Select Herbals Proposed as Beneficial in the Eradication of Small Intestinal Bacterial Overgrowth

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The small intestines begin at the duodenum, into which food from the stomach empties, followed by the jejunum, and finally the ileum, with the complete length being approximately twenty-one feet. The primary function of the small intestines is to digest and absorb food, and unlike the large intestines, the small intestines typically contain a low amount of microorganisms. In fact, according to Levitt[1], the primary site of hydrogen peroxide production by bacterial fermentation is limited to the distal gut, with the duodenum and jejunum being primarily sterile.

Small intestinal bacterial overgrowth (SIBO) refers to a condition in which abnormally large numbers of bacteria are present in the small intestine. According to most experts, the gold standard in the diagnosis of SIBO is a bacterial count greater than 10^5 CFUs/mL by small bowel culture.[2] In SIBO, as opposed to what would typically constitute the small intestine, the types of bacteria present typically resemble the bacteria of the colon. As a result of the presence of these bacteria in the small intestines, nutrient breakdown results in damage to the cells that line the intestinal wall, in turn making it more difficult for the body to properly absorb these nutrients. In addition, increased intestinal gas may be localized to the small, rather than the large intestine, resulting in abnormal gas retention.[2, 3] According to Park H,[4] SIBO is a hot topic of interests because of its potential role in the development of irritable bowel syndrome (IBS). In fact, the probability of SIBO being a major pathogenic mechanism underlying IBS has been proposed.[5] In patients with IBS, coupled with a high degree of bloating and flatulence, SIBO has been documented in a substantial percentage of these patients,[6] noted to be as high as 84% in patients with abnormal breath tests.[7]

The most common symptoms of small intestinal bacterial overgrowth include abdominal fullness, abdominal pain, cramps, bloating, and watery diarrhea.[8] Other symptoms may include flatulence, abdominal discomfort, steatorrhea, and weight loss, as well as associated micronutrient deficiencies in vitamins B_{12}, A, D, and E, as well as iron, thiamine, and vitamin B_3. Abnormal motility in the small intestines has also been implicated in patients with SIBO, which is proposed to occur due to reduced activity in the major migrating complex (MMC). "The MMC includes a period of powerful, lumen-obliterating contractions that propagates from the stomach or duodenum distally to the terminal ileum (phase III of MMC, also termed the intestinal housekeeper wave)."[3, 9] In addition to abnormal motility, bacterial translocation is also a known complication of SIBO. Translocation involves the "movement of gut bacteria from the lumen across the mucosal barrier,"[3, 10] resulting in immune activation. The hydrogen breath test is the most common indirect method for evaluating SIBO, as small bowel culture via jejunal aspirate is invasive, time-consuming, and has a high potential for contamination.[4]

There are a number of herbs recognized as beneficial agents in eradication of non-commensal bacteria, as well as in promoting the synergistic healing of damaged intestinal tissue. Subsequently, these herbs may assist in promoting the healing of the gastrointestinal tract, resulting in the elimination of non- commensal flora. These herbs include:

Dill (*Anethum graveolens*)(seeds) – As a popular flavoring agent, dill has a history of use as an aromatic herb and spice exceeding 2000 years.[11] It is said to have a calming effect on both the autonomic nervous and digestive systems, as well as having carminative and stomachic properties.[12] It is also indicated as a diuretic, antispasmodic and antibacterial agent, an expectorant, and as a pancreatic stimulant.[13]

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The fruit seed contains 1-4% essential oil, of which the primary compounds are corvone, limonene and α-phellandrene, representing 30-60%, 33% and 21%, respectively. [11, 14] Potent antibacterial activity has been demonstrated with both aqueous and organic extracts of the seeds.[15, 16, 17] The compounds D-limonene and D-carvone, have been demonstrated to possess strong activity against the species *Aspergillus niger*, *Saccharomyces cerevisiae* and *Candida albicans*.[18, 19, 20] Its activity against both Gram negative and Gram positive bacteria, as well as fungi and molds has also been demonstrated.[21] Aside from its beneficial attributes towards eradicating these species, its primary use is for the calming action it exerts on the digestive system, which aids in reducing gastrointestinal irritation.

