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Systematic review

Chinese herbal medicine versus probiotics for irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Chinese herbal medicine (CHM) and probiotics are two complementary and alternative approaches often used for irritable bowel syndrome (IBS). This study evaluates the efficacy and safety of CHM compared with probiotics for IBS.

Methods: 11 databases were searched (up until March 2020) for randomized controlled trials of IBS. Risk of bias was evaluated. RevMan 5.3 was used for data synthesis. Trial sequential analysis (TSA) was used to control for risk of random errors.

Results: A total of 47 trials were includedin the analysis. Unclear risk of bias was observed for most domains of included trials. CHM had advantages over probiotics for improving overall symptoms of IBS-Diarrhea (IBS-D) (RR 1.24, 95 % CI 1.18–1.30, 3207 patients, I^2 = 55 %, very low certainty). The heterogeneity might be associated with different diagnostic criteria, duration of treatment, probiotic composition and types of CHM. CHM might provide better outcomes than probiotics when the duration of treatment is more than 4 weeks (RR 1.26, 95 % CI 1.20–1.33, 2669 patients, very low), and the formulae represented by Tongxie Yaofang appeared to be better than triple Bifidobacterium preparations for improving overall symptoms of IBS-D (RR 1.33, 95 % CI 1.20–1.47, 476 patients). CHM might reduce relapse rate compared with probiotics (RR 0.27, 95 % CI 0.18 − 0.40, 382 patients, very low). Adverse events were mainly gastrointestinal symptoms.

Conclusions: Very low quality evidence suggests that CHM may be better than probiotics for improving overall symptoms of IBS-D when the duration of treatment lasted more than 4 weeks ; and CHM may be better than probiotics for reducing relapse rates of IBS-D.

1. Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder (FBD) that manifests as recurrent episodes of abdominal pain associated with altered bowel habits, accompanied by symptoms of abdominal bloating or distension. Symptoms occur for at least 6 months before diagnosis and during the last 3 months. According to an individual's abnormal bowel habits, IBS is divided into three main subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), and IBS with mixed bowel habits (IBS-M). Different subtypes can be transformed into each other over time [1].

The prevalence of IBS varies according to different diagnostic criteria. A general population survey using Rome IV criteria in the United States, United Kingdom and Canada showed that the prevalence of IBS was 5.7 % [2]. IBS can significantly reduce work efficiency and quality of life [3–6]. Conventional medications for IBS target the main bowel symptoms by using antidiarrheals, 5-HT_3 receptor antagonists, and antispasmodics for IBS-D; fiber supplements, laxative agents, and prosecretory agents for IBS-C; other symptomatic medications (such as antidepressants, antibiotics) [7].

As conventional medications are often symptomatic and have limited efficacy [8,9], Complementary and Alternative Medicine (CAM) is

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increasingly favored by IBS patients. An Australian study showed that about 20 % IBS patients had sought alternative health care approaches for gastrointestinal problems [10]. A UK study found that about 51 % of IBS outpatients had used CAM [11]. A prospective study in the United States showed that 35 % of patients with functional bowel diseases, including IBS, claimed to have used at least one type of CAM during a 6-month follow-up [12]. Probiotics and Chinese herbal medicines (CHM) are two commonly used CAM therapies for IBS [8,13–15]. Although actual clinical practice is always not consistent with evidence-based expert recommendations for the use of probiotics, one study showed that among surveyed doctors most recommended probiotics for IBS patients and believed that probiotics were safe for most patients with gastric problems [16]. Probiotics are living microorganisms that can bring health benefits to the host when administered in sufficient quantities. Synbiotics are a mixture of probiotics and prebiotics that have a synergistic effect on the growth and survival of beneficial organisms [17]. Meta-analysis showed that probiotics might play a beneficial role in improving some IBS symptoms [18,19]. The efficacy of CHM in the treatment of IBS has always received much attention. Since the first systematic review (SR) of herbal medicine for IBS published on Cochrane collaboration network in 2006 [20], a large number of randomized controlled trials (RCTs) [21–23] and SRs [24–27] of CHM for IBS have been published in recent years. CHM are generally considered effective for IBS, although the current quality of evidence is still low or very low [20,24–27].

However, there have been no studies comparing CHM and probiotics or synbiotics on the treatment of IBS. The aim of this systematic review and meta-analysis was to evaluate the efficacy and safety of CHM compared with probiotics or synbiotics for IBS.

2. Methods

The protocol of the review was registered in PROSPERO (CRD42019133253) on 20th of May 2019 (Available from: http://www.crd.york.ac.uk/PROSPERO/). Different clinical questions could be answered by different comparisons: in the comparison of CHM versus probiotics, the efficacy of CHM was observed and evaluated; in the comparison of CHM combined with probiotics versus probiotics alone, the efficacy of CHM as an adjuvant therapy was observed and evaluated. Only RCTs of CHM versus probiotics were included in this study. A systematic review comparing RCTs of CHM combined with probiotics versus probiotics alone has been published previously [28]. After the protocol was registered, we made some revisions of the previous version of the protocol regarding the comments of digestive clinical experts. Since psychological states are important factors in the occurrence and recurrence of IBS, we expanded the outcomes of relief of depression and anxiety as amendments. All the revisions had been pre-defined before conducting the review.

3. Eligibility criteria

3.1. Type of studies

RCTs were included in the review, irrespective of blinding, publication status and language. Randomized cross-over trials were included only if the trial reported a wash-out period to eliminate any carry-over effects from the first period of treatment before cross-over.

3.2. Type of participants

To be included in the review, the diagnosis of IBS had to be based on the Manning criteria, the Kruis criteria or the Rome I-IV criteria, but there were no restrictions on the patient's age, race or gender.

3.3. Type of interventions

The interventions of treatment groups were CHM. These could include single herbs (or extracts from single herbs), Chinese proprietary medicines, or mixtures of several herbs, irrespective of preparation (e.g., decoction, oral liquid, tablets, capsules, pills, powders, plasters or injections), means of delivery (e.g., oral, intramuscular or intravenous injection), dosage, and regimens of herbs. The control interventions were probiotics or synbiotics (any dose, strain, species, duration or treatment regime) alone. Co-interventions were allowed as long as all arms of the randomized allocation received the same co-intervention.

3.4. Type of outcomes

The primary outcomes were: (1) global improvements of symptoms: including overall symptoms improvement rate and overall symptoms scores; (2) quality of life (QOL). The secondary outcomes included: (1) relapse rates; (2) the improvement of predominant symptoms: including the scores of abdominal pain, distension and diarrhea; (3) psychological states: including depression and anxiety; (4) cost-effectiveness; (5) adverse events. The outcomes were measured at the end of treatment and at maximal follow-up after completion of the treatment.

With reference to [29], the overall symptoms improvement rate in this study was defined as more than 30 % improvement in overall symptoms scores or improved signs and symptoms. Overall symptoms improvement rate = [(overall symptoms scores before treatment - overall symptoms scores after treatment)/ overall symptoms scores after treatment] * 100 %. Overall symptoms scores were defined as: the sum of symptom scores of individual symptoms at least including diarrhea, abdominal pain and distension; or scores of scales that reflected the overall condition of IBS (e.g., IBS-SSS).

3.5. Search strategy

The following electronic databases were searched from their inception dates to March 2020: China National Knowledge Infrastructure (CNKI), Wanfang database, Chongqing VIP (CQVIP) and SinoMed; Ovid MEDLINE, Ovid Embase. Trial registers were also searched: the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane IBD Group Specialized Register, International Standard Randomized Controlled Trial Number Register (www.controlled-trials.com/), US National Institutes of Health Ongoing Trials Register (www.ClinicalTrials.gov) and World Health Organization International Clinical Trials Registry (www.who.int/ictrp/en/). In addition, we searched the reference lists of all included studies to identify any further relevant trials, conference full texts and dissertations. There were no restrictions on publication language. For details of the search strategy, see **Supplementary File 1**.

3.6. Study selection and data extraction

Two reviewers (FLB and RLC) independently screened and retrieved studies by reviewing titles and abstracts. If no decision was made for a particular study from the title and abstract, the full text would be available for further evaluation. The authors discussed any disagreements in order to reach a consensus, or a third (JPL) was called upon to adjudicate.

Two authors (RLC and ZYL) used standardized tables to extract data independently from the included studies. Disagreements were resolved through discussion and consultation. If consensus could not be reached, the opinion of a third author (HJC) was sought. Duplicate published studies were removed. For trials with unclear information, an attempt was made to contact the authors for further details. The following data were extracted: primary author, funding source, study setting, methodological characteristics, mean age, gender and ethnicity of patients, number of randomized patients, reason and number dropped out or lost

during follow-up, eligibility criteria, subtype of IBS, the diagnostic criteria, type of CHM, route of delivery, dosage, frequency and duration of intervention, probiotic/synbiotic strain, species, dosage, frequency and duration of intervention, co-interventions, details of the comparison regime, outcome measures (end of treatment and follow-up), and number and type of adverse events. Regardless of compliance or follow-up, data on the number of patients under each outcomes divided by the assigned treatment group was required for an intention-to-treat analysis. One author (ZYL) entered the data into Review Manager (RevMan 5.3, 2014) and another (NL) checked it.

3.7. Quality assessment

The risk of bias for each study was assessed by two authors (FLB and RLC) with the Cochrane risk of bias tool. After arbitration by one author (NR), any disagreements were discussed and consensus reached. Each domain was judged as 'low', 'high' or 'unclear': (1) random sequence generation; (2) allocation concealment; (3) blinding participants and evaluators; (4) blinding outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; (7) other bias: including eligibility criteria, baseline and conflicts of interests.

3.8. Data analysis

Dichotomous data was presented as risk ratio (RR) and continuous outcomes as mean difference (MD), with 95 % confidence intervals (CI). Intention-to-treat analyses were performed only for dichotomous outcomes where possible. For dichotomous outcomes, patients with incomplete or missing data were included in a sensitivity analysis by counting them as treatment failures in order to explore the possible effect of loss to follow-up on the findings ('worst-case' scenario).

The χ^2 test was used to evaluate heterogeneity. A P value of < 0.10 was considered to be statistically significant. When there was significant heterogeneity, the results of I^2 were quantified for each study and interpreted as a percentage of the total variation between studies caused by heterogeneity rather than chance [30]. Referring to the Cochrane Handbook 5.1.0, we defined I^2: < 25 % represented mild heterogeneity; 25 %–50 % represented moderate heterogeneity; > 50 % represented severe heterogeneity. When more than 75 %, no meta-analysis was performed. A random effects model was planned to use when the heterogeneity more than 25 %, otherwise the fixed effect model was used. Subgroup analysis was employed to explore potential sources of heterogeneity. If sufficient data were available, subgroup analyses were performed based on the types of probiotic/synbiotic strain, species, dose, different diagnostic criteria, duration of treatment and type of CHM. Sensitivity analyses were intended to be conducted so that robustness can be tested, in terms of random sequence generation (low or high) and selective reporting (low or high/unclear).

If there were at least 10 trials in one meta-analysis, publication bias was evaluated by constructing a funnel plot for each outcome. If the funnel plot was asymmetric, publication bias may be considered one of the reasons for the asymmetry of the funnel plot.

Trial Sequential Analysis (TSA) (version 0.9.5.10) was applied to calculate the required sample size in a meta-analysis and to detect the robustness of the results. For dichotomous outcomes, the diversity-adjusted required information size (DARIS) was planned to estimate based on the event proportion in the control group, a relative risk improvement of 10 %, an alpha of 5 %, a beta of 10 % [31], and diversity suggested by the trials in the meta-analysis [32,33]. For continuous outcomes, the DARIS was intended to estimate based on the standard deviation (SD) observed in the control group; a minimal relevant difference of 50 % of this SD; an alpha of 5 %; a beta of 10 % [31]; and diversity suggested by trials in the meta-analysis [32,33].

3.9. Evidence assessment

The Grades of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the quality of the evidence. We judged whether to downgrade the evidence of included RCTs and assessed the evidence as: high, moderate, low or very low.

