

## Review of Literature:

### I) Primary literature

1. May B, Köhler S, Schneider B. *Efficacy and tolerability of a fixed combination of peppermint oil and caraway oil in patients suffering from functional dyspepsia. Aliment Pharmacol Ther. 2000 Dec;14(12):1671-7. PubMed PMID: 11121917.*

#### • Study objectives :

- To investigate the efficacy and safety of enteric coated capsules with fixed peppermint and caraway combination in the treatment of functional dyspepsia.

#### • Methods

- Design:
  - Double blind, randomized controlled, parallel-group study
  - Intention-to-treat
- Allocation
  - 48 patients in each treatment group (treatment n= 48, placebo n= 48)
  - Computer-generated randomization procedure in blocks of four was used.
- Blinding
  - Double blind
- Follow-up period
  - 4 weeks (28 days) of treatment or placebo
- Setting
  - Out-patient setting, otherwise not specified, in seven centres in Germany
- Participants
  - 96 patients with secured diagnosis of functional dyspepsia; defined as “diffuse, unspecific, variable, moderately intense epigastric pain with at least four points on the visual analogue scale, at least one additional dyspeptic key symptom, organ pathology excluded by in-depth clinical examination sonography and oesophago-gastro-duodenoscopy”
  - At least 18 years old
  - Current episode lasting for at least 14 days
  - Exclusion criteria:
    - severe organic disorders, disorders that could cause gastrointestinal symptoms,
    - severe functional disorders other than dyspepsia,
    - severe diarrhea,
    - inability to discontinue concomitant medication that could be expected to interact with the assessment of the study’s outcome variables (e.g. prokinetics, agonists and antagonists of gastric hormones, acid-reducing drugs, bismuth preparations, sedatives, laxatives, non-steroidal antiphlogistics),
    - history of major gastrointestinal surgery,
    - presence of gastrointestinal ‘alarm symptoms’ pointing to a malignoma, ulcer, reflux oesophagitis, or reflux dyspepsia.
- Intervention
  - 2 × 1 enteric coated capsule PCC per day (one in the morning, one at lunch time), each containing 90 mg peppermint oil and 50 mg caraway oil; for 28 days
- Outcomes
  - Intensity of pain
  - sensation of pressure, heaviness and fullness between

- global improvement
- Patient follow-up
  - 28 days

- **Main results**

- The average intensity of pain was reduced by 40% vs. baseline in the PCC group and by 22% in the placebo group.
- With regards to pressure, heaviness and fullness, a 43% reduction was observed for PCC vs. 22% for placebo.
- In CGI item 2, “Global Improvement” 67% (PCC) vs. 21% (placebo) of the patients were described as much or very much improved.
- In all three target parameters, the superiority of PCC over placebo was statistically significant.
- Six patients (PCC: 5; placebo: 1) reported adverse events, either unrelated to the trial, or attributable to an aggravation of the disease under investigation.

- **Conclusions**

Overall, the authors concluded that based on the results, the reduction in intensity of pain, the reduction in sensation of pressure, heaviness and fullness, and the global improvement seen in the treatment group vs. the control in general were significant ( $p=0.002$ ).

- **Comments/critical appraisal** (including assessment of internal and external validity)

- Study design :
  - Double blind, randomized controlled, parallel-group study with intention-to-treat
- Limitations include:
  - The authors failed to describe the blinding and randomization processes.
  - The study used a combination therapy, making it difficult to determine which ingredient is responsible for the effect.
  - Small sample size.
  - Short follow up period
- Results point to peppermint showing efficacy in the treatment of dyspepsia, however, due to the overall weakness of the study, further research is warranted to be able to conclusively determine its efficacy.

2. *Barnick CG and Cardozo LD. The treatment of abdominal distension and dyspepsia with enteric coated peppermint oil following routine gynaecological intraperitoneal surgery. J Obstet.Gynecol 1990;10(5):423-424.*

- **Study objectives**

- To determine the efficacy of enteric-coated peppermint in the treatment of abdominal distention and dyspepsia following gynaecological intraperitoneal surgery.

