IRESPUB Journal of Life Sciences

Volume: 1 | Issue: 1 | SEP - OCT 2021 | Available Online: www.irespub.com

Influence of probiotics on inflammatory bowel disease

Claire W.E.
Independent researcher, Montpellier, France

ABSTRACT
Inflammatory bowel disease (IBD) is one of the crucial immune-mediated inflammatory diseases in which an imbalance occurs within the cellular inflammatory pathways. This article takes a look at what IBD is and the potentials of probiotic use in eradicating or curbing IBD, as well as its particular possible protective influence.

KEYWORDS
probiotics; inflammatory; immune-mediated

CORRESPONDING AUTHOR
Claire W.E.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) are a group of autoimmune conditions with similar inflammatory pathways of cellular homeostasis imbalance origin. These disorders include rheumatoid arthritis, IBD, psoriasis, ankylosing spondylitis, type 1 diabetes, and multiple sclerosis, and may afflict any system to cause morbidity, reduced quality of life, and premature death [1]. Other than usual biologic drugs developed to curb or eradicate IMIDs, which include Infliximab, Etanercept, Adalimumab, Rituximab, Abatacept, Efalizumab, Alefacept, and Anakinra, among others [1], probiotics were investigated for their potential immunomodulatory effects on IMIDs [2,3,4].

INFLAMMATORY BOWEL DISEASE COULD BE IMPROVED WITH PROBIOTICS

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder characterized by an imbalance between effector and regulatory mechanisms of the immune response [5]. The major representations of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which affect the gastrointestinal tract and, despite some similarities they present a variety of discrepancies regarding clinical manifestations and immune disturbances [6]. Despite the increasing prevalence rate of IBD, the exact biomechanism remains unknown. However, several studies have shown that the intestinal microbiota plays a crucial role underlying the disease because a disbalance (dysbiosis) of beneficial microbes in favor of harmful bacteria favors mucosal inflammation that progresses into IBD [7,8]. An active gut microbiota modulation might make use of antibiotics, diet, probiotics, or fecal microbiota transplant (FMT) for IBD prevention and treatment. Microorganisms involved in the pathogenesis of IBD and their mechanisms have been reviewed before [9,10], however it remains to be ascertained whether microbial dysbalances are cause or consequence of disease neither a causal link and a core microbiome associated with IBD has been defined. Table 1 is a collection of various findings on the effects of probiotics and their immunomodulatory mechanisms on inflammatory disease.

The treatment for IBD aims to control inflammation while maintaining and prolonging the episodes of remission, to which different therapeutic methods have been employed including aminosalicylates, corticosteroids, thiopurines, folic acid antagonists, and biological therapies [5]. The use of antibiotics and probiotics have been widely applied to modulate intestinal microbial populations for the sake of maintaining the native gut microbiota balance, except that long-term antibiotic uses tend to increase dysbiosis to negatively regulate immune responses [11]. Therefore, a regular administration of probiotics might contribute to endorsing the immune homeostasis by modulating microbial balance or by interacting with the gut mucosal immune system, explaining their potential effect in IBD. Supplementary probiotics can lead to the induction, maintenance of remission, and colitis-associated carcinoma chemoprevention, by targeting microbiome modulation [12].

The accumulation of probiotics in adequate number, and more especially in mixed strains will be beneficial to the host, as exemplified in the study of [14] who found out that probiotic cocktails could synergistically inhibit inflammation. Indeed, probiotics have been proposed as potential alternatives for IBD management. When dextran sulfate sodium (DSS)-induced colitis mice model was used to demonstrate the therapeutic effects of the probiotic ID-JPL934 mixture (Lactobacillus johnsonii IDCC9203, Lactobacillus plantarum IDCC3501, and Bifidobacterium animalis subspecies lactis IDCC4301) on IBD, there was a dose-dependent reduction of the disease activity index scores, improved colon length contraction and suppression of inflammatory lesions (such as infiltration of immune cells in mucosa and submucosa,

severe crypt damage, and loss of goblet and epithelial cells on the histological analysis) due to down-regulation of the expression of proinflammatory cytokines [15]. The findings showed both the immunomodulatory effect and therapeutic potential of the probiotic mix (ID-JPL934) for IBD.

