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The synergistic effect of herbal medicine and probiotics in pediatric functional constipation

A systematic review and meta-analysis

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Abstract

Background: Pediatric functional constipation (PFC) is a prevalent and persistent gastrointestinal disorder, that requires various treatments, including alternative approaches. This review assessed the synergistic efficacy of herbal medicine (HM) and probiotics for PFC.

Methods: We conducted a comprehensive search of 11 databases, including English, Chinese, and Korean databases, until June 29, 2023. The inclusion criteria were randomized clinical trials (RCTs) comparing the intervention of HM with probiotics to that of the same probiotics. Statistical analyses included calculation of the mean difference (MD), standardized MD, risk ratio (RR) with a 95% confidence interval (CI), and assessment of risk of bias using Review Manager Version 5.4 software. The Grading of Recommendations Assessment, Development, and Evaluation rating system was used to evaluate evidence quality. Potential publication bias was assessed using funnel plots, Egger test, the fail-safe N test, and Duval and Tweedie trim and fill method.

Results: A total of 22 RCTs involving 2228 patients were included in the meta-analysis. The HM and probiotics group exhibited superior outcomes compared to the probiotics alone group in various parameters: total effective rate (RR: 1.24, 95% CI: 1.19–1.29, $P < .001$), Bristol fecal Score (MD: 0.80, 95% CI: 0.71–0.89, $P < .001$), gastrointestinal peptide hormone (motilin) (MD: 35.37, 95% CI: 24.64–64.10, $P < .001$), inflammation indicator (nitrous oxide) (MD: –12.45, 95% CI: –15.12 to –9.77, $P < .001$), minimal sensitive volume of the rectum (MD: –8.7, 95% CI: –10.91 to –6.49, $P < .001$), and recurrence rate (RR: 0.30, 95% CI: 0.21–0.43, $P < .001$).

Conclusion: The combination of HM and probiotics may exhibit a synergistic effect on PFC. Nevertheless, it is imperative to undertake rigorously planned RCTs to comprehensively evaluate the synergistic efficacy of HM and probiotics.

Abbreviations: B = *Bifidobacterium*, CI = confidence interval, CNKI = China National Knowledge Infrastructure, E = *Enterococcus faecalis*, EMBASE = Excerpta Medica dataBASE, FC = functional constipation, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HM = herbal medicine, KCI = Korea Citation Index, KISS, Korean Studies Information Service System, KMbase = Korean Medical database, L = *Lactobacillus*, MD = mean difference, MSP = maximal systolic pressure of the anal sphincter, MSV = minimal sensitive volume of rectum, MTL = motilin, MTV = maximum tolerated volume of rectum, NO = nitrous oxide, OASIS = Oriental Medicine Advanced Searching Integrated System, PEG = polyethylene glycol, PFC = pediatric functional constipation, RCTs = randomized clinical trials, RISS = Research Information Sharing Service, ROB = risk of bias, RR = risk ratio, S = *Streptococcus thermophilus*, SMD = standardized mean difference, SP = Substance P, SS = somatostatin, TCM = Traditional Chinese Medicine, TER = total effective rate.

Keywords: children, functional constipation, herbal medicine, meta-analysis, probiotics, systematic reviews

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This is a systematic review of previously published studies, ethical approval is not required.

If further studies on the effects of combining HM and probiotics are conducted in the future, HM may be used more actively for constipation management in children.

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1. Introduction

Pediatric functional constipation (PFC) is a prevalent gastrointestinal disorder in children, with a global average prevalence of 9.5%.[1] The initial approach to managing PFC involves demystification, education, toilet training, and the use of laxatives such as polyethylene glycol (PEG).[2] PEG is the primary choice for both initially clearing large stool accumulation and providing ongoing maintenance therapy. If PEG is not available, lactulose may serve as a secondary maintenance treatment option.[3] Using laxatives can lead to various adverse effects, such as fecal incontinence, flatulence, abdominal discomfort, and nausea.[4] Therefore, patients with functional constipation (FC) typically adopt a self-management approach and explore complementary and alternative therapies.

Herbal medicine (HM) has been used as complementary approaches and has shown significant safety and effectiveness in the treat of gastrointestinal disorders.[5] Based on previous research that examined the effects of HM on PFC, it appears to provide potential advantages without leading to significant adverse effects.[6,7]

Probiotic strains, such as *Bifidobacterium* and *Lactobacilli* are known for their production of acetate and lactate, which can potentially stimulate gut motility by generating short-chain fatty acids that reduce the intestinal pH and enhance colon peristalsis. Therefore, probiotics have been proposed as a potential treatment option for children with FC.[8,9] However, the use of probiotics has not shown significant improvements in defecation frequency, and evidence supporting their sole use is limited in PFC.[10]

Therefore, our study aimed to analyze the synergistic effect of HM combined with probiotics in the treatment of PFC, by comparing it to the use of probiotics alone.

2. Methods

2.1. Study registration

The protocol for this systematic review was registered on INPLASY (INPLASY202370042) and is available at inplasy.com (https://doi.org/10.37766/inplasy2023.7.0042). This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11]

2.2. Criteria for study selection

2.2.1. Types of studies. Only randomized clinical trials (RCTs) on HM combined with probiotics for PFC were included. Non-RCTs, RCT protocols, animal studies, case reports, surveys, and reviews were excluded.

2.2.2. Types of participants. Patients included in this study met the diagnostic criteria for FC according to the Rome III and IV diagnostic criteria, or other published criteria, guidelines, or authors' definitions. Additionally, patients were required to be under 18 years of age. Patients with FC caused by other reasons (e.g., drugs, surgery, and other intestinal organic diseases) were excluded. Moreover, patients with major organ problems (e.g., heart, liver, and lung) or those with known allergies to drugs and probiotics were also excluded.

2.2.3. Types of interventions. Interventions in the experimental group included HM combined with probiotics. Only oral HM was allowed, with no limitations on the number of herbs, formulations (e.g., powder, pill, granules, capsule, decoction, and oral solution), dosages, or duration. All probiotic strains, doses, and formulations (capsule, powder, tablet, granules, and vitamin-containing compounds) were included. Concurrent interventions (e.g., conventional treatments, and basic treatments such as dietary adjustments) were acceptable, provided that identical co-interventions were administered to all groups within the randomized allocation.

2.2.4. Types of comparisons. The control group received the same probiotics as the experimental group. If conventional or basic treatment was administered to the experimental group, the same treatment was also administered to the control group.

2.2.5. Types of outcome measures. The main outcomes included the total effective rate (TER), indicating treatment efficacy, and the symptom scores included the Traditional Chinese Medicine symptom score (evaluating the overall condition by scoring multiple systemic indicators), Bristol fecal score, defecation frequency (per week), and defecation time. Additional analyses included serum indicators (related to gastrointestinal hormones or inflammatory markers), gut microbiota (including *Bifidobacterium,* and *Lactobacillus*), and anorectal dynamic parameters to assess the physiological movements and functions of the anus and rectum. Adverse events and recurrence rates were used for the data synthesis.

2.3. Data sources and search strategy

Eleven electronic databases were searched without language or year restrictions up to June 29, 2023. The search included 3 English databases (PubMed, Excerpta Medica dataBASE, and the Cochrane Central Register of Controlled Trials), 3 Chinese databases (China National Knowledge Infrastructure, Wan Fang Database, and Chinese Scientific Journal Database), and 5 Korean medical databases (Oriental Medicine Advanced Searching Integrated System, Korean Studies Information Service System, Korea Citation Index, Research Information Sharing Service, and Korean Medical database). We used the search terms "pediatric functional constipation" and "herbal medicine," which were adapted to suit the language specifications of each database. The details of the search strategies and outcomes for each database are provided in Supplementary File 1, Supplemental Digital Content, http://links.lww.com/MD/L441.

2.4. Study selection and data extraction

2.4.1. Study selection. After removing duplicates, 2 review authors (E.K. and S.C.) conducted a literature search by screening titles and abstracts, followed by a review of full-text articles using EndNote software (version 20; Clarivate Analytics, Philadelphia, PA). The 2 reviewers independently performed the selection process and crosschecked their decisions based on the predefined criteria. Disagreements between the 2 reviewers were resolved through consultation. If consensus could not be reached, a third reviewer (J.N.) was involved in reaching an agreement.

2.4.2. Data extraction. Data extraction from the included studies was independently conducted by 2 reviewers (E.K. and S.C.). All the authors participated in discussions to reach an agreement, in cases where discrepancies arose during data extraction. Any missing or unclear data were requested from the corresponding author of the study via email. Detailed data extraction results included the first author's name, publication year, sample size, duration of illness, total treatment period, participant details, treatment intervention and comparison, outcome measures and intergroup differences, adverse events, recurrence rate, and information for evaluating the risk of bias (Robs).

Table 1

The quality of evidence.

