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PROBIOTICS AS ADDITIONAL TREATMENT OF RHEUMATOID ARTHRITIS. A REVIEW.

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Abstract

Relevance. Rheumatoid arthritis (RA) is a condition with an unclear cause, marked by inflammation affecting the synovial tissue of joints, cartilage, and bone. RA can extend to areas outside the joints, autoantibodies production and progressive disability. Rheumatoid arthritis affects approximately 0.24% to 1% of adults globally, with women being affected 2 to 3 times more frequently than men. In recent years numerouse studies showed the significant role of micribiome in RA developement. Regardless of using disease-modifying anti-rheumatic drugs (DMARDs) and biologic therapies, a significant number of patients with RA fail to achieve remission. These two facts have prompted interest in targeting the microbiome as a therapeutic strategy for RA.

Aim: To analyze the effectiveness of probiotics in the treatment of RA according to contemporary literature.

Search strategy: A search for scientific publications was carried out in the following databases of scientific publications and specialized search engines: PubMed, Google Scholar, Web of Science Core Collection, Cochrane Library. A number of original publicly available publications on the research topic were analyzed. The search depth was 10 years. As a result of the search, we studied 579 foreign publications, of which 84 publications were included in this review. *Inclusion criteria:* meta-analyses, systematic reviews, cohort and cross-sectional studies. *Exclusion criteria:* short reports, newspaper articles and expert opinion in the form of short reports.

Results and conclusions: The review revealed that probiotics can influence the microbiome and immune system of RA patients through various mechanisms of action. In addition, it has been found that the use of L. Casei alone and in combination with L. acidophilus, L. Lactis, B. Lactis and B. bifidum, as well as Bacillus coagulans can improve the course of RA, reduce the level of inflammatory markers and pro-inflammatory cytokines. Given the conflicting evidence regarding the effectiveness of probiotics in the treatment of RA, further research is needed.

Key words: *rheumatoid arthritis, microbiome, probiotics, mechanism of probiotics effectiveness, role of probiotics in RA treatment.*

Резюме

ПРОБИОТИКИ КАК ДОПОЛНИТЕЛЬНОЕ ЛЕЧЕНИЕ РЕВМАТОИДНОГО АРТРИТА. ОБЗОР ЛИТЕРАТУРЫ.

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Актуальность. Ревматоидный артрит (РА) — заболевание с неясной этиологией, характеризующееся воспалением, поражающим синовиальную ткань суставов, хрящи и костей. РА может распространяться на области за пределами суставов, вырабатывать аутоантитела и приводит к инвалидности и ее прогрессированию. Ревматоидным артритом страдают примерно от 0,24% до 1% взрослых во всем мире, причем женщины страдают в

2-3 раза чаще, чем мужчины. В последние годы многочисленные исследования показали значительную роль микрибиома в развитии РА. Несмотря на использование модифицирующих заболевание противоревматических препаратов (БПВП) и биологической терапии, у значительного числа пациентов с РА не удается достичь ремиссии. Эти два факта вызвали интерес к использованию микробиома в качестве терапевтической стратегии при РА.

Цель: Провести анализ эффективности пробиотиков в лечении РА по данным современной литературы.

Стратегия поиска: Проведен поиск научных публикаций в следующих базах данных научных публикаций и специализированных поисковых систем: PubMed, Google Scholar, Web of Science Core Collection, Cochrane Library. Проанализирован ряд оригинальных публикаций, находящихся в открытом доступе по теме исследования. Глубина поиска составила 10 лет. В результате поиска нами было изучено 579 зарубежных публикаций, из них в данный обзор вошли 84 публикаций. *Критерии включения:* мета-анализы, систематические обзоры, когортные и поперечные исследования. *Критерии исключения:* краткие отчеты, газетные статьи и мнение экспертов в виде коротких сообщений.

Результаты и выводы: По результатам обзора выявлено, что пробиотики могут влиять на микробиом и иммунную систему больных РА различными механизмами действия. Кроме того, установлено, что применение L. Casei самостоятельно и в сочетании с L. acidophilus, L. Lactis, B. Lactis и B. bifidum, а также Bacillus coagulans может улучшить течение РА, снизить уровень воспалительных маркеров и про-воспалительных цитокинов. Учитывая противоречивые данные об эффективности пробиотиков при лечении РА, необходимы дальнейшие исследования.

