GI HEALTH

BIOTICS® RESEARCH CANADA

"The Best of Science and Nature"

SUPPLEMENTS TO SUPPORT GASTRO-INTESTINAL HEALTH

Address these stages of GI Health*

REMOVE → REPLACE → REINOCULATE → REPAIR

*These may not be in chronological order, depending on the specific GI issue.

REMOVE

Overgrown yeast and bacteria that may (or may not) normally live in the GI tract are removed using specific gluten free nutritional supplements, including a proven-effective patented formula.

A.D.P.®

Product Number: 1101 (60T) or 1104 (120T)

A.D.P.® is a proven-effective* patented formula. Utilizing micro-emulsification and delayed release technologies, A.D.P.® delivers standardized oil of oregano throughout the digestive tract, where it functions to impact undesirable intestinal organisms.

*Phytother Res 2000 May

Active Ingredients:

Oregano (Origanum vulgare) (standardized extract)

Supplement Facts

Serving Size: 1 Tablet

	Amount Per Serving
Oregano Oil (Origanum vulgare) (extract from leaf)	50 mg*

*** Daily Value not established**

Other ingredients: Cellulose, modified cellulose gum, potassium sorbate, stearic acid (vegetable source), silica, water and gum arabic.

A.D.P.® supplies oregano oil which is emulsified and processed in a sustained release form for optimal effectiveness. This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Patent #5,955,086

This product is gluten, dairy and GMO free.

BiomeBalance

Product Number: 7856 (120C)

BiomeBalance supplies a proprietary blend of herbs and herbal extracts to support normal gut health. Select herbs are recognized in promoting the synergistic healing of damaged intestinal tissue, resulting predominately from dysbiosis*. The combination of Eastern and Western herbs in this formula provides a broad anti-dysbiotic effect, even with low dosing.

*Glob Adv Health Med. 2014 May

Active Ingredients:

Proprietary Blend including Dill (Anethum graveolens) (seed), Stemona (Stemona sessilifolia) (root) (powder and extract), Wormwood (Artemisia absinthium) (shoot & leaf) (extract), Java Brucea (Brucea javanica) (fruit) (powder & extract), Chinese Pulsatilla (Pulsatilla chinensis) (rhizome) (powder & extract), Jamaica Quassia (Picrasma excelsa) (bark) (extract), Cutch Tree (Acacia catechu) (heartwood & bark) (powder & extract), Hedyotis (Hedyotis diffusa) (aerial part) (powder & extract), Yarrow (Achillea millefolium) (leaf & flower) (extract).

Supplement Facts

Serving Size: 2 Capsules
Servings Per Container: 60

	Amount Per Serving
Proprietary Blend	950 mg
Dill (Anethum graveolens) (seed) *	
Stemona (Stemona sessilifolia) (root) (powder and extract) *	
Wormwood (Artemisia absinthium) (shoot & leaf) (extract) *	
Java Brucea (Brucea javanica) (fruit) (powder & extract) *	
Chinese Pulsatilla (Pulsatilla chinensis) (rhizome) (powder & extract) *	
Jamaica Quassia (Picrasma excelsa) (bark) (extract) *	
Cutch Tree (Acacia catechu) (heartwood & bark) (powder & extract) *	
Hedyotis (Hedyotis diffusa) (aerial part) (powder & extract) *	
Yarrow (Achillea millefolium) (leaf & flower) (extract) *	

*** Daily Value not established**

Other ingredients: Capsule shell (gelatin and water) and magnesium stearate (vegetable source).

This product is gluten and dairy free.

Research shows that gut health is critical to overall health and that an unhealthy gut contributes to a wide range of diseases, conditions, an impaired immune and nervous system, and even hormonal imbalance. Supporting gastrointestinal health and restoring the integrity of the gut barrier are essential to optimizing overall health.

FC-Cidal™

Product Number: 6310 (100C)

FC-Cidal supplies a proprietary blend of herbs and herbal extracts, which function to support healthy GI function*. Herbs, spices and botanical preparations often exhibit antimicrobial properties due to a wide array of terpenoid and polyphenolic compounds. Culinary herbs have long been used to control pests and food-borne yeasts and molds in the context of food safety.

*Glob Adv Health Med. 2014 May

Active Ingredients:

Proprietary Blend including French Tarragon (Artemisia dracunculus) (leaf), Indian Tinospora (Tinospora cordifolia) (stem & root), Horsetail (Equisetum arvense) (whole herb), Thyme (Thymus vulgaris) (leaf), Pau D' Arco (Tabebuia impetiginosa) (inner bark), Stinging Nettle Extract (Urtica dioica) (root), Olive (Olea europaea) (leaf).

Supplement Facts

Serving Size: 1 Capsule

	Amount Per Serving
Proprietary Blend	500 mg
French Tarragon (Artemisia dracunculus) (leaf) *	
Indian Tinospora (Tinospora cordifolia) (stem & root) *	
Horsetail (Equisetum arvense) (whole herb) *	
Thyme (Thymus vulgaris) (leaf) *	
Pau D' Arco (Tabebuia impetiginosa) (inner bark) *	
Stinging Nettle Extract (Urtica dioica) (root) *	
Olive (Olea europaea) (leaf) *	

*** Daily Value not established**

Other ingredients: Capsule shell (gelatin and water), cellulose and magnesium stearate (vegetable source).

This product is gluten and dairy free.

Adjunct Products: Bio-HPF®, Berberine HCl, Caprin™, and Iodizyme-HP™

REPLACE

Bile salts, digestive enzymes, and hydrochloric acid levels are replaced using specific gluten free nutritional supplements in order to maintain and promote healthy digestion.

Beta-TCP™

Product Number: 1215 (90T) or 1216 (180T)

Beta-TCP™ supports both healthy bile flow, and the normal bile acid-to-cholesterol conversion. It contains both digestive and antioxidant enzymes, along with Taurine and organic beet concentrate.

Active Ingredients:

Vitamin C (ascorbic acid), Taurine, Pancrelipase (porcine), Organic Beet Concentrate** (Beta vulgaris) (whole), Superoxide Dismutase (raw organic vegetable culture†) and Catalase (raw organic vegetable culture†). †Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors. ** Whole beet concentrate from certified organically grown beets.

Supplement Facts

Serving Size: 1 Tablet

	Amount Per Serving	% Daily Value
Vitamin C (ascorbic acid)	60 mg	100%
Taurine	100 mg	*
Pancrelipase (porcine)	50 mg	*
Organic Beet Concentrate** (Beta vulgaris) (whole)	100 mg	*
Superoxide Dismutase (from vegetable culture †)	20 mcg	*
Catalase (from vegetable culture †)	20 mcg	*

*** Daily Value not established**

Other ingredients: Cellulose, stearic acid (vegetable source), magnesium stearate (vegetable source) and food glaze.

† Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

** Whole beet concentrate from certified organically grown beets.

This product is gluten and dairy free.

REPLACE (continued)

Beta Plus™

Product Number: 1210 (90T) or 1209 (180T)

Beta Plus™ is a source of bile salts, digestive enzymes and organic beet concentrate, along with SOD and catalase. Consider this product whenever the gallbladder has been removed, or the need for supplemental bile salts is indicated.

Active Ingredients:
Ox Bile Extract, Pancrelipase (porcine), Organic beet concentrate** (Beta vulgaris) (whole), Superoxide dismutase (raw organic vegetable culture†), Catalase (raw organic vegetable culture†). †Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors. ** Whole beet concentrate from certified organically grown beets.

Supplement Facts
Serving Size: 1 Tablet

	Amount Per Serving	% Daily Value
Ox Bile Extract	100 mg	*
Pancrelipase (porcine)	50 mg	*
Organic Beet Concentrate** (Beta vulgaris) (whole)	100 mg	*
Superoxide Dismutase (from vegetable culture †)	20 mcg	*
Catalase (from vegetable culture †)	20 mcg	*

*** Daily Value not established**

Other ingredients: Cellulose, stearic acid (vegetable source), magnesium stearate (vegetable source) and food glaze.

† Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

** Whole beet concentrate from certified organically grown beets.

This product is gluten and dairy free.

