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Probiotic Applications in Autoimmune Diseases

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Abstract

Evidences from animal models and humans have implied the involvement of alterations in the gut microbiota in development of some autoimmune diseases. Dysbiosis observed in autoimmune diseases is associated with decreased bacteria function and diversity, impaired epithelial barrier function, inflammation, and decreased regulatory T cells in the gut mucosa. Studies suggest that probiotics influence systemic immune responses, ensure the homeostasis of the healthy microbiota in the intestinal mucosa, and could, therefore, be used as adjuvant therapy to treat immune-mediated diseases. The mechanisms proposed to achieve this include mucus secretion; antimicrobial peptide production; the maintenance of the function of the gastrointestinal-epithelial barrier, ensuring adequate interactions between the gut microbiota and the mucosal immune cells; and, finally, helping the activation of host immune system in response to pathobionts. Here, we described several reports concerning probiotic applications in several animal models of autoimmune diseases and data of the main clinical trials concerning the applicability of probiotics in type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus.

Keywords: dysbiosis, barrier disruption, inflammation, autoimmunity, probiotics

1. Introduction

Thousands of years ago, Hippocrates, father of medicine, coined the concept that food would serve as medicine and postulated, "Let food be thy medicine, and let medicine be thy food." Nowadays, the concept of food as a medicine appeared as functional foods, referring to any foods or ingredients with nutritional value and that promote a health benefit to the host [1]. Probiotics, prebiotics, and synbiotics are the most popular ingredients used as functional foods and dietary supplements [2].

According to the World Health Organization (2002) and the International Scientific Association for Probiotics and Prebiotics (2013), probiotics is defined as "a live organism, which provides a benefit to the host when provided in adequate quantities" [2–4]. Most commonly used probiotic includes lactic acid-producing bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* species. Non-lactic acid-producing bacteria, such as *Bacillus* and *Propionibacterium*, species and nonpathogenic yeasts, including *Saccharomyces boulfecesardii*, non-spore-forming and non-flagellated rod or coccobacilli, and some helminths, such as *Trichuris suis ova*, could also been used as probiotics [5, 6]. Some of these strains were chosen based on origin, in vitro adherence to intestinal cells, and survival during passage through the gastrointestinal tract [5].

2. Intestinal dysbiosis in autoimmune diseases

Evidence from animal models has implied the involvement of intestinal dysbiosis in development of some autoimmune diseases [24–26]. Dysbiosis observed in autoimmune diseases is associated with decreased bacteria function and diversity, impaired epithelial barrier function, inflammation, and decreased regulatory T cells (Treg cells) in the gut mucosa [7, 8]. The hypotheses proposed to link dysbiosis with autoimmune diseases include molecular mimicry, bystander T cell activation, and the amplification of autoimmunity by pro-inflammatory cytokines, which is elicited by dysbiotic gut microbiota [9]. In 2016, Lerner and colleagues, from Institute Wendelsheim, in Germany, proposed the posttranslational modification of luminal proteins, promoted by enzymes from altered microbiota, which modify substrates in a different way than performed under homeostatic conditions. The defective posttranslational modification of luminal proteins could generate neo-epitopes that may become immunogenic and induce systemic autoimmunity and trigger autoimmune diseases [9].

Here, we described several reports concerning probiotic applications in several animal models of autoimmune diseases and data of the main clinical trials concerning the applicability of probiotics in type 1 diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus.

3. Probiotics in autoimmune diseases

Studies suggest that probiotics influence systemic immune responses, ensure the homeostasis of the healthy microbiota in the intestinal mucosa, and could, therefore, be used as adjuvant therapy to treat immune-mediated diseases [4]. The mechanisms proposed to achieve this include mucus secretion, antimicrobial peptide production, the maintenance of the function of the gastrointestinal-epithelial barrier, decreasing oxidative stress, ensuring adequate interactions between the gut microbiota and the mucosal immune cells, and, finally, helping the activation of host immune system in response to pathobionts [10].

3.1. Type 1 diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by autoimmune reactions against the insulin-secreting pancreatic β-cells, resulting in exogenous insulin dependence

to control blood glucose levels [11]. The etiopathogenesis may involve the interaction of pre-disposing human leucocyte antigens (HLA) alleles and environmental factors, such as viral infections, vitamin deficiencies, and disruption of the gut microbiota [12]. According to the International Diabetes Federation, more than 96,000 children and adolescents under 15 years will be diagnosed with T1D annually worldwide, and this number is estimated to be more than 132,600 when the age range extends to 20 years [13].

The role of the gut microbiota in T1D etiology has been the subject of research over the last decade to clarify its role in disease development and determine preventive approaches, such as diet manipulation and probiotic administration [12]. Several researches have been carried out to verify whether the administration of probiotics may improve the prognosis of diabetes through modulation of gut microbiota. Probiotics have been identified as effective adjuvants in insulin resistance therapies [14–16]. This health claims apparently stem from the ability of probiotics to secrete antimicrobial substances, competing with other pathogens, strengthening the intestinal barrier, and modulating the immune system [17].