Ключевые слова: *ревматоидный артрит, микробиом, пробиотики, механизм эффективности пробиотиков, роль пробиотиков в лечении РА.*

Түйіндеме

ПРОБИОТИКТЕР РЕВМАТОИДТЫ АРТРИТТІҢ ҚОСЫМША ЕМІ РЕТІНДЕ. ӘДЕБИЕТКЕ ШОЛУ.

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Өзектілігі. Ревматоидты артрит (РА) – буындардың, шеміршектің және сүйектің синовиальды тініне әсер ететін қабынумен сипатталатын, себебі түсініксіз жағдай. РА буындардан тыс аймақтарға, аутоантиденелер түзілуіне және прогрессивті мүгедектікке таралуы мүмкін. Ревматоидты артрит бүкіл әлем бойынша ересектердің шамамен 0,24% -дан 1% -ға дейін әсер етеді, әйелдер ерлерге қарағанда 2-3 есе жиі ауырады. Соңғы жылдары көптеген зерттеулер РА дамуында микробиоманың маңызды рөлін көрсетті. Ауруды өзгертетін ревматизмге қарсы препараттарды (АӨРҚП) және биологиялық терапияны қолдануға қарамастан, РА бар науқастардың айтарлықтай саны ремиссияға қол жеткізе алмайды. Бұл екі факт РА үшін терапевтік стратегия ретінде микробиомаға бағытталған қызығушылықты тудырды.

Мақсаты: заманауи әдебиет бойынша РА емдеудегі пробиотиктердің тиімділігі.

Іздеу стратегиясы: ғылыми жарияланымдарды іздеу келесі ғылыми басылымдар мен мамандандырылған іздеу жүйелерінің дерекқорларында жүргізілді: PubMed, Google Scholar, Web of Science Core Collection, Cochrane Library. Зерттеу тақырыбы бойынша көпшілікке қолжетімді бірқатар түпнұсқа басылымдар талданды. Іздеу терең дігі 10 жыл болды. Іздестіру нәтижесінде 579 шетелдік басылымды зерттедік, оның ішінде 84 басылым осы шолуға қосылды. *Қосылу критерийлері:* мета-талдаулар, жүйелі шолулар, когорттық және секциялық зерттеулер. *Алып тастау критерийлері*: қысқаша есептер, газет мақалалары және қысқа хабарламалар түріндегі сарапшылардың пікірі.

Нәтижелер мен қорытындылар: Шолу пробиотиктердің әртүрлі әсер ету механизмдері арқылы РА пациенттерінің микробиомасы мен иммундық жүйесіне әсер етуі мүмкін екенін көрсетті. Сонымен қатар, L. Casei-ді жалғыз және L. acidophilus, L. Lactis, B. Lactis және B. bifidum, сондай-ақ Bacillus coagulans біріктіріп қолдану РА ағымын жақсартуға, қабыну маркерлерінің және қабынуға қарсы цитокиндердің деңгейін төмендетуге болатыны анықталды. РА емдеудегі пробиотиктердің тиімділігіне қатысты қарама-қайшы дәлелдерді ескере отырып, қосымша зерттеулер қажет.

Түйінді сөздер: *ревматоидты артрит, микробиома, пробиотиктер, пробиотиктердің әсер ету механизмі, РА емдеудегі пробиотиктердің рөлі.*

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Introduction

Rheumatoid arthritis (RA) is a condition with an unclear cause, marked by inflammation affecting the synovial tissue of joints, cartilage, and bone. Occasionally, it extends to areas outside the joints, autoantibodies production and progressive disability [62,66]. Synovial hyperplasia is a key feature of RA and primarily drives the formation of an invasive pannus [66]. Rheumatoid arthritis affects approximately 0.24% to 1% of adults globally, with women being affected 2 to 3 times more frequently than men [17,53,64].

Overall heritability of RA in identical twins, which measures the extent to which genetic factors contribute to disease susceptibility, has been estimated at 66%. This underscores the significant role of genetic risk loci in RA [66,82]. However, the relatively low concordance in twins suggests that environmental factors, such as cigarette smoke, dust exposure, and notably, the microbiome, which serves as an internal environmental factor, also play a crucial additional role in the development of the disease [27,66,68].

Recently, there has been a resurgence in interest regarding the role of microbes in the development of RA. This renewed focus is partly driven by advancements in techniques for high-throughput DNA sequencing, which enable the detailed characterization of trillions of microorganisms - collectively known as the microbiota - residing within the human body under both healthy and diseased conditions. In Table 1 showed several microbial taxa that associated with RA development in animal models.

