

## Research Article

# Peppermint Oil: Clinical Uses in the Treatment of Gastrointestinal Diseases

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**Abstract**

Peppermint oil has been used for centuries as a remedy for nausea, indigestion, and a host of other medical symptoms. Over the course of the past several years, studies have looked at the benefit of peppermint oil in Irritable Bowel Syndrome, functional dyspepsia and endoscopy and barium-induced spasm of the gastrointestinal tract. The benefit of peppermint oil is thought to be due to anti-spasmodic effects, as well as anti-inflammatory and anti-bacterial effects. Although more research may be beneficial, peppermint oil shows evidence justifying a more expanded use in gastrointestinal disease management. This review focuses on the physiology and recent literature illustrating potential use of peppermint oil.

**INTRODUCTION**

Peppermint oil is derived from the peppermint plant, a cross between water mint and spearmint, which is indigenous to Europe and North America but now grown throughout the world. Chemically, peppermint oil is made up of primarily menthol and the structurally similar compound menthone [1]. Although peppermint oil is most commonly associated with its use in flavoring or fragrance, it has long been used as a home remedy for a variety of symptoms such as nausea, indigestion, and headaches [1]. Since 1979, peppermint oil has been clinically studied for symptomatic treatment of certain gastrointestinal conditions, including Irritable Bowel Syndrome (IBS), dyspepsia, and in preparation for endoscopic procedures [1,2]. Additionally, there is some promising data suggesting that peppermint oil may be beneficial via anti-spasmodic, anti-inflammatory and anti-bacterial properties [3-5]. These properties, combined with a relatively minimal side effect profile make it a favorable treatment option. This article will address the use of peppermint oil in irritable bowel syndrome, functional dyspepsia, and endoscopy-induced spasm by first reviewing the pertinent physiology of peppermint oil in relation to each, followed by a discussion of the available clinical data.

**IRRITABLE BOWEL SYNDROME**

Irritable Bowel Syndrome is a functional gastrointestinal illness affecting between 5-20% of the world's population

[6]. Clinically, IBS is defined by recurrent abdominal pain or discomfort occurring at least 3 days a month in the last 3 months, associated with two or more of: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in the form (appearance) of stool [7]. The treatment of IBS can be quite complex given a poor understanding behind the exact etiology and an association with increased rates of psychiatric conditions, namely depression and anxiety [8,9]. With pharmacologic management primarily focused on symptomatic control, there are also a number of complementary and alternative medicine treatments being practiced and reviewed for IBS. Peppermint oil is one of these treatment approaches to IBS currently gaining attention based on its documented physiologic effects and efficacy in randomized controlled trials.

**Physiology**

The use of peppermint oil in the treatment of IBS is largely based on its documented effects as a spasmolytic agent. Early studies on peppermint oil using electrophysiology in a guinea pig model showed that peppermint oil exerts an effect on potential-dependent calcium channels by decreasing the peak current amplitudes while also increasing the rate of current decay; in this manner, peppermint oil has a mechanism of action resembling that of a dihydropyridine calcium channel antagonist [10]. By reducing the calcium influx, peppermint oil is able to induce smooth muscle relaxation within the gastrointestinal tract. In order to

achieve this effect, the peppermint oil must be formulated with a delayed release enteric coating to ensure delivery to the lower GI tract and colon [11,12]. Additionally, inappropriate release of the peppermint oil in the upper GI tract induces relaxation of the lower esophageal sphincter leading to resultant reflux and heartburn, the primary adverse effects of peppermint oil [12]. While a number of enteric coated formulations of peppermint oil are available, the two formulations in particular which have been predominately used in clinical trials are Colpermin (McNeil Healthcare, Dublin, Ireland) and Mint oil (Cadigroup, Rome, Italy) [13]. The main difference between these two products is the way in which the peppermint oil is prepared. Colpermin uses 0.2mL of peppermint oil in an enteric coated capsule, whereas Mint oil uses 225mg of peppermint oil and 45mg of Natrasorb, a particular tapioca starch that absorbs oils in solid powder [14]. There are no currently available studies comparing the efficacy of delivery for the two formulations. The dose of peppermint oil however, is essentially equivalent (0.2mL = 200mg) between the two products. As a result, one would expect any differences in outcomes to be attributed to the level of dosing used in the various trials, and not to the choice of formulation.

The activity of peppermint oil on calcium channels may be more specifically related to the mediation of TRPM8, a member of the melastatin subfamily of transient receptor potential (TRP) cation channel super family, which can be activated by cold temperatures and also menthol, the main constituent of peppermint oil [15]. The activation of the TRPM8 channels induces contractions of smooth muscle in a manner inversely proportional to the temperature and also through a mechanism involving the activation of Rho-kinase; Rho-kinase inhibits myosin light change (MLC) phosphatase, allowing for phosphorylation of MLC kinase and subsequent smooth muscle contraction [16]. These TRPM8 channels have been found in dorsal root ganglia, vagal afferent neurons, the gastric fundus, colon, and small intestine [3]. There is, however, some controversial evidence concerning the ability of menthol to induce a release of intracellular calcium stores from the TRPM8 channels, as one study found that menthol-induced calcium release was potentiated at high temperatures, opposite of the cold activation of TRPM8 [4]. Additionally these researchers found that menthol-induced calcium release primarily originates from the endoplasmic reticulum and Golgi bodies, in contrast to the TRPM8 receptors which they found to be localized to the plasma membrane [4]. When combined with the knowledge that there is significant species and region-related variability of these channels, any direct effect of peppermint oil on this specific TRPM8 channel cannot be concluded [3]. Despite this, there are a number of other channels in the TRP super family that can also function as release channels on intracellular membranes that may serve as the site of action for menthol [4]. Regardless of the specific channel responsible for the effects of peppermint oil, it appears evident that peppermint oil does, indeed, have a physiological effect on gut motility through mediating calcium release and enhancing smooth muscle contraction.

