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Efficacy of *Lactobacillus plantarum* in prevention of inflammatory bowel disease

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ABSTRACT

The incidence of inflammatory bowel disease (IBD) is increasing globally. Altered gut bacteria and bacterial metabolic pathways are two important factors in the initiation and progression of IBD. *Lactobacillus plantarum* is distributed in a variety of ecological niches, has a proven ability to survive gastric transit, and can colonize the intestinal tract of human and other mammals. Several studies have described the effects of *L. plantarum* consumption on human physiology. This review summarizes the safety and the effects of *L. plantarum in vitro* and in animal models for the prevention and management of IBD. *L. plantarum* modulates the ratio of Th1 and Th2 cells by stimulating the production of different inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1β, IL-6, IL-10, IL-12, and interferon-gamma. The blocking of cyclooxygenase-2 in Th1 also is an apoptotic inhibition mechanism. This overview of the molecular studies addresses the activity of *L. plantarum* in the human gut environment and its' potential for remission of IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a global health issue. The incidence of IBD is increasing in western and developing countries [1]. The disease includes two major types. Crohn's disease (CD) affects the entire gastrointestinal tract. Ulcerative colitis (UC) affects the colon and rectum. IBD mainly affects young adults, increasing morbidity and the risks of developing colorectal cancer, dysplasia, and high-grade dysplasia. The etiology of IBD is multifaceted including genetic predisposition, external environment, intestinal microbial flora, and immune responses [2].

Research on probiotics has centered on their beneficial modification of intestinal microbial flora and the improved immune responses in patients with IBD [3,4]. Probiotics have been refined several times and today's definition is "live microorganisms, which when consumed in adequate amounts, confer a health effect on the host" [5]. Probiotics must be safe, genetically stable, and able to survive passage through the gastrointestinal tract [6]. Most of the probiotic strains belong to *Lactobacillus* spp. and *Bifidobacterium* spp. This review summarizes the most relevant preclinical studies describing the effects of *L. plantarum* on IBD. Further clinical studies are needed to better confirm the role of *L. plantarum* in IBD.

2. *L. plantarum* strains

L. plantarum is one of the most widely-known *Lactobacillus* species because of its distribution in a variety of ecological niches such as vegetables, fermented foods, and healthy human intestinal mucosa. It belongs to the phylum Firmicutes, which is one of the two major phyla that dominate the intestinal microbiota. Over 186 *L. plantarum* strains have been reported [7]. Genomic diversity may explain the wide distribution of *L. plantarum*. *L. plantarum* is frequently used in the food and pharmaceutical industries as starter cultures or probiotics because of its health benefit to the host. *L. plantarum* has health-promoting effects including management of the fecal flora composition [8], prevention and treatment of irritable bowel syndrome [9], IBD [10], cancer [11], coronary heart disease [12], and certain gastrointestinal symptoms [13].

3. Mechanisms of action of *L. plantarum* relevant to IBD

The mechanisms of action of *L. plantarum* on IBD are complex and not well understood. It was hypothesized that *L. plantarum* modulates the intestinal microbiota and suppresses pathogens (Table 1). These mechanisms were described in many *in vitro* studies [14–16]. The second mechanism is immunomodulation of the immune response of gut-associated lymphoid and epithelial cells. The introduction of *L. plantarum* can produce a protective effect through the mediation of T

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Table 1
Results of *Lactobacillus plantarum in vitro* studies.

Bacterial strains	Host cells	Duration	Effects	Reference
L. plantarum 299	Lamina propria cells	48 h	Increase IL-10 cytokines production	[14]
L. plantarum CM	Epithelial cell (YAMC), macrophage (RAW 264.7), primary culture murine dendritic cells	4 h	Inhibit NF-κB in YAMC, inhibits release of MCP-1	[31]
L. plantarum	Caco-2 cells	24 h	Inhibits TNF-α production, increase SMCT1	[18]
L. plantarum L2	Caco-2 cells	24 h	Inhibits TNF-α production, increase SMCT1	[32]
L. plantarum K8	Human monocytic THP-1 cells	24 h	Inhibits TNF-α, IL-1β, NF-κB, enhance MAPKs, inhibits NOD2 production	[15]
L. plantarum K8	HT-29 intestinal epithelial cells	24 h	inhibition of NF-κB and MAPKs	[2]
L. plantarum MYL26	Caco-2 cells	10 h	Inhibition of TOLLIP, SOCS1, SOCS3, and IκBα expression	[19]
L. plantarum Lp62	HT-29 intestinal epithelial cells, J774 macrophages	2 h	Inhibition IL-8 production TNF-α, IL1- β, and IL-17 production	[33]

cells that include Th1 and Th2. *L. plantarum* modulates the balance between Th1 and Th2 by stimulation and production of different cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-10, IL-12, and interferon-gamma (IFN-γ). The blocking of cyclooxygenase-2 (COX-2) in Th1 also is an apoptotic inhibition mechanism. However, the interaction between *L. plantarum* and the immune system remains to be clarified. To date, only lipoteichoic acid and plantaricin EF produced by *L. plantarum* have been investigated. Moreover, other probiotics improve barrier function by inhibiting the apoptosis of intestinal epithelial cells and promoting the synthesis of proteins that are critical components of tight junctions [17]. However, this effect has not been reported of *L. plantarum* species.

