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**Columns:** **META-ANALYSIS**

**Effectiveness of probiotics in all subtypes of irritable bowel syndrome: An updated systematic review with meta-analysis**

Didari T *et al.* Effectiveness of probiotics in IBS

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**Abstract**

**AIM**: To investigate the efficacy of probiotics in irritable bowel syndrome (IBS) patients, this meta-analysis was performed.

**METHODS**: For literature review PubMed, Cochrane library, Scopus, Google scholar and Clinicaltrial.gov were searched from September 2007 up to December 2013. The applied Mesh terms were “probiotics”, ”irritable bowel syndrome” and “irritable bowel syndrome treatment”. The collected data contained twenty-four clinical trials which fifteen were eligible for meta-analysis and nine were reviewed systematically. All studies were randomized placebo-controlled trials in patients with IBS that investigated the efficacy of probiotics in IBS improvement. Jadad score was used to assess the methodological quality of trials. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3. Relative Risk (RR) and Standardized effect size 95%CI and were calculated using Der Simonian-Laird method. Cochran *Q* test was used to test heterogeneity with P value 0.05 (*P* < 0.05). Egger and Begg-Mazumdar tests in funnel plot were calculated as publication bias indicators.

**RESULTS**: A total of 1793 patients were included in meta-analysis. The summary for RR of responders to therapies based on abdominal pain score in IBS patients for two included trials comparing probiotics to placebo was 1.96 with 95%CI: 1.14-3.36 (*P* = 0.01). RR of responders to therapies based on GSS in IBS patients for two included trials comparing probiotics with placebo was 2.43 with 95%CI: 1.13-5.21 (*P* = 0.02). For adequate general symptoms improvement in IBS patients the summary for RR of seven included trials comparing probiotics with placebo in six studies was 2.14 with 95%CI: 1.08-4.26 (*P* = 0.03). Distension, Bloating and Flatulence (DBF) were evaluated by IBS severity scoring system in three trials in two studies to compare the effect of probiotics therapy in IBS patients with placebo. The summary of standardized effect size of mean differences of DBF “∆DBF” for probiotics therapy was -2.57 with 95%CI: -13.05-(-7.92) (non- significant effect).

**CONCLUSION:** Probiotics reduced pain severity, symptom severity score. Collectively, the results demonstrated the beneficial efficacy of probiotics in IBS patients in comparison with placebo.

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**Key words;** Probiotics; Irritable bowel syndrome; Clinical trial; Meta-analysis; Irritable bowel syndrome; Systematic review; Meta-analysis; Evidence-based medicine

**Core tip:** Irritable bowel syndrome (IBS) is a gastrointestinal tract dysfunction with complicated etiology. Probiotics may influence IBS symptoms. The present meta-analysis included 1793 patients with all subtypes of IBS from fifteen randomized, double-blind clinical trials conducted during 2007-2013. Use of different scales to analyze the mean differences of symptoms in various studies has been the main limitations of all meta-analyses in IBS including the present one. Thus, further clinical trials are still needed to conclude the effectiveness of probiotics on special major IBS symptoms of patients. Probiotics may have beneficial therapeutic role in IBS patients in definite duration of administration.

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**INTRODUCTION**

Irritable bowel syndrome (IBS) is a gastrointestinal (GI) tract dysfunction with complicated etiology[1]. Prevalence of IBS varies between Asian and North American societies but the total range in general population is estimated 5%-11%[2-4]. Besides the interference with daily life of patients and caregivers, socioeconomic costs of IBS have been raised, as the majority of IBS patients are young population between 20 to 39 years old[2].

Abdominal pain, stool pattern alteration, distention, bloating, straining, abdominal discomfort and urgency are major symptoms observed in IBS[5,6]. Genetics background and environmental factors, history of inflammatory bowel disease (IBD) in a family member, psychological positions as stressful social activities are involved in the pathogenesis of IBS[7]. The level of severity score in patients with IBS depends on different factors such as chronic immunity reactions after intestinal microbiome alteration, visceral hypersensitivity associated with gut-brain pathways and impaired bowel permeability. It is believed that initiation of IBS in some people is associated with a post microbial infection[8,9]. However, the precise cause of IBS is unrecognized to date[10-14].

Pharmacologic, psychological, and complementary approaches are considered as therapeutic options in IBS patients[15]. Pharmacological medications include antispasmodics, selective serotonin reuptake inhibitors (SSRIs)[16], tricyclic antidepressants[17], 5-hydroxytryptamine type-3 (5-HT3) antagonists such as ramosetron and alosetrone[18], lubiprostone and linaclotide[19]. However, due to lack of favorable efficacy and associated adverse events with pharmacological treatments, some IBS patients look for alternative treatments such as herbal medications and Chinese acupuncture[2,20-22]. Probiotics are live microorganisms which have been demonstrated to exhibit potential effects on human health[23]. Probiotics may influence the IBS symptoms including abdominal pain, bloating, distension, flatulence, altered bowel movements and gut microbiota[24].

