# *Lactobacillus* as Probiotics against Different Health Issues

Subjects: Neurosciences

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Probiotics are microorganisms involved in the growth and development of other microorganisms, derived from a Greek word meaning "for life". The well-accepted definition of probiotics was given by Fuller, according to which "Probiotics are live microbial feed supplements which beneficially affect the host animal by improving microbial balance" . WHO redefines the term as “live microorganisms which when administered in adequate amounts confer a health benefit on the host". The concept of probiotics was introduced by Elie Metchnikoff in 1907. He introduced the idea that food microbes can modify the normal flora of the human body and that replacement of harmful microbes with beneficial microbes is possible. Based on this concept, the term “probiotics” was defined in different ways. The term probiotic was first used by Lilly and Stillwell in 1960. In 1857, Pasteur discovered the first bacteria that were lactic acid-producing. Then in 1878, Lister also separated and recognized these lactic acid bacteria. In 1889, Henry Tissier discovered Bifidobacterium and also found that these bacteria could be used to treat acute gastroenteritis caused by an imbalance of harmful microorganisms. The idea that probiotics could be friendly and used to treat certain intestinal diseases was also reported and presented by Tissier, in 1906. The most widely used microorganism as probiotics is *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*. *Lactobacillus* and *Bifidobacterium* are Gram-positive rods that are obligated facultative anaerobes and *S.boulardii* is a yeast.

Keywords: probiotics ; Lactobacillus probiotics ; Alzheimer’s disease ; depression

## 1. Effects on Gastrointestinal Tract (GIT)

*Lactobacilli* strains show good adherence to the epithelial cell layer of GIT and are thus protective. They show their effectiveness in intestinal diseases, travelers’ diarrhea, antibiotic-associated diarrhea, bowel disorders, allergy and so on. Probiotic Lactobacillus strains act in different ways by binding the epithelial cell surface of the host to minimize the harmful effects of bacterial enteric pathogens, by enhanced production of the protective mucus layer, by downregulation of inflammatory mediators and so on. [1]. They can induce the secretion and production of mucins from human epithelial cells of the intestine. This results in an increased production of mucus layer surrounding the gut that is protective and also enhances the removal of enteric pathogens [2]. Probiotic *Lactobacillus* strains also show an effective role in the prevention of adherence to the epithelial layer of the gastrointestinal tract. A study performed by Johnson-Henry KC et al. evaluated this effect and concluded that all *Lactobacillus helveticus* strains block the adherence of Escherichia coli with an epithelial barrier, which is an initiative of bacterial pathogenesis. This occurs via surface-layer proteins (slps) of the microbe [3]. Probiotic *Lactobacillus* strains can stimulate the expression of β-defensin mRNA and so have a valuable role against infectious enteritis [4][5]. The direct effect of *Lactobacillus* on the epithelial layer is also reported. Probiotic *Lactobacillus* strains decrease the production of TNF-α and inflammatory cytokines to enhance the integrity of the epithelial barrier. They may also increase the integrity and tightness of the epithelial barrier by inhibiting any kind of change in tight junction proteins of the GI tract [6]. They have a role in the reduction of apoptosis which is important to modify barrier resistance against proinflammatory cytokines [7]. Diarrhea may occur due to pathogenic microorganisms such as *Clostridium*, *Salmonella*, *Shigella*, *Rotavirus* and so on, variations in the immune system, and may also be due to physiological causes. These causes may have a link with an imbalance in human normal flora and can be treated with normal flora modifications. Approximately 50 to 80% of cases of traveler’s diarrhea are bacterial, while the remaining is due to virus and protozoa. It is reported that different *Lactobacillus* strains are effective in the reduction and prevention of traveler’s diarrhea as well as antibiotic-associated diarrhea. Randomized controlled trials performed by Hilton et al. show that ingestion of probiotic *Lactobacillus strain* is effective in reducing the daily risk of diarrhea development [8]. Different *Lactobacillus* strains, such as *L. rhamnosus*, *L. bulgaricus*, *L. acidophilus*, and *L. reuteri* along with *Bifidobacterium*, show their effectiveness in reducing the period of rotavirus infection in pediatric diarrhea [9]. Acute diarrheas in children are caused by rotavirus. A multicenter trial performed by Guandalini et al. (2000) examined the effect of oral rehydration