3.1.1. Probiotics in animal models of autoimmune diabetes

The intestinal microbiota might modulate the autoimmune T1D pathogenesis via two mechanisms, recently proposed by Knip and Honkanen [18], from the University of Helsinki, in Finland. In the first phase, an impaired tolerance process in infancy leads to a susceptibility to develop autoimmune diseases, such as T1D, and may result in appearance of autoreactive T cells and autoantibodies. At the second phase, the intestinal dysbiosis predisposes children with genetic susceptibility and positive autoantibodies to develop clinical disease [18].

The inflammasome signaling components are innate immune sensors that are highly influenced by the gut environment and play pivotal roles in maintaining intestinal immune homeostasis [19]. Previous studies suggested the involvement of the gastrointestinal tract in the pathogenesis of islet autoimmunity. Thus, the modulation of gut-associated lymphoid tissue may represent a means to affect the natural history of the disease. Oral administration of probiotics can modulate local and systemic immune responses [20].

The earliest study to evaluate the efficacy of probiotics in T1D was published in 2005. The study performed by Calcinaro and colleagues, in the University of Perugia, in Italy, investigated the effects of oral administration of the probiotic VSL#3 in nonobese diabetic (NOD) mice development. VSL#3 was administered to female NOD mice three times a week starting from 4 weeks of age. Early oral administration of VSL#3 prevented diabetes development in NOD mice. Protected mice showed reduced insulitis and a reduced β-cell destruction. Prevention was associated with an increased production of interleukin (IL)-10 from Peyer's patches and the spleen and with increased IL-10 expression in the pancreas, where IL-10-positive islet-infiltrating mononuclear cells were detected. The protective effect of VSL#3 was transferable to irradiated mice receiving diabetogenic cells and splenocytes from VSL#3-treated mice. Oral VSL#3 administration prevents autoimmune diabetes and induces immunomodulation by a reduction in insulitis. These data provide a sound rationale for future clinical trials of the primary prevention of T1D by oral VSL#3 administration [21].

Eleven years later, Kim and colleagues evaluated the effects of *Bifidobacterium lactis* HY8101 on insulin resistance induced by tumor necrosis factor-alpha (TNF-α) in the skeletal muscle

cell from L6 rat. The treatment using HY8101 improved the insulin-stimulated glucose uptake and translocation of GLUT4 via the insulin signaling pathways AKT and IRS-1(Tyr) in TNF-treated L6 cells. HY8101 increased the mRNA levels of GLUT4 and several insulin sensitivity-related genes in TNF-α-treated L6 cells. HY8101 improved diabetes-induced plasma total cholesterol and triglyceride levels and increased the muscle glycogen content. *Bifidobacterium lactis* HY8101 can be used to moderate glucose metabolism, lipid metabolism, and insulin sensitivity in mice and in cells. *Bifidobacterium lactis* HY8101 might have potential as a probiotic candidate for alleviating metabolic syndromes such as diabetes [22].

Another work, performed in Yale University, by Peng and colleagues, in 2014, demonstrated that the protection from T1D development observed in MyD88-deficient NOD mice (MyD88−/− NOD) could be transferred to wild-type NOD mice [23, 24]. The gut bacteria isolated from MyD88−/−NOD mice, administered over a 3-week period, altered the family composition of the gut microbiome, mainly increasing the *Lachnospiraceae* and Clostridiaceae members and decreasing *Lactobacillaceae* family members. The gut microbiota-transferred mice had a higher concentration of IgA and transforming growth factor-beta (TGF-β) in the lumen that was accompanied by an increase in CD8+CD103+ and CD8αβ T cells in the lamina propria of the large intestine. The data obtained in this study suggest that gut bacterial composition can be altered after the neonatal period, affects the mucosal immune system, and might delay the onset of autoimmune diabetes. These results have important implications for the development of probiotic adjuvant treatment for T1D [24].

In 2015, Le and colleagues, from the National Institute for Food Control, by using C57BL/6 J mice with streptozotocin-induced diabetes, evaluated whether *Bifidobacterium* species induce the expression of proteins of the insulin signaling pathway and enhance adipocytokine gene expression. Oral administration of *Bifidobacterium* species significantly reduced blood glucose levels and increased the protein expressions of insulin receptor beta, insulin receptor substrate 1, protein kinase B (Akt/PKB), IκB kinase alpha (IKKα), and nuclear factor-kappaB inhibitor alpha (IκBα). *Bifidobacterium* species also induce the adiponectin gene expression and decrease in macrophage chemoattractant protein-1 (MCP-1) and IL-6 expression. In conclusion, the results from this work suggest that *Bifidobacterium* species may be the promising bacteria for treat diabetes [25].

