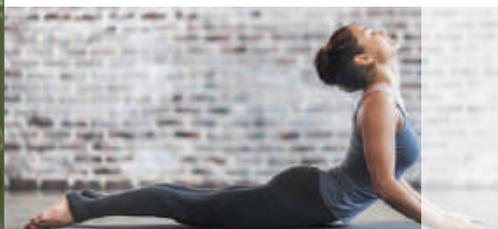


Gastro-AD® - A Natural Solution
for Digestive Discomfort

Lallemand  Health
Ingredients

LALLEMAND BIO-INGREDIENTS



**YEAST – A
NATURAL
SOLUTION**



LALLEMAND BIO-INGREDIENTS

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LALLEMAND

SUMMARY

Gastroesophageal Disease (GERD) is a common ailment which is growing in incidence with a global prevalence estimated between 10%-20%, and even higher in westernized countries. There is a need today for natural and effective treatments to address this burgeoning problem without the side effects of pharmacological solutions. **Gastro-AD®** is a food supplement based on non-GMO soy fermented by Lactobacillus strain *L. delbrueckii* R-187, whose story began more than 50 years ago in Bulgaria. This supplement has an excellent track record of safe and effective use for management of gastric discomfort and the relief of occasional heartburn, backed by several published studies, involving close to 600 subjects in total. Altogether these studies showed that this fermented soy-based solution is very well tolerated and leads to quick relief of symptoms including heartburn, gastric pain, vomiting, and nausea. **Gastro-AD®** represents a natural, safe and effective alternative to over-the-counter (OTC) digestive discomfort solutions with the extra nutritional benefits and healthy image of fermented soy.

GERD AND ITS SYMPTOMS – A COMMON HEALTH PROBLEM

Gastroesophageal Disease (GERD) is characterized by the frequent regurgitation or reflux of stomach acid back up into the esophagus from the stomach. The acid may irritate the lining of the esophagus. Many people experience occasional acid reflux, but GERD refers to mild acid reflux that occurs at least twice a week, or moderate to severe acid reflux that occurs at least once a week. Most people can manage the discomfort of GERD with lifestyle changes and over-the-counter (OTC) medications. But some people with GERD may need stronger medications or surgery to ease symptoms.

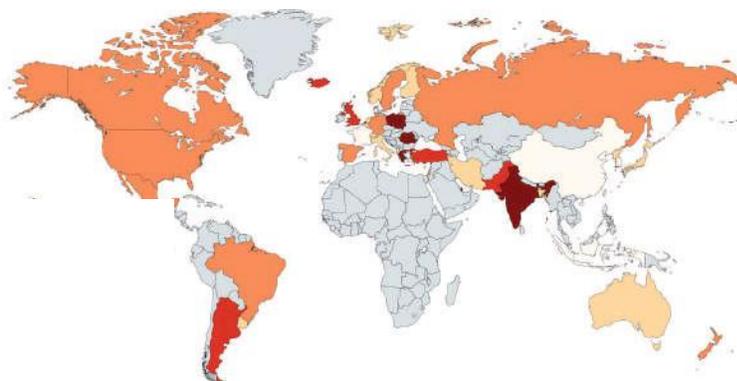
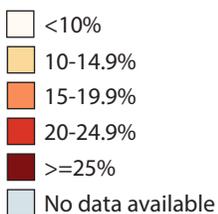
Symptoms of GERD may include: heartburn (a burning sensation in the chest area after eating), chest pain, difficulty swallowing, regurgitation or nausea.

What causes GERD? In general, everyday life stress may cause stomach hyperacidity. Increased secretion of stomach acid is also a side effect of some drug intake, or excess consumption of tobacco or alcohol. The continued surge in obesity is likely to increase acid reflux prevalence in coming years. However, all population groups can be affected by this condition, including seniors or young active women and men.

GERD AROUND THE WORLD

While overall worldwide prevalence is estimated to 10%-20%, this rate is even higher in westernized countries. A study by Kushner in 2010 reported that an estimated 42% of the United States population has experienced heartburn at some point. In Europe, a population based survey in Norway by Ness-Jensen in 2011 showed a substantial rise in gastro-oesophageal reflux symptoms in only ten years. Between 1995 and 2006, overall yearly prevalence increased by 30%, from 31.4% to 40.9%, while the prevalence of at least weekly symptoms increased by as much as 47%, from 11.6% up to 17.1%. The same study showed that the percentage of spontaneous disappearance of symptoms (without medication), was only around 2%.

