Botanicals in Clinical Practice: Part One: The GI

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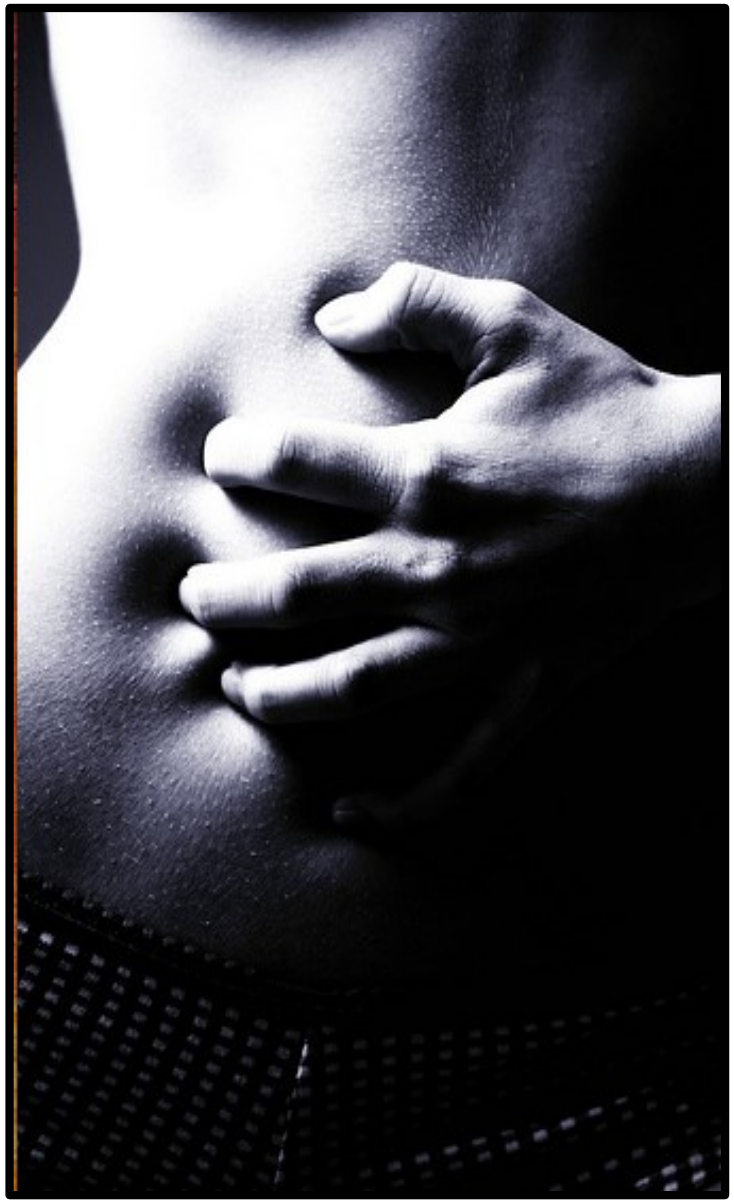
AARM
Association for the Advancement of Restorative Medicine

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

Andrographis
Artichoke leaf
Barberry
Boneset
Calamus
Cascara sagrada
Chamomile
Dandelion
Gentian
Goldenseal
Hops
Horehound
Motherwort
Oregon grape
Sage
Skullcap
Vervain
Wormwood
Yarrow

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.

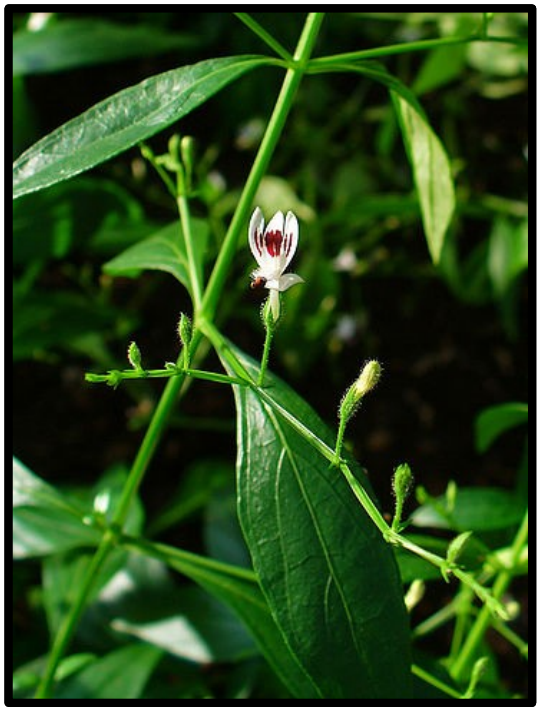
Clinical trials of botanical drugs in patients with inflammatory bowel disease.

Herbal preparation	Study design	Number of patients	IBD type	Dose	Comparator	Frequency	Endpoint	Reference
Aloe vera	Randomized, double-blind controlled study	44	UC	100 mL twice/day	Placebo	4 weeks	*Aloe vera* produced a significantly better clinical response than in those receiving placebo. The Simple Clinical Colitis Activity Index and histological scores decreased significantly during treatment with *Aloe vera* but not with placebo	[14]
Andrographis paniculata (HMPL-004)	Randomized, double-blind multicentre study	120	UC	1.2 g/day	Mesalazine (4.5 mg/day)	8 weeks	There were no significant differences between the two treated groups when considering the clinical efficacy rates or the safety profile	[15]
	Randomized, double-blind placebo-controlled study	224	UC	1.2 g/day and 1.8 g/day	Placebo	8 weeks	Patients treated with the extract, mainly at the highest doses, were more likely to achieve clinical response than those receiving placebo, whereas the incidence of adverse events was similar among groups, although the occurrence of rash was higher in the HMPL-004 extract groups	[16]
Artemisia absinthium	Randomized, double-blind multicentre study	40	CD	3 × 500 mg/day	Placebo	10 weeks	After 8 weeks of treatment with wormwood, there was almost complete remission of symptoms in 65% of the patients, whereas no beneficial effect was observed in those receiving the placebo	[17]
	Randomized, double-blind multicentre study	20	CD	3 × 750 mg/day (in addition to standard therapy)	Standard therapy + placebo	6 weeks	Wormwood administration promoted the clinical improvement of the symptoms in all the patients. The beneficial effect was associated with a significant decrease in TNFα serum levels in comparison with those obtained in the placebo group, where no amelioration in the disease was observed	[18]

From: Algieri F, et al. Botanical Drugs as an Emerging Strategy in Inflammatory Bowel Disease: A Review *Mediators Inflamm* 2015: 179616.

