A Meta-Analysis of Modified Sijunzi Decoction Combined with Tongxie Yaofang in the Treatment of IBS-D

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Abstract: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGD), among which the diarrhea-predominant (IBS-D) is the most common in China, significantly affecting patients' life and work due to its long course and easy recurrence. Herb medicine is a viable complementary and alternative treatment option for patients with IBS. Specifically, Sijunzi Decoction combined with Tongxie Yaofang is a clinical prescription commonly used in China for IBS-D. We retrieved randomized controlled trials (RCTs) of Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D from CNKI, WanFang Data, VIP, CBM, Pubmed and the Cochrane Library, and Embase database. And then we performed quality evaluation, data extraction and pooling. Stata software (version 15.0) was used to perform meta-analysis. Resultly, a total of 14 RCTs were included, including 1,032 subjects, with 522 cases in the test group and 510 cases in the control group. Meta-analysis showed the following results: (1) Clinical efficacy: Compared with conventional Western medicine treatment, the total clinical effective rate of modified Sijunzi Decoction combined with Tongxie Yaofang for IBS-D was significantly increased [RR= 1.229, 95% CI (1.162, 1.299)], and the difference was statistically significant (P<0.05); (2) Daily bowel frequency: Three RCTs counted the number of daily bowel movements before and after treatment, the results showed a more considerable improvement in the number of daily bowel movements in the test group than in the control group after treatment [SMD=-1.791, 95% CI (-3.130, -0.452)], and the difference was statistically significant (P<0.05); (3) Clinical symptom score: Six RCTs recorded clinical symptom scores of the subjects before and after treatment, and the results showed that the clinical symptoms of the subjects in both groups improved significantly after treatment compared with those before treatment, and the test group improved significantly more than the control group (P<0.05). In conclusion, Sijunzi Decoction combined with Tongxie Yaofang is effective in the treatment of IBS-D.

Keywords: IBS-D; Tongxie Yaofang; Sijunzi Decoction; Meta-analysis

1. Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGD) characterized by recurrent abdominal pain and changes in bowel habits [1]. The global prevalence of IBS is approximately 11.2% [2]. The incidence of IBS is about 10%-20% in Western urban areas and 6.5%-10.1% in Asian countries. In China, the incidence is about 4.6%-5.67%, in which female cases are more common than male cases [1,3]. IBS often occurs in people under 45 years old [3]. Clinically, this disorder can be divided into 4 subtypes, diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), unclassified IBS (IBS-U) and IBS with mixed bowel habits (IBS-M) [4], of which diarrhea-predominant (IBS-D) is the most common in China [5]. As a chronic functional disease, IBS has a long course of disease and is prone to recurrent episodes [6]. Nearly 75% of patients are still diagnosed with IBS after 5 years [7], which severely reduces patients' quality of life (QOL, SF36) [2,8,9], imposes a socioeconomic burden [10], and increases psychological problems [11,12]. It has been shown [13,14] that IBS patients are more likely to develop comorbid psychological and psychiatric disorders than non-IBS patients, and the severity of anxiety and depression in IBS patients is significantly higher than that in the healthy population. Patients with IBS attend more frequent clinic visits, consume more medications, are hospitalized more frequently, are less productive at work, have higher overall direct
costs, and occupy the healthcare system to a greater extent than patients without IBS [15].

IBS is considered as a non-organic syndrome, and modern medicine focuses on relieving symptoms by symptomatic treatment, but the long-term outcome is less than ideal [16-18]. When faced with a chronic disease with limited treatment options, many patients choose complementary and alternative medicine (CAM), and herbal medicine is the most widely used CAM for patients with IBS [19,20]. A systematic review [20] has demonstrated that TCM has distinctive features and advantages in treating IBS, with strengths in symptom improvement, safety, tolerance, and effectiveness, making it a feasible, effective, and safe treatment method.

Sijunzi Decoction is one of the famous traditional Chinese prescriptions composed of four common herbs: Ginseng Radix, Poria, Rhizoma Atractylodis Macrocephalae, and Glycyrrhiza [21]. Tongxie Yaofang is another regular clinical prescription for IBS in China. There have been some original studies on modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D, but the efficacy of this prescription is still unclear due to the lack of systematic assessment. This study aimed to evaluate the overall efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D through a meta-analysis of relevant literature to provide more evidence-based evidence for the clinical application of this classical prescription.

