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Probiotic Interventions in Systemic Sclerosis Patients: A Systematic Review and Future Prospects

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ABSTRACT

Background and Aims: Systemic sclerosis (SSc) is an uncommon autoimmune connective tissue disease distinguished by fibrosis and vascular abnormalities, often leading to gastrointestinal problems. This review explores the potential of probiotics in managing SSc-related gastrointestinal issues and modulating immune responses, highlighting the need for innovative treatments to improve patient well-being.

Methods: We performed an extensive literature search up to October 2023 in databases, including Web of Science, PubMed/MEDLINE, and Scopus.

Result: This review detected four articles that investigated the impact of probiotics on SSc. These studies, comprising non-randomized observational studies and randomized clinical trials, provide preliminary insights suggesting that probiotics may be efficacious in modulating the immune response and, consequently, in improving gastrointestinal symptoms in SSc patients.

Conclusion: The comprehensive review suggests that probiotics may aid in managing gastrointestinal symptoms and modulating immune responses in SSc. However, it is essential to acknowledge the limited existing evidence, underscoring the need for more rigorous randomized controlled trials to thoroughly assess their effectiveness.

1 | Introduction

Systemic sclerosis (SSc) is an infrequent autoimmune connective tissue disorder characterized by extensive fibrosis and vascular abnormalities. The annual incidence of SSc is 19.3 cases per million adult individuals in the United States, primarily affecting individuals aged 44–55, with a notably higher incidence in women [1, 2].

While the skin is often the most visibly and frequently affected organ, SSc commonly involves multiple internal organs, including the gastrointestinal tract, vasculature, and cardiopulmonary systems, leading to a wide range of clinical manifestations [3–5]. The combination of fibrosis, vascular dysfunction, autoimmune inflammation, and autonomic nervous system involvement in SSc can contribute to a range of gastrointestinal (GI) problems [2], such as meteorism

Abbreviations: B, *Bifidobacterum*; FMT, Fecal microbiota transplantation; GI, gastrointestinal; IL, interleukin; L, *Lactobacillus*; PICO, population, intervention, comparison, and outcomes; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RA, rheumatoid arthritis; RCT, randomized controlled trial; SIBO, small intestinal bacterial overgrowth; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; Th, T helper; UCLA GIT, University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument.

(bloating), esophageal dysmotility, dysphagia, heartburn, nausea, diarrhea, vomiting, and constipation [6–8]. These complications may lead to GI bleeding and malnutrition, with severe cases even resulting in fatal outcomes such as intestinal pseudo-obstruction [9]. These complications significantly impact patients' overall quality of life and contribute to considerable morbidity and mortality [1].

In recent years, significant progress has been made in understanding distinct subgroups of SSc patients with GI involvement and uncovering the underlying pathogenic mechanisms, often related to factors such as microbiota dysbiosis and GI dysmotility [10, 11].

The microbiome has been associated with the onset of autoimmune conditions; multiple studies have demonstrated changes in the composition of gut microbiota in conditions such as anti-phospholipid syndrome, Sjögren's syndrome, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and SSc [10, 12, 13]. Therefore, research suggests that the intestinal microbiome may play a role in regulating the immune system and the development of autoimmune disorders and allergic diseases [14–16].

Despite this, the use of probiotics in SSc patients remains an area of uncertainty, as the available evidence on their efficacy, particularly for GI complications in SSc, is limited [17].

However, a growing body of research suggests that probiotics may help mitigate GI symptoms associated with SSc, such as bloating, diarrhea, and malnutrition. Recent studies have examined the impact of probiotics on both the immune system and GI symptoms in SSc patients, particularly those with moderate to severe scores on the UCLA GIT 2.0 (University of California, Los Angeles Scleroderma Clinical Trial Consortium GI Tract) assessment [18].

Significant gaps in the data remain, particularly in randomized controlled trials examining the effects of probiotics in SSc populations. While studies on the general population have indicated potential benefits, whether these findings are applicable requires further investigation.

