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ORIGINAL ARTICLE

The therapeutic effect of probiotics on rheumatoid arthritis: a systematic review and meta-analysis of randomized control trials

Abdelrahman Tarek Mohammed[1] · Mohammed Khattab[1] · Ali Mahmoud Ahmed[1] · Tarek Turk[2] · Nora Sakr[3] · Adham M. Khalil[4] · Mohamed Abdelhalim[4] · Bisher Sawaf[5] · Kenji Hirayama[6] · Nguyen Tien Huy[7,8,9]

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Abstract Rheumatoid arthritis is an autoimmune disease in which probiotics appears to have an immune modulating action along with decreased inflammatory process. Therefore, we aim to investigate the efficacy of probiotics as an adjuvant therapy for rheumatoid arthritis. A comprehensive literature search was performed using nine databases including PubMed and Web of Science. Interesting data was extracted and meta-analyzed. We assessed the risk of bias using Cochrane Collaboration's tool. The protocol was registered in PROSPERO (CRD 42016036769). We found nine studies involving 361 patients who met our eligibility criteria. Our meta-analysis indicated that pro-inflammatory cytokine IL-6 was significantly lower in the probiotics compared with the placebo group (standardized mean difference = − 0.708; 95% confidence interval (CI) − 1.370 to 0.047, P = 0.036). However, there was no difference between probiotics and placebo in disease activity score (mean difference 0.023; 95% CI − 0.584 to 0.631, P = 0.940). Probiotics lowered pro-inflammatory cytokines IL-6 in RA; however, its clinical effect is still unclear. Hence, many high-quality randomized controlled trials (RCTs) are still needed to prove this effect.

Keywords Cytokines · Disease activity score · Meta-analysis · Probiotics · Rheumatoid arthritis · Systematic review

Introduction

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disease that affects multiple joints of the body causing erosion of cartilage, bone, and eventually joint deformities [1, 2]. The prevalence of rheumatoid arthritis ranges from 0.5 to 1% among adults worldwide, with a female-to-male ratio of 2:1 to 3:1 [3–5]. Despite the cumulative intensive work and reporting of many factors that can significantly contribute to

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✉ Nguyen Tien Huy
nguyentienhuy@tdt.edu.vn

[1] Faculty of Medicine, Al-Azhar University, Cairo 11884, Egypt

[2] Faculty of Medicine, Damascus University, Damascus, Syria

[3] Faculty of Medicine, Menoufia University, Menoufia, Egypt

[4] Faculty of Medicine, Zagazig University, Zagazig 44519, Egypt

[5] Faculty of Medicine, Syrian Private University, Damascus, Syria

[6] Department of Immunogenetics, Institute of Tropical Medicine (NEKKEN), Leading Graduate School Program, and Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan

[7] Evidence Based Medicine Research Group and Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam

[8] Department of Clinical Product Development, Institute of Tropical Medicine (NEKKEN), Leading Graduate School Program, and Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan

[9] Center for Molecular Bio-Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang, District 5, Ho Chi Minh 70000, Viet Nam

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initiation and propagation of RA, the exact etiology and physiopathology are still unknown [4, 6].

Human studies have shown some evidence of a relationship between altered intestinal microbiota and the development of RA [7, 8]. A study comparing germ-free rats with those raised under conventional conditions shows that the germ-free rats were vulnerable to development of a relatively more severe RA than those that were grown under conventional conditions which showed lesser incidence and milder disease [9]. Furthermore, it had been shown that 20% of patients with bowel inflammation in the form of Crohn's disease and ulcerative colitis developed joint inflammation [10]. These findings support the hypothesis that altered microbiota may have a role in RA development. Moreover, some studies indicate that fasting and vegan diet are associated with decreased RA activity, which can be attributed to altered gut microbes as well [11, 12]. It is suggested that patients with inflammatory arthritis have a high gut permeability, which allows more bacteria to enter the bloodstream [13]. The antigens of these bacteria are expected to trigger an immune response and, consequently, take a role in the pathogenesis of some autoimmune diseases including RA [14, 15].