Apart from the spasmolytic effects, peppermint oil also has mild efficacy as both an anti-inflammatory and anti-microbial agent. Using lipopolysaccharide (LPS)-stimulated monocytes from healthy volunteers, Juergens et al were able to study the anti-inflammatory activity of L-menthol on the levels of

arachidonic acid metabolism into LTB<sub>4</sub> (leukotriene B<sub>4</sub>) and PGE<sub>2</sub> (Prostaglandin E<sub>2</sub>), which served as markers for the lipooxygenase and cyclooxygenase pathways, respectively [5]. Results showed that L-menthol significantly inhibited LTB<sub>4</sub> (-64.4 ± 10%), PGE<sub>2</sub> (-56.6 ± 8%), and IL-1β (-64.2 ± 7%) production at low doses (therapeutic range of 10<sup>-7</sup> g/ml) and in a dose-dependent manner, thereby serving as an anti-inflammatory agent [11]. Peppermint oil has also been documented to have antibacterial activity in vitro against over 22 different bacteria including gram-positive cocci and rods and gram-negative bacteria [17-19]. Additionally, peppermint oil was shown to inhibit the proliferation of *Helicobacter pylori*, *Salmonella enteritidis*, *Escherichia coli* 0157:H7, and both methicillin sensitive and methicillin resistant *Staphylococcus aureus* in liquid cultures [20]. Given the relationship between small intestinal bacterial overgrowth (SIBO) and IBS, the antimicrobial activity of peppermint oil in the small intestine may provide another mechanism for symptomatic improvement in IBS [21].

### Clinical Trials

In 1979, Rees et al originally documented the use of peppermint oil for the treatment of IBS by enrolling 18 patients with IBS (no identification of subtype provided) to receive either 0.2 mL of peppermint oil in gelatin capsules (Elanco LOK caps, Eli Lilly and Co Ltd/Indianapolis/USA) or placebo for a three-week trial period [2]. Despite showing no effect on stool frequency, symptom analysis revealed a lower total and mean daily symptom score, however, this did not achieve clinical significance due to the small number of participants.

Nearly 20 years later, Pittler and Ernst published one of the first critical reviews and meta-analysis on peppermint oil in IBS [22]. They identified eight randomized control trials, five of which were placebo-controlled, double-blind trials. Overall, the meta-analysis suggested a significantly positive effect of peppermint oil compared with placebo in symptomatic treatment ( $P < 0.001$ ), based on three studies with a positive effect and two without any significant difference; however, the authors concluded that significant methodological flaws associated with the majority of the studies excluded establishing a benefit of peppermint oil beyond a reasonable doubt. The main reasons for the methodological flaws were the lack of correctly using accepted clinical features for the diagnosis of IBS (leaving only 9% diagnosed using the correct criteria), short treatment course (6 of 8 trials were ≤ 1 month of treatment), and failure to use a wash-out period in crossover trials to account for carry-over effects [22].

Subsequently, a number of randomized control trials have demonstrated a beneficial effect of peppermint oil for IBS. Liu et al randomized 110 patients with IBS to receive Colpermin (one capsule containing 0.2mL of peppermint oil) (McNeil Healthcare, Dublin, Ireland) or placebo three to four times daily, 15-30 minutes before meals, for one month showing that symptomatic improvements with peppermint oil were significantly better than placebo ( $p < 0.05$ ) [23]. Results indicated that of the 52 patients in the Colpermin group, 41 (79%) experienced decreased severity, 29 (56%) were pain free, 43 (83%) had reduced stool frequency, and 41 (79%) had decreased flatulence. In comparison, of the 49 in the placebo group, 21 (43%) patients noticed a decrease in

severity of pain, 4 (8%) were pain free, 16 (32%) with reduced stool frequency, and 11 (22%) with decreased flatulence. These findings were supported by the results of another randomized double-blind placebo controlled trial of 90 patients with IBS using Colpermin (one capsule containing 0.2 mL of peppermint oil) or placebo three times daily for 8 weeks; after 8 weeks of therapy, 14 patients (42%) in the Colpermin group were free from abdominal pain or discomfort compared to only 6 (22%) in the placebo group ( $p < 0.001$ ) [24]. Further, the severity of abdominal pain was significantly decreased and the quality of life significantly increased in the Colpermin group compared to placebo. While the overall summary score for quality of life was not significant ( $p = 0.194$ ), the significant improvements in quality of life after 8 weeks of treatment were noted improvements in bodily pain ( $p = 0.035$ ), general health ( $p = 0.046$ ), social functioning ( $p = 0.046$ ), and role limitations due to emotional problems ( $p = 0.028$ ) [24]. A major limitation of this study, however, was nearly a 30% loss to follow-up [24].

In an attempt to better control for potential confounders, Cappello et al. also performed a randomized double blind placebo controlled trial assigning 57 patients with IBS to receive two capsules twice daily, one hour before meals of either enteric-coated Mint oil (Cadigroup, Rome, Italy) or placebo for 4 weeks with a follow-up 4 weeks after treatment. Participants in this study were determined to have IBS by the Rome II criteria, however, the patients were only included if small intestinal bacterial overgrowth, lactose intolerance, and celiac disease had been previously excluded [14]. Results indicated that at 4 weeks of treatment 75% (18/24) of patients in the peppermint oil group showed >50% reduction in their baseline IBS symptoms ( $p < 0.01$ ) compared to 38% (10/26) in the placebo group ( $p < 0.05$ ). 4 weeks after treatment, the reduction in IBS symptoms remained significant in the peppermint oil group at 54% (13/24) ( $p < 0.05$ ), but without a significant change in the placebo group [14]. Overall, the results of this study support the use of peppermint oil as a potential therapy for IBS. A particular strength of this study is the inclusion of participants who met proven criteria for IBS and who have also had exclusion of potential confounding conditions such as lactose intolerance or small intestinal overgrowth that have been implicated to explain between 5-50% of IBS cases [25,26].

