SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

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BASTIDAS-GERGŐ DOROTTYA

Transzlációs és klinikai farmakológia

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ASSESSMENT OF EFFICACY AND SAFETY OF NATURAL PRODUCTS IN EVIDENCE-BASED MEDICINE

PhD Thesis

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Budapest
2025

“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

Marie Curie

TABLE OF CONTENT

1. LIST OF ABBREVATIONS

AB	Acute bronchitis
ADR	Adenoma detection rate
AE	Adverse event
APC	Adenoma per colonoscopy
AS	Antispasmodic scores
BSD	Big Stick Design
BSS	Bronchitis Severity Score
CI	Confidence interval
CINV	Chemotherapy-induced nausea and vomiting
COPD	Chronic obstructive pulmonary disease
CTM	Centre for Translational Medicine
DMB	Data Monitoring Board
EO	Essential oil
EMA	European Medicines Agency
ETC	Elixirium thymi compositum
FoNo	Formulae Normales
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HBB	Hyoscine-N-butyl bromide
IBS	Irritable bowel syndrome
MCID	Minimum clinically important difference
MD	Mean difference
NV	Nausea and vomiting

NVP	Nausea and vomiting in pregnancy
OR	Odds ratio
PNMP	Proportion of no or mild peristalsis
PNP	Proportion of no peristalsis
PONV	Postoperative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QoL	Quality of Life
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture system
SC	Steering committee
SD	Standard deviation
SE	Standard error
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

2. STUDENT PROFILE

2.1 Vision and mission statement, specific goals

My vision is that the evidence-based use of herbal products will be more widespread in medical practice. My mission is to provide scientific evidence for health professionals to facilitate their work and their evidence-based decision-making when applying herbal products. My specific goals were to systematically evaluate the efficacy and safety of peppermint in reducing nausea and vomiting, as well as L-menthol's antiperistaltic effect during endoscopic procedures. My third goal was to design a clinical trial to evaluate the efficacy and safety of a thyme-based herbal product in pediatric acute bronchitis (AB).

2.2 Scientometrics

Number of all publications:	12
Cumulative IF:	51.055
Av IF/publication:	4.255
Ranking (SCImago):	D1:2,Q1:9,Q2:1,Q3:,Q4:
Number of publications related to the subject of the thesis:	2
Cumulative IF:	5.8
Av IF/publication:	2.9
Ranking (SCImago):	D1:,Q1:2,Q2:,Q3:,Q4:
Number of citations on Google Scholar:	201
Number of citations on MTMT (independent):	115
H-index:	6

The detailed bibliography of the student can be found on pages 90-91.

2.3 Future plans

In the future, I plan to expand research on the clinical efficacy and safety of a wider range of herbal products to provide more evidence-based options for healthcare. I also aim to integrate the positive findings on L-menthol's antispasmodic effects during endoscopy into routine clinical practice. Additionally, I intend to carry out the planned clinical trial of a thyme-based herbal preparation in pediatric patients with AB and subsequently extend this research to adult populations to generate comprehensive safety and efficacy data across age groups.

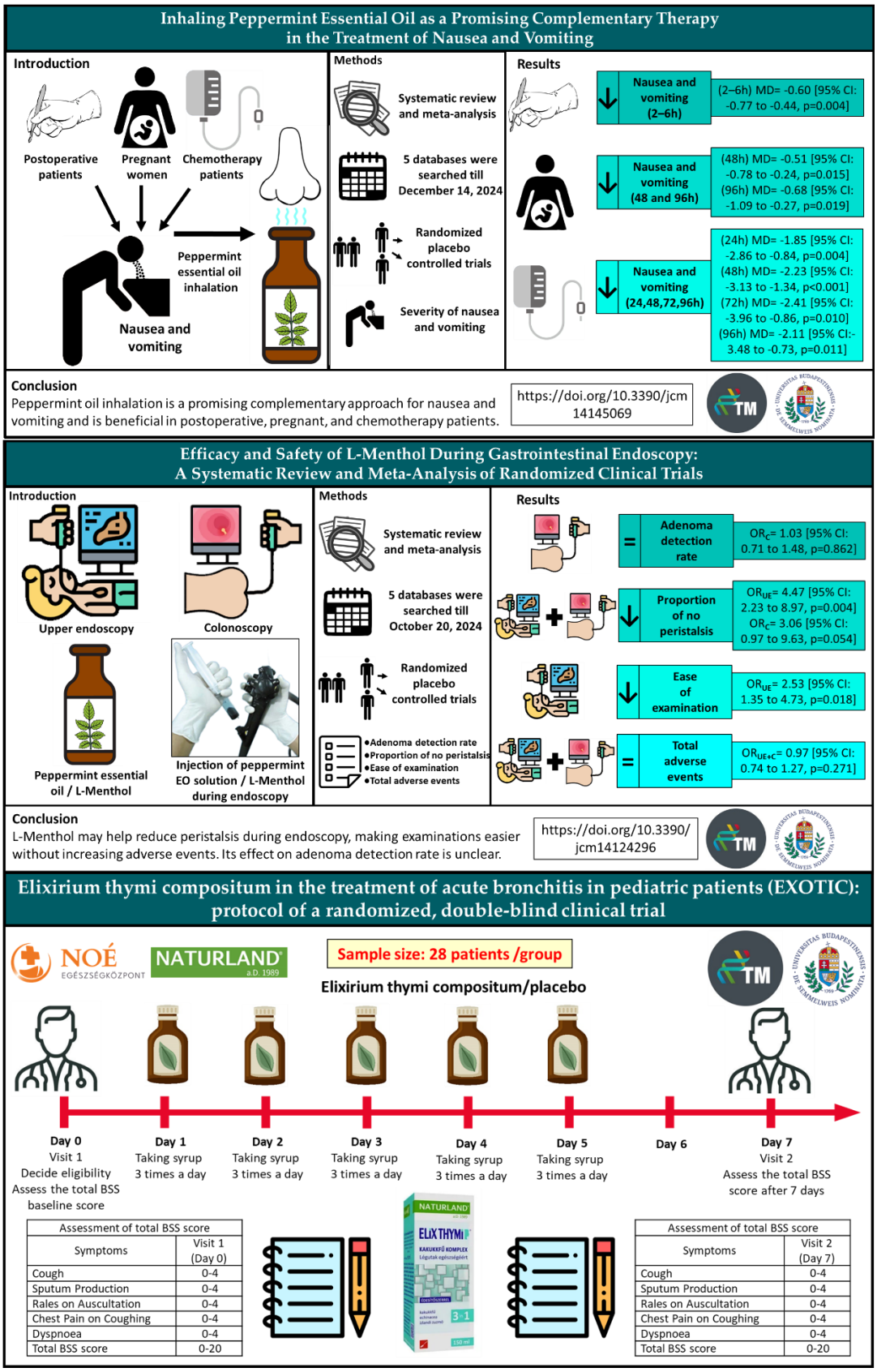
3. SUMMARY OF THE THESIS

Nausea and vomiting (NV) are common symptoms in various clinical situations, including postoperative recovery, chemotherapy and pregnancy. These symptoms impair patient comfort and quality of life (QoL). Conventional pharmacological treatments are not always effective and may cause side effects. This led to growing interest in complementary therapies, notably peppermint oil and its active component, L-menthol. We conducted our first systematic review and meta-analysis to evaluate the efficacy of peppermint oil for NV in postoperative, chemotherapy-induced, and pregnancy-related settings. The results show that peppermint oil inhalation may reduce NV severity within specific timeframes: 2–6 hours after surgery, 48–96 hours during pregnancy, and 24–96 hours in chemotherapy. The intervention is well tolerated, with few adverse events (AEs) and no significant safety concerns. However, the certainty of evidence is limited by small sample sizes and heterogeneity in outcome measures.

During endoscopic procedures, in elderly patients and in those with multiple co-morbidities, where standard pharmacological agents may be contraindicated, herbal options could represent a safer alternative. We analyzed L-menthol as a topical antispasmodic agent during gastrointestinal (GI) endoscopy in our second systematic review and meta-analysis. Our results showed that L-menthol effectively suppresses peristalsis, particularly during upper GI endoscopy, improving mucosal visualization and procedural ease. The effect is rapid and sustained, with a favorable safety profile. However, its impact on adenoma detection rate (ADR) during colonoscopy remains unclear, suggesting L-menthol can optimize procedural conditions but should not be solely relied upon for lesion detection.

Acute bronchitis (AB) in children is usually caused by a viral infection, in which case no outpatient cure is available, but symptom relief is the primary treatment. Appropriate symptomatic management can improve quality of life and reduce the risk of bacterial superinfection. Elixirium thymi compositum (ETC) (FoNo Editio VIII.), a traditional Hungarian herbal medicine containing thyme, is commonly used for symptom relief but its effectiveness is not supported by clinical trial data. We established a protocol for a randomized, double-blind, placebo-controlled trial to rigorously assess ETC’s efficacy and safety in pediatric patients, aiming to inform clinical guidelines and promote evidence-based herbal medicine.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

The focus of our research is the evaluation of selected herbal medicinal products that are applied for their effects on the respiratory and gastrointestinal systems. In these clinical areas, herbal products are traditionally used, but often lack robust scientific evidence. We assessed the efficacy and safety of peppermint oil, L-menthol, and ETC. This includes evaluating peppermint oil inhalation for the management of NV in postoperative, chemotherapy, and pregnancy settings; investigating L-menthol as an antispasmodic during GI endoscopy; and assessing ETC for the symptomatic treatment of AB in pediatric patients.

5.1.2 What is the problem to solve?

In certain vulnerable populations, such as pregnant women or patients with co-morbidities, the use of conventionally used anti-nausea medicines may pose safety concerns and are sometimes contraindicated. Herbal medicines with a more favorable safety profile may be an alternative to pharmaceuticals in such cases. Ginger (*Zingiber officinale*) is well-established for relieving motion sickness. Meta-analyses show that ginger effectively reduces the severity of PONV and may decrease the need for rescue antiemetic medications. However, based on limited safety data, the European Medicines Agency (EMA) generally advises caution regarding its use during pregnancy [1, 2]. Cannabinoids, particularly tetrahydrocannabinol (THC) and cannabidiol (CBD), have been used to manage chemotherapy-induced nausea and vomiting. Clinical evidence supports their efficacy in reducing nausea severity and improving appetite in cancer patients. However, their psychoactive effects, legal restrictions, and potential adverse reactions limit their broader clinical use [3]. Regardless of the cause of nausea, there is a need for agents that can provide an effective and safe alternative to currently available preparations.

GI endoscopy is a widely used examination method that requires the use of medication to facilitate the examination and reduce discomfort. Traditional antispasmodics used during GI endoscopy may present safety risks for certain patients, especially in elderly patients with co-morbidities [4]. Hyoscine butylbromide (Buscopan) may cause tachycardia,

hypotension, and anaphylaxis. Therefore, it should be used with caution in patients with cardiac conditions such as heart failure, coronary artery disease, arrhythmias, hypertension, or those undergoing cardiac surgery [5]. Glucagon is generally considered safe, with no severe adverse effects reported. However, in patients with diabetes, hyperglycemia followed by delayed hypoglycemia approximately two hours after administration has been described. Therefore, caution is advised when using glucagon in diabetic patients, although it is not contraindicated in this population [6].

The antiemetic and antiperistaltic effects of peppermint essential oil and menthol have been confirmed by several studies, but a critical evaluation of their clinical efficacy is lacking. Our aim was to fill this gap.

The causal treatment of acute bronchitis remains unresolved to this day, but certain medicinal herbs, such as thyme, play a significant role in symptomatic treatment [7]. Despite being widely used and available on the market for decades, ETC is primarily used based on tradition, with no clinical trials conducted to support its efficacy. Like many herbal medicines, the use of the main active ingredient (thyme) is supported by non-clinical studies and long-standing experience, qualifying it as a traditional herbal medicinal product with an EMA monograph [8]. The lack of robust clinical evidence supporting the efficacy and safety of peppermint oil, menthol and ETC leads to uncertainty among healthcare professionals regarding their integration into evidence-based practice.

5.1.3 What is the importance of the topic?

This topic is of major importance because nausea and vomiting are highly prevalent and distressing symptoms that negatively impact patient (QoL) and treatment adherence across multiple clinical scenarios, while AB remains one of the most common reasons for pediatric consultations. The limitations and side effects of standard therapies, as well as the public health threat posed by antibiotic overuse, underscore the need for effective, safe, and accessible alternative treatments. In the absence of high-quality clinical data, the adoption of herbal medicines such as peppermint oil, L-menthol, and ETC in mainstream medicine remains questionable.

5.1.4 What would be the impact of our research results?

The results of this research have the potential to directly inform clinical practice by providing high-quality evidence on the efficacy and safety of peppermint oil, L-menthol, and ETC in relevant patient populations. If reliable evidence is generated regarding the efficacy and safety of these products, they could be appropriately integrated into evidence-based medicine. Additionally, these findings could guide the development of clinical guidelines, influence policy decisions regarding the regulation and recommendation of herbal medicines, and highlight areas where further research is needed to optimize patient outcomes.

5.2 Inhaling Peppermint Essential Oil for the Treatment of Nausea and Vomiting

NV are frequent symptoms that can occur in various conditions, including the postoperative period, as a result of chemotherapy treatment, during pregnancy or in motion sickness. These symptoms result from continuous interactions among different parts of the gastrointestinal tract, including the enteric nervous system, the central nervous system, and the autonomic nervous system [9]. Postoperative nausea and vomiting (PONV) are common adverse events of anesthesia and surgery, occurring in approximately one out of three postoperative patients. The risk is higher in those with established risk factors, including female sex, non-smoking status, a history of PONV or motion sickness, or the use of postoperative opioids. Younger age is also associated with increased risk, with risk decreasing as age advances [10-12]. The type of surgery and the type of anesthesia, particularly the use of volatile anesthetics, further increase risk, while regional techniques are generally associated with a lower incidence of PONV [13-15]. In particular, for patients undergoing vitreoretinal surgeries, especially those with diabetes, PONV can lead to serious complications, such as suprachoroidal hemorrhage, potentially resulting in vision impairment [16, 17]. The relationship between obesity and PONV is controversial. Most evidence indicates that obese patients are not at increased risk and may experience a lower incidence, while underweight patients (BMI <19) may have a higher risk [18, 19]. The incidence of PONV may be further reduced by employing Surgical Pleth Index-guided opioid-free anaesthesia [20], or even lowered below 10% with Adequacy of Anaesthesia guidance [21]. Nausea and vomiting during pregnancy (NVP) typically begin in the first trimester and may last throughout the pregnancy. NVP

affects around 70-80% of pregnant women. It is thought to be caused by hormonal changes, particularly by an increase in human chorionic gonadotropin (hCG) and estrogen levels [22, 23]. NVP can cause discomfort, dehydration, and malnutrition and affect the quality of life of women [24]. Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing adverse event affecting 40–80% of chemotherapy patients [25]. CINV may compromise patient compliance with the chemotherapy regimen [26]. Consequently, CINV can decrease patients' quality of life [27].

While current pharmaceutical treatments have been clinically tested and approved, they can be associated with unpleasant adverse events [28, 29]. For instance, the 5-HT_3 (5-Hydroxytryptamine type 3) and NK1 (Neurokinin-1) receptor antagonists may cause constipation or headaches [30]. In pregnancy, antiemetic use is limited due to safety concerns [31]. Consequently, alternative therapies for NV are needed that may be more effective with fewer side effects. One alternative tool may be aromatherapy, which involves inhaling essential oils (EOs) and is considered a mild therapeutic modality without severe side effects. While robust clinical evidence supporting the efficacy of aromatherapy is still limited, preliminary studies suggest potential benefits [32].

Inhalation of peppermint essential oil can help alleviate nausea and vomiting through several mechanisms. Peppermint oil has been shown to block serotonin receptors in the gastrointestinal tract that trigger the nausea and vomiting reflex [33]. The active compounds of peppermint oil are menthol (35-45%) and menthone (10-30%), which exhibit antispasmodic effects [34]. These compounds help relax the smooth muscles of the gastrointestinal tract [35].

Several randomized controlled trials (RCTs) have been conducted to evaluate the effect of peppermint oil on PONV, NVP, and CINV. However, its clinical efficacy has not been established yet [36-41]. The major constituents of peppermint oil are menthol, ranging from 30-55%, and menthone, ranging from 14-32%. Other monoterpenes are limonene (1-3.5%), cineole (3.5-8%), menthofuran (1-8%), isomenthone (1.5-10%), menthyl acetate (2.8-10%), pulegone (maximum 3%), and carvone (maximum 1%). While peppermint oil is rich in menthol and menthone, compounds such as pulegone and menthofuran are present in smaller amounts and pose limited human safety data, particularly concerning use during pregnancy [42]. Consequently, the EMA does not recommend the oral use of peppermint oil in pregnant women [43]. While oral

administration is limited due to systemic absorption and potential adverse effects, inhalation or topical application is considered safer because these routes result in reduced systemic exposure [44]. In contrast to the EMA, according to the Australian Therapeutic Goods Administration Classification for Drugs in Pregnancy, peppermint oil is classified as category B2 for use in pregnancy. There is no evidence of an increase in birth defects or other harmful effects on the developing embryo for pharmaceuticals in category B2 [45].

5.3 L-menthol during GI endoscopy

GI endoscopy is an essential diagnostic tool [46] to identify and manage various GI diseases, such as colorectal cancer [47], inflammatory bowel disease [48], and peptic ulcer disease, highlighting its crucial role in clinical practice [49]. More than 7.4 million upper GI endoscopies [50] and more than 13 million colonoscopies are annually performed in the United States alone [51]. Factors like natural peristaltic movements, inappropriate bowel preparation or insufficient withdrawal time can affect the accuracy of endoscopic procedures by obstructing small lesions, thus decreasing diagnostic precision [52, 53]. Suppressing peristalsis is crucial for high-quality and accurate outcomes during endoscopic procedures [54, 55].

Hyoscine-N-butyl bromide (HBB) and glucagon are widely used during endoscopy to achieve optimal suppression of peristalsis. These agents have proven their ability to reduce peristaltic activity, thereby improving mucosal visualization and detection of polyps, including adenomas [56, 57]. However, HBB is associated with cardiovascular risks, such as tachycardia and arrhythmias, and is contraindicated in patients with conditions like myasthenia gravis and narrow-angle glaucoma [58]. Glucagon, on the other hand, can cause delayed hypoglycemia [59]. HBB requires intravenous administration, complicating its use in unsedated patients without a cannula [60]. It is costly and less suitable for elderly patients or those with co-morbidities [61-64]. The use of conventional antispasmodics is therefore limited due to these adverse effects, particularly in elderly individuals or those with co-morbidities, making it crucial to provide a safe and effective alternative as a growing number of elderly patients undergo endoscopic procedures [65, 66]. There is a critical need for a safe, effective, and cost-efficient alternative to suppress peristalsis during endoscopy.

Peppermint oil and its main component, L-menthol, extracted from the *Mentha* × *piperita* L. plant, have been considered potentially safer natural antispasmodics [61, 64].

Peppermint oil has been used traditionally to alleviate irritable bowel syndrome (IBS) symptoms, such as discomfort caused by spasms [62, 63]. Moreover, its efficacy is recognized as a "Well Established Use" (WEU) by the EMA [67]. This antispasmodic effectiveness is attributed to menthol, which acts as a calcium channel blocker to relax GI smooth muscles [68-71]. Recent studies have investigated the potential use of menthol during endoscopy and its ability to reduce peristalsis without adverse effects, unlike conventional antispasmodics. The potential benefits of using menthol during endoscopy include improving the lesion detection quality while minimizing the risk of AEs [72]. Notably, the use of menthol during upper GI endoscopy has already received approval in Japan [73].

5.4 Elixirium thymi compositum in the treatment of AB in pediatric patients

AB is a common disease predominantly affecting children, accounting for one of the most frequent reasons for pediatric doctor consultations. Approximately 5% of the population experiences AB each year, leading to around 10 million visits to the doctor annually only in the US [74, 75]. AB is among Western countries' costliest children's conditions [76]. The disease shows a seasonal pattern associated with pathogens such as respiratory syncytial virus, influenza viruses A and B, parainfluenza and rhinovirus [77]. AB is characterized by cough, sputum, wheezing and dyspnea [78]. Bacterial infections are rare, but when present, they often involve *Staphylococcus aureus* and *Streptococcus pneumoniae* [79]. Although there is no targeted therapy for viral infections of AB, antibiotics are frequently prescribed, which increases antibiotic resistance [80]. This disease starts with a dry/productive cough lasting less than three weeks [81]. The disease typically improves on its own and treatment primarily aims to alleviate symptoms [82]. Although there is no specific therapy for the disease, in some cases, antibiotics are used unnecessarily to treat patients [83]. Since antibiotic treatment is not only ineffective but also contributes to the spread of antibiotic resistance [84]. Therefore, integrating active substances used for symptomatic treatment into rational therapy requires careful evaluation of their efficacy and safety. For many active compounds, both synthetic and herbal, comprehensive clinical evidence supports their use [85, 86].

ETC is a traditional Hungarian herbal medicine indicated for the symptomatic treatment of inflammatory processes of the trachea and bronchi, as well as for the treatment of catarrhal cough. Thyme, the active ingredient, is known to promote the expectoration of viscous airway secretions, thereby supporting bronchial clearance [87]. ETC has been used medicinally since the 1940s [88]. Its composition has been modified since its original formulation to reflect advances in herbal pharmacology and regulatory standards. It is currently marketed as a traditional herbal medicinal product [89]. Its therapeutic indications are based on traditional use and experience [90]. Our study will therefore be the first RCT to evaluate the efficacy and safety of ETC in children with AB and aims to provide objective data on its therapeutic benefits and tolerability.

