Tropical Journal of Pharmaceutical Research February 2023; 22 (2): 399-406
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i2.24

Original Research Article

Benefits of probiotics in rheumatoid arthritis patients: A systematic review and meta-analysis

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Sent for review: 4 August 2022 *Revised accepted: 31 January 2023*

Abstract

Purpose: *To determine the efficacy of probiotics in the treatment of rheumatoid arthritis (RA).*
Methods: *Clinical trials were searched from online medicine databases. Outcomes such as changes in inflammatory cytokines and disability parameters such as American College of Rheumatology 20 % (ACR20) response, were analyzed.*
Results: *Nine trials were eligible, and 385 patients were included. Meta-analysis showed that probiotic consumption significantly improved 28-joint disease activity (DAS28) score and decreased levels of high-sensitivity CRP (95 % CI = -3.23, -0.80; p = 0.001), tumor necrosis factor-α (95 % CI = -1.40, -0.67; p < 0.00001), interleukin (IL)-1β (95 % CI = -11.37, -0.84; p = 0.02) and IL-12 (95 % CI = -94.91, -53.58; p < 0.00001) in RA patients when compared with placebo. However, probiotics did not affect ACR20 response, erythrocyte sedimentation rate, IL-6, and IL-10, when compared with placebo.*
Conclusion: *The effects of probiotic consumption on RA are very beneficial and have some reference significance for formulating treatment guidelines for RA. However, more trials are needed to confirm the influence of probiotics on RA patients. Furthermore, more clinical trials with larger sample sizes are needed to affirm the effectiveness of probiotics in mitigating disability and inflammatory status in RA patients.*

Keywords: *Disease activity score, Tumor necrosis factor-α, Interleukin-1β, Rheumatoid arthritis, Probiotics consumption*

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INTRODUCTION

Rheumatoid arthritis (RA) causes progressive articular damage and disability [1]. Biological disease-modifying anti-rheumatic drugs (DMARDs) have produced significant reductions in disability in RA patients [2,3]. The DMARDs relieve pain and reduce disability in RA patients, but also increase side effects such as cardiovascular diseases and mortality [2,4,5].

Probiotics have been used to prevent or treat infectious and inflammatory diseases [6,7]. Recent evidence has shown changes in the structure of gut microbiota in patients with autoimmune diseases, but probiotics ameliorated these changes [7-10]. Clinical trials showed that

probiotics supplementation reduced the frequency of abdominal pain in patients with RA [7] and improved disease activity scores in 28 joints (DAS28) [6,11]. Some trials showed that probiotics significantly changed high-sensitivity CRP (hs-CRP) levels [6,11-13]. However, the effects of probiotics on inflammatory responses in RA are debatable [7-9,14].

Some trials have shown that probiotics consumption decreased interleukin (IL)-10 in RA patients when compared with placebo [7,8], while others have shown that probiotics increased serum IL-10 [12]. Several meta-analyses of eligible studies showed that probiotics supplementation achieved less obvious improvements in RA therapy [15-17].

However, the number of patients (199-361) and studies (5 to 6) included in these meta-analyses were small [15-17]. A meta-analysis showed that synbiotics and probiotics reduced inflammatory status in patients with autoimmune diseases, when compared with placebo [10]. Therefore, the impact of probiotics on RA therapy should be updated as new data are published.

The purpose of this study was to analyze the effects of probiotics on disease activity and inflammatory responses of RA patients. A total of 385 patients in nine clinical trials reporting the efficacy of probiotics (*Lactobacilli*, *Bacillus coagulans*, and *Bifidobacterium bifidum*) on inflammatory responses and articular damage were included in this study. The systematical efficacy of probiotic consumption in RA patients was evaluated using meta-analysis. Moreover, these results are expected to provide pivotal information for formulating treatment guidelines for RA.

METHODS

We designed, conducted and prepared this study strictly following the PRISMA guidelines [18].

