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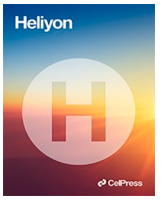

Review article

Effects of probiotics supplementation in gastrointestinal complications and quality of life of patients with systemic sclerosis: A systematic review

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ABSTRACT

Background: Systemic sclerosis (SSc), as an autoimmune rheumatic disease characterized by immune dysregulation and vasculopathy, affects multiple organs. Due to the high burden of its symptoms on the health care system, this study aims to investigate the effects of probiotic supplements in patients with SSc.

Methods: We searched electronic databases with predefined search terms in PubMed, Scopus, and ISI Web of Science up to June 2023. Randomized controlled trials that evaluated the effects of probiotic supplementation in adult patients suffering from SSc were included in the study. Results of the included studies were reported as weighted mean difference (WMD) with a 95 % confidence interval (CI).

Results: Four studies met the inclusion criteria and were included in the meta-analysis. There was a total of 176 SSc patients. The results show a significant effect of probiotics supplementation on gastrointestinal (GI) symptoms containing reflux (WMD: −0.36, 95 % CI: −0.51 to −0.22, p-value <0.001), gas and bloating (WMD: −0.88, 95 % CI: −1.05 to −0.7, p-value<0.001). However, the results for constipation (WMD: −0.12, 95 % CI: −0.27 to 0.04, p-value = 0.13), diarrhea (WMD: −0.14, 95 % CI: −0.31 to 0.03, p-value = 0.10), and fecal incontinence (WMD: 0.04, 95 % CI: −0.06 to 0.15, p-value = 0.43) were insignificant.

Conclusion: Supplementing with probiotics may alleviate a few numbers of GI complications in SSc. Nevertheless, due to the limited number of studies, more well-designed studies are needed to strengthen these results.

Abbreviations: SSc, systemic sclerosis; GI, gastrointestinal; SMR, standardized mortality ratio; GERD, gastroesophageal reflux disease; CI, confidence interval; SD, standard deviation; RCT, randomized control trial; GIT, The UCLA Gastrointestinal Tract Questionnaire; WMD, weighted mean difference; SIBO, Small intestinal bacterial overgrowth.

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1. Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease of rheumatoid connective tissue disorders, and it seems with chronic and progressive tissue and organ fibrosis [1]. SSc is characterized by the presence of autoantibodies, progressive micro vasculopathy, and abnormal production of extracellular matrix proteins in body tissues [2]. The apparent features of SSc include immune dysregulation, inflammation, vascular damage, anatomical and practical abnormalities, and systemic interstitial fibrosis of the body, which leads to multisystem organ destruction [3]. According to the findings of the most recent epidemiological studies, the prevalence of SSc is 17.6 per 100,000 people in the population, with an average incidence of 1.4 per 100,000 people [4]. A high mortality rate was demonstrated in SSc patients compared to other rheumatic diseases [5]. The standardized mortality ratio (SMR) of SSc is estimated to be over 4, with the five-year survival rate ranging from 50 % to 90 % depending on the study period and the specific population chosen [6].

The pathophysiology of SSc is complex, with potential triggers such as endothelial destruction, secretion of inflammatory markers, and fibrotic reactions, ultimately leading to systemic inflammation [5]. Many genes have been identified to be involved in the modulation of inflammation and autoimmune function and may be relevant to susceptibility to such illness [7]. In addition, environmental factors such as silica dust, drugs, smoking, stress, history of surgery, and diet have been identified to increase the incidence of SSc [8]. However, the precise way of action of most of these factors is not yet known; genetic sensitivity combined with extrinsic factors are important parts of the primary induction of the SSc [9]. It has been shown that pulmonary and renal involvement are the main predictors of mortality in SSc; emerging shreds of evidence show that involvement of the gastrointestinal (GI) tract can raise the morbidity and mortality of SSc patients [10]. GI problems, the most common type of organ involvement after skin fibrosis, occur in 90 % of SSc patients [11]. GI manifestations of SSc include gastroesophageal reflux disease (GERD), Barrett's esophagus syndrome, stricture, gastroparesis, false intestinal obstruction, esophageal dysphagia, esophageal dysphagia, intestinal malabsorption, constipation, diarrhea, or fecal soilage [6,12]. Bacterial overgrowth or reduced permeability in the small intestine may lead to malabsorption in these patients [13].

Probiotics have beneficial effects on human health [14]. These microorganisms, usually composed of the yeast Saccharomyces boulardi or lactic acid bacteria, are non-pathogenic and are prescribed to improve microbial balance, especially in the digestive system [15,16]. Prior studies have suggested using probiotics to enhance overall health and immunity, metabolic disorders, and inflammatory autoimmune and bowel disease [17–19]. A growing body of evidence has proposed the positive effects of probiotic supplementation in autoimmune disorders [20,21]. The potential anti-inflammatory and immune-modulating properties of probiotics show promise in complementing standard treatments for rheumatic diseases [22].