RECOMMENDATION: One (1) tablet with each meal as a dietary supplement

Hydro-Zyme™

Product Number: 1262 (90T) or 1263 (250T)

Hydro-Zyme™ provides digestive support via supplemental Betaine hydrochloride, Pepsin, Pancreatin, along with other known synergists. It may be considered when the need for supplemental hydrochloric acid and/or Pancreatin are indicated.

Active Ingredients:
Vitamin B6 (as pyridoxine hydrochloride), Betaine Hydrochloride, Glutamic acid (as L-Glutamic acid hydrochloride), Ammonium Chloride, Pancreatin 4X (porcine), Pepsin (1:10,000).

Supplement Facts
Serving Size: 1 Tablet

	Amount Per Serving	% Daily Value
Vitamin B6 (as pyridoxine hydrochloride)	2 mg	100%
Betaine Hydrochloride	150 mg	*
Glutamic acid (as L-Glutamic acid hydrochloride)	50 mg	*
Ammonium Chloride	35 mg	*
Pancreatin 4X (porcine)	10 mg	*
Pepsin (1:10,000)	10 mg	*

*** Daily Value not established**

Other ingredients: Vegetable culture †, cellulose, stearic acid (vegetable source), modified cellulose gum, silica and food glaze.

† Specially grown, biologically active vegetable culture (from organic Pisum sativum, Lens esculenta and/or Cicer arietinum) containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

This product is gluten and dairy free.

Intenzyme Forte™

Product Number: 1207 (50T), 1201 (100T) or 1202 (500T)

Intenzyme Forte™ is a broad spectrum proteolytic enzyme formulation, containing pancreatin, bromelain, papain, lipase, amylase, trypsin and alpha chymotrypsin. It may be utilized to support numerous protein metabolism pathways. Proteolytic enzymes are capable of exerting influence over a wide variety of physiological and biochemical processes. The benefits of Intenzyme Forte include its effect on muscle soreness and discomfort due to overexertion, the support of hormone processing, as well as providing support for healthy digestive, immune and circulatory functions.

Active Ingredients:
Pancreatin 4X (porcine), Bromelain (from pineapple), Papain (from papaya), Lipase (porcine), Amylase (porcine), Trypsin & Alpha Chymotrypsin (porcine), Superoxide Dismutase (from vegetable culture†), Catalase (from vegetable culture†) †Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

Supplement Facts
Serving Size: 1 Tablet

	Amount Per Serving	% Daily Value
Pancreatin 4X (porcine)	100 mg	*
Bromelain (from pineapple)	50 mg	*
Papain (from papaya)	50 mg	*
Lipase (porcine)	10 mg	*
Amylase (porcine)	10 mg	*
Trypsin & Alpha Chymotrypsin (porcine)	100 mg	*
Superoxide Dismutase (from vegetable culture †)	10 mcg	*
Catalase (from vegetable culture †)	10 mcg	*

*** Daily Value not established**

Other ingredients: Stearic acid (vegetable source), cellulose, magnesium stearate (vegetable source) and food glaze.

† Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

This product is gluten and dairy free.

RECOMMENDATION: One (1) tablet three (3) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

REINOCULATE

The restoration of optimal gut flora is done using a specific gluten free probiotic

BioDoph-7 Plus®

Product Number: 1285 (60C)

Probiotics are classically defined as "a preparation of, or a product containing viable, defined microorganisms in sufficient numbers, which alter the microbiota (typically by colonization) in a compartment of the host, and by that, exert beneficial health effects in this host".

BioDoph-7 Plus® supplies a blend of pro- and prebiotics, including Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium breve, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus salvarius, and Streptococcus thermophilus, along with the prebiotics Inulin (from chicory root), Arabinogalactans (from Larch), and Marshmallow root (extract).

GLUTEN FREE GUARANTEE

Supplement Facts

Serving Size: 1 Capsule

	Amount Per Serving
Proprietary Blend	400 mg
Inulin (from Chicory root)*, Arabinogalactans (from Larch)*, Marshmallow (Althea officinalis) (extract) (root)*, Bifidobacterium bifidum*, Bifidobacterium lactis*, Bifidobacterium breve*, Lactobacillus paracasei*, Lactobacillus plantarum*, Lactobacillus salivarius*, Streptococcus thermophilus*	

*** Daily Value not established**

Other ingredients: Vegetarian capsule shell (modified cellulose) and magnesium stearate (vegetable source).

Each capsule of **BioDoph-7 Plus®** contains more than 20 billion organisms at time of manufacture.

Contains an ultra-trace amount (0.3 ppm) of milk constituents which are used in the fermentation of probiotic ingredients.

This product is gluten free.

Active Ingredients:

Proprietary Blend including Inulin (from Chicory root), Arabinogalactans (from Larch), Marshmallow (Althea officinalis) (extract) (root), Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium breve, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus salivarius, Streptococcus thermophilus. Each capsule of BioDoph-7 Plus® contains more than 20 billion organisms at time of manufacture.

BioDophilus-FOS®

Product Number: 1205 (4oz)

BioDophilus-FOS™ is a pleasant tasting powder that supplies the probiotics Lactobacillus acidophilus (DDS-1 strain), and Bifidobacterium bifidum in a prebiotic base of fructooligosaccharides. Each 1/2 teaspoon supplies 3 billion organisms, along with 1,200 mg of beet-sourced Fructooligosaccharides.

Active Ingredients:

Lactobacillus acidophilus (DDS-1) and Bifidobacterium bifidum organisms, and Fructooligosaccharides (beet source).
Refrigeration is recommended to preserve the organisms.

GLUTEN FREE GUARANTEE

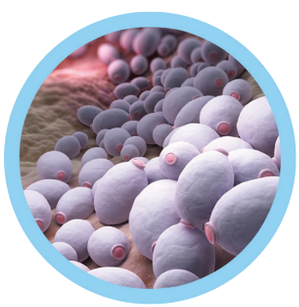
Supplement Facts

Serving Size: ½ Teaspoon (approx. 1.5 g)
Servings Per Container: 75

	Amount Per Serving	% Daily Value
Calories	5	
Total Carbohydrate	1 g	0% †
Sugars	0 g	*
Lactobacillus acidophilus (DDS-1) and Bifidobacterium bifidum organisms	3 billion	*
Fructooligosaccharides (beet source)	1,200 mg	*

†Percent Daily Values based on a 2,000 calorie diet.
*** Daily Value not established**

Ingredients: Fructooligosaccharides (beet source), Lactobacillus acidophilus (DDS-1) and Bifidobacterium bifidum.



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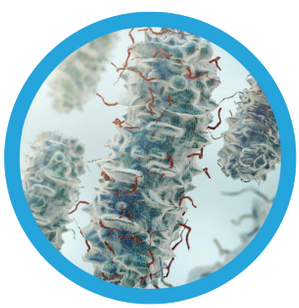
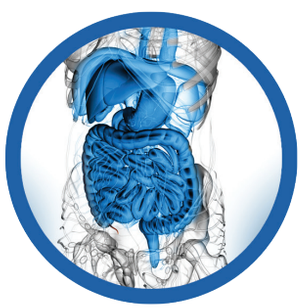


REPLACE

REINOCULATE



REPAIR

REPAIR

Specific gluten free nutritional supplements, including vitamins, minerals, amino acids, and EFAs, are essential to gut repair and healing the damaged intestinal lining.

BioMega-1000

Product Number: 1400 (100C)

BioMega-1000 supplies the highest quality, all-natural (not modified by distillation processes) fish oil, supplying EPA and DHA omega-3 fatty acids. BioMega-1000 fish oil surpasses all national and international standards for environmental pollutants, including dioxins, PCBs, pesticides and heavy metals. The most active and beneficial derivatives of marine derived ω-3 fatty acids are eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA), natural precursors that allow the body to make Specialized Pro-Resolving Mediators (SPMs), supporting healthy inflammatory responses. Both the brain and nervous system are higher in DHA, as compared to the rest of the body. As an omega-3 fatty acid, it has the ability to impact most physiological functions.

Supplement Facts

Serving Size: 1 Softgel Capsule

	Amount Per Serving	% Daily Value
Calories	15	
Calories from Fat	15	
Total Fat	1.5 g	2%*
Saturated Fat	<1 g	<3%*
Vitamin E (as mixed tocopherols)	4 mg	27%
Omega-3 fatty acids	1.14 g	†

*** Percent Daily Values based on a 2,000 calorie diet**
† Daily Value not established

Other Ingredients: Capsule shell (gelatin, glycerin and water).
Contains ingredients derived from Anchovy and Sardine.
This product is gluten and dairy free.

