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TITLE PAGE

Title: Systematic Review and Meta-analysis: Efficacy of Peppermint Oil in Irritable Bowel Syndrome.

Short title: Meta-analysis: Peppermint Oil for IBS.

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Abbreviations:

CI	confidence interval
FDA	Food and Drug Administration
IBS	irritable bowel syndrome

IBS-C	IBS with constipation
IBS-D	IBS with diarrhoea
NICE	National Institute for Health and Care Excellence
NNH	number needed to harm
NNT	number needed to treat
RCT	randomised controlled trial
RR	relative risk

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SUMMARY

Background: Irritable bowel syndrome (IBS) is one of the most common disorders of gut-brain interaction, with a complex pathophysiology. Antispasmodics are prescribed as first-line therapy because of their action on gut dysmotility. In this regard, peppermint oil also has antispasmodic properties.

Aims: We updated our previous meta-analysis to assess efficacy and safety of peppermint oil, particularly as recent studies have cast doubt on its role in the treatment of IBS.

Methods: We searched the medical literature up to 2nd April 2022 to identify randomised controlled trials (RCTs) of peppermint oil in IBS. Efficacy and safety were judged using dichotomous assessments of effect on global IBS symptoms or abdominal pain, and occurrence of any adverse event or of gastro-oesophageal reflux. Data were pooled using a random effects model, with efficacy and safety reported as pooled relative risks (RRs) with 95% confidence intervals (CIs).

Results: We identified 10 eligible RCTs (1030 patients). Peppermint oil was more efficacious than placebo for global IBS symptoms (RR of symptoms not improving = 0.65; 95% CI 0.43-0.98, number needed to treat (NNT) = 4; 95 % CI 2.5-71), and abdominal pain (RR of abdominal pain not improving = 0.76; 95% CI 0.62-0.93, NNT = 7; 95 % CI 4-24). Adverse event rates were significantly higher with peppermint oil (RR of any adverse event = 1.57; 95% CI 1.04-2.37).

Conclusions: Peppermint oil was superior to placebo for the treatment of IBS, but adverse events were more frequent, and quality of evidence was very low. Adequately powered RCTs of peppermint oil as first-line treatment for IBS are needed.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common disorders encountered by gastroenterologists, characterised by recurrent abdominal pain in association with abnormal bowel frequency and/or consistency.[1] Patients are divided into four subgroups based on their most common stool pattern: IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), IBS with mixed bowel habits (IBS-M), or IBS unclassified (IBS-U).[2] IBS is a chronic relapsing and remitting disease,[3] which affects between 4% and 10 % of the general population,[4,5] and can occur at any age, although it is more common among younger individuals and women.[4,6] Its high prevalence results in not only a substantial economic burden on the healthcare system and society,[7] estimated at between £1.3 and £2 billion per year in a recent UK study,[8] but also a considerable impact on quality of life,[9] a higher prevalence of psychological illness,[10] and a reduction in work productivity.[11]

The pathophysiology of IBS is not fully understood,[12] but it is classified as a disorder of gut-brain interaction (DGBI).[13] The term "gut-brain interaction" underlines the existing anatomical and bi-directional communication between the central nervous system and the gut, mediated by the autonomic nervous system, and explains some of the recognized mechanisms involved in the pathophysiology of IBS such as abnormal motility,[14] and altered visceral sensitivity,[15] which can be triggered by emotional or environmental stress. This complex pathophysiology is one of the reasons why we are still far from being able to treat patients with drugs targeting pathophysiological mechanisms, rather than symptoms.

Recommended first-line drug therapies for IBS include laxatives, anti-diarrheal drugs, and antispasmodic drugs,[16-18] with evidence for their efficacy coming from randomized controlled trials (RCTs) and meta-analyses,[19-21] although in the case of laxatives and anti-diarrheal drugs evidence for a benefit on global IBS symptoms is still lacking. Peppermint oil also has antispasmodic properties due to its active ingredient, L-menthol, which relaxes

gastrointestinal smooth muscle by antagonizing calcium channel receptors.[22,23] In addition, peppermint oil may have analgesic effects, via transient receptor potential channels.[23-25] Our prior meta-analysis examining the efficacy of peppermint oil in IBS concluded it was more efficacious than placebo,[21] with a number needed to treat (NNT) of 2.5. However, these trials were conducted prior to recommendations for the design of treatment trials for DGBI,[26] or used outdated diagnostic criteria for IBS. In addition, safety could not be assessed due to incomplete reporting of adverse events and due to the small number of trials the effect on global IBS symptoms or abdominal pain was pooled together, rather than examined separately. Finally, more recent RCTs have cast doubt on whether peppermint oil is truly an effective therapy for IBS.[27,28] We, therefore, updated our previous meta-analysis in order to examine the efficacy and safety of peppermint oil in IBS, in light of these, and other, trials published in the intervening years.

METHODS

Search Strategy and Selection Criteria

We updated a previous meta-analysis.[21] We searched MEDLINE (2007 to 2nd April 2022), EMBASE and EMBASE Classic (2007 to 2nd April 2022), and the Cochrane central register of controlled trials, as well as clinicaltrials.gov for unpublished trials or supplementary data for potentially eligible RCTs. We searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2007 and 2022 to identify trials published only as abstracts. Finally, we used bibliographies of all obtained articles to perform a recursive search.