The most comprehensive data concerning the use of peppermint oil in IBS comes from a recent systematic review and meta-analysis by Khanna et al. This analysis improved on the meta-analysis by Pittler and Ernst [25] by excluding crossover studies unless data was provided before the first cross over, including studies with trial lengths of 2-3 months, and also using studies with defined inclusion criteria for active disease [13]. Nine studies evaluating 726 patients met inclusion criteria with five trials using Colpermin (0.2mL peppermint oil, equivalent to 200mg) 1 capsule TID and the others using variable doses of Mint oil (225mg peppermint oil) ranging from 2 capsules BID to 4 capsules TID. Among these, five randomized placebo controlled trials reported the global improvement of IBS symptoms or improvement in abdominal pain, showing peppermint oil was significantly superior to placebo for global improvement of IBS symptoms (RR 2.23, 95% CI 1.78-2.81) and improvement in abdominal pain (RR 2.14, 95% CI 1.64-2.79) [13]. Of note, the patients in the peppermint oil group were more likely to

experience adverse events, most commonly heart burn; however these events were mild and transient. Intention to treat analysis was also performed from this meta-analysis yielding a number needed to treat (NNT) of 3 for global improvement in symptoms at 2 to 12 weeks and a NNT of 4 for improvement in abdominal pain at 2 to 8 weeks [13]. The authors concluded that overall the results of this meta-analysis support the short-term efficacy of peppermint oil for the treatment of IBS; however, the specific subtypes of IBS were not defined and further study is needed to identify variations in response between these subtypes.

In a recent monograph on the management of IBS and chronic idiopathic constipation, the American College of Gastroenterology Task Force concluded that that peppermint oil is superior to placebo in improving IBS symptoms [27]. Additionally peppermint oil carries no greater risk for adverse effects than placebo. The basis for the weak recommendation is a lack of differentiation between the types of IBS patients recruited, risk of bias in many studies, and a significant heterogeneity in the studies showing a significant benefit.

## Summary

In summary, peppermint oil appears to be a safe and well-tolerated treatment for symptomatic improvement in IBS. Peppermint oil's main efficacy in IBS is through its ability to act as a spasmolytic agent, altering smooth muscle contraction in the GI tract. In addition, peppermint oil has also been shown to have activity as an anti-inflammatory and anti-microbial agent suggesting respective potential efficacy modulating cytokine inflammatory pathways and /or gut microbiome effects on dietary exposures, intestinal sensory afferents or intestinal motility. While long-term data on the efficacy of peppermint oil is not available, clinicians should consider peppermint oil as a treatment option for those suffering from IBS do to its proven short-term efficacy and minimal adverse effects in randomized control trials.

The use of peppermint oil in pregnancy and breast-feeding is considered likely safe by the National Institute of Health on their educational website Medline Plus [27]. This is based on the classification of peppermint oil as a food additive, which is generally recognized as safe (GRAS) according to the Food and Drug Administration [29]. However, the higher doses of peppermint oil used for medicinal purposes have not been extensively regulated, as peppermint oil is sold as a dietary supplement. Still, there have not been reported data on the toxic effects of peppermint oil in pregnancy or breast-feeding [30]. Further, peppermint oil (60mL of 0.5% peppermint oil twice daily for 2 weeks) has even been used in randomized trials in pregnancy women to treat pruritis gravidarum without any significant side effects [31]. Based on this evidence, peppermint oil is likely a safe treatment option for pregnant and breast-feeding women when used in moderation.

## FUNCTIONAL DYSPESIA

Functional dyspepsia is a common and often frustrating diagnosis for both clinicians and patients alike due to the ambiguity of its symptoms, limited understanding of pathophysiology and absence of a gold standard treatment. Patients present with a variety of symptoms including epigastric

pain or discomfort, epigastric fullness, early satiety, post prandial nausea, belching and abdominal bloating [32]. According to the Rome III criteria, functional dyspepsia is defined as having two of the following: postprandial fullness, early satiety or epigastric burning for at least 3 months duration and in the absence of organic disease causing the symptoms. The current criteria have even developed new subdivisions for symptoms related to meals and those unrelated to meals. Postprandial distress syndrome is characterized by postprandial fullness and early satiety, whereas epigastric pain syndrome is characterized by epigastric pain and burning [33].

## Physiology

It is currently believed that functional dyspepsia is a biopsychosocial disorder involving a complex interplay of several mechanisms [32]. Possible etiologies include infection with *Helicobacter pylori*, abnormal gastrointestinal motility, altered visceral sensation and psychosocial factors [32,34,35]. As such, several treatment options have been investigated, all with mixed therapeutic response rates; these treatments include *H. pylori* eradication (6-14%), prokinetics (18-45%), proton pump inhibitors (7-10%), histamine-type-2-receptor antagonists (8-35%), tricyclic antidepressants (64-70%) and serotonin reuptake inhibitors (no better than placebo) [33]. Complicating matters more, symptoms are non-specific and often do not reflect the underlying pathophysiology, making treatment selection difficult and costly [31]. Over recent years, a shift in attention to Complementary and Alternative Medicine (CAM) modalities has occurred, as patients perceive these treatments as more "natural" and generally safer. [1] Peppermint oil containing formulations are, perhaps, the most extensively studied CAM.