To date, there has been no quantitative review conducted to assess the impact of probiotic supplementation on the symptoms of SSc. Given the gastrointestinal complications and elevated mortality rate observed in SSc patients, it is imperative to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the potential benefits of probiotic supplementation in this population.

2. Methods

2.1. Strategy of search

This meta-analysis has been done based on the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA) guideline. A systematic search was carried out using predetermined search terms in PubMed, Scopus, and ISI Web of Science up to June 2023 (table S1). S creening of titles and abstracts due to the predefined inclusion and exclusion criteria has been done to find eligible studies. Two authors independently assessed the full texts of the included studies for eligibility (M.R and F.N). Any controversies were resolved by a third reviewer (H.M.). Reference lists of relevant articles were screened to find further probable eligible studies.

2.2. Eligibility criteria

Criteria for inclusion and exclusion were defined according to the PICOS (population, intervention/exposure, comparator, outcome, and study design) framework (Table 1). In this quantitative review, eligible studies have the following criteria: 1) randomized controlled trials in adults aged over 18; 2) evaluated the effects of probiotics on symptoms of SSc patients; 3) reported mean and standard deviation (SD) of changes in symptoms of SSc patients; and 4) compared the effects of probiotics supplementation to placebo on systemic sclerosis patients. Moreover, articles were excluded if they were conducted on a population aged under 18,

Table 1
PICOS criteria for inclusion and exclusion of studies.

Parameter	Criteria
Population	Adults aged older than 18 suffering from SSc
Intervention	Probiotics
Control/comparator	Placebo
Outcomes	Reflux, gas and bloating, constipation, diarrhea, and fecal incontinence
Study design	Randomised controlled trails

Abbreviations: SSc, systemic sclerosis.

pregnant or lactating women.

2.3. Data extraction

Two authors independently (M.R and F.N) and in duplicate review the full text of potentially eligible articles. Furthermore, the citations of the included studies were reviewed to minimize the risk of overlooking any relevant studies. Any controversy about choosing the eligible studies has been resolved by a chief reviewer (H.M). For the studies that were to be considered eligible, two independent reviewers (M.R and F.N) were extracted: author name, year, location of study, study design and duration, mean age, baseline BMI and body weight, health status, total sample size, intervention characteristics (type and dose of probiotics supplementation), placebo in the control group, and results that we needed for the included outcomes.

2.4. Assessment of the risk of bias and certainty of the evidence

Cochrane Collaboration's tool was used for assessing the risk of bias in randomized trials for risk of bias assessment [23]. Each RCT was evaluated for the following biases: selection, performance, detection, attrition, and reporting bias. HM resolved discrepancies between the reviewers. M.R. and F.N. independently conducted a duplicate quality assessment. The certainty of evidence was evaluated using the GRADE approach.

2.5. Data synthesis and statistical analysis

The information required for statistical analysis was extracted from a predesigned table in Excel and then entered into Stata 14 software (Stata Corp, College Station, TX, USA). The statistical analysis utilized the appropriate effect size (mean or difference of means) along with their standard deviations. In cases where studies reported varying effect sizes, efforts were made to convert them into a common effect size, if feasible. Heterogeneity amongst studies was assessed using Cochran's chi-square test (Q) and the I^2 statistic indicated a low level of heterogeneity. In order to assess the source of heterogeneity in the studies included in the meta-analysis, statistical modeling approaches and sensitivity analysis were employed, depending on the amount of available

