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Probiotics as a complementary treatment in systemic lupus erythematosus: A systematic review

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that primarily affects young women. SLE has no recognized etiology but it is believed to be triggered by a number of factors, including genetic predisposition, hormonal influences, and environmental conditions. Dysbiosis in the gut microbiota has emerged as a potential mechanism connecting the intestinal microbiome to the breakdown of self-tolerance and chronic inflammation. This review aims to investigate the role of probiotics in modulating the gut microbiome and their potential therapeutic benefits in managing SLE, providing insights for future research and clinical practice.

Methods: We conducted a thorough search for papers published up to June 2023 in databases such as PubMed/MEDLINE, Web of Science, Scopus, and Cochrane Library.

Results: The systematic review identified 22 articles examining the effects of probiotics on SLE. These studies—which include in vivo tests, in vitro research, and clinical trials—indicate that probiotics may be effective against inflammation, and improve immunological responses and metabolic profiles in SLE patients. Most in vivo studies were assessed as medium to high quality, while the randomized controlled trial was deemed of high quality.

Conclusion: According to the findings of our systematic review, probiotics may be used in conjunction with other treatments to manage SLE. Nonetheless, current data is limited, and more randomized controlled trials would be required to fully examine their effectiveness.

KEYWORDS

prebiotics, probiotic, synbiotic, systematic review, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic illness with multi-system involvement that primarily affects young women. It is characterized by autoimmune intolerance to autoantigens, leading to the production of numerous antibodies and the activation of T cells that produce inflammation-promoting cytokines.[1]

While the etiology of SLE remains unknown, susceptibility to the disease may be correlated with factors such as immune intolerance, hormonal influences, and genetic predisposition. Additionally, various

environmental and psychological triggers, including the Epstein–Barr virus, cytomegalovirus, drugs, sunlight exposure, physical inactivity, psychological stress, and gut microbiota, have been implicated in the onset of the disease.[2]

The imbalance of microbial intestinal species (dysbiosis) can contribute to the development of autoimmunity by mechanisms such as molecular mimicry with self-antigens, epitope release, bystander activation, and bacterial translocation. These mechanisms may result in the loss of the immune system's self-tolerance, and the generation of autoantibodies which results in the destruction of the body's own tissues, thus triggering chronic inflammation.[3,4]

Therefore, the intestinal microbiota plays a key role in supporting several vital processes, including the maintenance of homeostasis, regulation of the immune system, preservation of the epithelial barrier, and metabolic functions. Intestinal homeostasis relies on the sophisticated interaction and cooperation of regulatory mechanisms within a cellular network that encompasses both innate and adaptive immune cells.[5,6]

The variety and composition of the microbiota found in the intestine depend on internal factors such as genetics as well as external factors such as lifestyle, diet, use of medication, and overall health condition.[7,8]

Probiotics are live microorganisms intended to be consumed as supplements to promote the growth of friendly bacteria, resulting in positive health effects on the host when taken in the appropriate quantities. The health benefits associated with probiotics have been demonstrated by numerous studies in recent years.[9] Specific strains of probiotics, especially those from the *Bifidobacteria* and *Lactobacillus* groups, have been particularly effective in providing protection against inflammatory and autoimmune illnesses.[10]

We aim to provide valuable insights into the potential benefits of probiotic interventions in managing SLE through the information presented in this review.

2 | METHOD

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11,12] and registered their study in PROSPERO, a global registry for systematic reviews, to ensure a systematic and transparent approach to their research. The review is assigned a unique identification number of CRD42023398876.

2.1 | Eligibility criteria

We utilized the Population, Intervention, Comparison, and Outcomes (PICO) framework to investigate the effects of probiotics on experimental SLE-induced mice, cells derived from SLE patients, and clinical trials in SLE patients. Our study population included various models of SLE-induced mice, including NZB/W, MRL/lpr, pristane-induced, and toll-like receptors (TLR)-7 activation, as well as SLE patients. The intervention involved administering probiotics; we compared various factors, such as severity, mechanisms, cell lines, probiotic strain(s), dosage, and duration of treatment. To report the outcomes, we assessed changes in clinical signs and symptoms and inflammatory markers from baseline to the last available follow-up. Additionally, we examined changes in cell surface markers to determine the outcomes.

2.2 | Search strategy

A comprehensive search of several databases, including PubMed/MEDLINE, Web of Science, Cochrane Library, and Scopus, was conducted from February 14, 2023, until the submission of this article, without imposing any language restrictions. The search terms used were "probiotic," "synbiotic," "prebiotic," "*Lactobacillus*," "*Bifidobacterium*," and "*Streptococcus thermophilus*," combined with the keywords "systemic lupus erythematosus," "Lupus," or "Lupus Erythematosus, Systemic" or "SLE." The review incorporated the most recently published article identified during the manual search, and the final search was conducted in June 2023.

2.3 | Study selection

The two reviewers independently screened articles by evaluating their titles and abstracts. After removing duplicates, studies deemed irrelevant based on title or abstract were excluded from further assessment. Excluded studies fell into two categories: (1) articles with an inappropriate format, such as books, review articles, letters to editors, guidelines, surveys, or those not in English, and (2) studies with irrelevant content, including those focusing on the microbiome of SLE patients or other diseases, as well as those unrelated to probiotics.

The full texts of the remaining studies were assessed to determine their final eligibility. These studies comprised both experimental and clinical studies that investigated the effect of probiotics on the prognosis of SLE. A flow diagram is included to provide a detailed overview of the entire study selection process (Figure 1).

