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Original Article

Effect of probiotic for maintenance of remission in adult ulcerative colitis: a meta-analysis

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Abstract: Purpose: Ulcerative colitis (UC) is a relapsing inflammatory bowel disease (IBD) with unknown aetiology. Studies suggest that probiotic could prove treatment effective for UC. The aim of this meta-analysis was to rationally evaluate the effect of probiotics for maintenance of remission in adult UC patients. Materials and methods: Medline, Embase, the Cochrane Controlled Trials Register, and China Journal Full text Database were retrieved for eligible clinical randomized controlled trials. Results: Seven randomized controlled trials met the inclusion criteria. Compared with non-probiotics group, the overall relapse rate of probiotics in maintaining remission in UC patients was no statistically significant difference (OR = 0.79, 95% CI 0.58-1.08, *P* = 0.14). Then we performed subgroup analysis, it showed a significant reduction in relapse rate in probiotics compared with placebo group (OR = 0.07, 95% CI: 0.02-0.26, P < 0.0001), but not with mesalazine group (OR:1.03, 95% CI 0.69-1.53, *P* = 0.89), and Bifidobacteria (OR = 0.03, 95% CI: 0.00-0.15, P < 0.0001) had a better therapeutic effect than E. coli (OR = 1.11, 95% CI: 0.72-1.74), *P* = 0.63) compared with non-probiotics group; there had no significant difference in maintaining remission of active UC (OR = 0.49, 95% CI: 0.09-2.57, *P* =0.40) than that of inactive UC (OR = 0.99, 95% CI 0.65-1.52, *P* = 0.98).The frequency of adverse effects was no significant difference (OR = 1.16, 95% CI: 0.92-1.47, p=0.22) in two groups. Conclusion: The present studies suggested that probiotics were not more safe and effective than mesalazine in maintenance remission of UC, but maybe more effective in maintaining remission in UC than placebo.

Keywords: Ulcerative colitis, probiotics, randomized controlled trail, meta-analysis

Introduction

Ulcerative colitis (UC) is a relapsing inflammatory bowel disease (IBD) characterised by bloody diarrhea and abdominal pain. Although it is assumed to be associated with infection, genetic, immune, food, environmental and psychological factors, the precise mechanisms underlying its pathogenesis remains unknown. Recently mounting studies suggested that dysfunction of the intestinal microbiota contributes to the pathogenesis of UC.

Mostly UC patients experience acute exacerbations and remission alternately. Maintenance of remission is important in UC treatment because up to 76% of patients relapse within a year without treatment [1], and many patients must be treated by surgery after recurrent attacks. Current effective maintenance treatment in UC is immunosuppressive agents [2-4]. However, the treatment is not always effective, and it has potential serious side effects that many patients cannot tolerate. Consequently treatments with better curative effect and fewer side-effects are needed.

Probiotics were defined as live microorganisms that was non-pathogenic to body and beneficial to the host's intestinal environment by regulating intestinal flora, thereby stabilizing the intestinal environment [5, 6]. It have been proved that probiotics was effective in the management of pouchitis [7, 8]. Many studies have indicated that probiotic preparations have positive effects for treating gastrointestinal diseases, including UC [9-11]. Several studies indicated that certain bacterial strains may be beneficial for maintenance of remission in UC, but one reported that it had no effects on relapse rates [12-15]. However, the data were derived from

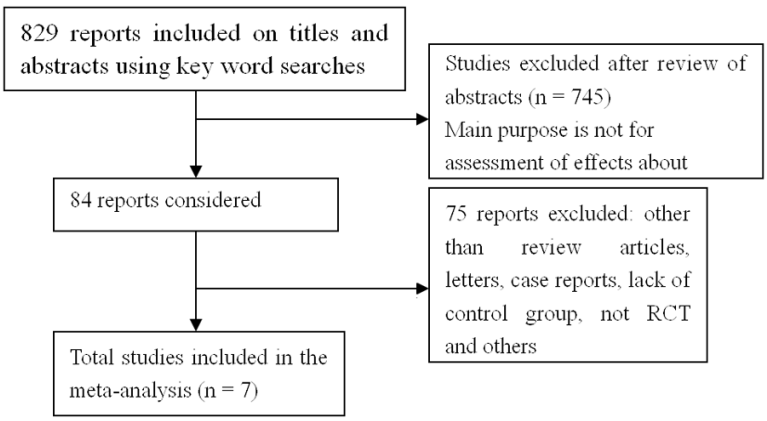

Figure 1. Flow diagram for studies evaluating probiotic for maintenance of remission in adult ulcerative colitis that were included in this meta-analysis.

relatively little studies, which were not sufficient to provide definitive evidence.

