

# LP299V® – Three decades of research

*Lactiplantibacillus plantarum 299v:*  
*The most clinically documented*  
*L. plantarum strain in the world*

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# 1. Summary

*Lactiplantibacillus plantarum* (*L. plantarum*) 299v, LP299V® (hereafter referred to by use of the trademark LP299V®) is the most clinically documented *L. plantarum* strain in the world. It has been described in more than 200 scientific publications out of which more than 65 are human clinical studies.

The probiotic strain LP299V® was isolated from healthy human intestinal mucosa three decades ago by scientists at Lund University, Sweden. Thirty years later, a wealth of data coming from *in vitro*, animal, and clinical studies exists. Intake of LP299V® has primarily been shown to support gastrointestinal health, such as reducing flatulence and abdominal pain in subjects with irritable bowel syndrome (IBS). The strain has also been shown to positively affect iron absorption as well as iron status, and has multiple other health benefits far beyond gut health.

Most importantly, LP299V® has been proven safe for human consumption and not to confer antibiotic resistance. The strain survives the harsh conditions of the human gastrointestinal tract and adheres to mannose residues on the intestinal epithelial cells. It has been re-isolated more than ten days after administration ceased. All studies conducted with LP299V® up until June 2020 have been summarized in a review by Arvidsson Nordström et al. The strain is patent protected for a wide range of indications and applications worldwide proving its excellent survivability, as well as trademarked as LP299V® and 299V®.



## 2. Meet one of the world's most studied probiotic strains

The story of LP299V® began in the 1980s, when a group of scientists at Lund University, in southern Sweden, was struggling to find ways to increase survival in intensive care unit (ICU) patients with multiple organ failure. These patients had signs of sepsis with failing respiratory, renal, and hepatic function, and high mortality rates, despite intensive care and antibiotic therapy. At the time, little was known about the gut microbial composition and its importance for health. It was hypothesized that something was missing in the intestines of the ICU patients; something that was abundant in the guts of healthy people. The scientists at Lund University, therefore, decided to take a new approach and investigate which gut bacteria that were most often seen in healthy individuals, and what would happen if these same bacteria were given to the severely ill ICU patients. Biopsies were taken from healthy intestinal mucosa and a vast number of bacterial strains were isolated and characterized. Various *Lactiplantibacillus plantarum* (*L. plantarum*) strains were found to frequently occur in the normal intestinal microbiota of healthy adults<sup>1</sup>. This laid the foundation for probiotic research as we know it today. Scientists were able to show that by adding these gut bacteria, mortality rates and critical illness significantly decreased in the ICU wards. The bacterial strain found to be the most prominent in the guts of healthy individuals, which was given to the ICU patients in the first trials, was named *Lactobacillus plantarum* 299v, later renamed *Lactiplantibacillus plantarum* 299v (LP299V®).

Today, we know that critical illness is often associated with significant gut overgrowth of typical ICU pathogens, such as *Clostridioides difficile* (*C. difficile*), Enterobacteriaceae and enterococci. Bacterial translocation over the intestinal wall may be a factor of importance in the pathogenesis of ICU-acquired infections. The intestinal microbiota therefore plays an important role in protecting the gut from colonization with pathogens as well as overgrowth of commensal bacteria. Treatment with antibiotics could partially be the cause of gut microbial imbalance since these disrupt the normal microbiota and promote colonization of pathogens<sup>2,3</sup>.

Probiotics are live microorganisms that confer health benefits on the host if given in adequate amounts<sup>4</sup>. They should be well defined with proven safety. The most common probiotics are lactic acid bacteria, for example different strains of lactobacilli and bifidobacteria. *L. plantarum* strains are common in traditional lactic acid-fermented foods of plant origin such as brined olives, capers, sauerkraut, sourdough and wine<sup>5</sup>.

As the intake of these foods has decreased and modern food processes tend to be done under 'sterile' conditions, it is likely that *L. plantarum* strains are now less prevalent in the microbiota of healthy as well as diseased people. The probiotic LP299V® strain has been studied in healthy individuals as well as in subjects with various health conditions. Among the clinically proven health benefits, LP299V® has primarily been shown to support gastrointestinal (GI) health. LP299V® is used in many different food applications as well as in various dietary supplements. In a freeze-dried format, LP299V® is robust and stable at room temperature, enabling long shelf-lives of consumer healthcare products such as capsules, tablets, or powder sachets.

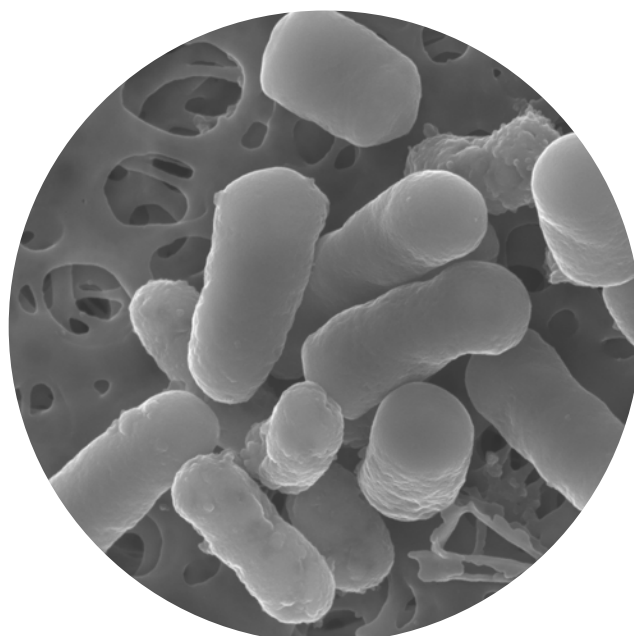
### 3. Isolation, taxonomy and intestinal persistence

The LP299V® strain was isolated from healthy intestinal mucosa<sup>1,6</sup> and has been re-isolated after consumption<sup>7</sup>. Multiple *in vitro* and clinical studies have shown that LP299V® survives the harsh conditions in the human GI tract<sup>7-16</sup>. It has also been shown to survive the passage through the GI tract irrespective of the gastric acidity<sup>13</sup>.

