CMMB
https://doi.org/10.31689/rmm.2026.33.2.145

ORIGINAL PAPERS

Exploring the Gut Microbiome-Immune Axis: Potential Benefit of Probiotics and Synbiotics in Systemic Lupus Erythematosus, a Meta-Analysis of Randomized Control Trials

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by periods of relapse and remission, in which gut microbiota imbalance plays a role in triggering and sustaining inflammation through pro-inflammatory cytokines. Therapeutic approaches targeting the gut microbiota, such as probiotics and synbiotics, have the potential to regulate disease activity by restoring microbial balance and reducing systemic inflammation. Several randomized controlled trials (RCTs) have explored the effects of microbiota-based interventions in autoimmune diseases; however, comprehensive meta-analyses summarizing their efficacy remain limited.
Objective: To explore the potential benefit of probiotics and synbiotics supplementation in improving SLE disease activity and inflammatory markers.
Methods: RCTs relevant to the treatment of SLE with probiotics and synbiotics were systematically retrieved from Pubmed, EMbase, Cochrane, Sinomed in accordance with the PRISMA guideline. The meta-analysis was performed using RevMan 5.4.1 software. A fixed-effects model was applied, Cochrane Risk of Bias 2 (ROB 2.0) was used as a bias assessment tool.
Results: Seven studies with a total 460 subjects were included in this meta-analysis. Data consisting of SLEDAI-2K, IL-17 and IgG from studies RCTs. The pooled analysis demonstrated that probiotic or synbiotic supplementation significantly reduced disease activity of SLE as assessed by the SLEDAI-2K score (MD = -2.33, 95% CI -2.49, -2.16; $P < 0.00001$; $I^2 = 61\%$). Similarly, the pro-inflammatory markers of IL-17 (MD = -1.04, 95% CI -1.55, -0.52; $P < 0.0001$) and IgG (MD = -2.64, 95% CI -2.77, -2.51; $P < 0.00001$) revealed a significant reduction compared to control group.
Conclusion: Gut microbiota-based therapies, including synbiotics and probiotics supplementation, demonstrate the potential benefit to reduce systemic inflammation and improve SLE disease activity through modulating gut microbiota composition and function. While promising as an adjunctive treatment for SLE, further studies are required to investigate its mechanisms and therapeutic efficacy.

Keyword: Systemic Lupus Erythematosus, Synbiotics, Probiotics, Gut Microbiome, Meta Analysis

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by periods of relapse and remission, involving multiple organ systems and the production of a wide array of autoantibodies. The precise etiology of SLE remains incompletely understood, but it is recognized as a multifactorial condition influenced by genetic, hormonal, and environmental factors. Recent advancements in research have increasingly highlighted the critical role of the gut microbiota (GM) in the pathogenesis and progression of SLE. An imbalance in the composition and function of the gut microbiota, termed dysbiosis, is now understood to contribute to the initiation and perpetuation of inflammation through the modulation of pro-inflammatory cytokines and immune responses (Parodi et al., 2025).

Evidence suggests that gut dysbiosis in SLE patients is characterized by reduced microbial diversity and alterations in the abundance of specific bacterial phyla, such as an increase in Proteobacteria and a decrease in Firmicutes and Bacteroidetes. These microbial shifts can lead to increased intestinal permeability, often referred to as a "leaky gut syndrome," which allows microbial antigens to translocate and trigger abnormal immune responses, thereby predisposing individuals to SLE and its complications, including lupus nephritis (LN) (Guo et al., 2021; Parodi et al., 2025). Specific bacterial species, such as *Bacteroides thetaiotaomicron* and *Ruminococcus gnavus*, have been implicated in driving autoimmune responses through mechanisms like molecular mimicry and immune dysregulation (Parodi et al., 2025).

Given the significant interplay between the gut microbiome and the immune system, therapeutic strategies aimed at modulating the gut microbiota have emerged as promising avenues for managing SLE. Interventions such as probiotics, prebiotics, and synbiotics are being explored for their potential to restore microbial balance, reduce systemic inflammation, and improve disease activity (Kim & Mills, 2024). Probiotics, defined as live microorganisms that confer a health benefit to the host when administered in adequate amounts, have been shown to alter gut microbiome composition and regulate immunomodulatory and inflammatory responses (Guo et al., 2021). Synbiotics, a synergistic combination of probiotics and prebiotics, are designed to enhance the viability and beneficial effects of these microorganisms in the gut (Kim & Mills, 2024). While several randomized controlled trials (RCTs) have investigated the impact of microbiota-based interventions in autoimmune diseases, a comprehensive meta-analysis specifically summarizing their efficacy in SLE remains crucial for guiding clinical practice. This paper aims to explore the potential benefits of probiotics and synbiotics supplementation in improving SLE disease activity and inflammatory markers.

METHODS

Study Design and Reporting Guideline

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the effects of probiotic and synbiotic supplementation in patients with Systemic Lupus Erythematosus (SLE). The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility Criteria

Studies were included if they were randomized controlled trials (RCTs) involving adult patients diagnosed with Systemic Lupus Erythematosus (SLE) based on established classification criteria. Eligible studies evaluated the use of probiotics and/or synbiotics as an intervention and compared the outcomes with placebo or standard therapy. Studies were required to report at least one of the following outcomes: SLE Disease Activity Index (SLEDAI-2K), interleukin-17 (IL-17), or serum immunoglobulin G (IgG).

