



Lincoln College of Postprofessional, Graduate and Continuing Education

Herbal Considerations to Effectively Treat SIBO and SIFO

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Herbal Considerations to Effectively Treat SIBO and SIFO

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Disclaimer

- ▶ CMO at SIBOtest.com
- ▶ I hold no financial interest in any of the information presented today

Pros and cons of herbal medicines

- ▶ Pros:
 - Herbs often have multiple effects, ie antibacterial and antifungal, antiinflammatory and antioxidant, etc
 - Mostly cause less damage to the microbiome
 - Have evolved with bacteria and thus have overcome many of their resistance strategies
 - Can be combined to address multiple issues
- ▶ Cons
 - Can be more costly due to length of treatment
 - Patients self medicating with inferior herbal products can be cause for concern due to contamination (heavy metals etc)
 - Allergies, salicylates, oxalates
 - Doses often vary depending on formulation (standardized extract vs whole plant)
 - Limited research in SIBO and SIFO, more research in IBS in general

Botanical Mechanisms of overcoming Bacterial Resistance

- ▶ Bacterial efflux pumps actively remove antibiotics and other substances out of the cell-
 - Examples of herbs which inhibit or down regulate these: Berberine containing plants, Thyme, Juniper, Licorice, Green Tea
- ▶ Alterations in bacterial cell wall permeability - gram neg bacteria down regulate porin expression which limits antibiotic entry into the cell.
 - Examples of herbs which alter bacterial cell wall: Bearberry, Goldenseal, Usnea
- ▶ Plasmids: strains of bacterial DNA that contain resistance information. Highly mobile and passed on to other bacteria
 - Examples of herbs that modulate bacterial DNA: Barberry, Golden Seal, Oregon Grape, Thyme

Antibiotics for SIBO- out of the frying pan and into the fire?

Long term damage to the microbiome with repeated antibiotic courses

“The fecal microbiome was severely affected by most antibiotics: for months, health-associated butyrate-producing species became strongly underrepresented. Additionally, there was an enrichment of genes associated with antibiotic resistance. Clearly, even a single antibiotic treatment in healthy individuals contributes to the risk of resistance development and leads to long-lasting detrimental shifts in the gut microbiome.”

Same Exposure but Two Radically Different Responses to Antibiotics: Resilience of the Salivary Microbiome versus Long-Term Microbial Shifts in Feces
Egija Zaura, a Bernd W. Brandt, a M. et al. Mbio November/December 2015 Volume 6 Issue 6 e01693-15

The Culprits

Predominant SIBO bacteria isolated on duodenal aspirate (Pimentel, 2015):

- ▶ **gram positive:**
 - Enterococcus spp
 - other studies also identified Streptococcus and Staphylococcus
- ▶ **gram negative:**
 - Proteus mirabilis
 - E.coli
 - Klebsiella pneumoniae
- ▶ Methanobrevibacter smithii (methane)

Co-morbid SIFO

candida spp and other fungal spp

The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: relationship with irritable bowel syndrome: Pylaris E, Giamerellos-Bourbouts EJ, Pimentel M, et al. Dig Dis Sci 2012 May;57(5):1321-9. doi: 10.1007/s10620-012-2033-7. Epub 2012 Jan 20.

Herbal uses in SIBO and SIFO

- ▶ Antimicrobials
 - Antibacterial/antifungals/antimethanogen
- ▶ Anti-inflammatory, antioxidants, Immune modulators:
 - curcumin, green tea
- ▶ Herbal Prokinetics
- ▶ Anti-spasmodics/carminatives: chamomile, caraway seeds

Anti-microbials

1. Berberine containing herbs
2. Garlic
3. Oregano
4. Clove
5. Pomegranate
6. Artemisia annua
7. Usnea
8. Horopito

Berberine containing herbs

Clinically well established for reducing hydrogen

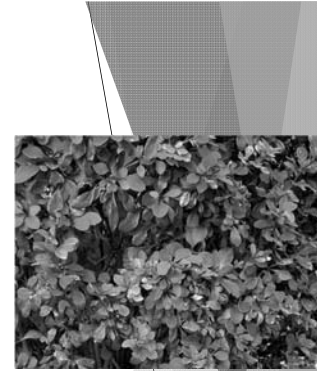
Phellodendron amurense, Mahonia aquafolium (Oregon grape), Coptis chinensis (Goldthread), Berberis vulgaris (Barberry), Hydrastis canadensis (Golden Seal)

