Botanicals in Clinical Practice:
Part One: The GI

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Disclosure

• Tieraona Low Dog, MD has the following to disclose:
  • Health Advisory Board: Pharmaca
  • Director of Scientific & Regulatory Affairs: Healthy Lifestyle Brands
  • Consultant/Spokesperson: FoodState

• This talk will not discuss off-label and/or investigational use of pharmaceuticals or devices not yet approved by the FDA.
Learning Objectives

• Participants will be able to discuss the evidence of safety and benefit for botanicals commonly used in the management of irritable bowel syndrome, GERD and inflammatory bowel disease.

• Participants will be able to identify physiologic actions of plants commonly used in herbal products.

• Participants will be able to discern different aspects of botanical product labels in order to more effectively counsel patients.
• GI complaints rank among the most frequent reasons for primary care visits in the US.

• Direct costs in excess of $85 billion annually, additional $20 billion indirect costs.

• But those are just the GI symptoms. From allergies to neurological disorders – the gut plays a central role.
Herbal Bitters: The Foundation

• Herbal bitters may be one our most important remedies in modern times if we believe that an optimally functioning digestive system is a key to good health.

• Compounds in the plants that bind bitter receptors increase salivation, stimulate the production of digestive juices from the stomach and pancreas, enhance bile flow from the gallbladder and increases the tone of the esophageal sphincter.

• Bitters enhance almost every aspect of digestion. ”Low GI fire leads to gut inflammation, allergies and food intolerances.”
Bitters: A Sampling

<table>
<thead>
<tr>
<th>Andrographis</th>
<th>Artichoke leaf</th>
<th>Barberry</th>
</tr>
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<tbody>
<tr>
<td>Boneset</td>
<td>Calamus</td>
<td>Cascara sagrada</td>
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<tr>
<td>Chamomile</td>
<td>Dandelion</td>
<td>Gentian</td>
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<tr>
<td>Goldenseal</td>
<td>Hops</td>
<td>Horehound</td>
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<tr>
<td>Motherwort</td>
<td>Oregon grape</td>
<td>Sage</td>
</tr>
<tr>
<td>Skullcap</td>
<td>Vervain</td>
<td>Wormwood</td>
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Andrographis Herb
(*Andrographis paniculata*)

- Andrographis is native to Taiwan, Mainland China, and India. In Unani and Ayurvedic medicine, it is one of the mostly used medicinal plants.
- The aerial part of AP is most commonly used.
- Andrographis has anti-inflammatory, as demonstrated in numerous clinical trials including two RCT for ulcerative colitis; neuroprotective, antifibrotic, and anti-fatigue effects in autoimmune diseases such as rheumatoid arthritis.
- Andrographolide, and its derivatives, potent inhibitors of NF-κB.
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Andrographis: MS

• RDBPCT: 170 mg of andrographis extract (total andrographolides: 85 mg per tablet; 10:1 extract, 75% ethanol) or placebo BID on relapse rate and fatigue using the Fatigue Severity Scores (FSS) over 12 months in 25 MS patients receiving interferon.

• Andrographis group showed significant reduction in their FSS score compared to placebo (44% reduction at 12 months).

• No statistically significant differences were observed for relapse rate or inflammatory parameters. One patient in active group presented with a mild and transient skin rash, alleviated with anti-histamine treatment.

Artichoke Leaf
(Cynara cardunculus var scolymus)

• Bitter, cholagogue, prokinetic
• Animal studies confirm effective against acute gastritis, increases gastric mucous secretion.
• Cynarin modify tastes receptors, making food/drinks seem sweet
• Hepatoprotective properties
• Rich source of FOS, has bifidogenic effect on gut bacteria
• Human studies show highly effective for relieving dyspepsia.

Impact on Lipids

- Cochrane review: 3 RCTs (N=262) concluded ”There is an indication that artichoke leaf extract has potential in lowering cholesterol levels, the evidence is, however, as yet not convincing”
- Since then, another 8-week RDBPCT of 92 overweight people with mild hypercholesterolemia given 500 mg artichoke leaf extract BID or placebo.
  - Significant increase in HDL-C (p=0.004) and improvement in LDL-C and total cholesterol/HDL ratio (p<0.001)
- Studies also show beneficial effects on liver enzymes in NAFLD.

Artichoke Details

• Dose of artichoke leaf extract:
  • 500-1500mg/d standardized 2-5% cynarin, 15% chlorogenic acid, and/or 5-7% caffeoylquinic acids
  • 3-5 ml BID-TID (1:5 tincture, 50% EtOH)
  • 1-2 grams powdered leaf day
• Predominant ingredient in Gallexier bitters
• Well tolerated.
• Allergy possible in those with daisy allergies.
Goldenseal & Oregon Grape Roots

Both used extensively by indigenous peoples of North America for infections, gonorrhea, skin conditions – similar to how we use antimicrobials today.
Berberine

• Isoquinoline alkaloid found at levels:
  • 0.5-6% in *Hydrastis canadensis* root (goldenseal)
  • 4-7% in *Coptis chinensis* rhizome (golden thread)
  • 7-16% in *Berberis aquifolium* root (Oregon grape)
  • 6.1% in *Berberis vulgaris* root (barberry)

• Antimicrobial activity against numerous bacteria, viruses, fungi, protozoans, helminths, and chlamydia.

• Berberine used as OTC antibacterial for diarrhea in China for decades.

