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Review article: The physiologic effects and safety of Peppermint Oil and its efficacy in irritable bowel syndrome and other functional disorders

Bruno P. Chumpitazi[1], **Gregory Kearns**[2], and **Robert J. Shulman**[1,3]

[1]Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

[2]Arkansas Children's Research Institute, Little Rock, AR, USA

[3]Children's Nutrition Research Center, Houston, TX, 77030

Abstract

Background—Peppermint oil has been used for centuries as a treatment for gastrointestinal ailments. It has been shown to have several effects on gastroesophageal physiology relevant to clinical care and management.

Aim—To review the literature on peppermint oil regarding its metabolism, effects on gastrointestinal physiology, clinical use and efficacy, and safety.

Methods—We performed a PubMed literature search using the following terms individually or in combination: peppermint, peppermint oil, pharmacokinetics, menthol, esophagus, stomach, small intestine, gallbladder, colon, transit, dyspepsia, and irritable bowel syndrome. Full manuscripts evaluating peppermint oil that were published through July 15, 2017 were reviewed. When evaluating therapeutic indications, only randomized clinical trials were included. References from selected manuscripts were used if relevant.

Results—It appears that peppermint oil may have several mechanisms of action including: smooth muscle relaxation (via calcium channel blockade or direct enteric nervous system effects); visceral sensitivity modulation (via transient receptor potential cation channels); anti-microbial effects; anti-inflammatory activity; modulation of psychosocial distress. Peppermint oil has been found to affect esophageal, gastric, small bowel, gallbladder, and colonic physiology. It has been used to facilitate completion of colonoscopy and endoscopic retrograde cholangiopancreatography. Placebo controlled studies support its use in irritable bowel syndrome, functional dyspepsia, childhood functional abdominal pain, and postoperative nausea. Few adverse effects have been reported in peppermint oil trials.

Corresponding Author: Bruno P. Chumpitazi, MD, MPH, Associate Professor of Pediatrics, 6701 Fannin Street, CCC 1010.03, Houston, TX 77030, chumpita@bcm.edu, Phone: 1-832-822-3131, Fax: 1-832-825-3633.

Guarantor of the article: Bruno P. Chumpitazi

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Conclusion—Peppermint oil is a natural product which affects physiology throughout the gastrointestinal tract, has been used successfully for several clinical disorders, and appears to have a good safety profile.

Keywords

Menthol; Diet; Irritable Bowel Syndrome; Dysphagia; Smooth muscle; Peppermint oil

INTRODUCTION

Peppermint is a perennial flowering plant that grows throughout Europe and North America. Peppermint (Mentha × piperita) is a (usually) sterile hybrid mint, a cross between Water mint (Mentha aquatica) and Spearmint (Mentha spicata) that is believed to have arisen naturally. Mint plants have a long history of medicinal use, dating to ancient Egypt, Greece, and Rome where they were used as stomach soothers.[1] Peppermint oil is obtained by steam distillation from the fresh leaves of peppermint.[2] Our goal was to review the literature on peppermint oil regarding its metabolism, effects on gastrointestinal physiology, clinical use and efficacy, and safety.

METHODS

A PubMed literature search was performed using the following terms individually or in combination: peppermint, peppermint oil, pharmacokinetics, menthol, esophagus, stomach, small intestine, gallbladder, colon, transit, dyspepsia, nausea, abdominal pain, and irritable bowel syndrome. Full manuscripts evaluating peppermint oil that were published through July 15, 2017 were reviewed. References from the selected manuscripts also were searched for additional relevant publications. A total of more than 2800 references were initially reviewed. Following removal of references overlapping between searches and those lacking original data, the authors agreed on inclusion of the 96 on which to base the information presented within this manuscript. When evaluating therapeutic trials for clinical disorders (e.g., irritable bowel syndrome), only randomized placebo controlled trials were included.

RESULTS

Pharmacokinetics

Pharmacokinetic data relating to peppermint oil in humans are limited.[3] The main constituent and active ingredient of peppermint oil appears to be menthol although it contains a large number (greater than 80) of other components.[3, 4] Studies in rats and limited data in humans demonstrate that peppermint oil is rapidly absorbed.[3, 5, 6] However, when taken in capsule form designed for delayed release, approximately 70% reaches the colon.[5] Though done in a small study (n=13), delayed release formulations of peppermint oil (vs. non-delayed release formulations) altered menthol urinary pharmacokinetics by increasing the apparent lag time and time to peak plasma concentrations. The delayed release formulation did not alter the absorption half-life or total area under the curve.[6] In healthy adults, an oral dose of 100 mg of menthol results in an average peak blood concentration of 16.7 ± 5.5 μmol/L and an apparent elimination $t_{1/2}$ of 56 ± 8 min.[7] However, as noted,

pharmacokinetics are greatly dependent on the formulation used.[6] A L-menthol preparation sprayed directly onto the gastric mucosa was rapidly absorbed with peak concentrations reached within one hour after administration.[8] In addition, development (reflected by age) may impact the pharmacokinetics of menthol as we showed in a pilot study in healthy children administered peppermint oil.[3]

Menthol is primarily metabolized in the liver via hepatic microsomal P450 enzymes and subsequently undergoes biotransformation via UDP-glucuronosyltransferases.[2, 3] Menthol is excreted into bile as menthol glucuronide.[3, 5] In particular, data show the importance of both CYP2A6 (the major P450 enzyme involved in menthol hydroxylation) and UGT2B7 expression in determining menthol clearance.[9, 10] Therefore there is the potential for pharmacogenomics and other substances which impact either CYP2A6 or UGT2B7 activity to alter peppermint oil's concentration-time curve. Following biliary excretion, menthol glucuronide undergoes enterohepatic circulation. Peppermint oil metabolites are excreted in the urine in part as glucuronic acid conjugates with ≥ 50% of a 100 mg oral dose of menthol appearing in urine as menthol glucuronide.[7, 8, 11]

Potential Mechanisms of Action

The Figure highlights several preclinical studies which lend insight into peppermint oil's potential relevance to gastrointestinal tract physiology and gastrointestinal disorders. Peppermint oil's benefit in functional gastrointestinal disorders such as the irritable bowel syndrome (**IBS**) has been ascribed primarily to its antispasmodic effect. The degree to which the other gastrointestinal effects of peppermint oil contribute to its clinical benefit remains unclear.