The nature of probiotics explains their beneficial role in intestinal function as they can protect against pathogenic bacteria via their antimicrobial properties[25]. Probiotics also amplify the intestinal tight junctions and stabilize the permeability. Moreover, probiotics stimulate goblet cells to produce mucus leading to enhance the intestinal barrier function, normalize bowel movements, and reduce visceral hypersensitivity[25] in pediatric and adult patients[26,27]. Several probiotics strains showed beneficial outcomes in IBS patients[28,29]. The present study was performed to update the previous meta-analysis[30] considering further clinical trials. A systematic review has been also conducted to assess the efficacy of probiotics in IBS patients in clinical trials that were not eligible for inclusion in meta-analysis.

**MATERIALS AND METHODS**

***Data sources***

In order to perform meta-analysis on the efficacy of probiotics in IBS management PubMed, Cochrane library, Scopus, Google scholar and Clinicaltrial.gov were searched from September 2007 up to December 2013. The applied Mesh terms were “probiotics”, ”irritable bowel syndrome”and “irritable bowel syndrome treatment”.

***Study selection***

Three reviewers inspected the topic and abstracts of all articles to eliminate identical studies, review articles, systematic reviews and meta-analysis investigations. All relevant characteristics of included trials such as IBS type, probiotics strain, dose of probiotics, trial and follow up duration, patient’s characteristics and outcomes were collected and summarized. All randomized controlled trials which considered IBS symptoms improvement as outcome of interest were included. The reference lists of searched articles were reviewed for further eligible articles.

***Assessment of trial quality***

Jadad score, which indicates the quality of studies based on their description of randomization, blinding, and dropouts (withdrawals) was used to assess the methodological quality of trials[31]. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

***Statistical analysis***

Data from selected studies were extracted in the form of 2 × 2 tables by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using Statsdirect software version 3.0.107. Relative Risk (RR) and 95% confidence intervals (95%CI) were calculated using DerSimonian-Laird (for random effects) method. Standardized effect size and 95% confidence intervals (95%CI) were calculated using Der Simonian-Laird (for random effects) methods. The Cochran Q test was used to test heterogeneity and *P* < 0.05 considered significant. In case of heterogeneity or few included studies, the random effects model was used. Egger and Begg-Mazumdar tests were used to evaluate publication bias indicators in funnel plot.

**RESULTS**

Based on the electronic search, 11748 publications were identified. The time arrangement (2007-2013) was applied to update the efficacy of probiotics in IBS. A total of 8719 studies found inappropriate because they did not clearly meet our inclusion criteria. The remained studies with lack of control group, using herbal medication in combination with probiotics, or combination of probiotics/prebiotics and unsuitable details about inclusion criteria were excluded. Furthermore, one trial that had applied likert score, two trials that were performed in pediatric patients and two cross-over trials were excluded (Figure 1). Fifteen trials met our criteria for meta-analysis. Rome criteria, ICHPP and WONCA were applied to include IBS patients. Seven trials with Rome II criteria, six with Rome III criteria and two with ICHPP and WONCA criteria were determined. The quality score of included trials were assessed and reported according to Jadad quality score. All trials had high quality with range of 3 to 5 score (Table 1). A total of 1793 patients with diarrhea predominant IBS (D-IBD), constipation predominant IBS (C-IBS) and alternative IBS (A-IBS) were included.

The characteristics of studies are scrutinized in Table 2. Nine other clinical trials which were not applicable for our meta-analysis were reviewed systematically. The characteristics and outcomes of these trials have been summarized in Table 3.

***Results of meta-analysis***

**Pain assessments in IBS patients for comparison of probiotics to placebo therapy:** Abdominal pain severity was evaluated by IBS severity scoring system in one study for 8 and 10 wk to compare the effect of probiotics therapy in IBS patients with placebo[32]. The reduction of abdominal pain severity was -23.42 ± 30.05 and -17.19 ± 27.73 for probiotics therapy group in 8 and 10 wk, respectively from baseline and -12.29 ± 30.08 and -8.06 ± 27.98 for placebo group at the same duration of therapy.

In another study that abdominal pain severity had been assessed by a 6-mo symptom diary with a 0 to 4 scale, the mean of severity reduction was -3 ± 9.95 in probiotics group in comparison with placebo therapy with mean of 0 ± 10.27[33].

**Abdominal pain improvement:** The RR for abdominal pain improvement in one trial was 1.1 with 95%CI of 0.77-1.60, a non-significant RR[34].

**Responders to therapies based on abdominal pain score:** The summary for RR of responders to therapies based on abdominal pain score in IBS patients for two included trials comparing probiotics to placebo was 1.96 with 95%CI: 1.14-3.36 (*P* = 0.01, Figure 2A)[35,36]. The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (*P* = 0.11, Figure 2B) and could be combined but because of few included studies, the random effects for individual and summary for RR was applied.

**Abdominal pain score by visual analogue scale:** The summary for standardized effect size of mean differences of abdominal pain score by visual analogue scale (VAS) ranging from 0-10 in IBS patients “∆AP” for probiotics therapy for two included trials comparing with placebo was -0.56 with 95%CI: -1.29-0.16 (*P* = 0.13, Figure 3)[37,38]. The Cochrane *Q* test for heterogeneity indicated that the studies are not heterogeneous (*P* = 0.73) and could be combined but because of few included studies, the random effects for individual and summary of effect size for standardized mean was applied.

In one study that abdominal pain score was evaluated by ranging of 0-100 of VAS, the mean score reduction was -7.65 ± 9.69 in probiotics group in comparison with placebo therapy with mean of -0.98 ± 7.67[39].