2.4 | Methodological quality assessment

We used various evaluation tools to assess the risk of bias in the animal experimental studies, in vitro studies, cross-sectional studies, and clinical trials included in this study. Specifically, we employed SYRCLE's RoB tool to evaluate animal experimental studies,[13] the operationalized Nature reporting checklist to evaluate in vitro studies,[14] the National Institutes of Health (NIH) quality assessment tool to evaluate cross-sectional studies, and the Cochrane risk of bias tool to evaluate clinical trials.[15]

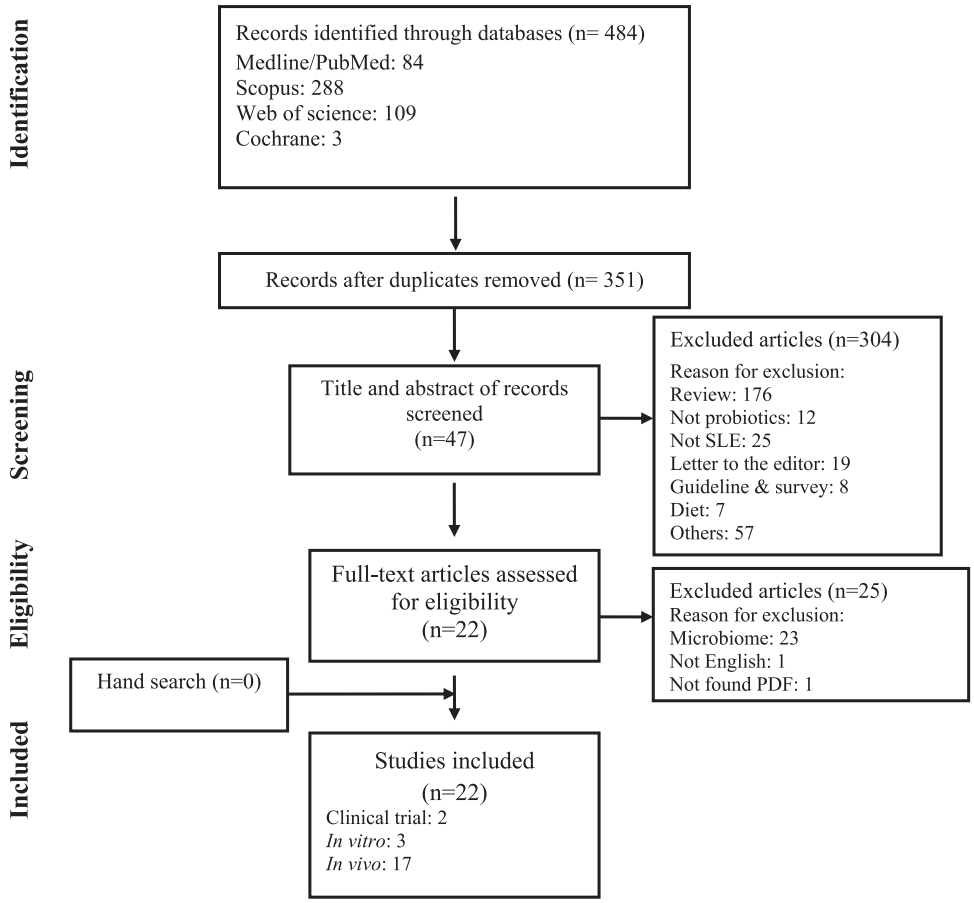

FIGURE 1 Flow chart of study selection for inclusion in the systematic review.

Two independent reviewers (A. F. and Z. M.) assessed the risk of bias in each paper included in the study. For attrition bias, we assumed no exclusion of animals when the number of animals per group specified in the materials and methods section matched the number stated in the results section. "Yes," indicated low risk of bias, "no" indicated high risk of bias, and "?" indicated undetermined risk. To mitigate items classified as "unclear risk of bias" due to inadequate reporting of experimental details, we introduced two additional reporting criteria: the reporting of any randomization measure and the reporting of any blinding measure. "Yes" indicated the measure was reported, while "no" indicated it was not. Detailed quality assessment of human and laboratory studies is available in the Supporting Information data section.

2.5 | Data extraction

Relevant data, including the author's name, publication date, animal model, cell line, group details, probiotic strains, probiotic dosage and duration, results, and mechanisms, were extracted and entered into a predefined Excel datasheet. Data screening was conducted independently by two reviewers, with discrepancies resolved through consensus. Our study's inclusion criteria were limited to experimental and clinical investigations, specifically examining the impact of probiotics on SLE prognosis.

3 | RESULT

3.1 | Study selection

We initially identified 484 articles through a comprehensive search across four databases: Medline/PubMed, Scopus, Web of Science, and Cochrane. After removing duplicates, 351 articles remained. Subsequently, we excluded 304 articles based on the inclusion criteria outlined in Figure 1, leaving us with 47 articles for full-text screening. Following a careful review of these articles, an additional 25 were excluded based on the criteria presented in Figure 1. Ultimately, we included 22 articles in our study, as they met all the inclusion criteria.

3.2 | Study characteristics

We classified the 22 included articles into 17 in vivo studies, three in vitro studies, and two clinical trials. Tables 1 and 2 present the

extracted data from in vitro and in vivo studies, respectively, including the animal model, cell type, group, probiotic strain, dosage, duration, result, and mechanism. Table 3 shows the data from clinical research, including the population, sex, probiotic strain, dosage, duration, and outcome.

Due to significant methodological variations and differences in outcome measurements among the included papers, performing a quantitative synthesis of the studies was not feasible. Therefore, the data in this study was generated solely using qualitative descriptive methods.

3.3 | Results of the in vitro studies

Esmaili et al. conducted two studies to assess the effects of *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus* on dendritic cells (DCs) in SLE patients compared to healthy individuals over a 2-day period. The researchers examined the expression of inflammatory chemokine receptors on the surface of tolerogenic DCs in both healthy and SLE donors, finding higher expression levels in individuals with SLE. Additionally, they observed an increase in interleukin (IL)-10 and indoleamine 2,3-dioxygenase (IDO) levels and a decrease in IL-12 levels.[16,17]

When *L. delbrueckii* and *L. rhamnosus* were used to treat peripheral blood mononuclear cells (PBMC) from SLE patients, Vahidi et al. found that the expression of miR-181a and miR-155 was reduced in comparison to the control group.[18] Table 1 provides a summary of the in vitro investigations' specifics.