Search strategy

Literature published up to May 2021 was retrieved from the following databases: PubMed, EMBASE, the Cochrane library and websites of clinical trial registers. The search terms were “rheumatoid arthritis”, “gut microbiota”, “intestinal microbiota” “probiotics”, “*Lactobacillus*”, “*Bifidobacterium*” and “microflora”.

Studies in the following categories were included: (a) trials designed as randomized controlled trials (RCT) or pilot studies published in English; (b) trials in which there were no restrictions on gender, nationality, or the usage of DMARDs, and (c) studies in which the intervention group received over 8 weeks of probiotics, while the control/placebo group received matching placebo agents or nothing.

Exclusion criteria

The exclusion criteria were: (a) trials that did not include control groups; (b) studies in which the subjects were not RA patients; (c) trials that included RA patients who had inflammatory bowel condition, and severe kidney and liver diseases; (d) duplicated articles or studies with overlapped cohorts; (e) publications without available outcome data, and (f) case reports, meeting summary and reviews.

Extraction of outcome data

The major outcomes were American College of Rheumatology 20 % (ACR20) response, DAS28 scores, swollen and tender joint counts, and the levels of ESR, hs-CRP, TNF-α, IL-6, IL-10, IL-12, and 1β in RA patients.

Assessment of article quality

Two reviewers independently assessed study quality using a modified 7-point Jadad scale that consists of 7 items (Table 1) [19]. Trials with scores ≥ 3 were of high-quality, while those with a scores ≤ 2 were of low-quality. Further reviews and dialogue were applied if there was any disagreement. The Begg’s test and Egger’s test were applied to evaluate publication bias.

Statistical and meta-analysis

Meta-analyses were performed using RevMan 5.0. Data heterogeneity was assessed using the inconsistency index (I^2), considering the *p* value of χ^2 test. Subgroup analysis was carried out to assess the source of heterogeneity. The fixed- and random-effects models were applied in the meta-analysis of homogeneous ($I^2 < 50$ %, $p < 0.1$) and heterogeneous ($I^2 \geq 50$ %, $p > 0.1$) data, respectively.

The evidence strength of meta-analysis was evaluated using the Cochrane Collaboration Grade Profiler (GradePro; http://ims.cochrane.org).

Table 1: Quality assessment of 9 included trials

Reference	RSG	AC	PB	OAB	IO	SR	Wd	Score
[9]	√	√	√	√	√	√	×	6
[8]	√	√	√	√	√	√	×	6
[14]	√	√	×	√	×	×	×	3
[12]	√	√	√	√	√	√	×	6
[13]	√	√	√	√	×	√	√	6
[6]	√	√	√	√	√	√	√	7
[20]	×	×	√	√	×	√	×	3
[7]	√	√	√	√	×	√	×	5
[11]	√	√	√	√	√	√	√	7

Abbreviations: AC = allocation concealment; IO = incomplete outcome data; OAB = outcome assessment blinded; PB = participants blinded; RSG = random sequence generation; SR, selective reporting; Wd = withdrawals

RESULTS

Study selection

The search identified 485 publications, including 189 duplicates. After reading of the title and abstract, 243 studies were excluded, leaving 53 studies for full-text review. Subsequently, 44 articles were discarded. Finally, 9 trials [6-9, 11-14, 20] were included in this study (**Table 2**).

Characteristics of studies

The articles were published between 1998 and 2017 (Table 2). Eight trials were RCTs, while one was designed as a pilot study. A total of 385 participants were included. The patients were Canadians [9], Iranians [6,8,11,12], Finns [14,20], Indians [7] and New Zealanders [13]. All patients suffered from RA for more than one year. Patients in the intervention group received 8 or 12 weeks of probiotics. The probiotics received by patients included *Lactobacillus rhamnosus*, *L. reuteri*, *L. dophilus*, *L. casei*, *Bacillus coagulans* and *Bifidobacterium bifidum*.