This systematic review aims to address this gap by providing a comprehensive analysis of the current evidence on the use of probiotics in SSc patients. Although prior research has largely focused on antibiotics and other therapies, this review centers on probiotics as a potential treatment option for managing GI symptoms in SSc. Given the significant impact of GI involvement on patients' quality of life, exploring all available therapeutic options is essential. The objective of this review is to evaluate the existing data and identify areas for future research, with the ultimate goal of improving the management of SSc-related GI complications and immune modulation.

2 | Materials and Methods

This systematic review adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was duly registered in PROSPERO, a worldwide prospective registry designed for systematic reviews. The review has been assigned a distinctive identification number, CRD42023398951.

2.1 | Eligibility Criteria

We used the PICO (Population, Intervention, Comparison, and Outcomes) framework to examine the effects of probiotics on GI symptoms and the immune system of SSc patients. Our study population consisted of SSc patients with GI involvement. The intervention consisted of administering probiotics; we assessed various factors, such as gender, disease status, probiotic strain(s), duration, and dose of treatment. To report the outcomes, we evaluated changes in GI symptoms using UCLA SCTC GIT 2.0 total score and changes in inflammatory markers observed from the baseline to the endpoint of the follow-up period. Search Strategy

The researchers conducted a comprehensive database search, encompassing Web of Science, PubMed/MEDLINE, and Scopus, from June 24, 2023, until the article submission date, without language restrictions. The keywords employed were "probiotic," "prebiotic," "synbiotic," "*Lactobacillus,*" "*Streptococcus thermophilus,*" and "*Bifidobacterium*" combined with the keywords "systemic sclerosis," "Scleroderma, Systemic," or "Sclerosis, Systemic" or "Systemic Scleroderma." This review included the last published article found during the manual search and the last search at the time of submission.

2.2 | Study Selection

Two reviewers independently screened articles by assessing their titles and abstracts. Following the removal of duplicates, any studies considered irrelevant based on their title or abstract were excluded from further evaluation. The studies that were excluded from further evaluation can be categorized into two groups: (1) articles with irrelevant formats, such as books, letters to editors, review articles, or surveys and case reports; and (2) studies with content unrelated, such as those related to the microbiome of SSc patients or animal studies, studies on other diseases, and those not relevant to probiotics.

We thoroughly reviewed the full texts of the remaining studies to determine their final eligibility. These studies contained clinical research focused on investigating the impact of probiotics on the prognosis of SSc. In addition, we have included a flowchart to provide a comprehensive overview of our study selection process.

2.3 | Methodological Quality Assessment

We used various assessment tools to appraise the risk of bias in the non-randomized observational studies and randomized clinical trials that were included in our study. Specifically, we applied ROBINS-I to evaluate non-randomized observational studies, and the Cochrane to assess randomized clinical trials.

Two reviewers (A.F. and Z.M.) individually assessed the potential for bias in every article included in the study. The

Cochrane tool comprises seven domains for assessing the risk of bias: allocation concealment, random sequence generation, selection reporting, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, and other potential sources of bias. Each domain is rated as "high risk," "low risk," or "unclear" for the article in question. Using this tool, an article is classified as "good quality" if it receives a "low risk" rating across all domains. An article assessed as "high risk" in a single domain or as "unclear" in two domains falls under the category of "fair quality." Lastly, an article that receives "unclear" or "high risk" assessments in two or more domains is deemed to have "poor quality".

In the assessment of the Risk of Bias (RoB) for non-randomized observational studies included in the research, the ROBINS-I tool was employed. This tool examines seven distinct domains for RoB, encompassing two domains associated with the pre-intervention phase, one domain related to intervention delivery, and four domains linked to the post-intervention phase. An RoB assessment was conducted for each of these domains, offering options such as low, moderate, serious, critical, or no information. Subsequently, a final RoB judgment for the entire study was determined by applying the same set of options, based on the cumulative findings from each domain.

The comprehensive information regarding the quality assessment of non-randomized observational studies and randomized clinical trials can be found in the Figure 1.

2.4 | Data Extraction

Important information, such as the country, author's name, date of publication, population, gender, criteria of inclusion and exclusion, disease status, probiotics dosage and duration, probiotic strains, and outcomes, was collected and entered into a predefined Excel spreadsheet. Data screening was conducted by two independent reviewers, and any discrepancies between them were resolved through consensus. The criteria for the inclusion of our study were restricted to clinical studies that specifically examined the effect of probiotics on the prognosis of SSc.