Probiotics, administrated live microbiota, are not only used to balance the gastrointestinal microbes but also have been suggested to be useful in controlling several disorders. Among all reported advantages of probiotics, regulation of immune system function remains the most beneficial function of probiotic bacteria. This effect on the immune system is different regarding the strain of the probiotic bacteria; some are used to stimulate the immune response and therefore can be beneficial for patients suffering from immune deficiencies, and some inhibit or down regulate the immune response and therefore can be beneficial for patients suffering from increased the immune response like RA [16, 17]. Probiotics have a large safety margin with minimal reported complications like constipation, nausea, and thirst [18]. Administration of probiotics, in a limited number of animal and human studies, has improved clinical manifestations, reduced pro-inflammatory cytokines, and increased regulatory cytokines [19, 20]. The anti-inflammatory effect of some strains of macrobiotics raised the question of whether these strains can alleviate the symptoms of RA. Securing the gut microbiome and solving the mystery of leaky gut syndromes can be a milestone on the path of providing highly effective and less-side-effect drugs that decrease RA activity [21]. In this study, we aim to systematically review and meta-analyze all relevant published clinical trials to investigate the effectiveness of probiotics in the treatment of RA.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22] (Supplementary PRISMA checklist S1). The study protocol was registered in PROSPERO (CRD 42016036769). The design does not require ethical approval according to our institution policy.

Eligibility criteria

We included any randomized or quasi-randomized clinical trial that discusses the efficacy of probiotics on humans as a treatment for RA. No restriction was taken regarding certain population, race, place, sex, age, ethnicity, language, or publication date. We excluded case reports, case series, letters, editorial comments, thesis, reviews, book chapters, news, or only abstracts. We also excluded papers if their data cannot be extracted.

Search strategy and study selection

A comprehensive literature search for relevant articles was performed up to October 2015 then updated in February 2017 using PubMed, Scopus, Web of Science (ISI), Google Scholar, Popline, Global Health Library (GHL), Virtual Health Library (VHL) including Cochrane database, NYAM (New York Academy of Medicine), and SIGLE (System for Information on Grey Literature in Europe). The used search string was ((“Rheumatoid arthritis” OR “atrophic arthritis”) AND (probiotics OR probiotic OR “faecal transplantation” OR “fecal transplantation” OR “feces transplantation” OR “faeces transplantation” OR “stool transplantation” OR “bacillus coagulans” OR microbiota OR excreta OR acidophilus OR prebiotic OR prebiotics OR lactobacillus OR microbiome OR flora OR microflora). This string was modified to match each database. A manual search was carried out through screening the references of the included studies and searching in the journals of nutrition and immunologic diseases. Search results were retrieved and duplicates were removed using EndNote X7.4 software for Windows. Three independent reviewers screened the proposed articles in order to include the relevant ones according to our inclusion and exclusion criteria. Screening title and abstract took place initially followed by full-text screening. Disagreement was resolved by discussion and consensus between reviewers and senior researchers.

Data extraction

Three independent reviewers extracted the data of interest from the included articles using the standardized extraction form. Any discrepancy was resolved by discussion to reach the consensus. The extraction form was developed by a pilot extraction of three randomly selected papers performed by all authors. The extracted variables included demographics of the included patients. We extracted clinical and laboratory

variables that assess the state of RA as disease activity score (DAS), health assessment questionnaire (HAQ), tender joints count (TJC), and swollen joints count (SJC). The level of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were extracted as well. In order to assess the inflammatory process and immunity, the pro-inflammatory cytokines like interleukin 1β (IL-1β), IL-6, IL-12, and tumor necrosis factor-α (TNF-α) were extracted. Also, IL-10 was assessed as an anti-inflammatory cytokine. If data was presented as graph only, it was extracted using PlotDigitizer software (http://plotdigitizer.sourceforge.net/).

Risk of bias assessment

Three independent authors assessed the risk of bias in the included RCTs using the Cochrane Collaboration's tool for risk of bias assessment. Any disagreement between them was resolved by discussion. Accordingly, seven items, random sequence generation, blinding of participants and personnel, incomplete outcome data, allocation concealment, selective outcome reporting, blinding of outcome assessments, and other risks of bias, were assessed.

Statistical analysis

Meta-analysis was performed by Comprehensive Meta-Analysis software (version 2). Fixed-effect model was used if there is no significant heterogeneity. In the case of significant statistical or clinical heterogeneity, random effect model was manipulated. Statistical heterogeneity was assessed using χ^2 test and I^2 statistics. Significant heterogeneity was considered when χ^2 test has a P value < 0.1 or I^2 test value > 50%. In the case of continuous data, mean difference (MD) along with 95% confidence interval (95% CI) were used in case of identical scales across studies; otherwise, standardized mean difference (SMD) was used. Sensitivity analysis was performed to examine the effect of one study removal on the results.