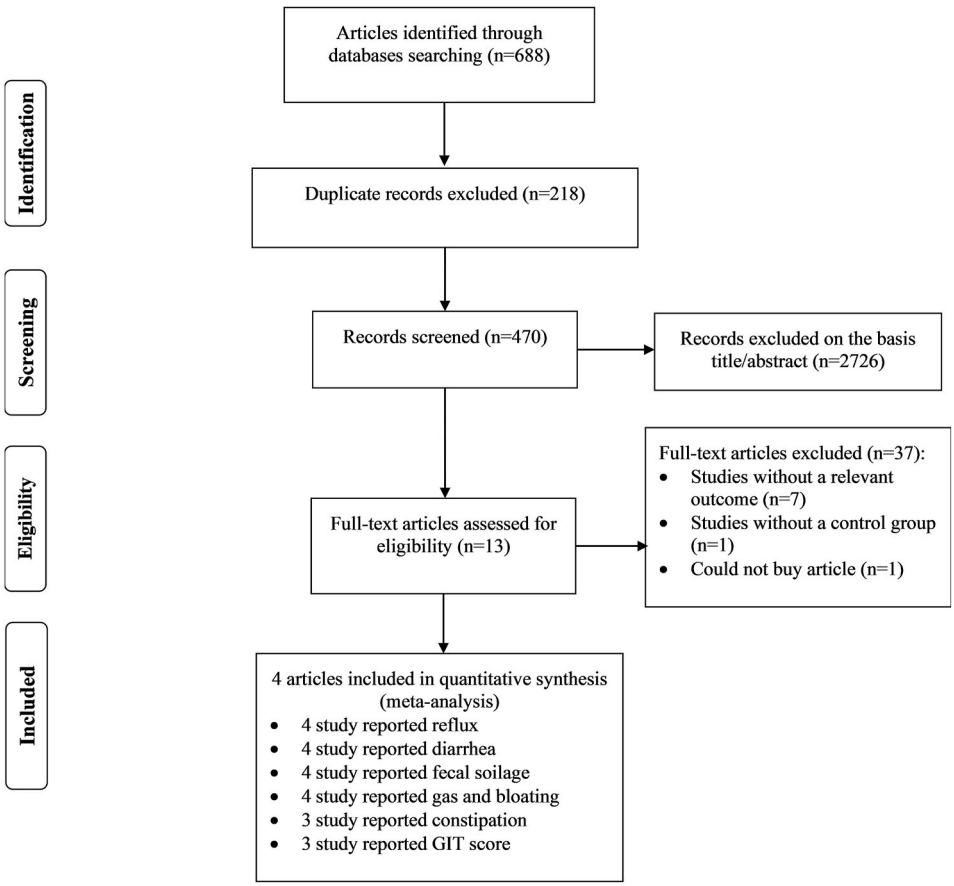

Fig. 1. Literature search and review flow diagram for selection of the studies.

information from the extracted studies. Publication bias was assessed by funnel curves, and the relative risk was presented against the reciprocal of the squared standard error. The statistical evaluation of funnel curve asymmetry was done by Egger regression.

This systematic review and meta-analysis study is registered at PROSPERO with the number: CRD42023388303.

3. Results

3.1. Selection and identification of studies

The detailed search strategy is included in Supplementary table 1. T he results of searching in electronic databases show 688 records have been found. From these records, 218 citations were duplicates. After screening, 466 publications were excluded. Overall, 4 records fulfilled the eligibility criteria and were entered in the meta-analysis [24–27]. Moreover, 5 records were included in the systematic review [24–28] (Fig. 1). The list of potential articles that were not entered in the second phase of screening is report ed in Supplementary table 2.

3.2. Characteristics of included studies

Characteristics of the included studies are represented in Table 2. The included studies were conducted between 2016 and 2020. There was a total of 176 people, including 89 people in the probiotic group and 87 in the control group. All studies were conducted on people suffering from SSc. These studies were conducted in Iran [24], Mexico [27], Singapore [26] and Brazil [25]. The duration of the intervention was 1 week in one study [27], and 8 weeks in other studies [24–26]. The type of probiotic used as an intervention was lactobacillus casei [24], a combination of Lactobacillus paracasei and rhamnose, and acidophilus and Bifidobacterium lactis [25], a combination of Lactobacillus Lactobacilli paracasei and plantarum and acidophilus and delbruecki subsp bulgaricus [26] and Saccharomyces boulardi [27].

3.3. Assessment of risk of bias

All included studies have random allocation. The method of random sequence generation has not been reported only in one study [25]. The risk of bias in the blinding of participants, personnel, and outcome assessors was low in two studies [24,26], unclear in one study [27], and in one trial blinding of participants and personnel had low risk but an unclear risk about the blinding of outcome assessors [26]. Regarding incomplete outcome data and selective outcome reporting, studies indicated a low or unclear risk of bias. Table 3 represents the details of the risk of bias assessment.

3.4. Effects of the probiotic supplement on the reflux of SSc patients

This outcome was examined in 4 arms of clinical trials. Pooled mean differences using the inverse variance method showed significant alteration in the reflux of SSc patients (WMD: −0.36, 95 % CI: −0.51 to −0.22, p-value <0.001) (Fig. 2). Moreover, between-study heterogeneity was considerable ($I^2 = 92.31$ %, $P < 0.001$).

3.5. Effects of probiotics on constipation of SSc patients

4 clinical trials investigated the effects of probiotics on the constipation of patients with SSc. Pooled mean differences using the inverse variance method showed no significant change in the constipation of patients with SSc (WMD: −0.12, 95 % CI: −0.27 to 0.04, p-value = 0.13) (Fig. 3). Considerable between-study heterogeneity was found ($I^2 = 97.17$ %, $P < 001$).

