

Gutgard® and Digestive Health

Flavanoid Rich Botanical
For Managing Gut Health



Botanicals and Digestive Health

While digestive health most readily conjures up thoughts of probiotics, herbs have been providing solace for grumpy guts since ancient times. Remedies like ginger, spearmint, and senna have been used for a variety of digestive ailments from heartburn to constipation. Licorice has been shown to be beneficial for digestive complaints, and recent research is illuminating its beneficial actions on gastric emptying as well as the interactions of its flavonols with the gut microbiome. Botanical extracts and bio actives under investigation in clinical trials show great potential for natural effects on digestive health. For these reasons, botanicals continue to be investigated for their therapeutic effects and are sought out for their benefits.

Digestive Problems Impact Quality of Life

Chronic digestive issues can have a significant impact on quality of life. Mild heartburn or indigestion can be very unpleasant and may require dietary and lifestyle changes such as avoiding fatty foods or not eating big meals late at night. Conditions like gastroesophageal reflux disease (GERD) and peptic ulcers are even more disruptive and may not respond to lifestyle changes alone. Conventional treatment includes over-the-counter antacids, prescription acid blockers, and/or antibiotics for relief. More serious conditions such as inflammatory bowel disease, diverticulitis, and gastrointestinal cancer are treated with potent pharmaceuticals and often require invasive surgeries.

Digestive Health Issues: A Closer Look



Upper Gastrointestinal Tract

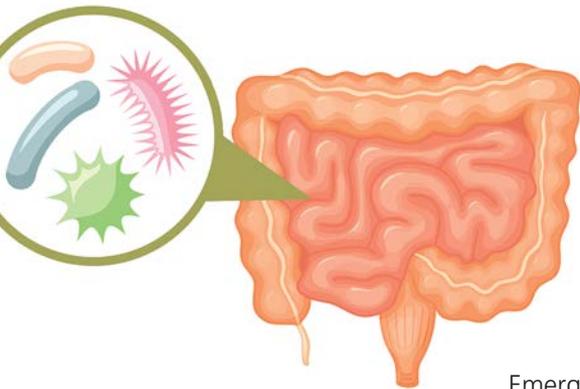
Indigestion, also called dyspepsia, is that unwelcome feeling of fullness, nausea, belching, and abdominal pain. There are two types of indigestion: “functional” and “organic”. Functional dyspepsia is common. It is related to slow gastric emptying after meals and includes heartburn or acid indigestion that causes a burning sensation in the chest or upper abdomen. Organic indigestion is associated with underlying conditions like GERD, gastroenteritis, peptic ulcers, anxiety, or food allergies.

Peptic ulcers are another troublesome condition of the upper gastrointestinal tract involving a breakdown of the lining of the stomach, esophagus, or duodenum. *Helicobacter pylori* and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) are the two most common causes.

Lower Gastrointestinal Tract

Digestive issues of the lower gastrointestinal tract can be of varying causes, including inflammation, a disrupted microbiome or autoimmune reactions. Inflammatory bowel disease (IBD) is a prevalent condition characterized by uncontrolled intestinal inflammation. Two main forms of IBD are Crohn’s disease and ulcerative colitis (UC). IBD is caused by a complex interaction of the immune system, gut microbiota, diet, and genetics leading to breakdown of the intestinal cell wall. IBD should not be confused with irritable bowel syndrome (IBS), a condition with some similar symptoms to IBD, but with no intestinal damage.

Antibiotics are well known to disrupt the gut microbiota, altering the diversity and/or number of resident bugs; this is known as antibiotic dysbiosis. The pattern of disruption is dependent on the type of antibiotic taken, how much is taken and for how long.¹ Disturbances can last for up to two months following dosing in adults, and for two years in children.² Opportunistic pathogens like *Clostridium difficile*, which causes severe diarrhea, are more likely to cause infection when this kind of disturbance is present.



The metabolism of gut bacteria is now thought to influence immune regulation and perhaps the whole immune system.

