

Herbal Antimicrobials for Intestinal Infections

BY MYRON LEZAK, M.D.

ABSTRACT: *Increases in international travel, immigration, animal transport, improper food handling, and drug-resistant bugs have led to an explosion in infectious disease of all types, as well as a need for new, safe antimicrobials. The gastrointestinal tract is called upon to function as an effective physical and immune barrier; and, because the intestinal tract can become a breeding ground for microbes, intestinal health is of critical importance. Imbalanced intestinal flora (dysbiosis) and intestinal infections not only cause localized problems, but can have*

systemic manifestations previously thought unrelated to intestinal health. With the involvement of gut origin (enteric) microbes in increasing numbers of disease processes, it becomes imperative to recognize, treat, and restore health to the intestinal tract. Herbs such as thyme, oregano, barberry, wormwood, garlic, and others appear efficacious as antimicrobial agents against the plethora of microbes threatening intestinal health; in addition, they benefit multiple organs and organ systems—a basic tenet of herbal therapy.

People need safe and effective substances to combat the rise in infectious diseases now evident in all parts of the world. Increases in mass population movements, international travel, and transportation of animals and animal products have helped carry diseases into areas where they've never been before. Furthermore, diseases can now be transported from one continent to another in a matter of hours, and infections commonly associated with "developing countries" are on the rise in America and Europe.¹ For instance, the incidence of intestinal parasitic infections has risen since the 1970s, and researchers conclude that intestinal parasitism should not be overlooked as a cause of gastrointestinal (GI) illness in the United States.^{2,3} Even the incidence of disease due to yeast (i.e., fungi) pathogens has increased.⁴ Furthermore, food-borne pathogens such as *Salmonella* and *Escherichia coli* continue to be a threat due to changes in food production, handling, and processing, as well as the international food trade.^{1,5}

With the arsenal of drugs available to treat infectious disease being progressively depleted as a result of microbial resistance, the need for alternative treatments is greater than ever.^{1,6} Fortunately, nature offers effective therapies that have been used for centuries in traditional medical practices to treat illness related to enteric, pathogenic organisms.^{7,8} Advances in the isolation, extraction, and verification of active compounds from various herbs allows for the production of safe, potent formulas that enhance the body's own defenses and have direct antimicrobial action.

Intestinal Ecology and the Link to Systemic Disease

To appreciate the need for safe antimicrobial agents with action in the GI tract, it is critical to understand the relationship between GI health and systemic disease. The gastrointestinal tract performs critical digestive, immunologic, and barrier functions.⁹ Both non-immunologic processes (i.e., gastric secretions, proteolysis, peri-

stalsis, mucous production, membrane composition) and the local mucosal immune system (gut associated lymphoid tissue or GALT) work in concert to form an effective barrier to the attachment and penetration of microorganisms, antigens, and toxins that are present in the gut environment at any given time.^{10,11}

In recent years, the deleterious consequences of imbalanced intestinal flora (dysbiosis), intestinal infection, and mucosal barrier dysfunction have become clear. Indeed, remote infection with an enteric organism can occur in other organs and systems (e.g., typhoid, paratyphoid, listeriosis, and hepatitis A and E), but reactionary mechanisms associated with their very presence in the intestines can have a systemic impact as well, leading to autoimmune pathology and other chronic diseases.^{12,13,17} For instance, reactive and septic arthritis have long been associated with enteric bacterial infections including *Salmonella*.¹⁷ More recently, they have been associated with a variety of GI parasites and *Candida* infection.^{18,17}

Published research has implicated intestinal dysbiosis and infection as the initiating step in a wide range of GI and systemic conditions including: pancreatic disease, irritable bowel syndrome, autoimmune arthropathies such as ankylosing spondylitis, psoriasis, eczema, cystic acne, chronic fatigue, uveitis, breast cancer, and chronic heart disease.^{11,19,21} According to Dr. Leo Galland, et al., "Intestinal dysbiosis should be considered as a mechanism promoting disease in all patients with chronic gastrointestinal, inflammatory or autoimmune disorders, food allergy and intolerance, breast and colon cancer, and unexplained fatigue, malnutrition, or neuropsychiatric symptoms."²³

Researchers postulate that interrelated mechanisms involved in the systemic manifestations of a dysbiotic or infected gut include inflammation, superantigens, molecular mimicry, and translocation, as discussed below.

