<u>Leaky Gut - Herbal, Nutritional, and Integrative Approaches</u> By Stephen Byers

WHAT IS "LEAKY GUT SYNDROME"?

DEFINITION:

Leaky Gut Syndrome – This term is not a medically recognized diagnosis. It uniquely refers to increased permeability or hyper-permeability of the intestinal walls which occurs when tight junctions of the epithelial cells become loosened or "leaky". This can allow undesired foreign substances, including undigested food particles to more easily pass through into the bloodstream. It is believed that this intestinal permeability (IP) can contribute to a cascade of imbalances in the function of the body leading to a variety of immune, hepatic, and/or lymphatic associated conditions. Due to the variety of ways Leaky Gut Syndrome can manifest, this article will predominantly refer to research and treatments for IP rather than specifically for the more broad umbrella term Leaky Gut Syndrome.

In response to the increasing public acceptance of Leaky Gut Syndrome, The UK National Health Service (2015) writes: "While it's true that some conditions and medications can cause a "leaky" gut (what scientists call increased intestinal permeability), there is currently little evidence to support the theory that a porous bowel is the direct cause of any significant, widespread problems. There is also little evidence that the "treatments" some people claim help to reduce bowel "leakiness", such as nutritional supplements and herbal remedies, have any beneficial effect for most of the conditions they supposedly help." It is true that research on direct medical treatments for IP specifically is limited, but there are currently decades of research trials pointing to a clear relationship between IP and numerous diseases and conditions.

Skeptics believe that the "Leaky Gut Syndrome" diagnosis is misguiding the public into following unnecessary elimination diets and purchasing diet books, nutritional supplements (i.e. probiotics), and herbal products that have not been proven to help this "alleged syndrome". And it is true that many people may be self-diagnosing and self-treating without proper testing, assessment, and guidance. Yet the incidence of chronic diseases, especially auto-immune diseases, is on the rise and in many auto-immune conditions, IP is a consistent and early feature of the disease process (Arrietta et al. 2006). In fact, there is increasing evidence that IP is both the cause or an associated symptom of many diseases so it makes sense that people would want to find ways to address gut-based issues accompanying these various chronic conditions with a personalized rather than broad spectrum approach.

Since the 1990's, it has been possible to test for and diagnose intestinal permeability with safe, non-invasive, and inexpensive methods. For the mainstream medical field, there is no proven treatment yet for IP and the diagnosis of IP may leave patients confused and dependant on limited generic approaches for digestive issues (i.e. anti-spasmodic, steroidal drugs, etc). In conjunction with proper testing and assessment, various "alternative" therapies have successfully used dietary protocols, stress reduction, herbal, and nutritional supplements to help people with IP to heal their gut and find resolve in many of their primary and secondary concerns.

INTRODUCTION TO THE GUT AND THE MECHANISMS INVOLVED IN INTESTINAL PERMEABILITY:

The intestinal lining is supported by complex mechanisms including probiotic bacteria, intestinal secretions (mucus, secretory IgA, mucine, defensine, lysozyme, phospholipase A2), bile acids, the mucosal epithelium, and lymphocytes (Peyer's Patches). Bile acids also help to inhibit the growth of bacteria, especially anaerobic bacteria. Amazingly, the healthy gut lining is able to allow the absorption of nutrients of food but prevent luminal antigens and toxins from entering through the mucosa. Mucus covering the epithelial layer prevents the colonization of pathogenic bacteria and also prevents the diffusion of toxins, particularly fatsoluble compounds, towards the surface of these sensitive mucosal cells. The pH of the gut is also regulated by bicarbonate ions in the mucus. The mucus and bicarbonate are stimulated by the release of endocrine and paracrine factors such as Prostaglandin E2 and prostacyclin, both of which can cause IP when in excess. Increased levels of cytokines, such as Tumor Necrosis Factor-α, negatively affect the intestinal wall by increasing inflammation and permeability. Anti-TNF-α treatments given to people with Crohn's Disease have been shown to improve healing of the intestinal barrier and reduce IP (Suenaert, 2002). It is well known that Type 1, 3, and 4 Hypersensitivities (often triggered by food) cause increased levels of inflammatory mediators, such as cytokines, prostaglandins, interleukin, and histamine.

Research in the last decade has shown that up to 1000 different species of microbes exist in the gut with a genetic population 10 times that of the human genome. It is now clear that bacteria in the gut can have a strong influence on the pathological development of allergies and auto-immune disorders. Gut bacteria has been shown to influence regulation of T lymphocytes, T helper cell (Th1, 2, & 17) activity, IgG antibodies, IgA antibodies, and impact the development of T and B cell compartments in gut-associated lymphoid tissue (GALT). A recent example of this has been revealed through research demonstrating that T helper cell 17 is activated via single strains of bacteria that drive auto-immune arthritis (Wu et al. 2010). Also, certain gut bacteria (as well as gluten) are known to trigger the innate immune response to release zonulin, the protein responsible for causing the tight-junctions in the mucosa to open (Fasano, 2011). It is clear that the microbiota of the gut directly regulate immune homeostasis and play a critical role in achieving health.

Second to these initial layers of protection, the liver is responsible for breaking down all substances passing through the intestinal lumen that come to it via the portal system. This is to protect other tissues and organs from exposure to potentially toxic proteins and macromolecules. Within the liver, Kupffer cells and hepatic enzymes work in concert with glutathione to alter chemical substrates from the gut to neutralize them for excretion via the bile and kidneys. In turn, the liver affects intestinal function and protection through bile secretion into the lumen of the gut. Also, gut bacteria are able to influence both bile acid metabolism and bile secretion from the liver (Sayin et al. 2013). If the liver is unable to neutralize toxins, they are returned to the blood, then the lymph, and eventually the connective tissue. In the case of IP, it is possible that this would be a perpetuating mechanism of IP, cyclically leading to further damage of the sensitive tissues in the gut and preventing much needed repair.

The integrity of the epithelial cells are tightly held together by many factors including trefoil proteins, occluden, and clauden. These tight junctions are known as "zonula occludens" and are regulated by the protein zonulin. It is released by the small intestine epithelial cells to help these tight junctions open and close in response to stimuli like food particles, humoral and neuronal signals, inflammatory mediators, mast cell products, and signals from microbial and viral activity (Arrieta et al, 2006). Zonulin is now a measured biomarker of IP for several auto-immune diseases, neurodegenerative conditions, and tumoral diseases (Fasano, 2011).

If the intestinal barrier is compromised, the level of reactive oxygen species, carcinogens, macromolecules, and other toxins pass through the intestinal wall and accumulate in the blood causing stress on the immune system and liver. The immune system is often pushed into a hypersensitive state resulting in increased environmental and food-based sensitivities. With damage to the tight junction between the enterocytes and increased IP, undigested proteins passing through cause higher levels of specific IgG antibodies which can lead to type 3 hypersensitivities (Frank et al. 2012). Additionally, this hyper-permeability can cause overstimulation of dendritic cells leading to classic hypersensitivity to foods, bacterial flora, and/or bacterial endotoxins. It is believed that this low-grade endotoxemia and/or dysbiosis can be one of the causes of auto-immune disorders and chronic GI-issues.