2. Materials and Methods

2.1. Search strategy

The following databases were searched from the inception of the database to November 20, 2022 by computer: CNKI, WanFang Data, VIP, CBM, and English databases Pubmed, Cochrane Library, and Embase. Chinese search terms included irritable bowel syndrome, irritable colon, Sijunzi decoction, tongxie-yaofang, etc. English search terms included irritable bowel syndrome, irritable colon, Sijunzi decoction, tongxie-yaofang, etc. The search method was "subject words + free words".

2.2. Inclusion and exclusion criteria

2.2.1. Study type

All RCTs of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D, with or without blinding masking, allocation concealment, and reporting of loss to follow-up and withdrawals, with no restriction on the type of literature.

2.2.2. Study subjects

All patients who met the diagnostic criteria for Rome II irritable bowel syndrome or Rome III irritable bowel syndrome and were clinically classified as diarrhea-predominant. Patients were of all ages and genders, but there was good agreement between groups at baseline. Subjects were free of severe immune system diseases, neurological diseases, organ insufficiency, or organic diseases. Subjects clearly understood the content of the trial and signed informed consent; the hospital's ethics committee approved the trial.

2.2.3. Interventions

The control group was treated with conventional Western medicine with no restriction on the drug type (montmorillonite powder, trimethobutine maleate tablets, and bifidobacteria-based microecologics, etc.). The test group was treated with modified Sijunzi Decoction combined with Tongxie Yaofang alone or was additionally treated with modified Sijunzi Decoction combined with Tongxie Yaofang on the basis of the control group with no restriction on the dosage (tablets, granules, etc.).

2.2.4. Exclusion criteria

Non-randomized controlled trials such as clinical reviews, animal studies, pharmacology, pharmacokinetics, basic studies, abstracts, and case reports; The diagnostic criteria for IBS of the diseases were unclear; The clinical diagnosis of the disease was IBS, but the clinical classification was not IBS-D; The experimental group used other combination therapies; The control groups did not receive conventional Western medicine treatment; The research results were incorrect and there was no argument to explain the reasons; The research replicated published literature.
2.2.5. Outcome indicators

Primary outcome indicators were clinical efficacy and total clinical symptom score. Secondary outcome indicators encompassed clinical symptom scores for each symptom, daily bowel frequency, quality of life assessment, biochemical indicators, adverse effects, and recurrence rate.

2.3. Literature screening and data extraction

After the literature search was done by one investigator, two investigators used Endnote X9 for literature screening according to the pre-defined exclusion/inclusion criteria. Firstly, duplicates were eliminated, and then the titles, abstracts, and full texts were read to determine the literature for final inclusion. In the case of disagreements, a third party was involved in order to obtain a final decision through discussion. Two investigators used pre-designed statistical tables to retrieve authors, year, sample size, diagnostic criteria, interventions, duration of treatment, and outcome indicators for the included literature.

2.4. Risk assessment for the included studies

A rigorous quality assessment was performed independently by 2 investigators using the Cochrane Risk of Bias Assessment Tool. The quality included 6 domains, including randomization plan, concealment scheme, intervention blinding, outcome data integrity, selective reporting, and other biases.

2.5. Statistical analysis

Stata (version 15.0) was used for meta-analysis, with risk ratio (RR) and 95% confidence interval (CI) as outcome statistics for dichotomous variables and weighted mean difference (WMD) and 95% CI as outcome statistics for continuous variables. Heterogeneity test is subject to the Q test and I² test. If P > 0.01 and I² < 50%, it means that the heterogeneity is small, and a fixed effect model is used for analysis. Otherwise, a random-effects model is used for analysis. Subgroup analysis, sensitivity analysis, or only descriptive analysis were performed for patients with obvious clinical heterogeneity. To detect publication bias, Stata (version 15.0) was used to plot funnel plots or performed the Egger's test. If the funnel plots were symmetrically distributed or P > 0.1, there was no significant publication bias.