3 | Result

3.1 | Study Selection

We conducted an exhaustive search across three databases: Scopus, Medline/PubMed, and Web of Science, which resulted in the identification of 298 articles. After removing duplicate records, we were left with 222 distinct articles. Among these initial articles, 156 were excluded based on the inclusion criteria detailed in Figure 2, leaving 22 articles for full-text screening. Following a meticulous evaluation of these articles, we excluded an additional 67 based on the criteria outlined in Figure 2. Finally, we included four articles in our study because they fully met all the inclusion criteria.

3.2 | Study Characteristics

We categorized the four articles that were included into three randomized clinical trials and one non-randomized observational study. Table 1 presents the extracted data from these trials, including information such as the country of origin, study design, population details (in case and control groups, if applicable), sex distribution (number of females and males in each group), eligibility and exclusion criteria, disease status, probiotic strain, duration, dosage, and outcomes.

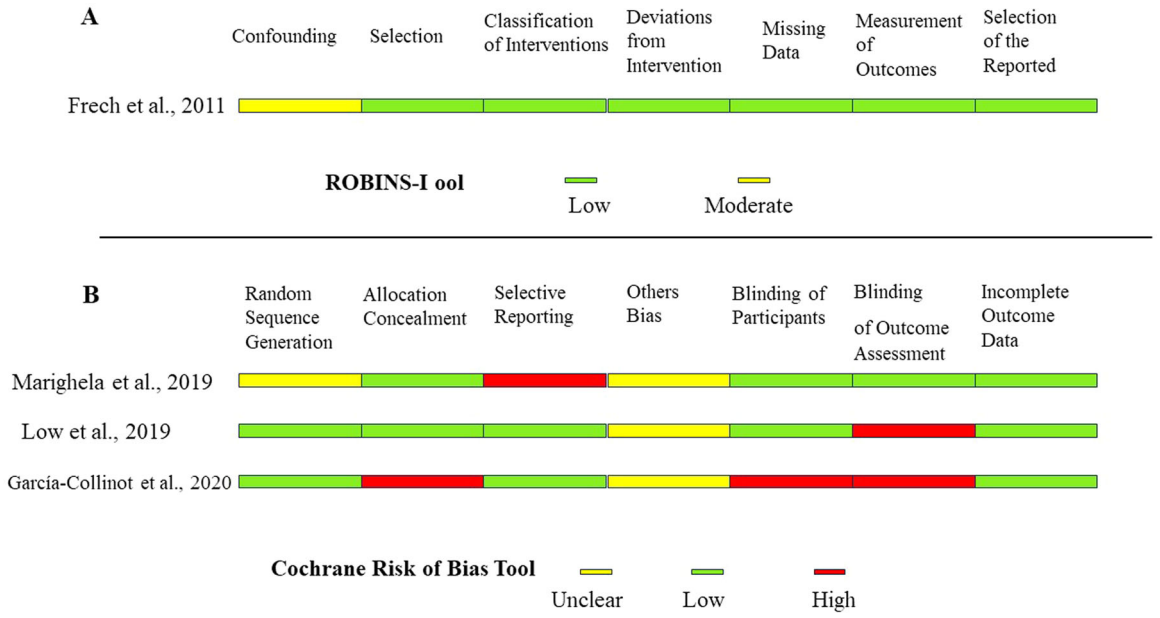

FIGURE 1 | Risk assessment scale of studies. (A) ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions): to assess non-randomized studies of interventions; (B) Cochrane Risk of Bias Tool: to assess randomized controlled trials (RCTs).

