important to know about the chemical composition of *M. spicata* essential oil.

The chemical compositions of *M. spicata* essential oil have been the subject of many studies (Table 1). Although, there is mix-up information on chemical composition of *M. spicata* essential oil, many investigations confirmed carvone as its main component.

M. spicata leaves essential oils at full flowering stage from North-West Himalayan region of India was containing carvone (49.62–76.65%), limonene (9.57–22.3%), and 1,8-cineole (1.32–2.62%) as the main components.[20]

Carvone (0–60.07%), pulegone (0–53.95%), and 1,8-cineol (2.04–28.81%) were the main components of *M. spicata* essential oil from Brazil.[21]

Carvone (78.8%), limonene (11.5%), and β-bourbonene (11.2%) were the main components of *M. spicata* essential oil from Gilan-E-Gharb city, Kermanshah province, west of Iran.[22]

M. spicata essential oil from southeastern USA with hot humid condition was containing carvone (35–62%).[23]

Carvone (40.8%), limonene (20.8%), 1,8-cineole (17.0%), β-pinene (2.2%), *cis* dihydrocarvone (1.9%), and dihydrocarveol (1.7%) were reported as the main components of Tunisian *M. spicata* aerial parts essential oil.[24]

In addition to carvone chemotype for *M. spicata* essential oil, there is pulegone/piperitone rich chemotypes for *M. spicata* essential oil.[25]

The chemical composition of *M. spicata* affects from environmental condition and harvesting seasons.[25,26]

The effect of environmental condition on chemical composition of *M. spicata* essential oil was confirmed in a field experiments on pulegone-piperitone rich chemotypes of *M. spicata* accession from Turkey. The yields of *M. spicata* essential oil varied between 2.41-2.74% (w/w) with the main components of pulegone (26.7–29.6%), piperitone (22.2–28.2%), limonene (3.2–5.2%), α-phellandrene (1.3–2.6%), trans-caryophyllene (5.2–8.0%) and germacrene D (3.08–5.32%).[25]

Harvesting season has essential effects on chemical composition of *M. spicata* essential oil. The essential oil contents of *M. spicata* can

Table 1
The chemical composition of *M. spicata* essential oil.

Place	Organ, stage	yield	Main components	References
North-West Himalayan region of India	Leaves, full flowering stage	0.57 ± 0.02%	Carvone (49.62–76.65%) Limonene (9.57–22.3%) 1,8-cineole (1.32–2.62%)	20
Turkish accession	earliest stage flowering	2.41–2.74%	Pulegone (26.7–29.6%) piperitone (22.2–28.2%) Limonene (3.20–5.2%) α-phellandrene (1.3–2.6%) trans-caryophyllene (5.2–8.0%) germacrene D (3.1–5.3%)	25
Brazil	leaves	0.02–0.17%	Carvone (0–60.1%) pulegone (0–54.0%) 1,8-cineol (2.04–28.8%)	21
Gilane Gharb city, Kermanshah province, west of Iran	leaves	–	carvone (78.7%) limonene (11.5%) β-bourbonene (11.2%)	22
southeastern United States	leaves		carvone (35–62%)	23
Faisalabad, Pakistan	Leaves-summer	12.0 g kg^{-1}	Carvone (59.5%) limonene (10.4%) 1,8-cineol (6.4%) borneol (1.4%)	26
Faisalabad, Pakistan	Leaves-winter	9.5 g kg^{-1}	Carvone (63.24%) limonene (9.1%) borneol (5.9%) 1,8-cineol (3.5%) linalool (3.1)	26
Tunisia	aerial parts	1.1%	carvone (40.8%) limonene (20.8%) 1,8-cineole (17.0%)	24
India	fresh leaves	6.5 ml kg^{-1}	carvone (48.6%) cis-carveol (21.3%) limonene (11.3%)	49

affect from harvesting time and varied from 9.5 to 12.0 g kg^{-1} in the winter and summer harvesting time, respectively. Carvone (59.5%), limonene (10.4%), 1,8-cineol (6.4%), borneol (1.4%), and linalool (0.7%) were the main components of essential oil from summer harvesting, while the corresponding amounts were 63.2%, 9.1%, 3.5%, 3.1%, and 5.9% in winter harvesting, respectively.[26]

