Botanicals and Nutritional Compounds to Support Gastrointestinal Health

Co-authored by
Donald R. Yance Jr., RH (AHG), CN and
Suzanne E. Sky, L.Ac., MTOM

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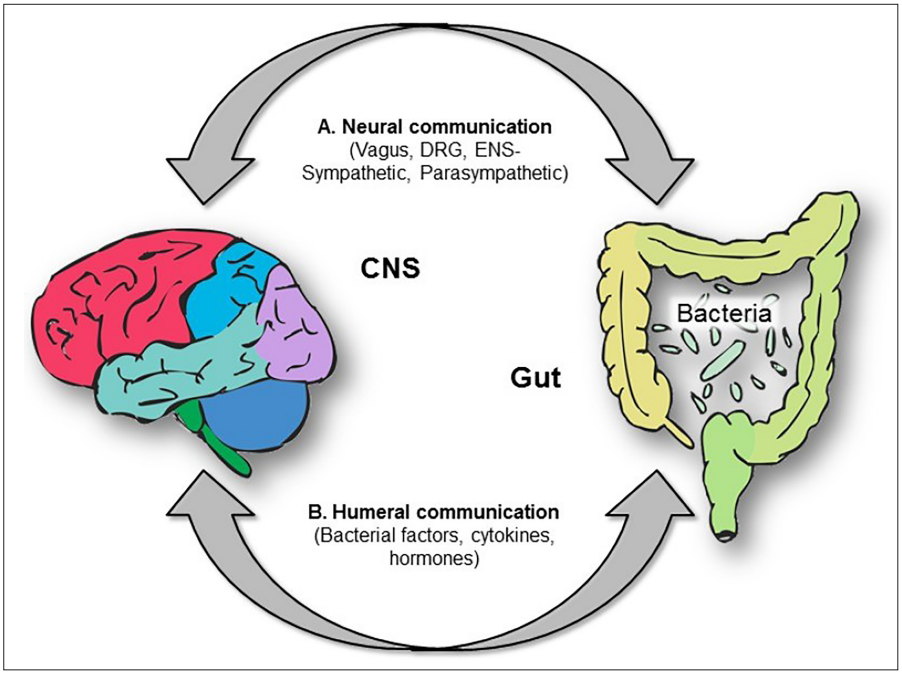
Gut Lining: Key to Gastrointestinal Health

The epithelial lining of the digestive tract, which extends from the esophagus through the anus, plays a key role in health and homeostasis. Comprised of multiple layers, it offers a protective barrier against harmful pathogens and facilitates nutrient absorption. Yet the integrity of these tissues is susceptible to damage through chronic inflammatory processes. This impairs tissue function and contributes to the formation of gastrointestinal, metabolic, and other chronic disease.

In the stomach, healthy gastric acid secretion begins the digestive process and provides the first line of defense against harmful microbes. Various factors, including inflammation and overgrowth of Helicobacter pylori, impair stomach functions and can lead to erosion of the gastric and duodenal mucosa.

A healthy intestinal lining is essential for overall health and homeostasis. It plays a vital role in the ongoing, complex, and dynamic communication between the gut, brain, nervous system, endocrine system, and immune system. The gut lining plays a determining role in effective gut-brain axis communication, nutrient absorption, and influences the vibrancy of the microbiome. The integrity of the epithelial lining, particularly the mucus layer, and permeability of the gut wall are essential to these homeostatic functions. Chronic inflammatory processes disrupt these functions, leading to a breakdown in homeostatic systems.

Botanical and nutritional compounds offer an ideal therapeutic approach to protect and support the integrity of the gut tissues. Through their ability to calm inflammatory processes and modulate the healing response, botanicals enhance the restoration of the ongoing processes that support the complex homeostatic dynamic. They also support and encourage the entire digestive process.



The Brain-gut Axis and the Bi-directional System of Communication.

Jenkins TA, Nguyen JC, Polglaze KE, Bertrand PP. *Influence of Tryptophan and Serotonin on Mood and Cognition with a Possible Role of the Gut-Brain Axis*. Nutrients. 2016 Jan 20;8(1).

Gastrointestinal Disease and Health

The digestive tract consists of the mouth, esophagus, stomach, small intestine, and large intestine; known collectively as the gastrointestinal (GI) tract. Gastrointestinal disease is widespread, affecting about 60 to 70 million Americans annually. This includes multiple conditions ranging from abdominal pain, heartburn, and indigestion to peptic and duodenal ulcers. It also includes cancers of the esophagus, stomach, and colon.[1] Inflammation is the primary factor that affects the epithelium of the esophagus, stomach lining, and intestines. Low-grade, chronic inflammation is widely recognized as a major determining factor in health, aging, and the development of disease.[2]

The stomach, as the gateway between the esophagus and intestines, plays a key role in promoting GI homeostasis. Factors such as inflammatory processes, gastric acid issues, and the bacteria *Heliobacter pylori* play a pivotal role in stomach health and disease. These factors adversely affect the esophageal lining and the small intestinal tract and also compromise the stomach's ability to digest nutrients. *H. pylori* is found to modulate gastric acid secretion.[3]

In the intestinal tract, inflammation sets the stage for increased permeability. Permeability is a delicate balance that allows ingestion of nutrients and at the same time, offers protection from influx of harmful pathogens or toxic metabolic byproducts. Increased permeability, linked with chronic inflammation and tissue injury, results in decreased nutrient absorption and protective capacity. Chronic inflammation of the GI lining disrupts gut homeostasis and impacts overall health.[2]

In addition, ongoing communication between the various parts of the nervous system, including the enteric nervous system, plays a dynamic role in health. It is well-known that stress negatively impacts the neuroendocrine system and GI health. Inflammatory processes in the large intestine lining adversely influence the colon microbiome, which is an intrinsic part of the enteric nervous system and ongoing communication process between the gut, brain, and immune systems.[4]

Gastric Disease and GERD

The primary GI symptom that brings people in to see a doctor is abdominal pain. Almost half these patients are diagnosed with gastroesophageal reflux (GERD). GERD affects about 20% of adults in the US.[5,6]

Patients may experience symptoms including heartburn, nausea, or bloating. Other symptoms of GERD can include laryngitis, hoarseness, chronic sinusitis, dental erosions, and cough. GERD is implicated in asthma, recurrent pneumonitis, and idiopathic pulmonary fibrosis. Epidemiological studies find that 34% to 89% of those with asthma have underlying GERD.[6]

While occasional dyspepsia is considered normal, it can become a chronic condition with severe symptoms. The chronic inflammation causes damage to the mucosal lining of the esophagus, stomach, and intestines. Structural changes at the gastro-esophageal sphincter can make a person more prone to stomach acids and undigested food rising up which causes burning of the esophageal tissues. Excess or chronic reflux of food, acid, and pepsin causes inflammation in the esophageal mucosa with resultant erosion or ulceration.[1,5,7,8]

GERD is considered to be a spectrum of disorders that progresses from non-erosive reflux disease (NERD) to more chronic, erosive conditions including erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. GERD incidence has risen significantly since 1970 and affects about 20%

of the population.[9] Of the 3.3 million Americans diagnosed with Barrett's, about 90% have nondysplastic Barrett's.[1]

Smoking and obesity are factors most commonly associated with higher risk for GERD. Genetics is considered to play a role in 18% to 31% of GERD incidence. The bacterium *Heliobacter pylori*, found in the mucus layer of the stomach, plays a key role in GERD. Although some studies find that eradication of *H. pylori* does not alleviate GERD, since chronic *H. pylori* infection is associated with other disease processes, including increased risk for peptic ulcers and gastric cancer, it is still considered a therapeutic target.[8]

Stomach Health and Gastric Acid

Studies find that up to 50% of gastric acid secretion occurs before food even enters the stomach. Stimulation in this anticipatory, or cephalic, phase of eating is primarily mediated through the vagus nerve, which links the brain, brainstem, and GI system. It activates digestive salivary secretions in the mouth and triggers activation of the stomach, pancreas, and gall bladder. It innervates regions of the GI tract that influence digestion, satiety, and caloric intake. The vagus nerve also promotes the expansion and contractions of the stomach along with the release of gastric acid for digestion.[3,10,11,16]

The mechanisms of gastric acid secretion, inhibition, and regulation involve complex, ongoing interactions between the endocrine, paracrine, nervous, and enteric nervous systems.[3] Gastrin and ghrelin, two factors that influence gastric secretions, are produced in the gastric mucosa and also by the hypothalamus.[3]

Gastric glands deep in the stomach's mucosal layer produce and secrete gastric acid (HCl), enzymes, hormones, protective mucus, and paracrine molecules. Gastric acid (HCl) secretion initiates the digestive process to break down proteins and other dietary components into smaller compounds.[10-13] Pepsinogen is converted to the proteolytic enzyme pepsin in the presence of HCl. Pepsin is most active at the acidic pH of 1.8 and is inactive in conditions of alkaline or neutral pH.[13]

Gastric acid secretion is correlated with gastric emptying. When food sits in the stomach longer than it should, this contributes to inflammation and disruption of normal gastric function. This also disrupts the normal inhibitory and stimulatory mechanisms. A study found that when gastric secretions such as HCl and pepsin were replaced in those with atrophic gastritis, emptying time and digestion of food improved.[3]

The peptide hormone gastrin, secreted from the stomach, stimulates gastric acid secretion and mucosal growth. Gastrin release is stimulated by the presence of amino acids and peptides in the stomach, by the sensation of stomach distension, and by coffee. Neural reflexes in the enteric and parasympathetic nervous system also stimulate the release of gastrin. These acidic secretions also function as part of the immune system as the strong acids provide a first line of defense that eliminate any food-borne pathogens or microbes and prevent them from entering the small intestine.[10,11]

The stomach's acid secretion is usually one to three liters a day and can bring the luminal pH down to 1.0. Bicarbonate, secreted with mucus, helps buffer the acids and protect the epithelium from damage. Studies find that the pH of the stomach's bicarbonate layer, just above the cell surface, is close to 7.0, even when the stomach lumen pH is highly acidic at pH 2.0.[14]

Lifestyle and nutritional factors greatly influence gastric acidity. Chronic stress, high intake of refined carbohydrates, and poor nutritional intake all contribute to disruption of normal gastric acid secretion.

Insufficient dietary B vitamins is linked with impaired gastric secretion.[12]
Gastric acid secretion naturally declines with age. About 30% of those over 60 years of age in the US have atrophic gastritis, in which there is little or no gastric acid secretion. Around 40% of postmenopausal women are found to have no basal gastric acid secretion.[12,13,17]

Low HCl secretion disrupts the absorption of multiple nutrients from the stomach and small intestines. This includes folic acid, B12 (cobalamin), minerals (such as calcium and iron), and impaired digestion of proteins; particularly tryptophan, tyrosine, and phenylalanine.[3,17,18]

There is a strong correlation between low levels of stomach acid with precancerous gastric conditions and with chronic atrophic gastritis.[10] Long-term decreased acid production (hypochlorhydria) is associated with increased risk of gastric cancer.[11] Chronic low-grade inflammation and decreased acid secretion in the stomach leads to the slow development of gastric cancer over many years.[10]

Dysfunctional HCl secretion can result in:[10]

1. Decreased acid secretion: chronic gastritis, dyspepsia, intestinal bacterial overgrowth, gastric cancer.
2. Increased acid secretion: GERD with epigastric pain, reflux, heartburn.
3. Abnormal acid secretion: GERD, peptic ulcer, gastric cancer.

