

Leaky Gut Syndrome, Part 1

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Abstract

The gastrointestinal mucosa deals with the variety of antigens it encounters in a highly controlled fashion. Antigens are transported via the transcellular route during which neuroendocrine and immune mediators are activated. Under certain pathological conditions the tight junctions between epithelial cells become "leaky," thus facilitating increased antigen uptake. This results in four vicious cycles, namely, allergy and inflammation, malnutrition, bacterial dysbiosis, and hepatic stress. These cycles play a role in the pathogenesis of disease or may contribute to their symptoms. The recognition, diagnosis, and treatment of "leaky gut syndrome" is imperative in complementary practice and forms an important part of the multifactorial model of pathogenesis and management of various disease entities.

Resumen

La mucosa gastrointestinal utiliza una manera sumamente controlada para dar trato a la variedad de antígenos que encuentra. Los antígenos se transportan vía el camino transcelular durante lo cual se activan los mediadores neuroendo-

crinas e inmunes. Bajo unas condiciones patológicas, las conexiones comienzan a tener agujeros, que facilita la captación aumentada de antígenos. Este resulta en cuatro ciclos viciosos: la alergia y la inflamación, la malnutrición, la disbiosis bacteriana, y la tensión hepática. Aquellos ciclos hacen un papel en la patogénesis de las enfermedades o pueden contribuir a sus síntomas. El reconocimiento, el diagnóstico, y el tratamiento del "síndrome de la barriga agujereada" son partes importantes del modelo multifactorial de la patogénesis y del manejo de una gran variedad de enfermedades.

Introduction

The role of the gut in systemic disease is not a new concept. The Austrian physician and researcher FX. Mayr (1875-1965) considered the gut "the root system of the human organism" and spent his life's work treating systemic disease via gut cleansing.¹ However, the linear model of disease was dismissed by modern medicine until recently, when researchers rediscovered the gut as a complex physiological entity and its role in disease.

The gut mucosa can be considered one of the sensory organs. The contents of the

gut are from outside the body and it is up to the gastrointestinal mucosa to recognize this multitude of substances as either noxious or useful to the body. Thus, the gut needs to act as both barrier and facilitator. To understand the mechanism involved in this complex task we need to examine the structure of the mucosa in greater detail.

Structural considerations

The gastrointestinal epithelium consists of a single layer of cells covering the villi and extends into the crypts. The majority of cells transport enterocytes among goblet cells, enteroendocrine cells, intraepithelial leukocytes, M cells, and Paneth granular cells. The epithelial cells are joined at their apices by the zona occludens or the so-called tight junctions and are supported beneath the lamina propria by a fibroblast sheath.² This paracellular pathway consists of two components, namely the tight junction and the subjunctional space.³ The tight junction is a narrow belt that circumferentially wraps the apical pole of the epithelial cells. The lateral membranes of adjacent cells form fusions that anastomose around the cell. These fusions are a meshwork of strands and grooves. The number of strands determines the resistance of the paracellular pathway. The strands have