According to the PDR, the amount of essential oil from *M. spicata* is between 0.8-2.5% and essential oil content of dried *M. spicata* in summer season was higher than its fresh ones. Carvone (40–80%), limonene (5–15%) are the main components of *M. spicata* essential oil. Carvone is responsible for the smell of *M. spicata* essential oil.[19] The chemical structure of main components of *M. spicata* essential oil are represented in Fig. 1.

5. Efficacy of *M. spicata* essential oil in treatment of flatulence

The main claim about *M. spicata* essential oil is its anti-bloating (anti-flatulence) effects. The use of *M. spicata* essential oil for treatment of flatulence and intestinal complaints is the subject of many studies. In one clinical study, the efficacy of *M. piperita* essential oil soft capsule and *M. spicata* essential oil oral drop was evaluated on 79 patients with functional dyspepsia. The patients were administered three capsule a day of *M. piperita* essential oil soft capsule ($n = 43$) or 30 drops of *M. spicata* essential oil liquid for 5 days ($n = 36$). The symptoms such as acid regurgitation, stomach pain, heart burn, upper abdominal bloating, nausea, practitioner and patient global index were evaluated before and after treatments in two groups. The adverse effects of treatment, biochemical, and hematological profiles of patients were evaluated for assessing the safety of treatments. The results showed *M. spicata* essential oil soft capsule and *M. piperita* essential oil oral drop was effective in reducing the subjective symptoms of functional dysfunction. Significant improvement was observed in 61.9% and 51.04% of patients symptoms in *M. piperita* essential oil soft capsule and *M. spicata* essential oil oral drop, respectively ($p > 0.05$). Both *Mentha* essential oil relived the acid regurgitation and heart burn from the first day. *M. spicata* essential oil relieved the feeling of acidity higher than that of *M. piperita* essential oil. Significant improvement was observed in appetite, stomach pain, upper abdominal dull ache, intensity of pain, nausea, fullness of stomach, flatulence and upper abdominal bloating for both essential oils, but *M. spicata* essential oil reduced the vomiting higher than *M. piperita* essential oil. Global evaluation of therapeutic response was the same in two groups.[27] The treatments were reported safe, but the authors not reported any results related to adverse effects of treatment.

In this study did not mention to chemical composition of *M. spicata* or *M. piperita* essential oil compositions. Also, two different forms of product including soft-capsule and oral drop were compared to each other. It was more interesting, if the daily dose of main components of each essential oil were mentioned and the effects of treatments on biochemical, and hematological profiles of patients under study were reported quantitatively.

A single blind clinical trial study were conducted on the anti-flatulence effects of *M. spicata* essential oil oral drop 2% (Supermint oral drop, BarijEssence Pharmaceutical Company, Kashan, Iran) in comparison with dimethicone on 60 patients with irritable bowel syndrome. The patients were divided in two groups and they treated with 40 mg chewable tablet of dimethicone or 40 drops of *M. spicata* essential oil oral drop after each meal for three weeks. The severity of symptoms was determined three times (after admission, two weeks after starting the treatment and one week after finishing the treatment). A visual analog scale graph (green: no flatulence, blue: very low flatulence, purple: low flatulence, yellow: moderate flatulence, orange: almost severe flatulence and red: severe flatulence) were given to patients as the assessment tools. The adverse effects of treatments such as headache, skin sensitivity, and itching were evaluated in two groups. There was no significant difference between two groups with regard to age, gender, flatulence duration ($p > 0.05$) in the baseline. No significant