4. *L. plantarum in vitro* studies

The effect of *L. plantarum* on IBD has been investigated in several *in vitro* studies. Some strains of *L. plantarum* were administered for between 2 and 48 h (Table 1). An early study Pathmakanthan, Li et al. [14] demonstrated beneficial immunomodulatory activity of *L. plantarum* 299 by increasing the production of the IL-10 cytokine in mononuclear cells (macrophages and T cells) derived from the inflamed colon of elder patients. Another study found that *L. plantarum* CM uniquely inhibits nuclear factor-kappa B (NF-κB) binding activity in response to TNF-α, which attenuates the release of monocyte chemotactic protein 1 (MCP-1), a proinflammatory chemokine and downstream gene target of NF-κB, and directly as well as reversibly inhibits proteasome function. *L. plantarum* CM inhibited NF-κB activation from TNF-receptor, MyD88-dependent, and MyD88-independent pathways, consistent with its downstream inhibitory effects on the proteasome in mice. Borthakur, Anbazhagan et al. [18] revealed that *L. plantarum* inhibited the TNF-α-induced production of MCP-1 in Caco-2 cells. A more recent study, Chiu, Lu et al. [19] provided evidence that *L. plantarum* MYL26 also impairs Toll-like receptor 4 (TLR4)-NFκb signal transduction through Tollip, SOCS-1, and SOCS-3 activation. In addition, lipoteichoic acid (LTA) derived from gram positive bacteria, observed that plays important roles in the maintenance of intestinal homeostasis [20]. *L. plantarum* LTA can significantly reduce NF-kappa B and mitogen-activated protein kinases [15], and the production of TNF-α and IL-1β [2]. These findings indicate an active role of the products released by *L. plantarum* against inflammation.

5. *L. plantarum in vivo* animal studies

In animal models, several studies used *L. plantarum* to induce spontaneous colitis in mice. The studies showed the beneficial effect of probiotics on gut bacteria (Table 2). Early studies in this field first confirmed that the decreased mucosal IL-12, IFN-γ, and immunoglobulin G2a had no protective effects [10]. Thus, the optimal dose and time of *L. plantarum* exposure is yet to be fully understood. In particular, the protection from visceral pain perception by *L. plantarum* was more evident in normal healthy mice induced with colorectal distension [21], supporting the hypothesis that *L. plantarum* can be protective against inflammation, although the mechanisms remain unknown. Subsequently, most studies showed that *L. plantarum* induces the secretion of IL-10 in splenocytes and mesenteric lymphocytes, blocks the expression of the proinflammatory cytokines, IL-1β, IL-6, TNF-α, COX-2, forkhead box P3 (Foxp3), suppressors of cytokine signaling 3 (SOCS3), and TLR4. Notably, only one study was conducted in gnotobiotic piglets [22]. After a 5-day treatment, *L. plantarum* Biocenol™ LP96 decreased IL-1a and IL-8 gene expression and increased IFN-c and cytokine IL-10 secretion. With respect to dosage, the most effective doses are 10^7–10^9 colony forming units/ml.

6. Is *L. plantarum* effective in humans?

To date, maintenance of remission and improved symptoms by probiotics in patients with UC, Crohn disease, and pouchitis has been the subject of several systematic reviews and meta-analyses [23]. However, data with *L. plantarum* are lacking. A recent study, Chermesh, Tamir et al. [24] used a combination of Synbiotic 2000 containing four probiotic bacteria and four prebiotics including *L. plantarum* 2362, *L. raffinolactis*, *L. paracasei* subsp. *paracasei* 19, *Pediacoccus pentoseceus*, β-glucans, inulin, pectin, and resistant starch in 30 patients with Crohn's disease. Unfortunately, Synbiotic 2000 showed no difference between the groups prior to surgery. Another study, Campieri, Rizzello et al. [25] assessed the impact of a probiotic preparation (VSL#3) combining eight different probiotic bacteria on 40 patients for 9 months. After 3 months of antibiotic treatment, a significantly higher recurrent Crohn's disease of 40% for the mesalamine therapy was evident compared with only 20% for those who received VSL#3. In a much smaller study of 29 consecutive patients, response to the IBD induction therapy was evident [26]. The emission rate seen in placebo and IBD therapy was lower than VSL#3 and IBD therapy (36.4% and 92.8%, respectively).

