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World J Clin Cases 2022 May 26; 10(15): 4713-5123





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#### **RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Ying-Yi Yuan, Production Department Director: Xiang Li, Editorial Office Director: Jin-Lei Wang.

#### **NAME OF JOURNAL**

World Journal of Clinical Cases

ISSN 2307-8960 (online)

#### **LAUNCH DATE**

April 16, 2013

#### **FREQUENCY**

Thrice Monthly

#### **EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja

#### **EDITORIAL BOARD MEMBERS**

https://www.wjgnet.com/2307-8960/editorialboard.htm

#### **PUBLICATION DATE**

May 26, 2022

#### COPYRIGHT

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https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wignet.com/bpg/gerinfo/208

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https://www.wjgnet.com/bpg/gerinfo/242

#### STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

#### **ONLINE SUBMISSION**

https://www.f6publishing.com

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World J Clin Cases 2022 May 26; 10(15): 4856-4877

DOI: 10.12998/wjcc.v10.i15.4856

ISSN 2307-8960 (online)

META-ANALYSIS

# Outcome of the efficacy of Chinese herbal medicine for functional constipation: A systematic review and meta-analysis

Zipan Lyu, Yibo Fan, Yang Bai, Tao Liu, Linda LD Zhong, Hui-Feng Liang

Specialty type: Gastroenterology and hepatology

#### Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

#### Peer-review report's scientific quality classification

Grade A (Excellent): 0 Grade B (Very good): B, B Grade C (Good): 0 Grade D (Fair): 0 Grade E (Poor): 0

P-Reviewer: Davis J, United States; Sánchez JIA, Colombia

**Received:** May 31, 2021 Peer-review started: May 31, 2021 First decision: June 25, 2021 **Revised:** July 14, 2021

Accepted: April 2, 2022 Article in press: April 2, 2022 Published online: May 26, 2022



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#### **Abstract**

#### **BACKGROUND**

Functional constipation (FC) is a common and chronic gastrointestinal disease and its treatment remains challenging.

To evaluate the efficacy and safety of Chinese herbal medicine (CHM) on efficacy rate, global symptoms, bowel movements and the Bristol Stool Scale score in patients with FC by summarizing current available randomized controlled trials (RCTs).

#### **METHODS**

RCTs with CHM to treat FC were identified by a systematic search of six databases from inception to October 20, 2020. Two independent reviewers assessed the quality of the included articles and extracted data. Meta-analyses were performed to odds ratio (OR), mean differences (MD) and 95% confidence interval (CI) using random-effects models. Subgroup analyses and sensitivity analyses were used to explore and interpret the sources of heterogeneity. The funnel plot, Begg's test and Egger's test were used to detect publication bias.

#### RESULTS

Ninety-seven studies involving 8693 patients were included in this work. CHM

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was significantly associated with a higher efficacy rate (OR: 3.62, 95%CI: 3.19-4.11, P < 0.00001) less severe global symptoms (OR: 4.03, 95% CI: 3.49-4.65, P < 0.00001) compared with control treatment, with the low heterogeneity between studies ( $I^2 = 0\%$ , P = 0.76). CHM was also associated with more frequent bowel movements (MD 0.83, 95% CI: 0.67-0.98, P < 0.00001), a lower score on the Bristol Stool Scale (OR: 1.63, 95%CI: 1.15-2.32, P < 0.006), and a not significant recurrence rate (OR: 0.47, 95% CI: 0.22-0.99, P = 0.05). No serious adverse effects of CHM were reported.

#### **CONCLUSION**

In this meta-analysis, we found that CHM may have potential benefits in increasing the number of bowel movements, improving stool characteristics and alleviating global symptoms in FC patients. However, a firm conclusion could not be reached because of the poor quality of the included trials. Further trials with higher quality are required.

**Key Words:** Functional constipation; Chinese herbal medicine; Efficacy; Systematic review; Meta-analysis

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Core Tip: In this meta-analysis, we found that Chinese herbal medicine may have potential benefits in increasing the number of bowel movements, improving stool characteristics and alleviating global symptoms in functional constipation patients. However, a firm conclusion could not be reached because of the poor quality of the included trials. Further trials with higher quality are required.

Citation: Lyu Z, Fan Y, Bai Y, Liu T, Zhong LL, Liang HF. Outcome of the efficacy of Chinese herbal medicine for functional constipation: A systematic review and meta-analysis. World J Clin Cases 2022; 10(15): 4856-4877

**URL:** https://www.wjgnet.com/2307-8960/full/v10/i15/4856.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v10.i15.4856

#### INTRODUCTION

Functional constipation (FC) is a common and chronic gastrointestinal disease. It has a prevalence of 14% in the population in Asia[1] and 15.6% of the population in Hong Kong[2], representing a huge care burden. It is estimated that about 3.2 million FC patients in the United States visited medical centers in 2012 and the direct cost per patient for chronic constipation ranged from \$1912 to \$7522 per year[3]. In addition, functional constipation greatly affects the quality of life of patients creating an important mental and physical burden[4].

The treatment of functional constipation remains challenging. Osmotic laxatives, irritant laxatives and stool softeners are commonly used to treat FC[5]. However, up to 47% of patients were not completely satisfied with such treatment mainly due to concerns about treatment efficacy, safety, adverse reactions and cost[6]. Therefore, patients with FC usually take a self-management approach and try to seek complementary and alternative therapy and Chinese herbal medicine is their usual choice.

Through a randomized controlled trial (RCT), McRorie et al[7] found that Psyllium, an herb, was superior to docusate sodium, a laxative, for the treatment of chronic constipation. Two systematic reviews reported that Chinese herbal medicine (CHM) was effective in treating constipation [8-9]. But they were not clear whether herbs improve bowel movement, increase the frequency of voluntary defecation or alleviate symptoms of constipation. Some people even have concerns about the safety of Chinese herbs. Therefore, the purpose of this review was to evaluate the efficacy and safety of CHM on efficacy rate, global symptoms, bowel movements and the Bristol Stool Scale score in patients with FC by summarizing current available RCTs.

#### MATERIALS AND METHODS

This systematic review was conducted following the guideline of Preferred reporting items for systematic review and Meta-analysis (PRISMA) statement[10].

#### Eligibility criteria

Studies meeting the following criteria will be included: (1) Participants: patients met established diagnostic criteria of FC, including Rome I, II, III, IV criteria, without restrictions for age, sex, ethnicity or setting type; (2) Type of studies: only randomized controlled trials were eligible; (3) Type of



intervention: studies compared any CHM with Western medicine (WM) or placebo. For studies using other agents as the third arm, only the two arms using CHM would be included for analysis; and (4) Type of outcome measurements: the efficacy rate (ER); the frequency of bowel movement (BM); the assessments of the global symptom (GS); the score of the Bristol Stool Scale (BSS); the recurrence rate (RR) within follow-up, and reported adverse effects (AEs).

#### Exclusion criteria

Trials were excluded: (1) Did not meet the criteria above; (2) Involved animal studies or in vitro studies; (3) Case series or reviews and conference abstracts; (4) Valid original data were unable to obtain even when contacting the author; and (5) Similar studies were reported without additional data to analyze and extract.

#### Search strategy and study selection

MEDLINE, Embase, SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang Database and China Science and Technology Journal Database (VIP) were searched. An electronic search of the databases was performed from 1994, the year of the establishment of Rome criteria, up to June 2020, using the following search terms: (functional constipation) AND (Chinese herbal medicine OR Chinese traditional medicine OR Oriental medicine OR complementary medicine). We also hand-searched conference abstracts. Reference lists of all retrieved articles and reviews were screened as well. We limited the literature search to RCTs on human subjects. No language restrictions were used. Search strategies used for the Medline database were as Supplementary material 1. Two reviewers (Lyu Z and Bai Y) independently read the title and abstract to initially select the studies that meet the eligibility criteria. Further reading of the full text was used to determine the included studies. If the reviewers had different opinions, the third researcher (Zhong LL) made the final decision.

#### Data extraction

Two reviewers (Lyu Z and Bai Y) independently extracted data on participant characteristics from the selected studies in a standardized data extraction form. We extracted the following information from each included article: first author, year of publication, publication language, number of participants, participant characteristics, duration of intervention and follow-up period, number of dropouts, controlled intervention and outcome data. Authors of trials were contacted for missing data and additional information. Any disparities between the two reviewers were discussed and resolved by consensus.

