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PROBIOTICS IN RHEUMATIC DISEASES: A SYSTEMATIC REVIEW

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Abstract. ***Background.*** Probiotic therapy (PB) has been used in several gastrointestinal disorders. Some studies evaluated PB in rheumatic diseases. However, there is no systematic review on this subject. ***Objectives.*** To perform a systematic review of the literature regarding the clinical, therapeutic, and outcome characteristics of patients with rheumatic diseases treated with PB. ***Methodology.*** A systematic review of "rheumatic diseases" and "probiotics" was done. The following databases were used: PubMed/MEDLINE, LILACS, SciELO, Scopus, RISC, Web of Science, and Cochrane, dating from 1966 to January 2023. No limitation in languages was applied. Although not in all, but in majority of clinical and experimental studies reviewed some favorable effects of probiotics in several rheumatic diseases were documented. Most probably, probiotic treatment is a useful and safe complementary therapy for rheumatic patients.

Key words: Rheumatic diseases; Probiotics; Rheumatoid Arthritis; Osteoarthritis; Fibromyalgia; Systemic Sclerosis; Spondyloarthritis; Gout; Autoimmunity; Sjögren Syndrome; Osteoporosis.

ПРОБИОТИКИ ПРИ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЯХ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Резюме. Пробиотическая терапия использовалась первоначально при желудочно-кишечных заболеваниях. Но существуют и работы по применению пробиотиков при ревматологической патологии. Однако систематического обзора по этому вопросу не проводилось. ***Цели.*** Провести систематический обзор литературы, касающейся клинических, терапевтических характеристик и результатов лечения пациентов с ревматическими заболеваниями, получавших пробиотики. ***Методология.*** Был проведен систематический поиск работ на входящий контекст «ревматические заболевания» плюс «пробиотики» по следующим библиографическим базам: PubMed/MEDLINE, LILACS, SciELO, Scopus, Web of Science, РИНЦ и Cochrane, датируемых периодом с 1966 года по январь 2023 года. Никаких языковых ограничений не применялось. Несмотря на неоднозначность результатов, в большинстве клинических и экспериментальных исследований получены позитивные эффекты пробиотиков в отношении ряда ревматических заболеваний. Скорее всего, пробиотики могут служить полезным и безопасным дополнением в комплексном лечении ревматологических больных.

Ключевые слова: ревматические заболевания; пробиотики; ревматоидный артрит; остеоартрит; фибромиалгия; склеродермия; спондилоартрит; подагра; аутоиммунитет; синдром Шёгрена; остеопороз.

INTRODUCTION

Probiotics have been defined as «live microorganisms which, when administered in adequate amounts, confer a health benefit on the host» by the Food and Agriculture Organization / World Health [1]. The genera most used in the formulations of probiotics are Lactobacillus and Bifidobacterium [2]. Several probiotics strains have demonstrated therapeutic benefits in a large sample of randomized clinical trials in infectious and systemic diseases [3–8].

Several research lines have demonstrated the influence of the microbiota on the regulation both in health and disease [9]. Since the immune system is essential in the pathophysiology of rheumatic diseases and the microbiota has a fundamental role in the maturation of the immune system, which is demonstrated in germ-free rats that are unable to develop immune maturation [9, 10]. Furthermore, it is known that 70% of the immune system is located in the lymphatic tissue associated with the intestine (GALT) [11]. Gut and oral microbiota may alter the course and risk of rheumatic diseases *via* various pathophysiological mechanisms, including molecular mimicry, production of immune suppressive and/or adjuvant-like metabolites, post-translational modification of human proteins with resulted formation of neo-antigens and through the modulation intestinal permeability, vitamins D and K metabolism, as well as intervention into extra-renal purine metabolites' excretion/absorption [12–15].

Probiotics have been recommended for several clinical conditions today. The primary accumulated evidence refers to gastrointestinal diseases, such as the prevention of antibiotic-associated diarrhea in children [16], prevent Clostridium difficile diarrhea associated with antibiotic use [17], shortening the duration, and reducing stool frequency in acute infectious diarrhea [18]. However, more recently, possible benefits have been found in the treatment of vulvovaginal candidiasis in non-pregnant women [19], allergic and atopic diseases in children [20], depression [21], and cardiovascular diseases [22].

Regarding rheumatic diseases and probiotics, several studies have evaluated the effects of these substances in diseases such as rheumatoid arthritis (RA), spondyloarthritis, and systemic sclerosis that will be reviewed in this study. However, the results of these works are still conflicting. But, to the best of our knowledge, no systematic reviews have been published until 2022 on this topic. We revealed only one Russian review of 2015 devoted to the etiologic role of microorganisms in rheumatic diseases, which is concluded with a short narrative section about their probiotic treatment, citing just 7 references on this matter [12].

The present study aims to perform a systematic review on the effects of probiotics in rheumatic diseases.

METHODOLOGY

Literature Review: A systematic review of the articles published in PubMed/MEDLINE, LILACS, SciELO, Scopus, Web of Science, RISC and Cochrane dating from 1966 to August 2020, was performed using the following search line, adapted to each database: (probiotics) AND (rheumatoid arthritis OR systemic sclerosis OR spondyloarthritis OR fibromyalgia OR arthritis OR Sjögren's syndrome OR osteopenia OR osteoporosis OR gout OR systemic lupus erythematosus OR dermatomyositis OR polymyositis OR juvenile idiopathic arthritis OR mixed connective tissue disease OR undifferentiated connective tissue disease OR Wegener's granulomatosis OR Takayasu arteritis OR giant cell arteritis OR Kawasaki disease OR polyarteritis nodosa OR Churg-Strauss syndrome OR Henoch-Schönlein purpura OR hypersensitivity vasculitis OR cryoglobulinemia OR Behçet's disease). It was added with a review of recent publications of 2021–2022 found with input context of (probiotics) AND (rheumatic diseases). No limitation in languages was applied.

The articles were independently reviewed by three authors (HMS, LPC and LNMF). The following information was collected: country, total sample number, and% of female patients, age, study design, probiotic features, duration of treatment, outcomes (statistical differences and no significant changes), and adverse events. A thorough analysis of each of these scientific articles and their list of references was conducted. Duplicate articles, insufficiently detailed or not informative enough, were excluded. This article followed the PRISMA guidelines [23]. The brief synopsis of collected information contain Tables I–III below.

RESULTS

By August 2020 we found 28 articles on RD who were treated with PB (Figure 1). There were 9 studies in rheumatoid arthritis (RA) and 18 in different diseases as follows: systemic sclerosis (n = 4), osteopenia (n = 4), spondyloarthritis (n = 2), juvenile idiopathic arthritis (n = 2), ulcerative colitis with psoriasis (n = 1), psoriatic arthritis (n = 1), fibromyalgia (n = 1), knee osteoarthritis (n = 1), Sjögren's syndrome (n = 1), and hyperuricaemia and/or gout (n = 1). One study was combined with involvement of RA, OA and gout patients (n = 1) [24].