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.



Bertoglio JC, Baumgartner M, Palma R, et al. Andrographis paniculata decreases fatigue in patients with relapsing-remitting multiple sclerosis: a 12-month double-blind placebo-controlled pilot study. *BMC Neurol.* 2016 May 23;16:77.

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.

Ishida K, et al. *Biol Pharm Bull* 2010; 33:223-9
Metwally NS, et al. *Eur Rev Med Pharamcol Sci* 2011; 15:1429-44
Sannia A, et al. *Minerva Gastroenterol Dietol* 2010; 56:93-9

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.

Rondanelli M, et al. *Int J Food Sci Nutr* 2012

Wider B, et al. *Cochrane Database Syst Rev* 2009 Oct 7;(4):CD003335

Rangboo V, et al. *Int J Hepatol* 2016; 4030476.

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

Liu Y, et al. *Evid Based Complement Alternat Med* 2013; 2013:308134.

Martinez-Abundis E, et al. *World J Diabetes* 2016; 7(7):142-52.

Wang H, et al. *Biomed Res Int* 2014: 798093

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.*

Liu X, et al. *Adv Dent Res* 2011; 23:56-60

Cybulska P, et al. *Sex Transm Dis* 2011; 38: 667-71

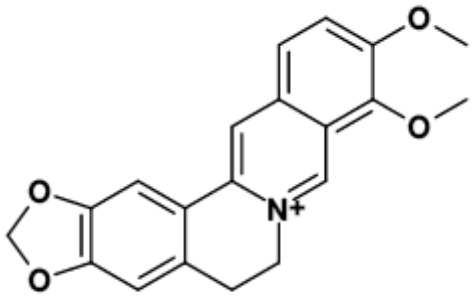
Chin, et al. *Arch Virol* 2010; 155:1933-41

Li N, et al. *Eur J Pharm Sci* 2010; 40:1-8

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.

Chen C, et al. *Phytother Res* 2015; 29(11):1822-7.



Berberine

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.

Song Y, et al. J Allergy Clin Immunol 2010; 126(6): 1208-17

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.

Tan XS, et al. PLoS One 2013; 8(10):e77969.

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.

Xin, et al. Find Exp Clin Pharmacol2006; 28: 25–29

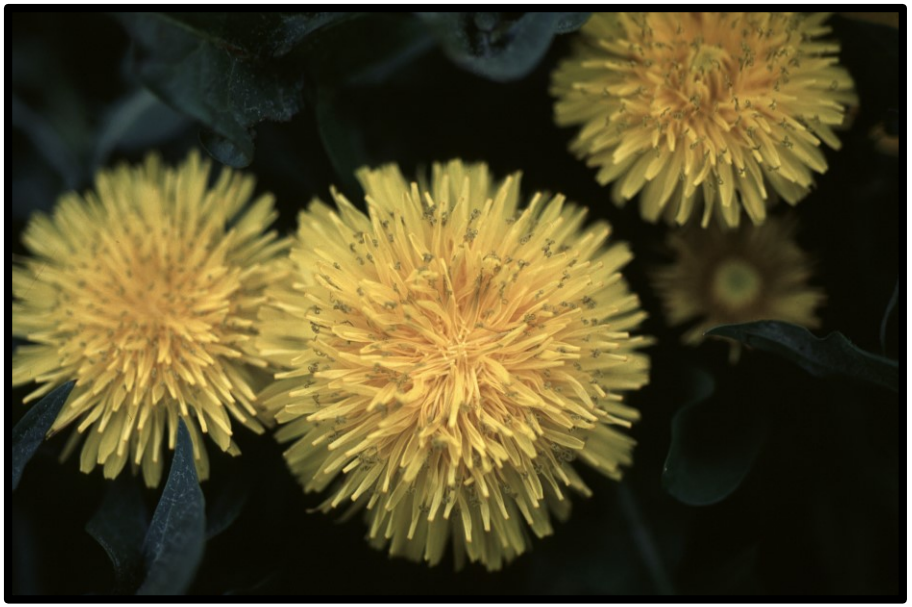
Wu, et al. Eur J Clin Pharmacol 2005; 61: 567–572

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-$\varkappa$B, TNF-alpha)
- Liver protectant in acetaminophen and alcohol models
- Prokinetic agent, rich source of inulin
- Leaf has demonstrated significant diuretic activity.



Colle D, et al. J Med Food 2012; 15:549-56
Jin YR, et al. Neurogastroenterol Motil 2011; 23:766
Park CM, et al. J Ethnopharmacol 2011; 133:834-42
Clare B, et al. J Altern Complement Med 2009; 15(8): 929–934.

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

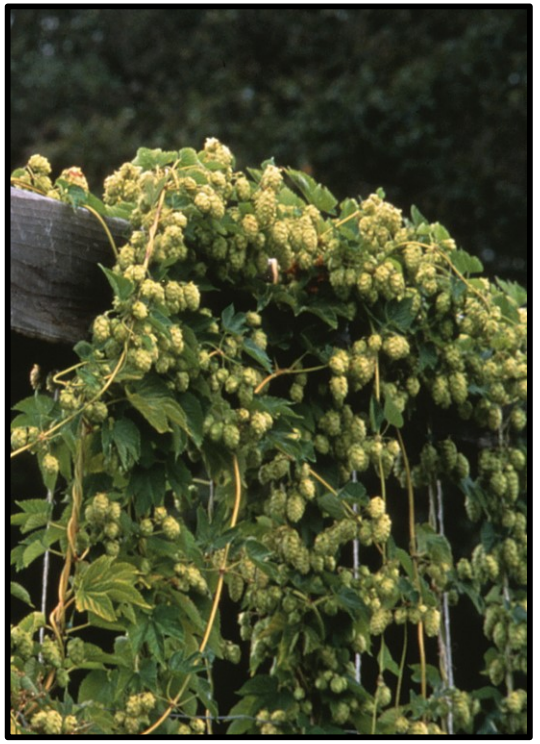
Dose for dandelion leaf

- 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.
- Official in USP 1860-1910. German authorities approve for gas, bloating, and poor appetite.
- 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.

