Lactiplantibacillus plantarum 299v (LP299V®): three decades of research

E. Arvidsson Nordström^{1*}, C. Teixeira¹, C. Montelius¹, B. Jeppsson² and N. Larsson¹

¹Probi AB, Ideongatan 1A, 22370 Lund, Sweden; ²Department of Surgery, Lund University, Universitetssjukhuset, 22184 Lund, Sweden; elisabet.nordstrom@probi.com

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REVIEW ARTICLE

Abstract

This review aims to provide a comprehensive overview of the *in vitro*, animal, and clinical studies with the bacterial strain *Lactiplantibacillus plantarum* 299v (*L. plantarum* 299v; formerly named *Lactobacillus plantarum* 299v) published up until June 30, 2020. *L. plantarum* 299v is the most documented *L. plantarum* strain in the world, described in over 170 scientific publications out of which more than 60 are human clinical studies. The genome sequence of *L. plantarum* 299v has been determined and is available in the public domain (GenBank Accession number: NZ_LEAV01000004). The probiotic strain *L. plantarum* 299v 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 exist, showing benefits primarily for gastrointestinal health, such as reduced flatulence and abdominal pain in patients with irritable bowel syndrome (IBS). Moreover, several clinical studies have shown positive effects of *L. plantarum* 299v on iron absorption and more recently also on iron status. *L. plantarum* 299v is safe for human consumption and does not confer antibiotic resistance. It survives the harsh conditions of the human gastrointestinal tract, adheres to mannose residues on the intestinal epithelial cells and has in some cases been re-isolated more than ten days after administration ceased. Besides studying health benefits, research groups around the globe have investigated *L. plantarum* 299v in a range of applications and processes. *L. plantarum* 299v is used in many different food applications as well as in various dietary supplements. In a freeze-dried format, *L. plantarum* 299v is robust and stable at room temperature, enabling long shelf-lives of consumer healthcare products such as capsules, tablets, or powder sachets. The strain is patent protected for a wide range of indications and applications worldwide as well as trademarked as LP299V®.

Keywords: irritable bowel syndrome, probiotic, digestive health, iron absorption

1. Introduction

The history of *Lactiplantibacillus plantarum* (*L. plantarum*) 299v 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. Critical illness is often associated with significant gut overgrowth of typical ICU pathogens, such as *Clostridioides difficile*, *Enterobacteriaceae* and enterococci, and bacterial translocation may be a factor of importance in the pathogenesis of ICU-acquired infections. The indigenous intestinal microbiota therefore plays an

important role in protecting the gut from colonisation with exogenous pathogens as well as overgrowth of endogenous commensal bacteria. Treatment with narrow or broad-spectrum antibiotics could partially be the cause of gut microbial imbalance since these disrupt the normal microbiota and promote colonisation of pathogens (Marshall *et al.*, 1993; Palleja *et al.*, 2018).

2. Isolation, intestinal persistence, and safety

L. plantarum 299v was isolated from healthy intestinal mucosa (Ahrné *et al.*, 1998; Molin *et al.*, 1993), and re-isolated after consumption (Johansson *et al.*, 1993). *L. plantarum* strains are common in traditional lactic acid-fermented foods of plant origin, such as brined olives,

capers, sauerkraut, sour-dough and wine (Molin, 2001), and different *L. plantarum* strains, including *L. plantarum* 299v, were found to frequently occur in the normal intestinal microbiota of healthy adults (Ahrné *et al.*, 1998). *L. plantarum* 299v has been characterised using different methods: restriction fragment length polymorphism (RFLP) (Johansson *et al.*, 1995a), restriction endonuclease analysis (REA) (Johansson *et al.*, 1995b), randomly amplified polymorphic DNA (RAPD) (Johansson *et al.*, 1995c; Nigatu *et al.*, 2001) and microarray analysis (Marco *et al.*, 2010; Molenaar *et al.*, 2005). Additionally, global gene expression profiles of *L. plantarum* 299v have been conducted on human intestinal tissue biopsies (Marco *et al.*, 2010).

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 (Zheng *et al.*, 2020). *Lactobacillus plantarum* was renamed *Lactiplantibacillus plantarum*.

Ability to survive and persist in the gastrointestinal tract

The strain *L. plantarum* 299v has been shown in multiple *in vitro* and clinical studies to survive the harsh conditions in the human gastrointestinal (GI) tract (Goossens *et al.*, 2003, 2005, 2006a,b; Hamon *et al.*, 2011; Jacobsen *et al.*, 1999; Jensen *et al.*, 2012; Johansson *et al.*, 1993, 1998; Onning *et al.*, 2003). When incubated at pH 2.5, *L. plantarum* 299v was found to survive for four hours (Jacobsen *et al.*, 1999). During a simulated transit through the upper GI tract, the viability of *L. plantarum* 299v was reduced after incubation with simulated gastric juice, but not with simulated small intestinal juice (Jensen *et al.*, 2012). Furthermore, *L. plantarum* 299v was one of the *L. plantarum* strains best suited to grow in culture broth supplemented with bile salts (Hamon *et al.*, 2011).

In a clinical setting, *L. plantarum* 299v in combination with either placebo or the proton pump inhibitor pantoprazole was given to 32 subjects, with the hypothesis that decreased stomach acid production by pantoprazole would increase survival of lactobacilli. *L. plantarum* 299v was found in all faecal samples, from the pantoprazole as well as the placebo group, during the week of probiotic administration. Hence, *L. plantarum* 299v survives the passage through the gastrointestinal tract irrespective of the gastric acidity (Goossens *et al.*, 2005).

Along with its ability to survive the harsh GI conditions, several clinical studies have demonstrated that *L. plantarum* 299v has excellent persistence capacity and can be re-isolated from mouth to rectum. *L. plantarum* 299v was one of the dominating lactobacilli strains in intestinal mucosa samples taken from the upper jejunum 11 days after the end of administration of a mix of 19 different strains (Johansson

et al., 1993). Moreover, the strain was re-isolated from faeces eight days after the last administration in a fruit drink (Johansson *et al.*, 1998) and four weeks after the last administration in an oat drink (Goossens *et al.*, 2005). Mucosal biopsies taken from both rectum and colon show that there is no difference in *L. plantarum* 299v prevalence or bacterial concentration between these two GI regions (Goossens *et al.*, 2006a).

Safety

L. plantarum 299v 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 recognised as safe and included on the Qualified Presumption of Safety (QPS) list in the European Union. To be on the QPS list, a microorganism must have a well-defined taxonomic identity and its safety must be well established. Moreover, the microorganism (strain) must not have any pathogenic properties (virulence factor or toxin production), it should have an acceptable antibiotic resistance profile (as defined by the European Food Safety Authority (EFSA, 2018)) and a clear intended use (EFSA, 2020). The Food and Drug Administration (FDA) in the United States has reviewed the evidence provided in the Generally Recognised as Safe (GRAS) determination notice for *L. plantarum* 299v and concluded they had no further questions about, nor any objection to, its intended use. For a substance to be considered GRAS it must be generally recognised, among qualified experts, as safe under the conditions of its intended use.

L. plantarum 299v has been safely administered to vulnerable populations, such as patients undergoing elective major abdominal surgery (McNaught *et al.*, 2002), critically ill patients (Klarin *et al.*, 2005, 2008; McNaught *et al.*, 2005; Oudhuis *et al.*, 2011), children as young as 6-12 months (Berggren *et al.*, 2003; Kingamkono *et al.*, 1999; Olek *et al.*, 2017), children congenitally exposed to HIV-1 who were diagnosed with failure to thrive (Cunningham-Rundles *et al.*, 2000, 2011), children with small bowel bacterial overgrowth (Vanderhoof *et al.*, 1998) and children and adolescents undergoing hematopoietic cell transplantation (Ladas *et al.*, 2016). The studies suggest that administration of *L. plantarum* 299v may even alleviate side effects coupled to invasive treatment (Ladas *et al.*, 2016) and positively influence growth and immune development in HIV-1 positive children (Cunningham-Rundles *et al.*, 2000; Cunningham-Rundles *et al.*, 2011). Moreover, *L. plantarum* 299v given to rats undergoing cancer chemotherapy improved food intake and body weight, as well as reduced the number of facultative anaerobes in the intestine, as compared to the control animals (Von Bultzingslowen *et al.*, 2003).

To further evaluate safety and risk of septic bacteraemia, an endocarditis animal model was used for a comparison between *L. plantarum* 299v and a *Staphylococcus lugdunensis* control group. 96 h 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 (Adawi *et al.*, 2002).