7. Safety of *L. plantarum*

L. plantarum has a long history of safe use. After decades of administration in food and clinical practice, there have been few reports of infections caused by *L. plantarum*. Some *L. plantarum* strains may potentially affect the elderly or individuals affected by deficiencies of their immune system, leading to the danger of blood clotting, resulting in aggregation of human platelets *in vitro* [27]. However, some studies have reported that *L. plantarum* does not cause infection when administered orally or via intravenous injection in mice [28,29]. Moreover, no bacteremia due to *L. plantarum* was evident in the post-market surveillance study [30].

8. Conclusion

For a decade, the use of probiotics has held promise for patients affected by IBD. Despite the effectiveness of *L. plantarum* against inflammation *in vitro* and in *in vivo* animal models, evidence supporting

Table 2
Results of *Lactobacillus plantarum in vivo* studies.

Bacterial strains	Mice strains	Daily dose	Duration	Effects	Reference
L. plantarum 299V	IL-10-/- mice	10^9 CFU/ml	4 weeks	decrease mucosal IL-12, IFN-γ, and immunoglobulin G2a levels	[10]
L. plantarum NCIMB8826	IL-10-/- mice	10^9 CFU/ml	4 days	no effects	[34]
L. plantarum NCIMB8826	Healthy mice	2×10^7 CFU/ml	9 days	decrease the activation-induced release of tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) from mesenteric T cells, interleukin 10 (IL-10) concentration in colonic tissue, increase IL-10 in splenocytes and mesenteric lymphocytes.	[21]
L. plantarum AK8-4	Healthy mice	10^8 CFU/ml	3 days	block the expression of IL-1β and TNF-α, cyclooxygenase-2 (COX-2) in the colon, block the expression of nuclear factor (NF-κB), toll like receptor 4 (TLR-4), decrease bacterial degradation activities of chondroitin sulfate and hyaluronic acid.	[35]
L. plantarum LP-Onlly	IL-10-/- mice	10^9 CFU/ml	8 weeks	decrease inflammatory scoring and histological injury, increase the numbers of beneficial total bifidobacteria and lactobacilli, decrease the numbers of potential pathogenic enterococci and *Clostridium perfringens*	[36]
L. plantarum K68	DSS-UC in BALB/c mice	10^9 CFU/ml	2 weeks	decrease TNF-α, IL-1β, and IL-6 production, decrease the expression of TNF-α, COX-2, forkhead box p3 (Foxp3), suppressors of cytokine signaling 3 (SOCS3), and TLR4	[37]
L. plantarum CGMCC 1258	IL-10-/- mice	10^9 CFU/ml	10 weeks	decrease IFN-c, TNF-α and MPO production	[38]
L. plantarum Lp91	IL-10-/- mice	10^9 CFU/ml	4 weeks	decrease expression of TNF-α and COX2, increase IL-10 production	[39]
L. plantarum Biocenol™ LP96	gnotobiotic piglets	10^9 CFU/ml	5 days	decrease expression of IL-1a and IL-8, increase IFN-c, IL-10 production	[22]
L. plantarum K8	Healthy mice	10^9 CFU/ml	2 weeks	decrease expression of TNF-α and IL-6	[40]
L. plantarum 21	Healthy mice	10^{10} CFU/ml	2 weeks	decrease TBARS, NO production, increase GSH concentration, decrease expression of IL-1β and TNFα, increase IL-10 production	[41]
L. plantarum LP3457	ZDF rat	10^8 CFU/ml	8 weeks	decrease IL-1β, IL-6, and CRP release, increase IL-10 levels	[42]
L. plantarum Sanriku-SU7	IBD Mouse	10^9 CFU/ml	4 weeks	recover the colon length	[43]
L. plantarum LP-Onlly	IL-10-/- mice	10^7 CFU/ml	4 days	Improve inflammation score and weight loss, regulate the abundance and diversity of gut microbiota	[44]
L. plantarum	BALB/c mice	10^9 CFU/ml	10 days	not protected against TNBS according lower proportions of *Mucispirillum*	[45]

human trials is limited. Most of the studies indicated that the administration of *L. plantarum* is clearly safe. However, the studies have varied in the experimental setup and quality due to the lack of a standard protocol. Better designed experiments with larger patient populations are needed to properly evaluate the beneficial effects of *L. plantarum* in IBD. Long-term studies are expected to contribute to the clarification of the mechanisms of the development of IBD. The availability of the complete genome sequence of *L. plantarum* makes it a suitable model to study the interaction between *L. plantarum* and host cells behind IBD. The hope is for a new generation of probiotics with a scientifically proven basis for the health benefits they provide.

Conflict of interest statement

We have no conflicts of interest to disclose.

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