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Meta Analysis

Comparison of maintenance effect of probiotics and aminosalicylates on ulcerative colitis: A meta-analysis of randomized controlled trials

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Abstract

Objective: To evaluate the maintenance effect of probiotics versus that of aminosalicylates on ulcerative colitis.

Methods: MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and the Chinese Biomedical Database were searched in English or Chinese. Data extracted were selected with strict criteria.

Results: In six randomized controlled trials (RCTs), a total of 721 participants were enrolled and the maintenance effect of probiotics ($n = 364$) versus that of aminosalicylates ($n = 357$) on ulcerative colitis was investigated. No significant difference was observed between probiotics and aminosalicylate groups (relative risk (*RR*) = 1.08; 95% confidence interval (*CI*): 0.91−1.28; $P = 0.40$). Three RCTs compared the incidence of adverse events with probiotics versus those with aminosalicylates. No significant difference was observed in the incidence of adverse events between the two groups (*RR* = 1.20; 95% *CI*: 0.92−1.56; $P = 0.17$).

Conclusions: Probiotics and aminosalicylates both showed a maintenance effect on ulcerative colitis. However, more well-designed RCTs are required.

Keywords: Maintenance effect; Probiotics; Aminosalicylates; Ulcerative colitis; Meta-analysis

Introduction

Ulcerative colitis (UC) is a relapsing, chronic, immune-mediated intestinal disease that mainly affects the large bowel, and whose causes and etiology remain unknown. Its main symptoms are watery or bloody stools, abdominal pain, urinary urgency and (or) tenesmus.[1] Consequently, UC severely affects patients' quality of life.

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Aminosalicylates are recommended for maintenance treatment in patients with UC.[2] However, many patients are intolerant to either classic aminosalicylate sulfasalazine or sulfur-free compounds. In addition, the potential side effects, costs, and a poor compliance to long-time therapy, have led researchers to look for novel therapeutic approaches.[3]

Probiotics are live microbial feed supplements, which beneficially affect the host by altering the enteric flora. Increasing evidence indicates the role of intestinal micro flora in the pathogenesis of UC.[4–6] Although several observations have suggested that some probiotics and aminosalicylates have comparable effects in the maintenance of remission in UC,[3,7–17] the evidence is based on a relatively few number of studies, which are not sufficient to determine whether they are definitely helpful or harmful. Therefore, the present meta-analysis systematically identifies and analyzes randomized controlled trials (RCTs) in order to evaluate the maintenance effect of probiotics versus that of aminosalicylates on UC.

Materials and methods

Search strategy

We searched for RCTs from the following databases: MEDLINE (1966 to August 2015), EMBASE (1980 to August 2015), the Cochrane Controlled Trials Register (1995 to August 2015), and the Chinese Biomedical Database (1981 to March 2015). The keywords used were probiotic, *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Escherichia coli*, yeasts, probiotic mixture VSL#3, mesalazine, osalazine, 5-aminosalicylic acid (5-ASA), balsalazide, and ulcerative colitis, maintenance of remission, or relapse. The studies were limited to those published in English or Chinese. Moreover, manual searching of reference lists, authors, and associated meeting reports or abstracts was also performed. Two participators (Yong Jiang and Ying Zhang) searched the results.

Selection criteria and quality assessment

The selection criteria were as follows: (a) They were RCTs; (b) Both adult and children studies were included; (c) Meeting reports or abstracts were included; (d) The studies compared the maintenance effect of probiotics to aminosalicylates with standard therapy for UC; (e) Patients who had UC used definite diagnostic standards; (f) Reviews and case reports were excluded.