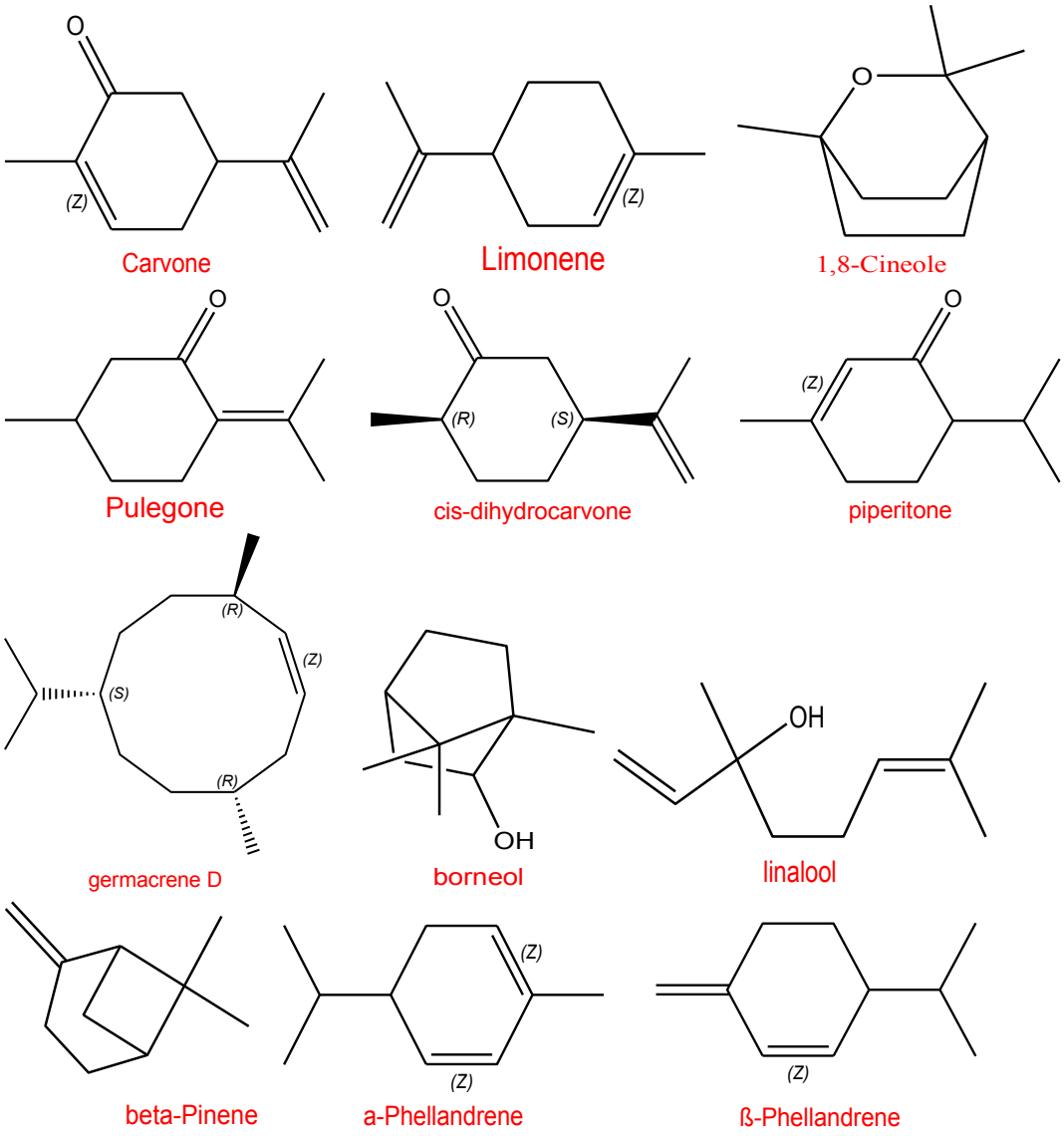

Fig. 1. The chemical structures of main components of *Mentha spicata* essential oils.

difference were observed between two groups in regard to dimethicone prescription and *M. spicata* essential oil oral drop for treatment of flatulence, in the admission time and two weeks after the treatment starting. After four weeks (one weeks after finishing the treatment), *M. spicata* essential oil oral drop was statistically superior than that of dimethicone ($p = 0.01$) in treatment of flatulence.[28] No adverse effects were reported for *M. spicata* essential oil group. The patients consumed 2 ml of *M. spicata* essential oil 2% (0.04 ml pure essential oil) after each meal that contain 0.6 mg carvone as the manufacturer claim.

