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Systematic review

Clinical effects and safety of Compound Glutamine Entersoluble Capsules for diarrhea-predominant irritable bowel syndrome: A systematic review and meta-analysis

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ABSTRACT

Introduction: Diarrhea-predominant irritable bowel syndrome (IBS-D) is a gastrointestinal disease with a high incidence and no effective drugs available. Compound Glutamine Entersoluble Capsules (CGEC) is a compound preparation integrating Sijunzi Decoction and L-Glutamine. The aim of this systematic review was to evaluate the clinical effects and safety of CGEC for IBS-D.

Methods: PubMed, Web of Science, the Cochrane library, CNKI, VIP and Wanfang Databases were searched from inception to June 30, 2019. Randomized controlled trials (RCTs) assessing the clinical effects and safety of CGEC for IBS-D were included. Global improvement of IBS-D symptoms was used as the primary outcome. The data were analyzed by RevMan5.3 software. Risk ratio (RR) calculations and 95% confidence intervals (CI) were used for dichotomous outcomes, and mean difference (MD) with 95% CI were used for continuous outcomes.

Results: Twelve RCTs involving 1232 participants were included. Compared with western conventional medicine (WCM) alone (i.e. gastrointestinal spasmodic and probiotics), CGEC demonstrated no significant differences in global improvement of IBS-D symptoms (RR 1.09, 95% CI [0.97, 1.23]), reduction in stool frequency (MD 0.14, 95% CI [−0.18, 0.46]) and relief of abdominal pain (MD 0.12, 95% CI [−0.27, 0.52]). The combination of CGEC and WCM had advantages over WCM alone in terms of global improvement of IBS-D symptoms (RR 1.37, 95% CI [1.25, 1.49]). Regarding the recurrence rate, both the CGEC group and the combined drug group were lower than the WCM group. In terms of safety, there is currently no evidence to suggest that CGEC can cause adverse reactions/events in patients with IBS-D.

Conclusions: Low or very low certainty evidence indicated that there was no difference between CGEC and WCM for the treatment of IBS-D. The combination of CGEC and WCM had a better therapeutic effect than WCM alone for the treatment of IBS-D.

1. Introduction

Irritable Bowel Syndrome (IBS) is a functional bowel disease characterized by recurrent abdominal pain associated with bowel movements or changes in bowel habits. Typical abnormal bowel habits can manifest as constipation, diarrhea, or alternating between constipation and diarrhea, with symptoms of abdominal distension [1]. It has been estimated that IBS affects approximately 11% of the global population [2]. IBS significantly reduces the quality of life of patients, their partners and caregivers, and affects the patient's daily activities [3,4]. According to the main symptoms of IBS, it can be categorized into four subtypes: constipation type (IBS-C), diarrhea type (IBS-D), mixed type (IBS-M) and undefined type (IBS-U) [1]. According to clinical epidemiological studies, IBS-D patients account for about 40% of all IBS

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patients [5].

At present, the specific pathogenesis of irritable bowel syndrome has not been defined and does not have specific effective drug treatment in the clinical setting [6]. Clinical treatment of western conventional medicine (WCM) is still based on symptomatic treatment. For example, some conventional drugs (e.g., antispasmodics and antidiarrheal drugs) have been tried but failed to achieve the desired clinical treatment effect [7]. Compound Glutamine Entersoluble Capsules (CGEC) is an integrated Chinese and western medicine compound preparation made of Sijunzi Decoction (*Ren shen, Bai Zhu, Fu Ling, Gan Cao*) and L-Glutamine. It has been used in clinical practice for more than 20 years and is widely used in the treatment of chronic intestinal diseases caused by various reasons. Modern pharmacological studies has demonstrated that CGEC can improve intestinal absorption and movement, promote the secretion of gastrointestinal hormones, and enhance intestinal immunity. It can also repair damaged intestinal mucosa and strengthen the defense function of the mucosal barrier [8].

Currently, many randomized controlled trials (RCTs) on CGEC for IBS-D have been conducted. In order to evaluate the effects and safety of CGEC for patients with IBS-D, we systematically reviewed the results of RCTs using CGEC in the treatment of IBS-D.