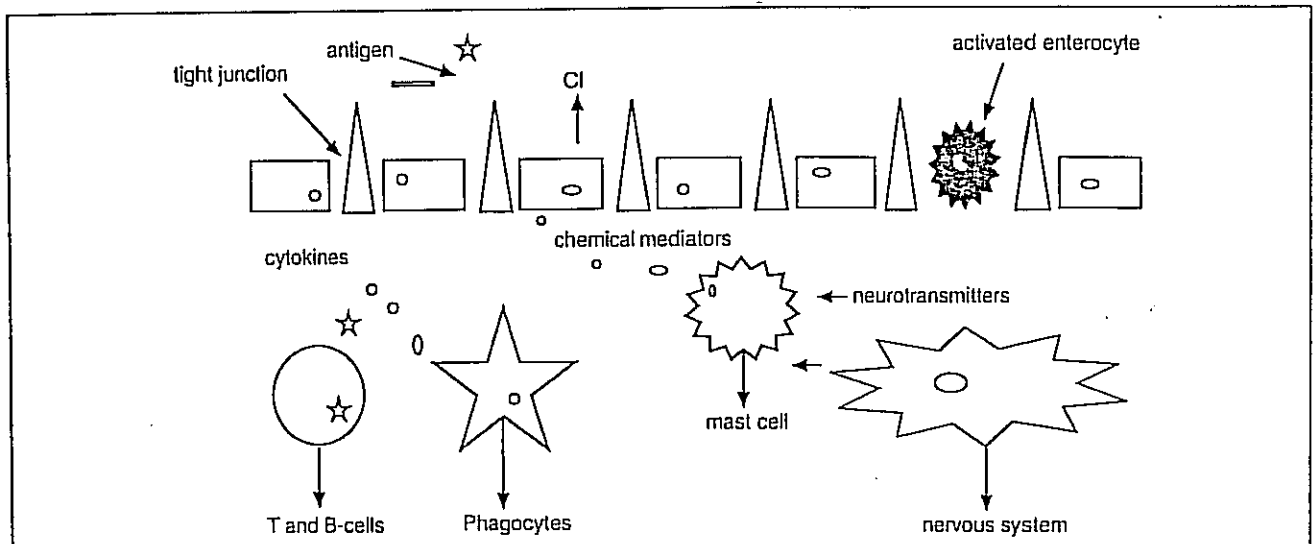


Figure: Neuro-endocrine-immune interactions in the gut mucosa.

channels or pores that can open or close. The pores may be influenced by intracellular events such as cyclic AMP, calcium, and protein kinases.³ The apical surface of epithelial cells also has a circumferential ring of actin and myosin that can be activated by phosphorylation, thereby altering the diameter of the paracellular pathway.

The lamina propria contains structural mesenchyme cells as well as the full complement of the immune armament.⁴ In fact, a large portion of the human immune system is located in the gut. The autonomic nervous system sends some fibers into this area and helps control intestinal transport.⁵

Functional considerations

The barrier function of the gut is a perfect example of psychoneuroendocrine immunology in action (Fig.). The extrinsic barrier is made up of the mucus layer and secretory IgA as well as the normal gut flora, which prevent toxins from having direct contact with the epithelial surface. The active barrier is more important and comprises the mucosal epithelium, ion secretion into the lumen, the intraepithelial lymphocytes, and the immune system in the lamina propria.^{2,6} These form a complex integrated network that responds to any noxious substance. The liver is part of the barrier function of the gut since all toxins not eliminated by the gut reach this organ via the portal system and have to be detoxified by phase I and phase II enzymes.⁷

Rather than being a passive transport medium, the enterocytes are truly pluripotential. An activated enterocyte can bind antigens, thus serving as an antigen-presenting cell, and display major histocompatibility complex markers on its surface. Presentation of the antigen to the population of CD8 cytotoxic suppressor cells in the lamina propria releases cytokines and activates the cellular immune response. It is also able to secrete ions such as chloride into the lumen that will wash away potential antigens by forcing fluid secretion into the gut. This is thought to play a major role in the control of the diameter of the paracellular pathways via the above-mentioned mechanisms.² Lastly, an enterocyte secretes IgA, contributing to the passive barrier of the gut.

Immune stimulation results in the release of chemical mediators, enzymes, oxidants, and neurotransmitters, many of which affect epithelial function. Neurotransmitters can also stimulate or inhibit ion transport. The autonomic nervous system endings often appear in close relation to certain immune cells such as mast cells in the lamina propria. Histamine from the latter activates the neural network to secrete ions into the lumen. Thus, to ward off noxious substances, the gut mucosa responds in a complex, highly integrated fashion.^{2,3,8,9}

However, the dysregulation of this very delicate system, which is sensitive to our modern lifestyle, may be the initiating factor in many modern diseases that defy identification of a single causative agent.

Pathological considerations

Antigens enter the gut mostly in a controlled fashion via the transcellular pathway by binding to enterocytes or M cells. In certain pathological states, however, paracellular transport is increased, thereby allowing unchecked entry of antigens into the body.¹⁰

Our modern lifestyle is not gut friendly. Infections, drugs, certain foods, and psychological stress can cause the paracellular

Intestinal disorders
Food allergy
Celiac disease
Chronic intestinal infection
Inflammatory bowel disease
Surgery
Systemic insults
Burns
Radiation
Septicemic shock
Hypovolemic shock
Malnutrition
Drugs
Nonsteroidal anti-inflammatory drugs
Ethanol
Cytotoxic drugs
Free radicals
Biliary
Foodborne

Table 1: Causes of increased antigen uptake in the intestinal mucosa.

pathway to become more permeable or leaky, thus resulting in the so-called leaky gut syndrome.¹¹⁻¹⁶ The causes of increased paracellular permeability are summarized in Table 1.