The bacterial content is high in the intestine and so is the likelihood of horizontal gene transfer between bacteria, such as those encoding antibiotic resistance. Re-isolated *L. plantarum* 299v from critically ill patients treated with broad-spectrum antibiotics were tested against 22 different antibiotics. There was no obvious decrease in susceptibility to 21 of the tested antibiotics and only a tendency towards decreased susceptibility to ampicillin. The authors therefore concluded that *L. plantarum* 299v is less likely to acquire antibiotic resistance when administered to critically ill patients treated with broad-spectrum antibiotics (Klarin *et al.*, 2019).

3. Mechanisms

L. plantarum 299v has been shown to benefit multiple areas of the body, especially the GI tract. Although not yet fully understood, maintenance and improvement of gut mucosal barrier function seems to be the core principle behind the GI health benefits of *L. plantarum* 299v. A healthy and more resilient mucosa can better tackle foreign elements (e.g. pathogens and their secreted substances), and in this way reduce local and systemic inflammation (Williams, 2003). Mucosal defence mechanisms include physical barriers, such as mucus secretion and selectively permeable epithelial cell layers with tight cell-cell connections, whereas non-physical barrier mechanisms include secretion of signalling molecules and respective receptors (Chaplin, 2010).

Adherence to epithelial cells

The ability of *L. plantarum* 299v to survive the passage through the GI tract and to adhere to epithelial cells is important for the health benefits of this strain and could explain the reduction of GI symptoms in irritable bowel syndrome (IBS) and the increased iron absorption, discussed in detail in later sections.

L. plantarum 299v adheres to the epithelial cells along the entire digestive tract in healthy adults (Johansson *et al.*, 1993, 1998; Mangell *et al.*, 2012; Nobaek *et al.*, 2000; Stjernquist-Desatnik *et al.*, 2000) and in critically ill patients (Klarin *et al.*, 2005). The mannose-binding mechanism is the best-known function enabling *L. plantarum* 299v to adhere to the intestinal epithelium (Adlerberth *et al.*, 1996). The binding mechanism is comprised of an adhesin present in the cell wall of the bacteria that attaches to mannose residues expressed on the surface of eukaryotic

cells, e.g. on intestinal epithelial cells. The gene encoding the mannose-specific adhesin (Msa; gene name *msa*) has been identified (Pretzer *et al.*, 2005) as the only responsible gene for this type of adhesion (Gross *et al.*, 2010), since its absence directly impairs the adhesion of *L. plantarum* 299v to yeast (rich in mannose residues), Caco-2 cells (Holst *et al.*, 2019), and HT29 cells (Mack *et al.*, 2003). Mannose-binding capacity was shown to vary between *L. plantarum* strains (Tallon *et al.*, 2007) and *L. plantarum* 299v seems to have higher capacity compared to the strain WCFS1 (Gross *et al.*, 2010). This variation of binding capacity between strains seems to be regulated by a promoter region upstream of the *msa* gene (Holst *et al.*, 2019), rather than the sole presence of *msa* itself (Pretzer *et al.*, 2005) or the domain composition of Msa protein (Gross *et al.*, 2010).

Although Msa protein is essential for binding to the epithelium, adhesion to the mucus layer is required to allow enough residence time for commensal bacteria to interact with the epithelial cells and thus exert their beneficial effects. *L. plantarum* 299v seems to adhere to mucus mostly due to electrostatic and hydrophobic interactions with the mucin (Buntin *et al.*, 2017). Surface-bound enzymes, such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH) possibly mediate these interactions by being able to bind to mucin, as shown in Caco-2 cells (Glenting *et al.*, 2013). Other cell surface molecules mediating the attachment of epithelial cells such as glycolytic enzymes, proteins involved in stress response and ribosomal proteins, have also been identified (Beck *et al.*, 2009; Glenting *et al.*, 2013; Gross *et al.*, 2008a; Izquierdo *et al.*, 2009; Saad *et al.*, 2009).

Pathogen inhibition

Competitive exclusion due to occupying binding sites, production of short-chain fatty acids (SCFAs) that lower the pH in the intestinal milieu, induced production of mucin and production of bacteriocins are some of the proposed mechanisms for pathogen inhibition by probiotics. Mucin production seems to be the strongest pathogen inhibition mechanism induced by *L. plantarum* 299v, followed by carboxylic acid production, whereas the results from studies on competition for binding sites are somewhat inconclusive. The mechanism can also be indirect, since *L. plantarum* 299v has been shown to affect the overall microbiota composition and increase diversity (Karlsson *et al.*, 2010), which is more thoroughly discussed in Section 4 – Potential mode of action.

Mucin production is a first line defence against pathogens in the intestinal lumen. The direct adherence of *L. plantarum* 299v to the epithelial cells seems to facilitate cellular communication with the epithelium to promote mucin production (Mack *et al.*, 1999, 2003) and could be one of the keys to promote intestinal barrier integrity. In the intestinal cell line HT29, *L. plantarum* 299v was shown to

rapidly upregulate mRNA expression of the mucin genes *MUC2* and *MUC3*, and consequently mucin production (Mack *et al.*, 1999). In contrast, when *L. plantarum* 299v lacked mannose-binding adherence ability (Mack *et al.*, 2003), or were heat-killed (Dykstra *et al.*, 2011), mRNA expression of *MUC3* was not upregulated (Mack *et al.*, 2003). *L. plantarum* 299v in combination with caprine milk carbohydrate fraction increased mRNA levels of *MUC4*, *MUC2* and *MUC5AC* in a co-culture of Caco-2 and HT29 cells. However, protein abundance was only confirmed for MUC4 mucin, one of the major components of the glycocalyx (Barnett *et al.*, 2018).

Bacterial fermentation products, such as the SCFAs acetic acid, butyric acid, and propionic acid contribute to a healthy intestinal barrier. SCFAs are partly absorbed by the intestinal cells to serve as energy to maintain cellular biological functions, and are partly accumulated in the intestinal lumen, contributing to pathogen inhibition by decreasing the pH. *L. plantarum* 299v is a lactic acid producer (Goossens *et al.*, 2006a) rather than a producer of SCFAs, however, lactic acid is a precursor of some SCFAs (Bourriaud *et al.*, 2005). Enhanced lactic acid production after intake of *L. plantarum* 299v may explain the significant increase in acetic acid and propionic acid production in healthy subjects (Johansson *et al.*, 1998), the significant increase in plasma propionic acid in men with stable coronary artery disease (Malik *et al.*, 2018) and the maintained, rather than decreased, faecal butyric acid levels in patients under antibiotic treatment (Wullt *et al.*, 2007). The latter result suggests that administration of *L. plantarum* 299v reduces the negative effects of antibiotic treatment on colonic fermentation.

Several pathogenic bacteria are known to have the same type of adherence to mannose as *L. plantarum* 299v (Stones and Krachler, 2015). Competition for the same binding sites on the intestinal cells, known as competitive exclusion, is one of the hypotheses for the defence mechanism of this strain (Gross *et al.*, 2010; Reid and Burton, 2002). *L. plantarum* 299v was found to inhibit the attachment of one strain of *Escherichia coli* to Caco-2 cells *in vitro* using Ussing chambers, but only when the probiotic bacteria were added before the *E. coli* infection (Michail and Abernathy, 2002). However, *L. plantarum* 299v did not inhibit phytohemagglutinin (PHA)-induced overgrowth of *E. coli* in suckling rats, although they were administered prior to PHA (Gross *et al.*, 2008b). In an *in vitro* study using the non-intestinal cell line HEP-2, expressing only minimal levels of *MUC2* and no *MUC3* mRNA, *E. coli* binding was not inhibited, nor dislodged, by *L. plantarum* 299v, possibly due to the low levels of mucin produced by these cells (Mack *et al.*, 1999). As discussed above, the promotion of MUC3 mucin by *L. plantarum* 299v appears to be of particular importance in pathogen inhibition and may be the main

mechanism for hindering *E. coli* adherence to the epithelial cells, rather than competitive exclusion. Clinical studies are necessary to evaluate the ability of *L. plantarum* 299v to inhibit attachment of *E. coli* in human intestine.

The interaction between *L. plantarum* 299v and other pathogenic bacteria that do not share the same binding mechanism has also been studied. In an *in vitro* study, *L. plantarum* 299v was shown to have intermediate antagonistic activity against *Helicobacter pylori* and *Salmonella enterica* ssp. *enterica* (Hutt *et al.*, 2006). However, another *in vitro* study did not show inhibition of *Salmonella enteritidis* 857 growth (Malago *et al.*, 2010), which was confirmed in a clinical setting where *L. plantarum* 299v was not able to accelerate clearance of *Salmonella* or reduce its associated symptoms (Lonnermark *et al.*, 2015). Further clinical studies are warranted to obtain conclusive results regarding the actions of *L. plantarum* 299v in *Salmonella* infections, and to investigate whether its efficacy could depend on the strain of the pathogen.