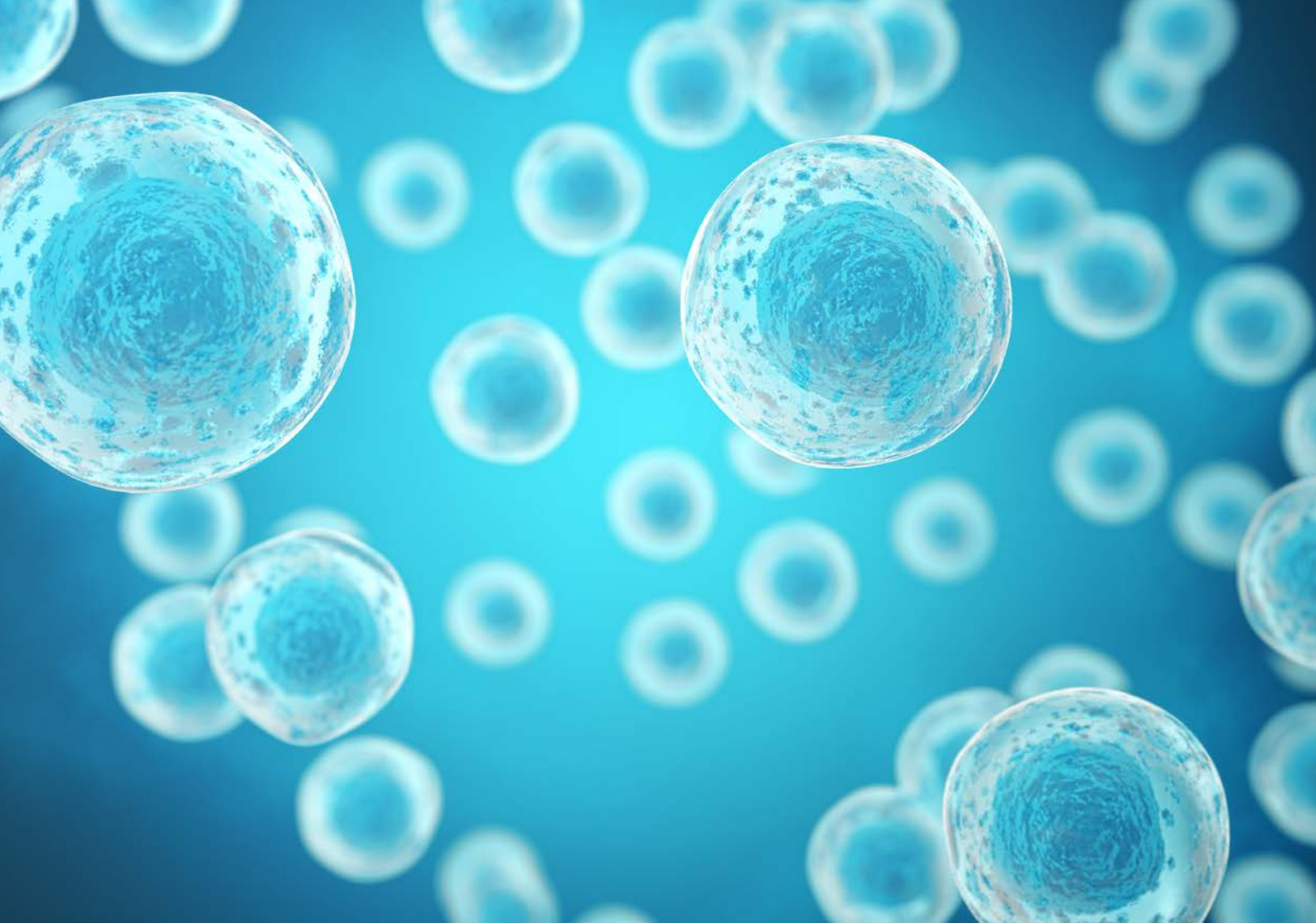
Several clinical studies have demonstrated that LP299V® has excellent persistence capacity and can be re-isolated all the way from the mouth to the rectum. The strain has even been re-isolated from intestinal biopsies taken 11 days after end of intake. When a mix of 19 different strains were given to healthy individuals, LP299V® was one of the dominating lactobacilli strains found in intestinal samples<sup>7</sup>.

LP299V® has been characterized using several different methods, such as restriction fragment length polymorphism (RFLP)<sup>17</sup>, restriction endonuclease analysis (REA)<sup>18</sup>, randomly amplified polymorphic DNA (RAPD)<sup>19,20</sup> and microarray analysis<sup>21,22</sup>. Additionally, global gene expression profiles of LP299V® have been conducted on human intestinal tissue biopsies<sup>21</sup>.

The rapid development of new sequencing technologies over the last few years has triggered the review of the taxonomy of microorganisms in more detail. As a result, a “reclassification” of certain *Lactobacillus* species into new genera has been made and *Lactobacillus plantarum* was renamed *Lactiplantibacillus plantarum*<sup>23</sup>.







## 4. Characteristics and mechanisms of LP299V®

LP299V® has beneficial effects in multiple parts of the body, especially in the GI tract. The core mechanism of the GI health benefits of this strain seems to be maintenance and improvement of the gut mucosal barrier function. A healthy and more resilient gut barrier can better tackle for example pathogens and foreign substances. LP299V® has the ability to bind to the intestinal epithelial cell layer by a mannose-dependent mechanism (Fig. 1). This trait, shared with only a few other probiotic strains, has been shown to be important for the majority of health benefits shown with this strain. Many studies have revealed the ability of LP299V® to decrease intestinal permeability, and the mannose-binding has been shown to be of greatest importance also for this mechanism.

Pathogen inhibition through many different actions is another mechanism. For LP299V®, the most prominent actions include promotion of mucin covering the intestinal cells, production

of lactic acid acting as a precursor for short chain fatty acids (SCFAs), as well as direct competitive exclusion of other bacteria to binding sites.

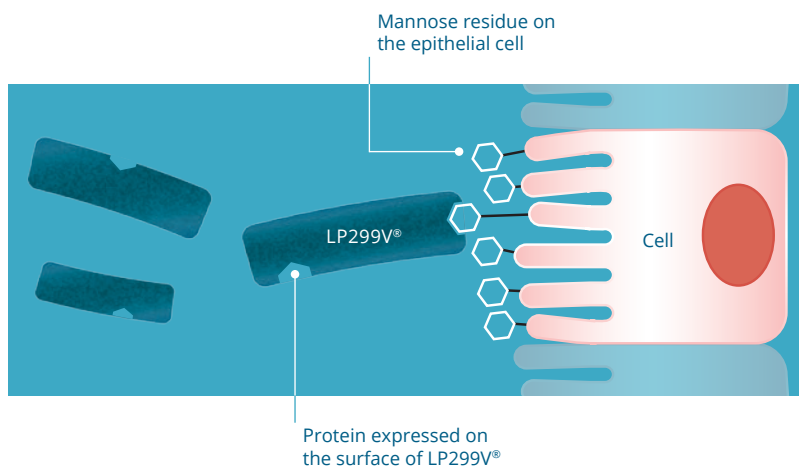
Apart from direct effects in the intestinal lumen, probiotic strains may also have immunoregulatory properties <sup>24</sup>. The mannose-binding seems to be important also for immune regulation by LP299V®, as the strain has been shown to positively impact immunoregulatory actions in both healthy and diseased states. The majority of immune regulation originates from the GI tract, and there is a constant interaction between the mucosal immune system and bacteria in the gut <sup>25</sup>. Probiotics may upregulate or downregulate pro- or anti-inflammatory responses aiming to maintain the balance between tolerance and defense <sup>26</sup>.