#### Definition of outcomes

The ER was considered a primary outcome. The frequency of BM, the assessments of the GS, the score of the BSS, the RR within follow-up and reported AEs were considered to be secondary outcomes.

ER: To access the efficacy of CHM on the number of participants with any self-assessed relief of constipation symptoms.

**BM:** To determine the efficacy of CHM on the frequency of BM per week, e.g., 4 times/week.

GS: To assess the efficacy of CHM on the number of participants with any self-assessed relief of global symptoms (including symptoms other than constipation).

BSS: To assess the efficacy of CHM on the number of participants with normal stool evaluated by Bristol Stool Scale ("soft sausage shape, soft lumps, muddy and watery stools" as normal stools).

RR: Recurrence means aggravation of constipation symptoms or reduction of BM to an untreated condition or less within the period of followed-up.

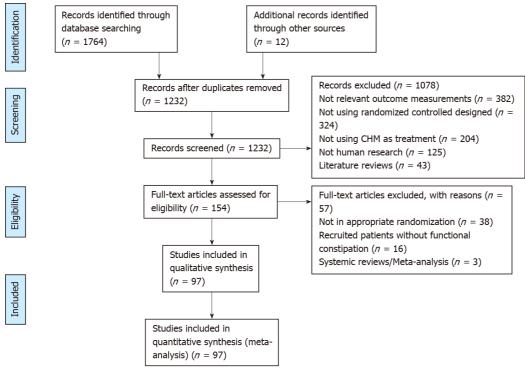
AEs: Including adverse events and clinical laboratory evaluations.

#### Risk of bias assessment

Two review authors (Lyu Z and Bai Y) assessed potential risks of bias for all included studies using Cochrane's tool for assessing the risk of bias. The tool assesses bias in six different domains: Sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Each domain receives a score of high, low or unclear depending on each review author's judgment. A third review author (Zhong LL) acted as an adjudicator in the event of a disagreement. Where doubt existed as to a potential risk of bias, we contacted the study authors for clarification. Results were tabulated into a "risk of bias graph" and a "risk of bias summary table".

#### Data synthesis

In this meta-analysis, odds ratio (OR) and 95% confidence interval (CI) was considered as the effect size



**DOI:** 10.12998/wjcc.v10.i15.4856 **Copyright** ©The Author(s) 2022.

Figure 1 Flow diagram of study selection.

for dichotomous outcomes; mean differences (MD) with 95%CI were calculated as the effect size for continuous outcomes. Forest plots were produced to visually assess the effect size and corresponding 95%CI using random-effects models. Heterogeneity between studies was assessed via the forest plot, while  $I^2$  values described the total variation between studies. When  $I^2$  values > 50%, it indicates high heterogeneity[11]. Subgroup analyses were used to explore and interpret the sources of heterogeneity; to evaluate whether the effects were modified by treatment characteristics and study quality, we specified it based on CHM ingredients, western medicine treatment and high-quality study. We used sensitivity analyses to explore the sources of high heterogeneity. Funnel plots, Begg's test, and Egger's test would be adopted to detect publication bias only when at least 10 studies were reporting the primary outcomes[12]. Statistical analysis was performed with RevMan software (version 5.4; The NordicCochrane Centre, The Cochrane Collaboration), and STATA software, version 13.0 (StataCorp, College Station, TX).

#### RESULTS

The meta-analysis outcomes of each outcome and subgroup are reported in Table 1.

#### Studies selection

There were 1764 studies via electronic databases and 12 trials by supplementary retrieval of reference lists of relevant literature. After the deletion of duplicate records, 1232 trials were screened, and 1078 trials were excluded by reviewing titles and abstracts. The remaining 154 trials were reviewed by full text. Ultimately, 97 trials involving 8693 FC patients were included in this work. The selection process of research was detailed by the PRISMA flow diagram as shown in Figure 1.

#### Description of trials identified

Ninety-seven studies were included based on the eligibility criteria in this work. The characteristics of the included studies are summarized in Table 1. As shown in Table 2, five studies [13,26,35,40,108] were published in English, the others in Chinese. Five studies [17,50,68,72,77] included patients using the Rome II criteria, 15 studies[16,25,36,38,42,44,49,58,62,63,67,82,83,90,95] using the Rome IV criteria, whereas the other 70 studies using Rome III criteria. The intervention of the treatment group was reported as CHM, and the ingredients were shown in Supplementary material 2. Besides, 6 types of intervention of the control group included PEG, mosapride, lactulose, phenolphthalein, probiotics and placebo. Duration in the retrieved studies ranged from 1 to 8 wk. Efficacy rate was reported in 97 studies and the global symptom was available in 69 studies. Bowel movement was reported in 15

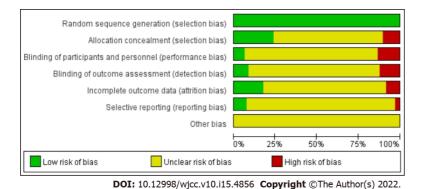


Figure 2 Risk of bias graph with the studies comparing Chinese herbal medicine with PEG/mosapride/lactulose/phenolphthalein/probiotics/placebo for the treatment of FC.

studies. The recurrence rate within the follow-up period was reported in 5 studies. Bristol Stool Scale was available in 7 studies while adverse effects of CHM were reported in 26 studies. Characteristics of the included trials are listed in Table 2 and quality evaluations of the included trials are shown in Table 2 and Figure 2.

#### Risk of bias

Among the 97 studies included, 3 trials[13,26,108] were found to be of high methodological quality. Thirteen trials[18,27,43,46,50,57,60,79,87,98,99,103,107] were deemed to have a high risk of bias. All trials mentioned "random" in terms of allocation, but 12 trials[18,43,46,50,57,60,79,87,98,99,103,107] didn't describe the specific method of randomization. Five trials[13,26,53,61,108] described allocation concealment and used blinding of participants, personnel or outcome assessors. Drop-outs and withdrawals were reported in 5 trials[13,19,24,26,108] which just left out the cases without qualified result data. We considered 8 trials[18,50,57,60,79,98,103,107] to be of selective reporting bias as these trials failed to report all the prespecified outcomes mentioned in their method section. Other potential sources of bias considered in all included studies were unclear. Therefore, study methodologies were incompletely described in majorities. The result of the assessment was showed in Figure 2, and the detail was showed in Supplementary material 3.

#### Efficacy rate

Ninety-seven studies measured ER (89.9%; 4007/4455) patients in the Chinese herbal medicine treatment group and 72.7% (3079/4238) patients with western medicine were measured. Results from 97 studies showed the treatment for FC was significantly in favor of CHM (OR: 3.62, 95%CI: 3.19-4.11, P < 0.00001) (Table 1 and Figure 3). There was no significant heterogeneity between studies ( $I^2 = 0\%$ , P =0.76).

In the subgroup analysis, CHM had a significant effect compared with PEG (OR: 2.42, 95%CI: 1.91-3.08, P < 0.00001), mosapride (OR: 3.49, 95%CI: 2.67-4.56, P < 0.00001), lactulose (OR: 3.71, 95%CI: 2.86-4.82, *P* < 0.00001), phenolphthalein (OR: 4.59, 95%CI: 2.71-7.76, *P* < 0.00001), probiotics (OR: 4.95, 95%CI: 3.21-7.65, *P* < 0.00001), and specifically compared with placebo (OR: 7.09, 95%CI: 4.83-10.43, *P* < 0.00001). There was no significant heterogeneity between studies in each subgroup (Table 1 and Figure 3).

#### Global symptom

Seventy-eight studies measured GS, and the results showed the treatment for FC was significantly in favor of CHM (OR: 4.03, 95%CI: 3.49-4.65, *P* < 0.00001) (Table 1 and Supplementary material 4). There was no significant heterogeneity between studies (P = 0%, P = 0.68). In the subgroup analysis, CHM had a significant effect compared with PEG (OR: 2.69, 95%CI: 2.06-3.51, P < 0.00001), mosapride (OR: 3.98, 95%CI: 2.93-5.41, *P* < 0.00001), lactulose (OR: 3.89, 95%CI: 2.97-5.09, *P* < 0.00001), probiotics (OR: 6.21, 95%CI: 3.60-10.70, *P* < 0.00001), and specifically compared with placebo (OR: 8.40, 95%CI: 5.64-12.52, *P* < 0.00001). There was no significant heterogeneity between studies in each subgroup (Table 1 and Supplementary material 4). However, there was only one study that compared the global symptom between CHM and phenolphthalein (OR: 5.85, 95%CI: 1.22-28.05).