Inflammation

The inflammatory response initiated by enteric microorganisms is recognized as a contributing factor to intestinal tissue destruction and mucosal barrier dysfunction.^{16,23} Stimulatory molecules that initiate mucosal immunologic and inflammatory events include microbial cell wall fragments (e.g., peptidoglycans, lipopolysaccharides) and toxic microbial byproducts (e.g., exotoxins, endotoxins) produced by the array of microbes present in the GI tract at any given time.^{16,24} These molecules stimulate the inflammatory process and can alter the balance of cellular mediators like prostanooids, cytokines, nitric oxide, leukotrienes, TNF-alpha, and interleukin 1 and 6, resulting in both local and systemic reactions. Overstimulation by microbial molecules results in increased circulation levels of these mediators, which are capable of tissue destruction.^{16,24,26} For instance, evidence increasingly suggests that tissue damage associated with irritable bowel disease might be caused by a non-specific hyper-responsive inflammation, and increased levels of these inflammatory molecules in circulation may even contribute to the progression of atherosclerosis.^{27,28} Often, attenuation of destructive inflammatory events occurs with resolution of infection.^{29,30}

Microbial Superantigens

Superantigens are thought to be one of the most powerful microbial stimulants that induce inflammatory and autoimmune reactions.^{31,32} These protein structures (e.g., enterotoxins) have the unique ability to nonspecifically activate large numbers of host T cells, inducing the copious production of cytokines—the factor largely responsible for all or part of their toxicity.³¹ They play a role in toxic shock syndrome and mucocutaneous lymph node syndrome, and are proposed to play a role in other systemic diseases.³² Superantigens have also been implicated in autoimmune disorders including rheumatoid arthritis, connective tissue disease, multiple sclerosis, and psoriasis.^{33,35} The effects of superantigens can be both acute and chronic; their role in pathogenesis is based on their unproductive, destructive stimulation of the immune system, including the activation of autoreactive T cells.^{34,35}

Molecular Mimicry

The term molecular mimicry describes an occurrence between pathogen and host in which the appropriate immune response against an organism (often of enteric origin) results in an inappropriate autoimmune reaction. This reaction is caused by the similarity between microbial antigens (proteins) and host cellular proteins.³⁶ As a result, the immune system's tolerance to self proteins breaks down, and the pathogen-specific immune response cross-reacts with host structures to cause tissue damage or disease.³⁷ Therefore, molecular mimicry is thought to be a mechanism in infectious disease-induced self-reactivity.³⁷ For instance, *Yersinia enterocolitica* has been implicated as a contributing factor in the development of thyroid autoimmunity (Graves' disease) due to its cross-reactivity with the thyroid stimulating hormone (thyrotropin) receptor.³⁸

Translocation

When mucosal barrier function is compromised, the opportunity for microbes, toxins, and antigens to exit the intestines and enter the blood, lymph, or visceral organs (translocation) increases. Although translocation occurs randomly in healthy individuals,

factors that promote increased rates of translocation include intestinal dysbiosis or infection, hyperimmune function, absence of bile in the intestines, injury to the gut mucosa, inflammation, and possibly portal hypertension.^{32,39,41} In an animal study of post-antibiotic shifts in the intestinal environment, disturbance of intestinal microflora appeared to be a greater promoting factor in translocation than inflammatory activity.^{41,48} Research indicates that bacteria, fungi, parasites, and viruses can translocate by similar mechanisms from the intestinal tract.⁴¹ Once in circulation, these materials have the ability to produce disease on various levels (e.g., widespread infection, immune system activation).⁴⁹

These data indicate the following scenario: when the intestinal flora is imbalanced or pathogenic organisms are present, a cascade of reactionary events occur that can affect the body on a local and systemic level through alterations in cell signaling or remote infection. These reactionary and interrelated events include inflammation and immune hyperresponsivity, antigen reactivity, and translocation. Moreover, they are all capable of inducing or exacerbating intestinal tissue damage, further aggravating these processes by increasing the systemic load of pathogenic, antigenic, immunologic, or inflammatory molecules.