The objective of this paper was to systematically evaluate probiotics' curative effects for maintenance of remission in adult UC patients based on data of random control trials.

Materials and methods

Search strategy

Eligible studies comparing the effects of probiotics with those of anti-inflammatory drugs or placebo for UC treatment were searched from Medline, Embase, the Cochrane Controlled Trials Register and China Journal Full text Database up to 1 may 2013. The language was limited to English and Chinese. The keywords used were below: inflammatory bowel disease, ulcerative colitis, probiotics, Escherichia coli, Lactobacillus, saccharomyces, Bifidobacterium, and yeasts. Moreover, we searched the reference lists of pertinent manuscripts in order to identify other potentially relevant articles.

Criteria for study selection

The inclusion criteria were as follows: (1) all were random control tests; (2) focused on adults; (3) the experiments compared probiotic use for the maintenance of remission with standard therapy or placebo for UC; (4) full texts were selected. Preclinical studies, reviews and case reports, not in the disease being studied were excluded.

Data extraction

Two reviewers selected the papers and evaluated the quality of selected papers, then extracted the data independently. A third person was consulted if there were any disagreements. Data on details pertaining to the patients, number of patients at the start of the study and completed subjects, treatment type, outcomes, adverse effects were extracted.

Methodological quality appraisal

The qualities of the selected data were assessed by the "risk of bias" method recommended by the Cochrane Collaboration [16]. The methodological quality of each study was evaluated according to the following items: (1) The adequacy of the randomization; (2) Allocation concealment; (3) Blind method; (4) ether lost or exit.

Statistical analysis

Statistical analyses were conducted by using the Review Manager Version 5.1 of Cochrane Collaboration. Relative risk (RR) and 95% confidence intervals (95% CI) were calculated as summary statistics. The estimate of RR from individual studies was calcultaed. Statistically heterogeneity was assessed by using the I^2 test to quantify heterogeneity across studies. If the results of heterogeneity were significant, the random effects model was used to perform analysis. Or else, the fix effects model was employed. Statistical significance was indicated by a *P* values less than 0.05.

Results

Characteristics of eligible studies

A total of 829 papers were initially identified by using the search strategy mentioned above. After a thorough screening of the papers, 7 studies were ultimately selected based on the inclusion/exclusion criteria (**Figure 1**). All of the eight papers assessed the recurrence rate, and two papers evaluated both the recurrence rate and remission rate. The duration of the research was 8 weeks to 12 months. The number of patients in each of including studies ranged from 22 to 327. All the papers were published in English. The Characteristics of the selected research were presented in **Table 1** [17-23].

Table 1. Characteristics of included studies

Study	Probiotic	Control group	Disease severity	Dose (n of probiotic/day)	Treatment duration	N (probiotic/ control group)	Maintenance of remission N (probiotic/ control group)
Kruis et al [17] 1997	E. coli Nissle 1917 serotype O6: K5: H1	Mesalazine	Inactive	50×10^9	12 wk	50/53	42/47
Rembac-ken et al [18], 1999	E. coli Nissle 1917 serotype O6: K5: H1	Mesalazine	Active	5×10^{10}	12 mo	36/43	10/11
Ishikaw-a et al [19], 2003	Bifidobacterium Breve Bifidobacterium Bifidum Lactobacillus acidophilus YIT 0168	BFM without these Bifidobacteria	Mild-to-moderate	10×10^8	12 mo	11/10	8/1
Cui et al [20], 2004	Bifidobacteria	Starch	Active	1.26 g/d	8 wk	15/15	12/1
Kruis et al [21], 2004	E. coli Nissle 1917	Mesalazine	Inactive	$2.5\text{-}25 \times 10^9$	12 mo	110/112	70/74
Zocco et al [22], 2006	Lactobacillus GG	Mesalazine	Inactive	18×10^9	12 mo	65/60/62	55/48/52
Wildt et al [23], 2011	Probio-Tec AB-25 (Lactobacillus acidophilus La-5 Bifidobacterium animalis subsp. lactis BB-12)	Placebo	Inactive	2.5×10^{10}	52 wk	20/12	5/1