3.6. Effects of probiotic supplementation on diarrhea of SSc patients

Probiotics administration had a non-significant effect on the diarrhea of patients with SSc (WMD: −0.14, 95 % CI: −0.31 to 0.03, p-value = 0.10) in 4 arms of clinical trials (Fig. 4). Moreover, heterogeneity between studies was remarkable ($I^2 = 96.73$ %, $P < 0.001$).

3.7. Effects of probiotic supplementation on gas and bloating of SSc patients

Our results show probiotics administration had a significant impact on gas and bloating of patients with SSc (WMD: −0.88, 95 % CI: −1.05 to −0.7, p-value<0.001) based on our analysis on 4 arms of clinical trials (Fig. 5). Moreover, remarkable heterogeneity between studies was seen ($I^2 = 98.75$ %, $P = 0.001$).

3.8. Effects of probiotic supplementation on fecal soilage of SSc patients

The results of our meta-analysis on 4 arms of clinical trials show that probiotic supplementation does not have a significant effect on fecal spoilage of patients with SSc (WMD: 0.04, 95 % CI: −0.06 to 0.15, p-value = 0.43) (Fig. 6). Between-study heterogeneity was not considerable ($I^2 = 0$ %, $P = 0.46$).

Table 2
Characteristics of the included studies.

	First author (Country; year)	RCT design (blinding)	Sex	Mean Age (year)	Type of probiotics	Sample size (supplement/ Placebo)	Duration (weeks)	Intervention		outcomes	Adverse events
								Dose of intervention	Control group (composition)		
1	García-Collinot et al. (Mexico; 2020)	Parallel	Both	50.5	Saccharomyces boulardi + metronidazole	26 (13/13)	1	400 mg	Placebo (metronidazole)	Reflux, diarrhea, constipation, fecal soilage, gas and bloating	Heartburn Flatulence Diarrhea Constipation
2	Marighela et al. (Brazil; 2019)	Parallel (Double)	Both (68 F/ 5 M)	46.9	Lactobacillus paracasei/ rhamnoses/acidophilous and Bifidobacterium lactis	73 (37/36)	8	10^9 CFU	Placebo (maltodextrin)	Reflux, diarrhea, constipation, fecal soilage, gas and bloating, GIT score	No adverse event
3	Ling Low et al. (Singapore; 2019)	Parallel (Double)	Both (35 F/ 5 M)	51.06	Lactobacilli paracasei/ plantarum/acidophilus/ delbrueckii subsp bulgaricus	40 (19/21)	8	1800 billion	Placebo (NR)	Reflux, diarrhea, fecal soilage, gas and bloating, GIT score	GI Infections Disease worsened Fatigue Headache Dizziness Joint pain/ body aches Others
4	Enteshari-Moghaddam et al. (Iran; 2018)	Parallel (Double)	Both (32 F/ 5 M)	46.3	lactobacillus casei	47 (20/17)	8	NR	Placebo (NR)	Reflux, diarrhea, constipation, fecal soilage, gas and bloating, GIT score	NR

Abbreviations: F, female; M, male; CFU, colony forming unit; NR, not report.

Table 3
Cochrane risk of bias assessment.

Study	Random Sequence Generation	Allocation concealment	Selective outcome reporting	Other sources of bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Overall quality
García-Collinot et al. (Mexico; 2020)	L	L	L	L	U	U	L	Some concerns
Marighela et al. (Brazil; 2019)	L	U	L	L	L	L	U	Some concerns
Ling Low et al. (Singapore; 2019)	L	L	L	L	L	U	L	Low risk of bias
Enteshari-Moghaddam et al. (Iran; 2018)	L	L	L	U	L	L	U	Some concerns

Abbreviations: L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

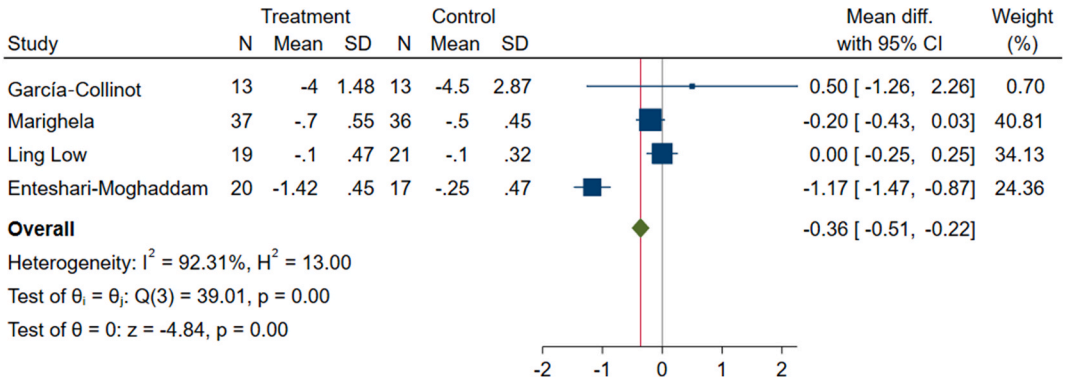

Fig. 2. Effects of probiotics on reflux of SSc patients.

