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 microflora 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
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 the 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 elderly 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 chemoattractant protein 1 (MCP-1), a proinflammatory chemokine and downstream gene target of NF-κB, and directly as well as reversibly inhibits pro tease activity. 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, Abazhagan 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 Bio cenol™ LP96 decreased IL-1α and IL-8 gene expression and increased IFN-γ 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 recurring 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 vivo animal models, evidence supporting
human trials is limited. Most of the studies indicated that the administra-
tion of \textit{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
data are expected to contribute to the standard protocol. Better designed experiments with larger patient
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Conflict of interest statement
We have no conflicts of interest to disclose.

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