The total number of patients included was 1,493. In RA, we detected 233 patients (of the 10 articles in RA, 4 of them referred to the same RA population), followed by knee osteoarthritis with 453, osteopenia with 230, spondyloarthritis with 210, systemic sclerosis with 163, juvenile idiopathic arthritis with 76, Sjögren's syndrome with 32, fibromyalgia with 31, ulcerative colitis with psoriasis with 26, hyperuricemia and/or gout with 45 and psoriatic arthritis with 10.

The study design was represented mainly by randomized double-blinded placebo-controlled studies in 20 articles, followed by t2 prospective open design, 1 randomized double-blinded (not placebo-controlled), 1 internet-based randomized placebo-controlled, 1 randomized crossover, 1 pharmacological, and 1 open-label, single-arm pilot study.

In the other rheumatic diseases, disease duration varied from 7.5 to 20 years, and female preponderance was detected between 0 to 100%. The age of the participants was found between 8 to 80 years old.

Regarding other RD, 6 studies used a single cepae, the other 12 studies used at least 2 cepaes. *L. acidophilus* was used in 8/18 studies, *B. infantis* in 5/18, *S. thermophilus* in 5/18, *L. rhamnosus* in 5/18, *L. delbrueckii* in 5/18, *L. paracasei* in 4/18, *L. casei* in 3/18, *B. breve* in 3/18, *B. longum* in 3/18, L. salivarius in 2/18, *B. bifidum* in 2/18, *B. lactis* in 2/18, *L. plantarum* in 2/18, *B. bifidus* in 1/18, *S. boulardii* 1/18, *L. gasseri* 1/18 and *L. reuteri* 1/18.

Four out of 9 RA articles refer to the same clinical trial [25–28]. Disease duration varied from 4.75 years (mean) to 19 years (mean), female sex prevalence was observed from 50 to 100%. Regarding cepae used in the RA studies, *L. casei* was employed in 5/9 studies, followed by *L. rhamnosus* in 2/9, *L. acidophilus* in 2/9, *B. bifidum* 1/9, *L. reuteri* 1/9, *B. lactis* in 1/9, *S. salivarius* in 1/9 and then *Bacillus coagulans* 1/9. 3/9 articles used 2 or more cepae in the same study. Significant differences were observed related to an improved DAS28 score in 3/3 articles [25, 28, 29] decreased levels of CRP or hs-CRP in 2/5 [28, 29] and no significant differences in 3/5 [30–32], HAQ score improvement in 1/2 [31], and no significant differences in 1/2 [30], and decreased levels of insulin and HOMA-B levels in 1/1[29].

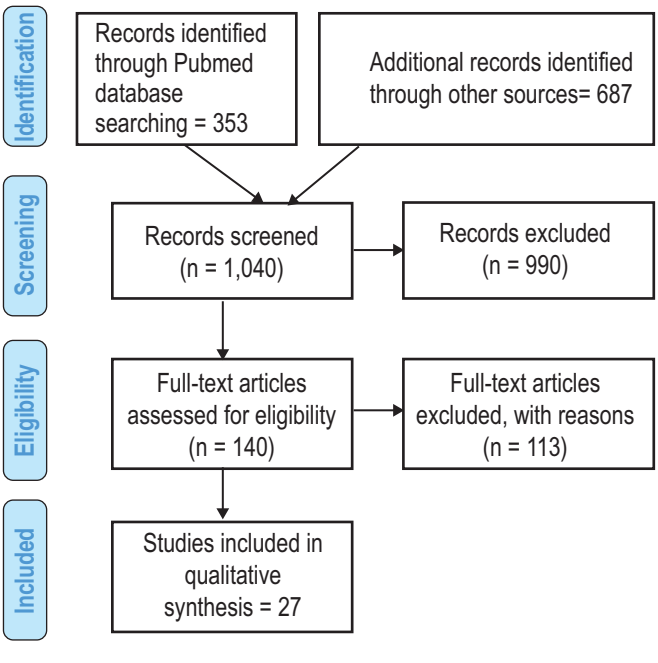

Figure 1. Flowchart of the included studies

Two articles demonstrated decreased levels of TNF-α and IL-12 and increased levels of IL-10, although they refer to the same population [25, 28]. One study revealed improvements in Patient Pain Assessment and Pain Scale scores [30]. In one article, a general well-being improvement was noted [32]. Single out of 4 articles demonstrated a decrease in number of tender and swollen joints [28], although 3/4 articles showed no significant changes [29, 31, 32]. Two studies showed no significant changes in lipid profile [27, 29]. Regarding adverse events in RA studies, five out of ten found no adverse events [24, 25, 27, 28, 31], although three of them are related to the same population [25, 27, 28]. 2/10 did not describe adverse events [26, 29]. In 2/10 RA articles, no adverse events related to probiotics were reported [30, 32]. The gastrointestinal disturbance was the most frequent adverse event.

In systemic sclerosis studies, 2/4 articles showed an improvement in gastrointestinal symptoms evaluated by SCTC GIT 2.0 score [33] and NIH-PROMIS GI score [34]. In 1/4 study [35], VAS-intestinal score and HAQ-DI results did not differ between groups, and it was observed an improvement on GIT score in reflux subdomain, but not in the total score. In 1/4 study [36], an improvement in GIT scores in both probiotics and placebo groups was observed similarly. Another study [34] observed a significant effect of probiotics on small intestinal bacterial overgrowth (SIBO) eradication. The effects on biomarkers observed a significant decrease in Th17 cells percentage and no significant changes on Th1, Th2, and Treg [36]. Fecal calprotectin (f-CP) levels were also evaluated, and no differences were observed [34].

In the spondyloarthritis studies [37–38], no differences were observed in symptoms between probiotics and placebo groups.

Regarding osteopenia, in 2/4 studies [39–40] there was observed a significant reduction in the loss of bone mineral density (BMD) in probiotics groups compared to placebo. In the other 2 studies, no significant effect was observed on BMD [41] and fractional calcium absorption [42]. A study that evaluated biomarkers [41] observed a significant decrease in BAP, serum CTX, PTH, and TNF-α levels in the PB group compared to the placebo group. There were no significant differences in OC, urinary DPD, RANKL, OPG, RANKL/OPG ratio, 25-OH vitamin D, alkaline phosphatase, albumin, urinary and serum magnesium, phosphorous, calcium, creatinine. Another study [40] showed no difference on HbA1c, N-telopeptide of type I collagen, BAP; hsCRP and TNF-α.