The Stomach Lining and Gastritis

The epithelial and mucosal lining of the stomach is influenced by the bacterial population, inflammatory factors, diet, and chemicals. When the stomach is irritated by compounds such as aspirin or alcohol, mucus secretion is increased.[14] Overuse of antibiotics and NSAIDs (nonsteroidal anti-inflammatory drugs) are well-known for their erosive action on the gastric and duodenal lining.[12,13] These compounds contribute to inflammation of the gastric mucosa. NSAIDs are considered to be the most common cause of gastric and peptic ulcers.[14,15] Gastritis, most commonly associated with *H. pylori*, can also arise due to chronic inflammatory conditions, Chron's disease, other autoimmune disorders, pernicious anemia, and damage of the stomach lining.[16]

Reduced gastric acid secretion increases the risk of bacterial overgrowth and influences the microbiome of the stomach and of the small and large intestines.[10,11,16] Duodenal acidity is directly influenced by the pH of the chyme that arrives from the stomach and determines the amount of alkaline fluids that are secreted. In both acute and chronic achlorhydria it is noted that the stomach and duodenum are quickly colonized with microbes from the colon with bacterial overgrowth and increased SIBO (small intestinal bacterial overgrowth). Colonic flora is found in the stomach of 25% of those with achlorhydria.[13,18]

***Heliobacter pylori* Influences Gastric Health**

For years, researchers assumed that any bacteria in the human stomach were merely transient, resulting primarily from ingested food. In the 1980s researchers began to realize that the stomach naturally contains a large bacterial community with hundreds of phenotypes.[11,16] One genomic study identified about 128 bacterial strains in the gastric flora.[3] Current studies explore the gastric microbiome and its role in digestion, health, and disease.[11]

Scientists are particularly interested in the bacteria *Helicobacter pylori*, which consists of over 20 recognized species. These are subdivided into groups according to the organ they inhabit, as *H. pylori* species are organ-specific to either the ileum, colon, biliary tree, liver, or stomach.[16] *H. pylori* is highly successful in colonizing the stomach. This spiral-shaped, gram-negative bacteria is able to live in the very acidic conditions of the stomach where it primarily colonizes the antrum and corpus and resides in the gastric mucosa.[11]

H. pylori is found in at least half and potentially in all human populations.[10,16] Some research states that humans have been colonized with *H. pylori* since our first ancestors.[10] While colonization of *H. pylori* itself is not considered a disease condition, it is highly correlated with the risk of developing a number of diseases.[18] The complex interaction between the host and *H. pylori* involves a constant interplay of factors including the host, the microbiome constituents, and gastric acid levels. These constitute contributing factors to disease proceses.[10,11,16]

H. pylori infection is the main etiological agent in numerous GI conditions including gastritis, Barrett's esophagus, peptic ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma.[19,20] It also plays a role in disorders of the upper GI and hepatobiliary tract.[5,16]

Gastric and duodenal ulcers are highly correlated with *H. pylori* infection. About 95% of duodenal ulcers and 85% of gastric ulcers are found to occur in relation to *H. pylori* infection.[16] It is estimated that those who test positive for *H. pylori* have about a 10% to 20% risk of developing some type of ulcer and 1% to 2% risk of developing distal gastric cancer.[16] *H. pylori* is the only bacteria formally recognized as a carcinogen as it is implicated as a direct causative factor for gastric cancer.[11,16]

There is an inverse relationship between *H. pylori* and GERD. While being overweight and obese are recognized risk factors for GERD, the dietary component is considered secondary to the role of *H. pylori*.[10] This is because *H. pylori* disrupts normal gastric physiology and gastric acid secretion.[11] Interestingly, while *H. pylori* is found to influence gastric acid secretion, the pattern of its influence varies with each individual.[3,18] This is further complicated by use of medications and dietary influences.

Long-term *H. pylori* infection is correlated with lower acid output.[3,10] Additionally, *H. pylori* is linked with atrophic gastritis, which results in lowered gastric acid.[19] A correlation is found between acid levels in the stomach and the distribution of gastritis. Since stomach acids keep a check on *H. pylori* growth, when stomach acids are low for any reason, *H. pylori* will proliferate and colonize large areas of the stomach. A condition known as *H. pylori* corpus gastritis is associated with hypochlorhydria. When *H. pylori* is eradicated, acid secretion is found to naturally increase.[16]

H. pylori causes numerous infections, is associated with chronic inflammation, and can contribute to hyperproliferation of epithelial cells.[16] Chronic inflammatory processes play a key role in the development of gastritis and duodenal ulcers.[3,16] This involves a complex interaction of proinflammatory and anti-inflammatory mediators including IL-1, and IL-1beta. High expression of IL-1 is linked with the reduced stomach acid output that facilitates the spread of *H. pylori*.[16]

Numerous compounds and herbs demonstrate an ability to inhibit *H. pylori*. We will later review several, including Ginger Root,[21] Mastic Gum,[22-25] Manuka Honey,[26] Licorice Root,[27] and Glutamine.[28] Most of these also exert a soothing and healing influence on epithelial tissues, which are prone to damage from inflammatory processes.

Inflammation and Tissue Integrity

A healthy intestinal lining is essential for overall health and homeostasis as it influences effective gut-brain axis communication, the capacity for nutrient absorption, and the vibrancy of the microbiome. The epithelial lining of the gut extends from the lower esophageal sphincter to the anus and plays a key role in physiological homeostasis. The epithelial tissues provide a dynamic interface for a vast communication network. Any disruption in tissue integrity impedes this vital, ongoing flow of information and signaling that mediates and modulates multiple funtions.[4,29,30]

The gut lining consists of the vascular endothelium, an epithelial cell lining, and a mucus layer. There is a constant, ongoing dynamic, communication process here involving digestive secretions, immune and inflammatory mediators, and cellular processes. These are all constantly responding to and interacting with the constant flow of stimuli from food moving through the digestive tract and other stimuli.[30]

The gut lining provides protection from compounds that can cause mucosal inflammation and plays a key role in transport functions.[29,30] It helps prevent microorganisms or harmful metabolic byproducts from entering the circulation. At the same time, it allows for absorption of fluids, electrolytes, and nutrients into the system. Thus, intestinal permeability plays a key role in health and disease. Loss of intestinal barrier function is correlated with inflammatory bowel disease, celiac disease, and other conditions. Upregulation of TNF, a powerful inflammatory mediator, is implicated in dysregulation of intestinal barrier.[31]

Mucosal Layer Transport and Role

Metabolic homeostasis is another parameter of allostasis. Metabolism is an ongoing, dynamic, biochemical process at the cellular level that sustains life through continual transformation of nutrients and molecular compounds. Metabolic balance influences endocrine function, immunity, cell proliferation, cellular communication, bioenergetics, mood, and behavior.[31-33]

The intestinal mucosa functions as an active and passive transport mechanism.[31] The viscous secretion of mucus serves as a protective coating over the mucosal layer of the GI tract. Normal secretion of mucus is modulated through interaction between parasympathetic innervation, genetic factors, gut microbes, and neuropeptides in the enteric nervous system.[14,30,32]

The mucosal layer is comprised mainly of glycoproteins known as mucins, which are made in specialized cells in the stomach, salivary glands, and intestines.[14,32] The mucosal layer consists of an inner and outer layer, which dynamically interact with the gut and microbiota.[4,32] The dense inner layer protects the epithelial layer from bacterial invasion. The outer layer hosts the majority of intestinal microbes and provides nutrients for them (mucin) in the absence of sufficient dietary fiber. The microbiota are found to modulate barrier function and intestinal permeability. Likewise, membrane permeability influences signaling pathways and communication within the microbiome.[4,30,34]

Excess mucus is secreted as a protective response to parasitic infection, injury, and ongoing inflammation.[14] There is also an ongoing modulatory process of inflammatory compounds in the intestinal mucosa including TNF, interferon-gamma, IL factors, and anti-inflammatory cytokines.[32] The cytokines play a key role in modulating inflammatory processes in the mucosal immune system.[32]

Intestinal Permeability and Tight Junctions

The primary component of the mucosal barrier is the intestinal epithelium, which consists of many types of specialized cells including enteroendocrine cells and immune cells. Cell cohesion and cellular permeability are supported by several types of junctions known as tight junctions, adherence junctions, and desmosomes.[33] Tight junctions are formed from complex protein structures.[34]

Generally, while the junctions between cells form a tight barrier in the stomach and large intestine, they are more open in the small intestine to allow greater absorption of nutrients, electrolytes, and water. Junction tightness has the quality of plasticity, is regulated through various mechanisms, and plays a role in immune homeostasis.[31,34,35]

Junctions, as dynamic areas of ongoing activity, are constantly responding to stimuli including nutrients, microbes, and neuronal, humoral, and inflammatory signaling. The junctions open and close, allowing nutrients and other cellular products to pass through while keeping microbes or other unwanted pathogens from entering the blood stream.[29,34,35]

Chronic inflammation compromises functional permeability. The mucosa usually heals rapidly, within minutes, to maintain an intact barrier. Prolonged inflammation contributes to erosions, ulcerations, and the loss of appropriate tissue permeability and resilience.[31] The resultant breach in the mucosal barrier is often referred to as a "leaky gut". Along with chronic inflammation it is a marker of multiple disease conditions, pain, and discomfort.[29,35] A large increase of inflammatory cytokines including TNF, IL-1beta, and IL-3 is noted in chronic intestinal inflammation.[30,33]

Factors that contribute to chronic inflammation include diet, genetic tendencies, intestinal microbiome constituents, and microbiota balance.[30] Changes in the intestinal microbiome are associated with gut barrier dysfunction.[34] Diets high in fat and sugars contribute to inflammatory processes and gut permeability.[30] A high-fructose diet is found to contribute to a loss of tight junction proteins in the duodenum and an increase of endotoxins in the portal vein.[30]

Stress and Intestinal Barrier Health

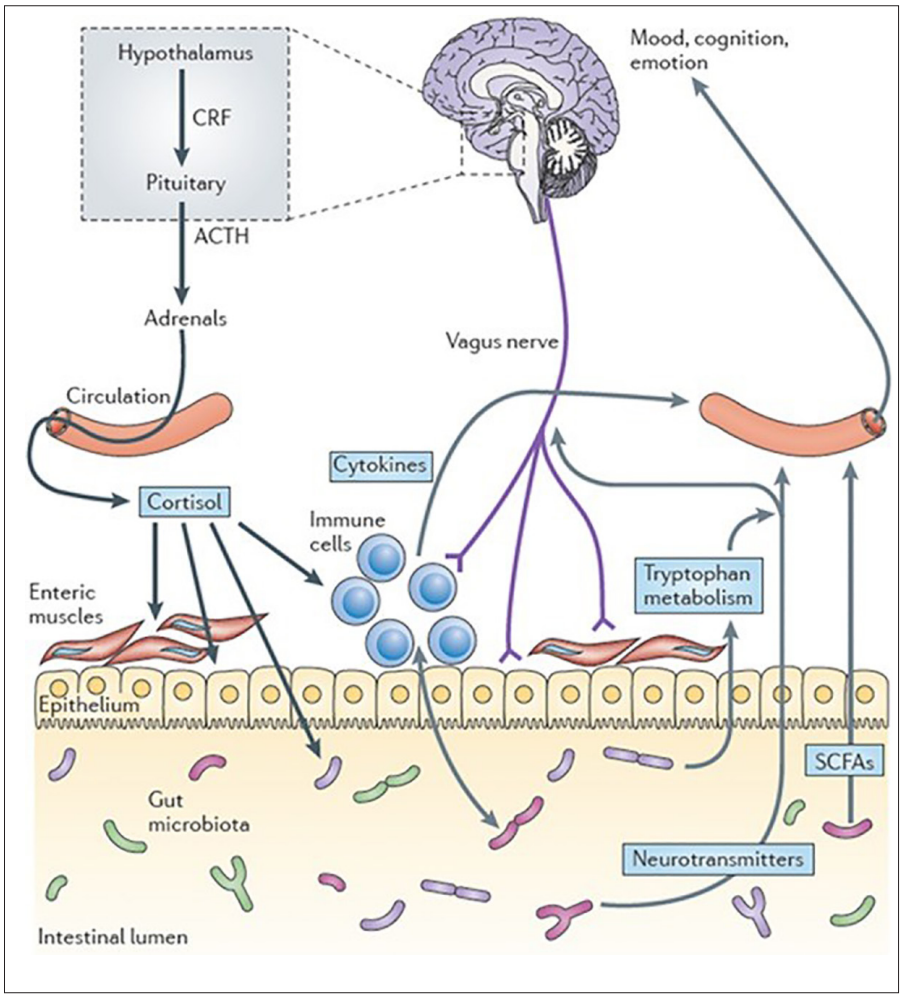
Stress is shown to affect the intestinal barrier and to be a contributing factor in the development of increased gut permeability and visceral sensitivity. This is partially mediated by CRF (corticotrophin releasing factor) and its receptors. The gut microbiome also influences host barrier function both directly and via its interaction with the HPA (hypothalamic-pituitary-adrenal) axis.[34;36-40]