3.4 | Results of the in vivo studies

Two studies have shown that combined oral gavage of all five species (*Lactobacillus oris*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus johnsonii*, *and Lactobacillus gasseri*) in 3-week-old female MRL/Mp mice had anti-inflammatory effects, as well as reductions in renal lymphadenopathy and splenomegaly.[19,20]

Three studies were conducted on the effect of *L. fermentum* in female mice for 8, 13, and 15 weeks through oral gavage. In the lymph nodes and kidneys, these studies generally found lower levels of proinflammatory cytokines, double-stranded (ds) deoxyribonucleic acid (DNA), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, and T helper (Th)1, and Th17 cells.[21–23]

According to Cheng et al., intraperitoneal injection of *L. plantarum* at a dose of 10^9 for 12 weeks reduced kidney damage, increased copper/zinc superoxide dismutase (Cu/Zn-SOD), and decreased inflammatory cytokines in lupus mice. In another study, *L. plantarum* demonstrated regulatory effects, including an increase in IL-10 and T regulatory (Treg).[24]

Studies have shown that the consumption of *L. casei*, *L. plantarum*, or *L. reuteri* in mice has anti-inflammatory, antiapoptotic, and modulatory effects and increases the lifespan of SLE mice.[24–26]

TABLE 1 Effect of probiotics in in vitro studies.

References, country	Cell type	Group	Probiotic strain(s)	Dose, duration	Result	Mechanisms
Esmaeili et al.,[16] Iran	Dendritic cells (human)	8 group healthy (IDC + LPS, IDC + RAM, IDC + DEL, IDC + MIX) SLE (IDC + LPS, IDC + RAM, IDC + DEL, IDC + MIX)	*Lactobacillus delbrueckii*, *Lactobacillus rhamnosus*	LPS (100 ng/mL), 2×10^6 bacteria per well, 2 days	↓Inflammatory responses ↑Production of regulatory Cells (DC)	↑IDO, IL-10 ↓IL-12
Esmaeili et al.,[17] Iran	Dendritic cells (human)	8 group healthy (IDC + LPS, IDC + RAM, IDC + DEL, IDC + MIX) SLE (IDC + LPS, IDC + RAM, IDC + DEL, IDC + MIX)	*L. delbrueckii*, *L. rhamnosus*	LPS (100 ng/mL), 2×10^6 bacteria per well, 2 days	↓Expression of inflammatory chemokine receptors on the surface of tolerogenic DCs in healthy and SLE donors (but in SLE was more)	↓CXCR3, CCR5, CCR4, and CCR3
Vahidi et al.,[18] Iran	PBMCs (human)	6 group control (*L. rhamnosus*, *L. delbrueckii*, and mix) SLE (*L. rhamnosus*, *L. delbrueckii*, and mix)	*L. rhamnosus*, *L. delbrueckii*	*L. rhamnosus* (10^7 Bac/mL) *L. delbrueckii* (10^5 Bac/mL), 2 days	*L. rhamnosus and L. delbrueckii* (mix): ↓Expression of miR-181a and miR-155 compared to the control group	-

Abbreviations: CCR, C chemokine receptor; CXCR, C-X-C chemokine receptor; DEL, *Lactobacillus delbrueckii*; IL, interleukin; IDC, immature dendritic cell; IDO, indoleamine 2,3-dioxygenase; miR, microRNA; MIX, both probiotics; PBMC, Peripheral blood mononuclear cells; RAM, *Lactobacillus rhamnosus*.

Kim et al. demonstrated that taking *L. acidophilus* with tacrolimus for a duration of 8 weeks decreased dsDNA and Th17 cells while increasing Treg cells in both the spleen and peripheral blood.[27]

Mu et al. observed that the simultaneous use of vancomycin with *L. animalis* increased the exacerbation of lupus in mice. They further demonstrated that this specific strain of *L. animalis* led to the inhibition of indoleamine 2,3-dioxygenase.[28]

Similarly, two other studies conducted on mice showed that the consumption of *L. rhamnosus* and *L. delbrueckii* caused a reduction in inflammatory cytokines, Th17 and Th1 cells, and an increase in Treg cells.[29,30] The details of animal studies are summarized in Table 2.

3.5 | Results of the human studies

In a randomized controlled trial (RCT) study, the effects of synbiotics were evaluated in 46 female SLE patients. The synbiotics, comprising *L. helicus*, *B. infantis*, *B. bifidum*, were administered daily at a dose of 3×10^9 colony forming units (CFU) for up to 3 months. Participants were divided into two groups: the synbiotic group and the placebo group. The study's findings revealed a significant reduction in IL-6 levels, an increase in the Firmicutes to Bacteroidetes ratio ($p = 0.48$), and a significant improvement in butyrate metabolism ($p = 0.037$). Furthermore, there was a decrease in amino sugar and nucleotide sugar metabolism ($p = 0.040$).[37]

In a cross-sectional study, Lu et al. treated 56 female SLE patients with probiotics. They noted a decrease in photosensitivity (odds ratio [OR]: 0.49; $p = 0.019$) and kidney involvement (OR: 2.43; $p = 0.026$) in the patients.[38] Table 3 provides a summary of the findings of these clinical trial studies.

3.6 | Risk of bias assessment

The risk of bias assessment was performed on the available in vivo studies using the SYRCLE risk of bias tool.[13] All studies, with the exception of those conducted by Manirarora et al., Kim et al., Mike et al., and Mardani et al., were found to have medium to high quality, as indicated in Table 4. A higher SYRCLE score corresponded to higher study quality.

The cross-sectional study (Lu et al.) included in the analysis was of good quality, as assessed by the National Institutes of Health (NIH) quality assessment tool.

The quality of the three in vitro studies, assessed using quality assessment tools for in vitro studies, is presented in the Supporting Information: Table S1.[14]

The RCT study conducted by Widhani et al., assessed using the Cochrane bias tool, was determined to be of high-quality.[15]

4 | DISCUSSION

In this systematic review, 17 animal studies, three laboratory studies, and two clinical trials were investigated. The majority of these studies demonstrated that administering probiotics at a dose of 10^8 to 10^9 CFU per day improved clinical outcomes in SLE patients and mice induced with SLE. SLE predominantly affects females, with a gender bias of 9:1, and the studies cited were primarily conducted on female subjects.[39] Based on the results of in vitro studies, animal models, and human intervention studies, probiotics seem to have preventive effects against SLE.