In juvenile idiopathic arthritis, the studies found no significant differences in clinical improvement by clinical judgment [43] or modified Juvenile Spondyloarthritis Disease Activity Index (mJSpADA) score [44] between probiotics groups compared to placebo. Regarding effects on biomarkers, it was observed an increase of ISC in the IgA class, increased sASC in the IgM class, a decrease of fecal urease activity, and

Table 1-1

Clinical, demographical, and therapeutic features of patients with rheumatoid arthritis who were treated with probiotics (Part 1)

First Author, year, [Reference]	Country	Total Sample Size (%Female)	Age (years)	Study Design	Probiotic Features
Zamani et al., 2016,(29)	Iran	60 (85%)	25–70 (range)	Randomized, double-blinded, placebo-controlled	*L. acidophilus* 2 bil, *L. casei* 2 bill, and *B bifidum* 2 bil
Vaghef-Mehrabany et al., 2014,(25)	Iran	46 (100%)	41.14 probiotic (mean) 44.29 placebo (mean)	Randomized, double-blinded, placebo-controlled	*L. casei* 01 1 bil
Pineda et al. 2011,(31)	Canada	29 (93%)	63.8 probiotic (mean) 59.1 placebo (mean)	Randomized, double-blinded, placebo-controlled	*L. rhamnosus* GR-1 2 bil and *L. reuteri* RC-14 2 bil
Vaghef-Mehrabany et al., 2016,(26)	Iran	46 (100%)	41.14 probiotic (mean) 44.29 placebo (mean)	Randomized, double-blinded, placebo-controlled	*L. casei* 01 1 bil
Alipour et al., 2014,(28)	Iran	46 (100%)	20–80 (range)	Randomized, double-blinded, placebo-controlled	*L. casei* 01 1 bil
Mandel et al., 2010,(30)	United States	45 (81.8%)	36–82 (range)	Randomized, double-blinded, placebo-controlled	*Bacillus coagulans* GBI-30 (6380) 2 bil
Hatakka et al. 2003,(32)	Finland	21 (57.14%)	50 probiotic (mean) 53 placebo (mean)	Randomized, double-blinded, placebo-controlled	*L. rhamnosus* GG (ATCC 53103) 2x/day
Lee et al., 2010,(66)	New Zeland	12 (50%)	56 (mean)	Pharmacological study: effects of probiotic administration on the metabolism of Sulfasalazine (SSZ)	*L. acidophilus* L10 (4×10^8 CFU), *B. lactis* B94 (4×10^8 CFU) and *S. salivarius* K12 (1×10^8 CFU) 2x/day
Vaghef-Mehrabany et al., 2017,(27)	Iran	46 (100%)	41.14 probiotic (mean) 44.29 placebo (mean)	Randomized, double-blinded, placebo-controlled	*L. casei 01* 10^8 CFU
Ziyaeva, Bektimirova, 2016, [24]	Uzbekistan	70 (66%)	44.4 (mean)	Randomized, pharmaco-therapeutical, comparison of routine treatment and the same schedule plus probiotics	*L. acidophilus*, strain 180 ($4x10^9$ CFU); B. longum, strain 17X (4x109 CFU)

N/D: not described; **PB**: probiotics; **bil**: billion (10^9); **RA**: rheumatoid arthritis; **DAS-28**: Disease Activity Score of 28 joints; **HOMA-B**: homeostatic model of assessment for B cell function; **hs-CRP**: high-sensitivity C-reactive protein; **QUICKI**: quantitative insulin sensitivity check index; **HOMA-IR**: homeostatic model of assessment for insulin resistance; **VAS**: visual analog scale; **STAI-Y**: State-Trait Anxiety Inventory Form Y; **IPAQ**: International Physical Activity Questionnaire; **HAQ**: Health Assessment Questionnaire; **ACR20**: American College of Rheumatology 20% improvement; **DAS:** Disease Activity Score; **EULAR criteria**: European League Against Rheumatism criteria; **CRP**: C-reactive protein; **ESR**: Erythrocyte Sedimentation Rate

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Table 1-2

Clinical, demographical, and therapeutic features of patients with rheumatoid arthritis who were treated with probiotics (Part 2)

First Author, year, [Reference]	Duration	Outcome (Statistical diferences)	Outcome (No significant change)	Adverse events
Zamani et al., 2016,(29)	8 weeks	Improved DAS28 score Decreased insulin levels Decreased HOMA-B and hs-CRP concentrations on the PB group.	Tender and swollen joint counts, lipid profile, nitric oxide, glutathione, malondialdehyde, QUICKI, HOMA-IR; energy and macronutrient intake	N/D
Vaghef-Mehrabany et al., 2014,(25)	8 weeks	Improved DAS28 score, decreased VAS score. Decreased levels of TNF-α, IL-12, and IL-6 Increased levels of IL-10 and of IL-10/IL-12 ratio on PB group.	IL-1 levels STAI-Y and IPAQ scores Energy and macronutrient intake	No adverse events were reported.
Pineda et al. 2011,(31)	3 months	HAQ improvement on PB group	ACR20 response CRP, IL-1a, IL-1b, IL-6, IL-8, TNF-a, IL-12p70, IL-15, IL-10, GM-CSF, G-CSF, IL-17, sCD40 ligand, MIP-1a, MIP-1b, MCP-1 levels DAS 64 swollen joint count and 66 tender joint count	No adverse events were reported
Vaghef-Mehrabany et al., 2016,(26)	8 weeks	Superoxide dismutase reduction on PB group Glutathione peroxidase was reduced in both groups.	Malondialdehyde levels, catalase activity, and total antioxidant capacity STAI-Y and IPAQ scores Energy and macronutrient intake Between-group differences for superoxide dismutase and glutathione peroxidase levels	N/D
Alipour et al., 2014,(28)	8 weeks	Improved DAS28 and global health scores, moderate EULAR response Decreased number of tender and swollen joints Decreased levels of hs-CRP, TNF-α, and IL-12 Increased levels of IL-10.	IL-1 and IL-6 levels STAI-Y and IPAQ scores Energy and macronutrient intake	No adverse events were reported.
Mandel et al., 2010,(30)	60 days	Improvement on Patient Pain Assessment and Pain Scale scores on PB group	Physician and global patient assessments, physician assessment of painful and swollen joints HAQ score CRP levels	Shingles, poison ivy, cold, leg edema (PB group) Gastrointestinal reflux, upper respiratory infection, and urinary tract infection (placebo group) These adverse events were deemed unrelated to the study treatment.
Hatakka et al. 2003,(32)	12 months	Well-being improvement on PB group Slightly increase in IL-1β levels in the PB group.	Number of swollen and tender joints Activity of RA Intake of energy, minerals, and vitamins ESR, CRP, IL-6, TNF-α, myeloperoxidase, IL-10, and IL-12 levels	No clinically relevant adverse effects were observed