Effects on Gastrointestinal Tract Neuromotor Function—Evidence suggests that peppermint oil acts as a smooth muscle relaxant.[3] Hawthorn et al. showed in guinea pig ileal smooth muscle in vitro that both peppermint oil and its constituent menthol were capable of blocking calcium channels.[12] *In vitro* studies using guinea pig colon and rabbit jejunum smooth muscle suggest peppermint oil reverses acetylcholine induced contraction and antagonizes serotonin-induced contraction through calcium channel blockade.[13] Amato et al., using samples obtained at the time of surgery, observed that menthol induces circular smooth muscle relaxation in human colon by directly inhibiting contractility through the blockade of Ca^{2+} influx through sarcolemma L-type Ca^{2+} channels.[14] Its action did not involve activation of the transient receptor potential cation channel subfamily M member 8 (**TRPM8**) channel or nitrous oxide.[14]

Peppermint oil may also directly affect the enteric nervous system. Using cultured murine small intestine interstitial cells of Cajal, Kim et al. showed via a whole cell patch clamp technique that menthol acts via the transient receptor potential cation channel, subfamily A, member 1 (**TRPA1**) receptor to induce membrane potential depolarization in a concentration dependent manner.[15] G protein stimulation as well as external Ca^{2+} and release from intracellular stores also appear to be involved.[15] Finally, Kim and colleagues also provided evidence that prostaglandin production also is involved in stimulating the effects of menthol on the interstitial cells of Cajal.

Effects on Gastrointestinal Visceral Sensation—Although peppermint oil (via menthol) is a well-known topical analgesic, rodent studies show that peppermint oil can decrease visceral pain when administered orally or intraperitoneally.[16–18] Recent studies suggest that the reduction in visceral pain is mediated through the TRPM8 and/or TRPA1 receptor of the transient receptor potential cation channel superfamily located in the gut.[19–22]

Antimicrobial/Antifungal Actions—Multiple studies have shown that peppermint oil (menthol) is one of the most potent antimicrobial/antifungal/antiviral botanicals.[23] Peppermint oil is active against obligate and facultative anaerobes.[24] It also is bactericidal to at least 20 common enteric pathogens including *Helicobacter pylori*, *Escherichia coli*, *Staphylococcus aureus*, Klebsiella sp., *Salmonella typhi*, *Shigella boydii*, and *Shigella flexneri*.[25–28] More recently it has been shown that menthol can inhibit quorum sensing activity of gram negative pathogens.[29] Peppermint oil also appears to have activity against fungal pathogens.[30] In a mouse model, a combination of menthol and menthone were effective in reducing the number of *Schistosoma mansoni* eggs in the feces, liver, and intestine and reducing the number of hepatic granulomas.[31]

Effects on Inflammation—Studies demonstrate that peppermint oil (menthol) possesses anti-inflammatory activity.[32] Oral administration of peppermint oil prevents both xylene induced gut inflammation in mice and acetic acid induced colitis in rats.[16, 32] *In vitro*, menthol suppresses the production of inflammatory mediators from human monocytes.[33] Immune cells also contain transient receptor potential cation channels. It is believed that the anti-inflammatory effects of peppermint oil may be mediated, in part, via TRPM8 as its activation down regulates chemically induced colitis in mouse models.[34, 35]

Effects on Behavior—Studies in humans demonstrated that inhalation of peppermint aroma improves attention but whether it improves mood remains unclear.[36–38] Studies in rodents, which suggest menthol has dose dependent anxiolytic effects, implicate involvement of dopamine pathways.[39–41] Given the potential role of psychosocial distress in the expression of functional gastrointestinal pain disorders symptoms, this may be another potential mechanism of action.

Peppermint Oil Effects on Gastrointestinal Physiology

Some older studies examining the physiologic effects of peppermint oil describe the administration of “drops” rather than a milligram dosage. Thus, the actual dose of peppermint oil can only be estimated. Our calculations are based on 20 drops/mL and a presumed concentration of 916 mg of peppermint oil per mL.[42] A caveat regarding this assumption is the recognition that concentrations may vary as a result of botanical source and/or preparation of the peppermint oil.

Peppermint oil effects on the Esophagus (Table 1)—The effects of peppermint oil on esophageal function have been studied in healthy adults. Using esophageal manometry Sigmund et al. demonstrated peppermint oil decreased lower esophageal sphincter pressure.[43] Peppermint oil increased the likelihood of reflux by causing equal pressures across the

esophageal body, lower esophageal sphincter, and stomach.[43] Using double contrast esophageal barium studies Mizuno et al. demonstrated peppermint oil (vs. saline) decreased esophageal spasms.[44]

Peppermint oil has been used as a spasmolytic agent in esophageal disorders though only in the short term. Using esophageal manometry in patients with diffuse esophageal spasm, Pimentel et al. found peppermint oil did not affect lower esophageal sphincter or esophageal body pressures but improved esophageal manometric findings.[45] Differences between Sigmund et al. and Pimentel et al. (e.g., lower esophageal sphincter pressure following peppermint oil) may relate to the larger dose of peppermint oil used in the Sigmund et al. study. Despite these promising data we did not identify long term studies using peppermint oil for hypercontractile disorders of the esophagus.

Peppermint oil Effects on Gastric Physiology and Gastric Emptying (Table 2)—Mizuno et al. in the same study which evaluated esophageal motor function using double contrast barium studies found peppermint oil given orally decreased spasms of the lower stomach.[44] During esophagogastroduodenoscopy investigators have found that peppermint oil/menthol sprayed on the mucosa decreased gastric peristalsis and increased pyloric ring diameter.[46, 47] Topical mucosa application is potentially appealing because systemic exposure to menthol is much reduced compared with oral administration.[2, 6, 8]

Peppermint oil sprayed on the mucosa during esophagogastroduodenoscopy was found to decrease peak power frequency on electrogastrography.[48] Manometry and/or barostat studies have identified the following peppermint oil effects: decreased intragastric pressure, decreased gastric motility index, no effect on gastric accommodation.[49–51] In healthy volunteers peppermint oil taken orally did not affect epigastric symptoms or satiation though there was decreased appetite (vs. placebo) during the fasting period.[50]

The effect of peppermint oil on gastric emptying has been evaluated with mixed results. Using a test meal of solids and nuclear scintigraphy Dalvi et al. demonstrated peppermint oil (vs. baseline) taken orally with water accelerated gastric emptying in both healthy adults and adults with dyspepsia.[52] In contrast, Goerg et al. used ultrasonography to demonstrate peppermint oil (taken orally in a non-enteric capsule) had no effect on gastric emptying of liquids (apple juice) .[53] Studying healthy adults via ^{13}C-acetic acid breath testing using a liquid test meal, Inamori et al. found peppermint oil (ingested as a solution with the test meal) caused a more rapid emptying in the early phase following a meal but this did not result in a difference in overall gastric emptying rate. Further investigation of the effect of peppermint oil on gastric emptying is needed given the differences in meal/liquids given and the differing methodologies employed in these previous studies.