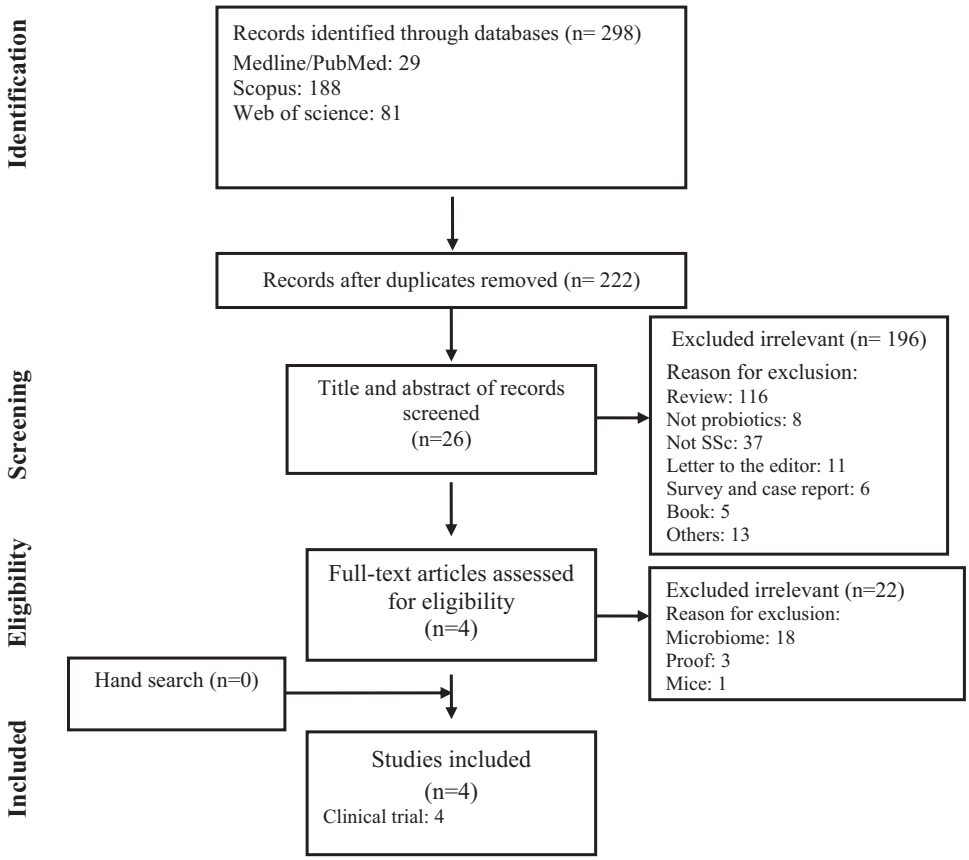

FIGURE 2 | Flow chart of study selection for inclusion in the systematic review and meta-analysis.

Due to significant methodological differences, variations in outcome measurement in the included articles, and the limited number of clinical trial articles, it was deemed impractical to perform a quantitative combination of studies. As a result, this document offers solely a descriptive qualitative analysis of the data.

The four included articles were conducted in Mexico, Singapore, Brazil, and the United States. The total number of patients involved was 163. Patients received their diagnoses from medical professionals, and these diagnoses were validated using the ACR-EULAR 2013 classification criteria.

3.3 | Risk of Bias Assessment

The evaluation of bias risk was carried out for the available non-randomized observational study using the ROBINS-I risk of bias tool [23]. Frech et al. study was determined to be of high quality.

The randomized controlled trial (RCT) conducted by Marighela et al., García-Collinot et al., and Low et al., assessed using the Cochrane risk of bias tool, were found to be of poor quality, with the exception of Low's study, which was rated as fair quality [24].

3.4 | Results of the Non-Randomized Observational Study

A study conducted by Frech et al. involved 10 SSc patients experiencing moderate to severe bloating. The researchers assessed the patients' GI symptoms before and after 2 months of daily probiotic use. The results revealed a considerable improvement in GIT 2.0 total scores, reflux, flatulence/distension, and affective scales, with the most substantial improvement observed in the bloating/dilation scale, showing an effect size of 1.76 [19].

3.5 | Results of the Randomized Clinical Trial

In a randomized clinical trial by Marighela et al., 73 patients with SSc were assigned to receive either a probiotic regimen (*Lactobacillus paracasei*, *L. acidophilus*, *L. rhamnosus*, and *Bifidobacterium lactis*) or a placebo for 8 weeks. Both groups exhibited significant improvements in the UCLA GIT 2.0 total score after 8 weeks, with no statistically significant differences between them. Symptoms such as abdominal distension, bloating, and reflux also improved in both groups. However, only the probiotic group demonstrated a significant reduction in T helper (Th)17 cells, suggesting an immunoregulatory effect not observed in the placebo group. There were no changes in Th1, Th2, or regulatory T cells, and no severe adverse events were reported [20].