The effect of *L. plantarum* 299v in *C. difficile* infections has also been investigated in both *in vitro* and clinical settings. Despite the lack of antagonistic activity against *C. difficile* *in vitro* (Hutt *et al.*, 2006), *L. plantarum* 299v was shown to reduce the incidence of *C. difficile* infections in several clinical studies (Dudzicz *et al.*, 2018; Klarin *et al.*, 2008; Kujawa-Szewieczek *et al.*, 2015). One clinical study included 3,533 hospitalised patients treated with immunosuppressive agents. It was found that the incidence of *C. difficile* infection in the ward was significantly reduced during the one-year period when supplementation of *L. plantarum* 299v was implemented, compared to the previous year (Kujawa-Szewieczek *et al.*, 2015). A follow-up study including in total 5,341 subjects showed that the incidence significantly increased again during the one year period after the supplementation ceased (Dudzicz *et al.*, 2018).

Permeability and bacterial translocation

The improvement of gut barrier function by *L. plantarum* 299v has been studied in different animal models assessing permeability and bacterial translocation. Similar to several other health benefits of *L. plantarum* 299v, reduction of permeability seems to be related to the mannose-binding property of this strain. Pre-treatment with *L. plantarum* 299v has been shown to prevent increased intestinal permeability induced by *E. coli* in healthy rat models (Mangell *et al.*, 2002), and to reduce lipopolysaccharide-induced bacterial translocation into mesenteric lymph node and liver of endotoxemic rats (Mangell *et al.*, 2006). This effect was only observed in *L. plantarum* 299v with adherence capacity, and not when the mannose-binding was lost (Mangell *et al.*, 2006). Moreover, an *ex vivo* study

showed that only *L. plantarum* 299v with adherence capacity decreased net fluid absorption over pig jejunal tissue (Gross *et al.*, 2008a). *L. plantarum* 299v also showed ability to enhance tight junction integrity as measured by the transepithelial electrical resistance in Caco-2 cells (Anderson *et al.*, 2010) and in a co-culture of Caco-2 and HT29 cells (Barnett *et al.*, 2018). Moreover, transcription levels of the plasma-membrane protein occludin (important for tight junction stability and barrier function) were increased in Caco-2 and HT29 cells during co-incubation of *L. plantarum* 299v with the carbohydrate fraction from caprine milk (Barnett *et al.*, 2018).

Bacterial translocation was reduced in rat models of acute pancreatitis (Mangiante *et al.*, 1999, 2001a) and acute liver failure with both rectal (Adawi *et al.*, 1997, 1998, 2001; Wang *et al.*, 2001) and oral (Kasravi *et al.*, 1997) administration of *L. plantarum* 299v. *L. plantarum* 299v also decreased permeability in rats with dextran sulphate sodium induced colitis (Osman *et al.*, 2004) and with methotrexate induced enterocolitis (Mao *et al.*, 1996a,b). *L. plantarum* 299v given to rat dams during the last week of gestation and during lactation colonised the dams as well as the pups and improved gut growth and gut barrier function in the pups (Fak *et al.*, 2008b). When the bacteria were fed directly to rat pups during the first week of life, gut barrier function was improved, with a more pronounced effect in the youngest pups (Fak *et al.*, 2008a). Furthermore, *L. plantarum* 299v was shown to be important in the maturation of gut function of suckling piglets (Wang *et al.*, 2019).

Clinical studies investigating intestinal integrity have primarily been done in patients rather than healthy volunteers. Pre-treatment with *L. plantarum* 299v reduced intestinal permeability in patients undergoing biliary drainage, measured by the lactulose/mannitol absorption test (Jones *et al.*, 2013). Using the same absorption test in critically ill patients, permeability was however only mildly reduced (Klarin *et al.*, 2008) or not affected (McNaught *et al.*, 2005). The discrepant results may be explained by the degree of disease severity, since the reliability of this test in critically ill patients has been contested (Fink, 2002; Oudemans-Van Straaten *et al.*, 2002). In two other clinical studies, the presence of bacteria in mesenteric lymph nodes isolated during surgery was used to measure bacterial translocation. In patients referred for colonic resection (Mangell *et al.*, 2012) and in patients with elective major abdominal surgery (McNaught *et al.*, 2002) bacterial translocation was not reduced by intake of *L. plantarum* 299v. Despite these results, *L. plantarum* 299v has been shown to affect overall intestinal barrier functions, such as mucin production and pathogen inhibition. The need for conclusive clinical studies on paracellular permeability *per se* has also been addressed by Ahrné and Hagslätt (2011).

Inflammatory response

In addition to effects on physical and non-physical mucosal defence mechanisms, probiotic strains may also have direct immunoregulatory properties such as enhancing the activity of macrophages and natural killer (NK) cells or modulating the secretions of antibodies or cytokines (La Fata *et al.*, 2018). There is constant interaction between the mucosal immune system and bacteria in the GI tract, and the immune homeostasis (the balance between tolerance and defence) is important (Peterson *et al.*, 2015). Probiotics may upregulate or downregulate pro- or anti-inflammatory responses aiming to maintain this balance (Isolauri *et al.*, 2001). The potential immunomodulatory activity of *L. plantarum* 299v has been evaluated in several clinical studies, as well as in animal and *in vitro* studies.

Studies using human mononuclear cells show that the immunomodulatory effects of probiotics differ and depend on immune system maturation and age (Peoples *et al.*, 2009; Tatad *et al.*, 2008), healthy versus diseased conditions (Pathmakanthan *et al.*, 2004; Van Hemert *et al.*, 2010), individual variations (Azad *et al.*, 2018; Van Hemert *et al.*, 2010) as well as strain-specific effects.

The importance of the mannose binding capacity of *L. plantarum* 299v for cytokine expression and secretion has been shown in several *in vitro* studies (Gross *et al.*, 2008a; McCracken *et al.*, 2002). This was, however, not confirmed in an *ex vivo* study using human colonic mucosa, since *L. plantarum* 299v showed down-regulatory effects on the immune system independent of the *msa* gene (Bauerl *et al.*, 2013). Moreover, in murine dendritic cells, lethally irradiated *L. plantarum* 299v was found to still affect cytokine secretion (Christensen *et al.*, 2002).

McCracken and colleagues (McCracken *et al.*, 2002) found that mRNA expression of the chemokine interleukin (IL)-8, was upregulated in HT29 cells incubated with *L. plantarum* 299v, and that the effect was even more pronounced when the bacteria were co-incubated with HT29 cells treated with the pro-inflammatory cytokine tumour necrosis factor alpha (TNF- α). Interestingly, this did not result in increased secretion of IL-8 protein, suggesting that *L. plantarum* 299v could exert a protective effect by preventing an excessive IL-8 secretion. Moreover, in monocytic cell lines *L. plantarum* 299v had little effect on the secretion of IL-8 and TNF- α (Jensen *et al.*, 2015).

In general, the immunoregulatory effects of *L. plantarum* 299v are anti-inflammatory in animal studies. In the IL-10-deficient mouse model for inflammatory bowel disease (IBD), oral administration of *L. plantarum* 299v caused a decrease in colonic mucosal interferon gamma (IFN- γ), IL-12 and immunoglobulin (Ig)-G2a levels (Schultz *et al.*,

2002). A slight downregulation of TNF- α and IL-10 was observed in liver perfusate from healthy rats who were fed *L. plantarum* 299v for seven days prior to laparotomy and bile duct ligation (Badger *et al.*, 2013). In pigs, *L. plantarum* 299v seemed to prevent the development of intestinal inflammation by inducing repression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B)-mediated transcription and peroxisome proliferator-activated receptor gamma (PPAR- γ) signalling (Hulst *et al.*, 2015).

IgA antibodies are thought to be increased as a response to enhanced intestinal immunity. Germ-free rats, supplemented with *L. plantarum* 299v together with *E. coli* O6:K13:H1 (originally isolated from urine of a patient with cystitis) resulted in significantly higher total serum IgA levels but only marginally higher IgM, compared to the rats given *E. coli* alone (Herias *et al.*, 1999). Enterocolitis rat models also showed increased ileal and colonic secretory IgA levels and increased numbers of T helper cells and cytotoxic T cells compared to control enterocolitis rats (Mao *et al.*, 1996b). In a study with preweaning calves, *L. plantarum* 299v given in the milk from seven days of age until start of weaning showed improved growth performance and increased immune capacity (increased plasma levels of IgG, IgA, total superoxide dismutase, IFN- γ and soluble CD4, and decreased IL-6) (Jiang *et al.*, 2020). However, in lupus-prone mice, *L. plantarum* 299v had only little effect on lupus progression and survival, in contrast to other *Lactobacillus* strains studied (Manirarora *et al.*, 2020).