- ▶ Berberine: different berberine alkaloids have different actions
- effective against: E.coli, Klebsiella p., P. aeruginosa, Staphylococcus spp, Streptococcus spp and candida spp
- interferes with the adhesion of LTA (lipoteichoic acid), a ligand responsible for the adherence of *Streptococci* to epithelial cells



Berberine - MOA

1. Efflux pump inhibition
2. Bacterial cell membrane permeability modification
3. Inhibition of biofilm formation
4. Inhibition of bacterial replication
5. Anti-virulence properties via quorum quenching



Buhner, S (2012) Herbal Antibiotics, USA; Storey Publishing

Goldenseal (*Hydrastis canadensis* L.) extracts synergistically enhance the antibacterial activity of berberine via efflux pump inhibition. Etefagh, KH et al. *Planta Med* 2011 May;77(8):835-40

Quorum quenching and antimicrobial activity of goldenseal (*Hydrastis canadensis*) against methicillin-resistant *Staphylococcus aureus* (MRSA). Cech NB, et al. *Planta Med*. 2012 Sep;78(14):1556-61

Berberine containing herbs

- poorly absorbed from GI thus ideal for local infections
- Mucous membrane “tonifying” effect
- Berberine is also
 - ▶ Antiinflammatory
 - ▶ Antioxidant

Ingredient in many “gut antimicrobial formulas” - ensure a daily dose of 2-3grams of berberine if included with other strong antimicrobials. Most herbal formulas only deliver around 500mg

Tincture: standard dose is 30-50ml a week, may have to go much higher than that

Caution:

High berberine can have hypoglycemic effects and also inhibit MOA enzyme



Berberine and hydrogen reduction on LBT

Sample	Sample #	ppm H2	ppm CH4	Combined
Control	1	4	7	11
20 min	2	5	9	14
40 min	3	5	9	14
60 min	4	21	11	32
80 min	5	41	14	55
100 min	6	37	13	50
120 min	7	28	13	41
140 min	8	58	15	73
160 min	9	36	13	49
180 min	10	46	13	59

Sample	Sample #	ppm H2	ppm CH4	Combined
Control	1	0	3	3
20 min	2	3	7	10
40 min	3	1	7	8
60 min	4	1	7	8
80 min	5	1	7	8
100 min	6	1	7	8
120 min	7	5	8	13
140 min	8	20	10	30
160 min	9	16	9	25
180 min	10	19	10	29

Allium sativum (Garlic)

- ▶ Allium sativum is antifungal, antibacterial, antiviral
- ▶ Allicin (diallyl thiosulphinate)- widely studied constituent of Garlic
 - Highly volatile compound (unstable) -
- ▶ Main MOA -inhibition of thiol containing enzymes which maintain intracellular redox state within bacterial cells.
- ▶ Disrupts electrochemical potential of yeast cells - causes apoptosis
- ▶ Do not use “aged garlic” or fresh garlic extracts- not as effective and contain Fructans (high FODMAP)
 - Allisure 360mg BID- TID
 - clinically proven to lower methane



Garlic extract and methane reduction

Sample	Sample #	ppm H2	ppm CH4	Combined
Control	1	0	35	35
20 min	2	1	23	24
40 min	3	1	24	25
60 min	4	0	29	29
80 min	5	0	33	33
100 min	6	10	39	49
120 min	7	29	66	95
140 min	8	26	73	99
160 min	9	49	130	179
180 min	10	27	72	99

Sample	Sample #	ppm H2	ppm CH4	Combined
Control	1	0	4	4
20 min	2	3	5	8
40 min	3	8	9	17
60 min	4	3	8	11
80 min	5	1	5	6
100 min	6	4	8	12
120 min	7	23	8	31
140 min	8	77	8	85
160 min	9	120	12	132
180 min	10	140	10	150

Syzygium aromaticum (Clove)

- ▶ contain 15-20% of clove is essential oil, primarily Eugenol.
- ▶ Anti-proliferative, antiinflammatory
- ▶ Active against a wide variety of gram (-) and (+) bacteria, including K.pneumoniae, E.coli, Proteus mirabilis, Streptococcus, Staphylococcus, Bacillus cereus, and H.pylori
- ▶ Broad spectrum anti-fungal - candida spp, Aspergillus, Dermatophytes (trichophyton etc)
- ▶ Anti-histamine: inhibits mast cell degranulation and reduction of mesenteric Mast cell infiltration



Syzygium aromaticum (Clove)

- ▶ Gastroprotective:
 - stimulates gastric mucous production
 - Antibacterial against H.pylori
- ▶ Motility
 - Helpful in IBS-C
 - Increase gastrointestinal muscle propulsion similar to metoclopramide and carbachol- cholinergic activity
- ▶ Dose
 - 10-15ml per week of a 1:2 extract
 - Caution - excess doses can increase bleeding time, some evidence of CYP3A4 inhibition



Antimicrobial agents from plants: antibacterial activity of plant volatile oils. Doorman HJ. J Appl Microbiol 2000 Feb;88(2):308-16.