4. Results

4.1. Searching and screening

A total of 1454 articles were identified and downloaded from 10 databases (search strategy details in **Supplementary File 1**). After excluding duplicates, 776 articles remained (647 Chinese and 129 English). After browsing the titles and abstracts and excluding articles that did not meet the inclusion criteria, 176 remained. After reading the full texts, 47 trials [34–80] (44 Chinese and 3 English) were finally included. (Fig. 1)

4.2. Study characteristics

Tables 1 and 2 showed the characteristics of the included trials. Tang JL 2011 [61] and Han SK 2011 [45] were the same trial, but had published different outcomes in two articles. Li DS 2017 [50] was a three-arm trial (Modified Buhuanjin Zhengqi San 2 vs Modified Buhuanjin Zhengqi San 3 vs triple Bifidobacterium preparations 2). Of the 47 trials included, 43 were IBS-D, 3 were IBS-C, and 1 was IBS-M. 32 trials used the Rome III as diagnostic criteria, 13 used Rome II, 1 used Rome IV, and 1 used Rome I. Sample sizes ranged from 23 to 175. The average age ranged from 18 to 65 years. The course of disease ranged from 6 months to 34 years. There were 47 CHM prescriptions involved (see **Supplementary File 2**) in 5 different dosage forms (decoctions, granules, bolus, capsules and oral liquids). The 47 CHM prescriptions were mainly divided into four categories according to their actions: soothing liver and invigorating spleen (SLIS) formulae (12 trials); invigorating spleen and resolving dampness (ISRD) formulae (8 trials); soothing liver, invigorating spleen and resolve dampness (SLISRD) formulae (4 trials); warming and invigorating spleen and kidney (WISK) formulae (6 trials) (and other prescriptions that cannot be categorized, 17 trials). The control group involved 12 probiotics (10 Chinese products, 1 Korean product and 1 Japanese product). No studies on synbiotics met the inclusion criteria. The duration of treatment was from 0.5 months to 2 months. Of the 47 trials, 44 reported overall symptoms improvement rate, 15 reported overall symptoms scores, 5 reported relapse rates, 5 reported QOL, 21 reported abdominal pain relief, 13 reported distension relief, 18 reported diarrhea relief, 1 reported constipation relief, 1 reported depression, 14 reported adverse events, and none reported cost-effectiveness.

4.3. Risk of bias of included trials

The included trials were judged to have unclear risk of bias in most domains. Almost all trials (46/47) had high risk of blinding of participants and personnel. More than half of the trials (25/47) might have high risk of selective reporting (Fig. 2). In the domain of random sequence generation, one trial [71] did not mention the recruitment in a 2:1 ratio, and the final reported number of cases was close to 2:1, which was considered to be high risk of bias. Fifteen trials referred to methods for generating random sequence with low risk. The rest of the trials had an unclear risk, as only the word "random" was mentioned. All trials did not describe allocation concealment, resulting in unclear risk. Only one trial [35] claimed to be blinded to trial-related personnel (including participants, researchers, clinicians, investigators, clinical research coordinator and clinical pharmacist) between the two groups, so both

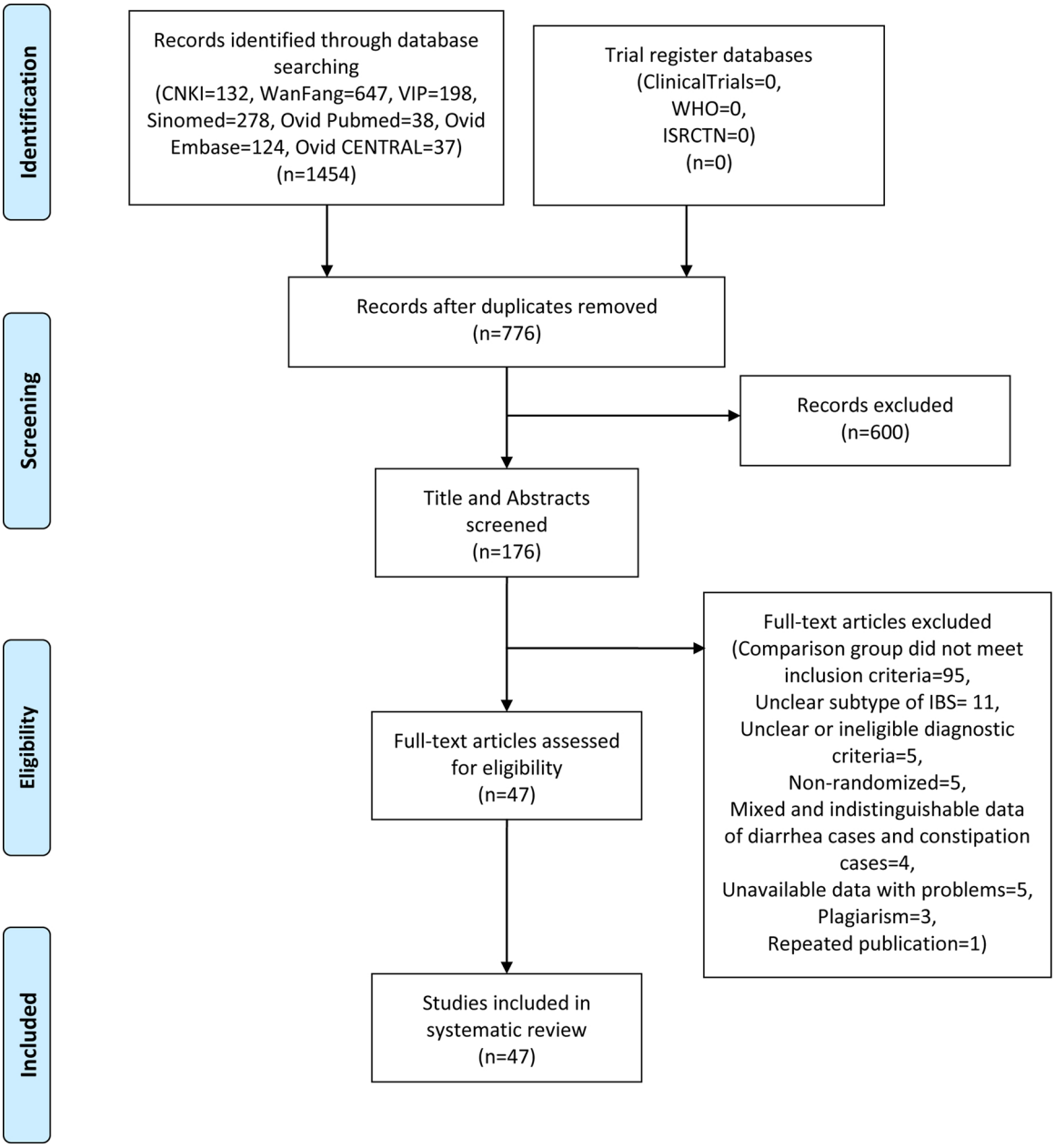

Fig. 1. Flow diagram.

blinding domains were rated low risk. The remaining trials had high risk of performance bias due to different dosage forms between the two groups, or unclear risk of detection bias due to lack of description of the evaluator blinding. In the domain of incomplete outcome data, three trials were deemed to have high risk due to a dropout rate of more than 10 %, and the other three trials had very few dropouts, which were low risk. The remaining trials did not mention whether there was attrition and was rated as unclear. Twenty-six trials were rated as high bias because they did not report any primary outcomes or the necessary specific symptoms (diarrhea/constipation, abdominal pain or distension) that were not contained in the definition of overall symptoms improvement rate (or overall symptoms scores). The remaining trials had low bias. One trial [35] was considered to have high risk of other bias due to funding from pharmaceutical companies. The five trials adequately reported for the funding, eligible standard and baseline situation and have low risk. The remaining trials had high risk due to insufficient reporting of the above three sets of data. (Fig. 3)

4.4. Effects of the interventions

4.4.1. IBS-D

Considering the general heterogeneity brought about by the different composition of CHM formulae, we finally adopted the random effect model in the meta-analysis. Meta-analysis was conducted only for overall symptoms improvement rate and relapse rate. Due to insufficient data, subgroup analysis and sensitivity analysis were only performed on overall symptoms improvement rate.

4.4.2. Primary outcomes

"4.4.2.1" should be "4.4.1.1.1".4.4.2.1 Global improvements of symptoms

4.4.2.1.1. Overall symptom improvement rate. A total of 41 trials reported overall symptom improvement rate: 1509/1665 (90.6 %) participants in CHM group versus 1109/1542 (71.9 %) participants in probiotics group. Compared with probiotics, CHM showed certain advantages in increasing overall symptom improvement rate (RR 1.24, 95 % CI 1.18–1.30, I^2 = 55 %, 41 trials). (Fig. 4)

Table 1
Characteristics of included trials.

Study ID	Funding	Type of IBS	Rome Criteria	Sample Size	Age(y)	Sex(M/F)	Course of disease	CHM
Al-Jassim ZG 2019	NR	C	III	I: 15 C: 15	NR	NR	NR	Ginger root powder
Bian YJ 2017	NR	D	III	I: 30 C: 30	I: 34.60 C: 36.03	I: 14/16 C: 17/13	I: 2.26y C: 2.40y	Modified Shenling Baizhu San combined with Sishen Wan
Cai T 2012	NR	D	III	I: 42 C: 41	NR	NR	NR	Huangqi Guizhi Wuwu Tang
Chen YB 2015	NR	D	III	I: 36 C: 30	I: 51 C: 49.2	I: 21/15 C: 14/16	NR	Tiaochang Fang
Ding ZY 2015	NR	D	III	I: 36 C: 36	I: 41.56 C: 40.22	I: 19/17 C: 18/18	I: 6.95y C: 6.75y	Modified Shenling Baishu San 1
Dong GF 2014	NR	D	III	I: 35 C: 35	I: 43 C: 42.5	I: 16/19 C: 17/18	I: 4.5y C: 4.1y	Modified Shenling Baishu San 2
Du YJ 2016	NR	D	III	I: 30 C: 30	I: 40.5 C: 42.67	I: 20/10 C: 15/15	I: 4.27y C: 5.27y	Modified Buhuanjin Zhengqi San 1
Gao Y 2013	NR	D	III	I: 60 C: 59	I: 42 C: 41	I: 31/29 C: 30/29	I: 5.2y C: 5.1y	Modified Wenshen Jianpi Fang
Gong JH 2013	NR	D	III	I: 56 C: 42	I: 24－50 C: 28－56	I: 26/30 C: 24/18	I: 6m－7y C: 6m－6.5y	Wangshi Yigan Fupi Tang
Guo JX 2016	NR	D	III	I: 34 C: 37	I: 19－58 C: 21－57	I: 16/18 C: 18/19	I: 7m－11y C: 8m－10y	Modified Tongxie Yaofang 1
He L 2012	NR	D	III	I: 36 C: 30	I: 18－64 C: 18－62	I: 11/25 C: 12/18	I: 1.2－6y C: 1.5－6y	Modified Qiwei Baizhu San combined with Tongxie Yaofang
Hu LJ 2014	Guangzhou University of Chinese Medicine Research Innovation Funding Project (No. 11CX024)	D	III	I: 50 C: 50	I: 40.3 C: 45.4	I: 22/28 C: 25/25	I: 6m－8y C: 6m－7y	Modified Tongxie Yaofang 2
Hu W 2006	NR	D	II	I: 50 C: 35	I: 36.1 C: 36.2	I: 13/37 C: 9/26	I: 2.9y C: 3.1y	Tiaogan Zhixie Tang
Ko SJ 2013	Cell Biotech Co., Ltd. (2011CBT- 001), and by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science, and Technology (2005－0049404)	D	III	I: 13 C: 14	I: 49.6 C: 47.1	NR	NR	Huoxiang Zhengqi San
Li CY 2012	NR	D	II	I: 95 C: 80	I: 34.6 C: 35.1	I: 46/49 C: 37/43	I: 3.23y C: 3.63y	Modified Tongxie Yaofang combined with Shenling Baizhu San 1
Li DS 2017 (a)	NR	D	III	I: 30 C: 30	I: 38.767 C: 45.03	I: 21/9 C: 17/13	I: 3.05y C: 2.733y	Modified Buhuanjin Zhengqi San 2
Li DS 2017 (b)	NR	D	III	I: 30 C: 30	I: 40.57 C: 45.03	I: 16/14 C: 17/13	I: 2.65y C: 2.733y	Modified Buhuanjin Zhengqi San 3
Li JH 2012	NR	D	III	I: 30 C: 30	NR	NR	NR	Modified Tongxie Yaofang combined with Banxia Xiexin Tang
Li QJ 2015	NR	D	III	I: 37 C: 33	I: 37.25 C: 40.25	I: 20/17 C: 19/14	I: 23.21m C: 22.94m	Shugan Jianpi Qufeng Tang
Liu F 2015	NR	D	III	I: 36 C: 35	I: 40.89 C: 38.14	I: 21/15 C: 24/11	NR	Modified Tongxie Yaofang combined with Shenling Baizhu San 2
Luo CM 2007	NR	D	II	I: 33 C: 35	I: 44.11 C: 42.78	I: 16/17 C: 19/16	I: 8.01y C: 7.89y	Modified Tongxie Yaofang 3
Meng YB 2009	NR	D	II	I: 30 C: 30	I: 19－64 C: 23－66	I: 10/20 C: 18/12	I: 41m C: 43m	Jianpi Huashi Fang
Miao C 2012	NR	D	III	I: 30 C: 30	I: 38.900 C: 38.770	I: 21/9 C: 21/9	I: 6.533y C: 5.5171y	Modified Lizhong Tang
Pan F 2009	Hangzhou Municipal Science and Technology Administration (No. 20070433Q24)	D	III	I:80 C:40	T: 39.2 C: 37.5	I: 33/47 C: 17/23	I: 6.3y C: 5.9y	Tongxie Yaofang
Qiao HJ 2015	NR	D	III	I: 43 C: 43	I: 45.44 C: 50.70	I: 23/20 C: 19/24	I: 3.05y C: 3.00y	Shuxie Fang
Rao J 2010	NR	D	III	I: 30 C: 30	I: 41.5 C: 40.6	I: 12/18 C: 13/17	I: 36.1m C: 36.4m	Changping Tang
Song Y 2015	NR	C	III	I: 38 C: 38	NR	NR	NR	Simo Tang Koufuye
Tang JL 2011, Han SK 2011	NR	D	III	I: 40 C: 40	I: 30.9 C: 32.4	I: 21/19 C: 20/20	I: 6.7y C: 7.4y	Jianpi Huazhuo Tongluo Fang
Wang HL 2006	NR	D	II	I: 30 C: 30	I: 18－60 C: 20－57	I: 13/17 C: 15/15	I: 0.5－10y C: 0.5－8y	Modified Qiwei Baizhu San