Emerging research suggests antibiotic dysbiosis, is correlated with a higher incidence of autoimmune diseases, allergies, and obesity, especially in young children.²

Celiac disease (CD) is an autoimmune disease of the small intestine induced by gluten, the storage protein in wheat, barley, rye, and oats. Research suggests CD is caused by a combination of genetics and an imbalance of gut microbes. In infants, this microbial imbalance coupled with use of antibiotics is thought to be one of the causes of CD.²

Digestive health is a key consumer concern and one of the fastest growing dietary supplement categories

Given the prevalence of digestive disorders and their impact on quality of life, consumers are actively pursuing the latest and most effective products to help maintain a healthy digestive system. In a 2015 Nutrition Business Journal survey, digestive issues ranked in the top ten consumer concerns; with over 10% of consumers reporting frequent digestive issues.³ Market reports rank digestive health products as one of the fastest growing end-use categories of dietary ingredients. Sales hit \$2.6 billion in 2016, with substantial growth expected for the next several years.^{3,4}

What's the connection between digestive health and other conditions?

The most recent research is finding intriguing links between the digestive system and many areas of health. The metabolism of gut bacteria is now thought to influence immune regulation and perhaps the whole immune system. This revelation has a profound impact on our understanding of autoimmune diseases, infectious disease, and other diseases related to immunology, including cancer. Digestive health may also affect other conditions like obesity, diabetes, depression and cognitive decline as well as the nervous system.^{5,6,7,8,9} A growing body of evidence also supports a complex connection between gut, microbiome, and brain.⁵

Insights into the gut-brain connection have revealed a complex communication system that not only ensures the correct continuance of gastrointestinal homeostasis but is seeming to have numerous effects on higher cognitive functions that link to the emotional and cognitive centers of the brain.³⁷

Overuse of Pharmaceuticals for Digestive Disorders



A host of pharmaceutical drugs are used to treat digestive disorders. Antacids, H2 blockers, and PPIs treat heartburn, GERD, and peptic ulcers. Antacids work to neutralize stomach acids. Their effectiveness is short lived and raising the stomach pH too high can trigger the release of more stomach acid. Bismuth subsalicylate (Pepto-Bismol) is used for temporary relief of indigestion and its associated symptoms. Pepto-Bismol overuse side effects can lead to tinnitus, rapid breathing, increased thirst, nausea, vomiting and severe headache.

H2 agonists, or H2 blockers (cimetidine, famotidine, and ranitidine) block the action of histamine in stomach cells. Long-term use can lead to a range of side effects including constipation, diarrhea, difficulty sleeping, trouble urinating and an increased risk of infections.

PPIs, like Prilosec or Prevacid block the gastric proton pump system in stomach cells. The irreversible binding of the proton pump enzyme system and antibiotic activity against *H. pylori*¹¹ makes PPIs more effective than H2 agonists. PPIs are typically prescribed for 7-14 days to treat peptic ulcers and GERD. Once the initial 7-14 day course is discontinued, stomach acid production surges. Rebound symptoms are often more severe, creating an endless cycle of medication dependency and nutrient depletion.¹⁰ The most common side effects reported with PPI's include headache, diarrhea, nausea, and vomiting. Reports of more serious side effects include kidney disease, fractures, and vitamin deficiencies, and are generally associated with long-term use.

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Gut Health and the Microbiome: How Are They Related?



Gut microbiota play an integral role in the proper functioning of a healthy gut. They contribute meaningfully to nutrient breakdown and absorption and even produce certain vitamins for the body. They also help to keep the intestine’s mucosal layer healthy and protect against the invasion of pathogenic bacteria.¹¹ The host’s immune system must learn to tolerate the presence of the microbiota while maintaining defense against pathogens. In turn, the microbes “train” the immune system to function properly.¹²

Flavonoids and polyphenols for Gut Health

Polyphenols are present in all plants and have many human health benefits. They can occur in high amounts in the digestive system and directly protect the gut through several mechanisms, including antioxidant defense.¹³ The gut microbiota break down and metabolically transform many dietary polyphenols, allowing them to be absorbed into the blood stream and be carried to their sites of action.¹¹ This increases their bioavailability and efficacy.¹⁴

Overall, the flavonoids of Gutgard® (Glycyrrhiza glabra) seems to help balance the gut microbiota by inhibiting opportunistic pathogen without affecting beneficial bacteria and also without much disturbance to the gastric pH.

