



Review

Probiotics and Amelioration of Rheumatoid Arthritis: Significant Roles of *Lactobacillus casei* and *Lactobacillus acidophilus*

Alok K. Paul ¹, Anita Paul ², Rownak Jahan ¹, Khoshnur Jannat ¹, Tohmina A. Bondhon ¹, Anamul Hasan ¹, Veeranoot Nissapatorn ³, Maria L. Pereira ⁴, Polrat Wilairatana ^{5,*} and Mohammed Rahmatullah ^{1,*}

¹ Department of Biotechnology & Genetic Engineering, University of Development Alternative, Dhaka 1207, Bangladesh; alokcpaul@gmail.com (A.K.P.); rownak86@hotmail.com (R.J.); jannat.koli.22@gmail.com (K.J.); afrozebondhon@gmail.com (T.A.B.); anamulhasanoris@gmail.com (A.H.)

² Department of Pharmacy, University of Development Alternative, Dhaka 1207, Bangladesh; anita.paul1988@gmail.com

³ School of Allied Health Sciences, World Union for Herbal Drug Discovery (WUHeDD), and Research Excellence Center for Innovation and Health Products (RECIHP), Walailak University, Nakhon Si Thammarat 80160, Thailand; nissapat@gmail.com

⁴ CICECO-Aveiro Institute of Materials & Department of Medical Sciences, University of Aveiro, 3810-193 Aveiro, Portugal; mlourdespereira@ua.pt

⁵ Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 73170, Thailand

* Correspondence: polrat.wil@mahidol.ac.th (P.W.); rahmatm@uoda.edu.bd (M.R.)



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Abstract: Rheumatoid arthritis is a chronic autoimmune disorder that can lead to disability conditions with swollen joints, pain, stiffness, cartilage degradation, and osteoporosis. Genetic, epigenetic, sex-specific factors, smoking, air pollution, food, oral hygiene, periodontitis, *Prevotella*, and imbalance in the gastrointestinal microbiota are possible sources of the initiation or progression of rheumatoid arthritis, although the detailed mechanisms still need to be elucidated. Probiotics containing *Lactobacillus spp.* are commonly used as alleviating agents or food supplements to manage diarrhea, dysentery, develop immunity, and maintain general health. The mechanism of action of *Lactobacillus spp.* against rheumatoid arthritis is still not clearly known to date. In this narrative review, we recapitulate the findings of recent studies to understand the overall pathogenesis of rheumatoid arthritis and the roles of *probiotics*, particularly *L. casei* or *L. acidophilus*, in the management of rheumatoid arthritis in clinical and preclinical studies.

Keywords: rheumatoid arthritis; probiotics; *Lactobacillus*; *Prevotella*; gut microbiota

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by swollen joints with chronic pain, stiffness, reduced functionality, osteoporosis, and cartilage degradation leading to a situation of disability [1,2]. RA is prevalent in 0.3–1.0% of adults aged 20–40 years globally, and it is very common among older adults aged 75 years or above [3,4]. Women are relatively more susceptible to RA [4]. RA patients experience age-related comorbidities such as diabetes, cardiovascular disorders, nephritis, chronic obstructive pulmonary disease (COPD), psychological distress, osteoporosis, asthma, and cancer, leading to a higher mortality rate [5].

RA is currently treated with nonsteroidal anti-inflammatory drugs (NSAIDs), as these drugs prevent prostaglandin synthesis by inhibiting the cyclooxygenase enzymes (COX-1 and COX-2) and thereby act against inflammation and pain. Drugs in this group include paracetamol, ibuprofen, naproxen, diclofenac, indomethacin, ketoprofen, meloxicam, and many more [6]. Besides NSAIDs, disease-modifying anti-rheumatic drugs like methotrexate

are used as a first-line drug for RA treatment, but 20 to 30% of RA patients could not continue its treatment for >12 months because of adverse reactions. The most common adverse effects of the drug are gastrointestinal toxicity (20–70% of RA patients experience nausea, vomiting, diarrhea, mucocutaneous ulcers), hepatotoxicity (~70% of RA patients), pulmonary toxicity, nephrotoxicity, and blood-related toxicity. The drug is teratogenic, carcinogenic, and anemic and causes patient non-compliance and discontinuation of the treatment [7]. Methotrexate treatment can increase the formation of rheumatoid nodules (lumps under the skin) [8]. Biological disease-modifying anti-rheumatic drugs are also widely used to treat RA, but Janus kinase (JAK) inhibitors like baricitinib and upadacitinib may cause venous thromboembolism [9].

Hydroxychloroquine and chloroquine are antimalarial drugs and are also used for the treatment of RA. The drugs prevent lysosomal degradation of antigens (prevents phagocytosis and autophagy pathways), inhibit the immune response by blocking the Toll-like receptor (TLR)-7 and TLR-9 receptors of dendritic cells by blocking the expression of major histocompatibility complex (MHC) class II molecules and thus modulating T-cells- and B-cells-mediated secretions of proinflammatory cytokines (IL-1, IL-6, and TNF- α) [10]. The drugs can produce retinopathy [10–13]. As the drugs are weak bases and have a long shelf life in the blood (~50 days), co-treatment with certain drugs with narrow therapeutic indices can create systemic toxicity in patients with hepatic and renal impairments [10].