Results

Search results and characteristics of included studies

The initial search of different databases, mentioned before, had identified 1948 reports from which 625 reports have been excluded by EndNote software as duplicates. The titles and abstracts of the remaining 1323 reports were screened. The full texts of the 60 reports, included from the title and abstract screening, were screened for eligibility criteria. After exclusion of 53 reports, we had seven papers for reviewing. The updated search revealed 368 reports of which two papers were added to the final included papers. The manual search of references of the included papers did not include any further papers. The meta-analysis was done on six papers (Fig. 1). The total number of patients with RA in the included studies was 361 patients. The six papers of meta-analysis compared probiotics (with 120 patients) with placebo (with 126 patients). Hatakka et al. [23] used *Lactobacillus rhamnosus* as a probiotic, Mandel et al. [24] used *Bacillus coagulans*, Alipour et al. [25] used *Lactobacillus casei*, Pineda et al. [26] used *Lactobacillus rhamnosus* and *Lactobacillus reuteri*, and Zamani et al. [27] used *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum.* The three papers were not included in the meta-analysis due to inconsistency with other papers and using different variables in assessing RA. One paper investigated the effect of probiotics on oxidative stress indices in RA patients [28], and the other two papers investigated the effect of diet rich in *Lactobacillus* on RA [29, 30]. Table 1 represents the characteristics and demographic data of the included papers.

Risk of bias assessment

The risk of bias assessment is illustrated in Fig. 2 and Supplementary Table S2. The assessment of results indicated that the quality of included papers ranges from moderate to high. Some key variables that should be present in such studies were not adequately reported like DAS and HAQ score which were neglected by some studies. The most items with high risk of bias is selective reporting and incomplete outcome data.

Outcomes

Any variable represented by two or more papers was eligible for meta-analysis. The meta-analyzed variables were DAS, CRP, ESR, HAQ, SJC, TJC, and cytokines (IL1β, IL6, IL10, IL12, and TNF-α). Table 2 represent the meta-analysis results of these variables.

Regarding DAS, there was no difference between probiotic group and placebo group (MD 0.023, 95% CI − 0.584 to 0.631, P = 0.940) (Table 2 and Fig. 3a).

Other clinical variables like HAQ, SJC, and CRP did not show a significant difference between both groups as shown from the pooled MD of the three variables, respectively (MD − 0.108, 95% CI − 0.229 to 0.013, P = 0.081; MD 0.171, 95% CI − 0.391 to 0.733, P = 0.551; MD − 1.401, 95% CI − 4.062 to 1.261, P = 0.302) (Table 2 and Fig. 3b) (Supplementary Fig. S3).

Interestingly, IL-1β showed a significant increase in the placebo against probiotics after removal of Hatakka et al. [23] (MD − 8.106, 95% CI − 13.843 to 2.369, P = 0.006) compared with no difference with including Hatakka's results (SMD 0.056, 95% CI − 0.995 to 1.107, P = 0.916) (Table 2) (Supplementary Table S4 and Fig. S5). IL-6 showed a significant difference between both groups (SMD − 0.708, 95% CI