Lopresti AL. Salvia (Sage): A Review of its Potential Cognitive-Enhancing and Protective Effects. *Drugs R D.* 2017 Mar; 17(1): 53–64.

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 world, described in different pharmacopoeias. Usually standardized based to dimeric guaianolides: absinthins (0.2%).
- Beneficial effect in IBD associated with a significant decrease in TNF-*a* serum levels in two clinical trials when compared to placebo.
- TNF-*a* 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-*a* inhibitors, like infliximab and adalimumab, for severe cases.

Algieri F, et al. Botanical Drugs as an Emerging Strategy in Inflammatory Bowel Disease: A Review *Mediators Inflamm* 2015: 179616.

Iberogast: Functional Dyspepsia

$33.00 for 100 ml

Supplement Facts

Serving Size: 20 drops (1 ml)

Servings Per Container: 100

	Amount per serving	% Daily Value
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	1 ml	**

**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)

12 years and over	20 Drops
6 to 12 years	15 Drops
3 to 6 years	10 Drops
3 months to 3 years	8 Drops
Under 3 Months, consult a physician	

Other Ingredients

Alcohol 31%

Gallexier: Non-Alcoholic Bitter

$21.75 for 250 ml

Supplement Facts		
Serving Size: 20 ml		
Servings Per Container: about 12		
	Amount Per Serving	**% Daily Value**
Calories	15	
Total Carbohydrate	4 g	2%*
Sugars	4 g	†
Sodium	5 mg	<1%
Proprietary blend 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.	1.611 g	†

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.

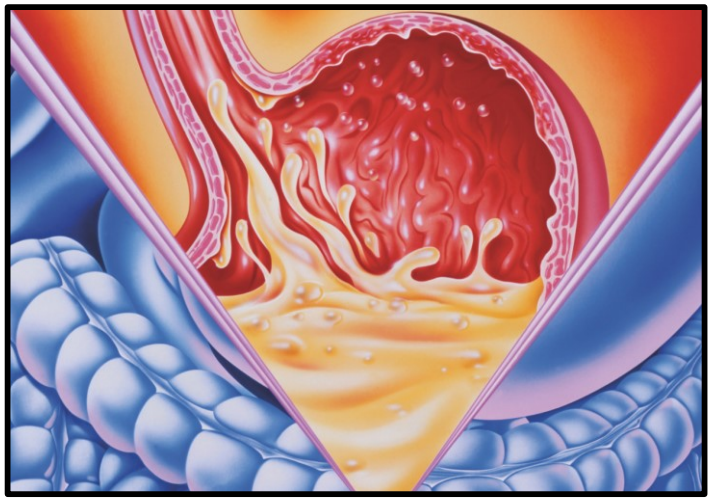
Gut Demulcents or Anti-Inflammatories

- Soothes, coats and/or protects GI mucosa

Aloe vera	Calendula
Chamomile	Comfrey
Holy basil	Licorice
Marshmallow	Meadowsweet
Slippery elm	Wild yam

Specifics: Gastroesophageal Reflux

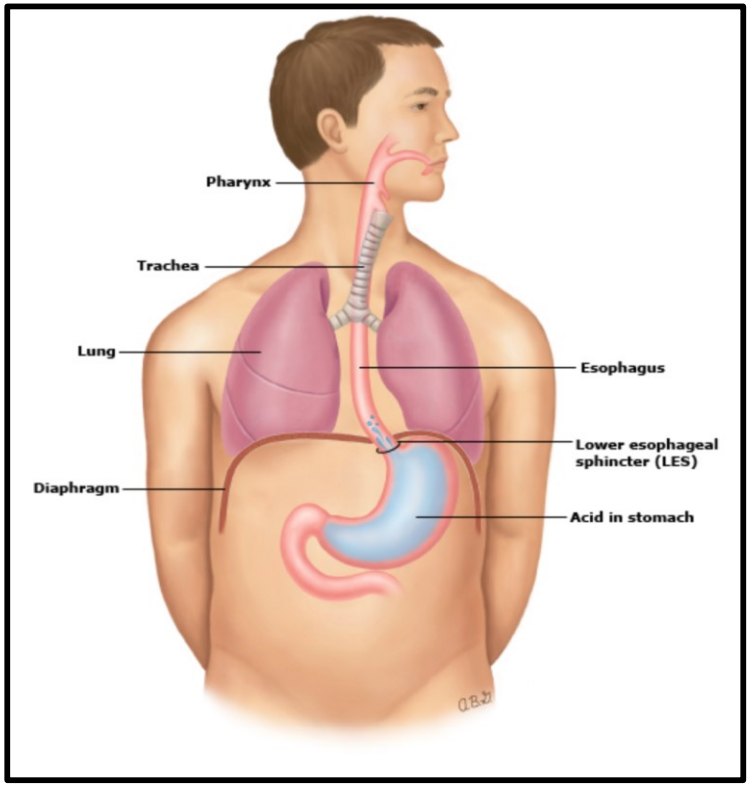
- Chronic condition in which contents of stomach flow back into esophagus, potentially causing symptoms (e.g., heartburn) and injury to esophagus.
- >60 million people report GERD symptoms at least weekly.
  - Symptoms include retrosternal burning, acid regurgitation, nausea, vomiting, chest pain, laryngitis, cough, and dysphagia.
- Incidence increasing: full-time physicians diagnose and treat 40-60 patients each month.



Anderson WD, et al. *Am Fam Physician*. 2015 May 15;91(10):692-697

What Causes GERD?