Postoperative abdominal discomfort and gastrointestinal distension is prevalence after Cesarean section.[29] *M. spicata* essential oil oral drop 2% can have potency in reducing the flatulence, pain and intestinal complaints after cesarean section.

The efficacy of *M. spicata* essential oil oral drop ($n = 60$) and placebo group ($n = 47$) was evaluated on the severity of flatulence, pain and intestinal complaints after cesarean on 107 cesarean women in double blind clinical trial study. There was no significant difference between two groups in regard to the anesthesia duration ($p = 0.57$), surgery duration ($p = 0.97$), and the kinds of anesthesia ($p = 0.83$). After leaving the operation room and stopping the hydration therapeutic, the cesarean women received three doses of *M. spicata* essential oil oral drop 2% or placebo ($n = 40$ drops) every 20 min. After 120 min, clinical questionnaires were completed. A significant difference was observed between the amounts of burp in *M. spicata* essential oil oral drop and placebo groups after 60 min, suggesting the effects of *M. spicata* on gas existence after administration.[30] Rather than the anti-flatulence effects of *M. spicata* essential oil, the oil had the efficacy in treatment of abdominal pain. The effects of *M. spicata* essential oil on pain severity and flatulence severity of cesarean women revealed *M. spicata* essential oil oral drop reduced the pain and flatulence severity and their differences was statistically significant with placebo group.[31] The flatulence severity decreased in *M. spicata* essential oil group after the first 20 min than before intervention.[32] The authors did not report any adverse effects during the study.

In folk believes, consuming the *M. spicata* water (Arag-E-Nana) during lactation can get rid of babies from colic after birth until 4 month.

Flatulence often accompanies by abdominal pain. *M. spicata* essential oil have shown efficacy in reducing the pain in clinical studies.

The efficacy of *M. spicata* essential oil on reducing the pain severity was compared to control group on 101 patients for abdominal pain during the colonoscopy. The average ages of patients were 10.13 ± 2.85 and 9.08 ± 2.55 in *M. spicata* essential oil oral drop 2% and control groups, respectively. There was no significant difference between the age and gender among two groups ($p > 0.05$). The patients in *M. spicata* essential oil oral drop group ($n = 51$) received 20 drops of oral *M. spicata* essential oil (2%), 30 min before the colonoscopy operations. The patients in control group did not receive any treatment. After colonoscopy, the pain severity and patient's satisfaction were determined by pain pediatric questionnaire. The averages of abdominal pain were 2.5 ± 0.527 and 1.625 ± 0.491 in *M. spicata* essential oil oral drop and control groups, respectively. Patients satisfaction scores were 2.67 ± 0.566 and 1.833 ± 0.389 in *M. spicata* essential oil oral drop and control groups, respectively ($p < 0.05$). The time for colonoscopy operations was significantly shorter in *M. spicata* essential oil oral drop group than that of control group. In total, there was a statistical significant difference between two groups in the average of pain severity and patients satisfaction ($p < 0.05$).[33] Therefore, *M. spicata* essential oil oral drop reduces the abdominal pain during the colonoscopy. According to the results of this investigation, the children that used the *M. spicata* essential oil before the colonoscopy operation have more satisfaction and experience lower pain than the control group.

Occurrence flatulence during menopause is accompanied with feeling of fullness in the abdominal area, feeling of tightness around the stomach and sharp stomachache. In this situation, the abdomens of dysmenorrheal patients swell and the flatulence and burping increase.

