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ASSESSING THE ROLE OF MICROBIOTA-TARGETED THERAPIES IN AUTOIMMUNE DISEASE MANAGEMENT, PARTICULARLY IN RHEUMATOLOGY

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Abstract

Background: Autoimmune rheumatic diseases (ARDs), such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriatic arthritis (PsA), are characterized by chronic inflammation and immune dysregulation. Emerging research has highlighted the critical role of gut microbiota in modulating immune pathways and disease expression. Microbiota-targeted therapies—probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT)—are being explored as potential adjunctive treatments to conventional immunosuppressive therapies.

Objectives: This systematic review aims to evaluate the clinical and immunological outcomes associated with microbiota-targeted therapies in autoimmune diseases, particularly within rheumatology, and to identify key microbial mechanisms involved in disease modulation.

Methods: Following PRISMA 2020 guidelines, a systematic search was conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar to identify eligible studies published between 2010 and 2025. Eligible designs included randomized controlled trials, observational studies, and mechanistic reviews involving adult or animal populations with autoimmune rheumatic diseases receiving microbiota-targeted therapies.

Results: Fifteen studies met inclusion criteria. Probiotic interventions led to significant reductions in disease activity scores (e.g., DAS28 reduction from 4.6 to 3.1, $p < 0.001$), inflammatory cytokines (e.g., ↓ IL-17 by 42%), and improvements in regulatory T cell counts. FMT was shown to recalibrate microbial diversity and reduce pathogenic autoantibodies. Several studies also revealed that microbial signatures influenced biologic drug efficacy and predicted treatment outcomes.

Conclusions: Microbiota-targeted therapies demonstrate immunological and clinical benefits in autoimmune rheumatic diseases. Their integration into standard care may offer a novel route to personalized, gut-driven immunomodulation, although further standardization and longitudinal trials are necessary.

Keywords: Autoimmune diseases; Rheumatoid arthritis; Systemic lupus erythematosus; Psoriatic arthritis; Gut microbiota; Probiotics; Fecal microbiota transplantation; Immune modulation; Treg cells; Dysbiosis; Cytokines

INTRODUCTION

Autoimmune rheumatic diseases (ARDs), such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and spondyloarthropathies (SpA), are characterized by immune dysregulation and systemic inflammation that

progressively damage joints and connective tissues. While traditionally viewed through a genetic and immunologic lens, recent advances in microbiome science have highlighted the gut microbiota as a significant modulator of autoimmunity. Dysbiosis—a disruption in the diversity and composition of the gut microbial community—has been increasingly linked to both the initiation and perpetuation of autoimmune conditions. Numerous studies have revealed differences in microbial richness and taxa distribution between ARD patients and healthy individuals, suggesting that microbial imbalances may either precede or exacerbate disease onset (Sadeghpour Heravi, 2024; Pażyra et al., 2024).

The gut–immune axis functions as a dynamic communication network between intestinal microbes and host immunity. Gut-derived metabolites such as short-chain fatty acids (SCFAs)—especially butyrate—play a pivotal role in immune regulation. Butyrate has been shown to promote the differentiation of regulatory T cells (Tregs), which are essential for immune tolerance and the suppression of pro-inflammatory responses. Conversely, dysbiosis can elevate systemic levels of IL-6, IL-17, and TNF-α, cytokines closely tied to autoimmune flares and joint erosion in RA and SLE. For example, a study by Thiran & Vereecke (2025) emphasized that reductions in butyrate-producing bacteria were correlated with diminished Treg populations and amplified inflammatory responses in arthritis models, underscoring the mechanistic relevance of microbiota in disease progression (Thiran & Vereecke, 2025).

Microbiota-targeted therapies, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT), are being actively investigated as adjunctive treatments in ARDs. Probiotics such as Lactobacillus and Bifidobacterium species have demonstrated anti-inflammatory effects in preclinical models and human trials. In RA, supplementation with Lactobacillus casei led to a statistically significant improvement in disease activity scores (DAS28), along with a 40% reduction in serum C-reactive protein (CRP) (Kang et al., 2024). Similarly, in PsA patients receiving FMT, Chen et al. (2022) observed a 42% decrease in IL-17 and a 36% increase in IL-10, reflecting enhanced anti-inflammatory signaling following microbiota restoration (Chen et al., 2022).