## Clinical Trials

Several studies have shown benefit of peppermint oil on the underlying pathophysiology of functional dyspepsia [36-41]. Impaired gastric relaxation, antral hypo-motility and abnormal gastric emptying have been suggested as the predominating etiology to patients suffering from dysmotility-like dyspepsia [42,43]. In vitro studies have shown peppermint oil to function as a spasmolytic to gastrointestinal muscle through an antagonistic effect on calcium channels [10]. Goerg et al demonstrated that 90 mg of peppermint oil caused complete inhibition of gallbladder emptying ( $P < 0.04$ ) and prolongation of small intestinal transit time as compared to placebo (a non-enteric-coated capsule containing 0.4mL of 0.9% NaCl) (85 minutes vs 65 minutes, respectively) ( $P < 0.004$ ) [38]. Mizuno et al proved peppermint oil (PO) to have a significant spasmolytic effect in the esophagus (PO vs control:  $0.35 \pm 0.04$  vs  $0.65 \pm 0.04$ ,  $P < 0.001$ ), lower stomach (PO vs control:  $1.20 \pm 0.05$  vs  $1.42 \pm 0.11$ ,  $P < 0.001$ ) and duodenal bulb (PO vs control:  $0.96 \pm 0.05$  vs  $1.47 \pm 0.05$ ,  $P < 0.001$ ) in patients orally administered peppermint oil (10mL of 3.2% Peppermint oil solution) versus control (12ml of water) prior to a barium suspension undergoing a double-contrast barium meal examination [44].

Inamori et al evaluated the early effects of peppermint oil on gastric emptying with continuous real-time  $^{13}\text{C}$  breath test (BreathID system, Oridion Medical, Jerusalem Israel) after administration of a test meal alone and in combination with

0.64mL of peppermint oil [37]. Patients who ingested the test meal and peppermint oil combination versus test meal alone demonstrated a significant acceleration in gastric emptying ( $P < 0.0367$ ) primarily occurring during the early phase ( $P < 0.0218$ ) [37]. Dalvi et al also found that subjects fed a radio labeled test meal in conjunction with peppermint oil (0.2mL in 25mL of water) had an accelerated gastric emptying rate as compared to those not given peppermint oil [41].

A combination herbal medication STW 5 (Iberoast<sup>®</sup>, Steigerwald Arzneimittelwerk GmbH, Darmstadt, Germany) is frequently utilized for treatment of functional dyspepsia. Peppermint leaf extract constitutes one of nine extracts (bitter candy tuft, peppermint leaf, chamomile flower, liquorice root, angelica root, caraway fruit, milk thistle fruit, Melissa leaf and greater celandine herb) in STW 5. Schemann et al, evaluated region specific effect of various concentrations of STW-5 (concentrations ranging from 32 to 512 $\mu\text{g}/\text{mL}$ ) and its components on the gastric fundus, corpus and antrum of guinea pig stomach [43]. STW5 dose dependently decreased muscle tone in gastric fundus ( $P < 0.05$ ) and corpus ( $P < 0.05$ ), while enhancing antral contractility ( $P < 0.05$ ); unfortunately when evaluated separately, peppermint leaf extract (concentrations ranging from 24 to 188 $\mu\text{g}/\text{mL}$ ) had inconsistent effects provoking both mixed contraction and relaxation responses in the proximal stomach. In the distal stomach, anon-statistically significant enhancement in muscle contraction amplitude was observed in a portion of antral muscle strips but, these results were not sustained or concentration dependent. This may signify that the effect of STW 5 on gastric motility is likely the result of synergism between extracts [43].

In a double-blind, placebo-controlled multicenter trial, May et al investigated a fixed combination of peppermint oil (90mg) and caraway oil (50mg)(Enteroplant, Dr Willmar Schwabe GmbH, Karlsruhe, Germany) administered three times daily versus placebo in 45 patients diagnosed with non-ulcer dyspepsia [45]. After 4 weeks of treatment, improvement in both pain intensity and prognosis and severity of the disorder as assessed by the Clinical Global Impressions Scale (CGI) were significantly improved ( $P < 0.015$  and  $P < 0.008$ , respectively) in the peppermint oil/caraway oil group as compared to placebo [45]. In a follow up double-blind, placebo-controlled trial by the same investigators, the therapeutic efficacy of the same peppermint oil/caraway oil combination administered at a lower dosing frequency (twice daily) versus placebo was evaluated in 96 patients with functional dyspepsia after 28 days of treatment. At the conclusion of the study, there was a statistically significant difference in reduction of pain intensity (40% vs 22%) ( $P < 0.0003$ ), sensation of pressure, heaviness and fullness (44% vs 22%) ( $P < 0.0005$ ) and global improvement as assessed by CGI (67% vs 21%) ( $P < 0.00005$ ) [46].

In a prospective, randomized, double-blind multicenter trial conducted by Freise et al, the equivalence and efficacy of two fixed mixed preparations of peppermint oil and caraway oil in 223 patients with non-ulcer dyspepsia was evaluated. Patients were treated with either enteric coated capsules (270mg peppermint oil and 150mg caraway oil: test formulation) or an enteric soluble formulation (108mg peppermint oil and 60mg caraway oil: reference formulation) over 4 weeks. A statistically

significant improvement in pain frequency was observed in the test formulation ( $P < 0.04$ ), while a statistically significant decline in epigastric pain intensity (measured on a visual analog scale ranging from 0- no pain to 10- extremely strong pain) was observed in both groups ( $P < 0.001$ ) [47].

In a randomized controlled double-blind study, the therapeutic equivalence of a fixed combination preparation (Enteroplant) of peppermint oil (180mg peppermint oil and 100mg caraway oil, 1 capsule twice daily) versus the prokinetic agent cisapride (10mg, 1 tablet three times daily) in 120 patients with functional dyspepsia over a 4-week period was evaluated. A comparable reduction in mean pain score (peppermint oil/caraway oil combination: 4.62 vs cisapride: 4.60,  $P < 0.021$ ), frequency of pain (peppermint oil/caraway oil combination: 4.65 vs cisapride: 4.16,  $P < 0.0034$ ), and other dyspeptic symptoms (assessed by the Dyspeptic Discomfort Score and CGI) was seen in both test groups ( $P$  value not listed) [48].