Two participants selected the articles after careful searching. We evaluated the quality of each selected article and verified the details. When discrepancies occurred, a third author (Feng-Xiang Qi) resolved them. The quality of the selected RCTs was assessed by the Cochrane Reviewer Handbook 5.0, RCTs' quality assessment standard, using the following criteria: sequence generation, allocation sequence concealment, blinding method, incomplete outcome data, and selective outcome reporting.[18] The Jadad score was used to evaluate the quality of every RCT. High-quality RCTs, which scored three points or more, were included in this meta-analysis.[19]

Statistical analysis

The statistical analysis was performed using Cochrane Collaboration's Revman 5.3 software. Relative risks (*RR*) with 95% confidence interval (*CI*) were calculated based on the studies. A statistical heterogeneity test was performed by using the Chi-square test and I^2 statistics, and an I^2 value of more than 50% was considered to have substantial heterogeneity. A random-effects model was selected when the heterogeneity test showed an I^2 value of more than 50%; otherwise, a fixed-effects model was used.[18] Subgroup analyses were used depending on species of probiotic. A funnel plot was used as an indicator of publication bias when the number of studies was 5 or more.

Results

We identified 4984 relevant studies from the literature searched. Nineteen potentially eligible studies[3,7–17,20–26] were initially identified; however, two studies[7,13] were excluded as they studied the maintenance effect of probiotics without aminosalicylates, four studies[14–17] were excluded as they were meta-analyses, and seven studies[20–26] were excluded as they only observed the induction of remission of UC (Table 1). Eventually, six RCTs[3,8–12] (four in English and two in Chinese) that satisfied the inclusion criteria were identified and included in the analyses (Fig. 1, Table 2).

Study characteristics

Six RCTs with a total of 721 participants were published during 1999–2009. The length of follow-up of these trials ranged from 3 to 12 months. Five studies[3,8–10,12] were conducted on adults, and one study[11] on children. Each of the five adult studies scored 4 points and the one pediatric study scored 3 points, respectively, based on the quality assessment criteria (Table 3).

Table 1
Characteristics of excluded studies.

Authors	Year	Journal	Reason for exclusion
Kruis et al[7]	1997	Aliment Pharmacol Ther	Did not compare to aminosalicylates
Miele et al[13]	2009	Am J Gastroenterol	Did not compare to aminosalicylates
Kato et al[20]	2004	Aliment Pharmacol Ther	Only studied the induction of remission
Tursi et al[21]	2004	Med Sci Monit	Only studied the induction of remission
Furrie et al[22]	2005	Gut	Only studied the induction of remission
Sood et al[23]	2009	Clin Gastroenterol Hepatol	Only studied the induction of remission
Matthes et al[24]	2010	BMC Complement Altern Med	Only studied the induction of remission
Ng et al[25]	2010	Inflamm Bowel Dis	Only studied the induction of remission
Tursi et al[26]	2010	Am J Gastroenterol	Only studied the induction of remission
Sang et al[14]	2010	World J Gastroenterol	Meta-analysis
Naidoo et al[15]	2011	Cochrane Database Syst Rev	Meta-analysis
Shen et al[16]	2014	Inflamm Bowel Dis	Meta-analysis
Fujiya et al[17]	2014	Clin J Gastroenterol	Meta-analysis