• Beneficial effects seen in metabolic syndrome. More than 46 research articles demonstrate impact on insulin/glucose metabolism

Berberine Rich Plants

- Berberine displays potent analgesic, anti-inflammatory, and antidiabetic activity.
- Hepatoprotectant.
- Strong anti-Candida activity
- Antiviral activity (HSV, influenza)
- Beneficial effect on atopic dermatitis both internally and topically.
- Licorice increases absorption of berberine.
- Restores intestinal barrier function from pro-inflammatory cytokines.

Berberine and IBS

• RDBPCT 132 patients IBS-D received 400 mg berberine HCl or placebo two times daily for 8 weeks.
• Reduction of diarrhea frequency (P = 0.032), abdominal pain frequency (P < 0.01) and urgent need for defecation frequency (P < 0.01) significantly superior in active group.
• Trend of improvement (P < 0.05) observed in berberine group for IBS symptom score, depression and anxiety scores and the IBS-QOL, compared with placebo.

Berberine and Allergies

• Food Allergy Herbal Formula 2 (water extract of 9 herbs) shown to prevent peanut anaphylaxis in mice.
• Researchers found berberine is most responsible for this effect, and to lesser extent palmatine and jatrorrhizine.

Berberine and Urinary Tract

• Multiple animal models show that berberine has significant renal protectant properties, including in diabetes and from numerous toxins.

• Oral administration shows concentration in liver and kidney.

• Berberine prevents adhesion of *E. coli* to uroepithelial cells.

Goldenseal Interaction: High

• Berberine and hydrastine inhibit CYP3A4 and CYP2D6.

• Cyclosporine serum concentration increased in healthy volunteers and renal transplant recipients after co-administration of 0.3g (single dose) or 0.2g (TID, 3 months) of goldenseal.

• Physicians recommending berberine generally unaware of any supplement-drug interaction.

Goldenseal, Oregon Grape Root, Barberry

- *Hydrastis* root
  - 2-3 ml [1:5, dried 70% alcohol] TID
  - 300-500 mg dried root TID
- *B. aquifolium* or *vulgaris*
  - 500 mg dried root TID
  - 2-4 ml (dried, 1:5 tincture, 50% EtOH) TID

- Not for use during pregnancy or lactation.
- Caution with herb-drug interactions.
Dandelion Leaf and Root
*(Taraxacum officinale)*

- Cholagogue, hepatic, bitter
- Entire plant is edible
- Significant anti-inflammatory activity (*NF-κB*, *TNF*-alpha)
- Liver protectant in acetaminophen and alcohol models
- Prokinetic agent, rich source of inulin
- Leaf has demonstrated significant diuretic activity.

Dosing Dandelion

Dose for dandelion root
• 500 mg TID of root
• 3-5 ml tincture (1:5 40%) TID
• Decoction: ¼ - ½ C. decoction TID root

Dose for dandelion leaf
• 500-1000 mg leaf TID
• 3-5 ml tincture (1:5 40%)
• Infusion: ½ cup TID

Note: Monitor patients who use leaf chronically for K loss. Encourage to eat potassium rich foods.
Hops Strobiles
(*Humulus lupulus*)

- Best known for bitterness in beer; long used to treat excitability and insomnia, improve appetite and digestion and relieve nerve pain.
- German health authorities endorse hops for "discomfort due to restlessness or anxiety and sleep disturbances."
- Research suggests sedative action may work in a similar way to melatonin. Three controlled studies have shown that the combination of hops and valerian is more effective than placebo and similar in effectiveness to prescription sleep medication for shortening the time it takes to fall asleep and improving sleep quality.
Horehound Herb
(Marrubium vulgare)

• Used as a cough and cold remedy for centuries. Widely used for children’s coughs and croup.
• Marrubiin and volatile oils responsible for its expectorant and cough relieving activity.
• Marrubiin acts as mucolytic, allowing thick secretions to be more easily expectorated. Mucilage may ease an irritated cough.
• Bitter taste explains its use as a digestive tonic.
• Not for use in pregnancy.
Sage Leaf
(Salvia officinalis, S. lavandulaefolia)

• Largest genus in the Lamiaceae family.
• Used traditionally for digestive and circulatory problems, bronchitis, coughs, asthma, memory problems, angina, mouth and throat inflammation, depression and excessive sweating.
• Research confirms S. officinalis, S. lavandulaefolia and S. miltiorrhiza have significant anti-inflammatory, antioxidant, anxiolytic, antidepressant, and acts as acetylcholine esterase inhibitors.

Sage

• 286 people with acute pharyngitis found 15% sage spray provided symptom relief within 2 hours. Similar results echinacea/sage spray compared to chlorhexadine/lidocaine in 154 patients.

• Aids digestion, stimulates digestive enzymes, and alleviates intestinal cramping. Cooked with beans or other gas-producing foods. Antibacterial activity explains its use in gastroenteritis.

• German health authorities endorse sage as a treatment for excessive sweating.

• Do not use in pregnancy.
Wormwood Leaves & Stems
(*Artemesia absinthium*)

- Wormwood species widely distributed around the world, described in different pharmacopoeias. Usually standardized based on dimeric guaianolides: absinthins (0.2%).
- Beneficial effect in IBD associated with a significant decrease in TNF-α serum levels in two clinical trials when compared to placebo.
- TNF-α is considered to play a key role in the pathogenesis of Crohn’s disease, which supports the high efficacy obtained with the biologicals acting as TNF-α inhibitors, like infliximab and adalimumab, for severe cases.