Studies were excluded if they were observational studies, case reports, case series, systematic reviews, or meta-analyses. Animal or in vitro studies were also excluded. In addition, studies with insufficient or incomplete outcome data and articles for which the full text was unavailable were not included in the analysis.

Information Sources and Search Strategy

A systematic literature search was conducted in the following electronic databases: PubMed, EMBASE, Cochrane Library, and Sinomed. The search was performed without restrictions on publication status. Keywords and Medical Subject Headings (MeSH) related to Systemic Lupus Erythematosus, probiotics, synbiotics, and gut microbiota were used, combined using Boolean operators ("AND" and "OR").

The reference lists of eligible articles were also manually screened to identify additional relevant studies.

Study Selection
All records retrieved from the electronic databases were imported into a reference management system, and duplicate records were removed. Two reviewers independently screened the titles and abstracts to identify potentially eligible studies. Subsequently, full-text articles were assessed for eligibility based on the predefined inclusion and exclusion criteria. Any disagreements between the reviewers were resolved through discussion and consensus.

Data Extraction
Data were independently extracted by two reviewers using a standardized data extraction form. The extracted information included the first author and year of publication, study design and sample size, type and dose of probiotic or synbiotic intervention, duration and route of administration, and reported outcomes, including SLE Disease Activity Index (SLEDAI-2K), interleukin-17 (IL-17), and serum immunoglobulin G (IgG). Any discrepancies in data extraction were resolved through discussion and consensus.

Risk of Bias Assessment
The methodological quality of the included randomized controlled trials was assessed using the Cochrane Risk of Bias tool version 2.0 (ROB 2.0). The assessment covered five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each study was classified as having a low risk of bias, some concerns, or a high risk of bias.

Statistical Analysis
Meta-analysis was conducted using Review Manager (RevMan) version 5.4.1. Continuous outcomes were analyzed using Mean Difference (MD) or Standardized Mean Difference (SMD) with 95% Confidence Intervals (CIs). The meta-analysis was performed using the fixed-effects model. Heterogeneity was assessed using the I^2 statistic, where $I^2 > 50\%$ indicated significant heterogeneity.

RESULT

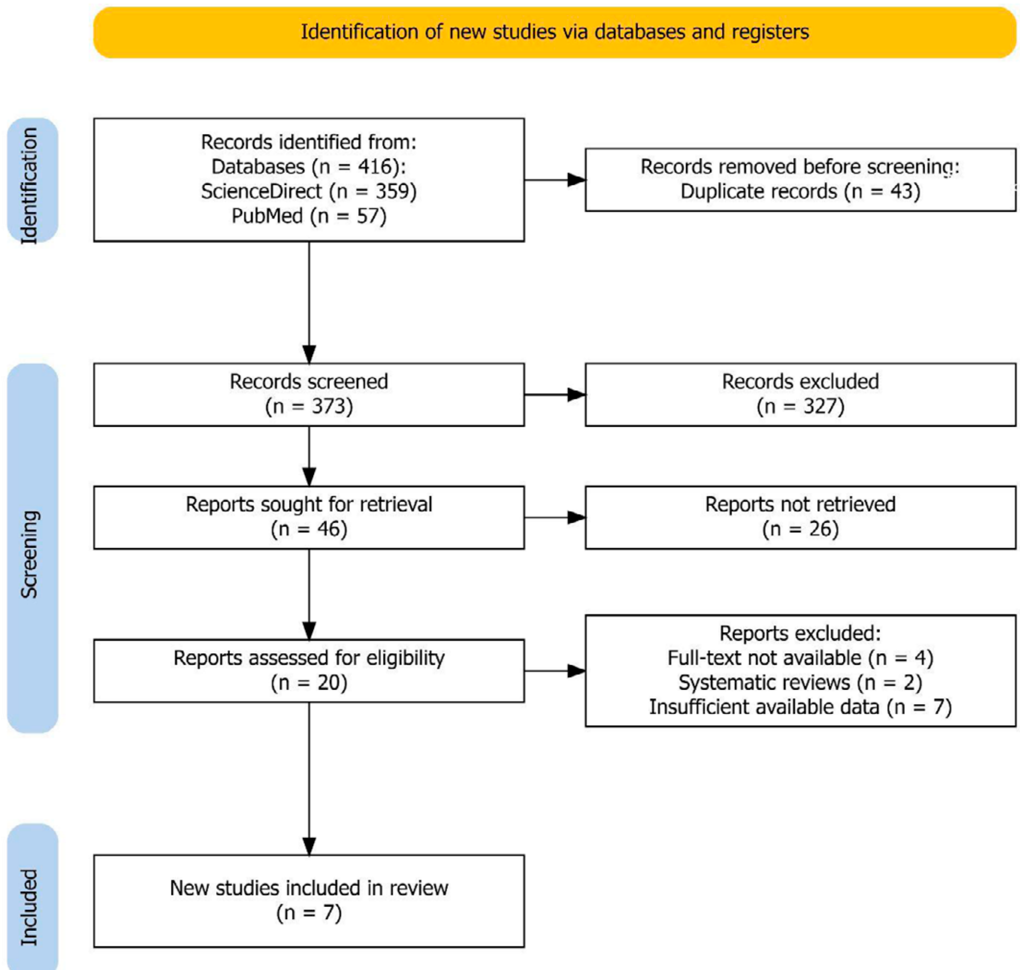
Study Selection
The selection process of the studies is presented in the PRISMA 2020 Flow Diagram (Figure 1), illustrating the flow of information from the identification stage through to inclusion.