Allopathic Treatment for Infection

There exists a vast array of prescription antimicrobial medications to treat all forms of infection. Although generally effective for managing acute infections, they not only can produce negative side effects (e.g., superinfections, GI irritation, renal and hepatic toxicity, anemia, etc.), but there is also an increasing resistance to them.⁴⁵ With the rise in new and old infectious diseases, and the mobility of microbes across the planet, mainstream medicine is becoming more receptive to the use of plant antimicrobials, which appear to be effective, even against drug-resistant microbes.⁴⁸

Combining Herbs for Effectiveness

For millennia, folk and ancient systems of medicine have used particular combinations and ratios of herbs to achieve the safest, most beneficial effect possible. Strategies for mixing plants were, and still are, tightly linked to the perceived cause of illness as originating in an unhealthy relationship between an individual, their predetermined nature (i.e., genetic make-up), and their immediate environment that results in physical and/or mental imbalance. Herbal formulas associated with traditional therapies generally seek to restore balance within and between organ systems responsible for the symptoms.^{47,48}

According to traditional Chinese medicine (TCM), successful herbal therapy means maximum benefits with minimal side effects.⁵⁰ To accomplish this, it is imperative to always distinguish the manifestation of the disorder from the root cause of a person's complaints. Both cause and effect are addressed by the herbal combination.

Because antimicrobial herbs need to be supplied at levels that can sometimes cause digestive upset, TCM guidelines of combining herbs are particularly useful in this model. To increase formula tolerance and efficacy, the chief or central herb(s) target the infection, while additional herbs modify the action of the chief herb and support other pathways known to be involved in the physical process of restoring and maintaining balance in the GI tract. This

traditional concept opposes Western herbology—supplying a single potent herb—which may cause side effects when used at high dosages. The TCM model of potency, balance, and efficacy combines antimicrobial herbs, allowing for better concentration of activity, while delivering additional benefits to the GI tract (i.e., digestive, purgative, secretory).^{3,51,52}

Antimicrobial Compounds from Plants

Substances synthesized by plants (phytochemicals) produce odors, pigments, and flavors, serving as plant defense mechanisms against microorganisms, insects, and herbivores. Various plant families including the mint, buttercup, ginger, lily, and rose yield potent compounds or metabolites, and have been used both empirically and clinically in humans for their antimicrobial activity, as well as for their beneficial effects on digestive secretions, peristalsis, and inflammation.^{5,62,56} Recent studies have validated empirical observations, isolated active metabolites, and demonstrated their toxicity to microbes both *in vitro* and *in vivo*.^{6,67-69}

Phenols

Plants have the ability to synthesize a vast array of aromatic substances, most of which are phenols—a group of bioactive phytochemicals classified according to their chemical structure. Plants in this group include those belonging to the *Lamiaceae* or mint family, such as red thyme (*Thymus vulgaris*), oregano (*Origanum vulgare*), sage (*Salvia officinalis*), and lemon balm (*Melissa officinalis*). The aromatic *Lamiaceae* family is one of the most popular worldwide for use as carminatives (to expel gas) and digestive aids, as well as for eliminating unwanted microbes.^{6,69} In addition to cleansing the GI tract, they also have an affinity for the respiratory tract and, as such, their oils have been traditionally inhaled to ward off pathogens.^{6,52} New technology has allowed for the combining of essential oils with dry plant extracts, heretofore not available in supplement form.

Red Thyme Oil (*Thymus vulgaris*)

The primary active in red thyme is thymol, whose action is focused on the upper respiratory and gastrointestinal tracts. Thyme extracts cause beneficial increases in mucous secretion of the bronchi, and have a tradition of use in bronchitis, sore throat, and whooping cough.⁹ When compared with several antibacterials, thyme extract also had a significant inhibitory effect on *Helicobacter pylori*.⁵⁴ Not only did it reduce the growth of *H. pylori*, it made it more susceptible to stomach acid.⁵⁶ In addition, volatile components of thyme showed a great range of inhibition against a variety of bacteria and fungi including *E. coli* and *Candida lypolytica*, as well as important food-borne pathogens.^{51,52,56} Formulas containing red thyme oil should be standardized to thymol for maximum efficacy.