***Distension / Bloating / Flatulence assessments in IBS patients for comparison of probiotics to placebo therapy***

**Distension / Bloating / Flatulence:** Distension / Bloating / Flatulence (DBF) were evaluated by IBS severity scoring system in three trials in two studies to compare the effect of probiotics therapy in IBS patients with placebo[32,40]. The summary of standardized effect size of mean differences of DBF “∆DBF” for probiotics therapy was -2.57 with 95%CI: -13.05-7.92 (*P* = 0.63, Figure 4). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (*P* = 0.64) and could be combined but because of few included studies the random effects for individual and summary of effect size for standardized mean was applied.

In another study that DBF had been assessed by a 6-mo symptom diary with a 0 to 4 scale, the mean severity reduction was -4 ± 11.36 in probiotics group in comparison to placebo therapy with mean of -2 ± 11.2[33].

**Flatulence improvement:** The RR for flatulence improvement in one trial was 1.2 with 95%CI of 0.85-1.77, a non-significant RR[34].

**Bloating improvement by VAS:** In one study that bloating improvement was evaluated by ranging of 0-100 of VAS, the mean score reduction was 0.34 ± 6.49 in probiotics group in comparison to placebo therapy with mean of 0.44 ± 5.25[39].

**Bowel habit dissatisfaction:** Bowel habit dissatisfaction (BHD) was evaluated by IBS severity scoring system in three trials in two studies to compare the effect of probiotics therapy in IBS patients with placebo[32,40]. The summary for standardized effect size of mean differences of BHD “∆BHD” for probiotics therapy was -5.31 with 95%CI: -13.87-3.25 (*P* = 0.22, Figure 5). The Cochrane *Q* test for heterogeneity indicated that the studies are not heterogeneous (*P* = 0.66) and could be combined but because of few included studies the random effects for individual and summary of effect size for standardized mean was applied.

***IBS improvement assessments in IBS patients for comparison of probiotics to placebo therapy***

**Global score improvement:** IBS improvement was evaluated by subjective global assessment (SGA) in one study for 4, 8 and 12 wk to compare the effect of probiotics therapy in IBS patients with placebo[41]. RR was 1.2 (95%CI: 0.89-1.60), 0.9 (95%CI: 0.63-1.2) and 0.9 (95%CI: 0.61-1.2) in 4, 8 and 12 wk, respectively.

**Sum score:** Sum score was evaluated by IBS symptom score (abdominal pain + distension + flatulence + rumbling) in one study for 4-5, 13-14, and 20 wk to compare the effect of probiotics therapy in IBS patients to placebo[33]. The reduction of sum score was -13 ± 24.4, -15 ± 26.84, and -14 ± 26.83 for probiotics therapy group in 4-5, 13-14, and 20 weeks, respectively from baseline and -6 ± 22.55, -6 ± 22.55, and -3 ± 21.97 in placebo group at the same duration of therapy.

***Responders to therapies based on global symptom score***

The summary for RR of responders to therapies based on GSS in IBS patients for two included trials comparing probiotics with placebo was 2.43 with 95%CI: 1.13-5.21 (*P* = 0.02, Figure 6A)[35,36]. The Cochrane *Q* test for heterogeneity indicated that the studies are not heterogeneous (*P* = 0.06, Figure 6B) and could be combined but because of few included studies, the random effects for individual and summary for RR was applied.

***Adequate general symptoms improvement***

The summary for RR of adequate general symptoms improvement in IBS patients for seven included trials comparing probiotics with placebo in six studies was 2.14 with 95%CI: 1.08-4.26 (*P* = 0.03, Figure 7A)[34,37,42-45]. The Cochrane *Q* test for heterogeneity indicated that the studies are heterogeneous non-combinable (*P* < 0.0001, Figure 7B) and thus the random effects for individual and summary for RR was applied. For evaluation of publication bias, Egger regression of normalized effect vs. precision for all included studies for “adequate general symptoms improvement” in IBS patients among probiotics *vs* placebo therapy was 4.34 (95%CI: -3.13-11.81, *P* = 0.2) and Begg-Mazumdar Kendall’s test on standardized effect *vs* variance indicated tau= -0.33, *P* = 0.38 (Figure 7C).

**Symptom severity score:** Symptom severity score was evaluated by IBS severity scoring system in one study for 8 and 10 wk to compare the effect of probiotics therapy in IBS patients with placebo[32]. The reduction of symptom severity score was -132.45 ± 118.30 and -93.49 ± 103.45 for probiotics therapy group in 8 and 10 weeks, respectively from baseline and -80.08 ± 116.16 and -58.67 ± 96.38 for placebo group at the same duration of therapy.

**Severity score improvement:** RR for severity score improvement in C-IBS and A-IBS types in one trial was 1.29 with 95%CI: 0.72-2.16, a non-significant RR[46].

The RR for severity score improvement in D-IBS types in one trial was 1.74 with 95%CI: 1.06-2.66, a significant RR[46].

**Results of systematic review:** A systematic review was performed to summarize non-eligible clinical trials for the meta-analysis that were excluded because of heterogeneity or different measurement scales for IBS symptoms. All the nine studies were classified as randomized placebo-controlled trials. Four, six, and eight weeks of treatment with probiotics were reported.