The role of the HPA axis and the immune system is widely recognized as the primary stress response system that coordinates an adaptive response.[34,37,38,40,41] Over the last decade research on the gut-brain axis finds that the gut microbiota mediates the interaction between the HPA axis and the immune response. Conditions such as IBS are recognized as a disorder of the brain-gut-microbiota axis and are most often concurrent with stress, dysbiosis, and increased intestinal permeability.[34] The intestinal barrier and microbiome are closely integrated with HPA axis, neurotransmitter systems, and immune function.[34;36-38] As such, these systems play an integral role in the stress response.[34,36,38,39]

The Gut Microbiome and the Enteric Nervous System

The gut microbiome is highly studied and recognized for the complex, dynamic, ongoing, and vital role it plays in maintaining homeostatic health throughout the human organism.[36,37,40,42] The gut microbiome is integrally linked with health while alteration in the gut microbiota is correlated with numerous disease conditions including IBD (inflammatory bowel disease), type 2 diabetes, obesity, allergies, and colorectal cancer.[43]

The human body is comprised of over 90% microbial cells living in symbiotic relationship. The most densely colonized areas are the small and large intestines.[34] There are about 1014 microbes, with over 500 species, colonizing the large intestines. Each person has their own unique bacterial microbiota profile, although it is noted that healthy persons show a similar distribution of phenotypes.[33,37,43] Composition of the microbiome is influenced by stress, diet, environmental factors, and by the host's genetics.[43]



Pathways Involved in Bi-directional Communication between the Gut Microbiota and the Brain

Bryon Petschow, et. al., *Probiotics, prebiotics, and the host microbiome: the science of translation* Ann N Y Acad Sci. 2013, Dec; 1306(1): 1–17

The Gut Microbiome's Role in Homeostasis

Scientists find the gut microbiome to be an integral part of the dynamic system that includes the gut lining, microbiome, brain, immune system, endocrine system, and nervous system.[4,33,35,44] Collectively referred to as the gut-brain axis or as the gut-brain-enteric-microbiota axis, this axis includes the CNS (brain and spinal cord), the neuroendocrine system, the neuroimmune system, the ANS (autonomic nervous system), the ENS (enteric nervous system), and the intestinal microbiota.[4;34,36-41;43] Ongoing communication between these systems is bidirectional and involves neural, endocrine, humoral, and immune signaling and mechanisms.[34,37,40,41]

A healthy microbiome is integral to and modulates the development and maturation of the immune system, the brain, and specifically of the HPA axis, which comprises the core neuroendocrine axis and primary stress response pathway.[34,38,40,41] The microbiome also influences CNS functions and CNS maturation.[41]

Gut bacteria play key roles in immunomodulation, adiposity, energy balance, and ENS activity.[38,44,45] The microbiota plays a vital role in supporting healthy digestion and metabolism.[40] It influences GI tract motility, epithelial barrier function, healthy digestion, and metabolism. Microbiota also regulates the mucosal immune system and helps prevents invasion or colonization of pathogens.[40,45] The gut lining contains the richest density of immune cells in the body – more than circulate in the blood or reside in the bone marrow.[4] The gut microbiota are key regulators of both systemic and mucosal immune function and of the inflammatory response.[34,41,43]

It is also found that the microbiome influences the development of chronic inflammatory disorders, and of mental/emotional conditions such as depression. A salient feature of aging is chronic low-grade inflammation generally characterized by increased levels of TNF, IL-6, and CRP (C-reactive protein). Each of these influences physiological disease states and also affect mood and cognition.[34]

Diseases linked to changes in intestinal microbiome include atopic diseases, IBD (irritable bowel disease), diabetes, obesity, cancer, and neuropathologies.[30,33,35] Diet is widely known as the primary factor that influences the microbiome, with resultant impact on the whole axis.[39]

The Enteric Nervous System

Neural networks that modulate digestive function include those in the central nervous system, the spinal cord, the prevertebreal sympathetic ganglia, and the enteric nervous system.[46] The enteric nervous system (ENS) is a complex, extensive neural network found in the entire GI tract walls from the esophagus to the anus.[45,46]

The autonomic nervous system regulates bodily processes. Its two main components are the sympathetic and parasympathetic nervous systems. The ENS is now recognized as the third division of the autonomic nervous system (ANS).[45,46] As part of the ANS, it influences motility, digestive secretions, blood flow, and immune response. The ENS plays a key role in epithelial barrier function, vasomotor activity, and GI immune function. It controls exocrine and endocrine secretions, the microcirculation of the GI, and regulates immune and inflammatory processes.[45-47] Disruption of gut-brain axis homeostasis results in IBS (irritable bowel syndrome) and other conditions.[45]

Known as the second brain, the microbiota and ENS produce a number of neurotransmitters including GABA, hydrotyrosine, tryptophan, serotonin, and dopamine.[42] Together, these systems are viewed

by researchers as a supercomputer with processing capabilities that rival that of the brain.[4] Though interconnected with the CNS, the ENS is noted for its ability to function independently of the CNS.[45,47] However, the ENS within the GI tract lining works in concert with the CNS and communication is constant and bidirectional.[48]

The vagus nerve, pelvic nerves, and sympathetic pathways carry information between the ENS and CNS.[48] The vagus nerve plays a crucial role in linking the GI tract, brain, and organs and helps regulate organ function. For example, the CNS exerts influence over the stomach, including stomach contractions and acid secretion, through the vagus nerve reflexes.[48]

The vagus nerve transmits information from the gut to regions of the brain including the hypothalamus and limbic system, which influence mood, cognitive function, appetite, and pain sensitivity. It is found that while the communication is bidirectional, about 90% of the signals travel through the vagus nerve from the gut to the brain with only 10% going in the other direction.[4]

Over 30 neurotransmitters and neuromodulators are released by the neurons of the ENS into the bloodstream. This includes serotonin, dopamine, and nitric oxide.[4,14] The serotonin signaling system is well-known for its key role in the gut-brain axis in relation to intestinal function, mood, digestive capacity, peristaltic reflex, pain sensitivity, and overall well-being.4 Endocannabinoids are also found to be vital neuromodulators in the CNS and to provide key regulatory functions in the GI tract. They regulate GI physiology, including motility, secretion, and energy balance. They also play a key regulatory role in ENS neurotransmission.[45]

The ENS is estimated to contain anywhere from 200 to 600 million neurons.[4,45,48] The majority of these are found in two major plexuses – the myenteric and the submucosal plexuses.[45,48] The myenteric plexus is located between the muscle layers and the submucosal plexus is in the submucosa of the GI tract.[45] The continuous network of the myenteric plexus extends from the upper part of the esophagus all the way to the internal anal sphincter.[48] The submucosal ganglia form plexuses with connecting fiber bundles. These are found only in the small and large intestines.[48]

Botanicals and Natural Compounds for GI Homeostasis

Health is an ongoing, dynamic process in which resiliency and adaptability help create the ongoing stability (homeostasis) maintained through allostasis.[49-52] Botanical medicines and natural compounds offer an excellent therapeutic approach to help calm inflammatory processes, promote tissue healing, restore gut homeostasis, and support a balanced neuroendocrine response to stress. The diversity of phytochemicals and nutrients naturally provide anti-inflammatory, antioxidant, antimicrobial, and anti-adhesive activity. They also provide a strong positive influence to support healthy digestive function, promote tissue healing, and support immune response.[4;53-55]

Botanical medicines and natural compounds have been used successfully for thousands of years to enhance healthy digestion and restore health to inflamed or damaged digestive tissues. The GI epithelium tissue is known to heal and regenerate quickly.[3] Soothing, demulcent botanicals exert a protective, restorative influence on the gut lining through multiple mechanisms.

Over the centuries, traditional herbalists have given herbal bitters to stimulate acid secretion and support healthy digestion. Dilutions of lemon juice or apple cider vinegar in water are also beneficial.[3] Nutrients such as B-vitamins in particular are found to be a key factors in functional HCl secretion.[13]

A number of botanicals influence both the digestive and nervous system. The connection between a distressed nervous system and digestive disorders has long been recognized. Today, we know that the enteric nervous system (ENS) functions as both an independent and integrated part of the autonomic nervous system. It is no surprise that herbs offering both calmative and digestive properties will benefit most gastrointestinal conditions.

In the following sections, we will discuss some well-known and unique botanicals and natural compounds that contribute vastly to digestive health.

Botanicals

Licorice Root (*Glycyrrhiza glabra*)

Licorice is highly valued for its demulcent qualities that soothe inflammation and nourish the mucus membranes of the intestinal tract. Licorice has a long history of use in Chinese, Ayurvedic, and European traditional medicines where it is combined with other herbs, playing a supportive, but powerful role.

Licorice Root *(Glycyrrhiza glabra)*

Research notes Licorice root for its anti-inflammatory activity and immunomodulatory influence.[27;56-58] Licorice is found to increase production of interferon and NK (natural killer) cells.[59]

Licorice contains an abundance of flavonoids, and many of those isolated from Licorice demonstrate broad-spectrum antibacterial activity.[60-64] Licorice root is found to be active against *H. pylori* in vitro.[64] It exerts antimicrobial activity and a protective influence on the oral mucosa.[65,66] A Licorice root mouthwash was found to help improve aphthous ulcers after one day of use, and many experienced clearing of the ulcers by day three.[67]

Deglycyrrhizinated Licorice (DGL) is a form of Licorice with the steroid-like component glycyrrhizin removed. DGL, noted for its soothing influence and ability to calm inflammation, is found to exert a protective influence on gastric mucosa against aspirin-induced damage.[68,69] It is used to support the healing of the epithelial mucosa tissues of the esophagus and stomach, especially when aggravated by GERD.[68,69]

Marshmallow Root (*Althaea officinalis*)

Marshmallow root is another highly-revered demulcent herb. It is traditionally used to soothe and promote the healing of the mucus membrane tissues of the GI system and urinary tract.[70] Studies find that Marshmallow root exerts significant anti-inflammatory activity.[71] It also exerts a beneficial influence on irritated mucosa.[70] Marshmallow extract is found to be protective against ethanol-induced ulcers. The flavonoid-rich mucilage from the roots soothes and coats inflamed tissues and mucosa to help facilitate tissue healing.[71]

A combination of Ginger and Marshmallow roots was found to be protective in rats with indomethacin-induced gastric ulcers.[72]

Chamomile (*Matricaria recutita* or *Chamomilla recutita*)

Chamomile *(Matricaria recutita* or *Chamomilla recutita)*

The small, bright yellow Chamomile flowers are known for their soothing, relaxing influence. They are traditionally used as an evening tea to relax the nervous system and facilitate a good night's sleep. Chamomile flowers are well-known for their ability to calm the nervous system and relieve anxiety.[73,74] Studies suggest that the flowers inhibit cortisol production.[75]

Chamomile flower tisane is traditionally used to alleviate nervous stomach upsets. Often used along with other herbs to treat colic in children, Chamomile also helps calm gastrointestinal muscle spasms.[73,74] Chamomile is found to be protective of the gut mucosa.[76]

Research highlights Chamomile flowers for their anti-inflammatory, antiseptic, carminative, sedative, and spasmolytic activity.[73,74] Active ingredients of Chamomile flowers include terpenoids, azulenes, flavonoids (including quercetin and apigenin), coumarins, and mucilage.[77,78]