Outcomes	Subgroup	No. participants (studies)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Heterogeneity (I^2)	Quality of evidence (GRADE)	Comments
			Risk with control group	Risk with intervention group				
Total effective rate subgroup	Total	1956 (19 RCTs)	758 per 1000	182 more per 1000 (144 more to 220 more)	RR 1.24 (1.19–1.29)	45	⨁⨁⨁⨁ High	Publication bias (0)*
	Mixture of 3 probiotics (B, L, S)	236 (3 RCTs)	805 per 1000	145 more per 1000 (56 more to 242 more)	RR 1.18 (1.07–1.30)	0	⨁⨁◯◯ Low	Risk of bias (–1)† Imprecision (–1)‡
	Mixture of 3 probiotics (B, L, E)	578 (5 RCTs)	799 per 1000	152 more per 1000 (88 more to 208 more)	RR 1.19 (1.11–1.26)	0	⨁⨁⨁⨁ High	—
	B quadruple probiotics	260 (2 RCTs)	792 per 1000	166 more per 1000 (79 more to 261 more)	RR 1.21 (1.10–1.33)	92	⨁◯◯◯ Very low	Risk of bias (–1)† Inconsistency (–1)§ Imprecision (–1)‡
	Clostridium butyricum and B	196 (2 RCTs)	510 per 1000	306 more per 1000 (153 more to 495 more)	RR 1.60 (1.30–1.97)	86	⨁⨁◯◯ Low	Inconsistency (–1)§ Imprecision (–1)‡
	Bacillus subtilis and E	434 (4 RCTs)	756 per 1000	196 more per 1000 (121 more to 280 more)	RR 1.26 (1.16–1.37)	0	⨁⨁⨁⨁ High	—
	Saccharomyces boulardii	178 (2 RCTs)	786 per 1000	157 more per 1000 (47 more to 275 more)	RR 1.20 (1.06–1.35)	0	⨁⨁◯◯ Low	Risk of bias (–1)† Imprecision (–1)‡
	C butyricum	74 (1 RCT)	757 per 1000	189 more per 1000 (23 more to 394 more)	RR 1.25 (1.03–1.52)	Not applicable	⨁⨁⨁◯ Moderate	Imprecision (–1)‡
Bristol fecal score	Total	460 (4 RCTs)	—	MD 0.8 higher (0.71 higher to 0.89 higher)	—	33	⨁⨁⨁◯ Moderate	Risk of bias (–1)†
MTL	Total	398 (4 RCTs)	—	MD 35.37 higher (24.64 higher to 46.1 higher)	—	0	⨁⨁⨁⨁ High	—
NO	Total	392 (4 RCTs)	—	MD 12.45 lower (15.12 lower to 9.77 lower)	—	0	⨁⨁⨁◯ Moderate	Risk of bias (–1)†
MSV	Total	158 (2 RCTs)	—	MD 8.7 lower (10.91 lower to 6.49 lower)	—	0	⨁⨁⨁◯ Moderate	Imprecision (–1)‡
MTV	Total	360 (4 RCTs)	—	MD 11.52 lower (17.14 lower to 5.9 lower)	—	66	⨁⨁⨁◯ Moderate	Inconsistency (–1)§
MSP	Total	284 (3 RCTs)	—	MD 10.87 lower (19.76 lower to 1.98 lower)	—	74	⨁⨁◯◯ Low	Inconsistency (–1)§ Imprecision (–1)‡
Recurrence rate	Total	1190 (11 RCTs)	200 per 1000	140 fewer per 1000 (158 fewer to 114 fewer)	RR 0.30 (0.21–0.43)	0	⨁⨁⨁◯ Moderate	Risk of bias (–1)† Publication bias (0)‖

B = *Bifidobacterium*, CI = confidence interval, E = *Enterococcus faecalis*, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, L = *Lactobacillus*, MD = mean difference, MSP = maximal systolic pressure of anal sphincter, MSV = minimal sensitive volume of rectum, MTL = Motilin, MTV = maximum tolerated volume of rectum, NO = nitrous oxide, OIS = optimal information size, RCT = randomized controlled trial, RR = risk ratio, S = *Streptococcus thermophilus*.

*Although the funnel plot for publication bias seemed to be asymmetry and the Egger regression test indicated probability for publication bias ($P < .001$), false-safe N was 771, and adjusted RR using the trim and fill method was consistent with that of the original analysis.

†The overall bias is high risk in half or more of the studies.

‡The sample size did not meet the OIS criterion.

§$I^2 > 50\%$, there are substantial heterogeneity.

‖The funnel plot distributions of outcomes seemed to be symmetrical. The overall bias is high risk in half or more of the studies.

2.5. Assessment of risk of bias

Two independent reviewers (E.K. and S.C.) conducted the quality assessment and categorized the included studies into 3 levels of bias (low, some concerns, and high risk of bias) using the Risk of Bias (RoBs 2) tool from the Cochrane Handbook for Systematic Reviews of Interventions.[12] The tool includes bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of reported results. Disagreements were resolved through discussions among all the authors.

2.6. Data synthesis and analysis

All included studies were analyzed qualitatively. When 2 or more studies reported the same continuous or dichotomous variables, a meta-analysis was performed using the RevMan software (version 5.4, Cochrane Collaboration, London, UK). For dichotomous outcomes, the risk ratio (RR) with 95% confidence intervals (CIs) was used, whereas for continuous outcomes, the standard mean difference or mean difference (MD) with 95% CIs was applied. The standard MD was used when the studies measured the same outcome but used different scales or units of measurement. The statistical heterogeneity was assessed using the I^2 index.[13] If I^2 values were >50%, substantial heterogeneity was considered to exist, and a random-effects model was used. Conversely, an I^2 value <50% indicated low heterogeneity, and a fixed-effects model was used. A subgroup analysis was used to investigate the potential origins of heterogeneity. When sufficient data were available, subgroup analyses were conducted based on the types of probiotic strains and species, with and without conventional treatment. A sensitivity analysis was performed by excluding 1 study at a time to assess the robustness of the meta-analysis results. The diverse compositions of HM used in the studies, along with the wide age range of the children, could lead to heterogeneity. Therefore, for cases with high heterogeneity ($I^2 \geq 75\%$) or inappropriate outcomes for conducting a meta-analysis, each study provided an effect size.

2.7. Assessment of reporting bias

As this review included more than 10 studies, publication bias was assessed using a funnel plot, which showed some asymmetry, prompting Egger test.[14] In case of suspected publication bias, the meta-analysis results were adjusted using the fail-safe N test[15] or the trim and fill method.[16] The assessment was performed using the R software (Version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria) and the R Studio program (Version 1.4.1106; Integrated Development for R, R Studio, PBC, Boston, MA) with the "meta" package as the default setting.

2.8. Quality of evidence

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) rating standards (available at http://gradepro.org). The following categories were assessed: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Using the GRADE system,[17] the level of evidence was classified as high, moderate, low, or very low (Table 1).

3. Results

3.1. Study selection

After removing duplicates, 1442 studies remained. After reviewing the titles and abstracts of these studies, 1362 were excluded, leaving 80 articles for further eligibility screening by full-text evaluation. Among these 80 articles, 58 were subsequently removed for the following reasons: 13 were not RCTs, 37 had inappropriate interventions (33 did not use HM combined with probiotics in the treatment group, 4 did not have HM orally administered), 5 had inappropriate control groups, and 3 used other therapies in addition to HM combined with probiotics. Finally, 22 RCTs[18–39] were included in the systematic review and meta-analysis (Fig. 1).

3.2. Characteristics of study

The 22 included RCTs were conducted in China. The publication years ranged from 2015 to 2023, and the sample size varied from 40 to 212 participants. The treatment duration ranged from 1 week to 2 months, and the age of the participants was 5 months to 15 years. The illness duration varied, with the shortest duration being 2.19 ± 0.97 (mean ± SD) months, while the longest duration was 15.25 ± 4.00 months (Table 2). Participants were diagnosed using the Rome II,[39] III,[20,22,28,36,37,39] IV,[18,19,21,24,26,29] other published criteria or guidelines,[23,25,31–34,38] and using the authors' definitions.[27,30,35]

3.3. Interventions

HM was administered orally in 22 of the included studies. The formulations employed consisted of decoctions,[18,22–26,29,31,33,35,38] capsules,[19,28,36] oral solutions,[20,34,37,39] granules,[21,30,32] and pills.[27] The compositions, dosages, and frequencies are listed in Table 3. *Aucklandiae Radix* and *Crataegi Fructus* were the most frequently used herbs, appearing in 7 studies, followed by *Raphani Semen*, *Ponciri Fructus Immaturus*, *Cannabis Fructus*, and *Arecae Semen*, each appearing 6 times (Supplementary File 2, Supplemental Digital Content, http://links.lww.com/MD/L442).

The probiotics used included a mixture of 3 probiotics (*Bifidobacterium longum, Lactobacillus bulgaricus*, and *Streptococcus thermophilus*),[18,28,35] another mixture of 3 probiotics (*Bifidobacterium*, *Lactobacillus acidophilus*, and *Enterococcus faecalis*),[19,21,25,26,30] *Bifidobacterium* quadruple viable tablets (*Bifidobacterium infantis*, *L acidophilus*, *E faecalis*, and *Bacillus cereus*),[24,34] *Clostridium butyricum* and *Bifidobacterium*,[20,23,38] *Bacillus subtilis* and *Enterococcus faecium* granules,[22,27,31–33] *Saccharomyces boulardii*,[36,37] *C butyricum*,[39] and live *Bacillus coagulans* tablets.[29] Dosages and frequencies are listed in Table 3.

In each study, the experimental and control groups were subjected to co-interventions, including conventional treatments. These include lactulose oral solutions[25,33,34,36] and vitamin B1, phenolphthalein and glycerol Enema.[35] Additionally, basic treatment was employed in 10 studies.[18–20,22,28,31,36–39] Detailed information is provided in Supplementary File 3, Supplemental Digital Content, http://links.lww.com/MD/L444.

3.4. Outcome measures

The primary outcome measure was the TER.[18,19,21–28,30,32,39] Each study employed various symptom scoring criteria, and selected an analyzable Traditional Chinese Medicine symptom score from among them.[18,22,24,26,37] For studies using the Bristol fecal score, which ranges from 1 to 7, with lower scores indicating severe constipation, 2 studies[28,36] were excluded from the meta-analysis due to outcome errors and 1 study[25] did not report scoring criteria, and 2 studies[19,23] excluded the use of the modified Bristol fecal score. Consequently, 4 studies[26,27,29,30] were included in the analysis. Defecation frequency per week was reported in 4 studies[23,26,29,30] and defecation time (the time it takes to have a bowel movement in minutes) was reported in 2 studies.[22,29]

