

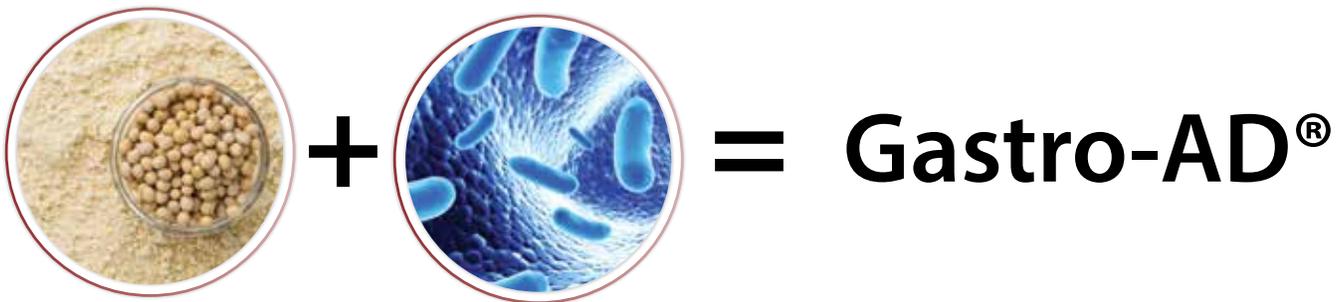
LALLEMAND HEALTH INGREDIENTS



**YEAST
A NATURAL
SOLUTION**

SUMMARY

The use of fermentation in food and beverage preparations, as a means to provide palatability, nutritive value, preservative, and medicinal properties, is an ancient practice. The enhanced nutritional and functional properties of fermented foods may be due to transformation of food molecules and the resulting formation of bioactive or bioavailable end-products. A more recent consideration that intersects with this traditional type of remedy is that of Gastroesophageal Reflux Disease (GERD). GERD is a modern-day common ailment which is growing in incidence with a global prevalence between 10%-20%, and even higher in westernized countries. Current remedies include synthetic pharmaceutical drugs and invasive surgery. There is a need for natural and effective options to address this burgeoning problem without the side effects of more radical solutions. **Gastro-AD®** is a food supplement based on non-GMO soy fermented by *Lactobacillus* strain *L. delbrueckii* R-187 (Rosell-187). It has an excellent track record of safe and effective use for management of symptoms of GERD including heartburn, gastric pain, vomiting, and nausea and has been backed by several published studies, in a total of 600 patients. **Gastro-AD®** represents a natural, safe and proven alternative to over-the-counter (OTC) remedies with the extra nutritional benefits of fermented soy. A current clinical trial is underway, with results expected in late 2019.



FERMENTED FOODS

Consumption of fermented foods is often associated with numerous health benefits resulting from fermentation-associated modifications to food components. Fermented foods and beverages were some of the first processed food products consumed by humans. Foods such as yogurt and cultured milk, wine and beer, sauerkraut and kimchi were initially valued because of their improved shelf life, safety, and organoleptic properties. However, we are developing a greater understanding that fermented foods may also have enhanced nutritional and functional properties due to transformation of carbohydrate and proteins and the resulting formation of bioactive or bioavailable end-products. There is evidence that these foods provide health benefits well-beyond their starting food materials. Techniques for preserving cereals, vegetables, and meat products are well developed in many Asian countries. For example, in Nepal, Korea, Vietnam and Thailand it is common to find rice, cabbage, fish, shrimp and pork fermented with lactic acid bacteria.

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. They 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:

It is known that during fermentation, LAB synthesize vitamins and minerals, produce biologically active peptides and remove some non-nutrients. **Gastro-AD®** comprises non-GMO soy flour fermented by *Lactobacillus delbrueckii*, R-187 (commercially known as Rosell-187). During fermentation of non-GMO soy flour by Rosell-187, it is postulated that bioactive molecules are being produced. Studies have shown that **Gastro-AD®** has proven health benefits, however it may also impart additional health advantages which have not yet been clearly elucidated.

WHY ROSELL-187?

