Probi Digestis® – The probiotic gastro concept

Restore peace in the gut
The importance of the intestinal system in health maintenance

Our intestinal system is host to an astounding number of bacteria. In fact, there are more bacteria in our gut than there are human cells in our body. These microorganisms form an ecosystem of their own, which just recently has been shown to be of great importance in various diseases and the maintenance of health. The intestinal ecosystem communicates with the host via the immune system, and this communication is increasingly believed to be important in “programming” the immune system to prevent chronic diseases such as rheumatoid arthritis, cardiovascular disease, diabetes, allergies etc.

Furthermore, when this sensitive ecosystem is disturbed and the abundance of “good” bacteria is reduced, disease-generating bacteria can colonize the gut, causing severe gastrointestinal disease. This brochure focuses on *Lactobacillus plantarum* 299v (LP299V®), one of the world’s most researched probiotics (more than 50 clinical studies). LP299V® has demonstrated broad health effects ranging from GI disorders to metabolic effects, nutrient uptake and the reduction of risk factors for cardiovascular disease.

**Proposed positioning**
- Reduction of abdominal pain.
- Reduction of bloating.
- Reduction of gas formation.
- Normalization of stool frequency.
- Improvement of IBS symptoms.

Probi Digestis® – A probiotic gastro concept based on *Lactobacillus plantarum* 299v
Intestinal microbiota

In the healthy gut, the microbiota and the host are separated by intestinal epithelium. The epithelium acts as a barrier, which prevents bacteria from entering the body and also prevents the host immune system from attacking the “good” bacteria. Over the past few decades, evidence has accumulated that the bacteria that are normally present in the gut also protect the host from infections caused by more aggressive, “pathogenic”, bacteria, by creating an environment in which the harmful bacteria cannot grow to disease-causing levels.

However, in various disease states, the epithelium breaks down, and the gut becomes permeable, being unable to keep toxins and pro-inflammatory substances, as well as disease-causing bacteria out of the body. This process is called translocation. Translocation of harmful substances from the gut has been associated with a range of serious conditions, such as sepsis.

In a number of clinical studies, LP299V® has shown that it can help create a healthier and more resistant gut.

Cross-section of gut epithelium, showing the process of translocation:

Aggressive, pathogenic bacteria 1 produce various toxins (A, B), which lead to production of TNF-alpha and proinflammatory interleukins 2. These compounds damage the epithelium and the tight junctions between cells are dissolved 3. The toxic substances as well as bacteria can reach the lymphatic system and the bloodstream, and can subsequently redistribute to other organs. If this process is not stopped, the epithelial cells may die, causing severe leakage 4.
**Lactobacillus plantarum**

The *lactobacillus* genus is a group of bacteria belonging to the lactic acid bacteria group, defined by its ability to produce lactic acid. These make up an important part of the intestinal microbiota. However, not all lactobacilli are the same. They bind to different receptors in the gut, which translates to different effects on the immune system, nutrient uptake, bacterial ecosystem etc. *Lactobacillus plantarum* is a member of this genus that has particularly interesting properties. Anthropologists estimate that *Lactobacillus plantarum* has been a part of our diet for 1.5 million years, since it is commonly found on plants and vegetables, where it helps preserve plant structure. With the introduction of modern preservation techniques such as refrigeration and freezing, our intake of *Lactobacillus plantarum* has decreased.

In the mid 1980s, researchers at Lund University found that *Lactobacillus plantarum* was common in healthy gut, but less frequent in diseased gut. Because of the great variety between strains in the same species, this finding prompted further research into different strains of *Lactobacillus plantarum*. The 299th strain was particularly promising as a potential therapy. It was found to resist breakdown by gastric enzymes and bile acids from the gall bladder, and it was present in the entire intestinal system – from the oral cavity to the colon! It was named LP299V®. These findings led to the founding of Probi in 1991.

**Probi’s strain LP299V®**

LP299V® is highly resistant to the digestive processes, which means that it does not need to be encapsulated to protect it from gastric or bile acids. It is also a very efficient colonizer of the gut, because it is able to bind strongly to a specific receptor – the mannose receptor – located on the epithelial cell. Most lactobacilli variants do not express the specific protein that makes mannose-receptor binding possible.

**Mannose-specific binding**

As opposed to most lactobacilli and bifidobacteria, LP299V® binds to epithelial cells via the mannose-containing receptor. This binding provides LP299V® with several unique properties. The binding occurs between the mannose-containing receptor and a protein expressed on the surface of LP299V®, which fits the receptor much like a key in a keyhole. This was first shown in a study by Probi.