Placebo-controlled trials examining the effect of peppermint oil in adults (≥18 years) with IBS of any subtype were eligible (Table 1). The first period of cross-over RCTs were also eligible if they provided efficacy data prior to cross-over. We considered definitions of IBS that included either a clinician's opinion, or those that met specific symptom-based criteria, for example the Rome criteria. We required a minimum treatment duration of 4 weeks.

Two investigators (MRI and ACF) conducted the literature search, independently from each other. We identified studies on IBS with the terms: *irritable bowel syndrome* or *functional diseases, colon* (both as medical subject heading and free text terms), or *IBS*, *spastic colon*, *irritable colon*, or *functional* adj5 *bowel* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *peppermint oil*, *menthol*, *mentha piperita*, *colpermin*, or *mintec* (as medical subject heading or free text terms). We did not apply language restrictions. Two investigators (MRI and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We

obtained all papers that appeared relevant, evaluating them in more detail against our eligibility criteria, using pre-designed forms. We translated foreign language papers, where required. We resolved disagreements between investigators (MRI and ACF) by discussion.

Outcome Assessment

We assessed the efficacy of peppermint oil in IBS, compared with placebo, in terms of failure to respond to therapy, according to the proportion of patients failing to achieve an improvement in either global IBS symptoms or abdominal pain severity at trial completion, but also according to each of these endpoints separately, as our primary outcomes. Other secondary outcomes assessed included total number of people experiencing any adverse event, as well as total number of people experiencing gastro-oesophageal reflux symptoms, if reported.

Data Extraction

Two investigators (MRI and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global IBS symptoms improved or not improved, abdominal pain improved or not improved). Where studies reported a dichotomous assessment of response to therapy according to these endpoints, for example a 50-point decrease in the IBS-SSS or a 30% improvement in abdominal pain severity (approximating Food and Drug Administration (FDA)-recommended endpoints in drug trials in IBS), we extracted these data from the article. For studies reporting mean global IBS symptom or abdominal pain severity scores at baseline together with follow-up mean symptom severity scores and standard deviation (SD) for these endpoints for each intervention arm, we imputed dichotomous responder and non-responder data using methodology previously described by Furukawa *et al*.[29,30] For example,

a 30% improvement in abdominal pain severity is derived from the formula: number of participants in each treatment arm at final follow-up x normal standard distribution. The latter corresponds to (70% of the baseline mean score – follow-up mean score) / follow-up SD. We contacted first and senior authors of studies to provide additional data for individual trials, where required.

We also extracted the following data for each trial, where available: country of origin, setting (primary, secondary, or tertiary care), proportion of female patients, criteria used to define IBS, and proportion of patients with IBS according to subtype. We also recorded the duration of treatment, release profile, and dosing schedule of peppermint oil or placebo. We extracted data as intention-to-treat analyses, assuming all dropouts to be treatment failures (i.e., no response to peppermint oil or placebo), wherever trial reporting allowed. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable data.

Risk of Bias and Quality of Evidence Assessment

We used the Cochrane risk of bias tool to assess risk of bias at the study level.[31] Two investigators (MIR and ACF) performed this independently; we resolved disagreements by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes. We summarised the quality of the evidence for the efficacy of peppermint oil in IBS using GRADE criteria.[32]

Data Synthesis and Statistical Analysis

We used a random effects model to pool data,[33] to give a more conservative estimate of the efficacy of peppermint oil in IBS. We expressed the impact of peppermint oil versus placebo as a relative risk (RR) of global IBS symptoms or abdominal pain not improving, separately along with 95% confidence intervals (CIs), where if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of peppermint oil over placebo. This approach is the most stable, compared with a RR of cure or improvement, or using the odds ratio, for some meta-analyses.[34] We also summarised adverse events data with RRs and 95% CIs. We calculated the NNT, and the number needed to harm (NNH), with a 95% CI, using the formula NNT or NNH = 1 / (assumed control risk x (1 – RR)).

We assessed heterogeneity between studies using both the χ^2 test, with a P value <0.10 used to define a significant degree of heterogeneity, and the I^2 statistic. The I^2 ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and ≥75% high heterogeneity.[35] We used Review Manager version 5.4.1 (The Cochrane Collaboration 2020) to generate forest plots of pooled RRs for primary and secondary outcomes with 95% CIs. We assessed funnel plots for evidence of asymmetry, where there were sufficient studies (≥10),[36] and therefore possible publication bias or other small study effects, using the Egger test.[37]

RESULTS

In the previous meta-analysis,[21] we identified four RCTs recruiting 392 patients.[38-41] The updated search generated 182 citations, eight of which appeared relevant and were retrieved for further assessment (Figure 1). Of these, we excluded two that did not fulfil eligibility criteria, leaving six new eligible trials.[27,28,42-45] Therefore, there were 10 eligible trials including 1030 patients,[27,28,38-45] 525 of whom were allocated to peppermint oil. Agreement between investigators for trial eligibility was perfect (kappa statistic = 1.00). Detailed characteristics of individual RCTs, including endpoints used, or imputed, are provided in Table 2. All trials were published in full. We obtained extra data from investigators of two RCTs.[27,44] Risk of bias for all included trials is reported in Table 3. Three RCTs were at low risk of bias across all domains.[28,42,44]