6. OBJECTIVES

6.1 Study I. – Inhaling Peppermint Essential Oil is Beneficial in the Treatment of Nausea and Vomiting

This systematic review and meta-analysis aimed to examine the efficacy of peppermint oil on nausea and vomiting symptoms compared to a placebo by systematically reviewing and meta-analyzing the available clinical data.

6.2 Study II. – Efficacy and safety of L-menthol during GI endoscopy

This systematic review and meta-analysis aimed to assess the efficacy and safety of menthol during upper and lower GI endoscopy, providing a comprehensive evaluation of its role in enhancing endoscopic outcomes.

6.3 Study III – Elixirium thymi compositum in the treatment of acute bronchitis in pediatric patients (EXOTIC)

This clinical trial aimed to evaluate the efficacy and safety of ETC for symptom relief in pediatric acute bronchitis, as measured by changes in the Bronchitis Severity Score and adverse event monitoring, with additional assessment of quality of life and use of concomitant medication.

7. METHODS

7.1 Study I.

The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline [91] and the Cochrane Handbook [92] were followed. No ethical approval was required, as all data were published in peer-reviewed journals. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022379103) on December 7, 2022.

7.1.1 Literature search and eligibility criteria

The systematic search was conducted on 26 November 2022 in five databases: Scopus, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via NCBI PubMed), and Web of Science, with an update on December 14, 2024. During the systematic search, the following search key was used: ((peppermint) OR (Mentha piperita)) AND ((nausea) OR (vomiting)) without any filtering option or restrictions. There were no language restrictions.

The PICO framework was used to answer the clinical question of the project. The population (P) included adult patients (> 18 years old) experiencing NV symptoms postoperatively, during pregnancy, or due to chemotherapy. In the intervention group (I), patients received peppermint oil by inhalation; in the control group (C), patients received a placebo. The primary outcome (O) was efficacy, characterized by the changes in the severity of nausea measured by the Visual analogue scale, the Rhodes Index, or the Pregnancy-Unique Quantification of Emesis and Nausea questionnaire for assessing nausea and vomiting.

7.1.2 Study selection and data extraction

In this study, RCTs were eligible. Studies were excluded from the systematic review and meta-analysis if; (1) they did not meet the inclusion criteria, (2) the intervention combined peppermint oil with other treatments, (3) the study design was: conference abstract, case reports, case series, and article with no original data or (4) desired outcomes could not be obtained from the published findings or upon request from the corresponding author.

The search results were first exported to the EndNote X9 citation manager (Clarivate Analytics, Philadelphia, PA, USA). Duplicates were removed by the author manually. Then, an additional independent review author co-performed selection by title and

abstract, then full-text using the online screening tool Rayyan [93] according to the inclusion criteria. In disagreements, a third independent review author made the final decision. Cohen's kappa coefficient was calculated at each selection step to evaluate the level of agreement between the authors. References from eligible studies were screened for eligibility manually and with an automated citation chaser [94].

Data were collected from eligible articles by two independent review authors; data were extracted manually from eligible articles, and then the authors cross-checked each other's datasets to ensure precision. Disagreements were resolved by consensus. Plot Digitizer (https://plotdigitizer.com, Version 2.6.9, 2020) was used to read data from plots. Microsoft Excel (Microsoft, Office 365, Redmond, WA, USA) was used for data collection. Study authors were approached to request any missing data.

The following data were extracted: study characteristics (first author, year of publication, country), study population (sample size, gender, age), intervention type and details (herbal medicine type, dose, duration), and the severity of NV as the primary outcome.

7.1.3 Quality assessment

Two review authors independently assessed the risk of bias using the Cochrane risk-of-bias tool (RoB2) [95]. Disagreements were resolved by consensus. The authors evaluated the bias through domains, such as bias due to randomization, deviations from the intended intervention, missing data, outcome measurement, and selection of reported results. The risk assessment conclusion categorized the risk of bias as 'low,' 'some concerns', or 'high'.

The GRADEpro tool (Guideline Development Tool) [96] was used to evaluate the quality of evidence. Two review authors independently performed the grading of the level of evidence. Each outcome was rated according to the following: risk of bias, inconsistency, indirectness, imprecision, publication bias, presence of a large effect, dose-dependent response, and plausible confounders ('not serious', 'serious', or 'very serious'). The final certainty of the evidence was categorized as 'very low', 'low', 'moderate', or 'high'.

7.1.4 Data synthesis and analysis

Both qualitative and quantitative synthesis of the data was performed. At least three studies with poolable effect sizes were required for statistical analysis. Meta-analyses

were conducted using the ‘meta’ [97] and ‘dmetar’ [98] packages in the R statistical environment [99].

To account for differences in pathophysiology and patient populations, separate meta-analyses for PONV, CINV, and NVP were conducted. The studies included slightly different numerical scales to quantify the severity of nausea and discomfort. All applied scales were converted to 0-10. Mean difference (MD) was used between the intervention and control groups' scales as an effect size measure (with 95% confidence intervals (CIs)). This approach could be applied to the further outcomes in the meta-analysis: NV scores and overall satisfaction levels. Sample size, means, and corresponding standard deviations (SD) were extracted from the studies separately for each group to calculate study and pooled MDs. After conversion to a scale of 0-10, the mean values of the control group were subtracted from the mean values of the experimental group. If quartiles were given instead of the mean, SD, or Standard error (SE) of the mean, the Luo and Shi methods were used [100, 101] to estimate the mean and SD, as implemented in the meta R package.

The random-effects model was chosen for the meta-analyses. The inverse variance weighting method was used to calculate the pooled MD. To estimate the heterogeneity variance measure (τ^2), the restricted maximum-likelihood estimator with the Q profile method was used for CIs [98, 102]. In individual studies, the t-distribution-based method was used for the CI of MD calculation.

Subgroup analysis was based on different follow-up intervals, which were determined after data had been extracted, as the data suggested this structure. In the subgroup analysis, a fixed-effects “plural” model (aka mixed-effects model) was used. Different τ^2 values were assumed in the subgroups.

Statistical heterogeneity was assessed using the Cochrane Q test and I^2 values [92]. Small study publication bias was evaluated by visual inspection of Funnel-plots and by calculating the classical Egger’s test p-value [103]. In addition, analyses of outlier and influential points were conducted following the methodologies proposed by Harrer et al. (2021) [98] and Viechtbauer and Cheung (2010) [104]. Results were considered statistically significant if the pooled CI did not contain the null value.

The findings from the meta-analysis were summarized in forest plots. Due to a low number of studies, prediction intervals were not reported. The time-related pattern in NV scores by study and treatment was plotted to visualize differences in trends between intervention and control groups.

7.2 Study II.

This study followed the PRISMA 2020 guideline [91] and the Cochrane Handbook [92]. No ethical approval was required, as all data were from peer-reviewed journals. The protocol was registered in the PROSPERO database (CRD42023430941) on May 30, 2023.

7.2.1 Literature search and eligibility criteria

The systematic search was conducted on May 31, 2023, in five databases (Scopus, Embase, CENTRAL, MEDLINE, and Web of Science) with an update on October 20, 2024. During the systematic search, the following search key was used: ('mint' OR 'peppermint' OR 'Mentha' OR 'L-Menthol' OR 'menthol') AND ('endoscope' OR 'endoscopy' OR 'colonoscope' OR 'colonoscopy' OR 'gastroscope' OR 'gastroscopy' OR 'esophagogastroduodenoscopy' OR 'enteroscope' OR 'enteroscopy' OR 'duodenoscope' OR 'duodenoscopy' OR 'esophagoscope' OR 'esophagoscopy' OR 'endoscopic ultrasound' OR 'Endoscopic Retrograde Cholangiopancreatography' OR 'ERCP' OR 'adenoma detection rate' OR 'ADR') without any filtering option or restrictions. There were no language restrictions.

7.2.2 Study selection and data extraction

RCTs, observational studies, case series, case-control studies, and conference abstracts were eligible. Reviews, meta-analyses, animal studies, *in vitro* studies, and guidelines were excluded. There were no language restrictions.

The search results were first exported to the EndNote 20 citation manager (Clarivate Analytics, Philadelphia, PA, USA). Duplicates were automatically and manually removed by the author. Then, two independent review authors did the title and abstract selection. Next, full-text selection was performed using the online screening tool Rayyan [93] according to the inclusion criteria. In disagreements, a third independent review author made the final decision. Cohen's kappa coefficient was calculated at each selection step to evaluate the level of agreement between the authors. The references from eligible

studies were screened for eligibility manually and with an automated citation chaser [105].

Two review authors independently extracted data, resolving disagreements by consensus. Plot Digitizer (https://plotdigitizer.com, Version 2.6.9, 2020) converted graphics to numerical values. Microsoft Excel (Microsoft, Office 365, Redmond, WA, USA) was used for data collection. Missing data were requested from the study authors.

The following data were extracted: study characteristics (first author, publication year, country, digital object identifier, study site, and study type), study population (sample size, gender, and age), endoscopy type, intervention type, and details (peppermint oil/L-menthol, dosage, and evaluation time point), and the ADR as the primary outcome with the experience level of the endoscopist(s). Secondary outcomes were peristalsis levels, withdrawal time, ease of examination reported by the endoscopist, and the total number of AEs and adverse drug reactions.

In upper GI endoscopy, the intervention was 20 mL of 0.8% L-menthol solution (160 mg) sprayed onto the gastric antrum or body via the endoscope's working channel before examination. The antiperistaltic effect begins within 30–90 s and is sustained throughout the procedure. Additional doses can be administered if peristalsis recurs during a more prolonged examination. For colonoscopy, the regimen is 20 mL of 0.8% L-menthol (160 mg) or 50 mL of peppermint oil solution sprayed or injected onto the colonic mucosa, particularly at the cecum, with additional doses as needed for persistent peristalsis. The antispasmodic effect occurs quickly (within 20–40 s) and lasts at least 15–20 min, covering the withdrawal phase.

ADR, a key performance indicator for colonoscopy, was analyzed as the proportion of procedures in which at least one adenoma is detected [106]. Peristalsis severity in upper endoscopy was assessed using Niwa's Classification, a five-point scale where Grade 1 indicates no peristalsis, Grade 2 mild, Grade 3 moderate, Grade 4 vigorous, and Grade 5 markedly vigorous peristalsis. For analysis, data were dichotomized as 'Grade 1' versus 'Grades 2–5' or 'Grades 1–2' versus 'Grades 3–5.' In colonoscopy, peristalsis or spasm severity was evaluated using the method described by Asao et al. (2001) [107]. The ease of examination is crucial for ensuring the quality of the endoscopy, as endoscopist fatigue may negatively impact outcomes [108]. The ease of examination was assessed by the

endoscopist using a standardized four-grade scale. This scale evaluates the degree to which gastric peristalsis interfered with the endoscopic procedure, and includes the following categories: ‘very easy’ (no peristalsis, no interference with observation), ‘easy’ (mild peristalsis, observation performed without interference), ‘slightly difficult’ (peristalsis slightly interfered with observation), and ‘difficult’ (marked peristalsis, observation significantly impaired). For statistical analysis, results were dichotomized as 'very easy' and 'easy' versus 'slightly difficult' and 'difficult.' Withdrawal time was defined as the duration from cecal intubation to scope withdrawal, including biopsy time. AEs and adverse drug reactions were assessed as the proportion of patients experiencing symptoms such as abdominal pain, nausea, diarrhea, rash, fever, or abnormal laboratory findings during or immediately after the endoscopic procedure.

7.2.3 Quality assessment

Two review authors independently assessed the risk of bias using the Cochrane risk-of-bias tool (RoB2) [95], applying the tool to assess the intention-to-treat effect in the included RCTs. Disagreements were resolved by consensus. Domains were evaluated, such as the randomization process, deviations from intended interventions, missing data, outcome measurement, and result selection. The risk was categorized as 'low,' 'some concerns', or 'high,' visualized using the robvis tool [109].

The GRADEpro tool [110, 111] was used to evaluate the quality of evidence. Two review authors independently graded each outcome. Discrepancies in GRADE (Grading of Recommendations, Assessment, Development and Evaluations) ratings were resolved through discussion or inclusion of a third independent review author. Grading started at ‘high’ for RCTs and downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias. Upgrading the certainty of evidence did not apply to RCTs. The final certainty was categorized as 'very low,' 'low,' 'moderate,' or 'high'.

7.2.4 Data synthesis and analysis

Both qualitative and quantitative synthesis were performed. At least three studies that reported clinically poolable effect sizes were a prerequisite for statistical poolability. Meta-analyses were conducted using the ‘meta’ [112] and ‘dmetar’ [98].

For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (95% CI) was used to measure the effect of the intervention. If not reported, these were calculated

from participant numbers and event occurrences [113-115]. For continuous outcomes, the MD between intervention and control groups was used with a 95% CI.

The random effects model was chosen for the meta-analyses. CIs were adjusted using the Hartung–Knapp method [116, 117]. For pooled results, the exact Mantel–Haenszel method without continuity correction was applied to manage zero cell counts [118, 119]. The τ^2 estimate utilized the Paule–Mandel method, and the CI for τ^2 was determined using the Q profile method [120, 121].

Statistical heterogeneity was assessed using the Cochrane Q test and I^2 values, with statistical significance at $p<0.1$ [92]. For subgroup analyses, if heterogeneity in a subgroup was low ($I^2 < 25\%$), a fixed-effects model (Mantel-Haenszel method) was used for that subgroup; otherwise, random-effects models were applied. Publication bias was assessed using funnel plots, and Egger's test was performed for outcomes with at least 10 studies. Outlier and influence analyses followed methodologies by Harrer et al. (2021) [98] and Viechtbauer and Cheung (2010) [104]. For subgroup analysis, a fixed-effects 'plural' model (aka mixed-effects model) was used, stratifying by procedure type (colonoscopy vs. upper endoscopy) and by time point of antiperistaltic effect measurement. It was assumed that subgroups share common τ^2 values. A Cochrane Q test assessed the difference between the subgroups. The null hypothesis was rejected at a significance level of 5%.

The analysis included studies using both spraying and direct application of peppermint oil. These methods were combined because the included studies used comparable peppermint oil concentrations and reported similar antiperistaltic effects, regardless of the delivery mechanism.

Peristalsis severity was assessed using Niwa's Classification [122], which categorizes peristalsis into five grades: Grade 1 (no peristalsis), Grade 2 (mild), Grade 3 (moderate), Grade 4 (vigorous), and Grade 5 (markedly vigorous). Two separate analyses were performed: data were dichotomized as 'Grade 1' versus 'Grades 2–5' or 'Grades 1 and 2' versus 'Grades 3–5,' with ORs calculated.

The ease of intragastric examination was evaluated on a four-grade scale: 'very easy', 'easy', 'slightly difficult', and 'difficult' [107]. The data were dichotomized as 'very easy' and 'easy' versus 'slightly difficult' and 'difficult,' with ORs calculated.

Withdrawal time was defined as the duration to remove the colonoscope from the cecum to the anus, including biopsy time. AEs and reactions were assessed as the proportion of patients experiencing symptoms.

7.3 Study III.

7.3.1 Study design

This is a single-center, randomized, controlled, double-blind superiority trial. The trial aims to evaluate the efficacy and safety of ETC in treating pediatric patients aged 6–17 years with AB. Eligible patients will be randomly assigned in a 1:1 ratio to either Group A (age-dependent doses of ETC (FoNo VIII., Naturland), 18–30 mL daily for five days) [87] or Group B (placebo matching the ETC in all ingredients except for the absence of thyme tincture, administered at the same dosage and schedule as ETC). The primary endpoint is improvement in AB symptom, measured by change in BSS on Day 7. Secondary endpoints include monitoring AEs to assess safety and tolerability and documenting the use of concomitant medications, dietary supplements, and antibiotics during treatment. The trial complies with EU Regulation 536/2014 on clinical trials [123] and follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement 2013 [124]. Prospective data collection during routine patient care is integrated into the study design, while anonymized data processing complies with applicable data protection regulations. Statistical analyses will be conducted after the last follow-up visit. Patient follow-up is integrated into the study design but does not interfere with routine care processes.

7.3.2 Setting

The EXOTIC (Elixirium thymi compositum in the treatment of AB in pediatric patients) trial will be conducted in Hungary between 2025 and 2027. It is coordinated by the Centre for Translational Medicine (CTM) at Semmelweis University, Budapest, which serves as the coordinating institution (www.tm-centre.org). CTM has been responsible for developing the study protocol, questionnaire, medical records, data processing, analysis, storage, and coordinating study logistics. The Hungarian Phytotherapy Study Group, affiliated with the Institute for Translational Medicine at the University of Pécs, is the guarantor of the trial (www.tm-centre.org/en/research/study-groups/hungarian-

phytotherapy-study-group). Naturland Magyarország Kft. is the sponsor, providing the investigational medicinal product and the placebo.

The trial will be conducted at Noé Medical Center, a private multidisciplinary healthcare facility established in 2011 in Szeged, Hungary. Pediatricians at the site will perform recruitment, randomization, intervention administration, storage of study medicines, and follow-up procedures after signing *Form 1: Declaration for joining*.

The steering committee (SC), chaired by Dezső Csupor (University of Szeged; specialist pharmacist in phytotherapy), includes Dorottya Gergő (medical biotechnologist, PhD student), Brigitta Teutsch (medical doctor), Zsolt Bella (otorhinolaryngologist, audiologist), Rita Román (pediatric pulmonologist), Attila Ványolós (pharmacist, assistant professor at Semmelweis University), and Péter Hársfalvi (biostatistician). The SC will provide overall supervision and final decision-making authority for the trial. Its responsibilities include reviewing trial progress, monitoring protocol adherence, and assessing blinded safety data. In the event of major safety concerns, the SC may request unblinding to review data and take appropriate action, including protocol modifications or early termination of the trial if necessary. The SC will also resolve disagreements within the research team or with the sponsor regarding data management or changes in protocol.

The Data Monitoring Board (DMB) will report directly to the SC, providing regular reports on blinded safety and data integrity. Any major safety concerns identified by the DMB will be immediately communicated to the SC, which is authorized to make final decisions.

The study protocol for the EXOTIC trial was designed by members of the SC following SPIRIT 2013 guidelines [124]. The study medication and placebo will be manufactured by Naturland Magyarország Kft., Hungary, under a partnership agreement. Notably, no sponsors or partners were involved in the study design.

Sponsors will not have access to the randomization code or the database generated during the trial to ensure independence of data management and analysis.

7.3.3 Ethics and patient consent

The study will follow the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines. The Hungarian Medical Research Council Ethics Committee for Clinical Pharmacology (ECCP) and the National Centre for Public Health and Pharmacy Institutional Committee of Science and Research Ethics (NNGYK) reviewed and approved the study protocol for scientific content and compliance with applicable research and human subject regulations (NNGYK/ETGY/03198-4/2025). The trial is registered at clinicaltrials.gov (NCT07030855).

Hungarian centres may participate on a voluntary basis. No financial payments or other material compensation are provided to investigators or participating sites. Investigators will be offered co-authorship in recognition of their contributions to patient enrolment and study conduct.

No special ancillary or post-trial care is planned due to the low risk of this trial. In case of harm related to trial participation, appropriate medical care and compensation will be provided according to national regulations.

Study participants, their parents, or legal guardians can recommend participant withdrawal from the study. All such requests will be documented and reviewed by the SC. Participants will be automatically withdrawn if they (1) experience severe adverse reactions, (2) miss multiple doses of the investigational product, (3) take additional medications from the exclusion list (e.g., antibiotics, immunostimulants, systemic steroids (past month), and antihistamines, expectorants, or local steroids (past two weeks)) or (4) withdraw consent at any time during the study. The SC may decide to exclude a participant from the per-protocol analysis if the deviation from the protocol is related to the intervention or significantly impacts the study outcome.

7.3.4 Participants

The study population will consist of pediatric patients aged 6 to 17 years diagnosed with AB, with a BSS total score ranging from 5 to 12. A BSS score of 5 to 12 corresponds to mild to moderate disease severity, ensuring inclusion of patients with clinically significant, but not extreme AB.

Patients will be identified and enrolled during routine pediatric consultations at Noé Medical Center, without active recruitment or advertising. When a child presents with respiratory symptoms, the outpatient pediatrician will screen for eligibility based on the inclusion criteria of the study during the physical examination. If eligible, the physician will explain the study design and intervention, provide *Form A: Patient information leaflet*, and answer any questions. Parents or legal guardians will then be invited to give written informed consent to participate with *Form B: Informed consent form*. The child will be formally enrolled in the study only after consent has been obtained. All enrollment procedures will take place within the framework of standard clinical practice. The clinical trial flow (including the inclusion and exclusion criteria), in accordance with the PRISMA 2013 statement, is shown in Figure 1.