TABLE 1: Pathogens involved in the pathogenesis of IBD and their mechanisms

Pathogen	Mechanism involved in pathogenesis
Protective role against IBD	
Intestinal parasites	Modulation of innate and acquired hosts' immune response which keeps mucosal inflammation in check
Helicobacter pylori	Increase in IL-18 production; Enhanced immune tolerance; Accumulation of suppressive regulatory T cells (Tregs); Reduces gastric secretion of leptin which has a proinflammatory effects
Predisposes for IBD	
Pseudomonas aeruginosa	Virulence-related attachment factor increases the paracellular permeability; Transform apical membrane of epithelial cells into basolateral membrane
Campylobacter	*Campylobacter* spp., in particular *C. concisus* increase the risk for IBD; Production of inflammatory cytokines; *C. concisus* has potential to invade Caco2 cells and secrete cytolethal distending toxin (CDT)-like toxin;
Fungal dysbiosis	Up-regulation of otherwise low level of TLR-4 expression in intestinal epithelium, which keeps the gut mucosal system in a state to tolerate commensal intestinal bacteria flora Anti-inflammatory effects in colitis models; Prevention of antibiotic-associated diarrhea, acute diarrhea, *Clostridium difficile* infection and enteral feeding-related diarrhea
Giardia duodenalis	Impairment of biofilm architecture; Destruction of mucus coating of the epithelium; Damage of epithelial cell barrier, physiology and survival; Induction of bacterial dysbiosis
Adherent–invasive *E. coli* (AIEC)	AIEC genes promote motility, capsule and lipopolysaccharide (LPS) expression, serum resistance, iron uptake, adhesion to and invasion of epithelial cell, biofilm formation, degradation of mucins protease; AIEC properties empower them to escape oxidative reactive species, tumor necrosis factor α (TNF-α) and other proinflammatory cytokines which enhances the dysbiosis; Exploitation of host mechanisms of apoptosis in favor of their own intracellular replication and prevention of antimicrobial response
Enterohepatic helicobacteria species (EHS), *i.e.* non-pylori *Helicobacter* members in Helicobacteraceae family	Regulates the switching of a 'healthy' colonic microbiota to IBD predisposing dysbiosis; Chronic infection with these species
Listeria monocytogenes	Weakens the defensive mucosal barrier, leading to invasive infection with *L. monocytogenes*

***Source**: [13]*

In another similar study, a probiotic cocktail dubbed Bifico (Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis) showed better down-regulation effects of proinflammatory cytokines (mainly IL-6 and C-reactive protein) as compared to mesalazine monotherapy [22]. Song et al. [23] described the impact of Bifico on the multiplication of lactobacilli in order to suppress cancer-related microbes, by down-regulating the production of CXC chemokines, the signaling protein molecules already implicated in intestinal inflammation and colorectal cancer. Although some studies demonstrated Bifico inhibitory effects on colon carcinogenesis in DSS-induced mice model [12], the validation challenge of its chemo-preventive effects on the carcinogenesis of IBD remains to be ascertained. Table 2 is a collection of various findings on probiotic strains involved in gut inflammation.

TABLE 2: Probiotic strains implicated in gut tissue inflammation and their outcomes

Probiotic strain/ administration	Study model	Outcomes/mechanisms
Lactobacillus gasseri SBT2055 (LG2055)	HFD mice fed with LG2055 (HFD-LG) for 21 weeks	HFD-LG intake significantly prevented HFD-induced increases in body weight, visceral fat mass, and the ratio of inflammatory-type macrophages to anti-inflammatory ones in adipose tissue. Elevations of intestinal permeability and anti-LPS antibody levels were significantly suppressed in mice fed the HFD-LG. Moreover, treatment with LG2055 cells suppressed an increase in the cytokine-induced permeability of Caco-2 cell monolayers. These results suggest that LG2055 improves the intestinal integrity, reducing the entry of inflammatory substances like LPS from the intestine, which may lead to decreased inflammation in adipose tissue.
Lactobacillus casei CRL431, CRL66, CRL72, CRL117, *L. acidophilus* CRL258, CRL1063, *L. fermentum* CRL1446, *Lactococcus lactis* CRL1434, *L. plantarum* CRL350, CRL352, CRL353, CRL355, *L. paracasei* CRL575, and *L. rhamnosus* CRL576	Mouse macrophage cell line RAW 264.7	Differential secretion profile of cytokines in macrophage cells induced by LAB strains was observed. In LAB-stimulated coculture cells (adipocytes and macrophages), differential production of leptin and cytokines were observed. Four clusters of strains were found related to their inflammatory profiles and leptin adipocyte production and leptin receptor expression in macrophages.
Lactobacillus plantarum HAC01	Diet-induced obesity (DIO) murine model	*L. plantarum* HAC01 reduced mesenteric adipose depot, the conjunctive tissue closely associated with the gastrointestinal tract, where lipid oxidative gene expression was upregulated compared to the control group. Metagenome analysis of intestinal microbiota showed that the strain HAC01 influenced specific bacterial families such as the *Lachnospiraceae* and *Ruminococcaceae* rather than the phyla Firmicutes and Bacteroidetes.