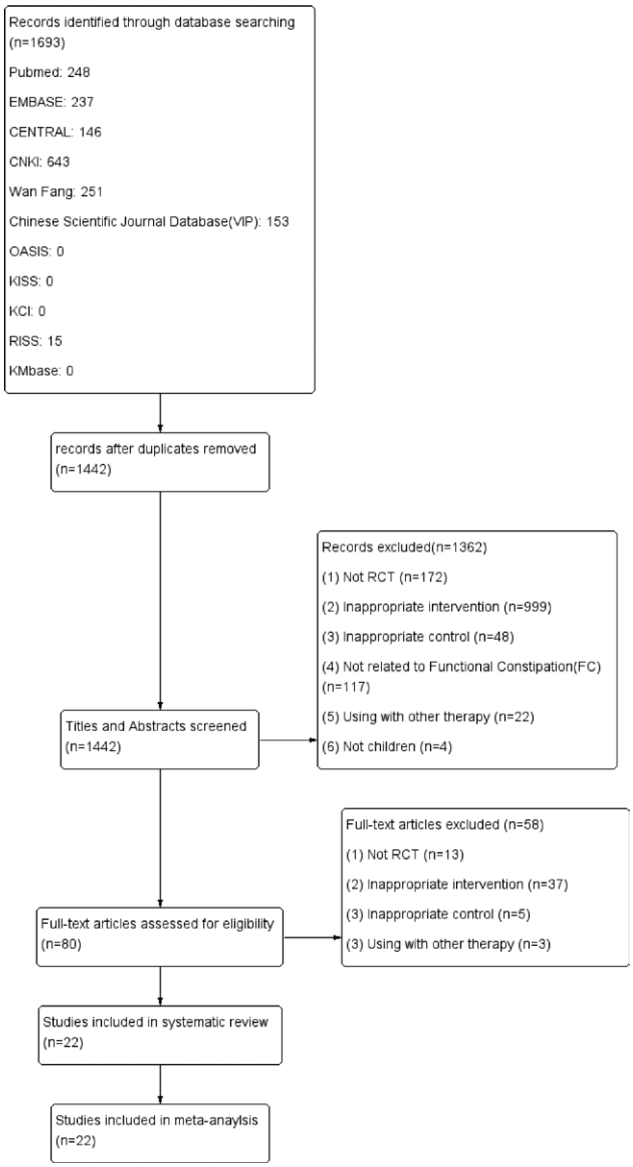

Figure1. Prisma flow diagram. C = control intervention, CENTRAL = Cochrane Central Register of Controlled Trials, CNKI = China National Knowledge Infrastructure, E = experimental intervention, EMBASE = Excerpta Medica dataBASE, HM = herbal medicine, KCI = Korea Citation Index, KISS = Korean Studies Information Service System, KMbase = Korean Medical database, OASIS = Oriental Medicine Advanced Searching Integrated System, RCT = randomized controlled trial, RISS = Research Information Sharing Service.

Regarding secondary outcomes, adverse events were reported in 12 studies,[18,19,22,24,26,28,29,32,34–36,38] and recurrence rates in 11 studies.[18,23,26,28,33–39] The recurrence rate was assessed at 2 weeks,[18] 4 weeks,[28,36] 8 weeks,[23] 3 months,[26,34,36,38] and 6 months[37,39] after treatment. One study[36] did not report a specific period. Serum indicators such as motilin (MTL),[20,25,29,32] nitrous oxide (NO),[21,28,29,36] substance P (SP),[18,21,25,28,29,32,34,36] gastrin (GAS),[20,25,29,32] and somatostatin (SS)[20,25,28,36] were reported. Furthermore, we examined changes in the gut microbiota, specifically focusing on *Bifidobacterium*[19–21,28,30] and *Lactobacillus*.[19–21,28–30] Anorectal dynamic parameters were also analyzed, including the minimal sensitive volume of rectum (MSV),[19,23] maximum tolerated volume of the rectum (MTV),[19,20,23,29] and maximal systolic pressure of the anal sphincter (MSP).[19,20,29] Comprehensive outcome details and *P*-values are consolidated in Supplementary File 4, Supplemental Digital Content, http://links.lww.com/MD/L446.

3.5. Quality assessment

In all the included studies, concealment of the allocation sequence was not reported, and evident baseline imbalances between the treatment and control groups were not observed. Therefore, all studies were evaluated as having some concerns of bias arising from the randomization process. Three studies[24,29,31] that had the withdrawal criteria were evaluated as having a low risk of bias due to deviations from the intended interventions. The remaining studies were evaluated with some concerns owing to insufficient related information. One study[31] was assessed as having a high risk of bias because of missing outcome data, whereas the other studies were evaluated as having a low risk of bias because they did not have any missing data. In 9 studies,[18,22,24,26,28,30,34,36,37] the assessment criteria (such as symptom scores) could have been subjective, and there was a high risk of bias when the outcome assessors were aware of the intervention, as this could have influenced the assessment. In contrast, in the remaining studies, the outcomes were evaluated using objective indicators, resulting in a low risk of bias. All studies except for 1[31] were evaluated with a low risk of bias due to preplanned analysis.

In the end, 10 studies[18,22,24,26,28,30,31,34,36,37] were determined to have a high risk of bias in at least 1 domain and were categorized with an overall bias rating of "at high risk." Conversely, 12 studies[19–21,23,25,27,29,32,33,35,38,39] that raise certain concerns in at least 1 domain but did not meet the criteria for a high risk of bias in any domain were evaluated as having an overall bias of "some concerns." The results are presented in Figure 2.

3.6. Synthesis of results

The varying compositions of HM used in the studies, coupled with the wide age range of the children, may have resulted in heterogeneity. As a result, a meta-analysis was conducted for TER, Bristol fecal score, serum indicators (MTL, NO), anorectal dynamic parameters (MSV, MTV, MSP), and recurrence rate. For other outcomes with significant heterogeneity ($I^2 \geq 75\%$) or those that were unsuitable for the meta-analysis, each study supplied the effect size (Supplementary Figure 1A–C, Supplemental Digital Content, http://links.lww.com/MD/L441, http://links.lww.com/MD/L461, http://links.lww.com/MD/L463, Supplementary Figure 2A–C, Supplemental Digital Content, http://links.lww.com/MD/L442, http://links.lww.com/MD/L465, http://links.lww.com/MD/L467, Supplementary Figure 3A and B, Supplemental Digital Content, http://links.lww.com/MD/L444, http://links.lww.com/MD/L469).

3.6.1. Total effective rate. A meta-analysis was conducted on 19 studies involving 1956 patients using a fixed-effects model. The pooled RR was found to be 1.24 (CI: 1.19–1.29). A subgroup analysis was performed based on the type of probiotics used. This analysis revealed that the combination of HM with corresponding probiotics may offer advantages when combined with *B subtilis* and *E faecium* (RR: 1.26, 95% CI: 1.16–1.37), as well as the mixture of 3 probiotics (B, L, E) (RR: 1.19, 95% CI: 1.11–1.26), compared to probiotics alone. However, the lower limit of the pooled RR for the mixture of 3 probiotics (B, L, S) and *S boulardii* subgroup was very close to the ineffective line, which might not hold clinical significance. Subgroups with significant heterogeneity (*Bifidobacterium* quadruple probiotics, *C butyricum*, and *Bifidobacterium*) or those with only 1 study (*C butyricum*) were not suitable for meta-analysis (Fig. 3). And when used in combination with both conventional medicine and probiotics, the addition of HM appeared to be more effective

Table 2

Basic characteristics of the included studies.

First author (yr)	Sample size (E/C)	Age (mean ± SD)	Gender (M/F)	Duration of illness (mean ± SD)
Du et al[18]	64 (32/32)	E: (3.85 ± 1.94) yr C: (3.73 ± 1.88) yr	E: 32 (13/19) C: 32 (11/21)	E: (4.19 ± 0.85) mo C: (3.78 ± 0.84) mo
Duan et al[19]	82 (41/41)	E: (6.1 ± 1.4) yr, 3–14 yr C: (5.8 ± 1.7) yr, 1–13 yr	E: 41 (22/19) C: 41 (21/20)	E: (6.9 ± 2.0) mo C: (7.2 ± 2.3) mo
Fang[20]	100 (50/50)	E: (5.72 ± 1.10) yr, 3–10 yr C: (5.71 ± 1.03) yr, 2–10 yr	E: 50 (26/24) C: 50 (30/20)	NR
Fu and Li[21]	78 (39/39)	E: (10.23 ± 3.10) yr, 3.1–14.2 yr C: (10.22 ± 3.09) yr, 3.1–14 yr	E: 39 (18/21) C: 39 (17/22)	E: (15.25 ± 4.00) mo C: (15.23 ± 4.01) mo
Gao et al[22]	98 (49/49)	E: (5.48 ± 2.52) yr C: (5.21 ± 2.48) yr	E: 49 (29/20) C: 49 (25/24)	E: (1.28 ± 0.56) yr C: (1.31 ± 0.58) yr
Hang and Tian[23]	76 (38/38)	E: (7.85 ± 1.34) yr, 10 mo–12 yr C: (8.02 ± 1.41) yr, 9 mo–12 yr	E: 38 (16/22) C: 38 (14/24)	E: (1.07 ± 0.23) yr C: (1.12 ± 0.26) yr
Li[24]	60 (30/30)	E: 4–8 yr, n = 13, 9–12 yr, n = 17 C: 4–8 yr, n = 16, 9–12 yr, n = 14	E: 30 (15/15) C: 30 (14/16)	E: ~6 mo, n = 10, 7–12 mo, n = 9, 12 mo, n = 11 C: <6 mo, n = 8, 7–12 mo, n = 10, >12 mo, n = 12
Li[25]	100 (50/50)	E: (5.13 ± 0.77) yr, 1–8 yr C: (5.09 ± 0.79) yr, 1–9 yr	E: 50 (30/20) C: 50 (29/21)	NR
Lu et al[26]	106 (53/53)	E: (6.87 ± 2.77) yr, 1–14 yr C: (6.76 ± 2.65) yr, 1–14 yr	E: 53 (27/26) C: 53 (25/28)	E: (7.35 ± 2.58) mo C: (7.25 ± 2.42) mo
Ma[27]	40 (20/20)	E: (7.16 ± 2.40) yr, 2–11 yr C: (7.3 ± 2.6) yr, 1–10 yr	E: 20 (14/6) C: 20 (13/7)	E: (4.8 ± 3.6) mo C: (5.3 ± 3.1) mo
Sheng et al[28]	94 (47/47)	E: (6.79 ± 1.18) yr, 4–10 yr C: (6.37 ± 1.16) yr, 4–9 yr	E: 47 (24/23) C: 47 (26/21)	E: (8.94 ± 1.48) mo C: (9.15 ± 1.53) mo
Tuo et al[29]	102 (51/51)	E: (7.25 ± 1.41) yr C: (7.07 ± 1.37) yr	E: 27/24 C: 22/29	E: (5.43 ± 7.79) mo C: (5.60 ± 1.86) mo
Wei et al[30]	212 (106/106)	E: (8.72 ± 3.11) yr, 1–12 yr C: (8.69 ± 3.15) yr, 1–12 yr	E: 106 (52/54) C: 106 (54/52)	E: (4.00 ± 1.41) mo C: (4.05 ± 1.52) mo
Wu et al[31]	70 (35/35)	E: (9.31 ± 1.24) yr, 3–12 yr C: (9.42 ± 1.27) yr, 3–13 yr	E: 35 (19/16) C: 35 (18/17)	E: (2.19 ± 0.97) mo C: (2.24 ± 0.88) mo
Yang and Zhu[32]	96 (48/48)	E: (9.14 ± 1.35) yr, 7–11 yr C: (7.52 ± 1.46) yr, 6–9 yr	E: 25/23 C: 26/22	E: (6.53 ± 1.69) mo C: (5.11 ± 1.57) mo
Zhang et al[33]	200 (100/100)	E: 1–3 yr, n = 56, 4–6 yr, n = 30, 7–14 yr, n = 14 C: 1–3 yr, n = 54, 4–6 yr, n = 31, 7–14 yr, n = 15	E: 100 (51/49) C: 106 (52/48)	E: (8.4 ± 1.2) mo C: (8.8 ± 1.4) mo
Zhang[34]	200 (100/100)	E: (7.22 ± 1.49) yr, 3–12 yr C: (7.39 ± 1.56) yr, 3–12 yr	E: 100 (52/48) C: 100 (53/47)	E: (7.86 ± 2.12) mo C: (7.54 ± 2.04) mo
Zhao[35]	78 (39/39)	E: (3.5 ± 2.4) yr, 5 mo–7 yr C: (3.5 ± 2.3) yr, 5.5 mo–6.5 yr	E: 39 (20/19) C: 39 (19/20)	E: (10.6 ± 0.7) mo C: (10.5 ± 0.8) mo
Zheng et al[36]	118 (50/68)	E: (5.30 ± 1.20) yr C: (5.00 ± 1.00) yr	E: 50 (28/22) C: 68 (37/31)	E: (8.60 ± 1.40) mo C: (8.80 ± 1.50) mo
Zhong[37]	60 (30/30)	E: (7.95 ± 1.15) yr, 3–10 yr C: (7.12 ± 1.06) yr, 3–9 yr	E: 30 (18/12) C: 30 (20/10)	E: (5.99 ± 1.95) mo C: (5.22 ± 1.92) mo
Zhou et al[38]	240 (60/60/60/60)	E1: (24.1 ± 7.79) mo, 1–3 yr E2: (25.8 ± 7.06) mo, 1–3 yr E3: (26.1 ± 7.18) mo, 9 mo–3 yr C: (25.7 ± 7.08) mo, 11 mo–3 yr	E1: 60 (28/32) E2: 60 (33/27) E3: 60 (30/30) C: 60 (31/29)	NR
Zhu[39]	74 (37/37)	E: (6.1 ± 1.4) yr C: (5.9 ± 1.6) yr	E: 37 (20/17) C: 37 (22/15)	E: (12.1 ± 2.6) mo C: (11.9 ± 2.4) mo