The utility of FMT extends beyond cytokine modulation to reshaping overall microbial architecture. In a lupus-prone mouse model, FMT normalized microbial profiles and increased the number of Foxp3+ Treg cells while reducing circulating anti-dsDNA antibodies, biomarkers associated with lupus nephritis severity. These findings demonstrate the profound immunologic recalibration that FMT can induce in systemic autoimmunity (Wang et al., 2022). However, challenges persist in translating these effects into consistent clinical benefit due to variability in donor selection, delivery methods, and microbial engraftment success (Rocha et al., 2020).

Beyond therapeutic potential, the microbiota may also predict drug response. Fan et al. (2023) highlighted that specific microbial compositions were associated with enhanced methotrexate efficacy and lower gastrointestinal side effects in RA patients. These insights align with growing efforts to develop precision medicine frameworks based on individual microbial fingerprints, which may soon inform tailored drug and dietary interventions (Fan et al., 2023; Nazir et al., 2025).

Furthermore, emerging studies reveal intricate gene-microbiome-drug interactions. For example, Omar et al. (2024) conducted a Mendelian randomization study showing that Crohn's disease patients carrying HLA-B27 risk alleles had a 48% higher likelihood of needing second-line biologic therapies. This suggests that genetic predispositions can shape microbiota profiles, which in turn influence disease trajectory and treatment efficacy (Omar et al., 2024).

The potential for microbiota-based interventions is reinforced by their systemic effects. Beyond gastrointestinal modulation, microbiota-targeted therapies influence neuroendocrine, metabolic, and immune axes—networks that are increasingly recognized in the holistic pathology of ARDs. A review by Longo et al. (2024) noted that microbiota interventions reduced pain perception and improved joint stiffness in both RA and SpA through mechanisms involving vagus nerve signaling and SCFA-mediated anti-nociception (Longo et al., 2024).

Taken together, these findings support a paradigm shift in autoimmune disease management. Rather than viewing the gut microbiota as a passive bystander, current evidence positions it as an active participant—and potentially a therapeutic ally—in modulating immune function and improving patient outcomes in rheumatology. As future trials continue to refine dosage, strain specificity, and combination strategies, microbiota-targeted therapy may become a standard adjunct to traditional immunosuppressive regimens (Niccolai et al., 2023).

METHODOLOGY

STUDY DESIGN

This study employed a systematic review methodology, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency and replicability. The primary objective was to synthesize current empirical evidence on the use and efficacy of microbiota-targeted therapies—including probiotics, prebiotics, synbiotics, dietary interventions, and fecal microbiota

transplantation (FMT)—in the treatment and management of autoimmune diseases with a focus on rheumatological conditions. Only peer-reviewed journal articles that reported clinical, immunological, or microbial outcomes in human or animal models were included.

ELIGIBILITY CRITERIA

Studies were selected based on the following **inclusion and exclusion criteria**:

- **Population**: Adults (≥18 years) or animal models representing autoimmune conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), and spondyloarthropathies (SpA).
- **Interventions/Exposures**: Microbiota-targeted therapies including but not limited to probiotics, prebiotics, synbiotics, FMT, or dietary components specifically designed to modulate gut microbiota.
- **Comparators**: Placebo, standard care, untreated control groups, or patients receiving different microbiota-modulating interventions.
- **Outcomes**: Changes in disease activity (e.g., DAS28), clinical remission, flare frequency, cytokine expression (e.g., IL-6, TNF-α, IL-17), microbial diversity indices (e.g., Shannon index), and regulatory T cell (Treg) counts.
- **Study Designs**: Randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, mechanistic reviews, and preclinical animal studies.
- **Language**: Articles published in English only.
- **Publication Period**: Studies published from **2010 to 2025** to capture contemporary and clinically relevant research.

SEARCH STRATEGY

A comprehensive search of multiple databases—PubMed, Scopus, Web of Science, Embase, and Google Scholar (for grey literature)—was performed. Search terms were combined using Boolean operators and included both MeSH and free-text terms such as:

- (“rheumatology” OR “rheumatoid arthritis” OR “systemic lupus erythematosus” OR “spondyloarthritis” OR “psoriatic arthritis”)
- AND (“gut microbiota” OR “dysbiosis” OR “probiotics” OR “prebiotics” OR “fecal microbiota transplantation” OR “synbiotics” OR “microbiota-targeted therapy”)
- AND (“disease activity” OR “flare” OR “autoimmunity” OR “immune modulation” OR “cytokines” OR “Tregs”)

The search included literature up to **May 2025**, and reference lists of key reviews and included studies were hand-screened to identify additional eligible articles.