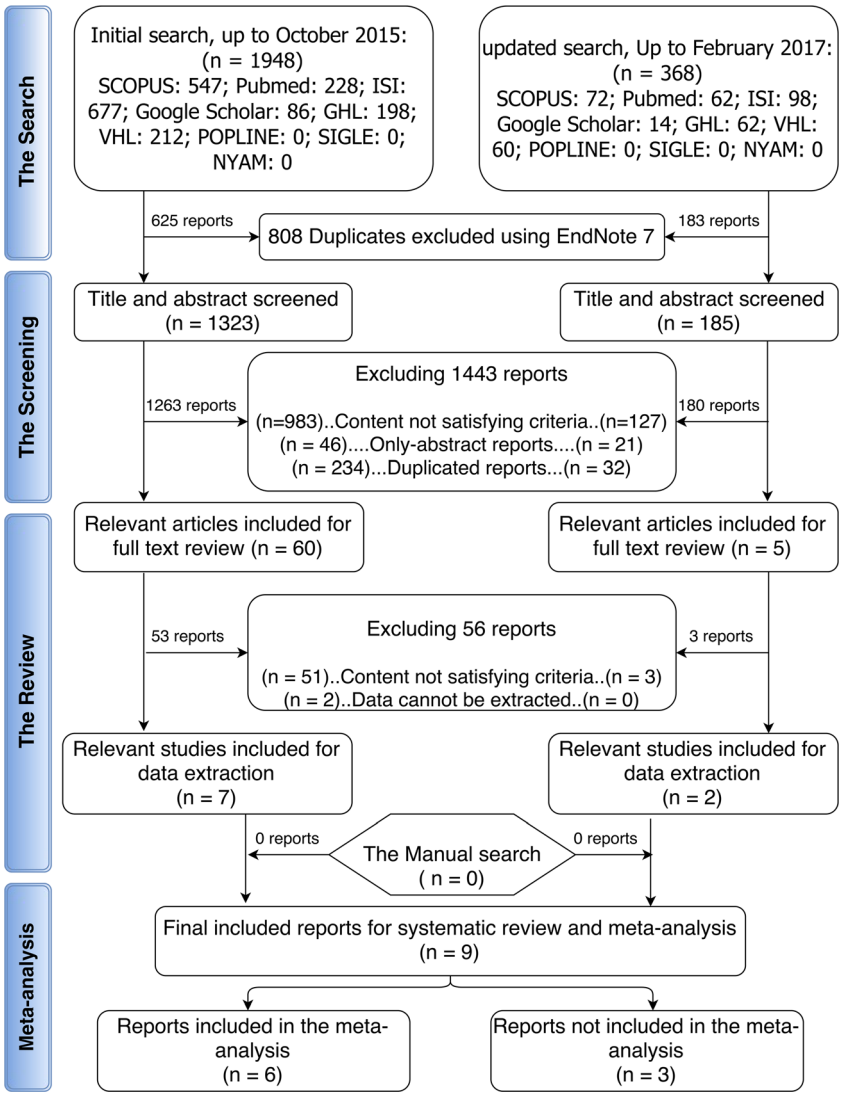

Fig. 1 Flow chart illustrating the sequence procedure of including articles

− 1.370 to 0.047, $P = 0.036$) (Fig. 3c), and this significant decrease in probiotics group remained after the removal of the results of Hatakka et al. [23], Pineda et al. [26], or Shukla et al. [31] (Table 2) (Supplementary Table S4). IL-10 did not have any difference between both groups (SMD 0.599, 95% CI − 0.719 to 1.917, $P = 0.373$) (Table 2) (Supplementary Table S4 and Fig. S5).

Discussion

Probiotics have been discussed as an adjuvant safe therapy of RA in many studies. They have shown a potential effect on RA. This potential effect acts mainly on the imbalance in cytokine level in RA patients. This imbalance of cytokine production leads to induction of inflammation and other immunity-related diseases. RA can be produced as a result of overproduction of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 and decrease in the production of anti-inflammatory cytokines like IL-10. Subsequently, the pro-inflammatory cytokines have an important role in the pathogenesis and assessment of the disease activity and inflammatory status [32].

The elevation of IL-6, as a pro-inflammatory cytokine, correlates with joints destruction and the progression of the disease [33]. In our case, IL-6 showed a significant decrease in probiotics group comparing with placebo. This significance was confirmed by the removal of Hatakka's or Pineda's results. Therefore, probiotics can show a potential therapeutic effect for RA based on IL-6 level. Regarding other pro-inflammatory cytokines, there was no significant difference between probiotics and placebo which gives rise to a controversy about the effect of probiotics.

After sensitivity analysis, the pro-inflammatory cytokines, except for TNF-α and IL-12, showed a significant decrease in the probiotics group comparing with placebo which indicates a positive effect of probiotics in improving the pathogenesis of RA. This is justified by the shifting in the results occurred by