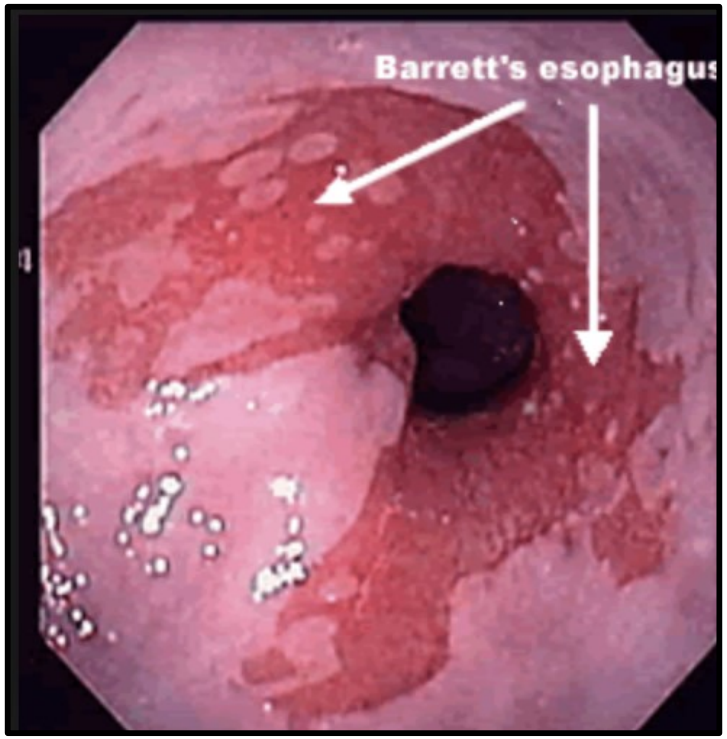
- Disturbed esophageal motility; anatomical disorders, such as hiatal hernia, increased obesity, defective mucosal integrity, and concomitant medications are all associated with increased risk of GERD.
- Problem is seldom excessive stomach acid production (except rare cases of Zollinger-Ellison syndrome).



Bashashati M, et al. *Ann NY Acad Sci* 2016; doi: 10.1111/nyas.13196.

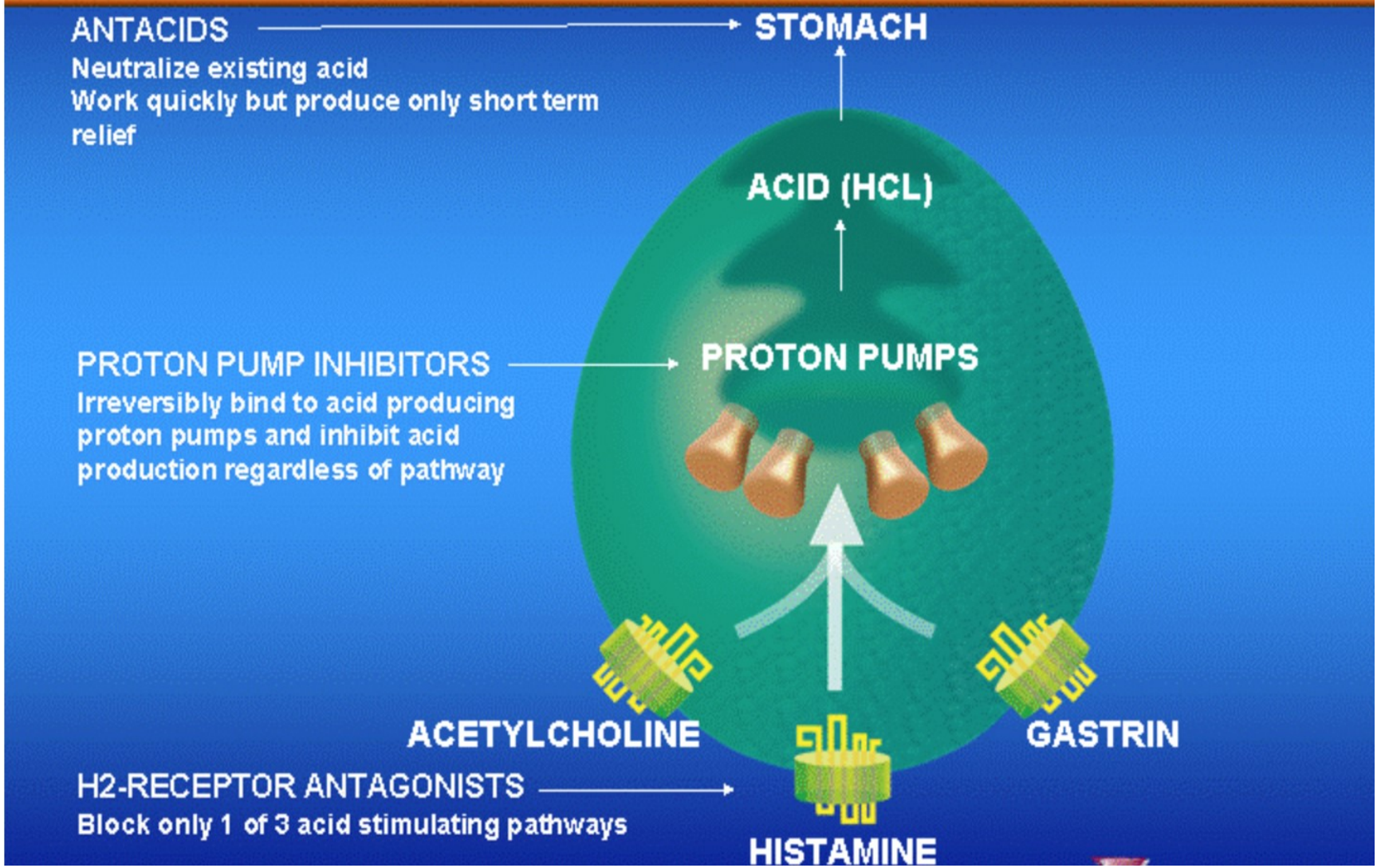
Barrett's Esophagus

- 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
Thrift AP. *Curr Opin Gastroenterol* 2016; 32(4):319-24.

Upper GI Products/Mechanisms



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)."

Boghhossian TA, et al. *Cochrane Database Syst Rev* 2017; Mar 16;3:CD011969.

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.

Choonhakam C, et al. *Br J Dermatol* 2008; 158:573-7
Worthington HV, et al. *Cochrane Database System* 2011; 4: CD 000978
Ali S, et al. *Oral Dis* 2016; doi: 10.1111/odi.12631.
Zhang Y, et al. *Nutrients* 2016; 8(7). pii: E388.