#### Bowel movement

Fifteen studies measured BM. Results from 15 studies showed the treatment for FC was significantly in favor of CHM (MD 0.83, 95%CI: 0.67-0.98, P < 0.00001) (Table 1 and Figure 4). There was significant heterogeneity between studies ( $I^2 = 80\%$ , P < 0.00001).

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### Table 1 Summary of meta-analysis results

	No. of studies in	No. of pa	rticipants	Results			Heterogeneit	у	
Outcomes	meta-analysis	Т	С	OR/MD	95%CI	P value	Chi- square test	p	P value
ER	97	4455	4238	3.62	(3.19, 4.11)	< 0.00001	85.79	0%	0.76
PEG	31	1429	1399	2.42	(1.91, 3.08)	< 0.00001	28.03	0%	0.57
Mosapride	21	881	834	3.49	(2.67, 4.56)	< 0.00001	14.87	0%	0.78
Lactulose	24	1102	1018	3.71	(2.86, 4.82)	< 0.00001	11.17	0%	0.98
Phenolphthalein	7	294	287	4.59	(2.71, 7.76)	< 0.00001	1.13	0%	0.98
Probiotics	8	410	362	4.95	(3.21, 7.65)	< 0.00001	0.63	0%	1
Placebo	6	339	338	7.09	(4.83, 10.43)	< 0.00001	4.84	0%	0.44
GS	78	3438	3288	4.03	(3.49, 4.65)	< 0.00001	70.74	0%	0.68
PEG	26	1078	1038	2.69	(2.06, 3.51)	< 0.00001	21.54	0%	0.66
Mosapride	17	714	673	3.98	(2.93, 5.41)	< 0.00001	10.92	0%	0.81
Lactulose	23	1046	978	3.89	(2.97, 5.09)	< 0.00001	8.08	0%	1
Phenolphthalein	1	57	57	5.85	(1.22, 28.05)	0.03	-	-	-
Probiotics	6	234	234	6.21	(3.60, 10.70)	< 0.00001	1.83	0%	0.87
Placebo	5	309	308	8.4	(5.64, 12.52)	< 0.00001	3.87	0%	0.42
BM	15	663	652	0.83	(0.67, 0.98)	< 0.00001	71.74	80%	< 0.00001
PEG	6	264	258	0.65	(0.28, 1.02)	0.0006	37.91	87%	< 0.00001
Mosapride	5	215	210	0.94	(0.64, 1.24)	< 0.00001	15.43	74%	0.004
Lactulose	1	55	55	0.98	(0.81, 1.15)	< 0.00001	-	-	-
Phenolphthalein	-	-	-	-	-	-	-	-	-
Probiotics	1	30	30	0.61	(0.39, 0.83)	-	-	-	-
Placebo	2	99	99	0.99	(0.87, 1.11)	< 0.00001	0	0%	1
BSS	7	303	284	1.63	(1.15, 2.32)	0.006	1.77	0%	0.94
PEG	4	187	183	1.48	(0.96, 2.28)	0.15	1.16	0%	0.76
Mosapride	2	60	61	1.88	(0.79, 4.44)	0.15	0.01	0%	0.92
Lactulose	-	-	-	-	-	-	-	-	-
Phenolphthalein	-	-	-	-	-	-	-	-	-
Probiotics	1	56	40	2.07	(0.90, 4.74)	0.09	-	-	-
Placebo	-	-	-	-	-	-	-	-	-
Recurrence	5	137	78	0.47	(0.22, 0.99)	0.05	4.42	9%	0.35
PEG	1	27	25	0.66	(0.20, 2.13)	0.49	-	-	-
Mosapride	-	-	-	-	-	-	-	-	-
Lactulose	1	42	40	0.31	(0.10, 0.91)	0.03	-	-	-
Phenolphthalein	-	-	-	-	-	-	-	-	-
Probiotics	-	-	-	-	-	_	-	-	-
Placebo	3	68	13	0.5	(0.08, 3.19)	0.46	3.47	42%	0.18

Ps: Data were meta-analyzed by using a random-effects model and are presented as OR or MD as appropriate. Statistical heterogeneity was assessed by using the chi-square test and quantified by using the  $l^2$  statistic. ER: Efficacy rate; PEG: Polyethylene glycol; GS: Global symptom; BM: Bowel movement; BSS: Bristol Stool Scale; RR: Recurrence rate; AEs: Adverse effects.

Table 2 Chara	cteristics of t	the included stu	dies								
Study	Language	Inclusion criteria	No. of participants	Age median (range)	Intervention of treatment group	Intervention of control group	Duration in wk	Assessment of outcomes	Follow-up in mo	Dropout (T/C)	Cochrane
Bian <i>et al</i> [13], 2014	English	Rome III	120	55.6 (18-75)	СНМ	Placebo	8	ER, BM, GS, ARs, RR	2	1/1	A
Bin <i>et al</i> [14], 2011	Chinese	Rome III	61	67.4 (60-85)	CHM	Mosapride	2	ER, BM, BSS, GS	NA	NA	В
Bu <i>et al</i> [15], 2019	Chinese	Rome III	57	57.9 (40-85)	CHM	Lactulose	4	ER, GS, ARs	NA	NA	В
Cai <i>et al</i> [16], 2020	Chinese	Rome IV	60	48.2 (45-78)	CHM	Lactulose	4	ER, GS	NA	NA	В
Cao <i>et al</i> [17], 2012	Chinese	Rome II	60	36.7 (18-65)	CHM	Peg	4	ER, GS	NA	NA	В
Chen <i>et al</i> [18], 2011	Chinese	Rome III	76	74.3 (60-92)	CHM	Peg	4	ER, GS	NA	NA	С
Chen et al[19], 2012	Chinese	Rome III	70	31.9 (28-75)	СНМ	Peg	4	ER, GS	NA	NA	В
Chen <i>et al</i> [20], 2014	Chinese	Rome III	120	69.3 (60-75)	CHM	Lactulose	4	ER, GS, ARs	NA	NA	В
Chen <i>et al</i> [21], 2014	Chinese	Rome III	88	25.1 (17-55)	СНМ	Mosapride	3	ER, GS	2	NA	В
Chen <i>et al</i> [22], 2016	Chinese	Rome III	112	62.5 (51-70)	СНМ	Lactulose	4	ER, BM, GS	NA	1/1	В
Chen <i>et al</i> [23], 2018	Chinese	Rome III	120	49.2 (25-77)	CHM	Lactulose	4	ER, GS	1	NA	В
Chen <i>et al</i> [24], 2020	Chinese	Rome III	88	66.9 (60-75)	CHM	Lactulose	4	ER, GS, RR	1	2/4	В
Chen <i>et al</i> [25], 2020	Chinese	Rome IV	160	48.3 (37-52)	CHM	Lactulose	4	ER, GS	NA	NA	В
Cheng et al[26], 2010	English	Rome III	120	33.5 (18-65)	СНМ	Placebo	8	ER, BM, GS, ARs, RR	2	9/8	A
Cheng et al[27], 2012	Chinese	Rome III	100	52.6 (23-67)	CHM	Mosapride	4	ER,GS	3	NA	С
Chi <i>et al</i> [28], 2010	Chinese	Rome III	70	NA	CHM	Peg	4	ER, BM, GS	NA	0/1	В
Deng et al[29],	Chinese	Rome III	96	70.2 (50-85)	CHM	Lactulose	4	ER, GS	1	3/3	В