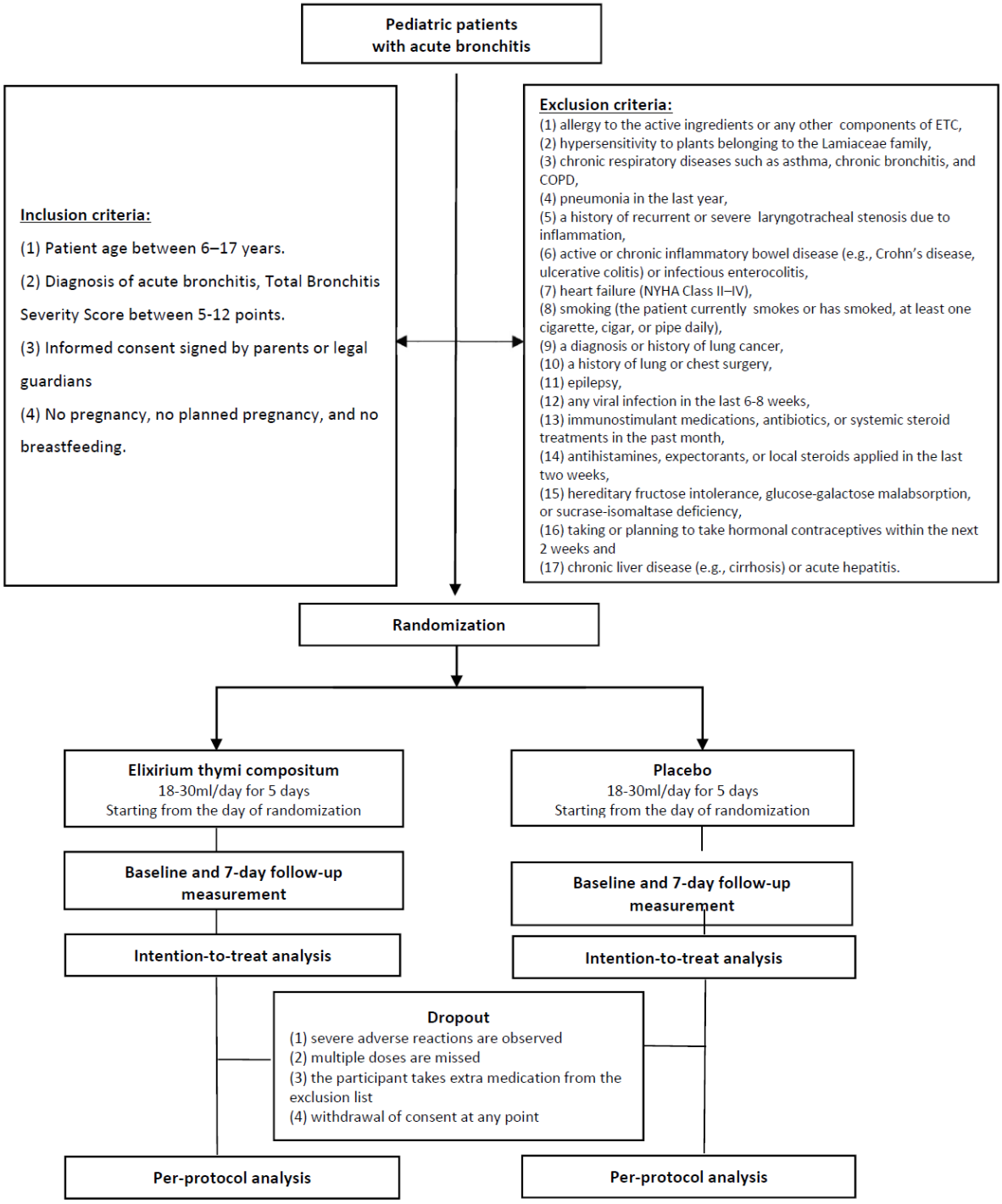


Figure 1. Flow chart of participants according to the SPIRIT 2013 Statement (COPD = chronic obstructive pulmonary disease, NYHA = New York Heart Association)

7.3.5 Interventions

The study drug is ETC (FoNo Editio VIII (OGYÉI-TN-73/01)) in a coded 150 ml brown glass bottle. One ml (= 1175 mg) oral solution contains 352.5 mg liquid extract of garden and Spanish thyme leaves and flowers (*Thymus vulgaris* L., or *Thymus zygis* L., herba) (1:3.45-3.85); extraction solvent: ethanol 27% (V/V). Other ingredients are sucrose, purified water, 96% ethanol, orange tincture, spicy tincture (alcoholic extract of cinnamon bark, orange peel, cardamom seed, and clove), methyl parahydroxybenzoate (E218), and sorbic acid (E200) [87].

The placebo is a syrup with a similar taste and color to the active treatment, without the active ingredient (thyme tincture) (provided by Naturland Magyarország Kft.). (Ingredients are spicy tincture (containing cassia cinnamon, orange peel, cardamom fruit, and cloves), orange tincture for syrup preparation, sorbic acid, sucrose, purified water, methyl parahydroxybenzoate, and 96% ethanol.)

Participants receive a single syrup dose as a self-administered intervention during the study. The dosage will be as follows, according to the Summary of product characteristics for children and adolescents: between 6-9 years of age, 6 ml 3 times a day; between 9-15 years of age, 8 ml 3 times a day; and between 15-17 years of age, 10 ml 3 times a day oral solution. The method of administration is oral, using an undiluted solution. A measuring cap is provided, graduated from 2.5 ml to 20 ml, to assist with dosing. After they have been opened, the investigational product and placebo should be stored in a refrigerator (2-8°C). The product should not be used for more than five days [34]. If AB symptoms become severe, consultation with a pediatrician is needed for further therapeutic management.

The alcohol content of the investigational product may interact with other medications and enhance the effects of alcohol consumed simultaneously; therefore, alcohol consumption is prohibited during treatment. Care providers must disclose any medications the children are taking, as specific treatments, such as immunostimulants, antibiotics, systemic steroids (in the last month), and antihistamines, expectorants, or local steroids (in the last two weeks) are exclusion criteria. Medications that are allowed include vitamins, vasoconstrictor nasal sprays, and antiseptic throat sprays/candies, provided the investigator is notified in advance.

7.3.6 Variables and data sources

The primary outcome of our study will be the efficacy as measured by the change in the total BSS score, assessed using the Bronchitis Severity Scale [125, 126]. The BSS is a validated clinical tool that assesses the severity of AB by evaluating five key symptoms: cough, sputum production, rales/rhonchi on auscultation, chest pain during coughing, and dyspnoea. Each symptom is rated on a 5-point verbal scale from 0 (absent) to 4 (very severe), resulting in a total score between 0 and 20 [127]. A clinically relevant difference in the change in BSS score was defined based on previous clinical trials. According to published data, the mean BSS change in the placebo group was 3.3 points and 5.7 points in the intervention group, resulting in a clinically meaningful difference of 2.4 points (SD=2.6) [128]. This difference was used to calculate the sample size and represents the minimal clinically important difference to demonstrate superiority in this study.

Change will be evaluated between enrollment (Day 0) and after 7 days of treatment (Day 7). The BSS is a validated tool that evaluates the five most important symptoms of AB: cough, sputum production, rales/rhonchi, chest pain during coughing, and dyspnea. The instrument is based on the clinical assessment of the investigator and the patient feedback. The investigator rates each component of the BSS using a 5-point verbal scale that ranges from 0 to 4 (0: absent; 1: mild; 2: moderate; 3: severe; and 4: very severe) [129]. The total score of the BSS is the sum of the ratings of the five symptoms, with a maximum score of 20. Investigators will be provided with a detailed guide entitled *Form 3: Instructions for evaluating the Bronchitis Severity Score* for accurate assessment of the BSS. Additionally, patients and parents will evaluate the BSS symptoms of the patient on Day 4, excluding auscultation for rales/rhonchi.

The secondary outcome is the assessment of safety and tolerability, as reported by the AEs. To assess safety and tolerability, patients and their parents will be given an AE form at the beginning of the study to record the missed doses, reasons for missed doses, any concomitant medications, and any AEs experienced. During the follow-up visit on Day 7, the investigator will review the completed AE form with the patient and parent, and will record the relevant information in the *Form G: Adverse Event Reporting Form* of the investigator.

QoL will be assessed using a modified Leicester Cough Questionnaire [130]. The questionnaire consists of 18 questions covering three domains and focuses on the physical, emotional, and social impacts of symptoms related to AB in the past 24 hours. QoL will be assessed by the investigator at the baseline and at the 7-day follow-up, and by the parent and patient on the morning of Day 4.

Parents or legal guardians of participants receiving either ETC or placebo will monitor the symptoms of their children daily using *Form E: Medication taking check-list, AEs and QoL*. This form contains a list of possible AEs, but parents/legal guardians are encouraged to report any additional symptoms not listed. Participants will document missed doses, reasons for missed doses, concomitant medications, and any experienced AEs. If allergic reactions, hypersensitivity, or intolerance occur, parents/legal guardians should stop the study medication immediately and notify the pediatrician. The pediatrician will assess and manage the reaction, provide appropriate treatment, and ensure the safety of the participant. Administration of the study medication will be discontinued, the event will be documented and reported according to protocol, and the participant will be monitored until symptoms resolve.

At follow-up visits on Day 7, pediatricians will assess the severity of recorded symptoms and categorize AEs as mild, moderate, or serious. They will also determine whether symptoms are attributable to the disease or the study product. Serious Adverse Events (SAEs) will be closely monitored to ensure participant safety.

Investigators should promptly report suspected Unexpected Serious Adverse Reactions (SUSARs) to the sponsor and relevant national authorities. Investigators are responsible for monitoring the condition of participants until the SAEs resolve or stabilize, unless a participant is lost to follow-up. Therapeutic interventions should be provided as needed during follow-up. SUSARs will be reported via email at clinadr@nngyk.gov.hu. All investigators should document AEs and SAEs. Confirmed events will then be reported to institutional and national ethics committees.

Participants will receive unique identification numbers to ensure confidentiality and tracking. Data collection will follow predefined forms. On the day of random assignment, pediatricians will complete *Form C: Medical history and eligibility of the patient* and *Form D: Baseline form for pediatrician*. During follow-up, parents/legal guardians will

fill out *Form E: Medication taking check-list, AEs and QoL* at home and bring it with them to the visit, where pediatricians will complete *Form F: Follow-up visit form* and, if applicable, *Form G: Adverse event reporting form*. All data will be entered into secure eCRFs by the principal investigator and subinvestigator, with the principal investigator responsible for verifying accuracy. Missing data will be referred to the principal investigator for resolution.

The practice staff will transfer collected data to the electronic Case Report Forms (eCRFs) created and managed using REDCap (Research Electronic Data Capture) electronic data capture tools at Semmelweis University. REDCap is a secure, web-based software platform to facilitate data collection for research studies. It provides an intuitive interface for data entry, tracks changes with audit trails, enables easy data export to statistical software, and supports integration with external data sources [131, 132].

Personal information will be replaced with codes, which are stored securely in encrypted files and locked cabinets and are only accessible to authorized personnel. Data transmission will use industry-standard encryption. Study data will remain stored for three years post-trial for research purposes only.

Informed consent will be obtained privately after study details, risks, benefits, and voluntary participation have been explained. Written consent from parents/legal guardians is required using *Forms B1-B3: Informed consent form*.

A Data Monitoring Committee (DMC) will oversee both participant safety and the scientific integrity of the study. The DMC will periodically review accumulating safety and efficacy data, including unblinded data if necessary, and make recommendations to the SC on continuation, modification, or termination of the trial.

Results will be reported to the Hungarian Medical Research Council and ClinicalTrials.gov. Qualified researchers may request anonymized datasets post-ethical approval, prioritizing participant privacy while enabling collaboration.

7.3.7 Bias and evidence synthesis

The study site will perform assessments at baseline (Day 0) and at follow-up (Day 7) after enrollment (see Table 1). Medical history will be recorded at the baseline visit. Physical examination of patients and QoL assessment will be completed at baseline (Day 0) and

during follow-up (Day 7). On Day 4, patients and parents will evaluate BSS symptoms (excluding auscultation for rales/rhonchi) and are asked to complete a QoL assessment.

Patients and their parents will log medication use, AEs, and concurrent medications on *Form E: Medication taking check-list, AEs and QoL*. These forms will be collected at the follow-up visit on Day 7.

During follow-up, the pediatrician will reassess the BSS score of the patient to measure clinical efficacy, defined as the change in total BSS score between Days 0 and 7. The pediatrician will also evaluate safety and tolerability based on AE reports of patients and parents. Any missed doses or use of concomitant medications will be documented.

After the diagnosis of AB and confirmation of eligibility, patients will be randomized into either Group A (ETC) or Group B (placebo) in a 1:1 allocation ratio on the day of the initial pediatric visit. Randomization will be performed in the REDCap system [131, 132] using the Big Stick Design (BSD) method. The BSD method is one of the Maximum Tolerated Imbalance procedures that can make the allocation process more unpredictable [133].

An unblinded site staff member will randomize the patients and fill out Form 2: Allocation form for the unblinded site staff members. The investigational product or placebo will be provided to patients in coded bottles, with administration handled exclusively by the unblinded staff member. A document detailing the allocation results and bottle coding will be securely stored in a location inaccessible to the pediatrician until the end of the study. Allocation concealment will ensure blinding throughout the study.

To ensure the blinding of both pediatricians and patients, along with their parents or legal guardians, syrups provided to the intervention and placebo groups will be identical in appearance and packaging. An independent individual, not involved in patient care or data analysis, will manage the decoding process to maintain blinding throughout the study.

Pediatricians conducting follow-up examinations should be unaware of the intervention received by patients. Data analysts responsible for comparing primary and secondary outcomes also remain blinded during statistical analysis to ensure unbiased interpretation of results.

Table 1. Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement.

	STUDY PERIOD						Form to use
	Enrollment	Allocation	Follow-up				
TIMEPOINT	Day 0 - first visit	Day 0 - first visit	Day 1 morning - home	Day 4 morning - home	Day 5 evening - home	Day 7- second visit	
Patient Information leaflet	X						Form A
Informed consent form	X						Form B
Eligibility screen	X						Form C
Baseline data	X						Form D
Randomization		X					Form 2
Follow-up data						X	Form F
[Intervention A Elixirium thymi compositum]			◆—	—	—◆		Form E
[Intervention B placebo]			◆—	—	—◆		Form E
[Evaluation of BSS - pediatrician]	X					X	Form D, F
[Evaluation of BSS – parent and patient]				X			Form E
[Quality of life - pediatrician]	X					X	Form D, F
[Quality of life – parent and patient]				X			Form E
[Reported adverse events - parent and patient]			◆—	—	—◆		Form E
[Reported adverse events - pediatrician]						X	Form G

7.3.8 Statistical methods

All statistical analyses and data processing will be performed using R software [134] under Windows 10 and/or MacOS 13 or later. The primary endpoint, the change in BSS from baseline to Day 7, will be analyzed in both the intention-to-treat (ITT) and per-protocol (PP) populations. For the primary hypothesis testing, mean changes in BSS between treatment groups will be compared using a two-sided Student's t-test if the data are normally distributed, or a Mann-Whitney U test if normality assumptions are not met.

For all statistical comparisons, significance will be declared if the two-sided p-value is less than 0.05. All p-values will be reported to two decimal places, except those less than 0.01, which will be reported to three decimal places.

Descriptive statistics will be used for baseline characteristics and safety evaluation. Continuous variables will be presented as the number of missing/non-missing values, mean, SD, median, interquartile range (Q1–Q3), minimum, and maximum. Categorical variables will be summarized with frequencies and percentages (excluding missing data from denominators).

Secondary continuous outcomes will be analyzed using either t-tests or Mann-Whitney U tests, depending on the distribution of the data. Categorical outcomes will be compared using chi-square tests or Fisher's exact tests, as appropriate. This approach ensures that the statistical methods are matched to the data characteristics and that the results are robust and reliable.

As the efficacy of ETC had not been previously evaluated in clinical trials, the sample size was estimated based on published data from studies of comparable plant extract-based products [128, 129, 135-147]. In these trials, the mean reduction in BSS was 5.7 points in the intervention group [141] and 3.3 points in the placebo group [128], with a SD of 2.6 points [128].

The superiority margin, defined as the minimum clinically important difference (MCID), was set at 2.4 points on the BSS. This threshold corresponds to the MD observed between the intervention and placebo groups in prior studies and aligns with clinically meaningful symptom improvements in pediatric AB. Although no formal MCID for pediatric BSS has been established, this margin balances feasibility and clinical relevance.

To detect this difference between groups with 90% power and a two-sided significance level of 0.05, a minimum of 15 participants per group was required. To account for attrition, a 20% post-enrollment dropout rate and a 25% screen failure rate were applied, estimating that 45% of enrolled patients would not complete the study. The final adjusted sample size was set at 28 participants per group, for a total of 56 patients. Table 2 summarizes the parameters and assumptions used for this calculation.

Table 2. Parameters used to calculate sample size

Number of groups	2
Relationship between groups	Parallel
Trial Objective (Hypothesis)	Superiority
Endpoint	BSS score
Summary Measure of Endpoint	Average of the BSS score decrease
Effect size	Mean BSS change Placebo = 3.3 [128] Mean BSS change Intervention = 5.7 [141]
Secondary Parameters	SD change = 2.6 [128]
Type I Error	0.05
Type II Error	0.1
Other Factors	Drop-out Rate 20% Screen Failure Rate 25%
Sample Size	28 patients / group

8. RESULTS

8.1 Study I: Inhaling Peppermint Essential Oil is Beneficial in the Treatment of Nausea and Vomiting

8.1.1. Search and selection

Our systematic search identified 1547 articles: Scopus (n=970), EMBASE (n=341), Cochrane Library (Trials) (n=93), Web of Science (n=78), and PubMed (n=65). After duplicate removal (n=483), title and abstract selection (n=1064), and full-text selection (n=71), we identified sixteen eligible articles (Figure 2). After our renewed systematic search, we found three more eligible studies. In total, seventeen publications were identified through an electronic search of databases, and two additional publications by the "citationchaser" tool [94] (eleven postoperative studies [36, 41, 151-159], five chemotherapy studies [38, 39, 157-159], and three pregnancy studies [37, 40, 160]). We included fourteen studies in the quantitative analysis (postoperative patients: [41, 148, 149, 151, 152, 153, 154, 155], chemotherapy patients: [38, 39, 157], and pregnant women: [37, 39, 160]). Five studies were included in the qualitative analysis (postoperative patients: [36, 150, 156], as well as chemotherapy patients: [158, 159]). The search results and the selection process are summarized in the PRISMA flowchart 2020 (Figure 2).

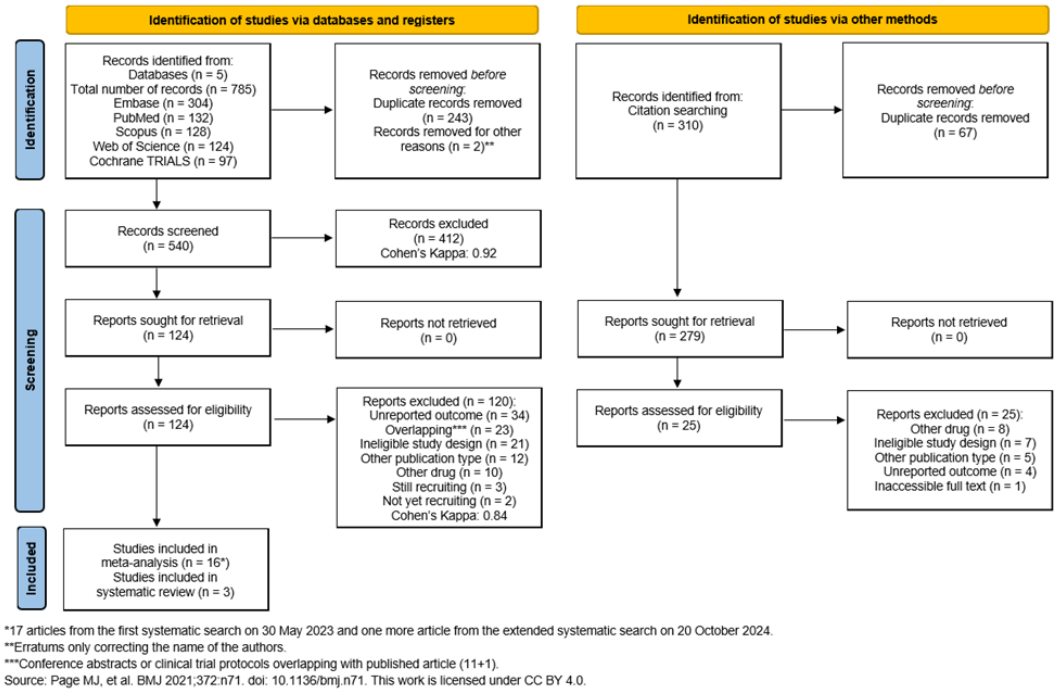


Figure 2. PRISMA 2020 flow diagram for searches in databases and other sources [91].

8.1.2. Basic characteristics of the included studies

The baseline characteristics of the studies included in the meta-analysis are detailed in Table S1. Types and original ranges of the NV measurement tools are detailed in Table S2. Postoperative studies were conducted across various countries, including Iran, the USA, Turkey, South Korea, and the UK. Sample sizes varied, ranging from 18 patients to over 1000. The mean age of patients ranged from the early 30s to the mid-70s, with most studies focusing on middle-aged adults. Gender distribution varied, with some studies including only female participants, while others were more balanced. Surgical procedures were diverse, with some studies involving abdominal, open-heart, laparoscopic, orthopedic, and gynecological procedures. Most studies used peppermint EO as an intervention, with a few using peppermint spirit. Peppermint spirit is a pharmacy-grade, alcohol-based solution containing approximately 82% ethyl alcohol, peppermint oil, peppermint leaf extract, and purified water [149, 156]. The follow-up periods ranged from 5-10 minutes up to 72 hours.