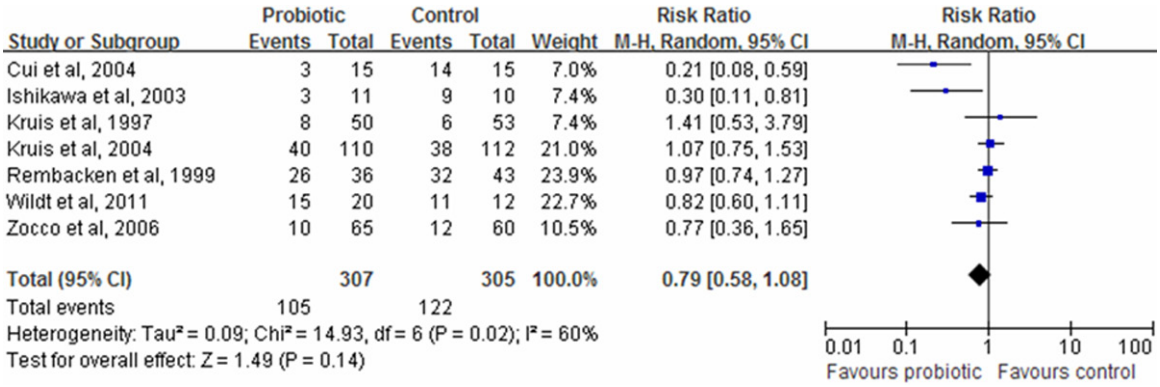

Figure 2. Relapse rate of probiotic group vs control group.

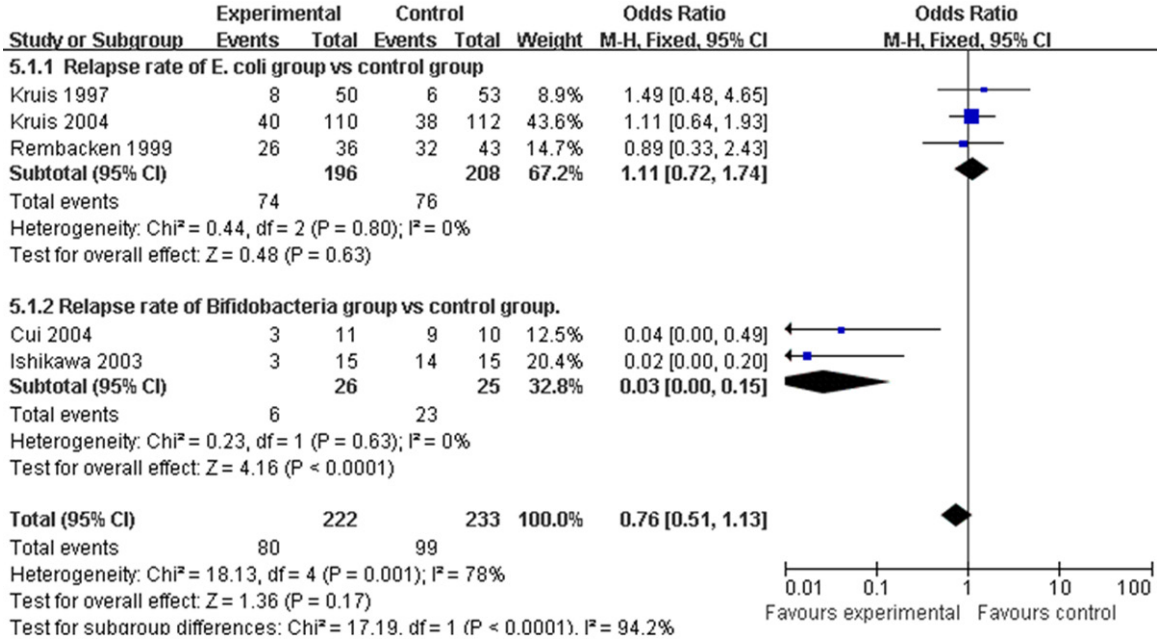

Figure 3. Relapse rate of E. coli group vs control group and Bifidobacteria group vs control group.