First Author, year, [Reference]	Duration	Outcome (Statistical diferences)	Outcome (No significant change)	Adverse events
Lee et al., 2010,(66)	1 week	No significant statistical changes were observed on the metabolism of SSZ	Sulfapyridine, N-acetyl-sulfapyridine, 5-aminosalicylic acid, and N-acetyl-5-aminosalicylic acid levels (all metabolites of SSZ) Changes in intestinal microbiota	Gastrointestinal disturbance (3), and flare of RA (1)
Vaghef-Mehrabany et al., 2017,(27)	8 weeks	No significant statistical changes were observed in lipid profiles in both groups.	TC, HDL-C, LDL-C, and TG levels STAI-Y and IPAQ scores Energy and macronutrient intake	No adverse events were reported.
Ziyaeva, Bektimirova, 2016, [24]	2 weeks L.acidophilus + 2 weeks B.longum	Statistically significant improvement in both clinical parameters and dysbacteriosis microbiological index, but of short duration (1 month)	Long-term clinical parameters and dysbacteriosis index	No adverse events were reported.

N/D: not described; **PB**: probiotics; **bil**: billion (10^9); **RA**: rheumatoid arthritis; **DAS-28**: Disease Activity Score of 28 joints; **HOMA-B**: homeostatic model of assessment for B cell function; **hs-CRP**: high-sensitivity C-reactive protein; **QUICKI**: quantitative insulin sensitivity check index; **HOMA-IR**: homeostatic model of assessment for insulin resistance; **VAS**: visual analog scale; **STAI-Y**: State-Trait Anxiety Inventory Form Y; **IPAQ**: International Physical Activity Questionnaire; **HAQ**: Health Assessment Questionnaire; **ACR20**: American College of Rheumatology 20% improvement; **DAS:** Disease Activity Score; **EULAR criteria**: European League Against Rheumatism criteria; **CRP**: C-reactive protein; **ESR**: Erythrocyte Sedimentation Rate

decreased levels of fecal TNF-α [43]. There were no significant differences in ESR/CRP; Th1, Th2, Th17, and Treg frequencies; IFN-γ, IL-4, IL-6, IL-17, IL-10, and TNF-α levels [44].

A study on ulcerative colitis with psoriasis using *B. infantis* found a reduction in CRP and TNF levels [45].

A study on fibromyalgia treatment with *L. rhamnosus, L. casei, L. acidophilus, and B. Bifidu*s observed significant cognition improvements by fewer impulsive choices and better decision-making. There are no differences between PB and placebo in pain, quality of life, fibromyalgia impact, or depressive or anxiety symptoms [46].

A study that tested *L. casei Shirota* for therapeutical effects on knee osteoarthritis [47] found symptoms improvements by significantly reducing WOMAC and VAS scores. It was observed that this effect had solid linear correlations with serum hs-CRP levels, which were significant reduced in the probiotics group compared to placebo. A study of deforming osteoarthritis documented short time positive effect of PB as regards to clinical judgment and microbiological dysbacteriosis index, but declining with longer time elapsed [24].

A psoriatic arthritis study [48] observed a significant decrease of fecal zonulin and calprotectin levels, decreased α1-antitrypsin levels in patients with high levels before treatment, and a decrease in intestinal permeability and amelioration of disease activity (post-treatment).

A study that tested therapeutical effects of *L. acidophilus, L. bulgaricus, S. thermophilus*, and *B. bifidum* on Sjögren's syndrome [49] found no significant differences between PB and placebo in NRS pain score or presence of erythematous candidosis and angular cheilitis. However, it was observed a significant reduction of the *Candida* load.

A study on hyperuricemia and/or gout using strains of *L. delbrueckii ssp., L. bulgaricus*, and *S. thermophilus* [50] evaluated serum uric acid (SUA) levels and their changes. There were no significant differences in SUA levels or changes in SUA in the complete sample analysis. However, in a subpopulation analysis, including only subjects within ± SD (1.0) of mean SUA level, a significant reduction in the probiotic group was observed compared to placebo. Another study of the scheme amended with PB therapy compared to routine treatment in gout revealed short time improvement of both clinical manifestations and microbiological dysbacteriosis index, later smoothed out [24]. Regarding other RD, 6/19 studies reported adverse events with no significant difference between PB and placebo groups. The most frequent events reported were nausea, diarrhea, and change in bowel habits. In 7/19 studies, there were no relevant adverse events reported, and 6/19 articles did not describe adverse events.

The present article is one of the first systematic reviews of PB's effects on rheumatic diseases, and a favored effect was observed in most studies. This study's strengths were the inclusion of all articles that evaluated probiotics and rheumatic diseases published in the literature. The second advantage was that most articles had a randomized placebo-controlled study design, which, in general, shows more precise results. The third advantage was that the authors followed the PRISMA guidelines [19].

Probiotics can influence the development of rheumatic diseases through the regulation of energy, essential nutrients metabolism, or modulation of the spectrum and strenth of immune system challenges (basing on neoantigen formation trans-barrier antigen and adjuvant penetration and molecular mimicry). They can contribute to prevention of obesity, which in turn is a significant risk factor for several rheumatic diseases [12–15, 24, 51–53]. The use of probiotics can increase butyrate production within the colon, generating immunomodulatory effects [54]. Butyrate has excellent anti-inflammatory potential, reducing levels of interleukin 1 beta (IL-1b), tumor necrosis factor (TNF), and nuclear transcription factor kappa b (NFkB), which are critical pro-inflammatory interleukins very important in rheumatic diseases. Together, butyrate can increase factors and increase anti-inflammatory factors such as interleukin 10 (IL-10) [55].

The primary disease studied so far was rheumatoid arthritis, being responsible for 10 of the 28 studies found between 1966 and 2020. The primary measure of continuous clinical evaluation of disease activity is DAS28, but it was only used in only 3 of the 10 articles [56]. Despite this, all 3 articles found significant improvements. These results corroborate the findings of decreased C-reactive protein levels, which was associated with a significantly increased risk of cardiovascular disease in patients with rheumatoid arthritis [57]. Besides, CRP has played an essential role in the direct differentiation of osteoclast precursors into mature osteoclasts and induction of RANKL expression, producing bone destruction in RA patients [58]. It can be hypothesized that part of the effects would be produced by an increase in the production of butyrate, which has the crucial anti-inflammatory role as previously mentioned, with Faecalibacterium prausnitzii being one of the leading producers of butyrate, which was observed a reduction in its abundance in patients with RA compared to healthy controls [59]. In systemic sclerosis, an improvement in symptoms, specifically, gastrointestinal symptoms were observed after PB. It is a logical result since it is expected an improvement in gastrointestinal manifestations after PB. A randomized study has demonstrated a significant improvement of gastroesophageal reflux after probiotics in patients with systemic sclerosis [60].