Chemotherapy studies were conducted in Turkey, Iran, the USA, and Indonesia. Sample sizes ranged from 80 to 285 patients. The mean age of patients was between 40 and 60 years. Most studies included a high proportion of female participants, with two studies focusing exclusively on breast cancer patients. Cancer types were diverse, including breast, liver, melanoma, lymphoma, sarcoma, cervical, lung, nasopharyngeal, and colon cancers. Follow-up periods ranged from 5 minutes to 5 days.

Pregnancy studies were conducted in Iran and Italy. Sample sizes ranged from 56 to 66 participants. The mean age of pregnant women was in their mid-20s. Gestational age at the time of intervention was primarily in the first trimester, averaging between 9 and 12 weeks. Follow-up periods ranged from 4 to 7 days.

8.1.3. Synthesis of the results

8.1.3.1 Efficacy of Peppermint Oil in Postoperative Patients

We analyzed the effects of peppermint oil on NV severity in postoperative patients across different time points, with a total of 453 participants at baseline (peppermint/control: 233/220), as shown in Figure 3. At 5 minutes after the intervention, no statistically significant difference was observed in the severity of NV between the peppermint and the control groups (MD=-1.59 scores, 95% CI: -9.29 to 6.10, p=0.467). A high heterogeneity

was observed (I^2=95%, CI: 89-98%). During the first two hours after the intervention, the MD was -0.87 scores (95% CI: -3.41 to 1.67, p=0.277), with higher heterogeneity (I^2=80%, CI: 36-94%). The most notable improvement occurred during the 2-6-hour period, where peppermint oil showed a statistically significant benefit (MD=-0.60 scores, 95% CI: -0.77 to -0.44, p=0.004), with no significant heterogeneity (I^2=0%, CI: 0-90%). During the 6-12-hour period, the effect size increased (MD=-0.82 scores, 95% CI: -2.65 to 1.02, p=0.251), but was not statistically significant, with high heterogeneity (I^2=81%, CI: 52-93%). This persisted through the 12-24-hour period (MD=-0.88 scores, 95% CI: -0.29 to 0.53, I^2=71%, CI: 18-90%, p=0.141). By 24-48 hours after intervention, the effect decreased (MD=-0.37 scores, 95% CI: -1.61 to 0.88, p=0.682), although heterogeneity was moderate (I^2=62%, CI: 0-89%). These findings suggest that peppermint oil in postoperative patients is the most effective in the 2-6 hours after intervention, with variable effects at other time points to reduce the severity of NV. The large heterogeneity at several time points is possibly due to differences in surgical procedures, patient populations, intervention type (peppermint EO or spirit), frequency of intervention, etc.

In some studies, PONV scores are reduced with peppermint oil at later time points (24-48 hours) [149, 154]. However, other studies show minimal differences [148, 155]. At early time points (5-10 minutes), some studies [152, 156] show an initial rapid decrease in nausea. Differences between studies may be due to differences in study design, patient population, or peppermint formulation.

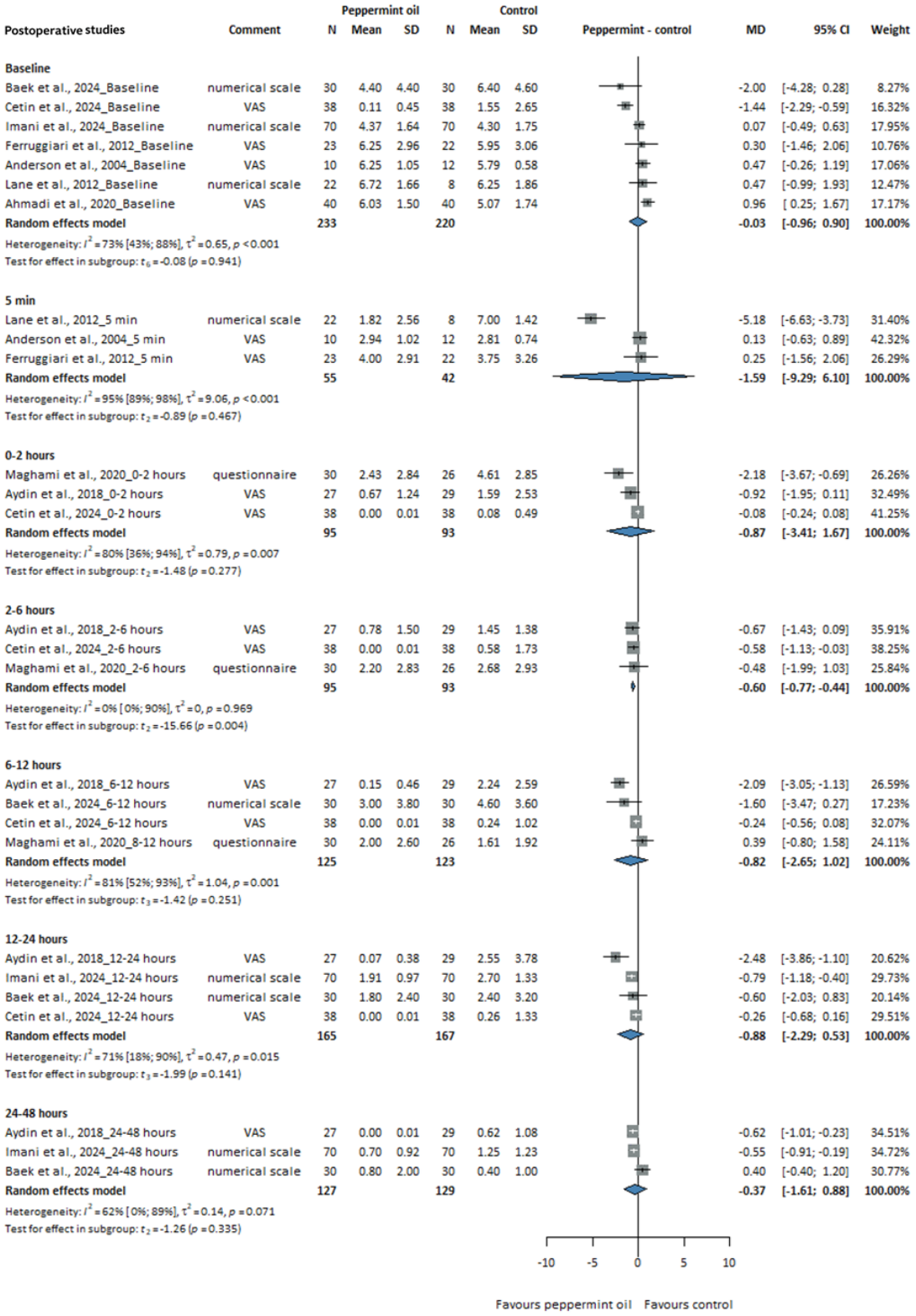


Figure 3. Severity of nausea and vomiting in postoperative patients (MD=mean difference, CI=confidence interval).

8.1.3.2 Efficacy of Peppermint Oil in Pregnant Women

Table S1 summarizes the key characteristics of NV studies on pregnancy. In the analyzed studies, pregnant women inhaled peppermint oil using varying regimens: some inhaled twice or four times daily, others breathed it in for the whole night. We analyzed the effect of peppermint oil on the severity of NV in pregnant women with a total of 283 participants at baseline (peppermint/control:189/94), as shown in Figure 4. Results varied, but heterogeneity remained insignificant (I^2=0%, CI: 0-90%) at different time points. At 24 hours, the MD was -0.09 scores (95% CI: -0.79 to 0.61), showing no significant difference between groups (p=0.638). At 48 hours, the MD was -0.51 scores (95% CI: -0.78 to - 0.24), showing a statistically significant improvement (p=0.015) in favor of peppermint oil. At 72 hours, the effect size decreased with an MD of -0.20 scores (95% CI: -1.02 to 0.62) with no statistical significance (p=0.400). At 96 hours, the MD was - 0.68 scores (95% CI: -1.09 to -0.27), showing a significant improvement (p=0.019) in favor of peppermint oil. These results suggest that peppermint oil may be effective in reducing NV in pregnant women, particularly at 48 and 96 hours after intervention. Consistent, non-substantial heterogeneity indicates reliable results across studies, although effect sizes varied at different time points.

Peppermint oil is associated with a more significant reduction in NV scores over time than the control, especially after day 2, indicating a potential benefit of peppermint oil in reducing NVP. Although there is some variability, there are reduced NVP scores with peppermint oil compared to the control group at seven days. The study by Pasha et al. 2012 [160] has the largest difference between the two groups.

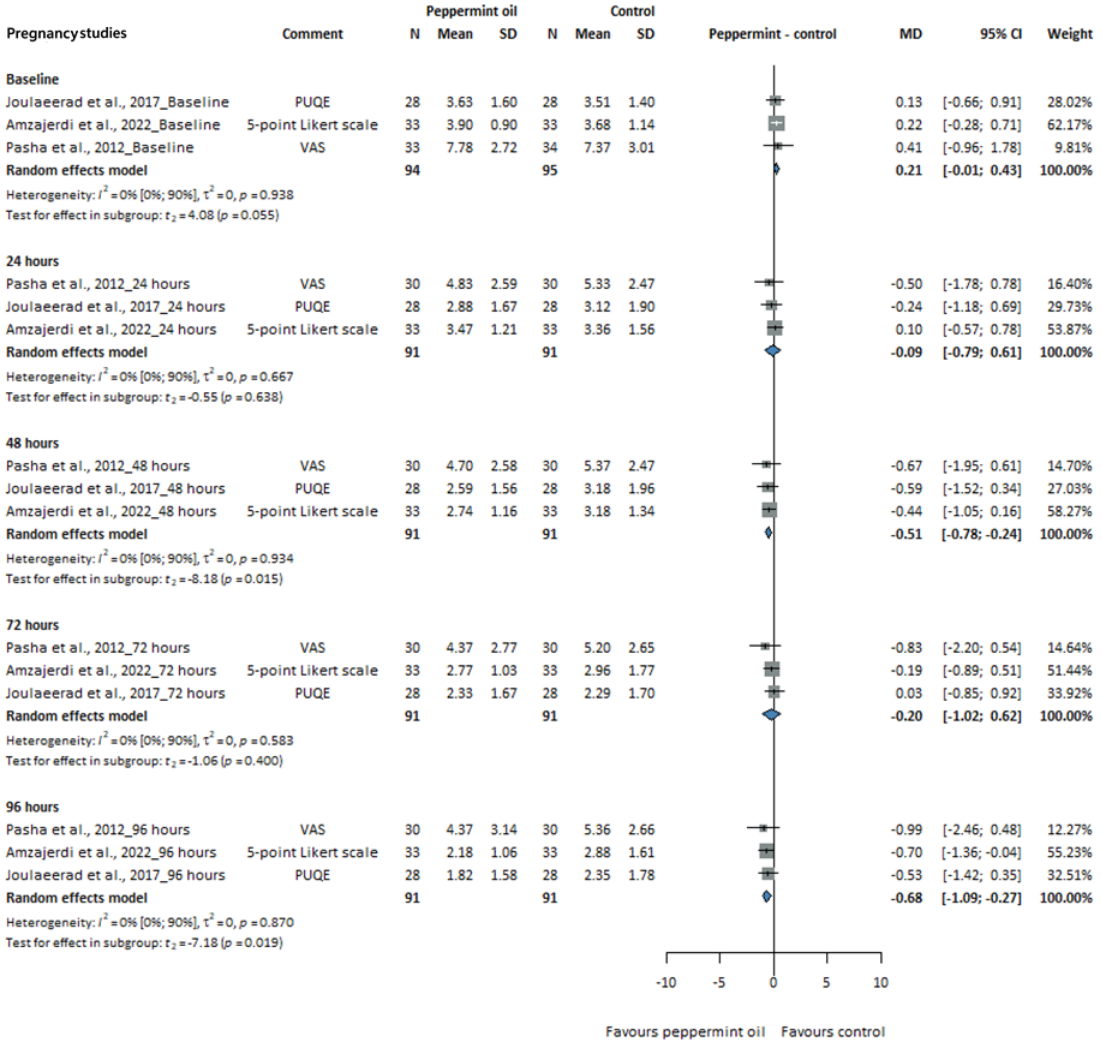


Figure 4. Severity of nausea and vomiting in pregnant women (MD=mean difference, CI=confidence interval).

8.1.3.3 Efficacy of Peppermint Oil in chemotherapy patients

Table S1 summarizes the key characteristics of CINV studies. We analyzed the effect of peppermint oil on the severity of NV in chemotherapy patients with a total of 264 participants at baseline (peppermint/control: 128/136) as shown in Figure 5. The analysis demonstrated consistently favorable results for peppermint oil at multiple time points. The difference between the effect of peppermint oil compared to placebo is statistically significant at 24 hours after intervention, with an MD of -1.85 scores (95% CI: -2.86 to

-0.84, p=0.004) with higher heterogeneity (I^2=83%, CI: 66-91%). At 48 hours, the improvement was maintained with an MD of -2.23 scores (95% CI: -3.13 to -1.34) with statistical significance (p<0.001) and moderate heterogeneity (I^2=63%, CI: 16-84%). The 72-hour assessment showed a consistent advantage with an MD of -2.41 scores (95% CI: -3.96 to -0.86) with statistical significance (p=0.010) and moderate heterogeneity (I^2=60%, CI: 3-84%). By 96 hours, while the effect size decreased slightly, it remained significant with an MD of -2.11 scores (95% CI: -3.48 to -0.73, p=0.011) and with higher heterogeneity (I^2=79%, CI: 55-91%). These results demonstrate that peppermint oil consistently reduced the severity of NV compared to placebo across all analyzed time points.

Patients receiving peppermint oil had lower nausea scores than the control group throughout the five-day observation period, indicating that peppermint oil has a potential benefit in reducing CINV. The study by Ertürk et al. 2021 [38] showed significantly lower nausea scores in the peppermint oil group using different chemotherapy regimens. It is important to note that in this study, the control group did not receive anything, which limits the ability to directly attribute the observed effects to peppermint oil compared to standard care or placebo. However, the studies of Jafarimanesh et al. 2020 [39] and Eghbali et al. 2017 [157] used a placebo control, and they showed smaller differences between the two groups. In most studies, there was a clear reduction in CINV scores with peppermint oil, but this varied depending on the type of chemotherapy.

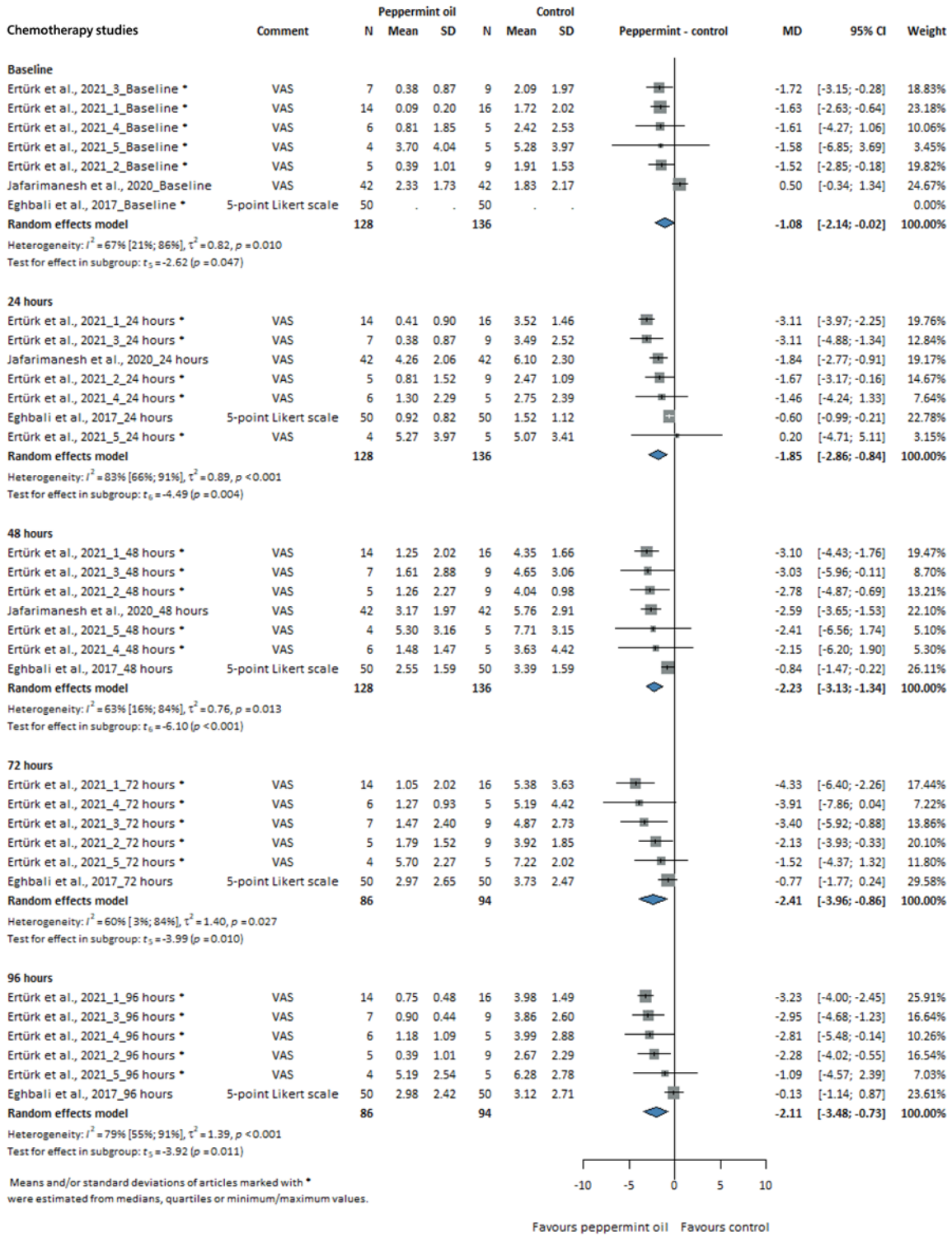


Figure 5. Severity of nausea and vomiting in chemotherapy patients (MD=mean difference, CI=confidence interval).

8.1.3.4 Adverse events

No AEs were reported in postoperative studies with the inhalation of peppermint oil [36, 41, 148-156]. In chemotherapy studies, few patients reported adverse events. In a study by Ertürk et al. 2021 [38], two of 36 patients in the intervention group had headaches, and 3 experienced increased frequency and severity of nausea. In a study by Mapp et al. 2020 [159], only 1 of the 36 patients reported feeling worse after inhaling peppermint. Chemotherapy studies by Jafarimanesh et al. 2020 [39] and Eghbali et al. 2017 [157] concluded that a standard dose of peppermint oil does not cause AEs. The study by Lestari et al. 2017 [158] did not report any AEs after peppermint treatment. Studies on pregnancy reported no AEs during the inhalation of peppermint oil [37, 40, 160].

8.1.3.5 Risk of Bias Assessment and Quality of Evidence

The risk of bias was a concern across all studies. While some studies were well-conducted, most had issues related to blinding participants and personnel because of peppermint oil's distinctive scent. Only a few postoperative studies achieved a low risk of bias across all domains, and pregnancy studies also had some concerns. In chemotherapy studies, intervention adherence and reporting were generally robust, but uncertainties in randomization remained. A summary of the risk of bias assessment is presented in Figure S1.

The GRADE assessment further shows that the certainty of evidence for peppermint oil inhalation in these settings was consistently low, mainly due to risk of bias and imprecision from small sample sizes. Although different measurement tools contributed to some heterogeneity, inconsistency, and indirectness were not major concerns. Overall, while peppermint oil inhalation may help reduce nausea and vomiting, confidence in these findings is limited. A summary of the GRADE findings is presented in Table S4.

These limitations highlight the need for cautious interpretation of the pooled results and underscore the importance of rigorous study design, including improved randomization, effective blinding, and comprehensive reporting. Larger, well-designed trials with standardized outcome measures and better blinding are needed in future studies.

8.1.3.6 Publication bias and heterogeneity

Egger's test for publication bias could not be performed as no outcome had enough studies (at least 10) to meet the test requirements. We found no evidence of publication

bias for the outcomes. However, our analysis was underpowered due to the small number of studies

8.2 Study II: Efficacy and Safety of L-Menthol During GI Endoscopy

8.2.1. Search and selection

The systematic search on 31 May 2023, identified 785 studies from five databases: EMBASE (n = 304), Scopus (n = 128), PubMed (n = 132), Web of Science (n = 124), and Cochrane Library (Trials) (n = 97). After removing 245 duplicates, 540 unique studies remained. Following title and abstract selection, 416 studies were excluded. After our renewed systematic search on 20 October 2024, we found one more eligible study. We also conducted a post hoc search of ClinicalTrials.gov on 25 October 2024. This search identified one additional eligible study.

Sixteen studies were included: 14 studies for quantitative analysis (colonoscopy: [107, 161-166], upper endoscopy: [167-173] and two studies for qualitative analysis (upper endoscopy: [174], colonoscopy: [175])

We used the ‘citationchaser’ tool [94] to explore more relevant studies; however, none were added. No meta-analyses were possible for ERCP and EUS due to the lack of available studies in the literature [176-180]. The search and selection process is summarized in the PRISMA-Flowchart 2020 (Figure 7).