Two studies used E. coli to be compared with mesalazine in inactive UC and one in active [17, 18, 21]. One study compared *Bifidobacteria* with placebo in patients with active UC and one compare them in mild to moderate UC [19, 20]. One study compared Lactobacillus GG alone or plus mesalazine with mesalazine [22]. One study used VSL#3 to be compared with placebo in patients with mild to moderate UC [23]. One study used Probio-Tec AB-25 to be compared with placebo in inactive UC [23].

Total effect of probiotics for maintenance of remission of ulcerative colitis

Among 612 patients included in seven reports, 307 of them received probiotics for maintenance treatment, and 305 received control medicine or placebo. Two studies reported a significantly higher maintenance rate of remission for UC in the probiotics treatment group than the control group [19, 20], four reports showed a trend of efficacy in the probiotics group and one did not show any significant difference [17, 18, 21-23], and one did not show any significant difference [17, 18, 21-23]. The total recurrence rate of UC in the probiotics maintenance therapy group was 34.2% and that in the control group was 40.0%. The pooled relative risk for the seven studies was 0.79 (95% CI 0.58-1.08, P = 0.14) (**Figure 2**). It showed there was no statistically significant difference between probiotic and control gro-

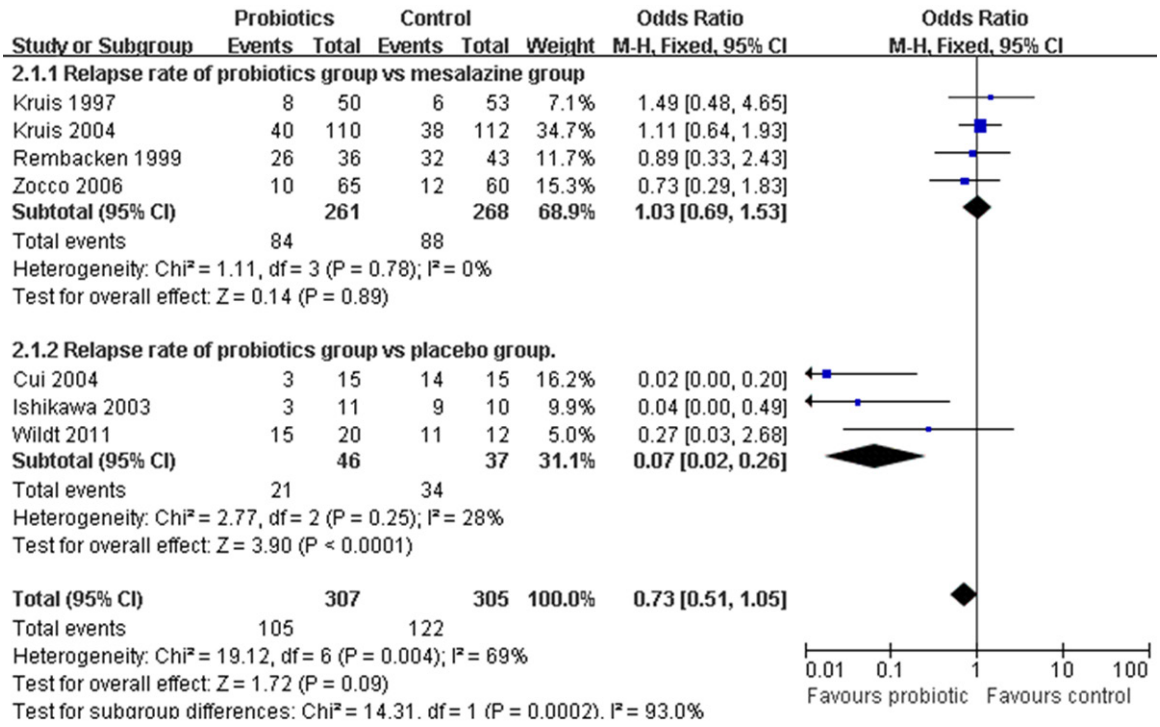

Figure 4. Relapse rate of probiotics group vs placebo group/mesalazine group.