3. Results

3.1. Literature search results

![Figure 1: Literature Screening Flow Chart]
Through literature search, a total of 108 relevant studies were preliminarily obtained (28 from CNKI, 32 from WanFang Data, 18 from VIP, and 28 from CBM). After eliminating duplicates, 40 studies remained. By reading the titles and abstracts, 17 were eliminated, leaving 23. Nine studies were excluded after reading the full text: 3 [22-24] did not specify the diagnostic criteria for IBS; 2 [25,26] did not specify the clinical classification of IBS as diarrhea-predominant; 1 [27] test group received combined emotional conditioning therapy; 1 [28] control group did not receive conventional Western medical treatment (massage therapy); and 2 [29,30] had incorrect and unexplained outcome data. Fourteen studies were eventually included [31-44], involving 1,032 patients with IBS-D. The flow of literature screening is detailed in Figure 1.

### 3.2. Basic characteristics of the included studies

A total of 14 studies were included, all of which were randomized controlled trials. There were 1,032 patients with IBS-D, with 522 in the test group and 510 in the control group. All studies reported the indicator of clinical efficacy. Nine of them [31,32,34,36,37,40,41,43,44] had the same evaluation criteria based on the Guidelines for Clinical Research on New Chinese Medicines [45], and the remaining 5 literatures had self-defined evaluation criteria. The basic characteristics of the literature are detailed in Table 1.

### Table 1: Basic Characteristics of the included studies

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Sample size (T/C)</th>
<th>Diagnostic criteria</th>
<th>Interventions</th>
<th>Duration of treatment</th>
<th>Outcome indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gong Yanhuan 2011</td>
<td>30/26</td>
<td>Rome II</td>
<td>Sijunzi Decoction combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Chen Yiliang 2014</td>
<td>35/35</td>
<td>Rome III</td>
<td>Sijunzi Decoction combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>1 month</td>
</tr>
<tr>
<td>Wang Yongqing 2014</td>
<td>58/58</td>
<td>Rome III</td>
<td>Sijunzi Decoction combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Wen Pei Yi 2014</td>
<td>42/42</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Yao Kaidong 2014</td>
<td>46/46</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Ji Jianghong 2015</td>
<td>34/32</td>
<td>Rome II</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Wang Changchun 2015</td>
<td>35/35</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Xue Desheng 2016</td>
<td>18/18</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Qi Zhijuan 2016</td>
<td>50/50</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Zhang Hongfei 2016</td>
<td>19/19</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Chen Tianliang 2016</td>
<td>43/43</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>1 month</td>
</tr>
<tr>
<td>Ye Tao 2019</td>
<td>40/40</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Zhao Bingfan 2019</td>
<td>27/26</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Liu Xiaoxi 2019</td>
<td>45/40</td>
<td>Rome III</td>
<td>Sijunzi Decoction Combined with Tongxie Yaofang</td>
<td>Conventional Western medicine</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Note: T = test group, C = control group; Conventional Western medicine includes montmorillonite powder, pinaverium bromide, bifidobacteria-based biologics, trimebutine, etc.

### 3.3. Quality evaluation for the included studies

The Cochrane Risk of Bias Assessment Tool was used to evaluate the quality of included studies. All 14 included studies [31-44] mentioned random assignment, of which 5 [33,34,39,41,44] used the random
number table method, and the other 9 did not describe the randomization method in detail. None studies stated whether allocation concealment and blinding masking were used. All eligible studies had complete outcome data and no selective reporting. All included studies mentioned baseline information such as patient age, gender, and course of disease, which were comparable. One study [44] reported case dropout and loss to follow-up, and the other 13 did not describe case dropout and loss to follow-up in detail. There was potential for bias in the included studies, such as dosage forms and single dosages of Chinese medicine and types and specifications of Western medicine. However, there was no evidence to suggest that these issues can cause bias. The quality evaluation of the included studies is detailed in Figure 2.

Figure 2: Literature Quality Evaluation

3.4. Meta-analysis of clinical efficacy

3.4.1. Heterogeneity test

The included 14 RCTs were analyzed in subgroups, of which 9 with consistent clinical efficacy evaluation criteria [31,32,34,36,37,40,41,43-45] were divided into group 1, and the remaining 5 with self-defined evaluation criteria were divided into group 2. The heterogeneity test indicated that there was homogeneity among the studies in group 1 (P=0.997, I²=0%), and also in group 2 (P=0.868, I²=0%), and there was homogeneity among 14 studies in both groups (P=0.0999, I²=0%). Therefore, a fixed effects model can be used for pooled analysis.