The immunomodulatory effects of *L. plantarum* 299v have also been investigated in clinical studies. In contrast to the animal studies discussed above, IgA antibodies were not affected in patients receiving *L. plantarum* 299v prior to elective abdominal surgery. Moreover, mucosal IgM levels were increased only in patients not receiving *L. plantarum* 299v, which may indicate increased bacterial translocation in these patients (Woodcock *et al.*, 2004). In critically ill patients treated with antibiotics, *L. plantarum* 299v significantly decreased serum levels of the pro-inflammatory cytokine IL-6 (McNaught *et al.*, 2005). A decrease in systemic IL-6 levels was also seen when the bacteria were given to smokers (Naruszewicz *et al.*, 2002), but not in men with atherosclerotic plaque (Karlsson *et al.*, 2010) or in subjects with major depressive disorders (Rudzki *et al.*, 2019).

An increased expression of IL-12 in peripheral blood mononuclear cells from healthy volunteers was observed when the cells were co-cultured with *L. plantarum* 299v (Rask *et al.*, 2013). However, in an uncontrolled study in men with coronary artery disease (CAD), supplementation with *L. plantarum* 299v for six weeks resulted in decreased plasma levels of IL-8 and IL-12 (Malik *et al.*, 2018). Since IL-12 contributes to the activation of phagocytes through

inducing IFN- γ production by T lymphocytes and NK cells, this contrast between healthy and diseased subjects may suggest that *L. plantarum* 299v assists the immune system in maintaining an alert and proactive immune regulation depending on need. This phenomenon can be seen in subjects suffering from IBS, where intake of *L. plantarum* 299v has been shown to result in dampening and relief of symptoms which are coupled to immune responses (discussed more thoroughly in Section 4). Hence, *L. plantarum* 299v seems to activate the immune system to maintain health but can also dampen the immune response in subjects with ongoing low-grade inflammation.

4. Irritable bowel syndrome

IBS is the most commonly reported GI disorder affecting 10-20% of the population worldwide (Canavan *et al.*, 2014). IBS is primarily characterised by recurrent abdominal pain or discomfort, associated with changes in bowel habits. Depending on the predominance of the bowel habit disorder, IBS can be classified as IBS-D with predominant diarrhoea, IBS-C with predominant constipation, or IBS-M with a combination of both diarrhoea and constipation. Although not required for an IBS diagnosis, abdominal bloating, straining during defecation, defecatory urgency, feeling of incomplete evacuation, or presence of mucus in the stool are common in people suffering from IBS (Mearin *et al.*, 2016; Quigley, 2008). The Rome IV Diagnostic Criteria have since 2016 been used to help diagnose functional GI disorders, such as IBS (Drossman and Hasler, 2016; Lacy *et al.*, 2016). The studies that will be discussed in this section were all performed before 2016, and therefore based on Rome II and Rome III criteria, in which abdominal pain and discomfort were considered main symptoms. In Rome III, the frequency of the symptoms required was 3 days per month during 3 consecutive months, but for clinical trials it was recommended to include subjects who had a frequency of at least two days a week.

The factors influencing the onset of IBS are not well known and can differ between individuals, but microbiota imbalance, also known as dysbiosis, may be one key parameter (Lacy *et al.*, 2016). A disturbed microbiota may over-activate the innate immune responses, which in turn could increase intestinal permeability and result in the GI symptoms typical in IBS (Simren *et al.*, 2013). This is discussed in more detail in Section 4 – Potential mode of action.

Bloating and flatulence

One of the earliest clinical studies with *L. plantarum* 299v in subjects with IBS aimed to understand the associated microbiota imbalance and changes with supplementation (Nobaek *et al.*, 2000). The study showed that a fruit drink with *L. plantarum* 299v was able to reduce flatulence and

number of days with abundant gas production significantly and more rapidly compared to placebo. This result was somewhat expected since in healthy volunteers, this strain had previously been shown to persist in the gut, reduce potentially gas producing bacteria and perceived flatulence, and increase faecal carboxylic acid concentration (Johansson *et al.*, 1998). A more recent and larger placebo-controlled study in IBS subjects given *L. plantarum* 299v in freeze-dried form (capsules) showed significant improvements in both severity and frequency of bloating (Ducrotte *et al.*, 2012). Moreover, upon intake of *L. plantarum* 299v in conjunction with lactulose, reduced breath hydrogen concentration in subjects with IBS was seen (Sen *et al.*, 2002). Hence, the above studies suggest decreased gas production in the colon caused by intake of *L. plantarum* 299v, which may be of importance in people with IBS since they often suffer from flatulence and bloating (King *et al.*, 1998).

Abdominal pain

The decreased flatulence shown in the studies by Nobaek *et al.* (2000) and Johansson *et al.* (1998) prompted further placebo-controlled clinical studies with focus on other IBS-related symptoms, such as abdominal pain. In the first study, subjects with IBS were randomised to receive either placebo or *L. plantarum* 299v for 4 weeks. The intervention resulted in resolution of abdominal pain, with a significant pain relief in 70% of the subjects in the active group after only one week of probiotic administration. At the end of the study, 55% of subjects in the placebo group still reported pain, in contrast to none of the subjects in the probiotic group (Niedzielin *et al.*, 2001). These results were confirmed in a larger placebo-controlled trial with 204 IBS subjects completing the intervention of 4 weeks. A significant reduction in abdominal pain severity and frequency was achieved, compared to placebo (Ducrotte *et al.*, 2012).

Bowel movement

L. plantarum 299v has been reported to improve stool frequency, both to reduce the bowel movement in those with at least three defecations per day (Ducrotte *et al.*, 2012), and to increase the bowel movement in those with constipation (Niedzielin *et al.*, 2001). Moreover, in an IBS mouse model, *L. plantarum* 299v was shown to normalise intestinal transit rates (Waugh *et al.*, 2009). Considering the results in these studies, it is suggested that *L. plantarum* 299v can normalise stool frequency independently of the IBS type. Some *L. plantarum* strains have been shown to catabolise arginine and thereby generate nitric oxide (NO), which may exert a positive effect on the motility of the large and small intestine. Hence, the mode of action may involve generation of NO (Jonsson *et al.*, 1983).

Overall symptoms

Changes in overall IBS symptoms were apparent in two of the studies described above. In the study by Niedzielin *et al.* (2001), 95% of the subjects receiving *L. plantarum* 299v showed an improvement of overall IBS symptoms, compared to 15% in the placebo group. These results were confirmed in the study by Ducrotte *et al.* (2012), where 78% of the subjects receiving probiotics rated their improvement of overall IBS symptoms as 'good' or 'excellent', in contrast with a positive rating of only 8% of the subjects in the placebo group. Moreover, the investigators assessed the improvement of symptoms similarly to the participants (Ducrotte *et al.*, 2012). Both the study participants and the investigators were blinded to the type of product that had been consumed when rating the efficacy of the product.

The IBS severity scoring system (IBS-SSS) was used by Stevenson *et al.* (2014) to assess the efficacy of *L. plantarum* 299v, compared to placebo, in an 8-week intervention. The authors are referring to abdominal pain relief although the IBS-SSS is comprised of five different symptom scores, and compare their results with those seen in the studies by Niedzielin *et al.* (2001) and Ducrotte *et al.* (2012). The results, not showing a superiority of *L. plantarum* 299v on total IBS-SSS, are however not comparable with the individual effects on symptom relief seen in the previous studies, since different parameters were evaluated. Moreover, a large placebo effect was seen in the study by Stevenson *et al.* (2014) and the authors suggested that this might be one of the main explanations for the lack of results. The study included several visits with clinicians, potentially explaining the big improvements in quality of life seen for all participants. The challenges of the large placebo effect often seen in IBS studies are further discussed in Section 4 – Challenges with IBS studies.

Potential mode of action

The mechanism by which probiotics may be able to alleviate symptoms of IBS is not clear, but the effects on each IBS symptom are believed to be strain specific (Ortiz-Lucas *et al.*, 2013). A low microbial diversity, particularly in the small intestine, has been associated with increased permeability, and consequently symptoms of GI disorders (Saffouri *et al.*, 2019). It has also been found that an altered mucosal barrier of the small intestine is a common factor regardless of IBS subtype (Gonzalez-Castro *et al.*, 2017). This is not surprising since the small intestine bears a higher exposure to environmental antigens than the colon and is where most of the immune responses to digestive contents occur (Santaolalla *et al.*, 2011). The impact of microbiota in the aetiology of IBS seems to start with dysbiosis, which in turn compromises integrity of the intestinal barrier, and ultimately affects immune modulation (Lacy *et al.*, 2016; Simren *et al.*, 2013).