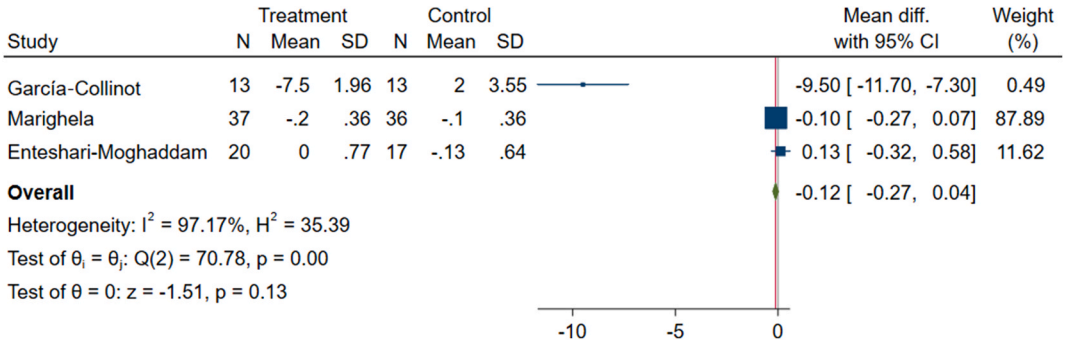

Fig. 3. Effects of probiotics on constipation of SSc patients.

3.9. Publication bias and sensitivity analysis

There was no evidence of publication bias for reflux (p = 0.977, Egger's test), diarrhea (p = 0.073, Egger's test), constipation (p = 0.442, Egger's test), gas and bloating (p = 0.292, Egger's test), and fecal soilage (p = 0.617, Egger's test). Moreover, the sensitivity analysis for diarrhea, constipation, fecal soilage, gas and bloating showed that the elimination of any study did not affect the overall results. However, the study by Enteshari-Moghadam et al. (WMD: −0.10, 95 % CI: −0.27, 0.07) affected the overall result regarding the effects of probiotics supplementation on reflux and turned it non-significant. So that may be a source of heterogeneity.

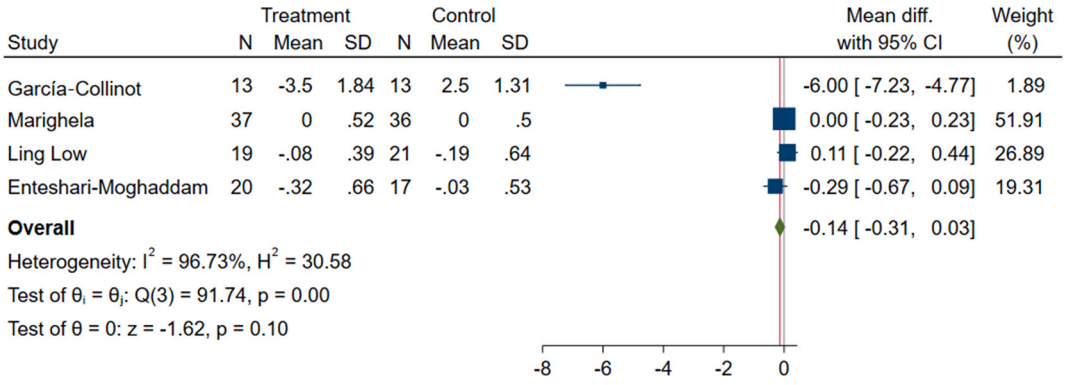

Fig. 4. Effects of probiotics on diarrhea of SSc patients.

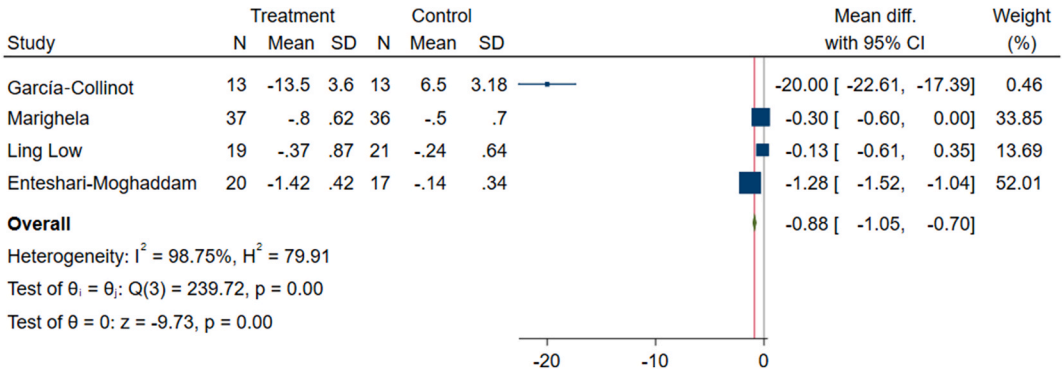

Fig. 5. Effects of probiotics on gas and bloating of SSc patients.