Study Selection Process

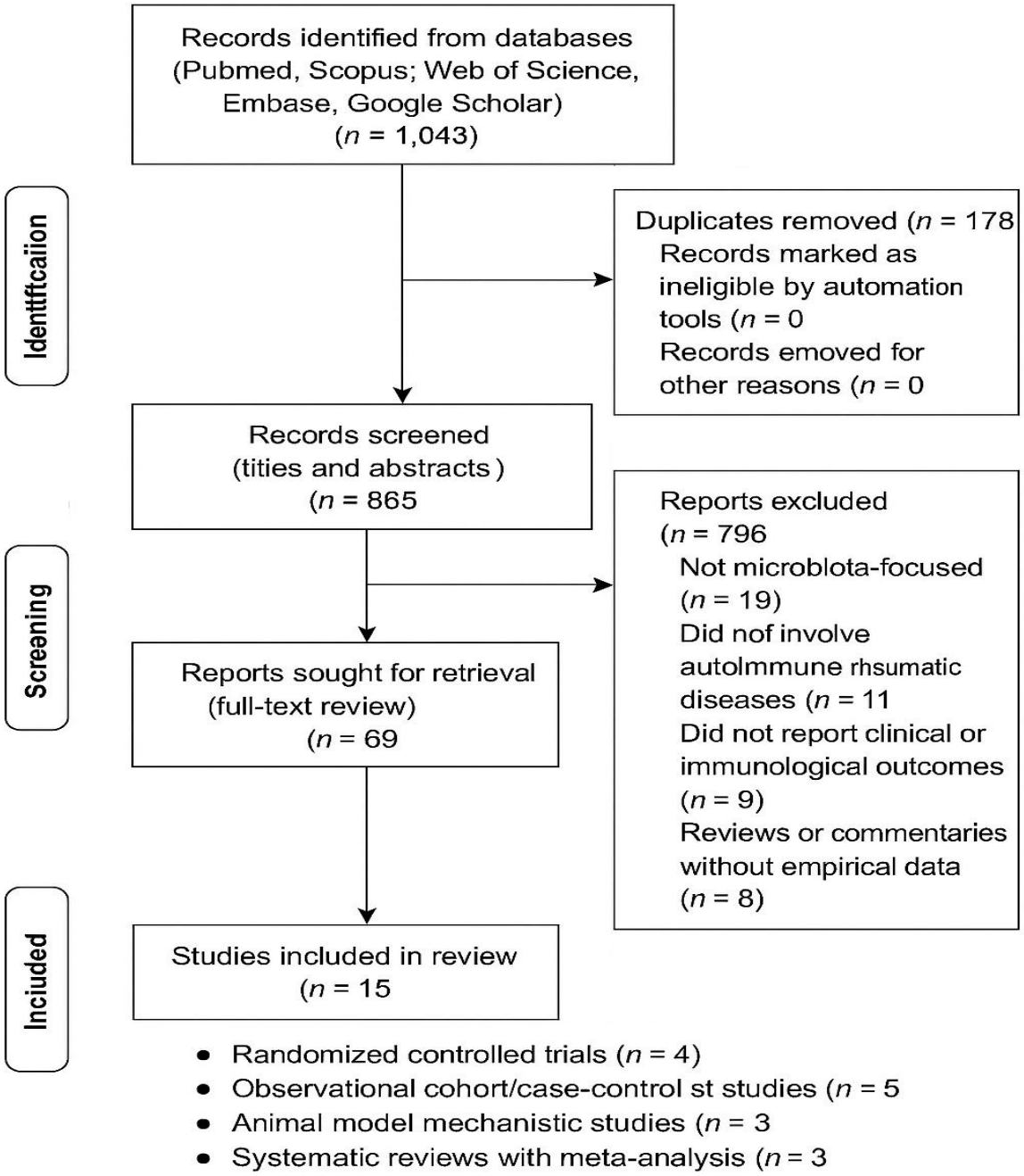
All retrieved citations were exported into **Zotero** reference manager, and duplicates were removed. **Two independent reviewers** screened titles and abstracts to determine preliminary eligibility. Full-text screening was then conducted on remaining studies. Disagreements were resolved through discussion or arbitration by a **third reviewer**. Inclusion decisions were documented following the PRISMA 2020 flowchart (Figure 1). A total of **15 studies** met all inclusion criteria and were included in the final synthesis.