TNF- α , a proinflammatory cytokine produced inside the body mainly by macrophages and lymphocytes, and induces inflammatory responses by activating nuclear factor-B, proteases, and protein kinases [14,15]. The combination of TNF- α inhibitors and methotrexate can reduce the chance of discontinuation of the therapy in patients with RA [16,17]. TNF- α inhibitor can cause pneumonia and bacterial, viral, and fungal infections, mainly in the respiratory tract, urinary tract, gastrointestinal tract, and skin [18,19]. These drugs need subcutaneous or intravenous administration and may create infections at the injection site [14,20]. TNF- α inhibitors may pose a risk for cancer development, although the findings are inconclusive [21–23].

Corticosteroids (especially glucocorticoids such as prednisone, hydrocortisone, and dexamethasone) are immunosuppressants and anti-inflammatory drugs, and these are used in combination with the disease-modifying anti-rheumatic drugs. The combined treatment provides a better onset of symptomatic treatment and reduces adverse reactions associated with the treatment of the disease-modifying anti-rheumatic drugs [24–26]. Glucocorticoid receptor usually remains in the cytoplasm in an inactive form, but glucocorticoids activate it. The interaction of glucocorticoids and glucocorticoid receptors suppresses the activity of NF- κ B and activator protein-1. This interaction, in turn, prevents the expression of inflammatory genes and transcriptions of proinflammatory cytokines (e.g., IL-1 β , IL-6, and TNF- α) [24,27]. Glucocorticoids can induce apoptosis of T-cells, neutrophils, and some other activated white blood cells, as well as increase the phagocytic capability of macrophages [27,28]. NF- κ B is expressed in osteoclast precursors, and it is a key regulator of osteoclastogenesis [29]. As glucocorticoids suppress NF- κ B expression, it may prevent osteoporosis, which is also a comorbidity of RA. Glucocorticoid use over a long time can cause adverse effects such as hyperglycemia, diabetes, weight gain, fat deposition on the upper body parts, and reduced calcium resorption (and osteoporosis), myopathy, and adrenal insufficiency [30]. Briefly, all the drugs available in the clinic RA treatment produce adverse reactions. A detailed understanding of RA pathogenesis will help us to develop alternative management strategies like using food supplements such as probiotics against the disease manifestation of RA.

2. Rheumatoid Arthritis: An Inflammatory Pathway

RA manifests with increased fluid retention, neuronal and inflammatory cell migration to the joints with increased secretion of proinflammatory cytokines (IL-1, IL-8, IL-12, IL-15, IL-17, IL-18, IL-29, and TNF- α) [31]. Studies have shown that TNF- α and IL-6 inhibitors are effective against RA [32–35]. The inflammatory process also results from reduced

production of immunomodulatory cytokines like IL-11, IL-13, and IL-10 [31]. Increased ratio of proinflammatory and anti-inflammatory cytokines causes chronic inflammatory conditions like RA, and the process is induced by helper T cell type 1 (Th1) [36–38]. Helper T17 (Th17) cells (that defend against extracellular microbes) produce inflammatory response TNF- α , IL-17A, IL-17F, and IFN γ (γ -interferon) that leads to the pathogenesis of RA [39] (Figure 1). RA is influenced by some receptors that can recognize pathogen-associated molecular patterns, such as Toll-like receptors (TLRs), which activate host-defense mechanisms and maintain innate immune responses [40–42]. TLRs (especially TLR-2, TLR-3, TLR-4, TLR-5, and TLR-7 in RA) regulate the nuclear factor kappa-B ligand (NF- κ B), generation of osteoclasts, and induce increased production of TNF- α , IL-6, IL-12, IL-18, and many other proinflammatory cytokines [40,43]. TLRs express in the synovial joints and cause inflammation that leads to swollen joints, pain, stiffness, and damage in cartilages and bones [44] (Figure 1). RA increases TNF- α and IL-1 β in blood and synovial tissues that accelerate activation of matrix metalloproteinase (MMP) enzymes (e.g., MMP-1, MMP-9, and MMP-13) that can decompose all components of extracellular matrix and cartilages of joints [45,46]. Early diagnosis and treatment are essential to managing RA as psoriasis and bone damage are irreversible [34].