# Important characteristics and mechanisms have been identified for LP299V®

1

## ADHERENCE TO EPITHELIAL CELLS

LP299V® adheres to the epithelial cells along the entire GI tract both in healthy adults<sup>7,11,27-29</sup> and in critically ill patients<sup>30</sup>. The mannose-binding mechanism enables LP299V® to adhere to the intestinal epithelium (Fig. 1).<sup>31</sup> LP299V® can also adhere to the mucus layer, mostly due to electrostatic and hydrophobic interactions with the mucin<sup>32</sup>. Adhesion to the mucus layer is required to allow enough residence time for the bacteria to interact with the epithelial cells.



*Fig. 1  
The probiotic strain LP299V® has the ability to bind to mannose residues on the intestinal epithelial cells. The binding is a prerequisite for many of the health benefits linked to intake of LP299V®.*

2

## INHIBITING PATHOGENS

Probiotics can exert pathogen inhibition by several different methods. Competitive exclusion due to occupying binding sites, production of SCFAs that lower the pH in the intestinal lumen, increased production of mucin and production of bacteriocins are some of the proposed mechanisms.

LP299V® has been shown to promote the **production of mucin**<sup>33-35</sup>. As the mucus layer is the first line of defence against pathogens in the intestinal lumen, this mechanism seems to be the strongest for pathogen inhibition and promotion of intestinal integrity.

The second most important mechanism for pathogen inhibition by LP299V® is **carboxylic acid production**<sup>11,36,37</sup>. LP299V® is a lactic acid producer<sup>14</sup> rather than a producer of SCFAs. However, lactic acid is a precursor of some SCFAs<sup>38</sup>. SCFAs include acetic acid, butyric acid, and propionic acid, all of which contribute to a healthy intestinal barrier and pathogen inhibition by decreasing the pH in the intestinal lumen. The lactic acid production by LP299V® may explain the significant increase in production of acetic acid and propionic acid found in healthy subjects<sup>11</sup>, as well as the significant increase in plasma propionic acid in men with stable coronary artery disease<sup>36</sup>. In patients under antibiotic treatment, levels of fecal butyric acid have been found to be maintained, rather than decreased<sup>37</sup>. This suggests that administration of LP299V® reduces the negative effects of antibiotic treatment on colonic fermentation.

**Competitive exclusion** for pathogens by LP299V® occurs by competition for binding sites on the intestinal cells<sup>33,39-42</sup>. Several pathogenic bacteria, such as *Escherichia coli* (*E. coli*), are known to have the same type of adherence to mannose as LP299V®<sup>43</sup>. *Helicobacter pylori* and *Salmonella* are pathogenic bacteria that do not share the same binding mechanism as LP299V®. The interaction between LP299V® and these bacteria has been studied<sup>44-46</sup>, as well as the effect of LP299V® in *C. difficile* infections. LP299V® did not inhibit *C. difficile in vitro*<sup>44</sup>, however, it was shown to reduce the incidence of *C. difficile* infections in several clinical studies<sup>47-49</sup>.

## PERMEABILITY AND BACTERIAL TRANSLOCATION

The effects of LP299V® on permeability and bacterial translocation have been studied in *in vitro*, *in vivo* and *ex vivo* studies<sup>35,40,50-65</sup>. Similar to several other health benefits of LP299V®, reduction of permeability seems to be related to the mannose-binding property of this strain. The prevention of bacterial translocation was only observed with LP299V® with adherence capacity, and not when the mannose-binding was lost<sup>66</sup>. Also in clinical settings, pre-supplementation with LP299V® was shown to reduce intestinal permeability (Fig. 2)<sup>47,67</sup>.

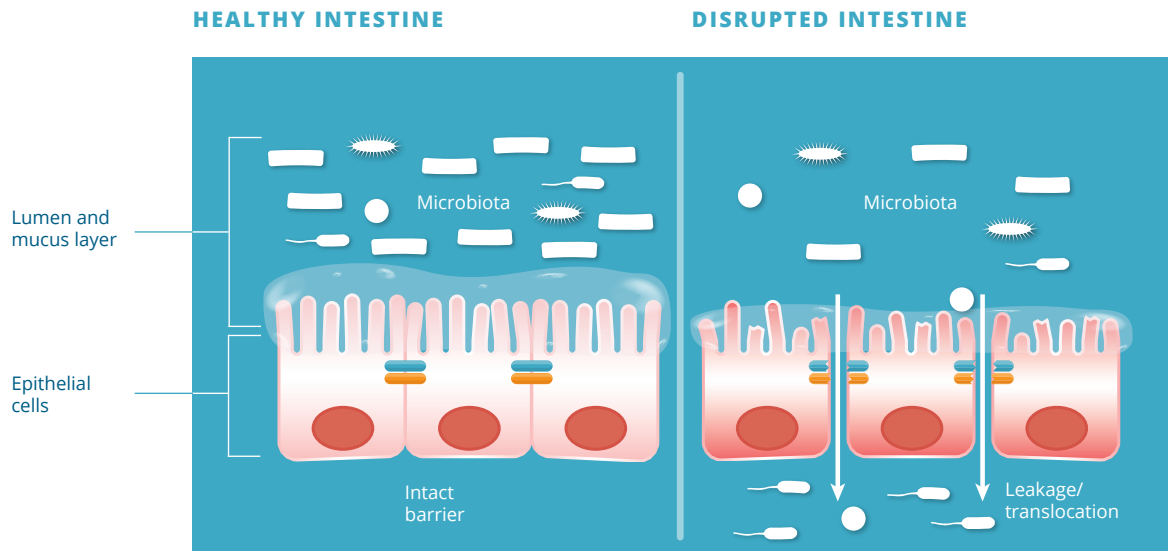


Fig. 2

A healthy intestine is composed of epithelial cells tightly connected to each other, preventing leakage over the intestinal wall. A thick mucus layer covers the finger-like structures, microvilli, and tight junctions hold the epithelial cells together (left side).

In a disrupted intestine, the mucus layer is thinner and more permeable. The microvilli may become damaged and the tight junctions are weakened, resulting in epithelial cells that are no longer bound to each other.