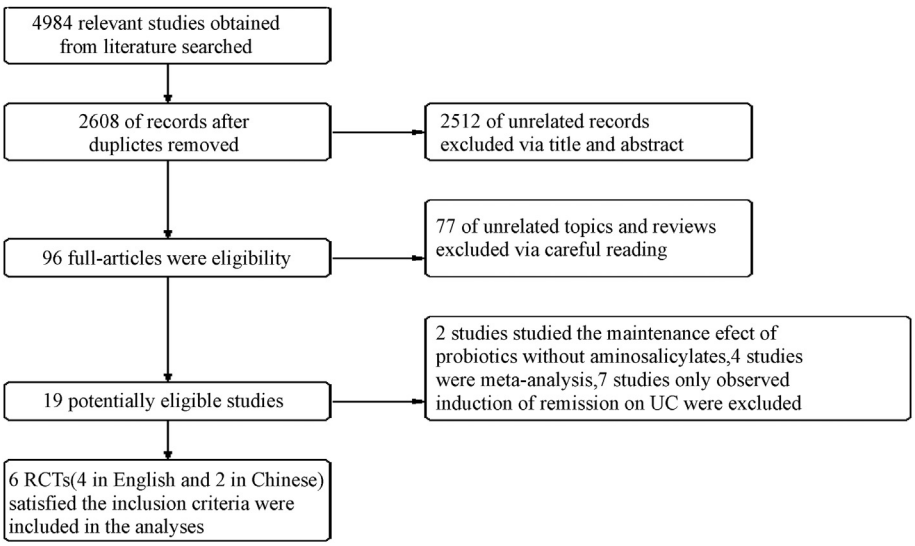

Fig. 1. Flowchart of selecting process for meta-analysis.

Effects of interventions

Six studies investigated the maintenance effect of probiotics versus that of aminosalicylates on UC. *Bifidobacterium longum* was used as the probiotic treatment in one study.[10] *E. coli* Nissle 1917 was used as the probiotic treatment in three studies.[8,9,11] The other two studies used *Lactobacillus* GG as the probiotic treatment.[3,12] Four studies[3,9,10,12] used mesalazine as the control intervention, and the other two

Table 2
Characteristics of included studies.

Authors	Year	Country	Probiotic	Control group	Dose of pro-biotic/day	Dose of mesalazine	Degree of UC	Treatment duration
Cui et al[10]	2007	China	*Bifidobacterium longum*	Mesalazine	6×10^7	500 mg tid	Mild to moderate	3 months
Henker et al[11]	2008	Germany	*E. coli* Nissle 1917	5-ASA	5×10^{10}	1500 mg/d	Not mentioned	12 months
Kruis et al[9]	2004	Germany	*E. coli* Nissle 1917	Mesalazine	$(2.5–25) \times 10^9$	500 mg tid	Not mentioned	12 months
Ma et al[12]	2009	China	*Lactobacillus* GG	Mesalazine	Not mentioned	420 mg bid	Not mentioned	12 months
Rembacken et al[8]	1999	United Kingdom	*E. coli* Nissle 1917	5-ASA	5×10^{10}	400 mg tid	Not mentioned	12 months
Zocco et al[3]	2006	Italy	*Lactobacillus* GG	Mesalazine	18×10^9	800 mg tid	Not mentioned	12 months

UC: ulcerative colitis; tid: three times a day; 5-ASA: 5-aminosalicylic acid; d: day; bid: twice a day.

Table 3
Methodological quality of the six RCTs.

Authors	Year	Random method	Allocation concealment	Blind method	Lost or exit	Inclusion/ exclusion criteria	Jadad score
Cui et al[10]	2007	High	Unclear	Unclear	Unclear	High	3
Henker et al[11]	2008	High	High	Unclear	Unclear	High	4
Kruis et al[9]	2004	High	Unclear	Unclear	High	High	4
Ma et al[12]	2009	High	Unclear	High	High	High	4
Rembacken et al[8]	1999	High	High	Unclear	High	High	4
Zocco et al[3]	2006	High	Unclear	Unclear	High	High	4

RCTs: randomized controlled trials.

studies[8,11] used 5-ASA as the control intervention. The observation intervals were 12 months in the five adult studies, and 3 months in the pediatric study. None of the studies showed significant difference in the maintenance effect between the experimental groups and control groups. The meta-analysis showed no significant difference between the probiotics groups and aminosalicylate groups ($P = 0.40$). The relapse rate was 40.4% (147/364) in the probiotics group, compared to 38.7% (138/357) in the aminosalicylate group. The pooled *RR* for the maintenance effect of probiotics versus that of aminosalicylates on UC was 1.08, with a 95% *CI* of 0.91−1.28. No significant difference was found in the heterogeneity of the total recurrence rate ($P = 0.69$, $I^2 = 0\%$) (Fig. 2).