As already mentioned in previous sections, *L. plantarum* 299v has been shown to increase the microbiota diversity (Karlsson *et al.*, 2010), promote intestinal barrier integrity through increasing mucin production (Dykstra *et al.*, 2011; Mack *et al.*, 1999, 2003), and increase the carboxylic acid concentration in faeces (Johansson *et al.*, 1998). Moreover, *L. plantarum* 299v has also been shown to affect immunomodulatory responses in various models, as discussed in Section 3 – Inflammatory response. Several proinflammatory cytokines are thought to contribute to the pathogenesis of IBS (Mitselou *et al.*, 2020; Vara *et al.*, 2018). One of these, IFN- γ , has been shown to be increased in the mucosa of IBS patients irrespective of IBS type (Barbaro *et al.*, 2016) and decreased by *L. plantarum* 299v in a mouse model of IBS (Vaughn *et al.*, 2009).

Challenges with IBS studies

Studies in subjects with IBS can be challenging due to the natural variation of the IBS symptoms over time and the large placebo effect related to the symptoms reported by the subjects. Many people suffering from IBS have had difficulties finding relevant professional consultation, treatment, and relief (Shah and Pimentel, 2014). Thus, the sheer participation in a clinical study focusing on IBS, with regular visits and study personnel showing an interest in the health status of the participant, may result in improved symptom scores by the subjects (McCarney *et al.*, 2007). Due to these specific conditions, a relatively large number of participants is required to give statistically reliable results (Shah and Pimentel, 2014). The lack of positive results for some symptoms in the above-described studies may therefore be due to the relatively low numbers of participants included, such as for overall IBS symptoms (Sen *et al.*, 2002; Stevenson *et al.*, 2014) and abdominal pain (Nobaek *et al.*, 2000).

Despite small differences in the settings and varied outcomes of different studies, they all point to an improvement of IBS symptoms by *L. plantarum* 299v, especially abdominal pain and bloating as mentioned in other review articles assessing the efficacy of probiotics (Bixquert Jimenez, 2009; Hoveyda *et al.*, 2009; McFarland *et al.*, 2018; Sniffen *et al.*, 2018; Zhang *et al.*, 2016).

5. 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 diarrhoea, abdominal pain, blood in stools, fatigue, and unintended weight loss, negatively affecting quality of life. UC causes ulcers in the colon and rectum, while the inflammation in CD affects primarily the small intestine.

The aetiology of IBD is not fully known but involves genetic, environmental, microbial, and immunological factors, described more in detail in the review by Zhang and Li (2014). The gut microbiome in IBD patients has been shown to be significantly less diverse than that of healthy controls (Joossens *et al.*, 2011), however, it is unclear whether the changes in microbiota composition are part of the cause, or rather a consequence, of IBD. A recent review article suggests that defects in communication between the innate immunity and the mucosal barrier are more important for the pathophysiology of IBD than the acquired immune system (Stange and Schroeder, 2019). The authors suggest that targeting the gut bacteria could prevent the development of inflammation in IBD and would be a better approach than trying to dampen an already established inflammation.

L. plantarum 299v has been shown to reduce histological scores and cytokine levels associated with IBD in different colitis animal models (Osman *et al.*, 2004; Schultz *et al.*, 2002). Slight improvement of colonic, rectal and caecal histological scores and a lower production of the cytokines IL-12 and IFN- γ were observed in IL-10 knockout mice with established colitis when treated with *L. plantarum* 299v for four weeks. However, when *L. plantarum* 299v was given as prevention, it did not show the same effectiveness (Schultz *et al.*, 2002). *L. plantarum* 299v has also been shown to significantly improve disease activity index in rats with dextran sulphate sodium (DSS) induced colitis (Osman *et al.*, 2004), but did not prevent relapse of colitis in a rat model under antibiotic treatment (Dieleman *et al.*, 2003). Although DSS administration is commonly used to induce colitis in animal models, the method has its drawbacks since it does not directly cause intestinal inflammation but rather chemical injury to the epithelium, which in turn triggers inflammation. Hence, there are several different models to study acute colitis, but neither of them truly resembles the chronic changes observed in human IBD (Low *et al.*, 2013).

Histological and immunological improvement in animal colitis models seems to agree with clinical studies. Patients with active UC taking oat gruel fermented with *L. plantarum* 299v significantly improved their symptoms during a 24-week intervention (Krag *et al.*, 2012). The results were confirmed in a randomised study comparing a drink containing *L. plantarum* 299v to a similar product without bacteria (Krag *et al.*, 2013).

The effects of *L. plantarum* 299v on symptoms of IBD seem to be partially explained by immune-related mechanisms and inhibition of translocation. Bacterial translocation induces inflammatory immune responses, which *L. plantarum* 299v has been shown to reduce in rats with enterocolitis (Mao *et al.*, 1996a). The mucus layer in IBD patients is more permeable than in healthy controls, thus, the epithelial barrier is weakened (Johansson *et al.*, 2014;

Salim and Soderholm, 2011). As previously mentioned, *L. plantarum* 299v has been shown to promote mucus production (Mack *et al.*, 1999, 2003), reduce translocation (Mangell *et al.*, 2006), and strengthen tight junctions (Barnett *et al.*, 2018), which may contribute to the beneficial effects on IBD symptoms.

Many IBD patients who suffer this chronic disease with a constant inflammation may have to undergo an intestinal resection during their lifetime (Sica and Biancone, 2013). Liu and colleagues studied the side-effects of external radiation on colonic anastomosis healing, and the impact of supplementation with *L. plantarum* 299v, in a rat model. The results suggest that administration of *L. plantarum* 299v might reduce the inflammatory reaction, increase collagen deposition, and improve colonic anastomotic healing (Liu *et al.*, 2001). Colonic anastomosis healing was also studied in rats fed either low fibre diet, normal chow, or normal chow with *L. plantarum* 299v. Compared to the low fibre diet, both normal chow and normal chow with *L. plantarum* 299v facilitated healing of colonic anastomosis (Mangiante *et al.*, 2001b).

6. Gastrointestinal infections

The effects of *L. plantarum* 299v on the incidence, symptoms and recurrence of antibiotic associated diarrhoea (AAD) and gastrointestinal infections, such as *C. difficile* infection (CDI), have been investigated in several clinical studies.

Antibiotic associated diarrhoea

AAD is often defined as three or more loose to watery stools within 24 h, starting after initiation of antibiotic treatment. Prevention of AAD is especially important in immunocompromised patients, for example after an organ transplantation, since diarrhoeal episodes can lead to reduced concentration of immunosuppressive agent in the blood, increasing the risk of acute rejection (Angarone and Ison, 2015).

L. plantarum 299v taken during antibiotic treatment reduced mild GI symptoms associated with antibiotic intake, such as loose/watery stools or nausea in adult patients (Lonnermark *et al.*, 2010), but had lower efficiency in children (Olek *et al.*, 2017). While the adult population included both hospitalised patients and outpatients, of which 45% were given antibiotics intravenously, the paediatric population was treated in primary healthcare settings due to infections of the respiratory tract, ear or urinary tract, and were otherwise healthy, which could explain the discrepancy of the probiotic efficiency in AAD. Furthermore, in these studies, the incidence of AAD was rather low compared to older studies (approximately 7% versus 16% and 3% versus 6% in adults and children,

respectively (Asha *et al.*, 2006; Damrongmanee and Ukarapol, 2007)), possibly due to different patterns of antibiotic use.

As previously mentioned, intake of *L. plantarum* 299v during antibiotic treatment also seems to help maintain the levels of butyric acid as well as total organic acids in comparison with placebo, which could indicate that *L. plantarum* 299v would help minimise disturbances to the microbiota during the course of antibiotic treatment (Wullt *et al.*, 2007).

Clostridioides difficile

C. difficile is currently the most frequently identified pathogen involved in the development of AAD (Dudzicz *et al.*, 2017). Infections by other microbes, such as *Staphylococcus aureus* and *Clostridium perfringens* have also been identified as causes (Boyce and Havill, 2005; Modi and Wilcox, 2001). *C. difficile* associated diarrhoea (CDAD) caused by CDI is associated with dysbiosis and occurs most frequently in patients under broad spectrum antibiotic therapy. The risk of CDI is increased in the elderly and patients with previous hospitalisations, comorbid conditions, or impaired immune system. CDAD does not necessarily occur due to the actual infection but rather to large clostridial toxins, that also cause inflammation and tissue necrosis. Thus, CDI is often diagnosed based on detection of these toxins in faeces. The cascades triggered by the toxins have been extensively reviewed by Smits and colleagues (2016).