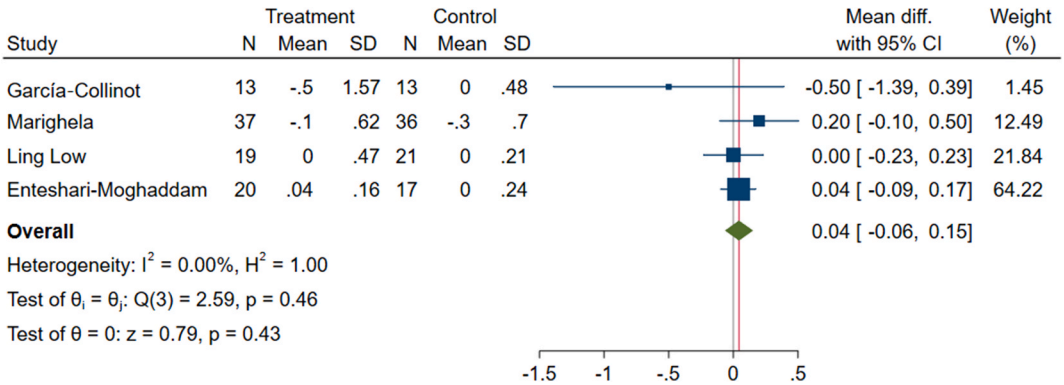

Fig. 6. Effects of probiotics on Fecal incontinence of SSc patients.

3.10. Grading of evidence

table S3 shows the detailed GRADE evidence for each outcome. Due to this approach, low certainty of evidence for reflux, diarrhea, constipation, and gas and bloating was found. Moreover, moderate certainty of the evidence for fecal soilage was reported.

3.11. Effects of probiotic supplementation on nausea, vomiting, and disrupted swallowing of SSc patients

Nausea and vomiting are among the complications of SSc. In most SSc patients with nausea and vomiting, this complication occurs with mild to moderate severity [29]. The results of a recent meta-analysis that examined the effects of probiotics on the symptoms of patients who undergo chemo or radiotherapy showed probiotics could have improved effects on nausea and vomiting [30]. According

to our systematic review, only one study has investigated the impacts of probiotics on nausea in patients with SSc. The results of the mentioned studies revealed no significant effect [27]. Dysphagia is a typical appearance of GI involvement in SSc [31]. Emerging pieces of evidence reported that dysphagia is because of esophageal dysfunction, but oropharyngeal involvement can also result in oropharyngeal dysphagia in SSc [32]. Our systematic review identified two studies that assessed the effects of probiotics on swallowing difficulties in patients with SSc [25,27]. The findings of these studies proposed an improvement in dysphagia; however, the result of one of them was significant [27].

3.12. Effects of probiotic supplementation on quality of life of outcomes SSc patients

Some characteristics of SSc patients, such as physical appearance, can subsequently interfere with social functioning by increasing the risk of depression and fatigue [33–35]. This disease is a comprehensive multidimensional problem that includes biological, psychological, and social aspects [36]. Previous studies have shown that probiotic supplementation in autistic children probably improved their social functioning [37]. Two studies evaluating the effect of probiotics on SSc patients [24,25] reported that the difference between the average scores of social functioning in the intervention group and the control group was statistically significant. Concerning emotional well-being, these studies concluded that probiotics supplementations have no significant effect on the emotional well-being of SSc patients. As previously mentioned, SSc may adversely impact the quality of life of those affected. A systematic review concluded that health-relevant quality of life in SSc patients was impaired. The authors also stated that there is a need to identify and implement interventions to improve the quality of life of SSc patients [38]. The evaluations conducted on the quality of life of patients with SSc concerning the effects of probiotics were carried out using a health assessment questionnaire in two studies [25,26]. Based on the findings of the mentioned studies, there was an insignificant reduction of decreased quality of life in the probiotic group compared to the control group [25,26]. The effects of probiotics on the visual analog scale were assessed in 2 studies, both of which did not demonstrate any significant effects [25,26].