① = total effective rate, ② = symptom score, ③ = Bristol fecal score, ④ = defecation frequency, ⑤ = defecation time, ⑥ = serum indicator, ⑦ = gut microbiota, ⑧ = anorectal dynamics parameters, ⑨ = adverse events, ⑩ = recurrence rate, B = *Bifidobacterium*, E = *Enterococcus faecalis*, L = *Lactobacillus*, S = *Streptococcus thermophiles*, NR = not reported.

Experimental intervention (E) Control intervention (C)	Total treatment periods	Outcome measurement	Adverse events
(C) + Tiaochang Tongbian decoction Mixture of 3 probiotics (B, L, S) + basic treatment	4 wk	①②⑨⑩	None
(C) + Liuwei Nengxiao capsule Mixture of 3 probiotics (B, L, E) + basic treatment	2 wk	①②③⑥⑦⑧⑨	None
(C) + Simotang oral solution *Clostridium butyricum* and B combined powders + basic treatment	6 wk	②⑥⑦⑧	NR
(C) + Huaiqihuang granules Mixture of 3 probiotics (B, L, E)	20 d	①②⑥⑦	NR
(C) + Xiaodaobiantong decoction *Bacillus subtilis* and *Enterococcus faecium* granules with multivitamins + basic treatment	2 wk	①②④⑤⑥⑨	E: 2 (1 diarrhea; 1 abdominal pain) C: 6 (3 diarrhea; 2 abdominal pain; 1 intestinal spasm)
(C) + Banxia Xiexin decoction *C butyricum* and B combined powders	4 wk	①③④⑧⑩	NR
(C) + Jiawei Zengye decoction B quadruple probiotics + conventional treatment + vitamin B	2 wk	①②⑨	None
(C) + Huangqi Baizhu decoction Mixture of 3 probiotics (B, L, E) + conventional treatment	1 mo	①②③④⑥⑧	NR
(C) + Xiaoji Daozhi decoction Mixture of 3 probiotics (B, L, E)	2 wk	①②③④⑨⑩	None
(C) + Maziren pill *B subtilis* and *Enterococcus* multidimensional granules	NR	①③	NR
(C) + Qingchang Tongbian capsule Mixture of 3 probiotics (B, L, S) + basic treatment	4 wk	①②③⑥⑦⑨⑩	E: 6 (1 nausea; 2 abdominal distention; 2 diarrhea; 1 rash) C: 4 (1 nausea; 2 abdominal distention; 1 diarrhea)
(C) + Jiawei Zengye decoction *Bacillus coagulans* tablets	1 mo	②③④⑤⑥⑦⑧⑨	E: 3 (1 abdominal distention; 1 lose weight; 1 flatus) C: 6 (2 abdominal distention; 1 anorexia; 1 lose weight; 1 flatus; 1 diarrhea)
(C) + Xiaoer Xiaoshi granules Mixture of 3 probiotics (B, L, E)	2 wk	①②③④⑦	NR
(C) + Modified Sijunzi decoction *B subtilis* and *Enterococcus* multidimensional granules + basic treatment	2 wk	②⑥	NR
(C) + Huaiqihuang granules *B subtilis* and *E faecium* granules with multivitamins	1 wk	①②⑥⑨	E: 7 (3 nausea; 2 anorexia; 1 vomiting; 1 dizziness) C: 3 (1 nausea; 1 anorexia; 1 vomiting)
(C) + Runzao Tongbian decoction *B subtilis* and *E faecium* granules with multivitamins + conventional treatment	4 wk	①②⑩	NR
(C) + Simotang oral solution B quadruple probiotics + conventional treatment	2 mo	①②⑥⑨⑩	E: 3 (1 nausea; 2 abdominal distention) C: 2 (1 nausea; 1 abdominal distention)
(C) + Zengye decoction Mixture of 3 probiotics (B, L, S) + conventional treatment	NR	①⑨⑩	E: 2 (1 abdominal pain; 1 vomiting) C: 9 (2 abdominal pain; 1 diarrhea; 3 nausea; 3 vomiting)
(C) + Qingchang Tongbian capsule *Saccharomyces boulardii* powder + conventional treatment + basic treatment	4 wk	①②③⑥⑨⑩	E: 6 (1 nausea; 2 diarrhea; 1 rash; 1 abdominal pain; 1 abdominal distention) C: 9 (2 nausea; 3 diarrhea; 1 rash; 3 abdominal distention)
(C) + Simotang oral solution *S boulardii* powder + basic treatment	4 wk	①②⑩	NR
E1: (C) + Zhishi Daozhi decoction + *C butyricum* and B combined powders E2: (C) + Zhishi Daozhi decoction E3: (C) + Live *C butyricum* and B combined powders Basic treatment	8 wk	①②⑨⑩	12 abdominal pain; 15 vomiting
(C) + Simotang oral solution *C butyricum* powder + basic treatment	6 wk	①⑩	NR

Table 3

Traditional herbal medicine and probiotics information.