- **Methods**

- Design:
  - Double-blind randomized, placebo-controlled
- Allocation
  - Admitted patients for surgery for benign pathology were recruited and randomly allocated to receive Colpermin® or placebo postoperatively.
- Blinding
  - Double blind

- Follow-up period
    - o 5 days
  - Setting
    - o N/A
  - Participants
    - o N=69, women, undergoing routine gynaecological intraperitoneal surgery for benign pathology; treatment given post-op
  - Intervention
    - o 2 capsules, three times daily of enteric-coated peppermint oil for 5 days post-operatively
  - Outcomes
    - o Self-assessed severity of symptoms, using visual analog scale
    - o Measured symptoms included: abdominal distention, flatulence, and pain.
  - Patient follow-up
    - o 5 days post surgery
    - o Ten patients withdrew from the study, as they had an epidural catheter inserted perioperatively for postoperative analgesia.
    - o Six (five from the placebo group) withdrew because of side effects.
  - **Main results**
    - No significant differences were found between the groups.
  - **Conclusions**
    - Authors concluded that no significant differences were found between the groups.
  - **Comments/critical appraisal** (including assessment of internal and external validity)
    - Limitations:
      - o Small sample size
      - o Unclear method of randomization
      - o VERY short study duration
    - Since results do not show efficacy in the treatment of dyspepsia and the study's sample size and duration reduce its validity, further research is warranted.
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3. *Madisch A, Heydenreich CJ, Wieland V, Hufnagel R, Hotz J. Treatment of functional dyspepsia with a fixed peppermint oil and caraway oil combination preparation as compared to cisapride. A multicenter, reference-controlled double-blind equivalence study. Arzneimittelforschung. 1999 Nov;49(11):925-32. PubMed PMID: 10604046.*

- **Study objective**
  - To investigate a peppermint oil and caraway oil combination in outpatients diagnosed with functional dyspepsia.
- **Methods**
  - Design:
    - o Reference-controlled, double-blind equivalence trial
  - Allocation
    - o Following surgery on the gastrointestinal tract, patients were given either an enteric-coated combination preparation (180mg of peppermint oil and 100mg of caraway oil) or Cisapride® treatment within seven days.
  - Blinding
    - o Double-blind

- Follow-up period
  - o 4 weeks
- Setting
  - o Multicenter
- Participants
  - o N= 120, outpatients diagnosed with functional dyspepsia
  - o N = 60 received treatment or N = 58 received Cisapride, daily for 4 weeks
  - o Excluded were patients with pregnancy, lactation, dementia, substance abuse, comorbid conditions, or intake of specified medication
- Intervention
  - o Fixed combination of enteric-coated peppermint and caraway oils preparation (180mg peppermint + 100mg caraway) vs. cisapride
- Outcomes
  - o Mean reduction in pain score
- Patient follow-up
  - o 4 weeks
- **Main results**
  - The mean reduction of the pain score was 4.62 in patients treated with the peppermint oil combination and 4.60 in the Cisapride® group (p=0.021 for both groups).
  - The combination of peppermint and caraway oil appeared to be equally effective with Cisapride®, and both medications were well tolerated with only minor side effects.
- **Conclusions**
  - Peppermint appears to be safe in a fixed combination of enteric-coated peppermint and caraway oils preparation of 180mg peppermint + 100mg caraway.
  - No difference was observed between the combination and Cisapride for dyspepsia.
- **Comments/critical appraisal** (including assessment of internal and external validity)
  - Limitations:
    - o Placebo not used
    - o Equivalency trial
    - o Short duration
    - o Inadequate descriptions of the randomization and blinding processes
  - These results do not show explicit efficacy in the treatment of dyspepsia due to the lack of placebo use in the study. Further more, although the study had a significantly larger sample size than other studies, the short duration and the simple fact that it was an equivalency trial, we cannot prove its efficacy in dyspepsia. Further research is warranted.

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4. May B, Kuntz HD, Kieser M, Köhler S. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. *Arzneimittelforschung*. 1996 Dec;46(12):1149-53. PubMed PMID: 9006790.

- **Study objectives**
  - to determine the efficacy and safety of an herbal combination of caraway oil and peppermint oil in the management of nonulcer dyspepsia
- **Methods**
  - Design