SUMMARY OF ACTIONS OF GUTGARD® AND ITS FLAVONOIDS

- Gutgard® improved gut mobility
- Isoliquiritigenin regulated bowel movements
- Isoliquiritigenin relaxed smooth muscle
- Gutgard® & its flavonoids inhibited *H. pylori*
- Gutgard® & its flavonoids inhibited pathogenic bacteria
- Gutgard® does not affect probiotic bacteria
- Gutgard® does not increase gastric pH
- Protects gastric mucosa

BENEFITS

- Manage Functional Dyspepsia and IBS symptoms
- Manage Functional Dyspepsia and IBS symptoms
- Helps to Manage pain in IBS
- Help reduce gastric *H. pylori* load
- Balance gut microbiota
- Balance gut microbiota
- Maintain normal digestion
- Maintain normal gut function

In fact, gut microbes are necessary to break down large molecules like ellagitannins and proanthocyanins before they can enter the blood.^{15,16} At the same time, this process provides nourishment to the gut microbes and regulates their metabolism. In a beautiful feedback loop, this metabolic regulation can enhance the host's immune system and trigger further metabolism of nourishing plant molecules.¹⁴ Clinical trials have shown polyphenol extracts from multiple botanical sources improve gut health in subjects with inflammatory bowel disease, improving symptoms.¹⁷ To date, the clinical trials have been small pilot studies, but the interventions show promise. For these reasons, botanicals continue to be investigated for their therapeutic effects and are sought out for their benefits.

Licorice and Gut Health

Licorice from the roots of *Glycyrrhiza glabra* (Family: Fabaceae) has a long history of use for treating digestive discomforts.¹⁸ Glycyrrhizin (also called glycyrrhizic acid), one of the best known active ingredients, is a triterpene saponin from licorice that has been used as an emulsifier and a sweetener by the food industry. Consuming too much licorice or foods with glycyrrhizin can produce serious adverse side effects such as elevated blood pressure and lowered potassium levels. As a result, deglycyrrhizinated licorice (DGL) is often sold to avoid these complications. *Glycyrrhiza glabra* (Yashtimadhu) is known for its anti-inflammatory and gastro-protective properties in the traditional systems of medicine (TSM) in India and China. Conventional methods extract glycyrrhizin and other polar components, leaving behind other constituents in the roots during processing. Classical deglycyrrhizinated extracts of licorice (DGL), with low content of glycyrrhizin, are common in the marketplace.



Gutgard® is entirely different from deglycyrrhized licorice (DGL) with respect to chemistry and composition, manufacturing process, mechanisms of action and physicochemical properties.

Rich in flavonoids: Gutgard®

Gutgard® is an innovative, clinically researched, bioactive for gut health. As opposed to focusing solely on deglycyrrhization, Gutgard® is a flavonoid-rich extract of *G. glabra* root. It is entirely different from deglycyrrhized licorice (DGL) with respect to chemistry and composition, manufacturing process, mechanisms of action and physicochemical properties.

Gutgard® is extracted using a soft and unique extraction process to capture the bioactive flavonoid chemistry of the plant. A classical extract like DGL does not contain any significant quantity of flavonoids. Most of the generic DGL-based extracts available in the market are by-products of a process to manufacture glycyrrhizin from licorice.

Gutgard® is standardized to contain $\geq 10\%$ total flavonoids (w/w) and also $\leq 0.5\%$ glycyrrhizin to avoid undesirable side effects. More than 50 flavonoids have been identified in Gutgard® by hyphenated analytical techniques like LC-MS, including isoflavans (glabridin), flavones (ex: licoflavone A), flavanones (ex: glabrol), chalcones (Ex: isoliquiritigenin), isoflavones (ex: Formononetin), etc.¹⁹ Batch to batch consistency of the flavonoid profile is monitored with the help of HPLC and other advanced analytical test methods.

Licorice flavonoids have been shown to have beneficial activity for digestive complaints. Gutgard® itself has been clinically tested and shown to have efficacy for addressing these complaints. Gutgard® (with LC-MS based identification of flavonoids) showed far superior antiulcer (in-house report) and anti-*Helicobacter pylori* activity³⁰ than regular aqueous based deglycyrrhized (DGL) extracts. Because of the concentrated nature of the flavonoids, the efficacious intake level for Gutgard® is much lower than that needed for DGL - 150 mg/day versus 1500 mg/day.