In another randomized, placebo-controlled trial by Low et al., 40 SSc patients were divided into two groups: one received probiotics for 120 days, while the other received a placebo for the first 60 days, followed by probiotics for the remaining 60 days. After 60 days, no significant differences were observed in GI symptoms between the two groups. However, after

TABLE 1 | Characteristics of the included studies.

Author, Country	Study design	Population		Sex		Criteria		Probiotics strain	Disease status	Dose, Duration	Outcome
		Case	Control	Case	Control	Eligibility	Exclusion				
Frech et al. [19]; United States	CT	10	—	F/M (9/1)	—	≥ 18 years with a diagnosis of SSc.	Any change in clinical interventions (dose of calcium channel blocker, immunosuppression, initiation of prokinetic or antibiotic).	*B. infantis* or *Lactobacillus GG*	Moderate-to-severe distention/bloating score	10^9 CFU, Daily, 8 weeks	Improvement in total GIT 2.0 score (ES = 0.82), reflux (ES = 0.33), bloating/distention (ES = 1.76), and emotional scales (ES = 0.18).
Marighela et al. [20]; Brazil	RCT	37	36 (placebo)	F/M (34/3)	F/M (34/2)	≥ 18 years, SSc diagnosis according to the classification criteria ACR-EULAR 2013, UCLA GIT 2.0 total score > 0.50, stable use of medication to treat SSc or GI symptoms for at least 8 weeks before entry.	Lactating or pregnant, active infections, malignancies, a diagnosis of IBD, overlapping syndromes with rheumatic diseases, active smoking, and using probiotics, cyclophosphamide, or antibiotics in the last 4 weeks.	*L. paracasei, L. rhamnosus, L. acidophilus,* and *B. lactis*	Moderate to severe	10^9 CFU, Daily, 8 weeks	No difference in UCLA GIT 2.0 score between the two groups, ↓ Th17 cells in the probiotic compared with the placebo group ($p = 0.003$).
Low et al. [21]; Singapore	RCT, computer-generated randomization	21 (2 Phase: probiotics and probiotics)	19 (2 Phase: placebo and probiotics)	F/M (16/5)	F (19)	≥ 18 years, SSc diagnosis according to the classification criteria ACR-EULAR 2013, UCLA GIT 2.0 total score > 0.10, GI medications, immunosuppressive or corticosteroid treatment, patients had to be on stable doses for 30 days before enrollment.	probiotics or antibiotics 30 days prior, infections requiring hospitalization, lactating or pregnant, a long-term indwelling vascular catheter, malignancy, or inflammatory bowel disease.	*L. paracasei, L. plantarum, L. acidophilus, L. delbrueckii, L. bulgaricus, B. longum, B. breve, B. infantis, and Streptococcus thermophilus*.	—	18×10^{11} CFU, Daily, 16 weeks (each phase 8 weeks)	Significant improvement of GIT-reflux in the probiotic group (0.22 vs. 0.05 vs. placebo-probiotics 0.05 vs. 0.07; $p = 0.004$), probiotics exhibited increasing stool microbiota diversity compared to the placebo-probiotics group.
García-Collinot et al. [22]; Mexico	RCT, computerized random numbers	SB, *n = 14* SB and M, *n* = 13	M, *n* = 13	—	—	≥ 18 years, SSc diagnosis according to the classification criteria ACR-EULAR	Any other chronic disease.	*Saccharomyces boulardii*	—	*SB*: 200 mg twice orally for 2 months,	The SB and M + SB groups had decreased abdominal

(Continues)

TABLE 1 | (Continued)

Author, Country	Study design	Population		Sex		Criteria		Probiotics strain	Disease status	Dose, Duration	Outcome
		Case	Control	Case	Control	Eligibility	Exclusion				
						2013, determine SIBO by the hydrogen breath test (HBT).				M: 500 mg daily	pain, diarrhea, and gas/ flatulence/ bloating, but M remained unchanged. ↓ Expired hydrogen at 45–60 min: M + SB 48% and 44%, M 18% and 20%, and SB 53% and 60%.