Iberogast: Functional Dyspepsia

$33.00 for 100 ml

Supplement Facts

Serving Size: 20 drops (1 ml)
Servings Per Container: 100

<table>
<thead>
<tr>
<th>Amount per serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml</td>
<td>**</td>
</tr>
</tbody>
</table>

Proprietary Blend of the following Herbal Extracts:
German chamomile (Matricaria recutita) flower, clown's mustard (Iberis amara) plant, angelica (Angelica archangelica) root and rhizome, caraway (Carum carvi) fruit, milk thistle (Silybum marianum) fruit, lemon balm (Melissa officinalis) leaf, celandine (Chelidonium majus) aerial part, licorice (Glycyrrhiza glabra) root, and peppermint (Mentha x piperita) leaf

**Daily Value not established.

Suggested Use
Shake bottle before use.
Iberogast is taken 3 times a day orally before or with meals. Iberogast may be mixed with your favorite drink (warm water is recommended)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 years and over</td>
<td>20</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>15</td>
</tr>
<tr>
<td>3 to 6 years</td>
<td>10</td>
</tr>
<tr>
<td>3 months to 3 years</td>
<td>8</td>
</tr>
<tr>
<td>Under 3 Months</td>
<td>Consult a physician</td>
</tr>
</tbody>
</table>

Other Ingredients
Alcohol 31%

Tierona Low Dog, M.D.
# Gallexier: Non-Alcoholic Bitter

**Supplement Facts**

- **Serving Size:** 20 ml
- **Servings Per Container:** about 12

<table>
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<tbody>
<tr>
<td>Calories</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>4 g</td>
<td>2%*</td>
</tr>
<tr>
<td>Sugars</td>
<td>4 g</td>
<td>†</td>
</tr>
<tr>
<td>Sodium</td>
<td>5 mg</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Proprietary blend</td>
<td>1.611 g</td>
<td>†</td>
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Artichoke leaf, dandelion leaf, gentian root, turmeric root, yarrow aerial parts, ginger root, chamomile flower, bitter fennel fruit, bitter orange peel, blessed thistle aerial, cardamom fruit, bog bean leaf.

**Description**

- Vegetarian Liquid Formula
- No Artificial Preservatives, Colors or Flavors
- Kosher Parve
- Liquid Extract Herbal Supplement
- With Artichoke, Dandelion and 10 Selected Herbs
- Beneficial After a Main Meal - The Perfect Accompaniment for Heavy Meals

**Suggested Use**

Take 1 cap 20 ml mark daily before meals as an appetizer or after meals as a herbal supplement.

Take Gallexier Herbal Bitters regularly.

**Other Ingredients**

Water, fructose

This product contains no alcohol or artificial preservatives, colors or flavors.
Gut Demulcents or Anti-Inflammatories

• Soothes, coats and/or protects GI mucosa

Aloe vera          Calendula
Chamomile         Comfrey
Holy basil        Licorice
Marshmallow       Meadowsweet
Slippery elm      Wild yam
Specifics: Gastroesophageal Reflux

• Chronic condition in which contents of stomach flow back into esophagus, potentially causing symptoms (e.g., heartburn) and injury to esophagus.

• >60 million people report GERD symptoms at least weekly.
  • Symptoms include retrosternal burning, acid regurgitation, nausea, vomiting, chest pain, laryngitis, cough, and dysphagia.

• Incidence increasing: full-time physicians diagnose and treat 40-60 patients each month.

What Causes GERD?

• Disturbed esophageal motility; anatomical disorders, such as hiatal hernia, increased obesity, defective mucosal integrity, and concomitant medications are all associated with increased risk of GERD.

• Problem is seldom excessive stomach acid production (except rare cases of Zollinger-Ellison syndrome).

Barrett’s Esophagus

• Up to 10% of patients with chronic reflux will develop Barrett’s esophagus.
• Those at highest risk:
  • Smokers with weekly GERD symptoms (OR = 51.4)
  • BMI > 30 with weekly GERD symptoms (OR = 34.4); likely mediated by high levels of leptin and insulin.
  • Over 50, white male, hiatal hernia.
• Annual risk of progression to esophageal adenocarcinoma is low (0.12-0.33% per year).

Zimmerman TG. *Am Fam Physician* 2014; 89(2):92-9
Upper GI Products/Mechanisms

ANTACIDS
Neutralize existing acid
Work quickly but produce only short term relief

STOMACH

ACID (HCl)

PROTON PUMP INHIBITORS
Irreversibly bind to acid producing proton pumps and inhibit acid production regardless of pathway

PROTON PUMPS

ACETYLCHOLINE

H2-RECEPTOR ANTAGONISTS
Block only 1 of 3 acid stimulating pathways

GASTRIN

HISTAMINE
Inappropriate Use

“Proton pump inhibitors (PPIs) are a class of medications that reduce acid secretion and are used for treating many conditions such as gastroesophageal reflux disease (GERD), dyspepsia, reflux esophagitis, peptic ulcer disease, and hypersecretory conditions (e.g. Zollinger-Ellison syndrome), and as part of the eradication therapy for Helicobacter pylori bacteria.

However, **approximately 25% to 70% of people are prescribed a PPI inappropriately.** Chronic PPI use without reassessment contributes to polypharmacy and puts people at risk of experiencing drug interactions and adverse events (e.g. *Clostridium difficile* infection, pneumonia, hypomagnesaemia, and fractures).”

Aloe vera

• Aloe gel may have beneficial effects on metabolic parameters.

• Cochrane review interventions in patients undergoing cancer treatment found statistically significant evidence of benefit for aloe preventing or reducing severity of mucositis.

• Aloe gel improved oral lichen planus with similar effects vulvar lichen planus. Not as effective as corticosteroids.

• Gel should be “aloin” free.

Clinical trials of botanical drugs in patients with inflammatory bowel disease.