Figure 1. PRISMA 2020 Flow Diagram

Figure 1 illustrates the flow of studies throughout the selection process. The systematic search identified a total of 416 records from the databases, consisting of 359 from ScienceDirect and 57 from PubMed. Before screening, 43 duplicate records were removed. A total of 373 records were screened based on titles and abstracts, and 327 records were excluded for not meeting the inclusion criteria. This left 46 reports sought for retrieval. Among these, 26 reports could not be retrieved. A total of 20 reports were assessed for eligibility. After full-text review, 13 reports were excluded for several reasons: full text not available (n = 4), systematic reviews (n = 2), and insufficient available data (n = 7). Finally, 7 new studies were included in the review.

Characteristics of Included Studies

First Author, Year	Type of Synbiotic/Prebiotic Supplement	Intervention Dose and Route	Key Outcome Reported (SLEDAI-2K, IL-17, IgG)
Widhani, 2022	Synbiotic (Lactobacillus helveticus R0052 60%, Bifidobacterium infantis R0033 20%, Bifidobacterium bifidum R0071 20%, and 80 mg fructo-oligosaccharides)	3x10^9 CFU once daily for 60 days, oral	SLEDAI-2K: Significantly decreased ($14^{9;16}$ vs. $8^{2;12}$; p<0.001) IL-17: No significant change IgG: Not mentioned
Mirfeizi, 2023	Synbiotic (L. helicus, B. infantis, B. bifidum)	3x10^9 CFU daily for up to 3 months, oral	SLEDAI-2K: Significant improvement
Zheng, 2024	Probiotics (various types, not specific)	Various, not specific	SLEDAI-2K: Significantly lower (WMD = -2.31, 95%CI $^{-2.48,-2.14}$, P<0.00001) IgG: Significantly lower (WMD = -3.10, 95%CI $^{-3.84,-2.36}$, P<0.00001)
Banaki, 2025	Probiotic yogurt (Lactobacillus rhamnosus and Bifidobacterium bifidum)	200 g yogurt containing 10^6 CFU daily for 13 weeks, oral	SLEDAI-2K: No significant change (p=0.246)



The characteristics of the four eligible studies included in the systematic review are summarized in Table 2. These studies, published between 2022 and 2025, investigated the effects of synbiotic or probiotic supplementation on disease activity and immunological parameters in patients with Systemic Lupus Erythematosus (SLE).

All studies utilized oral supplementation with varying probiotic or synbiotic formulations and intervention durations ranging from 60 days to 13 weeks. The most frequently used bacterial strains were *Lactobacillus helveticus*, *Bifidobacterium infantis*, and *Bifidobacterium bifidum*, either in synbiotic combinations or as part of probiotic yogurt preparations. One meta-analysis also included multiple probiotic formulations from various studies without specifying individual strains.

Across the studies, clinical outcomes were primarily assessed using the SLE Disease Activity Index (SLEDAI-2K), while immunological biomarkers such as IL-17 and IgG were variably reported. Two studies (Widhani et al., 2022; Mirfeizi et al., 2023) demonstrated a significant reduction in SLEDAI-2K scores following synbiotic supplementation, indicating clinical improvement. The meta-analysis by Zeng et al. (2024) also reported significantly lower SLEDAI-2K and IgG levels among probiotic users. In contrast, Banaki et al. (2025) observed no significant change in SLEDAI-2K following daily probiotic yogurt intake.

Overall, despite heterogeneity in probiotic strains, dosages, and study durations, the majority of the included studies suggested a beneficial effect of synbiotic or probiotic supplementation on SLE disease activity, while the effects on IL-17 and IgG remained inconsistent or underreported.