First author (yr)	Intervention	Type of formulation	Prescription/composition	Dosage	Frequency
Du et al[18]	Herbal medicine	Decoction	Tiaochang Tongbian *Raphani Semen* 20 g, *Chrysanthmi Flos*, *Sterculiae Lychnophorae Semen* 6 g, *Hordei Fructus Germinatus*, *Oryzae Fructus Germinatus* 12 g, *Rhei Radix et Rhizoma* 3.5 g, *Bupleuri Radix* 6 g, *Scrophulariae Radix* 15 g, *Scutellariae Radix* 3.5 g, *Ponciri Fructus Immaturus* 12 g, *Magnoliae Cortex*, *Phragmitis Rhizoma*, *Hordei Fructus Germinatus*, *Rehmanniae Radix*, *Oryzae Fructus Germinatus* 10 g	2–3 yr: 50 mL/time, 4–6 yr: 100 mL/time	3 times/d
	Probiotics	Tablet	Mixture of 3 probiotics (B, L, S) Golden Bifid: live combined B and L tablets (Inner Mongolia Shuangqi Pharmaceutical Co., Ltd., Inner Mongolia, China) *Bifidobacterium longum*, *Lactobacillus bulgaricus*, and S	2–3 yr: 2 tabs (1.0 g)/ time, 4–6 yr: 3 tabs (1.3 g)/time	3 times/d
Duan et al[19]	Herbal medicine	Capsule	Liuwei Nengxiao capsule (Tibet Tibetan Medicine Group Co., Ltd., Nyingchi, Xizang, China) *Rhei Radix et Rhizoma*, *Terminaliae Fructus*, *Zingiberis Rhizoma*, *Aucklandiae Radix*, *Halitum*, *Glauberite*	0.45 g/cap, 1–3 yr: 1/3 cap/time, 4–5 yr: 1/2 cap/time, 6–10 yr: 2/3 cap/time, 11–14 yr:1 cap/time	2 time/d
	Probiotics	Capsule	Mixture of 3 probiotics (B, L, E) BIFICO: live combined B, L, and *Enterococcus* capsules (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd., Shanghai, China) B, *Lactobacillus acidophilus*, and E	0.21 g/cap, 1–6 yr: 1 cap/time, 7–14 yr: 2 caps/time	3 times/d
Fang[20]	Herbal medicine	Oral solution	Simotang oral solution (Hunan Hansen Pharmaceutical Co., Ltd., Yiyang, Hunan, China) *Aucklandiae Radix*, *Aurantii Fructus Immaturus*, *Arecae Semen*, *Linderae Radix*	10 mL/time	3 times/d
	Probiotics	Powder	Live *Clostridium butyricum* and B combined powders (Shenzhen Sinovac Biopharmaceutical Co., Ltd., Shenzhen, China)	0.5 g/time	<6 yr: 2 times/d, ≥6 yr: 3 times/d
Fu and Li[21]	Herbal medicine	Granules	Huaiqihuang granules (Qidong Gaitianli Pharmaceutical Co., Ltd., Qidong, Jiangsu, China) *Huaier aqueous extract*, *Lycii Fructus*, *Polygonati Rhizoma*	10 g/time	2 times/d
	Probiotics	Powder	Mixture of 3 probiotics (B, L, E) Bifid. Triple viable powder: live combined B, L, and *Enterococcus* powders (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd.) B, *L acidophilus*, and E	1 g/time	3 times/d
Gao et al[22]	Herbal medicine	Decoction	Xiaodaobiantong *Atractylodis Rhizoma Alba*, *Crataegi Fructus*, *Poria Sclerotium*, *Paeoniae Radix*, *Massa Medicata Fermentata* 10 g, *Coicis Semen* 15 g, *Ponciri Fructus Immaturus*, *Pinelliae Tuber*, *Forsythiae Fructus*, *Raphani Semen* 6 g, *Magnoliae Cortex*, *Scutellariae Radix* 3 g	100 mL/time	2 times/d, given according to aged and symptoms
	Probiotics	Granules	Mamiai: live combined *Bacillus subtilis* and E granules with multivitamins (Beijing Hanmei Pharmaceutical Co., Ltd., Beijing, China)	1 g/ time	2 times/d
Hang and Tian[23]	Herbal medicine	Decoction	Banxia Xiexin *Scutellariae Radix* 9 g, *Crataegi Fructus* 15 g, *Pinelliae Tuber* 6 g, *Raphani Semen* 10 g, *Coptidis Rhizoma* 3 g, *Magnoliae Cortex*, *Aucklandiae Radix* 6 g, *Zingiberis Rhizoma* 5 g, *Codonopsis Pilosulae Radix* 12 g, *Galli Gigeriae Endothelium Corneum* 10 g, *Glycyrrhizae Radix et Rhizoma* 3 g, *Ponciri Fructus Immaturus* 10 g	33–55 mL/time	2 times/d
	Probiotics	Powder	Live *Clostridium butyricum* and B combined powders (Shenzhen Sinovac Biopharmaceutical Co., Ltd.)	<1 yr: 250 mg/time, 1–3 yr: 500 mg/time, 3–6 yr: 750 mg/time, 7–12 yr: 1 g/time	NR
Li[24]	Herbal medicine	Decoction	Jiawei Zengye decoction *Scrophulariae Radix*, *Rehmanniae Radix Recens*, *Liriopis seu Ophiopogonis Tuber*, *Poria Sclerotium*, *Cannabis Fructus*, *Uncariae Ramulus cum Uncus*, *Eriobotryae Folium* 10 g	40–50 mL/time	2 times/d
	Probiotics	Tablet	Siliankang: B quadruple viable tablets (Hangzhou Yuanda Bio Pharmaceutical Co., Ltd., Hangzhou, China) *Bifidobacterium infantis*, *L acidophilus*, E, and *Bacillus cereus*	0.5 g/tab, 4–8 yr: 2 tabs/time, 8–14 yr: 3 tabs/time	3 times/d
Li[25]	Herbal medicine	Decoction	Huangqi Baizhu decoction *Astragali Radix* 30 g, *Atractylodis Rhizoma Alba* 15 g, *Mel* 10 g, *Tetrapanacis Medulla* 5 g, *Persicae Semen* 10 g	100 mL/time	2 times/d
	Probiotics	Capsule	Mixture of 3 probiotics (B, L, E) BIFICO: live combined B, L, and *Enterococcus* capsules (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd.) *Bifidobacterium, L acidophilus* and E	0.21 g/cap, 1–2 caps/ time	2 times/d

(*Continued*)

Table 3

(*Continued*)

First author (yr)	Intervention	Type of formulation	Prescription/composition	Dosage	Frequency
Lu et al[26]	Herbal medicine	Decoction	Xiaoji Daozhi decoction *Amomi Fructus*, *Alismatis Rhizoma*, *Coptidis Rhizoma* 6 g, *Zizyphi Fructus*, *Atractylodis Rhizoma Alba*, *Aucklandiae Radix*, *Dioscoreae Rhizoma*, *Poria Sclerotium* 10 g, *Cannabis Fructus*, *Citri Unshius Pericarpium*, *Ponciri Fructus Immaturus* 12 g, *Massa Medicata Fermentata*, *Raphani Semen*, *Hordei Fructus Germinatus* 15 g	1–2 yr: 60 mL/d, 3–6 yr: 100 mL/d, 7–14 yr: 130 mL/d	1 time/d
	Probiotics	Capsule	Mixture of 3 probiotics (B, L, E) BIFICO: live combined B, L, and *Enterococcus* capsules (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd.) B, *L acidophilus*, and E	0.21 g/cap, 1–6 yr: 1 cap/time, 7–14 yr: 2 caps/time	2 times/d
Ma[27]	Herbal medicine	Pill	Maziren pill *Cannabis Fructus* 10 g, *Magnoliae Cortex*, *Ponciri Fructus Immaturus*, *Paeoniae Radix Alba* 5 g, *Armeniacae Semen*, *Rhei Radix et Rhizoma* 3 g	NR	2 times/d
	Probiotics	Granules	*Bacillus subtilis* and *Enterococcus* multidimensional granules (Beijing Hanmei Pharmaceutical Co., Ltd.)		2 times/d
Sheng et al[28]	Herbal medicine	Capsule	Qingchang Tongbian capsule (Kunming quanxinshengwu Biopharmaceutical Co., Ltd., Kunming, China) *Solanum erianthum, Scolopendra*, *Uncariae Ramulus cum Uncus*, *Saruma henryi Oliv, Amomi Tsaoko Fructus*	0.3 g/cap, 2 caps/time	3 times/d
	Probiotics	Tablet	Mixture of 3 probiotics (B, L, S) Golden Bifid: live combined B and L tablets (Inner Mongolia Shuangqi Pharmaceutical Co., Ltd.) *B longum*, *L bulgaricus* and S	≤5 yr: 1 g/time, >5 yr: 2 g/times	3 times/d
Tuo et al[29]	Herbal medicine	Decoction	Jiawei Zengye decoction *Scrophulariae Radix*, *Rehmanniae Radix*, *Liriopis seu Ophiopogonis Tuber*, *Cannabis Fructus*, *Eriobotryae Folium*, *Poria Sclerotium*, *Angelicae Gigantis Radix*, *Crataegi Fructus* 10 g	40–50 mL/time	2 times/d
	Probiotics	Tablet	Live *Bacillus coagulans* tablets (Qingdao Donghai Pharmaceutical Co., Ltd., Qingdao, China)	0.35 g/tab, 2 tabs/time	3 times/d
Wei et al[30]	Herbal medicine	Granules	Xiaoer Xiaoshi Granules (Hefei Lifang Pharmaceutical Co., Ltd., Hefei, Anhui, China) *Galli Gigeriae Endothelium Corneum*, *Crataegi Fructus*, *Massa Medicata Fermentata*, *Hordei Fructus Germinatus*, *Arecae Semen*, *Citri Unshius Pericarpium*	1.5–3 g/time	3 time/d
	Probiotics	Powder	Mixture of 3 probiotics (B, L, E) Bifid. Triple viable powder: live combined *B, L* and *Enterococcus* powders (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd.) *Bifidobacterium, L acidophilus*, and E	1 g/time	3 times/d
Wu et al[31]	Herbal medicine	Decoction	Modified Sijunzi decoction *Ginseng Radix* 10 g, *Poria Sclerotium*, *Atractylodis Rhizoma Alba* 12 g, *Glycyrrhizae Radix et Rhizoma* 6 g	100 mL/time	2 times/d
	Probiotics	Granules	*B subtilis* and *Enterococcus* multidimensional granules (Beijing Hanmei Pharmaceutical Co., Ltd.)	<2 yr: 1 g/time, ≥2 yr: 1–2 g/time	1–2 time/d
Yang and Zhu[32]	Herbal medicine	Granules	Huaiqihuang granules (Qidong Gaitianli Pharmaceutical Co., Ltd.) *Huaier aqueous extract*, *Lycii Fructus*, *Polygonati Rhizoma*	10 g/time	2 times/d
	Probiotics	Granules	Mamiai: live combined *B subtilis* and *Enterococcus faecium* granules with multivitamins (Beijing Hanmei Pharmaceutical Co., Ltd.)	1 g/time	2 times/d
Zhang et al[33]	Herbal medicine	Decoction	Runzao Tongbian decoction *Magnoliae Cortex*, *Raphani Semen*, *Ponciri Fructus Immaturus Persicae Semen*, *Armeniacae Semen*, *Perillae Fructus, Cannabis Fructus*, *Scrophulariae Radix*, *Liriopis seu Ophiopogonis Tuber*, *Phragmitis Rhizoma*, *Galli Gigeriae Endothelium Corneum*, *Crataegi Fructus*, *Glycyrrhizae Radix et Rhizoma* 3–10 g	25–75 mL/time	2 times/d
	Probiotics	Capsule	Mamiai: live combined *B subtilis* and *E faecium* granules with multivitamins (Beijing Hanmei Pharmaceutical Co., Ltd.)	<2 yr: 0.5 g/time, ≥2 yr: 1 g/time	2 times/d
Zhang[34]	Herbal medicine	Oral solution	Simotang oral solution (Hunan Hansen Pharmaceutical Co., Ltd.) *Aucklandiae Radix*, *Aurantii Fructus Immaturus*, *Arecae Semen*, *Linderae Radix*	10 mL/time	3 times/d
	Probiotics	Tablet	Siliankang: *B* quadruple viable tablets (Hangzhou Yuanda Bio Pharmaceutical Co., Ltd.) *B infantis*, *L acidophilus*, E, and *Bacillus cereus*	1 g/time	3 times/d
Zhao[35]	Herbal medicine	Decoction	Zengye decoction *Astragali Radix* 15 g, *Codonopsis Pilosulae Radix*, *Scrophulariae Radix*, *Rehmanniae Radix, Cannabis Fructus*, *Pruni Japonicae Semen* 10 g, *Hordei Fructus Germinatus*, *Crataegi Fructus*, *Bupleuri Radix*, *Cimicifugae Rhizoma*, *Liriopis seu Ophiopogonis Tuber* 5 g, *Glycyrrhizae Radix et Rhizoma* 3 g	100 mL/time	2 times/d
	Probiotics	Tablet	Mixture of 3 probiotics (B, L, S) Golden Bifid: live combined B and L tablets (Inner Mongolia Shuangqi Pharmaceutical Co., Ltd.) *B longum*, *L bulgaricus*, and S	Given according to aged and weight	Given according to aged and weight

(*Continued*)

Table 3

(*Continued*)