Active Ingredients: Vitamin E (as d-alpha tocopherol), Omega-3 fatty acids. Each softgel capsule of BioMega-1000 contains 1,000 mg of natural marine lipid
concentrate, providing a natural source of Omega-3 fatty acids; EPA (Eicosapentaenoic acid) 180 mg and DHA (Docosehexaenoic acid) 120 mg.

Gastrazyme™

Product Number: 1140 (90T)

Gastrazyme™ supplies specific nutrients including vitamin U complex, chlorophyllins and vitamin A, ingredients all known to support the health of GI tract, which may become stressed due to normal, everyday factors. Early studies have recognized the effectiveness of raw cabbage juice in normalizing gastric and intestinal function. Glutamine and methionine derivatives present in this juice are believed to be the active principles. Specific attention has focused on methionine S-methylsulfonium (MMS) in the chlorinated form. MMS occurs in a variety of fruits and vegetables, such as cabbage. Studies have demonstrated that MMS supports the normal healing process of the stomach following exposure to nonsteroidal anti-inflammatory agents (NSAIDs). Traditionally, this compound has been designated "Vitamin U", although it does not meet the classic definition of a vitamin.

Supplement Facts

Serving Size: 1 Tablet

	Amount Per Serving	% Daily Value
Vitamin A (as natural mixed carotenoids and palmitate) (IU ratio 2.5:1)	3,500 IU	70%
Gamma Oryzanol (from rice)	100 mg	*
Chlorophyllins (from Mulberry leaf)	20 mg	*
Vitamin U Complex (DL-methylmethionine sulfonium chloride)	10 mg	*
Superoxide Dismutase (from vegetable culture †)	15 mcg	*
Catalase (from vegetable culture †)	15 mcg	*

*** Daily Value not established**

Other ingredients: Cellulose, modified cellulose gum, modified cellulose, silica and magnesium stearate (vegetable source).

† Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

This product is gluten and dairy free.

RECOMMENDATION: One (1) tablet three (3) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

Active Ingredients:

Vitamin A (as natural mixed carotenoids and palmitate), Gamma Oryzanol (from rice), Chlorophyllins (from Mulberry leaf), Vitamin U Complex (as DL-Methionine methylsulfonium chloride), Superoxide Dismutase (from vegetable culture†), Catalase (from vegetable culture†). †Specially grown, biologically active vegetable culture containing naturally associated phytochemicals including polyphenolic compounds with SOD and catalase, dehydrated at low temperature to preserve associated enzyme factors.

IPS®

Product Number: 6415 (90C)

IPS® is a comprehensive Intestinal Permeability Support supplement, consisting of a proprietary blend of botanical compounds and amino acids, along with other synergistic constituents. It provides support for healthy gut function, specifically as it relates to permeability and intestinal mucosa integrity. It includes L-Glutamine, which is the preferred fuel for intestinal tissues, promoting repair and intestinal healing. L-Glutamine has also been demonstrated to be a functional component in the repair of ulcers, as well as a contributor to the healing of leaky gut conditions. When the intestinal epithelium becomes injured or compromised, chronic health disturbances may result. **IPS®** is a unique formula designed to address the specific issue of altered intestinal permeability. It supplies a comprehensive array of nutritional factors to support healthy intestinal function.

Supplement Facts

Serving Size: 1 Capsule

	Amount Per Serving
Proprietary Blend	600 mg
Jerusalem Artichoke (Helianthus tuberosus) (tuber)	*
L-Glutamine	*
Spanish Moss (Tillandsia usneoides) (whole)	*
Lamb Intestine Concentrate	*
Glucosamine Sulfate (from shrimp & crab shell)	*
Gamma Oryzanol (from rice)	*
L-Glutathione (reduced)	*
Cellulase	*

*** Daily Value not established**

Other ingredients: Capsule shell (gelatin and water) and magnesium stearate (vegetable source).

Substance with hair-like appearance is acturally Spanish moss fibers.

This product is gluten and dairy free.

RECOMMENDATION: One (1) capsule three (3) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

KEEP OUT OF REACH OF CHILDREN

Store in a cool, dry area.

Sealed with an imprinted safety seal for your protection.

Product # 6415 Rev. 05/13

Active Ingredients:

Proprietary Blend including Jerusalem Artichoke (Helianthus tuberosus) (tuber), L-Glutamine, Spanish Moss (Tillandsia usneoides) (whole), Lamb Intestine Concentrate, Glucosamine Sulfate (from shrimp & crab shell), Gamma Oryzanol (from rice), L-Glutathione (reduced), and Cellulase. Note: Substance with hair-like appearance is actually Spanish moss fibers.

L-Glutamine Powder™

Product Number: 5209 (500 g)

L-Glutamine is the most abundant amino acid in the body. Although the body manufactures glutamine during times of extreme stress (such as after very heavy exercise or an injury), in certain circumstances the body may need more glutamine than it can make. Most glutamine is stored in the muscles, followed by the lungs, where much of the glutamine is made. According to the University of Maryland Medical Center (https://umm.edu.com), glutamine functions as an important compound in removing excess ammonia (a common waste product in the body). It also assists in immune system functions, and appears to be needed for normal brain function and digestion. Glutamine helps to protect the gastrointestinal mucosa, and is a major fuel for enterocytes. It also supports tissues in the body that rapidly turn over, such as intestinal cells (intestinal epithelium). High levels of cortisol during times of stress can lower the body's stores of glutamine.

L-Glutamine Powder™ supplies 3g of L-Glutamine per teaspoon, as a nonhydrolyzed, free-form L-Amino Acid.

Supplement Facts

Serving Size: 1 teaspoon (approx. 3 g)
Servings Per Container: 166

	Amount Per Serving	% Daily Value
Glutamine (as L-Glutamine)†	3 g	*

*** Daily Value not established**

Ingredients: L-Glutamine.

† Non-hydrolyzed, naturally produced, free-form L-Amino Acid

CERTIFIED PURE

Contains no additives of any kind

This product is gluten and dairy free.

RECOMMENDATION: One (1) teaspoon (approx. 3 g) each day as a dietary supplement or as otherwise directed by a healthcare professional.

Active Ingredients:

Glutamine (as L-Glutamine). L-Glutamine is a non-hydrolyzed, naturally produced, free-form L-Amino Acid. CERTIFIED PURE. Contains no additives of any kind.

Adjunct Products: Aqueous Zinc™, Bio-Ae-Mulsion®, Bio-D-Mulsion®, Immuno-gG®, NAC, and Whey Protein Isolate

BIOTICS® RESEARCH CANADA

"The Best of Science and Nature"

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ORIGINAL RESEARCH

Herbal Therapy Is Equivalent to Rifaximin for the Treatment of Small Intestinal Bacterial Overgrowth

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Disclosures
The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none was reported.

ABSTRACT

Objective: Patients with small intestine bacterial overgrowth (SIBO) have chronic intestinal and extraintestinal symptomatology which adversely affects their quality of life. Present treatment of SIBO is limited to oral antibiotics with variable success. A growing number of patients are interested in using complementary and alternative therapies for their gastrointestinal health. The objective was to determine the remission rate of SIBO using either the antibiotic rifaximin or herbals in a tertiary care referral gastroenterology practice.

Design: One hundred and four patients who tested positive for newly diagnosed SIBO by lactulose breath testing (LBT) were offered either rifaximin 1200 mg daily vs herbal therapy for 4 weeks with repeat LBT post-treatment.

Results: Three hundred ninety-six patients underwent LBT for suspected SIBO, of which 251 (63.4%) were positive 165 underwent treatment and 104 had a follow-up LBT. Of the 37 patients who received herbal therapy, 17 (46%) had a negative follow-up LBT compared to 23/67 (34%) of rifaximin users (P=.24). The odds ratio of having a negative LBT after taking herbal therapy as compared to rifaximin was 1.85 (CI=0.77-4.41, P=.17) once adjusted for age, gender, SIBO risk factors and IBS status. Fourteen of the 44 (31.8%) rifaximin non-responders were offered herbal rescue therapy, with 8 of the 14 (57.1%) having a negative LBT after completing the rescue herbal therapy ,while 10 non-responders were offered triple antibiotics with 6 responding (60%, P=.89). Adverse effects were reported among the rifaximin treated arm including 1 case of anaphylaxis, 2 cases of hives, 2 cases of diarrhea and 1 case of *Clostridium difficile*. Only one case of diarrhea was reported in the herbal therapy arm, which did not reach statistical significance (P=.22).