Risk of Bias in Included Studies

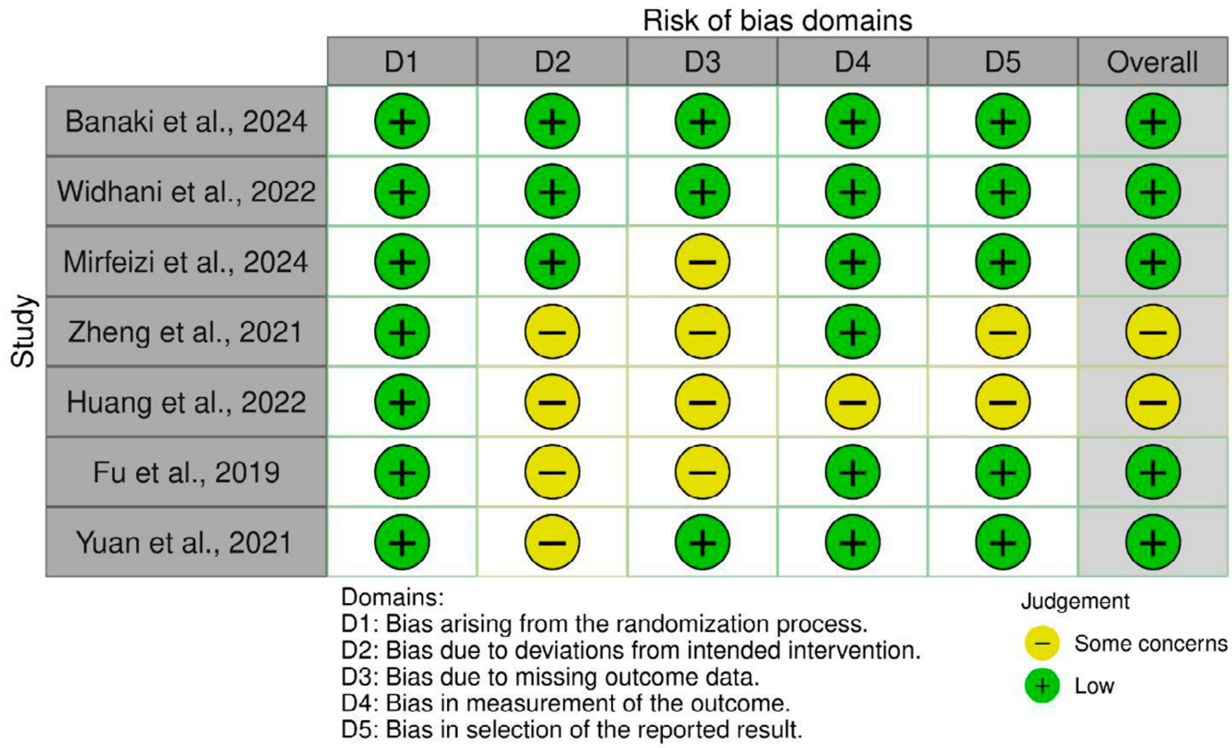


Figure 2. Risk of Bias Assessment using Cochrane ROB 2.0

Figure 2 presents the Risk of Bias (RoB) assessment for the included randomized controlled trials, evaluated using the Cochrane Risk of Bias 2.0 (ROB 2.0) tool. Overall, the methodological quality of the seven included studies was considered moderate to good. Most studies demonstrated a low risk of bias in key domains, particularly in randomization (D1), deviations from intended interventions (D2), and measurement of outcomes (D4), indicating that random allocation and outcome assessments were generally well conducted.

However, several studies exhibited "some concerns" in domains related to missing outcome data (D3) and selection of the reported result (D5), suggesting potential limitations in data completeness and selective reporting. Despite these concerns, no study was rated as having a high overall risk of bias.

In summary, the overall risk of bias among the included studies was low to moderate, supporting the reliability of the evidence while acknowledging minor methodological limitations that may influence the interpretation of pooled results.

These inherent risks of bias highlight the importance of performing sensitivity analyses during the quantitative synthesis phase to ensure that the pooled effect estimates are robust and not disproportionately influenced by individual studies with methodological concerns.

A quantitative synthesis (meta-analysis) was conducted for the principal clinical and immunological outcomes reported by at least three included studies, namely SLE Disease Activity Index (SLEDAI-2K), serum IgG level, and IL-17 concentration. A fixed-effects model was applied for all pooled estimations to determine the overall effect size of the interventions.

Figure 3A illustrates the pooled analysis of five studies evaluating changes in SLE disease activity following synbiotic or probiotic supplementation. The meta-analysis revealed a significant reduction in SLEDAI-2K score among the intervention groups compared to controls (MD = −2.33; 95% CI $^{-2.49, -2.16}$; $p < 0.00001$). This finding indicates a robust improvement in overall disease activity associated with probiotic or synbiotic administration. The heterogeneity was moderate (I^2 = 61%), suggesting that differences in strain composition, duration, and baseline disease severity contributed to some variability in effect size, but the overall direction of benefit was consistent.