The unprecedented onslaught of antigens results in four vicious cycles:

1) Allergy and inflammation

Considering the complex response of the mucosa toward an antigenic stimulus, it should be clear that food allergy increases mucosal permeability through inflammation, which in turn exacerbates food intolerance. Children with food allergies have increased intestinal permeability.^{17,18} The effect of the immune system activation is not, however, confined to the intestinal mucosa. The immune cells in the gut mucosa form part of the so-called mucosal-associated lymphoid tissue (MALT). Once the cells are sensitized in the gut they are absorbed into the bloodstream and move to other sites in the body where they degranulate and their chemical mediators cause inflammation. This forms the basis of asthma, urticaria, and skin disease in response to a food antigen. This concept is used in tests for food intolerance in which the degranulation of neutrophils in peripheral blood is examined following various food challenges.¹⁹

2) Malnutrition

Inflammation of the gut mucosa impairs the active transport of nutrients via the enterocytes. Many nutrients are carried over the membrane by a carrier protein often requiring binding to certain cofactors such as vitamins and trace elements.⁷ This disrupted mechanism results in malnutrition. Turnover of gut mucosa cells occurs every 3 to 6 days, resulting in high metabolic demand. When this demand is not met the epithelium becomes even more disrupted, resulting in exacerbation of the hyperpermeability.

3) Bacterial dysbiosis

Many causes of leaky gut syndrome also cause an imbalance between normal and pathogenic gut flora. Dysbiosis occurs when disease or dysfunction is induced by organisms of low virulence that alter the immunologic and metabolic responses of the host.¹¹ Bacterial endotoxins have been implicated in the pathogenesis of various

Abdominal
Pain
Diarrhea
Distention
Food intolerance
Immunological
Arthralgia
Myalgia
Skin rashes
Fever of unknown origin
Cerebral
Fatigue
Cognitive dysfunction
Memory loss
Mood swings
Other
Toxic feeling
Poor exercise tolerance
Shortness of breath

Table 2: Symptoms associated with increased intestinal permeability.

disease processes such as Crohn's disease, seronegative spondylarthropathies, and rheumatoid arthritis.^{20,21} The inflammation induced by the reaction to the bacterial antigens that enter the body unchecked further induces hyperpermeability, thereby setting up a vicious cycle.

4) Hepatic overload

When toxins are not barred by the intestinal mucosa or removed by the MALT, the liver has to deal with an increased toxin load. This will stress the phase I mixed function oxidases and can result in depletion of their cofactors such as iron, zinc, copper, manganese, and the B vitamins, among others. The phase II sulfur-containing amino acids, i.e., cysteine, glycine, and glutathione, are not regenerated during detoxification, leading ultimately to depletion of these substances that also play a major role in the scavenging of oxygen-derived free radicals. The result is an increase in dangerous intermediate substances such as acetaldehyde, which may be shunted into the bloodstream.

Due to the lipophilic nature of these toxic byproducts, the brain becomes a major target, resulting in various symptoms of cognitive dysfunction and fatigue. Reactive oxygen substances damage proteins and membranes, thereby exposing denatured proteins to the immune system,

which may cause autoimmunity and other degenerative diseases.

Hepatic overload with dietary toxins also decreases the liver's ability to deal with other exotoxins or endotoxins (for example, histamine), resulting in chemical sensitivity to previously tolerated substances or to up-regulation of the immune system.

Increased intestinal permeability and disease

Thus, it should be clear that leaky gut syndrome not only causes a host of symptoms in the gut and at distant sites, but also may play a major part in the development of various disease processes or sustain the mechanisms involved in these syndromes and diseases.

Studies on healthy relatives of patients with Crohn's disease, for instance, suggest that increased permeability exists in these families.²⁰ Intestinal permeability tests may also be used to predict exacerbations of Crohn's disease. The symptoms of leaky gut syndrome and the diseases associated with it are summarized in Tables 2 and 3.