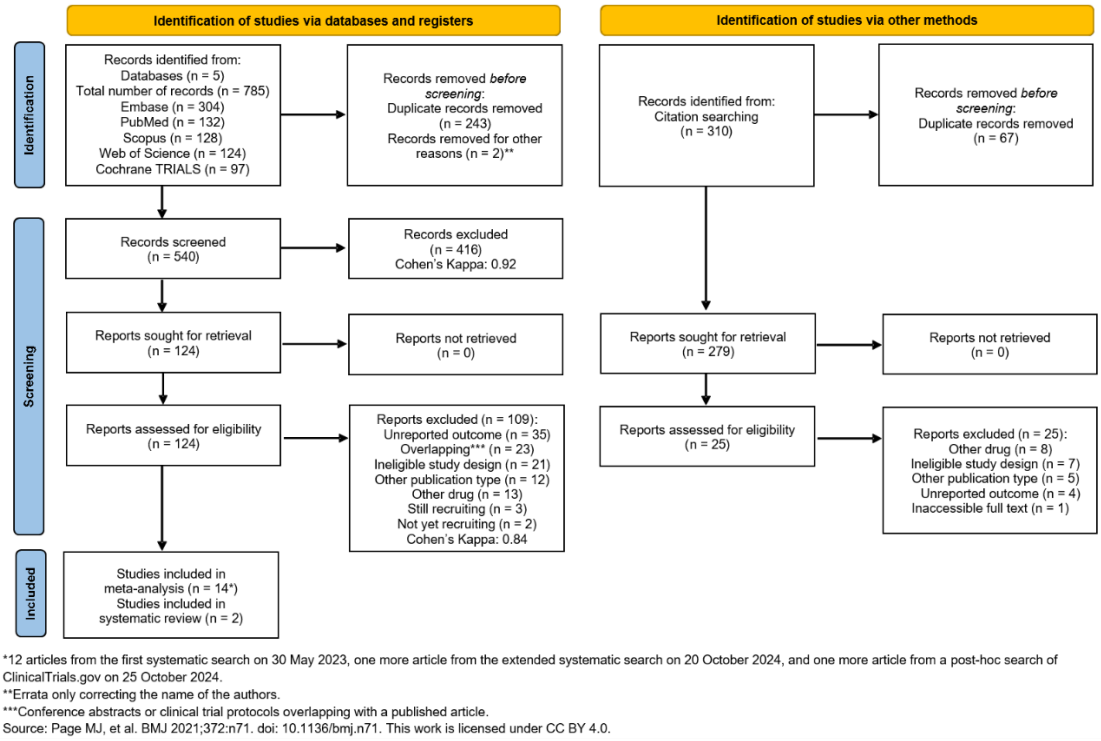


Figure 7. PRISMA 2020 flow diagram for searches in databases and other sources [91].

8.2.2. Basic characteristics of the included studies

Of the included studies, the majority were conducted in Asia, with 10 studies in Japan [107, 163, 164, 167-170, 172, 174, 175], one in China [171], one in Taiwan [173], one in Thailand [165], and one in Iran [181]. Three studies were conducted in North America: two in the USA [161, 165] and one in Canada [162].

Gastric peristalsis was evaluated using Niwa's Classification [122] or the modified version of Niwa's classification [168]. Colonic peristalsis was assessed using the method reported by Asao et al. (2001) [107]. The baseline characteristics of each study are detailed in Table S3.

8.2.3.1 Antiperistaltic Effect of L-Menthol

Ten studies [162-169, 171, 173] reported on the proportion of no peristalsis (PNP). PNP had a high overall heterogeneity (I^2=88%, p<0.001). For colonoscopy, the analysis of PNP data (405/716, 56.6%, OR=3.06, 95% CI: 0.97 to 9.63, p=0.054) indicates a trend toward efficacy that did not reach statistical significance. In studies of upper endoscopy (155/286, 54.2%, OR=4.47, 95% CI: 2.23 to 8.97, p=0.004), and overall PNP (560/1002, 55.9%,

OR=3.88, 95% CI: 2.13 to 7.07, p<0.001), L-menthol demonstrated a significantly higher antispasmodic effect compared to placebo, as shown in Figure 8.

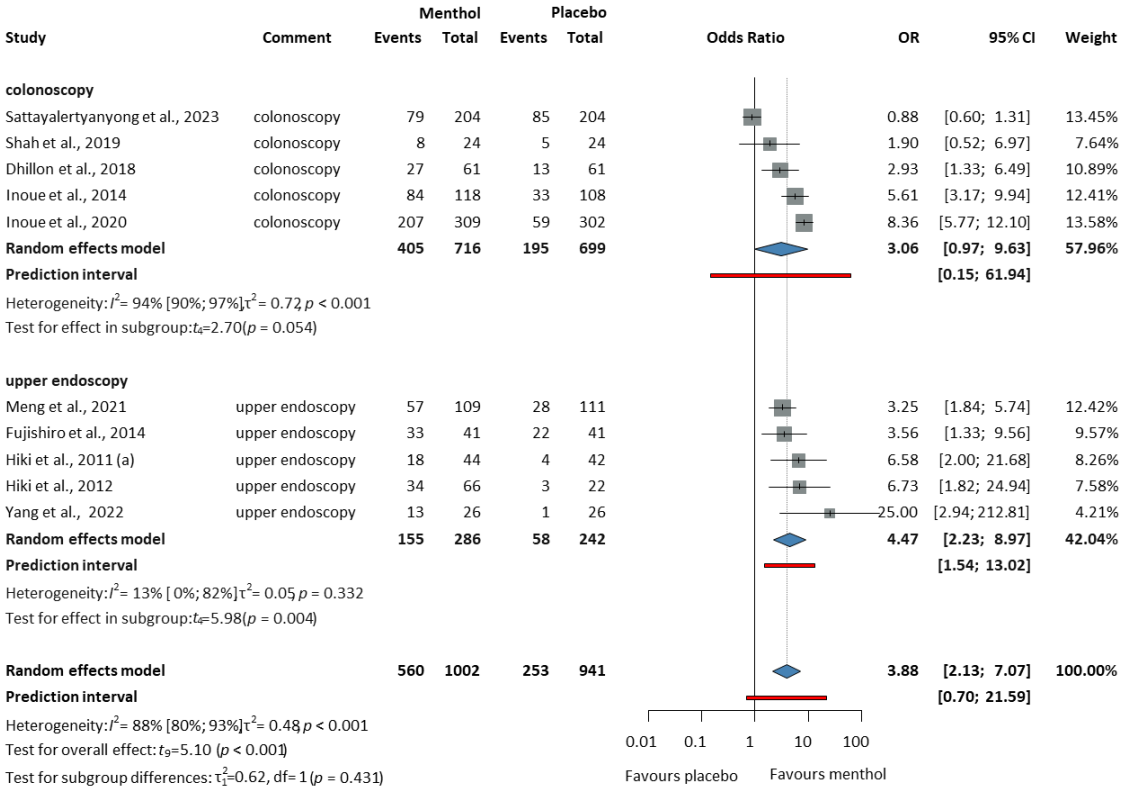


Figure 8. Forest plot of the proportion of no peristalsis (PNP) in colonoscopy and upper endoscopy showing pooled ORs with 95% CIs for menthol versus placebo. OR = odds ratio, CI = confidence interval, D = domain

Eleven studies [107, 163-169, 171-173] reported data on the proportion of no or mild peristalsis (PNMP). Heterogeneity was high (I^2=85%, p<0.001). For colonoscopy, the analysis of PNMP data (649/690, 94.1%, OR=3.36, 95% CI: 0.27 to 42.41, p=0.255) indicated no statistically significant antiperistaltic effect of L-menthol compared to placebo. In studies of upper endoscopy (251/335, 74.9%, OR=3.79, 95% CI: 0.91 to 15.82, p=0.062), a trend toward efficacy was observed, though this did not reach statistical significance. In the overall PNP (900/1025, 87.8%, OR=3.70, 95% CI 1.27 to 10.76, p=0.021),

Yoshida et al. (2014) [175] demonstrated a rapid antispasmodic effect of L-Menthol. It reduced peristalsis in 60.0% (39/65) of cases within 30 s and 70.8% (46/65) within 1 min, compared to 22.2% (6/27) and 29.6% (8/27) in the control group. Imagawa et al. (2012)

[174] assessed spasm severity using antispasmodic scores (1–5, where 5 indicates no spasm). This study reported higher scores in the peppermint oil group (4.025 (0.925), n=1893) compared to the placebo group (3.846 (1.073), n=156), indicating effective peristalsis reduction.

Subgroup analysis identified specific patient groups where L-menthol demonstrates superior efficacy. Unsedated upper GI procedures showed the strongest effects in elderly patients (mean age 81.7 vs. 82.6 years) [173], and in middle-aged participants (mean age 51.64 vs. 51.44 years) [171]. These findings suggest that L-menthol may benefit those with contraindications to antispasmodic drugs or sedation. In contrast, colonoscopy studies yielded more modest effects, likely due to greater procedural complexity and more common use of sedation or general anesthesia.

8.2.3.2 Ease of Examination for the Operator in Upper Endoscopy

Four upper endoscopy studies [168, 169, 171, 173] evaluated ease of examination, using a four-grade scale (very easy, easy, slightly difficult, and difficult) shown in Figure 9. There was no heterogeneity (I^2=0%, p=0.548). Thus, a fixed-effects model was used to pool data. The endoscopic procedure was significantly easier for the operator when L-menthol was applied (OR=2.53, 95% CI: 1.35 to 4.73, 206/256 subjects, p=0.018).

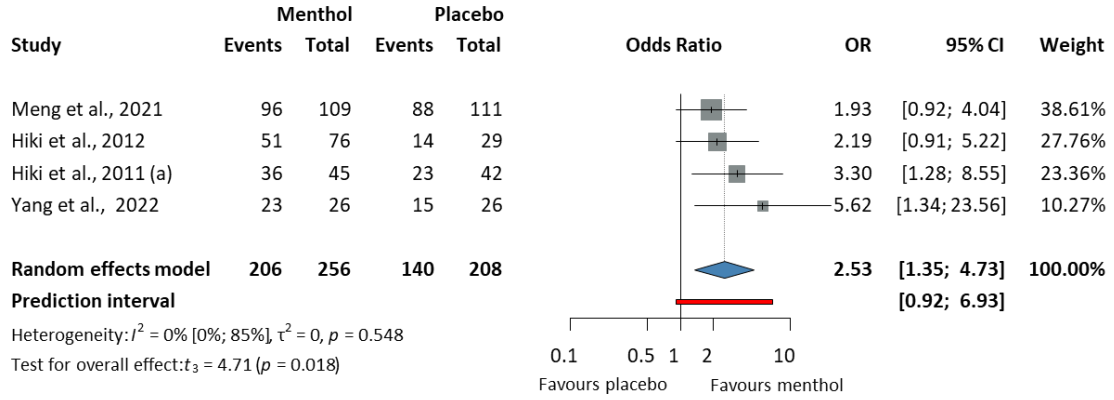


Figure 9. Forest plot of ease of examination for the operator in upper endoscopy showing pooled ORs with 95% CIs for menthol versus placebo. OR = odds ratio, CI = confidence interval, D = domain

This benefit was most evident in unsedated patients (improved ease for 88.1% vs. 79.3% patients [171]). Neither age, co-morbidities, nor gender moderated this effect, supporting L-menthol's broad applicability.

8.2.3.3 Total Adverse Events

Four studies reported no major [162], serious [172], or any [163, 164] AEs during the procedure. Nine studies [161, 165-171, 173] reported the number of AEs. Commonly reported GI symptoms included abdominal pain, nausea, diarrhea, heartburn, and bloating, observed in both colonoscopy and upper endoscopy studies. Some studies also noted dizziness, headache, and fever. Additionally, cardiovascular changes, including electrocardiogram ST-T changes, palpitations, and ventricular premature beats, were observed. Urinary tract infections or respiratory infections were observed as well. The pooled OR did not indicate a significant difference in total adverse events between the L-Menthol and the placebo groups (OR=0.97, 95% CI: 0.74 to 1.27, p=0.937), as shown in Figure 10.

Differences in AE proportions were observed when analyzing the data separately for colonoscopy and upper endoscopy groups. In the colonoscopy group, the proportion of patients experiencing AEs was 3.35% (20/597 patients) in the L-menthol group and 4.08% (24/588 patients) in the placebo group. In the upper endoscopy group, AEs were reported in 18.98% (71/374 patients) in the L-menthol group and 17.43% (53/304 patients) in the placebo group.

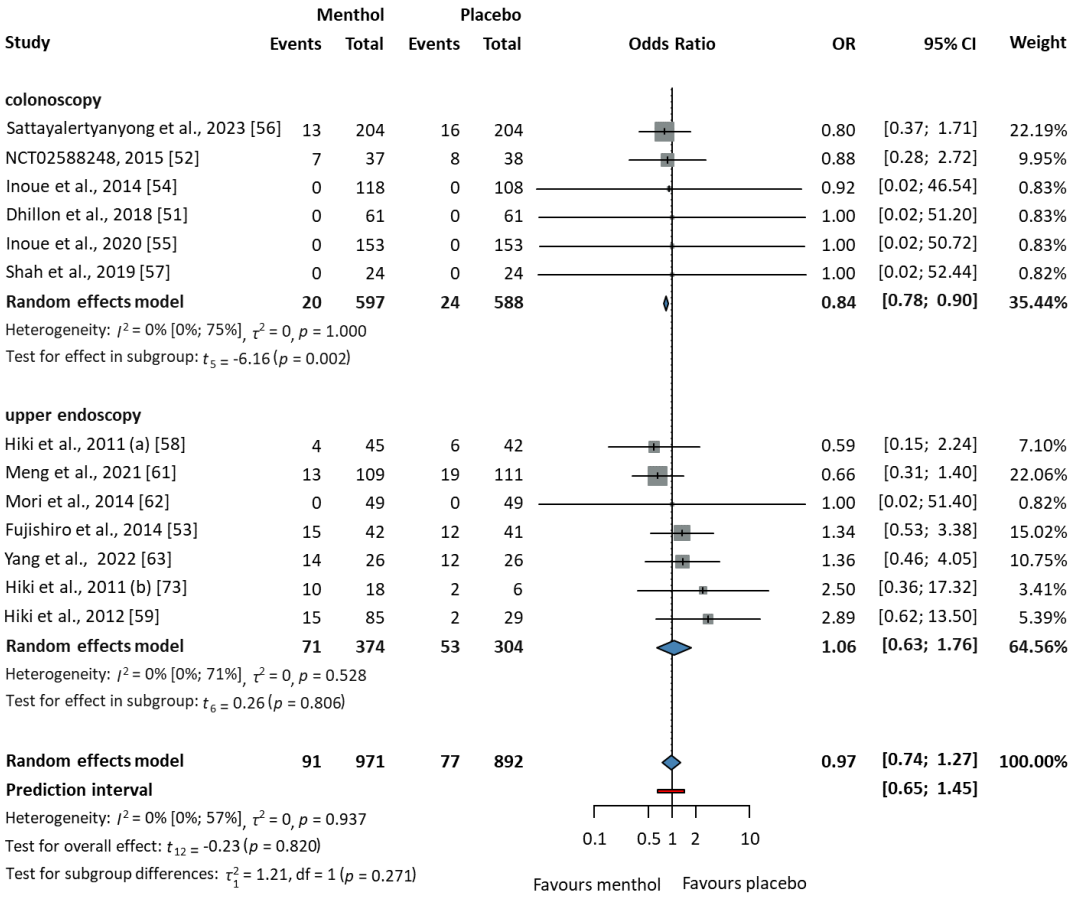


Figure 10. Forest plot of adverse events showing pooled ORs with 95% CIs for menthol versus placebo. OR = odds ratio, CI = confidence interval, D = domain

8.2.3.4 Studies with Peppermint Capsules

Three studies evaluated peppermint oil in orally administered formulations, specifically IBGard™ [182] and Colpermin® [183], both of which are frequently used to manage symptoms of IBS [184, 185]. Although these products and studies were not included in our main analysis, they are presented here to provide a more comprehensive overview of the therapeutic profile of peppermint EO.

Han et al. (2021) [186] found no significant difference in the ADR between the two groups (IBGard™: 47.8% vs. placebo: 43.1%; p=0.51). Shavakhi et al. (2012) [181] found significantly lower spasm scores in the Colpermin® compared to placebo (no movement: 25 vs. 0; any movement: 8 vs. 32). Al Moussawi et al. (2017) [187], however, reported no significant difference between the groups. In the ease of examination scores, Han et al. (2021) [186] reported no significant difference (p=0.23). Similarly, Al Moussawi et al. (2017) [187] found no significant differences in endoscopist satisfaction

scores between Colpermin® and placebo groups (p=0.8). Han et al. (2021) [186] observed slightly shorter withdrawal times in the placebo group compared to the IBGard™ group (14.5 min (10.3) vs. 16.5 min (8.3 min)), although this difference was not significant (p=0.31). For AEs, Shavakhi et al. (2012) [181] observed isolated cases of abdominal discomfort, nausea, blurred vision, and heartburn. Meanwhile, Al Moussawi et al. (2017) [187] and Han et al. (2021) [186] reported no AEs in either group.

8.2.3.5 Risk of Bias Assessment and Quality of Evidence

The risk of bias was assessed for each outcome using the RoB2 tool, and GRADE certainty was evaluated per outcome. For the ADR, most studies were rated as having "some concerns," primarily due to deviations from intended interventions, measurement of the outcome, and selection of the reported result. The assessment of the PNP showed greater variability; several studies exhibited "some concerns" or "high risk", while others demonstrated low risk across all domains. Outcomes such as ease of examination and AEs were generally associated with low risk of bias, though a few studies still showed "some concerns". Withdrawal time was often rated as having "some concerns," mainly due to issues with adherence to the intervention and outcome measurement. The RoB2 judgements are provided in Figure S4. The overall certainty for each outcome is summarized in Table S5, with detailed explanations provided.

8.2.3.6 Publication bias and heterogeneity

We included conference abstracts in our analysis and also attempted to contact the corresponding authors of included studies to identify unpublished data, although no additional information was obtained. To further mitigate publication bias, we conducted citation chasing using the Citationchaser tool [105] to identify relevant studies from the reference lists of eligible articles. We found no evidence of publication bias for the rest of the outcomes. However, our analysis was underpowered by the small sample size.

8.3 Study III: Elixirium thymi compositum in the treatment of acute bronchitis in pediatric patients

8.3.1 Planned Analyses

As of the current protocol stage, no study data have been collected or analyzed. Upon completion, the primary analysis will report the difference in mean BSS score change from baseline to Day 7 between the ETC and placebo groups. Secondary analyses will

summarize safety and tolerability outcomes, QoL scores, and patterns of concomitant medication use. These results will determine whether ETC provides a clinically meaningful benefit in the treatment of pediatric AB and will inform future clinical practice and guidelines.

8.3.2 Data Reporting

All collected data will be entered into secure electronic case report forms (eCRFs) and analyzed according to the statistical plan. The results will be reported to regulatory authorities and disseminated via peer-reviewed publications and scientific conferences.

8.3.3 Contextualization with Prior Evidence

Previous studies on thyme-based herbal medicines (e.g., thyme-ivy, thyme-primrose extracts) have shown significant reductions in BSS and cough frequency compared to placebo, with favorable safety profiles [137, 139]. The current trial seeks to build on this evidence by employing a rigorous, double-blind, placebo-controlled design in a pediatric population, thereby addressing a gap in the existing literature and providing high-quality evidence for clinical practice.

9. DISCUSSION

9.1 Summary of findings, international comparisons (including all studies)

Study I is the most comprehensive systematic review and meta-analysis on this topic to evaluate the efficacy of peppermint oil alone compared to control in three distinct patient populations – PONV, CINV, and NVP – with each group analyzed independently at multiple time points. As a result, peppermint oil inhalation may be a promising complementary approach in managing NV. There was a significant difference between the peppermint and the control groups in the reduction of PONV within 2-6 hours, NVP within 48 and 96 hours, and CINV from 24 to 96 hours, supporting the benefits of peppermint oil inhalation. However, it is important to emphasize that these findings should be considered exploratory, given the substantial methodological limitations and heterogeneity across the included studies. At all outcomes, the certainty of evidence was rated as low, primarily due to methodological concerns such as the difficulty of blinding (given peppermint's distinctive scent), inconsistency in measurement tools, and imprecision resulting from small sample sizes (Table S1). Nearly all included trials had some risks of bias, with many being open-label or lacking adequate blinding. The considerable heterogeneity among the studies, such as differences in the form of peppermint (essential oil vs. spirit), dosage, and frequency of inhalation, further complicates the interpretation of pooled results. High I^2 values in several analyses indicate divergent results between studies.

An additional challenge in interpreting these findings arises from the diversity of control interventions used across the included RCTs. While some studies employed placebos (such as saline or water), others used active comparators, including alternative essential oils or non-olfactory interventions like controlled breathing exercises. This variability makes it difficult to isolate the specific pharmacologic effect of peppermint oil from the general therapeutic context or non-specific effects. Additionally, as most included studies lacked blinding, patient awareness of receiving a fragrant intervention could enhance placebo responses or create positive expectations of symptom relief.