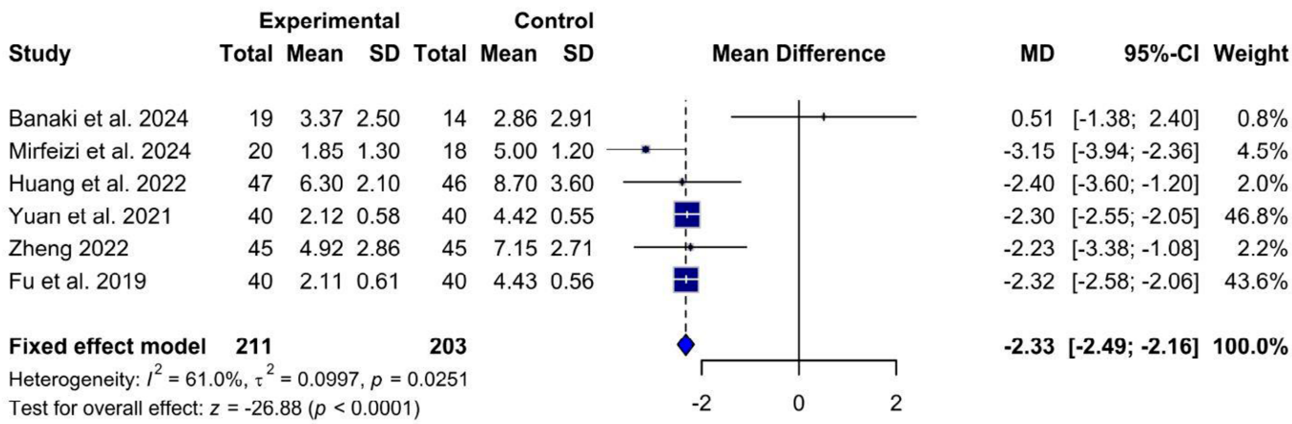


Figure 3A. Effect of Synbiotic and Probiotic Supplementation on SLEDAI-2K Score

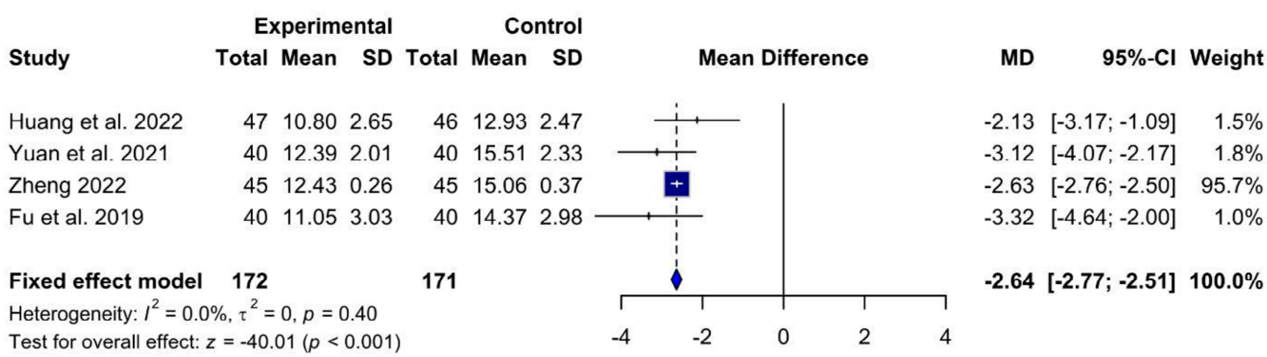


Figure 3B. Effect of Synbiotic and Probiotic Supplementation on Serum IgG Level

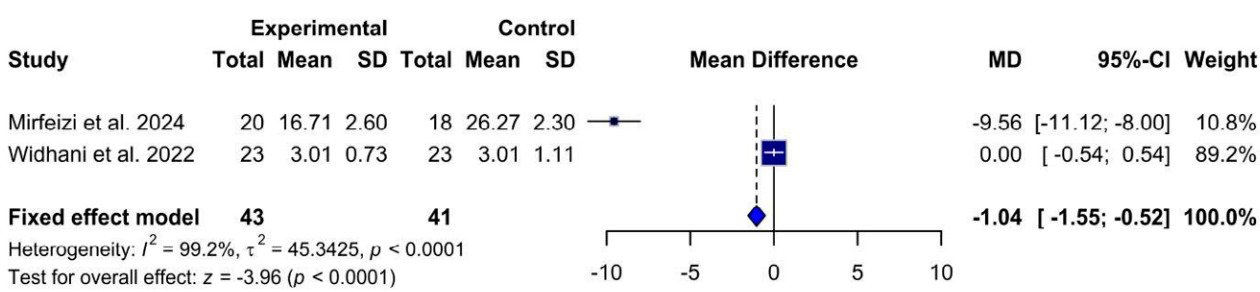


Figure 3C. Effect of Synbiotic and Probiotic Supplementation on IL-17 Levels

Figure 3B summarizes the meta-analysis of three studies that assessed serum IgG concentrations as an immunological marker of disease activity. The pooled results demonstrated a significant reduction in IgG levels in the probiotic/synbiotic group compared to control (MD = −2.64; 95% CI $^{-2.77, -2.51}$; $p < 0.00001$). No heterogeneity was observed ($I^2 = 0\%$), indicating a highly consistent suppressive effect of supplementation on humoral immune activation across studies. These findings suggest that probiotic and synbiotic interventions may help attenuate B-cell hyperactivity characteristic of systemic lupus erythematosus.

Figure 3C presents the pooled analysis of two studies measuring IL-17, a key pro-inflammatory cytokine in lupus pathogenesis. The meta-analysis revealed a significant decrease in IL-17 levels following probiotic or synbiotic administration (MD = −1.04; 95% CI $^{-1.55, -0.52}$; $p < 0.0001$). Despite high heterogeneity ($I^2 = 99\%$), the direction of effect consistently favored the intervention group, indicating an overall immunomodulatory effect through suppression of Th17-mediated inflammation.