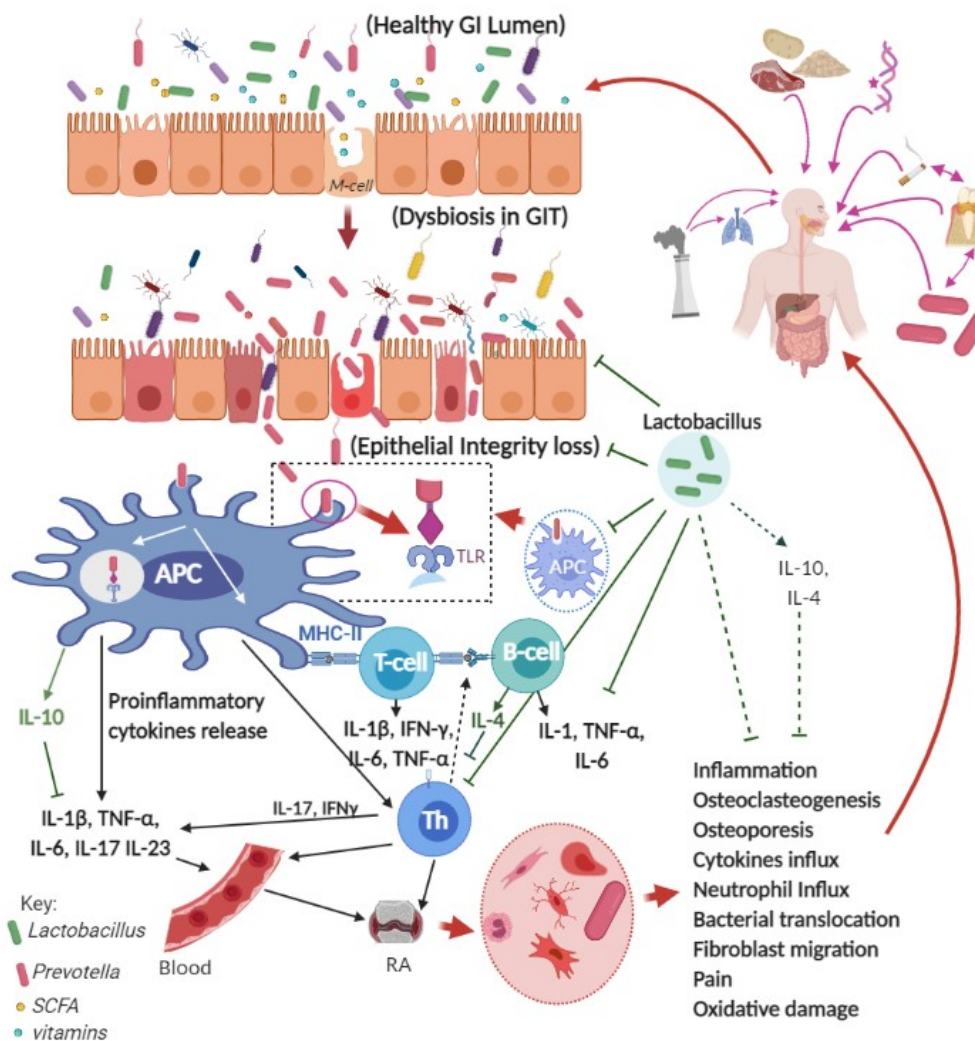


Figure 1. Possible mechanisms of Rheumatoid Arthritis (RA) and the role of *Lactobacillus* spp. Keys: APC, antigen-presenting cell; GI, gastrointestinal, GIT, gastrointestinal tract; IL, Interleukin; TNF- α , tumor necrosis factor alpha; IFN- γ , gamma interferon; M-cell, microfold cell; Th, Helper T cell; T-cell, T-cell lymphocytes, B-cell, B-cell lymphocytes; green rod-shaped bacteria, *Lactobacillus* spp.; red rod-shaped bacteria, *Prevotella* spp.; SCFA, short-chain fatty acids. Figure was made with www.biorender.com (access date: 14 April 2021).

Several genetic, environmental, and socioeconomic factors are associated with RA initiation and progression [44]. Fat-rich and low-vegetable diet, smoking, gut microbiota, periodontal diseases, bacterial or viral infections lead to different inflammatory conditions and results in RA [47–49] (Figure 1). RA is also influenced by gender as women are more susceptible to RA than men and several factors influence the disease, such as hormonal deficiency (estrogen deficiency in pre- and post-menopausal women), genetic factor (X-chromosome related), the prevalence of depression, neuropathic pain, fibromyalgia and osteoporosis (in post-menopausal women) [50–53]. Apart from environmental factors, increased citrullination is also observed in alveolar macrophages in smokers' lungs, and thus smoking may involve the pathogenesis of RA [47].

Citrullination is a peptidylarginine deiminase-mediated enzymatic conversion of arginine residues of protein to citrulline residues, and dysregulation of the peptidylarginine deiminases enzymes causes increased citrullination of protein in the joints of RA patients [54].

3. RA and Gastrointestinal Tract

The gastrointestinal tract is connected with the environment, and it is an essential gateway for the intake of beneficial and harmful microbes and their metabolites through food and drinks. The human gut harbors over 100 trillion bacteria, and these microbes have a potential role in the digestion, metabolism, nutrition, disease control, and maintenance of general well-being [55–58]. The epithelial cell barrier and intestinal single cell layer determine the rate of entry of microbes or antigens into the bloodstream [59,60]. Disturbance in the gastrointestinal homeostasis, especially massive changes in gut microbiota composition, results in diarrhea, dysentery, or inflammatory responses such as RA [61–64]. Increased bacterial lipopolysaccharides in the bloodstream and their deposition in the synovial fluids can cause proinflammatory responses (by releasing cytokines) and RA [65,66] (Figure 1).

Besides genetic, environmental, and physiological changes like citrullination of proteins and deposition in the joint tissues, RA is also believed to be caused by gut bacteria like *Prevotella*. *Prevotella* spp. are anaerobic, non-spore-forming bacteria, and these are part of normal gut flora. *Prevotella* contributes to polysaccharides breakdown, and their presence is relevant to the consumption of carbohydrate and high fiber diets [48]. *P. copri* is also responsible for the generation and progression of intestinal dysbiosis in people at their early stages of RA or risk on RA development [67–69]. Increased *Prevotella* spp. was found in the intestines of people carrying genotype of RA before developing clinical symptoms of the disease [70]. Increased abundance of *P. copri* and its antibodies are detected in patients with RA [71]. The increased population of *P. copri* in the intestinal lumen probably enables it to defend itself against myeloid cells and T cells that leads to immune responses [69] (Figure 1). *Prevotella* also activates the TLR-2 receptor of the intestinal epithelial cells and stimulates the release of proinflammatory cytokines such as IL-1 β , IL-6, and IL-23 and promotes the activation of Th17 cells that leads to massive production of IL-17, inflammation, and initiation of RA [72] (Figure 1).