2. Methods

2.1. Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) participants: IBS-D diagnosed according to the Rome criteria. Other types of IBS, such as IBS-M, were excluded. No restrictions on age, gender and race; (2) intervention: the treatment group used CGEC or added CGEC compared with the control group. The control group had no treatment, placebo or WCM. If the two groups received general adjuvant therapy at the same time, the adjuvant therapy should be identical in both groups. The course of treatment should be no less than 4 weeks; (3) type of study: RCT, language was limited to Chinese and English; (4) outcomes: the primary outcome was global improvement of IBS-D symptoms, measured by a validated scale or efficacy evaluation criteria. The secondary outcomes were specific symptoms (including stool frequency, stool consistency, abdominal pain) measured by score changes, quality of life, safety (adverse reactions/events) and recurrence rate.

Exclusion criteria were as follows: (1) the full text of the literature could not be obtained; (2) the literature was suspected of plagiarism; (3) any duplicated literature; (4) student dissertations.

2.2. Search strategy

PubMed, Web of Science, the Cochrane library, the Chinese National Knowledge Infrastructure Databases (CNKI), Wanfang Database and the Chongqing Chinese Science and Technology Periodical Database (VIP) were searched from inception to June 30, 2019. The subject/Mesh terms used for the searches were “glutamine”, “Irritable bowel syndrome” and “IBS”, and adjusted for use in the different databases.

For example, Pubmed was searched with the following terms: "glutamine" AND ("Irritable bowel syndrome" OR "IBS").

2.3. Study selection and data extraction

The imported records of retrieved literature were entered into NoteExpress 3.0 software. Two authors (S-B L and C-H L) independently screened the titles, abstracts and full texts of the literature, and selected the eligible literature according to the inclusion and exclusion criteria.

The data extraction table was established by using Excel 2010. Two authors (S-B L and S-H Y) independently extracted the data and checked the extraction results. The inconsistencies were discussed and resolved by the two authors and adjudicated by a third author. Specific extraction entries included; study titles, authors information, characteristics of participants, details of interventions and controls, outcomes with clear evaluation criteria, and information relevant to study design.

2.4. Risk of bias assessment

The risk of bias of each included trial was evaluated using the Cochrane risk of bias tool [9] by two authors (S-B L and Y-Q L) independently. The inconsistencies were discussed with the third author (J-P L). The evaluation items include: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) incomplete outcome data; (6) selective reporting; (7) other bias. Each item was judged as "low risk of bias", "high risk of bias" or "unclear risk of bias".

2.5. Data synthesis

The data were analyzed by RevMan5.3 software. Risk ratio (RR) calculations and its 95% confidence intervals (CI) were used for dichotomous outcomes, and mean difference (MD) with 95% CI were used for continuous outcomes. Statistical heterogeneity among the included trials was evaluated using the I^2 test: A fixed-effect model was used to pool the data if the statistical heterogeneity was small ($I^2 \leqq 25\%$); a random-effects model was used if the statistical heterogeneity was large ($25\% < I^2 \leqq 75\%$); and data were not pooled if there was a significant level of statistical heterogeneity($I^2 > 75\%$).

If the data could be obtained, this review conducted a subgroup analysis according to the type of comparison, severity of disease, age of participants. According to our protocol, a funnel plot would be applied to explore the possibility of publication bias, if ten or more trials were included in a meta-analysis of the primary outcome [10]. In addition, the certainty of evidence for each primary outcome was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation criteria) approach to conduct management recommendations by the GRADEpro Guideline Development Tool (GDT) online.

3. Results

3.1. Searching results

In total, 377 records were retrieved from the above-mentioned six databases and 324 were deleted as a result of screening the titles and abstracts. The remaining 53 records were selected for scrutinizing the full-texts. A further 41 records were excluded for various reasons. Finally, 12 articles involving 12 trials [11–22] were included. Fig. 1 provides the flow diagram of search, literature selection and reasons why articles were not included.