We divided pooled trials into three subgroups according to different species of probiotics (Fig. 3). The first subgroup compared the maintenance effect of *E. coli* Nissle 1917 to that of 5-ASA/mesalazine on UC. There was no significant difference in the maintenance effect between the two groups ($P = 0.32$) and the pooled *RR* was 1.11, with a 95% *CI* of 0.91−1.35. The second subgroup compared *Lactobacillus* GG to mesalazine, which showed that there was no significant difference between the two groups ($P = 0.67$); the pooled *RR* was 0.77, with a 95% *CI* of 0.36−1.65. The third subgroup compared *B. longum* to mesalazine, and found no significant difference between the two groups ($P = 0.57$); the pooled *RR* was 1.12, with a 95% *CI* of 0.76−1.64.

Adverse events

Three studies[8,9,12] investigated the incidence of adverse events between probiotics and aminosalicylates. Meta-analysis of the trials showed no significant difference between the interventions (*RR* = 1.20, 95% *CI*: 0.92−1.56, $P = 0.17$) (Fig. 4). Adverse events were reported in 33.2% (77/232) of patients treated with probiotics and in 27.6% (66/239) of patients treated with aminosalicylates. Adverse events included symptoms such as bloody stools,

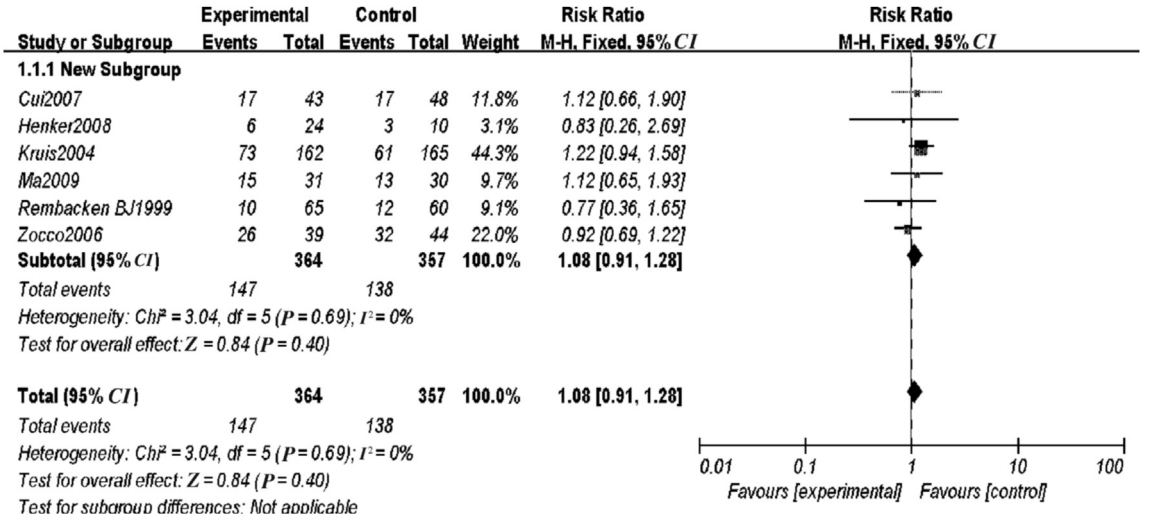

Fig. 2. The forest plot of relapse rate of probiotics group versus control group.