Stemona sessilifolia (root) - The active principals of *Stemona* are 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,[22] and worms (pinworms).[23, 24, 25]

Artemisia absinthium, *Wormwood* (shoot, leaf) – In Traditional Chinese Medicine (TCM) *Artemisia* has been used as an antiparasitic agent for more than 1,000 years,[26] as well as an antihelmintic since primordial times. Its parasitic properties are attributed partially to its α-santonin content.[27] It is also regarded as a potent and rapidly acting antimalarial herb.[28, 29] 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.[30] 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*,[31] and has a confirmed 94.5% success rate in hookworm eradication.[30] It has also been demonstrated to exhibit hepatoprotective activities, partially via its inhibition of microsomal drug metabolizing enzymes (MDME).[32]

Artemisia intake has also been demonstrated to have an action in the stimulation of 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.[33] 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 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."[34]

Brucea javanica (fruit) – The active constituents of *Brucea javanica* are the quassinoid compounds bruceantin and brucein C.[35] It possesses properties designated as beneficial 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.[36] *In vitro* studies have verified that *Brucea javanica* extracts are effective as amoebicides,[37] and clinical studies have shown it to be an effective agent in the treatment of amoebic dysentery[38, 39] and malaria.[40] 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.[41] 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*

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species *(V. cholerae, V. inaba* and *V. cholerae ogawa)*.[42]

Pulsatilla chinensis (rhizome) – The root (rhizome) of *Pulsatilla chinensis* has been described as possessing anodyne (pain relieving), anti-inflammatory, antispasmodic, astringent, and sedative properties.[43, 44, 45] It is noted as an effective agent for bacterial and amoebic dysentery,[44, 45] and is traditionally used in the treatment of malaria, nose bleeds, and hemorrhoids. It is also used externally to treat infestation with *Trichomonas vaginitis,*[44, 33] and believed to clear toxicity and lower fever.[46] The active compound in the root is the lactone protoanemonin, which is recognized as the bactericidal agent.[33]

Picrasma excelsa (bark) – Also referred to as Quassia, 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.[47] Orally it is used for anorexia, indigestion, constipation, fever, or as an anthelmintic for thread worms, nematodes, and ascaris.[48] A recent study with *P. excelsa* noted a moderate inhibition of the cytochrome P450 (CYP) enzyme 1A1. This enzyme is a known activator of carcinogens.[49]

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.[50] The chief phytoconstituents of the heartwood are catechin and epicatechin.

Hedyotis diffusa (whole herb)– *Hedyotis diffusa* is one of the most popular herbs used in traditional Chinese medicine (TCM). It has been demonstrated to possess antioxidant,[51] anti-inflammatory, hepatoprotective,[52] neuroprotective,[53] and antitumor properties.[54] Its active principles include anthraquinones,[55, 56] iridoid glucosides,[53, 51] triterpenoids,[57] and flavonoids.[53, 51]

Yarrow (*Achillea millefolium*) (leaf, flower) – The indications for the use of Yarrow, as approved by the German Commission E include loss of appetite, dyspeptic complaints 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.[30] Yarrow is recognized for its relaxant property on smooth muscles, thus may aide with the relief of stomach cramps[58] associated with dysbiosis. In one study utilizing Yarrow, an anti-Staphylococcal activity was demonstrated.[59] In Europe, yarrow is mainly used as a digestive aid, often in combination with mint.[60] It also aids in the relief of gas and bloating (carminative), improves appetite and alleviates gastric insufficiency and distress (stomachic), and promotes the flow of bile, including the promotion of fat digestion; also it may assist in the alleviation of fullness and constipation.[60]

French Tarragon *(Artemisia dracunculus) – A. dracunculus* is a culinary herb, which is also used medicinally. Its key biologically active secondary metabolites include the essential oils, the coumarins, the flavonoids, and the phenol-carbonic acids.[61] It is recognized as possessing antimicrobial activity against a wide variety of bacterial species, including *Staphyloccus aureus*, *Shigella* (RSHI) (Microbiology Laboratory Culture Collection of Refik Saydam Hifzisihha Institute), *Listeria monocytogenes*, *Pseudomonas aeruginosa, Staphyloccus epidermidis, Bacillus subtilis,* and *Escherichia coli* (RSHI, ATCC 25922).[61, 62] Its bactericidal activity against *H. pylori* has also been reported.[62] According to Web.MD.com (www.webmd.com), *A. dracunculus* is used to treat digestion problems, poor appetite, water retention, toothache, and is potentially beneficial in promoting sleep.[63] Its digestive therapeutic actions include appetite stimulation, and both spasm relieving (spasmolytic) and laxative properties.[61] It also possesses diuretic properties,[64] choleretic properties