2018											
Dou <i>et al</i> [30], 2014	Chinese	Rome III	90	58.7 (45-72)	СНМ	Lactulose	3	ER, GS	NA	NA	В
Fu <i>et al</i> [31], 2012	Chinese	Rome III	60	42.8 (18-65)	СНМ	Probiotics	4	ER, BM, GS	NA	NA	В
Gao et al[32], 2013	Chinese	Rome III	60	55.7 (18-70)	СНМ	Peg	8	ER, GS	NA	NA	В
Gao et al[33], 2015	Chinese	Rome III	80	58.3 (20-70)	CHM	Peg	2	ER, BM, GS	NA	NA	В
Gu et al[34], 2013	Chinese	Rome III	60	45.1 (21-60)	CHM	Lactulose	4	ER, GS, BSS, ARs	NA	0/1	В
Guo et al[35], 2010	English	Rome II	70	64.7 (21-79)	CHM	Placebo	4	ER, GS, RR, RR	NA	NA	В
Guo et al[36], 2018	Chinese	Rome IV	60	61.8 (18-80)	CHM	Peg	4	ER, GS	NA	1/1	В
He <i>et al</i> [37], 2015	Chinese	Rome III	80	71.4 (60-79)	CHM	Peg	2	ER, BM, GS	2	NA	В
He <i>et al</i> [38], 2019	Chinese	Rome IV	120	72.5 (65-80)	CHM	Peg	2	ER, GS, ARs	2	NA	В
Hu et al[39], 2018	Chinese	Rome III	238	3.84 (1-14)	CHM	Placebo	1	ER, GS	NA	NA	В
Huang <i>et al</i> [40], 2012	English	Rome III	60	71.8 (60-85)	CHM	Lactulose	4	ER, GS, ARs	NA	NA	В
Hui <i>et al</i> [41], 2018	Chinese	Rome III	62	68.1 (55-90)	CHM	Lactulose		ER, GS, ARs	NA	NA	NA
Jiang <i>et al</i> [42], 2020	Chinese	Rome IV	72	51.6 (22-73)	CHM	Lactulose	4	ER, GS	NA	NA	В
Jiao <i>et al</i> [43], 2018	Chinese	Rome III	120	58.7 (50-70)	CHM	Placebo	1	ER, GS	NA	0/4	С
Kong et al[44], 2020	Chinese	Rome IV	100	69.4 (60-83)	CHM	Mosapride	2	ER, GS	1	1/3	В
Lai et al[45], 2012	Chinese	Rome III	90	NA	CHM	Mosapride	4	ER, GS	NA	NA	В
Li et al[46], 2012	Chinese	Rome III	60	49.7 (18-65)	CHM	Peg	4	ER, GS	NA	NA	С
Li et al[47], 2015	Chinese	Rome III	166	51.9 (18-65)	CHM	Peg	4	ER, ARs	2	NA	В
Li et al[48], 2016	Chinese	Rome III	160	47.2 (23-68)	CHM	Peg	4	ER, BM	NA	0/6	В

Li et al[49], 2019	Chinese	Rome IV	120	55.1 (49-63)	CHM	Mosapride	2	ER, GS, ARs	NA	NA	В
Lin <i>et al</i> [50], 2009	Chinese	Rome II	120	68.5 (65-80)	СНМ	Peg	4	ER, ARs	NA	NA	С
Lin <i>et al</i> [51], 2012	Chinese	Rome III	80	47.1 (20-60)	CHM	Mosapride	6	ER, GS, ARs	NA	NA	В
Liu <i>et al</i> [52], 2013	Chinese	Rome III	66	49.6 (18-75)	CHM	Lactulose	4	ER, GS	NA	0/3	В
Liu <i>et al</i> [53], 2017	Chinese	Rome III	60	51.9 (18-65)	CHM	Mosapride	4	ER, GS, ARs	NA	NA	В
Liu <i>et al</i> [54], 2017	Chinese	Rome III	120	53.7 (45-64)	СНМ	Lactulose	2.1	ER, GS	NA	NA	В
Liu <i>et al</i> [55], 2018	Chinese	Rome III	244	2.6 (1-14)	CHM	Probiotics	4	ER	NA	NA	В
Lv et al[56], 2012	Chinese	Rome III	280	67.1 (19-82)	СНМ	Peg	3	ER	6	NA	В
Lv et al[57], 2018	Chinese	Rome III	80	54.9 (20-71)	СНМ	Probiotics	1	ER, GS	NA	NA	С
Mu et al[58], 2019	Chinese	Rome IV	90	68.7 (62-81)	СНМ	Peg	2	ER, GS, BSS	NA	NA	В
Qian <i>et al</i> [59], 2014	Chinese	Rome III	80	46.3 (18-65)	СНМ	Mosapride	8	ER, GS, ARs	NA	2/4	В
Que et al[60], 2018	Chinese	Rome III	80	45.8 (16-70)	СНМ	Lactulose	8	ER, GS	NA	NA	С
Ren <i>et al</i> [61], 2014	Chinese	Rome III	60	47.6 (18-65)	CHM	Peg	8	ER, GS, RR	1	NA	В
Shao <i>et al</i> [62], 2019	Chinese	Rome IV	100	67.9 (65-80)	СНМ	Mosapride	2	ER, GS	NA	NA	В
Su <i>et al</i> [63], 2019	Chinese	Rome IV	96	71.5 (64-78)	СНМ	Mosapride	2	ER, BM	1	NA	В
Sui <i>et al</i> [64], 2012	Chinese	Rome III	120	54.9 (18-79)	СНМ	Probiotics	2	ER, GS	NA	NA	В
Sun <i>et al</i> [65], 2011	Chinese	Rome III	80	68.3 (60-80)	CHM	Mosapride	1	ER, BM, GS	NA	NA	В
Tao <i>et al</i> [66], 2018	Chinese	Rome III	60	NA	СНМ	Peg	4	ER	NA	NA	В
Wang et al[67], 2020	Chinese	Rome IV	94	69.3 (66-85)	СНМ	Peg	4	ER, BM, GS	2	5/5	В

Wang et al[68], 2004	Chinese	Rome II	90	64.5 (56-75)	CHM	Phenolphthalein	4	ER	NA	NA	В
Wang et al[69], 2011	Chinese	Rome III	156	60.7 (NA)	CHM	Peg	2	ER, GS, BSS	NA	NA	В
Wang <i>et al</i> [70], 2013	Chinese	Rome III	112	73.6 (65-82)	СНМ	Lactulose	3	ER, ARs	NA	0/12	В
Wang <i>et al</i> [71], 2014	Chinese	Rome III	60	1.9 (1-7)	СНМ	Probiotics	8	ER	3	NA	В
Wang et al[72], 2015	Chinese	Rome II	116	66.7 (55-75)	CHM	Phenolphthalein	4	ER, GS	NA	1/1	В
Wu et al[73], 2008	Chinese	Rome III	54	76.4 (60-84)	CHM	Peg	4	ER, GS	NA	1/0	В
Wu et al[74], 2009	Chinese	Rome III	60	55.9 (50-75)	CHM	Probiotics	4	ER, GS, ARs	6	NA	В
Wu et al[75], 2013	Chinese	Rome III	60	56.3 (45-75)	CHM	Peg	4	ER, BM, ARs	NA	4/3	В
Wu et al[76], 2013	Chinese	Rome III	60	49.4 (NA)	CHM	Phenolphthalein	2	ER	NA	NA	В
Xin <i>et al</i> [77], 2008	Chinese	Rome II	130	66.8 (60-88)	CHM	Phenolphthalein	4	ER	NA	0/5	В
Xin et al[78], 2014	Chinese	Rome III	70	69.7 (60-85)	CHM	Phenolphthalein	4	ER	NA	NA	В
Xu et al[79], 2013	Chinese	Rome III	82	70.3 (NA)	СНМ	Lactulose	4	ER, GS	NA	NA	С
Xu et al[80], 2016	Chinese	Rome III	70	47.2 (18-75)	CHM	Peg	8	ER, GS	NA	5/5	В
Xu et al[81], 2018	Chinese	Rome III	80	41.8 (18-54)	CHM	Peg	4	ER, GS	1	8/10	В
Xu et al[82], 2019	Chinese	Rome IV	60	42.3 (25-64)	CHM	Mosapride	4	ER, GS	3	NA	В
Yan et al[83], 2020	Chinese	Rome IV	80	46.7 (16-70)	СНМ	Peg	4	ER, GS	2	NA	В
Yan et al[84], 2013	Chinese	Rome II	258	82.2 (80-93)	СНМ	Peg	4	ER	NA	NA	В
Yan et al[85], 2016	Chinese	Rome III	60	43.1 (32-62)	СНМ	Mosapride	4	ER, GS, BSS	1	NA	В
Yang et al[86],	Chinese	Rome III	80	67.4 (60-82)	СНМ	Peg	4	ER, GS	NA	NA	В