In Traditional Chinese Medicine, prolonged IP is believed to cause Spleen Qi deficiency because in TCM the Spleen is responsible for the repair of the Small Intestine. Nutrient deficiency can result due to damage from intestinal inflammation that reduces digestive enzyme function, dysregulates synergistic probiotic conversion of vitamins, and compromises "carrier protein" motility that normally assist in the absorption of essential vitamins and nutrients. The term "oral tolerance" describes the human function that naturally suppresses the immune response in the gut from and systemic immune system from reacting to food and bacteria so we can peacefully digest food and cohabitate with the microfora. It has also been documented that normal gut bacteria is supported by the immune system but IP mediated immune hypersensitivity persists, the immune system may actually start overreacting to the normal bacteria, further increasing immune hypersensitivity in the gut (Chistiakov et al. 2014). This hypersensitivity is chronically sustained when people continue to repeatedly eat foods they have unknowingly become sensitive to.

In humans with IP, intestinal Gram-negative bacteria can release an endotoxin called lipopolysaccharide (LPS) into the bloodstream, which is known to up-regulate gut and systemic inflammation. LPS has also been shown to increase permeability in the blood brain barrier in mice, an association, which has led some to assign "Leaky Brain" as a secondary symptom of Leaky Gut Syndrome. Higher levels of IgG and IgM antibodies to LPS have been correlated with major depression (Maes et al. 2008).

The Gut Brain Connection: The Enteric Nervous System

Often referred to as the "Second Brain" or "Gut Brain", the enteric nervous system is home to over 100 million neurons woven throughout the gut lining. Researchers have determined

that up to 95% of the serotonin in the body is produced in the gut as well as about 50% of our dopamine both of which influence mood and GI motility. Furthermore, studies reveal that disease-causing bacteria can alter brain chemistry in mice causing their behavior to become either more excited and bold or more fearful and anxious indicating a strong relationship between dysbiosis and mood (see further studies by Bercik). Additionally, compared to controls, mice fed probiotics like Lactobacillus have shown reduced levels of corticosterone and depression when faced with a stressful situation (the forced-swim test). Bacteria in the gut are believed to communicate with the brain via the Vagus nerve as their main mode of influence on neurotransmitter activity, though immunological stimulation is also suspected to have some influence. (Bienenstock, 2012). Bacterial influence on the brain is inactive in studies where the Vagus nerve has been severed. Gut bacteria not only produce neurotransmitters like GABA, serotonin, norepinephrine, dopamine, acetylcholine, and melatonin but they are also influenced by these neurochemicals themselves, suggesting an interesting host-guest interdependence.

Diseases/Syndromes/Sensitivities <u>Associated</u> With Leaky Gut Syndrome "All diseases begins in the gut" - Hippocrates

Many diseases, syndromes, and conditions have been associated with or directly linked to IP and Leaky Gut Syndrome. In TCM, IP can result from "microbial toxicosis" which creates a pattern known as "pathological endogenous autotoxicosis". This leads to the Leaky Gut Syndrome progression of various imbalances in the body. Due to either microbial toxicosis and/or metabolic toxicosis, the internal accumulation of harmful toxins can cause stagnation in the Liver, obstruction in the lymphatic tissue in the gut, and often present with localized or systemic signs of Damp Heat or Toxic Heat (Holmes, 1998). In reference to endogenous toxicosis, Peter Holmes writes, "Clinically, it is important to recognize that it's the toxicosis that is causing these diseases with its many confusing symptoms, not the disease causing the symptoms". Often it is true that many diseases are activated by the toxicosis and yet, there has been research proving that due to genetic factors, IP actually precedes the disease process of both Type 1 Diabetes and Crohn's Disease, meaning that it IP is initiating the progression of the disease.

Dr. Leo Galland, M.D., a leading expert in gastrointestinal dysregulation and chronic disease, has drawn attention to Leaky Gut Syndromes since the early 1990's and has been treating people with Leaky Gut Syndrome for over 20 years. In his flagship article on Leaky Gut Syndromes, he writes: "Hyperpermeability may play a primary etiologic role in the evolution of each disease, or may be a secondary consequence of it which causes immune activation, hepatic dysfunction, and pancreatic insufficiency, creating a vicious cycle. Unless specifically investigated, the role of altered intestinal permeability in patients with Leaky Gut Syndromes often goes unrecognized...Monitoring the intestinal permeability of chronically ill patients with Leaky Gut Syndromes can help improve clinical outcomes" (*Leaky Gut Syndromes: Breaking the Vicious Cycles*, 1993).

Dr. Galland says to suspect compromised intestinal permeability with the following conditions:

Inflammatory bowel disease	Infectious enterocolitis
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Spondyloarthropathies Acne Eczema Psoriasis

Urticaria AIDS/HIV infection
Pancreatic insufficiency Cystic fibrosis
Irritable bowel syndrome with food Hepatic dysfunction

intolerance Chronic arthritis/pain treated with

CFIDS Neoplasia treated with cytotoxic drugs NSAIDS Alcoholism

Celiac disease Dermatitis herpetiformis
Autism Childhood hyperactivity

Environmental illness Multiple food and chemical sensitivities

Other diseases associates with Leaky Gut Syndrome include: Asthma, Multiple Sclerosis, Vasculitis, Colitis, Addison's Disease, Lupus, Rheumatoid Arthritis and Thyroiditis (Fratkin, 2015).

Additionally, research has shown IP to be associated with Graft vs. Host disease, Type 1 diabetes, Multiple organ dysfunction syndrome, Acute Pancreatitis, Parkinson's Disease, Fibromylagia, Non-Alchoholic Fatty Liver Disease, and Alcoholic cirrhosis (Oldenwald & Turner, 2014). Other diseases include: IBS-D, Inflammatory arthritis, Juvenialle onset arthritis, Chronic Heart Failure, Ankolysing Spondylitis, Chemotherapy, and Pelvic Radiotherapy (Resnick, 2010).

These long lists of diseases and syndromes indicates the complex manifestations of Leaky Gut Syndrome but also highlights the importance of assessing the health of the gut, especially in people with chronic conditions.

Dr. Galland has produced the following list of symptoms associated with intestinal permeability:

Arthralgias (pain in multiple joints), myalgias, fever of unknown origin, food intolerance, abdominal pain, abdominal distension, diarrhea, chronic skin conditions, toxic feelings (i.e. chronic depression), cognitive and memory deficits, shortness of breath, malaise, and chronic fatigue. You should also suspect it if you drink heavy amounts of alcohol or take NSAIDS on a daily basis. He also lists the symptom of "feeling of being infected but your doctor can't find the infection" which is a trait people suffering from chronic illnesses may share in common.

Aviva Romm (2014) gives the following "10 Signs" of Leaky Gut Syndrome:

- 1. You struggle with digestive problems including gas, bloating, loose stools, or irritable bowel syndrome (IBS).
- 1. You have food intolerances or food sensitivities.
- 2. You suffer from seasonal allergies.
- 3. You have eczema, skin rashes, acne, or other chronic skin problems.
- 4. You have an autoimmune condition.
- 5. You're tired all the time.