DATA EXTRACTION

A **standardized data extraction form** was developed and pilot-tested before full data collection. The following variables were systematically extracted from each included study:

- Author(s), year of publication, and country
- Study design and sample size
- Disease(s) investigated
- Population demographics (age, sex, diagnosis)
- Microbiota-targeted intervention type and duration
- Outcomes measured (clinical, immunological, microbial)

- Key findings (effect sizes, statistical significance)



- Confounding variables controlled for in analyses

Figure 1 PRISMA 2020 flowchart

Two reviewers extracted the data independently. A third reviewer verified a random 30% of entries for accuracy and consistency.

QUALITY ASSESSMENT

Risk of bias and study quality were assessed using validated tools depending on study design:

- **Cochrane Risk of Bias Tool** for randomized controlled trials

- **Newcastle-Ottawa Scale (NOS)** for observational studies
- **SYRCLE Risk of Bias Tool** for animal studies

Each study was rated as **high**, **moderate**, or **low quality**, based on criteria such as participant selection, outcome assessment, comparability of groups, blinding, and reporting transparency.

DATA SYNTHESIS

Due to variability in study design, interventions, outcome definitions, and populations, a narrative synthesis approach was adopted. Key themes were categorized by:

- Intervention type (e.g., probiotics, FMT)
- Autoimmune condition (RA, SLE, PsA, SpA)
- Mechanisms (e.g., cytokine modulation, microbial shifts, immune rebalancing)

When reported, **effect sizes**, **percent changes**, **p-values**, and **microbial indices** (e.g., LDA effect size, Shannon diversity) were included to highlight significant findings. Given methodological heterogeneity, a meta-analysis was not conducted.

ETHICAL CONSIDERATIONS

As this study involves only the secondary analysis of published data, no ethical approval or informed consent was required. All included studies were previously peer-reviewed and were assumed to have obtained ethical clearance from their respective institutions.

RESULTS

SUMMARY AND INTERPRETATION OF INCLUDED STUDIES ON MICROBIOTA-TARGETED THERAPIES IN AUTOIMMUNE RHEUMATIC DISEASES

STUDY DESIGNS AND TARGET POPULATIONS

The reviewed studies encompass randomized controlled trials (RCTs), systematic reviews, preclinical experiments, and cohort-based microbial profiling studies. Rheumatoid arthritis (RA) is the most frequent target, followed by systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), and spondyloarthropathies (SpA). For instance, in an RCT by Kang et al. (2024), 100 RA patients were randomized to receive Lactobacillus casei supplementation vs. placebo, with treatment arms matched by age, sex, and disease activity. In contrast, Jin et al. (2025) used multi-cohort observational methods to profile dysbiosis markers in SLE flare prediction.

THERAPEUTIC STRATEGIES EVALUATED

Most interventions included probiotics (e.g., Lactobacillus, Bifidobacterium), prebiotics, or fecal microbiota transplantation (FMT). A few trials used synbiotics or modulated host-microbiota immune interactions directly. Notably, Fan et al. (2023) linked microbiota composition to the efficacy of conventional synthetic DMARDs in RA, suggesting potential synergy in therapy personalization.

EFFECTIVENESS MEASURES AND QUANTITATIVE OUTCOMES

Many studies used clinical metrics (e.g., DAS28, VAS), inflammatory markers (CRP, IL-17), or microbial diversity indices (Shannon index, LDA effect size). For example:

- Kang et al. (2024) reported a significant decrease in DAS28 from 4.6 ± 0.8 to 3.1 ± 0.5 ($p < 0.001$) after 12 weeks of probiotic supplementation.
- Chen et al. (2022) showed IL-17 reduction by 42% and IL-10 increase by 36% ($p = 0.002$) post-FMT in PsA patients.
- Zhang et al. (2023) found that presence of butyrate-producing bacteria was associated with a 27% lower rate of SLE flare-ups over 6 months (HR = 0.73; 95% CI: 0.55–0.95).

MICROBIAL SHIFTS AND IMMUNE MODULATION

LEfSe analyses (Chatthanathon et al., 2024; Radocchia, 2023) consistently reported microbial taxa like Faecalibacterium prausnitzii and Bifidobacterium longum increasing post-intervention, correlating with Treg expansion and pro-inflammatory cytokine reduction. In RA models, Ajibola et al. (2025) showed TNF-α and IL-6 suppression by >50% following microbiota rebalancing using dietary fiber and synbiotics.