2008											
Yang et al[87], 2012	Chinese	Rome III	66	71.5 (NA)	СНМ	Phenolphthalein	2	ER	NA	2/2	С
Yang et al[88], 2015	Chinese	Rome III	80	54.9 (NA)	CHM	Probiotics	4	ER, GS, BSS, ARs	NA	NA	В
Yao et al[89], 2016	Chinese	Rome III	160	66.1 (60-80)	CHM	Lactulose	4	ER, GS	NA	NA	В
Ye et al[90], 2020	Chinese	Rome IV	120	57.8 (18-78)	CHM	Peg	4	ER, GS	NA	NA	В
Ye et al[91], 2016	Chinese	Rome III	60	68.4 (60-85)	СНМ	Lactulose	4	ER, GS	NA	NA	В
Yuan et al[92], 2016	Chinese	Rome III	64	47.4 (30-75)	CHM	Peg	4	ER, GS, ARs	1	NA	В
Zeng et al[93], 2017	Chinese	Rome III	88	47.2 (18-65)	СНМ	Mosapride	4	ER, BM, GS	3	1/3	В
Zhan et al[94], 2016	Chinese	Rome III	60	56.3 (18-75)	СНМ	Lactulose	4	ER, GS, ARs	NA	NA	В
Zhang et al[95], 2020	Chinese	Rome IV	80	44.5 (18-65)	СНМ	Lactulose	4	ER, GS, ARs	3	5/5	В
Zhang et al[96], 2014	Chinese	Rome III	64	56.7 (18-75)	СНМ	Mosapride	4	ER, ARs	NA	NA	В
Zhang et al[97], 2014	Chinese	Rome III	104	68.2 (60-80)	СНМ	Mosapride	4	ER, GS, ARs	1	NA	В
Zhang et al[98], 2014	Chinese	Rome III	90	65.3 (NA)	СНМ	Peg	4	ER, GS	NA	NA	С
Zhang et al[99], 2018	Chinese	Rome III	60	72.4 (60-85)	СНМ	Phenolphthalein	4	ER	NA	NA	С
Zhang <i>et al</i> [100], 2018	Chinese	Rome III	106	33.5 (24-58)	CHM	Mosapride	8	ER, BM	1	0/2	В
Zhang <i>et al</i> [101], 2019	Chinese	Rome III	68	41.7 (19-69)	СНМ	Probiotics	4	ER, GS	3	NA	В
Zhao et al[102], 2009	Chinese	Rome III	76	42.4 (NA)	CHM	Mosapride	2	ER, GS	1	11/11	В
Zhao et al[103], 2014	Chinese	Rome III	76	56.7 (15-80)	СНМ	Peg	4	ER, GS	NA	NA	С
Zhao et al[104], 2015	Chinese	Rome III	68	51.4 (18-70)	СНМ	Mosapride	4	ER, GS, ARs	NA	NA	В

Zhao et al[105], 2015	Chinese	Rome III	100	4.2 (1-14)	CHM	Lactulose	8	ER, GS	14	1/2	В
Zhao et al[106], 2018	Chinese	Rome III	90	53.7 (23-67)	СНМ	Lactulose	8	ER, GS	NA	NA	В
Zhao et al[107], 2019	Chinese	Rome III	66	68.4 (65-84)	CHM	Peg	3	ER, BSS	3	0/1	С
Zhong <i>et al</i> [108], 2018	English	Rome III	194	44.6 (18-70)	CHM	Placebo	8	ER, BM, GS, ARs	2	3/7	A
Zhou et al[109], 2018	Chinese	Rome III	80	51.3 (30-70)	СНМ	Mosapride	4	ER, GS, ARs	NA	7/9	В

CHM: Chinese herbal medicine; PEG: Polyethylene glycol; ER: Efficacy rate; BM: Bowel movement; GS: Global symptom; BSS: Bristol Stool Scale; RR: Recurrence rate; AEs: Adverse effects; A: Methodology with a low risk of bias; B: Methodology with an unclear risk of bias; C: Methodology with a high risk of bias.

In the subgroup analysis, CHM had a significant effect compared with PEG (MD 0.83, 95%CI: 0.67-0.98, P < 0.0006), mosapride (MD 0.65, 95%CI: 0.28-1.02, P < 0.00001), and specifically compared with placebo (MD 0.99, 95%CI: 0.87-1.11, P < 0.00001). There was no significant heterogeneity between studies in the placebo subgroup (Table 1 and Figure 4). However, there was only one study that compared CHM with lactulose (MD 0.98, 95%CI: 0.81-1.15, P < 0.00001), and probiotics (MD 0.61, 95%CI: 0.39-0.83, P < 0.00001). No study in the phenolphthalein subgroup.

#### Bristol stool scale

A total of 7 studies compared CHM with western medicine and reported the Bristol Stool Scale. The results showed the treatment for FC was significantly in favor of CHM (OR: 1.63, 95%CI: 1.15-2.32, P < 0.006) (Table 1 and Supplementary material 5). There was no significant heterogeneity between studies (P = 0%, P = 0.94).

In the subgroup analysis, CHM had no significant effect compared with PEG (OR: 1.48, 95% CI: 0.96-2.28, P = 0.15) and mosapride (OR: 1.88, 95% CI: 0.79-4.44, P = 0.15). There was no significant heterogeneity between studies in the two subgroups (Table 1 and Supplementary material 5). However, there was only one study that compared CHM with probiotics (OR: 2.07, 95% CI: 0.90-4.74, P = 0.09).

#### Recurrence rate

Five studies compared CHM with western medicine and reported the RR. The results showed CHM was not superior to western medicine in controlling the recurrence rate of FC (OR: 0.47, 95% CI: 0.22-0.99, P = 0.05) (Table 1 and Figure 5). There was no significant heterogeneity between studies ( $I^2 = 9\%$ , P = 0.35).

In the subgroup analysis, CHM had no significant effect compared with placebo (OR: 0.5, 95%CI: 0.08-3.19, P = 0.46). There was no significant heterogeneity between studies in this subgroup (Table 1 and Figure 5). However, there was only one study that compared CHM with PEG (OR: 0.66, 95%CI: 0.20-2.13, P = 0.49), and lactulose (OR: 0.31, 95% CI 0.10-0.91, P = 0.03) (Table 1 and Figure 5).