A meta-analysis study showed that probiotic supplement helps reduce IL-6 levels in RA patients, which may help to manage RA. However, it did not reduce DAS scores of RA patients, and it may not be effective in established RA patients [73]. It is known that gut dysbiosis favors increased population growth of *Eggerthella lenta* or *Collinsella aerofaciens* bacteria in the gut [74]. A clinical study showed decreased population of *Faecalibacterium* (a Firmicutes bacteria abundant in healthy human gut) in people experiencing RA [75] (Table 1). *Faecalibacterium* is responsible for butyrate production [76] that stimulates mucin secretion and lubrication of inner gut epithelium. As the *Faecalibacterium* population decreases, the gut is more vulnerable to opportunistic organisms like *Collinsella* and *Eggerthella*. *Collinsella* induces the release of cytokines (e.g., IL-17 α) and chemokines (e.g., CXCL1 and CXCL5) that contribute to RA development by activating NF κ B and neutrophils [75]. *Eggerthella* causes the citrullination of proteins that contributes to RA development. RA-associated decreased population of *Streptococcus* and *Haemophilus* are also observed in the human

gut with the escalation of *Prevotella histicola* and *P. oulorum* numbers [77]. Higher fecal *Lactobacillus casei* was also reported in RA patients [78]. Thus dysbiosis-related changes in *Collinsella aerofaciens*, *Eggerthella lenta*, *Faecalibacterium* spp., *Haemophilus* spp., *Prevotella* spp., and *Streptococcus* spp. population induce loss of integrity of inner epithelium of gut and development of RA [75,77] (Table 1).

Table 1. The roles of some bacteria in RA pathogenesis.

Bacteria	Changes During Gut Dysbiosis	Roles in RA Pathogenesis or Prevention	Ref.
<i>Collinsella</i>	Increased population	<ul style="list-style-type: none"> reduces expression of tight junction protein in gut epithelial cells increases gut permeability releases proinflammatory cytokines (e.g., IL-17α) secretes chemokines (e.g., CXCL1 and CXCL5) cytokines and chemokines activate NFκB and neutrophils Inflammation in gut epithelium and RA development 	[75]
<i>Eggerthella</i>	Increased population	<ul style="list-style-type: none"> conversion of arginine residues of protein to citrulline residues increases citrullination of proteins in gut citrullination contributes to RA development 	[75]
<i>Faecalibacterium</i>	Decreased population	<ul style="list-style-type: none"> responsible for butyrate production butyrate stimulates mucin secretion and lubrication of gut epithelium reduced <i>Faecalibacterium</i>, reduces lubrication on epithelium and makes it vulnerable to pathogens reduced <i>Faecalibacterium</i> provides increased growth of <i>Collinsella</i> and <i>Eggerthella</i> 	[76]
<i>Prevotella</i>	Increased population	<ul style="list-style-type: none"> <i>Prevotella</i> spp. contributes to polysaccharides breakdown <i>P. copri</i> acts against immune responses of T-cells <i>P. copri</i> activates TLR-2 receptor of intestinal epithelial cells <i>P. copri</i> stimulate secretions of IL-1β, IL-6, IL-17, and IL-23 <i>P. copri</i> causes inflammation in GI lumen and initiates RA <i>P. histicola</i> releases antimicrobial compounds <i>P. histicola</i> and <i>P. intestinalis</i> have anti-inflammatory effects <i>P. histicola</i> increases expression of Treg cells and IL-10 Some effects are species-dependent 	[69,72,79–84]
<i>Lactobacillus</i>	Decreased population	<ul style="list-style-type: none"> reduces proinflammatory cytokines (e.g., IL-17, IL-1β, IL-6, and TNF-α) releases anti-inflammatory cytokines like IL-4 and IL-10 reduces oxidative stress reduces swelling and cartilage damages reduces lymphocyte infiltration in joints releases short-chain fatty acids reduces growth of <i>Bacteroides</i>, <i>Escherichia</i> and <i>Shigella</i> in gut some effects are species dependent 	[38,85–90]
<i>Porphyromonas gingivalis</i>	Increased population	<ul style="list-style-type: none"> oral <i>P. gingivalis</i> increases with concomitant growth of intestinal <i>P. copri</i> <i>P. gingivalis</i> possibly migrates to synovial tissues causes citrullination of proteins in synovial tissues produces inflammatory responses and RA 	[91–93]

The situation regarding the enteric biome is complicated by the presence of pathogenic and commensal enteric viruses (forming the enteric virome) and their effects on intestinal homeostasis and immune responses. Since the subject matter is still challenging like experimenting with mice infected with commensal enteric human viruses is still not a feasible experiment that has been done [94], and since existing literature lacks reports (to our knowledge) on any enteric viral biome effect on initiation and development of RA, this review will confine itself to enteric microbial biome (meaning enteric bacteria and does not take into account virome or fungal biome) and any disturbances in their homeostasis leading to RA. The main objective of this review is to take a close look at whether the administration of probiotics in the form of *Lactobacillus casei* and *Lactobacillus acidophilus* can cause amelioration of the RA. However, it is possible that disturbances in the pattern recognition receptors (PRRs) and their signaling pathways can lead to disruption of immune homeostasis, and which might act as a trigger for RA.