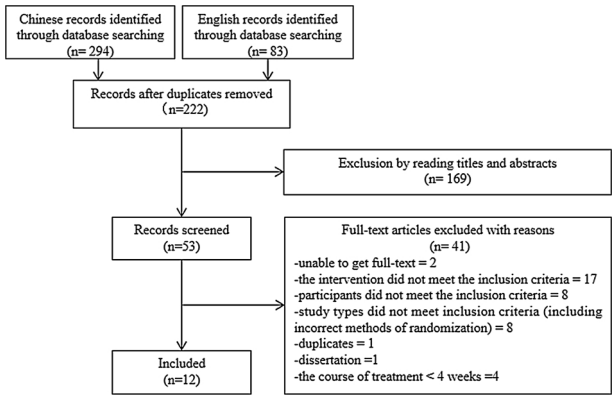

Fig. 1. Flow diagram of search and literature selection.

Table 1
The characteristics of included 12 trials.

Study ID	Sample size (M:F)		Age		Course of disease		Intervention		Common adjuvant therapy	Course of treatment	Outcomes
	T	C	T	C	T	C	T	C			
Xiu FX2016 [11]	44/40		42.6 ± 2.3 (18-72)Y		5.3 ± 1.2 (1-12)Y		CGEC (4capsules/time, t.i.d) + control group	Bifidobacterium triple viable enteric-coated capsules (2capsules/time, q.i.d)	Not mentioned	8W	①④⑤
Yang JD 2015-1 [12]	60	60	Not reported		Not reported		CGEC (2capsules/time, t.i.d)	Trimebutine maleate capsules (0.1 g/time, t.i.d)	Dietary guidance + psychological comfort	4W	①④
Yang JD 2015-2 [12]	60	60	Not reported		Not reported		CGEC (2capsules/time, t.i.d) + control group	Trimebutine maleate capsules (0.1 g/time, t.i.d)	Dietary guidance + psychological comfort	4W	①④
Feng XQ 2011-1 [13]	8/12	9/11	45Y	42.7Y	Not reported		CGEC (2capsules/time, t.i.d)	Compound lactobacillus capsules (2capsules/time, t.i.d)	Not mentioned	8W	①
Feng XQ 2011-2 [13]	8/12	9/11	43.6Y	42.7Y	Not reported		CGEC (2capsules/time, t.i.d) + control group	Compound lactobacillus capsules (2capsules/time, t.i.d)	Not mentioned	8W	①
Lu L2012 [14]	20/29	16/30	44.56 ± 13.2 (18-65)Y	45.74 ± 14.32 (20-65)Y	6.42 ± 3.11 (0.6-14)Y	7.15 ± 3.28 (0.6-15)Y	CGEC (4capsules/time, t.i.d) + control group	Bifidobacterium tetrad viable tablets (3capsules/time, t.i.d)	Not mentioned	6W	①④
Zhu KD2012 [15]	18/22	19/19	19-65Y	20-72Y	Not reported		CGEC (3capsules/time, t.i.d) + control group	Bifid triple viable capsules (3capsules/time, q.i.d)	None	4W	①④
Li KJ 2011-1 [16]	50	50	Not reported		Not reported		CGEC (4capsules/time, t.i.d)	Trimebutine maleate (200 mg/time, t.i.d)	Control diet + exercise properly	4W	④
Li KJ 2011-2 [16]	50	50	Not reported		Not reported		CGEC (4capsules/time, t.i.d) + control group	Trimebutine maleate (200 mg/time, t.i.d)	Control diet + exercise properly	6W	④
Lu CX 2010-1 [17]	18/28	21/25	32 (17-55)Y	31.4 (17-54)Y	2.7 (1.5-16)Y	2.8 (1.2-15)Y	CGEC (3capsules/time, t.i.d)	Compound lactobacillus acidophilus tablets (1000 mg/time, t.i.d)	None	4W	①④
Lu CX 2010-2 [17]	20/26	21/25	33.6 (19-57)Y	31.4 (17-54)Y	3 (1-18)Y	2.8(1.2-15)Y	CGEC (3capsules/time, t.i.d) + control group	Compound lactobacillus acidophilus tablets (1000 mg/time, t.i.d)	None	4W	①④
Yuan SF2010 [18]	14/16	13/17	45.4 ± 8.1Y	43.2 ± 8.4Y	7-15Y	7-15Y	CGEC (500 mg/time, t.i.d) + control group	Trimebutine maleate tablets (200 mg/time, t.i.d)	None	4W	①④
Ye LM2017 [19]	24/12	14/18	43.2Y	42.1Y	6.3Y	5.5Y	CGEC (2capsules/time, t.i.d) + control group	Trimebutine maleate tablets (200 mg/T, t.i.d)	Not mentioned	4W	④
Xu XY2007 [20]	102/48		22-75Y		1-22Y		CGEC (3capsules/time, t.i.d)	Ordibromine (40 mg/time, t.i.d)	Not mentioned	4W	②③④
Yan MZ2018 [21]	38/62		34 ± 15(19-49)Y		Not reported		CGEC (500 mg/time, t.i.d)	Clostridium butyricum tablets (2capsules/time, t.i.d)	Not mentioned	4W	①
Huang JC2010 [22]	48/21		18-64Y		0.5-26Y		CGEC (4capsules/time, t.i.d)	Bifid triple viable capsules (2 capsules/time, t.i.d)	None	6W	①④⑤