The specific strain, Rosell-187, has been characterized as *Lactobacillus delbrueckii*, *spp delbrueckii*. This particular strain, when heat-inactivated and incubated with intestinal epithelial cells, has been shown to up-regulate IL-6, a cytokine which stimulates antibody production. In this same system, the heat-inactivated bacteria has also been shown to down-regulate the cytokine IL-8, which has an inflammatory effect. Not only are LAB some of the most studied and familiar microorganisms in fermented dairy and other food, but this particular LAB strain, when heat-inactivated, has some very positive effects on intestinal epithelial cells. Overall, decades of research conducted on Rosell-187 have proven this strain to be superior to alternative strains for this application.

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 with many health benefits such as:

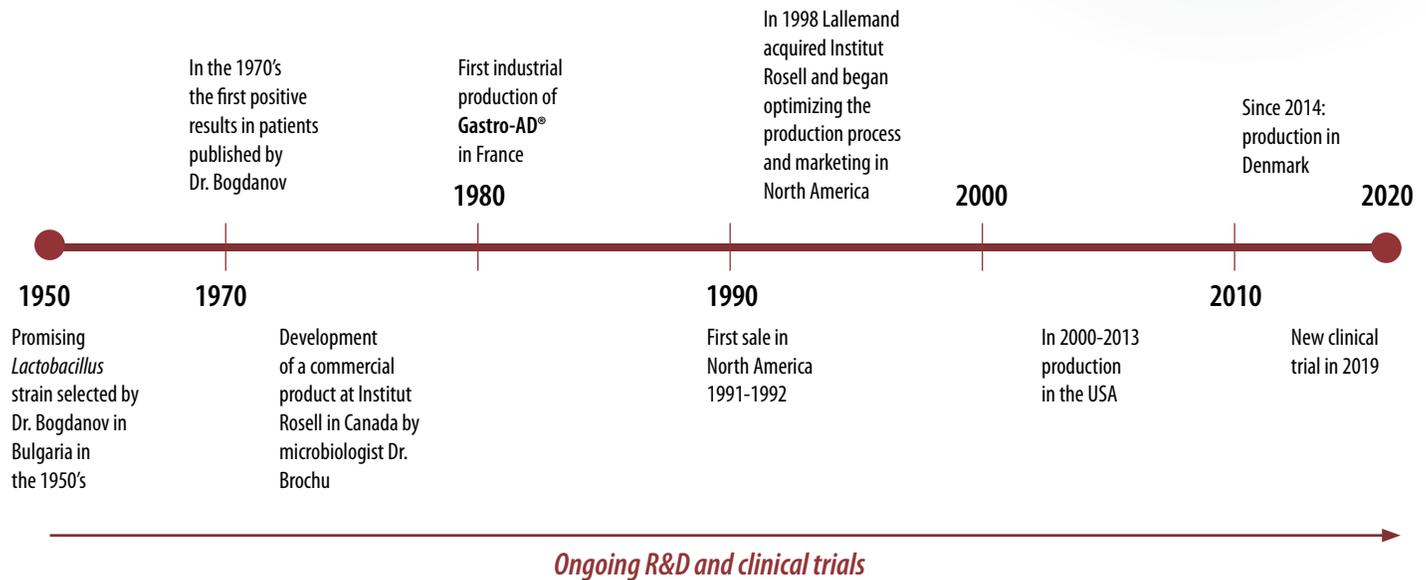
- ✓ Reduction of menopausal symptoms
- ✓ Antioxidant, cholesterol-lowering and anti-allergenic effects
- ✓ Reduced arterial stiffness in men
- ✓ Relief of gastritis (heartburn & stomach discomfort)

For example, fermented soybeans are rich in isoflavone genestein and gamma-polyglutamic acid (PGA). Isoflavone genestein may act as a chemopreventive agent against cancer, while PGA acts as dietary fiber to reduce the cholesterol level in serum and improves efficacy of calcium absorption.

The nutritional values of fermented soy are related to the specific microorganism used, which may enhance health benefits directly through the interaction with the host or indirectly through metabolites synthesized during fermentation. Bioactive compounds and other interactions within fermented food can add novel flavors to food and impart potential health benefits. Many scientific research studies have exhibited promising results related to these traditionally fermented food products.