The analysis of postoperative RCTs demonstrated significant reductions in nausea severity following peppermint oil inhalation [36, 41, 149, 152], while others reported only mild or non-significant effects but still showed potential benefits [151, 155, 156]. While peppermint oil inhalation was associated with statistically significant reductions in PONV

severity, the improvement was modest and generally below the established minimal clinically important difference (MCID) of approximately 1.5 points on a 0–10 nausea scale [188]. However, peppermint oil is primarily used as a complementary therapy when conventional antiemetics are contraindicated or not preferred. In these situations, even modest symptom relief may be valuable, especially given peppermint oil's favorable safety profile, low cost, and ease of administration.

Sites et al. (2014) [156] compared controlled breathing (CB) with peppermint spirit to CB alone in PONV management. After 10 minutes, there was no significant difference in efficacy (p=0.61) or antiemetic rescue medication use (p=0.76) between CB alone and CB with peppermint spirit. The study recommended CB as a first-line treatment while acknowledging the potential benefits of peppermint spirit. Tate et al. (1997) [150] compared peppermint oil, peppermint essence, and no treatment for PONV. By day 2, the peppermint oil group had zero nausea (0.00), compared to peppermint essence (0.05) and placebo (0.32). Patients in the peppermint oil group also required slightly less antiemetics.

A previous meta-analysis of Wang et al. (2024) [189] evaluated the effects of ginger, lavender, and peppermint aromatherapy on PONV. In their analysis, the most significant effect was observed with ginger. Peppermint oil and lavender oil also showed significant effects. In another meta-analysis by Hines et al. (2018) [190] with aromatherapy, peppermint oil did not affect the severity of nausea after treatment (4 studies, intervention/control:68/47, 5 minutes). These findings suggest that peppermint oil may be beneficial for managing PONV.

The analysis of the RCTs in pregnant women indicated that inhalation of peppermint oil can effectively reduce symptoms at specific time points, particularly at 48 and 96 hours. The peppermint intervention demonstrated a statistically significant reduction in NV severity compared to the placebo group [37, 40]. These findings suggest that peppermint oil may be a valuable non-pharmacological option for pregnant women experiencing NVP, especially given the limitations in treatment choices due to safety concerns [191]. Despite achieving statistical significance in NVP severity with peppermint oil inhalation in pregnant women, the magnitude of improvement was modest and generally below the MCID [188]. Still, the complementary use of peppermint oil is also relevant for pregnant women, especially when standard antiemetic medications are not suitable. In these

circumstances, even small improvements in symptoms may be meaningful. Two reviews mentioned the efficacy of peppermint oil on NVP. These studies are included in our analysis [192, 193]. Due to the paucity of studies, ours is the first meta-analysis on peppermint oil in NVP.

The analysis of the RCTs in chemotherapy patients demonstrated the potential of peppermint oil inhalation as a low-cost, non-invasive intervention for reducing the severity of CINV [194, 195]. Studies showed consistent benefits across multiple days, suggesting that peppermint oil was effective in acute and delayed CINV [196, 197].

A study by Mapp et al. (2020) [159] evaluated the efficacy of a cool, damp washcloth with peppermint EO versus a washcloth alone in managing CINV. After 30 minutes, the peppermint group reported significantly better improvement than the control group using the Baxter Retching Faces scale ($p=0.020$) [198]. Lestari et al. (2017) [158] compared peppermint oil to standard hospital care based on the Rhodes Index. After 5 minutes, peppermint aromatherapy reduced CINV symptoms more significantly than standard care ($p=0.001$ vs. $p=0.02$).

Standard pharmacological antiemetic prophylaxis often comes with adverse events. Commonly used agents such as ondansetron can cause arrhythmias [199], dexamethasone is associated with hypokalemia [200], and metoclopramide may induce extrapyramidal symptoms [201]. These adverse effects can limit the use of pharmacological antiemetics, particularly in patients with contraindications or those at higher risk for complications. In contrast, peppermint oil inhalation has a favorable safety profile and is generally well tolerated, without serious adverse events.

In a previous meta-analysis, Ahn et al. (2024) [196] examined the efficacy of EOs, including lavender, chamomile, peppermint, orange, ginger, damask rose, and sage. Peppermint oil was the most effective in reducing nausea and vomiting. Another meta-analysis by Toniolo et al. (2021) [197] on aromatherapy found peppermint and ginger promising in alleviating NV, while chamomile and ginger reduced nausea alone. These findings suggest that peppermint oil aromatherapy may be an effective complementary intervention for managing CINV in cancer patients undergoing chemotherapy.

Study II is the most comprehensive systematic review and meta-analysis on this topic to evaluate the efficacy and safety of L-menthol in both upper endoscopy and colonoscopy.

Although L-menthol did not consistently improve the ADR in colonoscopy, it may have beneficial effects in other areas, such as suppressing peristalsis and potentially improving the ease of examination for operators, particularly in upper endoscopy. However, L-menthol did not significantly impact withdrawal time in colonoscopy. Regarding safety, L-menthol showed a favorable profile, with AEs comparable to placebo and fewer adverse drug reactions. Although L-menthol induces spasmolytic effects in colon circular muscle by directly inhibiting GI smooth muscle contractility, the detailed mechanism remains unclear [68, 202].

L-menthol's antispasmodic properties make it a promising alternative for patients who cannot tolerate conventional agents, such as HBB or glucagon, which are associated with systemic side effects, including dry mouth, urinary retention, and hyperglycemia [56, 58, 62, 63]. Emerging alternatives to L-menthol include topical lidocaine and cool water irrigation, both of which have shown efficacy in reducing GI spasm. Topical lidocaine (2–4%) blocks mucosal sodium channels, offering more prolonged action and less rebound than peppermint oil without AEs. However, its effect is superficial, while L-menthol directly targets smooth muscle for more profound, sustained relief. Cool water (15–24°C) reduces peristalsis via TRPM8 activation but is less potent and more technique-dependent than L-menthol's targeted suppression [203, 204].

The ADR is a critical quality indicator for colonoscopy, reflecting the ability to detect adenomas, the precursors to colorectal cancer [106]. We analyzed data from six studies on L-menthol in colonoscopy, but only one (Inoue et al., (2014) [163]) reported a significant improvement in the ADR, suggesting that applying L-menthol does not consistently improve lesion detection. However, this outcome must be interpreted cautiously due to the primarily negative results on the ADR. The ADR may be affected by various factors, such as the number and experience level of endoscopists (years of practice and the number of procedures performed), the quality of equipment (e.g., high- or lower-definition scopes) [205], withdrawal time (more or less than 6 min), and procedural factors, e.g., bowel preparation) [206], etc. While procedural efficiency benefits from L-menthol's antiperistaltic effects—improving mucosal visualization and potentially reducing missed adenomas —the lack of ADR improvement limits its clinical utility as an additional measure to colonoscopy. Although the ADR remains the gold standard, recent studies suggest that complementary metrics, such as adenoma per

colonoscopy (APC) or procedural efficiency, may more comprehensively reflect the benefits of intervention, especially given the recognized limitations of the ADR as a standalone metric [207-209]. Although there is no evidence based on the studies analysed, ease of examination may affect the performance of the examiner when he or she performs several examinations in succession. Investigating this relationship may be the subject of future studies. While L-menthol's robust antiperistaltic effects and improved procedural conditions are well supported, we acknowledge the need for further research to establish its impact on lesion detection and colorectal cancer prevention.

L-menthol may improve endoscopic visibility during the procedure. Pooled analyses revealed a robust antispasmodic effect of L-menthol compared to placebo in both colonoscopy and upper endoscopy. While these procedures differ anatomically, the antispasmodic mechanism of L-menthol—mediated via TRPM8 activation and calcium channel blockade—is consistent across the GI tract [210, 211]. To ensure transparency, we conducted subgroup analyses by procedure type. The overlapping CIs support similar efficacy across GI segments (Figure 8). However, clinical heterogeneity, such as mucosal differences or procedural duration, may still influence outcomes.

Ease of examination by endoscopists is essential for procedure quality and can reduce operator fatigue [108]. Four upper endoscopy studies (Hiki et al. (2011) [168]; Yang et al. (2022) [173]; Meng et al. (2021) [171]; and Hiki et al. (2012) [169] demonstrated significantly easier examinations with L-menthol use. These findings highlight the role of L-menthol in enhancing procedural efficiency and increasing the number of daily procedures performed.

The reduction in withdrawal time between the L-menthol and the placebo group (MD=3.24 s) was not significant. This is not concerning, as the U.S. Multi-Society Task Force [207] recommends a withdrawal time of 6–10 min for an effective colonoscopy.

AEs were systematically reviewed, with no major, severe, or serious events reported. Commonly reported AEs included abdominal pain, nausea, diarrhea, and heartburn. Some studies also reported cardiovascular changes, such as electrocardiogram ST-T changes, palpitations, and ventricular premature beats; however, these events were not statistically associated with L-menthol use. The similar proportions of AEs in the L-menthol and placebo groups in both upper endoscopy and colonoscopy suggest a potentially safe usage

profile for L-menthol. Although some studies focused only on SAEs, others documented every occurrence. The overall results suggest that L-menthol has a favorable safety profile, as it does not result in more AEs than placebo. This supports its use as a safe alternative to antispasmodic agents for endoscopic procedures.

Four studies reported adverse drug reactions, with a pooled analysis indicating a significantly lower incidence in the L-menthol group. These findings highlight the equivalent safety profile of L-Menthol compared to placebo.

Previous meta-analyses have examined the antispasmodic effects of L-menthol and peppermint oil during endoscopy. Aziz et al. (2020) [210] focused on colonoscopy and included both oral and topical interventions, while You et al. (2020) [212] evaluated L-menthol for suppressing peristalsis primarily during upper endoscopy, with studies mostly from Japan. In contrast, the present study builds on and extends these works by focusing exclusively on topical application during both colonoscopy and upper endoscopy, incorporating a larger and more recent evidence base, and providing more detailed subgroup and safety analyses.

Based on current clinical evidence, the topical application (spraying directly onto the mucosa during endoscopic procedures) of L-menthol and peppermint oil seems to be reasonable to achieve an optimal antispasmodic effect. For upper GI endoscopy, the established regimen is to spray 20 mL of 0.8% L-menthol solution (160 mg) onto the gastric antrum or body via the endoscope's working channel before examination. The antiperistaltic effect begins within 30–90 s and is sustained throughout the procedure. Additional doses can be administered if peristalsis recurs during more prolonged examination. For colonoscopy, the regimen is 20 mL of 0.8% L-menthol (160 mg) or 50 mL of peppermint oil solution sprayed or injected onto the colonic mucosa, particularly at the cecum, with additional doses as needed for persistent peristalsis. The antispasmodic effect occurs quickly (within 20–40 s) and lasts at least 15–20 min, covering the withdrawal phase. This approach ensures rapid and sustained suppression of peristalsis, facilitating high-quality mucosal visualization and procedural efficiency, with a favorable safety profile.

The clinical trial planned according to **Study III**'s protocol will be the first RCT to evaluate the efficacy of ETC compared to placebo in treating AB in children aged 6–17

years. The primary outcome is the BSS change over seven days. On the basis of the long-term experience with the product, we hypothesize that ETC will significantly reduce BSS compared to placebo. Additionally, the study aims to assess safety and tolerability by monitoring AEs. If successful, this trial could provide robust evidence supporting the integration of ETC into clinical guidelines for the treatment of AB.

The findings of this study will contribute to the growing body of evidence on the use of herbal medicines for respiratory conditions. Previous studies on thyme-ivy combinations have demonstrated significant reductions in BSS and coughing fits compared to placebo, with excellent tolerability and minimal AEs. For example, a multicenter trial found that thyme-ivy syrup reduced coughing by 68.7% compared to 47.6% for placebo ($p < 0.0001$) and also improved other bronchitis symptoms more rapidly than placebo [139]. Similarly, another study on thyme-primrose extract showed a clinically significant reduction in BSS scores and shortened disease duration compared to placebo [136]. These results align with our expectations for ETC, which contains thyme as an active ingredient known for its expectorant and anti-inflammatory properties.

Our study builds on these findings and focuses on pediatric AB patients. By using a rigorous, double-blind, placebo-controlled design, we aim to provide higher-level evidence that addresses the limitations of observational data.

9.2 Strengths

9.2.1 Study I

One of the key strengths of our study is that it provides a comprehensive and systematic review of the literature on the effects of peppermint oil inhalation on NV symptoms across diverse patient populations, including pregnant women and postoperative and chemotherapy patients. The inclusion of only RCTs strengthens the reliability of our findings. In addition, the meta-analysis was restricted to RCTs that used peppermint oil as a single treatment, minimizing confounding factors from additional treatments.

9.2.2 Study II

This study is the first to comprehensively synthesize data on L-menthol's effects across various endoscopic procedures, covering outcomes such as the ADR, peristalsis suppression, ease of examination, and AEs. By including studies on both colonoscopy and upper endoscopy, the analysis provides a comprehensive view of L-menthol's

usefulness across various endoscopic procedures. Subgroup analyses and advanced statistical methods strengthen the findings.

9.2.3 Study III

This is the first clinical trial to evaluate the efficacy of Elixirium thymi compositum specifically for treating pediatric AB, using a single-center, randomized, controlled, and double-blinded approach. The study employs the Bronchitis Severity Scale, a widely validated tool that ensures a reliable measurement of therapeutic outcomes. By targeting the pediatric population, the study provides critical insights into the efficacy and safety of the treatment for this specific age group.

9.3 Limitations

9.3.1 Study I

A major limitation is that few clinical trials with small numbers of patients investigated the effectiveness of peppermint oil inhalation for NVP, which introduces imprecision and limits the certainty of the findings. The use of different measurement tools to assess the effect of the intervention, while allowing for scale conversion in analysis, introduced heterogeneity and inconsistency. Variations in peppermint oil interventions, including differences in dosage and, in some cases, type (peppermint oil or spirit), may also affect interpretation. Furthermore, studies used different types of control interventions, including placebo (normal saline, distilled water), standard care (routine antiemetics, routine nursing care), and other comparators (alternative oils, controlled breathing). In addition, the risk of bias was a concern in all studies, primarily due to the blinding of participants and personnel by the recognizable scent of peppermint oil. Furthermore, the open-label nature of most aromatherapy studies makes it possible that some observed benefits are due to placebo or expectation effects. Since patients might be aware that they are receiving a fragrant intervention, part of the effect may reflect relaxation or positive expectations rather than a direct pharmacologic action of peppermint oil. Additionally, the act of inhalation itself can provide symptom relief, regardless of the aroma, making it unclear how much benefit is due to peppermint oil's pharmacologic action versus nonspecific effects. The majority of included studies were conducted in Iran, Turkey, and the USA, which may introduce geographic and demographic biases. Differences in cultural practices, healthcare infrastructure, and patient populations could affect the applicability of our results to other settings. Future research should include more diverse

populations to enhance generalizability. The retrospective nature of meta-analyses, including the present study, introduces certain limitations. We are dependent on the quality and reporting of the included RCTs, and unmeasured confounders may remain present. Moreover, publication bias and selective reporting cannot be entirely excluded. The pooled effect estimates could be overestimated due to systematic biases and the limitations described above. We interpret our findings with caution and recommend that future research prioritize rigorous study design, adequate blinding, and standardized outcome measures to improve the reliability of evidence in this field. Despite these limitations, our study provides valuable insights into the potential efficacy of peppermint oil inhalation as a basis for future, more robust clinical trials.

9.3.2 Study II

Most studies were conducted in Asia, particularly Japan, and some in North America. This geographical concentration may limit the generalizability of our findings to other populations, as differences in genetics, healthcare systems, and endoscopic practice may influence the efficacy and safety of L-menthol. Further studies from diverse geographic regions are needed to confirm these findings and ensure their applicability to broader patient populations.

However, high heterogeneity was observed for both the ADR (I^2=51%) and PNP (I^2=94%) in colonoscopy, limiting the validity of our results. For the ADR, heterogeneity likely arises from differences in patient age and co-morbidity profiles, inconsistent sedation protocols, and variability in endoscopist experience, all known to affect detection rates. For PNP, the much higher heterogeneity reflects broader variations in patient age, sedation practices, and subjective differences in endoscopist assessments of peristalsis. Approximately one-third of included studies [107, 163, 164, 172, 174, 175] had inadequate blinding (e.g., single-blind or open-label designs), which may have introduced performance and detection bias, particularly for subjective outcomes such as ease of examination or peristalsis assessment. While some trials [167, 170] employed independent committees and reported moderate-to-good inter-observer agreement, most studies did not validate peristalsis grading scales or assess inter-rater reliability. The scale for the ease of examination outcome has not been formally validated, and subjective assessments by unblinded endoscopists may introduce measurement bias. Furthermore, while procedures were performed by experienced endoscopists in many trials,

heterogeneity in operator skill and training may have influenced outcomes. Future studies should prioritize standardized training for outcome assessors and report inter-observer agreement metrics to enhance reproducibility. AEs were only assessed during or shortly after the procedure; analysis of any delayed complications or mucosal injury was not possible due to a lack of data. The relatively small sample size of some included studies limits the generalizability and robustness of the conclusions. Furthermore, it was not possible to perform subgroup analyses by age or gender, as the included studies did not provide stratified outcome data [213]. Future studies should assess whether L-menthol's effects differ across demographic groups, such as older adults or between genders, to clarify potential differences in efficacy or safety. Four studies were sponsored by a pharmaceutical company [167-170], while others were funded by academic or hospital sources [161, 163, 166, 181, 186]. Two studies reported no funding [162, 165], the remaining studies did not report their funding sources [107, 164, 171-175, 187]. The cost-effectiveness of L-menthol use was not studied due to a lack of available data; it should be addressed in future research. It is also important to note that despite our broad inclusion criteria, we could not perform meta-analyses for ERCP and EUS due to a lack of available studies. This limitation highlights the need for further research into L-menthol's efficacy in these endoscopic procedures.

9.3.3 Study III

The focus on pediatric AB restricts the applicability of findings to other demographics or respiratory conditions. Subjectivity in self-reported symptom assessments, external factors such as concurrent diseases, and variability in treatment adherence may introduce biases and affect the reliability of results.

10. CONCLUSIONS

10.1 Study I

Peppermint oil inhalation may offer a complementary treatment for managing nausea and vomiting. However, the certainty of evidence is low due to methodological limitations, inconsistency, and imprecision. In PONV, peppermint oil inhalation appeared most effective in reducing nausea and vomiting severity within 2–6 hours after the intervention, with variable effects at other time points. In NVP, peppermint oil inhalation was associated with reduced severity of nausea and vomiting at 48 and 96 hours after intervention, though the evidence in this group is limited by small sample sizes and study heterogeneity. In CINV, peppermint oil inhalation consistently reduced the severity of nausea and vomiting at all analyzed time points, with the most notable effects observed at 48 and 72 hours, and sustained benefit through 96 hours. Nevertheless, these findings are based on low-certainty evidence. While some analyses demonstrated statistically significant reductions in symptom severity, these improvements did not reach thresholds considered clinically meaningful for PONV and NVP patients. However, the effects may be more promising for CINV patients. Given its favorable safety profile and accessibility, peppermint oil inhalation could be considered as an adjunct when conventional antiemetic options are limited or unsuitable. Further well-designed trials are needed to confirm the efficacy of peppermint oil and optimize its use in various clinical settings.

10.2 Study II

L-Menthol may have beneficial effects in GI endoscopy, particularly in reducing peristalsis and potentially facilitating easier examinations without an observed increase in AEs. Although its impact on the ADR remains inconclusive, probably due to variability in study designs and procedures, its possible antiperistaltic benefits and improved ease of examination highlight its potential in both colonoscopy and upper endoscopy. In addition, L-menthol offers a promising alternative antispasmodic option for patients who cannot receive pharmaceutical agents due to the risks of AEs or co-morbidities.

10.3 Study III

This randomized, double-blind, placebo-controlled trial will be the first to rigorously evaluate the efficacy and safety of ETC, a traditional Hungarian herbal medicine, for the treatment of AB in children aged 6–17 years. The study is designed to address the significant gap in high-quality clinical evidence for ETC, despite its long-standing use

and regulatory approval based on traditional experience. By employing validated outcome measures such as the Bronchitis Severity Scale and monitoring AEs, the trial aims to provide objective data on both the therapeutic benefits and tolerability of ETC in pediatric AB.

11. IMPLEMENTATIONS FOR PRACTICE

11.1. Study I

The findings from this systematic review and meta-analysis suggest that peppermint oil inhalation can be considered as a complementary intervention for managing nausea and vomiting in postoperative, chemotherapy, and pregnancy settings. Peppermint oil offers a non-pharmacological, low-cost, and generally safe option that may be especially valuable for patients who are unable or unwilling to use conventional antiemetic medications, such as pregnant women or those with contraindications to standard therapies. The minimal AEs reported, along with patient satisfaction in several studies, support its use as an adjunct to standard care. However, clinicians should be aware of the low certainty of evidence and apply peppermint oil inhalation with caution.

11.2 Study II

The evidence suggests that topical L-menthol or peppermint oil can be safely and effectively used to suppress peristalsis during upper and lower GI endoscopy, particularly in patients for whom traditional antispasmodics (e.g., HBB) are contraindicated or carry significant risks. In upper GI endoscopy, L-menthol may improve the ease of examination for endoscopists and facilitates mucosal visualization, which may enhance procedural efficiency and reduce operator fatigue. The antispasmodic effect is rapid and sustained, with a favorable safety profile and no significant increase in AEs compared to placebo. Standardized protocols for dosing and application (e.g., spraying 20 mL of 0.8% L-menthol solution onto the gastric or colonic mucosa) should be incorporated into endoscopy suites, especially for high-risk patients. However, clinicians should be aware that the impact of ADR remains inconclusive.