Quality of studies

The 9 trials had Jadad scores ranging from 3 to 7, with a median score of 5.3 (Table 1), suggesting that the included studies were of high quality.

Risk of study bias

The results of Begg's test (t = -0.93, p = 0.407, 95 % CI = -28.70, 14.34) and Egger's tests (P-Q = -7, z = 1.13, Pr > |z| = 0.260, continuity corrected) showed that the included studies were less likely to have publication bias.

Data from individual studies

In 9 studies included, 5 [6,8,11,12,20] reported that patients who received probiotics had decreased DAS28 scores (MD ranged from -1.6 to -0.25), when compared with placebo (MD ranged from -0.3 to 0.02). One study [9] showed that placebo achieved lower DAS28 scores than probiotics (-2.9 over -2.1, p = 0.77). The other three trials [7,13,14] did not report changes in DAS28 scores. Five studies [6,7,11,12,14] reported that probiotics led to significantly lower hs-CRP (MD ranged from -3.3 to 1.0) than placebo (MD ranged from -1.5 to 3.07), while one [9] reported the opposite result (1.2 for probiotic versus 1.8 for placebo). Three-to-five studies showed changes in swollen and tender joint counts, ESR and cytokine levels. Pineda *et al* [9] reported that changes in DAS28, SJC, ESR and cytokines (TNF-α, IL-6, IL-10 and IL-1β) favored placebo over anti-inflammatory drugs plus probiotics. Shukla *et al* [7] included only children (13 - 19 years old; Table 2).

Meta-analysis

The effect of probiotics on DAS28 scores, ACR20, number of swollen and tender joints, hs-CRP and cytokines were evaluated. Meta-analyses indicated that probiotics significantly changed DAS28 scores (I^2 = 88 %, mean difference, MD = -0.39, 95 % CI = -0.61, -0.17, p = 0.0005; Figure 1 A), hs-CRP (I^2 = 61 %, MD = -2.01, 95 % CI = -3.23, -0.80; p = 0.001; Figure 1 B), TNF-α (I^2 = 9 %, MD = -1.03, 95 % CI = -1.40, -0.67, p < 0.00001; Figure 2 A), IL-1β (I^2 = 27 %, MD = -6.10, 95 % CI = -11.37, -0.84; p = 0.02; Figure 2 B) and IL-12 (I^2 = 0 %, MD = -74.25, 95 % CI = -94.91, -53.58; p < 0.00001; Figure 2 C) in RA patients, when compared with placebo. Probiotics did not achieve significant changes in ACR20, ESR and IL-6/10 in RA patients.

Table 2: Characteristics of 9 studies included

Reference	Region	Design	Mean age (SD)	RA course (yr, mean/SD)	Participant (age, years)	Group size	Probiotics dose	Duration (week)
						Probiotic/placebo		
[9]	Canada	RCT	63.8 (7.5)	19 (12.4)	≥ 4 SJs and TJs (18–80)	15/14	*L. rhamnosus* GR-1, *L. reuteri* RC-14 (2×10^9 CFU, b.i.d.)	12
[8]	Iran	RCT	41.14 (12.65)	5.25 (3.75, 10.0)	inactive/moderate RA (20–80)	22/24	*L. casei* 01 (≥ 1×10^8 CFU, q.d.)	8
[14]	Finland	Pilot	50 (10)	8.3 (7.3)	≥ 1 year of RA, ≥ 3 months medication (18–64)	8/13	*L. rhamnosus* GG (≥ 5×10^9 CFU, b.i.d.)	12
[12]	Iran	RCT	41.14 (12.65)	5.25 (6.87)	≥ 1 year of RA, 3 months medication (20–80)	22/24	*L. casei* 01 (≥ 1×10^8 CFU, q.d.)	8
[13]	New Zealand	RCT	62.5 (36,82)	11.8 (5.4)	≥ 1 year of RA (≤ 80)	22/22	*B. coagulans* GBI-30, 6086 (2×10^9 CFU, q.d.)	8
[6]	Iran	RCT	52.2 (12.2)	7 (6.7)	moderate/acute RA (25–70)	30/30	*L. acidophilus*, *L. casei*, *B. bifidum* (2×10^9 CFU, q.d.)	8
[20]	Finland	RCT	49.1 (7.1)	12.6 (10.3)	≥ 3 SJs or ≥ 5 TJs (ESR > 20 mm/h or CRP > 10 mg/L)	19/20	*L. plantarum* and *L. brevis* NR	12
[7]	India	RCT	16 (13–19)	3 (1, 6)	≥ 1 SJ, enthesitis (MASES > 2), ESR >30 mm/h	23/23	Eight strains (112.5×10^9 BC)	12
[11]	Iran	RCT	49.3 (11)	7.7 (6.1)	moderate/severe RA (25–70)	27/27	*L. acidophilus*, *L. casei*, *B.bifidum* (2×10^9 CFU, q.d.)	8