Peppermint Oil Effects on Small Bowel Physiology and Transit Time (Table 3)—Peppermint oil appears to decrease small bowel contractility. The double contrast barium study by Mizuno et al. also demonstrated that the oral peppermint oil solution (vs. water) decreased spasm in the duodenal bulb.[44] Micklefield et al. found that duodenally instilled peppermint oil decreased duodenal contractions during phase III (but not phase I or II) of the fasting period.[51] Investigators using peppermint oil instilled into the duodenum during

endoscopic retrograde cholangiopancreatography noted subjective decreases in duodenal contractions and a trend for an overall decrease in duodenal contractions per minute.[54, 55] As might be anticipated, the timing of the effect of peppermint oil on duodenal contractility appears related to the peppermint oil formulation used. Using manometry Micklefield and colleagues using an enteric (vs. non-enteric) coated peppermint oil (both mixed with caraway oil) given orally noted that the decrease in duodenal contractions occurred later in the enteric vs the non-enteric coated preparation.[49]

Based on hydrogen breath testing peppermint oil has been found to slow orocecal transit.[53] Wildgrube et al. used carmine red to demonstrate that peppermint oil slowed whole intestinal transit.[56]

Peppermint Oil Effects on Gallbladder Emptying—Using ultrasound gallbladder volume measurements as a proxy for emptying following a liquid meal (400 mL apple juice) in 12 healthy volunteers, Goerg et al. reported that peppermint oil taken orally inhibited gallbladder emptying vs placebo (44.4% ± 14.0 increase in volume vs 28.6% ± 4.8 decrease in volume, P=0.04).[53]

Peppermint Oil Effects on Colonic Physiology (Table 4)—Using peppermint oil solution mixed with barium, several investigators have found peppermint oil decreased colonic spasm during barium enema.[57, 58] Investigators also have found that peppermint oil applied topically to the colonic mucosa inhibits colonic motor activity as measured by colonic manometry and ultrasound.[59, 60] Several endoscopy based studies have found peppermint oil (taken orally or administered topically within the colon) decreases colonic peristalsis and/or spasm.[61–64] Inoue et al. found a higher adenoma detection rate during colonoscopy in those receiving peppermint oil vs. placebo.[64] In contrast, peppermint oil administered intraluminally potentiated the activity of neostigmine given intramuscularly by further increasing the amplitude of sigmoid contractions in adults.[65] The dose used in this study by Rogers et al. was half that used in the study by Duthie et al. in which luminal peppermint oil inhibited all sigmoid motor activity following neostigmine injection.[53]

Peppermint Oil Usage During Endoscopic Procedures

As noted above, the anti-spasmodic properties of peppermint oil have been used successfully during both upper GI endoscopies, colonoscopies, and endoscopic retrograde cholangiopancreatography (**ERCP**) procedures. These studies are summarized in Table 5.

Peppermint Oil for Treatment of Gastrointestinal Disorders

Adult Irritable Bowel Syndrome (Table 6)—A number of trials have investigated peppermint oil for IBS. As can be seen in Table 6, the dosing and formulation for peppermint oil varied significantly. All but one study found peppermint oil more effective than placebo in reducing symptoms.[66] Similarly, 5 peppermint oil meta-analyses have found peppermint oil to be effective in IBS.[67–71] In the most recent meta-analysis, the number needed to treat was 3.[71] It should be noted that given the lack of negative studies there may be potential for publication bias to cause studies showing no benefit to be under-represented in the literature.

Pediatric Functional Abdominal Pain (Table 7)—Two peppermint oil randomized controlled pediatric trials have been carried out, both suggesting benefit. The study by Kline et al. was a double blind, randomized, placebo controlled trial that included children with both IBS and functional abdominal pain (J. Kline, 5/2007, personal communication).[72] The other trial was randomized and single blinded comparing peppermint oil to a probiotic and folic acid (presumably as a placebo).[72, 73]

Functional Dyspepsia (Table 8)—A number of randomized controlled trials have shown peppermint oil to be effective for functional dyspepsia when used in conjunction with other natural products (primarily caraway).[74–77] However, to our knowledge, peppermint oil has not been studied alone in a randomized, double blind trial. As an example, peppermint oil has been used within STW 5-II which also contains extracts from bitter candy tuft, matricaria flower, caraway, licorice root and lemon balm. In adults with functional dyspepsia, Madisch et al. reported that STW5-II was superior to placebo in both improvement of overall gastrointestinal symptom score and complete relief of symptoms (43.3% vs. 3.3%, $P<0.001$).[75]

Post-operative Nausea—Peppermint oil aromatherapy when blended with ginger, spearmint, and cardamom oil was found to be superior vs saline for postoperative nausea.[78] Peppermint oil aromatherapy was superior to placebo for post-operative nausea following caesarian section.[79] However two randomized double-blind trials did not find peppermint oil aromatherapy to be superior to saline or controlled breathing for post-operative nausea.[78, 80]

Safety

Menthol is listed as generally regarded as safe by the US Food and Drug Administration. The European Medicines Agency recently released their assessment and recommendations regarding peppermint oil (see below).[42]

Few adverse events have been reported in peppermint trials. In those studies reporting adverse events (see Table 2), no differences were noted between peppermint oil and placebo groups except in the study by Nash et al. in which heartburn was more common in the peppermint oil vs placebo group; however, the efficacy of the enteric coating used for the peppermint oil formulation in this study of 30 years ago is unknown. In theory, enteric coated formulations of peppermint oil facilitate release distal to the stomach – thereby minimizing the risk of gastroesophageal reflux.

The safety of peppermint oil also has been reviewed by the Cosmetic Ingredient Review Expert Panel.[81] In rat studies cystlike spaces have been identified in the cerebellum in some rat studies but not others at doses of ≥ 40 $mg \cdot kg^{-1} \cdot d^{-1}$.[81] Subsequently it was shown that the cystlike spaces were artifacts of poor tissue fixation.[82]

Pulegone, and its metabolite, menthofuran which are present in peppermint oil have been considered to be potentially toxic in high doses. In a rat study, ≥ 80 $mg \cdot kg^{-1} \cdot d^{-1}$ of pulegone was associated with vacuolization of hepatocytes.[81] In a more recent series of studies from the National Toxicology Program, liver necrosis and cytoplasmic vacuolization were only seen in rats given ≥150 $mg \cdot kg^{-1} \cdot d^{-1}$ of pulegone for 2 weeks.[83] In a 3-month administration

study in rats, bile duct hyperplasia, hepatocyte focal necrosis and hypertrophy and renal glomerulopathy were only seen at doses ≥75 mg·kg^{-1}·d^{-1} of pulegone.[83] In contrast, mice were more resistant to the effects than were rats with doses of 300 mg·kg^{-1}·d^{-1} of pulegone required to see hepatic injury at 2 weeks.[83] The European Medicines Agency statement points out that "prevailing opinion is that no certain cases of liver toxicity in humans are associated with the use of peppermint oil or mint oil."[42] In a case report of a woman suspected to have ingested peppermint oil in a suicide attempt, although comatose on arrival, she recovered without evidence of hepatic or renal injury.[84]

In a 2-year study in rats, pulegone was associated with an increased risk of bladder cancer at a 150 mg·kg^{-1}·d^{-1} dose. In contrast, in a 2-year study of mice, an increased risk for hepatoblastoma was found at the 75 mg·kg^{-1}·d^{-1} dose but not at the 150 mg·kg^{-1}·d^{-1} dose in males with no increased risk in females.[83] The European Medicines Agency statement posits that "non-relevance of rodent neoplasms to human carcinogenesis seems probable" in part, because of the long term sustained exposure required and doses which are not relevant in human situations.