The effects of *M. spicata* essential oil oral drop against pain and flatulence were confirmed in a clinical study on 100 girls (18–22 years old) with dysmenorrheal disease in contrast to 400 mg ibuprofen. The patients were randomly divided into groups. The patients received 40 drops of *M. spicata* essential oil oral drop at two cycles of pain, while other control group received the ibuprofen 400 mg, every 4 h (if needed). There was no significant difference between two groups in regard to first menstruation, the bleeding duration, pain severity and dysmenorrheal duration before administration of drug ($p > 0.05$). The severity of pain related to first dysmenorrhea significantly decreased in two groups in comparison with the baseline ($p = 0.0001$), while the average of pain reduction among two groups after treatment was not significant ($p = 0.486$). The average of menstruation cycle decreased from 60.4 ± 34 to 19.74 ± 21.88 h after administration of *M. spicata* essential oil oral drop, while ibuprofen decreased this average from 55.78 ± 25.13 to 27.74 ± 25.11 h. The difference between two groups was not significant ($p > 0.05$). The satisfied patients were 88% (22% (excellent), 62% (good) and 16% (unsatisfied)) in *M. spicata* essential oil, while the satisfaction was 90% (22% (excellent), 68% (good)) in ibuprofen group. There was no significant difference between the patients compliance in two groups ($p = 0.066$).[34]

According to the results of clinical trials, the patients with indigestion, IBS and flatulence severity can benefit from *M. spicata* essential oil. The women after their cesarean or the girls with dysmenorrheal diseases can profit the anti-flatulence effects of *M. spicata* essential oil. Also, *M. spicata* essential oil can reduce the pain severity during the colonoscopy and dysmenorrheal diseases.

6. Proposed mechanisms for anti-flatulence effects of *M. spicata* essential oil

A successful treatment of flatulence is possible, when a compound have carminative, anti-inflammatory, antiseptic, sedative, digestive and antispasmodic effects. The carminative effects of compound facilitate the exclusion of gases and avoid bloating. The sedative and anti-spasmodic effects of compounds reduce the stress and air swallow. The anti-inflammatory and digestive effects of compound prevent the bowel inflammation and digest the food better. For prediction of possible mechanisms, we searched these properties for *M. spicata* essential oil and components.

As BS ISO 3033-1:2005, (-)-carvone (monoterpene ketone) is the main component of native *M. spicata* essential oil. The amounts of carvone in *M. spicata* essential oil should be between 60-70%. Our investigations showed all present animals and *in vitro* studies have been focused on carvone and it seems the confirmed biological effects of *M. spicata* essential is related to carvone at first and with low importance to other components in its essential oil.

The antispasmodic effects of carvone have been confirmed on smooth muscle of intestine of guinea pig ileum. The anti-spasmodic effects of carvone in presence of histamine, carbachol, and $BaCl_2$ were compared with verapamil as calcium channel blocker. Carvone did not exert any relaxation response or direct contractile in smooth muscle. It is unlikely that carvone be potassium channel opener, because it did not change the K_{20} induced contraction in contrast to minoxidil as positive control. Carvone also reduced the spasmodic response in presence of carbachol, $Bacl_2$ and histamine and this reduction was higher for histamine, followed by carbachol and $BaCl_2$ elicited contractions. Therefore, the involvement of specific receptor or pathway in its antispasmoic actions is unlikely. Comparison of carvone and morphine on electrically elicited contraction showed carvone did not modify the neurogenic ileum contractions. Carvone reduced the high contractile response related to high carbachol concentrations, and had a dose relaxing response. Therefore, carvone acts as a Calcium Channel Blocker and its anti-spasmodic effects is almost 100 times more potent than verapamil.[35] According to above studies, carvone did not reduce the neurogenic contractions and also opiate antagonists did not reverse the antinociceptive effects of Calcium Channel Blockers and by this mechanism, it can be showed anti-spasmodic effects.