Abbreviations: b.i.d. = two times daily; CFU = colony-forming unit; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; q.d.= once a day; SJs =swollen joints; TJs = tender joints

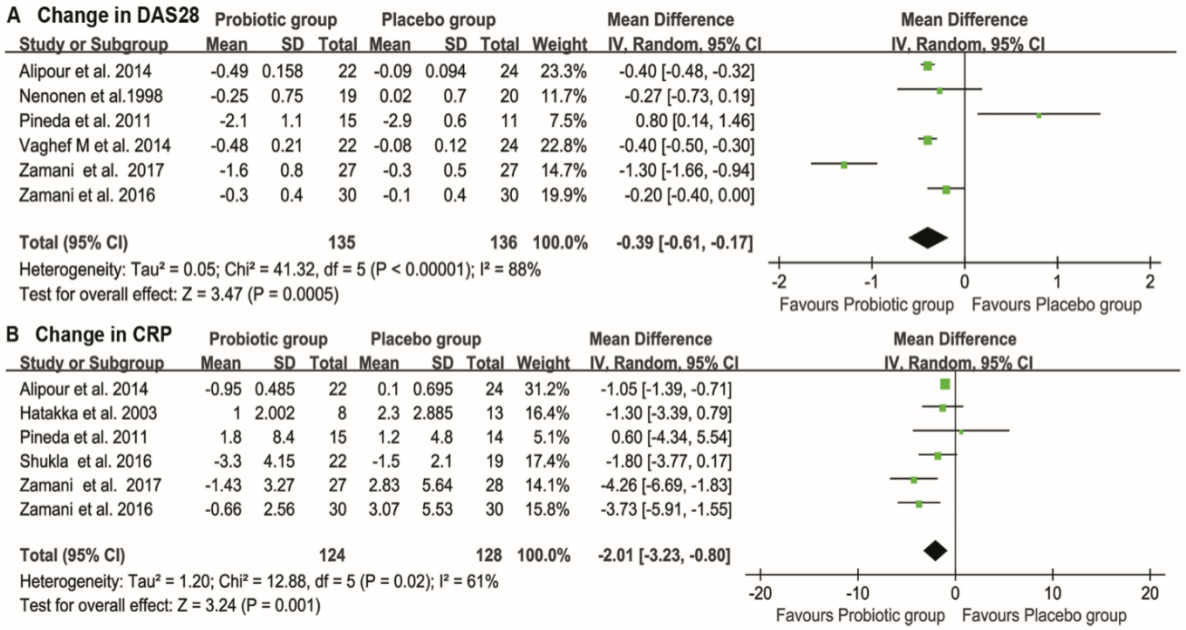

Figure 1: Effect of probiotics on disease activity scores in 28 joints (DAS28) and C-reactive protein (CRP, B) in rheumatoid arthritis patients. (CI = confidence interval; IV = inverse variance; SD = standard deviation)