Antimicrobial activity of five herbal extracts against multi drug resistant (MDR) strains of bacteria and fungus of clinical origin. Khan et al. Molecules. 2009 Feb 4;14(2):586-97

Antiproliferative and Molecular Mechanism of Eugenol-Induced Apoptosis in Cancer Cells. Jaganathan, SK et al. Molecules. 2012 May 25;17(6):6290-304.

Gastroprotective activity of essential oil of the Syzygium aromaticum and its major component eugenol in different animal models. Sein SK et al. Naunyn-Schmiedeberg's Arch Pharmacol 2011 Feb;383(2):149-58.

Gastrointestinal effects of Syzygium aromaticum (L) Merr. & Perry (Myrtaceae) in animal models. Agbaje EO. Nig Q J Med Hosp 2008 Jul-Sep;18(3):137-41.

Punica granatum (Pomegranate)

- ▶ Juice, rind and seed used
- ▶ Active constituents: ellagic acid glycosides and ellagitannins, other tannins, flavonoids
- ▶ *Gram-positive bacteria* : Staphylococcus aureus, Streptococcus, spp, and Bacillus spp
- ▶ *Gram-negative bacteria*: E.coli, Campylobacter jejuni, Salmonella spp, Shigella spp, Vibrio spp, Klebsiella pneumonia, Pseudomonas aeruginosa, Yersinia enterocolitica, H.pylori
- ▶ *Fungal*: candida spp
- ▶ *Parasitic infections*: Giardia spp, Blastocystis spp, Entamoeba h., Cryptosporidium parvum, and more..



Punica granatum (Pomegranate)

- ▶ “Significantly enhances growth of *Lactobacillus* spp, *Bifidobacterium breve* and *Bifidobacterium infantis* while inhibiting the growth of pathogenic clostridia and *Staphylococcus aureus*”
- ▶ Therapeutic Dose: 40-80ml/week (10ml daily) of a 1:2 tincture

Evaluation of antimicrobial activity of Punica granatum peel against enteric pathogens: an in vitro study. Pai V, et al *Asian Journal of Plant Science and Research* 1(2). 57-62

The Pomegranate: Effects on Bacteria and Viruses That Influence Human Health. Howel A, D'Souza D. *Evid Based Complement Alternat Med.* 2013; 2013: 606212.

The effect of pomegranate (*Punica granatum* L.) byproducts and ellagitannins on the growth of human gut bacteria. *Bialonska D, Kasimsetty SG, Schrader KK, Ferreira DJ Agric Food Chem.* 2009 Sep 23; 57(18):8344-9.



Artemisia annua (Qing Hao)

- ▶ Active constituents: essential oils and sesquiterpenoids (artemisinins)
- ▶ Classically used for parasites, malaria
- ▶ Antimicrobial activity against
 - Gram-positive bacteria* : Staphylococcus aureus, Streptococcus, spp, and Bacillus spp
 - Gram-negative bacteria*: E.coli, Salmonella spp, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus spp
- ▶ Antiparasitic against: Toxoplasma gondii, Schistosoma (blood fluke), Fasciola hepatica (liver fluke), Plasmodium f.



Artemisia annua (Qing Hao)

- ▶ Immunomodulation- inhibits NO, iNO and NF-kB
- ▶ Therapeutic Dose: 20-50ml/week 1:2 extract

Artemisinin Attenuates Lipopolysaccharide-Stimulated Proinflammatory Responses by Inhibiting NF-kB Pathway in Microglia Cells. Cansheng Zhu, et al. *PLoS One.* 2012; 7(4): e35125. Published online 2012 Apr 13. doi:

Essential Oil of *Artemisia annua* L.: An Extraordinary Component with Numerous Antimicrobial Properties. Bilita AR, et al. *Evid Based Complement Alternat Med.* 2014; 2014: 159819.