Probiotic strain/ administration	Study model	Outcomes/mechanisms
Lactobacillus kefiri DH5	*in vitro* screening and *in vivo* validation. Mice fed with 60% high fat diet (HFD-DH5)	Lactobacillus kefiri DH5 survived 100% in gastrointestinal environments. Body weight, epididymal adipose tissue weight, blood triglyceride and LDL-cholesterol levels were remarkably reduced in the HFD-DH5 group. Hepatic steatosis and adipocyte diameter also significantly reduced. *L. kefiri* DH5 upregulated PPAR-α, FABP4, and CPT1 expression in the epididymal adipose tissues, suggesting a reduction in adiposity by stimulating fatty acid oxidation.
Lactobacillus reuteri 263	Four groups of Sprague–Dawley rats (n=10/group) for 8 weeks	*L. reuteri* 263 increased oxygen consumption in white adipose tissue (WAT), improved obesity, serum levels of proinflammatory factors and antioxidant enzymes. It could have induced browning of WAT due to the higher mRNA levels of browning-related genes peroxisome proliferator-activated receptor-γ, PR domain containing-16, Pparγ coactivator-1α, bone morphogenetic protein-7 and fibroblast growth factor-21. *L. reuteri* 263 altered the expressions of genes involved in glucose and lipid metabolisms in WAT, including increasing the levels of glucose transporter type 4 and carbohydrate-responsive element-binding protein and decreasing the expression of Acetyl-CoA carboxylase-1.
Lactobacillus reuteri LR6	Protein energy malnourished (PEM) murine model comprising 30 male Swiss albino mice in five groups for 1 week	Probiotics feeding in PEM model as fermented product or bacterial suspension improved the intestinal health in terms of intact morphology of colonic crypts, normal goblet cells, and intact lamina propria with no inflammation in large intestine, absence of fibrosis, and no inflammation in spleen. The number of secretory IgA+ cells were also significantly higher.
Leuconostoc mesenteroides subsp. *mesenteroides* SD23	Mice randomly divided into four dietary groups: standard diet (C), HFD (OB), standard diet with L. mesenteroides SD23 (CP), and HFD with *L. mesenteroides* SD23 (OBP). Diets were maintained for 14 weeks	OBP reduced body weight, glucose, cholesterol, and leptin levels and improved glucose tolerance compared to OB. OBP also reduced liver steatosis, the number of larger adipocytes in adipose tissue, and reduced the villus height in the small intestine. OBP decreased expression of TNF-α and increased expression of IL-10 in liver.