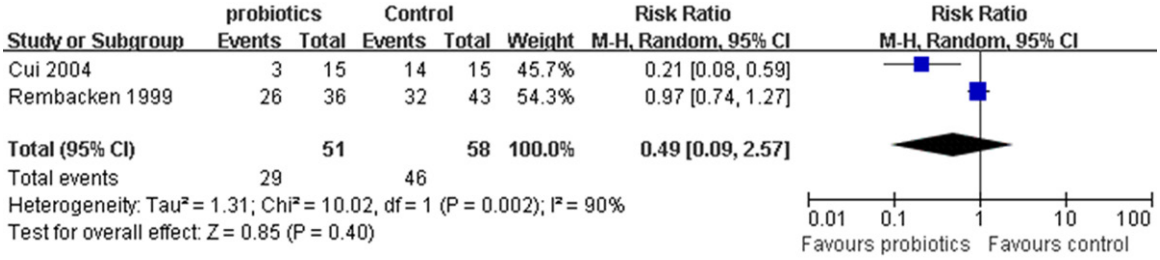

Figure 5. Relapse rate of probiotics group vs control group in active UC.

ups. The heterogeneity was detected between studies (I^2 = 60%).

Subgroups of studies

Type of probiotic and ulcerative colitis: There were four kinds of probiotics reported in included studies. Three studies reported *E. coli* and one reported *Lactobacillus*, both of which had equivalent effect to mesalazine for maintenance of remission in UC patients [17, 18, 21, 22]. Two reports showed that *Bifidobacteria* had more efficacy than placebo. One did not show Probio-Tec-AB-25 had any significant difference with placebo [19, 20, 23]. *E. coli* did not improve the effect significantly compared with control [OR: 1.11, (95% CI: 0.72-1.74), P = 0.63, I^2 = 0%] (**Figure 3**). But *Bifidobacteria* was significantly more effective than the control group (OR = 0.03, 95% CI: 0.00-0.15, P < 0.0001, I^2 = 0%) (**Figure 3**).

Probiotics vs mesalazine and vs placebo: Among seven studies, four reports compared probiotics with mesalazine and three articles compared probiotics with placebo. The included studies were then separated into a placebo control subgroup and a meselazine control subgroup. The pooled OR of the placebo control sub-group was 0.07 (95% CI: 0.02-0.26, P < 0.0001, I^2 = 28%) (**Figure 4**), showing a significant difference for maintenance of remission between probiotic and placebo. The mesalazine control subgroup's pooled OR was 1.03

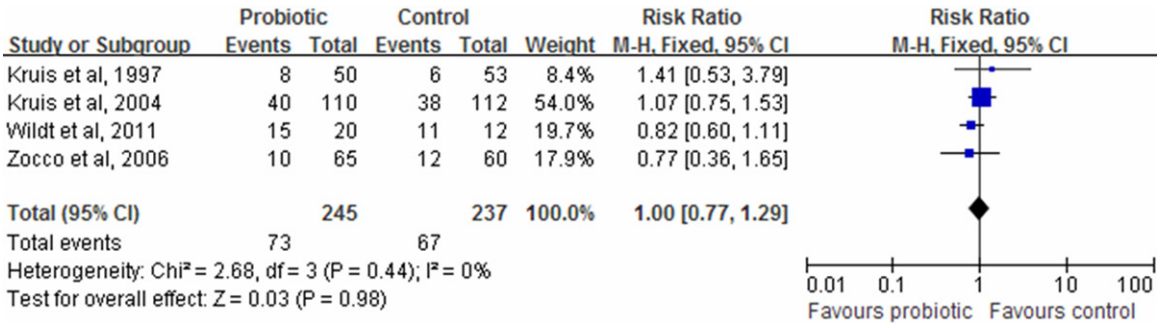

Figure 6. Relapse rate of probiotics group vs control group in inactive UC.