Study or Subgroup	Experime		Contr		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Ct
12.1.1 CHM vs PEG Cao[17] 2012	27	30	26	30	0.6%	1.38 [0.28, 6.80]	
Chen[18] 2011	29	37	26	39	1.5%	1.81 [0.65, 5.06]	+
Chen[19] 2012	35 33	40 35	22 31	30	1.1%	2.55 [0.74, 8.78]	
Chi[28] 2010 Gao[32] 2013	28	30	25	30	0.5%	1.60 [0.25, 10.21] 2.80 [0.50, 15.73]	
Gao[33] 2015 Guo[36] 2018	39 27	40 29	37 25	40 29	0.5%	3.16 [0.31, 31.78] 2.16 [0.36, 12.84]	
He[37] 2015	34	40	26	40	1.4%	3.05 [1.03, 9.02]	
He[38] 2019	59	60	47	60	0.4%	16.32 [2.06, 129.29]	
Li[46] 2012 Li[47] 2015	33 68	40 87	18 50	20 79	3.5%	0.52 [0.10, 2.79] 2.08 [1.05, 4.11]	
LI[48] 2016	79	80	61	74	0.4%	16.84 [2.14, 132.25]	
Lin[50] 2009 Lv[56] 2012	135	140	123	140	1.1%	3.50 [1.06, 11.57] 3.73 [1.34, 10.42]	
Mu[58] 2019	40	45	26	45	1.3%	5.85 [1.94, 17.60]	
Ren[61] 2014	27	30	25	30	0.7%	1.80 [0.39, 8.32]	
Tao[66] 2018 Wang[67] 2020	25 38	30 43	27 30	30 43	1.3%	0.56 [0.12, 2.57] 3.29 [1.06, 10.27]	
VVang[69] 2011	74	79	61	77	1.4%	3.88 [1.35, 11.20]	
Wu[73] 2008 Wu[76] 2013	26 26	26 26	25 23	27	0.2%	5.20 [0.24, 113.59] 10.15 [0.52, 198.63]	
xu[80] 2016	20	30	22	30	0.6%	5.09 [0.98, 26.43]	
Xu[81] 2018 Yan[83] 2020	31 39	32 40	29 37	30 40	0.2%	1.07 [0.06, 17.89] 3.16 [0.31, 31.78]	
Yan(84) 2013	62	72	76	88	2.0%	0.98 [0.40, 2.42]	
Yang(86) 2008 Ye(90) 2020	36 55	40 60	34 47	40 60	0.9%	1.59 [0.41, 6.12] 3.04 [1.01, 9.16]	
Yuan[92] 2016	32	32	30	32	0.2%	6.33 [0.26, 116.60]	
Zhang[98] 2014	17	20	12	20	0.7%	3.78 [0.83, 17.25]	
Zhao[103] 2014 Zhao[107] 2019	35 30	43 33	32 27	43 32	0.7%	1.60 [0.54, 4.21]	
Subtotal (95% CI)		1429		1399	28.1%	2.42 [1.91, 3.08]	
Total events Heterogeneity: Tau <sup>a</sup> =	1303 0.00: Ch8	- 28.03	1128	/P = 0.4	573: E = 09	6	
Test for overall effect:	Z = 7.23 (F	< 0.00	001)	0 - 0	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	~	
12.1.2 CHM vs mosap Bin[14] 2011	20	30	22	31	0.6%	5.73 [1.12, 29.25]	
Chen[21] 2014	41	44	34	44	0.9%	4.02 [1.02, 15.79]	
Cheng[27] 2012 Kong[44] 2020	47 45	52 49	27 38	48	1.4%	7.31 [2.47, 21.62] 2.66 [0.76, 9.34]	<del></del>
Lai[45] 2012	51	60	16	30	1.6%	4.96 [1.81, 13.59]	
Li[49] 2019 Lin[51] 2012	55 37	60 40	43 36	60 40	0.7%	4.35 [1.49, 12.73] 1.37 [0.29, 6.56]	
Liu[53] 2017	28	30	26	30	0.5%	2.15 [0.36, 12.76]	
Qian[59] 2014 Shao[62] 2019	36 43	38 50	32 21	36	1.7%	2.25 [0.39, 13.12] 8.48 [3.19, 22.52]	
Shao(62) 2019 Su(63) 2019	43	49	34	47	1.5%	8.48 [3.19, 22.52] 2.29 [0.82, 6.39]	+
Sun(65) 2011	36	40	31	40	1.0%	2.61 [0.73, 9.32]	
Xu[82] 2019 Yan[85] 2016	27 27	30	21 22	30	0.8%	3.86 [0.93, 16.05] 3.27 [0.77, 13.83]	
Zeng[93] 2017	39	43	28	41	1.196	4.53 [1.33, 15.35]	-
Zhang(100) 2018 Zhang(96) 2014	29 42	32 53	24	32 51	0.8%	3.22 [0.77, 13.50]	
Zhang(97) 2014	41	53	33	51	2.2%	1.86 [0.79, 4.41]	+
Zhao(102) 2009 Zhao(104) 2015	23 35	27 38	19	27 38	0.9%	2.42 [0.63, 9.29] 7.61 [1.98, 29.25]	
Zhou[109] 2018	32	33	24	31	0.3%	9.33 [1.08, 81.02]	
Subtotal (95% CI)	704	881		834	22.7%	3.49 [2.67, 4.56]	•
Total events Heterogeneity: Tau* =	784 0.00: Chi <sup>a</sup>	= 14.07	587 df= 20	(P = 0.7	70): I* = 0.9	No.	
Test for overall effect:	Z = 9.17 (F	× 0.00	001)				
12.1.3 CHM vs latulos	ie.						
Bu[15] 2019	28	29	24	28	0.3%	4.67 [0.49, 44.64]	
Cai[16] 2020 Chen[20] 2014	28 53	30 60	21 42	30 60	1.8%	6.00 [1.17, 30.72] 3.24 [1.24, 8.49]	
Chen[22] 2016	52	55	4.4	55	0.9%	4.33 [1.14, 16.52]	
Chen[23] 2018	55	60	46	60	1.4%	3.36 [1.12, 9.99]	
Chen[24] 2020 Chen[25] 2020	72	42 80	29 62	40 80	2.0%	2.81 [0.88, 8.99]	
Deng[29] 2018	44	4.5	40	45	0.3%	5.50 [0.62, 49.11]	
Dou[30] 2014 Gu[34] 2013	39 28	42 30	37 24	48 29	0.9%	3.86 [1.00, 14.96] 2.92 [0.52, 16.42]	
Huang[40] 2012	28	30	24	30	0.6%	3.50 [0.65, 18.98]	+
Hui[41] 2018	27 35	31 36	19 29	31	0.4%	4.26 [1.19, 15.25] 8.45 [0.98, 72.70]	
Jiang[42] 2020 Liu[52] 2013	27	33	23	30	1.196	1.37 [0.40, 4.66]	
Liu[54] 2017	80	90	14	30	1.7%	9.14 [3.46, 24.19]	
Que[60] 2018 Wang[70] 2013	39 54	40 55	33 31	40	0.4%	8.27 [0.97, 70.73] 7.84 [1.59, 38.61]	
Xu[79] 2013	35	43	22	39	1.6%	3.38 [1.25, 9.15]	
Yao[89] 2016 Ye[91] 2016	74 20	30	61 26	80	1.7%	3.84 [1.44, 10.22] 2.15 [0.36, 12.76]	
Zhan(94) 2016	26	30	22	30	0.9%	2.36 [0.63, 8.92]	
Zhang[95] 2020 Zhao(105) 2015	32 45	35 49	24 33	35 48	1.1%	4.89 [1.23, 19.47] 5.11 [1.55, 16.82]	
Zhao[106] 2018	40	46	32	44	1.4%	2.50 [0.85, 7.40]	
Subtotal (95% CI) Total events	1006	1102	762	1018	23.8%	3.71 [2.86, 4.82]	•
Total events Heterogeneity: Tau* =	0.00; Chi*		. df = 23	(P = 0.5	98); I* = 09	16	
Test for overall effect:							
12.1.4 CHM vs phenoi	lphthalein						
VVang[68] 2004	44	46	32	44	0.7%	8.25 [1.73, 39.44]	
Wang[72] 2015 Wu[76] 2013	55 27	57 30	47 21	57 30	0.7%	5.85 [1.22, 28.05] 3.86 [0.93, 16.05]	
30n[77] 2008	59	65	44	60	1.6%	3.58 [1.29, 9.88]	
Xin[78] 2014 Yang[87] 2012	33	35 31	28 17	35	1.0%	4.13 [0.79, 21.48] 5.56 [1.57, 19.72]	
Zhang[99] 2018	28	30	24	30	0.6%	3.50 [0.65, 18.98] 4.59 [2.71, 7.76]	
Subtotal (95% CI)	070	294	24.2	287	5.9%	4.59 [2.71, 7.76]	•
Total events Heterogeneity: Tau*=	273 0.00; Chi*	= 1.13	213 df= 6 (P	= 0.981	; I* = 0%		
Test for overall effect:	Z = 5.68 (F	< 0.00	001)				
12.1.5 CHM vs probio	tics						
Fu[31] 2012	27	30	21	30	0.8%	3.86 [0.93, 16.05]	
Liu[55] 2018 Lv[57] 2018	138	146	24	40	1.1%	4.70 [1.99, 11.13] 6.00 [1.79, 20.15]	
Sui[64] 2012	26	30	17	30	1.0%	4.97 [1.39, 17.82]	
Wang[71] 2014 Wu[74] 2009	28 56	30 60	21 47	30 60	1.2%	6.00 [1.17, 30,72]	
VVu[74] 2009 Yang[88] 2015	37	40	26	40	0.9%	3.87 [1.18, 12.68] 6.64 [1.73, 25.47]	
Zhang[101] 2019	31	34	23	34	0.8%	4.94 [1.24, 19.76]	
Subtotal (95% CI) Total events	379	410	256	362	8.6%	4.95 [3.21, 7.65]	-
Heterogeneity: Tau*=	0.00; Chi*	= 0.63,	df = 7 (P	= 1.00)	; I*= 0%		
Test for overall effect:	Z = 7.22 (F	< 0.00	001)				
12.1.6 CHM vs placeb							
Bian[13] 2013	34	39	26	39	1.2%	3.40 [1.08, 10.75]	
Cheng[26] 2010 Guo[35] 2010	26 32	60 35	18	80 35	0.9%	8.41 [2.95, 24.00] 10.07 [2.59, 39.11]	
Hu[39] 2018	93	115	41	118	4.5%	7.94 [4.36, 14.46]	
Jiao[43] 2018 Zhong[108] 2018	50 27	90 60	19	56 30	2.1%	9.74 [4.06, 23.38]	
Zhong[108] 2018 Subtotal (95% CI)	21	339	24	338	10.9%	7.09 [4.83, 10.43]	•
Total events	262		133				
Heterogeneity: Tau <sup>a</sup> = Test for overall effect:	Z= 9.97 /6	= 4.84, 2 < 0.00	ar= 5 (₽ 001)	= 0.44)	1 = 0%		
	2.31 (1						l .
Total (95% CI) Total events	4007	4455	3079	4238	100.0%	3.62 [3.19, 4.11]	
Heterogeneity: Tau* -	0.00; Chi2		. df = 96	(P = 0.7	76); I* = 09	16	0.005 0.1 1 10 200
Test for overall effect:	Z = 19.79	(P < 0.0)	0001)				Favours (experimental) Favours (control)
Test for subgroup diffi		45				and the same and	