Effect on Either Global IBS Symptoms or Abdominal Pain

All ten trials provided data for this endpoint.[27,28,38-45] There were 285 (54.3%) of 525 patients randomised to peppermint oil with unimproved global IBS symptoms or abdominal pain after treatment compared with 365 (72.3%) of 505 patients receiving placebo (RR of global IBS symptoms or abdominal pain persisting with peppermint oil versus placebo = 0.65; 95% CI 0.47 to 0.88, NNT = 4; 95% CI 3 to 11.5) (Figure 2). There was a high degree of heterogeneity between studies (I^2 = 93%) and evidence of funnel plot asymmetry (Egger test, p = 0.0007). Eight RCTs used small intestinal-release peppermint oil,[27,38-42,44,45] and one trial also randomised some patients to ileocolonic-release.[28] When only these trials were considered in the analysis the treatment effect increased slightly (RR = 0.64; 95% CI 0.47 to 0.87, NNT = 4; 95% CI 3 to 11). All three low risk of bias trials,[28,42,44] containing 351 patients, provided either global IBS symptom or abdominal pain data. However, peppermint oil was not superior to placebo in this analysis (RR = 0.86; 95% CI 0.62 to 1.20).

Effect on Global IBS Symptoms

Seven RCTs, containing 756 patients, 388 of whom received peppermint oil, provided extractable dichotomous data.[27,28,38,40,41,44,45] Overall, 217 (55.9%) of 388 patients assigned to peppermint oil therapy reported unimproved global IBS symptoms following therapy, compared with 259 (70.4%) of 368 allocated to placebo. The relative risk of global IBS symptoms persisting with peppermint oil versus placebo was 0.65 (95% CI 0.43 to 0.98) (Figure 3), but with statistically significant heterogeneity between studies (I^2 = 94%, P<0.001). The NNT with peppermint oil was 4 (95 % CI 2.5 to 71). There were too few studies to assess for publication bias. All seven trials used small intestinal-release peppermint oil,[27,28,38,40,41,44,45] although one trial also randomised some patients to ileocolonic-release.[28] When only data for the 693 patients randomised to small intestinal-release peppermint oil or placebo were included in the analysis the treatment effect increased slightly (RR = 0.65; 95% CI 0.45 to 0.94, NNT = 4; 95% CI 3 to 24). Only two RCTs at low risk of bias, containing 261 patients, provided global IBS symptom data.[28,44] In this analysis, peppermint oil was not superior to placebo for global IBS symptoms (RR = 0.77; 95% CI 0.28 to 2.08).

Effect on Abdominal Pain

Four trials reported data on effect on abdominal pain,[28,39,42,44] and data were imputed for a further three studies.[27,43,45] In total, these seven trials recruited 748 patients, 383 of whom received peppermint oil. Overall, 181 (47.3%) patients receiving peppermint oil had no improvement in abdominal pain following therapy, compared with 218 (59.7%) of 365 allocated to placebo. The relative risk of abdominal pain persisting with peppermint oil versus placebo was 0.76 (95% CI 0.62 to 0.93) (Figure 4), with moderate heterogeneity detected between studies (I^2 = 56%, P = 0.03). The number needed to treat with peppermint oil was 7 (95 % CI 4 to 24). Again, there were too few studies to assess for publication bias.

Six trials, recruiting 611 patients, used a small intestinal-release formulation of peppermint oil.[27,28,39,42,44,45] When only these trials were included in the analysis, the treatment effect was similar but the 95% CI widened (RR = 0.75; 95% CI 0.58 to 0.98, NNT = 7; 95% CI 4 to 89). All three low risk of bias trials,[28,42,44] containing 351 patients, provided abdominal pain data. Peppermint oil remained superior to placebo in this analysis (RR = 0.78; 95% CI 0.61 to 0.99, NNT = 7; 95% CI 4 to 155).

Adverse Events

There were seven studies reporting adverse events data,[27,39-42,44,45] including 720 patients. In total, 58 (17.1%) of 340 patients allocated to peppermint oil experienced any adverse event, compared with 46 (12.1%) of 380 assigned to placebo. The relative risk of experiencing any adverse event among those taking peppermint oil was 1.57 (95% CI 1.04 to 2.37) (Figure 5), with no heterogeneity detected between studies (I^2 = 13%, P = 0.33). The number needed to harm with peppermint oil was 14.5 (95% CI 6 to 206.5). Most adverse events were mild, with the commonest reported including symptoms of gastro-oesophageal reflux, dyspepsia, or flatulence. Eight trials, containing 973 patients, provided data for gastro-oesophageal reflux symptoms, with no heterogeneity between studies (I^2 = 0%, P = 0.44).[27,28,39-42,44,45] These were reported by 83 (17.9%) of 465 patient randomised to peppermint oil, versus 34 (7.7%) of 444 patients receiving placebo (RR = 1.67; 95% CI 1.18 to 2.38, NNH = 19.5; 95% CI 9.5 to 72.5) (Figure 6). Presence or absence of publication bias could not be assessed for safety analyses as there were too few studies.