T = test group; C = Control group. Outcomes: ①Clinical total efficiency; ②Stool frequency score; ③-Abdominal pain score; ④Safety indicators (adverse reactions / events); ⑤Recurrence rate.
CGEC: Compound Glutamine Entersoluble Capsule; Y: years old; M: months; W: weeks.

3.2. Characteristics of the included trials

All 12 trials [11–22] involving 1232 participants were conducted in China. All were published in Chinese between 2007 and 2018. Of all the participants, 713 were in the treatment group and 519 were in the control group. Of all trials, 8 RCTs [11,14,15,18,12–22] were two-armed trials and 4 RCTs [12,13,16,17] were three-armed trials. No trial provided evidence that the sample size had been calculated. According to the trials which reported the age of participants and the number of men and women, the age range of participants was 17–75 years old, and the ratio of men to women was 1.01:1. No trial reported the severity of the disease. Of all trials, ten [11,12,14–20,22] described baseline comparability or balance between the groups, but only in words (no data was presented in the tables), and the remaining two [13,21] did not mention the relevant information. The treatment groups of all included trials were treated with CGEC alone or combined with control drugs, and the control group was treated with WCM (gastrointestinal spasmodic or probiotics). No trial reported using no treatment or placebo in the control group. Table 1 shows the specific details of the included 12 trials.

3.3. Risk of bias of included trials

For random sequence generation, the method of random number tables was used in 2 trials [11,21], and the other 10 trials [12–20,22] only mentioned “random” or “randomization” without describing the specific methods. For allocation concealment, no trials reported relevant information. Therefore, the risk of selection bias for the majority of the included trials was unclear due to insufficient information. Judging by the interventions, it was considered impossible to implement blinding for participants and doctors for all trials. Therefore, the risk of performance bias for all trials was judged as “high risk”. The risk of detection bias was judged as “unclear” for all trials, due to the fact that they all failed to report whether the outcome assessors were blinded. Of all trials, one [20] was unable to determine whether any participants were lost to follow up, while the remaining trials did not lose any participants. Therefore, the attrition bias was low for the majority of trials. For the risk of reporting bias, all trials were judged as” unclear” due to they all did not report the information of study protocol and trial registration. Of all trials, ten [11,12,14–20,22] clearly reported that the baseline comparability or inter-group balanced and the remaining two [13,21] did not, so the other bias of the 10 trials were judged as “low risk” and the remaining two were “unclear”. Fig. 2 demonstrates the risk of bias graph of included trials.

3.4. Outcomes

3.4.1. Primary outcome (global improvement of IBS-D symptoms)

Of all the included trials, 9 trials [11–15,17,18,21,22] (including 6 two-armed trials [11,14,15,18,21,22] and 3 three-armed trials [12,13,17]) measured this outcome based on clear evaluation criteria. A total of 2 types of comparison: "CGEC alone *versus* WCM" and "CGEC + WCM *versus* WCM".

