Lactobacillus plantarum — A Literature Review Of Therapeutic Benefits

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Abstract

This article reviews scientific literature for evidence of the therapeutic value of *Lactobacillus plantarum* in treating inflammatory disease and mitigating pathogenic infection.

Reference

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Introduction

Inflammatory diseases of the cardiovascular system, the gut (including intestinal dysbiosis such as irritable bowel disease/syndrome (IBD/IBS), Crohn's disease and ulcerative colitis) and low immune function are becoming more common with current highly refined, processed Western diets(1). Probiotics have long been one of the first tools for nutritional treatment of intestinal dysbiosis of all types, but research is now uncovering wider applications for their use.

This paper reviews the literature for *Lactobacillus plantarum* 299v as a therapeutic agent in a number of conditions, including intestinal dysbiosis, inflammation and pathogenic infection. A Swedish product called Proviva (manufactured by Probi AB, Lund, Sweden) was used in many of the trials cited in the literature. This product is a fruit drink to which has been added a fermented oatmeal gruel which contains *L. plantarum* 299v[2]. It is available in Europe, but is not well-known in Australia.

Method

A search of PUBMED and CINAHL was carried out for papers covering the period 1995 to 2008 reviewing the effects of *Lactobacillus plantarum* in humans. Murine studies were only considered if the research had strong application to humans, but in general these studies were excluded, along with the studies of *L. plantarum* use or effects in animals and agriculture. With one exception, full texts of all of the articles were obtained. One paper published in 1993 was included because it was cited as an important reference by many other papers. In all, 29 papers were selected for review.

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The majority of these studies revealed their funding sources, most of which were from government and educational/research bodies, but eight investigations also disclosed a commercial source of funding, including Probi AB (Lund, Sweden) which provided sources of *L. plantarum* for two studies. The Danish Dairy Board and the New Zealand Dairy Board were also involved in funding some investigations.

Background

It is clear from clinical research over the last few decades that particular strains of *Lactobacillus* and *Bifidus* bacteria have different effects, which can be suited to various disease states[3—7]. *L. plantarum* appears to be an extremely adaptable and useful strain of *Lactobacillus* that has many modes of operation. In one review article, the authors stated that *L. plantarum* was the first of the *Lactobacillus* to have its genome sequenced[8]. They reviewed its considerable adaptability within a variety of habitats, such as foods, oral mucosa and the GI tract, and found it capable of synthesising most amino acids de novo via its elaborate proteolytic system.

Strains

Like most lactobacilli, *L. plantarum* is found in a number of strains. One which is commonly used in therapeutic tests and products is *L. plantarum* 299v, however, research continues into other potentially therapeutic strains of *L. plantarum* such as LA318 and DSM9843. This paper specifies which strain was used whenever possible, but this information was not always given.

Therapeutic Benefits

Relief from Inflammation and Pain

Beneficial effects of probiotics fall into two categories: recolonisation of the gut with friendly bacteria, or enhancement of the immune system from greater numbers of beneficial bacteria in the gut. In IBD, the mechanisms of action

include competition with microbes for receptors on the epithelium; stimulation of gut-associated lymphoid tissue (GALT) and other immune tissues; suppression of pathogenic growth through production of an acid environment; enhancement of the mucosal barrier function and induction of T-cell apoptosis in the lamina propria[9].

There are a number of species of lactobacillus that have beneficial effects on the gut. *L. plantarum* is one which has showed particular promise in a number of studies. A double-blind, randomised study of 40 patients who took Proviva for four weeks showed that all of the study group obtained relief from IBS symptoms, with a trend to normalisation of stool frequency in constipation. The authors postulated that these beneficial effects could be due to the unique ability of *L. plantarum* to catabolise arginine and generate nitric oxide (NO) which may have a positive effect on the motility of the intestines[10].

Similarly, significant findings of reduced pain and flatulence in IBS sufferers were found in another study of 60 patients who also received Proviva for four weeks, though the authors could not offer any real explanation for the improvement[11]. Both studies concluded that further research on larger cohorts is required.