DISCUSSION

This meta-analysis has evaluated the efficacy of peppermint oil in the treatment of IBS, updating our previous meta-analysis.[21] Six new eligible trials were added meaning that, in total, there were 10 studies and 1030 patients. Our updated results still demonstrate that peppermint oil is more efficacious than placebo in all 10 trials, in terms of improvement in either global symptoms or abdominal pain, with a NNT of 4, and for global IBS symptoms alone and abdominal pain alone, according to data from seven RCTs that reported on efficacy according to either of these endpoints, with NNTs of 4 and 7, respectively. When we included only low risk of bias trials in the analysis, peppermint oil was still more efficacious than placebo for abdominal pain alone, but not for either global IBS symptoms or abdominal pain, or global IBS symptoms alone. When we carried out a subgroup analysis including only trials that used small intestinal-release peppermint oil, similar efficacy was observed. The number of patients experiencing any adverse event, as well as gastro-oesophageal reflux symptoms, was significantly higher with peppermint oil compared with placebo, with a NNH of 14.5 and 19.5, respectively.

We used rigorous and reproducible methodology for this systematic review and meta-analysis. We reported our search strategy, which covered not only main bibliographic databases, but also the “grey literature”, such as conference proceedings and clinicaltrials.gov for unpublished data. Two investigators performed eligibility judging and data extraction independently, with all discrepancies resolved, and excellent agreement between them. We used an intention-to-treat analysis, with all dropouts assumed to be treatment failures, and a random effects model in order not to overestimate the efficacy of peppermint oil in IBS. We contacted authors to obtain supplementary data for some studies, as well as information about release profiles of peppermint oil formulations, where this was not stated in the article. We also imputed data from trials that only reported efficacy according to mean symptom scores,[27,43,45] increasing the number of trials, and patients, available for analysis. In our prior meta-analysis, the effect of peppermint oil on global IBS symptoms and

abdominal pain was pooled together to estimate efficacy, rather than being able to be analysed separately as well, unlike in this meta-analysis. In addition, we were able to assess safety of peppermint oil in this update, because most of the newly identified trials reported total numbers of adverse events. We also carried out an analysis concerning the occurrence of gastro-oesophageal reflux symptoms, which are often felt to be a treatment-related side effect of peppermint oil, perhaps due to its effects on smooth muscle in the lower oesophageal sphincter. This issue has not been examined systematically, to our knowledge, before. The current meta-analysis, therefore, represents an advance over our previous study, and other meta-analyses in this field,[46,47] which although they identified similar numbers of studies included data from cross-over trials, irrespective of whether data were reported prior to cross-over.

However, there was moderate to high heterogeneity detected between trials in all our symptom analyses, suggesting that the results should be interpreted with caution. There was evidence of funnel plot asymmetry, or other small study effects, when data from all 10 trials were pooled. Other limitations of this systematic review and meta-analysis are related to the trials themselves, which include small sample sizes, meaning that they are probably underpowered for efficacy, and the fact that only three RCTs were at low risk of bias, due to lack of information concerning the method of generation of the randomisation schedule and/or method of concealment of allocation in six trials. Studies that do not report such information tend to overestimate the efficacy of the active treatment.[48] In addition, many trials are outdated in terms of their methodology, including the use of historical definitions of IBS, failure to judge efficacy according to FDA-recommended endpoints for treatment trials in IBS, and a relatively short duration of treatment of 4 to 6 weeks in several studies. It is also important to point out that peppermint oil has an intrinsic risk of unblinding because of its smell and taste. Even if a placebo is manufactured to be the same size or shape, if the tablet is cut into, it will likely smell or taste “minty”. In this regard, only Capanni *et al.* mentioned that the placebo used in their trial had been imbued with a mint flavour.[40]

The current meta-analysis suggests that peppermint oil is an efficacious treatment for IBS. However, compared with our previous meta-analysis,[21] there is more uncertainty in terms of its efficacy, with a wide confidence interval around the NNTs for global IBS symptoms alone or abdominal pain alone, and high heterogeneity between all studies for either global IBS symptoms or abdominal pain, and between RCTs for global IBS symptoms only. The NNT has also increased from an estimated 2.5 in the prior version to 4 for global symptoms or abdominal pain, 5 for global symptoms, and 7 for abdominal pain. This is, in part due to the results from two recently published trials,[27,28] where no significant differences in efficacy were detected between peppermint oil and placebo. These are particularly relevant, because both trials were conducted using more rigorous endpoints and a contemporaneous definition of IBS.