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(bile/liver stimulant),[65] and is also noted to be an anti-inflammatory agent.[66] In the Northern district of India an extract of the whole herb is used as a vermifuge, as well as to treat various fevers,[67] while in cultures with high red meat consumption, it is commonly used to improve a malfunctioning digestive system by increasing appetite, and acting as a digestive stimulant. It also functions as an aide in flushing toxins from the body.[68, 69]

Indian Tinospora *(Tinospora cordifolia)* – *Tinospora cordifolia* is a well know bitter, and is considered a "detoxifying herb" due to its ability to scavenge free radicals and heavy metals. It also has recognized beneficial characteristics when used with fevers, dyspepsia, and diabetes. Additionally, it is documented as a favorable agent in the management of elevated cholesterol, allergic rhinitis (hay fever), upset stomach, gout, rheumatoid arthritis (RA), hepatitis, and peptic ulcer disease (PUD), and is also indicated as an effective immune system booster.[70] In the Ayurvedic system it is an acknowledged as an "indispensable herb of medicine,"[75] recognized for building up the immune system, particularly against infecting organisms.[71, 72] Its chemical composition includes the following active compounds: alkaloids including palmatine, berberine, and choline,[73] steroids including β-sitosterol,[73] and aliphatic compounds such as octacosanol.[73, 74] Its antimicrobial compounds include jatorrhizin, isocolumbin, and berberine, while its immunomodulatory compounds, include cordifolioside A, cordioside, ecdysterone, and tinosporaside (Cordiol).[75] *T. cordifolia* has also been noted to improve the "phagocytic function without effecting the humoral or cell mediated immune system,"[76] and to enhance humoral immunity.[67]

Horsetail (*Equisetum arvense*). – Traditionally used in Europe as an oral diuretic for the treatment of edema, Equisetum may also be used for diuresis, kidney and bladder stones, urinary tract infections, incontinence, and for general disturbances of the kidney and bladder.[77] The German Commission E expert panel has approved Horsetail for use as an oral diuretic. It contains the flavonoids apigenin, luteolin, kaempferol, and quercetin compounds, as well as caffeic acid derivatives, sterols, tannins, and saponins.[78, 79, 80] Additionally, it contains a significant amounts of silicon.[81]

Thyme (*Thymus vulgaris*). – Historically thyme is used for symptoms of bronchitis, whooping cough, and for general inflammation of the upper respiratory tract.[82] It has antiseptic, antispasmodic, tonic, and carminative properties, and is useful in cases of wind spasms and colic. It assists in promoting perspiration at the beginning of a cold, as well as in fever and general febrile complaints. It is also noted as a useful agent against septic sore throat, and as a vermifuge, to aide in the expulsion of parasites. Thymol, classified as a biocide, is one of the major monterpene phenols of *Thymus vulgaris*, consisting of 20 to 60 percent of the oil. It functions as a powerful antiseptic, used both internally and externally. A tea made from thyme is also a noted means to arrest gastric fermentation.[83]

Pau d'arco (*Tabebuia impetiginosa*). – Pau d'arco is a genus of tropical plants native to the rain forests of Central and South America.[84] The active constituents in Pau d'arco are believed to be the naphthoquinone derivative, lapachol, and its derivatives (ie. beta-lapchone).[85] It has antiangiogenic, antimetastatic, anti-invasive, apoptotic, anti-proliferative, and antimyelosuppressive properties, all of which have been documented *in vitro* and in animals. Additionally, antiplatelet, anti-inflammatory, immunomodulatory, and wound-healing effects have also been noted.[86]

As a folk medicine it has been used to treat bacterial infection, blood coagulation (platelet aggregation), cancer, inflammatory diseases, and peptic ulcers.[87, 88] Preparations made from the inner bark of Pau d'arco are presumed by herbal experts to be more effective than those made from the outer bark. It has also been reported that the beta-lapachone constituent of pau d'arco functions in the inhibition of viral enzymes, which are involved in DNA and RNA synthesis. As a result, the virus can neither replicate nor infect other cells.[86]

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Stinging nettle *(Urtica dioica)*. – Stinging nettle is a perennial plant that has been used as a medicinal agent since ancient times. The genus name *Urtica* comes from the Latin verb *urere*, meaning "to burn," named because of its urticate (stinging) hairs that cover the stem and underside of the leaves. The plant usually has male or female flowers, hence the name dioica, which means "two houses".