Diagnosis of leaky gut syndrome

A relatively noninvasive test exists to diagnose increased intestinal permeability.²² The test is performed by giving the patient a cocktail of 5g each of lactulose and mannitol. These innocuous sugars are not metabolized by humans so the amount absorbed is excreted in the urine in 6 hours. Mannitol is passively transported through the enterocyte; mean absorption is 14% of the administered dose (range, 5%-25%). The normal mucosa is impenetrable to lactulose, a disaccharide, and less than 1% of the administered dose is absorbed. The differential excretion of lactulose and mannitol in the urine is then measured (normal, <0.03%). A higher amount indicates an excessive absorption of lactulose through the paracellular pathway.

Treatment of leaky gut syndrome

Any patient presenting with the symptoms or diseases listed in Tables 2 and 3 should be suspected of having increased

intestinal permeability. The treatment is aimed at breaking the four vicious cycles including removal of causative factors, support and regeneration of the gut mucosa, and hepatic support.

Summary

Intestinal permeability to antigens is a well-controlled physiological process. Paracellular uptake of antigens increases under certain conditions, setting up four vicious cycles that can cause a host of symptoms and contribute to a number of disease processes. The recognition and management of increased intestinal permeability is imperative in the complementary treatment of these diseases and demonstrates the multifactorial causes of many modern diseases, a number of which have defied the linear model most commonly applied in conventional medicine.

Abdominal
Irritable bowel syndrome
Inflammatory bowel disease
Infectious enterocolitis
Celiac disease
Pancreatic insufficiency
Hepatic dysfunction
Skin disease
Eczema
Psoriasis
Urticaria
Acne
Dermatitis herpetiformis
Rheumatological
Rheumatoid arthritis
Spondylarthropathies
Pain treated with nonsteroidal anti-inflammatory drugs
Immunological
HIV / AIDS
Chronic fatigue syndrome
Multiple food and chemical sensitivities
Cerebral
Childhood hyperactivity
Autism
Other
Cystic fibrosis
Alcoholism
Neoplasia treated with cytotoxic drugs

Table 3: Diseases associated with increased intestinal permeability.

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Leaky Gut Syndrome, part II

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A leaky gut or altered intestinal permeability plays a major role in the causation and perpetuation of a host of diseases. In its own right altered intestinal permeability could explain the myriad of symptoms of the ever increasing number of ambulatory patients which cross our doors daily and who defy conventional diagnoses. Recognition and treatment of this syndrome is imperative in the management of these in order to maximize their outcome.

Diagnosis

The recognition of this syndrome requires firstly a high index of suspicion on the part of the practitioner. This should be the rule when one is faced with the diseases or with the symptom complex discussed in part one of this article (*BT* June 1999). If increased intestinal permeability is suspected, the history of the patient should be expanded to include a detailed dietary and lifestyle analysis e.g., drug and ethanol intake, stress levels, food craving, recurrent yeast infections, reactions to certain foods, intolerance to environmental chemicals, and cognitive dysfunction.

Direct diagnosis - The intestinal permeability test

The intestinal permeability test is a relatively non-invasive test utilizing the two innocuous sugars mannitol and lactulose. This test was first proposed by a French researcher, Claude André, who used the test as a sensitive screening test for food allergy.^{1,2}

The test is performed by giving the patient 5 grams of each of these sugars to ingest and then testing the urine via gas chromatography six hours later for their presence.³ Both are not metabolized in the human body and the amount absorbed is fully secreted in the urine within six hours. Mannitol is a monosaccharide which is passively transported through the enterocyte and about 14% of the ingested dose is normally absorbed (range is 5 - 25 %).

Lactulose is a large disaccharide which is absorbed by less than 1% through the intestinal mucosa. After ingestion the differential excretion of lactulose and mannitol is then measured in the urine.

The normal ratio of lactulose/mannitol in the urine is less than 0.03. If the ratio is higher it indicates that lactulose is absorbed via the disrupted tight junction, indicating that these have become "leaky." The test can also be performed after challenge with a suspected food allergen. An increase in permeability will indicate an allergy or intolerance to the particular food.⁴ Newer tests use innocuous sugars of variable size to determine the degree of disrupted permeability.