4. Adverse events

From the included studies, 2 studies reported adverse events [26,27], 1 stated there were no adverse events [25], and another one mentioned nothing about it [24]. In the study by García-Collinot et al. [27], 2 patients reported diarrhea, and 1 patient reported heartburn, flatulence, and constipation. However, in the control group, which consumed metronidazole like the intervention group, the incidence of heartburn and constipation were 5 and 2, respectively. In the study by Ling Low et al. [26], 25 patients reported GI adverse events compared to 21 in the placebo group. The number of infections and disease worsened were 16 and 1 in the probiotic group, and 8 and 1 in the placebo group, respectively. 1 patient in the placebo group reported fatigue. The number of patients who experienced headaches was 2 in probiotic and 1 in placebo groups. Nobody reported dizziness. Joint pain and body ache was seen in 2 patients in the placebo group and no one in the probiotic group. On the whole, 2 subjects in the placebo group (due to pneumocystis pneumonia and upper respiratory tract infection) and 1 subject in the intervention group (due to Herpes zoster infection) discontinued the study.

5. Discussion

This study summarizes the available evidence about the effect of probiotic supplements on patients suffering from SSc. To our knowledge, this study represents the first meta-analysis of randomized clinical trials investigating the effects of probiotic supplementation in SSc patients. The results obtained from this meta-analysis show that SSc patients experienced symptom improvement, including relief from reflux, and gas and bloating, following probiotic supplementation. Furthermore, no significant impact was seen regarding constipation, diarrhea, and fecal soilage.

Evidence shows probiotics can be used to treat and prevent chronic GI diseases and inflammatory disorders [39], such as diarrheal [40], necrotizing enterocolitis [41], inflammatory bowel disease [42], Irritable Bowel Syndrome [43], and many other conditions. Probiotics and gut microflora interact with the gut-associated lymphoid tissue (GALT), which plays a role in oral tolerance and mucosal immunity, and this interaction has a positive impact on the epithelium, helping to maintain digestive and overall health [44]. The general mechanisms of action of probiotics target two main aspects: (a) altering the composition and function of the gut flora and (b) enhancing gut mucosal immunity, leading to anti-inflammatory responses [45]. Therefore, the mechanisms of probiotic action include strengthening the epithelial barrier, increasing the insertion of beneficial probiotics to the mucous layer, inhibiting pathogen insertion to this layer, eliminating pathogenic microbes competitively, generating antimicrobial structures, and adjusting immune responses [46]. Moreover, there is increasing evidence of the effects of probiotics on autoimmune diseases [47]. The precise pathophysiology of autoimmune diseases is still unknown, but both innate and adventitious immunity may result in this phenomenon [48]. Regulating the autoimmune condition of the disease with no more immunosuppressive ways is a new aspect of curing autoimmune diseases [49]. Recently, the role of gut flora in the modulation of immune responses has been investigated, and the results show that establishing an equivalency between pro-inflammatory and anti-inflammatory gut bacteria can adjust and prevent autoimmune conditions [50]. Together, probiotics and commensal bacteria strengthen the mucosal surface function of the GI tract epithelium, enforce mucosal secretion, and stimulate the production of Immunoglobulin A (IgA), which eliminates pathogens in the GI tract [51]. Although the information is limited, there is increasing interest in the possible benefits of these microorganisms in rheumatic diseases [52]. A recent meta-analysis evaluated the safety and efficacy of probiotic supplementation in eight types of inflammatory arthritis. It concluded that probiotic supplementation may improve hyperuricemia, gout, inflammatory bowel disease, arthritis, juvenile idiopathic arthritis,

osteoarthritis, osteoporosis and osteopenia, psoriasis, rheumatoid arthritis and spondylarthritis [53]. The GI tract, which has unique microbial ecosystems, is considered one of the most active organs in immunity [54]. Studies show alterations in the microbial flora of patients with inflammatory arthritis at the preclinical stage. Moreover, according to the available evidence, intestinal dysbiosis causes inflammatory arthritis and chronic systemic inflammation [55–61]. A possible complex interaction between intestinal microbial disturbances and genetic factors may be the reason for the pathology of systemic inflammation in inflammatory arthritis [62–64]. SSc, as a rheumatic and autoimmune disease, can affect various internal organ systems, including the pulmonary system, peripheral vessels, kidneys, heart, and digestive system [65]. In the intestinal tract, SSc causes a disruption in the normal neuromuscular function of the intestine, resulting in motility disorders and subsequent alterations in the gastrointestinal tract's function [66]. Whether changes in GI tract flora in SSc may result in large clinical outcomes in these patients is still unclear [54], but observational cohort studies reveal unique differences in the microbial community of SSc patients versus healthy individuals [67–70].