Abbreviations: B, *Bifidobacteria*; L, *Lactobacillus*; M, Metronidazole; RCT, randomized clinical trial; SB, *Saccharomyces boulardii*.

120 days of probiotic treatment, the probiotics group showed a notable improvement in GI reflux symptoms. Additionally, stool sample analysis revealed increased alpha diversity in the microbiota of the probiotic group compared to the placebo group, supporting both the safety and potential gut microbiota benefits of multi-strain probiotics in SSc patients [21].

A third study by García-Collinot et al. evaluated the effectiveness of combining *Saccharomyces boulardii* with metronidazole compared to monotherapy in SSc patients with small intestinal bacterial overgrowth (SIBO). The combination therapy was more effective in eliminating SIBO and improving GI symptoms, including reduction in gas, bloating, abdominal pain, and diarrhea, compared to either treatment alone. It also led to a greater reduction in expired hydrogen levels, a marker for SIBO. Adverse events were mild and occurred across all groups, suggesting the combination treatment is both effective and relatively safe for SSc patients with SIBO [22].

4 | Discussion

This systematic review focused on evaluating the effects of probiotics in SSc patients by analyzing four studies—three randomized clinical trials and one non-randomized observational study—conducted in diverse geographic locations, including Mexico, Singapore, Brazil, and the United States, with a total of 163 patients. The studies examined different probiotic regimens and their impact on GI symptoms, microbiota composition, and immune modulation in SSc patients.

Microbiota-based therapeutics targeting the GI microbiome show promise for managing SSc symptoms and potentially modifying the disease course. Although antibiotics are frequently used to manage GIT symptoms in SSc, their long-term use may lead to dysbiosis and increased risk of infections [25].

Fecal microbiota transplantation (FMT) has shown promise in a small pilot study but requires further investigation to confirm its safety and efficacy [26]. Hoffman-Vold and Volkmann highlighted improved gut microbiota diversity and potential clinical benefits in SSc patients following FMT [27]. Dietary modifications present a lower-risk approach to addressing dysbiosis, with plant-based diets showing potential benefits [28]. Probiotics, primarily containing *Bifidobacterium* and *Lactobacillus* strains, have yielded mixed results in SSc studies, and prebiotics, such as inulin, also warrant further exploration. Overall, advancing our understanding GIT microbiota in SSc may help identify therapeutic targets and biomarkers, potentially improving patient outcomes [17, 27].

This study investigated the efficacy of probiotic treatments in alleviating GI symptoms in SSc patients, among whom small intestinal bacterial overgrowth (SIBO) affects up to 60%. SIBO is marked by excessive bacterial growth in the small intestine, leading to significant GI discomfort [22].

Recent studies have found that patients with SSc in the early stages of the disease (recently diagnosed) already showed dysbiosis in their GI microbiota. This suggests that perturbations in the GI microbiota may occur early in the course of SSc and

could potentially contribute to the development of the disease [29]. However, this trial had certain limitations, including heterogeneity between the two study sites and a small sample size in the early-stage population, which may limit the generalizability of these findings. Additional factors, such as diet and medications, may also influence the differences observed between controls and SSc patients, complicating the analysis. These limitations highlight the need for future studies to consider these variables and potentially include larger, more homogeneous populations to better understand the relationship between SSc and gastrointestinal microbial composition [29].

Probiotics offer several therapeutic benefits, such as anti-inflammatory effects, enhanced protein digestion, toxin neutralization, increased immunoglobulin secretion, and antioxidant activity. These properties make them a promising option for treating SSc patients with SIBO. *Saccharomyces boulardii*, either alone or combined with metronidazole, has been shown to be more effective in eliminating SIBO and alleviating GI symptoms than metronidazole alone [22].

Marighela et al. conducted an 8-week study to assess the effects of a daily probiotic mixture on GI symptoms in SSc patients.

The study found no significant difference in GI symptom improvement between probiotic and placebo groups, though a reduction in Th17 cells in the probiotic group suggested potential immunomodulatory effects [20].