THE HISTORY OF GASTRO-AD®



The modern-day 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"). In older literature it is also referred to as subspecies *bulgaricus* or *lactis*, but with continued improvement in technology over the years, it is now possible to clearly define the precise strain as subspecies *delbrueckii* and it 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 expertise and state of the art technology. It is produced from IP-certified non-GMO soy, fermented by Rosell-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.



GERD AND ITS SYMPTOMS – A COMMON HEALTH PROBLEM

Gastroesophageal Reflux 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, which normally does not come into contact with stomach acid, and has no protective mucosal layer to prevent it from burning. 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 – prescription - medications or surgery to ease symptoms.

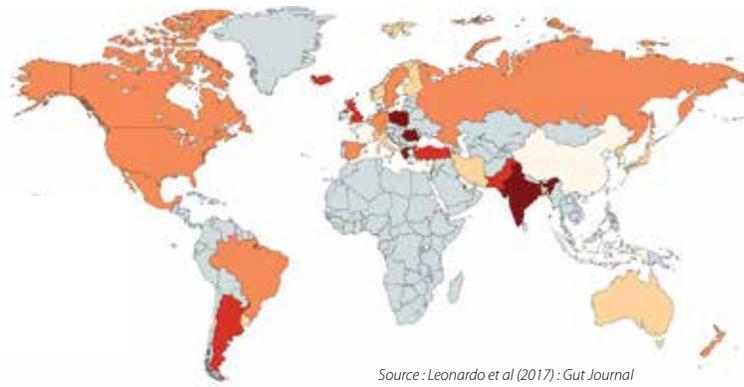
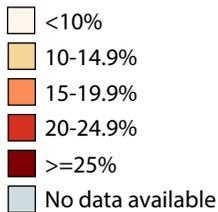
Symptoms of GERD may include: heartburn (a burning sensation in the chest area after eating), chest pain, difficulty swallowing, regurgitation or nausea.

What causes GERD? In general, everyday life stress causes 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

Gastroesophageal reflux disease is the most common gastrointestinal complaint seen across the world. It has often been perceived as Western disease due to its high prevalence of around 10–20%. In Asia, limited data showed that the prevalence was 2.5–6.7% and that most patients had mild disease. However, within the last decade, research in GERD showed that the prevalence of weekly heartburn in Asia ranges from 8 to 20%, which is higher than previous estimates. This increase in prevalence could be due to the changing dynamics mainly due to interaction of environmental, genetic, and recent socioeconomical development in Asia. It is estimated that 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%.

Prevalence of Gastro-oesophageal reflux symptoms

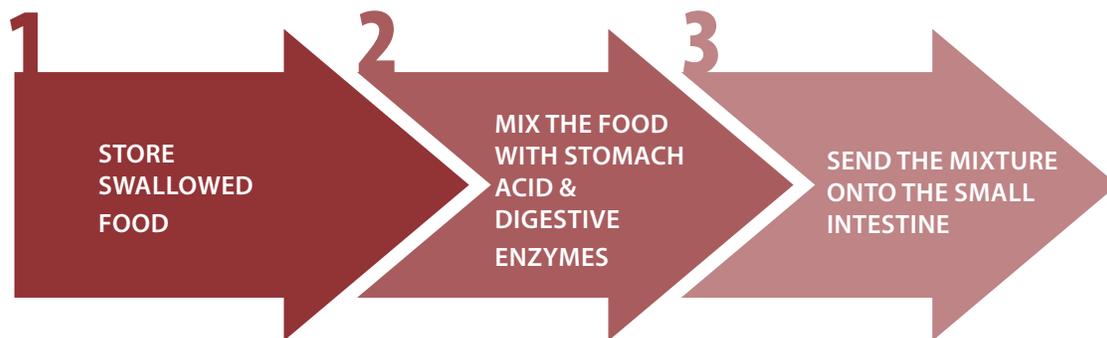


Source : Leonardo et al (2017) : Gut Journal

Some more recent statistics since 2017 show that in the U.S., those suffering from heartburn are even younger than expected. There is an increase in the proportion of 30-39 year olds suffering from heartburn. In Asia, the increase in weekly heartburn incidents has really happened within the last two years. The belief is that adoption of a more “western” lifestyle is having a negative impact on stress and health levels and resulting in digestive problems. GERD and heartburn are becoming bigger problems than ever before, and getting worse, quickly.