The amount of pulegone in peppermint oil can be reduced depending on how the peppermint is grown, when it is harvested, and how it is processed.[85] Peppermint oil normally contains a maximum of 0.1% pulegone and its metabolite menthofuran according to the European Pharmacopoeia (and more commonly 0.03-0.07%). The European Medicines Agency statement proposes a life-long exposure acceptable dose of 0.75 mg·kg^{-1}·day^{-1}.[42] As likely would be used to treat functional gastrointestinal disorders (oral use for less than one year or intermittently over several years) in adults, the European Medicines Agency statement proposes an acceptable exposure of pulegone plus menthofuran to be 75 mg/day.[42] The maximum usual dose of peppermint oil used to treat functional gastrointestinal disorders such as IBS is 540 mg/d which would deliver only 0.54 mg of pulegone and menthofuran combined. Pharmacokinetic data are needed from studies in children to understand the true systemic exposure to pulegone and menthofuran after "therapeutic" peppermint oil doses and how the aforementioned recommendations regarding exposure limits might apply to the pediatric population.

SUMMARY

Peppermint oil has been used for centuries to address gastrointestinal ailments. Peppermint oil's primary active ingredient is menthol which is metabolized in the liver via both P450 (primarily CYP2A6) catalyzed biotransformation and glucuronidation. Peppermint oil effects on neuromotor function and visceral sensation have been studied most extensively. However, more recent data demonstrate its antibacterial/antifungal effects, an ability to downregulate inflammation, and potentially affect attention, and possibly mood.

Peppermint oil affects esophageal, gastric, small bowel, gallbladder, and colonic physiology primarily as a function of its spasmolytic properties, with such effects seen throughout the gastrointestinal tract. These effects appear to facilitate the completion of endoscopic studies (e.g., colonoscopy, endoscopic retrograde pancreatography). Placebo controlled studies support its use in irritable bowel syndrome, functional dyspepsia, childhood functional

abdominal pain, and postoperative nausea though significant trial heterogeneity (e.g., peppermint oil dose and formulation) exists. It appears to be safe with few, if any side effects beyond those seen with placebo. Future studies should focus on understanding the pharmacokinetics of peppermint oil in children and its pharmacodynamics in children and adults. A clearer understanding of its modes of action in treating functional gastrointestinal disorders is needed. Finally, studies investigating its clinical utility beyond its spasmolytic effects are warranted.

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Abbreviations

PMO	Peppermint Oil
IBS	Irritable Bowel Syndrome

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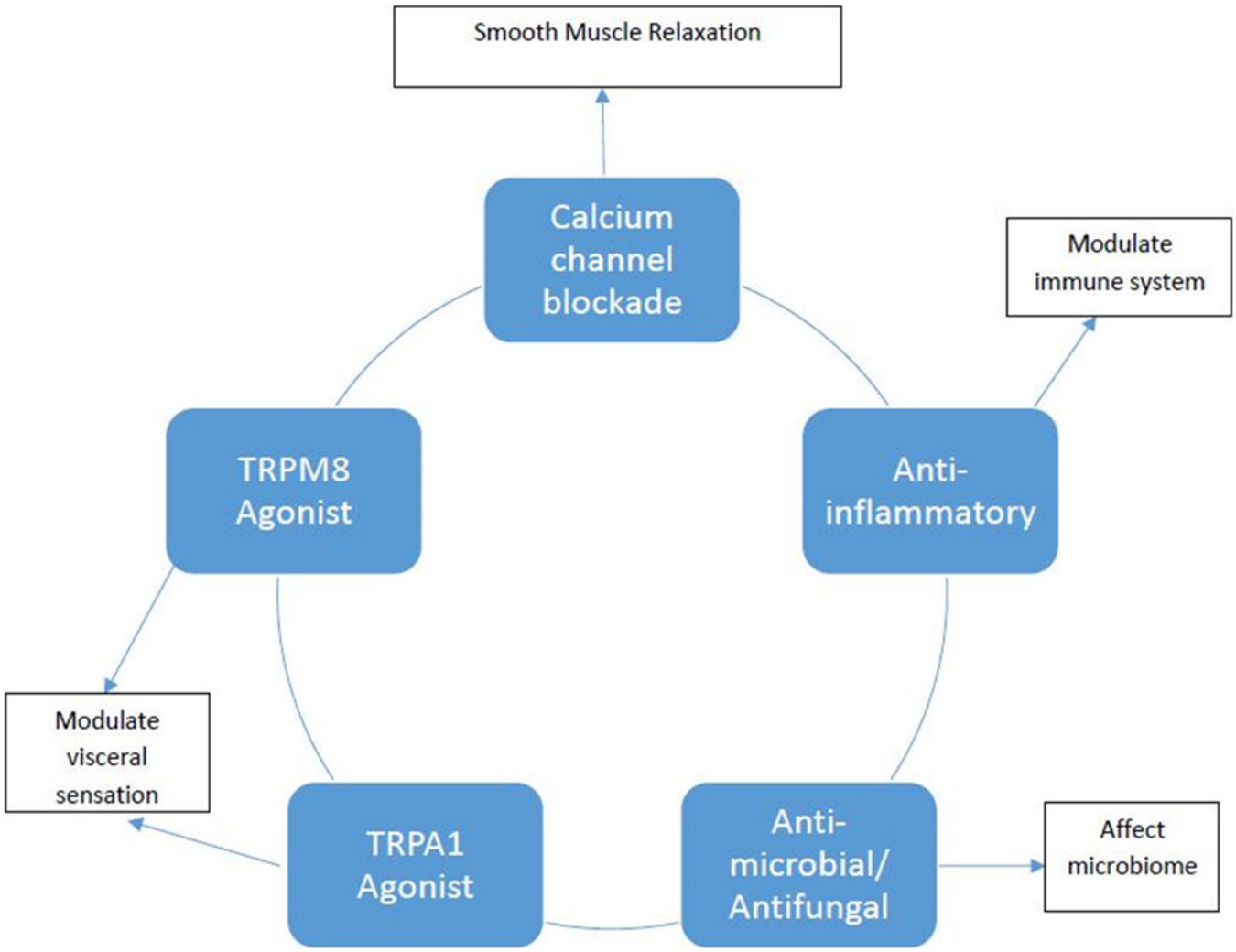

FIGURE. Potential peppermint oil mechanisms of action within the gastrointestinal tract
TRPM8 = transient receptor potential cation channel subfamily M member 8; TRPA1 = transient receptor potential cation channel, subfamily A, member 1