**Defense against harmful bacteria**

This strong mannose-dependant receptor binding has two main effects: 1) It makes it possible for LP299V® to “crowd out” harmful bacteria, such as *E Coli, Listeria, Salmonella* etc, which compete for the same receptor; and 2) LP299V® uses the mannose receptor to get close to the epithelial cells and facilitate cellular communication which e.g. increases their production and secretion of mucus. This mucus strengthens the intestinal wall and makes it even more difficult for harmful bacteria to invade the gut.
LP299V® creates a rainforest

Diversity is as important for the intestinal microbiota as for any other ecosystem, a rainforest for example. Variations within species help to create a balance, thus building resistance. The opposite may instead give rise to the overgrowth of a few organisms, usually undesirable. One example of this is that patients with chronic inflammatory disorders, such as ulcerative colitis and Crohn’s disease, often have a depleted intestinal flora with low levels of Lactobacillus. LP299V® has, in clinical studies, shown a unique ability to increase diversity and thereby create a flourishing, varied and resistant “rainforest”. LP299V® creates conditions for a healthy, well-functioning intestine.

Supporting a healthy intestinal microbiota

LP299V® also plays a role in keeping healthy bacteria – and the gut itself – nourished. By fermenting and digesting carbohydrates and polyphenols, LP299V® creates a nutrient-rich environment, which promotes bacterial diversity. Some of these bacteria in turn produce short-chain fatty acids, providing nutrients to the gut epithelium.

LP299V® has several important advantages over other lactobacilli

- Survives gastric acid and the digestive processes.
- Colonizes the entire gastrointestinal system – from the mouth to the colon.
- Crowds out aggressive, pathogenic bacteria.
- Strengthens the healthy bacterial ecosystem.
- Provides nutrients to the gut epithelium and other healthy bacteria.

Lactose intolerance

The name Lactobacillus derives from the capacity of these bacteria to metabolize lactose. Lactose intolerance is a condition where the body is unable to metabolize lactose. Lactobacilli are safe to consume for those who are intolerant to lactose, unless of course the food product itself contains lactose.
Clinical studies and results on intestinal health

The discovery and characterization of LP299V® is based on the work of over 200 researchers, documented in more than 100 publications. The characteristics of LP299V® are promising in theory, but clinical studies are required to investigate whether the properties of LP299V® translate to improved health in real life. More than 50 clinical studies have been conducted on humans to explore this question. This wealth of knowledge makes LP299V® one of the world’s most well-documented probiotic bacteria. Based on the clinical studies conducted, the recommended dose is $10^{10}$ CFU (colony forming units).

One of the world’s most well-documented probiotic bacteria

- Research on LP299V® is conducted in-house by Probi and in collaboration with contract research organizations (CROs).
- Probi collaborates with a number of International Universities.
- Several independent research groups conduct research on Probi’s bacterial strains.
- The current clinical data is compelling.
- The effects of LP299V® appear to be pleiotropic: A wide range of health benefits are observed in various disease states.
Irritable Bowel Syndrome (IBS)

Research into the field of IBS is intense. IBS is a syndrome encompassing various intestinal symptoms such as pain, bloating, diarrhea and/or constipation. According to some studies, 50% of patients seeing a gastroenterologist have symptoms associated with IBS, and some estimates indicate as many as 20% in the general population suffer from similar symptoms.

IBS is not a disease, but a syndrome associated with a number of symptoms. Typically, the diverse gastrointestinal symptoms means that patients need to undergo a lot of interventions, such as lifestyle changes, special diets, pharmacotherapy etc. Interestingly, patients suffering from IBS often have a disturbed intestinal bacterial ecosystem. The number of “unhealthy” and gas-promoting bacteria is greater in patients with IBS than in non-affected individuals. Three different studies, conducted by three different research teams, show that LP299V® improves the bacterial ecosystem and has a robust beneficial effect on the symptoms of IBS. Several studies have been conducted on IBS.

Study 1
(Nobaek et al., 2000)

Since pain and bloating are two hallmark symptoms of IBS, a research team at Lund University investigated whether a change in the intestinal bacterial flora could affect the symptoms. 60 patients with IBS were enrolled into a double-blind randomized, placebo-controlled, 4-week clinical study. To explore potential long-term effects, a follow-up assessment was done 12 months after stopping treatment.

Results:
After 10 days, LP299V® had colonized the gut in 84% of the active group. This corresponded with a decrease in gas-promoting bacteria and a reduction in symptoms. After 4 weeks, twice as many patients in the LP299V® group reported a 50% reduction in flatulence over placebo. The patients randomized to LP299V® also reported less pain, as well as an improved stool consistency and normalized bowel movement. Prior studies had indicated that LP299V® improved bacterial diversity and improved bacterial ecosystem and the researchers wanted to explore whether these effects were durable. After a follow-up period of 12 months after study treatment had been discontinued, the research subjects were asked to fill in the same questionnaires again. Just like after 4 weeks, there was a clear difference between the LP299V® and placebo groups. The LP299V® group still reported less pain and fewer symptoms in conjunction with their bowel movements. Symptoms related to gassiness were also reported as being less severe.
Study 2  
(Niedzielin et al., 2001)

Another team of gastroenterologists carried out a 4-week double-blind, randomized, placebo-controlled study of 40 patients with IBS.