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Aloe Vera

- Strong antimicrobial effects against *H. pylori*, reduces gastric acid secretion, and promotes the healing of gastric ulcers.

- 79 people with GERD (endoscopy) given either:
  - 10 ml/d aloe vera syrup (standardized to 5.0 mg polysaccharide per mL of syrup)
  - Omeprazole capsule (20 g/d)
  - Ranitidine tablet (150 mg in am and 150 mg 30 min before sleep) for 4 weeks.

- Frequencies of eight main symptoms of GERD (heartburn, food regurgitation, flatulence, belching, dysphagia, nausea, vomiting and acid regurgitation) were assessed at weeks 2 and 4 of the trial.

- Significant benefit seen in all three groups.

Table 2 Frequency of GERD symptoms in the study groups at baseline, and at weeks 2 and 4 of the trial [n (%)]

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<th>Ranitidine</th>
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<td>Baseline</td>
<td>Week 2</td>
<td>Week 4</td>
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<tr>
<td>Heartburn</td>
<td>17 (100.0)</td>
<td>4 (23.5)</td>
<td>5 (29.4)</td>
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<tr>
<td>Food regurgitation</td>
<td>10 (100.0)</td>
<td>1 (10.0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>12 (100.0)</td>
<td>4 (33.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>17 (100.0)</td>
<td>1 (5.9)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Belching</td>
<td>15 (100.0)</td>
<td>2 (13.3)</td>
<td>3 (20.0)</td>
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<tr>
<td>Nausea</td>
<td>5 (100.0)</td>
<td>1 (20.0)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (100.0)</td>
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<tr>
<td>Acid regurgitation</td>
<td>20 (100.0)</td>
<td>10 (50.0)</td>
<td>10 (50.0)</td>
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Notes: GERD: gastroesophageal reflux disease. *P < 0.05: within group comparison with respect to baseline value; †borderline significant difference versus A. vera group at the respective time point; ‡between-group comparison at respective time point (week 2 or 4) in the A. vera group.
Slippery Elm Inner Bark
(\textit{Ulmus fulva})

- Slippery elm is one of the few herbs approved by the FDA: recognized as a safe and effective non-prescription oral demulcent.
- High in fiber and mucopolysaccharides, the latter forms viscous, protective barrier on mucosa.
- Study 10 patients with IBS-C showed benefit with combination of powdered slippery elm bark, lactulose, oat bran, and licorice root.

Marshmallow Root  
(*Althaea officinalis*)

- Rich in mucilage, structurally similar to pectin
- Soothes and protects irritated skin and mucosa
- Used for sore throats, GERD, inflammatory bowel disease
- Very little modern research but strong herbal use.
Licorice Root
*(Glycyrrhiza glabra; G. uralensis)*

- Gastroprotectant effects of licorice root known for centuries.
- Research has shown licorice to be a useful anti-ulcer agent, similar efficacy as famotidine.
- Licorice root 5 HT3 antagonist
- Increases absorption berberine.
- Licorice often found in herbal formulations for cough, colds, sore throat, GERD, gastritis or IBD.

Licorice: Safety

• Licorice root likely safe in healthy adults when used at doses not exceeding 3 grams/d for periods up to 2 weeks.
  • Should limit licorice to < 1 gram longer periods.
  • Glycyrrhizin is the compound responsible for symptoms of pseudoaldosteronism with excess or prolonged ingestion.
  • Symptoms include hypertension, edema, hypokalemia
Licorice

• Licorice raises local concentration of prostaglandins that promote mucous secretion and cell proliferation in stomach, leading to healing of ulcers.

• Germany’s Commission E endorses use of licorice root for gastric and duodenal ulcers, as does The British Herbal Compendium, which also indicates use of licorice root for chronic gastritis.

• A special preparation, deglycyrrhizinated licorice (DGL), has had a minimum of 97% of glycyrrhizin removed, making it safer long-term.
  • 380-760 mg chewable tablets 20 minutes before meals.

European Medicines Agency March 12, 2013


**DGL Product**

**Suggested Use**

Chew two tablets twenty minutes before each meal.

**Supplement Facts**

<table>
<thead>
<tr>
<th>Supplement Facts</th>
<th>Amount Per 2 Tablets</th>
<th>%DV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serving Size 2 Tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Servings Per Container 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calories</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>5 mg</td>
<td>&lt;1%**</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>2 g</td>
<td>&lt;1%**</td>
</tr>
<tr>
<td>Sugars</td>
<td>&lt;1 g</td>
<td>t</td>
</tr>
<tr>
<td>Deglycyrhizinated Licorice (DGL) (Glycyrrhiza glabra) Root Extract 3:1</td>
<td>760 mg</td>
<td>t</td>
</tr>
<tr>
<td>Glycine</td>
<td>100 mg</td>
<td>t</td>
</tr>
</tbody>
</table>
Alginates

• Alginates work through an alternative mechanism by displacing the postprandial gastric acid pocket. Suppresses reflux after meals by creating a gel-like barrier that caps and displaces the acid pocket distal to the oesophago-gastric junction.

• Meta-analysis: 14 studies (N = 2095 subjects). Alginate-based therapies increased the odds of resolution of GERD symptoms when compared to placebo or antacids (OR: 4.42; 95% CI 2.45-7.97) with a moderate degree of heterogeneity between studies (I² = 71%, P = .001).

• Compared to PPIs or H2RAs, alginates appear less effective but the pooled estimate was not statistically significant.