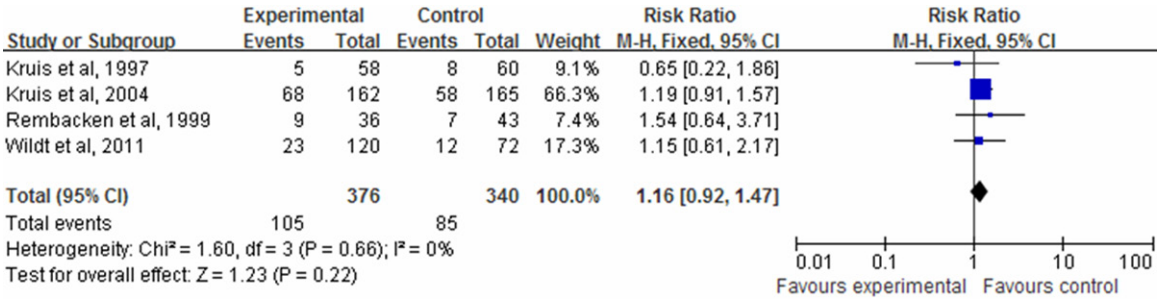

Figure 7. Adverse effects of probiotics group vs control group.

(95% CI 0.69-1.53, $P = 0.89$, $I^2 = 0\%$) (**Figure 4**), showing no significant difference between probiotic and mesalazine treatment. Both of heterogeneity was not significant.

Probiotics and severity of ulcerative colitis: Four studies compared probiotics with control treatment for inactive UC and two performed such comparison for active UC [17, 18, 20-23]. The included studies were then separated into an inactive UC subgroup and an active UC subgroup. The pooled RR of the active UC subgroup was 0.49 (95% CI: 0.09-2.57, $P = 0.40$, $I^2 = 90\%$) (**Figure 5**), showing no significant difference between probiotics with control treatment for maintenance of remission for active UC and heterogeneity was obvious. The inactive UC subgroup's pooled RR was 0.99 (95% CI 0.65-1.52, $P = 0.98$, $I^2 = 0\%$) (**Figure 6**), also showing no significant difference between them for inactive UC and heterogeneity was insignificant.

Adverse effects

Four of seven trials (71.4%) presented data on adverse effects, which were included in our analysis [17-19, 21-23]. The pooled RR of adverse effects for the four studies was 1.16 (95% CI: 0.92-1.47, P = 0.22) (**Figure 7**), showing no significant difference between probiotics and control treatment. A insignificant heterogeneity was found ($I^2 = 0\%$).

Publication bias assessment

Publication bias was assessed by funnel plot. The funnel plots showed asymmetry (**Figure 8**), indicating that there was publication bias among selected studies, which might be caused by a language bias, flawed methodological design, smaller studies, and/or a lack of publication of studies with opposite results.

Discussion

According to the results of this study, probiotics provided no additional benefit in maintenance of remission of UC compared with control treatments. A significant heterogeneity was found in total relapse rate analysis. The contradictory results might be related to methodological differences among selected studies, such as the type of probiotics used, the duration of treatment, the types of UC, the difference in the control groups, medication compliance of patients, and patient behavior. The simultaneously use of antibiotics together with probiotics, the analysis of the results, and the sample size may also cause heterogeneity for probiotic trials.