This enables leakage of bacteria and other harmful substances over the intestinal wall (right side). The probiotic strain LP299V® has been shown to support intestinal health by contributing to a balanced microbiota composition. Moreover, LP299V® stimulates the production of mucus and strengthens the tight junctions (holding the epithelial cells together), thereby preventing increased intestinal permeability and translocation.

## INFLAMMATORY RESPONSE

The importance of the mannose-binding capacity of LP299V® for immune responses has been shown in several *in vitro* studies<sup>40,68</sup>. Animal studies have shown that LP299V® has anti-inflammatory effects<sup>69-71</sup>. The levels of a specific type of antibody, called immunoglobulin A (IgA), increase as a response to enhanced intestinal immunity. LP299V® has been shown to affect IgA levels in several animal studies<sup>62,72</sup>.

The immunomodulatory effects of LP299V® have also been investigated in clinical studies. In critically ill patients treated with antibiotics, LP299V® significantly decreased levels of the pro-inflammatory cytokine interleukin (IL) 6<sup>73</sup>. A decrease in IL-6 levels was also seen when the bacteria were given to smokers<sup>74</sup>. In blood samples from healthy volunteers, LP299V® was shown to increase the expression of yet another cytokine, IL-12<sup>75</sup>. IL-12 is important for regulating immune responses. Based on these different studies, LP299V® helps to support natural immune regulation by maintaining an alert and proactive immune system.



## 5. Safety

LP299V® has been thoroughly tested in humans and proven to be safe for consumption by healthy adults and children as well as individuals with various health conditions. The species *L. plantarum* is recognized as safe and included in the Qualified Presumption of Safety (QPS) list in the European Union. To be in the QPS list, a microorganism must have a well-defined taxonomic identity and its safety must be well established. The Food and Drug Administration (FDA) in the United States has reviewed the evidence provided in the Generally Recognized as Safe (GRAS) determination notice for LP299V®. The FDA had no further questions about, nor any objection to, its intended use.

LP299V® has been safely administered to vulnerable populations such as patients undergoing elective major abdominal surgery<sup>76</sup>, critically ill patients<sup>30,47,73,77-79</sup>, children as young as 6-12 months<sup>80-82</sup>, children congenitally exposed to HIV-1<sup>83,84</sup>, children with small bowel bacterial overgrowth<sup>85</sup>, and children and adolescents undergoing hematopoietic cell transplantation<sup>86</sup>. The studies even suggest that administration of LP299V® may alleviate side effects coupled to invasive treatment<sup>86</sup> and positively influence growth and immune development in HIV-1 positive children<sup>83,84</sup>. In severely ill cancer patients, supplementation of LP299V® was shown to reduce GI side-effects coupled to enteral feeding<sup>79</sup>.

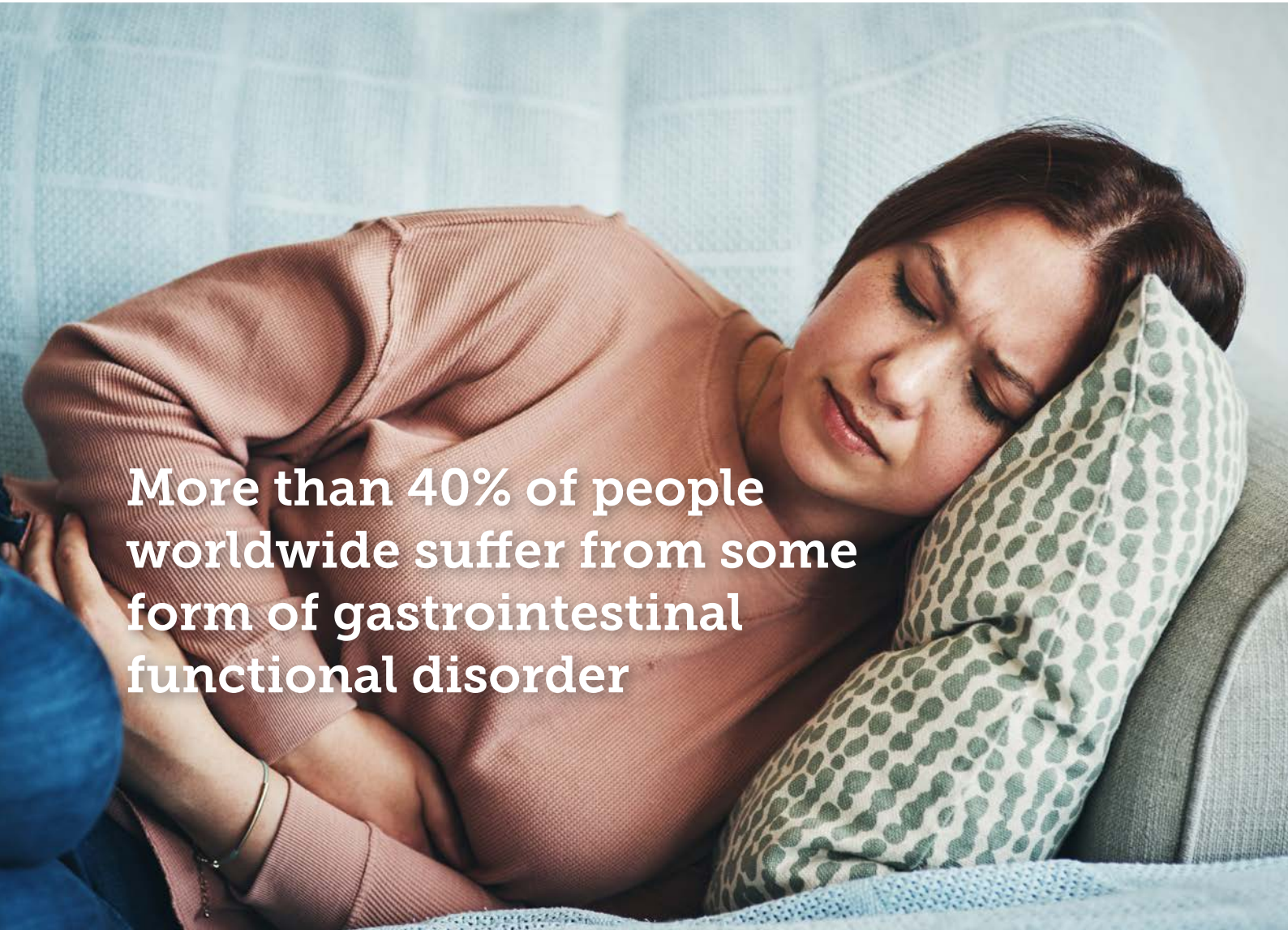
To further evaluate safety and risk of intestinal translocation causing septic bacteremia, an endocarditis animal model was used for a comparison between LP299V® and the pathogen *Staphylococcus lugdunensis*. Ninety-six hours after injection into the tail vein of rats, no lactobacilli were found in the heart, blood, or catheter, while *S. lugdunensis* was isolated from both blood and heart<sup>87</sup>. This showed that LP299V®, in the occasion of an intestinal leakage into the bloodstream, will not cause sepsis.