A study performed in Diabetes Research Institute, in Milan, Italy, by Dolpady and colleagues, in 2016, reported that the oral administration of a *Lactobacillaceae*-enriched probiotics VSL#3, alone or in combination with retinoic acid, protects NOD mice from diabetes by suppressing inflammasome activation and IL-1β expression and by inducing the immunomodulatory indoleamine 2,3-dioxygenase (IDO) and IL-33 secretion. In addition, VSL#3-treated NOD mice showed modulation of the gut immunity by promoting differentiation of CD103+ tolerogenic dendritic cells and suppressing the differentiation of inflammatory Th1 and Th17 subsets in the gut mucosa [26].

Accumulating evidence supports that the intestinal microbiome is involved in T1D pathogenesis through the gut-pancreas axis. A recent study, performed in the University of British Columbia, in Canada, Brown and colleagues [27], aimed to determine whether the gut microbiota in the NOD mice played a role in T1D through the gut mucosa. To examine the effect of the intestinal

microbiota on T1D onset, scientists manipulated gut microbes by fecal transplantation between NOD and resistant NOD mice (NOR) and by oral antibiotic and probiotic treatment of NOD mice. The intestinal microbiota from NOD mice harbored more pathobionts and fewer beneficial microbes in comparison with NOR mice. Fecal transplantation of NOD microbes induced insulitis in NOR hosts, suggesting that the NOD microbiome is diabetogenic. Moreover, antibiotic exposure accelerated diabetes onset in NOD mice accompanied by increased Th1 and Th17 cells in the mucosal-associated lymphoid tissues. The diabetogenic microbiome was characterized by a metagenome altered in several metabolic gene clusters. Furthermore, diabetes susceptibility correlated with reduced fecal short chain fatty acids. In an attempt to correct the diabetogenic microbiome, researchers administered VLS#3 probiotic to NOD mice and found that VSL#3 colonized the intestine poorly and did not delay diabetes onset. Authors concluded that NOD mice harbor gut microbes that induce diabetes and that their diabetogenic microbiome can be amplified early in life through antibiotic exposure. Protective microbes like VSL#3 are insufficient to overcome the effects of a diabetogenic microbiome [27].

Another recent work, performed in Jiangnan University, in China, Jia and colleagues [28], investigated whether administration of probiotic *Clostridium butyricum* CGMCC0313.1 (CB0313.1) could induce Treg cells in pancreas, and consequently inhibit the diabetes onset in NOD mice. CB0313.1 supplementation was delivered daily to female NOD mice from 3 to 45 weeks of age. Researchers observed that probiotic administration suppressed the insulitis, delayed the disease onset, and improved the glucose metabolism. These beneficial effects could involve the migration of intestinal Treg cells to the pancreatic lymph nodes and changes in the Th1/Th2/Th17 balance, favoring an anti-inflammatory milieu in the gut and pancreas. Additionally, probiotic supplementation increased the Firmicutes/*Bacteroidetes* ratio, *Clostridium* species, and butyrate-producing bacteria in the gut [28].

3.1.2. Probiotic applications in T1D patients

Probiotic supplementation has been hypothesized to affect innate and adaptive immune responses to environmental antigens by supporting healthy gut microbiota and could therefore be used to prevent the onset of T1D-associated islet autoimmunity and treat the stablished disease [29].

In humans, a TEDDY study group, published in JAMA Pediatrics in 2016, evaluated the association between probiotic supplementation and islet autoimmunity in children with genetic risk for T1D, during their first year of life. This multicenter prospective cohort study (United States, Finland, Germany, and Sweden) investigated 7473 children ranging from 4 to 10 years old. Early probiotic administration (0–27 days of life) was correlated with a decreased risk of islet autoimmunity when compared with the group that received probiotics after 27 days of life or no supplementation. This study concludes that early probiotic supplementation could decrease the risk of islet autoimmune reactions in children with high-genetic-risk alleles for T1D [30].

A current clinical trial, performed by Medical University of Warsaw, in Poland, involves the evaluation of the effect of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 on β-cell function in children with newly diagnosed T1D. The double-blind, randomized, placebo-controlled clinical trial included 96 children aged 8 to 17 years old. During 1 year, patients

received *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 at a dose of 10^9 colony-forming units or an identically appearing placebo, orally, daily, for 6 months. The follow-up will be for 12 months. The primary outcome measures will be the area under the curve of the C-peptide levels during 2 h response to a mixed meal [31].

The *Lactobacillus* and *Bifidobacterium* are the major bacteria genera that make up the colon microbiota in humans and help in the intestinal microbial homeostasis, inhibit growth of pathobionts, improve the gut mucosal barrier, and modulate local and systemic immune responses. Intestinal dysbiosis may influence the immune system by increasing gut permeability, intestinal inflammation, and impaired oral tolerance in T1D patients. Beneficial effect of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12 on β-cell function would create a rationale for its routine use in patients with newly diagnosed T1D [31]. Taken together, the studies imply that bacteriotherapy may potentially be used as a tool to modulate the immune system for preventing islet autoimmunity [31, 32].