**Abdominal pain:** Four weeks administration of probiotics ameliorated the abdominal pain in three clinical trials in comparison to placebo[37,42,45]. In one multi-centre cross-over study in children, probiotics alleviated the intensity and frequency of abdominal pain after six weeks. The mean reduction of abdominal pain score from baseline was 1.0 ± 0.2 and 0.5 ± 0.2 in probiotics and placebo groups, respectively[48]. Hun *et al*[50]reported the improvement of abdominal pain in probiotics arm. However, in placebo group, this symptom was improved after six and eight weeks of trial. Another study proved that abdominal pain score was significantly decreased in probiotic group. The mean abdominal pain score was decreased from baseline (53 ± 21.4) -26.0 and -29.5 after four and eight weeks of probiotics administration, respectively[51]. An evaluation of pain relief in a cross-over trial amongst children have reported improvement in 36 of 67 children at twelve weeks and 49 of 67 at twenty weeks in probiotics group. Placebo group showed improvement among 23 of 69 and 38 of 69 patients after twelve and twenty weeks of treatment[52]. Simren *et al*[40]have demonstrated the positive effect of probiotics in abdominal pain after one week treatment in comparison to placebo. However, there was no significant different between probiotics and placebo groups after eight weeks of treatment.

**Distension/Bloating/Flatulence:** Flatulence and bloating as undesirable symptoms of IBS were improved in probiotics-receiving adult patients after four weeks[37,44,45]. Moreover, probiotics alleviated distension and bloating in adult female patients with C-IBS[53]. Another investigation demonstrated that the mean abdominal distension/bloating in placebo group declined from baseline after eighth and ten weeks (-14.74 and -7.52, respectively). This reduction was -22.80 and -12.04 in probiotics group[32]. A cross-over clinical trial showed that bloating/gassiness in 42 of 59 IBS children was improved. Amongst 42 responders to probiotics, 16 were improved in placebo group. Overall assessment showed the effectiveness of probiotics on abdominal bloating rather than placebo in the six-week trial[48]. Simren *et al*[40]reported the significant reduction of bloating severity after two weeks of treatment with probiotics more than placebo, but no statistically significant difference was observed between two compared groups at the end of trial.

**Global IBS score:** The specific GI symptom rating scale-IBS score (GSRS-IBS score) was improved after eight weeks of probiotics digestion in D-IBS patients[49]. The daily symptom score did not change among probiotics- and placebo-received patients in a cross-over trial[54]. Probiotics were effective in reducing the global IBS score from baseline after four weeks[39]. In comparison to placebo group, 50% reduction was observed in global symptom score after probiotics ingestion[36]. In another clinical trial, IBS severity score was decreased by 40% in probiotics-received patients when the reduction was reported as 28% in placebo-received patients[46].

**IBS symptoms relief:** Four, six, and eight weeks of treatment with probiotics resulted in significant beneficial effects on IBS symptoms in comparison to placebo[35,41-44,48].

**Quality of life:** Probiotics administration decreased disease-associated complications in IBS patients after four weeks[37,44,47]. During a cross-over trial, the elevated quality of life (QoL) in children after six weeks of probiotics digestion was identified[48]. In 2008, Williams et al. reported that probiotics improved QoL from baseline rather than placebo[32]. Another study performed by Ki Cha *et al*[38] reported that the changes of QoL from baseline in follow-up period were statistically similar in probiotics- and placebo-received patients. Michail *et al*[49] showed significant positive effect on the overall average QoL score in both probiotics and placebo groups after eight weeks of treatment. QoL was improved from 3.0 ± 1.3 to 2.1 ± 0.8 in active treatment group and from 2.4 ± 1.0 to 1.8 ± 0.6 in control group after eight weeks. Twelve-week treatment with probiotics resulted in QoL improvement in placebo and probiotics groups similarly in D-IBS patients[34].

***Intestinal barrier function and gut microbiota***

In IBS patients, bowel function and gut microbiotaare changed. Probiotics are demonstrated to modify the impaired intestinal permeability in pediatric and D-IBS patients after 4 and 12 wk of treatment, respectively[39,52]. Furthermore, probiotics caused significant improvement on intestinal barrier function among IBS female patients in an eight-week trial[51]. Probiotics digestion alleviated the increased small bowel permeability in 28.6% of patients in comparison to 53.3% in placebo group. It was concluded that probiotics improved mucosal barrier function in D-IBS adult patients[39]. Steady state of gut microbiota in the probiotics-treated arm was increased, but it was decreased in placebo arm[33]. However, the balanced gut microbiota was not observed in probiotics-received patients in comparison to placebo after eight and twelve weeks of treatment[34,49].