Current management guidelines in the UK and USA recommend the use of peppermint oil for global IBS symptoms,[16,49] but this guidance was based on the results of prior meta-analyses. Our updated meta-analysis demonstrates that, although peppermint oil was more effective than placebo, there was inconsistency between individual study results, possible publication bias (or other small study effects), few RCTs were at low risk of bias, and there was uncertainty around the effect. As a result, and by GRADE criteria,[32] the quality of evidence would be judged as very low. In addition, adverse events and gastro-oesophageal reflux were significantly more likely with peppermint oil. Finally, given that peppermint oil is likely to be used early on in the treatment of IBS it is important to point out that only one trial was conducted partly in primary care.[44] We would still suggest that peppermint oil be used in IBS, and our meta-analysis demonstrates it is also effective for abdominal pain, an issue that we have not been able to examine previously. However, further adequately powered, and rigorous RCTs, using peppermint oil as a first-line treatment, particularly ones conducted in a primary care setting, and examining efficacy according to IBS subtype are needed.

In summary, this meta-analysis demonstrates that peppermint oil is efficacious for both global IBS symptoms and abdominal pain with NNTs of 4 and 7 respectively. However, uncertainty around

the effect estimate has increased, partly due to the recent publication of two larger, and negative, trials. Given the wide confidence intervals around the effect size now seen when incorporating these more rigorously designed RCTs it is possible that a future large negative trial, when pooled with the existing studies, would demonstrate that peppermint oil is not efficacious in IBS. In addition, adverse events, and specifically gastro-oesophageal reflux symptoms, were significantly more frequent with peppermint oil, and patients should be counselled regarding this. The results of future adequately powered studies will be important in increasing our confidence in the efficacy of peppermint oil in IBS.

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AUTHORSHIP STATEMENT

Specific author contributions: MRI, GI, JN, AJL, PM, CJB, and ACF conceived and drafted the study. MRI and ACF collected all data. MRI and ACF analysed and interpreted the data. MRI and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

Guarantor: ACF is guarantor.

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TABLES

Table 1. Eligibility Criteria.

Randomised controlled trials.
Adults (aged ≥18 years).
Diagnosis of IBS based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.
Compared peppermint oil with placebo.
Minimum duration of therapy of 4 weeks.
Dichotomous assessment of response to therapy in terms of effect on either global IBS symptoms or abdominal pain following treatment.†

*Manning criteria, Kruis score, Rome I, II, III, or IV criteria.

†Preferably patient-reported, but if this was not available then as assessed by a physician or questionnaire data.

Table 2. Characteristics of Randomised Controlled Trials of Peppermint Oil in IBS.

Study	Country and setting	Diagnostic criteria used for IBS, and number (%) with each subtype	Endpoint(s) used*	Sample size (% female)	Release profile and dosing schedule of active therapy (number of patients)	Duration of therapy
Lech 1988 [38]	Denmark, secondary care	Clinical diagnosis, subtype not stated	Improvement in global IBS symptoms	47 (77%)	Small intestinal-release peppermint oil (Mintoil) 200mg t.i.d. (23)	4 weeks
Liu 1997 [39]	Taiwan, secondary care	Clinical diagnosis, subtype not stated	Improvement in abdominal pain	110 (40%)	Small intestinal-release peppermint oil (Colpermin) 187mg t.i.d. or q.i.d. (55)	4 weeks
Capanni 2005 [40]	Italy, secondary care	Rome II, subtype not stated	Improvement in global IBS symptoms assessed by validated questionnaire	178 (75%)	Small intestinal-release peppermint oil (Mintoil) 2 capsules t.i.d. (91)	12 weeks
Cappello 2007 [41]	Italy, secondary care	Rome II, 25% IBS-C, 75% IBS-D	≥50% improvement in global IBS symptom scores from baseline	57 (unclear)	Small intestinal-release peppermint oil (Mintoil) 450mg b.i.d. (28)	4 weeks
Merat 2010 [42]	Iran, tertiary care	Rome II, subtype not stated	Free from abdominal pain or discomfort at study end	90 (75%)	Small intestinal-release peppermint oil (Colpermin) 187mg t.i.d. (45)	8 weeks

Alam 2013 [43]	Bangladesh, tertiary care	Rome II, 100% IBS-D	≥30% improvement in abdominal pain (imputed)	74 (13.5%)	Peppermint oil 2mls t.i.d. (37)	6 weeks
***Cash 2016** [44]	USA, primary and secondary care	Rome III, 53% IBS-D, 47% IBS-M	Any improvement in global IBS symptom severity score Any improvement in abdominal pain or discomfort	72 (75%)	Small intestinal-release peppermint oil (IBgard) 180mg t.i.d. (35)	4 weeks
Mosaffa-Jahromi 2016 [45]	Iran, tertiary care	Rome III, 34% IBS-C, 31% IBS-D, and 20% IBS-M	Free from global IBS symptoms at study end ≥30% improvement in abdominal pain (imputed)	80 (47.5%)	Small intestinal-release peppermint oil (Colpermin) 187mg t.i.d. (40)	4 weeks
Weerts 2020 [28]	Netherlands, secondary, and tertiary care	Rome IV, 22% IBS-C, 44% IBS-D, 21% IBS-M, and 13% IBS-U	Relief of global IBS symptoms ≥30% decrease in the weekly average of worst daily abdominal pain	189 (78%)	Small intestinal-release peppermint oil (Tempocol) 182mg t.i.d. (62) or ileocolonic-release peppermint oil (Tempocol) 182mg t.i.d. (63)	8 weeks

***Nee 2021** [27]	USA, tertiary care	Rome IV, 20% IBS-C, 41% IBS-D, 35% IBS-M, and 4% IBS-U	Moderate or substantial improvement in global IBS symptoms ≥30% improvement in abdominal pain (imputed)	133 (74%)	Small intestinal-release peppermint oil (Pepogest) 180mg t.i.d. (46)	6 weeks

*Full information not reported in published article, but obtained after correspondence with the authors.