Integrative Approach to GERD

• Weight loss (most evidence of benefit)
• Elevate the head of bed
• Smoking cessation
• Avoid tight fitting clothes
• Do not eat 3 hours before bed
• Do not eat right after exercising
• Eat smaller portions
• Avoid dietary triggers
Dietary Triggers

Low CARB DIETS have been shown to be beneficial. Certain foods and beverages may act as triggers, however studies are contradictory:

- Alcohol
- Carbonated beverages
- Chocolate
- Citrus fruits
- Drinks with caffeine
- Garlic and onions
- Peppermint
- Spicy foods
- Fatty or fried foods
- Tomato-based foods
Melatonin

- Melatonin detected in enteroendocrine (EE) cells of GI wall.
- Patients with GERD and recurrent duodenal ulcers have lower melatonin concentrations than healthy subjects.
- Melatonin prevents gastric damage: more effective than ranitidine but less effective than omeprazole in preventing stress ulcer. However, melatonin allows lower dose of omeprazole to be used.
- Short term use of melatonin even at very high doses has not been associated with any significant side effects.
- Long-term treatment is not associated with any significant side effects, comparable to placebo.

Andersen LP, et al. *Clin Drug Investig* 2015; Dec 21
Melatonin for GERD

• Study of 60 patients with GERD by endoscopy compared to controls. Received:
  • 3 mg melatonin
  • 20 mg omeprazole
  • 3 mg melatonin + 20 mg omeprazole

• Heartburn/epigastric pain decreased after 4 weeks and completely resolved in 8 weeks in all three groups.

• Only groups with melatonin has improved LES function.

Long Term Consequences

• Long-term PPI use has been linked to decreased microbiota diversity, increased *Clostridium difficile* infections, and SIBO.

• These effects are due to altering GI pH, as well as local hormonal and nutrient availability conditions.
  
  • Single oral PPI dose raised gastric pH in most patients from 2.0 to over 6.0, a 10,000-fold change.
  
  • Probiotics and correcting vitamin D status may have a significant protective effect decreasing the incidence of acid suppressing medication associated infections, especially in elders.


PPI and Bacterial Overgrowth

Prevalence of SIBO by Duration of Therapy

Clin Gastroenterol Hepatol 2010;8(6):504
Intestinal Permeability and SIBO

• L-glutamine is a major nutrient involved in maintaining/restoring intestinal barrier function.
• Depletion of glutamine results in decreased expression of tight junction proteins and increased intestinal permeability.
• For SIBO: rifaxamin, berberine, essential oils of thyme, oregano, etc.

Study Found Clinically Effective for SIBO

CandiBactin AR $39.95 60 caps

CandiBactin BR $39.95 90 tabs

**Benefits**

| Serving Size: | 1 Softgel |

**Ingredients**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyme (Thymus vulgaris) Oil [provides 55 mg thymol]</td>
<td>183 mg</td>
<td>*</td>
</tr>
<tr>
<td>Oregano (Origanum vulgare) Oil [provides 55 mg carvacrol]</td>
<td>100 mg</td>
<td>*</td>
</tr>
<tr>
<td>Sage (Salvia officinalis) Leaf 5:5:1 Extract</td>
<td>75 mg</td>
<td>*</td>
</tr>
<tr>
<td>Lemon Balm (Melissa officinalis) Leaf 5:1 Extract</td>
<td>50 mg</td>
<td>*</td>
</tr>
</tbody>
</table>

Ingredients: Rice bran oil, gelatin, thyme oil, glycerin, oregano oil, sage leaf extract powder, lemon balm leaf extract, water, silica, annatto extract (color), and lecithin (soy). Contains: soy.

Directions: Take one softgel three times daily before or with meals or as directed by your healthcare practitioner.

**Serving Size:**

2 Tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
<th>Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coptis (Coptis chinensis) Root &amp; Rhizome 12:1 Extract (containing berberine)</td>
<td>30 mg</td>
<td>*</td>
</tr>
<tr>
<td>Oregon Grape (Berberis aquifolium) Root 4:1 Extract</td>
<td>70 mg</td>
<td>*</td>
</tr>
<tr>
<td>Berberine HCl</td>
<td>400 mg</td>
<td>*</td>
</tr>
<tr>
<td>A 4:1† Proprietary Extract of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coptis (Coptis chinensis) Root &amp; Rhizome, Chinese Skullcap (Scutellaria baicalensis) Root, Phellodendron (Phellodendron chinense) Bark, Ginger (Zingiber officinale) Rhizome, Chinese Licorice (Glycyrrhiza uralensis) Root, Chinese Rhubarb (Rheum officinale) Root &amp; Rhizome</td>
<td>300 mg</td>
<td>*</td>
</tr>
<tr>
<td>Coptis (Coptis chinensis) Root &amp; Rhizome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese Skullcap (Scutellaria baicalensis) Root</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phellodendron (Phellodendron chinense) Bark</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginger (Zingiber officinale)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhizome, Chinese Licorice (Glycyrrhiza uralensis) Root</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese Rhubarb (Rheum officinale) Root &amp; Rhizome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Ingredients: Microcrystalline cellulose, croscarmellose sodium, silica, stearic acid (vegetable), magnesium stearate (vegetable), and coating (hypromellose, medium chain triglycerides, and hydroxypropylcellulose).

Directions: Take two tablets two to three times daily or as directed by your healthcare practitioner.
Berberine: Antimicrobial (500 mg TID)

Thorne Berberine 500  $32.60  60 caps

Solaray Berberine ~$20.00  60 caps

**Supplement Facts**

<table>
<thead>
<tr>
<th>Serving Size: Two Capsules</th>
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<tbody>
<tr>
<td>Servings Per Container: 30</td>
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Two Capsules Contain:

<table>
<thead>
<tr>
<th>Amount</th>
<th>% DV Per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberine HCl (from Indian Barberry extract) (root) (Berberis aristata)</td>
<td>1 g</td>
</tr>
</tbody>
</table>

*Daily Value (DV) not established
Berberis Concentrate Berberine HCl 85%.