The anti-spasmodic effects of carvone as calcium channel blockers also can be an explanation for its analgesic effects. The analgesic effects of 50, 100, 200 mg/kg (-)-carvone, 6 mg/kg morphine was investigated using acetic acid induced writhing test and formalin induced nociception tests. The writhe reduction of 100 mg/kg (-)-carvone in mice was similar to morphine (2.6 ± 1.1 vs. 3.3 ± 1.4) and their response was statistically significant than that of control group (14.4 ± 2.7). 50 mg/kg carvone did not exhibit any antinociceptive effects, while 200 mg/kg carvone caused writhe reduction (0.3 ± 0.1) higher than morphine. The licking responses to injected paw were 63.5 ± 6.4 s and 83.9 ± 39.4 s for 100 and 40.7 ± 8.5 s; 16.8 ± 16.4 s for 200 mg/kg carvone in comparison to its vehicle group (119 ± 9.9 s; 296.4 ± 31.8 s) in the first and second phases of formalin test. Morphine reduced the licking time in the first and second phases of formalin test (55.8 ± 9.0 s; 52.4 ± 15.3 s) and 100 mg/kg acetylsalicylic acid reduced licking time in second phase of formalin test (140.3 ± 34.3 s). The antinociceptive effects of morphine were reversed by 5 mg/kg naloxone, while this effect for carvone was not affected by naloxone treatment. Therefore, opioid system is not participated in antinociceptive activity. It has been showed *M. spicata* affects on calcium channels in neurons causes the Ca^{2+} currents, therefore neurons excitability and synaptic transmittance decreased and finally the pain reduces. The sedative and relaxing effects of (-)-carvone is higher than (+)-carvone the form founded in caraway oil.

The motor performance of treated mice with 50, 100 and 200 mg/kg carvone was not modified in Rota rod test, while these alterations were observed for 4 mg/kg diazepam.

Incubation of 10 mM Carvone with isolated peripheral nerve

reduced the CAP amplitude about 23.3 mv (50.8 ± 3.4 mV to 27.2 ± 7.1 mV). The hypothesis for antinociceptive effects of carvone is involvement of Na^+ channel blocking mechanisms of central and peripheral nervous system that finally reduce the peripheral nerve excitability.[36] 200 mg/kg carvone showed high sedative and antinociceptive effects in mice.[37]

The role of instability of gut microbial ecosystem in flatulence and influence of diet on gut microflora have been confirmed.[38] Gut microflora is a complex ecosystem with different microbial species that involve in protective, metabolic and trophic functions. Gas production is caused by interaction between gut microflora and substrates. Flatulence or other gastrointestinal symptoms are as the result of perturbation of equilibrium between enteric flora and ecosystems.[39] *M. spicata* with antiseptic effects[40,41] may have potential therapeutic role in patients with flatulence or gas related syndrome.

In order to determine the fermentation kinetic and digestibility effects of *M. spicata* essential oil, 250, 500, 750 and 1000 μg/ml of *M. spicata* essential oil was evaluated on rumen fluid. The gas production technique was employed to determine the gas production, asymptotic gas production, microbial biomass, rate of gas production, ammonia concentration, partitioning factor and digestibility. By increasing the *M. spicata* essential oil, asymptotic gas production and rate of gas production decreased. 250 and 500 μg/ml *M. spicata* essential oil increased partitioning factor, digestibility and ammonia concentration, but 1000 μg/ml decreased these above parameters. Higher partitioning factor was related to greater amount of digested organic matter and the higher growth of microbial cell. The increasing in ammonia production is as the result of microbial lysis. 1000 μg/ml *M. spicata* essential oil had inhibitory effects on microorganisms in the rumen. In other word, 250 and 500 μg/ml *M. spicata* essential oil by increasing the partitioning factor and digestibility modulated the rumen fermentation and improved dietary utilization.[42]

Therefore, *M. spicata* essential oil due to its carvone content has anti-spasmodic, analgesic, antiseptic and anti-bloating effects. I think the results of studies that compared different biological effects of *M. spicata* essential oil with carvone clear the exact role of components in *M. spicata* essential oil.