Table 1 Baseline characteristics of the patients in the included RCTs

Author, year	Probiotics bacterial strain	Dose	Groups	Sample	Age mean (SD)	Sex females *N* (%)	Duration of RA (months) mean (SD)	Current medication					Follow-up duration (days)
								DMARDs *N* (%)	Methotrexate *N* (%)	Corticosteroids *N* (%)	NSAIDs *N* (%)	Hydroxychloroquine *N* (%)	
Malin, 1997	*Lactobacillus GG*	2×10^{10} CFU	Probiotics	10	8 (1–-15)[b]	5 (50)	11 (2–21)[b]	4 (40)	0	NR	6 (60)	4 (40)	28
			Colostrum	10	8 (2–-15)[b]	6 (60)	11 (3–22)[b]	3 (30)	1 (10)	NR	6 (60)	4 (40)	
			Immune colos-trum	10	7 (2–-15)[b]	6 (60)	7 (1–18)[b]	1 (10)	2 (20)	NR	7 (70)	7 (70)	
Vaghef-Mehrabany, 2015	*Lactobacillus casei*	10^8 CFU	Probiotics	22	41.14 (12.-6)	22 (100)	63 (45–120)[c]	NR	15 (68.2)	21 (95.5)	NR	18 (81.8)	56
			Placebo	24	44.29 (9.7-7)	24 (100)	57 (36–108)[c]	NR	20 (83.3)	23 (95.8)	NR	18 (75)	
Mandel, 2010	*Bacillus coagulans*	2×10^9 CFU	Probiotics	22	NR	NR	NR	18 (81.8)	NR	NR	2 (9.1)	NR	60
			Placebo	22	NR	NR	NR	17 (77.3)	NR	NR	3 (13.6)	NR	
Alipour, 2014	*Lactobacillus casei*	10^8 CFU	Probiotics	22	41.14 (12.-6)	22 (100)	63 (45–120)[c]	NR	15 (68.2)	21 (95.5)	NR	18 (81.8)	58
			Placebo	24	44.29 (9.7-7)	24 (100)	57 (36–108)[c]	NR	20 (83.3)	23 (95.8)	NR	18 (75)	
Hatakka, 2003	*Lactobacillus rhamnosus*	10^{10} CFU	Probiotics	8	50 (10)	4 (50)	99.6 (87.6)	8 (100)	NR	6 (75)	6 (75)	NR	360
			Placebo	13	53 (7)	8 (61.5)	132 (98.4)	13 (100)	NR	8 (62)	10 (77)	NR	
Pineda, 2011	*L. rhamnosus and L. reuteri*	2×10^9 CFU	Probiotics	15	63.8 (7.5)	14 (93.-3)	228 (148.8)	NR	11 (73)	4 (26)	NR	6 (40)	90
			Placebo	14	59.1 (9.1)	13 (92.-8)	164.4 (100.8)	NR	11 (78)	3 (21)	NR	7 (50)	
Nenonen, 1998	*Lactobacillus plantarum* and *L. brevis*	NR	Probiotics	19	49.1 (7.1)	18 (95)	151.2 (123.6)	NR	10 (52.6)	10 (52.6)	16 (84.2)	NR	90
			Control	20	55.6 (10.-8)	19 (95)	193.2 (163.2)	NR	5 (25)	9 (45)	18 (90)	NR	
Shukla, 2016	Eight different strains[d]	112.5×10^9 BC	Probiotics	23	16 (1-3–1-9)	2 (8.7)	36 (18–60)	0	0	0	23 (100)	0	84

Table 1 (continued)

Author, year	Probiotics bacterial strain	Dose	Groups	Sample	Age mean (SD)	Sex females *N* (%)	Duration of RA (months) mean (SD)	Current medication					Follow-up duration (days)
								DMARDs *N* (%)	Methotrexate *N* (%)	Corticosteroids *N* (%)	NSAIDs *N* (%)	Hydroxychloroquine *N* (%)	
			Placebo	23	15 (1-4–1-6)	0	36 (12–72)	0	0	0	23 (100)	0	
Zamani, 2016	*L. acidophilus*, *L. casei*, *Bifidobacterium bifidum*	2×10^9 CFU/g each strain	Probiotics	30	52.2 (12.-2)	25 (83.-3)	84 (80.4)		29 (96.7)	27 (90)		20 (66.7)	56
			Placebo	30	50.6 (13.-1)	26 (86.-7)	84 (68.4)		29 (96.7)	28 (93.3)		21 (70)	

CFU, colony-forming unit; BC, bacterial cell; SD, standard deviation; RA, rheumatoid arthritis; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; NR, not reported

[a] Age and disease duration are presented as mean and standard deviation (SD). Sex and current medications are presented as number and percentage (%)

[b] Data presented as mean (range)

[c] Data are presented as median (IQR)

[d] The eight strains are *Streptococcus thermophilus*, *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, and *L. delbrueckii*