Another important safety factor for probiotics is the risk of antibiotic resistance. The bacterial content is high in the intestine and so is the likelihood of horizontal gene transfer between different bacteria. This means that bacteria that possess antibiotic resistance genes may transfer these genes to other bacteria, which may lead to antibiotic resistance in the host. If antibiotic resistance genes would be transferred to potentially pathogenic bacteria, this could have detrimental effects on the health of the host. LP299V® has therefore been thoroughly tested to make sure that the strain is sensitive to antibiotics, i.e., does not possess antibiotic resistance<sup>88</sup>.

**LP299V® has been thoroughly tested in humans and proven to be safe for consumption by healthy adults and children as well as individuals with various health conditions.**

## 6. Efficacy

The effects of LP299V® in different populations and on different health indications have been investigated in more than 65 human clinical studies. Its clinical efficacy has been shown for many indications, but mostly focused on supporting gastrointestinal health and increasing iron absorption. These two health areas are especially interesting and important since more than 40% of people worldwide suffer from some form of gastrointestinal functional disorder <sup>89</sup> and iron deficiency is the most common micronutrient deficiency in the world <sup>90</sup>.



**More than 40% of people worldwide suffer from some form of gastrointestinal functional disorder**

# Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) is the most commonly reported GI disorder affecting 10-20% of the population worldwide. Moreover, 50% of people seeing a gastroenterologist have symptoms associated with IBS<sup>91</sup>. IBS is primarily characterized by recurrent abdominal pain or discomfort, associated with changes in bowel habits. Other common GI symptoms are abdominal bloating or flatulence, straining during defecation, defecatory urgency, feeling of incomplete evacuation, or presence of mucus in the stool<sup>92,93</sup>.

The factors influencing the onset of IBS are not well known and can differ between individuals. An imbalanced microbiota, also known as dysbiosis, is however thought to be one key parameter<sup>94</sup>. A disturbed microbiota may over-activate immune responses. This may in turn increase intestinal permeability and result in the GI symptoms typical in IBS<sup>95</sup>.

## BLOATING AND FLATULENCE

The first clinical study with LP299V<sup>®</sup> in the IBS-related area was performed in healthy volunteers. The strain was shown to persist in the gut and reduce potentially gas producing bacteria. Moreover, perceived flatulence was significantly decreased in participants in the LP299V<sup>®</sup> group, both compared to baseline and to the placebo group. Increased levels of fecal carboxylic acid were also found<sup>11</sup>.

Several studies have been performed in IBS patients. One of the first clinical studies aimed to understand the microbiota imbalance and changes with supplementation<sup>27</sup>. The study showed that a fruit drink with LP299V<sup>®</sup> was able to significantly reduce flatulence (Fig. 3). Number of days with abundant gas production was also significantly and more rapidly decreased in the LP299V<sup>®</sup> group compared to placebo.

The effects of LP299V<sup>®</sup> in a freeze-dried (capsule) format given to IBS subjects have been evaluated in two larger clinical studies: one placebo-controlled including 204 subjects<sup>96</sup> (Fig. 4), and one in a real-life, non-placebo controlled study including 221 subjects<sup>97</sup>. Both studies found significant improvements in both severity and frequency of bloating and flatulence, as well as other effects described on page 12.