Prevalence of Gastro-oesophageal reflux symptoms



Source : Leonardo et al (2017) : Gut Journal

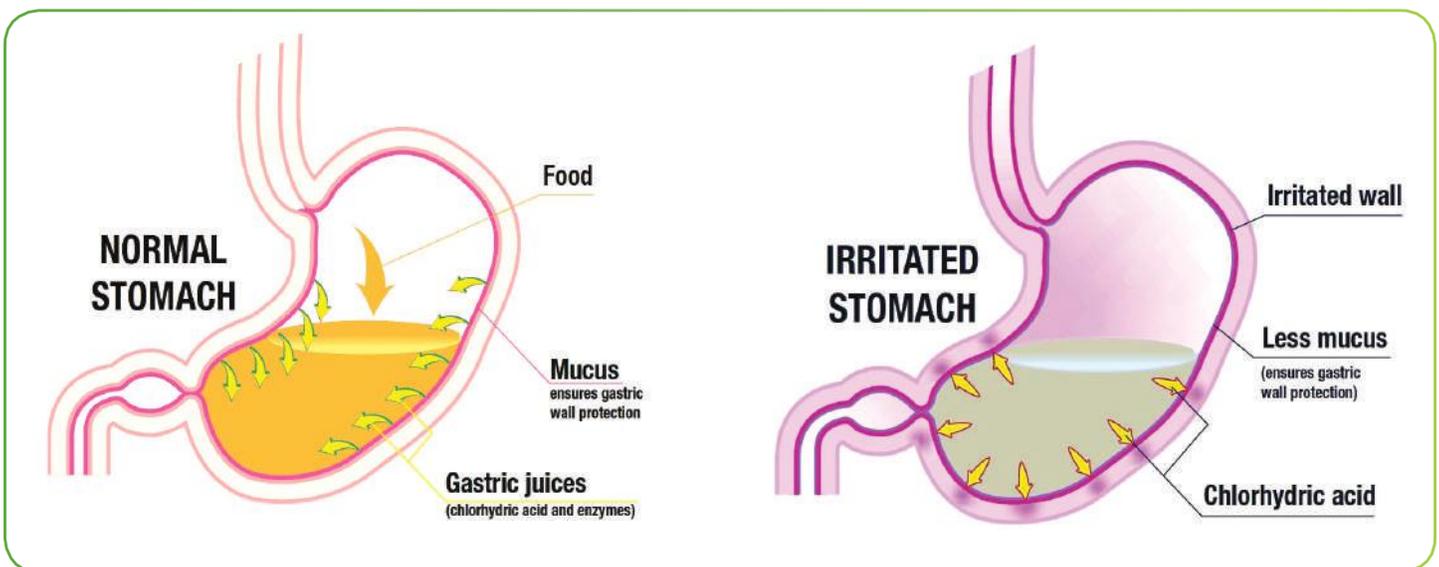
GERD AND THE STOMACH

THE STOMACH HAS THREE TASKS



THE STOMACH

- ✓ The stomach is a muscular pouch which receives swallowed food from the esophagus.
- ✓ Normally, the stomach lining is protected from the effects of gastric juices (HCL & proteolytic enzymes) by the mucosal barrier.
- ✓ Certain factors can alter the mucosal barrier: spicy, greasy, fried foods, citrus fruits, hypersecretion of HCL, stress, alcohol, tobacco, etc.
- ✓ The stomach acid and proteinases are indiscriminate in their activity and can degrade the stomach lining when the mucosal barrier is altered.



CURRENT SOLUTIONS FOR GASTRIC DISTRESS

Antacids: this refers to substances which neutralize stomach acidity and are used to relieve heartburn, indigestion or an upset stomach. These are commonly made with sodium bicarbonate or magnesium hydroxide. While they offer quick relief, this is often temporary and followed with side effects such as a reflexive increase of acid secretion into the stomach or diarrhea. Long term effects may include kidney stones or even osteoporosis.