(*continued on next page*)

Table 1 (*continued*)

Study ID	Funding	Type of IBS	Rome Criteria	Sample Size	Age(y)	Sex(M/F)	Course of disease	CHM
Wang JY 2008	NR	D	II	I: 50 C: 50	I: 45 C: 43	I: 23/27 C: 24/26	I: 30m C: 29m	Modified Tongxie Yaofang combined with Shenling Baizhu San 3
Wang W 2018	National Natural Science Foundation of China (81260532); Guangxi Traditional Chinese Medicine National Medicine Self-financing Fund Research Project (GZZC16－13)	D	III	I: 40 C: 40	I: 40.13 C: 40.27	I: 19/21 C: 20/20	I: 6.47y C: 6.28y	Modified Chaishao Liujun Keli
Wang XJ 2019	Changchun University of Chinese Medicine "JuJingBei" Academic Research Innovation Project (FK201815)	C	IV	I: 30 C: 30	I: 38.3 C: 37.6	I: 9/21 C: 11/19	I: 16.3m C: 20.4m	Modified Dachaihu Tang
Wen TY 2016	Zhengzhou Science and Technology Department Medical Fund Project (zzzx20140510)	D	III	I: 61 C: 61	I: 57.82 C: 56.49	NR	I: 2.26y C: 2.19y	Modified Fuzi Lizhong Tang combined with Sishen Wan
Wu HQ 2015	NR	D	III	I: 50 C: 50	I: 42.94 C: 42.16	NR	I: 9.62w C: 10.43w	Wenzhong Zhixie Tang
Wu WB 2012	NR	D	III	I: 35 C: 35	I: 38.26 C: 37.00	I: 15/20 C: 14/21	I: 2.51y C: 2.94y	Heganpi Yin
Xu XT 2009	NR	D	II	I: 60 C: 60	I: 47 C: 45	I: 25/35 C: 30/30	I: 30m C: 29m	Pinggan Zhixie Tang
Xu YJ 2015	NR	D	II	I: 40 C: 40	I: 21－66 C: 24－65	I: 16/24 C: 19/21	I: 10m－24y C: 5m－22y	Jianpi Huazhi Wan
Yang F 2009	NR	D	II	I: 54 C: 32	I: 37.4 C: 39.8	I: 30/24 C: 18/14	I: 8.5y C: 8.5y	Modified Sishen Wan
Yin LJ 2002	NR	D	I	I: 50 C: 50	I: 45 C: 43	I: 23/27 C: 24/26	I: 30m C: 29m	Erzhu Tang
Yu C 2013	NR	D	III	I: 30 C: 30	I: 48.10 C: 46.27	I: 9/21 C: 11/19	I: 2.77y C: 3.10y	Modified Sini San combined with Lizhong Tang
Yu HT 2007	funded by the Administration of TCM of Jilin Province (No. 2005)	D	II	I: 30 C: 30	I: 35.6 C: 36.7	I: 13/17 C: 19/11	I: 3.7y C: 3.6y	Modified Tongxie Yaofang 4
Yu SL 2007	NR	D	II	I: 39 C: 37	I: 38.65 C: 37.60	I: 16/23 C: 15/22	I: 4.35y C: 4.24y	Modified Jijiao Lihuang Tang
Zhang SS 2004	NR	D	II	I: 36 C: 36	I: 18－64 C: 24－65	I: 16/20 C: 18/18	I: 41m C: 43m	Jianpi Huashi Fang
Zhao CX 2015	NR	D	III	I: 35 C: 34	I: 34.69 C: 34.69	I: 21/14 C: 20/14	I: 13.94y C: 14.25y	Tongxie Sishen Tang
Zhao JP 2012	NR	M	III	I: 30 C: 30	I: 39 C: 40	I: 11/19 C: 10/20	I: 9y C: 8y	Modified Tongxie Yaofang 5
Zhou SF 2016	Guizhou Province Administration of Traditional Chinese Medicine Project	D	III	I: 20 C: 20	I: 22－50 C: 19－48	I: 7/14 C: 11/9	I: 6m－13y C: 8m－12y	Shenling Guchang Keli
Zhuang YH 2005	NR	D	II	I: 12 C: 11	I: 41.83 C: 42.81	I: 5/7 C: 4/7	I: 23.64y C: 21.10y	Shenqu

Study ID	CHM dosage form	CHM dosage	Probiotic	Probiotic dosage	Probiotic Frequency	Duration of Treatment	Follow-up	Outcome	Adverse event
Al-Jassim ZG 2019	capsule	1g	Brewer's yeast tablets	500mg	qd	20d	NR	⑤⑥⑧	NR
Bian YJ 2017	decoction	100－150ml	Triple Bifidobacterium preparations 1	0.5*4g	tid	4w	NR	①⑪	NS
Cai T 2012	decoction	150mL	Triple Bifidobacterium preparations 2	0.4g	bid	4w	NR	①	NR
Chen YB 2015	decoction	NR	Bacillus Licheniformis preparations	500mg	tid	14d	NR	①⑦⑪	NS
Ding ZY 2015	decoction	150mL	Triple Bifidobacterium preparations 3	210m-g*(2－3)	bid－tid	4w	NR	①②③⑦⑪	NS
Dong GF 2014	decoction	150mL	Bacillus Licheniformis preparations	0.25g*2	tid	4w	NR	①	NR
Du YJ 2016	decoction	200mL	Triple Bifidobacterium preparations 2	420mg	tid	4w	NR	①②③⑦⑪	NS
Gao Y 2013	decoction	NR	Mixture preparations of Bacillus Subtilis and Enterococcus Faecium	0.5g	tid	8w	NR	①	NR
Gong JH 2013	decoction	NR	Triple Bifidobacterium preparations 2	420mg	tid	6w	NR	①	NR
Guo JX 2016	decoction	NR	Bacillus Licheniformis preparations	0.25g*2	tid	4w	NR	①③⑦	NR
He L 2012	decoction	75mL	Mixture preparations of Bacillus Subtilis and Enterococcus Faecium	250mg*2	tid	4w	NR	①	NR
Hu LJ 2014	decoction	NR	Triple Bifidobacterium preparations 2	0.42g	tid	4w	NR	①	NR

(*continued on next page*)

Table 1 (*continued*)

Study ID	CHM dosage form	CHM dosage	Probiotic	Probiotic dosage	Probiotic Frequency	Duration of Treatment	Follow-up	Outcome	Adverse event
Hu W 2006	decoction	NR	Clostridium Butyricum preparations	1 – 2 capsule	tid	1m	6m – 1y	①⑪	NS
Ko SJ 2013	granule	1 package	mixture preparations of 7 probiotics	1 capsule	tid	8w	2w	②④⑤⑥⑪	I: Headache (2/13), Low-back pain (1/13), Constipation (1/13), Dysmenorrhea (1/13)
Li CY 2012	decoction	NR	Triple Bifidobacterium preparations 1	0.5g*4	tid	4w	4w	①③	NR
Li DS 2017 (a)	decoction	200mL	Triple Bifidobacterium preparations 2	420mg	tid	28d	NR	①②③⑦⑪	NS
Li DS 2017 (b)	decoction	200mL	Triple Bifidobacterium preparations 2	420mg	tid	28d	NR	①②③⑦⑪	NS
Li JH 2012	bolus	6g	Triple Bifidobacterium preparations 2	420mg	bid	2w	NR	①③⑥⑦⑪	NS
Li QJ 2015	decoction	NR	Bacillus Licheniformis preparations	0.25g*2	tid	8w	NR	①②	NR
Liu F 2015	decoction	NR	Triple Lactobacillus preparations	660mg	tid	4w	3m	①②③	NR
Luo CM 2007	decoction	NR	Triple Bifidobacterium preparations 2	420mg	tid	15d	NR	①⑪	NS
Meng YB 2009	decoction	100mL	Bifidobacterium adolescentis preparations	0.35g*2	bid	4w	NR	①⑪	I: Constipation (2/30), Nausea (1/30) C: Distension (5/30), Constipation (4/30), Dry mouth (2/30)
Miao C 2012	decoction	NR	Triple Bifidobacterium preparations 2	420mg	tid	1m	NR	①②④	NR
Pan F 2009	granule	NR	Clostridium Butyricum preparations	0.35g*2	bid	4w	NR	①②⑤	NR
Qiao HJ 2015	decoction	200mL	Triple Bifidobacterium preparations 2	0.63g	bid	4w	NR	①②④⑤⑥⑦⑪	NS
Rao J 2010	decoction	100mL	Triple Bifidobacterium preparations 3	210mg*2	bid	4w	8w	①②③⑤⑥⑪	NS
Song Y 2015	oral liquid	20mL	Triple Bifidobacterium preparations 2	210mg*4	bid	4w	NR	①	NR
Tang JL 2011, Han SK 2011	decoction	100mL	Bifidobacterium adolescentis preparations	2 capsules	tid	4w	NR	①②④⑤⑥⑦	NR
Wang HL 2006	granule	NR	Mixture preparations of Clostridium	3 capsules	bid	4w	NR	①⑤⑥⑦	NR
Wang JY 2008	decoction	NR	Triple Bifidobacterium preparations 2	210mg	bid	3w	NR	①	NR
Wang W 2018	granule	150mL	Triple Bifidobacterium preparations 2	210mg*4	bid	4w	2m	②⑤⑥⑦	NR
Wang XJ 2019	decoction	100mL	Triple Bifidobacterium preparations 1	0.5g*4	tid	2w	6w	①⑤⑦⑩	NR
Wen TY 2016	decoction	75mL	Mixture preparations of Bacillus Subtilis and Enterococcus Faecium	250mg*2	bid	6w	NR	①⑤⑦	NR
Wu HQ 2015	decoction	150mL	Quadruple Bifidobacterium infantis preparations	0.5g*3	tid	1m	NR	①⑦	NR
Wu WB 2012	decoction	250mL	Triple Bifidobacterium preparations 2	0.42g	bid	4w	NR	①②	NR
Xu XT 2009	decoction	NR	Triple Bifidobacterium preparations 2	210mg	bid	3w	NR	①	NR
Xu YJ 2015	bolus	10g	Triple Lactobacillus preparations	0.66g	tid	30d	NR	①⑤⑥⑦	NR
Yang F 2009	decoction	100mL	Triple Bifidobacterium preparations 1	0.5g*4	tid	1 – 2m	8m	①③	NR
Yin LJ 2002	decoction	NR	Bifidobacterium adolescentis preparations	0.35g*2	bid	2 – 5w	6m	①③	NR
Yu C 2013	decoction	150mL	Triple Bifidobacterium preparations 2	210mg*3	bid	4w	4w	①②④⑤⑥⑪	NS
Yu HT 2007	decoction	150mL	Bifidobacterium adolescentis preparations	50mg	tid	30d	NR	①	NR
Yu SL 2007	decoction	NR	Triple Bifidobacterium preparations 2	210mg*2	tid	4w	NR	①⑤⑥⑦	NR
Zhang SS 2004	decoction	100mL	Bifidobacterium adolescentis preparations	0.35m*2	bid	4w	NR	①⑤⑥⑦	NR
Zhao CX 2015	decoction	NR	Triple Bifidobacterium preparations 2	210mg*3	bid	4w	NR	①	NR
Zhao JP 2012	decoction	NR	Bacillus Licheniformis preparations	0.5g	tid	4w	1y	①	NR
Zhou SF 2016	granule	150 – 200m-L	Triple Bifidobacterium preparations 1	2g	tid	4w	NR	①②③⑥⑦	NR
Zhuang YH 2005	decoction	100mL	Bifidobacterium adolescentis preparations	0.7g	tid	2w	NR	①	NR