The ways in which the oral and intestine microbiome influence the RA formation are diverse. The subgingival microbiota associated with periodontitis, specifically the periodontal pathogens Porphyromonas gingivalis (P.gingivalis) may contribute to RA by promoting the production of anti-citrullinated protein antibodies (ACPA) through its peptidylarginine deiminase enzyme (PAD), which citrullinates proteins. On the other hand, Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans) has been implicated in RA by inducing excessive citrullination through leukotoxic mechanisms [22,25,33,42]. The study identified that Prevotella copri (P. copri) possesses a significant capacity to trigger the production of cytokines associated with Th17 cells, specifically IL-6 and IL-23. Elevated levels of Prevotella species have also been associated with increased mucosal inflammation, which occurs through Th17 pathways. These observations align with Prevotella species' notable ability to direct Th17 immune responses in experimental settings [47]. Collinsella appears to contribute to the disease by promoting gut permeability, as evidenced by reduced expression of tight junction proteins. Additionally, this bacterium influences the release of IL-17A from epithelial cells, further implicating it in the pathogenesis of RA [21].

Table 1.

Microbial taxa associated with autoimmune diseases development.

#	Taxa	Model	Phenotypes	Author, year
1	Prevotella copri JCM 13464	Zymosan-treated SKG mice (RA)	Increased Th17 cells in colon and popliteal lymph nodes	Maeda Y. et al., 2016 [47].
2	Collinsella aerofaciens VPI 1003	Collagen-induced arthritis in HLA-DQ8 transgenic mice (RA)	Increased gut permeability and IL-17-related cytokines	Chen J. et al., 2016 [21].
3	Akkermansia muciniphila BAA-835	K/BxN mice (RA)	Modestly increased ankle swelling	Stoll et al., 2019 [69].
4	Bifidobacterium adolescentis	K/BxN mice (RA)	Induced Th17 cells in small intestine	Tan T.G. et al., 2016 [71].
5	Bacteroidaceae, Lachnospiraceae, and S24-7	DBA1 mice (RA)	Increase cytokine interleukin-17 in serum and the proportions of CD8+T cells and Th17 lymphocytes in the spleen	Liu et al., 2016 [45].
6	SFBs	K/BxN mice (RA)	Induced gut Th17 cells that migrated to lung and recognized autoantigens	Bradley C.P. et al., 2017 [15].
		K/BxN mice (RA)	Drove differentiation and egress of Tfh cells in PPs	Teng F. et al., 2016 [72].

Despite the use of disease-modifying anti-rheumatic drugs (DMARDs) and biologic therapies, a substantial number of RA patients do not reach remission [2,31,60]. This has led to increased interest in targeting the microbiome as a potential therapeutic strategy for managing RA. Probiotics, defined as live microorganisms, primarily bacteria, that confer health benefits when consumed in adequate amounts (FAO/WHO, 2002), have emerged as a promising avenue. Published works have demonstrated that probiotics can modulate systemic immune responses and enhance gut barrier function by promoting a balanced gut microbiota ecosystem and fostering beneficial interactions between gut microbiota and mucosal immune cells [5,19,23,75].

In this review, we attempt to summarize the influence of probiotics to disease activity and microbiome of RA patients.

Aim. The aim of these work is to summarize the effect of probiotics on the RA course.

Research methods.

An exploration for scientific publications was done in the upcoming bibliography of scientific publications and particular search engines: PubMed, Google Scholar, Web of Science, Cochrane Library. A wealth of original publicly accessible publications on the research topic were investigated. The search depth was 10 years. As an outcome of the search, we studied 579 foreign publications, of which 84 publications were involved in this review. *Inclusion criteria:* meta-analyses, systematic reviews, cohort and cross-sectional studies. *Exclusion criteria:* short reports, newspaper articles and expert opinion in the form of short reports.