Antibacterial Activity of Essential Oils and Plant Extracts of Artemisia (*Artemisia annua* L.) In Vitro. Massiha A, et al. *Zahedan Journal of research in Medical Sciences,* 15(6), 14-18



Usnea spp (Old Man's Beard)



- ▶ Over 600 Usnea spp - found on every continent
- ▶ Primary active constituent: usnic acid
- ▶ Primarily active against gram positive bacteria:
 - Bacillus spp, Clostridium spp, Enterococcus spp, Listeria monocytogenes, Staphylococcus spp, Streptococcus spp, etc
- ▶ Some gram negatives: H.pylori, E. coli, Yersinia enterocolitica, Proteus mirabilis
- ▶ Antiparasitic
- ▶ Candida spp

Usnea spp (Old Man's Beard)



- ▶ Anti-inflammatory- in one study as or more effective as NSAID and hydrocortisone
- ▶ Anti-oxidant: activates superoxide dismutase (SOD) and glutathione s-transferase (GST) enzymes, protects against damage in mucosal cells
- ▶ Therapeutic Dose 10-15ml daily 1:2 extract

Buhner, SH (2012) Herbal Antibiotics: Natural Alternatives for treating Drug-Resistant Bacteria, 2nd ed, Massachusetts, USA : Storey Publishing, p.197

Contributions to the complex study of some lichens-Usnea genus. Pharmacological studies on Usnea barbata and Usnea hirta species. Dobrescu D, et al. Rom J Physiol. 1993 Jan-Jun;30(1-2):101-7

Effects of water extract of Usnea longissima on antioxidant enzyme activity and mucosal damage caused by indomethacin in rats. Halici, M, et al. Phytomedicine 2005 Sep;12(9):656-62.

SIFO - small intestinal fungal overgrowth

- ▶ Large intestinal fungal overgrowth also very common
- ▶ Issues with candida spp:
 - Often cause similar symptoms to SIBO
 - Commonly forms biofilm
 - Overgrowth easily evades detection

Dr Rao study

- ▶ SIFO co-morbid with SIBO in 20%
- ▶ SIFO found in 26% of patients with "unexplained GI symptoms"

Small intestinal fungal overgrowth. Erdogan A, Rao SS. Curr Gastroenterol Report. 2015 Apr;17(4):16

Antifungal herbs

- ▶ Many of the herbs discussed also exhibit antifungal properties
- ▶ Classic antifungal herbs include Pau D'Arco, Uva Ursi, Berberine herbs
- ▶ Essential oils of clove, oregano, and thyme are particularly useful
- ▶ Oregano
- ▶ Horopito



Oreganum vulgare (Oregano)



- ▶ Traditionally used for digestive, urinary, and respiratory disorders.
- ▶ Carvacrol main active antimicrobial constituent (mainly antifungal)
- ▶ Active against candida spp, but also *S. aureus*, *Pseudomonas a.*, and *Blastocystis hominis*
- ▶ Clinically shown to be effective for SIFO and methanogens
- ▶ Effective against candida biofilm
- ▶ antioxidant
- ▶ Usually dosed as oil of oregano (50-100mg 2x daily)

Mechanism of Antifungal Activity of Terpenoid Phenols Resembles Calcium Stress and Inhibition of the TOR Pathway. Rao A, et al. Antimicrob. Agents Chemother. December 2010 vol. 54 no. 125062-5069:

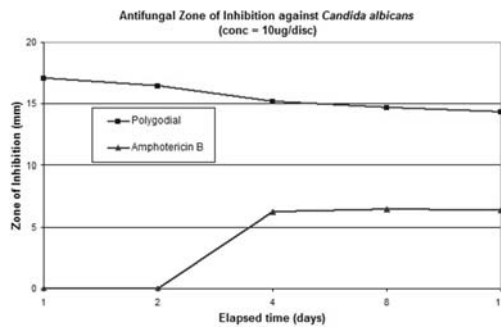
Pseudowintera colorata (Horopito)



- ▶ Native to New Zealand
- ▶ Active constituent: Polygodial
- ▶ strong antifungal activity against the yeast like fungi *C. albicans*, *C. utilis*, *C. krusei*, *Cryptococcus neoformans*, *S. cerevisiae* and also filamentous fungi including *T. mentagrophytes*, *T. rubrum* and *Penicillium marneffe*
- ▶ moderate antibacterial activity against both gram positive bacteria (including *Bacillus subtilis* and *Staphylococcus aureus*) and gram negative bacteria (including *Escherichia coli* and *Salmonella*)
- ▶ MOA: polygodial is a nonionic surfactant that damages the permeability barrier of yeast cells.

Mode of Action of Polygodial, an Antifungal Sesquiterpene Dialdehyde. Taniguchi, M, et al. Agricultural and Biological Chemistry, 52(61), 1409-1414.