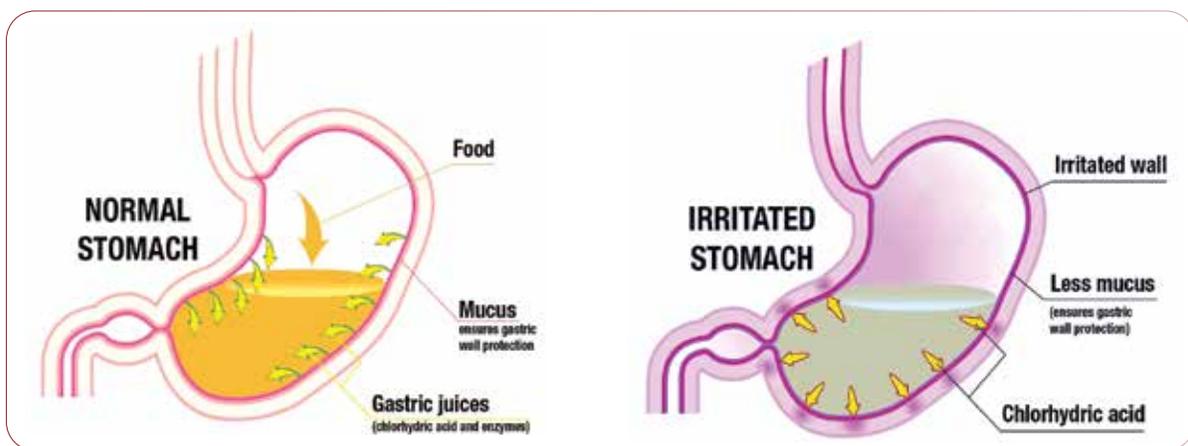
GERD AND THE STOMACH

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 (hydrochloric acid & proteolytic enzymes) by a thick mucosal barrier, which contains alkaline components.
- ✓ Certain factors can compromise this mucosal barrier: hypersecretion of stomach acid due to stress; intake of spicy/ greasy/fried foods, citrus fruits, alcohol; smoking and others.
- ✓ The stomach acid and proteases are indiscriminate in their activity and can degrade the stomach lining when they get through holes in the mucosal barrier.



CURRENT SOLUTIONS FOR GASTRIC DISTRESS

The current solutions available to treat heartburn symptoms include a range of effective synthetic solutions with negative side effects, and a handful of natural products that are ineffective.

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 prevent acid secretion in the stomach. While these may provide long term relief, side effects still exist, as we require stomach acid for digestion of proteins and absorption of some nutrients such as calcium and vitamin B12. Mild side effects may include constipation and diarrhea. More severe side effects might include increased risk for bone fractures and altered gut microbiota.

Herbal treatments: 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 try natural remedies and often suffer with no real relief.

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. Gastro-AD® has been proven to be effective, and is a natural option with no side effects, safe for all populations.

PROPOSED MECHANISMS OF ACTION OF GASTRO-AD®

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 still being investigated, **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 proven in vitro: **Gastro-AD®** has the ability to neutralize hydrochloric acid. As seen by X-ray and gastroscopic examination, **Gastro-AD®** also seems to heal ulcers directly, leading to remission of the disease. 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.

Heat-inactivated R-187 was able to suppress the cytokine, Interleukin-8, allowing for a reduction in inflammation. This stimulates an immune response. These combined actions on the expression of pro-inflammatory cytokines may help explain the how the gastric ulcers were healed. This feature reinforces the benefit of **Gastro-AD®** as a preventative product, supporting the immune system overall, not only for immediate heartburn relief.

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

In the absence of food protein, proteases in the stomach may act on proteins of the stomach lining, digesting them and causing pain. The soy peptides in **Gastro-AD®** seem to interact with the active area of these protein-degrading enzymes in a non-reversible way. These peptides block the protease activity and prevent them from degrading the patient's exposed stomach lining and causing pain. In this way, **Gastro-AD®** functions to provide immediate relief of pain and long-term alleviation of damage to the stomach lining and associated chronic pain.