According to the degree of improvement of the main symptoms (including stool frequency, stool consistency, abdominal pain, abdominal distension or other discomfort), all the trials divided the efficacy into three categories: significantly effective, slightly effective, and ineffective. To clearly describe the global improvement of IBS-D symptoms, we classified those categories into two levels: effective (including significantly effective and slightly effective) and ineffective. The effective rate = (number of significantly effective participants + number of slightly effective participants)/total number of participants × 100%. However, the evaluation criteria of effective and ineffective was different for some of the included trials, and data were divided into two types: evaluation criteria 1 and 2. Evaluation criteria 1: judgment based on changes in the efficacy index, efficacy index = (total score of main symptoms before treatment - total score of main symptoms after treatment)/total score of main symptoms before treatment × 100%. If the efficacy index was less than or equal to 50%, it was considered ineffective, otherwise effective. Evaluation criteria 2: according to the change of main symptoms, if the symptoms were not improved or even aggravated after treatment, it was considered ineffective, otherwise effective. This review conducted subgroup analyses based on different types of comparisons and different evaluation criteria.

3.4.1.1. CGEC alone versus WCM. A total of five trials [12,13,17,21,22] were involved this type of comparison and all of them adopted the evaluation criteria 2. Statistical heterogeneity among the seven trials was small (I^2 = 23), and the fixed-effect model was used for meta-analysis. The result (Fig. 3) showed there was no statistical difference (RR 1.09, 95% CI [0.97, 1.23], 5 RCTs) on the improvement of global symptoms between the CGEC alone and WCM.

3.4.1.2. CGEC + WCM versus WCM. A total of seven trials [11–15,17,18] were involved this type of comparison, of which two [14,18] adopted the evaluation criteria 1 and five [11–13,15,17] adopted the evaluation criteria 2. Statistical heterogeneity among the seven trials was small (I^2 = 15), and the fixed-effect model was used for meta-analysis. The result showed the combination of CGEC and WCM was superior to WCM alone (RR 1.37, 95% CI [1.25, 1.49], 7 RCTs) on the improvement of global symptoms, whether adopted the evaluation criteria 1 (RR 1.24, 95% CI [1.06, 1.44], 2 RCTs) or the evaluation criteria 2 (RR1.42, 95% CI [1.28, 1.57], 5 RCTs) (Fig. 4).

3.4.2. Secondary outcomes

3.4.2.1. Stool frequency. In terms of “CGEC alone *versus* WCM”, only one trial [20] reported this outcome. The result showed there was no statistical difference between CGEC alone and WCM (MD 0.14, 95% CI

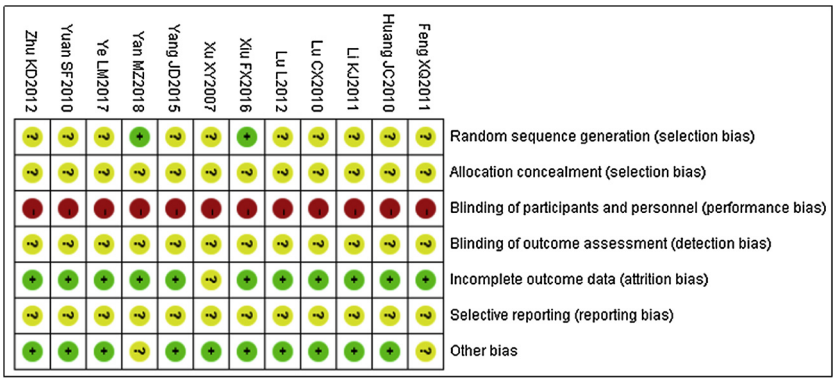

Fig. 2. The risk of bias of included trials.