Some studies revealed conflicting findings. For example, one uncontrolled, non-blinded, four week clinical trial of 12 patients found that *L. plantarum* 299v did not improve symptoms in patients with IBS[12]. Hydrogen production on the breath was just one of several parameters measured by end expiratory breath samples. Their findings for *L. plantarum* were not statistically significant compared to placebo.

Regulation of the Mucosal Immune System

An in vitro study in 2004 of inflamed human bowel tissue, gathered from seven patients during resection and treated with *L. plantarum* 299v, showed production of interleukin-10 (IL-10). The authors found that the ability of *L. plantarum* to induce human mononuclear lamina propria cells to produce cytokines such as IL-10 may provide this probiotic with a mechanism for reducing excessive inflammation at a mucosal level[13].

More recently, a study of the effects of *L. plantarum* on Caco-2 cells incubated with tumor necrosis factor–alpha (TNF-alpha) was completed. This study found that induction of epithelial barrier dysfunction and interleukin-8 (IL-8) secretion by TNF-alpha was inhibited by *L. plantarum*[14].

A study by Naruszewicz is also relevant. The six week study specifically studied the effects of *L. plantarum* 299v on cardiovascular risks in 36 smokers with no obvious disease symptoms[15]. The authors linked the anti-inflammatory effect of *L. plantarum* with propionic acid, also found in pharmaceutical non-steroidal anti-inflammatory drugs[16], which they found was generated from fermentation of dietary fibre in the colon. In this process, succinate is an intermediate product which is a precursor of propionate[17].

Decreases Fibrinogen and Lipid Levels

A 1997 study of diet supplementation with *L. plantarum* (Proviva) in 30 male subjects with elevated cholesterol found a statistically significant drop in fibrinogen levels after six weeks, but not the placebo group[18]. Cholesterol levels were also lowered in the study group.

The mechanism for lowering fibrinogen appears to be the modulation of immune response, which decreases synthesis of fibrinogen (an acute phase protein). No mechanism was discussed for the drop in cholesterol levels. While the findings are very important to cardiovascular disease, they are also relevant to inflammatory bowel conditions in dysbiosis, as minimisation of inflammation is one of the naturopathic treatments of first choice.

Rapid Inhibition of Many Pathogenic Microbes

L. plantarum's actions have been studied in vitro. It was found that *L. plantarum* produced antimicrobial compounds which were natural preservatives of very broad applications to the food and agriculture industries[19].

Some in vitro studies had positive findings for treatment of peptic ulcers. Rokka tested seven strains of the *L. plantarum* group which showed strong anti-*Helicobacter pylori* activity[20]. Another in vitro study tested a group of lactobacilli, including *L. plantarum* 299v, against six target pathogens which again showed strong anti-*Helicobacter* activity[21].

Listeria monocytogenes is a food-borne pathogen which is of concern because it grows in various foods at refrigeration temperatures, and in an acid pH environment. A study of the effect of *L. plantarum* on *L. monocytogenes* found that *L. plantarum* produces a bacteriocin which inhibits the pathogen.

The bacteriocin was inactivated by proteolytic enzymes, resistant to heat and stable over a wide pH range. As *L. plantarum* is produced naturally in many fermented foods, this finding has implications in prevention of food poisoning, and in the natural preservation of foods, particularly in the tropics[22].

Diarrhoea is often caused by *Clostridium difficile* infection, and can be recurrent due to overgrowth of the pathogen in the gut, particularly after prolonged antibiotic use. *L. plantarum* 299v, in a randomised, controlled trial for its effects on enhancing short chain fatty acids (SCFAs) in the gut, inhibited *C. difficile*.

Both groups began with *C. difficile*-associated diarrhoea. Ten patients received ongoing antibiotics with *L. plantarum* in a fruit drink, while nine were given the antibiotics and a placebo drink. The treatment group had higher levels of SCFAs and butyrate with no diarrhoea, compared to the placebo group who had a decreasing level of butyrate and continuing recurrence of diarrhoea[17].

Bacterial Translocation Risks Lowered

A prospective randomised trial of 172 patients following major abdominal surgery found that *L. plantarum* 299v was effective in reducing bacterial translocation[23]. Further positive findings showed in an Italian study of pancreatic necrosis in animals, where *L. plantarum* 299v was effective in reducing microbial translocation in experimental pancreatitis. Treatment with probiotic bacteria seems to be a promising alternative to antibiotic therapy[24].