Studies evaluating the efficacy of *L. plantarum* 299v for CDI prevention have shown promising results. A study by Wullt *et al.* (2003) demonstrated that *L. plantarum* 299v tended to reduce the incidence of recurrent CDI in adults. Prophylactic use of *L. plantarum* 299v significantly decreased CDI incidence in critically ill patients (Klarin *et al.*, 2008): 19% of the patients in the control group had a CDI compared to none in the *L. plantarum* 299v group. In another study performed over three twelve-month periods, hospitalised patients under antibiotic and immunosuppressive therapy were given either *L. plantarum* 299v or other probiotic formulations (Dudzicz *et al.*, 2018; Kujawa-Szewieczek *et al.*, 2015). The other probiotic formulations were given during the first and third years and *L. plantarum* 299v was given during the second year. A significant reduction of CDI incidence in the ward was observed during the second year when *L. plantarum* 299v was administered, compared to the first year (Kujawa-Szewieczek *et al.*, 2015), and the incidence of CDI increased again during the third year, after administration of *L. plantarum* 299v ceased (Dudzicz *et al.*, 2018). Interestingly, although *L. plantarum* 299v was only given to the patients treated with antibiotic and immunosuppressive therapy, the number of CDI cases in the entire ward also decreased

during the second year. Moreover, during the second year, fewer diarrheal days were reported than during the first year, when *L. plantarum* 299v was not administered (Kujawa-Szewieczek *et al.*, 2015).

7. Iron absorption

Iron deficiency is the most common cause of anaemia and explains approximately 50% of all cases of anaemia 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 anaemia in 2011 (WHO, 2015). The need for iron varies depending on age, gender, and physical status, where children, women of fertile age, and pregnant or lactating women have higher needs.

The typical Western diet contains approximately 14 mg of iron per 2,000 kcal (the average daily energy intake), but only 1–4 mg is absorbed (Weinborn *et al.*, 2017). There are two forms of dietary iron: haem iron, found in animal sources, and non-haem iron, found in both animal and plant-based foods. The comprehensive review by Beck and colleagues (2014) describes how different dietary components interact with non-haem iron in the intestine impacting iron absorption. Soy protein, legumes, cereals, eggs, and dairy products are examples of foods that decrease iron absorption to some extent, and phytic acid and phenolic compounds (found in plant seeds, tea and coffee) are dietary factors that inhibit the absorption. On the other hand, vitamin C, naturally present in fruits and vegetables, increases 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 anaemia, but are strongly associated with GI side effects, such as abdominal pain and constipation (Low *et al.*, 2016). This is due to the high concentration of iron present in the supplements and the low absorption rate in the intestine that will lead to a high iron content in the colon. Moreover, growth and adhesion of pathogenic bacteria, such as *Salmonella* Typhimurium have been shown to increase in response to high intestinal iron levels (Kortman *et al.*, 2012).

Insufficient iron levels is the most common micronutrient deficiency globally (Bailey *et al.*, 2015; World Health Organization, 2020) and given the very common side effects of iron supplements, finding ways to increase iron absorption, rather than only increasing the intake of iron, would be desirable. One way of increasing iron absorption is by increasing iron bioavailability through fermentation of foods. Fermentation is believed to increase iron absorption by increasing ferric iron (Fe^{3+}) released from the food matrix (Bering *et al.*, 2006; Scheers *et al.*, 2016). In foods rich in phytic acid, such as some pseudo cereals, fermentation results in lower pH, increasing the

activity of the endogenous enzyme phytase, which in turn improves iron bioavailability (Castro-Alba *et al.*, 2019). Added to the effect on food matrix, organic acids formed during fermentation may also prolong gastric emptying (Liljeberg and Björck, 1998), potentially increasing the exposure of iron to the intestinal epithelium (Salovaara *et al.*, 2002, 2003), hence enabling increased absorption.

Increased iron uptake independent of food matrix

L. plantarum 299v has been shown to increase iron absorption in several clinical studies in women of childbearing age (Bering *et al.*, 2006; Hoppe *et al.*, 2015, 2017) and improve iron status in clinical (Axling *et al.*, 2020, 2021; Korcok *et al.*, 2018) and animal (Adiki *et al.*, 2019) studies. The studies by Bering *et al.* (2006, 2007) and Hoppe *et al.* (2015, 2017) all made use of a double-isotope cross-over design method. The usage of this method is validated and generally accepted for the measurement of iron absorption. The order of the meals was randomised in the first study by Bering *et al.* (2006), but to avoid carry-over effects on the placebo meal after the intake of *L. plantarum* 299v, the sequence was altered to 2 days with the control, followed by 2 days with *L. plantarum* 299v in the latter study by Bering *et al.* (2007) and the studies by Hoppe *et al.* (2015, 2017).

Bering and colleagues investigated the potential of *L. plantarum* 299v to increase absorption of non-haem iron in humans by comparing four different oat gruels (Bering *et al.*, 2006). They found that oat gruel fermented with *L. plantarum* 299v significantly increased the absorption of iron from a test meal by 80%, compared to oat gruels that were either pasteurised after fermentation, non-fermented with adjusted pH, or contained added organic acids. In a follow-up study, Bering and colleagues compared the effect of a heat-inactivated fermented oat gruel with or without lyophilised *L. plantarum* 299v added to the cold gruel after pasteurisation (Bering *et al.*, 2007). However, with this setup, no significant difference in iron absorption between the test products was observed, with the authors hypothesising that the bacteria ‘were not in a comparable active state’, compared to the previous study.

The positive results from the first study by Bering *et al.* (2006) were later confirmed in four different trials (two in each publication) with a fruit drink (Hoppe *et al.*, 2015) and lyophilised bacteria in capsules (Hoppe *et al.*, 2017). In the first study by Hoppe *et al.* (2015), different doses of *L. plantarum* 299v added to an iron and ascorbic acid supplemented fruit drink increased iron absorption compared to the same fruit drink without added bacteria. In the second study, lyophilised *L. plantarum* 299v with added iron, folic acid and ascorbic acid in capsules were used in two separate identical trials, both showing a significantly increased iron absorption from a light meal,

compared to placebo (Hoppe *et al.*, 2017). These results are in contrast with the study above by Bering *et al.* (2007), where the lyophilised bacteria were added directly to a heat-inactivated fermented oat gruel with a low pH caused by the fermentation. As discussed in the study by Bering *et al.* (2007), later experiments showed that the metabolic activity of *L. plantarum* 299v in this oat gruel at 37 °C was delayed with approximately 1 h. This could explain why no effect on the iron absorption was shown in this study. In the study by Hoppe *et al.* (2017), the lyophilised bacteria were encapsulated and protected from the low pH in the stomach. The bacteria were therefore probably in a more active state once released into the neutral environment in the duodenum where the iron absorption takes place. These results suggest that live *L. plantarum* 299v was responsible for the increase of iron absorption, rather than reduced pH or organic acids, which is in line with the studies by Scheers *et al.* (2016) and Bering *et al.* (2006). Effects on iron absorption have also been investigated for other probiotic strains (Skrypnik *et al.*, 2019, 2020), however, the results suggest that the health-promoting effects on iron absorption described above may be a specific trait of *L. plantarum* 299v.

Long-term effects on iron status

Serum iron concentration rather than iron absorption was investigated in a small, exploratory study where lyophilised *L. plantarum* 299v combined with 10 mg sucrosomial iron and 15 mg of ascorbic acid were administered to healthy women of child-bearing age for 7 days and blood samples analysed 10–12 days after administration ceased. The study reported an 11% increase in serum iron concentration compared to the placebo group, however, it was underpowered, and no statistical analysis was shown (Korcok *et al.*, 2018).

The long-term effects of *L. plantarum* 299v on improving serum ferritin levels have been investigated in healthy pregnant women (Axling *et al.*, 2021) and in a group of healthy female athletes (Axling *et al.*, 2020). The female athletes had low iron stores but were not anaemic and were randomised to receive either one capsule daily containing 20 mg of iron (as ferrous fumarate) and *L. plantarum* 299v, or 20 mg of iron alone (placebo) for 12 weeks. In the group receiving *L. plantarum* 299v, plasma ferritin levels increased by 70%, compared to 42% in the placebo group, although the difference was not statistically significant. The effect was apparent already after four weeks, with a close to significant difference between groups, in favour of *L. plantarum* 299v (Axling *et al.*, 2020).

A population of 326 healthy, non-anaemic, pregnant women was studied in a prospective, multicentre trial. In this study, two capsules a day, one with each main meal, of placebo or lyophilised *L. plantarum* 299v with 4.2 mg of iron, 12

mg ascorbic acid and 30 µg folic acid were administered. The women received study product from gestational week 10–12 until the end of pregnancy, or until a potential need of conventional iron therapy. In the group receiving *L. plantarum* 299v, the pregnancy-related decreases in serum ferritin levels, total body iron status, and haemoglobin levels were mitigated, compared to the placebo group. Moreover, the study showed that supplementation with *L. plantarum* 299v, iron, ascorbic acid and folic acid resulted in reduced prevalence of iron deficiency and iron deficiency anaemia in late pregnancy (Axling *et al.*, 2021). It can thus be hypothesised that this could delay or even prevent the need for traditional iron therapy during pregnancy.