The following study summaries provide the evidence supporting these three proposed mechanisms of action.

SCIENTIFIC EVIDENCE OF EFFICACY

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

This study provides evidence for the buffering activity of **Gastro-AD®**.

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

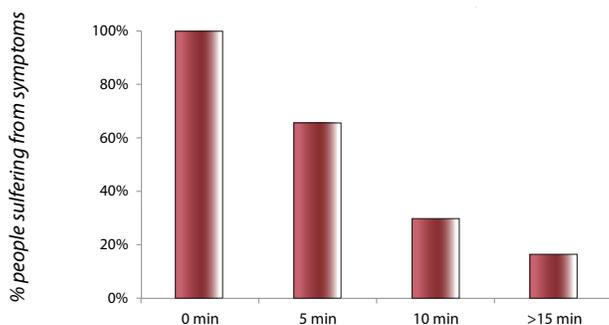
<u>360 patients suffering from:</u>	<u>Having symptoms for:</u>
Duodenal ulcers (238)	1 year (44)
Gastritis (93)	1-5 years (125)
Gastric ulcers (29)	5+ years (191)

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

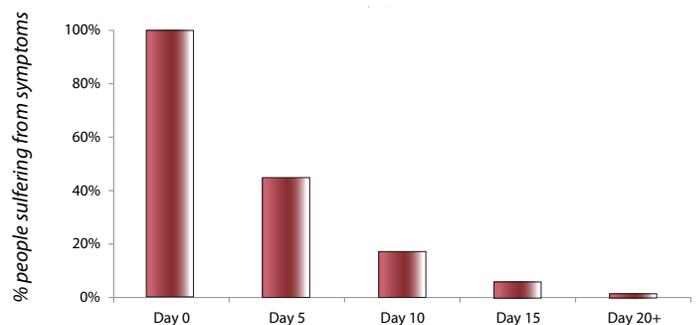
Results: rapid and long-lasting relief of painful symptoms:

- 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 heartburn/ulcer pain



Chronic relief from symptoms of ulcers



This 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 response to ulcer symptoms is significant. The effect on heartburn pain is also compelling: it is quick and dramatic, providing real relief to suffering patients.

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

This study also provides evidence for the buffering activity of **Gastro-AD®**.

DOSAGE

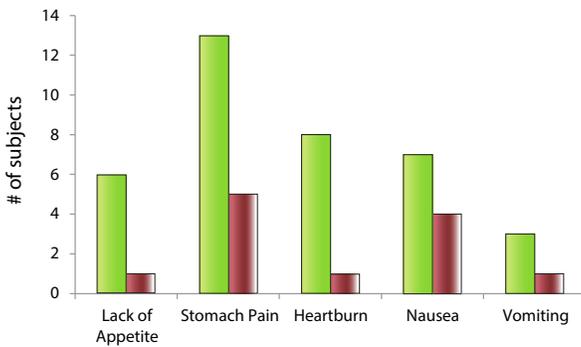
**2.0 g Gastro-AD®
x 3 times/day for 30 days**

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

Significant reduction of symptoms and long-term relief



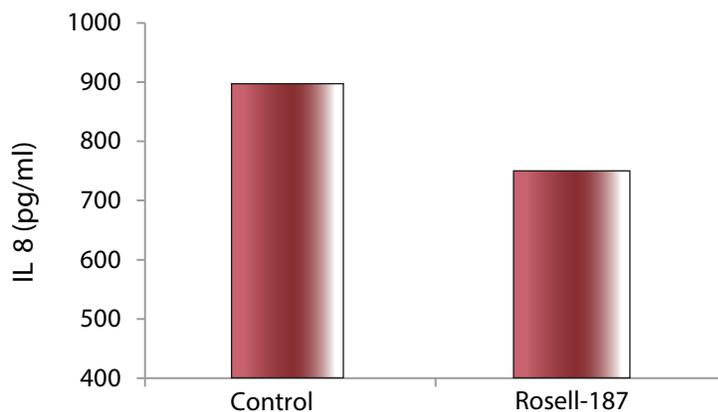
Reduction of heartburn	85% of patients
Appetite regained	83% of patients
Lessening of vomiting	67% of patients
Reduction of gastric discomfort	62% of patients

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

CLINICAL STUDY: WALLACE TD ET AL. INTERACTIONS OF LACTIC ACID BACTERIA WITH HUMAN INTESTINAL EPITHELIAL CELLS: EFFECTS ON CYTOKINE PRODUCTION. 2003.