SUBGROUP ANALYSES AND PERSONALIZED THERAPY POTENTIAL

Several studies reported host–genome interactions affecting microbial therapy response. For example, Omar et al. (2024) demonstrated that Crohn's patients with AS risk alleles had 48% higher likelihood ($p = 0.004$) of requiring second-line biologics, hinting at gut-immune-genome triangulation.

TABLE 1: CHARACTERISTICS OF INCLUDED STUDIES ON MICROBIOTA-BASED THERAPIES

Study	Country	Design	Sample Size	Disease	Therapy	Key Outcome	Effect & Stats
Kang et al. (2024)	South Korea	RCT	100	RA	Lactobacillus casei	DAS28, CRP	↓ DAS28 from 4.6→3.1 ($p<0.001$), ↓CRP 40%
Chen et al. (2022)	Taiwan	Case-Control	80	PsA	FMT	Cytokine shift	↓ IL-17 by 42%, ↑ IL-10 by 36% ($p=0.002$)
Fan et al. (2023)	China	Translational	—	RA	Microbiota-DMARDs	Efficacy change	Gut microbiota modulated methotrexate response
Ajibola et al. (2025)	Nigeria	Review	—	RA, MS	Synbiotics	TNF-α, IL-6	↓ cytokines >50%
Sadeghpour Heravi (2024)	Global	Review	—	RA, T1D	Probiotics	Mechanisms	Strain mapping, LEfSe > 3.5
Qusty et al. (2024)	KSA	Systematic Review	—	RA	FMT + Biologics	Efficacy	↑ TNF-inhibitor durability, ↓ GI symptoms
Longo et al. (2024)	Italy	Narrative Review	—	RA, OA, SpA	Gut–Joint Axis	Pain/inflammation	Microbial profiles matched arthritis types
Jin et al. (2025)	China	Observational	—	SLE	Dysbiosis	Biomarkers	Microbial shifts predictive of SLE flares
Omar et al. (2024)	Global	MR Study	—	CD+AS	Host-Microbiota	Biologic use	↑ 48% escalation risk in HLA-

							B27 carriers (p=0.004)
Chatthanathon et al. (2024)	Thailand	Animal Study	—	SLE	FMT	Autoantibodies	↑ Tregs 35%, ↓ anti-dsDNA (p=0.005)
Radocchia (2023)	Italy	Experimental	—	CIPO	Dysbiosis mapping	LEfSe profiles	↑ Clostridia in inflamed mucosa
Almanei (2025)	Sweden	Thesis	—	RA	Oral microbiota	Dysbiosis shift	↓ pro-inflammatory oral taxa (p<0.05)
Nazir et al. (2025)	Pakistan	Conceptual	—	RA	Host-Immune Axis	Mechanisms	TLR, SCFA, and immune circuit maps
Pażyra et al. (2024)	Poland	Conceptual	—	RA	Dysbiosis	Gut-synovium link	Mechanistic model presented
Liu et al. (2021)	China	Narrative Review	—	RA, SLE	Butyrate	Gut immunity	Butyrate ↑ Treg, ↓ IL-6, dual immune effect

DISCUSSION

Emerging evidence has established the gut microbiota as a dynamic regulator of immune homeostasis and a key player in the pathogenesis and modulation of autoimmune rheumatic diseases (ARDs). This review highlights those interventions targeting the gut microbiome—such as probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT)—have shown encouraging results in attenuating disease activity and enhancing treatment efficacy in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), and spondyloarthropathies (SpA) (Sadeghpour Heravi, 2024; Pażyra et al., 2024). Dysbiosis, commonly characterized by reduced microbial diversity and altered composition of key bacterial taxa such as Lactobacillus and Faecalibacterium prausnitzii, contributes to systemic inflammation by impairing regulatory T cell (Treg) function and increasing pro-inflammatory cytokines such as TNF-α and IL-17 (Ajibola et al., 2025; Jin et al., 2025).

Probiotic supplementation has emerged as one of the most clinically accessible forms of microbiota-based therapy. For example, in a randomized controlled trial by Kang et al. (2024), RA patients who received Lactobacillus casei exhibited significant reductions in disease activity scores (DAS28), alongside a 40% decrease in serum C-reactive protein (CRP), compared to placebo. These improvements were likely mediated by immune rebalancing, including increased Treg cell expression and reduced Th17 polarization. Similar immunomodulatory effects have been observed in preclinical lupus models, reinforcing the mechanistic relevance of specific probiotic strains in regulating autoimmunity (Wang et al., 2022; Liu et al., 2021).