Aloe Vera Gel (*Aloe barbadensis* Miller)

Aloe Vera Gel *(Aloe barbadensis* Miller*)*

Aloe Vera is revered for its powerful healing attributes in many traditions including Ayurveda, Chinese medicine, and in areas where it grows, including Africa, Hawai'i, and other tropical areas. A member of the Lily family (Liliaceae), Aloe was used as a medicine in ancient Egypt, where it is represented in temple engravings dating back to 4000 BC.[79]

Ayurvedic medicine considers Aloe as a restorative tonic herb. Traditionally, Aloe is used to clear heat, and to soothe and promote the healing of inflamed tissues and membranes. It is well-known for its ability to calm the pain, redness, and heat of sunburn and help restore healthy skin tissue. In the same way, Aloe is used to calm inflammation and soothe inflamed tissues of the gastrointestinal tract, especially the esophagus and stomach. It is found to benefit esophagitis, and acute and chronic gastric ulcers.[80-82]

Aloe is found to calm GERD symptoms including heartburn and food regurgitation. It is known to enhance wound healing and is also found to be beneficial for oral health care as a mouthwash.[82-85] Aloe gel is found to exert antibacterial, antiviral, antiseptic, antifungal, antioxidant, anti-inflammatory, and immunomodulatory activity.[82,83] Aloe is also found to deter *H.pylori*.[82]

High in chlorophyll, Aloe exerts a soothing, alkalinizing influence on the stomach and helps normalize stomach pH.[89,90] It is found to be beneficial for GI disorders and to enhance immune function.[82] Most research is done on the gel inside the leaves where over 200 biologically active substances are found.[82] Aloe gel is rich in polysaccharides. It also contains water- and fat-soluble vitamins along with minerals, enzymes, amino acids, enzymes, phenolic compounds, and organic acids. [82]

The gel polysaccharides are high in mannose along with some glucose. These compounds are referred to as "polymannans." Acemannan is a widely researched polymannan and is considered the primary polysaccharide in the inner leaf. It is found to enhance cellular immunity and to facilitate the humoral immune response.[82;86-88] However, the many benefits of Aloe leaf extracts are considered to be the result of the combined action of all its components.[82]

Ginger Root (*Zingiber officinale*)

Ginger root is renowned as a digestive tonic throughout the world. It has been used as a cooking spice, herbal home remedy, and revered medicine for centuries. It is a valued household remedy for digestive upset, sore throat, colds, and flu. It is known to alleviate infection, reduce pain and fever, and exert a mild sedative influence.[91,102]

Ginger Root *(Zingiber officinale)*

The American Eclectic and Physiomedical physicians used Ginger root as a stimulating tonic, stomachic, carminative, and antispasmodic. They found it useful for nausea, GI cramping, and loss of appetite.[92,93] Studies find that Ginger enhances gastric emptying in both healthy volunteers and in those with dyspepsia.[94,95]

Research finds that Ginger root is helpful to alleviate many types of nausea.[96,97] Ginger is found to be gastroprotective and to benefit stress-induced IBS.[21,98,99] Ginger's active ingredients include its many volatile oils.[99-102] It demonstrates powerful antioxidant and anti-inflammatory activity.[103-105]

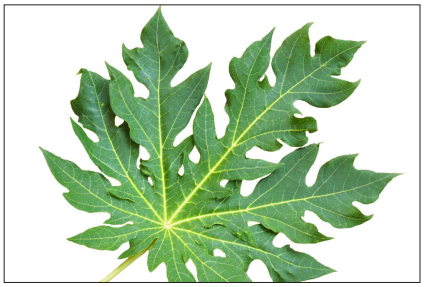
Lemon Balm Leaf (*Melissa officinalis*)

Lemon Balm, a member of the Mint family, easily grows in the garden. As a calmative, it is combined with other herbs to help calm anxiety, soothe the nervous system, and help promote sleep. Lemon Balm is traditionally used to calm nervous digestive disorders and to ease indigestion. It is often used to calm colic, irritable bowel disease, and gastritis.[108-111]

Lemon Balm is a mild, relaxing antispasmodic. It is rich in phenolic acids, especially rosmarinic acid, which is known to calm smooth muscle spasms. Lemon Balm is found to exert antioxidant, anti-inflammatory, and antiviral activity.[106-109] Studies find Lemon Balm to be calming while also increasing alertness and improving mood and cognition.[110,111]

Papaya Leaf (*Carica papaya*)

Papaya is best known for its delicious fruit that is enjoyed in the tropical and subtropical regions where it grows. Papaya leaf is traditionally used to treat indigestion and abdominal disorders. It is used for dyspepsia, hyperacidity, bloating, nausea, and flatulence.[112,113]



Papaya Leaf *(Carica papaya)*

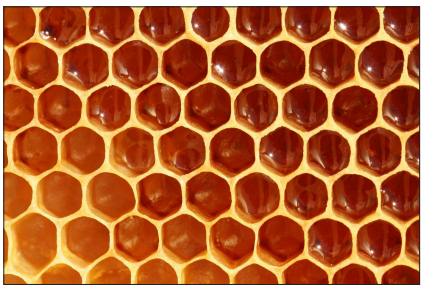
Papaya leaves contain papain, flavonoids, ascorbic acid, and other components with notable antioxidative activity. The enzyme papain is found in the Papaya bark, leaves, and fruit.[112-115] Studies find that Papaya leaf benefits those with gastric ulcers.[113] It is also found helpful in treating oral gingivitis.[116]

Mastic Gum (*Pistacia lentiscus*)
Mastic gum is the exudate of the Mastic tree (*Pistacia lentiscus*), which is native to the Greek Island of Chios in the Aegean Sea. Mastic has been used in the Mediterranean region to treat gastrointestinal disorders for several thousand years.[117,118] Mastic gum was prized by the Egyptians and Arabs for medicinal use. A shipwreck from the Bronze age was discovered in 1982 with a cargo of 100 jars of Mastic gum. The 13th century Arab physician Ibn Al-Baytar used Mastic gum to treat upper abdominal pain, heartburn, gastric ulcers, and intestinal ulcers.[22,117,118]

Studies report that Mastic is beneficial as a treatment for duodenal ulcers.[119,120] It is found to exert antibacterial activity and to be highly effective against *H. pylori* both *in vivo* and *in vitro*.[22,24,25,121-123] Mastic gum is also found to reduce harmful oral bacteria. It is often included in oral care products to help prevent periodontitis and gingivitis.[124]

Botanical Extracts/Compounds

Bee Propolis
The powerful medicinal properties of propolis were well-known by the ancient Greeks, Persians, Romans, and Egyptians. The Greek word propolis means defender of the city. These ancients valued the waxy resin as a powerful antiseptic to enhance wound healing. Propolis is made by bees from plant material they collect and use as a sealant to protect the hive.


Bee Propolis

The color and chemical composition of propolis varies widely with geographical location, botanical species, and even by the bee species itself. Crude propolis contains around 50% resin, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% other organic materials, such as wood fragments. Over 300 compounds have been found in propolis including flavonoids, aldehydes, amino acids, ketones, fatty acids, and vitamins. The flavonoids are among the most researched compounds.[125,126] The main flavonoid constituents include quercetin, baicalin, and chrysin.[125,126]

In modern times, propolis is recognized to offer powerful antimicrobial, anti-inflammatory, and immunomodulatory influence.[127] Propolis has a regenerative influence on tissues with wound-healing capacity. Studies find it beneficial for skin healing where it supports re-epithelization.[128,129] Propolis is found to help prevent canker sores and to speed healing of the ulcers. Because of its antimicrobial action, propolis is used in a mouth spray or mouthwash to encourage tissue healing after gum surgery or other dental work. In dentistry, propolis is found effective as an antibacterial to help address gingivitis and mouth ulcers.[130] It delays the growth and progression of skin changes in *Herpes simplex*. Propolis is found to benefit oral health in periodontal treatment as it helps prevent loss of alveolar process bone.[131,132]

Mucositis is a serious acute complication of radiotherapy that can cause oral mucosa ulceration. This induces severe pain and discomfort and can affect normal oral function. Propolis, rich in flavonoids, exerts antiulcer, antibacterial, antifungal, healing, and anti-inflammatory influence. A study with a water-based propolis extract found it to prevent and heal radiotherapy-induced mucositis.[133-135]

The polyphenol CAPE (caffeic acid phenethyl ester) is a bioactive compound found in propolis that demonstrates antimicrobial, antioxidant, anti-inflammatory, and cytoxic properties. It also exerts antiseptic, antibacterial, antifungal, astringent, and antiulcer qualities. Studies find that both propolis and CAPE inhibit the growth of *H. pylori*.[136-141]

Manuka Honey

Manuka is a unique, dark honey that is widely used and studied for its efficacy in wound healing.[26] The honey is derived from the Manuka tree, Leptospermum scoparium. The Manuka tree belongs to the family Myrtaceae in New Zealand and the Eastern region of Australia.

Manuka honey is found to be gastroprotective.[142,143] It is rich in methylgloyoxal (MGO), a compound formed in Manuka flower nectar and transferred into the honey by bees. This compound, unique to Manuka honey, is found protective against gastric damage in rats exposed to caustic agents.[144] In animal studies, it is noted to significantly promote healing from gastric ulcer lesions and to preserve gastric mucosal glycoprotein.[145]

Rich in flavonoids, Manuka honey exerts potent anti-inflammatory, antimicrobial, and antioxidant activity. Manuka is antimicrobial against a wide range of organisms including some antibiotic-resistant strains.[142,143,146] Manuka honey is found to help prevent gastric ulcer formation.[147,148] This is attributed to the actions noted above. It is also found beneficial to alleviate mucositis.[145,149]

D-Limonene from Orange Peel Oil

The monocyclic monoterpene D-limonene is noted for its lemony odor. It is a major constituent of the citrus family, including oranges, lemons, mandarins, and limes. Limonene demonstrates significant anti-inflammatory activity in vivo and in vitro.[150] It is found to calm inflammation in the intestinal walls.[150] An in vitro study finds that it coats the stomach wall and is protective of the stomach lining from gastric acid exposure. It is also known to exert a protective influence on epithelial tissues.[150-152]

Orange Peel

Limonene helps calm gastric acid, relieves heartburn, and supports healthy peristalsis.[151-154] It can dissolve cholesterol and is clinically used to help dissolve cholesterol-containing gallstones.[151-154] In clinical studies, D-limonene is found to significantly decrease symptoms of GERD and chronic heartburn. Some participants experienced complete relief.[155]

Sodium Alginate

Sodium alginate offers a unique protective action to the stomach and GI. Alginate-based, raft forming formulations have been used for over 30 years for their ability to offer relief from reflux.[156-161] Alginates are long-chain carbohydrates that naturally occur in brown seaweeds. Alginate naturally precipitates to form a thick gel when it contacts stomach acids and liquids. This thick gel expands to become a floating foam that sits in the stomach like a raft, forming a protective, pH-neutral barrier that absorbs excess acid.[156-160;162] This also protects the sensitive esophageal tissues because the gel foam prevents the stomach's contents from backing up into the esophagus.[156-159;162]

Because of their unique actions, alginates offer relief that is rapid, often within a few seconds; and long-lasting – usually for several hours.[156-160] Alginate-based formulations are used to relieve reflux symptoms in adults, children, and during pregnancy.[162]

Alginate contains D-mannuroic and L-glucuronic acids.[163] Alginate, a natural polymer, is used in many applications to support wound healing and is known for its excellent biocompatibility. It is also well-known for its ability to form hydrogel films, which are natural polymer networks that are used for both wound healing and drug delivery systems. Hydrogels are known for their ability to maintain their structure and provide a moist, protective environment in which wounds can heal well.[160,163]