Proton pump inhibitors (PPIs) and Histamine (H₂) receptor antagonists: these options inhibit acid secretion in the stomach. While these may provide long term relief, side effects still exist. Mild side effects may include constipation and diarrhea. More severe side effects might include decreased calcium and vitamin B12 absorption and a greater vulnerability to infections.

Natural treatments: Many people prefer to opt for a more natural approach to treating symptoms of GERD. A common recommendation is the ingestion of herbal preparations, such as ginger or peppermint to soothe the stomach. But generally these remedies do not provide relief and they have not been tested for efficacy or safety for long term use. Heartburn is common during pregnancy and often worsens over time. Pregnant women prefer to take natural remedies or often suffer with no medication

These solutions comprise either synthetic drugs or ineffective options. The market today demands natural and effective alternatives to address the growing issue of heartburn and gastric reflux.



INTRODUCING: GASTRO-AD®



THE LONG, STRONG HISTORY OF GASTRO-AD®

The story of **Gastro-AD®** started in the 1980s when Dr. Edouard Brochu from Institut Rosell in Canada met Dr. Ivan Bogdanov in Bulgaria, the country associated with the beginning of probiotics history.

Dr. Bogdanov focused on studying the properties of lactic acid bacteria isolated from Bulgarian yoghurt. He was also interested in the effects of different *Lactobacillus bulgaricus* strains, studying their properties in soy fermentation. He isolated a specific strain of *L. bulgaricus* in the 1950s, which has been demonstrated to possess anti-tumor effects in vivo on transplanted tumors in mice. This strain has also been used for cancer therapy in humans.

In parallel with the anti-tumor studies, Dr. Bogdanov demonstrated that soy fermented with this particular strain provided quick relief of heartburn, nausea, bloating after meals and most gastric and duodenal ulcer symptoms. **Gastro-AD®** was born. This whole fermented soy product was marketed in Bulgaria and Eastern Europe under the name "GastroPharm" for gastric comfort from the mid- 1950s in Bulgaria and Eastern Europe.

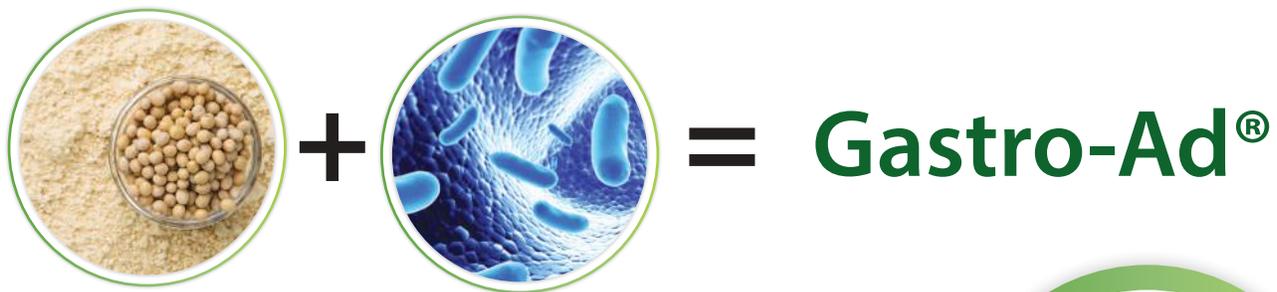
In the 1980s, following his exchange with Dr. Bogdanov, Dr. Brochu decided to extend this product to the North American market. Institut Rosell began to market the product as **Gastro-AD®** in North America and integrated the product and the strain into its research programs.

The specific *Lactobacillus bulgaricus* strain discovered by Dr. Bogdanov was historically known as "I. Bogdanov's strain 51" ("LB-51"). It has now been identified by Institut Rosell-Lallemand as *Lactobacillus delbrueckii subsp. lactis* (Rosell R-187) and is registered at the American Type Culture Collection under ATCC 21815.