It has been reported that the virome can have a profound influence on the composition and functional properties of the microbial biome, and in the practical sense, it alters the development and function of the immune system [95]. It remains for future studies to determine whether the predominance of *Prevotella* spp. in the human gut leading to RA is a result of gut virome alterations and whether taking probiotics like *Lactobacillus* can help the intestine to revert back to normal virome homeostasis. The question of gut inflammation, immunity, and the role of gut virome has been raised before [96], but any answer is yet to be found, and the topic falls outside the scope of this review. A very recent pre-print article reports dysbiotic oral and gut viromes in treated and un-treated RA patients [97]. Despite recent advances on gut virome and resultant pathogenesis if the homeostasis is disturbed, there is virtually no information on the role of gut virome dysbiosis and RA or even gut virome dysbiosis and consequential changes in the gut microbiome with *Prevotella copri* becoming the dominant oral and gut bacteria. It is left for scientists to discover to what extent gut microbiome and gut virome follow independent trajectories or have interacting trajectories; if interacting, when and where are the points of interaction?

4. *Prevotella* and RA Pathogenesis

Most likely, *P. copri* enter the bloodstream and infiltrate joints via phagocytic cells (such as macrophages, neutrophils, and dendritic cells) [71]. *P. copri* infection causes massive production of immunogenic helper T cell (Th17) cells, proinflammatory cytokines (such as IL-6, IL-17, and IL-23), leading to inflammation in the gut and that subsequently migrates to other organs and initiates RA as shown in a preclinical study [69,72]. An increased number of *P. copri* in the large intestine causes inflammatory responses in the gut. Th17 cells, IL-17, bacterial DNA, and possibly *Prevotella* spp migrate to the joints and induce joint inflammation and RA [79–81] (Figure 1). *Prevotella intermedia*, (another *Prevotella* bacteria) has been shown to increase prostaglandin E2 from arachidonic acid by activating cyclooxygenase-2 in the joints [98,99]. Noticeably, overexpression of the cyclooxygenase-2 enzyme was observed in RA [100]. Increased prostaglandins have multiple roles in RA pathogenesis, such as pain in the joints, inflammation, bone metabolism, and immune response [99].

Prevotella is also present in the oral cavity, and their presence increases in periodontal diseases, and thus RA is also correlated with periodontitis [49,101,102]. Periodontitis is highly correlated with RA in the clinic, and the oral bacterial population shift towards *Porphyromonas gingivalis* and other anaerobic bacteria such as *Prevotella* spp. [91,103] (Table 1). A concomitant increase in *Porphyromonas gingivalis* in the oral cavity and *P. copri* in the intestine is observed in patients who experience RA [92] (Figure 1). Serum samples from patients with RA showed positive responses to immunoglobulin G (IgG) antibody of *P. gingivalis* [104]. *P. gingivalis* from the oral cavity possibly migrate to the synovial tissues through phagocytotic capture of dendritic cells, and *P. gingivalis* also causes cit-

rullination of proteins in synovial tissues, which in turn, produce systemic inflammatory responses [91,93].

Besides these, *P. histicola* and *P. intestinalis* have shown immunomodulatory effects and reduced arthritis in mice similar to RA [82–84]. *Prevotella intestinalis* may cause a reduction in short-chain fatty acids and IL-18 production in the intestine, which reduces the abundance of acetate-producing bacteria like *P. copri* [82]. *P. histicola* protects the intestinal mucosal barrier by increased enzymatic expression of antimicrobial compounds. The bacteria also produce anti-inflammatory effects by reducing inflammatory responses of Th17 cells and increasing the number of regulatory T cells and IL-10 [83] (Table 1).

5. Roles of *Lactobacillus* Probiotics against RA in Preclinical Studies

Probiotics are live microorganisms intended to be administered orally to improve the host's gut microbiota [105,106]. Human gut microbiota sometimes becomes imbalanced and causes dysbiosis in situations like long-term treatment with antibiotics, NSAIDs, stress, and inflammatory conditions such as RA and osteoarthritis [107–109]. Bacteria like *Lactobacillus* spp. and *Bifidobacterium* spp. are widely used probiotics, and *Lactobacillus* spp. can survive in an acidic gastrointestinal environment, and the presence of glucose in the gut help their survival [106,110]. The efficacy of probiotics depends on the microbial strain or pathophysiologic conditions of the host [109].