Alginate and Aloe vera are used together to produce hydrogels to enhance wound healing.[163] Sodium alginate is found to help eradicate of *H. pylori* when combined with drug therapy.[157,159,164] Sodium alginate alleviates the pain of oral mucositis and reduces oral mucosa erosion due to radiotherapy.[165]

Researchers studied a compound containing sodium bicarbonate, alginate, Aloe gel, Propolis, and several herbs. Their clinical study lasted over six months. They found this combination effectively decreased incidence and symptoms of GERD and supported healing of mucosal lesions in the pharynx and esophagus.[161]

Nutritional Compounds

Potassium Bicarbonate
Potassium, an electrolyte, is essential for healthy muscular and digestive function. The bicarbonate form of potassium is found equal to or significantly better than antacids traditionally used to relieve heartburn symptoms. It is often combined with sodium alginate formulations to relieve heartburn and acid reflux. Bicarbonate has a very high buffering capacity.[166-169]

Zinc Carnosine
Bound together in equal proportions, zinc and carnosine form a unique ingredient that is found to benefit the gastric lining. It consists of a zinc ion, L-carnosine, a beta-alanine dipeptide, and L-histidine.[170] In vivo studies show this compound exerts a protective influence on the gastric mucosa and in the small intestine. It was also found to promote gut mucosal integrity and repair. Studies suggest its potential in preventing increased gut permeability.[171]

Zinc carnosine, considered an antiulcer compound, is found beneficial for gastric ulcers.[172] Zinc carnosine possesses antioxidant action, which contributes to its gastric protective effect.[173,174] Carnosine, a dipeptide with beta-alanine and L-histidine, is found in long-lived cells including muscle and nerve cells. It functions as an antioxidant.[171]

Zinc, a non-toxic, biologically-essential trace mineral, is vital for almost all physiological processes. The only metal that is a coenzyme to all classes of enzymes, zinc is a key component of over 300 metalloenzymes. Zinc is essential for over 2000 transcription factors involved with gene transcription and regulation of lipid, protein, and nucleic acid metabolism.[175-178]

Necessary to maintain the structural integrity of DNA, zinc also plays a role in cellular metabolism, immune function, wound healing, and acts as a messenger in signal transduction. Because of the far-reaching influence of zinc, even mild zinc deficiency is deleterious to numerous biochemical and immunological functions.[179]

Serum zinc status is indicative of gastric membrane protection from damage by *H. pylori*.[173] A meta-analysis of 19 studies involving an estimated 400,000 participants found zinc intake levels to be inversely associated with digestive tract cancers, especially colorectal cancer.[180]

Zinc is found to enhance gastrointestinal epithelial barrier function and is protective of mucosal cells.[151] Zinc supplementation is found to benefit the treatment of oral mucosal diseases.[181,182]

Glutamine

Glutamine

Glutamine, though not an essential amino acid, is the most abundant amino acid in the blood. Levels of glutamine markedly decline during periods of stress, injury, illness, trauma, and during radiation therapy. Since glutamine becomes essential during these times, it is considered conditionally essential.[183] Glutamine supplementation is found to enhance immune function. It reduces the rate of infection and degree of inflammation. It regulates intestinal barrier function and health and is protective of the intestinal mucosa.[184-186] Dysfunction of the intestinal mucosal barrier is associated with gut permeability and progression of multiple gastrointestinal diseases. Glutamine is found to promote intestinal mucosal cell differentiation and proliferation.[187-193]

Glutamine is utilized as a source of energy and for nucleotide synthesis by rapidly dividing cells, such as those of the intestinal lining and certain immune cells (thymocytes, lymphocytes, and macrophages). Glutamine supports intestinal function and is found to enhance healing from gastric and peptic ulcers. It is a vital nutrient used by both the intestinal immune cells (the lymphocyte-rich Peyer's patches) and mucosal cells.[183]

Glutamine exerts immunomodulatory activity. It demonstrates antioxidant activity and is a precursor amino acid for the production of glutathione.[192,193] Glutamine is also found to relieve radiation-induced oral mucositis.[194-197]

Conclusion

Our health is as an ongoing, dynamic process that creates ongoing stability (homeostasis) through allostatic processes. Our resilience and robustness depends on our ability to adapt and evolve with our constantly changing environment. The integrity of the GI tract influences the health of the whole system. The epithelial lining of the gut, which extends from the lower esophageal sphincter to the anus, plays a key role in physiological homeostasis. These epithelial tissues provide a dynamic interface for a vast communication network and play key roles in the gut-brain axis, ENS (enteric nervous system), immune response, and neuroendocrine system. Any disruption in tissue integrity impedes this vital, ongoing flow of information

and signaling that mediates and modulates multiple functions.

Since GI tissues are prone to inflammation, a thorough therapeutic approach focuses on both calming inflammatory processes and on supporting the integrity of the gut tissues themselves. These two therapeutic keys go hand-in-hand. Because inflammation causes damages to the tissues, normalizing those processes will relieve inflammatory stress on the gut lining. At the same time, compounds to promote the restorative process in the epithelial and mucosal gut lining are essential. Botanical and nutritional compounds offer

About the Authors

Donald R. Yance Jr., RH (AHG), CN

Donald R. Yance Jr., RH (AHG), CN, is a practicing Clinical Master Herbalist, Certified Nutritionist and the author of two books including his latest *Adaptogens in Medical Herbalism* (Healing Arts Press, 2013). Providing visionary leadership in the field of natural medicine, Yance has maintained a successful clinical practice for over two decades and trains practitioners worldwide in his therapeutic methodology for patient care. He is the founder and formulator of Natura Health Products, a line of botanical and nutritional formulas, which are based on key principles of Yance's Eclectic Triphasic Medical System.

Suzanne E. Sky, L.Ac., MTOM

Suzanne E. Sky, L.Ac., MTOM has been a Chinese medicine practitioner since 1989 and involved with herbs, nutrition and the healing arts since the mid-70s. She worked with Donald Yance as clinical associate for five years until 2004 and since then often as a writing associate.

With Chinese medicine as her framework, Suzanne integrates herbal, nutritional and lifestyle recommendations along with gentle energy work (Jin Shin Jyutsu) or acupuncture. Blending ancient Chinese wisdom with modern knowledge, her work focuses on supporting and nourishing each person's innate healing and regenerative capacity. Her clinic, Ashland Acupuncture, is located in Ashland, Oregon. She teaches Qi Gong and Chinese medicine classes.

References

Intro

1. Peery AF, Dellon ES, et al. *Burden of Gastrointestinal Disease in the United States: 2012 Update*. Gastroenterology. 2012 November. 143(5):1179-1187.e3 doi:10.1053/j.gastro.2012.08.002

2. Scrivo R, Vasile M, et al. *Inflammation as the "common soil" of the multifactorial diseases*. Autoimmune Rev. 2011 May. 10(7):369-374. doi: 10.1016/j.autrev.2010.12.006

3. Pohl D, Fox M, et al. *Do We Need Gastric Acid? Review*. Digestion 2008. 77:184-197. doi.org/10.1159/00142726

4. Mayer E. *The Mind-Gut Connection: How the Hidden Conversation Within Our bodies Impacts Our Mood, Our Choices, and Our Overall Health*. 2016. Harper Collins.

5. Kahrilas PJ. *Gastroesophageal Reflux Disease*. NEJM. 2008 October 16. 359(16):1700-1707.

6. Patrick K. *Gastroesophageal Reflux Disease (GERD): A Review of Conventional and Alternative Treatments*. Altern Med Rev. 2011. 16(2):116-133.

7. *Heartburn and GERD: Overview*. 2015 November 18. PubMed Health. Informed Health Online. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072438/

8. Fox M, Forgacs I. *Gastro-oesophageal reflux disease. Clinical review*. BMJ. 2006 January 14. 332:88-93.

9. Hershcovici T, Fass R. *Pharmacological management of GERD: where does it stand now?* Trends in pharmacological sciences. 2011 April. 32 (4): 258-264.

Stomach

10. Di Mario F, Goni Elisabetta. *Gastric acid secretion: changes during a century*. Best Practice and Research in Clinical Gastroenterology. 2014 October. doi:10.1016/j.bpg.2014.10.006

11. Hunt RH, Camilleri M, et al. *The stomach in health and disease*. Gut. 2015 October. 64(10):1650-1668. doi:10.1136/gutjnl-2014-307595.

12. Banoo H, Nusrat N. *Implications of low stomach acid: an update. Review Article*. RAMA Univ J Med Sci. 2016. 2(2):16-26.

13. Kelly GS. *Hydrochloric acid: physiological functions and clinical implications*. Alt Med Rev. 1997. 2(2):116-127.

14. Pearsons. Chapter 21: The Digestive System

https://www.pearson.com/content/dam/one-dot-com/one-dot-com/us/en/higher-ed/en/products-services/silverthorn-7e-info/pdf/sample-chapter--ch21.pdf

15. Mayo clinic online. http://www.mayoclinic.org/diseases-conditions/peptic-ulcer/home/ovc-20231363

16. Kusters JG, van Vliet AHM, Kuipers EJ. *Pathogenesis of Helicobacter pylori infection*. Clin Microbiol Rev. 2006 July. 19(3):449-490.

17. Champagne ET. *Low gastric hydrochloric acid secretion and mineral bioavailability*. Adv Exp Med Biol. 1989. 249:173-184.

18. Cater RE. *The clinical importance of hypochlorhydria (a consequence of chronic Helicobacter infection): its possible etiological role in mineral and amino acid malabsorption, depression, and other syndromes*. Med Hypotheses. 1992 Dec. 39(4):375-383.

19. Ye W, Held M, et al. *Helicobacter pylori infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia*. J National Cancer Institute. 2004 March 3. 96(5):388-396.

20. Rokkas T, Pistiola D, et al. *Relationship between Helicobacter pylori infection and esophageal neoplasia: a meta-analysis*. Clin Gastroenerol Hepatol. 2007 Dec. 5(12):1413-1417.

Herbs that Inhibit Hp

21. Siddaraju MN, Annaiah HN, Shylaja MD. *Gastroprotective Effect of Ginger Rhizome (Zingiber officinale) Extract: Role of Gallic Acid and Cinnamic Acid in H+, K+-ATPase/H. pylori Inhibition and Anti-oxidative Mechanism*. Evid Based Complement Alternat Med. 2009.6:1-13.

22. Dabos KJ , Sfika E, et al. *The effect of mastic gum on Helicobacter pylori: a randomized pilot study*. Phytomedicine. 2010 Mar. 17(3-4):296-299. doi: 10.1016/j.phymed.2009.09.010.

23. Paraschos S, Magiatis P, et al. *In Vitro and In Vivo Activities of Chios Mastic Gum Extracts and Constituents against Helicobacter pylori*. Antimicrob Agents Chemother. 2007. 51:551.

24. Miyamoto T, Okimoto T, Kuwano M. *Chemical Composition of the Essential Oil of Mastic Gum and their Antibacterial Activity Against Drug-Resistant Helicobacter pylori*. Nat Prod Bioprospect. 2014 Aug. 4(4):227-231. doi: 10.1007/s13659-014-0033-3.

25. Maron P, Bono L, et al. *Bactericidal Activity of Pictacia lentiscus Mastic Gum against Helicobacter pylori*. J. Chemother. 2001. 13:611-614.

26. Osato MS, Reddy SG, Graham DY. *Osmotic effect of honey on growth and viability of Helicobacter pylori*. Dig Dis Sci.1999. 44:462-464.

27. Krausse R, Bielenberg J, et al. *In vitro anti-Helicobacter*

pylori activity of Extractum liquiritiae, glycyrrhizin and its metabolites. J Antimicrob Chemother. 2004. 54(1):243-246.