The treatment of osteopenia with PB seems to be beneficial, with the improvement of bone mass. Ohlsson et al. performed a six-week study of L. paracasei from two weeks before ovariectomy in mice. They found that probiotics reduced

Table 2-1

Clinical studies that evaluated probiotics in other rheumatological diseases (Part 1)

First Author, year, [Reference]	Country	Disease	Disease duration, mean	Total Sample Size (% Female)	Age, years	Study Design	Duration
Frech et al., 2011,(33)	United States	Systemic sclerosis with moderate-to-severe distention bloat score	7.1 years	10 (90%)	51.7 (mean)	Prospective open	2 months
García-Collinot et al., 2019,(34)	Mexico	Systemic sclerosis with small intestinal bacterial overgrowth (SIBO)	13.5 years	40 (mostly women, not described)	53.2 (mean)	Open pilot, randomized, clinical trial with three different intervention groups (M, M + SB, and SB)	2 months: on the 1st week (group M and group SB) or the 1st and 2nd weeks of each month (group M + SB)
Low et al., 2019, [35]	Singapore	Systemic sclerosis with gastrointestinal symptoms	9.1 years (placebo-PB group); 5.588 years (PB-PB group)	40 (87.5%)	50.71 (placebo-PB group); 51.42 (PB-PB group)	Randomized, double-blinded, placebo-controlled, parallel-group phase II trial	4 months (T1 at 2 months, T2 at 4 months)
Mariela et al., 2019, (36)	Brazil	Systemic sclerosis	4.5 years (Probiotic group); 4.6 years (Placebo group)	73 (93,15%)	46.7 years (mean) in the PB group, 47.1 years (mean) in the placebo group	Randomized, double-blind, placebo-controlled trial	8 weeks
Brophy et al., 2008,(37)	United Kingdom	Spondyloarthritis	20.3 years	134 (29.85%)	44.8 probiotic (mean) 42.7 placebo (mean)	Internet-based, randomized, placebo-controlled (according to CONSORT)	3 months
Jenks et al., 2010,(38)	New Zeland	Spondyloarthritis	8.9 years	63 (36.5%)	43.3	Randomized, placebo-controlled	12 weeks
Lambert et al., 2017,(39)	Denmark	Postmenopausal Osteopenia	Not described	78 (100%)	62.85 control (mean); 60.84 RCE with probiotics (mean)	Randomized, double-blinded, placebo-controlled, parallel design trial	12 months
Cheung et al., 2011,(42)	Australia	Osteopenia	Not described	12 (100%)	54.8 years (mean)	Randomized crossover pilot study	Not described
Nilsson et al., 2018,(40)	Sweden	Osteopenia	Not described	90 (100%)	76.4 years (mean) in PB group; 76.3 years (mean) in the placebo group	Randomized, double-blind, placebo-controlled, single-center trial	12 months
Jafarnejad et al., 2017,(41)	Iran	Osteopenia	Not described	50 (100%)	58.85 years (mean) in the PB group; 57.29 years (mean) in the placebo group	Randomized, double-blind, placebo-controlled trial	6 months
Shukla et al., 2016,(44)	India	Juvenile idiopathic arthritis	3.5 years	46 (4.34%)	15 (mean)	Randomized, double-blinded, placebo-controlled	12 weeks
Malin et al., 1997,(43)	Finland	Juvenile idiopathic arthritis	11 months (*L. GG group*); 11 months (Colostrum group); 7 months (Immune colostrum group)	30 (56.66%)	8 (mean)	Randomized, double-blinded, with three different intervention groups (*L. GG*, Colostrum, and Immune colostrum groups)	2 weeks

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Table 2-1. Ending

Groeger et al., 2013,(45)	Ireland	Ulcerative, Psoriasis, Chronic Fatigue Syndrome		26 (not described)	18-60	Randomized, double-blinded, placebo-controlled	6-8 weeks
Roman et al., 2018,(46)	Spain	Fibromyalgia	8.56 years probiotic; 8.47 years placebo	31 (90.32%)	55 probiotic (mean); 50.27 placebo (mean)	Randomized, double-blinded, placebo-controlled	8 weeks
Lei et al., 2017,(47)	China	Knee osteoarthritis	Not described	433 (55,66%)	66.5 probiotic (mean); 67.2 placebo (mean)	Randomized, double-blinded, placebo-controlled	6 months
Haidmayer et al., 2020,(48)	Austria	Psoriatic Arthritis	11 years	10 (70%)	58 (mean)	Open-label, single-arm pilot study	12 weeks
Kamal et al., 2020,(49)	Egypt	Sjögren's syndrome	Not described	32 (100%)	43.2 probiotic (mean); 43.5 placebo (mean)	Randomized, double-blinded, placebo-controlled	5 weeks
Yamanaka et al., 2019,(50)	Japan	Hyperuricaemia and/ or gout	Not described	25 (0)	63.3 years (mean) in the total sample; 63.0 years (mean) in PB group; 63.6 years (mean) in the placebo group	Randomized, double-blind, placebo-controlled trial	8 weeks
Ziyaeva, Bektimirova, 2016, [24]	Uzbekistan	Gout and deforming osteoarthritis	Chronic, duration omitted	40 (2.5%) and 40 (66%)	41.2 and 44,4 (mean)	Randomized, pharmaco-therapeutical, comparison of routine treatment and the same schedule plus probiotics	2 weeks Lacto - + 2 weeks Bifido-

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Table 2-2

Clinical studies that evaluated probiotics in other rheumatological diseases (Part 2)