**DISCUSSION**

The present meta-analysis included 1793 patients with all subtypes of IBS in fifteen randomized, double-blind clinical trials from 2007 up to December 2013. The applied criteria were Rome criteria for thirteen trials and ICHPP and WONCA for two trials. Some trials were retrieved due to heterogeneity in assessing IBS symptom scores with different scales and questionnaires and therefore reviewed systematically and the outcomes were summarized. IBS is manifested with gut-brain axis interactions, changes in serological biomarkers, enhanced inflammatory indicators such as myeloperoxidase (MPO), tumor necrosis factor alfa (TNF-) and lipid peroxides, gut microbiome disruption and is also associated with genetics background and environmental factors[56,57,58,59]. Among all factors, change in intestinal microbial flora seems very important in initiation of IBS. As well, diet as an environmental factor influences the human’s microflora[60]. Despite of pharmacological approaches and novel drugs on IBS management, the experience on the use of probiotics in IBS has been good confirmed by recovery and gradually heals[61-63]. In the meantime, low grade inflammation resulting from immunity dysregulation in IBS is affected by probiotics in the way to acquire immune stability and enhancing cellular integrity to protect the colon[64,65]. Moreover, probiotics modify the intestinal microbiota leading to change of fermentation pattern inside the colon and reduction of flatulence[66]. Probiotics as the live microorganisms exert beneficial effects to the host but they can act as double edged sword because of having both negative and positive effects. Therefore, precaution is necessary before their administration[67]. Pain assessment analysis showed that probiotics significantly reduce pain severity[32,33] after eight and ten weeks of administration. However, the reduction rate was rather higher at week eight than that of week ten suggesting the lesser effectiveness of probiotics on pain severity in long-term use. The responder rate based on abdominal pain was significantly more than placebo[35,36]. Probiotics did not improve abdominal pain significantly vs. placebo in two trials[34,38]. Probiotics did not significantly affect the severity score of distension, bloating and flatulence[32,33,40]. Flatulence and bloating were not improved after probiotics treatment when compared with placebo[34,39]. Bowel habit dissatisfaction was not significantly different after probiotics and placebo treatment[32,40]. Global IBS symptoms were not improved[41] but IBS sum score was decreased after use of probiotics[33]. The responder rate was significantly higher in probiotics treated groups when global symptom improvement was considered[35,36]. Probiotics were effective to induce adequate general symptoms improvement in IBS patients[34,37,42-45]. The severity of symptom scores was decreased[32] but was not improved with probiotics *vs* placebo[46]. The same results of clinical improvement in previous meta-analysis demonstrated the effectiveness of probiotics on IBS symptoms[30].

The numbers of reported withdrawals are shown in Table 4. The most withdrawals were due to adverse events in probiotics and lack of efficacy in placebo groups. Four and seven patients in placebo and probiotics groups discontinued treatment due to adverse events[33,34,36]. Lack of efficacy was reported as the reason of withdrawal in three patients in two trials[34,35]. Symptom worsening was reported in five patients who received placebo in two trials[38,46] (Table 4). The results of systematic review demonstrated the beneficial effect of probiotics on QoL [32,34,37,38,44,47,48], abdominal pain[37,42,45,48,50-52], distension, bloating and flatulence[32,37,44,45,47,53], IBS diagnostic scores[36,3946,49,54] , and IBS total symptoms [33,35,42,44,48,55].

Generally, use of different scales to analyse the mean differences of symptoms in various studies has been the main limitation of all existing meta-analyses in IBS and the present one is not an exception. Thus, further clinical trials are still needed to better conclude the effectiveness of probiotics on special major IBS symptoms and QoL of patients. Collectively, probiotics may have beneficial therapeutic role in IBS patients in definite duration of administration.

**COMMENTS**

***Background***

Irritable bowel syndrome (IBS) is a gastrointestinal tract dysfunction which affects general population specially young people. This syndrome is manifested with abdominal pain, stool pattern alteration, distention, bloating, straining, abdominal discomfort and urgency. Genetics background and environmental factors have been known important in pathogenesis of IBS but the precise cause of IBS is still unknown. Because of adverse effects of pharmacological drugs, some physicians and IBS patients tend to use probiotics.

***Research frontiers***

Probiotics are live microorganisms which confers positive effects into the host after oral administration. Several probiotics strains have shown beneficial outcomes in IBS patients.

***Related publications***

Our study was performed to update the previous meta-analysis considering further clinical trials. Moreover systematic review conducted to assess the efficacy of probiotics in IBS patients in clinical trials that were not eligible for meta-analysis section.

***Innovations and breakthroughs***

A total of 11748 publications between 2007 and 2013 about the efficacy of probiotics in IBS were identified and studied. Of them, 8719 studies were found inappropriate because they did not clearly meet our inclusion criteria while fifteen trials met criteria of meta-analysis and included. Rome criteria, ICHPP and WONCA were applied to include IBS patients. Totally, 1793 patients with diarrhea predominant IBS (D-IBD), constipation predominant IBS and alternative IBS were included. Nine other clinical trials which were not applicable for our meta-analysis were reviewed systematically.

***Applications***

Pain assessment analysis showed that probiotics significantly reduce pain severity. The responder rate based on abdominal pain was significantly more than placebo. The responder rate was significantly higher in probiotics treated groups when global symptom improvement was considered. Probiotics were effective to improve general IBS symptoms. The most withdrawals were due to adverse events in probiotics and lack of efficacy in placebo groups. The results of systematic review demonstrated the beneficial effect of probiotics on QoL, abdominal pain, distension, bloating and flatulence, IBS diagnostic scores, and IBS total symptoms. Generally, use of different scales to analyse the mean differences of symptoms in various studies has been the main limitation of all existing meta-analyses in IBS. Thus, well-designed clinical trials are still needed to reach the consensus on the effectiveness of probiotics on special major IBS symptoms and QoL of patients. Collectively, probiotics seem having beneficial therapeutic role in IBS patients if administered accurately.