Table 1

Peppermint Oil (PMO) Effect on Human Esophageal Function

Reference	Population	Methods	Findings
Sigmund (1969)[43]	• Healthy subjects (n=27)	• Esophageal manometry measuring the lower esophageal sphincter (LES) and esophageal body • Completed following 15 drops of PMO (presumably ~687 mg). Most subjects also had air infused into the stomach (24 of 27). Controls (n=7) were given saline alone	• 22/24 subjects given PMO after air infusion demonstrated "reflux": decrease in LES pressure until equal pressure stomach and esophageal pressure • 3/3 given PMO without air prior had decrease in LES pressure • Mean duration before response to peppermint: 168.6 seconds ± 97.2 seconds • Duration of sphincter relaxation: 27.8 ± 8.8 seconds to PMO vs. 7.9 ± 3.8s with swallowing • No LES relaxation in controls (saline)
Pimentel (2001)[45]	• Adults with diffuse esophageal spasm (n=8)	• Esophageal manometry at baseline then 10 minutes after PMO • 5 drops of 11% PMO (presumably ~25 mg) in 10 mL water	• No effect on LES or esophageal body pressure • PMO decreased simultaneous esophageal contractions in all patients (P<0.01) and increased propagated body contractions (P<0.01); decreased contraction variability • Two of eight had improvement in chest pain
Mizuno (2006)[44]	• Adult patients undergoing upper double contrast barium study (n=420)	• Nonrandomized study: (n=205) given PMO: 10 mL of 1.6% solution vs. (n=215) given water • Degree of spasm for esophagus blindly scored (0-3 range, indicating none to severe)	• Fewer esophageal spasms seen in PMO group than in controls: 0.35 ± 0.04 vs 0.65 ± 0.04 (P<0.001)

Unless otherwise indicated data are presented as mean ± standard deviation.

Table 2

Peppermint Oil (PMO) Effect on Human Gastric Function and Gastric Emptying

Reference	Population	Methods	Findings
Dalvi (1991)[52]	• Healthy adults: 21-23 yrs., n=10; 35-45 yrs., n=10), and adults with dyspepsia (n=6).	• Solid meal gastric emptying scintigraphy at baseline and after 0.2 mL PMO	• Overall PMO-induced acceleration of gastric emptying ($T_{1/2}$) in both groups • Younger: 100.6 ± 5.8 min → 81.4 ± 10.0 (P<0.05) • Older: 160.0 ± 9.3 min → 109.9 ± 5.9 (P<0.02) • Dyspepsia: 227 ± 28.6 min. → 147.5 ± 28.9 (P<0.001)
Micklefield (2000)[49]	• Healthy adults (n=6)	• Enteric vs. non-enteric coated PMO (90 mg) (combined with caraway oil (50 g) • Gastroduodenal manometry measured migrating motor complex	• No difference in number of antral contractions between capsule types
Hiki (2003)[48]	• Adult patients undergoing endoscopy (n=100)	• Double blind randomized study comparing 20 mg intramuscular hyoscine (n=50) to 20 mL of 1.6% PMO sprayed twice around pyloric ring (n=50) • Subgroup completed electrogastrography (EGG) (n=20) • Endoscopy videotaped with both maximal and minimal pyloric ring diameter measured to calculate opening and contraction ratios during 4 minute assessment.	• Maximal opening ratio and was greater after PMO (P<0.0001) • Contraction ratio was smaller after PMO (P<0.0001) • Time required for disappearance antral contraction rings shorter in PMO (97.1 ± 11.4 s) vs. hyoscine (185.9 ± 10.1 s; P< 0.0001) • EGG: Peak power frequency 2 minutes after PMO administration decreased to 2 cycles per minute and resolved within

Reference	Population	Methods	Findings
			11.5 ± 0.8 minutes
Goerg (2003)[53]	• Healthy adult volunteers (n=12)	• 90 mg PMO (0.1 mL) or 50 mg caraway oil vs. control (0.9% sodium chloride) vs. 10 mg cisapride vs. 10 mg butylscopolamine • 400 mL apple juice given • Ultrasound assessment of gastric and gallbladder emptying based on cross-sectional areas and gallbladder emptying	• No effect of PMO vs placebo on gastric antrum cross-sectional area • Increased gallbladder cross-sectional area following PMO vs placebo (44 ± 14% increase)
Micklefield (2003)[51]	• Healthy volunteers (n=24)	MO: 90 mg and caraway oil infused into the duodenum • Gastroduodenal manometry	• During Phase I and II: PMO decreased stomach corpus contractions (P=0.042); no effect on antrum • During Phase III: PMO decreased frequency of contractions (particularly within the duodenum)
Mizuno (2006)[44]	• Adult patients undergoing double contrast upper barium study (n=420)	• Nonrandomized, (n=205) given PMO: 10 mL of 1.6% solution and (n=215) given water • Degree of spasm for lower stomach blindly scored (0-3 range, indicating none to severe)	• Less stomach spasm in PMO group vs. Controls: 1.20 ± 0.05 vs 1.42 ± 0.11 (P<0.001)
Inamori (2007)[86]	Healthy adults (n=10)	• Randomized crossover study receiving liquid test meal (200 kcal in 200 mL) with/ without 0.64 mL PMO • Gastric emptying measured with ^{13}C-acetic acid breath test	• Early phase of emptying more rapid (decreased lag time) with PMO 56.6 (36.7-71.2) vs 71.5 (47.3-87.6), median (range); P=0.037 • No difference in overall

Reference	Population	Methods	Findings
			gastric emptying rate
Hiki (2012)[46]	• Adult patients undergoing endoscopy (n=97)	• Double blind study randomly assigned to 20 mL of L-menthol spray (n=79): 0.4% vs. 0.8% vs. 1.6% vs. placebo (0% L-menthol) (n=18) • Endoscopy videotaped and amount of gastric peristalsis rated on 0-5 scale blindly	• Proportion of subjects with no peristalsis increased with increasing PMO dose (P=0.005) • Proportion of subjects with no peristalsis greater in 0.8% PMO (47.4%) and 1.6% PMO (52.9%) groups vs. placebo (5.6%) (P=0.015, P=0.009, respectively)
Imagawa (2012)[47]	• Adult patients undergoing upper endoscopy (n=8269).	• Groups included: PMO (n=1893); hyoscine (n=6063); Glucagon (n=157); Control (n= 156) • PMO: 20 mL 1.6% PO solution to antrum (32 mg) • Endoscopist's (n=29) unblinded antral spasm score (1-5; 5=no spasm)	• Trend for less antral spasm in PMO vs. Control (4.3 ± 0.9 vs. 3.8 ± 1.1, P=0.09)
Papathanasopoulos (2013)[50]	• Healthy volunteers (n=13)	• Randomized crossover study in healthy volunteers • 182 mg PMO vs. placebo with 50 mL water when fasting followed by nutrient drink given via pump over 60 minutes • Epigastric symptoms and satiation rated (n=5) and/or barostat (n=6) (with a total of n=7 doing both) measured intragastric pressure before and after nutrient drink	• PMO decreased intragastric pressure (P<0.0001) and gastric motility index (P<0.05) during fasting • Did not affect parameters during the nutrient drink or gastric accommodation • Did not affect epigastric symptoms or satiation, gastric compliance, or sensitivity • Reduced appetite vs. placebo during fasting

Unless otherwise indicated data are presented as mean ± standard deviation.