First Author, year, [Reference]	Probiotic Features	Outcome (Statistical differences)	Outcome (No significant changes)	Adverse events
Frech et al., 2011,(33)	*B. infantis* 1 bil or *Lactobacillus GG* 1 bil 1 x day	Improvement in total SCTC GIT 2.0 score and reflux, bloating/distention, and emotional scales	Fecal soiling, diarrhea, constipation, and social scales	Not described
García-Collinot et al., 2019,(34)	*S. boulardii 200mg 2x/day*	Eradication of SIBO on each group (%): M + SB (55%); SB (33%); M (25%). Group SB: decreases in gastroesophageal reflux, diarrhea, abdominal pain, and gas/bloating/ flatulence. Group M + SB: decreases in abdominal pain and gas/bloating/flatulence.	No significant changes were observed in Group M.	Heartburn (6 total), flatulence (2 total), diarrhea (4 total), constipation (3 total)
Low et al., 2019, [35]	*L. paracasei DSM24,733, L. plantarum DSM 24,730, L. acidophilus DSM24,735, L. delbrueckii subsp. Bulgaricus DSM24,734, B. longum DSM 24,736, B. breve DSM 24,732, B infantis DSM 24,737* and *S. thermophilus DSM 24,731* 1800 bil/day	(UCLA, SCTC, GITv2 was evaluated in this study) At T2, a reduction in the GIT-reflux score subdomain was observed in the PB-PB group. An abundance of *Odoribacter* and *Prevotella* were negatively associated with the total GIT score at T2; an abundance of *Bacteroides* was positively associated with the total GIT score.	No significant differences between groups in HAQ-DI, VAS-intestinal scores, or Fecal calprotectin levels. No significant improvements were observed between placebo-PB and PB-PB groups at T1 or T2 on total GIT and GIT-distension subdomain.	None related to the probiotics
Mariela et al., 2019, (36)	A daily dose of *Lactobacillus paracasei* (10^9 CFU), *Lactobacillus rhamnosus* (10^9 CFU), *Lactobacillus acidophilus* (10^9 CFU), and *Bifidobacterium lactis* *(10^9 CFU).*	Significant decrease in Th17 cell levels in the probiotic group.	Improvements on UCLA GIT 2.0 and HAQ-DI scores in both groups with no significant differences in the probiotic group compared to placebo. No significant changes were observed in the percentages of Th1, Th2, and Treg.	No serious adverse events were reported.
Brophy et al., 2008,(37)	*B. infantis* 1.25 bil *B. bifidum* 1.25 bil *L. salivarius* 6.25 bil *L. paracasei* 1.25 bil 1 x day	No significant statistical changes were observed.	No differences between PB and placebo were observed	6 PB group [stomach cramps (3), indigestion (1), painful spots (1), dizzy spells (1)] 5 placebo group [stomach cramps (3), indigestion (1), decline in well being (1)]
Jenks et al., 2010,(38)	*B. lactis* LAFTI B94 4 bil *L. acidophilus* 4 bil *L. salivarius* K12 1 bil 2 x day	No significant statistical changes were observed.	No differences between PB and placebo were observed on BASFI, BASDAI, pain, patient global VAS, MAF, DISQ, ASQol, joint count, MASES, CRP, and ASAS20 scores.	43.8% PB group vs. 38.7% Placebo group; no serious adverse events were reported
Lambert et al., 2017,(39)	Red Clover Extract (RCE) rich in isoflavone aglycones and a heterogeneous culture of probiotic lactic acid bacteria (no taxonomy details were described) 2x/day	Significant reduction in BMD loss at L2-L4 lumbar spine vertebra, femoral neck, and trochanter Decreased collagen type 1 cross-linked C-telopeptide plasma levels and increased isoflavone plasma levels. Improved estrogen metabolite profile (increased urinary 2-OH to 16α-OH ratio) and equol-producer status	No significant changes of plasma concentrations of the following bone turnover biomarkers: osteocalcin, procollagen type I N-terminal propeptide, RANKL, undercarboxylated osteocalcin, and osteoprotegerin.	No

Table 2-2. Ending

Cheung et al., 2011,(42)	Calcium-fortified soya milk fermented with *Lactobacillus acidophilus* ATCC 4962	No significant statistical changes were observed.	There were no significant effects observed in fractional Calcium absorption in fermented soya milk than non-fermented soya milk.	N/D
Nilsson et al., 2018,(40)	*Lactobacillus reuteri* ATCCPTA 6475 $1x10^{10}$ CFU/day	Significantly reduced loss of total vBMD was observed in the PB group compared to the placebo Significantly lower reduction of trabecular bone volume fraction in PB group compared to placebo in the per-protocol population.	There were no significant differences in BMD, trabecular bone volume fraction or microarchitectural bone indices, bone biomarkers, body composition, inflammatory markers, or HbA1c.	Adverse events did not differ between groups. The two most frequent were: Change in bowel habit 21 (47%) PB group vs 23 (53%) placebo; flatulence and related conditions 5 (11%) PB group vs 5 (11%) placebo;
Jafarnejad et al., 2017,(41)	Two daily doses of Multispecies probiotic capsules containing *Lactobacillus casei* 1.3 x 10^{10} CFU; *Bifidobacterium longum* 5 × 10^{10} CFU; *Lactobacillus acidophilus* 1.5 × 10^{10} CFU; *Lactobacillus rhamnosus* 3.5 × 10^{9} CFU; *Lactobacillus bulgaricus* 2.5 × 10^{8} CFU; *Bifidobacterium breve* 1 × 10^{10} CFU; and *Streptococcus thermophilus* 1.5 × 10^{8} CFU	A significant decrease in BAP, serum CTX, PTH, and TNF-α levels in the PB group was observed compared to the placebo group.	No significant effect was observed on mean BMD; There were no significant differences in OC, urinary DPD, RANKL, OPG, RANKL/OPG ratio, 25-OH vitamin D, alkaline phosphatase, albumin, urinary and serum magnesium, phosphorous, calcium, creatinine.	N/D
Shukla et al., 2016,(44)	*S. thermophilus, B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei and L. delbrueckii*	Lower IL-10 levels in probiotics group compared to placebo	No significant differences were observed in mJSpADA score; Th1, Th2, Th17, and Treg frequencies; IFN-γ, IL-4, IL-6, IL-17, and TNF-α levels	PB versus placebo, respectively (%): Diarrhea (36 vs 45%), abdominal pain (9 vs 20%), minor infections 4.5 vs 20%), flatulence (23 vs 15%)
Malin et al., 1997,(43)	*Lactobacillus GG*	The *Lactobacillus* group observed an increase of ISC response in the IgA class, increased sASC in the IgM class, a decrease of fecal urease activity, decreased levels of fecal TNF-α. Fecal urease activity increased in patients receiving bovine colostrum.	By clinical judgment, signs of inflammatory arthritis diminished in 16 patients, all study groups alike. No significant changes were observed on the IgM, IgG, TNF-α, cellular fatty acid profiles in feces and fecal α-1-antitrypsin levels.	N/D
Groeger et al., 2013,(45)	*B. infantis 35624* 1 bil	Significantly lower CRP levels in all diseases Significantly lower TNF-α levels in Psoriasis and Chronic Fatigue Syndrome patients Significant reduction of CRP and TNF-α levels after treatment in Psoriasis and Chronic Fatigue Syndrome patients Significant reduction of IL-6 levels after treatment in Chronic Fatigue Syndrome patients	Lower levels of IL-6 in Ulcerative Colitis and Chronic Fatigue Syndrome patients. Unchanged IL-6 levels in Psoriasis patients No significant changes in CRP levels in Ulcerative Colitis patients after 6 weeks of treatment No significant changes in TNF-α in Ulcerative Colitis patients after treatment No significant changes in IL-6 levels in Ulcerative Colitis and Psoriasis patients after treatment	N/D
Roman et al., 2018,(46)	*Lactobacillus Rhamnosus GG®, Casei, Acidophilus, and Bifidobacterium Bifidus*	Improvements in cognition (fewer impulsive choices and better decision-making)	No differences between PB and placebo in pain, quality of life, fibromyalgia impact, or depressive or anxiety symptoms No changes in VAS, FIQ, SF-36, BDI, STAI, and MMSE scores	N/D