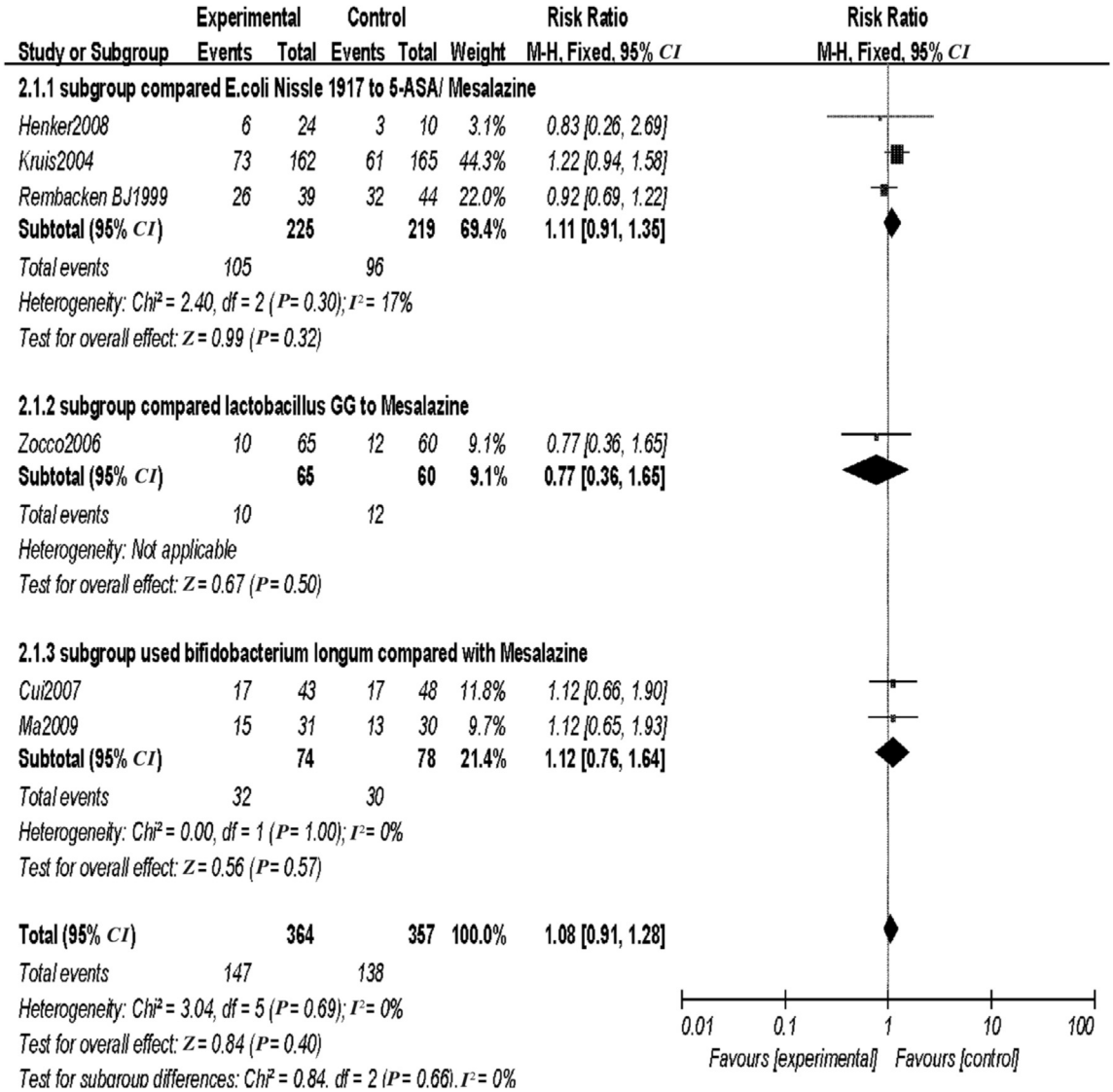

Fig. 3. The forest plot of relapse rate of diffident probiotic group versus control group (subgroup).