Table 3

Peppermint Oil (PMO) Effect on Human Small Bowel Physiology and Transit Time

Reference	Population	Methods	Findings
Wildgrube (1988)[56]	• Adult IBS patients (n=40)	• Enteric coated PMO vs. placebo × 2 weeks • Oro-cecal transit (lactulose 3-hr breath hydrogen) • Total GI transit time (Carmine red)	• Oro-cecal transit increased from 43 to 86 min. vs. placebo 56 to 64 (P<0.05) • Whole intestinal transit time increased from 39.0 to 46.5 hr. vs. placebo 8 to 8 (P<0.05) • No change in stool frequency • Decreased breath hydrogen production from 17,005 to 12,718 ppm/3 hr. vs placebo 13,908 to 11,820 (P<0.05)
Micklefield (2000)[49]	• Healthy adults (n=6)	• Gastroduodenal manometry to measure migrating motor complex • Enteric vs. non-enteric coated PMO (90 mg) combined with caraway oil (50 mg)	• Increase in duodenal contractions with enteric- vs. non-enteric coated capsules
Goerg(2003)[53]	• Healthy volunteers (n=12)	• 90 mg PMO (0.1 mL) or 50 mg caraway oil vs. placebo vs. 10 mg cisapride vs. 10 mg butylscopolamine given in randomized order with 2-day washout • Lactulose breath test (10 mL)	• Prolonged orocecal transit time with PMO vs. placebo (85.0 ± 7.8 min vs. 65.0 ± 6.1, P=0.004) based on 15 ppm over baseline value
Micklefield (2003)[51]	• Healthy volunteers (n=24)	• Gastroduodenal manometry to study intra-duodenal PMO: 90 mg and caraway oil	• During Phase I and II: No PMO effect on the duodenum • During Phase III: PMO decreased frequency of contractions (particularly within the duodenum)
Mizuno (2006)[44]	• Adult patients undergoing upper double contrast barium study (n=420)	• Nonrandomized, (n=205) given PMO: 10 mL of 1.6% solution and (n=215) given water • Degree of spasm and contrast filling of	• Less duodenal spasms in PMO group vs. Controls: 0.96 ± 0.05 vs 1.47 ± 0.0 (P<0.001)

Reference	Population	Methods	Findings
		distal duodenal loops of duodenum blindly scored (0-3 range, indicating none to severe)	• PMO inhibited barium flow to distal duodenum (P<0.001)

Unless otherwise indicated data is presented as mean ± standard deviation.

Table 4

Peppermint Oil (PMO) Effect on Human Colonic Function

Reference	Population	Methods	Findings
Duthie (1981)[59]	• Healthy subjects (n=6)	• Open label randomized to 0.2 mL PMO or placebo • Given 0.5 mg neostigmine and 15 min later motility measured by triple lumen motility catheter	• PMO inhibited motor activity for a mean of 12 min (P<0.05 vs placebo)
Taylor (1983)[87]	• Healthy subjects (n=14)	• Given either PMO 0.2 mL (n=6) or 0.1 mL citral (found in citrus oils) (n=8) following stimulation of motility by neostigmine • Rectosigmoid motility measured using triple lumen tube	• Complete inhibition of motor activity by both oils
Rogers (1988)[88]	• Healthy subjects (n=5)	• Given neostigmine to simulate motility followed 30 min. later by crossover of PMO 0.1 mL in 20 mL normal saline vs. placebo (saline) • Distal colonic manometry	• 4/5 subjects had cramps/pain/urge to defecate after PMO associated with high amplitude (150-390 mm Hg) pressure waves • Activity (motility) index with PMO > placebo
Sparks (1995)[58]	• Adult patients undergoing barium enema (n=141)	• Double blind study with randomization to PMO (30 mL placed in the barium and 10 mL in the enema tube; n=70) or barium alone (n=71) • Incomplete studies (n=3) and those receiving hyoscine (n=14) subsequently excluded • Assessed colonic spasm (present vs. absent) and exam quality (excellent, good, poor) • Patient symptom questionnaire	• 39/60 (65%) controls vs. 23/64 (36%) PMO with spasm (P<0.001) • No marked difference in study quality • No marked difference in patient symptoms/ acceptability
Asao (2003)[57]	• Adult patients undergoing barium enema (n=383)	• Assigned to: 1) No treatment (n=97); 2) hyoscine IM (n=105); 3) PMO (30 mL of 8 mL PMO in 100 mL water) via enema tube n=90; 4) PO (30 mL of 8 mL PMO in 100 mL water) in barium • Radiologist blinded to treatment assessed spasm in ascending, transverse, descending colon graded none, mild, severe	• PMO via enema tube reduced spasms throughout the colon vs. no treatment • PMO as effective as hyoscine given IM PMO

Reference	Population	Methods	Findings
		• Blinded radiologist assessed for spasm	

Unless otherwise indicated data are presented as mean ± standard deviation.

TABLE 5

Peppermint Oil Usage During Endoscopic Procedures

Reference	Population	Design	Findings
Leicester (1982)[62]	• Adult patients undergoing colonoscopy (n=20)	• PMO administered during colonoscopy • Primary objective: Relief of colonic spasm	• Colonic spasm relieved within 30 seconds in all patients
Asao (2001)[61]	• Adult patients undergoing colonoscopy (n= 445)	• Open label study of PMO (n=409) vs. control (n=36) • 8 mL PMO and 0.2 mL Tween 80 mixed in 1 L water. Given throughout colon and patients repositioned as needed. • Primary objective: Control of colonic spasm. • Colonic spasm assessed during colonoscopy (graded 0-3 indicating no movement (contractions) to severe spasm)	• Satisfactory (Grade 0 or 1) spasmolytic effect seen in 362 (88.5%) of PMO vs. 12 (33.3%) control (P<0.0001).an time to PMO onset 21.6 ± 15 sec (tested in n=31). Effect continued for at least 20 minutes (assumed - not measured based on colonoscopy time)
Yamamoto (2006)[54]	• Adult patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) (n=40)	• 4 groups: Group 1, 20 mL 1.6% PMO to papilla (n=10); Group 2, 40 mL 1.6% PMO to antrum and papilla (n=9); Group 3, 20 mL 3.2% PMO to papilla (n=10); Group 4, 20 mL 3.2% PMO to antrum and papilla (n=10). Compared with historical group (n=20) • Primary objective: To investigate PMO as an antispasmodic for ERCP • Endoscopist's subjective duodenal motility scores during ERCP graded 0-3 indicating none to severe. • Number of duodenal movements per minute	• Subjective score of grade 0 or 1 made in 7 (70%) of Group 1, 6 (66.7%) of Group 2, 8 (80%) of Group 3, and 5 (50%) of Group 4 vs. 11 (58.8%) in Controls. • Non-significant reduction in duodenal contractions with PMO (6.1 ± 3.8 to 4.4 ± 2.9 per minute, P=0.39) with no differences between groups