Indirect diagnosis - The metabolic questionnaire

If the intestinal permeability test is not available a detailed questionnaire can be used to cover all the organ systems affected by a leaky gut as discussed in part one. These questionnaires can be linked to a point scale in order to assess severity and by redoing them during treatment to monitor progress.⁵

Detection of food intolerance

Measurement of sensitization of peripheral blood lymphocytes to certain food allergens forms the basis of newer food intolerance tests available in selective centers.⁶ Transdermal screening with an electro-acupuncture device offers a practical alternative with the advantage of testing the individual for intolerance to medication that is going to be used. If neither of these two methods are available a bit more detective work is required. The patient should be encouraged to keep an accurate food diary in order to try and pinpoint any adverse symptoms to food. This could be misleading however as there are other variables such as psychological stress, drugs, and environmental toxins which can produce adverse symptoms.

Detection of bacterial overgrowth

A stool sample and in females a vaginal swab will often reveal bacterial or fungal overgrowth. These should be sent to selective laboratories dealing with the detection of dysbiosis. Dysbiosis should be suspected if there is a history of frequent antibiotic use, fungal vaginitis, or symptoms like abdominal bloating and anal itching as well as symptoms of auto intoxication.

The four vicious cycles characteristic of a leaky gut can be demonstrated and quantified in a loose manner with a variable microscope. The presence of fungus and bacteria points to dysbiosis. Evidence of maldigestion suggests pancreatic involvement. Liver overload can be seen as liver spicules and allergy and inflammation will be apparent on the dry smear. This can be repeated at regular intervals to monitor progress.

Management of leaky gut syndrome

The treatment of increased intestinal permeability is aimed at breaking the four vicious cycles of inflammation and allergy, malabsorption, hepatic overload, and dysbiosis. Lastly the repair of the intestinal mucosa is undertaken. In practice I find the approach of Eleanor Barrager of Healthcomm International the most useful.⁵ This is based on the so-called 4-R approach, namely:

- Remove
- Replace
- Reinoculate
- Repair

REMOVE

This refers firstly to the treatment of dysbiosis. If the condition has been present for a long time it is usually not enough to just support the natural defense mechanisms of the gut and active treatment of pathogens is required. Fungal overgrowth

is normally the most difficult to treat and requires optimum individualization and cooperation from the patient.

This is best approached with two natural products, namely citrus seed extract (Citricidal[®]) in a dose of two drops b.i.d. working up to six drops b.i.d. and Caprilic acid (Caprilix[®]) six tabs daily. All yeast and fermented food should be cut out of the diet for three months. In severe cases treatment with a broad spectrum anti-fungal like nystatin for five days or more may be required. I prefer this to the systemic variants, as it is not absorbed. Other infections like parasites and enteropathogens should be treated accordingly.

The second aspect of removal pertains to all dietary and other factors that cause or sustain an increased intestinal permeability. If a direct investigation for food intolerance is done the patient should follow a diet absolutely free of any of the intolerant foods for at least twelve weeks. This is usually sufficient to calm down the sensitized immune system and to reverse the local inflammation in the gut. If these tests are not available one should start to eliminate the most common culprits, namely the protein fraction of wheat and dairy products. Refined sugar should also be avoided as it forms a substrate for fungal growth and sugar may bind to connective tissue proteins thereby impairing repair of the mucosa.

Other factors that may contribute to a leaky gut should also be avoided, for example alcohol, caffeine, and NSAIDs. Indomethacin, for instance, is concentrated in the bile, thereby creating a toxic bile which damages the small bowel mucosa. Nabumetone is the only available non-steroidal which does not increase intestinal permeability.⁴

REPLACE

This refers to the replacement of digestive factors and/or enzymes. These may be lacking or dysfunctional due to a change in the bowel milieu, for instance, hypochloridia caused by an overgrowth of *H. pylori*. If hypochloridia is present bacterial overgrowth will recur a few weeks after the removal regimen. Low grade pancreatitis and a disruption of the mucosa

may lead to a deficiency in dietary enzymes. Hydrochloric acid may be given orally or if not available L-histidine, an essential fatty acid, can be given in a dose of 500 mg b.i.d. The latter probably will increase gastric histamine levels.⁴ Enzymatic replacement with pancreatic enzymes or plant derived proteases, amylases lipases and cellulases is of benefit especially if malabsorption is suspected.⁵ The symptoms of enzyme deficiency include a prolonged feeling of fullness following meals, belching, abdominal bloating, undigested food particles in the stool, steatorrhea, and diarrhea or loose stools.