solution containing *Lactobacillus rhamnosus* strain GG in comparison to simple ORS in pediatric diarrhea. It was concluded that administration of oral rehydration solution containing *Lactobacillus rhamnosus* strain GG in children suffering from acute diarrhea is safe. Compared to the ORS, it results in lowering the duration of the diarrhea period along with faster recovery and discharge from the hospital [10]. A meta-analysis performed by VanNiel et al. (2002) examined the safety and efficacy of probiotic *Lactobacillus* strain therapy in children suffering from acute infectious diarrhea. The results of the meta-analysis also confirm the safety, effectiveness, reduced duration, and reduction in stool per day [11]. Another probiotic strain of *Lactobacillus*, i.e., *Lactobacillus reuteri* strain, when administered with zinc showed a beneficial role in the maintenance of acute pediatric diarrhea. This was verified by a randomized, double-blind trial in 2018 [12]. Shornikova AV et al. performed a randomized trial to check the effectivity of the *Lactobacillus reuteri* strain in *Rotavirus* infection. After administration, the *Lactobacillus reuteri* strain successfully colonizes the GIT, effectively reducing the watery diarrheal duration caused by *Rotavirus* [13]. Some chronic conditions of the gastrointestinal tract involve Crohn's disease and ulcerative colitis. The symptoms of these conditions include inflammation and diarrhea. In the case of Crohn's disease, inflammation occurs in the colon, mucosa, and submucosa, while in the case of ulcerative colitis it remains only in the mucosa and submucosa. The combination of both of these chronic conditions is called inflammatory bowel disease (IBD). VSL # 3 sachet is a combination of 900 billion lyophilized bacteria including four strains of *Lactobacillus*, i.e., (*L. casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*), three strains of *Bifidobacterium* i.e., (*B. longum*, *B. breve*, and *B. infantis*), and one strain of *Streptococcus salivarius* subsp. *thermophilus.* It was concluded that *Lactobacillus* along with other probiotics species is effective in the treatment and maintenance of the remission state of Crohn's disease and ulcerative colitis [14]. Irritable bowel syndrome (IBS) is another chronic condition of GIT affecting the large intestine. Symptoms include abdominal pain, cramps, diarrhea, bloating, and gas. A randomized blinded trial involving 50 adults with IBS concluded that there is a beneficial and effective role of *lactobacillus Plantarum* in reducing pain in patients suffering from IBS [15].

## 2. Lactobacillus as Immune Modulators

*Lactobacilli* can influence the innate as well as adaptive immune system by acting as phagocytic cells, natural killer cells, and cytotoxic T cells, as a result enhancing the production of IgA antibodies and activating Toll-like receptors. This occurs by attachment with pattern recognition receptors (PRR) on immune cells as well other tissues of the intestinal epithelium. Attachment of opportunistic pathogens to epithelium is also prevented via the production of lactic acid and reactive oxygen species [16]. Different strains of probiotics show variable results based on the type of microorganism used as probiotics, dose, route of administration, and immunological condition of the patient. Different species of *Lactobacillus* are used to evaluate their effectiveness in allergic rhinitis. They show beneficial results due to their immunomodulation properties [17]. A study performed on 31 adult volunteers suffering from allergic rhinitis shows the beneficial role of *Lactobacillus paracasei*. The level of cytokines was measured in nasal fluid, and it was concluded that *Lactobacillus paracasei* can lower the amount of IL-5, IL-8, and IL-10 that are the immune markers [18]. Another report shows that oral administration of *Lactobacillus plantarum* results in the amelioration of symptoms of Birch pollen-induced allergic rhinitis by boosting Th-1 type immune response. This results in the recovery of the Th1/Th2 balance [19]. Anti-inflammatory properties of *Lactobacillus* species are also reported. By activation of Treg cells and dendritic cells, they are used to prevent and treat inflammation related diseases [20]. A study was conducted to elucidate the induction of oral tolerance in the case of rheumatoid arthritis with the help of *Lactobacillus casei*. It was concluded that this species of *Lactobacillus* proved to be effective in the potentiation of oral tolerance via up-regulation of foxp3 expression along with downregulation of Th1 type-based immune response [21]. In 2008, Jae-seon et al. elucidated the beneficial role of *L. casei* in an autoimmune disorder called rheumatoid arthritis. They deduced that *L. casei* can efficaciously lower the level of proinflammatory cytokines along with suppression of Th1 mediated cellular as well as humoral immune response [21].

## 3. Roles of Lactobacillus against Skin Diseases

Lactic acid bacteria can reduce the inflammatory response and hypersensitivity reactions by reducing the inflammatory mediators i.e., cytokines.