Today, **Gastro-AD®** is a food supplement produced by Lallemand under strict quality control standards and benefits from the company's fermentation know-how and state of the art technology. It is produced from IP-certified non-GMO soy, fermented by *L. delbrueckii* R-187. **Gastro-AD®** is entirely of biological origin, without any alkalizing, local anesthetic and/or anti-spasmodic agents. The gentle processing conditions used during production help to preserve **Gastro-AD®**'s biologically active metabolites and soy nutritional qualities.

FERMENTED FOODS

Fermented foods have been commonly consumed as part of the human diet for thousands of years, even without a clear appreciation for, or an understanding of, their benefits and underlying microbial functionality. Fermented foods have unique functional properties which impart some health benefits to consumers due to the presence of functional microorganisms possessing probiotic activity, antimicrobial and antioxidant function, peptide production, etc. Health benefits of some fermented foods may include synthesis of nutrients, prevention of cardiovascular disease, gastrointestinal disorders, allergic reactions, diabetes, and others.



Lactic acid bacteria (LAB) have been some of the most studied microorganisms in fermented foods:

During fermentation, these bacteria synthesize vitamins and minerals, produce biologically active peptides and remove some non-nutrients.

Gastro-AD® is non-GMO soy flour fermented by *Lactobacillus delbrueckii*, R-187. Even though it has some clear benefits, as previously discussed, it may potentially impart additional health benefits which have not yet been clearly elucidated.

Fermented non GMO soy as found in Gastro-AD® represents a natural, nutritional and safe food product.

ABOUT SOY AND FERMENTED SOY

Soy is considered as an alternative to animal-based products, and is highly regarded for its oil and high protein content. Soybean contain 30-46% proteins and provide 8 essential amino acids.

Moreover, soy is associated with many health benefits but certain factors present in soy products can limit its consumption: indigestible carbohydrates, proteins, lectins, allergens, etc. Soy fermentation might provide a solution to reduce the negative effects of these anti-nutritional factors

Fermented soy is recognized as healthy, nutritive ingredient, which has been part of Asian culture for thousands of years (e.g. miso, natto, soy sauce...) and associated to many health benefits:

- Reduction of menopausal symptoms
- Antioxidant, cholesterol-lowering and anti-allergenic effects
- Relief of gastritis (heartburn & stomach discomfort)

SCIENTIFIC EVIDENCE OF EFFICACY

CLINICAL STUDY: DR. BOGDANOV, TREATMENT OF GASTRIC AND DUODENAL ULCERS WITH GASTROPHARM. 1978.

Gastro-AD® has been tested in several clinical studies, in approximately 600 subjects. It was shown to be very well tolerated, with results showing that it provided quick relief from ulcer symptoms including heartburn, pain, vomiting, and constipation.

DOSAGE

2.5 to 5.0 g Gastro-AD® x 3 times/day, 30 min before meals. Duration: 30 days

DESIGN

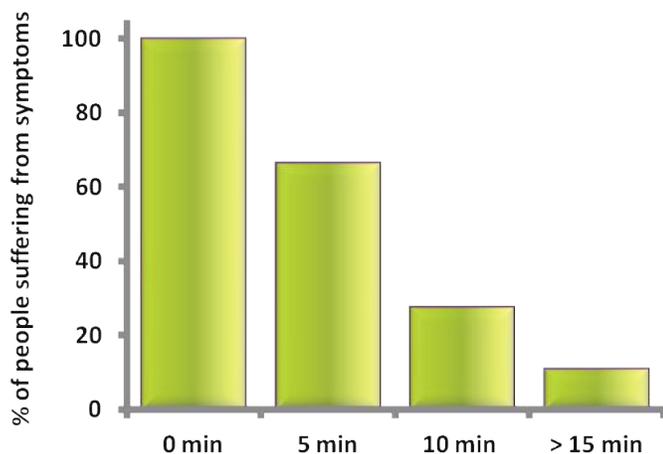
<u>360 patients suffering from:</u>	<u>Having symptoms for:</u>
Duodenal ulcers (238)	1 year (44)
Gastritis (93)	1-5 years (125)
Gastric ulcers (29)	5+ years (191)

Symptoms monitored: acidity, nausea, stomach pain, heartburn.