Oregano (*Origanum vulgare*)

Like red thyme, the primary active in oregano is thymol. In several studies, oregano has exhibited high levels of antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria, parasites, and fungi.^{55,59,60} Oregano has been traditionally consumed in teas to treat stomach and gallbladder disorders, diarrhea, coughs, and asthma.^{6,67}

Sage (*Salvia officinalis*)

Phenolic glycosides found in sage are potent antioxidants that support the health of mucosal surfaces; not surprisingly, sage was often used in native cultures to prevent drying of the mucosa.^{60,61} According to the German Commission E, sage is antibacterial, fungistatic, virostatic, astringent, and secretion-promoting.⁶² Sage is indicated for use in digestive complaints, flatulence, inflammation of the intestines, and diarrhea.^{56,61}

Lemon Balm (*Melissa officinalis*)

Lemon balm supplies flavonoids—metabolized in the body to phenols—which support the action of the immune system. Phenolic tannins found in lemon balm display potent antiviral activity; for example, among other mechanisms, they neutralize viruses on contact by attaching to them and preventing their union with cell receptors.^{67,68}

According to TCM, a combination of these aromatic, phenolic compounds has the potential to assist digestion while harmonizing healthy gut and respiratory environments.^{18,61} Because the aromatic mint family has an affinity for the respiratory tract, the individual with gut problems who is susceptible to lung infections, or those with chronic lung conditions that may be secondary to gut infection, would find a combination of these herbs especially useful. The relationship between the GI tract and lung conditions is well recognized in traditional medical systems as well as Western medicine (e.g., bacterial translocation to the lungs).^{7,65,61}

Alkaloids

Alkaloids—heterocyclic nitrogen compounds—deliver a bitter flavor, and for this reason, plants high in alkaloids are often referred to as bitter herbs. Diterpenoid alkaloids are commonly isolated from the *Ranunculaceae*, or buttercup, family and are strongly microbiocidal.⁹ Berberine is a key representative of the alkaloid group, and is present in medicinal plants such as *Coptis chinensis* and barberry (*Berberis aristata*).^{6,66} For nearly 3,000 years, extracts and decoctions of these plants have been used in Ayurvedic and Chinese medicine.

Berberine

Berberine has been shown to have significant activity against bacteria, fungi, parasites, worms, and viruses.⁶⁴ It not only exhibits a broad spectrum of antibiotic activity, but it also inhibits toxin formation as well as antagonizes formed toxins at the site of target tissues.^{6,65,66} In one study, *Coptis* showed an inhibitory effect on a variety of toxigenic fungi, not only inhibiting its growth but inhibiting its toxin production as well.⁶⁷

Berberine sulfate was studied in 165 patients with infectious diarrhea due to enterotoxigenic *E. coli* and *Vibrio cholerae*.⁶⁸ At a dosage of 400 mg, the *E. coli* group had a significant reduction in stool volume during three consecutive 8-hour periods after administration as compared to controls; 42% stopped having diarrhea within 24 hours. Stool volume in the *V. cholerae* group significantly decreased in the second 8-hour period after administration. These results indicate that berberine sulfate is a safe and effective agent against *E. coli* diarrhea, and to a lesser degree, in patients with severe cholera. *In vitro* experiments on the effects of berberine on the growth and structure of parasites indicate that growth

inhibition is dose dependent, inducing morphological changes (e.g., clumping of chromatids, formation of autophagic vacuoles, etc.) in common human parasites.⁴⁸ Furthermore, berberine proved more effective than prescription antimicrobials in clearing patients of *Plasmodium falciparum* (malaria), and when combined with pyrimethamine (an antiparasitic drug) delivered the best results in drug-resistant strains.⁴⁹