4.1 | Effects of probiotics on in vitro studies

Previously, Dong et al. demonstrated that a mixture of probiotics, including *L. casei*, *L. rhamnosus*, *L. plantarum*, *L. reuteri*, *Bifidobacterium longum*, *and B. bifidum*, had a modulatory effect on PBMCs of healthy individuals.[40] Some studies in autoimmune diseases have shown that *L. rhamnosus* and *L. delbrueckii* can increase the levels of inhibitory cytokines in T cells and PBMCs, while reducing the production of inflammatory molecules.[41–44]

Our findings suggest a decrease in inflammatory cytokines and chemokines in DCs and PBMCs obtained from SLE patients and healthy control subjects, after exposure to *L. delbrueckii* and *L. rhamnosus*.[16,17] Furthermore, the expression of miR-181a and miR-155 was lower in the probiotic group compared to the control group.[18]

4.2 | The role of gut microbiota in the progression of SLE

The study of the gut microbiota and its potential role in the development of SLE has become a prominent area of research. The onset and progression of many autoimmune illnesses are attributable to the activities of gut microbiota. Studies have found a significant association between the consumption of dietary supplements, disease activity, and the composition of gut microbiota in both animal models prone to lupus and individuals diagnosed with SLE.[3,45–52] Notably, recent research has unveiled a connection between dietary supplement intake, disease activity, and the composition of the intestinal microbiota in both lupus-prone animal models and individuals with SLE.[53,54]

4.3 | Effects of probiotics on in vivo studies

Cabana-Puig et al. demonstrated that oral administration of a mixture comprising five different *Lactobacillus* species, namely *L. rhamnosus*, *L. gasseri*, *L. johnsonii*, *L. reuteri*, and *L. oris* was effective in ameliorating lupus-like clinical signs by reducing lymphadenopathy and splenomegaly. Interestingly, none of the individual strains could reproduce the same positive effects observed in the mixed *Lactobacillus* species. These findings suggest a potential cooperative interaction among the species, enhancing the overall effectiveness by multiplying each individual strain's strength.[31] Furthermore, Mu et al. found that combining five with the *lactobacillus* mentioned earlier caused IL-6 levels in SLE mice to decrease and IL-10 levels to rise.[20]

TABLE 2 Effect of probiotics in in vivo studies.

Author, country	Animal model	Group	Probiotic strain(s)	Dose, duration	Result	Mechanisms
Cabana-Puig et al.,[31] USA	3-week-old MRL/lpr mice, Female	7 group ($n \geq 7$) PBS, *L. reuteri*, *L. oris*, *L. johnsonii*, *L. gasseri*, *L. rhamnosus*, Mix of all 5 species	*Lactobacillus reuteri*, *Lactobacillus oris*, *Lactobacillus johnsonii*, *Lactobacillus gasseri*, *Lactobacillus rhamnosus*	10^9 CFU, 100 µL at 3 weeks of age, 150 µL at 4 weeks of age, and 200 µL for the remaining weeks, 15 weeks (frequency of twice a week), oral gavage	↓Renal lymphadenopathy and splenomegaly (mix of all 5 species vs. PBS)	CX3CR1-dependent mechanism ↓Central memory T cells ↑Effector memory T cells in the lymphoid organ
Cheng et al.,[24] China	6-week-old C57BL/J6 mice (lupus nephritis), Female and Male	5 group ($n = 10$) normal group, model group, drug positive control group, low concentration treatment with LP-HFY15 group, high concentration treatment with LPHFY15 group	*Lactobacillus plantarum HFY15*	Low: 10^8 CFU/kg daily High: 10^9 CFU/kg daily, 12 weeks, intraperitoneally injected	High dose and prednisolone: ↓Urinary protein ↓IL-6, IL-12, TNF-α, and IFN-γ in serum and kidney tissue ↓Serum creatinine, BUN, TC, TG, TP, albumin, dsDNA, inflammatory infiltration, and the glomerulus morphological incompleteness. ↑Expression of IκB-α, Cu/Zn-SOD, and Mn-SOD	↓Expression of TGF-β1, VEGF, and NF-Kb ↑Expression of IκB-α, Cu/Zn-SOD, and Mn-SOD
de la Visitación et al.,[21] Spain	8-week-old BALB/cByJRj mice without or with the agonist of TLR-7 Imiquimod (mouse lupus model induced by TLR-7 activation), Female	4 group Ctrl ($n = 8$), IMQ ($n = 12$), IMQ-LC40 ($n = 10$), IMQ-BFM ($n = 10$)	*Lactobacillus fermentum CECT5716 (LC40), Bifidobacterium breve CECT7263 (BFM)*	10^9 CFU/mL daily, 8 weeks, oral gavage	LC40 and BFM: Endothelial dysfunction and hypertension	↑Expression of TLR9 ↓T cells activation, and Th17 in mesenteric lymph nodes ↓dsDNA
de la Visitación et al.,[22] Spain	20-week-old NZBWF1 (SLE) and NZW/LacJ (Ctrl) Mice, Female	4 group Ctrl ($n = 8$), Ctrl-treated ($n = 5$), SLE ($n = 9$), SLE-treated ($n = 8$)	*L. fermentum CECT5716 (LC40)*	5×10^8 CFU daily, 13 weeks, oral gavage	Renal injury associated with hypertension	↓Pro-inflammatory cytokines, NADPH oxidase activity, anti-dsDNA, immune-complexes deposition, infiltration of Th1 and Th17 cells in kidney
Mike et al.,[26] Japan	4-week- old MRL/lpr mice, female	2 group ($n = 25$) Ctrl, *Lactobacillus casei*	*L. casei*	Once a week, 18–20 weeks, intraperitoneally injected and orally	Diet: ↑the lifespan of MRL/lpr mice Intraperitoneally:	Expansion of $B220^+$ T cells

TABLE 2 (Continued)