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.

Santhosh Kumari CH, et al. *Int J Pharma Bio Sci* 2010; 1(2): 124.
Keshavarzi Z, et al. *Avicenna J Phytomed* 2014; 4(2): 137-143.
Panahi Y, et al. *J Tradit Chin Med* 2015; Dec;35(6):632-6.

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

Item	Aloe vera			Omeprazole			Ranitidine		
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4
Heartburn	17 (100.0)	4[a] (23.5)	5[a] (29.4)	24 (100.0)	13[ab] (54.2)	15[ab] (62.5)	25 (100.0)	9[a] (36.0)	13[ab] (52.0)
Food regurgitation	10 (100.0)	1[a] (10.0)	1[a] (10.0)	11 (100.0)	2[a] (18.2)	2[a] (18.2)	16 (100.0)	1 (6.3)	2[a] (12.5)
Dysphagia	12 (100.0)	4[a] (33.3)	4[a] (33.3)	12 (100.0)	1[a] (8.3)	1[a] (8.3)	9 (100.0)	0 (0.0)	2 (12.5)
Flatulence	17 (100.0)	1[a] (5.9)	2[a] (11.8)	21 (100.0)	5[a] (23.8)	9[ac] (42.9)	23 (100.0)	12[ac] (52.1)	7[ac] (30.4)
Belching	15 (100.0)	2[a] (13.3)	3[a] (20.0)	19 (100.0)	7[a] (36.8)	10[ab] (52.6)	21 (100.0)	3[a] (14.3)	7[a] (30.4)
Nausea	5 (100.0)	1[a] (20.0)	1[a] (20.0)	12 (100.0)	4[a] (33.3)	4[a] (33.3)	15 (100.0)	8[a] (53.3)	10[a] (66.7)
Vomiting	1 (100.0)	1 (100.0)	1 (100.0)	3 (100.0)	2[a] (66.7)	2[a] (66.7)	6 (100.0)	2[a] (33.3)	4[a] (66.7)
Acid regurgitation	20 (100.0)	10[a] (50.0)	10[a] (50.0)	20 (100.0)	12[a] (60.0)	13[a] (65.0)	24 (100.0)	10[a] (41.7)	16[a] (66.7)

Notes: GERD: gastroesophageal reflux disease. [a]$P < 0.05$: within group comparison with respect to baseline value; [b]borderline significant difference versus A. vera group at the respective time point; [c]between-group comparison at respective time point (week 2 or 4) in the A. vera group.

Panahi Y, et al. *J Tradit Chin Med* 2015; Dec;35(6):632-6

Slippery Elm Inner Bark (*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.

Hawrelak JA, et al. *J Altern Complement Med* 2010; 16: 1065-71

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.

Aly AM, et al. *AAPS PharmSciTech.* 2005; 20;6(1):E74-82 .

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

www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2012/08/WC500131285.pdf

Blumenthal M, Goldberg A, Brinckmann J (eds). Herbal Medicine: Expanded Commission E Monographs. 1st ed.

DGL Product

Suggested Use

Chew two tablets twenty minutes before each meal.

Supplement Facts

Supplement Facts		
Serving Size 2 Tablets		
Servings Per Container 50		
	Amount Per 2 Tablets	**%DV****
Calories	10	
Sodium	5 mg	<1%**
Total Carbohydrate	2 g	<1%**
Sugars	<1 g	†
Deglycyrrhizinated Licorice (DGL) (Glycyrrhiza glabra) Root Extract 3:1	760 mg	†
Glycine	100 mg	†

Alginates

- Aginates 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.

Leiman DA, et al. Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis. Dis Esophagus 2017 May 1;30(5):1-9.

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.

Bandyopadhyay D, et al. *J Pineal Res* 2002, 33(1):1–7

Kandil TS, et al. BMC Gastroenterology 2010;10:7

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.

Kandil TS, et al. *BMC Gastroenterol* 2010; 10:7.

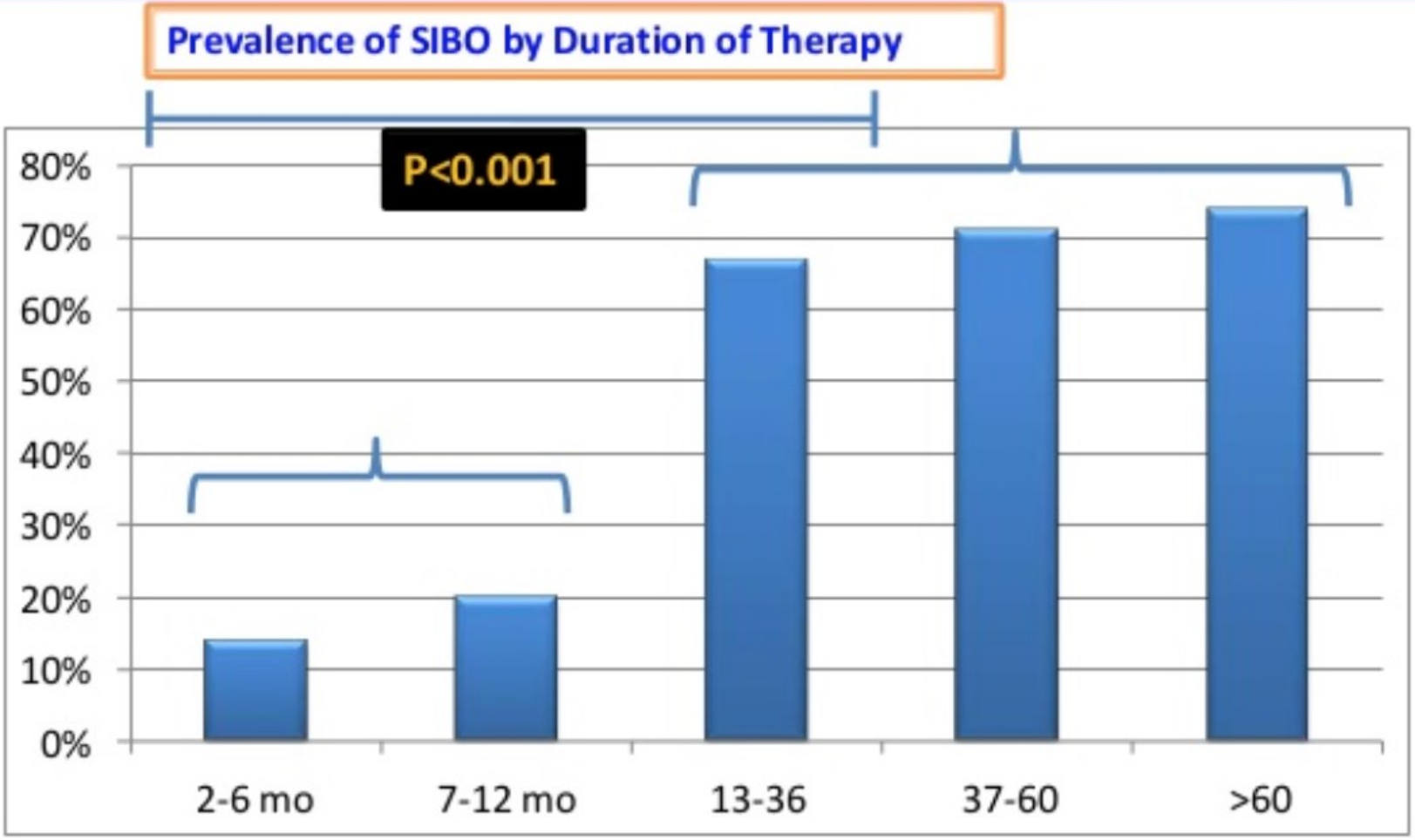
Brzozowska I, et al. *Curr Pharm Des* 2014; 20(30):4807-15