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Figure 3 Forest plot of randomized controlled trials in patients with functional constipation comparing Chinese herbal medicine with PEG/mosapride/lactulose/ phenolphthalein/ probiotics/ placebo. Odds ratio (95%Cls) for effective rate are shown.

#### Adverse events

Ten trials[13,17,19,26,33,38,46,79,81,90] reported digestive symptoms when using CHM, including abdominal pain or bloating, nausea, stomach discomfort, diarrhea and passing of gas. There were also other adverse effects recorded in CHM groups, such as headache [17,81], transient hypertension [35] and insomnia[81]. While 21 studies[13,15,19,25,26,29,33,35,38-39,46,54,55,68,70,79,81,85,86,94,107] had digestive symptoms in Western medicine group and these mainly occurred when using mosapride and lactulose.

#### Subgroup analysis

Three studies were evaluated as high quality with a low risk of bias in their methodology. Their compared CHM with western medicine and reported ER. Results showed the treatment for FC was significantly in favor of CHM (OR: 2.89, 95% CI: 1.29-6.46, P < 0.01) (Table 1 and Figure 6). There was no significant heterogeneity between studies ( $I^2 = 0\%$ , P = 0.94).

Two CHM ingredients commonly used in the treatment of functional constipation, Cannabis Fructus and Cistanche, were analyzed in a subgroup by measuring ER. In the Cannabis Fructus subgroup, the results showed Cannabis Fructus had no significant effect compared with western medicine (OR: 1.88, 95% CI: 0.97-3.65, P = 0.06). There was significant heterogeneity between studies ( $I^2 = 61\%$ , P = 0.08) ( Supplementary material 1 and Figure 7). In the Cistanche subgroup, the results showed Cistanche had a significant effect compared with western medicine (OR: 3.49, 95% CI: 2.76-4.41, P < 0.0001). There was significant heterogeneity between studies ( $I^2 = 0\%$ , P = 0.71) (Supplementary material 1 and Figure 8).

#### Publication bias and sensitivity analyses

Visual inspection of funnel plots (Figure 9), Begg's test (P = 0.31), and Egger's test (P = 0.26) revealed no evidence of publication bias for the examined primary outcomes. We did sensitivity analyses by excluding seven trials[17,19,64,76,87,96,103] using the decoction; the outcome showed that the results did not change.

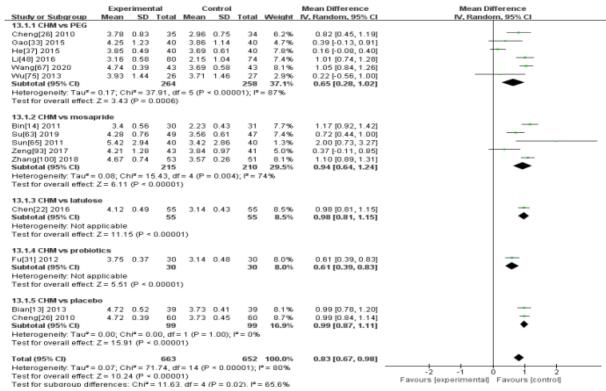
#### **DISCUSSION**

A total of 97 RCTs involving 8693 patients with FC were recruited in the review. Pooled data showed a tendency for improvement of clinical efficacy in the CHM group, compared with most Western medicine, such as PEG, mosapride, lactulose, phenolphthalein, probiotics and placebo. The results showed that CHM was significantly superior to western medicines in improving efficacy rate, the frequency of bowel movement, global symptom assessment, and Bristol Stool Scale score of FC. However, there was significant heterogeneity between the 7 studies that reported the frequency of bowel movement ( $I^2 = 80\%$ , P < 0.00001). Besides, five studies compared CHM with western medicine and reported the recurrence rate showed the treatment for functional constipation was not significantly in favor of CHM.

Our study found that CHM treatment of FC significantly improved physical symptoms, including constipation-related symptoms (abdominal distension, reduced bowel frequency, difficulty defecating) and systemic symptoms (dry mouth, insomnia, and dyspepsia), compared to Western medicine or placebo. Similar findings have been found in related studies[110,111]: They found that herbal medicine can produce synergistic therapeutic effects, such as spasmolytic, tonifying, wind-repelling, anti-inflammatory and local analgesia. We believe that TCM can effectively address the challenge of simultaneously addressing multiple symptoms other than constipation faced by Western medicine in the treatment of FC. However, how to evaluate and quantify the improvement of functional constipation symptoms from the perspective of TCM. Huang et al[112,113] proposed the use of Multidimensional Item Response Theory to solve the problem of standardized results of TCM symptoms.

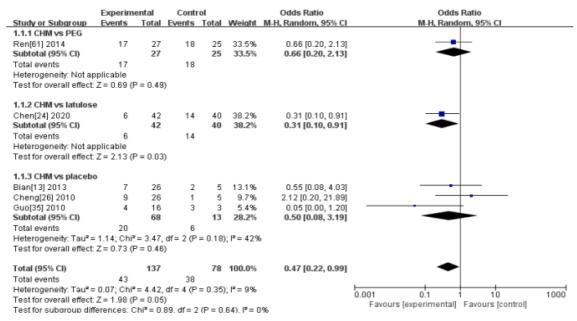
The normal frequency of defecation is 3 to 21 times per week [114,115]. A recent meta-analysis showed that osmotic and irritant laxatives increased stool frequency by 2.5 times per week in patients with FC [116]. Our study found that CHM had a significant effect compared with PEG (MD 0.83, 95%CI: 0.67-0.98, *P* < 0.0006). However, six studies were included in this meta-analysis, and significant heterogeneity between studies ( $I^2 = 87\%$ , P < 0.00001). The strong conclusion that CHM improves defecation frequency needs to be validated by more high-quality studies. At the same time, we found that many current RCTs recorded stool frequency, but translated into effective results at the time of reporting. This leads to a lack of detailed data on stool frequency. Our study, therefore, suggests that similar future studies should report detailed stool frequency and compare them to baseline, such as Zhong et al's study [108].

Despite beneficial findings from meta-analyses, the results of these trials should be interpreted with caution due to the generally low methodological quality of the included studies. Although only RCTs were included, with insufficient information on how the random allocation was generated and/or concealed in most studies, it was uncertain about selection bias. Secondly, considering clinical efficacy was a subjective index and it could introduce performance bias and detection bias without blinding participants, healthcare providers and assessors. Thirdly, missing data due to attrition or exclusions was found in some studies but only a few handled it appropriately. Finally, protocols were not available to



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Figure 4 Forest plot of randomized controlled trials in patients with functional constipation comparing Chinese herbal medicine with PEG/mosapride/lactulose/probiotics/placebo. Mean differences (95%Cls) for bowel movement are shown.