Author, country	Animal model	Group	Probiotic strain(s)	Dose, duration	Result	Mechanisms
					Lymphadenopathy	↓IL-6 in peritoneal macrophages, modulates macrophage recruitment
Hsu et al.,[32] Taiwan	6-week-old NZB/W F1 mice, female	4 group ($n = 8$) Ctrl, GMNL-32, GMNL-89, GMNL-263	*Lactobacillus paracasei* GMNL-32 (GMNL-32), *L. reuteri* GMNL-89 (GMNL-89) *L. reuteri* GMNL-263 (GMNL-263)	10^9 CFU daily, 12 weeks, oral gavage	In all three groups of probiotics: ↓Inflammatory indicators (MMP-9, CRP, NO, IL-1β, IL-6 and TNF-α) and hepatic apoptosis	NF-κB and mitogen-activated protein kinase pathways
Hu et al.,[33] Taiwan	12-week-old NZB/W F1 mice, female	2 group ($n = 10$) Ctrl, GMNL-32	*L. paracasei* GMNL-32 (GMNL-32)	10^9 CFU/mL daily, 3 weeks, oral gavage	Impressive protective effect on cardiac cells	↓Cardiac cell apoptosis ↑Antiapoptotic proteins
Mu et al.,[20] USA	3-week-old MRL/Mp (MRL), MRL/Mp-Faslpr (MRL/lpr or lpr, stock number 000485) mice, female	2 group ($n = 4–10$) Ctrl, Mix of 5 Lactobacillus	*L. oris*, *L. rhamnosus*, *L. reuteri*, *L. johnsonii*, *L. gasseri*	0.2 mL, oral, 11 weeks, gavage	Mix of 5 Lactobacillus: Anti-inflammatory (Beneficial effects were shown in female)	↓IL-6, IgG2a ↑IL-10
Tzang et al.,[34] Taiwan	6-week-old NZB/W F1 mice, female	4 group ($n = 8$) Ctrl, GMNL-32, GMNL-89, GMNL-263	*L. paracasei* GMNL-32 (GMNL-32), *L. reuteri GMNL-89* (GMNL-89) *L. reuteri* GMNL-263 (GMNL-263)	10^9 CFU/mL daily, 12 weeks, oral gavage	In all three groups of probiotics: Antioxidant activity Anti-inflammation	↓IL-6, TNF-α, MyD88 and TLR ↑Treg
Khorasani et al.,[30] Iran	3 to 5-week-old BALB/c mice, female	10 group ($n = 6$) Prophylactic effect (*L. delbrueckii*, *L. rhamnosus*, *or L. delbrueckii* + *L. rhamnosus*, Prednisolone) Therapeutic effect, SLE-induced (*L. delbrueckii*, *L. rhamnosus*, or L. delbrueckii + L. rhamnosus, Prednisolone) SLE-induced control group, Negative control group	*L. delbrueckii*, *L. rhamnosus*,	10^8 CFU/mL, prednisolone (5 mg/kg), 2 months, intraperitoneal injection	*L. delbrueckii* and *L. rhamnosus*: ↑Tregs ↓Inflammatory cytokines and disease severity	↓lipogranuloma, anti-dsDNA, and ANA ↑Expression level of Foxp3 ↓IL-6
Manirarora et al.,[25] USA	4-week-old (NZBxNZW) F1 (BWF1) and BALB/cxNZW (BaWF1) mice, female	4 group ($n = 5–10$) *L. casei*, *L. reuteri*, *L. plantarum*, PBS	*L. casei* B255, *L. reuteri* DSM *17509* *L. plantarum* LP299v	10^9 CFU/mL twice a week, 10 months, gavaging needle	*L. casei* or *L. reuteri*: increased survival and delayed lupus onset. *L. plantarum*: had a small impact	↑percentages of Tregs (upregulation B7-1 and B7-2) ↑IL-10

(Continues)

TABLE 2 (Continued)

Author, country	Animal model	Group	Probiotic strain(s)	Dose, duration	Result	Mechanisms
Kim et al.,[27] South Korea	8-week-old MRL/lpr mice	3 group ($n = 5$) Vehicle, LA, Tac + LA	*L. acidophilus* (LA) Tacrolimus (Tac)	50 mg/kg of LA, 5 mg/kg of Tac, 8 weeks, daily, orally	LA + Tac: ↓Double negative T cells in the spleens and peripheral blood Renal pathology scores	↓Immunoglobulin G2a and anti-dsDNA ↓Th17 ↑Treg
Yeh et al.,[35] Taiwan	12-week-old NZB/W F1 mice, female	2 group ($n = 5$) Ctrl, *L. reuteri*	*L. reuteri GMNL-263*	10^8 cell/mL daily, 16 weeks, oral gavage	↓Abnormal myocardial structures and enlarged interstitial spaces in the hearts	↓Mitochondrial- and fas-dependent apoptotic signaling
Mu et al.,[28] USA	11 weeks old MRL/MpJFaslpr/J mice, female	2 group ($n = 6$–12) Postpartum (PP; pregnancy and lactation), Ctrl (naïve; without pregnancy or lactation)	*L. animalis* (35046), Vancomycin (2 g/L)	Once a week, 9 weeks of age until 15 weeks, oral gavage	Administration of *L. animalis* along with vancomycin causes exacerbation of lupus in PP versus control group.	*L. animalis* inhibits indoleamine 2,3-Dioxygenase.
Toral et al.,[23] Spain	18-week-old NZBWF1 [systemic lupus erythematosus (SLE)] and NZW/LacJ (control) mice, female	4 groups ($n = 4$–8) Ctrl, Ctrl-treated (Ctrl + LC40), SLE, SLE-treated (SLE + LC40)	*L. fermentumCE*CT5716(LC40)	5×10^8 CFU daily, 15 weeks, oral gavage	LC40 treatment in SLE mice: ↓Blood pressure, lupus disease activity, splenomegaly, renal and cardiac hypertrophy vascular disorders ↑Bifidobacterium count in gut microbiota	↓Proinflammatory cytokines ↓Oxidative stress (NADPH, Enos) ↓B, T, regulatory T cells, and T helper-1 cells in mesenteric lymph nodes
Mardani et al.,[29] Iran	4–6-week-old BALB/c mice, female	8 groups ($n = 8$) Pretreatment groups*: (Injection of pristane + oral administration of *L. delbrueckii*, Injection of pristane + oral administration of *L. rhamnosus*, Injection of pristane + oral administration of prednisolone). Treatment groups*: (Injection of pristane + oral administration of *L. delbrueckii*, Injection of	*L. rhamnosus* *L. delbrueckii*	10^8 CFU daily, 4 weeks, Oral administration	Prednisolone and probiotics could delay SLE in treatment and pretreatment mice groups in comparison with the positive control	↓Anti-RNP, anti-dsDNA, ANA, and mass of lipogranuloma ↓Th1–Th17 cells ↓IFN-γ, IL-17