- 6. You have chronic fatigue syndrome or <u>fibromyalgia</u>.
- 6. You struggle with anxiety, depression, or erratic moods.
- 7. You've been diagnosed with yeast (Candida) overgrowth or SIBO (small intestinal bacterial overgrowth).
- 8. You can't lose weight in spite of an excellent diet.
- 9. Your joints ache and swell.
- 10. You have trouble concentrating, with your memory, or notice other cognitive changes.

Determining whether someone truly has IP can only be medically diagnosed with lab tests. Otherwise, a judicial and experienced analysis of the signs and symptoms of Leaky Gut Syndrome are needed before creating a treatment protocol for it.

TRIGGERS FOR INTESTINAL PERMEABILITY (IP):

Infections: Exposure to infectious agents (viral, bacterial, protozoan) and candida overgrowth can cause IP.

Drugs: Substances such as ethanol, NSAIDS (which inhibit protective prostaglandin mucus secretion), or cytotoxic drugs (antibiotics) can cause inflammation, dysbiosis of the gut microbiome, and disrupt epithelial integrity leading to increased permeability. Some medications used to treat rheumatoid arthritis can cause IP. Researchers have documented that 50-70% of people taking conventional NSAIDS routinely will have IP (Smale et al. 2003). Antacids and long term contraceptive pill use have also been linked to promoting IP.

Alcohol: Alcohol is metabolized by bacteria in the large intestine into Acetaldehyde, which can causes IP. It also increases bacterial overgrowth leading to increased endotoxins also known to cause increased IP. Alcohol consumption also increases endothelial nitric oxide (NO) which can lead to IP. Liver cirrhosis is associated with IP.

Digestive Conditions: Digestive issues such as Celiac disease, Crohn's disease, IBS, and IBD are associated with the occurrence of IP. Interestingly, the IP associated with Type 1 Diabetes and Crohn's Disease has been found to precede the pathological presentation of the disease due to the genetic nature of the disease, which predisposes people to IP in the gut. This suggests that IP isn't always caused by external factors. Insufficient digestive and pancreatic enzymes have been associated with Leaky Gut Syndrome. Intestinal inflammation and mucosal oxidative stress are the two most primary causative mechanisms in the pathophsyiology of IP (Resnick, 2010).

Diet, Food Allergens & Food Sensitivities: Diets high in refined carbohydrates and sugars has been associated with leaky gut syndrome. Food additives such food dyes have also been blamed. Caffeine also irritates the intestinal wall. Exposure to food allergens can cause IP through excited mast cell release of chemical mediators such as serotonin and histamine. Cow's Milk, Gluten and gliadin have been shown to cause IP. While food intolerances such as lactose intolerance have not been shown cause IP, food sensitivities and food allergies can cause IP through Type 1,3, and 4 Hypersensitivity mechanisms.

Stress: Chronic stress causes reduced circulation to the gut, dysregulates important growth factors and insulin, and increases inflammation in the body. Stress induces IBS and stress can also induce IP (Lambert, 2009).

Detoxification: Environmental pollutants can cause increased IP. Also poor liver function and compromised detoxification capacity is closely associated with IP. Liver function is often moderately to severely compromised in people with Leaky Gut Syndrome.

LAB TEST OPTIONS:

Testing enhances clarity of the etiology of one's condition and saves time in treatment efforts but also enhances client compliance and acceptance of protocol, which in some cases can require long term commitment and extensive efforts on the part of the client.

Testing can be used to rule out Candida overgrowth, immune deficiency (low IgA), intestinal permeability and inflammation, and food allergy and sensitivity testing.

If the client chooses not to do any testing but you as the practitioner still want assess the possibility of IP, ask questions in regards to inflammation. Also refer to the associated symptoms and diseases listed above.

- 1. History of antibiotic use? More than 1x in a lifetime is believed to be enough to cause Candida overgrowth or dysregulation in the microbiome.
- 2. Signs of inflammation on the skin (acne, eczema, psoriasis, rash) then it is likely that there is inflammation in the small intestine (the GI tract can technically be considered a barrier to the external environment just like the skin). In TCM, these presentations would often be symbolic of damp heat and would be treated as such. Red cheeks/flushed cheeks, especially after eating, would also be an indicator of inflammation as this is where the stomach meridian goes through. Jake Paul Fratkin, an expert in TCM approaches to Leaky Gut Syndrome uses TCM skin formulas for several intestinal damp heat.

**Interestingly, gut research shows that external burn injury can cause mesenteric vasoconstriction and cellular hypoxia in the gut (Magnotti, 2005) and stress to the epithelial barrier causing IP and bacterial translocation to the mesenteric lymph nodes (Choudhry, 2004). Burn injury can cause dysregulation of the gut microbiome indicating that increased inflammation can signal and strengthen certain bacteria in a inflamed and physically stressed state as well as allow bacterial translocation from the gut, through the blood, to the burn site causing higher incidence of sepsis (Earley et al. 2015).

LABORATORY MEASURES OF INTESTINAL PERMEABILITY:

It is important to determine the permeability of the gut in chronic conditions in order to more accurately assess appropriate treatment protocols. Several methods of measuring intestinal permeability have been considered including blood zonulin levels and urinary lactulose/mannitol ratio levels.

Lactulose/Mannitol (L:M) tests demonstrate both increased intestinal permeability and reduced absorption. This is a widely used oral challenge test that measures two sugars that normally pass through the gut without absorption. Years of research trials seeking to measure IP in various diseases has shown the test to be valid but does have limited sensitivity and specificity in certain conditions.

COST OF TEST:

- Truehealthlabs.com offers a \$150 lactulose:mannitol ratio kit which includes a one on one data review from their doctors.
- Genova L:M test retails for \$104.

In a 2013 Clinical Gastroenterology and Hepatology journal review, Oldenwald & Turner write,

"Most importantly, while permeability by these measures [Lactulose/Mannitol test] is increased in Crohn's Disease, IBS, and other diseases, it is well recognized that disease processes, such as pro-inflammatory cytokine release, can impact intestinal permeability. This makes it impossible to separate cause from effect... both human and mouse studies have made it clear that intestinal barrier loss alone, whether from tight junction dysregulation or epithelial damage, is insufficient to cause disease in an otherwise healthy individual."

Zonulin: This is the protein released from the tight junctions holding the epithelial cells together. Increased levels of zonulin indicate increased IP. This test has become a recent addition to the methods used to diagnose IP and other autoimmune conditions. Cyrex labs offers a zonulin/occludin test.

OTHER DIGESTIVE ASSESSMENT TESTING OPTIONS

Candida – Stool test to evaluate the need for treatment. If low, there is no concern but high levels would require assertive treatment efforts with diet, herbs, and possibly supplements. Genova and Diagnos-Techs are two labs to try. If Candida is present, it is important to follow a protocol aimed at eliminating this pathogen. This can take weeks or even months so it is critical that client compliance is consistent with diet, herbs, biofilm breakdown protocols, and supplements as Candida overgrowth can be difficult to reduce.