Reference	Population	Design	Findings
Shavakhi (2012)[63]	• Adult patients undergoing colonoscopy (n=65)	• Double blind randomized study • Given PMO premedication (n=33) vs. placebo (n=32) 4 hrs. prior to colonoscopy • Primary objective: Efficacy (total procedure time and time required for intubation to the cecum) of enteric-coated PMO as orally administered antispasmodic premedication before colonoscopy	• PMO vs. Placebo decreased: – Total procedure time (minutes) 12.2 ± 1.8 vs 15.9 ± 2.8 (P<0.001) – Cecal intubation time (minutes) 6.87 ± 1.63 vs. 10.6 ± 2.8 (P<0.001) More patients 30/33 (90%) receiving PMO vs. 6/32 (19%) receiving placebo willing to repeat the colonoscopy
Sola-Bonada (2012)[55]	• Adult patients undergoing ERCP (n=8)	• Patients received 20 ml of 1.6% PMO to the duodenum • Effectiveness of PMO rated from 0 to 5 indicating absence of effect to disappearance of peristaltic movement	• 7/8 had decreased duodenal peristalsis • PMO effect started in 2-5 minutes of administration
Inoue (2014)[64]	• Adult patients undergoing colonoscopy (n=226)	• Single-blind placebo-controlled • 20 mL (1.6%) L-menthol (n=118) vs. placebo (n=108) sprayed onto colonic mucosa • Primary objectives: Adenoma detection rate • Secondary objective: No peristalsis	• Adenoma detection rate significantly higher with L-menthol (vs. placebo): 71 (60.2%) vs. 46 (42.6%) (P<0.01). • Proportion of patients with no peristalsis after treatment higher with PMO (vs. placebo): 84 (71.2%) vs. 33 (30.9%) (P<0.0001).

Table 6

Peppermint Oil (PMO) Randomized Double Blind Controlled Trials for Adult Irritable Bowel Syndrome (IBS)

Reference	Population	Design	Findings	Adverse Events
Rees (1979)[89]	• Adults with IBS (n=18); 2 withdrawals	• Double blind cross-over trial comparing PMO 0.2 mL 1-2 caps TID vs placebo × 3 weeks • Primary objective: Overall symptoms graded from on 5-point scale (+2 to −2 being excellent to terrible)	• More subjects had excellent or good outcomes while on PMO vs. placebo [9 (50%) vs. 2 (12.5%)], P< 0.01	• PMO with heartburn, n=2
Dew (1984)[90]	• Adults with IBS (n=29)	• Double blind crossover multicenter study comparing PMO 0.2 mL 3-6 caps/day vs placebo × 2 weeks • Primary objective: Severity of daily abdominal symptoms (graded 0-3; asymptomatic to severe)	• More subjects (12/29) on PMO vs. Placebo (3/29) with excellent or good overall abdominal symptoms (P<0.001)	• Not reported
Nash (1986)[66]	• Adults with IBS (n=41) with pain as a major symptom; 8 withdrawals: 6 failed to complete diary cards and 2 because of nausea and vomiting with PMO	• Double blind crossover study: PMO 0.2 mL 2 caps TID vs placebo × 2 weeks each • Primary outcome: Daily pain recorded on visual analogue scale and 4 category scale (0-3; “no pain” to “a great deal of pain”)	No difference in primary outcomes (raw data not presented)	• PMO with nausea/ vomiting, n=2 • PMO with heartburn, n=6
Wildgrube (1988)[56]	• Adult IBS patients (n=40)	• Double-blind randomized study	• Median scores for fullness decreased from 39.0 to 27.5 vs.	• “Heartburn or belching either did not occur or if it did was minimal”

Reference	Population	Design	Findings	Adverse Events
	• 1 placebo dropout	• PMO vs. placebo × 2 weeks • Primary outcome: Compared fullness, flatulence, bowel sounds, abdominal pain from the 1st to 2nd week	placebo 42 to 44; flatulence from 50 to 28.5 vs. placebo 46 to 47; bowel sounds from 34.0 to 22.5 vs. placebo 34 to 33; and abdominal pain from 25.0 to 16.5 vs. placebo 24 to 30; all (P<0.05) • See also Wildgrube in Table 3	(unclear which group) • Slight burning during defecation, n= 5 (unclear which group)
Liu (1997)[91]	• Adults with IBS (n=110); 9 withdrawals	• Double-blind parallel group study: PMO 187 mg TID to QID (n=52) or placebo (n=49) × 4 weeks • Primary Objective: Response in 5 symptoms graded on 4-point scale (+2 marked improvement to −1 worsening of symptoms) at one month	Higher proportion of subjects with PMO vs. placebo with a marked or moderate improvement in pain [41 (79%) vs. 21 (43%)], distention [43 (83%) vs. 14 (29%)], stool frequency [43 (83%) vs. 16 (33%)], borborygmi [38 (73%) vs. 15 (31%)], and flatulence [41 (79%) vs. 11 (22.5%)], all comparisons P < 0.05.	• PMO with heartburn, n=1; skin rash, n=1
Capanni (2005)[92]	Adult IBS (n=178); 5 withdrawals	• Double-blind parallel group study PMO 225 mg 2 cap bid (n= 91) vs. placebo (n=87) × 12 weeks • Primary objective: Global improvement in IBS symptoms	• Proportion with global IBS symptom improvement greater in PMO (73/91) vs. placebo (31/87), P<0.02	• Placebo drop out for 'non-IBS related reasons,' n=2 • PMO drop out for 'non-IBS related reasons,' n=1; heartburn, n=2
Cappello (2007)[93]	• Adults with Rome II IBS (n=57)	• Double-blind parallel group study: PMO 225 mg 2 caps BID (n=24) vs. placebo (n=26) × 4 weeks • Primary objective:	• 18 (75%) of the patients in the PMO group vs. 10 (38%) placebo had a >50% reduction of total IBS symptoms score at week 4 (P<0.01).	• PMO with prolonged heartburn, n=1