The healing of a wound involves three main steps

- Inflammatory response
- Cell multiplication
- Remodeling of extracellular matrix

Atopic dermatitis is a chronic inflammation of the skin. It may result in a reduced antimicrobial response. *Lactobacillus* has a beneficial role in the treatment of atopic dermatitis with the help of its immunomodulatory role as shown by the following studies [22][23].

## 4. Metabolic Disorders

Metabolic syndrome is a cluster of conditions that occur together, increasing your risk of heart disease, stroke, and type 2 diabetes. The cardinal features of metabolic syndrome are elevated blood pressure, dyslipidemia, obesity, and an increase in fasting blood glucose. Different clinical trials show a link between human intestinal normal flora and metabolic syndromes such as obesity, diabetes and so on. A report by Larsen et al. shows that changes in gut microbiota including *Lactobacillus* species may result in improved glucose tolerance, which is the main cause of diabetes mellitus. How glucose tolerance was improved was not shown in the given article, which may be considered for future studies. It was also suggested that by regulating the gut flora there is reduced insulin resistance and overall reduced symptoms associated with diabetes mellitus type-2 [24].

## 5. Effects of Lactobacillus against Neurodegenerative Diseases

### 5.1. Microbiota–Gut–Brain (mgb) Axis

Normal flora of the GIT tract can affect and influence the functioning and development of the human brain [25]. This occurs with the help of regulatory signals among both the gut and the brain. CNS can affect the normal flora of GIT via the autonomic nervous system and hypothalamus-pituitary-adrenal association [26][27]. HPA-axis is a response system for stress that is activated by some physical or psychological stresses. As a result of stress, the hypothalamus produces and discharges a corticotrophin-releasing hormone that results in the induction of the pituitary gland and adrenal cortex to secrete adrenocorticotrophic hormone and glucocorticoids, respectively [28]. Alteration in HPA-axis, and the microbiome is one of the causes implicated and reported in affective disorders including depression, anxiety, and bipolar disorders [29]. It is reported that the altered HPA-axis can be regained by the use of Lactobacillus species. In this case, Lactobacillus reduced the permeability of the intestine and makes the HPA-axis functional [30]. Brain-derived neurotrophic factors (BDNF) are involved in brain plasticity and N-methyl-D-aspartate (NMDA) is a glutamate receptor associated with memory and synaptic plasticity. Decreased activities of both of these are reported in stressed mice. To reduce stress and anxiety-like behavior, these changes must be reversed. *Lactobacillus farciminis* treatment can result in attenuation of the hypothalamic-pituitary-adrenal (HPA) axis to reduce the stress induced in mice. As a result, it reduces the increased level of ACTH, cortisone, as well as CRF expression in the hypothalamus [31]. A study by S. Liang et al. found that *Lactobacillus helveticus* treatment shows similar results. Its chronic administration results in beneficial effects such as anti-anxiety, antidepressant, improvement in memory, and decrease in CORT and ACTH [32]. The vagus nerve also has a role in this association. *Lactobacillus* can influence the vagus nerve and results in stimulation of GABAergic receptors transcription. In this way, it induces marked changes in behavioral and psychological responses. By modulation of host immune system and by prevention of inflammatory responses *Lactobacillus* can prevent immune-mediated diseases.

### 5.2. Protective Effects of Lactobacillus against Multiple Sclerosis

An autoimmune disease triggered by aberrant T cells mediated immune response against myelin antigens. It is characterized by axonal damage, demyelination, and progressive neurological disability [33][34]. In 2018, Stephanie K. Tankou et al. evaluated the effect of probiotics including *Lactobacillus* species on gut microbiota and peripheral immune function in patients with relapsing-remitting multiple sclerosis and healthy controls. They concluded that probiotic administration results in synergistic effects with already given MS therapies by modulating immune response and also by reducing the expression of MS risk allele HLA-DQA [35]. Yuying Liu et al. in 2019 evaluated the effect of *Lactobacillus reuteri* in mice models of experimental autoimmune encephalomyelitis (EAE). This model is widely used to study multiple sclerosis and this is based on Th1 and th17 cells. They concluded that treatment with *Lactobacillus reuteri* results in a reduction of Th1/ Th17 cells and their amalgamated cytokines IFN-γ/IL-17 in EAE. They added that probiotic *L. reuteri* treatment results in changed gut microbiota to regulate immune responses in this EAE model of MS [36]. In 2018, Maya Yamashita et al. evaluated the effect of *Lactobacillus helveticus* by IP administration in a mice model of EAE and concluded that it results in reduced frequency and a clinical score of disease. Moreover, it significantly reduced IL6 production and also down-regulated Th17 differentiation and infiltration of the spinal cord, consequently relieving EAE symptoms [37]. Zohre Salehipour et al. used the combination of *Lactobacillus Plantarum* and *Bifidobacterium* species to evaluate their therapeutic potential in the EAE model of MS in 2017. It was concluded that this combination modulates immune response by enhancing anti-inflammatory cytokines while decreasing disease associated cytokines. Mononuclear infiltration of CNS, which is a pathological feature of MS, was also significantly reduced by this combinational approach.