11.3 Study III

A clinical trial with ETC, based on the clinical trial protocol presented in this thesis, will be an essential contribution to ensuring that this medicine, which has been used for decades, is given its rightful place in the evidence-based medicine system.

12. IMPLEMENTATION FOR RESEARCH

12.1 Study I

There is a need for larger, well-designed RCTs with standardized dosing, frequency, and duration of peppermint oil inhalation across diverse populations. Research should explore the mechanisms underlying peppermint oil's antiemetic effects, investigate its impact on QoL, and assess patient-reported outcomes such as satisfaction and preference. Additionally, studies in broader geographic and demographic populations are needed to enhance the generalizability of findings and to address methodological limitations such as blinding and heterogeneity in outcome measures.

12.2 Study II

Future research should focus on large, multicenter RCTs that standardize L-menthol dosing, delivery, and outcome measurement across diverse populations and endoscopic procedures. Studies should aim to clarify the true impact of L-menthol on ADR and other clinically relevant outcomes such as APC, procedural efficiency, and patient comfort. Research should also address the cost-effectiveness of L-menthol versus standard antispasmodics.

12.3 Study III

Depending on the results of the clinical trial, it may be appropriate to study the efficacy and safety of ETC in larger patient groups (e.g., adults).

13. IMPLEMENTATION FOR POLICYMAKERS

13.1 Study I

Given the low cost, accessibility, and favorable safety profile of peppermint oil inhalation, policymakers may consider supporting its integration as a complementary therapy in clinical guidelines for nausea and vomiting, particularly where conventional pharmacological options are limited or not preferred. However, policy recommendations should be made cautiously, reflecting the current low certainty of evidence and emphasizing the need for further high-quality research. Policymakers could also support funding and infrastructure for large-scale, multicenter trials and encourage the inclusion of patient-centered outcomes in future studies. Clear regulatory guidance on the quality and standardization of peppermint oil products for clinical use would further ensure patient safety and efficacy.

13.2 Study II

Given L-menthol's favorable safety profile, rapid onset, and ease of administration, policymakers should consider supporting its inclusion as an alternative to traditional antispasmodics in endoscopic procedural guidelines. This is particularly relevant for patients with contraindications to standard agents or in settings where intravenous administration is impractical. Policymakers should encourage the development of consensus protocols for L-menthol use, ensure regulatory clarity regarding product quality and standardization, and support funding for further research, especially cost-effectiveness and real-world implementation studies.

13.3 Study III

This clinical trial could be the first step towards evidence-based clinical recommendations for ETC, which could also have an impact on therapeutic guidelines for AB.

14. FUTURE PERSPECTIVES

14.1 Study I

Peppermint oil inhalation holds promise as a complementary therapy for nausea and vomiting across multiple clinical contexts. It may become a routine adjunct in perioperative care, oncology supportive care, and obstetric practice, particularly for patients seeking non-pharmacological options. Future perspectives include the development of standardized protocols for administration and integration into multimodal antiemetic strategies. With more robust evidence, peppermint oil could be positioned as one of the first-line or adjunctive therapies in specific patient populations, improving patient comfort and satisfaction while reducing reliance on pharmacological agents.

14.2 Study II

L-menthol and peppermint oil are on track to become integral components of modern endoscopic practice, especially as patient populations age and the prevalence of co-morbidities increases. These agents may be routinely used to optimize procedural conditions and improve both patient and operator experience. Future studies may also clarify their role in capsule endoscopy and other minimally invasive diagnostic modalities. Ultimately, the integration of L-menthol into clinical guidelines and practice will depend on continued high-quality research and real-world effectiveness data.

14.3 Study III

The symptomatic treatment of AB is often empirical, and the efficacy and safety of the products used are not supported by modern clinical trials. In this context, a clinical trial with an ETC could be an important step, which could be followed by further trials (same product in other patient groups, other products with similar indications). This is an important step in promoting evidence-based medicine.

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APPENDICES

TABLE S1. BASIC CHARACTERISTICS OF THE INCLUDED NAUSEA AND VOMITING STUDIES.

First Author, Publication year	Country	Nausea type	Surgical procedure¥/ gestational age^/ cancer type^Δ	Drug type	Dosage	Follow up period	Frequency of intervention	Sample size (intervention /placebo)	Age (years; mean ± SD)	Sex (female % of total)
Ahmadi et al. 2020 [36]	Iran	PONV	abdominal¥	peppermint EO	2 drops (0.1mL) of 10% EO +2cc DW	10 minutes	once for 5 minutes	40/40	46.4 ±12.1	50.8
Maghami et al. 2020 [41]	Iran	PONV	open-heart¥	peppermint EO	0.1mL of EO plus 10mL DW	0-4, 4-8 & 8-12 hours	10 minutes before every examination	30/26	I: 62.4 ±10.22 C: 57.54 ±8.94	30.4
Ferruggiari et al. 2012 [155]	USA	PONV	any¥	peppermint EO	2 drops (0.1mL) of EO and 5mL of 0.9% normal saline	5 and 10 minutes	once for 5 minutes	23/22	ND	100
Aydin et al. 2018 [152]	Turkey	PONV	head, neck, eye, ear, and intraabdominal¥	peppermint EO	EO was diluted to 1/10 with wheat oil	0-2, 2-6, 6-12, 12-24, and 24-48 hours	5 times in every 30 min	27/29	I: 50.56 ±20.81 C:48.14 ±23.1	48.2
Lane et al. 2012 [149]	USA	PONV	post C-section¥	peppermint spirit	1mL peppermint spirit	2 and 5 minutes	at baseline, at 2 minutes and at 5 minutes	22/8	31.3 (ranged from 22 to 43 years)	100

Anderson et al. 2004 [151]	USA	PONV	any¥	peppermint EO	0.2mL of EO and 2mL of isotonic saline	2 and 5 minutes	once, taking three slow, deep breaths	10/12	I: 42±6 C: 44±5	63.6
Baek et al. 2025 [153]	South Korea	PONV	total knee arthroplasty¥	peppermint EO	5 drops (0.25mL) of 100% pure aroma oil	24, 48, 72 hours	at least 5 nasal inspirations	30/30	I: 75.4 ± 6.4 C: 73.8 ± 8.4	15
Imani et al. 2024 [148]	Iran	PONV	laparoscopic cholecystectomy¥	peppermint EO	3 drops (0.15mL) of 100% EO	24, 48 hours	5 minutes repeated 3 times	70/70	I: 51.92±15.62 C: 51.47±13.25	72.14
Cetin et al. 2024 [154]	Turkey	PONV	cervical¥	peppermint EO	5 drops (0.25mL) of EO	5, 35, 65, 95 minutes, 2, 6, 12, 24 hours	replaced every 30 minutes	38/38	I: 42.11±7.13 C: 44.89±9.57	50
Sites et al. 2014 [156]	USA	PONV	laparoscopic, ear, nose and throat, orthopedic, or urological¥	peppermint spirit	0.5mL peppermint spirit	5 and 10 minutes	3 repetitions of deep breathing	26/16	I: 47.8±15.3 C: 45.7±17.1	88.1
Tate et al. 1997 [150]	UK	PONV	gynecological¥	peppermint EO, peppermint essence	not defined	24, 48 hours	inhaled from the bottle when feeling nauseous	6/6/6	I1: 45.5 I2: 43.2 C: 54.0	100
Amzajerdi et al. 2022 [37]	Iran	NVP	I: 10.31±2.50 C: 10.64±2.34^	peppermint EO	4 drops (0.2mL) of EO diluted to 10% in sesame oil	7 days	twice a day	33/33	I: 26.30 ±4.57 C: 27.79 ±3.51	100

Joulaeerad et al. 2017 [40]	Italy	NVP	I: 12.4±3.77 C: 12.1±4.06↟	peppermint EO	5 drops (0.25mL) of EO diluted to 10% in sweet almond oil	4 days	4 times a day	28/28	I: 26.39 ±4.27 C: 27.79 ±3.51	100
Pasha et al. 2012 [160]	Iran	NVP	I: 9.07±1.31 C: 9.73±2.21↟	peppermint EO	4 drops (0.2mL) of EO in a bowl of water	4 days	whole night under the bed	30/30	I: 24.8 ±3.56 C: 25.1 ±4.76	100
Mapp et al. 2020 [159]	USA	CINV	any, except head and neck[A]	peppermint EO	cool damp washcloth with two drops (0.1mL) of EO	30 minutes	once	37/42	I: 51.0±15.2 C: 54.1±13.8	72.16
Lestari et al. 2017 [158]	Indonesia	CINV	liver, cervical, lung, nasopharyngeal, breast, colon, melanoma, lymphoma, sarcoma[A]	peppermint EO	EO dropped onto a cotton ball	5 minutes	once	150/135	I: 21-70 C: 31-70	81.3
Ertürk et al. 2021 [38]	Turkey	CINV	any[A]	peppermint EO, sweet almond oil	1 drop (0.05mL) of aromatic mixture	5 days	3 times a day	36/44	I: 49.94 ±10.47 C: 54.63 ±10.15	67.5
Jafarimanesh et al. 2020 [39]	Iran	CINV	breast[A]	peppermint extract in tap water	40 drops (2mL) of peppermint extract in 20cc of tap water	1 and 2 days	every 8 hours	42/42	I: 49.6 ±11.78 C: 51.9 ±9.52	100

Eghbali et al. 2017 [157]	Iran	CINV	breast[Δ]	peppermint EO	2 drops (0.1mL) of EO	1-5 days	20 minutes three times a day	50/50	47.86±9.52	100

PONV=POSTOPERATIVE NAUSEA AND VOMITING, NVP=NAUSEA AND VOMITING IN PREGNANCY, CINV=CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING, EO=ESSENTIAL OIL, I=INTERVENTIONAL GROUP, C=CONTROL GROUP, ML=MILLILITER, CC=CUBIC CENTIMETER, DW=DISTILLED WATER.

TABLE S2. TYPES AND ORIGINAL RANGES OF MEASUREMENT TOOLS EVALUATING NAUSEA AND VOMITING

Study	Nausea and vomiting type	Scale type	Range	Scale description
Ahmadi et al. 2020 [36]	PONV	Visual analog scale for nausea	0-100	Zero is equivalent to the absence of nausea, and one hundred indicates the highest severity of nausea.
Maghami et al. 2020 [41]	PONV	Nausea and vomiting assessing scale	0-100	The nausea severity scores ranged from zero (no nausea) to 100 (most severe nausea)
Ferruggiari et al. 2012 [155]	PONV	Visual analog scale for nausea	0-200	The degree of nausea ranged from „no nausea" at the 0-mm mark to „worst possible nausea" at the 200-mm mark.
Aydin et al. 2018 [152]	PONV	Visual analog scale for nausea	0-100	The patient was asked to mark his/her condition on a 100 mm scale. 0-1: no nausea, 2-4: mild, 5-7: moderate, and 8-10: severe nausea.
Lane et al. 2012 [149]	PONV	6 points descriptive ordinal rating scale	0-5	The scale measured the participants' subjective perceptions of nausea and vomiting symptoms from "I am not experiencing any nausea" to "I vomited."
Anderson et al. 2004 [151]	PONV	Visual analog scale for nausea	0-100	The patients marked their symptoms on a 100-mm long line on paper. The two ends were marked as "no nausea" and "worst possible nausea."
Baek et al. 2024 [153]	PONV	Halpin nausea and vomiting scale	0-5	Each rating corresponds to the frequency and intensity of vomiting episodes over a 12-hour period, ranging from no vomiting (0) to severe intractable vomiting with more than 7 episodes (5).
Imani et al. 2024 [148]	PONV	Likert scale	0-10	Numerical rating scale, the Likert-type scale scored from zero (minimal or no symptom) to four (worst symptom)
Cetin et al. 2024 [154]	PONV	Visual analog scale for nausea	0-10	A scale from 0 (no nausea) to 10 (very severe nausea).
Sites et al. 2014 [156]	PONV	Descriptive ordinal scale	0-10	On the scale, 0 represented the absence of symptoms, and 10 denoted the most severe symptoms.
Tate et al. 1997 [150]	PONV	Nausea score	0-4	The scale is from 0, as I am not experiencing any nausea, to 4, I am so nauseated, I feel I am about to vomit
Amzajerdi et al. 2022 [37]	NVP	Rhodes nausea and vomiting questionnaire	0-32	Eight 5-point self-report items. Likert-type scale for each item is scored from zero (minimal or no symptom) to four (worst symptom). The item scores are summed for a total score.
Joulaeerad et al. 2017 [40]	NVP	Pregnancy Unique Quantification of Emesis/Nausea Questionnaire	3-15	Three PUQE questions. Each has a rating from 1–5. A total score between 3–6 points is mild, 7–12 points is moderate, and ≥13 points is severe NVP.
Pasha et al. 2012 [160]	NVP	Visual analog scale for nausea	0-10	Scores 0 and 10 are respectively indicative of the best and the worst conditions.
Ertürk et al. 2021 [38]	CINV	Visual analog scale for nausea	0-10	The patient was asked to place a mark on the 10cm scale to indicate the level of intensity of his/her nausea. 0 means no nausea, and 10 means severe nausea.
Jafarimanesh et al. 2020 [39]	CINV	Visual analog scale for nausea	0-10	A 10-centimeter line ranged from "0 = no feeling of nausea" to "10 = severe feeling of nausea".
Eghbali et al. 2017 [157]	CINV	Rhodes' index	0-4	The patient completed the questionnaire with a score from minimal or no signs (score 0) to the most severe condition (score 4).
Mapp et al. 2020 [159]	CINV	Baxter Retching Faces pictorial scale	0-10	The 6-point pictorial scale depicts varying stages of nausea with possible scores from 0 (neutral) to 10 (emesis).
Lestari et al. 2017 [158]	CINV	Rhodes Index Nausea, Vomiting, and Retching	0-32	0= not Nausea and Vomiting; 1-8 = Lightweight; 9-16 = medium; 17-24 = heavy; 25-32 = bad

NV = nausea and vomiting, PONV = postoperative NV, CINV = chemotherapy-induced NV, NVP = pregnancy-related NV

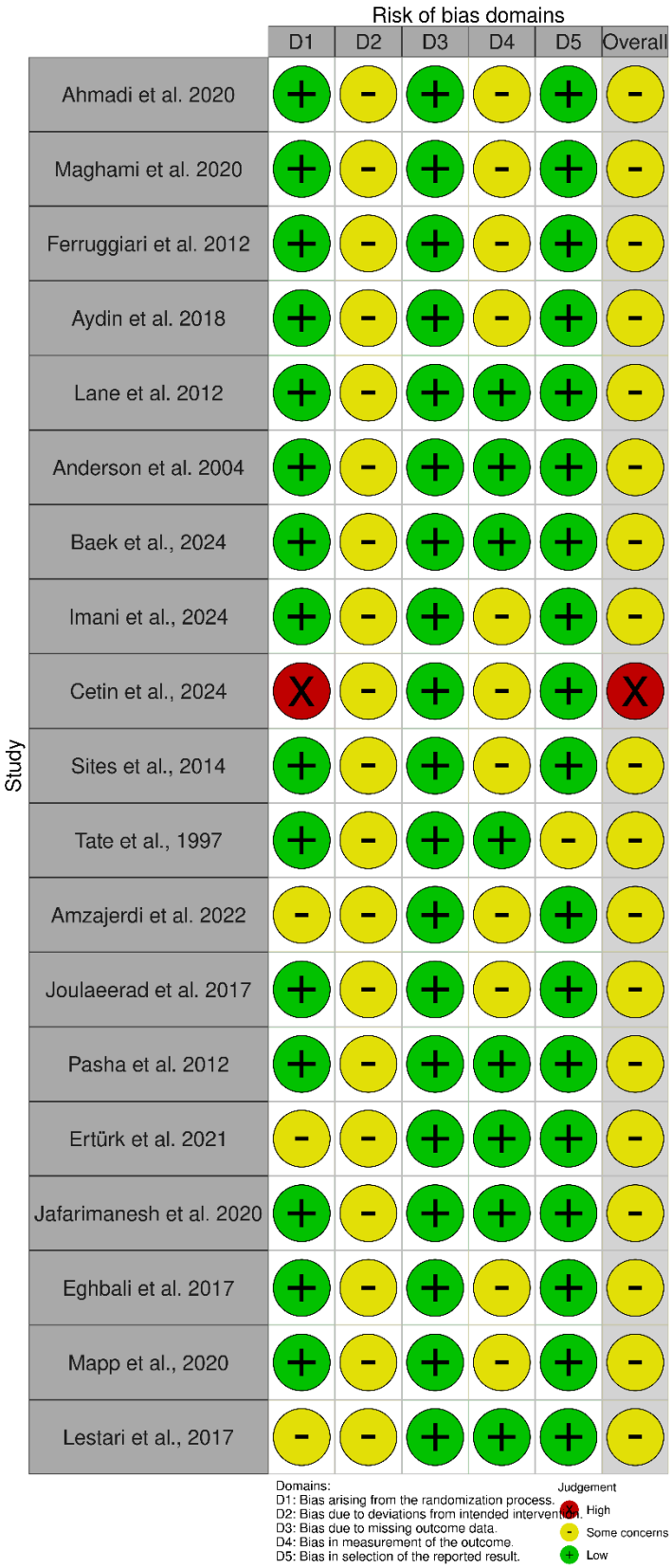
Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Ahmadi et al. 2020
Maghami et al. 2020
Ferruggiari et al. 2012
Aydin et al. 2018
Lane et al. 2012
Anderson et al. 2004
Baek et al., 2024
Imani et al., 2024
Cetin et al., 2024
Sites et al., 2014
Tate et al., 1997
Amzajerdi et al. 2022
Joulaeerad et al. 2017
Pasha et al. 2012
Ertürk et al. 2021
Jafarimanesh et al. 2020
Eghbali et al. 2017
Mapp et al., 2020
Lestari et al., 2017
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended interventions.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
High
Some concerns
Low

FIGURE S1. RISK OF BIAS ASSESSMENT OF THE INCLUDED STUDIES USING THE REVISED COCHRANE RISK-OF-BIAS TOOL (ROB2) [95].

TABLE S3. BASELINE CHARACTERISTICS OF THE RCTS WITH COLONOSCOPY AND UPPER ENDOSCOPY PATIENTS INVESTIGATED IN THE SYSTEMATIC REVIEW AND META-ANALYSIS.