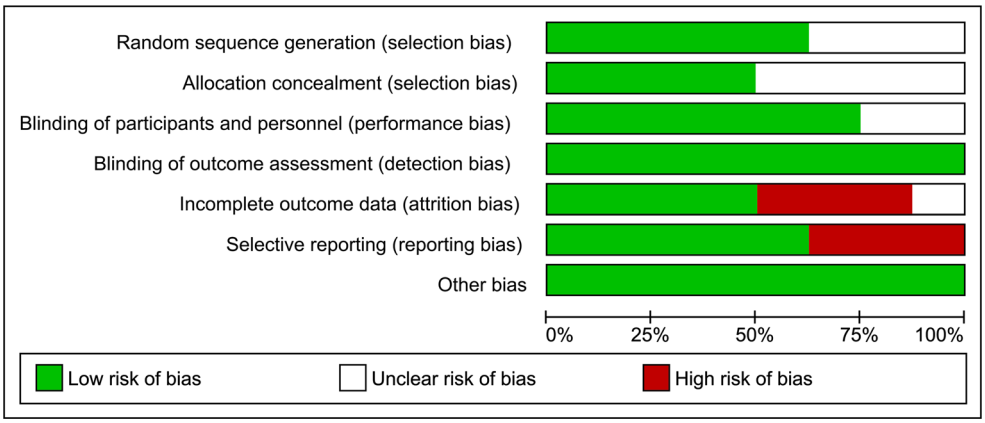

Fig. 2 Summary of risk of bias assessment according to Cochrane Collaboration tool

Hatakka et al. [23], which has a small number of patients and very weak power with a weak presentation of data. This also indicates that this significance is not convinced and needs more studies to be confirmed.

The effect of the pro-inflammatory cytokines is antagonized by the anti-inflammatory cytokines like IL-10. So increase in the level of IL-10 would restore the balance and control of the inflammatory progress [33]. In our study, the regulatory cytokines IL-10 did not show a significant increase in the probiotics group over the placebo.

The absence of significance for many clinical and laboratory variables was mainly due to large variability between studies. This can be justified by the usage of different strains of probiotics which affects the immunological response derived from each study. Also, the dosages used in these studies were different from each other. The

Table 2 Meta-analysis of the change in the clinical and laboratory parameters in rheumatoid arthritis patients

Variable	Number of studies	Total sample size Probiotics/placebo	Heterogeneity		Model	Overall effect	
			P value	I^2		*P* value	Mean difference (95% CI)
DAS	3	67/65	0.025	73	Random	0.940	0.023 (− 0.584 to 0.631)
CRP	5	96/95	<0.001	82.3	Random	0.134	− 2.660 (− 6.144 to 0.823)
HAQ	2	23/24	0.806	0	Random	0.081	− 0.108 (− 0.229 to 0.013)
ESR	4	65/64	0.032	66.0	Random	0.565	1.861 (− 4.481 to 8.202)
SJC	5	96/95	0.070	53.9	Random	0.551	0.171 (− 0.391 to 0.733)
TJC	5	96/95	0.007	71.5	Random	0.437	0.379 (− 0.578 to 1.336)
IL-1β	3	43/44	0.006	80.4	Random	0.916	0.056[a] (− 0.995 to 1.107)
IL-6	4	64/63	0.028	66.9	Random	0.036	− 0.708[a] (− 1.370 to 0.047)
IL-10	4	64/63	<0.001	91.2	Random	0.373	0.599[a] (− 0.719 to 1.917)
IL-12	3	43/44	0	92.7	Random	0.754	− 0.287 (− 2.087 to 1.512)
TNF-α	4	64/63	0.001	80.5	Random	0.831	− 0.092[a] (− 0.940 to 0.756)

Effect measure was calculated as mean difference with 95% confidence intervals (95% CI). Heterogeneity is measured using χ^2 test and I^2 test

[a] Data presented as standardized mean difference (95% CI)