Probiotic strain/ administration	Study model	Outcomes/mechanisms
Lactobacillus plantarum A29	3T3-L1 adipocytes cell lines and high-fat diet (HFD)-fed mice	Treatment of 3T3-L1 adipocytes with the cell-free metabolites of *L plantarum* inhibited their differentiation and fat depositions *via* downregulating the key adipogenic transcriptional factors (PPAR-γ, C/EBP-α, and C/EBP-β) and their downstream targets (FAS, aP2, ACC, and SREBP-1). Moreover, supplementation with *L plantarum* reduced the fat mass and serum lipid profile concurrently with downregulation of lipogenic gene expression in the adipocytes, resulting in reductions in the bodyweight of HFD-fed obese mice. It also attenuated the development of obesity in HFD-fed mice *via* the activation of p38MAPK, p44/42, and AMPK-α by increasing their phosphorylation. Further analysis revealed that the probiotic modulated gut-associated microbiota composition.
Lactobacillus amylovorus KU4	High-fat diet (HFD)-fed mice	*L. amylovorus* KU4 enhanced mitochondrial levels and function, as well as the thermogenic gene program (increased Ucp1, PPARγ, and PGC-1α expression and decreased RIP140 expression), in subcutaneous inguinal WAT of HFD mice.
Lactobacillus pentosus GSSK2, *Lactobacillus fermentum* PUM and *Lactobacillus plantarum* GS26A	High-fat diet (HFD)-fed Sprague Dawley rats for 12 weeks	*L. pentosus* GSSK2 showed maximum reduction in weight gain while maximum decrease in abdominal circumference, Lee's index, BMI and visceral fat deposition was observed in *L. plantarum* GS26A compared with HFD animals. Both *L. pentosus* GSSK2 and *L. plantarum* GS26A exhibited improved glucose tolerance, liver biomarkers, alleviated oxidative stress and restored the histoarchitechture of adipose tissue, colon and liver compared with HFD animals.
Lactobacillus brevis OPK-3 (KLAB)	Male C57BL/6 mice (n = 10) divided into four groups: normal diet with distilled water (NDC), high-fat diet with distilled water (HDC), high-fat diet with L-ornithine (OTC) or high-fat diet with KLAB	The KLAB supplement resulted in significantly lower body weight, lower epididymal fat tissue mass, and lower serum and hepatic TG levels than the HDC. KLAB supplementation improved serum cytokines, and real-time polymerase chain reaction (PCR) analysis showed significantly lower inflammatory cytokine mRNA levels in epididymal adipose tissue. These results suggest that the administration of KLAB inhibits the induction of inflammation in adipose tissue along with the inhibition of weight gain.

Probiotic strain/ administration	Study model	Outcomes/mechanisms
Lactococcus lactis NZ3900	*In vivo* study of Db/Db mice	Human fibroblast growth factor 21 (FGF21) expressing *L. lactis* strain was constructed and fed to Db/Db mice. Compared with the control group, the body weight of mice in the experimental group was significantly reduced, and the overall homeostasis was improved in mice treated with human FGF21. Moreover, the activity of brown adipose tissue was enhanced.
Lactobacillus rhamnosus PL60	Diet-induced obese (DIO) mice fed for 8 weeks	Reduction of body weight without reducing energy intake, and specific reduction of white adipose tissue (epididymal and perirenal). Also, apoptotic signals and UCP-2 mRNA levels increased in adipose tissue.
Lactobacillus paracasei CNCM I-4270 (LC), *L. rhamnosus* I-3690 (LR) and *Bifidobacterium animalis subsp. lactis* I-2494 (BA)	High-fat diet (HFD)-fed mice (10^8 cells day^{-1}) for 12 weeks	Each strain attenuated weight gain and macrophage infiltration into epididymal adipose tissue and markedly improved glucose-insulin homeostasis and hepatic steatosis.
Lactobacillus and *Bifidobacterium* strains	High-fat diet (HFD)-fed wild-type C57/BL6J mice for 14 weeks	The tested probiotic mixture significantly attenuated the increase in body weight, serum glucose concentration and insulin resistance induced by the high-fat diet. It significantly reduced the up-regulation of expression of several genes encoding pro-inflammatory adipokines and leukotriene pathway enzymes (CCL-2, IL-6 and leukotriene C4 synthase in adipose tissue, leukotriene C4 synthase and leukotriene A4 hydrolase in the gut). Finally, it also significantly counteracted the down-regulation of adipose tissue gene expression related to the anti-inflammatory adipokine adiponectin.
Lactobacillus casei CRL 431	High-fat diet (HFD)-fed BALB/c mice for 60 days	*L. casei* CRL 431 exerted an anti-inflammatory response in mice fed an HFD, evidenced mainly by decreasing proinflammatory cytokines, such as interleukin (IL)-6, IL-17, and tumor necrosis factor-α. Also, there were fewer immune-infiltrating cells in the liver of mice that received the HFD and decreased secretion of MCP-1 by the adipocytes.
Bifidobacterium bifidum, Lactobacillus casei, and *L. plantarum*	High-fat diet (HFD)-fed C57BL/6N mice for 6 weeks	Reduction of HFD-induced body weight gain, hyperlipidemia, liver fat accumulation, levels of serum alanine aminotransferase (ALT), lipopolysaccharide (LPS), liver tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS) production.