Note: D, IBS-D; C, IBS-C; M, IBS-M; I, Rome I; II, Rome II; III, Rome III; IV, Rome IV; y, year; m, month; w, week; NR, not reported; NS, not serious.
Outcomes: ①Overall symptoms improvement rate, ②Overall symptom scores, ③Relapse rates, ④Quality of life, ⑤Abdominal pain relief, ⑥Distension relief, ⑦Diarrhea relief, ⑧Constipation relief, ⑨Anxiety scores, ⑩Depression scores, ⑪Adverse events, ⑫Cost-effectiveness.

Table 2
Composition of probiotics.

Probiotics	Product names	Manufacturers	Composition and dosage
triple Bifidobacterium preparations 1	JinShuangQi	Inner Mongolia Shuangqi Pharmaceutical Co., Ltd., Inner Mongolia, China	Bifidobacterium longum (0.5×10^7 CFU), Lactobacillus bulgaricus (0.5×10^6 CFU) and Streptococcus thermophiles (0.5×10^6 CFU)
triple Bifidobacterium preparations 2	PeiFeiKang	Shanghai Xinyi Pharmaceutical Co., Ltd., Shanghai, China	Bifidobacterium (1.0×10^7 CFU), Lactobacillus (1.0×10^7 CFU) and Enterococcus (1.0×10^7 CFU)
triple Bifidobacterium preparations 3	BeiFeiDa	Jincheng Haelsth Pharmaceutical Co., Ltd., Shanxi, China	Bifidobacterium longum (1.0×10^6 CFU), Lactobacillus acidophilus (1.0×10^6 CFU) and Enterococcus faecalis (1.0×10^6 CFU)
Lactobacillus acidophilus preparations	YiJunKang	Tonghua Golden-horse Pharmaceutical Group Co., Ltd., Jilin, China	Lactobacillus acidophilus (5×10^6)
Bifidobacterium adolescentis preparations	LiZhuChangLe	Livzon Pharmaceutical Group Co., Ltd., Guangdong, China	Bifidobacterium adolescentis (0.5×10^8)
Clostridium Butyricum preparations	Miyarisan	Miyarisan Pharmaceutical Co., Ltd., Nagano, Japan	Clostridium Butyricum MIYAIRI 588 (0.35×10^6 CFU)
mixture preparations of 7 probiotics	Duolac7s	CellBiotechCo.,Ltd., Gimpo, Korea	Lactobacillus acidophilus (7×10^8), Lactobacillus plantarum (7×10^8), Lactobacillus rhamnosus (7×10^8), Bifidobacterium breve (7×10^8), Bifidobacterium lactis (7×10^8), Bifidobacterium longum (7×10^8) and Streptococcus thermophiles (7×10^8)
quadruple Bifidobacterium infantis preparations	SiLianKang	Hangzhou Grand Biologic Pharmaceutical INC., Hangzhou, China	Bifidobacterium infantis (0.5×10^6 CFU), Lactobacillus (0.5×10^6 CFU), Enterococcus (0.5×10^6 CFU) and Bacillus cereus (0.5×10^5 CFU)
Saccharomyces boulardii preparations	YiHuo	Laboratoires BIOCODEX, France	Saccharomyces boulardii (1.3×10^9 CFU/g)
mixture preparations of Clostridium Butyricum and Bifidobacterium infantis	ChangLeKang	Shandong Kexing Biological Products Co., Ltd., Shandong, China	Clostridium Butyricum (1.0×10^7 CFU/g) and Bifidobacterium infantis (1.0×10^6 CFU/g)
Bacillus Licheniformis preparations	ZhengChangSheng	Northeast Pharmaceutical Group Co., Ltd., Shenyang, China	Bacillus Licheniformis (2.5×10^8)
triple Lactobacillus preparations	JuKe	Jiangsu Meitong Pharmaceutical Co., Ltd., Jiangsu, China	Lactobacillus lactis (≥70), Lactobacillus acidophilus ($\geq 7 \times 10^3$) and Streptococcus lactis($\geq 1.4 \times 10^4$)
mixture preparations of Bacillus Subtilis and Enterococcus Faecium	MeiChangAn	Beijing Hanmei Pharmaceutical Co., Ltd., Beijing, China	Bacillus Subtilis R-179 (5.0×10^7) and Enterococcus Faecium R-026 (4.5×10^8)

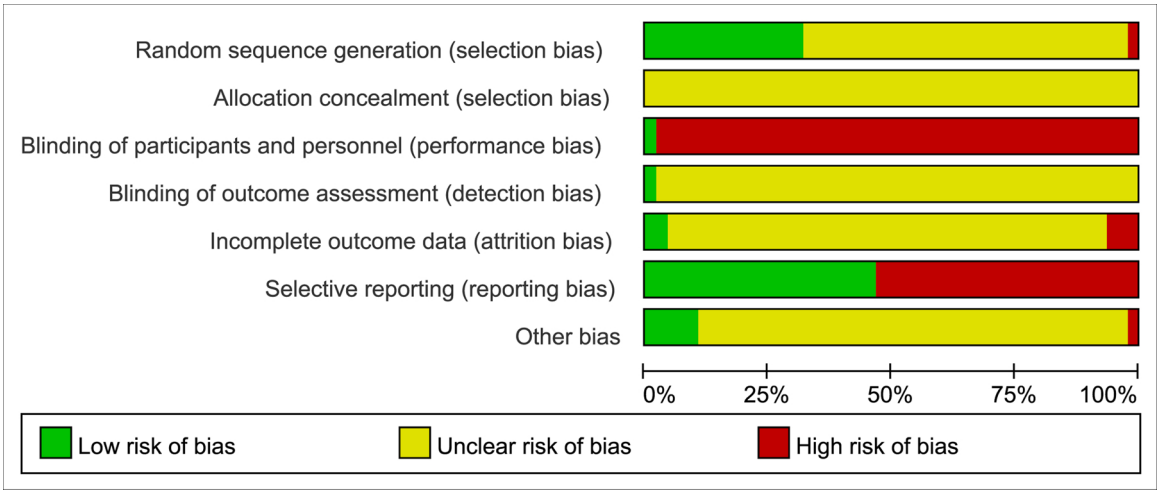

Fig. 2. Risk of bias graph.

4.4.2.1.1.1“4.4.2.1.1.1” should be "①".. Sensitivity analysis

‘Low risk’ showed that random sequence generation bias did not influence the above results (RR 1.21, 95 % CI 1.13–1.29, $P = 0.09$, $I^2 =$ 37 %, 13 trials, 1153 participants). ‘Low risk’ showed that selective reporting bias did not influence the above results (RR 1.24, 95 % CI 1.13–1.36, $P < 0.00001$, $I^2 = 74$ %, 18 trials, 1478 participants). (Table 3)

“4.4.2.1.1.2” should be "②".4.4.2.1.1.2. Subgroup analysis

Due to the significant heterogeneity ($I^2 = 55$ %), subgroup analysis was performed according to the registered protocol.

There was a statistically significant difference between subgroups on the effect of CHM on overall symptoms improvement rate, when comparing trials with different Rome criteria (test for subgroup differences: $P < 0.00001$, $I^2 = 92$ %; Rome II: RR 1.32, 95 % CI 1.22–1.43, $I^2 = 28$ %, 1066 participants; Rome III: RR 1.20, 95 % CI 1.15–1.26, $I^2 = 28$ %, 2041 participants) (**Supplementary File 3**); when comparing trials assessing the duration of treatment within 4 weeks versus 4 weeks to 6 months (test for subgroup differences: $P =$ 0.04, $I^2 = 76.4$ %; 4w-6m: RR 1.26, 95 % CI 1.20–1.33, $I^2 = 44$ %, 2669 participants) (**Supplementary File 4**); when comparing trials assessing single strain versus multi-strain probiotics (test for subgroup differences: $P = 0.05$, $I^2 = 73.1$ %; multi-strain probiotics: RR 1.27, 95 % CI 1.21–1.32, $P < 0.20$, $I^2 = 18$ %, 2333 participants) (**Supplementary File 5**); when trials compared SLIS formulae with different probiotics (test for subgroup differences: $P = 0.002$, $I^2 = 76.8$ %) (Fig. 5). The CHM prescriptions used in the trials included in this

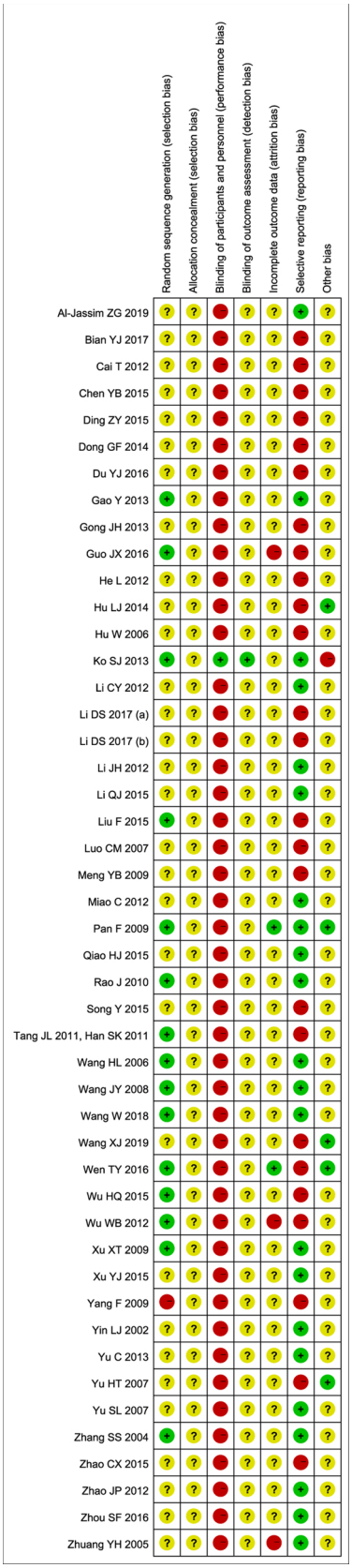

Fig. 3. Risk of bias of summary.

study could be mainly divided into four categories according to their actions: SLIS formulae; ISRD formulae; SLISRD formulae; WISK formulae. Subgroup analysis based on the same type of formulae with the same probiotics showed that SLIS formulae might be better than triple Bifidobacterium preparations 2 for improving the overall symptoms of IBS-D (RR 1.33, 95 % CI 1.20–1.47, $P < 0.51$, $I^2 = 0$ %, 6 trials, 476 participants) (Fig. 5).

However, it must be recognized that the quality of the evidence in the above subgroups analysis was very low (Table 6).