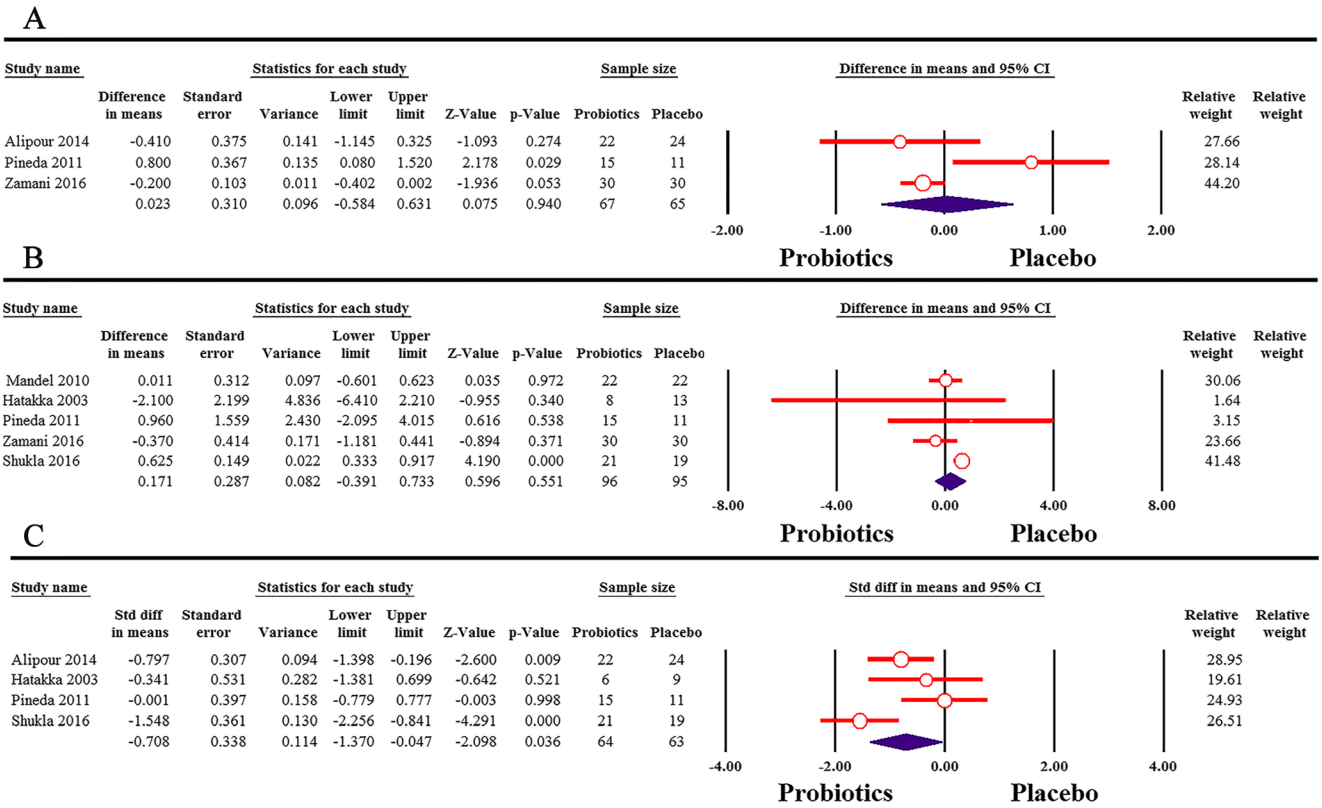

Fig. 3 Forest plot of the change in the clinical and laboratory parameters between probiotics and placebo. **a** Change in the DAS score. **b** Change in the SJC. **c** Change in IL-6 level

inflammatory parameters CRP and ESR did not show enough difference between probiotics and placebo. Some groups showed normal baseline values of both CRP and ESR which indicates stability of patients' conditions. This made it hard for probiotics to produce a change in inflammatory parameters and can explain these results. Also, clinically HAQ which is validated measure in assessing patient status and activity [34] along with DAS did not show a significant difference, but these two variables need to be assessed in more studies. Probiotics could not produce a significant difference regarding oxidative stress in RA [28]. It was only for a short term, about 8 months, and against the results of many previous studies. So, long-term trial is needed to accurately provide an evidence for oxidative stress.

Diets rich in probiotics have shown the ability to relieve the symptoms of RA patients and also shown an affection against gut defense mechanisms [29, 30]. This relationship between probiotics and RA is mainly attributed to the dysregulation of gut mucosal barrier mechanisms [7]. Gut is the main reservoir of antigens and toxins especially the large intestine. The internal environment is protected from these harmful antigens by various physical, biological, and immunological defense mechanisms [35]. Dysregulation of these defense mechanisms and disturbance of immune response may contribute to the development of autoimmune diseases like RA [36]. Probiotics administration can restore the normal mucosal barrier function [29] through keeping the balance between intestinal microflora and resistance against harmful bacterial colonization, adherence, and translocation. Probiotics can also promote mucus secretion from intestinal epithelial cells enhancing the physical barrier function [35]. The same mechanism should be examined in other autoimmune diseases in which it can lead to a new strategy and revolution in this field [37].