Conclusion: SIBO is widely prevalent in a tertiary referral gastroenterology practice. Herbal therapies are at least as effective as rifaximin for resolution of SIBO by LBT. Herbals also appear to be as effective as triple antibiotic therapy for SIBO rescue therapy for rifaximin non-responders. Further, prospective studies are needed to validate these findings and explore additional alternative therapies in patients with refractory SIBO.

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is defined as an increase in the concentration of bacteria of more than 100000 colony-forming units per mL of proximal jejunal fluid.[1] Although the overall prevalence of SIBO in the general public is unknown, a meta-analysis has shown that the prevalence of SIBO is approximately 56% among patients with irritable bowel syndrome (IBS).[2] At present, the prevalence of SIBO in the community or in a tertiary-care gastroenterology referral practice remains unknown. SIBO is becoming an increasingly significant problem in clinical practice as its manifestations can be protean and range from a full-blown enteropathy causing profound malabsorption and malnutrition simulating celiac disease to mild symptoms that overlap with IBS.[1] There are several factors involved in the pathogenesis of SIBO that have in common a disruption in the natural protective antibacterial mechanisms of the gut as shown in Tables 1-3.[3] These factors, alone or in combination, can predispose the gut toward dysbiosis and favor the growth and colonization of aerobes and anaerobes in the proximal jejunum and may provide barrier(s) from achieving durable remission of symptoms following treatment.[10]

What is the current knowledge?

Small intestinal bacterial overgrowth (SIBO) is widely prevalent among patients with the irritable bowel syndrome (IBS) and is associated with a worsening of symptoms and quality of life.

Current treatment of SIBO is presently limited to antibiotics with a variable response rate and none have been approved by the US Federal Drug Administration (FDA).

SIBO is often treated with a course of rifaximin 1200 mg/day for 10-14 days, which is expensive and not routinely covered by many commercial health plans in the United States.

The majority of IBS patients use complementary and alternative therapies to control symptoms and are often looking for more "natural" options to treat their disease.

What is new here?

The high prevalence rate for SIBO of 64% in a tertiary care referral gastroenterology practice.

The response rate for normalizing breath hydrogen testing in patients with SIBO was 46% for herbal therapies vs 34% for Rifaximin.

Herbal therapy may be an effective treatment for patients with SIBO.

Patients with SIBO refractory to rifaximin can be given the choice of herbal therapy as rescue therapy.

Currently, lactulose breath testing (LBT) is the most commonly used procedure for diagnosing SIBO.[11,12] LBT is useful as an indirect testing method for SIBO, given that the human gastrointestinal (GI) tract does not absorb or use lactulose, which is metabolized by bacteria to produce hydrogen and methane gas. These gases are then measured by gas chromatography.[13] Once suspected SIBO is diagnosed, it should be treated to prevent its myriad of adverse consequences.[14-17]

The current state-of-the-art treatment of SIBO is the provision of a short course (10-14 days) of antibiotics (Table 4). Thus far, rifaximin, a rifampin derivative, is the antibiotic that has been most widely recognized and published for its use in the treatment of SIBO.[19] Additionally, SIBO has been implicated as a major contributing pathophysiological factor in IBS. Over the past decade, patients with IBS are increasingly turning to complementary and alternative medicine (CAM) options for symptoms relief and disease management.[20] Herbal remedies and nutraceutical supplements continue to dominate as the most common forms of CAM used for IBS patients.[21] A number of herbs have a long tradition of antimicrobial activity,[22] thus we hypothesized that the use of plant extracts possessing antimicrobial activity would be as effective as antibiotic therapy for patients with an abnormal LBT and the diagnosis of SIBO.

Table 1 Conditions That Predispose Toward the Development of Small Intestine Bacterial Overgrowth[4-7]

Achlorhydria (surgical, iatrogenic, autoimmune)
Motor abnormalities
Scleroderma
Intestinal pseudo-obstruction
Diabetic enteropathy
Vagotomy
Abnormal communication between colon and small bowel
Fistulas between colon and small bowel
Resection of ileocecal valve
Structural abnormalities
Systemic and intestinal immune deficiency states
Surgical loops (Billroth II, entero-entero anastomosis, Rou-en-Y)
Duodenal or jejunal diverticula
Partial obstruction of small bowel (stricture, adhesions, tumors)
Large small Intestine diverticulosis
Systemic diseases (celiac disease, cirrhosis, pancreatic exocrine insufficiency, non-alcoholic fatty liver disease)
Alcoholism

Table 2 Protective Factors That Protect Against the Development of Small Intestine Bacterial Overgrowth[4,8,9]

• Gastric acid
• Pancreatic enzymes
• Bile acids
• Cholecystectomy
• Motility
• Migrating motor complex
• Biofilm
• Secretory immunoglobulin A

Table 3 Extrinsic Factors That Alter the Gut Microbiome and May Influence the Development of Small Intestine Bacterial Overgrowth[4]

FODMAPs[a] (fructose, lactose, galactans, fructans, sugar alcohols)
Proton pump inhibitors
Anti-motility agents
Fiber
Prebiotics
Probiotics
Antibiotics

[a] FODMAPs is an acronym for a group of highly fermentable foods (Fermentable Oligo-, Di-, Monosaccharides and Polyols).

METHODS

Study Participants

The medical records at a single tertiary-care referral center from October 2006 to November 2010 were reviewed as part of an institutional IRB-approved protocol. Study participants were included in the analysis if they had: (1) symptoms suggestive of SIBO, (2) an initial positive LBT, (3) completed a prescribed regimen of either rifaximin or herbal therapy, and (4) received a post-treatment LBT. Symptoms considered to be suggestive of SIBO included otherwise unexplained abdominal discomfort, cramping, bloating, flatulence, eructation, diarrhea, worsening of symptoms after meal ingestion, and low serum B_{12}. Criteria considered to be risk factors for SIBO included prior history of gastric bypass surgery, known gastrointestinal motility disorder, collagen vascular disease, IBS (association), pancreatic insufficiency, and chronic proton-pump inhibitor (PPI) use. Exclusion criteria included those patients aged <18 or >85 years, use of antibiotics within 3 months, and failure to comply with regimen or to have a follow-up LBT. A subset of patients who (1) completed the rifaximin regimen, (2) had persistently positive post-treatment LBT, (3) subsequently completed a prescribed herbal or triple antibiotic regimen, and (4) had a post-herbal therapy LBT were defined as "rifaximin non-responders."

Lactulose Breath Testing Protocol

Study participants followed a standard preparation protocol prior to the procedure.[23] No laxatives were to be taken for at least a week prior to the test. One day prior, test subjects were advised to avoid high-fiber foods, butter, margarine, and sodas and asked to fast for 12 hours before the test, consuming no food except water. Subjects were advised not to smoke, sleep, or exercise vigorously up to 30 minutes before or at any time during the test.

Table 4 Antibiotic Regimens Used for Small Intestine Bacterial Overgrowth[18]

Agent	Dose	Frequency
Amoxicillin-clavulanate	500 mg PO	3 times/day
Cephalexin	250 mg PO	4 times/day
Chloramphenicol	250 mg PO	4 times/day
Ciprofloxacin	500 mg PO	twice daily
Doxycycline	100 mg PO	twice daily
Metronidazole	250 mg PO	3 times/day
Neomycin	500 mg PO	twice daily
Norfloxacin	400 mg PO	twice daily
Rifaximin	400 mg PO	3 times/day
Tetracycline	250 mg PO	4 times/day
Trimethoprim-sulfamethoxazole	1 double-strength tablet PO	twice daily

Abbreviation: PO, per os (by mouth).