3.2. Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune disease that affects the central nervous system (CNS) and is characterized by immune reactions against myelin proteins and gangliosides. Susceptible HLA alleles and environmental factors, such as virus infection, a hypercaloric diet, vitamin D deficiency, and intestinal dysbiosis, have been implicated in triggering MS [33]. MS promotes disability in young adults and affects twice more women than men. According to the Multiple Sclerosis International Federation and World Health Organization, the prevalence of MS increased from 2.1 million in 2008 to 2.3 million in 2013 [34].

Studies have shown that gut microbiota can affect the development of MS, and these works implicated intestinal dysbiosis as one of the possible causes of extraintestinal disease development [35]. The colonization of germ-free mice with segmented filamentous bacteria promotes an increase in the number of Th17 cells in the lamina propria and CNS, worsening disease severity in experimental autoimmune encephalomyelitis (EAE), a MS animal model [36]. Likewise, the colonization of the same mice with *Bacteroides fragilis* and polysaccharide A (PSA), which induces Foxp3+ Treg cell differentiation, decreases symptoms in EAE mice [37].

3.2.1. Probiotics in experimental autoimmune encephalomyelitis

Several studies in experimental autoimmune encephalomyelitis (EAE) mice reported the immunomodulatory functions of probiotic administration. Treatment with *Lactobacillus* species, *Pediococcus acidolactici*, *Bifidobacterium bifidum*, *Bifidobacterium animalis*, and *Bacteroides fragilis* decreased CNS inflammation through the induction of Treg cells in the gastrointestinal mucosa, IL-10 and TGF-β secretion, and decreased expansion of Th1 and Th17 inflammatory subsets [37–40].

In previous studies, performed in National Institute for Public Health and the Environment, in the Netherlands, in 2008, Ezendam and colleagues evaluated the effect of the probiotic *Bifidobacterium animalis* on Th1- and Th2-mediated immune responses, including a rat EAE model. *Bifidobacterium animalis* administration started when the rats were 2 weeks old and EAE were induced when the animals were 6–7 weeks old. *Bifidobacterium animalis* significantly

reduced the duration of clinical symptoms by almost 2 days in males and improved the body weight gain during the experimental period compared with the control group [41]. In the same year, Maassen and colleagues presented data showing that strain-specific differences on the effect of commercially available probiotic depend on physiological use (normal route, dose, growth phase, specific strain, or substrain/species) and overwhelm (high dose) or circumvent natural immune processing [42].

Two years later, Lavasani and colleagues, from Lund University, in Sweden, evaluated the effect of five daily-administered *Lactobacillus* strains in inhibiting disease onset in EAE mice. The *Lactobacillus paracasei* DSM 13434 and *Lactobacillus plantarum* DSM 15312 and DSM 15313 diminished autoreactive T cell responses and inflammation in the CNS. *Lactobacillus paracasei* and *Lactobacillus plantarum* DSM 15312 induce Treg cells in mesenteric lymph nodes and TGF-β secretion. *Lactobacillus plantarum* DSM 15313 induces increase in the IL-27 serum concentrations. The isolated *Lactobacillus* strains failed to be therapeutic in EAE mice. On the other hand, the combination of three strains inhibited the disease progression and reversed the clinical and histological signs of EAE, probably by suppressing inflammatory Th1 and Th17 pathways and inducing regulatory mechanisms [43].

In 2010, Kobayashi and colleagues, from Yakult Central Institute for Microbiological Research, in Japan, evaluated the safety of two probiotic bacterial strains, *Lactobacillus casei* strain Shirota (LcS) and *Bifidobacterium breve* strain Yakult (BbY), that were orally administered to EAE Lewis rats. EAE was induced with a homogenate of guinea pig spinal cord as the sensitizing antigen, and LcS was orally administered from 1 week before this sensitization until the end of the experiment. The oral administration of LcS tended to suppress the development of neurological symptoms. Differences in neurological symptoms between the control group and the administration groups did not reach statistical significance and support the notion that neither LcS nor BbY exacerbates EAE [44].

Two years later, Kobayashi and colleagues investigated the safety use of *Lactobacillus casei* strain Shirota (LcS) in prevention of EAE in a relapse and remission models. LcS was administered 1 week prior antigen sensitization until the end of the experiments. Probiotics did not exacerbate neurological symptoms or histopathological changes of the spinal cord in either model. LcS administration transiently induces IL-17 production by antigen-stimulated lymphocytes 7 days after sensitization. Increased production of IL-10 and an increase in the percentages of CD4+CD25+ Treg cells were observed. Strong expression of IL-17 mRNA was detected in the spinal cord of mice that displayed severe neurological symptoms on day 12, but this expression was not enhanced by LcS administration [45].

