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

PhD Thesis Booklet

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1. Introduction

1.1 What is the topic?

Our research focuses on assessing the efficacy and safety of selected herbal products, specifically peppermint oil (PO), L-menthol, and Elixirium thymi compositum (ETC). This includes evaluating PO inhalation for managing nausea and vomiting (NV) in postoperative, chemotherapy, and pregnancy settings; investigating L-menthol as an antispasmodic during gastrointestinal (GI) endoscopy; and assessing ETC for symptomatic treatment of acute bronchitis (AB) in pediatric patients.

1.2 What is the problem to solve?

In vulnerable populations, such as pregnancy and breastfeeding, conventional anti-nausea medicines may be dangerous or contraindicated. Traditional antispasmodics for GI endoscopy also present safety risks, especially for elderly patients with co-morbidities; therefore, PO is used in clinical practice even though its efficacy is not fully supported. Similarly, despite decades of use, clinical data does not support ETC's efficacy. The lack of robust clinical evidence supporting the efficacy and safety of these products leads to uncertainty among healthcare professionals regarding their integration into evidence-based practice.

1.3 What is the importance of the topic?

This topic is of importance because NV are prevalent and distressing symptoms that negatively impact patient quality of life and treatment adherence across multiple scenarios. At the same time, AB remains a common reason 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. Without high-quality clinical data, the adoption of herbal medicines such as PO, L-menthol, and ETC in mainstream medicine remains controversial.

1.4 What would be the impact of our research results?

The results of this research could directly inform clinical practice by providing high-quality evidence on the efficacy and safety of PO, L-menthol, and ETC in relevant patient populations. If an evidence-based picture of the efficacy and safety of these products can be developed, they could have a proper place in evidence-based medicine. Additionally, these findings could guide the development of clinical guidelines, influence policy decisions regarding regulating and recommending herbal medicines, and highlight areas where further research is needed to optimize patient outcomes.

2. Objectives

2.1. 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 PO on nausea and vomiting symptoms compared to a placebo by systematically reviewing and meta-analyzing the available clinical data.

2.2. 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.

2.3. Study III. – Elixirium thymi compositum in the treatment of acute bronchitis in pediatric patients

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

3. Methods

3.1. Study I.

This systematic review and meta-analysis adhered to PRISMA 2020 and the Cochrane Handbook guidelines. The protocol was registered on PROSPERO (CRD42022379103). A comprehensive search was conducted in five databases (Scopus, Embase, CENTRAL, MEDLINE, Web of Science) without language restrictions. The following search key was used: ((peppermint) OR (Mentha piperita)) AND ((nausea) OR (vomiting)). Studies included randomized controlled trials with adults experiencing nausea or vomiting postoperatively, during pregnancy, or from chemotherapy, comparing inhaled PO to a placebo.

Two reviewers performed selection and data extraction independently, with disagreements resolved by a third. Data collected included study characteristics, participant demographics, intervention details, and nausea/vomiting severity. Risk of bias was assessed using the Cochrane RoB2 tool, and evidence quality was rated with GRADEpro. Both qualitative and quantitative syntheses were performed; meta-analyses used a random-effects model, with subgroup and publication bias analyses conducted as appropriate.

3.2. Study II.

This systematic review and meta-analysis followed PRISMA 2020 and the Cochrane Handbook, with the protocol registered on PROSPERO (CRD42023430941). A systematic search was conducted in five databases (Scopus, Embase, CENTRAL, MEDLINE, Web of Science) without language restrictions, using terms related to mint, menthol, and various endoscopic procedures. Eligible studies included RCTs, observational studies, case series, case-control studies, and conference abstracts. Two reviewers independently screened titles, abstracts, and full texts, resolving disagreements with a third reviewer.

Data extracted included study characteristics, population details, intervention specifics, and outcomes such as adenoma detection rate (ADR), peristalsis severity, withdrawal time, ease of examination, and adverse events. Risk of bias was assessed using RoB2, and evidence quality was graded with GRADEpro. Both qualitative and quantitative syntheses were performed. Meta-analyses used random-effects models, with odds ratios for dichotomous outcomes and mean differences for continuous outcomes, assessing heterogeneity, publication bias, and subgroup effects.

3.3. Study III.

This single-center, randomized, double-blind, placebo-controlled superiority trial evaluates the efficacy and safety of Elixirium thymi compositum (ETC) for acute bronchitis (AB) in pediatric patients aged 6–17 years. Conducted at Noé Medical Center in Szeged, Hungary (2025–2027), the trial is coordinated by the Centre for Translational Medicine at Semmelweis University and sponsored by Naturland Magyarország Kft. Participants are randomized 1:1 to receive age-adjusted doses of ETC or placebo syrup for five days. The primary endpoint is the change in Bronchitis Severity Score (BSS) from baseline to Day 7; secondary endpoints include adverse events (AEs), use of concomitant medications, and quality of life (QoL) measured by a modified Leicester Cough Questionnaire.

Hungarian authorities obtained ethical approval, and the study is registered on ClinicalTrials.gov (NCT07030855). Informed consent is required from parents/legal guardians. Patients are recruited during routine pediatric consultations, with eligibility based on clinical criteria and BSS scores (5–12). Exclusion criteria include recent use of antibiotics, immunostimulants, or certain other medications.