Coptis Decoction

TCM practitioners familiar with the application of bitter plants such as coptis, skullcap, phellodendron, and rhubarb, and their bitter principles such as berberine, suggest that these plants be tempered with additional herbs like ginger and licorice, which are added to complement the bitter herbs and stabilize stomach and intestinal function. A decoction of these plants not only provides additional antibiotic activity and antioxidants, it improves the utilization of, and tolerance to, berberine through its protective effects on the lining of the stomach and intestines, thus complementing any formula containing high levels of berberine.⁷³⁴

Other Antimicrobial Herbs

In addition to phenols and alkaloids, foods and herbs commonly consumed in Asia and the Mediterranean including garlic, ginger, sour plum, and wormwood have strong digestive, microbicidal, and cleansing activity.

Garlic (*Allium sativum*)

The use of garlic to fight pathogens has a long and varied history. Its use against amoebic dysentery, cholera, and other infectious intestinal diseases is repeatedly discussed in the scientific literature.^{47,504} In fact, enterotoxigenic *E. coli* strains and other pathogenic intestinal bacteria, which are responsible for diarrhea in humans, are more easily inhibited by garlic than microbes that are part of the normal gut flora.⁷⁹ Garlic also has significant activity against pathogenic fungi and parasites, and has proven to be a potent inhibitor of two common, opportunistic human gastrointestinal pathogens (*Klebsiella* and *C. albicans*).^{76,75} Allicin, a primary active isolated from garlic, along with its metabolites (e.g., ajoene) are responsible for its antimicrobial activity.⁷²

Ginger (*Zingiber officinale*)

Recently, the number of *Anisakis* (parasite) infections in the United States has markedly increased due to the popularity of eating Japanese foods like raw-fish dishes.⁷³ *Anisakis* is found in many kinds of fish including mackerel, pollack, cuttlefish, halibut, tuna, flatfish, and codfish. Ginger has a potent lethal effect on *Anisakis* larvae—eliminating its viability and infectivity—substantiating the rationale for its traditional consumption with raw-fish dishes.⁷⁹ Furthermore, ginger's inhibitory effect on both Gram-positive and Gram-negative bacteria has been validated through *in vitro* experimentation.^{81,75} In the digestive arena, ginger has anti-ulcer effects, enhances the secretion of bile, and promotes gastrointestinal motility.⁷⁶ Anti-inflammatory properties of ginger may also be beneficial in reducing the load of inflammatory molecules associated with intestinal infection.^{47,76} Components of ginger, such as gingerol and shogaol, have been identified as active principles, demonstrating the importance of standardization.^{73,78}

Sour Plum (*Prunus mume*)

In a search for less toxic anthelmintics (deworming agents), the effects of sour plum have been studied extensively on *Clonorchis sinensis*—larvae found in raw or undercooked fish. Its suppression of egg laying capacity, as well as the killing of worms, was shown to be extensive.⁷⁷ In TCM, sour plum is used to treat diarrhea and dysentery, as well as expel hookworms and roundworms.^{74,72} The herb also stimulates purging of parasites from the gallbladder, bile duct, and intestines.⁴⁹ In addition, decoctions of sour plum have displayed *in vitro* inhibitory effects against various strains of food-borne pathogens and other common bacteria and fungi.⁷¹

Wormwood (*Artemisia annua*)

Wormwood has been used for the treatment of fevers in China for over 1,500 years; traditionally it was recognized as a treatment for worms—consequently the name “wormwood.”⁸⁰ The majority of current research on wormwood revolves around its use as an antiparasitic therapy. Artemisinin, an isolated compound of wormwood, has repeatedly proven to be effective in clearing two forms of virulent malaria; in fact, it has been shown to be effective against drug-resistant strains.^{78,79} According to hospital controlled clinical trials, artemisinin and its derivatives are the most rapidly effective of all the antimalarial treatments.⁷⁹

Herb Safety

In choosing herbal products for antimicrobial use, there are certain factors that should be considered. Foremost, because high doses of active principles are required for an antimicrobial effect, formulas should be combined properly to promote safety and efficacy. In multi-herb formulas, the rationale for each plant should be clearly stated. The correct species and safety of each plant should be verified by routine independent testing for pesticides and/or contamination. Whenever possible, a manufacturer's Certificate of Analysis should confirm extract specifications, herbs should be standardized to provide levels of active principles congruent with research and traditional use, and herb potency should be verified by third party analysis.