Stinging nettle is commonly used for the treatment of arthritis, allergies, pain, cough, tuberculosis, and urinary tract disorders. It is also frequently used as a diuretic. Stinging nettle has anti-inflammatory actions, which have been attributed its inhibitory effect on the activation of NF-kappaB.[89] Additionally, there is some data supporting the use of nettle in the treatment of symptoms of benign prostatic hyperplasia (BPH). Because it is a vegetable, it is classified as GRAS status (generally regarded as safe).

Olive leaf (*Olea europaea*). – The olive tree (*Olea europae*) is a tree native to the Mediterranean. While olives are used primarily as a food, the leaf is used medicinally, predominantly as a tea.[90] *In vitro* studies have demonstrated the antibacterial, antifungal, and antioxidant properties of *Olea europae*.[91, 92] Even at concentrations as low as 0.6% (w/v) olive leaf water extract was effective in eradicating both *C. albicans* and *E. coli*.[91] Sudjana, AN, et al. reported that olive leaf extract was active against *Campylobacter jejuni*, *Helicobacter pylori,* and *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA), with the minimum inhibitory concentrations (MICs) as low as 0.31-0.78% (v/v).[93] Olive leaf has also been noted to reduce viral loads,[94] thus may also possess anti-viral properties. Additionally, it has also been demonstrated to be effective against HIV-1 via its inhibition of cell-to-cell transmission and replication in infected H9 cells.[95]

Oregano (*Origanum vulgare*). Oregano is a perennial herb commonly used as a culinary spice and preservative agent in foods. Its active compounds are the phenolic compounds carvacrol and thymol. Traditionally is has been used to treat respiratory and gastro-intestinal disorders, as well as menstrual irregularities.[96] Research in humans has examined oregano for reducing cardiovascular disease risk, as a dental adjuvant, and as an antiparasitic. It is also identified as an agent that possessing antifungal, antioxidant, antibacterial, and insect-repelling properties.[96] In a recent study, Nostro A. demonstrated that subinhibitory doses (1/2, 1/4 and 1/8 MIC) of carvacrol reduced *Staphylococcus epidermidis* biofilm at neutral pH. The authors stated that carvacrol caused "a potentiated inhibitory effect … on established biofilm," resulting in "a strong reduction of biomass (>50%) and bacteria attached to polystyrene (>7 log units)."[97] Utilizing an emulsified, sustained release preparation of Oregano may be most beneficial, as this type of preparation has been demonstrated to be effective in the elimination of both parasites[98] and Candidia.[99]

By virtue of the combination of Eastern and Western herbs, the select botanicals discussed above afford a broad anti-dysbiotic 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.[100]
- **Yarrow** is contraindicated with blood thinners, particularly coumarin type compounds (coumadin). As it contains simple coumarin components,[101, 102] it may interfere with anticoagulants and blood pressure medications. Additionally, yarrow may be contraindicated concurrently with the use of drugs that minimize or reduce the production of stomach acid.[58]

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- **Equisetum** is possibly unsafe when used in patients with pre-existing thiamine deficiency, chronic alcoholism, malnutrition, renal insufficiency, or cardiac arrhythmias due to theoretical risks of thiamine deficiency, hypokalemia, and nicotine toxicity. It is not recommended in pregnancy or lactation.
- **Pau d'arco** (*Tabebuia* spp) is possibly unsafe when used in patients taking antineoplastic agents, as well as immunosuppressant agents. As Pau d'arco has blood thinning properties, it is likely unsafe when used in patients with blood disorders, those who are having surgery, or those who are taking anticoagulant or antiplatelet medications due to the theoretical increased risk of bleeding. Also, it is not recommended for women who are pregnant or trying to become pregnant, due to fetotoxic and abortifacient effects, based on animal studies. Additionally, allergy/hypersensitivity to Pau d'arco, its constituents, or members of the Bignoniaceae family has been reported.
- **Stinging nettle** *(Urtica dioica)* is possible unsafe when used in patients with diabetes, as nettle may increasing blood sugar levels. Should also be used with caution in conjunction with anticoagulants, antihypertensives and diuretics, as constituents in the nettle plant may potentiate or attenuate the effects of these medications. Stinging nettle is not recommended during pregnancy, as uterine contractions have been observed in animals.[103]
- **Indian Tinospora** (*Tinospora cordifolia*) is contraindicated when used along with diabetes medications, as its use might lower blood sugar levels. It is not recommended in those with autoimmune diseases, such as MS, lupus, or rheumatoid arthritis (RA), as it may cause the immune system to become more active. Additionally, it is recommended that *Tinospora cordifolia* be discontinued at least 2 weeks prior to surgery, as it may affect blood sugar control.

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