Trypsin/Chymotrypsin level: Chymotrypsin is a pancreatic enzyme that can be measured as an indicator of pancreatic function. In conjunction with Candida testing, a high Candida level with a low chymotrypsin level could indicate Leaky Gut Syndrome (Fratkin, 2014). A low chymotrypsin level alone has been associated with diabetes, cystic fibrosis, chronic pancreatitis, and most generally: malabsorption with symptoms of loose stool, undigested food in the stool, bloating, distension, GERD, and nausea. These are symptoms of Spleen Qi deficiency. There are also newer tests that can be used to assess pancreatic function such as the pancreatic elastase which is also a stool test.

Parasitic Infection: Genova and Diagnos-techs offer parasite, ameobic, and bacterial infection tests that could be useful to determine underlying weaknesses fueling the pathological progression of the condition and IP. Positive identification can assist treatment success and avoid protocols that may actually drive the symptoms deeper. For example, it is critical to deal with EXCESS presentations first that may stem from a parasite/ameobic infection. If you simply tonify the person because they have fatigue, then you will increase stagnation in the body. First, move the excess, disperse the stagnant Qi or Blood, eliminate parasites/amoeba, and then deal with the layered complaints (fatigue, poor sleep, bloating, ect).

Comprehensive Digestive Stool Testing:

In tough cases, I recommend extensive GI function panels such as the Comprehensive Digestive Stool Anaylsis by Genova, which will provide details on fungal, parasitic, fat/protein metabolism, immunologic markers, and absorption issues.

Food Sensitivity Testing: Mediator Release Test (MRT): This is considered to be the most advanced food sensitivity test for measuring non-specific IgE inflammatory mediators in the blood such as cytokines, prostaglandins, histamine, serotonin, and interleukin. The developer of the ALCAT test recognized the limitations in that test and created the MRT to more precisely identify non-specific IgE (Type 3 and 4 Hypersensitivities) reactions to foods and chemicals. This test can measure reactivity levels in up 120 foods and 30 chemicals. It has been clinically shown to especially help people with chronic migraines, fibromylagia, IBS, and chronic digestive disorders while also by far outperforming the ALCAT and ELISA IgG in test reliability, sensitivity, and specificity. The benefits of identifying the reactive foods not only greatly improves client compliance in dietary changes but also helps to avoid the guess work involved in multiple food-sensitivity elimination diets. Often more obscure sensitivities can also be discovered. This is an invaluable tool for the clinical practice working with chronically ill people. A dietary protocol based on the results (to know what should and shouldn't be eaten) is highly suggested though it does require a committed effort for 3-6 months. Cost: \$295

In review, there are several inflammatory mechanisms involved in IP. It is critical to identify these mechanisms through various methods of testing and elimination diets as needed. This chart reminds us of the various inflammatory pathways involved in allergies and sensitivities:

Hypersensitivity	Type 1	Type 3	Type 4
Type:			
Mediator Cells	Mast Cell	Neutrophil	Neutrophil
Involved in the	- Histamine	Basophil	Basophil
Inflammatory	Prostaglandin D2	Macrophage	Macrophage
Response	Basophil	Natural Killer Cell	Natural Killer Cell
	Eosinophil	Eosinophil	Eosinophil
		Monocyte	Monocyte

			T-Cells
Mechanism Involved	IgE	IgG Complement	T-Cell Mediated
in Mediator Release		IgM C3,C4	
Examples of	Food and	IBS, Rheumatoid	Auto-Immune
Associated Diseases	Environmental	Arthritis, Lupus,	Diseases, Crohn's
	Allergies, IgA	Food Sensitivities	Disease, Peripheral
	nephropathy		Neuropathy, MS,
			Food Sensitivities
Testing Options	Skin Prick Test	IgG Blood testing	MRT
	Total IgE (blood)	ELISA IgG,	
	RAST/ELISA	MRT	
	Oral Challenge		

THE HERBALIST'S ASSESSMENT:

The following areas should be included in the Leaky Gut Assessment:

Pulse	Digestive Complaints	Heavy Metals
Tongue	History	Hormones
Nails	Parasite Exposure	Thyroid
Face	Environmental	Lymph
Family History	Exposures	Liver
Genetics	Skin Issues	Spleen
Ancestral Dietary	Drug Exposures	Kidney
Patterns	Stress	Heart
Diet/Deficiencies	Mood Disorders	

DIETARY APPROACHES - Beyond the one-size fits all approach

"A common error among Western practitioners of Chinese medicine is to focus on elimination diets (avoiding, for example, dairy, wheat, meat, etc.) rather than to focus on nutritious diets." – Subhuti Dharmandha

Any client with IP who wants to heal their gut must consider a plan for addressing nutrient deficiencies and food allergies and/or sensitivities. We are living in a day and age where the contents, quality, and safety of our food system is held in great suspicion. Sadly, the relationship that many people have learned to have with food has become one of distrust and confusion, especially for those with undiagnosed chronic conditions, multiple food sensitivities, or even people who have become "excessively internet educated" by blogs, podcasts, and food summits on the web. It is not that the information is wrong or misleading (usually), but many people are not able to see the bigger picture and get quickly swept into inappropriate diets that could wosrsen rather than help their conditions, resulting in nutrient deficiencies, overspending on superfoods and products, and cause a loss of hope and social isolation because their food list is so restricted.

As herbalists, our goal is to help people deepen awareness of their own body's needs and helping them to expand their potential as humans, both individually and in community. This means that part of our work is to help people extend their trust and knowledge of food in a positive and healthy way. In efforts to heal the gut, some people (practitioners included) have become malnourished by intense efforts that try to identify food allergies and sensitivities. It is important to challenge these fad-diets with tradition and research to avoid getting stuck into a paradigm of excessive limitation, even in addressing IP. Elimination diets can be of great benefit but great care is needed to avoid eating our way into a new sensitivity from overconsumption of one thing to avoid another (Ex: glutenfree dieters tend to eat more corn chips).

We are reminded that our ancestors once ate nutrient dense, seasonal, local, chemical-free and whole food diets. For some, this included whole grains, like wheat. A 2013 study looked at 75 post-menopausal women eating a diet with either whole-grain wheat or refined wheat flour for 12 weeks. The results showed that those on the whole-grain wheat diet had an increased level of bifidobacteria as well as improved integrity of the intestinal wall. (Christensen et al, 2013). Note the study was conducted in Europe where the grain has a less likelihood of being sprayed with glyphosate. At the same time, we remember that gluten proteins can trigger the release of zonulin leading to increased IP. It is true that many of our main grains (wheat, corn, soy, rice) have been hybridized to have more gluten and/or genetically modified making them more difficult to digest. So we must hold this new knowledge and traditional wisdom of eating in balance and consideration of each individual's specific dietary needs.