In 2013, Kwon and colleagues, from School of Life Sciences and Immune Synapse Research Center, in Republic of Korea, evaluated the prophylactic and therapeutic actions of a mixture of five probiotics (IRT5) in EAE mice. IRT5 includes *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*. IRT5 prior treatment, before EAE induction, abrogated the disease development and delayed the EAE onset. Furthermore, the inflammatory subset Th1 and Th17 polarization was suppressed by the administration of IRT5 probiotic. These actions were due probably by induction of CD4+Foxp3+ Treg cells and IL-10 secretion at sites of inflammation and peripheral lymph nodes [46].

Three years later, Abdurasulova and coworkers, from Institute of Experimental Medicine, in St. Petersburg, Russian Federation, evaluated the effect of probiotic *Enterococcus faecium* strain L-3 that was studied in EAE rats. Glatiramer acetate (GA) was used as control drug. *Enterococcus faecium* strain L-3 and GA were able to reduce the severity of EAE. Both approaches prolonged the inductive phase of EAE and reduced the disease duration. Study of the phenotypes of immune cells in the blood revealed the differences in immunoregulatory pathways that mediate the protective action of probiotic or GA treatment of EAE. The presence of pronounced protective and immunomodulating effects of the probiotic *Enterococcus faecium* strain L-3 opens an opportunity of its application for the adjuvant treatment of MS [47].

The Goudarzvand group [48], from School of Medicine, in Karaj, Iran, investigated the effect of *Lactobacillus plantarum* (LP) and *Bifidobacterium* B94 (BB94) on acquisition phase of spatial memory in the local demyelination of rats' hippocampus. Thirty-two male Wistar rats were divided into control, damage group and treatment group. After the induction of demyelination, probiotics were administered by gavage for 28 days. Findings demonstrated that probiotics have no significant effect on swimming speed compared with lesion and saline groups. According to some studies, probiotics have a positive impact on improving the performance of spatial memory and learning, although this current study could not indicate finality of this assumption [48].

A recent study, performed by Secher and colleagues [49], from the University of Toulouse, in France, evaluated the effects of the probiotic *Escherichia coli* strain Nissle 1917 (ECN) in EAE model. The daily oral administration of ECN significantly decreased the disease severity induced by myelin oligodendrocyte glycoprotein (MOG) peptide mice immunization. The therapeutic effects could be explained by the increase in the IL-10 anti-inflammatory cytokine and reduction in inflammatory cytokines in the CNS and in the periphery. They also observed a decreased frequency of MOG-specific CD4+ T cells in the CNS, suggesting that ECN modulate the T cell homing from the lymph nodes to the CNS by affecting their activation and differentiation. In this study, authors showed that EAE trigger is associated with increased gut permeability [49].

Another recent study, performed in Immunology Research Center, in Mashhad, Iran, Salehipour and colleagues [50], evaluated the therapeutic effect of probiotic strains, *Lactobacillus plantarum* A7, *Bifidobacterium animalis* PTCC 1631, or both. Probiotics were administered orally for 22 days starting at same time with the induction of EAE in female C57BL/6 mice. Results showed that treatment with both strains caused a more significant delay in the time of disease onset and clinical score compared with strains used alone. Mononuclear cell infiltration into the CNS was significantly inhibited by the combinational approach. The treatment with both strains enhanced the population of CD4+CD25+Foxp3+ Treg cells in the lymph nodes and spleen. Additionally, *Lactobacillus plantarum* A7 and *Bifidobacterium animalis* ameliorated EAE condition by inhibiting IL-6 production, decreasing the release of IFN-γ, a Th1-type cytokine, and IL-17, a Th17 pro-inflammatory molecule, and increasing the secretion of IL-4, a Th2-type cytokine, and IL-10 and TGF-β, anti-inflammatory cytokines, in the lymph nodes and spleen. The treatment with *Bifidobacterium animalis* induced a downregulation of transcription factors T-bet and ROR-γt that generate Th1 and Th17 inflammatory subsets, in the brain and spleen, and promoted an upregulation of GATA3 and Foxp3, which contributes for the Th2 and Treg cell differentiation [50].

3.2.2. Probiotic applications in MS patients

Probiotic applications based on the hygiene hypothesis, such as administration of the eggs from nonpathogenic helminth *Trichuris suis ova* (TSO), have proven safe and effective in autoimmune inflammatory bowel disease. Based on this, Fleming and colleagues [6], from the University of Wisconsin, in the United States, evaluated the safety and effects of TSO administration in newly diagnosed, non-treated relapsing-remitting MS patients. Researchers conducted the phase 1 helminth-induced immunomodulatory therapy (HINT 1) study by enrollment of five MS patients that took orally 2500 TSO, every 2 weeks, for 3 months. The preliminary outcomes showed increase in the serum levels of IL-4 and IL-10 cytokines and decreased in the mean number of new gadolinium-enhancing magnetic resonance imaging (MRI) lesions. TSO was well tolerated in this first human study of the probiotic application in relapsing-remitting MS, and favorable trends were observed in exploratory MRI and immunological parameters [6].