Research results

Probiotics and their mechanisms of action

The recognition of probiotics as natural and beneficial gastrointestinal microbiota dates back to the late 19th century, when the colonization of microorganisms in the digestive tracts of asymptomatic healthy individuals was first described [52]. Now, it is well known that probiotics are supplements that contain live microorganisms capable of changing the composition of microbiota. When taken in sufficient quantities, they provide a health benefit to the host [18,24,37,80]. Probiotics have been proposed as effective against various disorders with their ability to affect immune system function. Numerous studies have identified probiotics that stimulate the immune system locally and also influence both innate and adaptive immune responses systemically [38,75]. The most frequently presented microbes as probiotics are Lactic Acid Bacteria (LAB) and Bifidobacteria [8]. Additionally, microorganisms such specific strains of Streptococcus [12,40,59], Escherichia [54], Enterococcus [9,55], Bacillus, and Saccharomyces [1,63] are less commonly used for probiotic purpose. Latterly, these microorganisms have gained medical attention due to their antagonistic effects against numerous human pathogens. Probiotic LAB has been shown to inhibit the growth of several Gram-positive and Gram-negative pathogenic bacteria, including Staphylococcus aureus, Salmonella typhimurium, Escherichia coli (E. coli, a conditionally pathogenic bacterium), and Enterococcus faecalis [10,34,55]. A critical factor in selecting probiotics is choosing strains that can survive and thrive in the intestinal environment they encounter [13,16].

Probiotics exert their effects through various probable mechanisms, including:

a) Regulation of the composition of the intestinal microbiota. Scientists provided gnotobiotic mouse model by colonization germ-free mice with Bacteroides thetaiotaomicron, a prominent component of the adult human gut microbiota, and Bifidobacterium longum, which is a less abundant member of the gut microbiota but commonly used as a probiotic. A controlled study demonstrated how a resident symbiont and a probiotic species adapt their substrate utilization in response to each other. This highlight both the broad applicability and specific dynamics of the interactions between a host, a component of its microbiota, and intentionally consumed microbial species [48]. Li J. et al. additionally found that probiotics induced changes in gut microbiota composition, promoting the growth of specific beneficial bacteria such as Prevotella and Oscillibacter, which are recognized for producing anti-inflammatory metabolites [44].

b) Influence on the metabolic profile of both intestinal microbiota and the host. The alteration in fecal metabolic profiles induced by the concurrent administration of Bifidobacterium longum and Lactobacillus helveticus closely resembled the changes observed following supplementation with Lactobacillus helveticus alone, particularly in terms of reducing pyridine levels and increasing butyrate levels [20,70,79].

c) Production of antimicrobial substances. Bacillus clausii strains, in their vegetative forms, are capable of inducing NOS II synthetase activity, IFN-γ production, and CD4+ T-cell proliferation [30]. Probiotics produce low molecular weight compounds, such as organic acids, and high molecular weight antimicrobial compounds known as bacteriocins [13]. Some examples of bacteriocins produced by probiotics include lactacin B from Lactobacillus acidophilus, bifidocin B from Bifidobacterium bifidum NCFB, plantaricin from Lactobacillus plantarum, and nisin from Lactococcus lactis [67].

d) Competition for nutrients and ecological niches with other microorganisms. The study offers a scientific foundation for screening and selecting probiotics that compete with specific groups of pathogens for adhesion to intestinal surfaces. For instance, Lactobacillus rhamnosus GG competes with Escherichia coli and Salmonella spp [4,11].

e) Improvement of intestinal barrier function and integrity. The activation of Pattern Recognition Receptors (PRRs) in the intestinal mucosa by Microbe-Associated Molecular Patterns (MAMPs) derived from probiotics can strengthen intestinal barrier function [83]. This activation may occur through mechanisms such as upregulating the synthesis of tight junction proteins and/or enhancing their functionality [36,58,81]. Probiotics have also been shown to enhance the intestinal barrier by increasing the number of Goblet cells, which subsequently strengthen the mucus layer [30]. Additionally, several Lactobacillus species have been found to improve mucin expression in human intestinal cell lines. Scientists reported that VSL#3 probiotics both in vitro and in vivo activate the p38 and ERK signaling pathways which leads to protection of the epithelial barrier and boost the expression of tight junction proteins [48].

f) Production or induction of molecules that affect humoral and cellular immune responses. Probiotics exert beneficial effects on the intestinal mucosa by downregulating the production of pro-inflammatory cytokines such as IL-12, IL-6, TNF-α, and IFN-γ. This is primarily achieved by inducing the differentiation and enhancing the activity of regulatory T cells in the intestinal mucosa [52].