Significant complications in SSc patients are known to be associated with esophageal disease such as erosive esophagitis, stricture formation, and Barrett's esophagus that may transform malignant to adenocarcinoma [66,71]. A systematic review assessing the impact of probiotics on GERD concluded that probiotics have beneficial effects on reflux symptoms, including heartburn [72].

Constipation in these patients is the result of several factors, including impaired gastric reflexes that lead to prolonged transit time and reduction of contractions in the colon [73]. SSc patients experiencing constipation are typically treated similarly to patients without SSc through medications that can impair GI motility [74]. Recent studies showed an improvement in constipation in the overall population and concluded that some probiotics may improve stool frequency and constipation symptoms [75]. Moreover, another meta-analysis reported that the effectiveness of probiotics is controversial. In the same study, the findings revealed that supplementation with certain specific probiotics has shown significant beneficial effects, while others have demonstrated minimal impact [76].

The etiology of diarrhea in SSc has many causes [77]. The primary cause of diarrhea in SSc is a small intestinal bacterial overgrowth or SIBO; however, screening examinations for other causes of diarrhea, such as stool microscopy and *Clostridium difficile* toxin testing, are recommended in these patients [78]. The prevalence of SIBO, which results from an increase in the size or type of microorganisms in the small intestine, is significantly higher in these patients, ranging from 30 % to 60 %, compared to 0 %–12.5 % in healthy individuals [79,80]. A recent meta-analysis found that probiotics are effective in alleviating the bacterial load in SIBO patients and reducing their symptoms [81]. On the other hand, one study stated that the consumption of probiotics in SIBO patients led to the worsening of gas, bloating, and brain fogginess symptoms [82].

About 50 % of patients report signs of gastric dysfunction with early bloating and abdominal discomfort [83,84]. Frech et al. conducted a pilot study to evaluate the effects of probiotics for curing SSc-associated GI bloating and distension [28]. This study was the first to examine the effects of probiotics in patients with SSc. Results of the mentioned study showed a significant improvement in the bloating and distention scores of SSc patients. This study did not have a control group; therefore, we did not include it in our meta-analysis.

Fecal incontinence sometimes may be severe, with a prevalence of 27–38 % in SSc [85,86]. internal anal sphincter atrophy was reported in SSc patients [87]. Evidence suggests that the neurogenic process may be more clinically important, especially in the beginning. In addition, the absence of rectoanal inhibitory reflex (RAIR) has been seen in 71.4 % of these patients. There was a meaningful association between fecal incontinence in SSc and RAIR disorder. RAIR represents a local nerve reflex that is most relevant to Hirschsprung's disease, and the relationship between its absence and fecal incontinence or constipation is unknown in this context [88]. Studies have concluded that fecal incontinence in these patients mostly results from neuropathy to sphincter atrophy and fibrosis [89].

Of the studies included in this review, just 2 of them reported adverse events. A wide range of side effects were reported, nevertheless, most of them were mild to moderate events. Adverse events after intake of probiotics are likely to happen [90]. GI problems including diarrhea, constipation, and bloating are common, especially if taken in high doses or with a sensitive gut in patients [91]. Due to the results of the included studies, the incidence of GI adverse events was not significantly higher in the probiotic groups. The biggest difference was seen in the infection of the intervention group compared to the placebo. As Rafael Lessa Costa et al. mentioned in a meta-analysis in this field, the use of probiotics is not without risks and should be thoroughly assessed for certain patient populations [92]. It should be taken into consideration that SSc patients are more likely to develop infections [93], and since the evidence about the safety of probiotics in these patients is scarce, there is a need for more studies to assess adverse events in SSc.

The strengths of our meta-analysis include conducting a comprehensive search strategy and evaluating the effects of probiotic supplementation on SSc patients for the first time. In addition, there was no limitation on the publication date and we assessed the reported adverse events. Moreover, we assess the certainty of evidence through the GRADE approach. The limitations of our study include the small number of pooled data due to the lack of clinical trials in this regard. It is worth noting that there were notable differences in the intervention doses across these studies; however, the effect of different types of probiotic spices was not detected as the number of studies for each type of species was insufficient, and only four RCT studies were included. In addition, the optimal timing, dosage, and mode of probiotic administration in SSc patients remain unanswered.

6. Conclusion

In total, there was a lack of evidence for the significant effect of probiotic supplementation on GI complications of SSc patients. Due to the small number of studies, more well-designed studies are needed to assess the effects and safety of probiotics in these patients.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committees of the School of Medicine- Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1401.376)

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Mahsa Ranjbar: Writing – original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Fatemeh Naeini:** Writing – review & editing. **Abdolrahman Rostamian:** Validation, Methodology. **Kurosh Djafarian:** Visualization, Supervision. **Hamed Mohammadi:** Validation, Supervision, Resources, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36230.

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