**Supplement Facts**

<table>
<thead>
<tr>
<th>Serving Size: 1 Vegetarain Capsule</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberine HCl (from Indian Barberry (Berberis aristata) (root extract))</td>
<td>250 mg</td>
</tr>
<tr>
<td>Oregon Grape (Berberis aquifolium) (root)</td>
<td>150 mg</td>
</tr>
</tbody>
</table>

* Daily Value not established.
Post-Infectious IBS

• Studies show 3-36% of enteric infections lead to persistent new IBS symptoms; the precise incidence depends on the infecting organism.

• Mechanisms are unknown but likely include residual inflammation or persistent changes in mucosal immunocytes, enterochromaffin and mast cells, enteric nerves, and the gastrointestinal microbiota.

• Consider berberine, EO of thyme, oregano, etc. Astringent AND Antimicrobial!

Gut Antispasmodics

- Inhibit intestinal contractions via a number of mechanisms. Most carminatives fall into this category.

Anise      Caraway      Chamomile
Dill       Fennel       Ginger
Hops       Lemon balm   Peppermint
Sage       Thyme        Wild yam
Some Carminatives and Secondary Benefits

• Angelica
  • Warming carminative, digestive stimulant

• Anise
  • Congestion, cough, asthma

• Basil
  • Anti-inflammatory, antimicrobial

• Caraway
  • Increases salivation, gastric motility, cholagogue

• Catnip
  • Nervine relaxant

• Cinnamon
  • Insulin resistance, aromatic

• Dill
  • Epigastric fullness, enterospasm, lactagogue

• Fennel
  • Expectorant, URI, increase gastric motility, gut spasm

• Ginger
  • Prokinetic, antiemetic, URI

• Iberis
  • Bitter, demulcent, nervine relaxant

• Lemon balm
  • Anxiolytic, functional GI disorders, insomnia

• Peppermint
  • IBS, antiemetic, upper GI spasm, URI, cough

• Sage
  • Dyspepsia, hot flashes, sore throats, antibacterial

• Thyme
  • Bronchitis, pertussis, antimicrobial, intestinal spasm
# Efficacy of IBS Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trials</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peppermint oil</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Hycosamine</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Alosetron</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Peppermint Essential Oil for IBS

• Sustained-release formulation of peppermint oil (0.2 ml) demonstrated efficacy in IBS. Must be enteric coated.

• Antispasmodic (calcium channel blocking properties), peppermint oil and L-menthol normalize orocecal transit time, κ-opioid and 5-HT$_3$ antagonism.

• Abdominal pain/discomfort, bloating, pain at evacuation, and urgency are symptoms most improved.

Peppermint Oil Safety

• Daily dose is 0.6 ml of peppermint oil (enteric coated). This provides average of 16 mg/kg pulegone and ~42 mg/kg menthofuran.

• The NTP study set the LOAEL at 20 mg/kg/bw for these constituents.

• There have been no confirmed cases of liver or kidney toxicity reported.

• However, it raises the question of long-term safety and use in children.

Caraway Essential Oil
(Carum carvi)

• Caraway oil displayed high degree of selectivity, inhibiting growth of potential bacterial intestinal pathogens at concentrations that had no effect on beneficial bacteria.
• Increases mucin secretion and PGE2 in stomach, protecting against NSAID damage.
• Carminative, antispasmodic
• Spirit of caraway – 1 ounce EO in 10 ounces vodka. 5-10 drops PRN
Ginger Rhizome

(Zingiber officinale)

• Ginger has beneficial effect on lipids, elevated blood sugar, oxidative stress and inflammation.
• Studies also suggest that ginger can be beneficial in those with arthritis.
• Ginger at doses of 1-2 grams of dried rhizome per day has not been associated with adverse effects.
• Doses higher than 4 grams/day dried can have a negative impact on blood clotting.

Ginger and the Gut

• Ginger is a prokinetic agent. Study in 24 healthy human volunteers found 1200 mg dried ginger accelerated gastric emptying and stimulated antral contractions greater than placebo.

• Ginger benefits those with gastroparesis with symptoms such as heartburn, early satiety, abdominal bloating, and nausea and/or vomiting several hours after eating a meal.

Ginger for Nausea and Vomiting

• Nine RCT show ginger (1.0-1.5 g dried rhizome) is effective for reducing NVP.

• Ginger did not increase the risk of pregnancy complications, pregnancy outcome, and congenital abnormalities. No difference in mean birth weight, birth length, and head circumference for babies of mothers having taking ginger.

• Effect of ginger on chemotherapy induced nausea and vomiting and motion sickness yield conflicting results.

Ginger & URI

• Antiviral, mucolytic and potent anti-inflammatory activity.
• Throat swabs from 333 people with URI found ginger highly active against Streptococcus pneumoniae, Strep pyogenes, Haemophilus influenzae, Staph aureus.
• Fresh, not dried, ginger highly active against RSV induced plaque formation on airway epithelium - blocks viral attachment and internalization.

Ginger & Arthritis

• Meta-analysis RCTs comparing ginger with placebo in OA patients aged >18 years.
• Following ginger intake, a statistically significant reduction in pain and disability.
• “Ginger was modestly efficacious and reasonably safe for treatment of OA.”
• GI upset was very common at high doses – ginger patients twice as likely to discontinue than placebo.