Mechanism of probiotics effect on RA

Although the local effects of probiotics on gut health are well established, the mechanisms underlying their broader anti-inflammatory and immunomodulatory properties remain largely unclear. Due to challenges in directly assessing the role of probiotics in RA within the immune systems of human subjects, most data on the influence of these beneficial microorganisms come from experimental studies. Consequently, numerous studies have suggested the potential use of probiotics as an adjunct therapy for the therapeutic management of RA.

Nowadays, Bifidobacterium and Lactobacillus genera are widely used probiotics [26,57]. Research involving Lactobacillus species or strains has shown that their ability to exert anti-inflammatory effects on RA can vary depending on the specific strain used, with different strains inhibiting various inflammatory pathways. Thus, Lactobacillus helveticus and strains seem to protect against invasion by pathogenic bacteria and may induce regulatory CD11c+ dendritic cells, thereby enhancing the production of the anti-inflammatory cytokine IL-10 [39,41]. Whereas Lactobacillus salivarius UCC118 and Lactobacillus plantarum WCFS1 significantly increased the levels of the anti-inflammatory cytokine IL-10, decreased pro-inflimatory IL-17 and TNF-α cytokine levels by reduction Th17 cells and increasing Treg cell proportions in the spleen [46,76]. Furthermore, Lactobacillus casei decrease levels of IFN-gamma, IL-6, IL-17, IL-1beta, TNF-alpha, and serum anti-CII IgG, increase levels of IL-4 and IL-10, inhibits of nuclear translocation of NF-κB and cyclooxygenase-2 (COX-2) [7,28,32,76,78]. Fan et al investigated that Lactobacillus reuteri decrease levels of IFN-gamma, IL-12, IL-17, IL-21, IL-6, TNF-alpha, IL-10 and serum anti-CII IgG levels. Also reduce the relative abundance of Bifidobacterium and increase TGF-beta [76]. Treatment of adjuvant-induced arthritis (AIA) murine with Lactobacillus casei ATCC 334 inhibited joint swelling, reduced arthritis scores, lowered levels of pro-inflammatory cytokines, and mitigated bone destruction [56]. After treatment with Lactobacillus spp., anti-inflammatory cytokines such as Interleukin-4 and Interleukin-10 were similarly elevated in the body fluids [14]. Several Lactobacillus species, notably L. casei, L. reuteri, L. fermentum, and L. rhamnosus, have been shown to reduce collagen-induced arthritis (CIA) in female rat models. They achieve this by altering the gut microbiome composition (increasing Lactobacillus species), inhibiting inflammatory cells, modulating antibody production, influencing the immune response via Th1/Th17 pathways, and potentially through other mechanisms [6,61].

In a different rodent model of RA showed that there was a shift towards a T regulatory (Treg) phenotype with a decrease in Th17 cells, alongside suppression of pro-inflammatory cytokines [43]. Results of several studies underscored that early treatment with Bifidobacterium adolescentis in RA may represent an optimal timing for alleviating symptoms. Prophylactic treatment with Bifidobacterium adolescentis resulted in milder arthritis symptoms, decreased concentrations of anti-CII IgG and anti-CII IgG2b antibodies, restored immune balance by increasing Tregs, and suppressed the production of pro-inflammatory cytokines. Rats that received oral gavage of B. adolescentis before immunization showed significantly higher frequencies of Tregs and lower levels of TNF-alpha compared to those treated later with B. adolescentis. Tregs were found to promote bone health by inhibiting osteoclastogenesis, whereas Th17 cells were implicated in promoting osteoclastogenesis and bone loss [3,77].

Management of butyrate-producing Clostridia such as Faecalibacterium prausnitzii and Butyricicoccus pullicaecorum to animal models of inflammation appears to reduce the occurrence of macroscopic lesions in the intestinal mucosa. Oral administration of Prevotella histicola, whether as a preventive or therapeutic measure, reduces arthritis severity, modulates adaptive immune responses in DQ8 mice, increases regulatory T cells (Tregs), and decreases Th17 responses in the intestine [45,65].

Probiotics' Efficacy in the RA treatment

Currently, the growing interest among patients in complementary therapies for RA is driven by the numerous side effects associated with conventional disease-modifying anti-rheumatic drugs (DMARDs) and symptomatic treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). Probiotics have emerged as a potential alternative and complementary therapy to standard drugs used in managing rheumatic conditions. However, according to several meta-analyses since 2000, there have been relatively few randomized clinical trials (RCTs) investigating the effectiveness of probiotics in RA treatment [53,57,65]. These studies involved a total of 293 participants, with 142 in the intervention group receiving probiotic supplementation and 151 in the control group without probiotic supplementation. The types of probiotic species used and their dosages varied across the different studies. Other main data of RCTs are shown in table 2. Statements from RCTs on probiotics for RA are highly heterogeneous. This heterogeneity pertains to the populations studied, the specific characteristics of RA and the outcomes related to disease activity scores and inflammatory markers.