Two years later, Rosche and colleagues, from the Department of Neurology and Experimental Neurology, in Berlin, Germany, evaluated the administration of 2500 *Trichuris suis ova* eggs orally, every 2 weeks, for 12 months, in relapsing-remitting MS patients. Fifty patients with relapsing-remitting MS with clinical activity, not undergoing any standard therapies, were enrolled. The safety, tolerability, and effect on disease activity and in vivo mechanisms of action of TSO in MS will be assessed by neurological, laboratory, and immunological exams and MRI throughout the 12-month treatment period and over a follow-up period of 6 months. No adverse effects were observed, and the *Trichuris suis ova* group was more effective than the placebo in preventing new T2 and gadolinium-positive lesions, quantified by MRI. Authors also expect the Th1 and Th17 pro-inflammatory responses polarize toward the anti-inflammatory Th2 response [51].

In a recent study, Kouchaki and colleagues [52], from School of Medicine from Kashan, in Islamic Republic of Iran, reported improved Expanded Disability Status Score (EDSS), insulin resistance, and a decrease in inflammatory markers in MS patients treated with probiotic supplementation containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum*. This randomized double-blind, placebo-controlled clinical trial analyzed probiotic intake for 12 weeks in 60 MS patients. Compared with the placebo group, probiotic administration improved EDSS, beck depression inventory, general health questionnaire, and depression anxiety and stress scale. Furthermore, changes in high-sensitivity C-reactive protein, plasma nitric oxide metabolites, and malondialdehyde in the probiotic group were significantly different from the changes in these parameters in the control group. In addition, the probiotic intake significantly decreased insulin levels and total high-density lipoprotein (HDL) cholesterol and significantly increased quantitative insulin sensitivity check index and HDL-cholesterol levels compared with the placebo [52].

Another recent randomized, double-blind, placebo-controlled clinical trial, performed in Islamic Republic of Iran, by Tamtaji and colleagues [53], evaluated the role of probiotic administration on gene expression associated to inflammatory, glucose, and lipid signaling pathways in MS patients. The study included 40 patients with MS. Participants were randomly assigned into two groups to receive either a probiotic capsule containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* (2×10^9 colony-forming units/g each) or placebo, for 12 weeks. Researchers observed that probiotic administration

downregulated gene expression of IL-8 and TNF-α mRNA in peripheral blood mononuclear cells of MS patients. On the other hand, probiotics did not affect the gene expression of IL-1, peroxisome proliferator-activated receptor gamma (PPAR-γ), or oxidized low-density lipoprotein receptor (LDLR) in peripheral blood mononuclear cells of MS patients [53].

3.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by chronic inflammation of multiple joints, bone erosion, and cartilage destruction. Moreover, RA can affect internal organs such as the lungs, heart, and kidneys. Anti-cyclic citrullinated peptide and rheumatoid factor are the most important autoantibodies in RA and can be found before disease onset [54]. The disease is three times more common in women, and according to the World Health Organization, the worldwide prevalence, which is between 0.3 and 1%, ranks the disease among the most common autoimmune disorders. The triggering of RA involves the interaction of HLA genes and environmental factors, such as smoking and infections [55]. Among environmental factors, dysbiosis has been identified as a possible trigger factor for autoimmunity and RA development [56].

3.3.1. Probiotics in animal models of RA

Experiments in animal models suggest that gut microbiota influences local and systemic immunity and might trigger joint inflammation [57]. Studies in collagen-induced arthritic (CIA) mice showed that the administration of antibiotics exacerbates the disease and increases the level of IL-6, IFN-γ, and IL-17 pro-inflammatory cytokines. Further study showed differences in the gut microbiota composition between CIA-susceptible and CIA-resistant mice, with a prevalence of *Desulfovibrio*, *Prevotella*, *Parabacteroides*, *Odoribacter*, *Acetatifactor*, *Blautia*, *Coprococcus*, and *Ruminococcus* genera in arthritic mice, in addition to increased levels of serum IL-17 and CD4 Th17 cells in the spleen [58].

The study performed by Abhari and colleagues [59], in Shiraz University, in Iran, investigated the possible role of probiotic *Bacillus coagulans* and prebiotic inulin on the downregulation of immune responses and the progression of RA, by using rat models of the disease. The spore-forming probiotic strain *Bacillus coagulans* has an anti-inflammatory and immunomodulatory effects in animals and humans. The treatment with the probiotic and prebiotic significantly inhibits serum amyloid A in arthritic rats, and a significant decrease in the secretion of the pro-inflammatory TNF-α was detected [59].