TABLE 2 (Continued)

Author, country	Animal model	Group	Probiotic strain(s)	Dose, duration	Result	Mechanisms
		pristane + oral administration of *L. rhamnosus*, Injection of pristane + oral administration of prednisolone). SLE-induced (positive) group. Negative control group.				
Li et al.,[36] China	C57BL/6 J control mice (8-week-old), B6. MRL-Faslpr/J lupus-prone mice (8-week-old)	4 group Control (PBS, *Bacteroides fragilis*), SLE (PBS, *Bacteroides fragilis*)	*Bacteroides fragilis*	200 μL PBS, 5×10^8 CFU/mouse, every other day for 1-month, oral gavage.	↓Levels of autoantibodies and symptoms of lupus nephritis.	↑CD1d expression in B cells via Est-1 pathway CD86 expression by SHP-2 signaling pathway to restore the immune response of B cells Th17/Treg balance

Abbreviations: ANA, antinuclear antibody; BFM, Bifidobacterium breve; BUN, blood urea nitrogen; Ctrl, control; Cu/Zn-SOD, copper/zinc superoxide dismutase; dsDNA, double-stranded deoxyribonucleic acid; Enos, Endothelial nitric oxide synthase; IFN-γ, interferon γ; IL-6, interleukin-6; IMQ, TLR7agonist; imiquimod; IκB-α, inhibitor of NF-Kb; L, Lactobacillus; LC40, Lactobacillus fermentum; MMP-9, matrix metalloproteinase-9; Mn-SOD, manganese superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-Kb, nuclear factor kappa-B; PBS, phosphate buffered saline; pretreatment, pristane intraperitoneal injection and simultaneous reception of probiotics or prednisolone from day 0 and daily; RNP, ribonucleoprotein; SLE, Systemic lupus erythematosus; TC, total cholesterol; TG, triglyceride; TGF, transforming growth factor; TLR, toll like receptors; TNF-α, tumor necrosis factor alpha; TP, total protein; Treatment: received prednisolone or probiotics 2 months after pristane injection; Treg, T regulatory; USA, United States; VEGF, vascular endothelial growth factor.

TABLE 3 Effect of probiotics in human studies.

Author, country	Study design	Population		Sex		Probiotics strain	Dose, duration	Result
		Case	Control	Case	Control			
Lu et al.,[38] Taiwan	Cross-sectional study	56	-	F	-	-	-	Photosensitivity (OR: 0.49; $p = 0.019$), Renal involvement (OR: 2.43; $p = 0.026$)
Widhani et al.,[37] Indonesia	RCT	23	23 (placebo)	F	F	*Lactobacillus helveticus, Bifidobacterium infantis, Bifidobacterium bifidum*, and 80 mg fructo-oligosaccharides	3×10^9 CFU, Daily, 60 Days	Synbiotic group: ↓IL-6 ($p = 0.02$) change in IL-17 and hs-CRP level (no sig) ↑Firmicutes:Bacteroidetes ratio ($p = 0.48$) and butyrate metabolism ($p = 0.037$) ↓Amino sugar and nucleotide sugar metabolism ($p = 0.040$).

Abbreviations: CFU, colony forming units; CRP, C-reactive protein; F, female; OR, odds ratio; RCT, randomized clinical trial; sig, significant; SLEDAI-2K, SLE disease activity index 2 K.

TABLE 4 The risk of bias assessment in vivo studies using the SYRCLE risk of bias tool.

SYRCLE risk of bias tool	1	2	3	4	5	6	7	8	9	10	Total score
Cabana-Puig et al.[19]	?	+	+	_	+	?	-	?	+	+	5
Cheng et al.[24]	+	+	?	+	-	+	-	-	+	+	6
De La Visitación et al.[21]	+	+	?	+	-	+	-	-	+	+	6
De La Visitación et al.[22]	+	+	+	+	+	+	-	+	+	+	9
Mike et al.[26]	?	+	?	-	-	?	-	?	+	+	3
Hsu et al.[32]	+	+	?	+	-	+	-	+	+	+	7
Hu et al.[33]	+	+	?	+	-	+	-	+	+	+	7
Mu et al.[20]	?	+	?	-	+	?	+	?	+	+	5
Tzang et al.[34]	+	+	?	+	-	+	-	+	+	+	7
Khorasani et al.[30]	+	+	?	+	-	+	-	+	+	+	7
Manirarora et al.[25]	?	+	?	-	-	?	-	?	+	+	3
Kim et al.[27]	?	-	?	-	-	?	-	+	+	+	3
Yeh et al.[35]	+	+	?	+	-	+	-	+	+	+	7
Mu et al.[28]	?	+	?	-	+	?	+	?	+	+	5
Toral et al.[23]	+	+	?	+	-	+	-	?	+	+	6
Mardani et al.[29]	?	+	?	-	-	?	-	+	+	+	4
Li et al.[36]	+	+	?	+	+	+	-	?	+	+	7

Manirarora et al. indicated that mice fed *L. casei* or *L. reuteri* before disease onset exhibited a delayed onset of lupus and increased survival, whereas *L. plantarum* feeding had little effect. In vitro, treatment of BWF1 dendritic cells with *lactobacilli* strains (*L. casei*, *L. reuteri*, and *L. plantarum*) upregulated IL-10 production to varying degrees, with *L. casei* being the most effective.[25]

Visitación et al. presented novel findings demonstrating that the long-term administration of *L. fermentum* or *B. breve* effectively decreased hypertension and preserved endothelial function in a mouse model of lupus induced by TLR-7 activation. Furthermore, the researchers observed that *L. fermentum* and *B. breve* treatments induced the activation of TLR9, resulting in a substantial reduction in T cell activation and the polarization of Th17 cells in the mesenteric lymph nodes.[21]