***Peer review***

In this study we concluded that probiotics confers beneficial effects on IBS symptoms alleviation. Generally, use of different scales to analyse the mean differences of symptoms in various studies is the main limitation of all existing meta-analyses in IBS. Further well-designed clinical trials are still needed to better conclude about the effectiveness of probiotics on special major IBS symptoms and the QoL of patients.

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**P-Reviewer:** Hauser G **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Figure1 Flow diagram for study selection.**

Potentially relevant articles in electronic search

(n= 11748)

Potentially relevant eligible studies

(*n*= 170)

Excluded because of duplication,

Lack of control group,

Prebiotic in combination with probiotic,

Herbal treatments plus probiotics,

Meta-analysis and review articles

(n= 146)

Excluded because of:

Likert score evaluation (n= 1)

Pediatric patients (n=1)

Cross-over studies (n = 2)

Lack of proper evaluation, figures and tables for analysis (n =5)

Eligible studies to include in meta-analysis

(*n*=15)

Excluded due to time limitation

(n=2859)

Clearly not eligible trials (n= 8719)

Trials which met eligible criteria

(*n*=24)

**Figure 2** **Responders to therapies based on abdominal pain score.** A: Individual and pooled relative risk for the outcome of “Responders to therapies based on abdominal pain score” in the studies considering probiotics comparing to placebo therapy in IBS patients; B:Heterogeneity indicators for the outcome of “Responders to therapies based on abdominal pain score” in the studies considering probiotics comparing to placebo therapy in IBS patients.



A



B

**Figure 3 Individual and pooled effect size for standardized mean for the outcome of “∆AP” in the studies considering probiotics comparing to placebo therapy in IBS patients.**



**Figure 4 Individual and pooled effect size for standardized mean for the outcome of “∆DBF” in the studies considering probiotics comparing to placebo therapy in IBS patients.**



**Figure 5 Individual and pooled effect size for standardized mean for the outcome of “∆BHD” in the studies considering probiotics comparing to placebo therapy in irritable bowel syndrome patients.**



**Figure 6 Responders to therapies based on global symptom score.**A: Individual and pooled relative risk for the outcome of “Responders to therapies based on global symptom score” in the studies considering probiotics comparing to placebo therapy in IBS patients; B: Heterogeneity indicators for the outcome of “Responders to therapies based on global symptom score” in the studies considering probiotics comparing to placebo therapy in IBS patients.



A



B

**Figure 7 Adequate general symptoms improvement.** A: Individual and pooled relative risk for the outcome of “adequate general symptoms improvement” in the studies considering probiotics comparing to placebo therapy in IBS patients; B: Heterogeneity indicators for the outcome of “adequate general symptoms improvement” in the studies considering probiotics comparing to placebo therapy in IBS patients; C: Publication bias indicators for the outcome of “adequate general symptoms improvement” in the studies considering probiotics comparing to placebo therapy in IBS patients.



A



B



C

**Table 1 Jadad quality score of randomized controlled trial included in the meta-analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Randomization** | **Blinding** | **Withdrawals and dropouts** | **Total score** |
| Kajander *et al*[33] | 2 | 2 | 1 | 5 |
| Williams *et al*[32] | 1 | 2 | 1 | 4 |
| Zeng *et al*[39] | 1 | 2 | 1 | 4 |
| Enck *et al*[35] | 1 | 1 | 1 | 3 |
| Drouault-Holowacz *et al*[37] | 2 | 2 | 1 | 5 |
| Sinn *et al*[42] | 2 | 2 | 1 | 5 |
| Enck *et al*[36] | 1 | 2 | 1 | 4 |
| Simren *et al*[40] | 2 | 2 | 1 | 5 |
| Sondergaard *et al*[43] | 2 | 2 | 1 | 5 |
| Guglielmetti *et al*[44] | 2 | 2 | 1 | 5 |
| Ducrotte *et al*[45] | 1 | 2 | 1 | 4 |
| Kruis *et al*[34] | 2 | 2 | 1 | 5 |
| Ki cha *et al*[38] | 2 | 2 | 1 | 5 |
| Dapoigny *et al*[46] | 1 | 2 | 1 | 4 |
| Roberts *et al*[41] | 2 | 2 | 1 | 5 |