First author (yr)	Intervention	Type of formulation	Prescription/composition	Dosage	Frequency
Zheng et al[36]	Herbal medicine	Capsules	Qingchang Tongbian capsule (Kunming quanxinshengwu Biopharmaceutical Co., Ltd.) *Solanum erianthum, Scolopendra, Uncariae Ramulus cum Uncus, Saruma henryi Oliv, Amomi Tsaoko Fructus*	0.3 g/cap, 2–3 caps/time	2–3 time/day
	Probiotics	Powder	*Saccharomyces boulardii* powder (French Laboratoires Biocodex Co., Ltd., Hunan, China)	0.25 g/time	1 time/d
Zhong[37]	Herbal medicine	Oral solution	Simotang oral solution (Hunan Hansen Pharmaceutical Co., Ltd.) *Aucklandiae Radix, Aurantii Fructus Immaturus, Arecae Semen, Linderae Radix*	10 Ml/time	3 times/d
	Probiotics	Powder	*Saccharomyces boulardii* powder (French Laboratoires Biocodex Co., Ltd.)	0.25 g/time	2 times/d
Zhou et al[38]	Herbal medicine	Decoction	Zhishi Daozhi decoction *Raphani Semen* 12 g, *Cyperi Rhizoma, Aurantii Fructus, Arecae Semen, Crataegi Fructus* 6 g, *Rhei Radix et Rhizoma* 4 g	NR	2 times/d
	Probiotics	Powder	Live *Clostridium butyricum* and B combined powders (Shenzhen Sinovac Biopharmaceutical Co., Ltd.)	0.5 g/time	3 times/d
Zhu[39]	Herbal medicine	Oral solution	Simotang oral solution (Hunan Hansen Pharmaceutical Co., Ltd.) *Aucklandiae Radix, Aurantii Fructus Immaturus, Arecae Semen, Linderae Radix*	3–10 mL/time	3 times/d
	Probiotics	Powder	Live *Clostridium butyricum* powder	0.5 g/time	<6 yr: 2 times/d, ≥6 yr: 3 times/d

B = *Bifidobacterium*, cap = capsule, E = *Enterococcus faecalis*, L = *Lactobacillus*, NR = not reported, S = *Streptococcus thermophilus*, tab = tablet.

(RR: 1.19, 95% CI: 1.12–1.26), showing low heterogeneity ($P = .17$, $I^2 = 38\%$).

3.6.2. Bristol fecal score. Four studies involving 460 patients, assessed the Bristol fecal score. The meta-analysis revealed that the treatment for FC significantly favored the use of HM combined with probiotics (MD: 0.80, 95% CI: 0.71–0.89), utilizing a fixed-effects model. No notable heterogeneity was observed among the studies ($I^2 = 33\%$, $P = .21$, Fig. 4).

3.6.3. Serum indicators. MTL, a gastrointestinal peptide hormone that stimulates smooth muscle contractions and promotes gastrointestinal motility, was assessed in 398 patients in 4 studies. According to the meta-analysis results, the pooled mean MD (95% CI) indicated a value of 35.37 (24.64, 46.10). The combination of HM and probiotics significantly increased MTL levels compared to probiotics alone. No significant heterogeneity was observed among the studies ($I^2 = 0\%$, $P = .90$, Fig. 5A). Four studies involving 392 patients assessed NO levels, which can serve as an indicator of oxidative stress and inflammation. The meta-analysis showed a pooled MD (95% CI) of −12.45 (−15.12, −9.77). The combination of HM and probiotics resulted in significantly reduced NO levels compared to probiotics alone. No significant heterogeneity was observed among studies ($I^2 = 0\%$, $P = .47$, Fig. 5B).

3.6.4. Anorectal dynamic parameters. Anorectal dynamic parameters evaluate the function and pressure of the anal and rectal muscles, offering insights into conditions such as constipation and fecal incontinence. In PFC, there was a tendency for higher MSV, MTV, and MSP with increasing constipation severity.[40] The meta-analyses of MSV (2 studies with 158 patients, MD: −8.7, 95% CI: −10.91 to −6.49), MTV (4 studies with 360 patients, MD: −11.52, 95% CI: −17.14 to −5.9), and MSP (3 studies with 284 patients, MD: −10.87, 95% CI: −19.76 to −1.98) indicated that the combination of HM with probiotics had a more pronounced effect compared to probiotics alone. While no heterogeneity was observed for MSV ($I^2 = 0\%$, $P = .78$), both MTV ($I^2 = 66\%$, $P = .03$) and MSP ($I^2 = 74\%$, $P = .02$) displayed significant heterogeneity (Fig 6A–C).

3.6.5. Recurrence rate and adverse events. Eleven studies involving 1190 patients measured the recurrence rate, using a fixed-effects model. The meta-analysis of the recurrence rate (RR: 0.30, 95% CI: 0.2–0.43) demonstrated that the combination of HM with probiotics might reduce recurrence rate by 70%. There was no significant heterogeneity among the studies ($I^2 = 0\%$, $P = .87$, Fig. 7). Furthermore, when used in combination with both conventional medicine and probiotics, the addition of HM appears to be more effective (RR: 0.22, 95% CI: 0.12–0.42), showing low heterogeneity ($I^2 = 0\%$, $P = .98$).

Twelve studies involving 1218 patients (600 in the experimental group and 618 in the control group) reported on adverse events. Four of these studies[18,19,24,26] reported no adverse events. Among 7 studies[22,28,29,32,34–36] that reported adverse events, the experimental group encountered 29 events, whereas the control group had 39 events. In the experimental group, the most commonly reported adverse events were abdominal distention (6 cases), nausea (6 cases), and diarrhea (5 cases). Conversely, in the control group, diarrhea (9 cases), abdominal distention (8 cases), and nausea (8 cases) were the most prevalent. In 1 study,[38] abdominal pain was reported in 12 cases, and vomiting in 15 cases, without specifying whether they belonged to the experimental or control group (Table 2). No severe adverse effects were reported in any study.

3.7. Assessment of reporting bias

The funnel plot of the TER showed potential asymmetry (Fig. 8), and Egger regression test provided evidence of possible publication bias ($t = 6.05$, $P < .001$) (Supplementary Figure 4, Supplemental Digital Content, http://links.lww.com/MD/L446). However, the fail-safe N test results were 771, surpassing the recommended cutoff of 105 (5 k + 10, where k represents the number of studies included in the meta-analysis). Furthermore using the trim and fill method, 9 artificial studies were included in the meta-analysis to adjust for funnel plot asymmetry. The adjusted fixed-effects (RR: 1.15, 95% CI: 1.11–1.18, $P < .001$) evaluated using the trim and fill method was aligned with original analysis (RR: 1.19, 95% CI: 1.15–1.23, $P < .001$) (Supplementary Figure 5A and B, Supplemental Digital Content, http://links.lww.com/MD/L448, http://links.lww.com/MD/L471). Additionally, a sensitivity analysis of the TER was conducted using the "leave 1 out" method because of the potential for reporting bias. This analysis did not affect the overall combined estimates (Supplementary File 5, Supplemental Digital Content, http://links.lww.com/MD/L448).

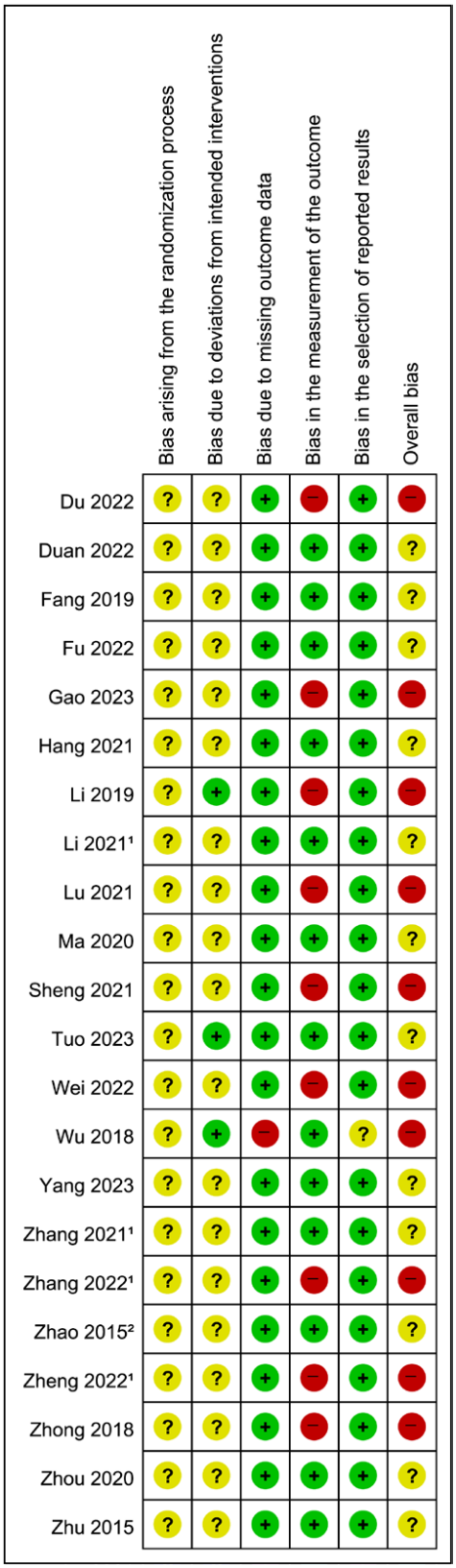

Figure 2. Risk of bias summary.

3.8. GRADE certainty of evidence

The level of confidence in the evidence for the combination of HM and probiotics in relation to TER and MLT was categorized as "high." For the Bristol fecal score, NO, anorectal dynamic parameters (MSV, MTV), and recurrence rate, the level of confidence was labeled as "moderate." The detailed reasons for downgrading are listed in Table 1.

4. Discussion

4.1. Summary of this review

This review aimed to investigate the effectiveness of HM in PFC. Following a comprehensive search, 22 RCTs, involving 2228 participants, were included in the analysis.

The combination of HM with probiotics may yield significantly greater benefits for TER, especially when HM is combined with *B subtilis* and *E faecium*, as well as a mixture of 3 probiotics (B, L, E), compared to probiotics alone. In the Bristol fecal score, serum indicators (MTL, NO), and anorectal dynamics parameters (MSV), the combined intervention of HM and probiotics also demonstrated positive effects. Furthermore, HM combined with probiotics could potentially reduce the recurrence rate by 70% compared to probiotics alone. This remains consistent even when conventional treatments and probiotics are used, as the inclusion of HM shows enhanced effectiveness in the TER and recurrence rate.