Treatment with *L. casei* or *L. acidophilus* over a period of 28 days reportedly prevented the development of arthritis in a preclinical model that reduced arthritic scores and proinflammatory cytokines such as IL-17, IL-1 β , IL-6, and TNF- α , similar to that of indomethacin treatment [38]. The treatment with the *Lactobacillus* spp. also increased the release of anti-inflammatory cytokines like IL-4 and IL-10 in the body fluids [38]. Consumption of *L. acidophilus* and *L. casei* reduces the oxidative stress of animals with collagen-induced arthritis [38]. Oral *L. casei* treatment also induced anti-inflammatory effects in rats in a collagen-induced arthritis model by inhibiting the COX-2 enzyme by reducing the proinflammatory cytokines [111]. Another preclinical study showed that intragastric administration of *L. casei* prevented the development of *Salmonella enterocolitis*-induced arthritis and reduced expression of proinflammatory cytokines (e.g., IL-1 β , IL-6, IL-17, IL-23, and TNF- α) [85]. Treatment of *L. casei* at the initial stage of adjuvant-induced arthritis (AIA) model (similar to RA) in rats inhibited the development of arthritis that was comparable to methotrexate with normalization of gut microbiota and an increment of *L. acidophilus* population [86]. *L. acidophilus* treatment showed anti-inflammatory properties as it suppressed Th17 cell-mediated secretion of proinflammatory cytokines (IL-1 β , IL-6, TNF- α , IL-17, and IL-23), but increased secretion of the anti-inflammatory cytokine (IL-10) [87,88]. Another study showed similar changes in the profile of cytokines along with reduced swelling, cartilage damage and lymphocyte infiltration in joints after *L. casei* treatment in collagen-induced arthritic rats [89].

Several *Lactobacillus* spp., especially *L. casei*, *L. reuteri*, *L. fermentum* and *L. rhamnosus* reduced collagen-induced-arthritis (CIA) in female Wistar rats by modifying gut microbial population (increasing *Lactobacillus* spp.), preventing proinflammatory cytokines, releasing antibodies, antibiotic substances and short-chain fatty acids, or modulating Th1/Th17 responses [90]. Noticeably, these effects are species dependent. *L. acidophilus* produces antibacterial substances, which are effective against in vitro Gram-positive and Gram-negative pathogenic bacteria, but not effective against normal gut flora [112,113].

On the negative side, *L. casei* [114], *L. bifidus*, *L. salivarius*, *L. iners*, and *L. ruminis* are connected with pathogenesis of RA and increased populations of these bacteria have been observed in RA patients in comparison to healthy people [78]. Another study also showed that oral supplementation of *L. casei* and *L. acidophilus* increased phagocytic and lymphocytic activity in the intestinal mucosa of Swiss albino mice [115]. Therefore, the consumption of *L. casei* and *L. acidophilus* can sometimes but rarely produce harmful effects, which is probably due to the increased population of these bacteria in the human gut. There are variations of effects between *Lactobacillus* spp., treatment protocols and induction

of experimental rheumatoid arthritis, animal species, and measurement parameters as reported previously [78]. Therefore, the outcome of these studies is quite inconclusive, but we hypothesize that a moderate population of *L. casei* and *L. acidophilus* produces beneficial effects. However, an increased population may cause infiltration of these bacteria from the gut to other organs, thereby producing harmful effects.

6. Roles of *Lactobacillus* Probiotics against RA in the Clinic

Patients with RA showed an increased presence of *Bacteroides*, *Escherichia*, and *Shigella* bacteria in the gut with a marked decrease in *Lactobacillus* spp. [116]. A well-balanced gut microflora provides essential vitamins like B-vitamins B3, B5, B6 (pyridoxal phosphate), B7, and B12, folate, tetrahydrofolate, and vitamin-K [58]. Low plasma vitamin-B6 has been observed in inflammatory conditions like RA, and long-term treatment with NSAIDs such as cyclooxygenase inhibitors prevented vitamin-B6 metabolism and thus reduced pyridoxal phosphate concentration from blood [117]. Impaired secretion of these essential vitamins (in conditions like gut dysbiosis), especially vitamin-B6 deficiency, can cause RA and cardiovascular complications [118,119]. Adequate colonization of *Lactobacillus* spp can improve the epithelium's integrity, and it becomes less susceptible to *Bacteroides*, *Escherichia*, and *Shigella* infections and their translocation into the intestinal lumen [120–123]. The bacteria secrete multiple short-chain fatty acids (e.g., lactic, acetic, and polyglutamic acid) and vitamins that provide nutritional support and decrease the pH of the intestinal lumen that prevent the colonization of harmful bacteria [124–126].

L. casei treatment over a period of 8 weeks improved RA-related pathophysiological parameters in a randomized clinical trial [127]. *Lactobacillus* spp also acts as an antimicrobial agent against different microorganisms [124,128]. Patients with RA show increased nitric oxide and reactive oxygenated species in blood and synovium, which cause degradation of lipids, other macromolecules, and matrix of the affected person [129,130].

Once daily administration of *L. casei* in capsule (contained 10^8 colony-forming unit) consumption treatment over a period of 8 weeks reduced the swelling of joints, arthritis-related disease activity score-28, serum high-sensitivity C-reactive protein (hs-CRP) levels, and proinflammatory cytokines, especially TNF- α and IL-12 in women with RA relative to the placebo-treated control group. *L. casei* increased plasma IL-10 levels after the treatment but caused no changes in IL-1 β and IL-6 levels [131]. Similarly, another study with a similar *L. casei* treatment protocol on a smaller number of patients found similar changes in the cytokines profile of RA patients [132]. The same dose of *L. casei* administered over eight weeks did not change the oxidative stress indicators or lipid profiles of RA patients [133,134]. Regular consumption of *L. casei* preserves the gastrointestinal diversity and prevents gastrointestinal dysbiosis, physiological stress, RA, and other inflammatory disorders [107]. *L. acidophilus* supplements in diabetic patients ($n = 48$, $p = 24$, $c = 24$) over a period of 4 weeks did not modify systemic inflammatory responses (induced by *Escherichia coli* lipopolysaccharide injections) and insulin sensitivity [135] (Table 2). The randomized clinical trials of probiotics are not readily comparable among these, as there are variations in the patient selection, probiotic formulation, experimental parameters, dose, and frequencies of probiotic treatment, and all these can potentially affect the experimental outcomes (Table 2).