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.

Freedberg D, et al. The Impact of Proton Pump Inhibitors on the Human Gastrointestinal Microbiome, Clinics in Laboratory Medicine, Volume 34, Issue 4, December 2014, Pages 771-785.
Fisher L, et al. Acid-Suppressive Therapy and Risk of Infections: Pros and Cons. *Clin Drug Investig* 2017 Mar 30. doi: 10.1007/s40261-017-0519-y.

PPI and Bacterial Overgrowth



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.

Chedid V, et al. *Glob Adv Health Med* 2014; 3(3): 16–24.
Achamrah N, et al. *Curr Opin Clin Nutr Metab Care* 2017; 20(1):86-91
Shu XL, et al. *Exp Ther Med* 2016; Dec;12(6):3499-3506

Study Found Clinically Effective for SIBO

CandiBactin AR $39.95 60 caps

Benefits | Ingredients

Serving Size:
1 Softgel

Ingredient	Amount	Daily Value
Thyme (*Thymus vulgaris*) Oil [provides 55 mg thymol]	183 mg	*
Oregano (*Origanum vulgare*) Oil [provides 55 mg carvacrol]	100 mg	*
Sage (*Salvia officinalis*) Leaf 5.5:1 Extract	75 mg	*
Lemon Balm (*Melissa officinalis*) Leaf 5:1 Extract	50 mg	*

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.

CandiBactin BR $39.95 90 tabs

Benefits | Ingredients

Serving Size:
2 Tablets

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

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

Supplement Facts

Serving Size: Two Capsules

Servings Per Container: 30

Two Capsules Contain:	**Amount Per Serving**	**% DV**
Berberine HCl (from Indian Barberry extract) (root) (Berberis aristata)	1 g	*

*Daily Value (DV) not established

Berberis Concentrate Berberine HCl 85%.

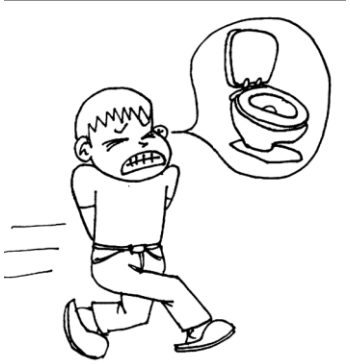
Solaray Berberine ~$20.00 60 caps

Supplement Facts

Serving Size: 1 Vegetarain Capsule

	Amount Per Serving	**% Daily Value***
Berberine HCl (from Indian Barberry) (Berberis aristata) (root extract)	250 mg	*
Oregon Grape (Berberis aristata) (root)	150 mg	*

* 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!

Spiller R, et al. Gastroenterology. 2009 May;136(6):1979-88.

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

Therapy	Trials	NNT
Peppermint oil	8	2
Hycosamine	22	11
Alosetron	6	7
Tegaserod	8	17
Tricyclics	8	4

Ford AC, et al. British Medical Journal 2008; 337:a2313

Peppermint Essential Oil for IBS

Cash BD, et al. *Dig Dis Sci.* 2016;61(2):560–571.
Chey WD, et al. J*AMA* 2015;313(9):949–958.

- 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, $\varkappa$-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.

Public statement on the use of herbal medicinal products containing pulegone and menthofuran, European Medicines Agency, EMA/HMPC/138386/2005 Rev. 1; 24 November 2014.

Caraway Essential Oil (*Carum carvi*)

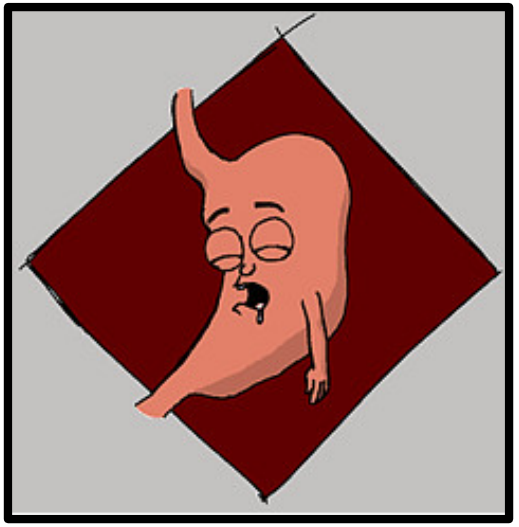
- Caraway oil displayed high degree of selectivity, inhibiting growth of potential bacterial intestinal pathogens at concentrations that had no effect on beneficial bacteria.
- Increases mucin secretion and PGE2 in stomach, protecting against NSAID damage.
- Carminative, antispasmodic
- Spirit of caraway – 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.