## REDUCTION IN FLATULENCE

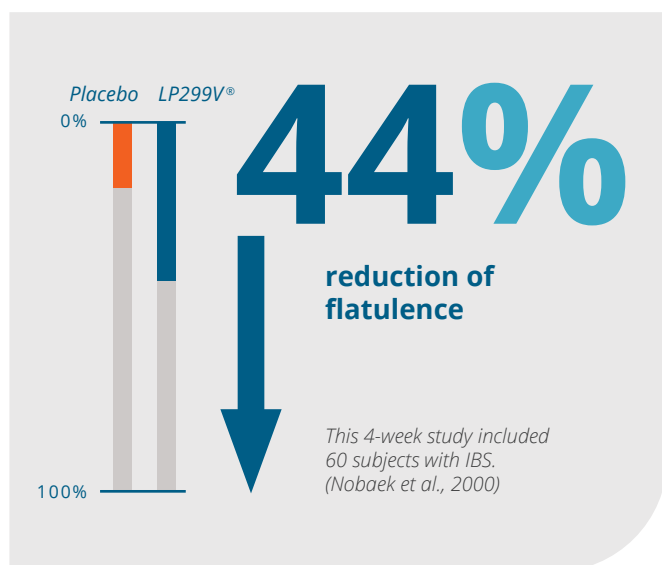


Fig. 3

## SIGNIFICANTLY LESS SEVERE ABDOMINAL BLOATING

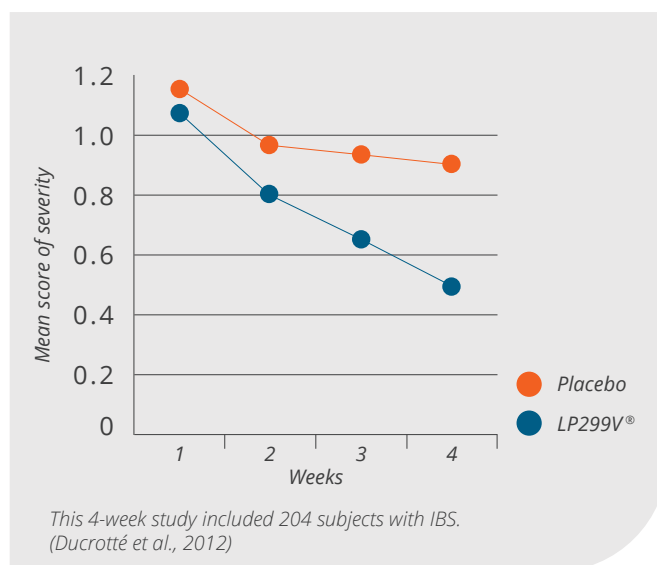


Fig. 4



## HELPS 9 OUT OF 10 WITH IBS

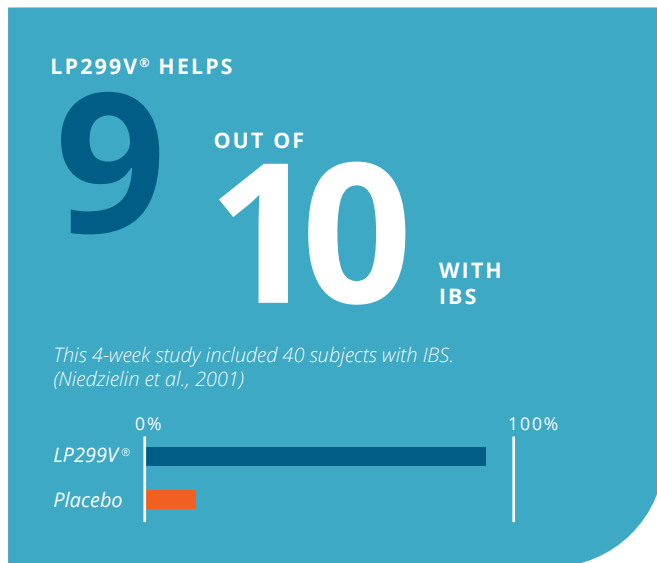


Fig. 5

## ABDOMINAL PAIN

Abdominal pain is a very common symptom in IBS subjects. LP299V<sup>®</sup> has successfully been shown to reduce both the severity and frequency of pain in several studies. In the first study, subjects received either placebo or LP299V<sup>®</sup> for 4 weeks in a fruit drink. Already after one week of intake, 70% of the subjects in the LP299V<sup>®</sup> group reported a significant pain relief. At the end of the study, complete resolution of abdominal pain was found in the LP299V<sup>®</sup> group, compared to 55% of the subjects receiving placebo who still reported pain<sup>98</sup>. The studies by Ducrotté et al. and Krammer et al. confirmed these results, showing significantly reduced severity and frequency of abdominal pain<sup>96,97</sup>.

## BOWEL MOVEMENT

Improved stool frequency is another effect seen in IBS subjects after intake of LP299V<sup>®</sup>. Reduced bowel movement in those with at least three defecations per day<sup>96</sup> and increased bowel movement in those with constipation<sup>98</sup> have been shown. The same results were confirmed in the real-life study by Krammer et al. Severity of constipation as well as severity and frequency of diarrhea were significantly decreased, with a higher resolution of the symptoms with time<sup>97</sup>. Urgency of defecation and incomplete evacuation are two other very distressing symptoms of IBS. These were also significantly reduced in the participants who received LP299V<sup>®</sup> in the two studies by Ducrotté and Krammer<sup>96,97</sup>. Considering these results, it is suggested that LP299V<sup>®</sup> can normalize stool frequency independently of the IBS subtype; diarrhea-predominant (IBS-D) or constipation-predominant (IBS-C).

## 78% OF THE SUBJECTS RATED THE EFFICACY AS GOOD OR EXCELLENT

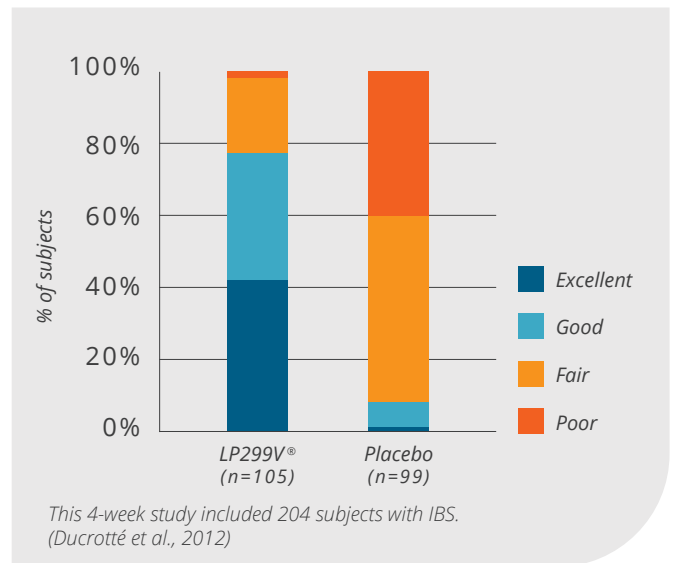


Fig. 6

## OVERALL SYMPTOMS

Changes in overall IBS symptoms were shown in three of the studies described. In the study by Niedzielin et al., 95% of the subjects receiving LP299V<sup>®</sup> showed an improvement of overall IBS symptoms, compared to 15% in the placebo group (Fig. 5)<sup>98</sup>. These results were confirmed in the study by Ducrotté et al., where 78% of the subjects receiving LP299V<sup>®</sup> rated the overall efficacy as “good” or “excellent”. In the placebo group, a positive rating of only 8% was seen (Fig. 6)<sup>96</sup>. The study participants were blinded to the type of product that had been consumed when rating the efficacy of the product. In the real-life study by Krammer et al., the overall symptoms reduced significantly with time. The significant improvement was seen after just 4 weeks and continued to improve significantly until the last timepoint (12 weeks). The subjects in the Krammer study were also asked whether they would recommend the product to others and at the end of the study, 83% of the subjects answered that they would recommend LP299V<sup>®</sup> to others suffering from IBS<sup>97</sup>.

## Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) refers to chronic relapsing inflammation of the intestines and includes the disorders ulcerative colitis (UC) and Crohn's disease (CD). Symptoms of CD and UC are severe diarrhea, abdominal pain, blood in stool, fatigue, and unintended weight loss. All these symptoms negatively affect quality of life. The etiology of IBD is not fully known but involves genetic, environmental, microbial, and immunological factors<sup>110</sup>. The gut microbiome in IBD patients has been shown to be significantly less diverse than that of healthy controls<sup>111</sup>.

LP299V<sup>®</sup> can reduce signs of inflammation associated with IBD, as shown in different colitis animal models<sup>61,69</sup>. The improvements seen in the animal models agree with

the results from clinical studies. Patients with active UC, supplemented with an oat gruel fermented with LP299V<sup>®</sup>, had significantly improved symptoms during a 24-week intervention<sup>112</sup>. The results were confirmed in a randomized study comparing a drink containing LP299V<sup>®</sup> to a similar product without bacteria<sup>113</sup>.

The mechanisms previously described for LP299V<sup>®</sup> may also explain the beneficial effects on symptoms of IBD. Studies show links between improvement of IBD symptoms and immune-related mechanisms, production of mucus, strengthening of tight junctions, and inhibition of translocation<sup>33-35,62,66,114,115</sup>.

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## Gastrointestinal infections

The effects of LP299V<sup>®</sup> on the incidence, symptoms and recurrence of antibiotic associated diarrhea (AAD) and gastrointestinal infections, such as *C. difficile infection* (CDI), have been investigated in several clinical studies<sup>47-49,82,116,117</sup>.