Table 2. Effects of probiotics in clinical trials.

Sample Size	Probiotic Type, Control and Duration	Measurement Parameters	Brief Outcome	Ref.
RCT, 54 (C: 27, P:27)	P: <i>L. acidophilus</i> (2×10^9 cfu/g), <i>L. casei</i> (2×10^9 cfu/g), <i>B. bifidum</i> (2×10^9 cfu/g), 0.8 g inulin C: starch Duration: 8 weeks, Dose: 1 cap/day	DAS-28, hs-CRP, VAS, NO, insulin levels, HOMA-IR, HOMA-B, GSH levels	Improved: hs-CRP, DAS-28, VAS, NO, insulin levels, HOMA-IR, HOMA-B, and GSH levels	[136]
RCT, 60 (C: 30, P: 30)	P: <i>L. acidophilus</i> (2×10^9 cfu/g), <i>L. casei</i> (2×10^9 cfu/g), <i>B. bifidum</i> (2×10^9 cfu/g) C: cellulose, Duration: 8 weeks, Dose: 1 cap/day	DAS-28, HOMA-B, hs-CRP, insulin levels	Improved: DAS-28, Decreased: insulin, HOMA-B, and hs-CRP levels	[127]
RCT, 46 (C: 24, P: 22)	P: <i>L. casei</i> 01 (10^8 cfu), C: maltodextrin Duration: 8 weeks Dose: 1 cap/day	MDA, TAC, SOD, GPx, CAT	No changes observed.	[133]
RCT, 46, (C: 24, P: 22)	P: <i>L. casei</i> 01 (10^8 cfu), C: maltodextrin Duration: 8 weeks Dose: 1 cap/day	DAS28, serum cytokines (IL-1 β , IL-6, IL-10, IL-12 and TNF- α), EULAR	Increased: IL-10, Reduced: TNF- α and IL-12	[131]
RCT, 46 (C: 24, P: 22)	P: <i>L. casei</i> 01 (10^8 cfu), C: maltodextrin Duration: 8 weeks Dose: 1 cap/day	Cytokines (TNF- α , IL-6, IL-12)	Increased: IL-10, IL-10:IL-12 ratio. Reduced: TNF- α , IL-6 and IL-12	[132]
RCT, 29 (C: 14, P: 15)	P: <i>L. rhamnosus</i> GR-1, <i>L. reuteri</i> RC-14 (total: 2×10^9 cfu) C: dextrose, starch, mcc, magnesium stearate Duration: 3 months Dose: 2 caps/day	ACR20 responses, cytokine levels	No changes observed.	[137]
RCT, 44 (C: 22, P: 22)	P: <i>Bacillus coagulans</i> GBI-30,6086, green tea extract, msm, vitamins (A, B, C, D, E), Se, C: mcc Duration: 2 months Dose: 1 cap/day	ACR, HAQ-DI, ESR, CRP	Reduced: CRP, and pain scores	[138]
RCT, 21 (C: 13, P: 8)	P: <i>L. rhamnosus</i> GG (5×10^9 cfu), C: placebo (no info), Duration: 12 months Dose: 4 caps/day	RA activity, HAQ index, CRP, ESR cytokines (IL-6, TNF- α , MPO, IL-10 and IL-12)	No changes observed.	[139]
RCT, 48 (C: 24, P: 24)	P: <i>L. acidophilus</i> NCFM (1 g, 10^{10} cfu), C: placebo (silicium dioxide and lactose, 1:1), Dose:	Systemic inflammatory response (by <i>E. coli</i> LPS), insulin resistance	No changes observed	[135]

RCT, randomized control trial; C, control (or placebo) group; P, probiotic (treatment) group; B., *Bifidobacterium*; L., *Lactobacillus*; DAS-28, Disease Activity Score of 28 joints; ACR, American College of Rheumatology criteria (e.g., ACR20), HOMA-B, homeostatic model assessment-B homoeostatic model assessment- β -cell function; hs-CRP, serum high-sensitivity C-reactive protein; HOMA-IR, homoeostasis model of assessment estimated insulin resistance; RA, rheumatoid arthritis; VAS, visual analogue scale of pain; NO, nitric oxide; MDA, serum malondialdehyde; TAC, total antioxidant capacity; SOD, erythrocyte superoxide dismutase; GPx, glutathione peroxidase; CAT, catalase; EULAR, European League Against Rheumatism response; HAQ-DI, Stanford Health Assessment Questionnaire Disability Index, mcc, microcrystalline cellulose; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HAQ, Health Assessment Questionnaire; MPO, myeloperoxidase; Se, selenium; LPS: lipopolysaccharides; FA, folic acid; msm, methylsulfonylmethane.