This study provides evidence that Rosell-187 suppresses Interleukin-8.

Rosell -187 has a beneficial effect on the immune system



The Wallace study from 2003 was able to show that the heat-inactivated Rosell -187 strain of lactic acid bacteria had a suppressive effect on interleukin-8, the inflammatory cytokine, in intestinal cells. So, by reducing this cytokine, we presume reduction of inflammation of the intestinal cells. Heat-inactivated Rosell-187 comprises a significant proportion of **Gastro-AD**®.

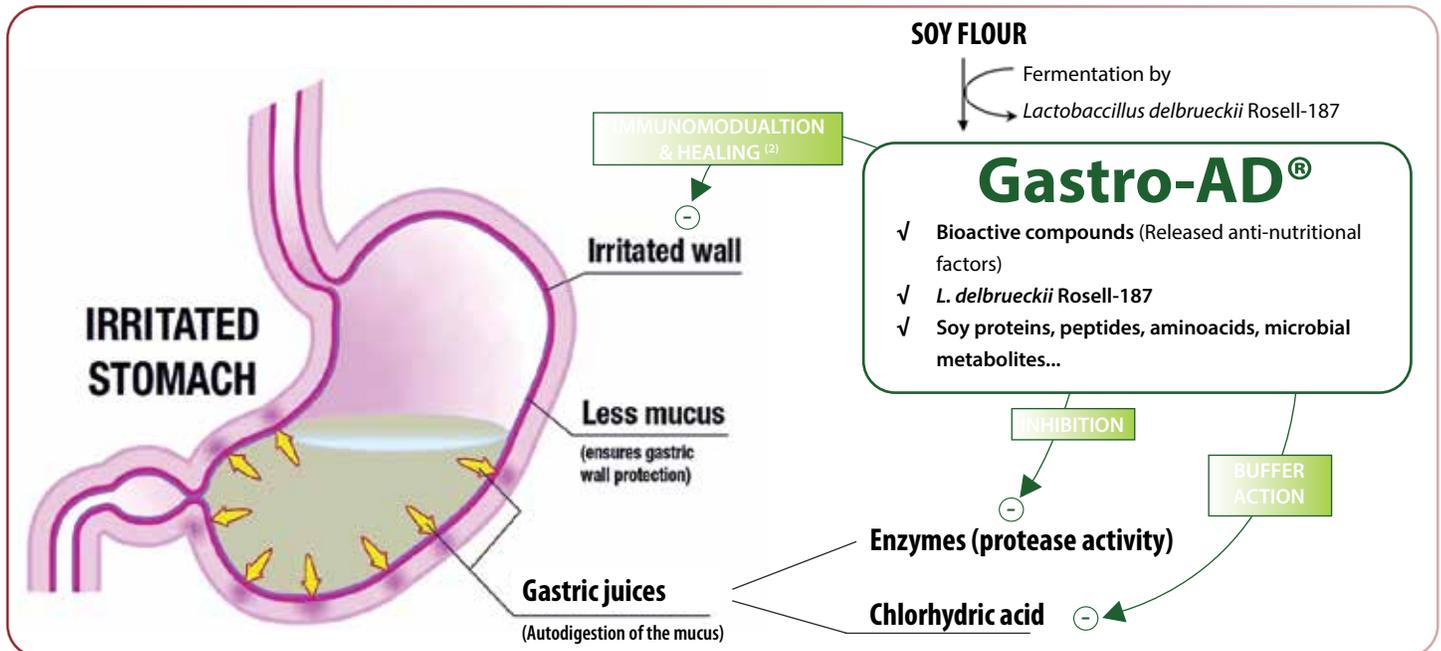


STUDY: AHMARANI, J. EFFECTS OF SOY FLOUR FERMENTED BY *LACTOBACILLUS DELBRUECKII* SSP. *LACTIS* R0187. 2006.