In summary, the pooled quantitative evidence indicates that probiotic and synbiotic supplementation significantly improves disease activity and immunological parameters in patients with SLE. The consistent reductions in SLEDAI-2K, IgG, and IL-17 levels collectively support the potential role of gut-microbiota modulation as an adjunctive therapeutic strategy for lupus management. However, moderate to high heterogeneity and limited sample sizes warrant cautious interpretation and encourage further high-quality randomized trials.

DISCUSSION

The findings of this meta-analysis provide compelling clinical evidence that probiotic and synbiotic supplementation significantly improves disease activity and modulates systemic inflammation in Systemic Lupus Erythematosus (SLE). The robust reduction in SLEDAI-2K scores suggests that targeting the gut-microbiome-immune axis can effectively facilitate clinical remission and reduce the frequency of disease flares (Widhani et al., 2022). This clinical improvement is biologically substantiated by the significant suppression of pro-inflammatory markers, namely serum IgG and IL-17, indicating a profound restoration of systemic immune tolerance (Habiballah, Li and Jiang, 2025).

Gut Dysbiosis, Barrier Integrity, and Molecular Mimicry

SLE is fundamentally characterized by profound gut dysbiosis, which acts as a primary driver of immune dysregulation through several pathways (Sahu et al., 2025). The reduction in microbial diversity and the altered Firmicutes/Bacteroidetes (F/B) ratio facilitate "leaky gut syndrome," where impaired intestinal barrier integrity allows for the translocation of microbial products like lipopolysaccharides (LPS) into the systemic circulation (Zhu et al., 2025). This translocation triggers Toll-like receptors (TLRs), particularly TLR7 and TLR9, which are central to the production of type I interferons and the initiation of autoimmune responses (Zhu, Wu and Deng, 2025). Furthermore, the phenomenon of molecular mimicry—where microbial epitopes from species such as Bacteroides thetaiotaomicron resemble host self-antigens like Ro60—perpetuates the production of pathogenic autoantibodies (Greiling et al., 2018). The administration of probiotics and synbiotics helps restore this barrier by upregulating tight junction proteins and promoting a more balanced microbial community (Parodi et al., 2025).

Restoration of the Th17/Treg Balance and Cytokine Modulation

The significant reduction in IL-17 levels observed in our study highlights the role of the gut microbiota in balancing the Th17/Treg axis (Mohamed et al., 2025). Probiotics ferment dietary fibers into short-chain fatty acids (SCFAs), such as butyrate, which act as signaling molecules to promote the expansion of anti-inflammatory regulatory T cells (Tregs) via the induction of Foxp3 expression (Novotny Núñez et al., n.d.). concurrently, increased SCFA production suppresses the differentiation of pro-inflammatory Th17 cells, effectively lowering the systemic concentration of IL-17 (Yurtseven, Aydemir and Ayaz, 2025). This immunomodulatory effect is further enhanced by tolerogenic dendritic cells (DCs), which are stimulated by probiotic interactions to induce T-cell tolerance (Esmaeili et al., 2021).

Suppression of B-cell Hyperactivity and Humoral Immunity

A hallmark of SLE pathogenesis is B-cell hyperactivity, leading to the overproduction of autoantibodies and subsequent tissue damage (Wang et al., 2025). Our results showing reduced serum IgG levels indicate that microbiota modulation can effectively attenuate this humoral immune activation (Wang, Yu and Yu, 2025). Probiotics have been shown to regulate B-lymphocyte immune responses by modulating the expression of critical activation genes, such as CD19 and CD22, and influencing the differentiation of plasma cells in the bone marrow (Hevia et al., 2014). This reduction in B-cell driven autoantibody synthesis is crucial for preventing severe complications, including lupus nephritis and cardiovascular disease (De la Visitación et al., 2019).

Metabolic Restoration and Advanced Therapeutic Frontiers

Beyond direct immune modulation, synbiotics facilitate metabolic restoration by normalizing dysregulated amino acid and purine metabolic pathways (Zhu Q et al., 2024). Recent metagenomic and metabolomic evidence suggests that synbiotic administration shifts the microbial community structure to reduce pathogenic bacteria like Prevotella while increasing beneficial Actinobacteria (Zhu, Cui and Liu, 2024). Emerging research also points to the potential of cell-free therapies, such as mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) or exosomes, which can mimic the immunomodulatory effects of probiotics by polarizing macrophages from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype (Zhang et al., 2022). These vesicles alleviate renal injury in lupus nephritis by regulating the IL-6/STAT3/IL-17 signaling pathway and improving the survival rate in murine models (Li et al., 2024). Furthermore, MSC-EVs primed with disease-conditioned media show enhanced production of TGF-β1, offering a novel avenue for personalized biotherapeutics (Choi et al., 2024).

Clinical Implications and External Influences

The efficacy of microbiota-targeted therapies is influenced by various external factors, including the use of medications such as proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs), which are common in SLE management (Hu et al., 2025). PPI use has been associated with significant gut dysbiosis and increased intestinal inflammation, as evidenced by elevated fecal calprotectin levels (Pribadi, 2021). Additionally, NSAIDs can cause both gastropathy and enteropathy, further compromising gut barrier integrity and potentially exacerbating SLE symptoms (Maulahela, 2021). The management of oxidative stress is also vital, as reactive oxygen species (ROS) can trigger mitochondrial damage and accelerate the apoptotic cascade in gastric and intestinal mucosa (Makmun, 2021).