Moreover, this combination effectively diminished EAE development as well as fortifying the regulatory T- cells' polarization [38]. Kobayashi et al. indicated in their work that *Lactobacillus Casei* administration results in up-regulation of IL-17 and IFN-γ on days 7 and 12. On day 7 levels of IL-10, CD4+ CD25+ T-reg cells up-regulated. Contradictory to this, on day 12 level of CD8+ T-cells decreased in the spleen [39]. A randomized, placebo-controlled trial was conducted by Kouchaki E et al., to evaluate the clinical and metabolic effects of probiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium*, and *Lactobacillus fermentum* in patients with MS. They concluded that this combination showed favorable effects on the expanded disability status scale (EDSS), parameters of mental health and inflammation, insulin resistance markers, and MDA levels [40].

### 5.3. Protective Effects of Lactobacillus against Alzheimer's Disease

AD is a neurodegenerative disorder characterized by a prominent symptom of dementia in older people with progressive loss of cholinergic neurons. The prevalence of the disease was 44 million people in 2015. Neuropathological characteristics of AD are due to the accumulation of extracellular β-amyloid protein, senile plaques, and neurofibrillary tangles intracellularly [41][42][43][44][45]. Different species of *Lactobacillus* were evaluated to find any effectiveness in AD. Most notable of these are as follows.

A diagram showing the rescuing effects of *Lactobacillus* against Alzheimer-associated neurodegenerative conditions. Here, it is presented that a diet with probiotics may reduce neurodegeneration by regulating the accumulation of Aβ, reducing the expression of inflammatory mediators, and enhancing cognitive functions.

### 5.4. Protective Effects of Lactobacillus against Depression

Depression is a common psychological disorder that affects 350 million people worldwide of all ages, disturbing the social functioning and quality of life of patients [46][47]. Depression is a serious, recurring, lethal, and debilitating neuropsychological disorder [48][49], characterized by loss of interest, low mood, feeling of guilt, hopelessness, change in sleep and appetite, sexual dysfunction and so on. [50]. It is the leading cause of disability and a major contributor to the global burden of disease, affecting women twice more than men (World Health Organization, 2020). Current antidepressant treatment focuses on the amending activity of a neurotransmitter in the brain. However, these treatments take weeks to produce an antidepressant effect, with severe adverse effects such as headache, agitation, nausea, sexual dysfunction, and sedation [51]. Different species of probiotics are utilized to find any effectiveness in amelioration of disease symptoms including many strains of *Lactobacillus*.

### 5.5. Protective Effects of Lactobacillus against Parkinson's Disease

PD is a neurodegenerative disorder that is mainly due to the loss of dopaminergic neurons in substantia nigra pars compacta, characterized by various motor as well as non-motor symptoms [52]. It is predicted that the disease will affect more than 10 million people worldwide by the year 2030 [53]. The disease is characterized by the aggregation of α-synuclein/Lewy bodies in the substantia nigra of the central nervous system. α-synuclein pathology is considered to be initiated in the enteric nervous system and then via vagus nerve spread in the central nervous system [54]. The pathology of PD is thought to be associated with oxidative stress [55], toxic agents, metabolic disorders, genetic factors, and neuroinflammation [56]. Gut microbiota plays important role in PD pathogenesis. Results of multiple studies showed that dysbiosis of gut microbes including *Lactobacillus*, *Bifidobacterium* and so on. is related to disease pathology via the gut-brain axis [57][58][59][60]. In 2020, Liao et al., evaluated the effect of *Lactobacillus Plantarum* PS128 in MPTP induced Parkinson's disease rodent model. They concluded that supplementation with PS128 significantly alleviated the motor deficit, corticosterone elevation, nigrostriatal, and striatal dopaminergic loss. It also attenuated oxidative stress and neuroinflammation. The fecal analysis showed that the level of *L. Plantarum* was enhanced with a reduced level of *Enterobacteriaceae*. Glial cell hyperactivation was reduced. Norepinephrine and neurotrophic factors were enhanced [61].

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