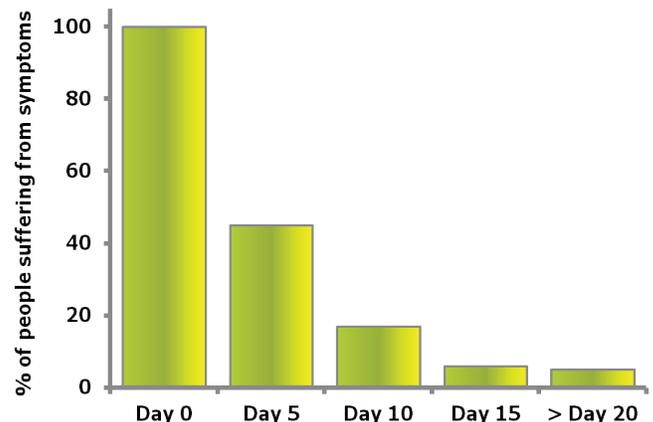
Results: rapid and long-lasting relief of painful symptoms:

- 85% of patients experienced relief from heartburn pain in 15 minutes or less
- 95% of patients found relief from ulcer symptoms in 15 days or less
- Gastro-AD® is very well tolerated

Short term relief of pain/heartburn ulcer



Chronic relief from symptoms of ulcers



The first study, from 1978 was actually done in patients with ulcers in their stomachs and small intestines. At the time, the Gastro-AD® was called "Gastropharm" but it is the same product. 360 patients were involved in the study. Most had ulcers and some had gastritis without ulcers. Most of them had been suffering from pain for over 5 years. The dosage used in the study was high, because the study focused on ulcer patients.

CLINICAL STUDY: Y. HIRATA AND A. UCHIDA. CLINICAL EFFECTS OF GASTRO-AD FOR GASTRITIS PATIENTS. 2002

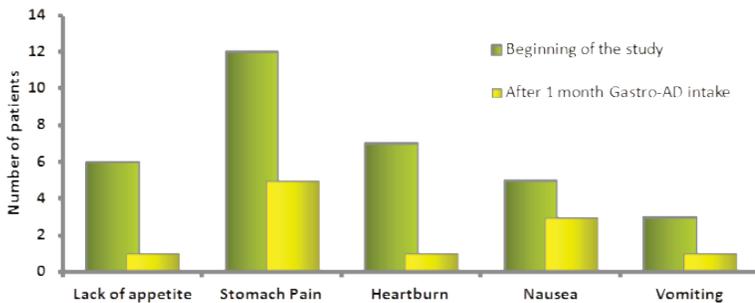
DOSAGE

2.0 g Gastro-AD®
x 3 times/day for 30 days

DESIGN

12 patients (22-75 years)
Suffering from gastritis and other gastroenteropathy
Symptoms : lack of appetite, nausea, stomach pain, heartburn

Results: significant reduction of symptoms and long-term relief



Reduction of heartburn	85% of patients
Appetite regained	83% of patients
Lessening of vomiting	60% of patients
Reduction of gastric discomfort	58% of patients



The Hirata study in 2002 also used a high dosage and this study focused on patients suffering from gastritis (inflammation of the stomach lining due to compromised mucosa). Again, a relatively high dosage was used because of the patients' disease condition. Results showed significant and continued reduction of heartburn, vomiting and gastric discomfort, and regained appetite in these patients after 1 month of treatment.

A few other smaller studies were conducted by Litiniskaya in 1981, Potashov in 1981, Daskalov in 1994 and Yanev in 1994. All patients suffered from duodenal and/or stomach ulcers. All studies showed similar results: most patients had a disappearance of symptoms within a week and some within 25 days, and a good tolerance for **Gastro-AD®** up to 15g per day.

In the various studies, it appeared that patients who did not respond to **Gastro-AD®** treatment were found to suffer from more severe afflictions, such as pyloric stenosis, a penetrating ulcer to the pancreas or a carcinoma.

Altogether, these various trials (almost 600 subjects in total) showed that **Gastro-AD®** is very well tolerated and leads to a quick relief of ulcer symptoms including heartburn, pain, vomiting, and constipation.