Wang J, et al. Beneficial effects of ginger Zingiber officinale Roscoe on obesity and metabolic syndrome: a review. *Annals of the New York Academy of Sciences* 2017; May 15. doi: 10.1111/nyas.

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.

Wu KL, et al. Eur J Gastroenterol Hepatol. 2008 May;20(5):436-40. d

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.

Palatty PL, et al. Crit Rev Food Sci Nutr 2013; 53(7):659-69

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.

Chang JS, et al. *J Ethnopharmacol* 2013; 145(1):146-51
Akoachere JF, et al. *East Afr Med* 2002; 79(11):588-92.

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.*

Bartels EM, et al. Osteoarthritis Cartilage 2015; 23(1):13-21

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.

Kunnumakkara AB, et al. *Br J Pharmacol* 2016; Sep 17. doi: 10.1111/bph.13621.

Prasad S, et al. *Biotechnol Adv* 2014; 32(6):1053-1064

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.

Irving GR, et al. Cancer Prev Res 2013; 6(2):119-28.

Shanmugam MK, et. Al. *Molecules* 2015, *20*(2), 2728-2769

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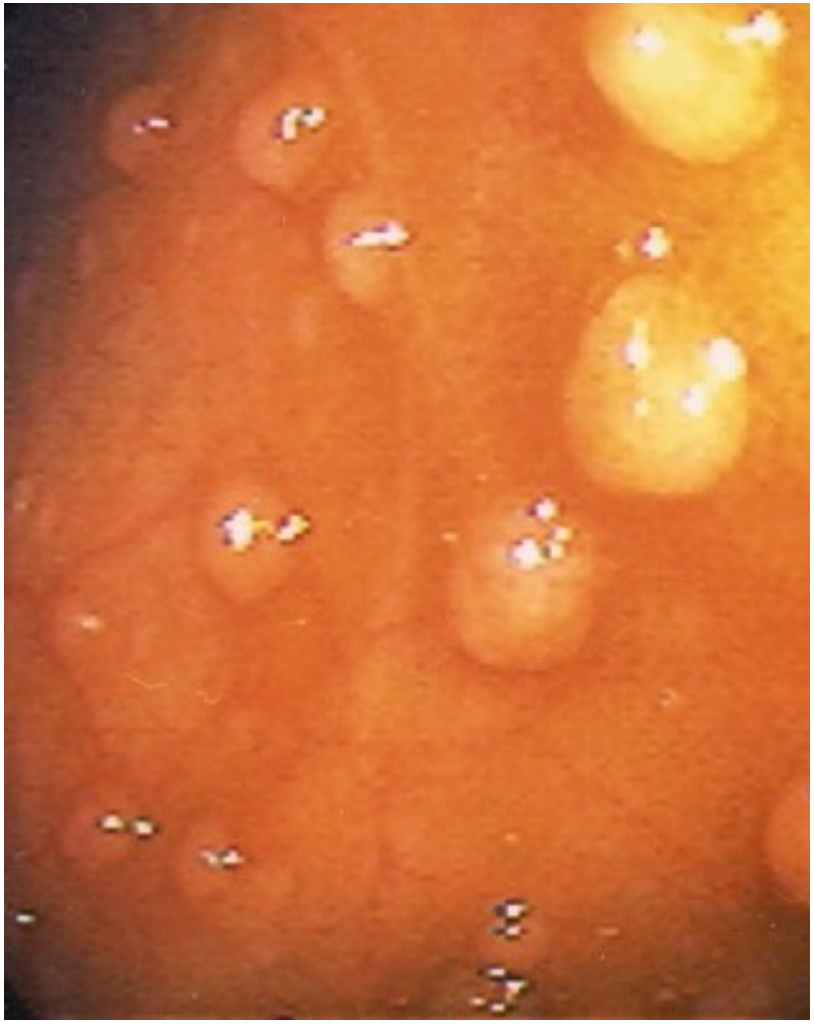
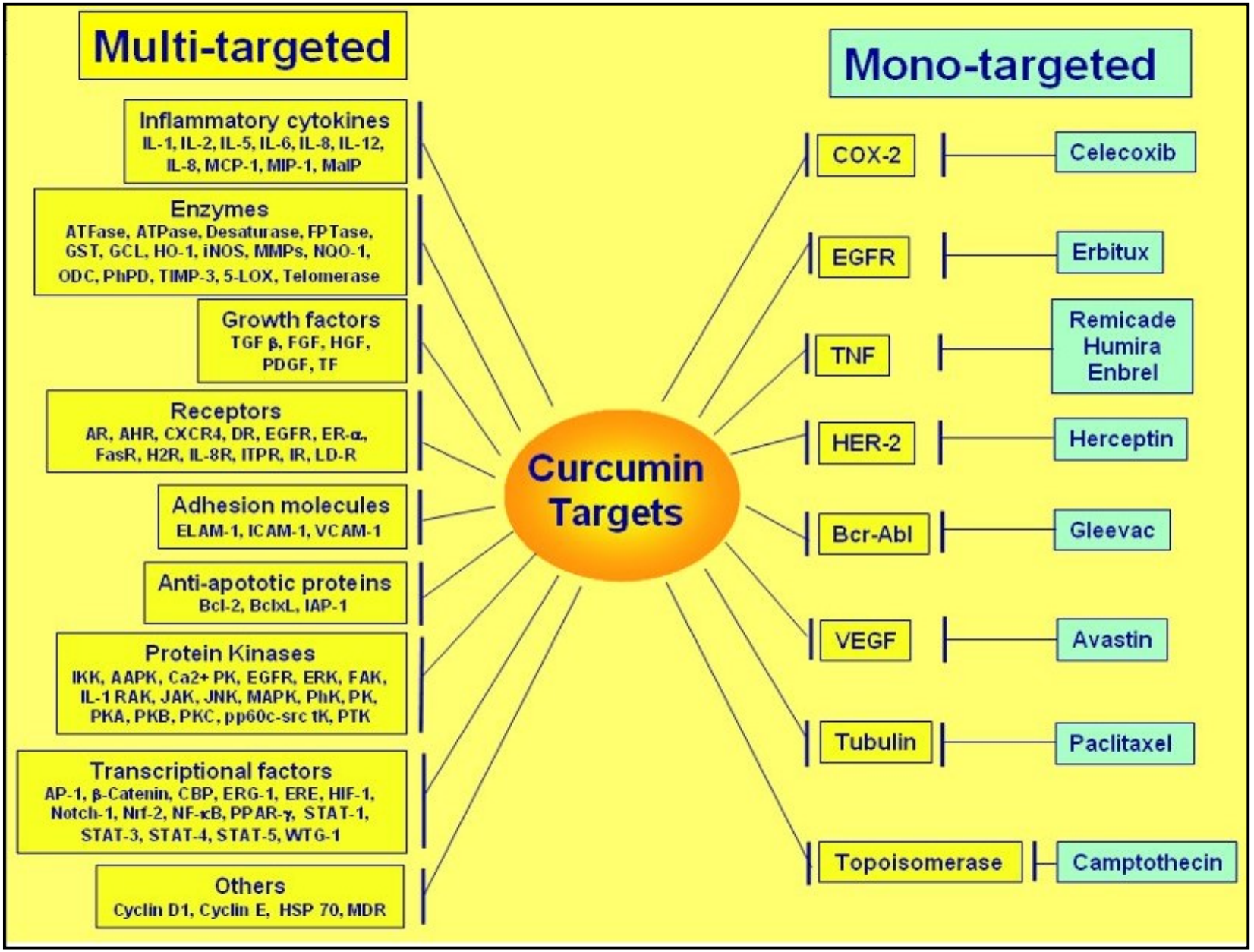
Early Investigation