**Table 2 Characteristics of studies included in the meta-analysis**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Type of IBS** | **Criteria** | **Age**  **(probiotic)** | **Age**  **(placebo)** | **Sex (M/F)**  **(Probiotic)** | **Sex(M/F)**  **(Placebo)** | **Probiotic** | **Probiotic dosage** | **Duration of treatment** | **Follow up** | **outcome** |
| Kajander  *et al*[33] | All IBS  types | Rome II | 50 | 46 | 2/41 | 4/39 | *L.rhamnosus*GG, *L.rhamnosus*Lc705, *P.freudereichii*  *Ssp. Sehrmanii*JS,  *B. animalis*  *Ssp.lactis*Bb 12 | 1 × 107 CFU | 20 wk | 3 wk | ↑ Stabilization of intestinal microbiota, ↓distension and abdominal pain in probiotic group,  ↓IBS symptoms |
| Williams  *et al* [32] | All IBS  types | Rome II | 40 | 38 | 3/25 | 8/20 | *L.acidophilus*CUL60,  *L.acidophilus*CUL21,  *B.lactis*CUL34,  *B.bifidum*  CUL20 | 2.5 × 1010  CFU | 8 wk | 2 wk | ↑QOL, ↓symptom severity, bloating did not improved |
| Zeng  *et al*[39] | D-IBS | Rome II | 44.6 | 45.8 | 10/4 | 9/6 | *S.thermophilus;*  *L.bulgaricus, L.acidophilus, B.longum* | 1 × 108CFU;1 × 107CFU | 4 wk | - | mucosal barrier function and bowel symptoms improved, ↓small bowel permeability |
| Enck  *et al*[35] | All IBS  types | ICHPPC and WONCA | 49.8 | 49.4 | 76/72 | 75/75 | Symbiflor2, (*E.coli)* | 1.5-4.5 × 10 7 CFU | 8 wk | ND | ↓Typical symptoms of IBS patients |
| Drouault-Holowacz  *et al*[37] | All IBS  types | Rome II | 47 | 44 | 8/40 | 16/36 | *B.longum*LA101,*L.acidophilus* LA102,*L.lactis*LA103  *,S.thermophilus*  LA104 | 1 × 10 10  CFU | 4 wk | - | ↑QOL , ↓flatulence , ↓abdominal pain and bloating |
| Sinn *et al*[42] | All IBS  types | Rome III | 41.9 | 47.5 | 6/14 | 8/12 | *L.acidophilus-* SDC 2012,2013 | 2 × 109  CFU | 4 wk | - | ↓IBS symptoms, abdominal pain and discomfort |
| Enck  *et al*[36] | All IBS  types | ICHPPC and WONCA | 49.8 | 49.4 | 77/72 | 73/75 | Pro symbiflor, (*E.coli*, *E.faecalis)* | 3-9  × 10 7  CFU | 8 wk | - | ↓50% global symptom score and abdominal pain score |
| Simren  *et al*[40] | All IBS  types | Rome II | 42 | 44 | 11/26 | 11/26 | *L.paracasei*F19,  *L.acidophilus*La5,  *B.lactis* Bb12 | 5 × 107  CFU | 8 wk | 8 wks | In both group improvement reported in Symptoms like pain frequency, pain severity,  bloating severity, satisfaction with bowel habits, interference  with daily life |
| Sondergaard*et al*[43] | IBS (ND) | Rome II | 53.9 | 48.5 | 7/20 | 6/19 | *L.paracasei*F19, *L.acidophilus* La5,  *B.lactis* Bb12 | 5 × 107  CFU  (500 mL) | 8 wk | 8 wk | Adequate symptom relief increased in both groups.No difference between treatment with probiotics and placebo group |
| Guglielmetti*et al*[44] | All IBS  types | Rome III | 36.65 | 40.98 | 21/41 | 19/41 | *B.bifidum*MIMBb75 | 1 × 109  CFU | 4 wk | 4 wk | ↓IBS symptoms like;pain,discomfort distension, bloating, digestive disorders, ↑QOL |
| Ducrotte  *et al*[45] | D-IBS (in majority of patients) | Rome III | 36.53 | 38.40 | 70/38 | 81/25 | *L.plantarum*  299v | 10  Billon CFU | 4 wk | 3 wk | ↓Abdominal pain and bloating |
| Kruis  *et al*[34] | D-IBS | Rome II | 46.3 | 45.1 | 12/48 | 16/44 | *E.coli*Nissle 1917 | 2.5-25 × 109  CFU | 12 wk | - | Did not show significant effects on probiotic group in IBS general symptom but enteric flora altered due to gastroenterocolitis or administration of antibiotics before IBS initiation |
| Ki Cha  *et al*[38] | D-IBS | Rome III | 37.9 | 40.3 | 12/13 | 14/11 | *L.acidophilus,*  *L.plantarum,*  *L.rhamnosus,*  *B.breve,*  *B.lactis,*  *B.longum, S.thermophilus* | 1 × 1010  CFU | 8 wk | 2 wk | ↑QOL |
| Dapoigny  *et al*[46] | All IBS  types | Rome III | 46.1 | 48.8 | 5/20 | 10/15 | *L.caseirhamnosus*(LCR 35) | 6 × 108  CFU  (250 mg) | 4 wk | 2 wk | ↓ IBS patients complaining of diarrhea  ↓50% reduction in IBS severity score in probiotic arm |
| Roberts  *et al*[41] | C-IBS, A-IBS | Rome III | 44.66 | 43.71 | 14/74 | 14/77 | *B.lactis*CNCMI-2494 | 1.25 × 1010  CFU | 12 wk | - | Significant improvement showed in probiotics and placebo groups on IBS symptoms |

CFU: Colony Forming Unit; IBS: Irritable bowel syndrome; A-IBS: Alternating irritable bowel syndrome; C-IBS: Constipation-predominant irritable bowel syndrome; D-IBS: Diarrhea-predominant irritable bowel syndrome; ND: Not determined; Probiotics abbreviation: *B., Bifidobacterium; E.coli, Escherichia coli; E.faecalis, Enterococcus faecalis; L., Lactobacillus; P., Propionibacterium; S.,Streptococcus*; VSL#3: A probiotic combination of *L. casei, L.plantarum, L. acidophilus, L. delbrueckii subsp. bulgaricus, B. longum, B. breve, B. infantis, S. thermophiles;* QOL: Quality of life.