Microbes including fungi, bacteria, viruses, parasites, and worms will gladly infest and impede the function of the gastrointestinal tract given the opportunity, leading to systemic manifestations of all kinds. Plants, which must themselves combat infection and predation, offer humans compounds with both specific and general actions that eliminate these microbes, while promoting the health of the digestive system. By concentrating and utilizing phenolic and alkaloid substances, effective and safe therapies can be realized. While the aromatic phenols harmonize and cleanse the gut and respiratory tract, alkaloid substances are best utilized to harmonize and cleanse the gut and excretory organs including the liver, gallbladder, and bladder. Substances such as garlic, wormwood, ginger, and sour plum can then be added to achieve greater cleansing activity or to reduce the risk of acute infection, such as, in the traveler. Furthermore, the concurrent use of prebiotics and probiotics can help establish healthy gut ecology and support local immunity. (Refer to CNI 505: Intestinal Health). From the omnipresent threat and increasing incidence of intestinal infections, to the building scientific evidence of systemic diseases of gut origin, intestinal health cannot be minimized as a priority in modern health care.

Antimicrobial Herb Profile 7-9,46-51,53-79

Herb	Class	Active compound(s)	Primary microbes targeted	Primary antimicrobial mechanism(s)
Red Thyme Oil (<i>Thymus vulgaris</i>)	Phenols	Thymol	Viruses, bacteria, fungi, worms	Toxic to microorganisms (possibly through enzyme inhibition or nonspecific interactions with microbial proteins)
Oregano Leaf (<i>Origanum vulgare</i>)	Phenols, flavonoids	Thymol, carvacrol, rosmarinic acid	Bacteria, fungi	Refer to Red Thyme Oil
Sage Leaf (<i>Salvia officinalis</i>)	Phenols, flavonoids	Thujone, rosmarinic acid	Bacteria, fungi, viruses	Refer to Red Thyme Oil
Lemon Balm Leaf (<i>Melissa officinalis</i>)	Phenols, flavonoids	Carvacrol, thymol	Viruses	-Stimulation of phagocytic cells -Thought to occupy viral receptors
Coptis Root & Rhizome (<i>Coptis chinensis</i>)	Alkaloids	Berberine	Parasites, viruses, bacteria	-Intercalates into cell wall and/or DNA -Inhibits microbial carbohydrate metabolism & protein synthesis -Improves immune function and phagocytosis -Stimulates bile production
Barberry Root (<i>Berberis aristata</i>)	Alkaloids	Berberine	Parasites, viruses, bacteria	Refer to Coptis
Wormwood (<i>Artemisia annua</i>)	Sesquiterpene lactone containing an endoperoxide moiety	Artemisinin	Worms, parasites, bacteria	-Blocks utilization of host's erythrocyte protein
Ginger Root & Rhizome (<i>Zingiber officinale</i>)	Phenols, monoterpenes, sesquiterpene hydrocarbons and alcohol	Gingerols (pungent principles), shogaols (formed by loss of water from gingerols)	Worms, bacteria	-Reduces production of eggs -Destroys larvae -Inhibits infection -Promotes gastric secretions
Sour Plum (<i>Prunus mume</i>)	Fruit acids and sugars, vitamin C, & plant sterols	Succinic acid, citric acid, malic acid, tartaric acid, oleanolic acid, β -sitosterol	Worms, bacteria, fungi	-Suppresses egg-laying capacity -Stimulates purging of the bile duct and intestine
Garlic (<i>Allium sativum</i>)	Sulfur compounds	Allicin	Bacteria, fungi, virus, parasites	-Enzyme inhibition -Inhibits DNA, RNA, & protein synthesis

Note: This chart is specific to antimicrobial activity. For a complete constituent, action, and mechanism profile of each herb, please refer to the references.

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