Potential mode of action

The mechanism behind increased iron absorption driven by *L. plantarum* 299v needs to be further investigated, but it has been suggested that the effects are mediated via the Fe³⁺/Duodenal cytochrome B (DcytB) axis (Sandberg *et al.*, 2018). *L. plantarum* 299v increased the Fe³⁺ form of iron in a simulated GI digestion of a test meal with capsules, oat drinks or fruit drinks, compared to samples without the bacteria. In the same study, human intestinal co-cultures of enterocytes and goblet cells (Caco-2/HT29 MTX cells) had higher levels of the ferric reductase DcytB in the presence of *L. plantarum* 299v, while the levels of the ferrous iron (Fe²⁺) importer, the divalent metal ion transporter 1 (DMT1), were not affected. This increase in DcytB seems to be a response to the increased ferric iron made available by *L. plantarum* 299v and not a direct effect of *L. plantarum* 299v.

Bering and colleagues (2007) showed that there is no absorption of iron in the distal intestine. The reduction of Fe³⁺ to Fe²⁺ required for uptake via DMT1 takes place in the duodenum, which suggests that *L. plantarum* 299v must be active in the most proximal small intestine to have an impact on iron absorption. Lyophilised bacteria are in a resting state and need to be rehydrated to become active, in contrast to the already active bacteria in the oat gruel and fruit drinks used in the studies by Bering *et al.* (2006) and Hoppe *et al.* (2015), respectively. The difference between the active and resting (lyophilised) bacteria in food and capsules may explain why more iron was absorbed with fruit drinks (Hoppe *et al.*, 2015) than with capsules (Hoppe *et al.*, 2017).

When evaluating the effect of *L. plantarum* 299v on iron absorption, the amount of iron seems to be an important factor. High doses of iron, like those found in conventional iron supplements, may result in no further increase of iron absorption by *L. plantarum* 299v for two main reasons: iron self-regulation mechanisms, and the presumed role of *L. plantarum* 299v to increase iron availability rather than absorption itself. Firstly, supplementation of iron increases the levels of hepcidin (a protein that helps regulate

the uptake of iron), resulting in a decreased potential to absorb iron (Moretti *et al.*, 2015). Secondly, since *L. plantarum* 299v seems to primarily increase availability of iron from the food matrix (Sandberg *et al.*, 2018), the bacteria would not be able to further increase iron absorption when a high load of iron is already available. This could be a potential explanation of the results in the study by Rosen and colleagues in which *L. plantarum* 299v was administered together with iron and ascorbic acid to iron-deficient children for 6–8 weeks (Rosen *et al.*, 2019). The iron supplementation was dependent on the weight of the children (3 mg/kg) up to a maximum of 65 mg/day in both the placebo and *L. plantarum* 299v groups. Although considered a low dose by the authors, the amount of iron administered in the study is high compared to the recommended daily intake for this age group (5–18 years; 11–13 mg per day (EFSA Panel on Dietetic Products and Allergies, 2015)). Naturally, ferritin levels increased significantly in both groups (slightly more in the probiotic group) and were positively correlated with the amount of iron administered. Although hepcidin levels were not measured in the study, it can be hypothesised that the high iron doses might have caused an increase in hepcidin preventing further iron absorption, and therefore the possibility for *L. plantarum* 299v to additionally increase iron uptake and consequently ferritin levels would be low.

The same reasoning as above regarding iron limiting the effect of *L. plantarum* 299v on iron absorption might also explain the rather small difference seen between the groups of athletes in the study referred to above (Axling *et al.*, 2020), and could suggest that a lower dose of supplementary iron could have resulted in a more pronounced effect in the probiotic group. Taking into account the possible harmful side effects of high-dose iron supplements, *L. plantarum* 299v could be considered a novel strategy to safely increase iron uptake and potentially prevent iron deficiency without the side effects.

8. Other indications

L. plantarum 299v has been used to investigate the effects on other indications as well, such as psychological or mental health (the so-called gut-brain axis), metabolic health and oral health. Moreover, *L. plantarum* 299v has been used 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 and autism spectrum disorders) (Cheng *et al.*, 2019). Moreover, animal experiments have shown that mental stress increases

the transepithelial permeability and translocation, and that probiotic administration can ameliorate bacterial translocation and reduce levels of stress hormones (Gareau *et al.*, 2007).

L. plantarum 299v has been used in two clinical studies in the area of mental health. The first study including 41 students with an upcoming school exam showed that intake of *L. plantarum* 299v for two weeks significantly decreased saliva cortisol, compared to placebo (Andersson *et al.*, 2016). The second study investigated the effect of cognitive function and biochemical parameters in subjects suffering from major depression. *L. plantarum* 299v or placebo was given to 60 subjects, all undergoing treatment with selective serotonin reuptake inhibitors, for a period of 8 weeks. The probiotic intake significantly improved cognitive performance, compared to placebo (Rudzki *et al.*, 2019).

Metabolic health

The GI microbiota has been shown to have a direct role in human metabolic regulation through various types of interactions between the bacteria and the host. Dysbiosis and reduced bacterial diversity, as well as increased transepithelial permeability, have also been shown to be related to metabolic health (Boulangier *et al.*, 2016). *L. plantarum* 299v has been shown to affect certain factors coupled to metabolic health, including postprandial insulin responses, concentration of blood lipids and endothelial function (Bukowska *et al.*, 1998; Granfeldt and Björck, 2011; Malik *et al.*, 2018; Naruszewicz *et al.*, 2002; Xu *et al.*, 2018). Two meal studies, each including 11 healthy subjects, investigated the effect of beverages composed of different berries and fruits as well as oatmeal fermented with *L. plantarum* 299v on postprandial glucose and insulin responses. Both studies found that the beverages resulted in decreased insulin responses but had no effect on the glycaemic response compared to reference bread or a glucose drink (Granfeldt and Björck, 2011; Xu *et al.*, 2018). Another meal study investigated the effect of barley kernels on blood glucose regulation and appetite regulating hormones with or without supplementation of different probiotics, including *L. plantarum* 299v. The results showed that probiotic intake for 14 days increased the plasma levels of glucagon-like peptide 2 (Nilsson *et al.*, 2016), a peptide which has been shown to improve intestinal integrity (Cani *et al.*, 2009), after a standardised breakfast.

Ischaemic heart disease and stroke are the top two causes of death globally (WHO, 2018). Atherosclerotic dysfunctions are strongly associated with these diseases, and the risk for atherosclerosis is mediated by, among others, blood lipid profiles, blood pressure, fibrinogen levels and vascular endothelial function. In recent years there has been a growing interest in the possible effect of probiotics on metabolic parameters, and to date five studies

have investigated the potential use of *L. plantarum* 299v. Three of these were clinical studies with *L. plantarum* 299v supplementation in fruit drinks for six weeks. The first study included 30 men with moderately elevated cholesterol levels. The probiotic group showed significantly reduced total and low-density lipoprotein cholesterol levels, as well as decreased fibrinogen levels compared to baseline, while no changes were seen in the placebo group (Bukowska *et al.*, 1998). In the second study, 36 smokers were included, both men and women. Intake of *L. plantarum* 299v significantly reduced the systolic blood pressure, leptin, fibrinogen, and IL-6 levels, while no effects were seen in the placebo group. Moreover, the adhesion of monocytes, isolated from the subjects, to native and stimulated human umbilical vein endothelial cells was significantly reduced in the probiotic group, suggesting an impact on atherosclerotic plaque formation (Naruszewicz *et al.*, 2002). In the third clinical study all 20 men with stable coronary artery disease received the probiotic drink; hence, the study was not placebo controlled. Supplementation resulted in a significantly improved brachial artery flow-mediated dilation and decreased circulating levels of IL-8, IL-12, and leptin (Malik *et al.*, 2018).

In addition to the three clinical studies summarised above, two animal studies investigating effects of *L. plantarum* 299v on ischaemia/reperfusion have been done. The first study was a rat model of myocardial infarction after antibiotic-induced intestinal dysbiosis. Supplementation of *L. plantarum* 299v for 14 days before induced ischaemia/reperfusion resulted in decreased circulating leptin, smaller myocardial infarcts, and better recovery of mechanical function, compared to control (Lam *et al.*, 2012). In the second study, ischaemia/reperfusion injury was induced in mice supplemented with both *L. plantarum* 299v and rosehip. The combination of rosehip and *L. plantarum* 299v reduced lipid peroxidation, however, the effect seemed to be primarily coming from rosehip, rather than *L. plantarum* 299v (Hakansson *et al.*, 2006).