This study was able to demonstrate that the soy peptides in **Gastro-AD®** block the active sites of proteases and inhibit their activity. These soy peptides are the result of fermentation of soy flour specifically by Rosell-187. So this is not a result we would expect from soy flour fermented with any other LAB. We can infer from this that the third mechanism of action of **Gastro-AD®** is to prevent degradation of the stomach lining by these proteases.

Some other 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 inflections, 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.

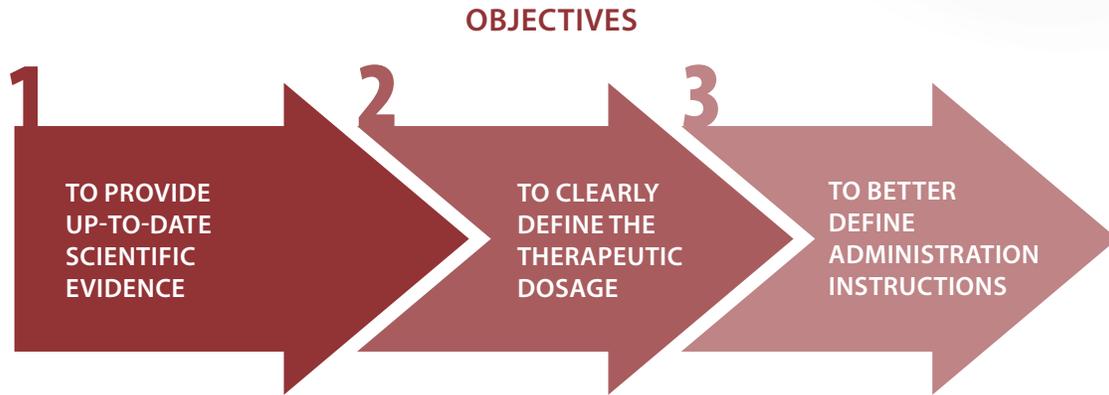
On-going promising investigations should lead to an even better understanding of the molecules involved in **Gastro-AD®** mechanism of action.



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

NEW CLINICAL TRIAL – MAY 2019

Lallemand Bio-Ingredients is conducting the latest clinical trial in 2019. Details of the study design are shown below. Results expected in late 2019.



TITLE: “The Effect of Fermented Soy Supplementation on Occasional Heartburn Symptom Relief: A Randomized, Placebo-Controlled, Double-blind Trial.”

OBJECTIVE: Evaluate the effect of **Gastro-AD®** on heartburn symptom relief and time to onset.

HYPOTHESIS: The consumption of 1-3g per day of **Gastro-AD®** will relieve heartburn symptom severity.

DESIGN: A randomized, double-blind, placebo controlled, 2-arm parallel study

PARTICIPANTS:

- a) 50 participants divided between the **Gastro-AD®** and placebo groups
- b) ≥18 and ≤60 years of age
- c) Experience heartburn symptoms min 2 days/week for the past 3 months
- d) Use OTC product(s), supplements, or dietary manipulation to relieve heartburn symptoms in the last 3 months (not prescription medication)
- e) Willing to take **Gastro-AD®** before resorting to OTC product(s) to control heartburn symptoms.

DOSAGE: 1g **Gastro-AD®**/ placebo

OUTCOMES:

- a) Measure time to onset of heartburn relief
- b) % diary-recorded heartburn symptom-free days during intervention
- c) % participants reporting ≤ 1 day with heartburn during the first and final weeks of intervention

DIRECTIONS:

- a) Participants consume 1g of the investigational product (IP) upon heartburn symptoms incidence.
- b) Participants record & score their heartburn symptoms at 5, 15 and 30 minutes after IP consumption.
- c) If the IP does not fully alleviate the heartburn symptoms by 30min, participants may repeat steps a) and b)
- d) If heartburn symptoms still have not been alleviated within 30 minutes, participants can either take a third dose of the IP or resort to an OTC product following their regular routine upon heartburn incidence.

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 include: acute toxicity, repeat-dose toxicity, reproductive toxicity

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.