“4.4.2.1.1.3” should be "⑤".4.4.2.1.1.3. Trial sequential analysis

The DARIS was calculated to be 3584 participants, based on an event rate in the control group of 72.8 %, a risk ratio reduction (RRR) of 10 %, a two-sided alpha of 5.0 %, a beta of 10 %, and observed diversity of 60 %. TSA showed that the Z-curve crossed the benefit boundary but did not reach the required information size. This indicates that CHM versus probiotics results in a 10 % or greater RRR among IBS-D. The TSA-adjusted CI was 1.17 to 1.31. (Fig. 6)

“4.4.2.1.1.4” should be "④".4.4.2.1.1.4. Publication Bias

There were some signs of asymmetry in the visual inspection of the funnel plot, indicating a high risk of publication bias. (Fig. 7)

“4.4.2.1.1.5” should be "⑤".4.4.2.1.1.5. Quality of the evidence

Summary of findings for the overall symptoms improvement rate provides detailed information on the evidence assessment. The results of several subgroup analyses had very low quality evidence. (Table 6)

4.4.2.1.2. Overall symptoms scores. Fifteen trials [35,39,41,50,52,53,56–59,61,64,68,74,79] reported overall symptoms scores, and meta-analysis was not performed given that they used different custom scoring criteria. Twelve trials favored CHM to reduce overall symptoms scores (but three of them [35,39,79] showed no statistical difference between two groups). Almost all of the trials were small sample sizes (Table 4).

4.4.2.2. “4.4.2.2” should be "4.4.1.1.2". Quality of life. Only one trial [58] reported that a modified Tongxie Yaofang could reduce the total score of IBS-QOL scale by 32.96 (RR 32.96, 95 % CI 4.64–61.28) compared with triple Bifidobacterium preparations 2.

4.4.3. Secondary outcomes

“4.4.3.1” should be "4.4.1.2.1".4.4.3.1 Relapse rates. Five trials reported relapse rates. Considering the insufficient data, subgroup analysis and sensitivity analysis were not meaningful (Fig. 8), although the results showed that CHM might reduce the relapse rate to 27 % compared with probiotics (RR 0.27, 95 % CI 0.18 − 0.40, 5 trials, 382 participants). The follow-up time points of the five trials were all different (After the trial: Li CY 2012 [49]: 1st month, Liu F 2015 [53]: 3rd month, Rao J 2010 [59]: 2nd month, Yang F 2009 [71]: 8th month, Yin LJ 2002 [72]: 6th month), and the results were interpreted with caution due to their clinical heterogeneity.

4.4.3.1.0.1. Quality of the evidence. The certainty of evidence for relapse rate was defined as very low. (Table 6)

“4.4.3.2” should be "4.4.1.2.2".4.4.3.2 Predominant symptom relief. Due to the significant differences in the scoring criteria, no meta-analysis were performed for the following outcomes. The results of qualitative synthesis are shown in Tables 4 and 5.

4.4.3.2.1. Abdominal pain relief. “4.4.3.2.1.1” should be "①".4.4.3.2.1.1. Effective rate of abdominal pain relief

Six studies [52,62,70,74–76] reported improvement in abdominal pain in the form of ratios (Table 5). No significant statistical differences between the two groups were found in the two trials. Although the four trials [52,70,75,76] supported CHM, limited to the small sample size and nearly invalid CI lower limit, this result should be treated with caution.

“4.4.3.2.1.2” should be "②".4.4.3.2.1.2. Abdominal pain scores

17 trials [35,36,39,41,44,45,50,51,57–59,61,64,66,74,79] measured abdominal pain scores. In the CHM group, abdominal pain was

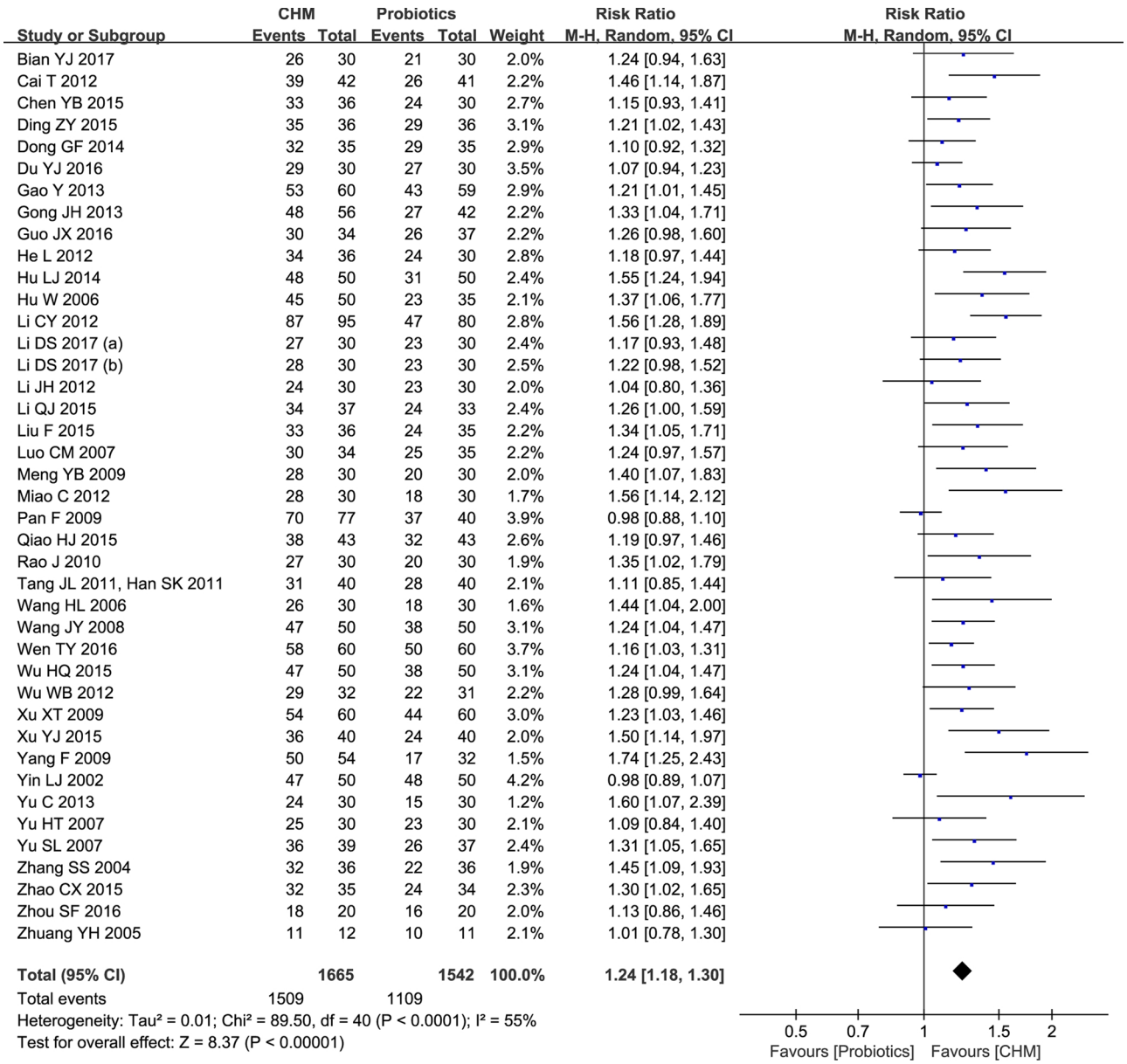

Fig. 4. Forest plot of overall symptoms improvement rate.

relieved to varying degrees, but 8 studies [35,36,39,41,45,50,51,61] did not demonstrate statistically significant differences between two groups (Table 4).

4.4.3.2.2. Distension relief. “4.4.3.2.2.1” should be "①".4.4.3.2.2.1. Effective rate of distension relief

Five trials [52,62,70,75,76] measured changes of distension in the form of ratios. Although each trial showed that CHM could relieve abdominal pain to varying degrees, the lower CI limits for all trials were close to the invalid line, and there was no statistically significant difference between the two groups in one trial [76]. (Table 5)

"4.4.3.2.2.2” should be "②".4.4.3.2.2.2. Distension scores

Nine trials [35,45,51,57–59,61,64,79] measured distension scores. Four trials [35,51,57,79] showed no statistical difference between CHM and probiotics, and the lower limit of the four RR was close to the ineffective line. (Table 4)

4.4.3.2.3. Diarrhea relief. "4.4.3.2.3.1” should be "①".4.4.3.2.3.1. Effective rate of diarrhea frequency relief

Four trials [45,52,61,70] measured changes of diarrhea frequency in the form of effective rates. One study had reported different outcomes in two separate articles [45,61]. Although each trial showed that CHM could alleviate the frequency of diarrhea in different degrees, there was no statistical difference in one trial [45,61], and the lower limit of CI in one trial [52] was almost close to the invalid line. (Table 5)

4.4.3.2.3.2“4.4.3.2.3.2” should be "②".. Diarrhea frequency scores

Seven trials [39,41,44,50,58,64,66] measured the scores of diarrhea frequency. Although each trial showed that CHM reduced frequency scores to varying degrees, five trials [39,41,44,50,66] showed no statistical difference between two groups. (Table 4)

“4.4.3.2.3.3” should be "③".4.4.3.2.3.3. Effective rate of improvement in stool consistency

Four trials [45,52,61,70] reported changes of the stool consistency in the form of effective rates. Although the trials showed that the stool consistency were relieved to varying degrees, two trials [45,61] were not statistically different between two groups, and the CI lower limit of one trial [52] was nearly ineffective. (Table 5)

“4.4.3.2.3.4” should be "④".4.4.3.2.3.4. Stool consistency scores

Seven trials [39,41,44,50,57,64,66] reported stool consistency scores. Although each trial showed a reduction in stool consistency scores to varying degrees, three trials showed no statistical difference

Table 3
Summary of findings for IBS RCTs comparison of CHM vs probiotics.