Reference	Population	Design	Findings	Adverse Events
		Remission of IBS symptoms (>50% improvement of the overall IBS symptom score from baseline to 4 and 8 weeks).	• 13 (54%) PMO subjects vs. 3 (11%) placebo subjects had a >50% reduction in total IBS symptoms score at week 8 (P<0.01).	
Merat (2010)[94]	• Adults with Rome II IBS (n=90); 30 withdrawals	• Double-blind parallel group study of PMO 187 mg (0.2 mL) TID (n=27) vs. placebo (n=33) × 8 weeks • Primary objective: Number of patients free from abdominal pain or discomfort	• Greater proportion free from abdominal pain or discomfort at week 8 in PMO group (14/33) vs placebo (6/27) (P < 0.001).	• No significant adverse events reported • No differences in adverse event frequency between groups
Alam (2013)[95]	• Adults with Rome II IBS (n=74); 9 withdrawals	• Double-blind parallel group study of PMO 2 mL TID (n=33) vs. placebo (n=32) × 6 weeks • Primary objective: Assess changes in symptoms and quality of life at 3 week intervals and 2 weeks after treatment completed	• No significant difference at 3 weeks • PMO improved abdominal pain (4.94 ± 1.30; mean ± SD) vs. placebo (6.15 ± 1.93; P<0.001) at 6 weeks. • No significant difference 2 weeks after treatments ended • No improvements in quality of life	• No significant adverse events occurred
Cash (2016)[96]	Adults with Rome III IBS-diarrhea or IBS-mixed (n=72)	• Randomized double blind trial PMO 180 mg TID (n=35) vs placebo (n=37) × 4 weeks • Primary objective: Change from baseline in the Total IBS Symptom Score after 4	• Total IBS Symptom Score decreased more relative to baseline in PMO vs. placebo (40.0% vs 24.3%, P=0.025)	• No significant differences between groups

Reference	Population	Design	Findings	Adverse Events
		weeks of therapy		

Unless otherwise indicated data are presented as mean ± standard deviation.

Table 7

Peppermint Oil (PMO) Randomized Controlled Trials for Childhood Functional Abdominal Pain

Reference	Population	Design	Findings	Adverse Events
Kline (2001)[72]	• Childhood IBS and FAP; n=50; 8 withdrawals	• Double-blind parallel group study comparing PMO 187 mg or 0.1mL/capsule; 2 capsules TID (>45kg) or 1 capsule TID (30-45 kg) (n=21) vs. placebo (n=21) × 2 weeks • Primary objective: Achieving a “better” or “much better” symptom score at 2 weeks	A greater number of subjects receiving PMO vs. placebo achieved a better or much better symptom score [15 (71%) vs. 9 (42.8%), P<0.01]	• No adverse events identified
Asgarshirazi (2015)[73]	• Children with FAP (n=120); 32 excluded because they didn’t complete the trial	• Three group unblinded parallel randomized study comparing PMO 187 mg TID (BID for children < 45 kg) (n=34) vs. probiotic/ prebiotic tablet (*Bacillus coagulans* and fructooligosaccharides) (n=29) vs. placebo (1 mg folic acid) (n=25) × 1 month • Primary objective: Assessment of abdominal pain severity (0-10 scale), duration, and frequency after one-month	• Decrease in pain duration (26.2 ± 11.6 vs. 51.6 ± 23.7 minutes, P<0.001), severity (3.1 ± 1.4 vs. 4.2 ± 1.3, P<0.01), frequency (2.0 ± 1.0 vs. 3.4 ± 1.4 episodes per week, P<0.001) greater with PMO compared with placebo	• No adverse events identified

FAP = Functional abdominal pain

Table 8

Peppermint Oil (PMO) Randomized Double Blind Controlled Trials for Functional Dyspepsia

Reference	Population	Design	Findings	Adverse Events
Madisch (1999)[74]	Adults with functional dyspepsia (n=120); 2 withdrawals	• Double-blind randomized 4 week study comparing PMO/ Caraway oil (90mg/50mg) (n=60) vs. cisapride (10 mg tid) (n=58) × 4 weeks • Primary objective: Mean reduction in pain score using a visual analogue scale	No significant differences between groups (4.6 vs. 4.6)	• Frequency of adverse events similar; PMO, n=12; cisapride, n=14
May (2000)[76]	• Adults with functional dyspepsia (n=96)	• Double-blind randomized trial comparing PMO/ Caraway oil () vs. placebo × 28 days • Primary outcome was intra-individual change in pain intensity; sensation of pressure, heaviness, and fullness; global improvement using a clinical global impressions item 2) on day 29	• Average intensity of pain was reduced further relative to baseline in the PMO/ Caraway oil group vs. placebo (40% vs. 22%, P<0.005)) • Sensation of pressure, heaviness, and fullness was reduced further relative to baseline in the PMO/ Caraway oil group vs. placebo (43% vs. 20%, P<0.005) • Using CGI item 2, more patients receiving PMO/ Caraway oil vs. placebo were described as much or very much improved (67% vs. 21%, P<0.005).	• PMO adverse events unattributed to study drug, n=5
Madisch (2004)[75]	• Adults with	• Double-blind, randomized, placebo-	• PMO vs. placebo at 4 weeks had	• No differences

Reference	Population	Design	Findings	Adverse Events
	functional dyspepsia	controlled trial comparing herbal combination (contains bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root, and lemon balm) vs. placebo. Four treatment groups random herbal vs. placebo 4 week treatment period combinations. • Primary objective: Standardized gastrointestinal symptom score at 4 and 8 weeks	lower mean symptom score (6.2 ± 5.1 vs. 12.3 ± 5.6, P<0.001) • PMO for full 8 weeks vs. placebo had a lower mean symptom score (3.9 ± 3.8 vs. ± 9.7 ± 4.9, P<0.001)	between groups

Table 9

Peppermint Aromatherapy Randomized Controlled Trials for Post-operative Nausea

Reference	Population	Design	Findings	Adverse Events
Lane (2012)	Women following a caesarian section (n=35)	• Aromatherapy comparing three groups: peppermint spirits inhalation (n=22) vs. placebo inhalation (n=8) vs. standard antiemetic therapy (n=5) • Primary objective was nausea severity at 2 and 5 minutes after intervention using a 6 point nausea scale	• Greater proportion of participants in the peppermint spirits group had no nausea or only slight nausea at 2 minutes vs. placebo (14 (63.6%) vs. 0) and vs. standard antiemetics (0). • Greater proportion of participants in the peppermint spirits group had no nausea or only slight nausea at 5 minutes vs. placebo (17 (77.2%) vs. 0) and vs. standard antiemetics (0).	• Not reported
Hunt (2013)	• Adults with nausea after ambulatory surgery (n=303); 2 withdrawals	• Randomized trial of aromatherapy of three groups: 1) essential oil of ginger (n=76); 2) blend of ginger, spearmint, peppermint, and cardamom oils (n=74); 3) isopropyl alcohol (n=78); 4) saline (n=73) • Primary objective: Reduction in post-operative nausea using a 0-3 scale at 5 minutes.	• More subjects had an improvement in nausea with the aromatherapy blend vs. saline [61 (82.4% vs. 29 (39.7%), P<0.001] and vs. alcohol [61 (82.4%) vs. 40 (51.3%), P<0.001)] • No difference found between ginger vs. blend	• Not reported
Sites (2014)	• Adults with postoperative nausea and/or vomiting (n=42)	• Single blind randomized control trial comparing controlled breathing alone (n=16) vs. peppermint aromatherapy (n=26) • Primary objective was absence of	• No differences between groups in resolving nausea [10 (62.5%) vs. 15 (57.7%), P=0.76)]	• Not reported

Reference	Population	Design	Findings	Adverse Events
		nausea 10 minutes after intervention		