Adverse food reactions are one of the most clinically overlooked (or poorly addressed) issues contributing to disease. Diet is the most important influential factor in regulating the intestinal microbiome and Leaky Gut Syndrome. This has been demonstrated by dozens of studies on the positive effects (probiotics, prebiotics, and fiber) and negative effects (high-fat diets) diet can have on the gut microbiome and IP. In 2008 Belgian researchers published several articles demonstrating evidence of IP in people with chronic fatigue syndrome as well as in people with major depressive disorder (Maes et al. 2008). Interestingly, the research showed that treatment with dietary protocols and specific nutrients both reversed IP and also improved symptoms of fatigue, malaise, and depression in those with chronic fatigue syndrome. Additionally, IgG related migraines and IBS sufferers have found great relief on intentional food elimination-rotation diets in double blind placebo controlled cross over trials (Alpay et al. 2010, Aidenpar et al. 2013)

Here is a list of several diets being used with various success by people looking to heal their IP and Leaky Gut Syndrome. I will highlight a few and how they may be indicated. Generally, these diets are used for a period of time to support healing. Clients can be reminded that these are not "forever diets" and once the gut heals and food sensitivities have been identified, they can expand their food options again.

Low Histamine and/or Low Tyramine Diet	Low-Carbohydrate Diet
Paleo Diet	Specific Carbohydrate Diet

Paleo Auto-Immune Diet	GAPS – Gut and Psychology Syndrome
Candida Diet	Low Inflammatory Diet
FOD-MAPS	Body Ecology Diet

The Specific Carbohydrate Diet

<u>WHO TO SUGGEST IT TO:</u> People with IBS, IBD, chronic gastrointestinal issues, eczema, asthma, behavior issues, and/or allergies.

<u>WHAT IS IT ABOUT:</u> Eliminating bacterial overgrowth and creating an environment that does not support intestinal yeast. Unlike the Paleo diet, it does allow some low-lactose dairy items.

<u>HOW DOES IT WORK:</u> Limiting larger carbohydrates such as processed and canned fruits, starchy vegetables, all grains, processed meats, and most milk products. Easier to digest carbs are eaten such as fresh/frozen fruits, non-starchy vegetables, meat, fish, eggs, some cheeses, yogurt, some juices and raw nuts.

Candida Diet

WHO TO SUGGEST IT TO: People who have tested positively for Candida overgrowth. People with digestive and skin issues who are untested for Candida but have a history of antibiotic use (2+ times).

WHAT IS IT ABOUT: Eating food that will not feed Candida, yeasts, and bad bacteria in the gut. It may often be combined with an anti-fungal/microbial herbal & supplemental protocol or used in combination with drugs like Nystatin. ***I suggest taking a product called InterPhase (Klair Labs) which is a capsule of enzymes that breakdown bacterial and yeast-created biofilms. This is important to consider for people with chronic conditions and high levels of Candida in the gut.

<u>HOW DOES IT WORK:</u> Avoid eating sugars, yeasts, refined white flour products, vinegar, fermented foods (sauerkraut/miso), and processed fruits (fruit juice/canned fruit).

Again, it is important to work closely with clients on dietary efforts to avoid malnutrition or pushing them into such a restricted diet that they eat themselves into developing a new food sensitivity. This can most easily be avoided by creating a plan with a rotation schedule every 3-4 days of food groups based on families of foods as well as good menu planning and monthly reviews of their diet.

Using Food Sensitivity Testing Options such as the **Mediator Release Test** can be useful for preventing poor compliance, improving clarity of dietary needs, and avoiding guesswork that can sometimes leave people confused and malnourished. This is especially helpful for clients who aren't convinced that their diet is contributing to their symptoms.

GENERAL RECOMMENDATIONS ON A DIET FOR HEALING IP:

Foods to Eliminate from Diet:

Refined carbohydrates, refined sugars, artificial sweeteners, artificial food dyes, artificial flavorings, artificial preservatives (sulfites, nitrates, benzoate), MSG, and oxidized fats

(fried foods, hydrogenated oils), and alcohol (for at least 1 month). Also, eliminate use of NSAIDs completely.

**Foods sprayed with glyphosate (i.e Round-Up and others), especially wheat, have been indicated in the increased incidence of Celiac Disease (Samsel & Seneff, 2013). A GMO-free diet would be highly encouraged as well, in addition to avoiding glyphosate sprayed foods. At the least, avoid eating the "Dirty Dozen" most heavily sprayed fruits and vegetables if eating organic foods isn't an option.

Foods to Consider for Temporary Elimination (1-6 months – longer is better)

Before beginning any elimination diet, encourage people to reduce that food gradually and then eventually eliminate it after a few weeks. This is much less stressful than going cold turkey and can help compliance. Yet if the client is willing, get them started ASAP. Consider these to be reactive foods until proven otherwise by elimination/rechallenge or MRT testing.

Common Allergenic and Food Sensitivities:

1. Dairy	5. Beans (especially soy, lentil, and kidney)
2. Gluten grains (wheat, rye, spelt, barley)	6. Peanuts
3. Eggs	7. Fish (especially shellfish)
4. Tree nuts	8. Corn

Foods to Generally Increase As Appropriate

Organic	Whole and unprocessed	Eat with Positive
Low Glycemic Index	foods	Thoughts/Intentions
Foods	Diversity of colorful fruits	Bone Broth
Nutrient Dense Foods	and vegetables	Fiber (bind endotoxins in
Organ meats	Lacto-fermented foods**	gut**
Grass fed butter/ghee	Prebiotic Rich Foods**	Colostrum

**Use these in moderation and gradually increase. In cases of dysbiosis and IP, the sensitivity of the gut may not be able to tolerate much of these. Certainly utilize as a part of the maintenance plan once signs of inflammation and reactivity have been subdued. It is more important to identify food sensitivities before worrying about which prebiotics or lacto-fermented foods need to be a part of the diet. This is a common mistake that can end up causing more aggravation in a sensitive gut. When the gut is ready, larger amounts of dietary fiber will help to restore the gut and has in many cases shown to help reduce symptoms in IBS, IBD, Ulcerative Colitis, and other GI-based issues.

Sauerkraut and Lacto-fermented foods

Use these foods slowly and gradually increase, especially once inflammation is reduced. These foods help to heal the gut and contain a rich source of probiotics (including *Lactobacillus plantarum*) and Butyric Acid. Both have research and traditional use confirming their benefit in healing the gut.

Grass Fed Butter/Ghee: Grass fed sources of butter and Ghee contain butyrate which helps to heal the gut and regulate the microbiome. In fact, "BUTRY-ate" comes from the Greek word for Butter. For those who cannot tolerate dairy, Ghee may be more tolerated and agreeable because it does not contain lactose or casein.

HERBAL APPROACHES

NOTE: Due to the complexity of Leaky Gut Syndromes, avoid suggesting generic approaches such as L-glutamine powder and DGL licorice as "a place to start". Often these are the reserved for later stages of healing. Always remember to "treat the person and not the problem". For this reason, I am listing herbs below by their herbal actions rather than writing down a protocol to follow. Custom tailoring the dietary and herbal actions will greatly enhance your work with each individual. Remember, no two people are the same, especially no two people with Leaky Gut Syndrome. Here are two examples I have summarized for consideration in creating protocols for Leaky Gut Syndrome.