28. Beth Israel Deaconess Medical Center. *Glutamine Supplements Show Promise In Treating Stomach Ulcers*. ScienceDaily. 2009 May 22. Retrieved February 7, 2010, from http://www.sciencedaily.com/releases/2009/05/090515104223.htm#

Intestinal Permeability

29. Arrieta MC, Bistritz L, Meddings JB. *Alterations in Intestinal Permeability*. Gut. 2006. 55:1512-1520. doi: 10.1136/gut.2005.085373

30. Bischoff SC, Barbara G, et al. *Intestinal permeability – a new target for disease prevention and therapy*. BMC Gastroenterology. 2014. 14:25 pages

31. Turner JR. *Molecular Basis of Epithelial Barrier Regulation: from basic mechanisms to clinical application*. Amgen Award Lecture. Am J Pathology. 2006 December. 169(6):1901-1909.

32. Ardizzone S, Bianchi Porro G. *Biologic therapy for inflammatory bowel disease*. Drugs. 2005. 65(16):2253-2286.

33. Michielan A, D'Inca R. *Intestinal permeability in inflammatory bowel disease: pathogenesis, clinical evaluation, and therapy of leaky gut. Review Article*. Hindawi Publishing Corporation. Mediators of Inflammation. 2015. Article ID 628157. 10 pages.

34. Kelly Jr, Kennedy PJ, et al. *Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders*. Frontiers in Cellular Neuroscience. 2015 October 14. 9:Artcle 302

35. Ahmad R, Sorrell MF, et al. *Gut permeability and mucosal inflammation: bad, good or context dependent*. Mucosal Immunology. 2017 March. 10:307-317

36. Rea K, Dinan TG, Cryan JF. *The microbiome: A key regulator of stress and neuroinflammation*. Neurobiology of Stress. 2016. 4:23-33.

37. Carabotti M, Scirocco A, et al. *The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Review*. Annals of Gastroenterology. 2015. 28:203-209.

38. Sarkar A, Lehto SM, *Psychobiotics and the manipulation of bacteria-gut-brain signals. Review*. Trends in Neurosciences. 2016 November. 39(11):763-781.

39. Foster JA, Rinaman L, Cryan JF. *Stress & the gut-brain axis: Regulation by the microbiome*. Neurobiology of Stress. 2017. 1-13.

40. Grenham S, Clarke G, et al. *Brain-gut-microbe communication in health and disease*. Frontiers in Physiology. 2011 December. 2(Article 94):1-15.

41. Wang Y, Kasper LH. *The role of microbiome in central nervous system disorders*. Brain Behav Immun. 2014 May. 38:1-12.

42. Yadav H, Jain S, et al. *Gut microbiome derived metabolites to regulate energy homeostasis: how microbiome talks to host.* Metabolomics. 2016. 6(2):2pages.

43. Stecher B. *The roles of inflammation, nutrient availability and the commensal microbiota in enteric pathogen infection*. Microbial Spectrum. 2014. 3(3):MBP-000i.

44. Blum S, Schiffrin EJ. *Intestinal microflora and homeostasis of the mucosal immune response: implications for probiotic bacteria?* Curr Issues Intest Microbiol. 2003 September. 4(4):53-60.

ENS, Microbiome & Digestive Homeostasis

45. Trautmann SM, Sharkey KA. *The Endocannabinoid System and Its Role in Regulating the Intrinsic Neural Circuitry of the Gastrointestinal Trac*t. Chapter Three. International Review of Neurobiology. 2015. Elsevier Inc. 125:85-126.

46. Hansen MB. *The Enteric Nervous System I: Organisation and Classification*. Pharmacology & Toxicology. 2003. 93:105-113.

47. Goyal RK, Hirano I. *The Enteric Nervous System. Review Article*. NEJM. 1996 April 25. 334:1106-1115.

48. Furness JB, Callaghan BP, et al. *The enteric nervous system and gastrointestinal innervation: integrated local and central control*. Adv Exp Med Biol. 2014. 817:39-71. doi: 10.1007/978-1-4939-0897-3_3

Herbs for Digestive Health

49. Stroeve JHM, van Wietmarschen H, et al. *Phenotypic flexibility as a measure of health: the optimal nutritional stress response test*. Genes Nutr. 2015. 10:13. 21 pages.

50. Chan S. *Complex Adaptive Systems*. 2001. ESD.83 Research Seminar in Engineering Systems.

51. Kruse K, Julicher F. *Oscillations in cell biology*. Current Opinion in Cell Biology. 20015 17:20-26. doi:10.1016/j.ceb.2004.12.007

52. McEwen BS, Wingfield JC. *The concept of allostasis in biology and biomedicine*. Horm Behav. 2003 Jan. 43(1):2-15.

53. Fahey JW, Talalay P, Kensler TW. *Notes from the field: "green" chemoprevention as frugal medicine*. Cancer Prev Res. 2012; 5(2):179-188. 49.

54. Liu H, Dinkova-Kostova AT, Talalay P. *Coordinate regulation of enzyme markers for inflammation and for protection against oxidants and electrophiles*. Proc Natl Acad Sci USA. 2008; 105(41):15926-15931.

55. Fahey JW, Stephenson KK, Wallace AJ. *Dietary amelioration of Helicobacter infection*. Nutr Res. 2015 Jun. 35(6):461-473. doi: 10.1016/j.nutres.2015.03.001. Epub 2015 Mar 6.

Licorice

56. Herold A, Cremer L, et al. *Hydroalcoholic plant extracts with anti-inflammatory activity*. Roum Arch Microbiol Immunol. 2003 Jan-Jun. 62(1-2):117-129.

57. Kwon HM, Choi YJ, et al. *Blockade of Cytokine-Induced Endothelial Cell Adhesion Molecule Expression by Licorice Isoliquiritigenin Through NF-{kappa}B Signal Disruption*. Exp Biol Med (Maywood). 2007 Feb. 232(2):235-245.

58. Khan R, Khan AQ, Lateef A. *Glycyrrhizic acid suppresses the development of precancerous lesions via regulating the hyperproliferation, inflammation, angiogenesis and apoptosis in the colon of Wistar rats, PLoS One*. 2013. 8(2):e56020. doi: 10.1371/journal.pone.0056020. Epub 2013 Feb 14.

59. Shibata S. *A drug over the millennia: pharmacognosy, chemistry, and pharmacology of lic*orice. Yakugaku Zasshi 2000 Oct;120(10):849-862 (ISSN: 0031-6903) Actual study-http://www.ncbi.nlm.nih.gov/pubmed/11082698

60. Xing GX, Li N, et al. *Advances in studies on flavonoids of licorice*, Zhongguo Zhong Yao Za Zhi. 2003 Jul 28. (7):593-597. Review. Chinese.

61. Hatano T, Aga Y, et al. *Minor flavonoids from licorice*. Phytochemistry 2000 Dec. 55(8):959-963 (ISSN: 0031-9422)

62. Fukai T, Marumo A, et al. *Antimicrobial activity of licorice flavonoids against methicillin-resistant Staphylococcus aureus*. Fitoterapia 2002 Oct. 73(6):536 (ISSN: 0367-326X)

63. Song NR, Kim JE, et al. *Licochalcone A, a Polyphenol Present in Licorice, Suppresses UV-Induced COX-2 Expression by Targeting PI3K, MEK1, and B-Raf*. Int J Mol Sci. 2015 Feb. 20:16(3):4453-4470. doi: 10.3390/ijms16034453.

64. Tanaka Y, Kikuzaki H, Fukuda S. *Antibacterial compounds of licorice against upper airway respiratory tract pathogens*. J Nutr Sci Vitaminol (Tokyo) 2001 Jun. 47(3):270-273. (ISSN: 0301-4800).

65. Messier C, Epifano F, et al. *Licorice and its potential beneficial effects in common oro-dental diseases*. Oral Dis. 2012. 18(1):32-39.

66. Ahn SJ, Cho EJ, et al. *The antimicrobial effects of deglycyrrhizinated licorice root extract on Streptococcus mutans UA159 in both planktonic and biofilm cultures*. Anaerobe. 2012 Dec. 18(6):590-596. doi: 10.1016/j.anaerobe.2012.10.005. Epub 2012 Oct 30.

67. Das SK, Das V. *Deglycyrrhizinated liquorice in aphthous ulcers*. J Assoc Physicians India. 1989 Oct. 37(10):647.

68. Dehpour AR, Zolfaghari ME, et al. *The protective effect of liquorice components and their derivatives against gastric ulcer induced by aspirin in rats*. J Pharm Pharmacol. 1994 Feb. 46(2):148-149.

69. Russell RI, Morgan RJ, Nelson LM. *Studies on the protective effect of deglycyrrhinised liquorice against aspirin (ASA) and ASA plus bile acid-induced gastric mucosal damage, and ASA absorption in rats*. Scand J Gastroenterol Suppl. 1984. 92:97-100.

Marshmallow Root

70. Deters A, Zippel J, et al. *Aqueous extracts and polysaccharides from Marshmallow roots (Althea officinalis L.): cellular internalisation and stimulation of cell physiology of human epithelial cells in vitro*. J Ethnopharmacol. 2010 Jan 8. 127(1):62-69. doi: 10.1016/j.jep.2009.09.050. Epub 2009 Sep 30.

71. Hage-Sleiman R, Mroueh M, Daher CF. *Pharmacological evaluation of aqueous extract of Althaea officinalis flower grown in Lebanon*. Pharm Biol. 2011 Mar. 49(3):327-333. doi: 10.3109/13880209.2010.516754. Epub 2011 Feb 1.

72. Zaghlool SS, Shehata BA, et al. *Protective effects of ginger and marshmallow extracts on indomethacin-induced peptic ulcer in rats*. J Nat Sci Biol Med. 2015 Jul-Dec. 6(2):421-428. doi: 10.4103/0976-9668.160026.

Chamomile

73. Singh O, Khanam Z, et al. *Chamomile (Matricaria chamomilla L.): An overview*. Pharmacogn Rev. 2011 Jan-Jun. 5(9): 82-95. doi: 10.4103/0973-7847.79103

74. Gardiner P. *Complementary, holistic, and integrative medicine: chamomile*. Pediatr Rev. 2007 Apr. 28(4):e16-18.

75. Mao JJ, Xie SX, et al. *Long-term chamomile (Matricaria chamomilla L.) treatment for generalized anxiety disorder: A randomized clinical trial*. Phytomedicine. 2016 Dec 15. 23(14):1735-1742. doi: 10.1016/j.phymed.2016.10.012.

76. Jabri MA, Aissani N, et al. *Protective effect of chamomile (Matricaria recutita L.) decoction extract against alcohol-induced injury in rat gastric mucosa*. Pathophysiology. 2016 Dec 21. pii: S0928-4680(16)30047-5. doi: 10.1016/j.pathophys.2016.11.001.

77. Viola H, Wasowski C, et al. *Apigenin, a component of Matricaria recutita flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects*. Planta Med. 1995. 61:213-216.

78. Amsterdam JD, Li Y, et al. *A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract therapy for generalized anxiety disorder*. J Clin Psychopharmacol. 2009 Aug. 29(4):378-382. doi: 10.1097/JCP.0b013e3181ac935c.

Aloe Vera Gel

79. Park YI, Lee SK (ed). *New perspectives on Aloe*. 2006. Springer. New York. p204.

80. Subramanian S. Kumar DS, et al. *Evaluation of anti-ulcerogenic potential of Aloe vera leaf gel extract studied in experimental rats*. J. Pharmacol. Toxicol. 2007. 2, 85-97.

81. Avijgan M, Kamran A, Abedini A. *Effectiveness of Aloe Vera Gel in Chronic Ulcers in Comparison with Conventional Treatments*. Iran J Med Sci. 2016 May. 41(3):S30.

82. Radha MH, Laxmipriya NP. *Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review*. J Traditional and Complementary Medicine. 2015. 5:21-26.

83. Ulbricht C, Armstrong J, et al. *An evidence-based systematic review of Aloe vera by the natural standard research collaboration*. J Herb Pharmacother. 2007. 7:279-323.

84. Jain S, Rathod N, et al. *Antibacterial Effect of Aloe Vera Gel against Oral Pathogens: An In-vitro Study.* J Clin Diagn Res. 2016 Nov. 10(11):ZC41-ZC44. doi: 10.7860/JCDR/2016/21450.8890.