Most studies had unclear biases in terms of the randomization process and deviations from intended interventions. The methodological quality of the included RCTs was poor, with 10 studies[18,22,24,26,28,30,31,34,36,37] rated as having a high risk of bias, and the remaining 12 studies[19–21,23,25,27,29,32,33,35,38,39] having some concerns. Publication bias was not suspected. This review, as the first study to analyze the synergistic effects of combining HM with probiotics, which are commonly used for treating PFC, offers valuable insights to clinicians.

4.2. Clinical implication

Chronic constipation lacks an identifiable organic cause in more than 90% of children and typically arises from functional factors.[41,42] The underlying factors of FC are complex and not fully understood. Significant contributors include withholding behavior, psychological aspects and social circumstances.[43,44] Importantly, constipation can result in painful defecation, leading children to avoid defecation to alleviate ongoing discomfort, and potentially worsening their condition.[45]

The most frequently used herb in the included studies, *Aucklandiae Radix*, functions as a cholinergic and calcium antagonist, displaying spasmolytic effects on gastrointestinal motility by inhibiting muscarinic and 5-HT receptors.[46] Furthermore, it exhibits antibacterial properties against a range of pathogenic bacteria, including *Staphylococcus aureus*, *S. epidermidis*, and *E faecalis*.[47] *Crataegi Fructus* also possess laxative effects,[48] demonstrating greater efficacy in enhancing dyspepsia by improving digestion and alleviating stagnation.[49]

Fibers and prebiotics promote fecal bulkiness through their mass and the capacity of insoluble fibers to bind water directly.[50] Insoluble fibers induce a laxative effect by stimulating and irritating the gut mucosa, leading to increased secretion and peristalsis.[51,52] In constipation, the mechanism primarily attributed to HM is fiber-related.[53] HM might also act as a potential prebiotic with the ability to encourage the growth of beneficial microbial strains, including *Bifidobacterium* spp., *Lactobacillus* spp., and *Bacteroides* spp., within the gastrointestinal tract, thereby offering potential advantages to the host.[54,55] Consequently, the combined use of HM and probiotics may amplify the effects of the latter.

4.3. Limitations and suggestions for further studies

This study had several limitations. The meta-analysis, restricted to 22 RCTs conducted in China from 2015 to 2023, may have geographic limitations. Participants,

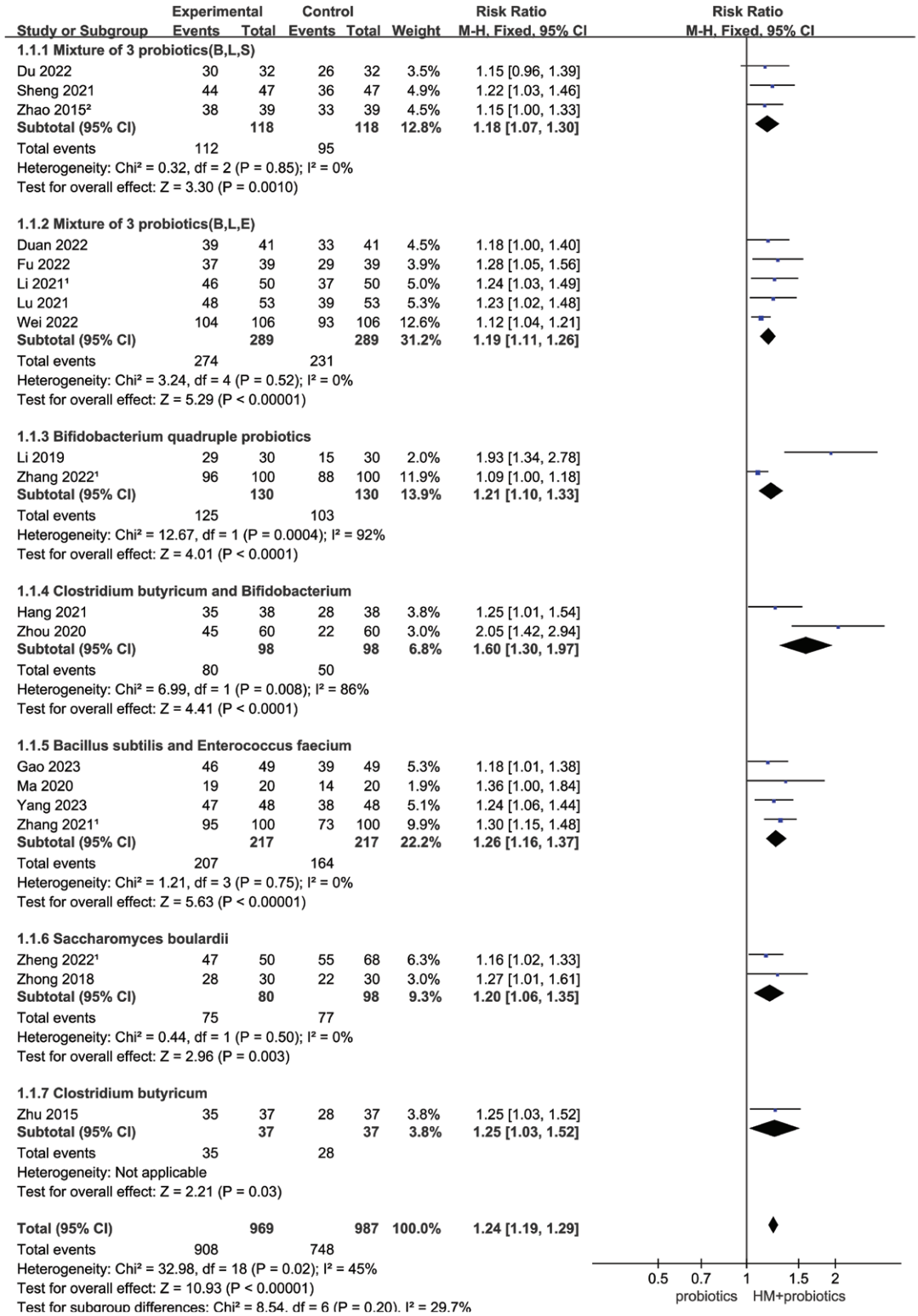

Figure 3. Forest plot of the total effective rate. [1]Add-on treatment: HM + probiotics + lactulose versus probiotics + lactulose. [2]Add-on treatment: HM + probiotics + (vitamin B1 + phenolphthalein + glycerol enema) versus probiotics + (vitamin B1 + phenolphthalein + glycerol enema). HM = herbal medicine.

personnel, and outcome assessors were not blinded in any of the included studies. The diverse compositions of HM used in these studies, combined with the broad age range of the children, could introduce heterogeneity. Additionally, owing to the various evaluations based on diverse criteria, some outcome measurements could not be performed meta-analysis.

In a previous study,[56] it was observed that elderly individuals showed a decrease in *Bifidobacterium* and an increase in *Lactobacillus*, *Streptococcus*, *Enterobacteriaceae*, and *Clostridia*, including *Clostridium perfringens*, in compared with infants. Another study[57] analyzing the gut microbiota in children with FC revealed that *Bacteroides fragilis*, *Bacteroides ovatus*, *B longum*, and *Parabacteroides* species

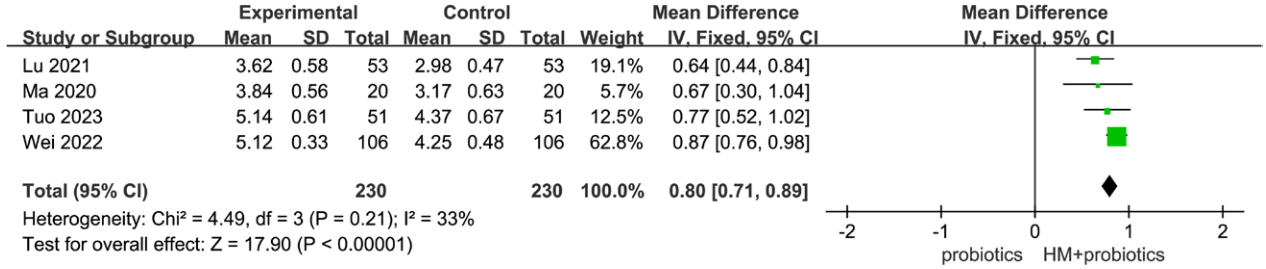

Figure 4. Forest plot of the Bristol fecal score.

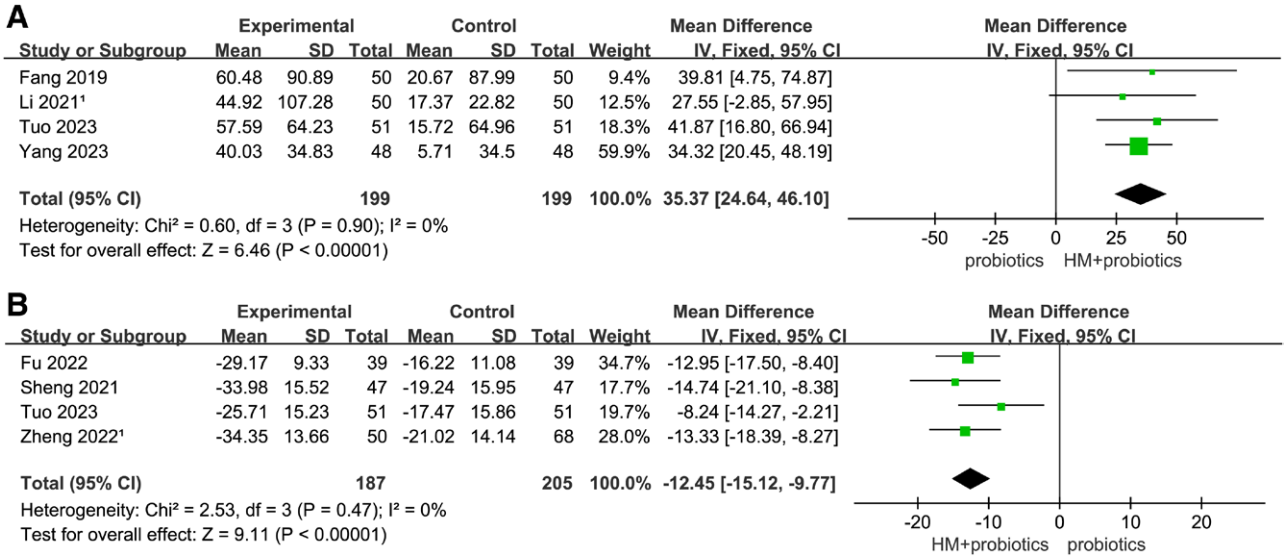

Figure 5. (A, B) Forest plot of the serum indicators (A: MTL, B: NO). [1]Add-on treatment: HM + probiotics + lactulose versus probiotics + lactulose. HM = herbal medicine, MTL = motilin, NO = nitrous oxide.