A Functional Medicine Approach to Leaky Gut Syndrome: The 4 R Program

- 1. REMOVE A) Pathogenic factors like yeast, parasite, bacteria. B) gastric irritants alcohol/caffeine/drugs. C) food allergens/sensitivities. In identifying these foods, also try to identify if it is dose dependent (what amount or accumulation over time is needed to trigger a response).
- 2. REPLACE Where there is weak digestion, integrate Betaine HCl, bile salts, digestive enzymes, or 1 T. apple cider vinegar
- **3.** REINOCULATE Replenish good bacteria into the gut with probiotic supplementation and prebiotic rich foods/herbs/supplements.
- **4.** REPAIR- Give the gut nutrients to repair itself. Often recommendations are made for supplementation of zinc, L-glutamine, Omega 3 fish oils, DGL licorice, Slippery Elm, Aloe vera, Vit. A, C, E, D, and B-vitamins.

A Traditional Chinese Medicine Approach to Leaky Gut Syndrome

Jake Paul Fratkin, OMD, R.Ac., has outlined the following organ systems to address generally in the order listed for Leaky Gut Syndrome. Here is an adapted summary I utilize myself.

**REMEMBER: Always treat areas of excess first before building up deficiency. If initial efforts only focus on tonification when patterns of excess are present, the treatment will potentially strengthen the pathology as well. For example, if someone with stagnation of Qi or Blood is tonified with herbs, it will create further stagnation unless efforts to move the stagnation are initiated first or at least used in combination with tonifying herbs in more mild cases.

1. LIVER

In Leaky Gut Syndrome, a lot of toxins get dumped in the liver. Poor sleep, fatigue, menstrual irregularities, cramps, bloating, headache, and constipation may be associated with Liver patterns.

Three areas of imbalance may manifest: Gynecological, Digestive, and/or Lymphatic (signs of fatigue, lymphatic swelling, and/or low grade fever). Identify which area(s) are out of balance. Identify damp heat or toxic heat.

- Herbal Goals: Clear Heat, Invigorate the Blood, Move the Qi. Focus on strengthening the eliminatory pathways instead of purging them with a "heavy detox".
- 2. SPLEEN Identify the energetic presentation with questions, pulse, tongue, and tests such as Comprehensive Digestive Stool Analysis, Chymotrypsin, Lactulose/Mannitol, Candida, Parasite, and food sensitivity testing (MRT). The Spleen Qi is often deficient in people with IP because the Spleen is responsible for repair of the intestinal wall.
 - A. If present, create a plan to eliminate pathogenic factors including fungus, parasite, food allergies/sensitivities, and eliminate NSAIDS.
 - B. Assess digestive ability of client. Tonify? Stimulate Digestive Fire? Is the pulse strong/weak?
 - Herbal Goals: Use Spleen Qi Tonics (Prebiotic rich/mucilaginous), Digestive Bitters, and Heat Clearing Herbs (Anti-inflammatory).
- 3. KIDNEY Chronic Leaky Gut Syndrome often leads to adrenal fatigue and Kidney deficiency. Adrenal herbs that tonify Kidney Yang are contraindicated in early stages of Leaky Gut treatment. Often Kidney Yin is depleted first and then Kidney Yang. Differentiate if only or both KD Yin and Yang are depleted.
 - Herbal Goals: Tonify Kidney yin and/or yang as needed.
- 4. HEART Symptoms of Disturbed Shen present in people with Leaky Gut Syndrome as poor/restless sleep, dream-disturbed sleep, slow/dull thinking, brain-fog, anxiety, insomnia, palpitations, and people who are jumpy or easily frightened. Often, these symptoms are resolved by the time the Liver, Spleen, and Kidney patterns of imbalance have been addressed as well as identification of food sensitivities.
 - Herbal Goals: Calm the shen (nervines and trophorestoratives)

HERBAL ACTIONS

The following actions are listed in order of general suggested use. Remember to save Tonics for later stages.

PREPARATIONS: The following herbs can be used in various forms. I recommend powdered forms often mixed with milk or water and encapsulated herbs. Also teas/infusions are excellent if taste is acceptable and client has compliance. Tinctures can be used though do so with caution in people with very sensitive guts.

1st . HERBS FOR REMOVING PATHOGENIC HEAT and INFLAMMATION

Anti-Microbial	Anti- Inflammatory
(bacterial/parasitic/ameobic)	Alder Bark
Andrographis	Amla Fruit
Baptisia	Baikal Scullcap
Black Walnut	Bupleurum- Chai hu
Elecampane	Butterfly Bush flower
Oldenlandia	Chamomille Flower
Isatis	Dan Shen
Barberry	Gotu Kola
Eucalyptus	Sarsparilla
Goldenseal	Calendula
Oregon Grape Root	Cayenne
Chapparal	Meadowsweet
Eclipta	Myrrh
Japanese Honeysuckle	Boswellia
Neem	Gum Guggul
Prickly Ash	Pine
Propolis	Plantain leaf
Rosemary	Purple Loosestrife
Sage	Rose
Spilanthes	Lady's Mantle
Thuja	Yarrow
Usnea	Goldenrod
Violet	Chrysathemum
White Mulberry Leaf	Sumach Berries/Bark
Wormwood	Triphala
	Tulsi

Additional Anti-Inflammatory Herbal Seed Oils

Borage Oil, Evening Primrose Oil, Black Currant Seed Oil, Flax Seed Oil

$2^{\rm nd}$. HERBS FOR MOVING LYMPHATIC AND LIVER STAGNATION

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Lymphatic	Chologogue/Hepatoprotective/Bitter
Cleavers	Stimulant
Echinacea	Angelica
Figwort	Mugwort
Poke	Orange Peel
Red Root	Turmeric Root
Ocotillo	White Peony

Stillingia	Yellow Dock
- 6	

3rd. IMMUNE REGULATION AND ADRENAL SUPPORT

Immune Amphoteric/Regulator	Adaptogen/Adrenal Support
Astragalus	Amla
Una de Gato – Cat's Claw	Codonopsis
Licorice Root	Cordyceps
Maitake	Schisandra
Resihi Mushroom	Eleuthero
Turkey Tail	Rhodiola
Guduchi – Tinospora	Jiaogulan
Unprocessed Rehmania	Shatavari

4th . HERBS FOR REPAIR AND NUTRITION:

Nutritive Herbs:	Tissue Demulcent:
Burdock Root	Aloe Vera
Chickweed	Sassafras bark/leaf
Irish Moss	Marshmallow Root
Nettle leaf	Slippery Elm bark
Horsetail	Comfrey Root/leaf (cold infuse)
Dandelion Leaf	Kudzu Root
Milky Oats	Jujube Fruit
Red Clover	Evening Primrose leaf/flower/root
Beet Root	Fenugreek

5th . KIDNEY YIN and YANG TONICS

Kidney Yin Tonic	Kidney Yang Tonic
Tian Men Dong – Chinese Asparagus Root	Ashwagandha
Cordyceps	Epimidium – Horny Goat Weed
Processed Rehmania	Morinda root
Solomon's Seal	Psoralea Seed – Bu Gu Zhi
Nettle Leaf/Seed	Cordyceps

Animal Studies:

Many studies have been conducted on herbs and food using mice. The gut microbiome of mice and humans is very similar and has produced informative correlations about IP in humans and mice based on specific known pathways causing IP. Unfortunately, the only direct research on the influence herbs can have on IP have been in-vitro and animal studies (which is also unfortunate for the animals harmed). Here are some examples to consider extrapolating on for human use.