Study ID	Participants	RR[95 %CI] or MD[95 %CI]
IBS-D		
Overall symptoms improvement rate		
Bian YJ 2017	60	1.24 [0.94, 1.63]
Cai T 2012	83	1.46 [1.14, 1.87]
Chen YB 2015	66	1.15 [0.93, 1.41]
Ding ZY 2015	72	1.21 [1.02, 1.43]
Dong GF 2014	70	1.10 [0.92, 1.32]
Du YJ 2016	60	1.07 [0.94, 1.23]
Gao Y 2013	119	1.21 [1.01, 1.45]
Gong JH 2013	98	1.33 [1.04, 1.71]
Guo JX 2016	71	1.26 [0.98, 1.60]
Guo YC 2013	60	1.00 [0.91, 1.10]
He L 2012	66	1.18 [0.97, 1.44]
Hu LJ 2014	100	1.55 [1.24, 1.94]
Hu W 2006	85	1.37 [1.06, 1.77]
Li CY 2012	175	1.56 [1.28, 1.89]
Li DS 2017 (a)	60	1.17 [0.93, 1.48]
Li DS 2017 (b)	60	1.22 [0.98, 1.52]
Li JH 2012	60	1.04 [0.80, 1.36]
Li QJ 2015	70	1.26 [1.00, 1.59]
Liu F 2015	71	1.34 [1.05, 1.71]
Luo CM 2007	69	1.24 [0.97, 1.57]
Meng YB 2009	60	1.40 [1.07, 1.83]
Miao C 2012	60	1.56 [1.14, 2.12]
Pan F 2009	117	0.98 [0.88, 1.10]
Qiao HJ 2015	86	1.19 [0.97, 1.46]
Rao J 2010	60	1.35 [1.02, 1.79]
Tang JL 2011, Han SK 2011	80	1.11 [0.85, 1.44]
Wang HL 2006	60	1.44 [1.04, 2.00]
Wang JY 2008	100	1.24 [1.04, 1.47]
Wen TY 2016	120	1.16 [1.03, 1.31]
Wu HQ 2015	100	1.24 [1.04, 1.47]
Wu WB 2012	63	1.28 [0.99, 1.64]
Xu XT 2009	120	1.23 [1.03, 1.46]
Xu YJ 2015	80	1.50 [1.14, 1.97]
Yang F 2009	86	1.74 [1.25, 2.43]
Yao M 2002	64	1.15 [0.91, 1.45]
Yin LJ 2002	100	0.98 [0.89, 1.07]
Yu C 2013	60	1.60 [1.07, 2.39]
Yu HT 2007	60	1.09 [0.84, 1.40]
Yu SL 2007	76	1.31 [1.05, 1.65]
Zhang SS 2004	72	1.45 [1.09, 1.93]
Zhao CX 2015	69	1.30 [1.02, 1.65]
Zhou SF 2016	40	1.13 [0.86, 1.46]
Zhuang YH 2005	23	1.01 [0.78, 1.30]
Overall symptoms scores		
Ding ZY 2015	72	−2.52 [−5.14, 0.10]
Du YJ 2016	60	−2.54 [−3.65, −1.43]
Guo YC 2013	60	−3.80 [−5.10, −2.50]
Li DS 2017 (a)	60	−3.17 [−4.86, −1.47]
Li DS 2017 (b)	60	−3.60 [−5.26, −1.94]
Liu F 2015	71	−2.17 [−3.87, −0.47]
Miao C 2012	60	−3.37 [−5.18, −1.56]
Pan F 2009	117	0.20 [0.09, 0.31]
Qiao HJ 2015	86	−48.49 [−74.02, −22.96]
Rao J 2010	60	−7.10 [−10.21, −3.99]
Wang W 2018	80	−2.07 [−3.09, −1.05]
Wu WB 2012	70	−1.22 [−2.32, −0.12]
Yu C 2013	60	−4.27 [−7.04, −1.50]
Zhou SF 2016	40	−0.80 [−3.63, 2.03]
QOL		
Qiao HJ 2015	86	32.96 [4.64, 61.28]
Relapse rate		
Li CY 2012	175	0.29 [0.16, 0.52]
Liu F 2015	8	0.60 [0.06, 6.44]
Rao J 2010	47	0.44 [0.12, 1.65]
Yang F 2009	67	0.19 [0.06, 0.58]
Yao M 2002	53	0.23 [0.07, 0.74]
Yin LJ 2002	85	0.19 [0.08, 0.46]
Effective rate of abdominal pain relief		
Guo YC 2013	60	1.07 [0.94, 1.23]
Li QJ 2015	51	1.39 [1.03, 1.88]
Wang HL 2006	55	1.25 [0.98, 1.60]
Xu YJ 2015	73	1.95 [1.38, 2.77]
Yu C 2013	60	1.04 [0.92, 1.16]
Yu SL 2007	71	1.32 [1.06, 1.65]
Zhang SS 2004	65	1.32 [1.02, 1.71]
Abdominal pain scores		
Bian YJ 2017	60	−0.30 [−0.79, 0.19]
Ding ZY 2015	72	−0.19 [−0.87, 0.49]
Du YJ 2016	60	0.00 [−0.41, 0.41]
Guo JX 2016	71	−0.37 [−0.71, −0.03]
Guo YC 2013	60	−0.57 [−0.86, −0.28]
Li DS 2017 (a)	60	−0.47 [−0.93, −0.00]
Li DS 2017 (b)	60	−0.73 [−1.14, −0.33]
Li JH 2012	60	−0.14 [−0.72, 0.44]
Pan F 2009	117	0.12 [0.01, 0.23]
Qiao HJ 2015	86	−11.62 [−17.06, −6.18]
Rao J 2010	60	−0.87 [−1.25, −0.49]
Tang JL 2011, Han SK 2011	80	−0.04 [−0.21, 0.13]
Wang W 2018	80	−1.78 [−1.96, −1.60]
Wen TY 2016	122	−0.72 [−0.77, −0.67]
Yu C 2013	60	−0.56 [−0.98, −0.14]
Zhou SF 2016	40	−0.90 [−1.77, −0.03]
Effective rate of distension relief		
Li QJ 2015	41	1.59 [1.10, 2.30]
Wang HL 2006	51	1.63 [1.11, 2.40]
Xu YJ 2015	38	3.70 [1.21, 11.38]
Yu SL 2007	74	1.26 [1.03, 1.55]
Zhang SS 2004	57	1.23 [0.95, 1.60]
Distension scores		
Guo YC 2013	60	Not estimable
Li JH 2012	60	0.04 [−0.57, 0.65]
Pan F 2009	117	0.07 [−0.03, 0.17]
Qiao HJ 2015	86	−8.14 [−13.53, −2.75]
Rao J 2010	60	−0.80 [−1.18, −0.42]
Tang JL 2011, Han SK 2011	80	−0.34 [−0.59, −0.09]
Wang W 2018	80	−0.30 [−0.47, −0.13]
Zhou SF 2016	40	0.45 [−0.37, 1.27]
Diarrhea frequency scores		
Ding ZY 2015	72	−0.65 [−1.05, −0.25]
Du YJ 2016	60	−0.20 [−0.53, 0.13]
Guo JX 2016	71	−0.26 [−0.56, 0.04]
Li DS 2017 (a)	60	−0.27 [−0.61, 0.08]
Li DS 2017 (b)	60	−0.27 [−0.61, 0.08]
Qiao HJ 2015	86	−0.65 [−1.02, −0.28]
Wang W 2018	80	−0.45 [−0.61, −0.29]
Wen TY 2016	122	−0.06 [−0.12, 0.00]
Effective rate of diarrhea frequency relief		
Li QJ 2015	70	1.38 [1.06, 1.79]
Tang JL 2011, Han SK 2011	80	1.09 [0.76, 1.56]
Xu YJ 2015	62	1.89 [1.28, 2.80]
Stool consistency scores		
Ding ZY 2015	72	−0.74 [−1.32, −0.16]
Du YJ 2016	60	−0.40 [−0.90, 0.10]
Guo JX 2016	71	−0.26 [−0.61, 0.09]
Li DS 2017 (a)	60	−0.87 [−1.32, −0.42]
Li DS 2017 (b)	60	−0.67 [−1.18, −0.15]
Pan F 2009	117	−0.02 [−0.15, 0.11]
Wang W 2018	80	−0.36 [−0.56, −0.16]
Wen TY 2016	122	−0.74 [−0.79, −0.69]
Effective rate of stool consistency relief		
Li QJ 2015	62	1.32 [1.03, 1.69]
Tang JL 2011, Han SK 2011	80	1.53 [1.00, 2.34]
Xu YJ 2015	73	2.47 [1.58, 3.87]

(*continued on next page*)

Table 3 (*continued*)

Study ID	Participants	RR[95 %CI] or MD[95 %CI]
Diarrhea scores (not distinguishing between frequency or consistency)		
Bian YJ 2017	60	−0.18 [−0.70, 0.34]
Chen YB 2015	66	−0.16 [−0.51, 0.19]
Guo YC 2013	60	−0.30 [−0.56, −0.04]
Li JH 2012	60	−0.10 [−0.98, 0.78]
Rao J 2010	60	−0.94 [−1.37, −0.51]
Tang JL 2011, Han SK 2011	80	−0.02 [−0.26, 0.22]
Wu HQ 2015	100	−0.88 [−1.24, −0.52]
Yu C 2013	60	−0.60 [−1.04, −0.16]
Zhou SF 2016	40	−1.20 [−2.09, −0.31]
Effective rate of diarrhea relief (not distinguishing between frequency or consistency)		
Guo YC 2013	60	1.04 [0.92, 1.16]
Wang HL 2006	60	1.04 [0.89, 1.21]
Yu C 2013	60	1.61 [1.19, 2.17]
Yu SL 2007	76	1.29 [1.00, 1.66]
Zhang SS 2004	72	0.97 [0.83, 1.13]
Depression scores		
Guo YC 2013	60	−3.29 [−6.16, −0.42]
Anxiety scores		
Guo YC 2013	60	−5.34 [−8.27, −2.41]
IBS-C		
Overall symptoms improvement rate		
Wang XJ 2019	60	1.04 [0.84, 1.29]
Abdominal pain scores		
Al-Jassim ZG 2019	30	5.07 [2.95, 7.19]
Distension scores		
Al-Jassim ZG 2019	30	5.00 [2.82, 7.18]
Constipation scores		
Al-Jassim ZG 2019	30	6.20 [4.04, 8.36]
Depression scores		
Wang XJ 2019	60	−1.00 [−2.48, 0.48]
IBS-M		
Overall symptoms improvement rate		
Li XY 2011	56	1.52 [1.10, 2.09]
Zhao JP 2012	60	1.47 [1.10, 1.97]
Overall symptoms scores		
Li XY 2011	56	−4.70 [−6.55, −2.85]
Stool consistency scores		
Li XY 2011	56	−0.49 [−1.23, 0.25]
Effective rate of stool consistency relief		
Li XY 2011	56	1.99 [1.18, 3.37]

between the two groups. The forest plot showed a large heterogeneity between trials. (Table 4)

“4.4.3.2.3.5” should be "⑤".4.4.3.2.3.5. Effective rate of diarrhea (not distinguishing between frequency or consistency) relief

Four trials [62,74–76] reported the effective rate of diarrhea. Only one trial [74] showed a positive result for CHM, and the remaining trials showed no significant statistical difference between the two groups. (Table 5)

“4.4.3.2.3.6” should be "⑥".4.4.3.2.3.6. Diarrhea scores (not distinguishing between frequency or consistency)

Nine trials [36,38,45,51,59,61,67,74,79] reported diarrhea scores. The trials showed that CHM could reduce the diarrhea scores to varying degrees, but five trials [36,38,45,51,61] showed no significant statistical difference between the two groups. (Table 4)

4.4.3.3. “4.4.3.3” should be "(4)". Psychological states and cost-effectiveness. None of trials for IBS-D reported the outcome of psychological states and cost-effectiveness.

“4.4.3.4” should be "(5)".4.4.3.4 Adverse events. Thirteen trials [35,36,38,39,41,48,50,51,54,55,58,59,74] reported adverse events, 11 [36,38,39,41,48,50,51,54,58,59,74] of which claimed no adverse events in both groups, and 2 [35,55] reported detailed types and case number of adverse events, mainly for gastrointestinal symptoms such as constipation (Table 1).

4.4.4. Summary of findings table

Only overall improvement rate of symptoms and relapse rate were evaluated by GRADE (See Table 6). For the evaluation of the subgroup results for overall symptoms improvement rate see **Supplementary File 6**.

4.5. 4.4.2 IBS-C

Meta-analysis was only performed for overall symptoms improvement rate [60,65]. There was no statistically significant difference between CHM and probiotics in improving overall symptoms improvement rate for IBS-C (RR 1.19, 95 % CI 0.86–1.63, $P = 0.09$, $I^2 = 66$ %, 2 trials, 136 participants). Al-Jassim ZG 2019 [34] showed that ginger was less effective in relieving abdominal pain, distension and constipation than Brewer’ s yeast at 20 days after treatment. Wang XJ 2019 [65] showed that Dachaihu Tang might be able to lower the HADS score more than triple Bifidobacterium preparations 1, but the difference was not statistically significant. (Table 7)

4.6. 4.4.3 IBS-M

Only one trial [78] reported overall symptoms improvement rate. The results based on a very small sample size (I/C 30/30) showed that modified Tongxie Yaofang might be superior to Bacillus Licheniformis preparations in improving the overall symptoms of IBS-M (RR 1.47, 95 % CI 1.10–1.97).

5. Discussion

5.1. Summary of main results

Of the 47 RCTs (3551 participants) included in this systematic review, most used self-customized and composite outcome measurements. Almost all of the trials reported overall symptoms improvement rate (44/47), which was a composite outcome. However, there were fewer studies concerned with QOL (5/47), relapse rate (5/47), relief of specific symptoms (abdominal pain (21/47), distension (13/47), diarrhea (18/47), or constipation (1/47), psychological states (1/47), adverse events (14/47) and health economic indicators (0/47). Meta-analysis, subgroup analysis and sensitivity analysis were conducted on overall symptoms improvement rate. Only meta-analysis was performed on relapse rate. Unclear risk of bias was in almost domains of included trials. The high risk of blinding participants and personnel existed in almost all trials, and the high risk of selective reporting was present in more than half of the trials. In general, very low quality evidence showed that CHM might be superior to probiotics in alleviating overall symptoms and reducing relapse rates for IBS-D. Due to the small number and sample size of included studies on IBS-C and IBS-M, there was limited evidence of the efficacy of CHM versus probiotics for IBS-C and IBS-M.