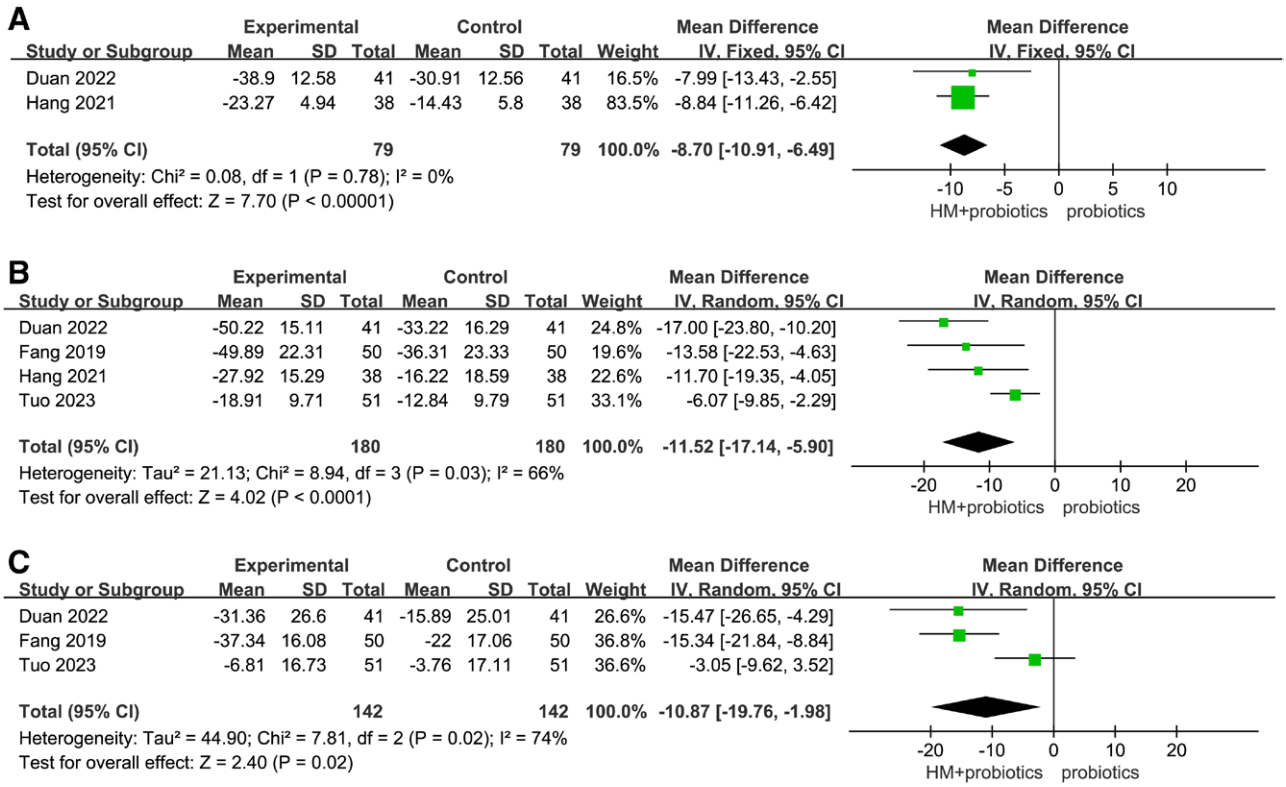

Figure 6. (A–C) Forest plot of the anorectal dynamics parameters (A: MSV, B: MTV, C: MSP). MSP = maximal systolic pressure of the anal sphincter, MSV = minimal sensitive volume of rectum, MTV = maximum tolerated volume of rectum.

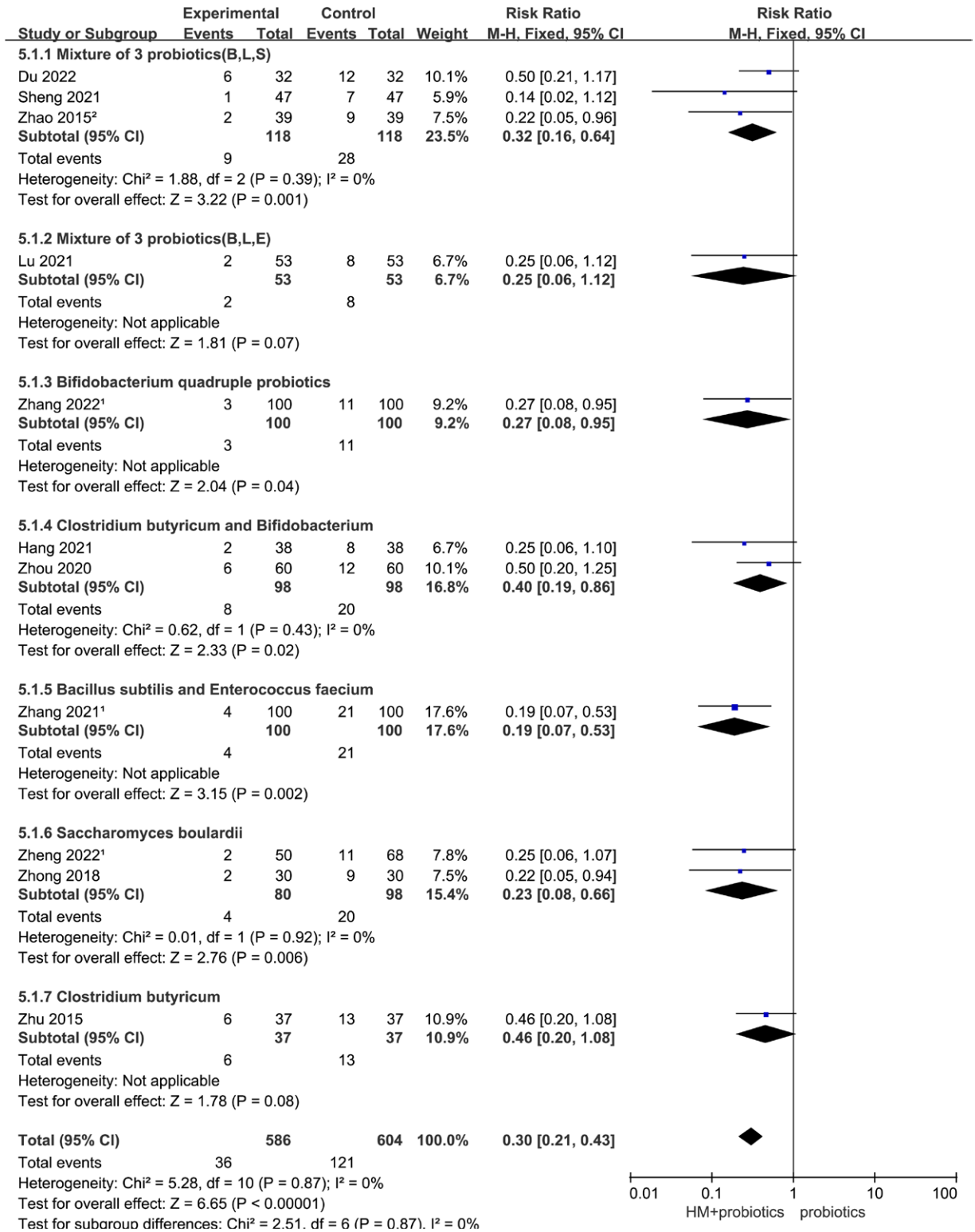

Figure 7. Forest plot of the recurrence rate. [1]Add-on treatment: HM + probiotics + lactulose versus probiotics + lactulose. [2]Add-on treatment: HM + probiotics + (vitamin B1 + phenolphthalein + glycerol enema) versus probiotics + (vitamin B1 + phenolphthalein + glycerol enema). HM = herbal medicine.

increased, while *Alistipes finegoldii* decreased. In this study, we had planned to analyze the changes in the gut microbiota as an outcome measurement. Because of the diverse age range of the participants (1–14.2 years), which induced heterogeneity, we were unable to conduct a meta-analysis. However, a trend was observed towards an increase in *Bifidobacterium* and *Lactobacillus*, accompanied by an improvement in constipation symptoms, in the HM and probiotics group compared with the group treated with probiotics alone. Conducting well-designed RCTs to analyze the synergistic effects of HM and probiotics through gut microbiota analysis would be beneficial. This enhanced understanding may pave the way for improved probiotic strategies, with the aim of effectively treating FC in children.

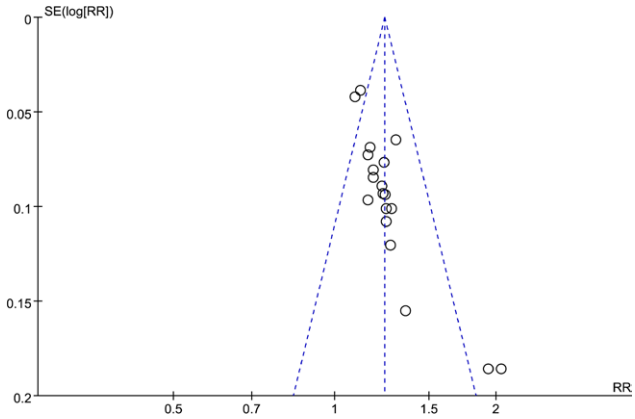

Figure 8. Funnel plot of total effective rate.

5. Conclusion

In conclusion, based on this meta-analysis, we observed that HM could potentially offer advantages in enhancing the efficacy rate and Bristol fecal score, influencing gastrointestinal peptide hormones (MTL), decreasing inflammation indicators (NO), increasing the MSV, and lowering the recurrence rate among children with FC.

Author contributions

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Writing—review & editing: Eunjin Kim, Seokjoo Chang, Sang Yeon Min.
Visualization: Seokjoo Chang.
Project administration: Sang Yeon Min.
Supervision: Sang Yeon Min.

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