PROPOSED MECHANISMS OF ACTION

Since the early days of Dr. Bogdanov further studies have been conducted to try to elucidate the exceptional benefits of **Gastro-AD®**.

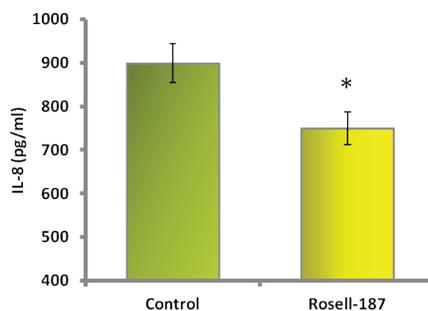
While the exact mechanism of activity is unknown, Gastro-AD® has three possible modes of action.

1 The soy peptides provide buffering activity, which neutralizes stomach acid.

The rapid relief of heartburn can be explained by a buffer effect of the product on the stomach pH. It appears that after intake of **Gastro-AD®**, there is a temporary decrease in stomach acidity, which quickly alleviates patients' heartburn and stomach burning sensations. This buffer effect has been shown in vitro: **Gastro-AD®** has the ability to neutralize hydrochloric acid. This effect is due to the high concentration of proteins/metabolites in the fermented soy product.

2 The Rosell-187 boosts the immune system, by reducing inflammation and supporting a healthy stomach mucosa.

Lactobacillus delbrueckii R-187's ability to moderate the immune response was assessed in vitro by Wallace et al. in 2003 and Easo et al. in 2002. The bacterial component was able to down-regulate the expression of the inflammatory cytokine, Interleukin-8, by colonic epithelial cells, which would boost an immune response. It also had a moderate to weak effect on TNF α expression. These combined actions on proinflammatory cytokines expression could help explain the product effect on gastric ulcerations healing process.