Excellent Adhesion Characteristics

Studies have shown that *L. plantarum* is able to adhere to various surfaces where other probiotics do not. *L. plantarum* has been isolated from jejunal and rectal biopsies as long as 11 days after administration, indicating that this strain may be very well adapted to the human intestine[25,26].

Kinoshita carried out a Biacore analysis of human tissue for adhesion of various lactobacillus strains. Biacore is a Swedish company with technology to measure the binding and adhesion affinity of proteins and other molecules, based on the ability of the biomolecule of interest to interact with a specific binding partner. Of the various strains, *L. plantarum* LA318 showed the highest adhesion to human colonic mucin[27].

L. plantarum 299v also adheres to gut mucosa. While it adheres in healthy patients, a study of critically ill patients who had undergone antibiotic treatment showed promising results[25]. A total of 15 patients completed the controlled study, with 240 cultures performed from biopsies. In the treatment group, no bacterial growth was found, while the control group had growth in five of 32 samples. The study found that repeated administration was required, but that the adherence of *L. plantarum* to gut mucosa was effective[28].

Adherence to the oral mucosa was also demonstrated. Stjernquist-Desatnik measured the persistence of *L. plantarum* DSM9843 on the human tonsillar surface, and found that this strain does adhere well to the tonsillar mucosa. This has implications for the treatment of tonsillitis and the control of pathogenic organisms in the oral cavity[29]. Recent murine studies have also demonstrated similar effects which may have application to oral peptide delivery[30].

Increased Bioavailability of Iron

L. plantarum has also been found to increase absorption of iron (Fe) from normally low iron bioavailability meals. A study by Bering ran a cross-over trial of 24 healthy women and concluded that *L. plantarum* 299v increased non-haem Fe absorption from a phytate-rich meal in young women[31]. This indicated a specific effect of live *L. plantarum* 299v and not only an effect of the organic acids.

Their discussion explored the idea that colonisation of the duodenal mucosa by *L. plantarum* would create a greater concentration of lactic and other organic acids, decreasing pH and the chelation of iron, leading to increased absorption.

Conclusion

L. plantarum has the ability to adhere to the epithelial tissue and the mucosa, to generate anti-inflammatory substances such as propionic acid, to increase IL-10 synthesis and reduce pathogenic infections.

While more research is needed on this and other useful *Lactobacillus* strains, it is possible to conclude from current and past research that *L. plantarum* would be a safe and efficacious treatment for various types of intestinal dysbiosis, with beneficial effects to the immune and cardiovascular systems, with promise as a delivery mechanism for other therapeutic substances.

Summary of the Therapeutic Benefits of *Lactobacillus plantarum.*

Therapeutic Uses	Action/Mechanism of *Lactobacillus plantarum*
Benefits immune function	Stimulates GALT and other lymphoid tissues. Creates an acidic environment in the gut which is unfriendly to many pathogens. Enhances mucosal barrier function. Induces T-cell apoptosis in the lamina propria.
Relief from IBS/IBD symptoms	Catabolises arginine and generates nitrogen oxide to assist motility of intestines.
Inhibits inflammatory cytokines	Induces production of IL-10. Inhibits epithelial barrier dysfunction. Generates propionic acid, a powerful anti-inflammatory by fermenting dietary fibre in the colon.
Decreases fibrinogen levels	Modulates immune response so that production of acute phase proteins is not stimulated.
Rapid inhibition of pathogens	Competes with pathogens for receptor space on epithelial tissue, depleting the space for pathogens to grow. Shows strong anti-*Helicobacter pylori* activity. Produces a bacteriocin which inhibits *Listeria monocytogenes*. Reduces *Clostridium difficile*-associated diarrhoea by stimulating butyrate and short chain fatty acid production.
Lowers risks of bacterial translocation	Competes with pathogens for receptor space on epithelial tissue, depleting the space for pathogens to grow.
Potential delivery mechanism for therapeutic substances	Strong ability to adhere to various bodily surfaces including oral and gut mucosa.
Increases absorption of iron from low Fe-bioavailability meals	Colonisation of duodenum increases lactic and organic acids and decreases Fe chelation to assist absorption of iron.

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