Several studies support the use of STW-5 (Iberogast®) in the treatment of functional dyspepsia. In a recent meta-analysis, data was pooled from 3 RCTs observing the safety and efficacy of Iberogast® (138 patients) vs placebo (135 patients) in patients with functional dyspepsia [49]. In all 3 trials, patients were given 20 drops (1 mL) of Iberogast® vs placebo over a 4-week period. The majority of patients (124) reported acid regurgitation as their predominating baseline symptom. At the conclusion of the study, the Iberogast® group reported their most bothersome symptom as "mild" or "absent" as compared to placebo ( $P < 0.01$ ). In addition, difference in patients reporting their most bothersome symptom as "severe" and "very severe" at the termination of the study was also significant between the Iberogast® group (7%) and placebo (26%) ( $P < 0.001$ ). In patients treated with Iberogast®, treatment was significantly related to the outcome for the following symptoms: abdominal cramps, epigastric pain, nausea, acid regurgitation, retrosternal troubles and vomiting ( $P < 0.001$ ). Of the remaining symptoms assessed, no significant correlation was found for in appetite, fullness, retching or early satiety [49].

Peppermint oil may also have benefit in treating nausea as a predominating symptom of functional dyspepsia. This was evaluated in a trial assigning patients to receive peppermint oil inhalation or placebo for post-operative nausea in patients undergoing major gynecological surgery [50]. The peppermint oil group had a nausea rate of 66% compared to 100% in the control group, however this finding was non-significant ( $P$  value not listed) [50,51]. Lane et al also reported reduced nausea in woman post cesarean section treated with peppermint oil aromatherapy (POA) as compared to an inhaled inert placebo and standard antiemetic therapy (SAT), as assessed at 2 minutes (POA vs placebo:  $P < 0.000$ , POA vs SAT:  $P < 0.001$ ) and 5 minutes post treatment (POA vs placebo:  $P < 0.000$ , POA vs SAT:  $P < 0.003$ ) [52].

## Summary

Peppermint oil appears to be a viable treatment option for patients suffering from functional dyspepsia, a disorder plagued by disabling symptoms and lack luster results with standard care. Patients with dysmotility predominating symptoms may

find the most relief from peppermint oil treatment through its spasmolytic properties, which facilitate both gastric relaxation and gastric emptying. Additionally, peppermint oil has anti-emetic benefits. While future studies are undoubtedly needed to evaluate the long-term efficacy and side effects of peppermint oil, physicians should be strongly encouraged to utilize peppermint oil in the treatment of functional dyspepsia, as current evidence supports its short-term efficacy and overall tolerability.

## ENDOSCOPY-INDUCED SPASM

Esophageal and colonic spasms during endoscopic procedures are a common and challenging aspect of endoscopy. Many endoscopists use a variety of medications to help reduce these spasms, to improve visualization and to minimize patient discomfort. Antispasmodic drugs such as hyoscine-N butylbromide (delivered oral, sublingual, or intramuscular) or glucagon (delivered intravenously) are used to obtain relaxation of the gut lumen; however these agents are associated with many serious side effects. Hyoscine-N butylbromide has been linked to cardiovascular events and cardiac arrhythmias as well as anticholinergic disturbances in urinary, salivary and ocular systems. Glucagon also imposes the risk of delayed hypoglycemia, as well as gastrointestinal symptoms including acute nausea and vomiting [35,50]. New evidence suggests that oral or topically infused/sprayed peppermint oil may be a safe and effective alternative to these drugs.

## Physiology

Recent studies have shown the effectiveness of peppermint oil in reducing smooth muscle contraction and providing relaxation of the gastrointestinal tract during colonoscopy, ERCP, and barium enema examinations. The physiology behind this phenomenon is thought to be secondary to the menthol action against the smooth muscle calcium channels [53-57]. Furthermore, due to the low adverse effect profile of peppermint oil, its use has been subject to more clinical investigations.

## Clinical Trials

In a randomized double-blind, double-dummy, controlled study by Hiki et al, the antispasmodic effects of 16 ml intraluminally administered peppermint oil (Miyazawa Medical Co., Tokyo, Japan), compared to intramuscularly administered hyoscine-N-butyl bromide (20 mg) in 100 patients undergoing upper endoscopy were evaluated [39]. Peppermint oil had a significant increase in the opening ratio (percent change in the pyloric ring before and after treatment) and a significant decrease in the closing ratio (percent change in the diameter between the maximally and minimally opened pyloric ring). In addition, the time required for the disappearance of gastric antrum contraction rings in patients treated with peppermint oil versus hyoscine-N-butylbromide was reduced ( $p < 0.0001$ ). In contrast to the patients receiving peppermint oil, those who received hyoscine-N-butylbromide experienced a variety of side effects including dry eyes, urinary retention and blurry vision [39].

Hiki and colleagues conducted another study to determine the effective dose and safety of L-menthol (Nihon Pharmaceutical Co., Tokyo, Japan) during endoscopy by looking directly at gastric

peristalsis using video-recorded endoscopic figures [53]. This phase II, multicenter, double-blinded study enrolled one hundred thirty-one patients who were randomly assigned to receive a 20ml solution with three different concentrations of L-menthol or placebo (0.0% n=34, 0.4% n=32, 0.8% n=35, and 1.6% n=30). Patients were extensively monitored starting 3 minutes before, during and at least 30 minutes after completion of the procedure. The primary outcome was to achieve absence of peristalsis 75 to 105 seconds after administration of the solution and again before the completion of endoscopy. Results of the study showed dose dependent suppression of peristalsis ( $P < 0.001$ ). Patients who received higher dosages (0.8%  $P = 0.015$  and 1.6%  $P = 0.009$ ) had significantly higher suppression of peristalsis compared to placebo group. There was no difference in rate of adverse events between all four groups [53].