Table 3. Risk of Bias of Randomised Controlled Trials of Peppermint Oil in IBS.

Study	Method of Generation of Randomisation Schedule Stated?	Method of Concealment of Treatment Allocation Stated?	Blinding?	No Evidence of Incomplete Outcomes Data?	No Evidence of Selective Reporting of Outcomes?
Lech 1988 [38]	Unclear	Unclear	Low	Low	Low
Liu 1997 [39]	Unclear	Unclear	Low	High	Low
Capanni 2005 [40]	Low	Unclear	Low	Low	Low
Cappello 2007 [41]	Low	Unclear	Low	High	Low
Merat 2010 [42]	Low	Low	Low	Low	Low
Alam 2013 [43]	Low	Unclear	Low	Low	Low
***Cash 2016** [44]	Low	Low	Low	Low	Low
Mosaffa-Jahromi 2016 [45]	Low	Unclear	Low	Low	Low
Weerts 2020 [28]	Low	Low	Low	Low	Low
***Nee 2021** [27]	Low	Low	Low	High	Low

*Full information not reported in published article, but obtained after correspondence with the authors.

FIGURES

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

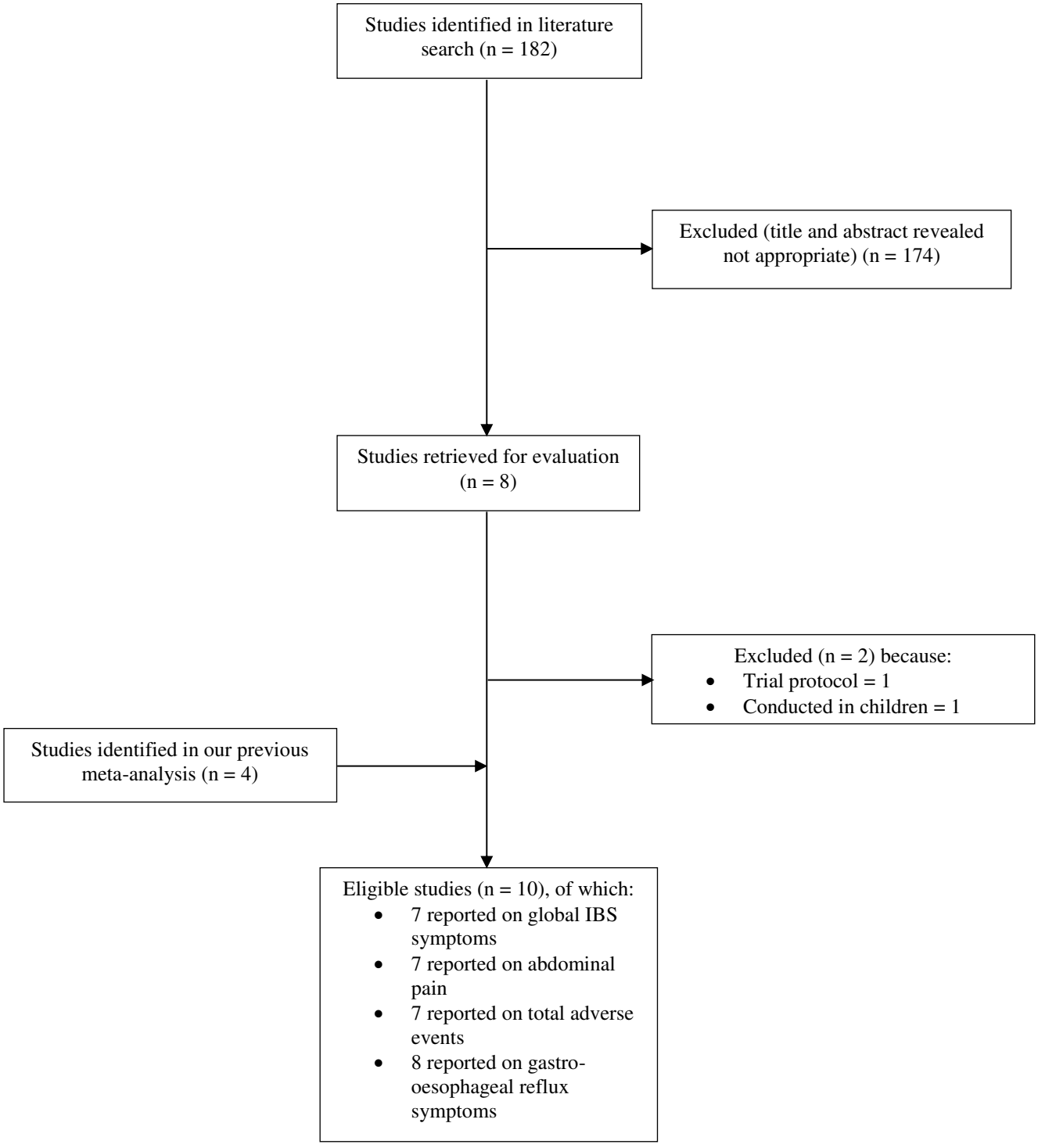

Figure 2. Forest Plot of Randomised Controlled Trials of Peppermint Oil in IBS: Effect on Global IBS Symptoms or Abdominal Pain.