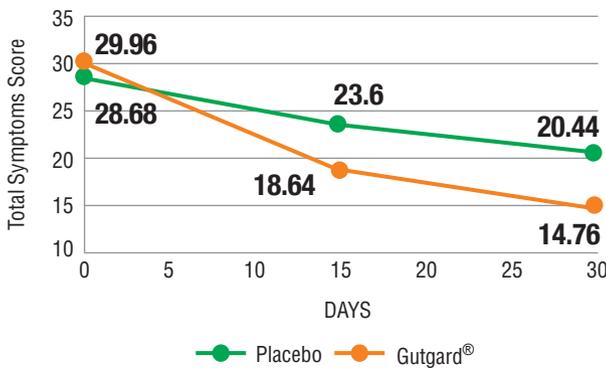
Gutgard® for Occasional Indigestion and Heartburn

A recent randomized, double blind, placebo controlled study showed that Gutgard® is beneficial for occasional indigestion.²⁰ Subjects received either 75 mg Gutgard® (n=25) or placebo (n=25) orally twice daily with water after food for 30 days. At day 0, 15, and 30 of the study, subjects were assessed on the severity of upper abdominal complaints and their quality of life. After 15 and 30 days, the severity of complaints and quality of life significantly improved in the Gutgard® group compared to the placebo group.²⁰

Following on the heels of this study is a clinical trial for heartburn, already in progress.

Effects of Gutgard® on Functional Dyspepsia

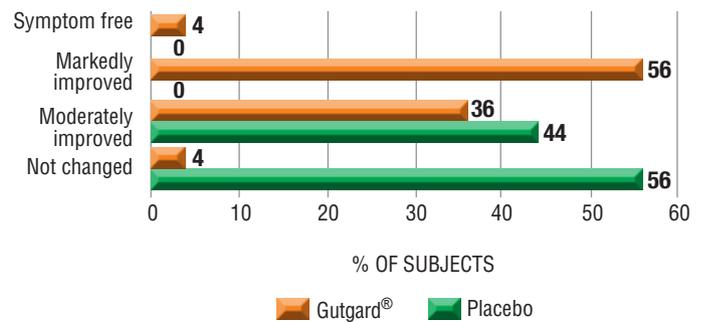
Functional Dyspepsia symptoms



#p≤0.05 versus placebo

- Gutgard® showed 51% reduction in the total symptoms score compared to placebo (29%).

Overall response to Gutgard®



#p≤0.05 versus placebo

- 56% of subjects in the Gutgard® group showed marked improvement compared to placebo (0%).

Gutgard® for Management of *H. pylori*

In 1982, scientists discovered the bacteria *H. pylori* living in the stomach of patients with chronic peptic ulcers. This was the first time microbial infection was considered as the cause of peptic ulcers. Most people with *H. pylori* develop chronic gastritis with no symptoms. But *H. pylori* can also cause painful peptic ulcers and gastric cancers.²¹

Gutgard® has been shown to successfully manage *H. pylori*.²² In a 2013 randomized, double blind, placebo controlled study²², participants with *H. pylori* infection received either 150 mg of Gutgard® (n=55) or placebo (n=52) orally once daily for 60 days. Before the study, all subjects tested positive for *H. pylori* using stool antigen test (HpSA), and ¹³C-urea breath test (¹³C-UBT¹³). After 60 days, 28 subjects in the Gutgard® group had a negative HpSA, compared to 2 subjects with negative HpSA in the placebo group. Results of ¹³C-UBT were negative for 24 subjects in the Gutgard® group compared to one subject in the placebo group. *In vitro* studies also performed using Gutgard® provide additional evidence that it is capable of controlling *H. pylori* growth.^{23,24} Caffeic acid esters from licorice have demonstrated anti-*H. pylori* activity.²⁵ They also inhibit neutrophil-derived elastase and oxidative stress, two contributors to gastric damage.²⁶

Randomized double blind placebo controlled clinical study in subjects with *H. pylori*

Condition	Subjects with gastric load of <i>Helicobacter pylori</i>
Dose	150 mg/day before breakfast
Participants	107 subjects (Age: ≥55 years)
Duration	60 days
Evaluation	On day 30 and day 60 using ¹³ C-UBT and HpSA test
Outcome	Gutgard® showed 41% reduction in <i>H. pylori</i> load compared to placebo. 48% of the population in the Gutgard® group got relieved from <i>H. pylori</i> as assessed by ¹³ C-UBT.