*C. difficile* is currently the most frequently identified pathogen involved in the development of AAD<sup>48</sup>. Microbial dysbiosis is common in *C. difficile* associated diarrhea and occurs most frequently in patients under broad spectrum antibiotic therapy. LP299V<sup>®</sup> taken during antibiotic treatment reduced mild GI symptoms associated with antibiotic intake such as loose or watery stools and nausea in adult patients<sup>116</sup>.

LP299V<sup>®</sup> also tended to reduce the incidence of recurrent CDI in adults<sup>117</sup> and significantly decreased CDI incidence in critically ill patients<sup>47</sup>. In a study performed over three consecutive years, which included a total of more than 5000 individuals, hospitalized patients under antibiotic and immunosuppressive therapy were given LP299V<sup>®</sup> only during the second year<sup>48,49</sup>. A significant reduction of the incidence of CDI in the ward was observed during the year when LP299V<sup>®</sup> was administered, compared to the first<sup>49</sup> and third<sup>48</sup> years.

## Iron absorption

Insufficient iron is the most prevalent micronutrient deficiency globally <sup>118,119</sup>, in both developed and developing countries. Iron deficiency is the most common cause of anemia worldwide. According to the World Health Organization (WHO), around 500 million women, more than 30 million pregnant women and almost 300 million children suffered from anemia in 2011 <sup>90</sup>. Iron deficiency often stems from low iron absorption. When the iron uptake from food does not meet nutritional requirements, iron deficiency may develop.

Iron supplements effectively reduce iron deficiency, and consequently the prevalence of anemia. The supplements are, however, strongly associated with GI side effects such as abdominal pain and constipation <sup>120</sup>. This is due to the high concentration of iron present in the supplements, and the low absorption rate in the intestine, which leads to high iron levels in the colon. Given these very common side effects of iron supplementation, finding ways to increase iron uptake, in addition to intake, is desirable.

According to the World Health Organization (WHO), around

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## INCREASED IRON UPTAKE, INDEPENDENT OF FOOD MATRIX

The effect of LP299V® on iron absorption has been studied in several clinical studies in women, as well as in animal studies. LP299V® has been proven to increase iron absorption<sup>121-123</sup> and improve iron status<sup>124-126</sup>. Iron uptake seems to be a strain-specific property of LP299V®. Researchers have investigated numerous other strains but were unable to show an effect on iron uptake or iron status<sup>128,129</sup>.

Bering and colleagues investigated the potential of LP299V® to increase iron absorption in women of childbearing age, by comparing different oat gruels<sup>121</sup>. They found that oat gruel with live LP299V® significantly increased the absorption of iron from a test meal, compared to oat gruels without live LP299V®. The results were later confirmed in studies with a fruit drink<sup>122</sup> and capsules with lyophilized bacteria<sup>123</sup>. Depending on the food matrix, increased iron absorption rates of 23% to 80%, compared to control were observed (Fig. 7).

## LONG-TERM EFFECTS ON IRON STATUS

The long-term effects of LP299V® on improving iron status have been investigated in a group of healthy female athletes<sup>125</sup> and in healthy pregnant women<sup>126</sup>. The female athletes had low iron stores but were not anemic. They were given either one capsule daily containing 20 mg of iron and LP299V®, or 20 mg of iron alone (placebo) for 12 weeks. Plasma ferritin levels, as a measure of iron status, increased in both groups. However, an increase of 70% was seen in the

LP299V® group, compared to 42% in the placebo group. The effect occurred within four weeks<sup>125</sup>.

A population of 326 healthy, non-anemic, pregnant women was followed from gestational week 10-12 until eight weeks after delivery. The women were given two capsules a day of either placebo or LP299V® with added iron (4.2 mg), ascorbic acid and folic acid. The women received the study product until the end of pregnancy, or until a potential need for conventional iron therapy. In the LP299V® group, the expected pregnancy-related decreases in serum ferritin levels, total body iron status, and hemoglobin levels improved, compared to the placebo group. Supplementation with LP299V®, iron, ascorbic acid and folic acid also resulted in reduced prevalence of iron deficiency (Fig. 8) and iron deficiency anemia in late pregnancy<sup>126</sup>.

## HOW DOES IT WORK?

The mechanism behind increased iron absorption driven by LP299V® needs to be further investigated. It has, however, been suggested that LP299V® increases the bioavailability of iron that can be absorbed<sup>130</sup>. Taking into account the possible harmful side effects of high-dose iron supplements, LP299V® is a novel strategy to safely increase iron uptake and potentially prevent iron deficiency, without the side effects of iron supplementation.

## SIGNIFICANTLY INCREASED IRON ABSORPTION

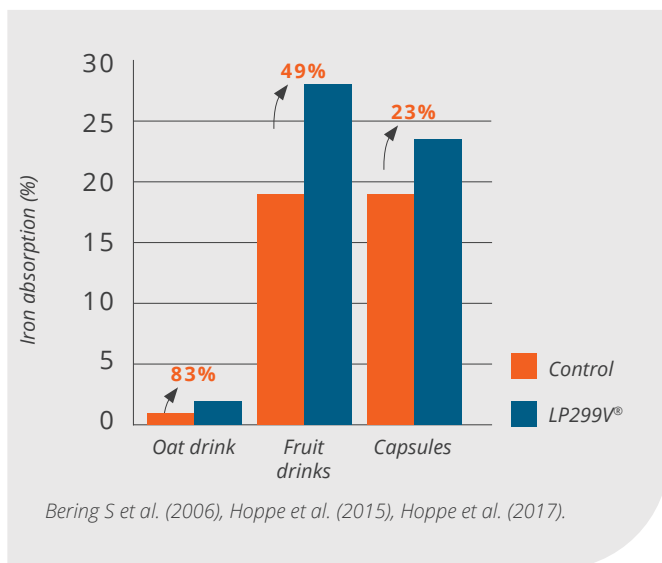


Fig. 7

## REDUCED INCIDENCE OF IRON DEFICIENCY DURING PREGNANCY

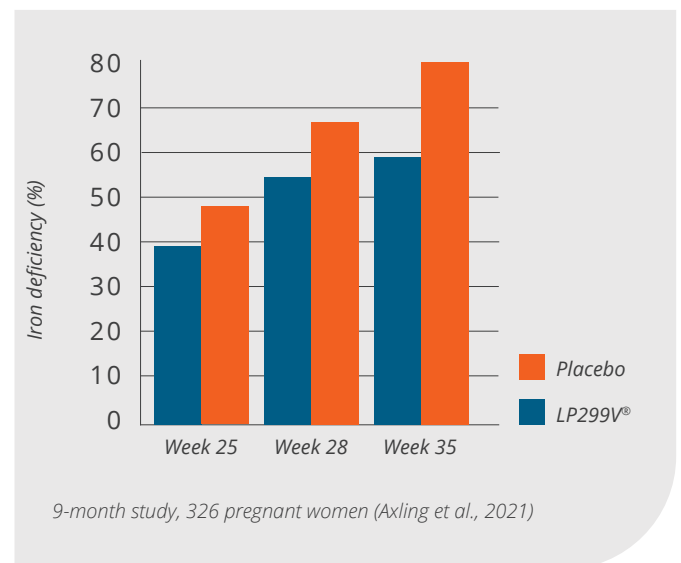


Fig. 8

## Additional indications

LP299V® has been investigated in other health areas as well, such as psychological or mental health (the so-called gut-brain axis) and metabolic health. Moreover, LP299V® has been broadly studied in various food applications.