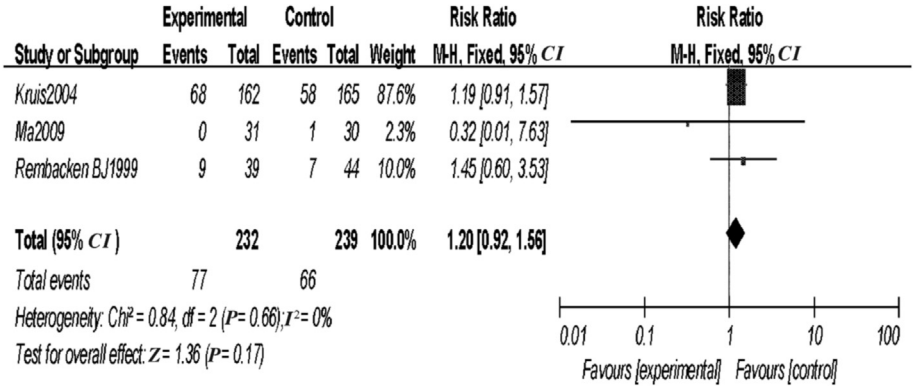

Fig. 4. The adverse events between probiotics and control group.

diarrhea, and abdominal pain. Non-intestinal adverse events included headaches, nausea, or viral infections.

Qualitative evaluation of publication bias

An inverted funnel plot can analyze the results of a fixed-effects model. Fig. 5 shows a symmetrical inverted funnel plot, indicating that there was no visible publication bias in the relative remission rates between the probiotics group and control group.

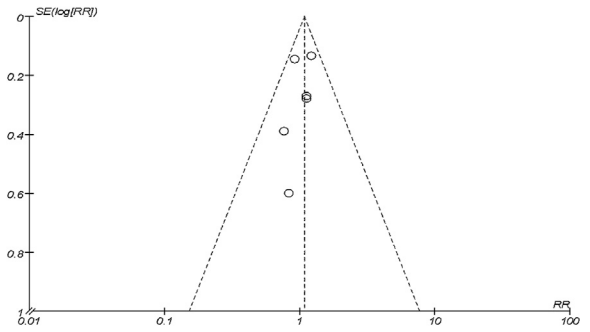

Fig. 5. Inverted funnel plot analysis of the relative of remission rate between probiotics group and control group.

Discussion

UC is a chronic relapsing disease that mainly affects the large bowel, which can negatively affect patients' quality of life. The ideal definition of relapse prevention includes longer symptom-free intervals with fewer adverse events. Standard maintenance therapy involves a variety of treatments including aminosalicylates, biological agents, and immunosuppressant therapy. However, these treatments are expensive, and have potential adverse events and high non-adherence rates, and as such, alternative medications are required. Probiotics are thought to have fewer adverse effects than current medications and have been proposed as an alternative treatment option. Recent evidence has supported the potential therapeutic role of probiotics in the treatment of UC. Several mechanisms have been proposed, including inhibiting the growth of pathogenic bacteria,[27] reinforcing the function of intestinal barriers,[28] and protecting immune responses through immunization.[29] However, the clinical results of probiotic treatments for UC are still unclear. Thus, more research is required before probiotics can be accepted as a standard medication for treating UC.

The results from this meta-analysis showed that probiotics reduced the recurrence of UC and might be as effective as aminosalicylates. To study the effect of different species of probiotics (*E. coli* Nissle 1917, *Lactobacillus* GG, *B. longum*) on maintaining the remission of UC, we divided the pooled trials into 3 subgroups. None of the studies showed significant difference in the maintenance effect between experimental groups and control groups. However, the number of patients in the pooled analysis was relatively small; therefore, it is difficult to conclude if probiotics can have a meaningful impact in clinical practice.

Persborn et al[28] observed the effect of probiotics on barrier function and mucosal pouch microbiota in cases of UC, and found that probiotics restored the mucosal barrier of *E. coli* and horseradish peroxidase in patients with pouchitis, which may influence the prevention of UC recurrence during maintenance treatment. Adam et al[30] showed that the maintenance effect of the probiotic *E. coli* Nissle on UC was as effective as standard mesalazine. Other studies found that *E. coli* Nissle can prevent the intrusion of *Salmonella typhimurium* to the intestinal tract, inhibit the intrusion of pathogenic enterobacteria,[31] and reduce intestinal flora constituents in patients with UC.[32] Thus, there is evidence to support the efficacy of *E. coli* in UC maintenance treatment.