A QuinTron Gas Microanalyzer (QuinTron Instrument Company, Inc, Milwaukee, Wisconsin) was used to detect breath hydrogen in samples. Baseline breath hydrogen was obtained on all subjects prior to the ingestion of 10 gm of lactulose in 30 cc of water. Serial breath hydrogen analysis was obtained every 20 minutes after ingestion of lactulose up to a maximum of 3 hours. The test was considered positive if it showed one or more of the following[24]: (1) a baseline breath concentration of >10 parts per million (ppm) for hydrogen or >7 ppm for methane only if patients were compliant with their preparation or (2) an increase within 90 minutes (small intestine) that was followed by a larger peak (colonic), indicative of a positive study (with a decrease of at least 5 ppm following the first peak). The first increase had to have one of the following to be considered positive: (1) an increase of at least 12 ppm methane over the baseline by 90 minutes or (2) if producing hydrogen only, an increase of at least 20 ppm hydrogen over the baseline by 90 minutes. All breath tests were evaluated by a single experienced reader who was blinded to the treatment regimen (GM).

Treatment

Subjects with newly diagnosed SIBO by LBT were given two open-label treatment choices based upon individualized treatment preference; either two 200 mg rifaximin tablets three times daily (TID) or 2 capsules twice daily of the following commercial herbal preparations; Dysbiocide and FC Cidal (Biotics Research Laboratories, Rosenberg, Texas) or Candibactin-AR and Candibactin-BR (Metagenics, Inc, Aliso Viejo, California) for 4 consecutive weeks immediately followed by a repeat LBT. Table 5 illustrates the details regarding the composition for each herbal preparation. The cost of herbal therapy was no more than $120 for a 30-day supply. The primary outcome was the proportion of patients in each group who had a negative post-treatment LBT. Rifaximin non-responders were then prescribed either the herbal protocol or triple antibiotics (clindamycin 300 mg TID, metronidazole 250 mg TID, neomycin 500 mg TID) for 4 additional weeks. The statistical methods applied to analyze the results were the student *t*-test and chi-squared test. The study was approved by the Johns Hopkins University (Baltimore, Maryland) Internal Review Board.

RESULTS

A flow chart of the study design and results are shown in the Figure. Three hundred ninety-seven

Table 5 Herbal Preparations for the Treatment of Small Intestine Bacterial Overgrowth

FC Cidal	Dysbiocide	Candibactin-AR	Candibactin-BR
Proprietary blend - 500 mg: 1 capsule	Proprietary Blend 950 mg per 2 capsules	One Capsule contains:	Two Capsules contain:
Tinospora cordifolia (stem)	Dill seed	Red Thyme oil (thymus vulgaris, providing 30%-50% thymol) 0.2 mL	Coptis root and rhizome extract (coptis chinensis, containing berberine) 30 mg
Equisetum arvense (stem)	Stemona Sessilifolia powder and extract	Oregano Oil (origanum vulgare, providing 55% to 75% carvacrol) 0.1 mL	Indian Barberry root extract (berberis aristata, containing berberine) 70 mg
Pau D'Arco (inner bark)	Artemisia Absinthium shoots and leaves extract,	Sage leaf 5.5:1 extract (salvia officinalis) 75 mg	Berberine Sulfate 400 mg • Proprietary 4:1 Extract 300 mg: Coptis root and rhizome (coptis chinensis)
Thymus vulgaris (aerial part)	Pulsatilla Chinensis rhizome powder and extract	Lemon Balm leaf 5:1 extract (melissa officinalis) 50 mg	Chinese Skullcap root (scutellaria baicalensis)
Artemisia dracunculus (leaf)	Brucea Javanica powder and extract		Philodendron bark (phellodendron chinense)
Sida cordifolia (aerial part)	Picrasma Excelsa bark extract		Ginger rhizome (zingiber officinale)
Olea europaea (leaf)	Acacia Catechu stem extract		Chinese Licorice root (glycyrrhiza uralensis)
	Hedyotis Diffusa powder and extract		Chinese Rhubarb root and rhizome (rheum officinale)
	Yarrow leaf and flower extract (achillea millefolium).		Chinese Rhubarb root and rhizome (rheum officinale).

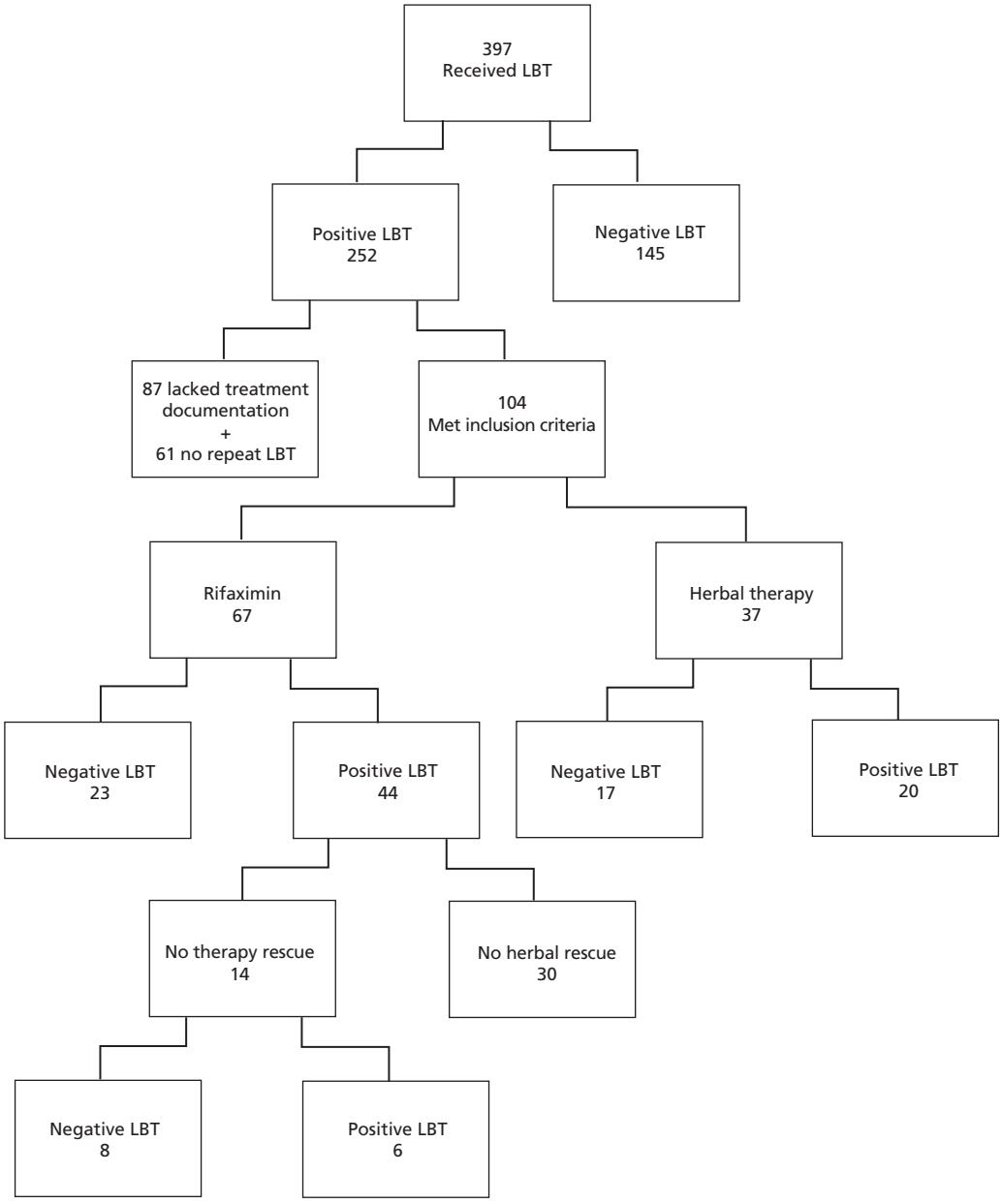

Figure Flow chart of the study design: 397 patients were recruited to participate in the study and underwent lactulose breath hydrogen testing (LBT), 252 were found to be LBT positive while 145 were negative. Due to lack of protocol adherence, only 104 of those who were had positive LBT met our inclusion criteria for the study, with 67 opting for Rifaximin therapy and 37 preferring herbals. Forty-four of the 67 (65.7%) subjects treated with Rifaximin failed to respond and had positive LBT after therapy with only 34.3% responding. Herbal therapies were associated with a (17/37) 45.9% response rate with (20/37) 54.1% having post-treatment positive LBT. For those who failed the first round of Rifaximin therapy, a crossover trial showed a 8/14 (57.1%) response rate for herbals in those who failed Rifaximin.