Japanese Honeysuckle Buds (Lonicera japonica) A study using a water extract of Flos Lonicera was shown to reduce endotoxemia and improve intestinal wall integrity in mice

(Wang et al. 2014). Interestingly, it has been used in TCM for clearing blood heat (infections), fire poison (toxins), pathogenic fire, abdominal distension, nausea, and fevers with stomach pain.

Quercitin/Resveratrol: Mice fed a high-fat diet (known to induce microbiome dysbioisis) had reduced dysbiosis after the administration of quercetin. Additionally, resveratrol either in combination with the quercitin or alone was found to reduce inflammation in the intestinal wall by altering mRNA expression of tight-junction proteins and cytokines. (Etxeberria et al. 2015)

Prebiotics: Mice fed prebiotics showed lower levels of inflammatory cytokines, oxidative stress markers, and reduced levels of plasma lipopolysaccharides (endotoxins released by Gram-negative bacteria through intestinal wall) indicating a reduction in intestinal permeability compared to controls. (Cadi et al. 2009)

Reishi (*Ganoderma lucidum*) – A water extract of Reishi mycelium was fed to mice on a high-fat diet (HFD) that is known to cause dysbiosis and obesity. Not only did the Reishi reduce inflammation, weight-gain, and insulin resistance, it also reversed HFD-induced dysbiosis, preserved intestinal barrier integrity, reduced metabolic endotoxemia, and had a modulating effect on the microbiome (Chang et al. 2015).

SUPPLEMENTAL SUPPORT

Consider some basic supplementation for healing the gut. These have been popularly used by many practitioners in the herbal, naturopathic, and functional medicine fields.

Probiotics:

-Genestra Human Strain Probiotics – I recommend the Intensive capsule (25 Billion CFU) 1 cap 1x/day for 1 month or the Replenish capsule 1 cap 1x/day (100 Billion CFU) with a 2 week supply.

-VSL#3 – This is a pharmaceutical grade probiotic that has been shown to have some of the best efficacy for treating IBS, ulcerative colitis, and dysbiosis. A written prescription can be obtained from GI-Specialists or you can buy it on Amazon though the concentration is lower (112.5 Billion CFU) where as the written prescription can contain various levels up to 450 Billion.

Digestive Enzymes: In chronic digestive conditions, digestive enzymes have been found to offer relief and improve healing. While I am not a fan of long-term dependency on these enzymes, they are helpful for healing the gut. Find digestive enzymes supplements with: protease, amylase, lipase, lactase, sucrase, maltase, phytase, and cellulase. *Remember that digestive bitters can stimulate the secretion of several of these enzymes.

1.2 appropriate in comparably recommended with each recal

1-2 capsules is generally recommended with each meal.

L-Glutamine: 750-1500mg/day

Butyric Acid – In-vitro and animal studies have shown promising evidence that Butyric acid can help heal tight junctions and reduce IP. It is important in the regulation of the cellular regeneration and apoptosis in the GI-tract and also influences microflora diversity. Butyric acid has been shown to help regulate the immune system and has an anti-inflammatory effect in the gut. While human research is still limited, it may be beneficial in treating people with IBS (Zaleski et al. 2013). It can be taken in the form of calcium and magnesium butyrate.

600 mg butyrate TID with meals

Phosphatidylcholine – This has been shown to increase remission times in people with ulcerative colitis and is an essential component in cell membrane formation, especially in the gut. 2-6g/day.

B-Vitamins – Food based B-vitamins are preferred over synthetic forms. Daily B-vitamins are sufficient though B-12 should be taken in a sublingual form for best absorption. This will improve tissue repair and cellular detoxification.

Vitamin C (w/ bioflavonoids): 1000-2000mg/day.

Vitamin D – 5000 IU/day

Vitamin E (d-alpha tocopheryl succinate): 200-400 mg/day

Zinc – Zinc picolinate or zinc L-carnosine – Supports immune function, helps to heal skin and gut tissue, and is needed in DNA/RNA synthesis. Take 30-90 mg/day

Quercitin: 400-800 mg/day

Omega 3 Fatty Acids – Long Chain Fatty Acids are metabolized by specific Lactobacillus in the gut and promote their population growth as well as protect against alcohol induced liver damage in humans and mice (Chen et al. 2015). Omega 3 fish oil is an essential component in reducing inflammatory mediators contributing to IP. 3-6 g/day

LIFESTYLE RECOMMENDATIONS

A large amount of evidence shows that stress can induce dysregulation in the gut and contribute to the onset and perpetuation of IBS symptoms. Stress reduction is especially needed as nueroimmunological dysregulation is easily remembered by the gut and stressors from diet, work, family, and society can reawaken the old patterns. Making positive changes in the life of a person with IP is crucial for avoiding stressful triggers that can perpetuate dysfunction in the gut. Getting 8-9+ hours of sleep every night is also recommended. Yoga, Tai Chi, and Qi Gong have also been associated with helping to reduce stress and healing the gut. Mindfulness meditation is also beneficial in healing the gut. Finally, taking time to appreciate the food we put in our body is paramount in

healing the gut. Mindfulness in eating foods that heal the gut, avoiding food sensitivities, and holding the whole experience with thankfulness is going to help the healing journey.

OUTCOME:

Leaky Gut Syndrome is determined by the presence of IP. Following a focused and personalized approach is the key to success in healing the intestinal wall and regulating the gut microbiome. By addressing factors leading to IP and maintaining an elimination of food allergens/food sensitivities, clients can expect to heal the gut generally within 2-6 months depending on severity of symptoms. Remember that all imbalances in the body are messages for individuals, acting as a signal for a need to change something. "Life as usual" will look different as care and attention need to be maintained in regards to diet, stress, environment, drug use, and outlook on life. Utilizing an integrative approach with many tools is going to bring the best success for these chronic conditions.

OTHER RESOURCES FOR MORE ON LEAKY GUT SYNDROME:

Casey Resnick, ND: Nutritional Protocol for the Treatment of Intestinal Permeability Defects and Related Conditions:

http://natural medicine journal.com/journal/2010-03/nutritional-protocol-treatment-intestinal-permeability-defects-and-related

Jake Paul Fratkin: Leaky Gut Syndrome: A Modern Epidemic http://drjakefratkin.com/articles/leaky-gut-syndrome-a-modern-epidemic

REFERENCES

Aydinlar EI, Dikmen PY, Tiftikci A, Saruc M, Aksu M, Gunsoy HG, et al. IgG-based elimination diet in migraine plus irritable bowel syndrome. Headache. 2013;53:514–525.