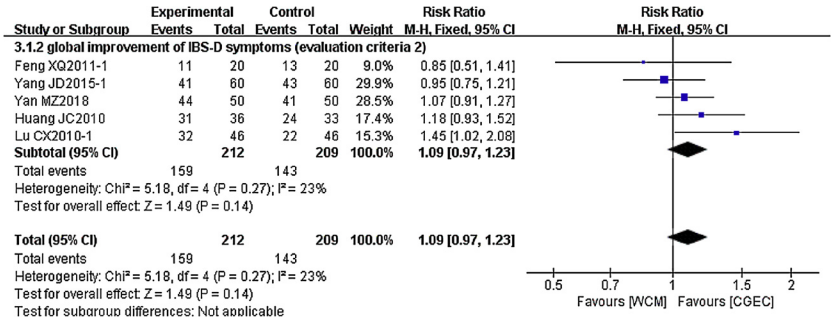

Fig. 3. The global improvement of IBS-D symptoms: CGEC alone *versus* WCM.

[−0.18, 0.46]). This result is consistent with that of the trial itself.

In terms of "CGEC + WCM *versus* WCM", no trial reported this outcome.

3.4.2.2. Stool consistency. No trial reported this outcome measured by score changes.

3.4.2.3. Abdominal pain. In terms of "CGEC alone *versus* WCM", only one trial [20] reported this outcome. The result showed there was no statistical difference between CGEC alone and WCM (MD 0.12, 95% CI [−0.27, 0.52]).

In terms of "CGEC + WCM *versus* WCM", no trial reported this outcome.

3.4.2.4. Quality of life. No trial reported this outcome.

3.4.2.5. Safety (adverse reactions/events). In terms of "CGEC alone *versus* WCM", five trials [12,16,17,20,22] reported this outcome. Among the five trials, four [12,16,17,22] reported no adverse reactions/events in the treatment group and the control group. Another trial [20] reported that no adverse reactions occurred in the CGEC group, while 4 participants in the control group (Otibromide group) had adverse reactions (2 cases of headache and 1 case of abdominal distention, with mild symptoms and no influence to continue taking the medicine; 1 case had constipation at 2 weeks and stopped taking the medication).

In terms of "CGEC + WCM *versus* WCM", eight trials [11,12,14–19] reported this outcome. Among the eight trials, seven [11,12,14–18] reported no adverse reactions/events in the treatment group and the control group and one trials [19] reported adverse reactions in both the treatment group and the control group. The trial [19] reported that 3 participants in the combined drug group had adverse reactions (2 cases of dry mouth, 1 case of dizziness), and 2 participants in the control group had adverse reactions (1 case of dry mouth, 1 case of headache), and their symptoms disappeared without special treatment.

3.4.2.6. Recurrence rate. In terms of "CGEC alone *versus* WCM", one trial [22] reported this outcome. The result showed that there was a statistical difference (RR 0.26, 95% CI [0.06, 1.17]) between the CGEC alone group and WCM group. The recurrence rate of half-year follow-up after treatment in the CGEC alone group was less than that in the WCM group.

In terms of "CGEC + WCM *versus* WCM", one trial [11] reported this outcome. The result showed that there was statistically difference (RR 0.35, 95% CI [0.08, 1.53]) between the combined drug group and WCM group. The recurrence rate of 6–12 months follow-up after treatment in the combined drug group was less than that in the WCM group.

3.5. Certainty of evidence (GRADE)

Using the GRADE system recommendation approach, certainty of evidence for primary outcomes were all evaluated as "low" or "very low". The certainty of evidence was downgraded mainly due to high risk of bias, high statistical heterogeneity (a small of total events or small sample size) and publication bias. Table 2 showed the details of the certainty of available evidence.

3.6. Additional analysis

Due to the limitation of data acquisition, this review failed to conduct subgroup analysis according to the severity and age of the participants according to the preset condition. According to the protocol, a funnel plot would be applied to explore the possibility of publication bias, if ten or more trials were included in a meta-analysis of the primary outcome. However, there was no meta-analysis meeting the above requirements in this review, so no funnel plot was conducted.