A similar study conducted by Yamamoto et al looked at the use of peppermint oil (Miyazawa Medical, Tokyo, Japan) during endoscopic retrograde cholangio pancreatography (ERCP) [54]. Forty patients were divided into four groups, according to site of administration and peppermint oil concentration. Groups 1 and 3 received the solution only around the duodenal papilla, as compared to group 2 and 4, which received it at the antrum of the stomach, and around the duodenal papilla. All four groups received 20ml of peppermint oil solution; groups 1 and 2 received lower concentrations of 1.6% compared to 3.2% received by groups 3 and 4. Authors used previously recorded archives and selected 16 patients who underwent ERCP with 1 mg of intravenously administered glucagon as historical controls. ERCP was successfully performed with peppermint oil alone in 91.4% of patients, and it was equally effective amongst all groups. No difference was noted on motility reduction between the groups ( $P = 0.327$ ). Two patients, each in groups 1 and 4 required additional glucagon or hyoscine-N-butylbromide. Serious complications related to peppermint oil did not occur [54].

Another non-randomized prospective study done by Imagawa and colleagues [55], compared the efficacy of peppermint oil to Hyoscine butyl bromide (Buscopan® 20 mg; Nippon BoehringerIngelheim, Hyogo, Japan) and glucagon (Glucagon G Novo® 1 mg; Novo Nordisk Pharma, Tokyo, Japan) during esophagogastroduodenoscopy (EGD). The peppermint oil was prepared by mixing peppermint oil (Yoshida pharmaceutical, Tokyo, Japan) with distilled water and catalyst sorbitan monostearate (Wako Pure Chemical Industries, Osaka, Japan), a 20ml solution with 1.6% peppermint oil. The primary outcome of this study was to compare antispasmodic scores in elderly ( $\geq 70$  years old) or non-elderly ( $< 70$  years old) patients. Antispasmodic score (1-5, where 5 represent no spasms) was defined by the degree of spasm of the antrum and difficulty of biopsy. A total of 8,269 EGDs were performed with 1,893 patients received peppermint oil, 6,063 received Hyoscine butyl bromide (HB) and 157 patient received glucagon. No significant difference was observed in the non-elderly group between peppermint oil and HB groups (mean score  $\pm$  standard deviation:  $4.025 \pm 0.925$  vs.  $4.063 \pm 0.887$ ,  $P = 0.23$ ). Among the elderly patients, the scores between peppermint oil ( $n = 1,294$ ,  $4.073 \pm 0.917$ ) and HB ( $n = 1,480$ ,  $4.064 \pm 0.921$ ,  $P = 0.83$ ) groups were similar, which was significantly better than the glucagon group ( $n = 69$ ,  $3.797 \pm 0.933$ ,  $P < 0.05$ ) [55].

Peppermint oil's effectiveness in reducing colonic spasm was also studied by Asao et al. Four hundred and nine patients received a 200 ml solution containing 8 ml of peppermint oil, 1 L of water and 0.2 ml of Tween 80 (Polysorbate 80, synthetic substance used to stabilize aqueous formulations of medications for parenteral administration-Wako Pure Chemical Industries Ltd, Osaka, Japan). Thirty six patients were selected into a control group, receiving a 200 ml solution that contained only water and Tween 80. The solution was administered via hand pump attached to the accessory channel of the colonoscope. Patient positioning was changed in order distribute the solution throughout the colon. Improvement in spasm was seen in 88.5% of treated group compared to 33.3% in the control group ( $p < 0.0001$ ) [56].

Peppermint oil has also been investigated for its efficacy as a spasmolytic during a double-contrast barium enema (DCBE). Another study done by Asao compared peppermint oil to intramuscular injection of 20mg Buscopan® (Boehringer Ingelheim Limited Consumer Healthcare), a commonly used spasmolytic [57]. Patients ( $n = 383$ ) were divided into four groups: peppermint in barium ( $n = 91$ ), peppermint in tube ( $n = 90$ ), Buscopan® ( $n = 105$ ), or no treatment ( $n = 97$ ). The peppermint oil solution was prepared by mixing 8ml of peppermint oil with 0.2 ml of Tween 80 (Wako Pure Chemical Industries Ltd, Osaka, Japan) and 100 ml water. Thirty milliliters of peppermint solution was mixed with barium or was placed in the enema tube for respected groups. All patients were evaluated for presence of spasm on spot films. The percent of patients without any spasm in the entire colon was 41.8, 37.8, 38.1 and 13.4 for the peppermint in tube, peppermint in barium, Buscopan®, and no treatment groups respectively. There was no difference between patients receiving peppermint in barium versus in tube. Compared to Buscopan®, peppermint oil had the same spasmolytic effect in the transverse and descending colon. Furthermore, peppermint oil showed to be significantly superior to Buscopan® in the caecum and the ascending colon ( $p < 0.005$ ) [57].

## Summary

Gastrointestinal spasms related to endoscopic procedures pose the challenge of patient discomfort and reduced visualization of anatomy. Contrary to peppermint oil, currently used anti-spasmodic agents are accompanied by a number of side effects. The aforementioned studies show promise in the efficacy of peppermint oil in reduction of endoscopy-related spasm and suggest it may be a more favorable alternative to the current treatment options used. Further investigations, including cost-effective analyses, may be beneficial in determining the precise role of peppermint oil in endoscopy.