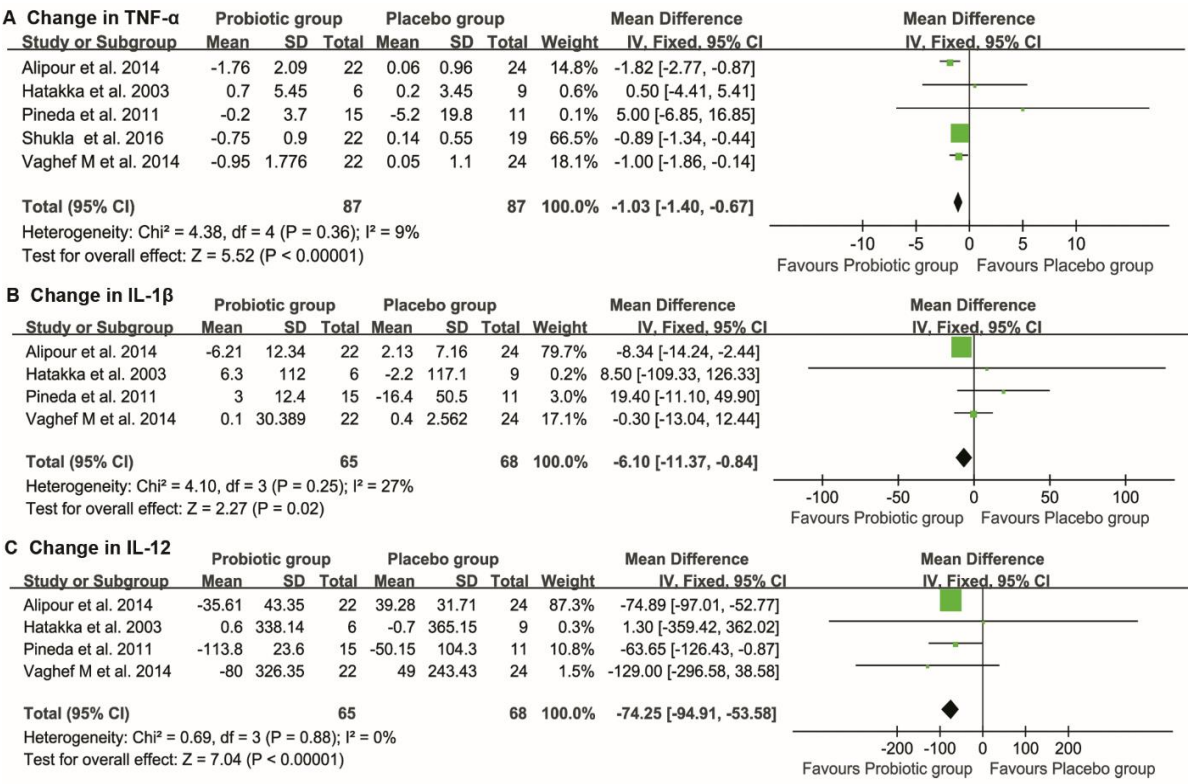

Figure 2: Effect of probiotics on TNF-α (A), IL-1β (B) and IL-12 (C) in rheumatoid arthritis patients. (CI = confidence interval; IV = inverse variance; SD = standard deviation)

DISCUSSION

This meta-analysis of 9 clinical trials and 385 patients showed that probiotics consumption significantly changed DAS28 scores and levels of hs-CRP, TNF-α, IL-1β and 12 in RA patients, when compared with placebo. However, the effects of probiotics on ACR20, ESR, IL-6 and 10 were not obvious. These results show that probiotics supplementation produced considerable effect on RA.