Polygodial



McCallion et al 1982. Planta Medica, vol 44, pp134-138

Liquid antimicrobial formula

- ▶ SIBO formula- 7.5ml 2 x daily
 - Oregon grape (or Coptis/Goldenseal)
 - Pomegranate
 - Artemisia
 - Burr Marigold
- ▶ SIBO/SIFO formula - 7.5 ml 2 x daily
 - Pomegranate
 - Usnea
 - Horopito
 - Oregon grape (or Coptis/Goldenseal)

Curcumin- anti inflammatory and antioxidant

- ▶ Curcumin is one of the active constituents of Turmeric
- ▶ Widely studied herb with multiple applications
- ▶ Anti-inflammatory effect very well established, both in research and clinically
 - Inhibits NFkb, COX2, LOX, MMP, TNFa, PGE2
- ▶ stimulates the gallbladder to produce bile.
- ▶ The German Commission E, which determines which herbs can be safely prescribed in Germany, has approved turmeric for digestive problems. And one double-blind, placebo-controlled study found that turmeric reduced symptoms of bloating and gas in people suffering from indigestion.



Curcumin in IBS

- ▶ 2004 study of 207 randomized patients received either 1.8g or 3.6g of dried turmeric daily for 8 weeks
- ▶ "IBS prevalence decreased significantly in both groups between screening and baseline (41% and 57%), with a further significant drop of 53% and 60% between baseline and after treatment, in the one- and two-tablet groups respectively ($p < 0.001$). A post-study analysis revealed abdominal pain/discomfort score reduced significantly by 22% and 25% in the one- and two-tablet group respectively, the difference tending toward significance ($p = 0.071$). There were significant improvements in all but one of the IBSQOL scales of between 5% and 36% in both groups, approximately two thirds of all subjects reported an improvement in symptoms after treatment, and there was a favorable shift in self-reported bowel pattern. There were no significant differences between groups"

Turmeric extract may improve irritable bowel syndrome symptomatology in otherwise healthy adults: a pilot study. J Alt Complement Med. Bundy R, et al. 2004 Dec;10(6):1015-8.

Herbal Prokinetics

- ▶ Dr. J's Herbal Bitters formula:
 - Oregon grape/Gentian/Baical Skullcap/Dandelion root: 2-3 whole droppers in water 15 min before meals
 - Dandelion root: cholagogue
 - Gentian, Oregon Grape: bitters stimulate HCL secretion, possibly motility
 - Baical skullcap: anti-inflammatory, antioxidant
- ▶ Formula IG - Iberis amara, Angelica archangelicacarum carvi, Silybum marianum, Melissa officinalis, chelidonium majus, Mentha piperitae, Glycerrhiza
 - ▶ 20 drops 3 x daily before meals and before bed. Or 60 drops at bed time
- ▶ Formula MP: Ginger, 5HTP, acetyl L carnitine, P5P, dose 3 caps morning and night
- ▶ Clove extract?

GI Antispasmodics and Carminatives

- ▶ Spasmolytics help with regulating motility and abdominal hypersensitivity
- ▶ Chamomile - also anxiolytic
 - a- bisabolol reduce visceral nociception
 - Apigenin - mild anxiolytic via benzodiazepine receptors, anti-inflammatory - inhibits IL-6 and TNF-a
 - Traditionally used for nervous diarrhea - binds to 5HT 4 receptors
 - 2-3 tsp of flowers per cup of tea to be taken TID ic
 - Tincture- 1-2ml TID pc



Carminatives- gas removal from GI tract

- ▶ Caraway seed - very effective carminative and spasmolytic
 - Active constituents: Carvol and d-limonene (carvene)
 - Relaxant effect on smooth muscle response to acetyl choline
 - Used as tea or in tincture
- ▶ Fennel
 - Fenchone and anethol

Carminative Tea - In equal parts:

- Caraway seeds
- Fennel seeds
- Anise seeds
- ▶ 1 teaspoon, crush seeds and steep for 20 minutes in 1 cup of water
- ▶ Drink after each meal

Relaxant effect of ethanol extract of *Carum carvi* on dispersed intestinal smooth muscle cells of the guinea pig. Al-Essa, MK et al. *Pharm Biol* 2010 Jan;48(1):76-80.



Parting Thoughts

- ▶ Use herbs before microbiome-disrupting antibiotics.
- ▶ Only use herbal medicines from reputable manufacturers who test batches frequently
- ▶ Herbs can be combined to make patient specific medicines
- ▶ Prescribe from professional brands only

Thank You