Hattaka K. et al. conducted a study comparing the effects of the probiotic Lactobacillus rhamnosus GG with a placebo in stable RA patients who were not receiving DMARDs but were predominantly on glucocorticoids (GC) and non-steroidal anti-inflammatory drugs (NSAIDs). The intervention group received two capsules of L. rhamnosus GG (Gefilus®, Valio Ltd.; ≥5 × 10^9 colony-forming units (CFU) per capsule) twice daily for 12 months. The placebo group received identical capsules without Lactobacillus rhamnosus GG. Between the groups in clinical parameters, biochemical variables, or Health Assessment Questionnaire (HAQ) scores, inflammatory markers were no statistically significant differences. Interestingly, despite the lack of measurable differences in disease activity, more participants in the probiotic group reported subjective improvements in well-being compared to the placebo group [35].

Table 2.

Other main data of RCTs.

№	Author, year	Design	Participant description (age in year)	Sample size		Current medication	Probiotic Strains (dose, CFU)	Duration (weeks)
				EG	CG			
1	Alipour B. et al., 2014 [5]	Double-blind RCT	Patients with RA of ≥ 1 year duration, stable medication for 3 months (20–80)	22	24	under treatment with DMARDs and not receiving NSAIDs) or cytokine inhibitors	L. casei 01-10^8 CFU	8
2	Hatakka K. et al., 2003 [35]	Double-blind RCT	Patients with RA of ≥ 1 year duration, stable medication for at least 3 months (18–64)	8	13	stable antirheumatic medication for at least 3 months	L.rhamnosus GG, ATCC 53103- ≥5 × 10^9 CFU	48
3	Maria de los Angeles Pineda et al., 2011 [50]	Double-blind RCT	RA patients with at least four swollen and tender joints (18–80)	15	14	DMARDs, steroids and/or NSAIDs for at least one month prior to randomization	L.rhamnosus GR1 and L.reuteri R- 2 × 10^9 CFU	12
4	Zamani B. et al., 2016 [84]	Double-blind RCT	Patients with moderate and severe RA (25–70)	30	30	DMARDs, biologic therapies, GC	L. acidophilus, L.casei and Bifidobacterium bifidum- 2 × 10^9 CFU	8
5	Mandel D.R. et al., 2010 [49]	Double-blind RCT	Patients with RA of at least 1 year duration (≤ 80)	23	22	DMARDs, biologic therapies, GC	Bacillus coagulans- 2 × 10^9 CFU	8
6	Vaghef-Mehrabany E. et al., 2014 [73]	Double-blind RCT	RA patients with inactive to moderate condition (20–80)	22	24	stable medication for at least the prior 3 months entered the study	L. casei 01 - ≥ 1 × 10^8 CFU	8
7	Vaghef-Mehrabany E. et al., 2015 [74]	Double-blind RCT	RA patients with inactive to moderate condition (20–80)	22	24	not receiving NSAIDs or cytokine inhibitors	Lactobacillus casei 01- 1 × 10^8 CFU	8

Pineda M. et al. conducted a placebo-controlled RCT combining Lactobacillus rhamnosus GR-1 with Lactobacillus reuteri RC-14. Participants had been taking DMARDs, steroids, and/or NSAIDs for at least one month prior to the study. The probiotic group received capsules containing L. rhamnosus GR-1 and L. reuteri RC-14, each at a dose of 2 × 10^9 CFU per capsule, taken twice daily for 3 months. The study reported a reduction in serum levels of various cytokines in both groups. In the probiotic group there were statistically significant decrease of IL-1α, IL-6, IL-10, IL-12p70, and TNF. Interestingly, in the placebo group there were a significantly greater decrease in the production of IL-6, IL-12p70, TNF, IL-15, and IL-17 compared to the probiotic group. As for clinical symptoms there were no statistically significant differences between the probiotic and placebo groups, including the HAQ score. However, a significant improvement in the HAQ score was observed within the probiotic group itself [50].