**Results:** In this study, all patients treated with LP299V® reported resolution of abdominal pain, significantly more than in the placebo group. With regards to all IBS symptoms, 95% of the patients in the LP299V® group improved, whereas only 15% reported improvement in the placebo group ($p < 0.0001$). Thus significantly reduced overall IBS symptoms and abdominal pain in the LP299V® group compared to the placebo group.

This 4-week study included 40 patients with IBS.
Study 3  
(Ducrotté et al., 2012)

In this double-blind study, 214 patients with IBS were randomized to either placebo or LP299V® and treated for 4 weeks.

Results: Symptom improvement was reported as “good” or “excellent” by 78% of the patients randomized to LP299V®, but only 8% of those randomized to placebo. This difference was significant (p < 0.01). At the end of the treatment period, pain severity and stool frequency were also significantly lower in the LP299V® group than in the placebo group. Similar significant results were observed for bloating.

The explanations underlying the results of the IBS-studies, as proposed by the researchers, are the following:

- LP299V® improves the bacterial ecosystem by increasing healthy bacteria and reducing the number of pathogenic bacteria.
- LP299V® increases the digestive breakdown of foodstuffs into short-chain fatty acids, which serves as a nutrient to the gut epithelium and reduces gas formation, pain and discomfort.
- LP299V® modulates the gastrointestinal immune system, changing the environment from pro-inflammatory to anti-inflammatory.
Inflammatory Bowel Disease (IBD)

The most common inflammatory bowel diseases are Crohn’s disease and ulcerous colitis. A number of studies in animal models suggested that LP299V® had potential in this field, which prompted a pilot study in 2012. Patients with IBD can suffer from a variety of symptoms, including diarrhea (often bloody), abdominal cramping, fever, fatigue and weight loss.

Study 1
(Krag et al., 2012)
This pilot study included 39 patients in Copenhagen, who received Profermin, an oat beverage containing LP299V®.

Results: After 6 months, at the end of the study, 24 out of 39 patients reported at least 50% reduction of symptoms.

The vast majority of patients reported significant symptom improvement after treatment with LP299V®

This 6-month pilot study included 39 patients with IBD.
Study 2
(Krag et al., 2013)
This study, from the same group as the pilot study, included 73 patients in a cross-over design. Patients were given either Profermin (LP299V®) or Fresubin (ordinary dietary treatment for IBD, not containing LP299V®) for an 8-week period. At the conclusion of the first 8 weeks, patients switched to the other beverage, which they took for another 8 weeks.

Results: This study showed significantly better effects using Profermin, containing LP299V®. More than half of the patients reported at least 50% improvement of symptoms after 8 weeks with LP299V®, as opposed to just over a quarter of patients reporting the same level of improvement after 8 weeks of the non-LP299V®-containing beverage.

Significant symptom improvement was observed after 8 weeks of treatment with LP299V®

This 8-week study included 73 patients with IBD.
LP299V® protects the bacterial ecosystem during antibiotics treatment

(Lönnemark et al., 2009)

Approximately 60% of all patients treated with antibiotics develop some kind of gastrointestinal problems. This is at least partly due to the fact that the antibiotics also kill “good bacteria” in the bacterial ecosystem. Furthermore, and perhaps more alarmingly, a course of antibiotics has a long-standing effect on the bacterial ecosystem – often times many years after stopping treatment.

A placebo-controlled study of 163 patients investigated the effect of LP299V® during a course of antibiotics and a week thereafter.

**Results:** The risk of developing nausea was significantly reduced by 50% and the risk of developing loose or watery stools was reduced by 30% in patients receiving LP299V® compared to patients receiving placebo.

LP299V® may reduce the risk of *Clostridium difficile* infection

(Klarin et al., 2008)

*Clostridium difficile* infection is a common cause of severe, long-standing and difficult to treat diarrhea in critically ill patients undergoing antibiotic treatment.

In a double-blind study, 44 critically ill patients were randomized to either LP299V® or placebo for the duration of their stay in the intensive care unit. It should be acknowledged that this study used a very high dose of LP299V®, which may be necessary when critically ill patients are involved. (Significant results were also seen with the dose $10^{10}$ in a study conducted on 3533 patients).