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Figure 5 Comparison of Chinese herbal medicine vs Chinese herbal medicine with PEG/ lactulose/ placebo. Odds ratio (95%Cls) for recurrence rate are shown.

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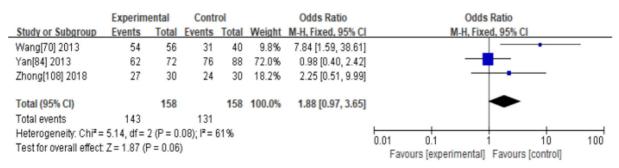
confirm free of selective reporting. For all these reasons, further validation of the findings is necessary. Besides, longer follow-up (> 12 wk) is necessary taking the placebo effect into account[117].

For the safety of CHM, adverse effects were reported, such as abdominal pain or bloating, nausea, stomach discomfort, diarrhea and passing of gas. But there were only 12.4% (12/97) of studies mentioned the safety of interventions or the AEs investigated as one of the main outcome indicators. In

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
Bian[13] 2013	34	39	26	39	45.0%	3.40 [1.08, 10.75]		
Cheng[26] 2010	28	30	25	30	22.5%	2.80 [0.50, 15.73]		
Zhong[108] 2018	27	30	24	30	32.4%	2.25 [0.51, 9.99]		
Total (95% CI)		99		99	100.0%	2.89 [1.29, 6.46]	•	
Total events	89		75					
Heterogeneity: Chi <sup>2</sup> =	0.19, df = 3	2 (P = 0)	.91);  2=	0%			0.01 0.1 1 10	100
Test for overall effect:	Z= 2.59 (F	P = 0.01	0)				Favours [experimental] Favours [control]	100

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Figure 6 Forest plot of high-quality randomized controlled trials in patients with functional constipation. Odds ratio (95%Cls) for effective rate are shown.



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Figure 7 Comparison of Cannabis Fructus vs western medicine. Odds ratio (95%Cls) for effective rate are shown.

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bian[13] 2013	34	39	26	39	4.1%	3.40 [1.08, 10.75]	
Cai[16] 2020	28	30	21	30	2.1%	6.00 [1.17, 30.72]	
Chen[20] 2014	53	60	42	60	5.9%	3.24 [1.24, 8.49]	<del>-</del>
Chen[23] 2018	55	60	46	60	4.6%	3.35 [1.12, 9.99]	
Deng[29] 2018	44	45	40	45	1.1%	5.50 [0.62, 49.11]	-
Dou[30] 2014	39	42	37	48	3.0%	3.86 [1.00, 14.96]	-
Hui[41] 2018	27	31	19	31	3.4%	4.26 [1.19, 15.25]	
Kong[44] 2020	45	49	38	47	3.5%	2.66 [0.76, 9.34]	-
Lai[45] 2012	51	60	16	30	5.4%	4.96 [1.81, 13.59]	
Li[47] 2015	68	87	50	79	11.7%	2.08 [1.05, 4.11]	-
Lv[56] 2012	135	140	123	140	5.2%	3.73 [1.34, 10.42]	_ <del></del>
Mu[58] 2019	40	45	26	45	4.5%	5.85 [1.94, 17.60]	_ <del></del>
Shao[62] 2019	43	50	21	50	5.7%	8.48 [3.19, 22.52]	
Su[63] 2019	42	49	34	47	5.2%	2.29 [0.82, 6.39]	+
Sui[64] 2012	25	30	22	30	3.5%	1.82 [0.52, 6.38]	<del></del>
Tao[66] 2018	25	30	27	30	2.3%	0.56 [0.12, 2.57]	-
Wang[68] 2004	44	46	32	44	2.2%	8.25 [1.73, 39.44]	
Xin[77] 2008	54	56	31	40	2.2%	7.84 [1.59, 38.61]	
Xin[78] 2014	59	65	44	60	5.3%	3.58 [1.29, 9.88]	
Yan[85] 2016	33	35	28	35	2.0%	4.13 [0.79, 21.48]	-
Yang[86] 2008	27	30	22	30	2.6%	3.27 [0.77, 13.83]	
Yao[89] 2016	36	40	34	40	3.0%	1.59 [0.41, 6.12]	
Zeng[93] 2017	74	80	61	80	5.7%	3.84 [1.44, 10.22]	<del></del>
Zhang[97] 2014	29	32	24	32	2.7%	3.22 [0.77, 13.50]	-
Zhao[104] 2015	35	38	23	38	3.0%	7.61 [1.98, 29.25]	
Total (95% CI)		1269		1210	100.0%	3.49 [2.76, 4.41]	•
Total events	1145		887				
Heterogeneity: Tau* =	0.00; Chi <sup>2</sup>	= 19.70	), df = 24	(P = 0.1)	71); $I^2 = 0$	%	0.01 0.1 1 10 100
Test for overall effect:	Z = 10.47	(P < 0.0	0001)				
							Favours [experimental] Favours [control]

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Figure 8 Comparison of cistanche vs western medicine. Odds ratio (95%Cls) for effective rate are shown.

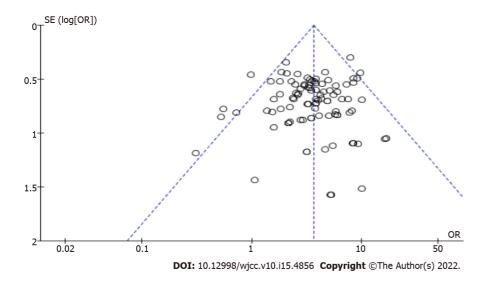


Figure 9 Funnel plots of comparison between Chinese herbal medicine and western medicine.

addition, many traditional Chinese medicines have been widely used by Chinese traditional medicine practitioners for nearly two millennia. This supports their security. Therefore, more attention should be paid to recording and reporting the harmful effects of these interventions.

#### Limitation

We searched main English and Chinese databases under well-designed searching strategies and made the comparison between CHM and different WM therapies clearer. There are several limitations to this systematic review. Firstly, missing articles that might be relevant. Although we searched through databases and did not limit the language of the article, we may still miss relevant articles in regional journals. Because the articles published in these regional magazines are not included in the database we searched. Secondly, most of the studies we included were published only in Chinese, which limited readers' review of the original research. This situation may be improved with the worldwide promotion of CHM. Thirdly, the studies we included were all conducted in the Asian region so the extrapolation of these results is limited by geography.

#### CONCLUSION

In conclusion, in this meta-analysis, we found that CHM may have potential benefits in increasing the number of bowel movements, improving stool characteristics, and alleviating global symptoms in FC patients. However, a firm conclusion could not be reached because of the poor quality of the included trials. Well-designed and high-quality reported RCTs are needed to confirm more definitive conclusions in the future.

#### **ARTICLE HIGHLIGHTS**

#### Research background

Well-designed and high-quality reported randomized controlled trials (RCTs) are needed to confirm more definitive conclusions in the future.

#### Research motivation

A firm conclusion could not be reached because of the poor quality of the included trials.

#### Research objectives

Chinese herbal medicine (CHM) may have potential benefits in increasing the number of bowel movements, improving stool characteristics and alleviating global symptoms in functional constipation (FC) patients.

#### Research methods

To evaluate the efficacy and safety of CHM on efficacy rate, global symptoms, bowel movements, and

the Bristol Stool Scale score in patients with FC by summarizing current available RCTs.

#### Research results

This review aimed to evaluate the efficacy and safety of CHM in patients with FC.

#### Research conclusions

To evaluate the efficacy and safety of CHM in patients with FC.

#### Research perspectives

FC is a common and chronic gastrointestinal disease.

#### **FOOTNOTES**

**Author contributions:** Lyu Z and Bai Y contributed toward the concept and data analysis; Lyu Z and Fan Y contributed toward manuscript writing; Zhong LL, Liu T, and Liang HF contributed toward concept and manuscript review; In addition, Lyu Z, Fan Y and Bai Y made equal contributions; Zhong LL and Liang HF should be considered as co corresponding authors.

Supported by the Hong Kong Chinese Medicine Development Fund (19B2/057A). The fund agency has no role in conducting the research.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Wu YXJ L-Editor: Filipodia P-Editor: Wu YXI

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