Ginger Tea

• 2 inch piece of fresh sliced ginger
• 4 cups water
• Honey and lemon

Simmer ginger for 15 minutes. Strain. Add honey and lemon. Drink as desired for colds, coughs, congestion, etc.
Turmeric Rhizome
(Curcuma longa and others)

• Rhizomes provide bright yellow-orange culinary spice and dye.
• Yellow pigments = curcuminoids, one example is curcumin.
• Long history of medicinal use for respiratory, skin, digestive and inflammatory conditions in India.
• More than 65 clinical trials have shed light on its potential role in CVD, diabetes, cancer, fatty liver, arthritis, neuro/psych disorders.

Curcumin

• Effective anti-inflammatory; strong inhibitor NF-kB very favorable clinical trials in knee osteoarthritis.

• 25 clinical trials using curcumin in a variety of cancers, curcumin is the most promising polyphenol as possible future adjuvant in colorectal cancer management.

Colonic polyps are a precursor to colorectal cancer.

A small pilot study of 5 patients with familial adenomatous polyps found that after six months of taking 480 mg of curcumin and 20 mg quercetin taken three times a day, polyp numbers were reduced by 60%.

Curcumin Targets

**Multi-targeted**

- Inflammatory cytokines: IL-1, IL-2, IL-5, IL-6, IL-8, IL-12, IL-8, MCP-1, MIP-1, MalP
- Enzymes: ATPase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, iNOS, MMPs, NQO-1, ODC, PI3PD, TIMP-3, 5-LOX, Telomerase
- Growth factors: TGF β, FGF, HGF, PDGF, TF
- Receptors: AR, AHR, CXCR4, DR, EGFR, ER-α, FasR, H2R, IL-8R, ITPR, IR, LD-R
- Adhesion molecules: ELAM-1, ICAM-1, VCAM-1
- Anti-apoptotic proteins: Bcl-2, Bcl-xl, IAP-1
- Protein Kinases: IKK, AAPK, Ca2+ PK, EGFR, ERK, FAK, IL-1 RAK, JAK, JNK, MAPK, PKC, PKA, PKB, PKC, pp60c-src tk, PTK
- Transcriptional factors: AP-1, β-Catenin, CBP, ERG-1, ERE, HIF-1, Notch-1, Not-2, NF-κB, PPAR-γ, STAT-1, STAT-3, STAT-4, STAT-5, WTG-1
- Others: Cyclin D1, Cyclin E, HSP 70, MDR

**Mono-targeted**

- COX-2: Celecoxib
- EGFR: Erbitux
- TNF: Remicade, Humira, Enbrel
- HER-2: Herceptin
- Bcr-Abl: Gleevac
- VEGF: Avastin
- Tubulin: Paclitaxel
- Topoisomerase: Camptothecin
Inflammatory Bowel Disease (IBD)

- IBD is a chronic gastrointestinal inflammatory disorder characterized by alternating relapses and remissions. Two most common types are Crohn's disease (CD) and ulcerative colitis (UC), characterized by exacerbated uncontrolled intestinal inflammation that contributes to worsening of QOL and prolonged medical and/or surgical interventions.

- IBD is the result of a complex combination of four main factors: multiple genetic variations, alterations in the composition of the intestinal microbiota, changes in the surrounding environment, and over-reactivity of the intestinal mucosal immune response.

• The physical barrier of the intestinal epithelium is complemented by a well-evolved mucosal innate immune system, which is poised to defend against pathogenic incursions, and limits inflammatory responses to maintain a state of hyporesponsiveness to commensal bacteria.

• The following herbs have been shown to be beneficial in randomized controlled trials for IBD but also consider berberine, probiotics, glutamine, etc.:
  • Aloe vera
  • Andrographis
  • Boswellia
  • Psyllium
  • Turmeric
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Patients</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label pilot study</td>
<td>5</td>
<td>UC 1.100 g/day (550 mg × 2) for 1 month, then 1.650 g/day (550 mg × 3) for 1 month, and then 1.440 g/day for two months</td>
<td>2 months</td>
<td>Improved serological parameters (erythrocyte sedimentation rate and C-reactive protein) as well as the disease activity index, with a reduction in the dose of medication, or even suppression. In the CD group, patients reported fewer bowel movements, less diarrhoea, and less abdominal pain and cramping.</td>
</tr>
<tr>
<td>Randomized, double-blind multicentre placebo-controlled study</td>
<td>89</td>
<td>UC 2 g/day plus sulfasalazine or mesalazine</td>
<td>6 months</td>
<td>Relapse rate was significantly higher in the placebo group, receiving only the aminosalicylate (20.5%), compared to the curcumin-treated cohorts (4.7%). During the period of the study, a marked reduction of the disease-associated clinical activity index and the endoscopic index scores was reported.</td>
</tr>
</tbody>
</table>

Curcumin and IBD

- Curcumin has been shown to be a potent modulator of NF-κB activation and can modify multiple signaling pathways, especially the kinases MAPK and ERK, thus affecting the expression of different proteins implicated in the intestinal inflammatory cascade, like MPO, COX-2, iNOS, or LOX.

- Distribution studies show curcumin preferentially accumulates in intestine, colon and liver.

- Consider standardized extracts of turmeric a safe and effective approach for maintaining remission and preventing relapse in patients with IBD.

- For systemic absorption consider using preparation with piperine or phytosome bound or nanoparticles.

Absorption and Safety Issues

• Low aqueous solubility of curcumin and its rapid metabolism and elimination from the body have constituted major obstacles to clinical use.