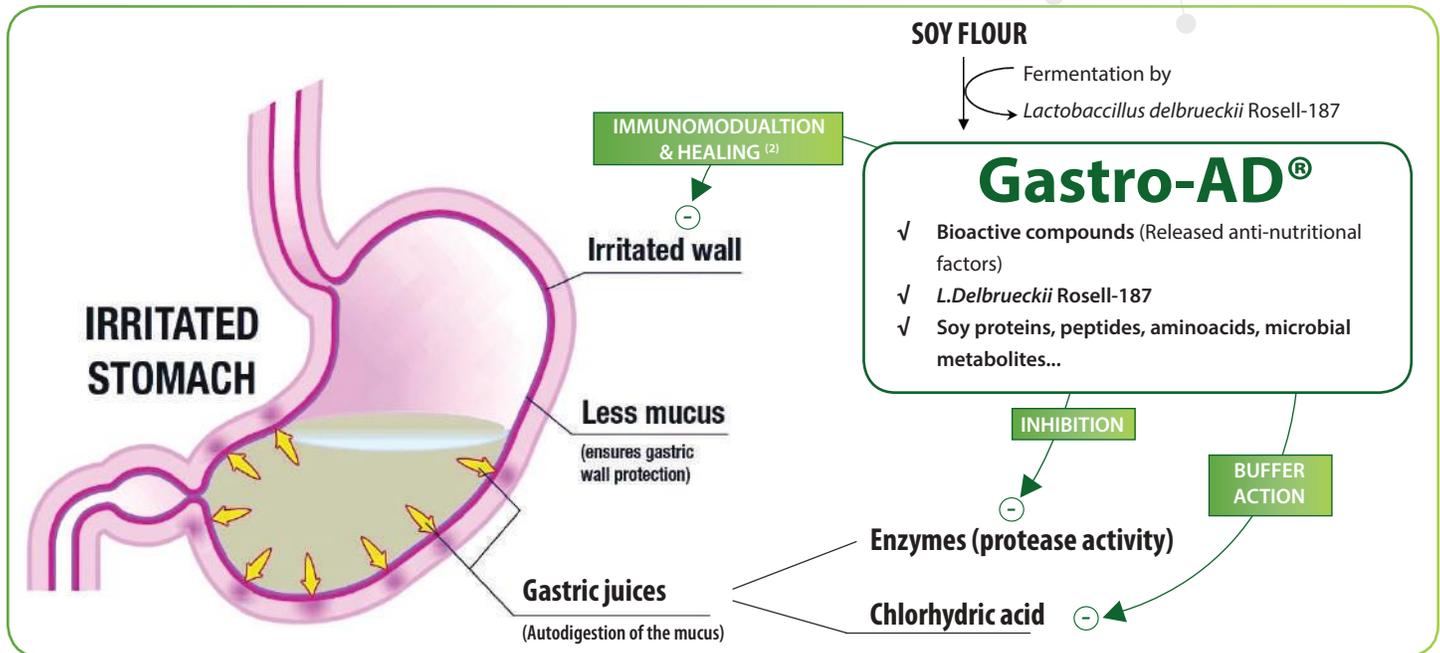


The ability of Rosell-187 to heal gastric mucosa may be partially **due to its suppressive effect on the interleukin IL-8**

3 The fermented soy peptides inhibit proteases from degrading the stomach lining and causing further pain.

Soy proteins contain regions which have anti-nutritional properties, called "anti-nutritional peptides". When digested and released in the stomach, these peptides inhibit stomach and duodenal proteases which normally promote the degradation of food protein. Because these soy peptides cannot be further degraded by the proteases, they block their active sites, thereby inhibiting further action of the enzyme. In the absence of food protein, these proteases may act on proteins of the stomach lining, digesting them and causing pain. It was shown that soy fermentation by *Lactobacillus delbrueckii* R-187 releases such anti-nutritional factors, which thus inhibit the action of the enzymes on the stomach lining. As a result, the stomach lining is protected from the action of these proteases, tissue degradation stops immediately and pain is reduced.

On-going promising investigations should lead to an even better understanding of the molecules involved in Gastro-AD® mechanism of action.



Summary of Gastro-AD® possible modes of action in the stomach

SAFETY AND QUALITY

Lallemand has many years of experience in specialty fermentation. Gastro-AD® is controlled at all stages of production:

- IP-certified non-GMO soy
- *Lactobacillus delbrueckii* Rosell-187 strain selection
- Fermentation monitoring
- Bacteriological control
- Yield rate analysis

There are no viable micro-organisms left from the fermentation process – the entire culture is pasteurized, harvested, and spray-dried. No solvents or additives are used during fermentation. Gastro-AD® powder is tested for heavy metals.

IP certificate and GMP statements are available.

Safety studies completed: acute toxicity, repeat-dose toxicity, reproductive toxicity.

RECOMMENDED INTAKE:

Gastro-AD® is available in powder form, suitable for chewable tablets or orodispersible delivery.

Based on existing studies, for occasional heartburn it is recommended to take 1g before each meal. When heartburn occurs frequently (more than twice a week) and is accompanied by other symptoms, it is recommended to consult a doctor.

COMING IN 2019:
NEW CLINICAL TRIAL

To provide
up-to-date
scientific
evidence

To clearly define
a therapeutic
dosage more
precisely

To better define
administration
instructions

Stay tuned! Lallemand Bio-Ingredients will be providing updates about the new study.

For more information, or to receive a sample of Gastro-AD[®], please contact your Lallemand sales representative or distributor, or e-mail info@bio-lallemand.com



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ABOUT US

Lallemand Inc. is a privately held Canadian company, founded at the end of the 19th century, which specializes in the development, production and marketing of yeasts and bacteria. Today, Lallemand is present through plants, distribution centers or representation offices in 40 countries on the 5 continents.

Lallemand Bio-Ingredients (LBI) develops, manufactures and markets high-value yeast products from *Saccharomyces cerevisiae* and Torula yeast, including whole cell nutritional yeast, yeast extracts and yeast derivatives. The know-how and experience acquired since its beginnings, as well as its high quality, high production standards and technical knowledge have allowed LBI to increase its presence in the food, health and fermentation industries.

OUR MISSION

We take pride – individually and collectively – in the quality of our work, the advanced processes we use, the products and services we provide, and in the recognized and validated efficacy of our continuous improvement program. We take pride in meeting selected customer needs ahead of our competition. We take pride in achieving and sustaining levels of financial returns as a measure, beyond the numbers, of the value our customers agree we create.