patients were offered LBT for suspected SIBO, of which 252 (63.5%) were positive; 87 of these patients did not pursue treatment, and 61 of those who underwent therapy did not undergo repeat LBT. The remaining 104 patients were provided the option of two treatment arms as per the patients' choice and underwent post-treatment LBT. Rifaximin was completed by 67 patients, and 37 completed herbal therapy. Results were tabulated only for those who completed therapy. There was no difference in the mean age of patients who chose rifaximin (47.55 ± 15.73) and those on herbal therapy (41.6 ffl 16.3) (P=.30). There was a gender skewing of participants as 48/67 (71%) of the rifaximin arm and 29/37 (78%) of the herbal arm were females (Table 6). Of the 67 patients who completed the rifaximin arm, 9 (13%) had risk factors for SIBO (diabetes mellitus, gastroparesis, narcotics, connective tissue disease, etc) while 7 (19%) in the herbal arm had risk factors (P=.46). Of the 252 individuals who tested positive for SIBO by LBT, 160 (63.5%) had IBS as diagnosed by the Rome III criteria. Of the 37 patients who received herbs, 17 (46%) had a negative follow-up LBT

Table 6 Demographic Information of Rifaximin vs Herbal Users

	Rifaximin (n=67)	Herbal (n=37)	*P* value
Age (yrs)	47.55 ± 15.73	41.6 ± 16.3	.07
Percent female	48 (71%)	29 (78%)	.45
Risk Factors for SIBO	9 (13%)	7 (19%)	.46
Diabetes mellitus	4 (6%)	0 (0%)	.12
Gastroparesis	2 (3%)	1 (3%)	.93
Narcotic	1 (1%)	3 (8%)	.09
CTD	2 (3%)	4 (11%)	.1
Any risk factor	9 (13%)	7 (19%)	.46
IBS	53 (79%)	25 (68%)	.19
Distribution of IBS by Subtypes			**.08**
None	14 (21%)	12 (32%)	
Diarrhea predominant	22 (32%)	6 (16%)	
Constipation predominant	16 (24%)	12 (32%)	
Mixed	14 (21%)	4 (11%)	
Unclassified IBS	1 (1%)	3 (8%)	
Negative LBT after Rx	23 (34%)	17 (46%)	.24

Table 7 Results of IBS Subjects Undergoing Intervention for Positive Lactulose Breath Hydrogen Testing for Small Intestine Bacterial Overgrowth (n=104)

Characteristics	Rifaximin	Herbs	*P* value
Number	67	37	N/A
Age (y), SD, range	44.4 ± 14.8 (19-81)	41.3 ± 14.8 (19-76)	.33
Gender **Female, n (%)** **Male, n (%)**	 48 (71) 19 (29)	 29 (78) 8 (22)	 .97
Responses (n)	26	15	N/A
Response Rate (%)	34	46	.24
Adverse Events (n, %)	2, 2.9	1, 2.7	.83

compared to 23/67 (34%) of rifaximin users (*P*=.24) (Table 7). The odds ratio of having a negative LBT if on herbal therapy as compared to rifaximin was 1.85 (CI=0.77-4.41, *P*=.17) once adjusted for age, gender, SIBO risk factors, and IBS status (Table 8). Fourteen of the 41 (34.1%) rifaximin non-responders were offered herbal rescue therapy; 8 of the 14 (57.1%) had a negative LBT after completing the rescue herbal therapy. Ten of the 41 (24.4%) rifaximin non-responders were offered rescue therapy with triple antibiotics, and 6 of the 10 (60%) had a negative LBT after completing the rescue herbal therapy. Rescue therapy with herbals in rifaximin non-responders was not different (*P*=1.0). The average age of those SIBO patients who cleared the LBT post-rescue herbal therapy was 37.4 ± 17 years, which was not different than non-responders (41.5 ffl 11.6, *P*=.62) (Table 9). The prevalence of IBS subtype, known risk factor(s) for SIBO, or gender status did not predict response to herbal rescue therapy (Table 9). Adverse effects (AE) were reported among the rifaximin treated arm (6/67; 9.0%) including 1 case of anaphylaxis, 2 cases of hives, 2 cases of diarrhea, and 1 case of *Clostridium difficile* (post-treatment). One case of diarrhea (non–*Clostridium difficile*) was reported in the herbal therapy arm (1/37; 2.7%) (*P*=.22)

Table 8 Odds Ratios (OR) for Negative LBT Comparing Herbal Therapy to Rifaximin

	OR	Confidence Interval	*P* value
Unadjusted	1.63	0.72 - 3.70	.24
Adjusted for Age and Gender	1.62	0.70 - 3.77	.16
Fully Adjusted*	1.85	0.77 - 4.41	.17

*Adjusted for age, gender, small intestine bacterial overgrowth risk factors, and irritable bowel syndrome status.

DISCUSSION

There is an ongoing resurgence of interest in the role of gut microbiota-host interactions in both health

Table 9 Demographic Information of Rifaximin Nonresponders After Herbal Rescue Therapy

	Responder (n=8)	Nonresponder (n=6)	*P* value
Age +/- SD	37.4 +/- 17	41.5 +/- 11.57	0.62
Female (%)	5 (62.5%)	4 (67%)	0.87
IBS subtype			0.74
None	1 (12.5%)	1 (16.7%)	
Diarrhea predominant	1 (14%)	2 (40%)	
Constipation predominant	3 (43%)	1 (20%)	
Mixed	3 (60%)	2 (40%)	
Any Risk Factor for SIBO[a]	2 (25%)	1 (17%)	0.71

[a] Defined as narcotic use, gastroparesis, diabetes mellitus, and connective tissue disease.

and disease.[25] The gut microbiota is a finely balanced ecosystem that helps regulate key vital functions for the host, including immunity, barrier defense, biotransformation of toxins and carcinogens, and much more.[26] As discussed in more detail by Okeke et al in this issue of *Global Advances in Health and Medicine*, imbalances in the gut microbiome (also known as dysbiosis) have been linked to the development of disorders of mood and behavior, Alzheimer's disease, and numerous gastrointestinal and systemic disorders including inflammatory bowel disease, diabetes, obesity, and cardiovascular disease.[27,28] Bacterial dysbiosis in SIBO can disrupt epithelial tight junctions increasing small intestine paracellular permeability, translocation of endotoxin, and induction of proinflammatory cytokines.[29-31] SIBO can have a number of extraintestinal manifestations such as rosacea, restless legs syndrome,[17,32] arthralgias, anemia, interstitial cystitis,[33] chronic prostatitis,[34] and polyneuropathy.[1] A large body of work has linked bacterial dysbiosis of the small bowel and endotoxemia to non-alcoholic steatohepatitis and progression of alcoholic liver disease, non-alcoholic fatty liver disease, obesity, and others.[35-38] SIBO is a widely prevalent condition in the practice of gastroenterology that is chronic and recurrent for patients and lacks clear treatment guidelines for practitioners. Given the role of the gut microbiome in health and dysbiosis in disease, SIBO is an important entity in clinical practice to recognize and treat.

Rifaximin is the most commonly studied antibiotic treatment for SIBO, with an overall breath test resolution rate of 49.5% (95% confidence interval, CI 44.0-55.1) in 8 clinical trials.[18] A recent meta-analysis reported that the therapeutic efficacy of rifaximin to treat SIBO in the setting of IBS showed benefit; however, the therapeutic gain was only 9.8%, and the number needed to treat is 10.2 with mild heterogeneity (P=.25, I(2)=26%).[39] Additionally, rifaximin is currently not approved by the US Food and Drug Administration (FDA) for the treatment of SIBO and is only labeled for hepatic encephalopathy. Furthermore, a month's supply of rifaximin retails for $1247.39, and according to Medicare part D, a patient's copay in 2014 will be $638.09 for preferred ($703.70, non-preferred) pharmacy or mail-in.[40] Antibiotics may also produce a wide range of toxicity (*Clostridium difficle* colitis, antibiotic induced diarrhea, anaphylaxis, Steven's Johnson reactions, hemolytic-uremic syndrome, etc).[41] Antibiotics have also been postulated to have pervasive adverse effects on the gut microbiome and protective biofilm layer.[42] In fact, a 7-day course of clindamycin has been shown to reduce commensal flora and gut microbial diversity and select antibiotic-resistant genes for over 2 years.[43] Thus, research into more effective and safer therapeutic options for SIBO are ongoing.