- Double-blind, placebo-controlled randomized trial
  - Allocation
    - Not mentioned
  - Blinding
    - Double-blind
  - Follow-up period
    - 4 weeks
  - Setting
    - N/A, Multicenter
  - Participants
    - N=45, outpatients diagnosed with nonulcer dyspepsia
    - Excluded were pregnant or lactating women and patients with dementia or substance abuse
  - Intervention
    - treatment group: 3 capsules daily for 4 weeks of a combination of 90mg of peppermint oil and 50mg of caraway oil.
  - Outcomes
    - Pain and clinical global impression
  - Patient follow-up
    - 4 weeks
  - **Main results**
    - After 2 weeks:
      - 42% of patients in the treatment group were pain free (vs. 5% in the placebo group) ( $p = 0.002$ ).
    - After 4 weeks:
      - 63.2% of patients in the treatment group were pain free (vs. 25%, in the placebo group).
      - Moderate to severe pain was still reported in 10.6% of the treatment group and 55% of the placebo group.
      - Decrease in pain was significantly greater in the treatment group than the placebo group (84.2% vs. 50% at 15 days,  $p = 0.002$ ; 89.9% vs. 45% at 29 days,  $p = 0.015$ ).
    - Overall, 95.7% of treated patients reported improvement after 4 weeks, vs. 55% in the placebo group.
  - **Conclusions**
    - The herbal combination of peppermint oil and caraway oil showed significant reduction of gastrointestinal symptoms.
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  - **Comments/critical appraisal** (including assessment of internal and external validity)
    - Limitations:
      - Unclear methods of randomization
      - Short duration
      - Small sample size
      - Combination product used
    - These results show efficacy of peppermint in a combination product for the treatment of dyspepsia. Due to having used a combination product, the efficacy cannot be explicitly attributed to peppermint alone. Although the results for peppermint are positive, due to the limitations of the study, further research is warranted.
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5. Freise J, Köhler S. [Peppermint oil-caraway oil fixed combination in non-ulcer dyspepsia--comparison of the effects of enteric preparations]. *Pharmazie*. 1999 Mar;54(3):210-5. German. PubMed PMID: 10192108.

- **Study objectives**

- Evaluate the equivalence and efficacy of a peppermint oil and caraway oil-fixed combination therapy in the management of nonulcer dyspepsia

- **Methods**

- Design
  - o Prospective, randomized, double-blind, multicenter equivalence trial
- Allocation
  - o N/A
- Blinding
  - o Double-blind
- Follow-up period
  - o 28 days
- Setting
  - o N/A
- Participants :
  - o N=223, patients diagnosed with dysmotility-type, essential or "idiopathic" dyspepsia with IBS
- Intervention
  - o Fixed combination of peppermint oil and caraway oil (90mg + 45mg) daily vs.
  - o Fixed combination of peppermint oil and caraway oil (36mg + 20mg) daily
- Outcomes
  - o Measure of difference in pain intensity at the beginning and end of therapy
- Patient follow-up
  - o 28 days

- **Main results / Conclusions:**

- A statistically significant decline in pain intensity was observed in both groups from baseline ( $p < 0.001$ ).
- Both preparations were found to be of equivalent efficacy ( $p < 0.001$ ) and were well tolerated.

- **Comments/critical appraisal** (including assessment of internal and external validity)

- Strong points:
  - o Larger sample size
- Limitations:
  - o Unclear methods of randomization and blinding
  - o No placebo group, unable to determine whether improvement was due to "placebo-effect"
  - o Combination product used instead
- Due to the limitations of the study, further research is warranted. Need a placebo-controlled randomized double-blind trial.

## II) Systematic reviews and meta-analyses

Thompson Coon J, Ernst E. *Systematic review: herbal medicinal products for non-ulcer dyspepsia. Aliment Pharmacol Ther.* 2002 Oct;16(10):1689-99. Review. PubMed PMID: 12269960.

### Study objectives:

- This systematic review aimed to critically assess the evidence that supports and refutes the use of specific herbal products for the treatment of non-ulcer dyspepsia.

### Scope - describe the scope of included studies (ex. patients, interventions, outcomes, duration, etc.)

- Only randomized clinical trials were included. These were placebo controlled or equivalent trials.
- Treatments of herbal remedies were administered as supplements to patients.
- Patients included had a diagnosis of non-ulcer dyspepsia or functional dyspepsia.
- Data relating to sample size, diagnosis of patients, intervention and control, treatment duration, primary outcome measures and results were extracted by the first author and validated by the second author.
- The methodological quality of each randomized clinical trial was assessed using the scoring system of Jadad et al.<sup>10</sup> This scale ranges from 0 (poorest) to 5 (highest) and assesses methods of randomization and blinding and the description of withdrawals and dropouts
- A total of 9 trials were included in which peppermint (*Mentha piperitae*) and caraway (*Carum carvi*) were constituent ingredients.
- The number of patients ranged from 45 to 223.
- The duration of the trials ranged from 2 to 4 weeks.
- The Jadad score of the studies ranged from anywhere from 2 to 5, averaging at 3.