7. Possible Effector Molecules of *Lactobacillus* Species

Intestinal microbes and their gene products can interact with PRRs, including C-type lectin receptors, including the specific intracellular adhesion molecule-3 grabbing non-integrin homolog-related 3 (SIGNR3) [140,141]. Any disruption of the delicate balance between the intestinal biome and their various gene product interactions can lead to disruptions in signal-transducing, giving rise to diseases like irritable bowel syndrome [142]. *Lactobacillus acidophilus* NCFM has been described as a model probiotic strain [143]. The strain is distinguished by its several surface (S) layer proteins. The S layer is encoded by three Slp-encoding genes: slpA (LBA0169), slpB (LBA0175), and slpX (LBA0512). SlpA, a probiotic factor, can bind to the host immune receptor SIGNR3, a C-type lectin. The binding affects modulatory signals, resulting in the mitigation of colitis, maintenance of a healthy gut biome, and protection of gut mucosal barrier function [143]. Other documented effector molecules (besides SlpA) in various species of *Lactobacillus* and *Bifidobacterium* strains have been reviewed by Lebeer and colleagues [143]. These molecules include specific pili (*Lactobacillus rhamnosus* GG), S-layer proteins (*Lactobacillus acidophilus* NCFM), exopolysaccharides and muropeptides. Various metabolites like tryptophan- and histamine-related metabolites (*Lactobacillus reuteri* 6475), CpG-rich DNA, and enzymes like lactase and bile salt hydrolases can also act as effector molecules.

Lactobacillus, often neglected because of the notion that they are transient passengers of the gut [144], now are regarded as important members of the gut microbiome, because they can form up to 5% of the gut microbiota and up to 99% of vaginal microbiota [145]. However, not much study is available on the effector molecule(s) of *Lactobacillus casei* and *Lactobacillus acidophilus* that may play a significant role in the attenuation of RA. Consumption of *Lactobacillus casei* fermented milk reportedly prevented *Salmonella enteritidis* reactive arthritis [85]. Such prevention occurred through modulation of IL23/IL17 expression. On the other hand, adhesion of probiotic bacteria to the gastrointestinal surface is considered a prerequisite for the exclusion of competitive pathogens [146], which would suggest that *Lactobacillus casei* adhesion molecules like fucose may play the part of an effector molecule [85].

8. Conclusions

In summary, preclinical studies mainly focus on the preventative roles of *Lactobacillus* spp in various experimental models of RA. In contrast, several clinical studies have investigated this bacteria's role in the improvement of the symptoms and diagnostic parameters after RA establishment. *L. casei* or *L. acidophilus* supplementation (in the form of food, drink, or pharmaceutical dosage forms) may not have an immediate favorable impact against RA. It ameliorates gut dysbiosis and consequential RA pathogenesis after repeated long-term use. However, an increased population of *Lactobacillus salivarius* was recorded in the gut, teeth and saliva of RA patients and *L. salivarius* and some other *Lactobacillus* spp. could be associated with RA pathogenesis [145,147]. Long-term high-dose consumption of some *Lactobacillus* spp. may induce rare complications like liver abscess and bacteremia [148–150]. Therefore, the benefits of *Lactobacillus* probiotic supplements depend on the *Lactobacillus* species. Since *L. casei* and *L. acidophilus* have anti-inflammatory, antimicrobial, antioxidant properties, these bacteria act symbiotically in the gut to establish their colonization and thus increase the integrity of cellular layers (of the gastrointestinal tract), maintain nutritional support of the host, and reduce the severity of inflammatory conditions like RA.

It has been put forward that the therapeutic use of probiotics and prebiotics in the case of obesity-related non-alcoholic fatty liver disease did not demonstrate any major benefits in high-quality clinical trial studies [151]. A number of factors are involved in probiotic studies, namely the initial composition of the patient's gut and possibly oral microbiome, the nature of probiotic administered, the progress of the disease at the time of probiotic administration, and the continuation of the diet and the probiotic along with any other medications. Every disease possibly has its own probiotics regimen and the initial microbiome of the patient, which brings in not one but two factors. As such, probiotics

can be and more possibly should be regarded as nutraceutical supplements, and it will be somewhat futile to presume that what will not work for obesity-related non-alcoholic fatty liver disease will also not work for, say RA.

Probiotics can be used as nutritional supplements to manage inflammatory disorders like rheumatoid arthritis, diarrhea, dysentery, irritable bowel syndrome, diabetes, but the effectiveness in clinical trials is yet to be proved. Probiotic supplements should be considered as a functional food which has some therapeutic benefits. The quality of probiotic products is currently examined based on the number of viable colonies of certain probiotic bacteria (e.g., *L. acidophilus*) in the product [152]. However, the number of colonies cannot represent the effectiveness of the bacteria for inflammatory disorders like RA. Physical parameters, such as stability in a low pH environment (e.g., gastric lumen), physical stability, viability and proper storage condition, should be monitored to maintain good quality products [153]. In vitro laboratory assessments like adhesion capabilities of probiotic bacteria to human intestinal epithelial cells (such as Caco-2 cell line) and the capability to contribute to the lubrication of inner gut walls (in vivo) needs to be taken into account [152,154,155]. New quality control parameters should be implemented to maintain an optimum standard of probiotic products for consumers.

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