Hsu et al. provided evidence that the oral administration of *L. paracasei (GMNL-32)*, *L. reuteri (GMNL-89)*, or *L. reuteri (GMNL-263)* effectively alleviated hepatic apoptosis and various inflammatory indicators in mice prone to lupus, including matrix metalloproteinase-9 (MMP)-9 activity, C-reactive protein (CRP) expression, and inducible nitric oxide synthase (iNOS) expression. Additionally, the administration of NZB/W F1 with GMNL-32, GMNL-89, or GMNL-263 in mice regulated MAPK/NF-B inflammatory pathway and as a result, reduced the

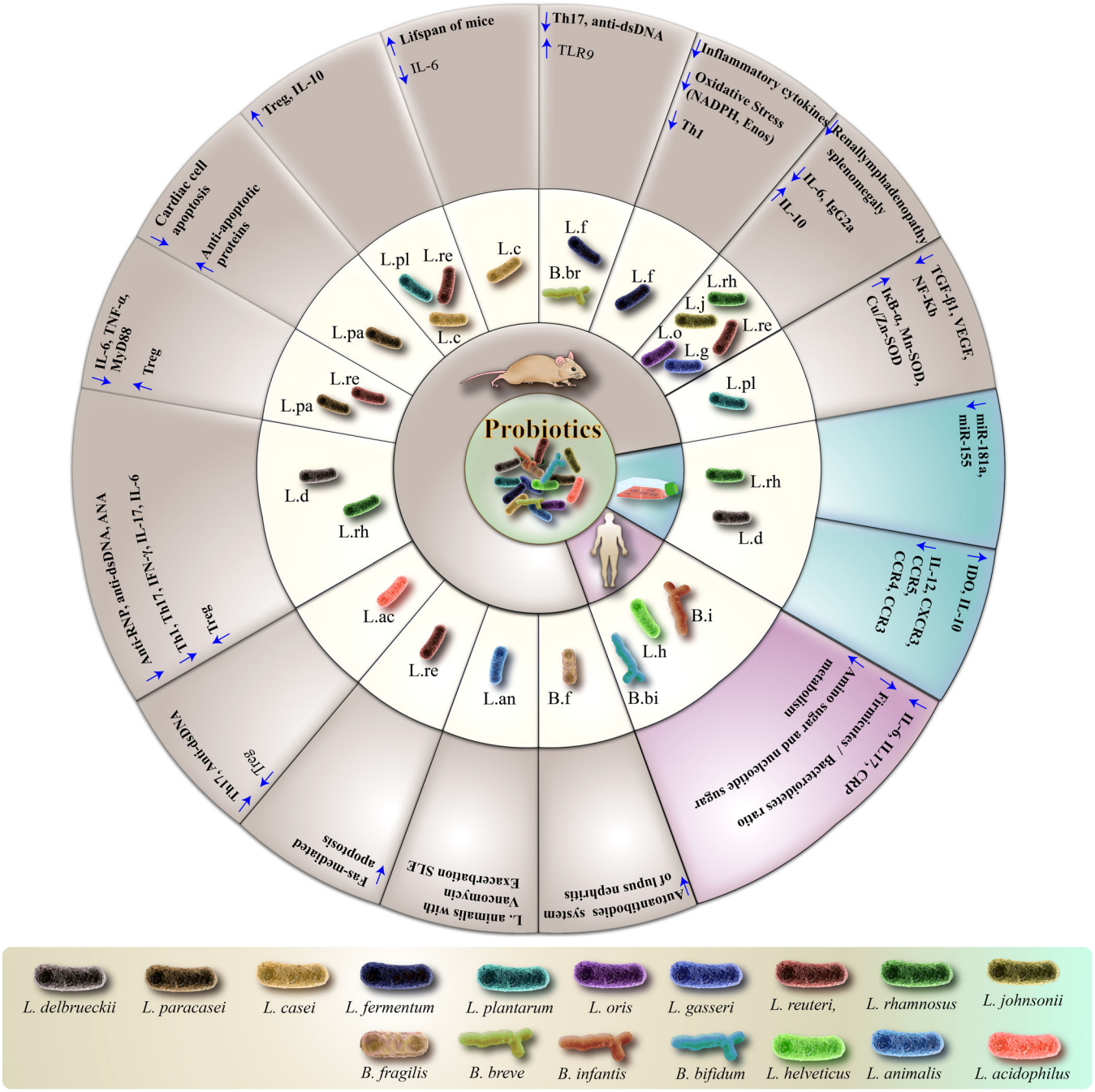

FIGURE 2 Overview of the effects of probiotics in various studies of SLE disease. ANA, antinuclear antibody; B.bi, *Bifidobacterium bifidum*; B.br, *Bifidobacterium breve*; B.f, *Bacteroides fragilis*; B.i, *Bifidobacterium infantis*; CCR, C chemokine receptor; Cu/Zn-SOD, copper/zinc superoxide dismutase; CXCR, C-X-C chemokine receptor; dsDNA, double-stranded deoxyribonucleic acid; Enos, Endothelial nitric oxide synthase; IDO, Indoleamine 2,3-dioxygenase; IFN-γ, interferon γ; IL, interleukin; IκB-α, inhibitor of NF-Kb; L.ac, *Lactobacillus acidophilus*; L.an, *Lactobacillus animalis*; L.c, *Lactobacillus casei*; L.d, *Lactobacillus delbrueckii*; L.d, *Lactobacillus delbrueickii*; L.g, *Lactobacillus gasseri*; L.h, *Lactobacillus helveticus*; L.j, *Lactobacillus johnsonii*; L.o, *Lactobacillus oris*; L.pa, *Lactobacillus paracasei*; L.pl, *Lactobacillus plantarum*; L.re, *Lactobacillus reuteri*; L.rh, *Lactobacillus rhamnosus*; miR, microRNA; Mn-SOD, manganese superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-Kb, nuclear factor kappa-B; RNP, ribonucleoprotein; SLE, Systemic lupus erythematosus; TGF, Transforming growth factor; Th, T helper cell; TLR, toll like receptors; TNF-α, tumor necrosis factor alpha; Treg, T regulatory; VEGF, vascular endothelial growth factor.