Probiotic strain/ administration	Study model	Outcomes/mechanisms
Lactobacillus rhamnosus, L. acidophilus and *Bifidobacterium bifidumi*	High-fat diet (HFD)-fed Swiss mice for 5 weeks	The probiotics reverse HFD induced huge alterations in gut microbiota accompanied by increased intestinal permeability, LPS translocation and systemic low-grade inflammation, resulting in decreased glucose tolerance and hyperphagic behavior. The probiotics also induced an improvement in hypothalamic insulin and leptin resistance.
Bifidobacterium longum	66 patients received *B. longum* for 24 weeks	Significant group differences in the AST, LDL cholesterol, CRP, TNF-α, HOMA-IR, serum endotoxin, and steatosis
Lactobacillus rhamnosus CGMCC1.3724 (LPR)	Obese men and women for 24 weeks	Changes in body weight and fat mass during the weight-maintenance period were similar in men in all groups. LPR-induced weight loss in women was associated not only with significant reductions in fat mass and circulating leptin concentrations but also with the relative abundance of bacteria of the *Lachnospiraceae* family in faeces.
Lactobacillus acidophilus La5*, Bifidobacterium* BB12, and *Lactobacillus casei* DN001	75 healthy overweight and obese individuals for 8 weeks	A reduction in BMI, fat percentage, and leptin level, and gene expression of ROR-γt was observed. The reduction in serum levels of hs-CRP was also evident.
Bifidobacterium lactis HN019	51 patients with metabolic syndrome (MetS) were selected and divided into a control group (n = 25) and a probiotic group (n = 26) who consumed fermented probiotics for 45 days	Daily ingestion of 80 mL fermented milk with 2.72×10^{10} cfu of *B. lactis* HN019 showed significant reduction in BMI, total cholesterol, and low-density lipoprotein compared with baseline and control group values. Furthermore, a significant decrease in tumor necrosis factor-α and interleukin-6 proinflammatory cytokines was observed.

Source: *[13]*

VSL#3 is a famous probiotic mix supplement (L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp.bulgaricus, B. longum, B. breve, B. infantis, and Streptococcus salivarius subsp. thermophiles) widely investigated to help in this regard. It is also used to induce remission in mild to moderate active Ulcerative colitis (UC) [16]. The VSL#3 cocktail reduced clinical scores after daily ingestion of 4 sachets containing each 9 × 1011 viable lyophilized bacteria by patients [16]. Patients also had an earlier remission response, better efficacy in symptoms, endoscopic, and histologic evaluation [17]. When VSL#3 dosage of 3.6 × 109 CFU/day was later used for 8 weeks, by 65 UC patients, the probiotic mix was still found though marginally effective but superior in clinical scores reduction such as UC disease activity index (UCDAI) [18].

Unlike UC, Crohn's disease (CD) has not elicited similar efficacy from VSL#3 probiotic cocktail or other probiotics. For instance, while it was demonstrated that after 90 days of administration of the probiotic mix by CD patients who underwent ileocolonic resection and re-anastomosis, their inflammatory cytokine levels reduced as compared to placebo [19], but oral treatment with L. johnsonii, LA1 Nestle (1010 CFU/day) and LGG (2 × 109 CFU/day) were not effective to prevent early endoscopic recurrence at 12 weeks or 6 months after ileo-caecal resection in CD patients [20]. Interestingly, a synergistic combo of B. longum and the prebiotic Synergy 1 reduced the activity and histological scores of CD, as well as down-regulated TNF-α expression on intestinal mucosa after ingestion by human volunteers for 3 months; yet without substantial changes after 6 months [21].

This also suggests a noteworthy limitation associated with probiotic treatment in IBD and its effects on CD.

Inconsistencies of therapeutic response in patients with distinct clinical entities suggest a sophisticated strategy to distinguish patients with proper and unique phenotypes who may benefit from supplementary probiotics [12]. Irrespective of the probiotic organism used in IBD treatment, their efficacy against disease relapse and improvement of clinical and histological conditions is promising but needs to be further deciphered. The limitation is that the findings positively gear towards UC, rather than CD patients. Therefore, investigation of the disparities and conditions warranting the discrepancies on the same probiotics interventions in UC and CD is highly recommended.

CONCLUSIVE REMARKS

There is a huge potential in the protective effect of probiotics on inflammatory bowel diseases amongst other immune mediated chronic diseases such as UC and CD.

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