REINOCULATE

This refers to the reintroduction of so-called "friendly bacteria" or "probiotics." These include the best known Acidophilus and Bifidobacteria species. There are several formulations available, but care should be taken to use only live bacteria and to inoculate preferably after removal and replacement has taken place. Another factor to consider is that these are live culture products and conditions during shipping and storage, i.e., refrigeration, should be optimized to ensure viability. Certain strains seem to be more effective in their action, namely the *Lactobacillus acidophilus* (LA, NFCB1748), *Lactobacillus GG*, *Lactobacillus casei shirota*, and *Bifidobacterium bifido*.⁷ The addition of fructooligosaccharides to the diet supports the growth of these bacteria.

REPAIR

This refers to the nutritional and medication support to ensure regeneration and healing of the gut mucosa. The need for intervention and progress can be elucidated by the intestinal permeability test or via a metabolic questionnaire as discussed above. A hypo-allergenic diet is of utmost importance. Rice protein seems to be the least allergenic substance and can provide a basis for many diets.

Specific nutrients which have been shown to support intestinal repair and function include:

- L-Glutamine

Glutamine is a non-essential, neutral amino acid which is considered to be the principal carrier of nitrogen from the periphery to the internal organs. The enterocytes and many of the components of the MALT use glutamine as a preferred respiratory fuel. Due to its role in protein regulatory functions its demand goes up in stress states associated with injury, sepsis, and inflammation. It is available in powdered and capsule form and should be taken in doses of 3600 mg per day during the initial phases of therapy.^{4,5,8}

• Vitamins

Vitamin B5, Vitamin C, and beta carotene as well as Vitamin E should be replaced as they play a pivotal role as antioxidants and in tissue repair.

• Zinc

Zinc also plays a pivotal role in tissue repair and has been shown to increase metallothionein and super oxide dismutase, two powerful antioxidants containing zinc and copper.⁹

• Gamma linoleic acid (GLA)

Intake of GLA promotes the synthesis of E-series prostaglandins, which decreases permeability. This should be taken as six capsules daily.^{4,8}

• Fiber

The effect of fiber on intestinal permeability is complex. Low fiber may increase intestinal permeability while supplementation with highly soluble fiber has the same effect. Hypoallergenic insoluble fiber has the best effect.

• Glutathione and N-acetyl cysteine

The selenium-dependent protein glutathione and N-acetyl cysteine are the main components of phase II detoxification in the liver. They are also major antioxidants but are lost through the kidneys in the process. Glutathione is poorly absorbed in the gut and therefore should be given with two of its building blocks, cysteine and lysine.¹⁰ All these are available in capsule form.

• Inulin

This carbohydrate from flowering plants e.g. Jerusalem artichoke, provides a substrate for the intestinal flora which then

produce short chain fatty acids which in turn provide the enterocytes with 70% of their energy fuel.

- Gamma-Oryzanol

This is rice bran oil which has been shown to be beneficial in repairing gastrointestinal mucosa especially in individuals with autonomic instability. In my experience this is present in most patients with leaky gut syndrome.

- Mucosa compositum® (Heel)

The formula of this complex homeopathic preparation contains mucosal extracts in homeopathic form to stimulate repair of the mucosa. I have used it with good results in my practice. The vials should be given orally three times a week on an empty stomach for two weeks.

Putting it all together

It is obvious from the above that treating altered intestinal permeability is no simple matter. However, a product called Ultra Clear®, developed by Healthcomm International Inc. combines all the above except Mucosa compositum® in one single powdered formulation which is then used in conjunction with the metabolic questionnaire and/or the intestinal permeability test to treat and monitor this syndrome. Because the gastro-intestinal mucosa is part of the matrix the treatment of this syndrome would be incomplete without treatment of the terrain, or constitution of the patient. Homeopathy, acupuncture, and ozone therapy form powerful adjuncts to the above treatment. By taking a good holistic history, treatment for each patient can be individually worked out to obtain the best results.

Again, these nutrients should be considered for repair:

L-glutamine
Vitamins C, E, B5
Beta carotene
Zinc
GLA
Glutathione
Inulin
Gamma-Oryzanol
Fiber

Homeopathic preparations useful in the treatment of leaky gut syndrome include:

Liver overload
Nux vomica-Homaccord®
Hepeel®

Gut repair
Mucosa compositum®

Pancreatic support
Leptandra compositum

Inflammation
Traumeel®

Detoxification
BHI Body Pure

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