production of hepatic IL-1, IL-6, and tumor necrosis factor (TNF)-proteins.[32] In this regard, Tzang et al. demonstrated that each of the three aforementioned probiotics possesses anti-inflammatory, antioxidant, and modulatory properties.[34]

On the other hand, certain bacterial strains, such as *L. animalis*, indirectly decrease the abundance of Treg cells while promoting inflammation.[55] In this regard, Mu et al. showed that the administration of *L. animalis*, along with vancomycin, exacerbated lupus in

pregnant and lactating mice compared to the control group. This exacerbation was associated with the inhibition of 2,3-indoleamine dioxygenase by *L. animalis*.[28]

Khorasani et al. and Mardani et al. demonstrated the effectiveness of *L. rhamnosus* and *L. delbrueckii in* increasing Tregs, reducing inflammatory cytokines, and decreasing disease severity in SLE-induced mice.[29,30]

Other studies conducted on various types of bacteria, such as *Bacteroides fragilis*,[36] *L. fermentum*,[22,23] *L. reuteri*,[35]*L. acidophilus*,[27] *L. paracasei*,[33] *L. plantarum*,[24] or *L. casei*,[26] as a tolerogenic probiotic, have individually demonstrated anti-inflammatory, antioxidant, or antiapoptotic effects in mice with SLE.

In general, in animal studies, strains of *L. fermentum*, *L. casei*, *L. plantarum*, *L. paracasei*, and *L. reuteri*, whether administered alone or in combination with other strains, demonstrate anti-inflammatory properties. Conversely, *L. animalis*, whether used alone or in conjunction with vancomycin, exacerbates lupus by inhibiting 2,3-indoleamine dioxygenase.[28] Therefore, further research is warranted to assess the effects of *L. animalis* and caution should be exercised regarding its use.

In research focused on studying lupus in mice, several methods are employed to induce lupus-like conditions. These approaches encompass genetic manipulation, chemical induction, hybrid strains, spontaneous models, immunization, hormonal manipulation, and viral infections. The selection of a particular method depends on the research goals and the desired characteristics of the lupus model under investigation. Genetic manipulation involves modifying mouse genes to express lupus-associated factors, while chemical induction employs certain substances (such as pristane and mercury compounds) to trigger lupus-like symptoms. Hybrid strains result from crossbreeding lupus-prone mice with other strains (e.g., NZB/W F1 hybrid), and spontaneous models involve mice that naturally develop lupus-like symptoms (e.g., MRL/lpr and NZB/W F1 mice). Immunization exposes mice to self-antigens, such as DNA or histones, hormonal manipulation alters hormone levels (particularly estrogen), and viral infections induce lupus-like autoimmune responses. Each method offers distinct advantages and limitations, allowing researchers to tailor their approach to the specific objectives of their study, which can range from elucidating disease mechanisms to evaluating potential treatments and understanding disease progression.

4.4 | Effects of probiotics on human studies

Currently, there is limited research on the use of probiotics as complementary treatments for SLE patients with clinical and laboratory manifestations. However, a cross-sectional study carried out by Lu et al. in Taiwan linked the use of probiotics with reduced photosensitivity (OR: 0.49; $p = 0.019$) and renal involvement (OR: 2.43; $p = 0.026$).[38]

Additionally, Widhani et al. conducted a double-blind randomized clinical trial in Indonesian adult SLE patients to investigate the effects of a symbiotic supplement containing *L. helveticus*, *B. infantis*, *B. bifidum*, and fructo oligosaccharides for 2 months. Their findings indicated that the administration of synbiotic supplementation had the potential to decrease systemic inflammation, mitigate SLE disease activity, and induce changes in both the composition and functions of the gut microbiota.[37] According to previous studies, SLE patients have lower Firmicutes to Bacteroidetes ratios than healthy individuals.[48] This suggests that increasing this ratio could potentially help restore balance to the gut microbiota. The study mentioned earlier found that taking synbiotics resulted in an increase in the Firmicutes to Bacteroidetes ratio and improved butyrate metabolism.[37] Butyrate has anti-inflammatory properties and works by inhibiting the translocation of nuclear factor kappa-B to the nucleus. This leads to a reduction in the transcription of genes responsible for producing proinflammatory molecules, such as IL-6.[56] Figure 2 summarizes the positive findings of the studies.

This systematic review was conducted to evaluate the effect of probiotic supplements on SLE, using three in vitro studies, 17 in vivo studies, and two clinical trials. However, due to significant differences in methodology and outcome measures in the included articles, a quantitative synthesis of the findings could not be performed. Therefore, only qualitative descriptive methods were used to generate the data for this research. Figure 2 shows an overview of the effects of probiotics in various studies of SLE disease.

5 | CONCLUSION

In conclusion, the results of the present systematic review highlight significant advantages associated with the use of probiotics, either in isolation or in combination, for the treatment of SLE. Probiotic administration has demonstrated noteworthy anti-inflammatory, regulatory, and antiapoptotic effects, along with improvements in clinical symptoms, both in SLE mouse models and SLE patients. These findings underscore the potential of probiotic interventions as a promising complementary approach for managing SLE and enhancing patient outcomes. Nonetheless, it is important to exercise caution in the application of the *L. animalis* strain due to its adverse results in the animal lupus model. To establish the most effective probiotic regimens for SLE therapy, further research and clinical studies are imperative to gain a deeper understanding of the underlying mechanisms responsible for these effects.

AUTHOR CONTRIBUTIONS

Zahra Mirfeizi: Conceptualization; methodology; project administration; validation; writing—original draft. **Mahmoud Mahmoudi**: Conceptualization; investigation; validation; writing—review and editing. **Arezoo Faridzadeh**: Data curation; investigation; methodology; software; supervision; visualization; writing—original draft; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

As this study is a systematic review, no original data are available and all extracted data are available in the original and supplementary data.

ETHICS STATEMENT

All authors have read and approved the final version of the manuscript. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. This systematic review was registered in the PROSPERO by a unique identification number of CRD42023398876.

TRANSPARENCY STATEMENT

The lead author Arezoo Faridzadeh affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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