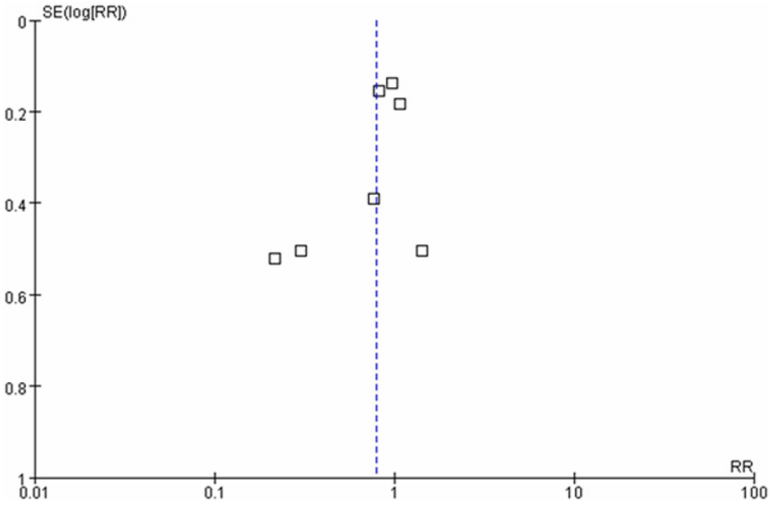

Figure 8. Publication bias was assessed by funnel plot.

It has been reported that different types of probiotic had different effectiveness for maintenance of remission of UC [24, 25]. Subgroup analysis demonstrated that *Bifidobacteria* were likely to be effective for maintenance of remission of UC. However, *E. coli* did not improve effect significantly compared with mesalazine. *Bifidobacteria* may not only normalize the intestinal flora and decrease the relative number of *B. vulgatus* (percentage) in bacteroidaceae in faeces [19], but also could impede the activation of NF-kB, decrease the expressions of TNF-α and IL-1β and elevate the expression of IL-10 [20]. In addition, *Bifidobacteria* may improve epithelial function via increasing concentrations of faecal short chain fatty acids (SCFAs) [26], which are the major energy source for colonocytes and may suppress proinflammatory cytokines through the inhibition of NF-kB activation to regulate immunological [27]. All three trials with *E. coli* included in present study compared the effectiveness of probiotic with mesalazine, while trials for bifidobacteria compared the effectiveness of probiotic with placebo. As a consequence, it was difficult to conclude whether *E. coli* is effective in maintenance remission of UC or not.

The therapeutic effect of probiotics was not significantly different with that of mesalazine, but was obviously better than that of placebo group. It may be related to the different types of probiotics which were employed in different studies. Three of four trials in the mesalazine group used *E. coli* and two of three used *Bifidobacteria* in placebo group as a probiotic. As mentioned above, Bifidobacteria showed better effect than *E. coli*. However, the results showed a similar effectiveness between probiotics and mesalazine. In addition, probiotics was showed to provide beneficial in maintaining remission of UC.

Subgroup analysis demonstrated that the probiotics group was showing no significant difference in maintaining remission of active UC than that of inactive UC. A significant heterogeneity was found in active UC group. It may be due to the number of patients included in active UC was relatively small. And simultaneously use of other medicine together with probiotics may also provide contributions to the result.

Safety is an equally important consideration for efficacy of any treatment. Considering that probiotics are living microorganisms given to patients, there may be risk to adverse reactions to UC patients. The majority of adverse events reported in the studies we evaluated were gastrointestinal disorders (bloody stools, nausea, diarrhea), abdominal pain, non-intestinal adverse events (viral infections, nausea, headache). Concerning the adverse effects, there were no significant differences between probiotics and the control treatment. Since no significant heterogeneity was detected among studies, it seemed that the kinds of probiotic, the severity of UC, methodological differences, or other differences of the trails were not likely to influence the overall significant level of the adverse effects.

Probiotics were supposed to be effective for many cause of diarrhoea both in children and adult since it can resist gastric acid, bile, antibiotics, and also modify immune processes to normalize the intestinal flora [28-31]. Compared with many pharmaceutical treatment, probiotics does not affect the function of normal mucosa during active therapy, and rarely induce serious adverse effects because they are well tolerated and safe [25, 32]. Moreover, probiotics must be nonpathogenic in order to overcome potential gastrointestinal infections.

The results of the present study suggested that probiotics are not more safe and effective than control treatment in maintenance of remission of UC. However, the results showed that there was a significant heterogeneity. According to subgroup analysis on the kind of probiotic, the serious of UC, or the control treatment, probiotics may be more effective.

In conclusion, whether the use of probiotics is safer and effective in reducing relapse than non-probiotics therapy is still not uncertain and desired to be further investigated in clinical research by large number of well-designed RCTs.

Disclosure of conflict of interest

None.

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