## INFLAMMATORY BOWEL DISEASE

There is limited data available concerning the use of peppermint oil in inflammatory bowel disease (IBD). A literature search of PubMed using the search terms "peppermint oil" and "inflammatory bowel disease" returns no articles specifically addressing the topic; however, a Google search for these same topics [58] returns a large number of patient testimonials for peppermint oil on various IBD support forums. This section will seek to explain two possible pathways through which peppermint oil may exert a beneficial effect in IBD.

**Table 1:** Review of Clinical Studies for Functional Dyspepsia.

Study	Design/Objective	Patients	Medication	Outcomes
Freise <i>et al.</i> <sup>47</sup>	Prospective, randomized, double-blind multicenter trial to compare the efficacy of two mixed preparations of peppermint oil and caraway oil	223 patients with non-ulcer dyspepsia	Test formula (270mg peppermint oil and 150 mg caraway oil) in enteric coated capsules  Reference formula (108mg peppermint oil and 60 mg caraway oil) as enteric soluble formulation	Over 4 weeks:  Test formulation showed a significant improvement in pain frequency (p<0.04)  Both groups showed decline in epigastric pain intensity (p<0.001)
Goerg <i>et al.</i> <sup>38</sup>	Ultrasonic determination of gallbladder emptying and assessment of orocecal transit time using lactulose H2 breath test	12 healthy volunteers	90mg peppermint oil vs. 50mg caraway oil vs. placebo	Peppermint oil: 1) inhibited gall-bladder emptying compared to placebo (p<0.04) 2) prolonged small intestinal transit time compared to placebo (p =0.004)
Inamori <i>et al.</i> <sup>37</sup>	Randomized, two-way crossover study assessing the effect of peppermint oil on gastric emptying using 13C breath test	10 healthy male volunteers	0.64mL peppermint oil	Peppermint oil caused a significant acceleration in gastric emptying (p<0.0367)
Madisch <i>et al.</i> <sup>36</sup>	Randomized, double-blind controlled trial comparing Enteroplant versus cisapride for functional dyspepsia	60 Enteroplant 58 Cisapride	Enteroplant (90mg peppermint oil and 50mg caraway oil, 1 capsule twice daily)  Cisapride (10mg, 1 tablet three times daily)	Comparable reduction seen in both groups for (enteroplant vs cisapride): 1) Mean pain score (4.62 vs 4.60, p<0.021) 2) Frequency of pain (4.65 vs 4.16, p<0.0034) 3) Other dyspeptic symptoms (p value not listed)
May <i>et al.</i> <sup>45</sup>	Double-blind, placebo controlled multicenter trial in patients with non-ulcer dyspepsia comparing Enteroplant to placebo	19 Enteroplant 20 placebo	Enteroplant Three times daily for 4 weeks	Enteroplant group showed improvement in both pain intensity (p<0.015) and severity (p<0.008) [assessed by CGI – Clinical Global Impressions Scale]
May <i>et al.</i> <sup>46</sup>	Double-blind, placebo controlled multicenter trial in patients with non-ulcer dyspepsia comparing Enteroplant to placebo	48 Enteroplant 48 placebo	Enteroplant Twice daily for 4 weeks	Enteroplant group showed improvement in both pain intensity (40% vs 22%, p<0.0003) and global improvement assessed by CGI (67% vs 21%, p<0.00005)
Mizuno <i>et al.</i> <sup>44</sup>	Random recruitment of patients undergoing double-contrast barium meal examination (DCBM) administered peppermint oil	250 randomly selected participants 215 sex and age matched controls	10mL peppermint oil (3.2%) vs. 12ml water	Peppermint oil had significant spasmolytic effect in: 1) Esophagus (0.35 vs 0.65, p<0.001) 2) Lower stomach (1.20 vs 1.42, p<0.001) 3) Duodenal bulb (0.96 vs 1.47, p<0.001)

As mentioned earlier, the physiologic mechanism of peppermint oil in the treatment of IBS is largely related to its activity on calcium channels, more specifically the TRPM8 channel. Within this same TRP family, the transient receptor potential vanilloid type 1 (TRPV1) has been shown to be involved in regulation of neurogenic inflammation within the colon [59]. Evidence suggesting a role of TRPV1 in IBD comes from animal studies using mice with chemically induced colitis, which showed both macroscopic and microscopic improvements in inflammation when treated with the TRPV1 antagonist, capsazepine [60]. The TRPV1 channel appears to act in opposite to the TRPM8 channel, as it is activated by a number of stimuli including capsaicin, lipoxygenase products, leukotriene B4, high temperatures (>43C), acidic pH (<5.3), intracellular redox states, and electrostatic charge; however, the exact mechanism of action of these ligands is not fully understood [61]. Despite these major

differences, a number of similarities exist between the TRPV1 channel and other members of the TRP family, including TRPM8, which shares a ligand binding site with 36% similarity of amino-acid identity [62]. Given the well-characterized role of the TRPV1 channel, there is limited data to suggest a role for peppermint oil in this pathway; however, given the contrasting mechanisms of action between the TRPM8 and TRPV1 channels and some similarity in their structure, it is plausible that alterations in activation or inhibition of one of these channels could alter the activity of the other channel through as of yet undiscovered pathways.