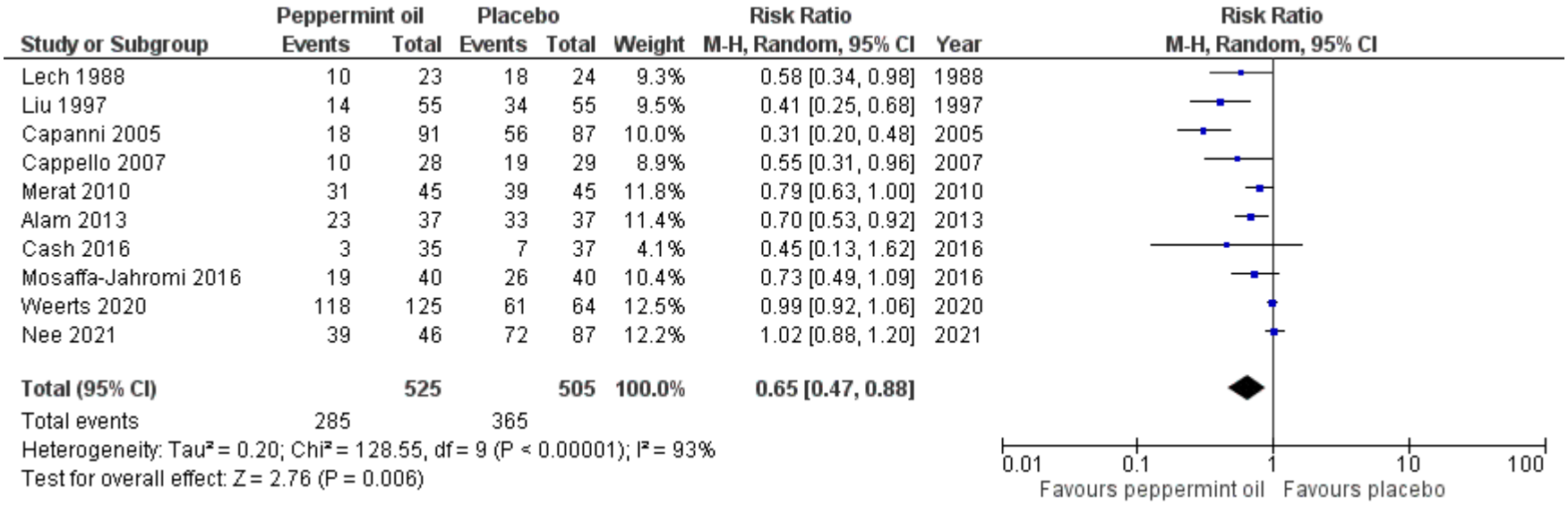

Figure 3. Forest Plot of Randomised Controlled Trials of Peppermint Oil in IBS: Effect on Global IBS Symptoms.

Study or Subgroup	Favours peppermint oil Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Lech 1988	10	23	18	24	14.0%	0.58 [0.34, 0.98]	1988
Capanni 2005	18	91	56	87	14.9%	0.31 [0.20, 0.48]	2005
Cappello 2007	10	28	19	29	13.5%	0.55 [0.31, 0.96]	2007
Cash 2016	3	35	7	37	6.6%	0.45 [0.13, 1.62]	2016
Mosaffa-Jahromi 2016	19	40	26	40	15.4%	0.73 [0.49, 1.09]	2016
Weerts 2020	118	125	61	64	17.9%	0.99 [0.92, 1.06]	2020
Nee 2021	39	46	72	87	17.6%	1.02 [0.88, 1.20]	2021
Total (95% CI)		**388**		**368**	**100.0%**	**0.65 [0.43, 0.98]**	
Total events	217		259				

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 100.32$, $df = 6$ ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: $Z = 2.06$ ($P = 0.04$)

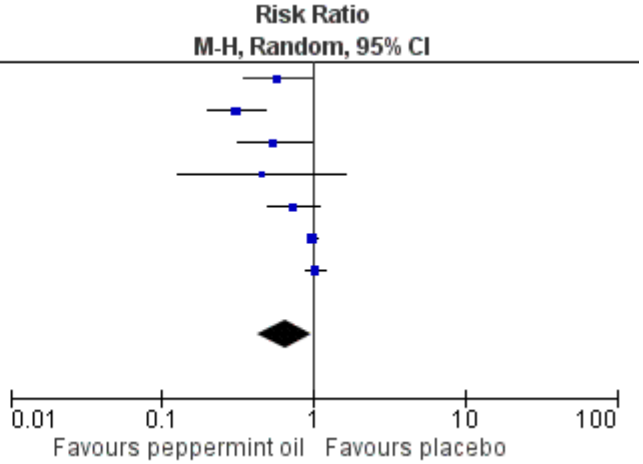

Figure 4. Forest Plot of Randomised Controlled Trials of Peppermint Oil in IBS: Effect on Abdominal Pain.