Another work, performed in the Department of Probiotics Immunology, Sapporo University, in Japan, Yamashita and colleagues [60], evaluated the effect of the oral administration of *Lactobacillus helveticus* SBT2171 on CIA development and on the regulation of antigen-specific antibody production and inflammatory immune cells, implicated in the RA development. Probiotic administration promotes decrease in joint swelling, body weight loss, and the serum level of bovine type II collagen (CII)-specific antibodies in the CIA mouse model. In addition, the intraperitoneal inoculation of *Lactobacillus helveticus* SBT2171 also decreased the arthritis incidence, joint damage, and serum concentrations of IL-6. Furthermore, the numbers of total immune cells, total B cells, germinal center B cells, and CD4+ T cells in the draining lymph nodes were decreased following intraperitoneal inoculation of *Lactobacillus helveticus* SBT2171. Findings of this study

demonstrated the ability of *Lactobacillus helveticus* SBT2171 to downregulate the abundance of immune cells and the subsequent production of CII-specific antibodies and IL-6, thereby suppressing the CIA symptoms, indicating its potential for use in the prevention of RA [60].

Lactobacillus helveticus SBT2171 (LH2171) is a lactic acid bacterium with high protease activity and used in starter cultures in the manufacture of cheese. Scientists have demonstrated that LH2171 inhibited the proliferation of lipopolysaccharide (LPS)-stimulated mouse T and B cells and the human lymphoma cell lines, Jurkat and BJAB. The findings of this study suggest that LH2171 inhibits the proliferation of lymphocytes through the suppression of the JNK signaling pathway and exerts an immunosuppressive effect in vivo, reinforcing their use in treatment of immune-mediated diseases [61].

Intestinal dysbiosis has been previously identified in patients with RA, and the administration of certain probiotics showed an improvement in RA. Study from Gohil and colleagues [62], from the Institute of Pharmaceutical Education and Research, in Gujarat, India, was designed to find out the antiarthritic activity of cell wall content of *Lactobacillus plantarum* in complete Freund's adjuvant (CFA)-induced arthritis in rats. The change in body weight, paw volume and arthritic index, joint stiffness, gait test, mobility test, erythrocyte sedimentation rate, serum C-reactive protein level, serum rheumatoid factor, and serum TNF-α was measured on day 21. Cell wall content of *Lactobacillus plantarum*-treated animals showed improvement in all the parameters as compared to that in CFA-treated animals and exert antiarthritic activity [62].

3.3.2. Probiotic applications in RA patients

Some performed studies evaluating the effect of probiotics as an adjuvant therapy for RA treatment have shown no significant results, and some of these conducted studies have smaller number of patients and a short period of evaluation [63, 64].

The earliest study to evaluate the efficacy of probiotics in RA was performed in Rheumatism Foundation Hospital, in Finland, and was published in 2003. In a pilot study, Hatakka and colleagues evaluated 25 non-treated RA patients that were randomized to receive either two capsules of a *Lactobacillus rhamnosus* or placebo, twice daily for a year. Overall, no statistically significant differences were seen between the case and the placebo. Both groups had a decline in tender and swollen joints, and the physician global scores improved in the probiotic group. Mean erythrocyte sedimentation rates and C-reactive protein levels remained normal in both groups. The serum concentrations of IL-1β increase in patients treated with *Lactobacillus* species; however, this increase was not associated with any detectable change in disease status. Fecal sampling showed an increase in the presence of *Lactobacillus rhamnosus* in the probiotic group at 1 year. Based on these results, researchers concluded that *Lactobacillus rhamnosus* preparation did not alter RA activity. However, study cohort was small, and enrolled patients have low disease activity [65].

A double-blind, placebo-controlled clinical trial, performed in the University of Western Ontario, Canada, by Pineda and colleagues [63], evaluated the effect of the oral administration of *Lactobacillus rhamnosus* and *Lactobacillus reuteri* for 3 months to 29 RA patients. Fifteen patients were randomized to the probiotic group and 14 to placebo. Alterations in cytokines favored placebo over probiotic group. There was a significant improvement in the Health Assessment Questionnaire score in the probiotic group. Although researchers did not detect

clinical improvement, measured by the American College of Rheumatology criteria, authors reported functional improvement within the probiotic supplementation group compared with the placebo [63].

Another randomized, double-blind placebo-controlled trial, performed in Tabriz University of Medical Sciences, in Iran, by Vaghef-Mehrabany and colleagues [64], investigated the role of *Lactobacillus casei* 01 intake in 46 RA patients for 8 weeks. This clinical trial showed improvement in disease activity score, increased levels of serum IL-10, and decreased levels of pro-inflammatory TNF-α, IL-6, and IL-12 cytokines in treated patients. In this study, scientists concluded that supplementation improved the disease activity and inflammatory status in RA patients [64].

Another clinical trial, with the same study design, performed by Zamani and colleagues [66], in Kashan University of Medical Sciences, Iran, evaluated the effect of probiotic administration on clinical and metabolic parameters in RA patients. Sixty patients aged 25–70 years were enrolled into two groups to receive either probiotic or placebo. Probiotic group received a daily capsule containing three strains: *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*, for 8 weeks. After intervention, probiotic administration improved Disease Activity Score of 28 joints (DAS-28). In addition, a significant decrease in serum insulin levels, homeostatic model assessment-B cell function (HOMA-B), and serum high-sensitivity C-reactive protein concentration was also observed in the probiotic group [66].