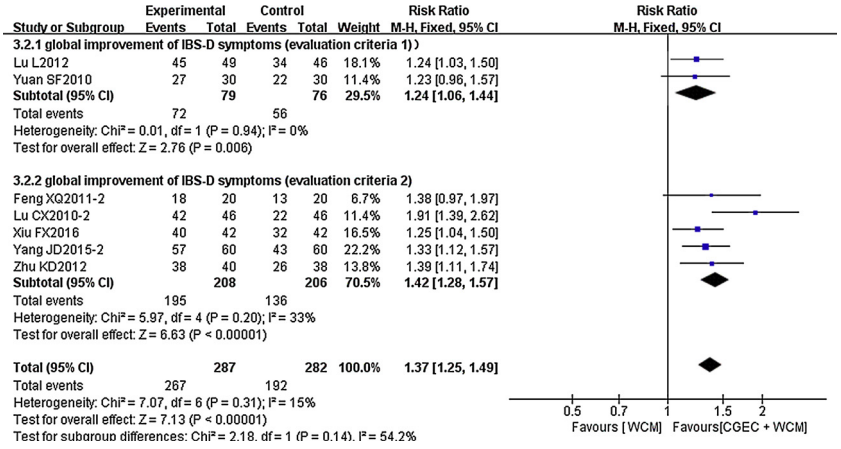

Fig. 4. The global improvement of IBS-D symptoms: CGEC + WCM *versus* WCM.

Table 2
GRADE evaluation form of evidence certainty.

Patient or population: adult patients with IBS-D
Setting: outpatients and wards
Intervention of treatment group: CGEC alone, or CGEC + WCM
Comparison: WCM

The type of comparison	Anticipated absolute effects* (95% CI)		RR(95% CI)	No. of participants (studies)	Certainty of the evidence
	Risk with control group	Risk with treatment group			
1. CGEC *versus* WCM - the global improvement of IBS-D symptoms	684 per 1000	746 per 1000 (664 to 842)	RR 1.09 (0.97, 1.23)	421 (5 RCTs)	⊕⊕◯◯ Low certainty[ac]
1.1. Evaluation criteria 1	No study was included.				
1.2. Evaluation criteria 2	684 per 1000	746 per 1000 (664 to 842)	RR 1.08 (0.97, 1.23)	421 (5 RCTs)	⊕⊕◯◯ Low certainty[ac]
2. CGEC + WCM *versus* WCM - the global improvement of IBS-D symptoms	681 per 1000	933 per 1000 (851 to 993)	RR 1.37 (1.25, 1.49)	569 (7 RCTs)	⊕⊕◯◯ Low certainty[ac]
2.1. Evaluation criteria 1	737 per 1000	914 per 1000 (781 to 1000)	RR 1.24 (1.06, 1.44)	155 (2 RCTs)	⊕◯◯◯ Very low certainty[abc]
2.2. Evaluation criteria 2	660 per 1000	937 per 1000 (845 to 1000)	RR 1.42 (1.28, 1.57)	414 (5 RCT)	⊕⊕◯◯ low certainty[ac]

*The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
GRADE Working Group grades of evidence:
Low certainty (⊕⊕◯◯): Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect;
Very low certainty (⊕◯◯◯): We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
a. high risk of performance bias (no trial achieved blinding to participants and personnel); **b.** imprecision (a small of total events or small sample size); **c.**publication bias.
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **RCT:** Randomized controlled trial; **CGEC:** Compound Glutamine Entersoluble Capsules; **WCM:** western conventional medicine.

4. Discussion

4.1. Summary of the main findings

The studies were screened and the literature selected strictly according to the inclusion/exclusion criteria, and finally included 12 studies [11–22]. The results showed that:

(1) For global improvement of IBS-D symptoms, there was no difference between CGEC alone and WCM. However, global improvement for the combination of CGEC and WCM was about 1.4 times higher than that of WCM alone.
(2) In terms of specific symptoms, CGEC showed no differences in reducing stool frequency and relieving abdominal pain compared with WCM.
(3) For safety of CGEC, there is currently no evidence that CGEC can cause adverse reactions/events in patients with IBS-D.
(4) For recurrence rate, both the CGEC alone group and the combination of drugs group was less than that of the WCM group.