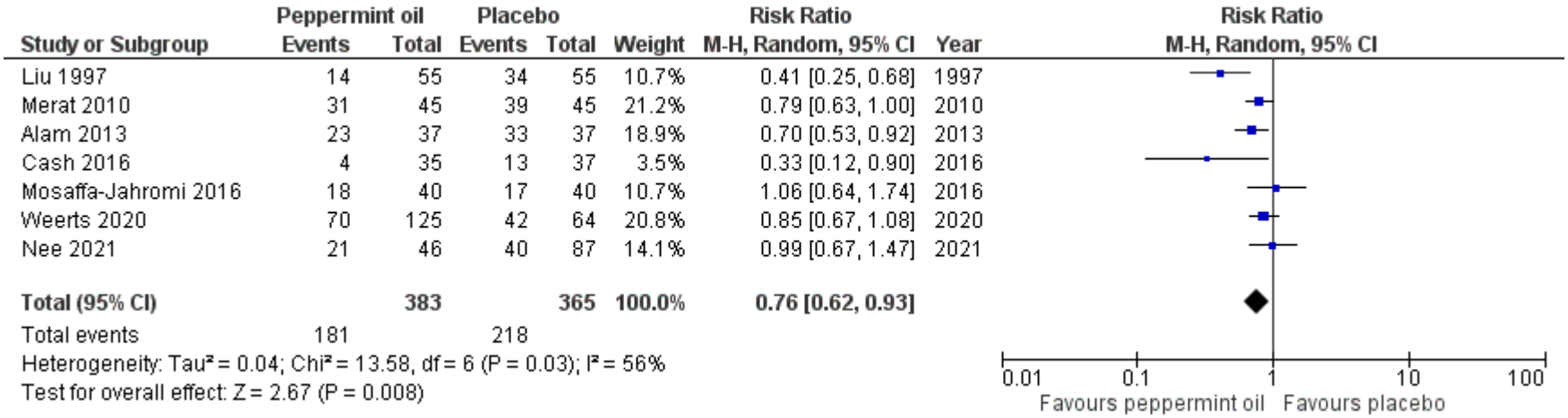

Figure 5. Forest Plot of Randomised Controlled Trials of Peppermint Oil in IBS: Total Adverse Events.

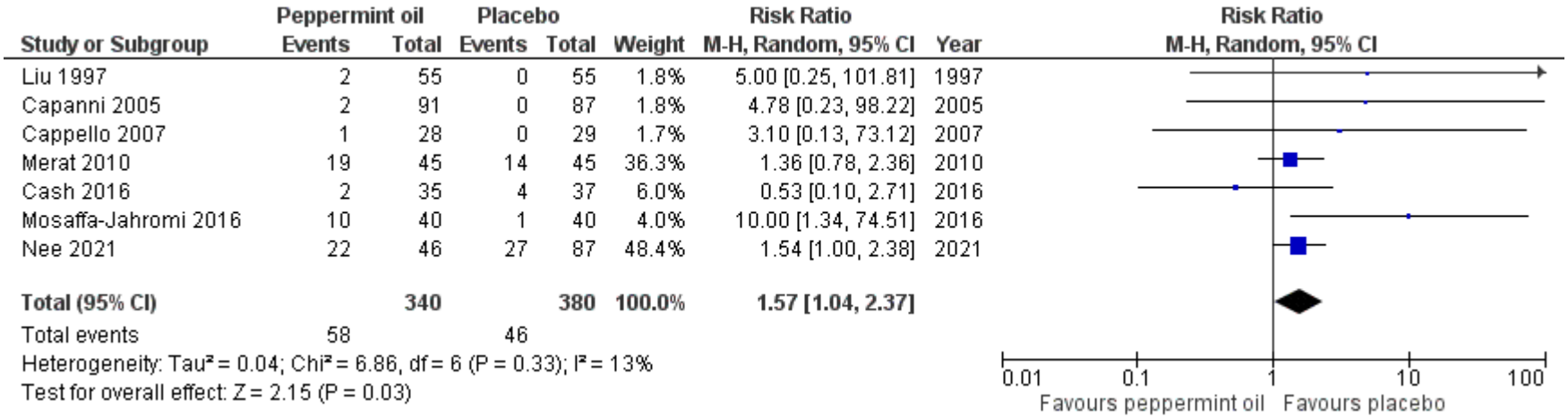

Figure 6. Forest Plot of Randomised Controlled Trials of Peppermint Oil in IBS: Gastro-oesophageal Reflux Symptoms.