### Methods – describe how studies were identified, number and type of trials included, and any other relevant information regarding the methods

- Systematic literature searches were conducted using Medline, Embase, CINAHL, Amed, Cochrane Library and CISCOP up until September 2011.
- The search terms used were: non-ulcer dyspepsia, functional dyspepsia, dyspepsia, reizmagen, idiopathic dyspepsia, phytomedicine, herbal medicine, botanical medicine, complementary medicine, phytotherapy.
- All retrieved data, including uncontrolled trials, case reports, preclinical and observational studies, were reviewed for safety information and possible mechanisms of action.
- No language restrictions were imposed.
- Studies were not exclusive to peppermint; many other herbal interventions were included.
- An in-depth literature search of the reference lists of all papers was also done.
- Experts in the field and manufacturers of herbal products were contacted to provide published and unpublished material.
- Seventeen randomized controlled trials were included, 9 of which included peppermint as the herbal product of interest. Peppermint was never studied as a monopreparation; however, it was always in combination with caraway, and in 5 trials out of 9, with multiple other herbals as well.

### Main results

- A reduction in symptoms was noted in all trials, ranging from 67% improvement in symptoms to 95% improvement.
- A reduction in symptoms was also noted with placebo; ranging from 20-55%.
- There were statistically significant differences in the reduction of pain intensity, and sensation of pressure, heaviness and fullness between the peppermint / caraway- and placebo-treated patients, with

an overall median rating of “much improved” for the peppermint / caraway group and “minimally improved” for the placebo group.

- Improvement in pain intensity after 4 weeks of treatment was significantly greater in the peppermint / caraway-treated patients than in those treated with placebo.
- Statistically significant reductions in pain intensity were seen.
- Improvements in epigastric pain intensity, pain frequency, dyspeptic discomfort was also noted.

### **Conclusions**

- Non-ulcer dyspepsia treatment with peppermint in combination with caraway seems to be effective and safe for improving dyspeptic symptoms. However, considering the many study flaws that exist, studies of better quality are needed to determine the true efficacy of peppermint in dyspepsia.

### **Comments/critical appraisal (including assessment of internal and external validity)**

- The quality of the trials included in the review were low.
- Only one study had a Jadad score of 5.
- The exact symptoms vary across studies.
- GERD, IBS or both diseases were neither included or excluded. Herbal products may affect either or both IBS and GERD, leading to confounding results.
- Tests/diagnostic procedures/screening used to define patients with non-ulcer dyspepsia are not defined.
- Majority of studies included were small and of short duration.
- Validated symptom measures were not used in many of the studies.
- No monopreparations of peppermint were studied; making it impossible to judge whether the positive effect is due to the peppermint, the caraway or any other active ingredient within the combination products.



## II) Tertiary Literature:

1. American Botanical Council – *HerbClip on Peppermint*(2008). *HerbClip: Systematic Review of Peppermint*. <http://cms.herbalgram.org/herbclip/365/review060586-365.html> Accessed 2/29/2012, 2012.

### Peppermint:

Peppermint (*Mentha x piperita*) is a perennial herb with a long history of use for digestive disorders. There is clinical and in vitro research supporting this use. Peppermint oil is from the above ground parts. The principal active components of peppermint oil are menthol, menthone, and menthyl acetate. Laboratory studies indicate that peppermint oil may have analgesic, anticancer, antimicrobial, antiparasitic, antitussive, gastrointestinal, and respiratory effects. This report is a systematic review of peppermint.

### Indication:

There were no indications for use of peppermint rated Grade A.

There is however Grade B evidence for its use in: colonic spasm (colonoscopy or barium enema), cough, ***dyspepsia***, gastric spasm (endoscopy), irritable bowel syndrome, and tension headache (topical).

### Efficacy:

There is insufficient evidence to determine the efficacy or recommend peppermint oil for colonic spasm during barium enemas or colonoscopies, cough management, ***dyspepsia*** (upper abdominal pain and bloating), gastric spasm during endoscopy, irritable bowel syndrome, tension headache, abdominal distention, esophageal spasm, intestinal spasm, nasal congestion, pre-herpetic neuralgia, post-operative nausea, stroke recovery-hemiplegic shoulder pain, tuberculosis, and vigilance improvement in brain injury.

### Safety:

Peppermint is generally regarded as safe when taken in small doses (up to 270 mg) and in an infusion. Peppermint oil is likely safe in children when used orally in amounts commonly found in food. It is possibly safe when used orally or topically at medicinal doses.