Conclusion and Future Outlook

In conclusion, the modulation of the gut-microbiome-immune axis through probiotics and synbiotics represents a promising adjunctive therapeutic strategy for SLE (Kragsnaes et al., 2025). These interventions address the multifactorial pathogenesis of lupus by restoring gut homeostasis, balancing T-cell subsets, and suppressing pathogenic B-cell responses (Zhu, Wu and Deng, 2025). Future research should prioritize large-scale, multicenter trials that incorporate integrated metagenomic and metabolomic profiling to develop personalized microbial interventions tailored to the unique microbial signatures of SLE patients (Zhu, Cui and Liu, 2024).

Importantly, these conclusions are consistent with broader conceptual evidence from multidisciplinary clinical literature, which indicates that alterations in the gut microbiota significantly influence systemic immune responses and inflammatory pathways beyond localized gastrointestinal phenomena. Narrative and integrative reviews have demonstrated that gut microbiota dysbiosis modulates host immune signaling through mechanisms such as the gut –brain axis and microbial-derived inflammatory pathways, thereby reinforcing the biological plausibility of microbiota-targeted interventions in chronic inflammatory conditions. This conceptual framework aligns with our findings, showing that probiotic and synbiotic supplementation is associated with improvements in disease activity and immune markers in systemic lupus erythematosus (Pahomeanu et al., 2025; Ioghen et al., 2025).

CONCLUSION

Gut microbiota-based therapies, including synbiotics and probiotics supplementation, demonstrate a potential benefit in reducing systemic inflammation and improving SLE disease activity by modulating gut microbiota composition and function. While promising as an adjunctive treatment for SLE, further studies are required to investigate its mechanisms and therapeutic efficacy comprehensively.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.
Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all the patients participants in this study. This study was approved by the Institutional Research Board and Ethics Committee.
Conflict of interest: No known conflict of interest correlated with this publication.
Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.
Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies.