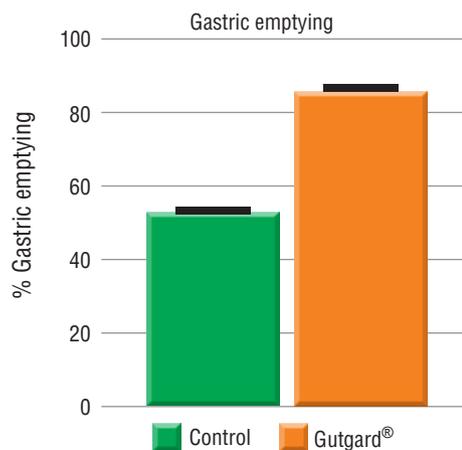
¹³C-UBT: ¹³C-urea breath test; HpSA: *H. pylori* stool antigen

Gutgard® Mode of Action

Gutgard® improves gut health by affecting gastric emptying and regulating bowel movement. Animal studies on Gutgard® and licorice actives glabridin and glabrol have shown to increase gastric emptying and gastrointestinal transit in rats,²⁷ with Gutgard® causing 86% gastric emptying compared to 53% in the control group. Delayed gastric emptying is one of the primary causes of functional dyspepsia, leading to upper abdominal discomfort. Faster emptying of the stomach and gastrointestinal tract can help to alleviate discomfort and regulate bowel motility.

In addition, Gutgard® preserves a healthy pH in the intestine (1.5-3.5), unlike antacids and proton pump inhibitors, which change the pH to over 4. An overly high pH increases the risk of opportunistic pathogens and discourages the normal digestive process. By contrast, Gutgard® (in-house report) and its flavonoids^{28,29} have been shown to inhibit the growth of pathogens such as *Staphylococcus aureus* in *in vitro* studies,

Gutgard® regulates bowel movement – Results from new preclinical research³



Gutgard® showed 86% gastric emptying compared to control group, which showed only 53% gastric emptying³

*p < 0.05 compared to control group; Gutgard® tested at 12.5 mg/ kg p.o

but not that of friendly bacteria such as *Lactobacillus casei* MTCC 1423, *Lactobacillus fermentum* MTCC 903, *Lactobacillus plantarum* MTCC 1325 and *Streptococcus thermophiles* MTCC 1938.³⁰ Accordingly, Gutgard® may help balance the gut microbiota by inhibiting opportunistic pathogens without affecting beneficial bacteria and without extensive disturbance to the gastric pH. In clinical studies Gutgard® has been shown to interrupt the inflammatory cascade^{32,33} and possess antioxidant properties.³⁴

Emerging research has also demonstrated Gutgard® has anti-*H. pylori* activity in clinical¹⁴, in vivo³¹, and in vitro studies.²³ It exerts anti-*H. pylori* activity by inhibiting protein synthesis, DNA gyrase, and dihydrofolate reductase.²³ It also interrupts the inflammatory cascade^{32,33} and possess antioxidant properties.³⁴

The safety of Gutgard® has been well studied, with no safety concerns noted. Two recent Gutgard® clinical trials reported no adverse events at 150 mg Gutgard®/day for 30 days. Rodent toxicity studies have been conducted using acute oral toxicity, 14-day repeated dose toxicity, and 90-day repeated dose oral toxicity models. The No Observed Adverse Effect Level (NOAEL) was 1000 mg/kg rat (unpublished data). Furthermore, Gutgard® did not show any genotoxic activity in bacterial reverse mutation test (Ames II), chromosome aberration, or micronucleus test performed on hamster ovary CHO-K1 cells *in vitro*.³⁵

Trends and Opportunities

Aside from its health benefits, Gutgard® has a number of features that make it attractive and easy for new product development and formulation. Gutgard®'s powder form, pleasant neutral taste and small dose load (150 mg) provide flexibility in formulation, making it suitable for tablets, capsules, gummies, stick paks, functional foods, and beverages. Its low water activity ensures compatibility with prebiotics, probiotics, and digestive enzymes; laboratory studies have confirmed that Gutgard® does not affect the viability of these ingredients when formulated together.³⁶

Gutgard® is kosher and Halal certified, GMO-free, irradiation-free, and follows all international regulatory requirements to ensure the highest quality product. GRAS status is in progress.

About Natural Remedies

Natural Remedies is a global research-driven botanical healthcare company whose core competency lies in manufacturing standardized herbal extracts. Its branded products, which include Gutgard®, are clinically-substantiated, scientifically-validated innovations. Known as a leader in scientifically based botanical extracts, Natural Remedies has contributed to various international pharmacopoeia including over 100 monographs internationally and over 220 phyto- compounds isolated for global reference standards. Its vision is to harness nature and apply science for health and happiness.

Write to us to know more on the benefits of Gutgard®; HHP@naturalremedy.com

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