Study	(1) Country, (2) Number of Centers, (3) Registration Number	Study Type	Endoscopy Type	Purpose of Endoscopy	Criteria Used to Evaluate Peristalsis	Sample Size (n)	Intervention Type, Dosage	Application Site	Outcomes
Al Moussawi et al. 2017 [187]	Lebanon, 1, NI	double-blind RCT	colonoscopy	diarrhea, bloody diarrhea, iron deficiency anemia, abdominal pain, rectorrhagia	degree of colonic spasm (no movement, minimal, mild, moderate, or marked)	I: 39 C: 39	I: Colpermin® 374 mg C: placebo comprised of vitamin B12	orally	PNP, EIE, TAE
Asao et al. 2001 [107]	Japan, 1, NI	cohort	colonoscopy	positive test for occult blood in feces, abnormal barium enema, or surveillance after previous polypectomies	NI	I: 409 C: 36	I: peppermint oil solution C: placebo	cecum	ADR, TAE,
Dhillon et al. 2018 [162] ‡	Canada, 1, NI	double-blind RCT	colonoscopy	screening	NI	I: 61 C: 61	I: L-menthol solution; C: placebo (water +simethicone)	cecum	ADR, PNP
Fujishiro et al. 2014 [167]	Japan, 8, NCT 01411176	double-blind RCT	upper endoscopy	determine the treatment strategy (EMR or ESD)	the modified version of Niwa's Classification	I: 42 C: 41	I: L-menthol solution; 160 mg (0.8%, 20 mL); C: placebo	gastric antrum	PNP, PNMP, TAE, TADR
Han et al. 2021 [186]	USA, 1, NA	double-blind RCT	colonoscopy	screening, positive fecal occult blood test or fecal immunochemical test, surveillance for	classification of colonic peristalsis (0–2)	I: 102 C: 90	I: IBGard™ 180 mg C: placebo containing sucrose	orally	ADR, EIE, WT, TAE

				history of colorectal polyps					
Hiki et al. 2011 [168]	Japan, 6, NCT 00742599	double-blind RCT	upper endoscopy	required treatment or follow-up for confirmed or suspected upper GI disease	the modified version of Niwa's Classification	I: 45 C: 42	I: L-menthol solution; 160 mg (0.8%, 20 mL); C: placebo	gastric mucosa/antrum	PNP, PNMP, EIE, TAE, TADR
Hiki et al. 2011 [170]	Japan, 6, NI	double-blind RCT	upper endoscopy	assessing the tolerability and pharmacokinetics of the intervention	NI	I1: 6 I2: 6 I3: 6 C: 6	I: L-Menthol solution; 80 mg (10 mL) 160 mg (20 mL) 320 mg (40 mL) C: placebo	gastric mucosa	GPPM, TAE
Hiki et al. 2012 [169]	Japan, multi, NI	double-blind RCT	upper endoscopy	required gastric endoscopy	Niwa's Classification	I: 87 C: 29	I: L-menthol solution; 80 mg (0.4%, 20 mL); 160 mg (0.8%, 20 mL); 320 mg (1.6%, 20 mL) C: placebo	gastric antrum	PNP, PNMP, EIE, TAE, TADR
Imagawa et al. 2012 [174] ◆	Japan, 2, UMIN 000004710	non-randomized prospective study	upper endoscopy	scheduled to undergo EGD were recruited	Niwa's Classification	I: 1893 C: 156	I: L-menthol solution; 1.6%, (20 mL) C: placebo	gastric antrum	AS
Inoue et al. 2014 [163]	Japan, 1, UMIN 000007972	single-blind prospective RCT	colonoscopy	screening, positive fecal occult blood test follow-up, or postendoscopic resection surveillance	classification of colonic peristalsis (0–3)	I: 118 C: 108	I: L-menthol solution; 320 mg (1.6%, 20 mL); C: placebo (water + dimeticone)	cecum	ADR, PNP, PNMP, WT, TAE, TADR
Inoue et al. 2020 [164]	Japan, 1, UMIN 000023383	single-blind prospective RCT	colonoscopy	screening, positive fecal occult blood test follow-up, or postendoscopic resection surveillance	classification of colonic peristalsis (0–3)	I: 309 C: 302	I: L-menthol solution + CO2/air; 160 mg (0.8%, 20 mL) C: placebo (water + dimeticone) + CO2/air	cecum	ADR, PNP, PNMP, WT, TAE

Meng et al. 2021 [171]	China, 5, NCT 03263910	double-blind RCT	upper endoscopy	advised for UE examination or follow-up for confirmed or suspected upper GI disease	modified version of Niwa's classification	I: 109 C: 111	I: L-menthol solution; 160 mg (0.8%, 20 mL); C: placebo	gastric mucosa	PNP, PNMP, EIE, TAE, TADR
Mori et al. 2014 [172]	Japan, 1, UMIN 000010859	prospective open-label RCT	upper endoscopy	scheduled to screening or follow-up for upper GI disease	modified version of Niwa's classification	I: 49 C: 49	I: L-menthol solution; 160 mg (0.8%, 20 mL); C: placebo (water + dimeticone)	gastric mucosa	PNMP, TAE
NCT 02588248, 2015 [161] §	USA, 1, NCT 02588248	prospective, double-blind RCT	colonoscopy	primary colorectal cancer screening or survillance	NI	I: 37 C: 38	I: peppermint oil solution (0.8% L-menthol, 20 mL) + simethicone C: simethicone	cecum	ADR, WT, TAE
Sattayaler-tyanyong et al. 2023 [165] ‡	Thailand, 1, NCT 05559814	double-blind RCT	colonoscopy	screening endoscopy	classification of colonic peristalsis (0–3)	I: 204 C: 204	I: peppermint oil solution (0.8% L-menthol, 50 mL) + simethicone C: simethicone	cecum	ADR, PNP, PNMP, EIE, WT, TAE
Shah et al. 2019 [166]	USA, 1, NCT 03286764	double-blind RCT	colonoscopy	initial screening colonoscopy	classification of colonic peristalsis (0–3)	I: 24 C: 24	I: peppermint oil solution (0.8% L-menthol, 50 mL) C: placebo (water + simethicone)	cecum	ADR, PNP, PNMP, WT, TAE
Shavakhi et al. 2012 [181] ❖	Iran, 1, IRCT201107056957N1	prospective, double-blind RCT	colonoscopy	diagnostic or screening colonoscopy	colonic spasm score (0–4)	I: 33 C: 32	I: Colpermin® 374 mg C: placebo with lactulose	orally	PNP, TAE
Yang et al. 2022 [173]	Taiwan, 1, NCT 04593836	prospective, double-blind RCT	upper endoscopy	screening endoscopy	modified version of Niwa's classification	I: 26 C: 26	I: L-menthol solution; 160 mg (0.8%, 20 mL); C: placebo (olive oil)	gastric mucosa	PNP, PNMP, EIE, TAE

Yoshida et al. 2014 [175]	Japan, 1, UMIN 000008317	retrospective study	colonoscopy	patients with severe colonic spasm	NI	I: 65 C: 27	I: 0.8% L-menthol solution C: water	cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum,	TAE, PNP

ADR: ADENOMA DETECTION RATE; AS: ANTISPASMODIC SCORES; C: CONTROL; EGD: ESOPHAGOGASTRODUODENOSCOPY; EIE: EASE OF THE INTRAGASTRIC EXAMINATION; EMR: ENDOSCOPIC MUCOSAL RESECTION; ESD: ENDOSCOPIC SUBMUCOSAL DISSECTION; GI: GASTROINTESTINAL; GPPM: GASTRIC PERISTALSIS PER MINUTE; I: INTERVENTION; NI: NO INFORMATION; PNMP: PROPORTION OF NO OR MILD PERISTALSIS; PNP: PROPORTION OF NO PERISTALSIS; TADR: TOTAL ADVERSE DRUG REACTION; TAE: TOTAL ADVERSE EVENT; WT: WITHDRAWAL TIME. ⁋ STUDY INCLUDED ONLY IN THE SYSTEMATIC REVIEW. ‡ CONFERENCE ABSTRACT. § UNPUBLISHED STUDY FROM CLINICAL TRIAL REGISTRY WITH REPORTED RESULTS.

TABLE S4. SUMMARY FOR QUALITY OF EVIDENCE, GRADE ASSESSMENT FOR POSTOPERATIVE, PREGNANCY AND CHEMOTHERAPY STUDIES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	peppermint oil	placebo	Relative (95% CI)	Absolute (95% CI)		
PONV: Severity of nausea (follow-up: 5 minutes; assessed with: VAS/numerical scale; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	55	42	-	MD **1.59 lower** (9.29 lower to 6.1 higher)	⨁⨁◯◯ Low[a,b,c]	CRITICAL
PONV: Severity of nausea (follow-up: range 0 hour to 2 hours; assessed with: VAS/questionnaire; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	95	93	-	MD **0.87 SD lower** (3.41 lower to 1.67 higher)	⨁⨁◯◯ Low[a,b,c]	CRITICAL
PONV: Severity of nausea (follow-up: range 2 hours to 6 hours; assessed with: VAS/questionnaire; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	95	93	-	MD **0.6 lower** (0.77 lower to 0.44 lower)	⨁⨁◯◯ Low[a,b,c]	CRITICAL
PONV: Severity of nausea (follow-up: range 6 hours to 12 hours; assessed with: VAS/numerical scale/questionnaire; Scale from: 0 to 10)												
4	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	125	123	-	MD **0.82 lower** (2.65 lower to 1.02 higher)	⨁⨁◯◯ Low[a,b,c]	CRITICAL
PONV: Severity of nausea (follow-up: range 12 hours to 24 hours; assessed with: VAS/numerical scale; Scale from: 0 to 10)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	peppermint oil	placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomized trials	serious[a]	not serious	not serious	serious[d]	none	165	167	-	MD **0.88 lower** (2.29 lower to 0.53 higher)	⨁⨁◯◯ Low[a,d]	CRITICAL
PONV: Severity of nausea (follow-up: range 24 hours to 48 hours; assessed with: VAS/numerical scale; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[d]	none	127	129	-	MD **0.37 lower** (1.61 lower to 0.88 higher)	⨁⨁◯◯ Low[a,d]	CRITICAL
PONV: Overall patient satisfaction (follow-up: at discharge; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[d]	none	110	112	-	MD **0.68 higher** (0.41 lower to 1.78 higher)	⨁⨁◯◯ Low[a,d]	IMPORTANT
NVP: Severity of nausea and vomiting (follow-up: 24 hours; assessed with: VAS/Likert scale/PUQE; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	91	91	-	MD **0.09 lower** (0.79 lower to 0.61 higher)	⨁⨁◯◯ Low[a,b,c]	CRITICAL
NVP: Severity of nausea and vomiting (follow-up: 48 hours; assessed with: VAS/Likert scale/PUQE; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	91	91	-	MD **0.51 lower** (0.78 lower to 0.24 lower)	⨁⨁◯◯ Low[a,b,c]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	peppermint oil	placebo	Relative (95% CI)	Absolute (95% CI)		
NVP: Severity of nausea and vomiting (follow-up: 72 hours; assessed with: VAS/Likert scale/PUQE; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	91	91	-	MD **0.2 lower** (1.02 lower to 0.62 higher)	⊕⊕◯◯ Low[a,b,c]	CRITICAL
NVP: Severity of nausea and vomiting (follow-up: 96 hours; assessed with: VAS/Likert scale/PUQE; Scale from: 0 to 10)												
3	randomized trials	serious[a]	not serious	not serious	serious[b,c]	none	91	91	-	MD **0.68 lower** (1.09 lower to 0.27 lower)	⊕⊕◯◯ Low[a,b,c]	CRITICAL
CINV: Severity of nausea and vomiting (follow-up: 24 hours; assessed with: VAS/Likert scale; Scale from: 0 to 10)												
3*	randomized trials	serious[a]	not serious	not serious	serious[e,f]	none	128	136	-	MD **1.85 lower** (2.86 lower to 0.84 lower)	⊕⊕◯◯ Low[a,b,c]	CRITICAL
CINV: Severity of nausea and vomiting (follow-up: 48 hours; assessed with: VAS/Likert scale; Scale from: 0 to 10)												
3*	randomized trials	serious[a]	not serious	not serious	serious[e,f]	none	128	136	-	MD **2.23 lower** (3.13 lower to 1.34 lower)	⊕⊕◯◯ Low[a,b,c]	CRITICAL
CINV: Severity of nausea and vomiting (follow-up: 72 hours; assessed with: VAS/Likert scale; Scale from: 0 to 10)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	peppermint oil	placebo	Relative (95% CI)	Absolute (95% CI)		
2*	randomized trials	serious[a]	not serious	not serious	serious[e,f]	none	86	94	-	MD **2.41 lower** (3.96 lower to 0.86 lower)	⨁⨁◯◯ Low[a,b,c]	CRITICAL

CINV: Severity of nausea and vomiting (follow-up: 96 hours; assessed with: VAS/Likert scale; Scale from: 0 to 10)

2*	randomized trials	serious[a]	not serious	not serious	serious[e,f]	none	86	94	-	MD **2.11 lower** (3.48 lower to 0.73 lower)	⨁⨁◯◯ Low[a,b,c]	CRITICAL

CI: confidence interval; MD: mean difference

Explanations:

a. In the articles blinding was questionable as peppermint has a distinctive scent.

b. Different measurement tools were used in the articles.

c. Low patient number in all the articles.

d. Low patient number in some of the articles

e. In the Eghbali article different measurement tool was used compared to the other articles.

f. Low patient numbers in the Ertürk subgroups.

*The Ertürk study analyzed subgroups with different chemotherapeutic agents; every subgroup had an individual control group for comparison.

Endoscopy type	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Colonoscopy	Dhillon_2018	L-Menthol	Placebo	Adenoma Detection Rate	+	!	+	+	!	!
Colonoscopy	Inoue_2014	L-Menthol	Placebo	Adenoma Detection Rate	+	+	+	!	+	!
Colonoscopy	Shah_2019	Peppermint oil	Placebo	Adenoma Detection Rate	+	!	+	+	+	!
Colonoscopy	Inoue_2019	L-Menthol	Placebo	Adenoma Detection Rate	+	+	+	!	+	!
Colonoscopy	NCT02588248_2015	L-Menthol	Placebo	Adenoma Detection Rate	+	+	+	+	+	+
Colonoscopy	Sattayalertyanyong_2023	Peppermint oil	Placebo	Adenoma Detection Rate	+	!	+	+	!	!
Colonoscopy	Asao_2001	Peppermint oil	Placebo	Adenoma Detection Rate	!	!	+	!	+	!
Colonoscopy	Han_2020	IBGard	Placebo	Adenoma Detection Rate	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interver
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Endoscopy type	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Colonoscopy	Dhillon_2018	L-Menthol	Placebo	Proportion of Peristalsis	+	!	+	+	!	!
Colonoscopy	Inoue_2014	L-Menthol	Placebo	Proportion of Peristalsis	+	+	!	!	+	!
Colonoscopy	Shah_2019	Peppermint oil	Placebo	Proportion of Peristalsis	+	+	!	+	+	!
Colonoscopy	Asao_2001	Peppermint oil	Placebo	Proportion of Peristalsis	-	!	!	-	-	-
Colonoscopy	Inoue_2019	L-Menthol	Placebo	Proportion of Peristalsis	+	+	+	!	+	!
Colonoscopy	Yoshida_2014	L-Menthol	Placebo	Proportion of Peristalsis	-	-	+	-	+	-
Colonoscopy	Sattayalertyanyong_2023	Peppermint oil	Placebo	Proportion of Peristalsis	+	!	+	+	!	!
Colonoscopy	Al Moussawi_2017	Colpermin	Placebo	Proportion of Peristalsis	+	+	+	+	+	+
Colonoscopy	Shavakhi_2012	Colpermin	Placebo	Proportion of Peristalsis	+	+	+	+	+	+

Endoscopy type	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Upper endoscopy	Fujishiro_2013	L-menthol	Placebo	Proportion of Peristalsis	+	+	+	+	+	+
Upper endoscopy	Hiki_2011a	L-Menthol	Placebo	Proportion of Peristalsis	+	+	+	+	+	+
Upper endoscopy	Hiki_2012	L-Menthol	Placebo	Proportion of Peristalsis	+	+	+	+	+	+
Upper endoscopy	Meng_2021	L-Menthol	Placebo	Proportion of Peristalsis	+	+	+	+	+	+
Upper endoscopy	Mori_2014	L-Menthol	Placebo	Proportion of Peristalsis	+	+	+	+	+	+
Upper endoscopy	Yang_2022	L-Menthol	Placebo	Proportion of Peristalsis	+	+	+	+	+	+

Endoscopy type	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Upper endoscopy	Hiki_2011a	L-Menthol	Placebo	Ease of Examination	+	+	+	+	+	+
Upper endoscopy	Hiki_2012	L-Menthol	Placebo	Ease of examination	+	+	+	+	+	+
Upper endoscopy	Meng_2021	L-Menthol	Placebo	Ease of Examination	+	+	+	+	+	+
Upper endoscopy	Yang_2022	L-Menthol	Placebo	Ease of Examination	+	+	+	+	+	+
Colonoscopy	Sattayalertyanyong_2023	Peppermint oil	Placebo	Ease of examination	+	!	+	+	!	!
Colonoscopy	Al Moussawi_2017	Colpermin	placebo	ease of examination	+	+	+	+	+	+
Colonoscopy	Han_2020	IBGard	placebo	ease of examination	+	+	+	+	+	+

Endoscopy type	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Colonoscopy	Inoue_2014	L-Menthol	Placebo	Withdrawal Time	+	+	+	!	+	!
Colonoscopy	Shah_2019	Peppermint oil	Placebo	Withdrawal Time	+	+	+	+	+	+
Colonoscopy	Inoue_2019	L-Menthol	Placebo	Withdrawal time	+	+	+	!	+	!
Colonoscopy	NCT02588248_2015	L-Menthol	Placebo	Withdrawal time	+	+	+	+	+	+
Colonoscopy	Sattayalertyanyong_2023	Peppermint oil	Placebo	Withdrawal time	+	!	+	+	!	!
Colonoscopy	Han_2020	IBGard	Placebo	Withdrawal time	+	+	+	+	+	+

Endoscopy type	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Colonoscopy	Asao_2001	Peppermint oil	Placebo	Adverse events	!	!	+	!	!	!
Colonoscopy	Yoshida_2014	L-Menthol	Placebo	Adverse events	!	!	+	!	!	!
Colonoscopy	Sattayalertyanyong_2023	Peppermint oil	Placebo	Adverse events	+	!	+	+	!	!
Colonoscopy	NCT02588248_2015	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+
Colonoscopy	Inoue_2014	L-Menthol	Placebo	Adverse events	+	+	+	!	+	!
Colonoscopy	Dhillon_2018	L-Menthol	Placebo	Adverse events	+	!	+	+	!	!
Colonoscopy	Inoue_2019	L-Menthol	Placebo	Adverse events	+	+	+	!	+	!
Colonoscopy	Shah_2019	Peppermint oil	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Imagawa_2012	Peppermint oil	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Hiki_2011a	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Meng_2021	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Mori_2014	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Fujishiro_2013	L-menthol	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Yang_2022	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Hiki_2011b	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+
Upper endoscopy	Hiki_2012	L-Menthol	Placebo	Adverse events	+	+	+	+	+	+

FIGURE S2. RISK OF BIAS ASSESSMENT OF THE ANALYZED STUDIES (ROB2) [95]

TABLE S5 SUMMARY FOR QUALITY OF EVIDENCE, GRADE ASSESSMENT

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With L-menthol	Relative effect (95% CI)	Risk with placebo	Risk difference with L-menthol
Quality of endoscopy in colonoscopy (assessed with: Adenoma detection rate)											
1490 (6 RCTs)	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low[a,b,c]	338/737 (45.9%)	351/753 (46.6%)	**OR 1.06** (0.69 to 1.64)	338/737 (45.9%)	**14 more per 1000** (from 90 fewer to 123 more)
Proportion of no peristalsis in colonoscopy + upper endoscopy											
1943 (10 RCTs)	serious[d,e]	not serious	serious[f]	not serious	none	⨁◯◯◯ Very low[d,e,f]	253/941 (26.9%)	560/1002 (55.9%)	**OR 3.88** (2.13 to 7.07)	253/941 (26.9%)	**319 more per 1000** (from 170 more to 453 more)
Proportion of no or mild peristalsis in colonoscopy + upper endoscopy											
1990 (11 RCTs)	serious[e,g]	not serious	serious[h]	not serious	none	⨁◯◯◯ Very low[f,g,h]	719/965 (74.5%)	900/1025 (87.8%)	**OR 3.70** (1.27 to 10.76)	719/965 (74.5%)	**170 more per 1000** (from 43 more to 224 more)
Proportion of no peristalsis in upper endoscopy (after application of L-menthol)											
626 (6 RCTs)	serious[e]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate[f]	156/291 (53.6%)	251/335 (74.9%)	**OR 3.79** (0.91 to 15.82)	156/291 (53.6%)	**278 more per 1000** (from 24 fewer to 412 more)
Proportion of no peristalsis in upper endoscopy (at the end of endoscopy)											
516 (5 RCTs)	serious[e]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate[f]	113/236 (47.9%)	227/280 (81.1%)	**OR 6.17** (2.00 to 18.99)	113/236 (47.9%)	**371 more per 1000** (from 169 more to 467 more)
Ease of examination for operator in upper endoscopy											
464 (4 RCTs)	serious[e]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate[f]	140/208 (67.3%)	206/256 (80.5%)	**OR 2.53** (1.35 to 4.73)	140/208 (67.3%)	**166 more per 1000** (from 62 more to 234 more)

Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With L-menthol		Risk with placebo	Risk difference with L-menthol
Total adverse events in colonoscopy + upper endoscopy											
4449 (16 RCTs)	not serious	serious[i]	not serious	not serious	none	⨁⨁⨁◯ Moderate[j]	77/1111 (6.9%)	91/3338 (2.7%)	**OR 0.93** (0.69 to 1.24)	77/1111 (6.9%)	**5 fewer per 1000** (from 20 fewer to 15 more)
Total adverse drug reactions in colonoscopy + upper endoscopy											
672 (5 RCTs)	not serious	serious[i]	not serious	not serious	none	⨁⨁⨁◯ Moderate[j]	14/331 (4.2%)	8/341 (2.3%)	**OR 0.57** (0.37 to 0.87)	14/331 (4.2%)	**18 fewer per 1000** (from 26 fewer to 5 fewer)
Withdrawal time (assessed with: seconds)											
1368 (5 RCTs)	serious[i]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate[j]	676	692	-	676	MD **0.7 seconds higher** (69.54 lower to 70.94 higher)

CI = confidence interval, RCT = randomized controlled trial, OR = odds ratio, MD = mean difference

Explanations

a. Downgraded once due to concerns in RoB2 Domains 2 (deviations from interventions), 4 (outcome measurement), and 5 (selective reporting) in 5/6 studies. These issues introduce uncertainty in the estimated effect.

b. Downgraded once due to heterogeneity in the clinical methods (screening vs. follow-up colonoscopies), limiting generalizability.

c. Downgraded once because confidence intervals crossed the null effect in 5/6 studies, indicating uncertainty about benefit or harm.

d. Downgraded once for colonoscopy studies (concerns in RoB2 Domains 2, 3, 4, 5). Upper endoscopy studies had low risk.

e. Downgraded once due to unblinded outcome assessment (grading variability among endoscopists), affecting outcome measurement (RoB2 Domain 4).

f. Downgraded once for colonoscopy studies due to mixed populations (screening vs. follow-up). Upper endoscopy studies had homogeneous indications.

g. Downgraded once for colonoscopy studies (concerns in RoB2 Domains 2, 3, 4, 5). Upper endoscopy studies had a low risk.

h. Downgraded once for colonoscopy studies due to mixed populations (screening vs. follow-up). Upper endoscopy studies had homogeneous indications.

i. Downgraded once due to heterogeneity in adverse event measurement methods (e.g., patient-reported vs. observed), leading to unexplained variability.

j. Downgraded once for RoB2 Domain 4 (lack of blinding for colonoscopists), introducing performance bias.