The microbiota significantly influences immune responses, particularly impacting the development and function of Th17 cells, a T helper cell subset involved in producing interleukin-17 (IL-17) and maintaining mucosal barrier integrity. Primarily within the GI tract, which hosts the highest density of commensal microbes, the microbiota plays a crucial role in supporting Th17 cell homeostasis. Through cytokines such as IL-17

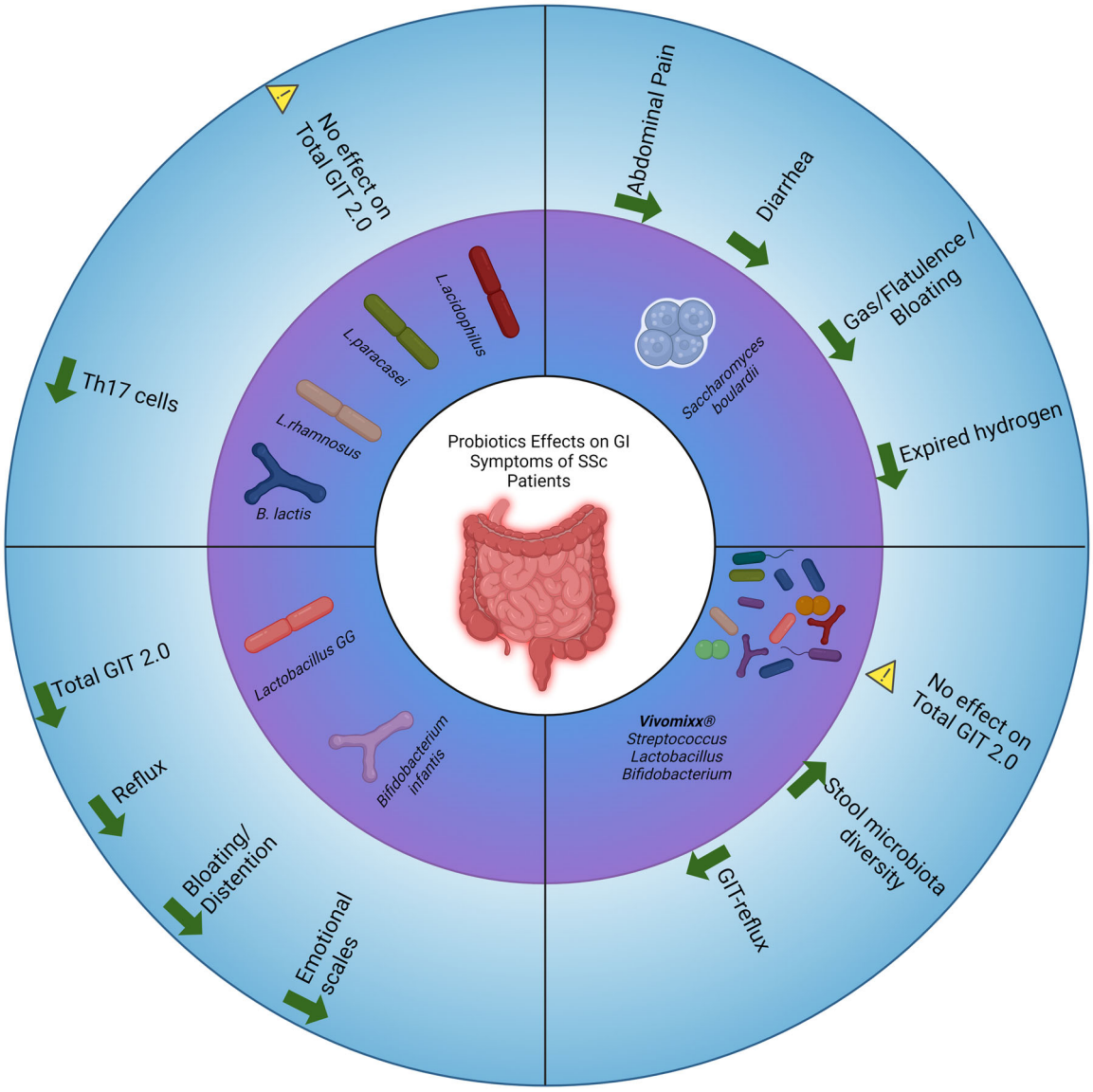

FIGURE 3 | Summary of the Impact of Probiotic Ingestion on Patients with Systemic Sclerosis (SSc). B, *Bifidobacterium*; GIT, gastrointestinal tract; L, *Lactobacillus*; Th, T cell helper.

and IL-22, Th17 cells regulate epithelial function, antimicrobial peptides, mucus production, and wound repair, helping to maintain microbial communities in distinct ecological niches within the GI tract [30–32].