**Table 3** **Characteristics of studies included in the systematic review**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Type of IBS** | **Criteria** | **Age**  **(probiotic)** | **Age**  **(placebo)** | **Sex (M/F)**  **(Probiotic)** | **Sex(M/F)**  **(Placebo)** | **Probiotic** | **Probiotic dosage** | **Duration of treatment** | **Follow up** | **outcome** |
| Agrawal  *et al*[53] | C-IBS | Rome III | Total | | 0/19 | 0/19 | *B.lactis*DN-173010 | 1.25×1010 CFU | 4 wk | 1 wk | ↓Abdominal distension and bloating |
| 39.6 | |
| Hun *et al*[50] | D-IBS | Rome II | Total | | Total | | *B.coagulans*  GBI-30,6086 | 800××106  CFU | 8 wk | - | ↓Bloating and abdominal pain |
| 48.36 | | 9/41 | |
| Dolin  *et al*[55] | D-IBS | Rome III | 52.3 | 44.0 | 7/19 | 6/23 | *B.coagulans*  GBI-30,6086 | 2×10 9  CFU | 8 wk | 2 wk | ↓Number of daily bowel movements in D-IBS patients |
| Guandalini  *et al*[48] | All IBS  types | Rome II | 4-18 years | | Total | | VSL#3 | 450 billion bacteria | 6 wk | 6 wk after 2 wk wash out | ↓ Percentage of symptoms , severity and frequency of the abdominal pain and abdominal bloating  ↑QOL |
| 31/28 | |
| Ligaarden  *et al*[54] | All IBS  types | Rome II | 18-75  46.5 | | Total | | *L. plantarum*  MF1298 | 1010 CFU | 3 wk | - | Daily symptom scores was not different between probiotic and placebo groups |
| 5/11 | |
| Francavilla*et al*[52] | IBS (ND)  children group | Rome II | 6.5 | 6.3 | 43/24 | 35/23 | *L.rhamnosus*  *(L.*GG*)* | 3×109  CFU | 12 wk | 8 wk | ↓ frequency and severity of pain and intestinal permeability improved |
| Hong  *et al*[51] | All IBS  types | Rome III | 33 | 33 | 12/25 | 10/26 | *Lactobacillus sp.*HY7801*, B.longum*HY804*,*  *L.brevis*  HY7401 | 4×109  CFU | 8 wk | - | ↑ Intestinal barrier function in female IBS patients, ↓pain and flatulence defection |
| Choi *et al*[47] | D-IBS, A-IBS | Rome II | 40.2 | 40.6 | 18/17 | 19/20 | *S.boulardii* | 2×1011  CFU | 4 wk | - | ↑QOL |
| Michail  *et al*[49] | D-IBS | Rome III | Total :  21.8±17 | | 5/10 | 3/6 | VSL#3 | 900 billion bacteria | 8 wk | - | ↑QOL,  gut microbiota did not change,↑specific GSRS-IBS scores |

CFU: Colony Forming Unit; IBS: Irritable bowel syndrome; A-IBS: Alternating irritable bowel syndrome; C-IBS: Constipation-predominant irritable bowel syndrome; D-IBS: Diarrhea-predominant irritable bowel syndrome; Probiotics abbreviation: *B., Bifidobacterium; L., Lctobacillus;S.boulardii, Saccharomyces boulardii;* VSL#3*:* A probiotic combination of *L. casei, L.plantarum, L. acidophilus, L. delbrueckii subsp. bulgaricus, B. longum, B. breve, B. infantis, S. thermophiles;* QOL: Quality of life.

**Table 4 Numbers and causes of reported withdrawals in the included clinical trials in the meta-analysis**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cause of withdrawal** | | **Adverse effect** | **Non- compliance** | **Lack of efficacy** | **Symptom worsening** |
| **Study** | **Group (N)** |
| Drouault-holowacz *et al*[37] | Placebo (53) | NR | 1 | NR | NR |
| probiotic (53) | NR | 5 | NR | NR |
| Kajander *et al*[33] | Placebo (43) | 2 | NR | NR | NR |
| probiotic (43) | 2 | NR | NR | NR |
| Kruis *et al*[34] | Placebo (60) | NR | NR | 2 | NR |
| probiotic (60) | 2 | NR | NR | NR |
| Enck *et al*[35] | Placebo (148) | NR | 1 | 1 | NR |
| Probiotic (149) | 2 | NR | NR | NR |
| Enck *et al*[36] | Placebo (150) | 2 | NR | NR | NR |
| Probiotic (148) | 3 | NR | NR | NR |
| Dapoigny *et al*[46] | Placebo (26) | NR | NR | NR | 3 |
| Probiotic (26) | NR | NR | NR | NR |
| Kicha *et al*[38] | Placebo (25) | NR | NR | NR | 2 |
| Probiotic (25) | NR | NR | NR | NR |

NR: Not report.