7. Toxicological effects

As the results of above clinical studies, No hazardous or adverse effects have been reported after consumption 0.24 ml of pure *M. spicata* essential oil daily for three continuous weeks.[28,34]

Survey in other studies showed few toxicological investigations were found for *M. spicata* essential oil in the published scientific literatures. Testing *M. spicata* essential oil and carvone in the Ames assay for mutagenicity to *S. typhimurium* Strain TA100 and TA98 and in assay for clastogenic potential in the chromosomal aberration assay by CHO cell culture and in the mouse micronucleus assay showed no evidence of mutagenic and clastogenic potential. Carvone in the Ames assay for mutagenicity to *S. typhimurium* Strain TA100 and TA98, TA1535, TA1537 and in Wing Somatic Mutation and recombinant test using *Drosophila melanogaster* for genotoxicity revealed no mutagenic and genotoxic potential, but it can induce a weak malsegregation in *Saccharomyces cerevisiae*[43] The result is in contrast to the results of older study that confirm that *M. spicata* essential oil showed some mutagenic activity in *D. melanogaster*.[44]

Evaluation the acute toxicity of (-)-carvone showed the LD_{50} 426.6 mg/kg in Male Swiss mice. The LD_{50} of orally administered *M. spicata* essential oil in rat is 5000 mg/kg.[45]

Contact allergy and sensitivity reactions to *M. spicata* essential have been reported in certain individuals especially in children. There was no information about the administration of *M. spicata* essential oil in pregnancy or lactation. In a double blind randomized crossover clinical trial about ingesting 500 mg of *M. spicata* essential oil on lower esophageal sphincter function and acid reflux in healthy volunteer showed *M. spicata* essential oil did not affect on lower esophageal sphincter and acid reflux.[46]

For evaluating the toxicity of carvone in metabolic environment of mammals, the investigators applied an *in silico* program (Osiris program) and they found carvone had low theoretical risk of toxicity.[47] No health hazards or side effects are known with the proper administration of designated therapeutic dosages.

Also, the safety of *M. spicata* ethanol extract has been the subject of toxicological purposes. The effects of different concentrations of *M. spicata* (0, 10, 20 and 40 mg/kg) ethanol extract orally was evaluated on the reproductive system, fertility and number of offspring of adult Wistar male rats for 45 days. There was no significant difference in serum testosterone concentration, sperm count and sperm motility (fast, slow or non-progressive movement, immotile sperm) among the treated group and control group. The structure of reproductive tissues (seminiferous tubules of testis tissue, spermatogenic cells, epididymal tissue, seminal vesicle, prostate tissue) did not change in treated groups, when compared to control group. Consumption of *M. spicata* extract had no significant effect on the weight and crown-rump length of offspring and the pregnancy outcome in comparison with control group. Therefore, *M. spicata* ethanol extract at used dosage had no anti-fertility effect in adult male rats.[48]

The results of studies showed no health hazards or side effects are known with the proper administration of designated therapeutic dosages of *M. spicata* essential oil.

8. Conclusion

M. spicata essential oil is used traditionally for treatment of flatulence. Some therapeutic effects of *M. spicata* essential oil can help to its anti-flatulence effects. There are some commercial products from *M. spicata* essential oil in markets in two forms of oral drop (Supermint oral drop, BarijEssence, Kashan, Iran) and soft capsule (Supermint soft capsule). Supermint oral drop is prepared from 2% of *M. spicata* essential oil and is standardized on the base of 11–15 mg carvone in each ml of product and is prescribed to use of 20 drops of product after meals. It is recommended for treatment of flatulence, and indigestion. Supermint soft capsule 20 mg contains 10–12 mg carvone and has the application such as Supermint oral drop.

The properties such as digestive, analgesic and anti-spasmodic effects synergistically act and reduce the flatulence severity in the stomach. Irritable bowel syndrome (IBS) as a long-lasting, relapsing disorder with abdominal pain/discomfort can be the subject of other more studies of *M. spicata* essential oil. Although, there are some clinical studies that evaluate the efficacy of *M. spicata* essential oil oral drop in treatment of intestinal diseases especially flatulence and intestinal pain, but there are needed many other pharmacological and clinical studies for evaluating the efficacy of different formulations of *M. spicata* essential oil.

Conflict of interest

No conflict of interest is declared by the author of this manuscript. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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