Low et al. conducted a study evaluating the effects of a high-dose probiotic supplement containing multiple bacterial strains on GI symptoms in SSc patients. Overall, probiotics showed promise for reflux symptom relief but had no effect on overall GI health [21].

Frech et al. conducted a study to evaluate the effectiveness of probiotics in alleviating GI symptoms in SSc patients. They found that probiotics, particularly Align (*Bifidobacterium infantis*) and Culturelle (*Lactobacillus GG*), significantly improved GI symptoms, including bloating and distention, in SSc patients [19].

The variability in probiotic effects across studies may be attributed to factors such as probiotic strain selection, patient diversity, study design, and the complexity of the gut microbiome [15]. Differences in baseline microbiota, disease heterogeneity, dosage, duration, and concurrent treatments further influence outcomes. Additionally, Study design, outcome measures, and interactions between probiotics contribute to this variability. Publication bias, favoring positive results, may distort perceptions of probiotic efficacy.

In summary, this systematic review highlights the variable efficacy of probiotics in alleviating gastrointestinal symptoms in SSc patients across various studies, with some evidence suggesting benefits, particularly for conditions like SIBO. Immunosuppressive therapy can increase the risk of infections from probiotics and worsen dysbiosis by altering gut microbial balance. Careful consideration is necessary when using probiotics in immunosuppressed patients, and further research is needed to better understand the safety and efficacy of probiotics in this context. Variability in outcomes may be attributed to differences in probiotic strains, dosages, study designs, patient demographics, and concurrent treatments. While some studies demonstrate improvements in specific symptoms, such as reflux, bloating, and immune modulation (e.g., reductions in Th17 cells), others report no significant changes in overall GI health. This inconsistency underscores the need for well-designed, larger studies to elucidate the therapeutic potential of probiotics more fully in SSc, accounting for disease heterogeneity, strain-specific effects, and comprehensive patient assessments to support personalized treatment strategies. Figure 3 provides a summary of the effects of different probiotic strains on patients with SSc, as reported in clinical trials.

5 | Conclusion

In conclusion, microbiota-based therapies hold promise for managing SSc GI symptoms and may have potential implications for disease progression. While antibiotics are commonly used, they carry the risk of dysbiosis, making alternative approaches—such as FMT and plant-based diets—attractive low-risk options. Probiotics, *Bifidobacterium*, and *Lactobacillus* have garnered interest in SSc studies, while prebiotics warrant further investigation. A deeper understanding of the GI microbiota in SSc could reveal new therapeutic targets. Probiotics, especially *Saccharomyces boulardii*, demonstrated potential in alleviating SSc-related GI symptoms, though variations in their effects require careful consideration. The integration of probiotic therapy may complement the comprehensive management of SSc, but further randomized controlled trials are needed to establish their efficacy.

Author Contributions

Zahra Mirfeizi: conceptualization, methodology, project administration, validation, writing – original draft. **Mahmoud Mahmoudi:** conceptualization, validation, writing – review and editing, investigation. **Marzieh Monemi:** methodology, writing – review and editing, supervision. **Amin Tajerian:** methodology, writing – original draft, software, validation. **Arezoo Faridzadeh:** data curation, investigation, methodology, software, supervision, visualization, writing – original draft, writing – review and editing.

Ethics Statement

All authors have read and approved the final version of the manuscript. The corresponding author had full access to all 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 registered in the PROSPERO by a unique identification number of CRD42023398951.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Since this study is a systematic review, no original data is available, and all the extracted data is in the main manuscript and tables.

Transparency Statement

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

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