- 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%.

Cruz-Correa M, *Clin Gastroenterol Hepatol.* 2006;4:1035–1038



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.

Strober W., Fuss I. J. Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. *Gastroenterology*. 2011;140(6):1756–1767.

- 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

Curcuma longa	Open-label pilot study	5	UC	1.100 g/day (550 mg × 2) for 1 month, then 1.650 g/day (550 mg × 3) for 1 month and 1.080 g/day (360 mg × 3) for 1 month, and then 1.440 g/day for two months	—	2 months	The results from this study revealed that the treatment of these patients with curcumin for two months resulted in an overall improvement in all the patients, as evidenced by amelioration of the serological parameters evaluated (erythrocyte sedimentation rate and C-reactive protein) as well as the disease activity index followed, together with a reduction in the dose of medication, or even suppression. In the CD group, all patients also reported fewer bowel movements, less diarrhoea, and less abdominal pain and cramping	[24]
	Open-label pilot study	5	CD		—	3 months		
	Randomized, double-blind multicentre placebo-controlled study	89	UC	2 g/day plus sulfasalazine or mesalazine	Placebo plus sulfasalazine or mesalazine	6 months	The relapse rate was significantly higher in the placebo group, receiving only the aminosalicylate (20.5%), than in 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	[25]

From: Algieri F, et al. Botanical Drugs as an Emerging Strategy in Inflammatory Bowel Disease: A Review *Mediators Inflamm* 2015: 179616.

Curcumin and IBD

- Curcumin has been shown to be a potent modulator of NF-$\varkappa$B 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 nanoparicles.

Algieri F, et al. A Review *Mediators Inflamm* 2015: 179616.

Dulbecco P, et al World J Gastroenterol 2013; 19(48): 9256–9270.

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.

Gurley BJ, et al. Planta Med 2012; 78(13):1490-514

Bedada SK, et al. Drug Res 2016; Oct 24

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

Boswellia serrata (Gum resin)	—	?	UC	750 mg (3 × 250 mg)	Sulfasalazine 3 g (3 × 1 g)	6 weeks	All parameters tested improved after treatment with *Boswellia serrata* 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%	[19]
(Gum resin)	—	30	UC?	900 mg (3 × 300 mg)	Sulfasalazine 3 g (3 × 1 g)	6 weeks	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 *Boswellia serrata*	[20]
(Boswelan)	Randomized, double-blind, multicentre placebo-controlled study	82	CD	2.4 g/day	Placebo	12 months (52 weeks)	Boswelan showed a safety profile during the long-term therapy but the results obtained did not show a higher efficacy when compared with placebo	[21]
Cannabis sativa	Retrospective observation study	30	CD	—	—	—	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	[22]
	Prospective Placebo-controlled study	21	CD	2 cigarettes containing 115 mg of THC/day	Placebo	8 weeks	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	[23]

From: Algieri F, et al. Botanical Drugs as an Emerging Strategy in Inflammatory Bowel Disease: A Review *Mediators Inflamm* 2015: 179616.

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 (*Agrimonia eupatoria*)

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

Ivanova D, et al. *Arch Physiol Biochem* 2013; 119(1):32-7
Yoon SJ, et al. *Food Chem Toxicol* 2012; 50(7): 2335-41

Nervines

Nervine Relaxant Mild	Nervine Relaxant Moderate	Nervine Relaxant Strong	Nervine Tonic
Cramp bark	Black cohosh	Hops*	Saint John's wort
Lavender	Vervain*	Passionflower	Saffron

*Nervine with benefit for gastrointestinal tract.

Ashwagandha Root (*Withania somnifera*)

White PT, et al. *Adv Exp Med Biol* 2016;928:329-373.
Yenisetti SC, et al. *Recent Pat CNS Drug Discov.* 2016;10(2):204-215.
Pratte MA, et al. *J Altern Complement Med.* 2014 Dec;20(12):901-8.
Choudhary D, et al. *J Diet Suppl* 2017; 14(6):599-612.

- 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 (*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.

Shakeri A, et al. J Ethnopharmacol 2016; 188:204-8

Supplement Facts		
Serving Size: 1 Cup Brewed Tea		
Serving Per Container: 16		
	Amount Per Serving	**%DV**
All Herbal Ingredients:		
Organic lemon balm leaf [PhEur] **	1500 mg	†

† Daily Value (DV) not established.
**This is the pharmacopoeial quality standard we use because quality matters.

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

John Burroughs