First Author, year, [Reference]	Probiotic Features	Outcome (Statistical differences)	Outcome (No significant changes)	Adverse events
Lei et al., 2017,(47)	*Lactobacillus casei Shirota* *6 x 10^9 CFU 2x/day*	Significant reduction of WOMAC total score and all subscales scores in probiotics group; Significant reduction in VAS scores in probiotics group; Significant reduction in serum hs-CRP in probiotics group; Linear solid correlations between serum hs-CRP levels and WOMAC, VAS scores	-	No serious adverse events were observed
Haidmayer et al., 2020,(48)	Nine bacterial strains of *Lactobacillus* and *Bifidobacterium*, 7.5bil per portion	Elevated gut permeability/inflammation in PsA patients (baseline). Significant decrease of fecal zonulin and calprotectin levels. Decrease of α1-antitrypsin levels in patients with high levels before treatment. A decrease in intestinal permeability and amelioration of disease activity (post-treatment).	No significant changes were observed in CD14 and lipopolysaccharide-binding protein concentrations.	No adverse events were reported.
Kamal et al., 2020,(49)	*L. acidophilus, L. bulgaricus, S. thermophilus,* and *B. bifidum*, 4 bil 2x/day	A significant reduction of the candidal load was observed in the PB group.	There are no differences between PB and placebo about the NRS pain score or the presence of erythematous candidosis and angular cheilitis.	No adverse events were reported.
Yamanaka et al., 2019,(50)	200g/day of yogurt (PA-3Y) containing *Lactobacillus gasseri* PA-3 at 8.5x10^7 cfu/g or more, made from milk fermented with strains *Lactobacillus delbrueckii ssp. bulgaricus* and *Streptococcus thermophilus.*	In a subpopulation analysis including only subjects within ± SD (1.0) of mean SUA level, it was observed a significant reduction in SUA levels of the probiotic group compared to placebo.	There were no significant differences in SUA levels or changes in SUA in the sample analysis.	No adverse events were reported.
Ziyaeva, Bektimirova, 2016, [24]	*L. acidophilus,* strain 180 (4×10^9 CFU); *B. longum,* strain 17X (4×109 CFU). 5 doses twice daily.	Significant improvement of dysbacteriosis microbiological index and clinical status, but for short duration only	Effect markedly decreased with time	No adverse events were reported.

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TNF-α and IL-1β expression and prevented cortical bone loss [61]. Furthermore, Britton et al. found that probiotics in ovariectomized mice decreased the osteoclastic bone resorption markers [TRAP5 and receptor activator of nuclear factor-kappa-B ligand], suppressed the increase of CD4+T lymphocytes, and prevented bone loss [62].

Interestingly, in fibromyalgia, a cognitive improvement was observed in the patients with PB. In gout, in a subgroup analysis, it was noted a reduction in uric acid. This fact might occur due to the positive effect of probiotics producing neuromodulatory effects on serotonin and dopamine *via* the vagus nerve and the hypothalamus [63]. Also, microbiota may modulate the extrarenal uric acid excretion and purine absorption rates [14].

On the contrary, no differences were seen in patients treated with PB in spondyloarthritis and juvenile idiopathic arthritis compared to the controls. In psoriatic arthritis subjects, an improvement in dysbiosis with reduction of calprotectin was detected. In Sjogren's syndrome, the treated groups also did not show differences, although reduced the Candida load. This fact is interesting since few studies have demonstrated an improvement in dysbiosis with PB use [24, 64]. Regarding side effects, all these manifestations were not described and possibly not noted in the patients or were mild. It is in line with the idea of PB use. In fact, studies have shown the safety of this intervention [65] although rarely some adverse effects, mostly gut-related were reported [66].

The limitations of the articles included in this systematic review were the lack of standardization of the parameters used to evaluate the results. Second, there was a disparity between the sample of patients in the studies, with the smallest sample having 10 patients [33, 48] and the largest, involved 433 patients [47]; some diseases have presented just few studies so far, such as fibromyalgia; the heterogeneity of the interventions used, with different strains, as well as very versatile parameters checked, which can be a significant confounding factor.

RECENT ADVANCES AND RECOMMENDATIONS

In 2021–23 the publishing activity in this field has been increased in spite of COVID-19 pandemic. Hence, we were able to identify 20 more reviews and original papers on the topic. In particular, it is worth to mention a recent systematic review and meta-analysis by group of French authors dedicated to efficacy of PB in rheumatoid arthritis and spondyloarthritis, also briefly concerned psoriatic arthritis [67]. The merit of this paper is that it covered not only articles in periodicals, but also abstracts of the leading international conferences on PB topic. Totally 173 references were summarized. The conclusion, however was not very optimistic; meta-analysis just showed a statistically significant decrease of C-reactive protein level with PB in rheumatoid arthritis patients. However, after excluding high-risk-of-bias trials of meta-analysis, there was no difference between PB and placebo on DAS28. The studies on spondyloarthritis and psoriatic arthritis patients showed no efficacy of PB. With such a background it is not surprising, that the latest dietary recommendations from the French Society for Rheumatology, published in March, 2022 [68] insisted that in chronic inflammatory rheumatic diseases "the use of PB … is not recommended given the limited or disparate data". The general principle of this document is a statement: "that nutritional advice is not a substitute for pharmacological treatment of inflammatory rheumatic diseases and that it is an integral part of the patients' overall care, which could help the patient actively participate in their care" [68]. But, few scholars from other countries were more enthusiastic as regards to PB therapy in rheumatology. Thus, an international group from Romania, India, Singapore and Malaysia in a narrative review [69] summarized the results of experimental animal and clinical human studies of PB effects in rheumatoid arthritis or its models. The authors concluded that PB may cause some reliable positive effect in rheumatoid arthritis, at least in short term perspective. Among other already mentioned above sanogenic mechanisms of PB action, the review emphasized the influence of PB on polarization of Th-cells counteracting to autoimmunity. This aspect of PB action in rheumatic diseases is stressed also in a recent narrative review from Byelarus [70]. The author mentioned several possible mechanisms of PB action in rheumatic diseases, including not only Th-cells polarization shift, but also translocation of epitopes and even trans-kingdom interactions, when bacteria alter rheumatic disease pathogenesis indirectly *via* their influences on phages, Viruses, Protozoa, Fungi or helminths. The review confirmed the effectiveness of PB in therapy of rheumatoid arthritis, psoriatic arthritis, osteoarthritis and spondyloarthritis. A Mexican team insists in their recent review [71] that PB may "significantly impact the preclinical stage of arthritis, based on the fact that dysbiosis occurs before clinical arthritis. The effects of interventions to modulate the microbiota could not reverse arthritis". So, their conclusion is that PB and similar interventions "may decrease the disease's incidence rather than treat or cure it" [71]. Reviewing the pathophysiology of gut-microbiota-immune system interplay in ankylosing spondylitis [72], the author emphasized the concept of dysbiosis, related chronic gut inflammation and intestinal wall leakage in provocation of autoimmune diseases, but referred to studies, which failed to prove the clinical effectiveness of PB in this disease. A list of original clinical and experimental studies of PB effect in all other above mentioned rheumatic diseases also has been replenished during 2021–23.