The present study demonstrates that herbal therapy may be as effective as antibiotic therapy in the treatment of SIBO, as indirectly measured by normalization of the lactulose breath test abnormalities. Complementary and alternative medicine has gained wide popularity among the United States population, with up to 50% of patients using at least one form of alternative therapy.[44] In addition, it has been noted that the majority of alternative medicine users are patients with chronic conditions. Examples include relaxation techniques and acupuncture for migraines, chiropractic for back problems, and herbal therapy and relaxation for digestive problems.[44] Drossman et al reported based on an international survey that approximately 37% of patients with functional digestive disorders seek complementary and alternative therapies to control their symptoms.[45] More recent data indicates that up to 51% of patients with IBS report using CAM.[20,21] Since CAM has gained popularity among patients with gastrointestinal diseases, especially functional disorders, physicians should familiarize themselves with available CAM therapies.[46] Alternative therapies commonly used by IBS patients that have some level of scientific basis in the literature include acupuncture, fiber, peppermint oil, herbal, traditional, yoga, massage, meditation, mind, relaxation, probiotics, hypnotherapy, psychotherapy, cognitive therapy, and behavioral therapies.[47] The use of antimicrobial herbs to treat SIBO has not been previously reported in the literature. A number of herbs exist that have known antimicrobial activity.[48-53] In the current study, we chose a combination of herbal preparations to provide broad-spectrum coverage against enteric coliforms.[54,55] Oil of

oregano (*Origanum vulgare*) is a well-documented botanical that directly kills or strongly inhibits the growth of intestinal microbes.[56,57] Oil of oregano has other beneficial properties such as inducing apoptosis in human colon cancer caco2 cells.[58] Berberine extracts and thymus vulgaris are also well known for their broad antibacterial activities.[56,59-61] Wormwood (*Artemisia absinthium*) has substantial antimicrobial and anti-inflammatory properties that may be important to the pathogenesis of SIBO and has been used to successfully induce remission of Crohn's Disease.[37,62] There are other herbals used in our study that have noteworthy properties. Lemon balm offers anti-anxiety and antidepressant effects that may benefit patients with IBS, while coptis root has growth-inhibitory effects on human bacteria.[63-65] Red thyme essential oil inhibits the growth of *Escherichia coli O157: H7* and *Staphylococcus aureus*.[66] Indian Barbarry root extract (*Berberis aristata*) contains berberine and has antimicrobial, anti-inflammatory, and antidiarrheal properties.[67] *Equisetum arvense L.* was shown to possesses a broad spectrum of a very strong antimicrobial activity against a variety of enteric microorganisms including *Staphylococcus aureus* (*S aureus*), *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella enteritidis* and the fungi *Aspergillus niger* and *Candida albicans*.[68] *Thymus vulgaris* has potent antimicrobial and anti-inflammatory actions.[69-72] *Olea europaea* inhibits the growth of a number of staphylococcal species including *S aureus*.[73]

Rifaximin is a non-absorbable oral antibiotic, first introduced in Italy in 1987 and in the United States in 2004, that has been approved for a variety of indications and is presently an antibiotic of choice for SIBO.[74] Rifaximin is presently the best studied antibiotic with an overall breath test resolution rate of 49.5% (95% confidence interval, CI 44.0-55.1).[18] Lauritano et al in 2009 showed that rifaximin is superior to metronidazole in the treatment of SIBO; however, recurrence rates after treatment with antibiotics is high as evidenced by high breath test positivity.[75] In our study, we demonstrated that 46% of patients normalized their LBT with herbal therapy. There was no statistical difference between antimicrobial herbs (46%) and rifaximin (34%) (P=.24). Patients were offered the choice of either therapy. SIBO tends to be a recurrent disease, and frequent antibiotic use may have long-term adverse effects on the gut microbiome and be costly; thus, herbal therapy may be a reasonable treatment option for patients with SIBO. In our study, the side effect profile of herbs when compared to rifaximin was not statistically different with a P=.22. However, the prevalence of side effects in the Rifaximin group was 9% (6/67) including *C difficile* and 2 non-*C difficile*–associated diarrhea. In the herbal group, only 1 case of non-*C difficile*–associated diarrhea (1%) was observed. These observations are contrary to popular beliefs. Perhaps the herbal therapies are less disruptive to the gut microbiome and while producing efficacy in resolving SIBO there appears to be less risk of *C difficile*; extended trials will need to confirm this hypothesis. The fear of bacterial resistance including opportunistic infections such as *Clostridium difficile* raises concerns among recurrent antibiotic users. The rifaximin non-responders who received herbal therapy were equally successful in resolving SIBO via the LBT as were triple antibiotics, which had much higher cost and risk of toxicity. Thus, herbal therapy appears to be effective in the treatment of SIBO patients that is initially refractory to rifaximin. Patients who were treated with herbs were not different than those who received rifaximin with respect to the number of predisposing factors for SIBO, and thus the equivalence in response was not due to disparities in underlying conditions. Induction of achlorhydria by acid-suppressive medications (eg, PPIs) has been studied as a potential risk factor for SIBO, with a recent meta-analysis of 11 studies revealing that a pooled OR of SIBO in PPI users vs nonusers was 2.282 (95% confidence interval [CI], 1.238-4.205) when duodenal/jejunal aspirate culture was used to diagnose SIBO but not for glucose hydrogen breath testing.[76] In contrast, in our study, concurrent PPI use did not appear to influence response to either herbal therapies (P=.27) or rifaximin (P=.10).

Limitations of this study include the fact that it was a retrospective chart review and not a prospective, randomized controlled trial. Furthermore, there was heterogeneity and multiplicity of herbs used and, additionally, diet was not controlled. Our patients were also not formally assessed for symptom resolution using a standardized questionnaire. The cost of the herbal regimen is traditionally not covered by commercial insurance; however, the cost of the herbals is relatively low and many individuals did find coverage through their flexible spending accounts.

In summary, we conclude that in the setting of SIBO, patients can be given the choice of antibiotic or herbal therapy depending on their individual preference with similar response rates and safety profiles. In addition, patients who are refractory to rifaximin can receive herbal therapy as a potential rescue therapy with equivalent results to triple antibiotics. This decision is left at the discretion of the treating physician and the patient depending on the clinical setting and the patient's inclination. Future prospective studies that consolidate the antimicrobial herbal regimen to a single agent would potentially enable randomization and blinding, improve patient compliance, and diminish associated costs in this challenging gastrointestinal disorder.

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Select Herbals Targeted to Eradicating Gastrointestinal Dysbiosis.

By: Rachel Olivier, MS, ND, PhD

Dysbiosis is the classic term for an imbalance of gastrointestinal microflora, indicating an increase in abnormal or noncommensal flora, with a coinciding decrease in commensal or normal flora. An increase in pathogenic bacteria, including *Shigella flexneri* and *Salmonella enteritidis*, opportunistic bacteria, including *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Clostridium difficile,* and yeasts, including *Candida albicans* in the lower bowel is typically associated with dysbiosis.[1] In addition to the intestinal tract, dysbiosis of the mouth is also known to occur, and is associated with dental carries.[2] There are numerous factors correlated with dysbiosis, including a poor diet, physical and/or psychological stress, and the overuse of antibiotics, which in turn results in depressed immunity. Psychological stress has been demonstrated to decrease the level of secretory IgA, resulting in decreased mucosal immunity.[3] In addition to other coinciding factors, intestinal dysbiosis has been implicated as the root cause of bowel inflammation.[4] The root cause of many chronic degenerative diseases is correlated to the health of the bowel; consequently optimizing bowel health offers a significant advantage for long lasting health benefits.