Oral health

Oral health, and more precisely dental plaque development, caries, and lesions, can be affected by the oral microbial composition. Probiotic bacteria for oral health promotion should be able to attach to the oral mucosa and dental tissues to become a part of an oral biofilm and compete with the growth of oral pathogens (such as *Streptococcus mutans* and *Candida albicans*). *L. plantarum* 299v has been investigated for usage in oral formulations in several studies. Different oromucosal delivery formats have also been investigated, with promising results (Hoffmann and Daniels, 2018; Pandey *et al.*, 2016). Independently of the administration mode (from gargling of oat-gruel to drinking a fruit juice), *L. plantarum* 299v was found to attach to the human tonsillar surface and remain for up to

8 h (Stjernquist-Desatnik *et al.*, 2000). Binding-capacity of *L. plantarum* 299v to saliva-coated surfaces *in vitro* and survival of the strain in saliva after a 24 h incubation period have been shown (Haukioja *et al.*, 2006). *In vitro* studies have demonstrated *L. plantarum* 299v to co-aggregate with selected oral pathogens to form a biofilm (Twetman *et al.*, 2009), inhibit salivary mutant streptococci biofilm, and affect the pathogenesis of dental caries (Soderling *et al.*, 2011). *L. plantarum* 299v also completely inhibited growth of all five mutant streptococci strains tested, and reduced the growth of *C. albicans* almost completely (Hasslof *et al.*, 2010).

The production of lactic acid and subsequent reduction in pH is a beneficial trait in the GI tract but could be a negative effect in the oral cavity since a low pH could lead to progression of dental caries. *L. plantarum* 299v has been found to significantly decrease pH levels after incubation with different sugars and sweeteners (Haukioja *et al.*, 2008; Hedberg *et al.*, 2008; Keller and Twetman, 2012). Additional studies are needed to further elucidate the potential usage of *L. plantarum* 299v for improved oral health, despite its pH-lowering effects.

Various food applications

The first food application for *L. plantarum* 299v was a fermented oat-meal beverage, developed as a new concept for enteral feeding. The formulation of this beverage was later optimised by Marklinder *et al.* regarding pH, viability of the strain as well as addition of phytase to not interfere with iron and zinc absorption (Marklinder and Johansson, 1995; Marklinder and Lönner, 1994; Marklinder *et al.*, 1995). The fermented oat-meal beverage is still used in the production of the fruit beverages ProViva® and GoodBelly® (Molin, 1994). ProViva® is often administered to patients in hospitals in Sweden and the rosehip-based drink was used in a study investigating tablet dissolution. Rosehip, rather than *L. plantarum* 299v, explained the slow dissolution of paracetamol tablets seen in the study (Akerman and Edvinsson, 2009).

Over the years, the general interest in probiotics has increased and *L. plantarum* 299v has been used in various applications related to food production. Already in 1995, Marklinder *et al.* showed that *L. plantarum* 299v could be used as a starter culture for production of barley sour dough (Marklinder and Johansson, 1995). Probiotic pineapple juice (Nguyen *et al.*, 2019) and orange juice (Barbosa *et al.*, 2015), quinoa juice (Canaviri Paz *et al.*, 2020), legume sprouts (Swieca *et al.*, 2018, 2019, 2020), fermented cauliflower and white beans (Thompson *et al.*, 2020), dark chocolate (Mirkovic *et al.*, 2018), bovine salami (Blaiotta *et al.*, 2018) and button mushroom fruiting bodies (Jablonska-Rys *et al.*, 2016) are other examples of food products where *L. plantarum* 299v has been used as either 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.

Other studies have used *L. plantarum* 299v to obtain secondary metabolites, such as potentially antihypertensive peptides from fermented pea seeds (Jakubczyk *et al.*, 2013), and to metabolise theaflavins from black tea to smaller, more bioavailable, polyphenols (Chen *et al.*, 2012). When used together with adzuki and mung bean sprouts, higher antioxidant capacity and especially cytotoxic and cytostatic activity against human gastric cancer cells were observed (Świeca *et al.*, 2020). *L. plantarum* 299v was found to successfully produce volatile sulphur compounds, important for food flavouring and aroma, from cysteine and methionine (Sreekumar *et al.*, 2009). Moreover, studies have shown that *L. plantarum* 299v is able to grow on different prebiotic substrates, for example galacto-oligosaccharides produced from whey permeate (Golowczyc *et al.*, 2013) and short-chain fructo-oligosaccharides (Saulnier *et al.*, 2008). *L. plantarum* 299v has also been evaluated in combination with a microalga (*Chlorella sorokiniana*) in a dairy product (flan), where it showed anti-microbial effects against rotavirus (Cantu-Bernal *et al.*, 2020). *L. plantarum* 299v incorporated in animal feed resulted in reduced oxidative stress, increased antioxidant capacity and improved growth rate of chickens (Khanian *et al.*, 2019), as well as improved fish performance in Atlantic salmon (Rodriguez *et al.*, 2020).

The viability of *L. plantarum* strains in calcium alginate beads has been found to be improved when whey proteins were used as coating material during encapsulation (Gbassi *et al.*, 2009). Successful co-delivery of bioactive hydroxytyrosol from a standardised extract of *Olea europaea* leaves (olive leaves) with *L. plantarum* 299v has been shown using novel food-grade granules (Aponte *et al.*, 2018). Another possible application for *L. plantarum* 299v is the preservation of cereal crops, as Zhao *et al.* (2017) showed that the strain possesses anti-*Fusarium* activity. More recently, *L. plantarum* 299v was found to successfully catalyse the hydration reaction of the most commonly consumed unsaturated fatty acids; oleic, linoleic, and linolenic acids (Serra *et al.*, 2020). This may be interesting for the food industry, since using probiotics to stabilise various food applications, such as emulsions, is not very common today.

L. plantarum 299v, being a well-known and characterised probiotic strain, has also been used as a positive control in various studies. One example is the study by Castro-Rodríguez *et al.* (2015) who used *L. plantarum* 299v to compare the viability and probiotic potential of strains found in agave, a component of a Mexican beverage (pulque). Gotteland *et al.* (2014) used *L. plantarum* 299v as a positive control for a safety evaluation of bacterial strains found in human breast milk, faeces, and goat

cheese. Melgar-Lalanne *et al.* (2013) used *L. plantarum* 299v and *Lacticaseibacillus casei* Shirota as comparisons to halotolerant lactobacilli isolated from ripened tropical Mexican cheese.

9. Conclusions

L. plantarum 299v was first discovered as a health-supporting probiotic strain more than 30 years ago and continues to be extensively researched around the world. This review aimed to describe and discuss all published research studies (up until June 2020) concerning the effects of *L. plantarum* 299v. *In vitro* and animal studies have helped to better understand various characteristics of this strain and reveal potential modes of action for many promising results obtained in clinical studies. It is important to remember that probiotics are not pharmaceutical drugs but are intended to support and help maintain health or be used for preventative purposes. Despite this, intake of *L. plantarum* 299v has been shown to provide relief of symptoms for those suffering from IBS and IBD and to mitigate iron deficiency.

IBS is the most commonly reported GI disorder globally. Repeated studies have shown that intake of *L. plantarum* 299v results in decreased severity and intensity of IBS symptoms such as abdominal pain, flatulence, bowel habits and bloating. Moreover, intake of *L. plantarum* 299v has been shown to increase bacterial diversity in the intestine, provide relief for those suffering from IBD, as well as decrease the incidence of CDI for those prescribed antibiotics.

Iron deficiency explains approximately 50% of all cases of anaemia worldwide and is often caused by poor iron absorption. Traditionally, iron supplementation is used as treatment of iron deficiency. However, *L. plantarum* 299v has been shown to significantly increase iron absorption, likely due to an increase in iron bioavailability, and recently to improve long-term iron status in healthy female athletes and non-anaemic pregnant women. These results suggest that *L. plantarum* 299v is a novel approach to preventing iron deficiency and iron deficiency anaemia.

The World Health Organization (WHO) classifies probiotics as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' and additional requirements have been described recently (Binda *et al.*, 2020). The bacterial strain *L. plantarum* 299v is well characterised, has a clinically proven dosage and has been shown to support health for a broad range of indications. Since the 1990s, *L. plantarum* 299v has been incorporated in functional food products and food supplements in more than 40 markets worldwide.

To conclude the various effects of *L. plantarum* 299v 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 *L. plantarum* 299v has been shown to affect pathogen inhibition, intestinal barrier function, and the immune system. The to date more than 60 published human clinical studies performed with *L. plantarum* 299v have demonstrated several health benefits, where the strongest evidence for the effectiveness is within gastrointestinal health and iron absorption.

Conflict of interest

The strain *L. plantarum* 299v, LP299V® is proprietary to Probi AB, Sweden. EAN, CT, CM and NL are employed by Probi AB. BJ is a senior scientific advisor to Probi AB.

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