Strengths

This is the first systematic review and meta-analysis that discusses the role of probiotics as an adjuvant therapy for rheumatoid arthritis. So our results are more reliable and evident than separated studies. Also, RCTs were only included which have a relatively good quality; therefore, we can rely on their results.

Limitations

Our limitations are the small sample size which can affect the reliability and validity of the results. Also, we had a small number of RCTs which is eligible for analysis with high heterogeneity which affects the conclusion of our study and

Table 3 Guidelines for future trials investigating the effect of probiotics in rheumatoid arthritis patients

Population	
Patient demographics	Document to control for factors that affect morbidity
Enrolled patients	Patients enrolled in the study should be diagnosed as rheumatoid arthritis using American College of Rheumatology (ACR) criteria
	Differentiate patients and outcomes according to severity and activity of rheumatoid arthritis
	Differentiate according to the type and dose of probiotics
Design details	
Sampling	The sample size should be appropriate and calculated with 5% type I error rate and 20% type II error rate. Considering a dropout rate of 10% is advisable
Randomization	A computer-generated stratified randomization should be used to assign patients to each group and stratification should be made according to type and dose of probiotics classification
Blinding	Blinding at the level of both outcome assessors and participants (double blinding)
Allocation	Allocation should be concealed from each patient
Multicenter	Recruitment of more than 5 large academic centers able to host data coordinating center
Follow-up	Follow-up at multiple points 30 days and 3 months, 6 months, and 12 months for all outcomes through a clinical visit
	Report the follow-up lost patients with the reason for each lost patient
Study arms	
Probiotics	Should use different doses of probiotics to report the efficacy of it using 10^8, 10^9, 10^{10} CF
	Should use different species of probiotics especially *Lactobacillus* including the strains *L. rhamnosus*, *L. casei*, and *L. reuteri* and *Bacillus* including *B. coagulans*
Placebo	Patient should not have intra-articular injection or other treatments of RA like DMARDs
Active control	Patients should choose a treatment strategy according to the severity of RA like DMARDs, corticosteroids, etc.
Combined therapy	Patient received both probiotics and active control
Duration of therapy	Should continue the therapy for at least for 12 weeks
Outcomes	Should report each outcome at the baseline and at each time point along with the change of each time point from the baseline
Quality of life	Assess the quality of life using health assessment questionnaire (HAQ)
DAS	Use disease activity score to report clinical symptoms of rheumatoid arthritis
Morning stiffness	Time and duration of morning stiffness should be calculated by an independent blinded physician
Pain	Should be measured using visual analog pain score
C-reactive protein and ESR	Should be measured at each time point by independent blind laboratory
Interleukins	Should investigate and report IL-1 (α and β), IL-6, IL-8, IL-10, IL-12, IL-15, IL-17, TNF-α, GM-CSF, G-CSF, sCD40 ligand, MIP-1a, MIP-1b, MCP-1
	Should be measured at baseline and each time point along with the change from baseline to each time point
Swollen and tender joint counts	Should be measured and reported by an experienced independent blinded physician
Financial aspect	Report the cost and financial value of the probiotics compared with other groups
Morbidity	Detect all the complications that appeared during the follow-up period
Mortality	Report the cause of death and whether related to the rheumatoid arthritis or probiotics in each patient

prohibits us from assessing the publication bias. Usage of different strains and dosages in each study is another limitation. So, we enhance future RCTs in this area because it still needs much more studies and evaluation in order to specifically recognize this relationship which may lead to a new strategy in the treatment of autoimmune disease. Table 3 highlights the items that should be covered in the future ideal RCTs that investigate the efficacy of probiotics as a dietary supplement for RA.

Conclusion

Probiotics lowered the pro-inflammatory cytokine IL-6, which is an indicator for joint destruction in RA; however, the clinical effect of probiotics is still unclear. Therefore, this study area still needs more high quality, suitably powered RCTs in order to reach the exact effect of this promising treatment for rheumatoid arthritis patients.

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Compliance with ethical standards

Disclosures None.

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