Select herbs are well recognized in promoting the synergistic healing of damaged intestinal tissue, resulting predominately from dysbiosis. These herbs include:

Stemona sessilifolia (root) - The active principals of *Stemona* are its alkaloids. These alkaloids exert antifungal, antibacterial and pesticidic properties. It is typically indicated for acute and chronic cough; cough in phthisis (wasting syndrome), whooping cough, cough occurring with or after the common cold, and for cough due to exopathogens. Its action is said to be warm in nature, rather than dry, and its use is considered calming to the entire respiratory center. It also has proven effectiveness for the eradication of louse, parasites,[5] and worms (pinworms).[6, 7, 8]

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Artemisia absinthium, *Wormwood* (shoots, leaves) – In Traditional Chinese Medicine (TCM) *Artemisia* has been used as an antiparasitic agent for more than 1,000 years,[9] as well as an antihelmintic since primordial times. Its parasitic properties are attributed partially to its α-santonin content.[10] It is also regarded as a potent and rapidly acting antimalarial herb.[11, 12] Its primary actions are noted to include cholagogue (inducing bile flow), digestive, appetite stimulating and wound healing, of which all are attributed to its essential oils and amaroids.[13] Following ingestion, the artemisinins are rapidly absorbed and subsequently penetrate the blood-brain barrier, and as in the case of malaria, accumulate into parasite infected erythrocytes. In turn these parasite infected erythrocytes are phagocytized by the leukocytes, thus subsequently eliminated.

In addition to its antiparasitic properties, the essential oil also possesses antimicrobial activity. *In vitro*, its use has been demonstrated to retard the growth of the parasite *Plasmodium falciparum*,[14] and has a confirmed 94.5% success rate in hookworm eradication.[13] It has also been demonstrated to exhibit hepatoprotective activities, partially via its inhibition of microsomal drug metabolizing enzymes (MDME).[15]

Artemisia intake has also been demonstrated to have an action in the stimulation the bitter receptors in the taste buds of the tongue, which in turn triggers a reflexive increase in stomach acid secretion. With intake a significant increase in the production of alpha-amylase, lipase, and other digestive secretions has been demonstrated.[16] Bitter taste receptor activation has been associated with a rapid change in the level of second messengers. Recent research has correlated the ingestion of bitter stimuli with an initiation of both a cellular and molecular responses in the endocrine cells of the GI tract, postulating that "some elements of taste-specific signaling are operative in enteroendocrine cells."[17]

Brucea javanica (fruit) – The active constituents of *Brucea javanica* are the quassinoid compounds bruceantin and brucein C.[18] It possesses properties designated as beneficial

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to multiple bodily systems, including the digestive and circulatory systems, and the large intestines. Both the roots and fruits of *Brucea javanica* are used as popular agents against diarrhea, dysentery and fever.[19] *In vitro* studies have verified that *Brucea javanica* extracts are effective as amoebicides,[20] and clinical studies have shown it to be an effective agent in the treatment of amoebic dysentery[21, 22] and malaria.[23] In animal studies *B. javanica* has been demonstrated to play a role in immunological regulation, as evidenced by its killing effect on the cysts associated with Pneumocystis carnii pneumonia.[24] Other reports have illustrated its activity against various non-commensal organisms including *Shigella* species *(S. shiga, S. flexneri, S. boydii), Salmonella* species *(S. lexington, S. derby, S. typhi* type II) and *Vibrio* species *(V. cholerae, V. inaba* and *V. cholerae ogawa).*[25]

Pulsatilla chinensis (rhizome) – The root (rhizome) of *Pulsatilla chinensis* has been described as possessing anodyne (pain relieving), anti-inflammatory, antispasmodic, astringent and sedative properties.[26, 27, 28] It is noted as an effective agent for bacterial and amoebic dysentery,[27, 28] and is traditionally used in the treatment of malaria, nose bleeds and hemorrhoids, as well as externally to treat infestation with *Trichomonas vaginitis.*[27, 16] It is also thought to clear toxicity and lower fever.[29] The active compound in the root is the lactone protoanemonin, which is recognized as the bactericidal agent.[16]

Picrasma excelsa (bark) – Also referred to as Quassia, this herb is considered a powerful simple bitter, hence its use as a digestive aide. The two main ingredients are quassin and neoquassin. Traditional use is as a remedy for roundworms, as an insecticide, and as a remedy for headlice. It is also used as a remedy for digestive disorders, and for parasites.[30] Orally it is used for anorexia, indigestion, constipation, fever, or as an anthelmintic for thread worms, nematodes, and ascaris.[31] A recent study with *P. excelsa*

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[31] http://www.naturaldatabase.com/Quassia

noted a moderate inhibition of the cytochrome P450 (CYP) enzyme 1A1. This enzyme is a known activator of carcinogens.[32]

Acacia catechu (stem) – The herb *Acacia catechu* is typically utilized for its astringent and antioxidant properties. The catechins isolated from this herb have significant antioxidant and antimicrobial properties. In many parts of the world chewing sticks are made out of the stem, and because of its antimicrobial properties it is considered a valuable component for dental care.[33] The chief phytoconstituents of the heartwood are catechin and epicatechin.

Hedyotis diffusa – *Hedyotis diffusa* is one of the most popular herbs used in traditional Chinese medicine (TCM). It has been demonstrated to possess antioxidant,[34] anti-inflammatory, hepatoprotective,[35] neuroprotective,[36] and antitumor properties.[37] Its active principles include anthraquinones,[38, 39] iridoid glucosides,[36, 34] triterpenoids,[40] and flavonoids.[36, 34]

Yarrow (*Achillea millefolium*) (leaf, flower) – The indications for the use of Yarrow, as approved by the German Commission E include loss of appetite, dyspeptic complains and liver/gallbladder issues. The actions of its flavonoids are indicated as cholagogic (bile flow stimulant), and as a vitalizer in increasing the production of stomach acid. It also possesses both anti-edema and anti-inflammatory attributes.[13] Yarrow is recognized for its relaxant property on smooth muscles, thus may aide with the relief of stomach cramps[41] associated with dysbiosis. In one study utilizing Yarrow, an anti-Staphylococcal activity was demonstrated.[42]

Dill (*Anethum graveolens*)(seeds) – As a popular flavoring agent, dill has a history of use as an aromatic herb and spice exceeding 2000 years.[43] It is said to have a calming effect on both the autonomic nervous and digestive systems, as well as having

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carminative and stomachic properties.[44] It is also indicated as a diuretic, antispasmodic and antibacterial agent, an expectorant, and as a pancreatic stimulant.[45]

The fruits (seeds) contain 1-4% essential oil, of which the primary compounds are corvone, limonene and α-phellandrene, representing 30-60%, 33% and 21%, respectively.[43, 46] Potent antibacterial activity has been demonstrated with both aqueous and organic extracts of the seeds.[47, 48, 49] The compounds D-limonene and D-carvone, have been demonstrated to possess strong activity against the species *Aspergillus niger*, *Saccharomyces cerevisiae* and *Candida albicans*.[50, 51, 52] Its activity against both Gram negative and Gram positive bacteria, as well as fungi and molds has also been demonstrated.[53] Aside from its beneficial attributes towards eradicating these species, its primarily use is for the calming action it exerts on the digestive system, and as such aids in reducing gastrointestinal irritation.

By virtue of the combination of Eastern and Western herbs, the select botanicals discussed above afford a broad anti-dysbiosic effect, even with low dosing. In addition to providing an unfriendly environment for bowel pathogens, this combination of herbs is safe for continual use for up to eight weeks, as it has a low toxicity, and affords minimal irritation to the gut lining. By providing constituents to support the healing and maintenance of the digestive epithelial lining, as well as to eradicate non-commensal flora, the above mentioned herbals affords potent healing properties.

Cautions:

- Artemisia is not recommended concurrently with drugs that thin the blood, drugs that reduce stomach acid, or drugs that prevent or lessen seizures. Additionally, consumption may intensify the effects and side effects of alcohol.[54]
- Yarrow is contraindicated with blood thinners, particularly coumarin. As it contains simple coumarin components,[55, 56] it may interfere with anticoagulants and blood

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pressure medications. Additionally, yarrow may be contraindicated concurrently with the use of drugs that minimize or reduce the production of stomach acid.[41]

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