• Nanoencapsulation, curcumin complexed with phosphatidylcholine, and inclusion of the black pepper alkaloid, piperine, enhance tissue distribution and bioavailability.

• Note: Piperine causes inhibition of CYP3A4 and at doses of 20 mg can cause clinically relevant drug interactions especially for drugs with narrow therapeutic indices.

• Dose generally 1200-1500 mg per day of turmeric extract standardized to 95% curcumin, taken in divided doses.

Boswellia serrata

- The oleo-gum resin from *Boswellia*, or Indian frankincense, is a traditional Ayurvedic remedy used to treat inflammatory diseases, including asthma and IBD.

- In Germany, approximately 36% of IBD patients have been administered with *Boswellia serrata* extracts to treat their intestinal condition, reporting positive therapeutic effects.

- Boswellic acids inhibit 5-lipoxygenase pathway, which can account in the beneficial effect showed by this botanical drug since leukotrienes have been clearly involved in the pathogenesis of IBD.
<table>
<thead>
<tr>
<th>Drug/Type of Treatment</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Boswellia serrata</em> (Gum resin)</td>
<td>Randomized, double-blind, multicentre placebo-controlled study</td>
<td>UC 750 mg (3 × 250 mg)</td>
<td>Sulfasalazine 3 g (3 × 1 g)</td>
<td>6 weeks</td>
<td>All parameters tested improved after treatment with <em>Boswellia serrata</em> gum resin, with the results being similar compared to controls: 82% out of treated patients went into remission; in case of sulfasalazine remission rate was 75%</td>
</tr>
<tr>
<td>(Gum resin)</td>
<td></td>
<td>UC? 900 mg (3 × 300 mg)</td>
<td>Sulfasalazine 3 g (3 × 1 g)</td>
<td>6 weeks</td>
<td>Patients showed an improvement in several parameters: stool properties, histopathology, and scanning electron microscopy, besides haemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes, and eosinophils. The remission was higher in patients treated with <em>Boswellia serrata</em></td>
</tr>
<tr>
<td>(Bosweljan)</td>
<td></td>
<td></td>
<td>Placebo</td>
<td>12 months (52 weeks)</td>
<td>Bosweljan showed a safety profile during the long-term therapy but the results obtained did not show a higher efficacy when compared with placebo</td>
</tr>
<tr>
<td><em>Cannabis sativa</em></td>
<td>Retrospective observation study</td>
<td>CD —</td>
<td>—</td>
<td>—</td>
<td>Cannabis administration was associated with an improvement in disease activity and a reduction in the need of other medications, as well as a reduced risk of surgery</td>
</tr>
<tr>
<td></td>
<td>Prospective Placebo-controlled study</td>
<td>CD 2 cigarettes containing 115 mg of THC/day</td>
<td>Placebo</td>
<td>8 weeks</td>
<td>A significant amelioration of the CD activity index has been reported in the majority of the subjects after cannabis treatment in comparison with placebo administration; in fact, complete remission was achieved in half of the subjects in the cannabis group, whereas it only occurred in 10% of the placebo group patients</td>
</tr>
</tbody>
</table>

Gut Astringents

• Astringents have a 'binding' action on tissue, usually due to tannins. Reduce irritation, inflammation, create protective barrier.

  Agrimony          Bayberry
  Blackberry        Cranesbill
  Goldenseal        Horse chestnut
  Meadowsweet       Oak leaf/bark
  Plantain          Raspberry leaf
  Sage              Tea
  Vervain           Witch hazel
  Wood betony       Yarrow
Agrimony Herb
\textit{(Agrimonia eupatoria)}

- Tonic astringent
- Anti-inflammatory
- IBS-mixed or IBS-D
- Acute diarrhea
- Gargle sore throat or laryngitis
- Topical antiseptic & vulnerary
- \textit{Infusion}: 2-4 ounces TID
- \textit{Tincture}: (1:5, 40\%) 2-4 ml TID

## Nervines

<table>
<thead>
<tr>
<th>Nervine Relaxant Mild</th>
<th>Nervine Relaxant Moderate</th>
<th>Nervine Relaxant Strong</th>
<th>Nervine Tonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramp bark</td>
<td>Black cohosh</td>
<td>Hops*</td>
<td>Saint John’s wort</td>
</tr>
<tr>
<td>Lavender</td>
<td>Vervain*</td>
<td>Passionflower</td>
<td>Saffron</td>
</tr>
</tbody>
</table>

*Nervine with benefit for gastrointestinal tract.
Ashwagandha Root
(*Withania somnifera*)

- Rasayana that normalizes physiological function disturbed by chronic stress by correcting imbalances in the neuroendocrine and immune system.
- Powerful anti-inflammatory working through numerous pathways.
- "*Somnifera*" means "sleep-inducer," which probably refers to its extensive use as a remedy against stress and anxiety.
- May enhance immediate and general memory in people with MCI, improve executive function, attention, and information processing speed.

Lemon Balm Leaf
(\textit{Melissa officinalis})

- “Gladdening herb” and “Heart’s delight.”
- Strong digestive affinity, can be helpful for functional GI disorders, IBS, etc.
- Carminative: improves colic in breastfed babies, especially when combined with chamomile and/or fennel.
- Calms disordered energy. Good for those who lose focus when over-stimulated.
- Exhibits numerous pharmacological effects, from which anxiolytic, antiviral and antispasmodic activities, as well as its effects on mood, cognition and memory have been shown in clinical trials.

I go to nature to be soothed and healed, and to have my senses put in order.

John Burroughs