5.2. Compared with previous studies

Although there was evidence of CHM [21–27] for IBS or probiotics for IBS [81–87], no direct evidence to evaluate CHM and probiotics for

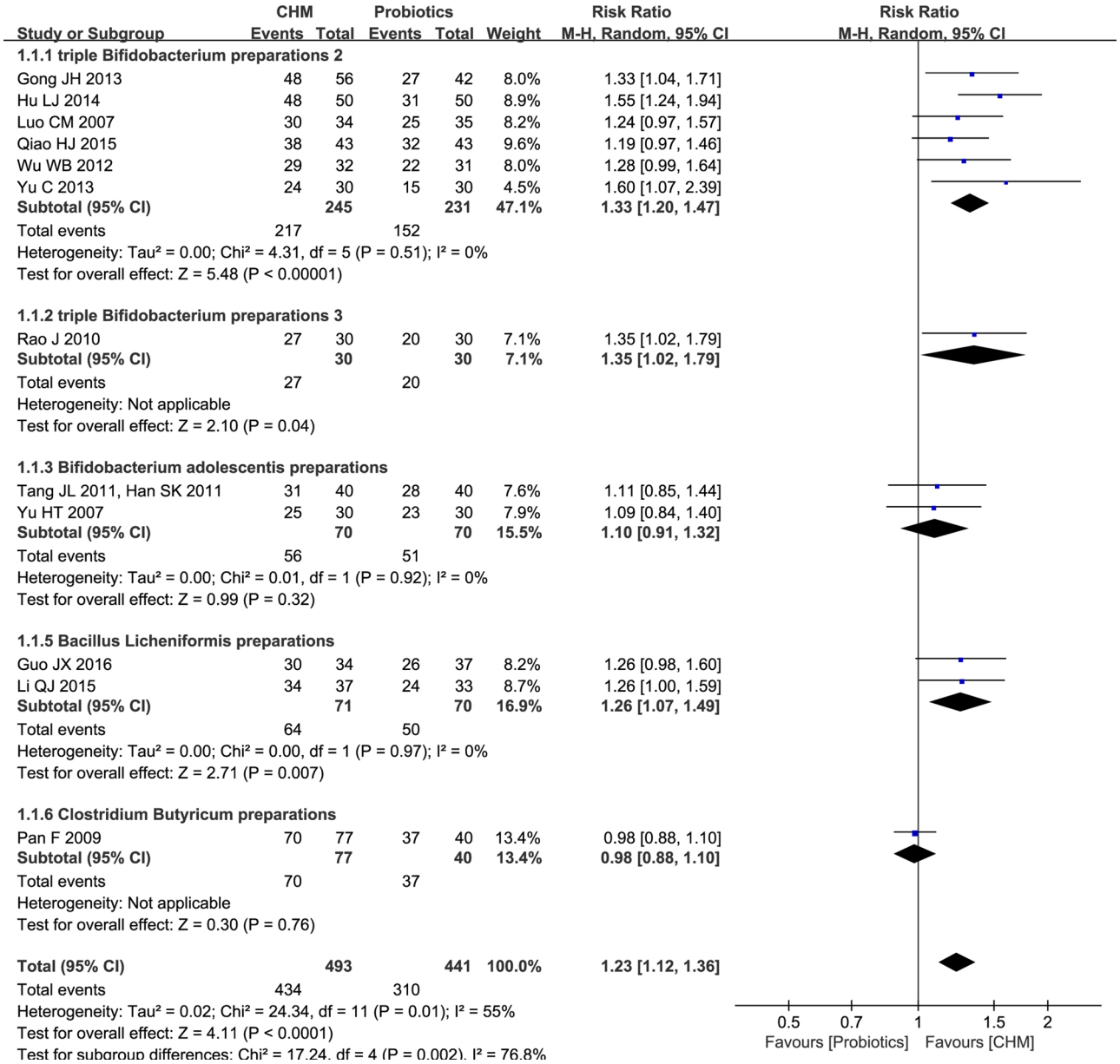

Fig. 5. Forest plot of subgroup analysis according to SLIS formulae for overall symptoms improvement rate.

IBS was identified. But high quality original studies and systematic reviews comparing CHM with placebo and probiotics with placebo were searched for indirect evidence. A primary study [88] published in JAMA showed that standard CHM formula (a modified Tongxie Yaofang) was significantly beneficial for improving overall symptoms of IBS compared with placebo (RR 2.15, 95 %CI 1.26–3.65). A systematic review [19] including 19 RCTs showed that probiotics significantly improved overall symptoms of IBS over placebo (RR 1.59, 95 %CI 1.33–1.89). Based on the above indirect comparisons, the difference of RR between CHM and probiotics in improving overall symptoms is about 0.56. This is quite different from the results of this study (SLIS vs triple Bifidobacterium preparations 2 for IBS-D, overall symptoms improvement rate: RR 1.33). This may be due to the fact that the results of the study [19] are based on multiple IBS subtypes patients and a variety of probiotics, which may make the results from indirect comparisons less reliable than this study.

5.3. Limitations

Race [89,90], age [91,92], diet [93,94] and concomitant medications (such as antibiotics and antacids) [95] during the trial which may have an effect on intestinal flora were not investigated. This could be a potential confounder due to lack of reported dietary and medication data. The probiotics involved were almost all Chinese products of mixed strain preparations, which may conceal or even confuse the effect of individual strain but may also limit the international promotion of these results. The included trials mostly used composite outcomes, which makes it impossible to answer whether CHM or probiotics effect specific symptoms.

Although we have used a random effects model to pool data to avoid overestimating the efficacy, included trials are almost all performed in China which supports CHM. This may have exaggerated the actual efficacy of CHM. Probiotics may only be used alone in clinical trials,

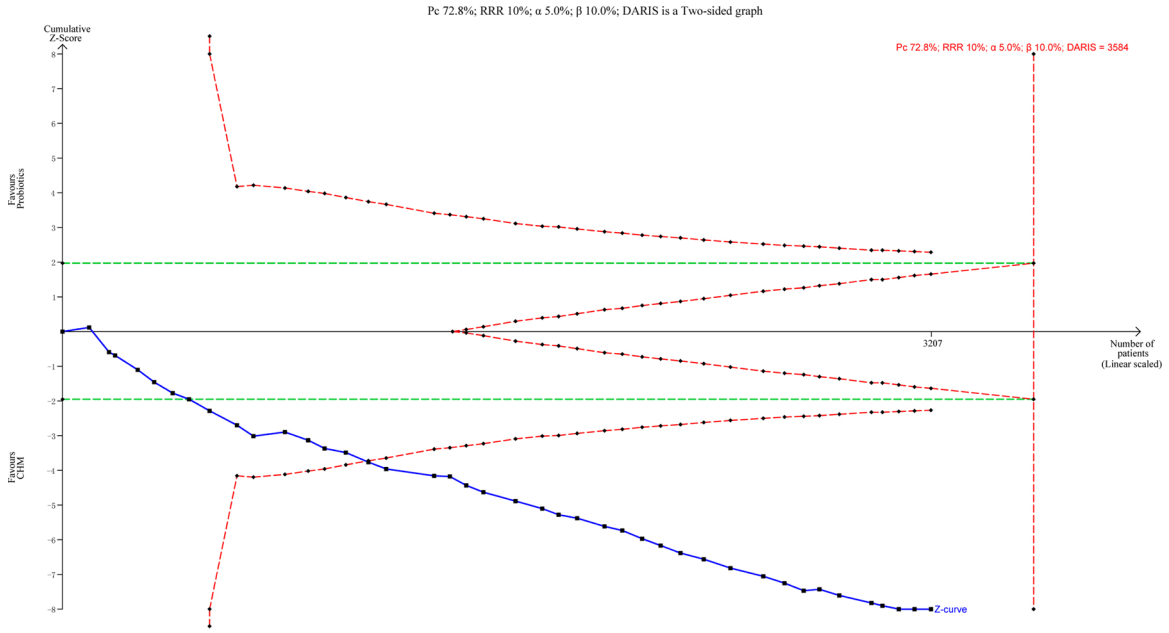

Fig. 6. Trial Sequential Analysis on overall symptoms improvement rate for IBS-D (41 trials).

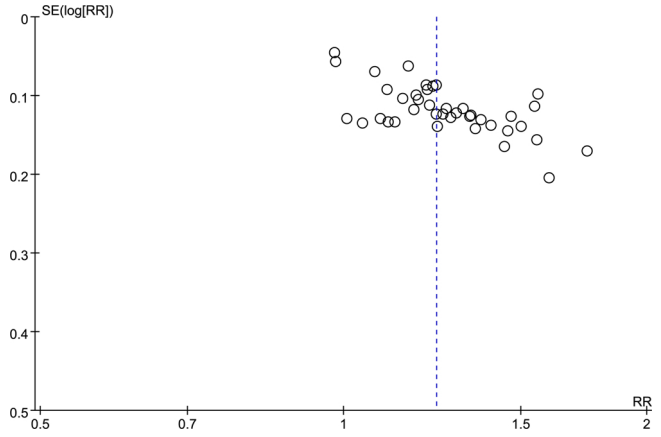

Fig. 7. Funnel plot for overall symptoms improvement rate (41 studies).

however in clinical practice, they are often used as complementary medicines in combination with other conventional medicines.

The CHM formulae involved in this study were divided into four categories according to their core composition and the efficacy, but they were completely different. According to the CHM, efficacy, duration and frequency of administration, clinical effectiveness will vary greatly. So the resulting clinical heterogeneity cannot be ignored. More importantly, the difference in underlying etiologies is one of the important potential sources of heterogeneity in the population. Unfortunately, the design of the included trials failed to further report some data that could reflect this heterogeneity, so these results may still have a confounding effect.

5.4. Implications for future research

Future research should try to recruit patients based on different etiologies and IBS subtypes, involving all ages, especially children and the elderly. Data on relevant confounding factors (such as diet and concomitant medications) during the trial should be recorded and reported. For setting outcomes, more attention should be paid to individual symptoms, psychological state, adverse events and health economics. For measuring outcomes, internationally recognized scales (especially Patient-Reported Outcome scales) should be used, such as IBS-SSS, IBS-QOL, HAMA and HAMD. In order to focus on long-term efficacy and safety, the trial should be conducted for at least 6 months. It is essential to pre-register a protocol and report it in any publication. The generation and concealment of random sequences and the implementation of blinding methods should be adequately reported. The composition and dosage of CHM and probiotics should also be reported in detail. Multi-center, multi-ethnic, large-sample, well-designed clinical trials should be conducted in the future. Although the results of TSA did not reach the required information size, the Z-curve crossed the benefit boundary. It suggested that no more studies were needed. But considering the low quality of the included studies, more studies and larger sample sizes are still needed in the future.

5.5. Implications for clinical practice

Limited data from the subgroup analysis showed that SLIS formulae may not be inferior to triple Bifidobacterium preparations (composition: Bifidobacterium, Lactobacillus and Enterococcus) for improving the overall symptoms of IBS-D. The typical representative of the SLIS formula is Tongxie Yaofang (composition: *Atractylodis Macrocephalae Rhizoma*, *Paeoniae Radix Alba*, *Citri Reticulatae Pericarpium*, and *Saposhnikoviae Radix*).

6. Conclusions

Very low quality evidence suggests that CHM may be better than probiotics when the duration of treatment lasted more than 4 weeks and SLIS formulae may be better than triple Bifidobacterium preparations for improving the overall symptoms of IBS-D; and some CHM may be more advantageous for reducing relapse rates of IBS-D than probiotics, but this needs to be confirmed by large sample size trials in the future, and it is not clear which categories of formula is more advantageous than which probiotics. Although individual studies have

Table 4
Effect size of other continuous outcomes.