Peppermint oil is unsafe when used by patients with gastroesophageal reflux disease (GERD), hiatal hernia, or kidney stones.

Oral peppermint oil can cause tongue spasms, apnea (stop breathing), laryngeal and bronchial spasm, and acute respiratory distress/arrest in infants and small children.

### Pregnancy:

Peppermint oil is unlikely safe when used orally in pregnant women in large doses.

2. *MicroMedex – PEPPERMINT* from AltMedDex® Evaluations. *Alternative Medicine detail - MICROMEDEX® 2.0*  
Available at: <http://www.thomsonhc.com> . Search word: Peppermint. Accessed 2/29/2012, 2012.

**Class:** antispasmodic

**Dosage:**

- A. Adult:
1. Irritable bowel syndrome, oil: 1 to 2 capsules (0.2 milliliter (ml)/capsule) three times daily between meals.
  2. General use, tincture (1:5 preparation, 45% ethanol): 2 to 3 ml, three times daily.
  3. Analgesic, topical: menthol (1.26% to 16%) applied to the affected area no more than 3 or 4 times daily.
- B. Pediatric: dosing not available.

**Administration:** oral, topical.

**Supplied:** bulk herb, oil, enteric-coated soft-gelatin capsule, tincture, and as a liquid. Menthol preparations are available as cream, ointment, or lotion).

**Uses:**

1. Scientific evidence: several clinical studies have demonstrated enteric-coated peppermint oil is possibly effective in reducing the abdominal symptoms of irritable bowel syndrome. Clinical studies showed an effective reduction in spasms during barium enemas and endoscopies, relieving *dyspepsia*, and alleviating headaches. Rowachol(r), a volatile oil, should be considered in treating common bile duct stones but careful attention to possible complications is necessary while the stones persist.
2. Complementary and alternative medicine indications: treatment of irritable bowel syndrome, intestinal colic, gallstones, musculoskeletal pain, the common cold, digestive disorders (*dyspepsia*, flatulence, gastritis, enteritis), and externally for rheumatic complaints, pruritus, and urticaria.

**Contraindications:** hypersensitivity or known allergy to peppermint, menthol, or any other member of the mint family. Not to be used in patients with biliary duct occlusion, gall bladder inflammation, or severe liver damage. Topical application should not be used on the nose, face, or chest of infants or small children. It should not be used on open skin areas.

**Adverse effects:** hypersensitivity reactions (skin rash), abdominal pain, heart burn, and perianal burning.

**Drug/food interactions:** no human drug interaction data available. Peppermint tea extract inhibited cytochrome p450 1a2 and 2e in rats. Caution is advised if peppermint is used with other drugs metabolized by these enzymes.

**Pregnancy/lactation:** should not be used in excess amounts during pregnancy. Scientific evidence for the safe use of peppermint during lactation is not available.

3. *Web Source - NaturalStandard.com: PEPPERMINT.pdf Available at: <http://naturalstandard.com/demo/PEPPERMINT.pdf>. Accessed 2/29/2012, 2012. Natural Standard Research Collaboration. 2011.*

**Background:**

Peppermint is a flowering plant that grows throughout Europe and North America.

OIL: Peppermint oil has been used historically for numerous health conditions, including common cold symptoms, cramps, headache, indigestion, joint pain, and nausea.

LEAF: Peppermint leaf has been used for stomach or intestinal disorders and for gallbladder disease.

**Supplied:**

Peppermint oil is available in bulk herb oil, enteric-coated capsules, soft gelatin capsules, and in liquid form. In small doses, such as in tea or chewing gum.

**Grade B Evidence for use in Indigestion (non-ulcer dyspepsia)**

There is preliminary evidence that a combination of peppermint oil and caraway oil may be beneficial for dyspepsia (heartburn) symptoms. It should be noted that heartburn can actually be a side effect of taking oral peppermint oil. Patients with chronic heartburn should be evaluated by a qualified healthcare provider.

**Dosing:**

The doses are based on scientific research, publications, traditional use, or expert opinion. Peppermint oil should be used cautiously, as doses of the constituent menthol over 1 gram per kilogram of body weight may be deadly.

For intestinal or digestion disorders, doses of 0.2 to 0.4 milliliters of peppermint oil in enteric-coated capsules, dilute preparations, or suspensions have been taken three times daily by mouth.

**Pregnancy:**

Peppermint preparations are commonly used during pregnancy for conditions like morning sickness; however, data are limited regarding safety and efficacy.