**Results:** In the placebo group, 19% of patients developed an infection with *Clostridium difficile*, similar to the number expected based on scientific literature. In the group treated with LP299V®, no patients were infected with *Clostridium difficile*. 
Increased diversity in the bacterial ecosystem in the gut may improve the immune system
(McCracken et al., 2002, McNaught et al., 2005)

Studies indicate that LP299V® has immunological and anti-inflammatory properties that may be relevant to patients with gastrointestinal disorders, but it should not primarily be viewed as an immune modulator. A healthy bacterial ecosystem in the gut may also have an anti-inflammatory effect.

**Results:** In vivo and in vitro studies show that LP299V® reduces important pro-inflammatory cytokines IL-6 and IL-8. This was, among others, shown in a study in 103 critically ill patients, who were randomized to “standard care” or “standard care” with addition of LP299V®. On day 15, the latter group had significantly lower levels of IL-6. According to the researchers, this suggests lower inflammatory response, in turn suggesting lower risk of serious infection and organ failure.

Choosing the right strain
(Rask et al., 2013)

In a study including 57 individuals, the effects of several different probiotic strains on the immune system were investigated.

**Results:** LP299V® was the only strain that increased markers of both “killer” (CD8+) and “helper” (CD4+) T-cells. No other strain was able to induce a significant increase on either marker. Furthermore, these in vivo results were not predicted by in vitro characteristics, which highlights the need for clinical trials to elucidate the effects of different bacterial strains.

LP299V® improves nutrient uptake
(Bering et al., 2006)

Iron deficiency anemia is very common, especially in women of childbearing age. A disturbed bacterial ecosystem in the gut often causes reduced nutrient uptake. An important part of the recovery process is to improve nutrient uptake by reestablishing the bacterial ecosystem.

Several studies have been conducted on iron uptake and have shown to increase iron uptake. In one of the studies, 24 young women were randomized to drinking an oat-based beverage with or without the addition of LP299V®, and the uptake of iron was measured. The study subjects were included in a cross-over study with 4 arms, each consisting of a controlled meal. With all of their meals, they received an oat-based beverage, and on one occasion for each subject, the beverage was fortified with LP299V®. The study showed that the uptake of iron in connection with LP299V® intake was significantly increased vs the meals consumed without the intake of LP299V®.

**Results:** LP299V® was shown to increase iron uptake significantly.
It started with a vision of saving lives

In the mid 1980s, a team of surgeons, microbiologists and nutritional physiologists in Lund studied the fact that many patients were dying after difficult but clinically successful surgical procedures. The patients suffered from sepsis and subsequent organ failure.

The team’s hypothesis was that the sepsis was caused by bacterial translocation. This means that the intestines, weakened for example by fasting, tube-feeding and medications before and after surgery, had begun to leak toxins and harmful bacteria into the body.

Can bacteria heal a damaged intestine?

Due to the wide range of expertise in the team, a bold idea was born: to solve the problem by introducing bacteria that could build up the intestinal flora and strengthen the intestinal wall, thus reducing the leakage of toxins and pathogens. An untested hypothesis.

After many years of work comparing hundreds of samples, the researchers finally identified bacteria that was common in healthy intestines, but less common in a diseased environment – *Lactobacillus plantarum*.

*Lactobacillus plantarum* becomes LP299V®

But the identification of *Lactobacillus plantarum* was not enough. The species has hundreds of strains, all with somewhat different effects – so the work continued.

After many attempts, the researchers finally identified a strain with promising medicinal properties that also proved robust. It successfully passes through the low pH of the stomach and the bile acids in the duodenum. Most importantly, it colonizes the entire gastrointestinal tract, meaning not only the small intestine, but also in the mouth and the colon. This was due to the ability of LP299V® to survive both anaerobic and aerobic environments. Because the discovery was made on the 299th attempt, the bacterial strain was named LP299V®.

All patients recovered

The first trial with LP299V® was conducted on five critically ill patients suffering from multiple organ failure. Their antibiotic therapy was terminated and replaced by LP299V® diluted in an oatmeal base. The results were dramatic. All five patients recovered and were able to leave the intensive care unit.

(Bengmark S et al., 1996)

And this was just the beginning...
References


Probi – A world Leader in probiotic research and development

Probi was founded in the early 1990s, by a group of physicians and researchers with a clear vision – to be able to save lives through the use of probiotic bacteria. Several of the researchers are still active in the company.

Science and research are as important today as when the company was founded. Our products must be scientifically proven, without compromise. Probi provides consumers worldwide with the opportunity to improve their health through clinically tested, effective probiotics.

Today, Probi is active in more than 40 markets around the world within the fields of Consumer Healthcare and Functional Food. Our main focus areas are improving gastrointestinal health, strengthening the immune system and optimizing nutrient uptake.

A one-stop shop offer

- Global market knowledge.
- Broad R&D expertise.
- Strong know-how in microbiology.
- Long experience in the field of nutrition.
- Application and product development.
- Regulatory support.
- Consumer focus.

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