Kato et al[20] found that supplementation with bifidobacteria-fermented milk products is safe, and more effective than conventional treatments alone in patients with active UC. Cui et al[33] also observed that bifidobacteria can impede the activation of nuclear factor-κB, decrease the expressions of tumor necrosis factor-α and interleukin-1β, and elevate the expression of interleukin-10 in patients with UC. These results suggest that bifidobacteria are effective in preventing flare-ups of chronic UC and may have potential in UC maintenance treatment.

VSL#3, a mixture of eight different probiotic bacteria, has successfully been used in the clinic to treat UC. Some *in vitro* studies have implicated that VSL#3 can suppress lipopolysaccharide-induced chemokine production by inhibiting signal transducer and activator of transcription 1 phosphorylation.[34] Mariman et al[35] studied C57BL/6 and BALB/c mice, and found that VSL#3 mediated both pro- and anti-inflammatory responses in bone marrow-derived dendritic cells. Dai et al[36] demonstrated that VSL#3 exerted anti-inflammatory activity via the phosphoinositide 3-kinase/protein kinase B and nuclear factor-κB pathway in a rat model of dextran sulfate sodium-induced colitis. A meta-analysis[37] of VSL#3 added to conventional therapies (at a daily dose of

3.6×10^{12} CFU/d), found that VSL#3 combination therapy was safe, and more effective than conventional therapy alone in achieving higher responses and remission rates in mild to moderately active UC.

Kumar et al[38] reported that when histopathological changes were induced by trinitrobenzenesulfonic acid, *Lactobacillus* attenuated the macroscopic colonic damage. Furthermore, Lactobacillus significantly decreased thiobarbituric acid reactive substances and nitric oxide production and increased glutathione concentrations, as well as down-regulated the expressions of interleukin-1β and tumor necrosis factor-α, whereas protein and mRNA expression of interleukin-10 were up-regulated. A randomized clinical trial[39] with children having active distal UC was conducted and rectal infusion of *Lactobacillus reuteri* was found to be effective in improving mucosal inflammation and altering mucosal expression levels of some cytokines involved in the mechanisms of inflammatory bowel disease. Thus, there is evidence that *Lactobacillus* may be a useful medication in the treatment of UC.

Probiotics appear to be well tolerated. No difference in the incidence of adverse events was observed between probiotics and aminosalicylates. In a meta-analysis of adverse events performed by Naidoo et al,[15] no statistically significant difference in the incidence of side effects was observed between the probiotic group and the mesalazine group on maintaining the remission of UC. Serious adverse effects from probiotics are rarely reported because they are well tolerated and safe.[40] These findings indicate that probiotics are very safe in clinical usage.

Future studies on the value of probiotics for the maintenance of remission in patients with UC should consider the effects of different kinds of probiotics, as different types of UC may benefit from probiotic use.

Several limitations exist in our meta-analysis. Firstly, we cannot eliminate publication bias, despite attempting to find both positive and negative results. Second, only six trials satisfied the inclusion criteria and were included in our study. Moreover, the number of patients included in these studies is relatively small, and thus they are not considered optimal-quality studies. Third, there are limited reports of side effects in the included studies (only three articles mentioned any). Fourth, mixed probiotics, such as VSL#3, may be more effective than singular probiotics; however, we did not find any RCTs that compared mixed probiotics with aminosalicylates. Lastly, the majority of the studies we analyzed did not indicate the type of UC or whether patients had multiple treatments. The initial treatments of mild UC often show self-healing tendencies, and therefore, it may be more significant to compare the maintenance effect of medications in patients with moderate to severe UC.

In conclusion, probiotics, as well as aminosalicylates, showed therapeutic effects on UC. However, the number of patients in the studies analyzed was relatively small, the quality of the RCTs was inadequate, and there was no information regarding whether patients were receiving initial treatments or multiple treatments. Thus, more well-designed RCTs are required.

Conflicts of interest

The authors declare that they have no conflicts of interest concerning this article.

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