### GUT-BRAIN AXIS

In recent years, the interest in how GI health may affect psychological health has increased. A disturbed GI microbial balance and decreased bacterial diversity have been coupled to mental health in several conditions (such as Parkinson's, Alzheimer's, major depression, autism spectrum disorders) <sup>131</sup>. Moreover, studies have shown that mental stress increases intestinal permeability and translocation <sup>132</sup>.

LP299V® has been used in two clinical mental health studies. The first study including 41 students with an upcoming exam showed that intake of LP299V® for two weeks significantly decreased saliva cortisol, compared to placebo <sup>133</sup>. The second study investigated the effect of cognitive function and biochemical parameters in subjects suffering from major depression. Intake of LP299V® for 8 weeks significantly improved cognitive performance, compared to placebo <sup>134</sup>.

### METABOLIC HEALTH

Ischemic heart disease and stroke are the top two causes of death globally <sup>135</sup>. In recent years there has been a growing interest in the possible effect of probiotics on metabolic parameters. The GI microbiota has a direct role in human metabolic regulation through interactions between the bacteria and the host. Dysbiosis and reduced bacterial diversity, as well as increased intestinal permeability, are also related to metabolic health <sup>136</sup>. LP299V® has been shown to affect certain factors coupled to metabolic health.

Fruit beverages with LP299V®, given to healthy individuals, resulted in decreased insulin responses compared to control <sup>137,138</sup>. In a study including 30 men with moderately elevated cholesterol levels, LP299V® significantly reduced total and LDL cholesterol levels. Moreover, fibrinogen levels decreased compared to baseline. No changes were seen in the placebo group <sup>139</sup>. Another study, which included 36 smokers, showed that intake of LP299V® significantly reduced systolic blood pressure, leptin, fibrinogen, and IL-6 levels. Again, no effects were seen in the placebo group <sup>74</sup>. Significantly improved brachial artery flow-mediated dilation, and decreased circulating levels of inflammatory markers, were found in men with stable coronary artery disease who were given LP299V® <sup>36,140</sup>.

### LP299V® IN FOOD

The first food application for LP299V® was a fermented oat-based beverage, developed as a new concept for enteral feeding <sup>141-143</sup>. The fermented oat beverage is still used as a base in the production of probiotic fruit beverages <sup>144</sup>.

Over the years, the general interest in probiotics has increased, and LP299V® has been used in various applications related to food production. In 1995, it was used as a starter culture for the production of barley sourdough <sup>143</sup>. Probiotic pineapple juice <sup>145</sup>, orange juice <sup>146</sup>, quinoa juice<sup>147</sup>, legume sprouts <sup>148-150</sup>, fermented cauliflower and white beans <sup>51</sup>, dark chocolate <sup>152</sup>, bovine salami<sup>153</sup> and button mushroom fruiting bodies <sup>154</sup> are other examples of food products where LP299V® has been used either as a fermenter or simply added to obtain a probiotic food product. Good viability of the probiotic bacteria has been obtained in all the above-mentioned studies.







## 7. Conclusion

LP299V® was first discovered as a health-supporting probiotic strain more than 30 years ago and continues to be extensively researched around the world. *In vitro* and animal studies have helped increase the understanding of various characteristics of this strain. Beneficial effects have been described in clinical studies, both in healthy and diseased individuals. All published studies up until June 2020 have been summarized in a review paper by Arvidsson Nordström and colleagues<sup>155</sup>. The role of LP299V® in promoting health in various vulnerable states has been summarized in another review paper by Kazmierczak-Siedlecka and colleagues<sup>156</sup>.

The strain LP299V® is a true probiotic. It is well characterized, has a clinically proven dose and has been shown to support health for a broad range of indications in humans. Since the 1990s, LP299V® has been incorporated in functional food products and food supplements in more than 40 markets worldwide.

Repeated studies have shown that the intake of LP299V® results in decreased severity and frequency of IBS symptoms, including abdominal pain, flatulence, bowel habits, and bloating. Moreover, LP299V® can increase bacterial diversity in the intestine, provide relief for those suffering from IBD, and decrease the incidence of CDI for people who have been prescribed antibiotics.

Iron absorption is another area where LP299V® has been proven to have significant effects, likely due its ability to increase iron bioavailability. The increased iron absorption leads to significantly improved long-term iron status, as shown in both healthy female athletes and pregnant women. These results suggest that LP299V® offers a novel approach to preventing iron deficiency and iron deficiency anemia.

It is important to remember that probiotics are not pharmaceutical drugs, but instead are intended to support and help maintain health. Despite this, LP299V® has been shown to have significant effects in IBS and IBD, and on iron absorption, as described above.

To conclude the various effects of LP299V® described herein, studies have shown the safety of use, survival through the GI tract, binding mechanism, and robust effects for improved human health of this strain. Intake of LP299V® has been demonstrated to affect pathogen inhibition, intestinal barrier function, and the immune system. Human clinical studies performed with LP299V® show several health benefits, where the strongest evidence for its effectiveness is gastrointestinal health and iron absorption.

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A photograph of a field of orange flowers, likely poppies, under a warm, golden light. In the foreground, a young child with blonde hair, wearing a blue dress, is seen from behind, looking towards the field. In the middle ground, two adults, a man and a woman, are standing and talking. The background shows a vast field of green grass and some trees under a clear sky.

# About Probi

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Probi® is a global company focused exclusively on researching, manufacturing, and delivering probiotics for supplements and functional food. We are experts at managing stable, live bacteria from R&D through every stage of the manufacturing process, and are dedicated to making the health-enhancing benefits of probiotics available to people everywhere. Our health concepts, formulations, and formats are supported by robust clinical documentation. Since our founding in 1991 at Sweden's Lund University, Probi has expanded its operations to more than 40 markets. We hold more than 400 patents globally.

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