Thus, in experimental rat collagen-induced rheumatoid arthritis a Chinese group showed the sanogenic effect of *Lactiplantibacillus plantarum*, caused by anti-inflammatory modulation of the cytokine spectrum and inhibition of spleen cell apoptosis [73]. Similar clinical data obtained a Brazil group explored in a double-blind placebo-controlled study in 42 rheumatoid ar-

Table 3

Rheumatic disease in which probiotics were not studied yet

Diseases in which probiotics have not been studied yet
Systemic lupus erythematosus
Dermatomyositis
Polymyositis
Mixed connective tissue disease
Undifferentiated Connective tissue disease
Wegener's granulomatosis
Takayasu arteritis
Giant cell arteritis
Kawasaki disease
Polyarteritis nodosa
Churg-Strauss syndrome
Henoch-Schönlein purpura
Hypersensitivity vasculitis
Cryoglobulinemia
Behçet's disease

thritis patients the effect of 2 months treatment with a mixture of 5 different *Lactibacullus* and *Bifidobacterium* strains versus placebo [74]. The PB group showed a significant reduction in white blood cell count, tumor necrosis factor-α and interleukin-6 plasma levels, lower nitric oxide metabolites and higher sulfhydryl group as well as total radical-trapping antioxidant blood parameters. However, no differences between the two groups were observed in concentrations of interleukin-10, adiponectin, C-reactive protein, lipid hydroperoxide and protein carbonyl, as well as in erythrocyte sedimentation rate, ferritin, or DAS-28 score. Finally, an Iranian group has just started a trials of a PB cheese consumption versus placebo in rheumatoid arthritis patients, yet no results are obtained so far [75].

Different groups reported the results of PB treatment in fibromyalgia: improvement of attention with no change of memory in a randomized controlled trial [76], and use of PB in 40% of fibromyalgia cases observed in a Canadian naturopathic clinic [77]. In relation to gout, a Chinese researchers showed in mice that *Limosilactobacillus fermentum* JL-3 strain from fermented souherb noodles is able to destroy uric acid in gut and decrease its blood concentration, along with decrease of some pro-inflammatory blood parameters [78]. Similarly, a Korean group documented decrease of uric acid level and even reversal of kidney damage in experimental mice gout under the influence of *Lactobacillus brevis MJM60390*, a promising PB [79]. A narrative review from Singapore provided an abstract of up-to-date animal and human studies on the gut microbiome and its link with osteoarthritis [80]. The authors analysed 19 articles of recent period and concluded that PB can favorably modulate the course of osteoarthritis in animal models, but "current evidence in human studies is limited". An Italian author [81] expressed similar doubts in adequacy of animal model data translation in human settings as regards to PB effectiveness in osteoarthritis.

Nevertheless, a year of 2023 brought several promising experimental studies in the field. Thus, in mice two groups demonstrated the effectiveness of probiotics in experimental model of RA, as regards to both inhibition of cartilage damage [82] and prevention of the experimental RA by a single bacteria *Bifidobacterium pseudocatenulatum via several mechanisms*: by protecting the intestinal barrier and reshaped gut microbial composition, thereby elevating bile salt hydrolase (BSH) enzyme activity and increasing the levels of unconjugated secondary biliary acids to suppress aberrant T-helper 1/17-type immune responses [83]. In another experimental work a Texan group has constructed an inducible system in the probiotic *Lactobacillus reuteri* to secrete the Kv1.3 potassium blocker ShK-235 (LrS235). They showed that LrS235 culture supernatants block Kv1.3 currents and preferentially inhibit human T-effector memory (TEM) lymphocyte proliferation in vitro with a preventive effect against experimental RA [84]. Some recent clinical studies and reviews include an article from Hungary reported the effect of probiotic supplementation and fecal microbiota transplantation on the therapeutic efficacy of non-steroid anti-inflammatory drugs and opioids (able to alter microbiota) in rheumatic diseases [85]. A Chinese group introduces the presumable pathways forming the "gut dysbiosis-ocular surface-lacrimal gland axis" and discusses the advantages of restoring intestinal microecology to treat dry eye by fecal microbiota transplantation or probiotics in Sjogren's syndrome [86]. It is worth to mention also a Russian review on the role of microbiota and pathways of its probiotic correction in the ankylosing spondylitis [72].

CONCLUSION

Future studies with a more significant number of participants using a higher dosage of probiotics are desired. Furthermore, studies of probiotics in other rheumatic diseases in which these substances were not used so far, such as lupus, rheumatic fever, myositis, and vasculitis, are needed.

We reviewed the literature for all published articles on PB use in rheumatic diseases in the present study. Improvements of DAS28 inflammatory markers were noted in most studies after at least 8 weeks of PB, with no or minimal side effects. Therefore, PB might be a complementary therapy for patients with rheumatic diseases, although not a substitute for basic rheumatological treatment.

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Authors contributions:

CMG: literature screening, manuscript preparation.

HMS: Literature screening, data curation, manuscript review, manuscript writing.

LNMF: Literature screening, data curation, manuscript review.

LPC: manuscript review, pathophysiological commentaries, analysis of RISC database and recent references of 2021-23, paper submission.

JFC: Conceptualization, literature screening, and data curation, manuscript writing.

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