85. Nair GR, Naidu GS, et al. *Clinical Effectiveness of Aloe Vera in the Management of Oral Mucosal Diseases A Systematic Review*. J Clin Diagn Res. 2016 Aug. 10(8):ZE017. doi:10.7860/JCDR/2016/18142.8222. Epub 2016 Aug 1.

86. Vogler B.K, Ernst E. *Aloe vera: A systematic review of its clinical effectiveness*. Br. J. Gen. Pract. 1999. 49:823-828.

87. Boudreau MD, Beland FA. *An evaluation of the biological and toxicological properties of Aloe barbadesis (Miller)Aloe vera*. J. Environ. Sci. Health. 2006. 24:103-154

88. Hamman JH. *Composition and applications of Aloe vera Leaf gel*. Molecules. 2008.13:1599-1616.

89. Sinnott RA, et.al. *Utilization of Arabinogalactan, Aloe vera Gel Polysaccharides, and a Mixed Saccharide Dietary Supplement by Human Colonic Bacteria In Vitro*. Int J Probiotics and Prebiotics. 2007. 2(3): 97-104.

90. Panahi Y, Khedmat H, et al. *Efficacy and safety of Aloe vera syrup for the treatment of gastroesophageal reflux disease: a pilot randomized positive-controlled trial*. J Tradit Chin Med. 2015 Dec. 35(6):632-636.

Ginger Rhizome

91. Kalra M, Khatak M, Khatak S. *Cold and flu: conventional vs botanical & nutritional therapy*. Int J Drug Dev & Res. 2011 Jan-Mar. 3(1):314-327.

92. Lyle TJ. *Physio-medical therapeutics, materia medica and pharmacy*. 1897. p343.

93. Valussi M. *Functional foods with digestion-enhancing properties.* Int J Food Sci Nutr. 2012 Mar. 63 (Suppl 1)82-89. doi: 10.3109/09637486.2011.627841. Review.

94. Hu ML, Rayner CK, et al. Effect of ginger on gastric motility and symptoms of functional dyspepsia. World J Gastroenterol. 2011 Jan 7. 17:105-110. doi: 10.3748/wjg.v17il.105

95. Wu KL, Rayner CK, et al. Effects of ginger on gastric emptying and motility in healthy humans. Gastroenterol Hepatol. 2008 May. 20(5):436-440.

96. Sharma SS, Kochupillai V, et al. *Antiemetic efficacy of ginger (Zingiber officinale) against cisplatin- induced emesis in dogs.* J Ethnopharmacol 1997. 57:93-96.

97. Pecoraro A, Patel J, et al. *Efficacy of ginger as an adjunctive anti-emetic in acute chemotherapy-induced nausea and vomiting*. ASHP Midyear Clinical Meeting. 1998. 33:P-429E.

98. Banji D, Banji OJ, et al. *Zingerone regulates intestinal transit, attenuates behavioral and oxidative perturbations in irritable bowel disorder in rat*s. Phytomedicine. 2014 Mar 15. 21(4):423-429. doi: 10.1016/j.phymed.2013.10.007

99. Kumar A, Rao ChV, et al. *Anti-ulcerogenic and ulcer healing effects of Zingiber officinale (L.) On experimental ulcer models: Possible mechanism for the inhibition of acid formation*. Int J Pharm Res. 2010. 1:75–85.

100. Connell D, Sutherland M. *A re-examination of gingerol, shogaol and zingerone, the pungent principles of Ginger (Zingiber officinale Roscoe).* Aust J Chem. 1969. 22:1033-1043.

101. Yoshikawa M, Hatakeyama S. *Qualitative and quantitative analysis of bioactive principles in Zingiberis Rhizoma by means of high performance liquid chromatography and gas liquid chromatography. On the evaluation of Zingiberis Rhizoma and chemical change of constituents during Zingiberis Rhizoma processing*. Yakugaku Zasshi. 1993. 113:307-315.

102. Connell D. *The chemistry of the essential oil and oleoresin of ginger (Zingiber officinale Roscoe*). Flavour Industry. 1970. 1:677-693.

103. Sujatha R, Srinivas L. *Modulation of lipid peroxidation by dietary componenets*. Toxicology in vitro. 1995. 9:231-236.

104. Zhou Y, Xu R. *Antioxidative effect of Chinese drugs*. Chung Kuo Chung Yao Tsa Chih 1992. 17:368-369, 373. inside backcover.

105. Cao ZF, Chen ZG, et al. *Scavenging effects of ginger on superoxide anion and hydroxyl radical.* Zhongguo Zhong Yao Za Zhi. 1993. Dec. 18(12):750-751, 764.

Lemon Balm

106. *Monograph: Lemon Balm*. Health Canada. 17 March 2008. Retrieved Feb. 1, 2017

107. Mazzanti G, Battinelli L, et al. *Inhibitory activity of Melissa officinalis L. extract on Herpes simplex virus type 2 replication*. Nat Prod Res. 2008. 22(16):1433-1440.

108. Zorić Z, Markić J, et al. *Stability of Rosmarinic Acid in Aqueous Extracts from Different Lamiaceae Species after in vitro Digestion with Human Gastrointestinal Enzymes*. Food Technol Biotechnol. 2016 Mar. 54(1):97-102.

109. Madisch A, Holtmann G, et al. *Treatment of functional dyspepsia with a herbal preparation. A double-blind, randomized, placebo-controlled, multicenter trial*. Digestion. 2004. 69(1):45-

52.

110. Kennedy DO, Little W, et al. *Anxiolytic effects of a combination of Melissa officinalis and Valeriana officinalis during laboratory induced stress*. Phytother Res. 2006. 20(2):96-102.

111. Akhondzadeh S, Noroozian M, et al. *Melissa officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomised, placebo controlled trial*. J Neurol Neurosurg Psychiatry. 2003. 74(7):863-366.

Papaya Leaf

112. Aravind G, Bhowmik D, et al. *Traditional and Medicinal Uses of Carica papaya.* J Medicinal Plants Studies. 2013. 1(1):7-15. ISSN: 2320-3862.

113. Otsuki N, Dang NH, et al. *Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects*. J Ethnopharmacol. 2010 Feb 17. 127(3):760-767. doi:10.1016/j.jep.2009.11.024. Epub 2009 Dec 2.

114. Seigler DS, Pauli GF, et al. *Cyanogenic allosides and glucosides from Passiflora edulis and Carica papaya*. Phytochemistry. 2002. 60:873-882.

115. Indran M, Mahmood AA, Kuppusamy UR. *Protective effect of Carica papaya L leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats*. West Indian Med J. 2008 Sep. 57(4):323-326.

116. Dejoie S, Boulmane R, et al. *Anti-inflammatory activity of a Carica papaya leaf extract used to prevent occasional gingivitis*. Planta Med. 2016 Dec. 81(S 01):S1-S381.

Mastic Gum

117. Thomas S, Stefanos D, et al. *Distribution, Development and Structure of Resin Ducts in Pistachia lentiscus var. chia Duhamel*. Flora. 2000. 195:83-94.

118. Riddle JM. History as a tool in identifying "new" old drugs. In Buslig B, Manthey J, eds. *Flavonoids in Cell Function.* pp 89-94. Kluwer/Academic/Plenum Publishers. New York. 2002.

119. Huwez FU, Al-Habbal MJ. *Mastic in Treatment of Benign Gastric Ulcers*. Gastroentrol (Japan). 1986. 21:273-274.

120. Al-Said MS, Ageel AM, et al. *Evaluation of Mastic, a Crude Drug obtained from Pistachio lentiscus for Gastric and Duodenal Anti-Ulcer Activity*. J. Ethnopharmacol. 1986. 15:271-278.

121. Paraschos S, Mitakou S, Skaltsounis AL. *Chios gum mastic: A review of its biological activities*. Curr Med Chem. 2012. 19(14):2292-2302. Review.

122. Mouhajir F, Hudson JB, et al. *Multiple antiviral activities of endemic medicinal plants used by Berber peoples of Morocco*. Pharmaceut Biol. 2001. 39(5):364-374.

123. Sharifi, MS, Vagg WJ, Hazell SL. *Characterization of mastic gum in relation to anti- Helicobacter pylori activity*. J. World Chem. 2001. 560.

124. Koychev S, Dommisch H, et al. *Antimicrobial Effects of Mastic Extract Against Oral and Periodontal Pathogens*. J Periodontol. 2017 Jan. 8:1-11. doi: 10.1902/jop.2017.150691.

Propolis

125. Tulsani SG, Chikkanarasaiah N, et al. *The effect of Propolis and Xylitol chewing gums on salivary Streptococcus mutans count: A clinical trial*. Indian Journal of Dental Research. 2014. 25 (6):737-741.

126. Kuropatnicki AK, Szliszka E, Krol W. *Review Article: Historical Aspects of Propolis Research in Modern Time*s. Evidence-Based Complementary and Alternative Medicine. 2013. Article ID 964149. 11 pages. doi. org/110.1155/2013/964149.

127. Neiva KG, Catalfamo DL, et al. *Propolis decreases lipopolysaccharide-induced inflammatory mediators in pulp cells and osteoclasts*. Dent Traumatol. 2014 Feb 6. doi: 10.1111/edt.12096

128. Hashem A, Abd-Allah EF, et al. *Effect of propolis on growth, aflatoxins production and lipid metabolism in Aspergillus parasiticus spear*. Pak. J. Bot. 2012. 44(3):1153-1158.\

129. Martinotti S, Ranzato E. *Propolis: a new frontier for wound healing?* Burns & Trauma. 2015. 3:9 DOI: 10.1186/s41038-015-0010-z

130. Santos VR. *Chapter 7. Propolis: Alternative Medicine for the Treatment of Oral Microbial Diseases*. p133- 169 © 2012 Santos; licensee InTech. http://dx.doi.org/10.5772/54003

131. Nakamura T, Ohta Y, et al. *Protective Effect of Repeatedly Preadministered Brazilian Propolis Ethanol Extract against Stress-Induced Gastric Mucosal Lesions in Rats*. Evid Based Complement Altern Med. 2014. 2014:383482. doi: 10.1155/2014/383482. Epub 2014 Feb 3.

132. Więckiewicz W, Miernik M, et al. *Does propolis help to maintain oral health?* Evid Based Complement Alternat Med. 2013:351062. doi: 10.1155/2013/351062.

133. AkhavanKarbassi MH, Yazdi MF, et al. *Randomized Double-Blind Placebo-Controlled Trial of Propolis for Oral Mucositis in Patients Receiving Chemotherapy for Head and Neck Cancer*. Asian Pac J Cancer Prev. 2016. 17(7):3611-3614.

134. Javadzadeh Bolouri A, Pakfetrat A, et al *Preventing and Therapeutic Effect of Propolis in Radiotherapy Induced Mucositis of Head and Neck Cancers: A Triple-Blind, Randomized, Placebo-Controlled Trial*. Iran J Cancer Prev. 2015 Oct. 8(5):e4019. doi: 10.17795/ijcp-4019.

135. Eslami H, Pouralibaba F, et al. *Efficacy of Hypozalix spray and propolis mouthwash for prevention of chemotherapy-induced*

oral mucositis in leukemic patients: A double-blind randomized clinical trial. J Dent Res Dent Clin Dent Prospects. 2016 Fall. 10(4):226-233. doi: 10.15171/joddd.2016.036.

136. Murtaza G, Karim S, et al. *Review Article: Caffeic acid phenethyl ester and therapeutic potentials*. BioMed Research International. 2104. Article ID 145342. 9 pages. doi. ort/10.1155/2014/145342

137. Baltas N, Karaoglu SA, et al. *Effect of propolis in gastric disorders: inhibition studies on the growth of Helicobacter pylori and production of its urease*. J Enzyme Inhib Med Chem. 2016. 31(sup2):46-50.