Study	CHM			Probiotics			Mean Difference [95 %CI]
	Mean	SD	Total	Mean	SD	Total	
Overall symptomsscores							
Ding ZY 2015	2.57	4.28	36	5.09	6.77	36	−2.52 [−5.14, 0.10]
Du YJ 2016	3.13	1.74	30	5.67	2.58	30	−2.54 [−3.65, −1.43]
Ko SJ 2013	30.98	17.43	14	31.55	17.98	14	−0.57 [−13.69, 12.55]
Li DS 2017 (a)	4.7	3.45	30	7.867	3.256	30	−3.17 [−4.86, −1.47]
Li DS 2017 (b)	4.267	3.3	30	7.867	3.256	30	−3.60 [−5.26, −1.94]
Liu F 2015	4.83	3.3	36	7	3.96	35	−2.17 [−3.87, −0.47]
Miao C 2012	3.3	3.053	30	6.67	4.037	30	−3.37 [−5.18, −1.56]
Pan F 2009	10.06	0.23	77	9.86	0.32	40	0.20 [0.09, 0.31]
Qiao HJ 2015	85.23	63.13	43	133.72	57.52	43	−48.49 [−74.02, −22.96]
Rao J 2010	3.4	3.93	30	10.5	7.76	30	−7.10 [−10.21, −3.99]
Wang W 2018	5.46	2.21	40	7.53	2.44	40	−2.07 [−3.09, −1.05]
Wu WB 2012	1.84	2.14	35	3.06	2.54	35	−1.22 [−2.32, −0.12]
Yu C 2013	4.4	4.056	30	8.67	6.609	30	−4.27 [−7.04, −1.50]
Zhou SF 2016	8.2	4.77	20	9	4.34	20	−0.80 [−3.63, 2.03]
Abdominal pain scores							
Bian YJ 2017	0.67	0.84	30	0.97	1.07	30	−0.30 [−0.79, 0.19]
Ding ZY 2015	1.15	1.44	36	1.34	1.51	36	−0.19 [−0.87, 0.49]
Du YJ 2016	0.4	0.814	30	0.4	0.814	30	0.00 [−0.41, 0.41]
Guo JX 2016	0.79	0.729	34	1.16	0.727	37	−0.37 [−0.71, −0.03]
Ko SJ 2013	27.97	18.35	14	28.45	18.55	14	−0.48 [−14.15, 13.19]
Li DS 2017 (a)	1.4	1.192	30	1.867	0.507	30	−0.47 [−0.93, 0.00]
Li DS 2017 (b)	1.133	1.008	30	1.867	0.507	30	−0.73 [−1.14, −0.33]
Li JH 2012	2.63	1.13	30	2.77	1.17	30	−0.14 [−0.72, 0.44]
Pan F 2009	2.82	0.38	77	2.7	0.24	40	0.12 [0.01, 0.23]
Qiao HJ 2015	11.05	13.7	43	22.67	11.97	43	−11.62 [−17.06, −6.18]
Rao J 2010	0.2	0.55	30	1.07	0.91	30	−0.87 [−1.25, −0.49]
Tang JL 2011, Han SK 2011	0.85	0.42	40	0.89	0.37	40	−0.04 [−0.21, 0.13]
Wang W 2018	1.21	0.56	40	2.99	0.15	40	−1.78 [−1.96, −1.60]
Wen TY 2016	0.77	0.09	61	1.49	0.18	61	−0.72 [−0.77, −0.67]
Yu C 2013	0.37	0.49	30	0.93	1.081	30	−0.56 [−0.98, −0.14]
Zhou SF 2016	1.4	1.31	20	2.3	1.49	20	−0.90 [−1.77, −0.03]
Distension scores							
Ko SJ 2013	25.65	15.1	14	31.81	18.4	14	−6.16 [−18.63, 6.31]
Li JH 2012	1.47	1.22	30	1.43	1.19	30	0.04 [−0.57, 0.65]
Pan F 2009	2.65	0.29	77	2.58	0.26	40	0.07 [−0.03, 0.17]
Qiao HJ 2015	11.63	13.75	43	19.77	11.65	43	−8.14 [−13.53, −2.75]
Rao J 2010	0.33	0.61	30	1.13	0.86	30	−0.80 [−1.18, −0.42]
Tang JL 2011, Han SK 2011	0.83	0.58	40	1.17	0.54	40	−0.34 [−0.59, −0.09]
Wang W 2018	0.92	0.31	40	1.22	0.46	40	−0.30 [−0.47, −0.13]
Zhou SF 2016	1.85	0.99	20	1.4	1.6	20	0.45 [−0.37, 1.27]
Diarrhea frequency scores							
Ding ZY 2015	0.45	0.13	36	1.1	1.21	36	−0.65 [−1.05, −0.25]
Du YJ 2016	0.13	0.507	30	0.33	0.758	30	−0.20 [−0.53, 0.13]
Guo JX 2016	0.71	0.579	34	0.97	0.726	37	−0.26 [−0.56, 0.04]
Li DS 2017 (a)	0.133	0.507	30	0.4	0.814	30	−0.27 [−0.61, 0.08]
Li DS 2017 (b)	0.133	0.507	30	0.4	0.814	30	−0.27 [−0.61, 0.08]
Qiao HJ 2015	1.72	0.77	43	2.37	0.95	43	−0.65 [−1.02, −0.28]
Wang W 2018	1.02	0.34	40	1.47	0.38	40	−0.45 [−0.61, −0.29]
Wen TY 2016	1.49	0.17	61	1.55	0.18	61	−0.06 [−0.12, 0.00]
Stool consistency scores							
Ding ZY 2015	0.31	0.93	36	1.05	1.52	36	−0.74 [−1.32, −0.16]
Du YJ 2016	0.73	0.98	30	1.13	1.001	30	−0.40 [−0.90, 0.10]
Guo JX 2016	0.79	0.77	34	1.05	0.743	37	−0.26 [−0.61, 0.09]
Li DS 2017 (a)	0.333	0.758	30	1.2	0.997	30	−0.87 [−1.32, −0.42]
Li DS 2017 (b)	0.533	1.042	30	1.2	0.997	30	−0.67 [−1.18, −0.15]
Pan F 2009	2.46	0.28	77	2.48	0.36	40	−0.02 [−0.15, 0.11]
Wang W 2018	1.17	0.49	40	1.53	0.4	40	−0.36 [−0.56, −0.16]
Wen TY 2016	0.85	0.1	61	1.59	0.17	61	−0.74 [−0.79, −0.69]
Diarrhea scores (not distinguishing between frequency or consistency)							
Bian YJ 2017	1.27	0.83	30	1.45	1.2	30	−0.18 [−0.70, 0.34]
Chen YB 2015	0.85	0.61	36	1.01	0.81	30	−0.16 [−0.51, 0.19]
Li JH 2012	3.9	1.69	30	4	1.8	30	−0.10 [−0.98, 0.78]
Rao J 2010	0.13	0.43	30	1.07	1.11	30	−0.94 [−1.37, −0.51]
Tang JL 2011, Han SK 2011	0.87	0.71	40	0.89	0.31	40	−0.02 [−0.26, 0.22]
Wu HQ 2015	0.86	0.88	50	1.74	0.94	50	−0.88 [−1.24, −0.52]
Yu C 2013	0.3	0.651	30	0.9	1.029	30	−0.60 [−1.04, −0.16]
Zhou SF 2016	1.1	1.02	20	2.3	1.75	20	−1.20 [−2.09, −0.31]

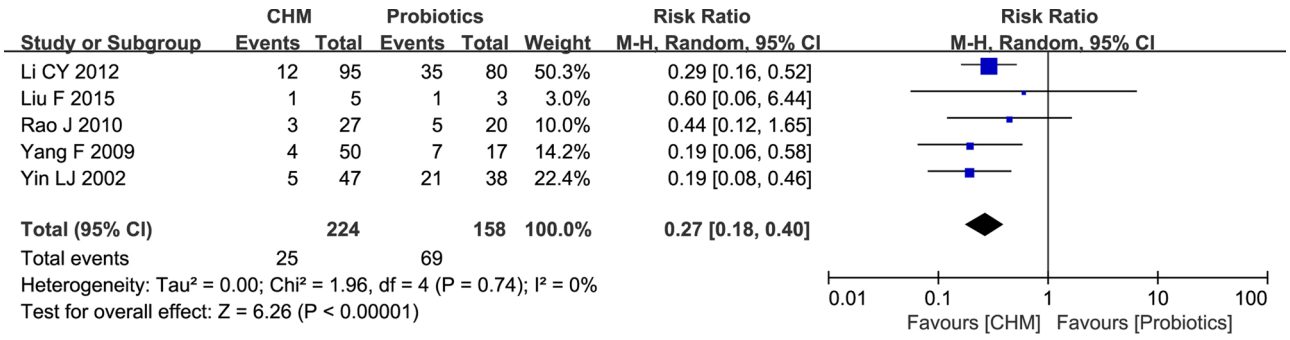

Fig. 8. Forest plot of relapse rates for IBS-D.

Table 5
Effect size of other dichotomous outcomes.

Study	CHM		Probiotics		Risk Ratio [95 %CI]
	Events	Total	Events	Total	
Effective rate of abdominal pain relief					
Li QJ 2015	25	27	16	24	1.39 [1.03, 1.88]
Wang HL 2006	26	28	20	27	1.25 [0.98, 1.60]
Xu YJ 2015	36	38	17	35	1.95 [1.38, 2.77]
Yu C 2013	29	30	28	30	1.04 [0.92, 1.16]
Yu SL 2007	34	36	25	35	1.32 [1.06, 1.65]
Zhang SS 2004	30	33	22	32	1.32 [1.02, 1.71]
Effective rate of distension					
Li QJ 2015	20	21	12	20	1.59 [1.10, 2.30]
Wang HL 2006	22	25	14	26	1.63 [1.11, 2.40]
Xu YJ 2015	10	18	3	20	3.70 [1.21, 11.38]
Yu SL 2007	36	38	27	36	1.26 [1.03, 1.55]
Zhang SS 2004	25	28	21	29	1.23 [0.95, 1.60]
Effective rate of diarrhea frequency relief					
Li QJ 2015	34	37	22	33	1.38 [1.06, 1.79]
Tang JL 2011, Han SK 2011	25	40	23	40	1.09 [0.76, 1.56]
Xu YJ 2015	34	36	13	26	1.89 [1.28, 2.80]
Effective rate of improvement in stool consistency					
Li QJ 2015	32	34	20	28	1.32 [1.03, 1.69]
Tang JL 2011, Han SK 2011	26	40	17	40	1.53 [1.00, 2.34]
Xu YJ 2015	33	37	13	36	2.47 [1.58, 3.87]
Effective rate of diarrhea (not distinguishing between frequency or consistency)					
Wang HL 2006	28	30	27	30	1.04 [0.89, 1.21]
Yu C 2013	29	30	18	30	1.61 [1.19, 2.17]
Yu SL 2007	34	39	25	37	1.29 [1.00, 1.66]
Zhang SS 2004	32	36	33	36	0.97 [0.83, 1.13]

Table 6
Summary of findings table.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95 % CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Probiotics	Risk with CHM			
Overall symptomsimproving rate	719 per 1000	892 per 1000 (849–935)	RR 1.24 (1.18–1.30)	3207 (41 RCTs)	⨁◯◯◯ VERY LOW [a,b,d]
Relapse rate	437 per 1000	118 per 1000 (79–175)	RR 0.27 (0.18 –0.40)	382 (5 RCTs)	⨁◯◯◯ VERY LOW [a,c]

GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanations.

[a] Downgraded by two levels: inadequate concealment of allocation, unblinded participants and personnel, and unblinded assessment of outcome.

[b] Downgraded by one level: asymmetric funnel plot.

[c] Downgraded by one level: total number of events is less than 300.

[d] Downgraded by one level: I2 > 50 %.

* The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI). CI: Confidence interval; RR: Risk ratio.

Table 7
Effect size of studies for IBS-C.

Study	CHM		Probiotics		Risk Ratio [95 %CI]
	Events	Total	Events	Total	
Overall symptoms improvement rate					
Song Y 2015	31	38	22	38	1.41 [1.03, 1.92]
Wang XJ 2019	26	30	25	30	1.04 [0.84, 1.29]
Total events	**57**	**68**	**47**	**68**	**1.19 [0.86, 1.63]** *
Abdominal pain scores					
Al-Jassim ZG 2019	31.73	3.21	15	26.66	5.07 [2.95, 7.19]
Distension scores					
Al-Jassim ZG 2019	50.0	2.88	15	45.0	5.00 [2.82, 7.18]
Constipation scores					
Al-Jassim ZG 2019	49.13	2.73	15	42.93	6.20 [4.04, 8.36]
Anxiety and Depression scores					
Wang XJ 2019	9.8	3.2	30	10.8	−1.00 [−2.48, 0.48]

* Random effect model; RR: Risk Ratio; MD: Mean Difference.

shown that CHM may be superior to probiotics in improving specific symptoms to varying degrees, due to insufficient data, certainty of evidence is not yet available. Also, due to limited data, the efficacy of CHM versus probiotics on IBS-C and IBS-M is not yet apparent.

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Data availability

Data can be supplied on request to the authors.

CRediT authorship contribution statement

Fan Long Bu: Writing - original draft. **Zi Yi Lin:** Software. **Hui Juan Cao:** Methodology, Writing - review & editing. **Nicola Robinson:** Methodology, Writing - review & editing. **Ning Liang:** Supervision. **Jian Ping Liu:** Methodology, Writing - review & editing.

Declaration of Competing Interest

Prof Nicola Robinson is Editor in Chief of the European Journal of Integrative medicine. Jian-Ping Liu is an associate Editor of the European Journal of Integrative Medicine.

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Appendix A. Supplementary data

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