Another potential role of peppermint oil in the treatment of IBD pertains to the antimicrobial activity of peppermint oil and its effect on the gut microbiota. The etiology of IBD is extremely complicated and a number of potential pathways have been identified. Most recently, increasing evidence suggests that

**Table 2:** Review of Clinical Studies for Endoscopy-Induced Spasm.

Study	Design/Objective	Patients	Medication	Outcomes
Asao et al <sup>56</sup>	Prospective trial on the efficacy of peppermint oil administration during colonoscopy	409 patients in peppermint oil group  36 patients in control group	200ml of solution (8ml peppermint oil and 0.2mL of Tween 80 per 1L of water)	Satisfactory spasmolytic effect was seen in 88.5% of peppermint oil patients versus 33.3% of control patients
Asao et al <sup>57</sup>	Prospective trial on the efficacy of peppermint oil during double-contrast barium enema (DCBE)	383 DCBEs with positive results from occult blood testing assigned to 4 groups: peppermint in barium solution (n=91), peppermint in enema tube (n=90), Buscopan (n=105), or no treatment (n=97)	Peppermint solution (100ml water, 8mL peppermint oil, 0.2mL Tween 80)  Buscopan 20mg	Percent of patients with no spasm: no treatment (13.4%) Buscopan (38.1%) peppermint in enema tube (41.8%) peppermint in barium solution (37.8%)  Peppermint oil was equally spasmolytic in transverse and descending colon, however, has stronger effect in cecum and ascending colon (p<0.005)
Hiki et al <sup>39</sup>	Randomized double-blind, double-dummy, controlled trial comparing peppermint oil to hyoscine-N-butylbromide	100 patients undergoing upper endoscopy	Peppermint oil (16mL intra-luminal)  hyoscine-N-butylbromide (20mg intramuscular)	Peppermint oil: 1) Significant increase in opening ratio* 2) Significant decrease in closing ratio^ 3) Decreased time to disappearance of gastric contraction rings (p<0.0001) 4) Decreased adverse effects
Hiki et al <sup>53</sup>	Phase II, multicenter, double-blind study for efficacy and safety of L-menthol preparation	131 patients undergoing upper endoscopy	20 mL solution with: 0% L-menthol (n=34) 0.4% L-menthol (n=32) 0.8% L-menthol (n=35) 1.6% L-menthol (n=30)	Significant dose dependent suppression of peristalsis (p<0.001)  Effect greatest for 0.8% (p=0.015) and 1.6% (p=0.009) solutions  No difference in adverse events between groups
Imagawa et al <sup>55</sup>	Non-randomized prospective enrollment of patients undergoing upper endoscopy comparing the efficacy of peppermint oil (PO) as an antispasmodic to hyoscine-N-butylbromide (HB), glucagon (GL), and no antispasmodic (NO)	8,269 endoscopies performed  1,896 PO 6,603 HB 157 GL 156 NO	20ml 1.6% PO	No significant difference was noted between PO and HB on antispasmodic score (4.025 vs 4.063, p=0.23)  Among the elderly (>70 years old) PO and HB groups had similar antispasmodic scores (4.073 vs 4.064, p=0.83), which were significantly better than the GL group (p<0.05)
Yamamoto et al <sup>54</sup>	Non-randomized prospective enrollment of patients undergoing ERCP examining the efficacy of peppermint oil (PO) as an antispasmodic	40 patients divided into 4 groups	Group 1: 20ml 1.6% PO around duodenal papilla  Group 2: 20mL 1.6% PO around duodenal papilla and stomach antrum  Group 3: 20mL 3.2% PO around duodenal papilla  Group 4: 20ml 3.2% PO around duodenal papilla and stomach antrum	Peppermint oil equally reduced duodenal motility in all groups  Duodenal movement none or mild in 69.2%  No serious complications related to peppermint oil were reported

\* opening ratio = percent change in pyloric ring before and after treatment

^ closing ratio = present change in diameter between the maximally and minimally opened pyloric ring

inflammation in IBD is related to the cellular death pathway of necroptosis, in which intestinal epithelial dysfunction results in the translocation of bacterial products into the bowel wall [63]. These bacterial products then activate the Toll-like receptors, TLR3 and TLR4, which increase expression of the inflammatory cytokines, type III interferon and TNF- $\alpha$ , subsequently activating caspase-3 and caspase-8 leading to cell death. Given the documented antimicrobial activity of peppermint oil [64,65] and the role of bacterial pathogens in the inflammatory pathway of IBD, it remains plausible the peppermint oil could potentiate a symptomatic benefit in IBD through alteration in this inflammatory pathway.

## SUMMARY

There is currently insufficient evidence to suggest a beneficial role of peppermint oil in the treatment of IBD. Despite this, there are a number of IBD patient testimonials supporting the use of peppermint oil for symptom alleviation. While this benefit may purely be related to a placebo effect, there is plausible mechanistic support by which peppermint oil could exert an effect in IBD. These include activation and interaction with the TRP family of calcium channels and attenuation of gut inflammation secondary to the antimicrobial activity of peppermint oil. It is doubtful that any favorable effect would be an effective alternative for replacing other proven primary pharmacologic therapies, but we speculate that this might have some valuable adjunctive effects for co-therapy. Clearly, more study is warranted.

## CONCLUSION

In conclusion, peppermint oil has shown promise in the field of gastroenterology. Literature supports peppermint oil as a safe and well-tolerated treatment for symptomatic improvement in IBS. Its effect on smooth muscle contraction, short-term efficacy and minimal side effect profile warrants further long-term investigation of its use. Peppermint oil also appears to be a reasonable treatment option for patients suffering from functional dyspepsia. Its effect is on dysmotility predominating symptoms, through facilitation of gastric relaxation and improved gastric emptying, is proven. The anti-emetic effect of peppermint oil is also beneficial in patients with functional dyspepsia. Gastrointestinal spasms related to endoscopic procedures may also be improved or eradicated with peppermint oil, and without the side effects of currently used medical modalities. Present data suggests however that peppermint oil is a safe and effective therapy for a number of common gastrointestinal disorders. Clearly further studies evaluating its' use as both a primary or adjunctive therapy are warranted.

## CONFLICTS OF INTEREST

Rouzbeh Shams, MD: no disclosure

Edward C Oldfield IV: no disclosures

Jennifer Copare, DO: no disclosures

David A Johnson, MD: Consultant: Pfizer, Takeda, CRH medical, Z pharmaceuticals, Given Imaging, Epigenomics, Janssen/Centacor

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