Alpay K, Ertas M, Orhan EK, Ustay DK, Lieners C, Baykan B. Diet restriction inmigraine, based on IgG against foods: a clinical double-blind, randomized, cross-over trial. Cephalalgia 2010;30:829-37.

Arrieta, MC et al. 2006. Alterations in intestinal permeability. Gut. 2006 Oct; 55(10): 1512–1520.

Bienenstock, J. (2012). Commensal communication to the brain: pathways and behavioral consequences. *Microbial Ecology in Health and Disease*, 23, 10.3402/mehd.v23i0.19007. doi:10.3402/mehd.v23i0.19007

Cani, PD et al. 2009. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009;58:1091-1103 doi:10.1136/gut.2008.165886

Carpenter, S. 2012. "That Gut Feeling" The American Psychology Association. September 2012, Vol 43, No. 8. Retrieved on 7/26/15 from: http://www.apa.org/monitor/2012/09/gut-feeling.aspx

Cesaro C. et al. 2011. Gut microbiota and probiotics in chronic liver diseases. Dig Liver Dis. Jun;43(6):431-8. doi: 10.1016/j.dld.2010.10.015

<u>Chang CJ</u> et al. 2015. Ganoderma lucidum reduces obesity in mice by modulating the composition of the gut microbiota. <u>Nat Commun.</u> 2015 Jun 23;6:7489. doi: 10.1038/ncomms8489.

Chen, P. et al. 2015. Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. Gastroenterology. Jan;148(1):203-214.e16.

<u>Chistiakov</u>, DA et al. 2014. Intestinal mucosal tolerance and impact of gut microbiota to mucosal tolerance. Front Microbiol; 5: 781. Published online 2015 Jan 13. doi: 10.3389/fmicb.2014.00781

Choudhry MA, Rana SN, Kavanaugh MJ, Kovacs EJ, Gamelli RL, Sayeed MM. Impaired intestinal immunity and barrier function: A cause for enhanced bacterial translocation in alcohol intoxication and burn injury. Alcohol. 2004;33: 199–208.

Christensen EG, Licht TR, Kristensen M, Bahl MI: Bifidogenic effect of whole-grain wheat during a 12-week energy-restricted dietary intervention in postmenopausal women. *Eur J Clin Nutr*; 2013 Dec;67(12):1316-21

Denno, DM. et al. 2014. Use of the Lactulose to Mannitol Ratio to Evaluate Childhood Environmental Enteric Dysfunction: A Systematic Review. Clinical Infectious Diseases Volume 59, Issue suppl 4Pp. S213-S219.

Dharmananda, Subhuti. Chapter 6 *Xuedao Zheng*, *Baihe Bing*, *Meihe Qi*. [blood course syndrome, lily disease, plum-pit qi] Retrieved from: http://www.itmonline.org/shen/chap6.htm. 7/26/15.

<u>Earley</u>, ZM et al. 2015. Burn Injury Alters the Intestinal Microbiome and Increases Gut Permeability and Bacterial Translocation. PLoS One; 10(7): e0129996.

Etxeberria U. et al. 2015. Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats. J Nutr Biochem. Jun;26(6):651-60. doi: 10.1016/j.jnutbio.2015.01.002. Epub 2015 Feb 26.

Fasano A. 2011. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. *Physiol Rev. Jan*; 91(1):151-75.

Frank, M. et al. IgG-dependent food allergy and its role in selected dieases. Pediatr Pol 2012; 88(3):252-7

Fratkin, Jake Paul. 2014. "Leaky Gut Syndrome: A Modern Epidemic". Website: The Environmental Illness Resource. Retrieved on 7/26/15 from: http://www.ei-resource.org/articles/leaky-gut-syndrome-articles/leaky-gut-syndrome-diagnosis-and-treatment/

Galland, L. 1995. "Leaky Gut Syndromes: Breaking the Vicious Cycles." *Townsend Letter for Doctors*, August/September p. 63.

Galland, L. 2010. "Do you have Leaky Gut Syndrome?". Huffington Post. 09/10/2010. Retrieved from: http://www.huffingtonpost.com/leo-galland-md/do-you-have-leaky-gut-syn_b_688951.html

Genova Diagnostics. 2008. Intestinal Permeability Assessment. g.ig.ip.071008

Holmes, Peter. 1998. The Energetics of Western Herbs. Volume 2. Ref. P. 669.

Lambert GP. Stress-induced gastrointestinal barrier dysfunction and its inflammatory effects. *J Anim Sci.* 2009;87(14 Suppl):E101-108

Maes M, Kubera M, Leuins JC. The Gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro Endorinol Lett 2008; 29(1):117-24

Maes M, Coucke F, Leunis JC. "Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome." Neuro Endocrinol Lett. 2007 Dec;28(6):739-44.

Magnotti LJ, Deitch EA. Burns, bacterial translocation, gut barrier function, and failure. J Burn Care Rehabil. 2005;26: 383–391.

Oldenwald, M.A., Turner, J.R. 2013. Intestinal permeability defects: Is it time to treat? Clin Gastroenterol Hepatol. 2013 Sep; 11(9): 1075–1083.

Maes M, Leunis JC. 2008. "Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: effects of age, duration of illness and the translocation of LPS from gram-negative bacteria." *Neuro Endocrinol Lett*. Dec;29(6):902-10.

Resnick, C. 2010. Nutritional Protocol for the Treatment of Intestinal Permeability Defects and Related Conditions. Natural Medicine Journal. <u>March 2010 Vol. 2 Issue 3</u>

Romm, Aviva. 2014. "10 Signs That You May Have Leaky Gut Syndrome and How to Heal It." May 4, 2014 // posted in blog, children's health, food & health, women's health. Retrieved from: http://avivaromm.com/10-signs-leaky-gut

Samsel A, Seneff S. 2013. Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. <u>Interdiscip Toxicol.</u> Dec;6(4):159-84. doi: 10.2478/intox-2013-0026. Sears, R.W., Sears, W. 2015. The Allergy Book. Little, Brown and Company. New York.

Smale S, Bjarnason I. Determining small bowel integrity following drug treatment. *British Journal of Clinical Pharmacology*. 2003;56(3):284-291.

Wu, H.-J., Ivanov, I. I., Darce, J., Hattori, K., Shima, T., Umesaki, Y., ... Mathis, D. (2010). Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. *Immunity*, *32*(6), 815–827. doi:10.1016/j.immuni.2010.06.001

<u>Suenaert P</u>. 2002. Anti-tumor necrosis factor treatment restores the gut barrier in Crohn's disease. Am J Gastroenterol. Aug;97(8):2000-4.

<u>Wang JH</u> et al. 2014. Flos Lonicera ameliorates obesity and associated endotoxemia in rats through modulation of gut permeability and intestinal microbiota. <u>PLoS One.</u> Jan 24;9(1):e86117. doi: 10.1371/journal.pone.0086117.

Załęski A, Banaszkiewicz A, Walkowiak J. Butyric acid in irritable bowel syndrome. *Przegla* □ *d Gastroenterologiczny*. 2013;8(6):350-353. doi:10.5114/pg.2013.39917.