Few studies have examined the effectiveness of Lactobacillus casei alone and in combination with different taxa. For example, *Vaghef-Mehrabany E. et al.* made RTC where the probiotic group included patients with inactive to moderate RA with consistant medication regimens (DMARDs and GC, but not NSAIDs or biologics). The probiotic group received a daily capsule of Lactobacillus casei 01 (>10^8 CFU/capsule) for eight weeks. Authors reported that probiotic supplementation significantly decreased serum levels of three pro-inflammatory cytokines: TNF, IL-6, and IL-12. Additionally, there was a significant increase in serum levels of the anti-inflammatory cytokine IL-10 in the probiotic group compared to baseline. Furthermore, by the end of the study the pain Visual Analogue Scale (VAS) score decreased by 43.96% in the probiotic group, while it decreased by only 5.99% in the placebo group [73]. Later, *Vaghef-Mehrabany E. et al.* investigated the effects of Lactobacillus casei 01 on oxidative stress in patients with RA. In a secondary analysis, the authors concluded that this intervention did not significantly impact oxidative status compared to the placebo [74]. However, in another study by *Alipour P. et al.,* who also investigated Lactobacillus casei 01 supplementation in RA patients, significant improvements were observed in several disease-related parameters. Specifically, there was a statistically significant reduction in serum high-sensitivity C-reactive protein (hs-CRP), global health score assessed by VAS, Disease Activity Score based on 28 joints (DAS-28), and levels of IL-10, IL-12, and TNF-alpha ($P < 0.05$). Additionally, reductions in the counts of tender and swollen joints were noted [5]. *Zamani M. et al.* evaluated a combination of Lactobacillus casei, Lactobacillus acidophilus, and Bifidobacterium bifidum in patients with moderate to severe RA (DAS-28 > 3.2). The intervention group received a daily capsule containing L. casei (2 × 10^9 CFU/g), L. acidophilus (2 × 10^9 CFU/g), and B. bifidum (2 × 10^9 CFU/g) in addition to their conventional medications (DMARDs and GCs) for eight weeks. Results showed that in the probiotic group, at the end of the trial the mean DAS-28 score decreased from 4.0

± 0.7 at baseline to 3.7 ± 0.7 (p= 0.01). Additionally, there was a significant decrease in serum hs-CRP concentrations in the probiotic group (-6.66 ±2.56 vs. +3.07 ± 5.53 mg/L, P < 0.001) [84]. *Cannarella L. et al.* carried out the study where Lactobacillus casei LC-11 was tested in combination with other strains including Lactobacillus acidophilus LA-14, Lactococcus lactis LL-23, Bifidobacterium lactis BL-04, and Bifidobacterium bifidum BB-06 as adjunctive therapy for RA. The main group consumed a daily sachet containing 10^9 CFU/g of each probiotic strain for 60 days. Both groups remained on their standard medications during the study. The probiotic group demonstrated a significant reduction in white blood cell counts (p=0.012), TNF levels (p=0.004), and IL-6 plasma levels (p=0.039) compared to the placebo group. However, there was no statistically remarkable change in DAS-28, IL-10, CRP and erythrocyte sedimentation rate (ESR) between the probiotic and placebo groups. These results suggest that application L. Casei itself and in combination with L. acidophilus, L. lactis, B. lactis and B. bifidum may provide clinical and laboratory benefits in RA [19].

Another taxa observed as additional treatment of RA is Bacillus coagulans. *Mandel et al.* conducted a RCT in RA patients who resieved Bacillus coagulans with green tea extract, methylsulfonylmethane, vitamins, and minerals, alongside conventional DMARDs. The placebo consisted of microcrystalline cellulose. The study demonstrated a statistically natable reduction in Patient Pain Assessment score (P = .052) and Pain Scale (P = .046) vs placebo. Additionally, a reduction in CRP levels was observed, along with greater improvements in patient global assessment, self-reported disability, ability to walk two miles, and engagement in daily activities compared to the placebo group [49].

Conclusions

Based on the results of the review, it was revealed that probiotics can affect the microbiome and immune system of patients with RA via different mechanisms. Additionally, results of article suggest that application of L. Casei itself and in combination with L. acidophilus, L. lactis, B. lactis and B. bifidum, Bacillus coagulans may improve the course of RA and reduce the level of inflammatory markers and pro-inflammatory cytokines. Given the mixed results regarding the effectiveness of probiotics in RA treatment, further research is needed.

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