4.2. Main problems of the included trials

All of the included trials had the following problems:

(1) Random allocation may not have been implemented correctly. Correct implementation of randomized allocation is crucial in RCT, and mainly relies on the correct generation of random allocation sequences and the correct implementation of allocation concealment [23–25]. The role of effective randomization is to achieve a balance between several influencing factors and measurement factors between groups, and to enhance the comparability between groups [26]. However, the majority of the included trials only mentioned “random” or “randomization” without describing the specific methods, and all trials did not mention allocation concealment. Therefore, we were unable to confirm that these trials have actually or effectively implemented randomized allocation.
(2) The blinding of participants, personnel and outcome assessors was not implemented. Successful implementation of blinding can control bias (e.g., performance bias) in multiple stages of RCT and reduce the variance assessment of outcome events [27,28]. According to the specific intervention measures of the treatment group and the control group, all the trials did not effectively implement the blinding of participants and personnel. Furthermore, all the included trials did not mention the relevant information about the blinding of outcome evaluators.
(3) Baseline data reporting was inadequate. Baseline data is an essential reference for judging whether the participants are comparable. Majority of the included trials only described the baseline comparability in the text. The baseline information of the treatment group and the control group was not thoroughly compared in the form of a table, and some trials failed to mention baseline comparability.
(4) Sample size was not estimated for all trials, and most trials were small sample studies. Sample size estimation is an important measure and premise to ensure the reliability and validity of the study results. Too small a sample size may lead to the study of false-negative results. If the sample size is too large, it will increase the difficulty of implementation and waste additional human resources, material resources, and financial resources [29,30].
(5) Lack of clinical trial protocols and registration information. The formulation and registration of clinical trial protocols can not only reflect the prospective nature of clinical trials, but also improve the transparency of clinical trials. Thereby reducing reporting bias and publication bias, and improving the authenticity of trial results [31]. However, all trials did not mention this relevant information.
(6) None of the included trials reported information about the source of funding. Adequate funding is one of the conditions to ensure the smooth running of the trial. Reporting the source of funding is important information for readers to evaluate the authenticity of the trial results [32]. Therefore, researchers should report relevant information to help readers evaluate the test results. Whether or not the research is funded, researchers should specifically report this

information to ensure transparency.

4.3. Implications for future research

In the future, large sample, multi-center and high-quality RCTs should be rigorously designed and conducted. Before the official start of the trial, a detailed trial protocol should be developed and registered. The protocol can be formulated with reference to the Standard Protocol Items: Recommendations for Interventional Trials 2013 [33].

Also, future trials should estimate sample size and recruit adequate participants, and pay more attention to study methods (especially randomization, blinding and missing data management). At the same time, it is suggested that the standardized report should be made with reference to the Consolidated Standards of Reporting Trials (CONSORT) statement [34].

5. Conclusion

Low or very low certainty evidence indicated that there was no difference between CGEC and WCM (gastrointestinal spasmodic or probiotics) in the treatment of IBS-D. Regardless of the global improvement of IBS-D symptoms, the combination of CGEC and WCM can provide a better therapeutic effect than WCM alone. However, in view of the poor methodological quality of the included trials, and most being small sample trials, may have affected the reliability of conclusions. Moreover, the GRADE evidence level is low or very low. Therefore, the conclusions of this review can only provide a reference for clinical practice, but cannot be directly used to guide clinical practice.

Future large sample, multi-center and high-quality RCTs should be rigorously designed and implemented to evaluate and confirm the clinical effects and safety of CGEC in the treatment of IBS-D.

Author contributions

J-P L and S-B L conceived and designed the review. S-B L and C-H L were responsible for the searching, screening and selecting studies. S-B L, S-H Y and Y-Q L participated in data extraction and assessed study quality. S-B L performed the statistical analysis. S-B L drafted the manuscript. C-H L assisted the writing of the manuscript. Z-Y T completed the PRISMA checklist. Z-Y T and NR revised the format of references. J-P L and NR were involved in critically revising the manuscript. All authors have read and approved the final manuscript. All authors approved the final version of the article, including the authorship list.

Declaration of competing interests

The authors have no conflicts of interest to declare.

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