Randomization and allocation concealment are managed via the REDCap system using the Big Stick Design method. Blinding is maintained for patients, parents, pediatricians, and data analysts. Data are collected using standardized forms and entered into secure electronic case report forms (eCRFs). The Data Monitoring Committee oversees safety and trial integrity. Statistical analysis will compare mean BSS changes between groups using appropriate tests (Student's t-test or Mann-Whitney U), with significance set at $p<0.05$. The sample size (56 total) was calculated to detect a clinically meaningful difference (2.4 points on BSS) with 90% power, accounting for attrition. Results will inform clinical practice regarding ETC's role in pediatric AB management and will be disseminated through regulatory and research channels.

Parameters used to calculate sample size

Number of groups	2
Relationship between groups	Parallel
Trial Objective (Hypothesis)	Superiority
Endpoint	BSS score
Measure of Endpoint	Average of the BSS score decrease
Effect size	Mean BSS change Placebo = 3.3 Mean BSS change Intervention = 5.7
Secondary Parameters	SD change = 2.6
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

4. Results

4.1. Study I.

4.1.1 Study Selection and Characteristics

Systematic search identified 19 studies on inhaled PO for nausea and vomiting (NV) in postoperative, chemotherapy, and pregnancy contexts. Fourteen studies were included in quantitative analyses.

4.1.2 Postoperative Patients

NV Severity: Significant reduction in NV severity was observed 2–6 hours after PO inhalation. Effects at other time points (5 min, 2 hours, 6–24 hours) were variable and often not statistically significant, with high heterogeneity between studies.

4.1.3 Pregnant Women

NV Severity: PO inhalation led to significant reductions in NV at 48 and 96 hours post-intervention. No significant effects were seen at 24 or 72 hours. Heterogeneity was low, indicating consistent results across studies.

4.1.4 Chemotherapy Patients

NV Severity: PO consistently and significantly reduced NV severity at 24, 48, 72, and 96 hours compared to placebo. Effect sizes were largest at later time points, though some heterogeneity was present.

4.1.5 Safety and Adverse Events

AEs were rare and mild. In postoperative and pregnancy studies, no AEs were reported. In chemotherapy studies, a few patients reported headaches or increased nausea, but overall, PO was well-tolerated.

4.1.6 Risk of Bias and Evidence Certainty

Most studies had some risk of bias, primarily due to difficulties with blinding (distinctive scent of peppermint). Some studies also had concerns regarding randomization and reporting. The overall certainty was rated as low, mainly due to risk of bias and small sample sizes. Measurement tool differences contributed to heterogeneity, but inconsistency and indirectness were minor concerns.

4.2. Study II.

4.2.1 Study Selection and Characteristics

A systematic search identified 16 studies (14 quantitative, 2 qualitative) evaluating L-menthol's antispasmodic effects during gastrointestinal endoscopy, including colonoscopy and upper endoscopy. Most studies were conducted in Asia, with a few from North America. Gastric and colonic peristalsis were assessed using standardized classifications.

4.1.2 Antiperistaltic Effect

L-menthol significantly increased the proportion of procedures with no peristalsis, especially in upper endoscopy, but effects in colonoscopy were less pronounced and did not reach statistical significance. Rapid peristalsis reduction was observed within 1 minute in some studies. Subgroup analyses showed the strongest benefits in unsedated upper GI procedures, particularly among elderly and middle-aged patients.

4.1.3 Ease of Examination

L-menthol made upper endoscopy significantly easier for operators, with benefits most evident in unsedated patients. Age, comorbidities, and gender did not affect this benefit.

4.1.4 Safety and Adverse Events

Adverse events (AEs) were similar between L-menthol and placebo, and adverse drug reactions were significantly lower with L-menthol.

4.1.5 Risk of Bias and Evidence Certainty

Most outcomes had low risk of bias, though some concerns existed for certain endpoints. Certainty of evidence varied by outcome. Some publication bias was possible, but analyses were underpowered.

4.3. Study III.

No data have yet been collected or analyzed. The primary analysis will compare mean changes in Bronchitis Severity Score (BSS) from baseline to Day 7 between ETC and placebo groups. Secondary analyses will assess safety, tolerability, quality of life, and medication use. All data will be securely recorded in electronic case report forms and analyzed per protocol, with results reported to authorities and published. This rigorously designed, double-blind, placebo-controlled trial builds on prior positive findings for thyme-based herbal medicines, aiming to provide high-quality evidence for pediatric acute bronchitis treatment.

5. Conclusions

5.1 Study I.

PO inhalation may be a useful complementary option for NV, mainly in chemotherapy patients, but the evidence is of low certainty due to methodological limitations and small sample sizes. Effects in postoperative and pregnant populations were modest and often not clinically significant. Given safety, PO could be considered when standard antiemetics are unsuitable, though further high-quality studies are needed.

5.2 Study II.

L-Menthol appears beneficial in GI endoscopy by reducing peristalsis and easing procedures, without increasing adverse events. Its effect on ADR remains unclear, likely due to study variability, but its antispasmodic properties make it a promising alternative for patients unable to use standard agents.

5.3 Study III.

This randomized, double-blind, placebo-controlled trial will be the first to rigorously assess the efficacy and safety of ETC, a traditional Hungarian herbal medicine, for acute bronchitis in children. By using validated outcome measures and monitoring adverse events, the study aims to provide objective evidence on the benefits and tolerability of ETC in pediatric care.

6. Bibliography

6.1 Publications related to the thesis:

1. **Gergő D,** Garmaa G, Tóth-Mészáros A, Do To UN, Fehérvári P, Harnos A, Hegyi P, Nagy R, Bánvölgyi A, Ványolós A, Csupor D. Inhaling Peppermint Essential Oil as a Promising Complementary Therapy in the Treatment of Nausea and Vomiting. J. Clin. Med. 2025;14(14):5069.

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