3.4. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune and heterogeneous disease characterized by damage to the skin, kidneys, lungs, joints, heart, and brain [67]. The disease affects mainly females, and its worldwide prevalence varies from 30 to 60 per 100,000 in the United Kingdom and the United States [68]. SLE pathogenesis may involve genetic and environmental factors, such as viral infections, defective apoptosis, elevated oxidative stress, and solar exposure to ultraviolet-B waves. Regarding immune response, it is known that autoantibodies bind mainly with nuclear and cytoplasmic antigens [69]. Moreover, increased evidence has emerged in a recent year that suggests the role of intestinal dysbiosis in SLE development [70].

3.4.1. Probiotics in animal models of SLE

In female lupus-prone mice, Zhang and colleagues [71] reported a decrease in the relative abundance of *Lactobacillus* species and an increase in *Lachnospiraceae* members when compared with controls. Early disease onset and severe symptoms correlated with increased *Lachnospiraceae* reads in female lupus-prone mice. Additionally, the number of Clostridiaceae and *Lachnospiraceae* reads increased at specific time points during disease progression [71]. Another study reported that dietary intervention, such as caloric restriction, in NZB/WF1 mice promoted changes in the intestinal microbiota and delayed disease progression in this animal model [72].

In a lupus-like animal model, the administration of retinoic acid restored *Lactobacillus* species and improved lupus symptoms, suggesting the use of these species as a probiotic to diminish

inflammation in SLE patients [71]. Some *Lactobacillus* species have been demonstrated to have immunomodulatory properties in the host gut mucosa, such as inhibiting neutrophil extracellular trap formation, improving antioxidant status, and increasing the expression of adhesion molecules in the gut [73, 74].

In a recent study, performed by Tzang and colleagues [75], in Chung Shan Medical University, in Taiwan, scientists investigated the effects of oral administration of *Lactobacillus paracasei* GMNL-32, *Lactobacillus reuteri* GMNL-89, and *Lactobacillus reuteri* GMNL-263 in NZB/W F1 mice. When researchers evaluated the administration of the three probiotic strains, they observed a significant decrease in IL-6 and TNF-α serum concentrations and increase in antioxidant activity in serum and liver samples (higher glutathione GSH and 1,1-diphenyl-2-picrylhydrazyl levels and lower malondialdehyde levels). Additionally, the supplementation with *Lactobacillus reuteri* GMNL-263 significantly increased the differentiation of CD4+CD25+FoxP3+ Treg cells in NZB/W F1 mice, suggesting that these strains could be used as adjuvant treatment of SLE patients [75]. Another investigation from the same group demonstrated that supplementation with these three probiotic strains ameliorates hepatic apoptosis, matrix metalloproteinase-9 activity, C-reactive protein, and inducible nitric oxide synthase expressions. In addition, probiotics decrease the gene expression of hepatic IL-1β, IL-6 and TNF-α proteins, by suppressing the mitogen-activated protein kinase and NF-κB signaling pathways [76].

Although some studies in SLE animal models showed promising results using probiotic supplementation, currently, there are no clinical trials reported at clinicaltrials.gov investigating the role of probiotics as an adjuvant therapy in the treatment of SLE patients.

4. Conclusions

Evidences associate intestinal dysbiosis with autoimmune disease pathogenesis. Impaired gut microbiota function and diversity could represent a trigger site of autoimmunity by neoantigen generation under dysbiotic conditions. Emerging findings point to the use of probiotics as a preventive functional food and as adjuvant treatment of autoimmune diseases. However, further clinical trials, with large cohorts, to evaluate the security and efficacy of the probiotic administration in patients with autoimmune diseases are needed.

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Conflict of interest

The author reports no conflict of interest.

Appendices and nomenclature

Treg	T regulatory cells
T1D	Type 1 diabetes
NOD mice	Nonobese diabetic mice
IL	Interleukin
TNF-α	Tumor necrosis factor-alpha
TGF-β	Transforming growth factor-beta
MCP-1	Macrophage chemoattractant protein-1
IDO	Indoleamine 2,3-dioxygenase
NOR mice	Resistant NOD mice
TEDDY	The Environmental Determinants of Diabetes in the Young
MS	Multiple sclerosis
CNS	Central nervous system
EAE	Experimental autoimmune encephalomyelitis
PSA	Polysaccharide A
GA	Glatiramer acetate
MOG	Myelin oligodendrocyte glycoprotein
TSO	*Trichuris suis ova*
MRI	Magnetic resonance imaging
EDSS	Expanded Disability Status Score
HDL	High-density lipoproteins
RA	Rheumatoid arthritis
CIA mice	Collagen-induced arthritic mice
LPS	Lipopolysaccharide
CII	Type II collagen-specific antibodies
NZB	New Zealand black mice

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