The dysbiosis of gut microbiota is associated with a variety of autoimmune diseases such as pemphigus vulgaris, ankylosing spondylitis, RA, systemic lupus erythematosus and inflammatory bowel disease [21-25]. The T cell sub-populations may be influenced by the abundance of microbiota or alterations in their compositional diversity [26,27]. Disruptions in intestinal microbiota composition increased T-helper (Th)17 cells and IL-17 in gnotobiotic mice [28]. Evidence has shown that high salt diet-induced reduction in the gut *L.* sp. induced exacerbation of colitis in mice [29]. The study by Miranda *et al* [29] indicated that the consumption of high-salt diet stimulated IL-7, Rac1, Mapk3, and Map2k1, and suppressed IL-1β. Additionally, DMARDs administration partially reversed the alterations in the gut microbiota in RA patients [30,31]. These evidences show the vital function of gut microbiome in immune system.

Probiotics benefit the host through the following three pathways: interference with potential pathogens, antimicrobial effect, improvement of barrier function, production of neurotransmitters, and immunomodulation [32,34]. Current animal experiments and clinical trials have demonstrated the therapeutic efficacies of probiotics, especially *Bifidobacterium* and *Lactobacillus,* on inflammation and autoimmune ailments [35,36]. It was found that the intestinal flora was imbalanced *via* feeding *L. reuteri*, resulting in improved mouse survival period [37,38]. *Lactobacillus reuteri* decreased the occurrence and extent of experimental necrosis-inducing enterocolitis, and decreased IL-1β and $Foxp3^{+}$-regulating T cells [37,38]. These studies showed that probiotic supplementation benefits the immune system in the host.

A meta-analysis by Pan *et al* [17] showed that probiotic supplementation significantly reduced hs-CRP, TNF-α, IL-12 and 1β in RA patients. However, the other two meta-analysis studies [15,16] showed that probiotics did not change the levels of inflammatory parameters. A meta-analysis showed that synbiotics and probiotics reduced hs-CRP and cytokine levels in RA and systemic lupus erythematosus patients, when compared with placebo [10]. The present meta-analysis of 9 clinical trials and 385 patients reported the efficacy of probiotics such as *Lactobacilli*, *Bacillus coagulans*, and *Bifidobacterium bifidum* in RA patients. We found that probiotics consumption significantly decreased DAS28 scores, hs-CRP, TNF-α, IL-1β, and 12 in RA patients, when compared with placebo, but did not change other inflammatory cytokines. These results show that probiotic intervention had non-negligible effect on RA. Therefore, the efficacy of probiotics in RA therapy should be explored and updated systematically with more trials and larger sample sizes.

The limitations that exist in this study are the small number of trials included (n = 9) and low number of patients included in each trial (21 - 60 patients). The limitations prevent us from unhesitatingly confirming the efficacy of probiotics in improving in the disability and inflammatory status in RA patients.

CONCLUSION

This meta-analysis of 9 trials and 385 patients shows that probiotics significantly change levels of DAS28, hs-CRP, TNF-α, IL-12 and 1β in RA patients. However, probiotics exhibit less obvious effect on ESR, IL-6 and IL-10. This study shows that the efficacy of probiotics intervention in RA patients is beneficial, and has some reference significance for formulating drugs for RA treatment. However, more clinical trials with larger sample sizes are needed to affirm the effectiveness of probiotics in mitigating the disability and inflammatory status in RA patients.

DECLARATIONS

Acknowledgements

This study was supported by the National Natural Science Foundation of China (NSFC; no. 81774104).

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this

article will be borne by the authors. Concept and design of this study: Ya-Qi Yuan and Wei Ji; Acquisition, analysis, or interpretation of data: Ya-Qi Yuan, Wei Ji, Zhi-Guo Lin, and Ke Gan. Statistical analysis: Ya-Qi Yuan. Manuscript drafting: Ya-Qi Yuan. Manuscript revision: Wei Ji, Zhi-Guo Lin, and Ke Gan. All authors approved of the final version.

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