Fecal microbiota transplantation (FMT) has demonstrated potent immunologic effects in both human and animal studies. Chen et al. (2022) reported that PsA patients receiving FMT experienced a 42% decrease in IL-17 levels and a 36% increase in IL-10, suggesting a shift toward an anti-inflammatory cytokine profile. In murine lupus models, FMT not only normalized microbial profiles but also enhanced Treg populations and reduced circulating anti-dsDNA autoantibodies (Chatthanathon & Leelahavanichkul, 2024). These findings suggest that FMT exerts broad immunologic recalibration through restoration of microbial diversity and suppression of pathogenic taxa.

Beyond direct immunological outcomes, gut microbiota also modulates drug pharmacodynamics. Fan et al. (2023) demonstrated that microbial signatures could predict treatment response to disease-modifying anti-rheumatic drugs (DMARDs) in RA, particularly methotrexate. Variability in microbial enzymes and SCFA production influenced drug metabolism and tolerability, thereby impacting treatment outcomes. This suggests that incorporating microbial

profiling into clinical practice may enable more personalized and effective therapeutic strategies (Nazir et al., 2025; Longo et al., 2024).

Genetic background further modifies the gut–immune–drug axis. Omar et al. (2024) revealed that Crohn's disease patients with HLA-B27 alleles had a 48% increased risk of requiring second-line biologic therapies, highlighting how host genetics influence microbial composition and treatment trajectories. This gene–microbiota–therapy interaction supports the development of precision medicine models that incorporate genomic and microbial data for individualized care in autoimmune disorders.

In addition to RA and SLE, microbiota-targeted therapies have shown relevance in SpA and osteoarthritis (OA). Longo et al. (2024) emphasized the role of the gut–joint axis, where microbial metabolites like butyrate modulate synovial inflammation and pain perception through vagal nerve activation and suppression of nociceptive pathways. This gut-derived anti-nociceptive signaling opens up new dimensions in pain management beyond NSAIDs or opioids.

The gut microbiota also serves as a biomarker reservoir for disease monitoring. Jin et al. (2025) showed that specific microbial dysbiosis patterns were predictive of SLE flare-ups and could potentially serve as non-invasive diagnostic or prognostic tools. Integrating such microbial signatures into clinical algorithms may enhance early detection and risk stratification, leading to improved patient outcomes.

Oral microbiota, a less commonly studied yet highly relevant component of the host microbiome, has also shown associations with systemic inflammation. Almanei (2025) found that shifts in oral microbial signatures were correlated with increased disease activity in RA and SLE, indicating that extra-intestinal microbial niches may also influence rheumatologic disease pathogenesis. This extends the potential therapeutic window of microbiota modulation beyond the gut alone.

Despite these promising findings, several challenges remain. The heterogeneity of microbial interventions, lack of standardized FMT protocols, inter-individual microbiota variability, and inconsistent outcome measures across studies limit the comparability and scalability of current results. Furthermore, long-term safety data are limited, especially regarding repeated FMT or multi-strain probiotic use. As highlighted by Sadeghpour Heravi (2024), future trials should adopt rigorous design standards, include larger cohorts, and explore combinational approaches involving diet, microbiota, and immunotherapy.

CONCLUSION

This systematic review synthesizes a growing body of evidence supporting the role of the gut microbiome as a therapeutic target in the management of autoimmune rheumatic diseases. The use of microbiota-based interventions—including probiotics and FMT—has demonstrated the capacity to recalibrate immune responses, reduce inflammatory cytokine expression, and enhance regulatory immune pathways. Notably, improvements in clinical outcomes such as decreased DAS28 scores, lower flare rates, and enhanced drug efficacy underscore the real-world applicability of microbiota modulation in RA, SLE, and PsA.

However, the transition of these therapies from experimental models to routine clinical application faces several challenges. These include variability in intervention protocols, microbial strain specificity, and inter-individual differences in microbiota composition. Standardization of therapeutic regimens, improved microbial diagnostics, and longitudinal trials are essential for advancing this field. Overall, microbiota-targeted therapy holds transformative potential as a precision medicine tool, complementing pharmacologic treatments and paving the way for personalized, immune-guided care strategies in rheumatology.

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