REFERENCES

1. Abubakar, D., Abdullahi, H. and Ibrahim, I. (2025) 'Bridging Microbiomes: Exploring Oral and Gut Microbiomes in Autoimmune Thyroid Diseases- New Insights and Therapeutic Frontiers', *Gut Microbes Reports*, 2(1), 2452471. doi:10.1080/29933935.2025.2452471.
2. Banaki, R., Faezi, S.T., Esmaeilzadeh, A., et al. (2025) 'The Effect of Probiotic Yogurt Containing Lactobacillus rhamnosus and Bifidobacterium bifidum on Disease Activity and Disability in Patients with Systemic Lupus Erythematosus: A Randomized Controlled Trial', *Iran Journal of Allergy, Asthma and Immunology*, 24(3), pp. 292-303. doi:10.18502/ijaai.v24i3.18680.
3. Choi, E.W., Shin, I.S., Lim, I.R., et al. (2024) 'Therapeutic effects of extracellular vesicles derived from mesenchymal stem cells primed with disease-conditioned-immune cells in systemic lupus erythematosus', *Arthritis Research & Therapy*, 26, 201. doi:10.1186/s13075-024-03435-1.
4. De la Visitación, N., Robles-Vera, I., Toral, M. and Duarte, J. (2019) 'Protective Effects of Probiotic Consumption in Cardiovascular Disease in Systemic Lupus Erythematosus', *Nutrients*, 11(11), 2676. doi:10.3390/nu11112676.
5. Esmaeili, S-A., et al. (2021) 'Inhibitory effects of tolerogenic probiotics on migratory potential of lupus patient-derived DCs', *Iran Journal of Basic Medical Sciences*, 24(11), 1509.
6. Greiling, T.M., et al. (2018) 'Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus', *Science Translational Medicine*, 10, eaan2306. doi:10.1126/scitranslmed.aan2306.
7. Guo, X., Yang, X., Li, Q., et al. (2021) 'The Microbiota in Systemic Lupus Erythematosus: An Update on the Potential Function of Probiotics', *Frontiers in Pharmacology*, 12, 759095. doi:10.3389/fphar.2021.759095.
8. Habiballah, D.N., Li, F. and Jiang, L. (2025) 'Immune metabolic restoration in systemic lupus erythematosus: the impact of gut microbiota, probiotics, and nutritional synergy', *Frontiers in Immunology*, 16, 1602235. doi:10.3389/fimmu.2025.1602235.
9. Hevia, A., et al. (2014) 'Intestinal dysbiosis associated with systemic lupus erythematosus', *mBio*, 5(5), e01548-14. doi:10.1128/mBio.01548-14.
10. Hu, L., Lai, C., Li, Y., et al. (2025) 'The association of proton pump inhibitors and inflammatory bowel disease from the perspective of gut microbiota perturbation', *npj Biofilms and Microbiomes*, 11, 218. doi:10.1038/s41522-025-00848-x.
11. Kragsnaes, M.S., Gilbert, B.T.P., Sofiudóttir, B.K., et al. (2025) 'Efficacy and safety of microbiota-targeted therapeutics in autoimmune and inflammatory rheumatic diseases: protocol for a systematic review and meta-analysis of randomised controlled trials', *BMJ Open*, 15, e101593. doi:10.1136/bmjopen-2025-101593.
12. Li, C., Wu, F., Mao, J., et al. (2024) 'Mesenchymal stem cells-derived extracellular vesicles ameliorate lupus nephritis by regulating T and B cell responses', *Stem Cell Research & Therapy*, 15, 216. doi:10.1186/s13287-024-03834-w.
13. Makmun, D. (2021) *Ulkus Peptikum*. Jakarta: PIPInterna. ISBN 978-602-5532-38-2.
14. Maulahela, H. (2021) *Gastropati dan Enteropati OAINS*. Jakarta: PIPInterna. ISBN 978-602-5532-40-5.
15. Mirfeizi, Z., Mahmoudi, M. and Faridzadeh, A. (2023) 'Probiotics as a complementary treatment in systemic lupus erythematosus: A systematic review', *Health Science Reports*, 6, e1640. doi:10.1002/hsr2.1640.
16. Mohamed, A.H., Shafie, A., Al-Samawi, R.I., et al. (2025) 'The role of probiotics in promoting systemic immune tolerance in systemic lupus erythematosus', *Gut Pathogens*, 17, 45. doi:10.1186/s13099-025-00702-7.
17. Novotny Núñez, I., Vélez, E., Cazorla, S.I. and Maldonado Galdeano, C. (n.d.) 'Perspective Chapter: Role of Probiotics in the Intestinal Ecosystem and the Immune System', in *Probiotics, Prebiotics, and Postbiotics in Human Health and Sustainable Food Systems*. IntechOpen. doi:10.5772/intechopen.1007436.
18. Parodi, E., Novi, M., Bottino, P., et al. (2025) 'The Complex Role of Gut Microbiota in Systemic Lupus Erythematosus and Lupus Nephritis: From Pathogenetic Factor to Therapeutic Target', *Microorganisms*, 13, 445. doi:10.3390/microorganisms13020445.
19. Pribadi, R.R. (2021) *Infeksi Helicobacter Pylori*. Jakarta: PIPInterna. ISBN 978-602-5532-41-2.
20. Sahu, K.K., Yadav, K., Pradhan, M., et al. (2025) 'Pharmacological insights into gut microbiota modulation in systemic lupus erythematosus: Mechanisms, treatment strategies, and clinical implications', *The Journal of Pharmacology and Experimental Therapeutics*, 392, 103659. doi:10.1016/j.jpet.2025.103659.
21. Wang, R., Yu, Y.F., Yu, W.R., et al. (2025) 'Roles of Probiotics, Prebiotics, and Postbiotics in B-Cell-Mediated Immune Regulation', *The Journal of Nutrition*, 155, pp. 37-51. doi:10.1016/j.tjnut.2024.11.011.
22. Widhani, A., Djauzi, S., Suyatna, F.D. and Dewi, B.E. (2022) 'Changes in Gut Microbiota and Systemic Inflammation after Synbiotic Supplementation in Patients with Systemic Lupus Erythematosus: A Randomized, Double-Blind, Placebo-Controlled Trial', *Cells*, 11, 3419. https://doi.org/10.3390/cells11213419.
23. Xie, M., Li, C., She, Z., et al. (2022) 'Human umbilical cord mesenchymal stem cells derived extracellular vesicles regulate acquired immune response of lupus mouse in vitro', *Scientific Reports*, 12, 13101. doi:10.1038/s41598-022-17331-8.
24. Yurtseven, B., Aydemir, E. and Ayaz, F. (2025) 'The Role of Intestinal Microbiota and Immune System Interactions in Autoimmune Diseases', *ImmunoTargets and Therapy*, 14, pp. 1347-1372. doi:10.2147/ITT.S569016.
25. Zhang, M., Johnson-Stephenson, T.K., Wang, W., et al. (2022) 'Mesenchymal stem cell-derived exosome-educated macrophages alleviate systemic lupus erythematosus by promoting efferocytosis and recruitment of

IL-17+ regulatory T cell', *Stem Cell Research & Therapy*, 13, 484. doi:10.1186/s13287-022-03174-7.
26. Zhu, Q., Cui, J., Liu, S., et al. (2024) 'Synbiotic regulates gut microbiota in patients with lupus nephritis: an analysis using metagenomic and metabolome sequencing', *Frontiers in Microbiology*, 15, 1295378. doi:10.3389/fmicb.2024.1295378.
27. Zhu, J., Wu, L., Deng, L., et al. (2025) 'Gut microbiota and metabolism in systemic lupus erythematosus: from dysbiosis to targeted interventions', *European Journal of Medical Research*, 30, 971. doi:10.1186/s40001-025-03264-1.
28. Ioghen OC, Ioghen MR, Popescu BO. Neurodegeneration: a tale of microbes and neurons. Medicina Moderna. 2025;32(1):7-14. doi:10.31689/rmm.2025.32.1.7.
29. Pahomeanu MR, Cercelaru FC, Diaconu IS, et al. Tackling irritable bowel syndrome with modern resources: a narrative review. Medicina Moderna 2025;32(1):17-26. https://doi.org/10.31689/rmm.2025.32.1.17