138. Banskota AH, Tezuka Y, et al. *Hepatoprotective and anti-Helicobacter pylori activities of constituents from Brazilian propolis*. Phytomedicine. 2001. 8:16-23.

139. Boyanova L, Derejian S, et al. *Inhibition of Helicobacter pylori growth in vitro by Bulgarian propolis: preliminary report*. J Med Microbiol. 2003. 52:417-419.

140. Kunqiang C, Weiqiang L, et al. *Caffeic acid phenethyl ester (CAPE), an active component of propolis, inhibits Helicobacter pylori peptide deformylase activity*. Biochemical and Biophysical Research Communications. 2013. 435:289-294.

141. Itoh K, Amamiya I, et al. *Anti-Helicobacter pylori substances in Propolis 1124*. Honeybee Science. 1994. 15(4):171-173.

Manuka Honey

142. Kato Y., Umeda N., et al. *Identification of a novel glycoside, leptosin, as a chemical marker of manuka honey*. J Agricultural and Food Chemistry. 2012. 60(13):3418-3423. doi: 10.1021/jf300068w.

143. Tonks AJ, Cooper RA, et al. *Honey stimulates inflammatory cytokine production from monocytes*. Cytokine. 2003. 21: 242-247.

144. Al. Shabanah O. *Inhibition of gastric mucosal damage by Methylglyoxal pretreatment in rats*. Food and Chemical Toxicology. 2000. 38(7):577-584.

145. Motallebnejad, M, Akram S, et al. *The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial*. J Contemp Dent Pract. 2008 Mar 1. 9(3):40-47.

146. Almasaudi SB, El-Shitany NA, et al. *Antioxidant, Anti-inflammatory, and Antiulcer Potential of Manuka Honey against Gastric Ulcer in Rats.* Oxid Med Cell Longev. 2016. 3643824. doi: 10.1155/2016/3643824.

147. Mota KS, Dias GEN, et al. *Flavonoids with gastroprotective activity*. Molecules. 2009. 14(3):979-1012. doi: 10.3390/molecules14030979.

148. Jubri Z, Abdul Rahim NB, Aan G J. *Manuka honey protects middle-aged rats from oxidative damage*. Clinics. 2013. 68(11):144-1454. doi: 10.6061/clinics/2013(11)11.

149. Maiti PK , Ray A, et al. *The effect of honey on mucositis induced by chemoradiation in head and neck Cancer*. J Indian Med Assoc. 2012 Jul. 110(7):453-456.

D-Limonene

150. de Almeida AAC, de Carvalho RBF, et al. *Potential antioxidant and anxiolytic effects of (+)-limonene epoxide in mice after marble-burying test*. Pharmacology, Biochemistry and Behavior. 2014 118: 69-78.

151. Lis-Balchin M, Ochocka RJ, et al. *Bioactivity of the enantiomers of limonene*. Med Sci Res 1996. 24:309-310.

152. Patrizia A. d'Alessio RO. *Oral administration of d-Limonene controls inflammation in rat colitis and displays anti-inflammatory properties as diet supplementation in humans*, Life Sciences 2013. 92:1151–1156.

153. Jidong Sun, *D-Limonene: Safety and Clinical Applications*. Alter Med Rev. 2007. 12(3)

154. Lu XG, Zhan LB, et al. *Inhibition of growth and metastasis of human gastric cancer implanted in nude mice by d-limonen.* World J Gastroenterol. 2004 Jul 15. 10(14):2140-2144.

155. Patrick K. *Gastroesophageal Reflux Disease (GERD): A Review of Conventional and Alternative Treatments*. Altern Med Rev. 2011. 16(2):116-133.

Sodium Alginate

156. KG, Daggy BP, et al. *Review article: alginate-raft formulations in the treatment of heartburn and acid reflux*. Aliment Pharmacol Ther. 2000 Jun. 14(6):669-690.

157. Adebisi AO, Laity PR, Conway BR. *Formulation and evaluation of floating mucoadhesive alginate beads for targeting Helicobacter pylori*. J Pharm Pharmacol. 2015 Apr. 67(4):511-524. doi: 10.1111/jphp.12345.

158. Dios P, Nagy S, et al. Preformulation studies and optimization of sodium alginate based floating drug delivery: a system for eradication of Helicobacter pylori. Eur J Pharm Biopharm. 2015 Oct. 96:196-206. doi: 10.1016/j. ejpb.2015.07.020.

159. Katayama H, Nishimura T, et al. *Sustained release liquid preparation using sodium alginate for eradication of Helicobacter pylori.* Biol Pharm Bull. 1999 Jan. 22(1):55-60.

160. Mandel KG, Daggy BP, et al. *Review article: alginate-raft formulations in the treatment of heartburn and acid reflux.* Aliment Pharmacol Ther. 2000. 14:669-690.

161. Savarino E, de Bortoli N, et al. *Alginate controls heartburn in patients with erosive and nonerosive reflux disease*. World J Gastroenterol. 2012 August 28. 18(32):4371-4378.

162. Kim HM. Raft formation of sodium alginate in the stomach. J Neurogastroenterol Motil. 2016 October. 22(4):705-706.

163. Pereira R, Mendes A, Bartolo P. *Alginate/Aloe hydrogel*

films for biomedical applications. Procedia CIRP 5. 2013. 210-215.

164. Diós P, Nagy S, et al. *Preformulation studies and optimization of sodium alginate based floating drug delivery system for eradication of Helicobacter pylori*. Eur J Pharm Biopharm. 2015 Oct. 96:196-206. doi: 10.1016/j.ejpb.2015.07.020.

165. Oshitani T, Okada K, et al. *Clinical evaluation of sodium alginate on oral mucositis associated with radiotherapy*. Nihon Gan Chiryo Gakkai Shi. 1990 Jun 20. 25(6):1129-1137. Japanese.

Potassium Bicarbonate

166. Ribeiro MD, Silva AS, et al. *Buffer Therapy for Cancer*. J Nutr Food Sci. 2012 Aug. 15:2:6.

167. McCarty MF, Whitaker J. *Manipulating tumor acidification as a cancer treatment strategy*. Altern Med Rev. 2010 Sep. 15(3):264-272.

168. Schieszer J. *Neutralizing Intratumoral pH May Improve Responses to Immunotherapy*. Published 05/2016 on OncoTherapy Network (http://www.oncotherapynetwork.com)

169. Zhang H. *Will cancer cells be defeated by sodium bicarbonate?* Sci China Life Sci. 2017 Jan 4. doi: 10.1007/s11427-016-0373-3.

Zinc Carnosine

170. Yoshikawa T, Naito Y, et al. *The antioxidant properties of a novel zinc-carnosine chelate compound, N-(3-aminopropionyl)-L-histidinato zinc.* Biochim Biophys Acta. 1991. 1115(1):15–22.

171. Mahmood A, FitzGerals AJ, et al. *Zinc carnosine, a health food supplement that stabilizes small bowel integrity and stimulates gut repair processes*. Gut. 2007. 56:168-175. doi: 10.1136/gut.2006.099929

172. Hill TL, Blikslager AT. *Effect of a zinc L-carnosine compound on acid-induced injury in canine gastric mucosa ex vivo.* Am J Vet Res. 2012. 73(5):659–663.

173. Prasad AS. *Zinc: mechanisms of host defense*. J Nutr. 2007 May. 137(5):1345-1349.

174. Yoshikawa T, Yamaguchi T, et al. *Effect of Z-103 on TNB-induced colitis in rats*. Digestion. 1997 58:464-468.

175. Haase H, Rink L. *Multiple impacts of zinc on immune function*. Metallomics. 2014 Feb 17.

176. Gupta M, Mahajan VK, et al. *Zinc therapy in dermatology: a review*. Dermatol Res Pract. 2014. http://dx.doi.org/10.1155/2014/709152

177. Web: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

178. Franklin RB, Costello LC. *The important role of the apoptotic effects of zinc in the development of cancers*. J Cell Biochem. 2009 April 1. 106(5):750-757.

179. Prasad AS. *Zinc in human health: effect of zinc on immune cells*. Mol Med. 2008 May-Jun. 14(5-6):353-7. doi: 10.2119/2008-00033.Prasad.

180. Li P, Xu J, et al. *Association between zinc intake and risk of digestive tract cancers: a systematic review and meta-analysis*. Clin Nutr. 2014 Jun. 33(3):415-420. doi: 10.1016/j.clnu.2013.10.001. Review.

181. Bao ZX, Yang XW, et al. *Serum zinc levels in 368 patients with oral mucosal diseases: A preliminary study*. Med Oral Patol Oral Cir Bucal. 2016 May 1. 21(3):e335-340.

182. Hayashi H, Kobayashi R, et al. *Preparation and clinical evaluation of a novel lozenge containing polaprezinc, a zinc-L-carnosine, for prevention of oral mucositis in patients with hematological cancer who received high-dose chemotherapy*. Med Oncol. 2016 Aug. 33(8):91. doi: 10.1007/s12032-016-0795-z.

Glutamine

183. Shabert, J. *The Ultimate Nutrient Glutamine: The Essential Non-essential Amino Acid*. 1994. Avery Publishing Group, NY

184. Hyeyoung K. *Glutamine as an Immunonutrient*. Yonsei Med J. 2011. 52(6):892-897.

185. Kelly D, Wischmeyer PE. *Role of L-glutamine in critical illness: new insights*. Curr Opin Clin Nutr Metab Care. 2003 Mar. 6(2):217-222.

186. Beth Israel Deaconess Medical Center. *Glutamine Supplements Show Promise In Treating Stomach Ulcers*. ScienceDaily. 2009 May 22. Retrieved February 7, 2010, from http://www.sciencedaily.com/releases/2009/05/090515104223.htm#

187. Achamrah N, Déchelotte P, Coëffier M. *Glutamine and the regulation of intestinal permeability: from bench to bedside*. Curr Opin Clin Nutr Metab Care. 2017 Jan. 20(1):86-91.

188. Wang B, Wu G, et al. *Glutamine and intestinal barrier function*. Amino Acids. 2015 Oct. 47(10):2143-2154. doi: 10.1007/s00726-014-1773-4. Review.

189. Sellmann C, Jin CJ, et al. *Oral Glutamine Supplementation Protects Female Mice from Nonalcoholic Steatohepatitis*. J Nutr. 2015 Oct. 145(10):2280-2286. doi: 10.3945/jn.115.215517.

190. Shu XL, Yu TT, et al. *Effect of glutamine on intestinal barrier function following liver transplantation in rats*. Eur Rev Med Pharmacol Sci. 2014. 18(14):2058-2064.

191. Lima AA, Anstead GM, et al. *Effects of glutamine alone or in combination with zinc and vitamin A on*

growth, intestinal barrierfunction, stress and satiety-related hormones in Brazilian shantytown children. Clinics (Sao Paulo). 2014. 69(4):225-233.

192. Andrews FJ, Griffiths RD. *Glutamine: essential for immune nutrition in the critically ill*. Br J Nutr. 2002. 87:S3-S8.

193. Cao Y, et al. *Glutamine enhances gut glutathione production*. J Parenter Enteral Nutr. 1998. 22(4): 224-227.

194. Leung HW, Chan AL. *Glutamine in Alleviation of Radiation-Induced Severe Oral Mucositis: A Meta-Analysis*. Nutr Cancer. 2016 Jul. 68(5):734-742. doi: 10.1080/01635581.2016.1159700.

195. Saadeh CE. *Chemotherapy- and radiotherapy-induced oral mucositis: review of preventive strategies and treatment*. Pharmacotherapy. 2005 Apr. 25(4):540-554. Review.

196. Gul K, Muge A, et al. *Oral glutamine supplementation reduces radiotherapy- induced esophagitis in lung cancer patients*. Asian Pac J Cancer Prev. 2015. 16(1):53-58.

197. Fukui T, Itoh Y, et al. *Elental prevented and reduced oral mucositis during chemotherapy in patients esophageal cancer*. Gan To Kagaku Ryoho. 2011 Dec. 38(13):2597-2601.