3.4.2. Meta-analysis of clinical effects

The results of meta-analysis showed that there was a statistically significant difference between the modified Sijunzi Decoction combined with Tongxie Yaofang group and the conventional Western medicine treatment group in group 1 (P<0.01) [RR=1.247, 95% CI (1.156, 1.347)]. The results of group 2 also showed a statistically significant difference between the test group and the control group (P<0.01) [RR=1.208, 95% CI (1.114, 1.309)]. There was a statistically significant difference (P<0.01) between the test group and the control group for a total of 14 studies in the two groups [RR=1.229, 95% CI (1.158, 1.306)].

Figure 3: Meta-Analysis of Clinical Efficacy

The results of meta-analysis showed that there was a statistically significant difference between the modified Sijunzi Decoction combined with Tongxie Yaofang group and the conventional Western medicine treatment group in group 1 (P<0.01) [RR=1.247, 95% CI (1.156, 1.347)]. The results of group 2 also showed a statistically significant difference between the test group and the control group (P<0.01) [RR=1.208, 95% CI (1.114, 1.309)]. There was a statistically significant difference (P<0.01) between the test group and the control group for a total of 14 studies in the two groups [RR=1.229, 95% CI (1.158, 1.306)].
CI (1.162, 1.299)]. It suggested that the clinical effect of modified Sijunzi Decoction combined with Tongxie Yaofang on IBS-D was significantly superior to that of conventional Western medicine, as shown in Figure 3.

3.4.3. Sensitivity analysis

Based on the meta-analysis results of the clinical efficacy of the modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D, sensitivity analysis was conducted by excluding the included studies one by one, and the results did not significantly change. This indicated that the meta-analysis results of clinical efficacy of the modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D were stable and reliable (Figure 4).

3.4.4. Publication bias

As more than 10 studies were included in the analysis, a publication bias analysis was conducted. Using the RR values of the included studies as horizontal coordinates and the inverse of the logarithmic standard error SE(log[RR]) as vertical coordinates, a funnel plot was generated for the clinical efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D. The funnel plot was not perfectly symmetrical, suggesting a possible publication bias, as shown in Figure 5. An Egger test based on Figure 5 yielded P=0.114>0.1, indicating no publication bias in the 14 included studies.

3.5. Meta-analysis of daily bowel frequency

Three RCTs [33,37,38] reported the daily bowel frequency before and after treatment in 302 patients with IBS-D, with 151 in the test group and 151 in the control group. There was heterogeneity among the three studies (P=0.000, I²=95.8%), as shown in Figure 6. The heterogeneity may be related to
patient age, course of disease, severity of disease, and patient expression, so a random-effects model was used for the pooled analysis, with SMD as the effect indicator. The results showed that the improvement in daily bowel frequency in the test group was higher than that in the control group, [SMD=-1.791, 95% CI (-3.130, -0.452)], and the difference was statistically significant (P<0.05).

![Figure 6: Meta-Analysis of Daily Bowel Frequency](image)

### 3.6. Clinical symptom scores

Six publications [32,34,37,42-44] measured the clinical symptom scores of subjects before and after treatment, and a decrease in the scores indicated an improvement in clinical symptoms. Due to the small number of included studies and inconsistent criteria for scoring, a descriptive analysis was performed to analyze the results. Three studies [32,37,43] calculated the total clinical symptom score before and after treatment, of which 2 [32,37] had the same criteria for scoring. The total clinical symptom score after treatment in all three studies decreased compared to before treatment, and the test group showed a significant decrease compared to the control group (P<0.05). 3 studies [42-44] calculated the stool trait, frequency of defecation, and abdominal pain before and after treatment, of which 2 [42,44] had the same criteria for scoring. The scores of stool traits, frequency of defecation, and abdominal pain after treatment in all 3 studies decreased compared to before treatment, and the test group showed a significant decrease compared to the control group (P<0.05). Another study [34] calculated the integral difference of stool trait, frequency of defecation and abdominal pain before and after treatment, and the difference of the test group was more significant than that of the control group (P<0.05). All 6 studies reported the improvement degree of clinical symptoms of the subjects before and after treatment, and the results showed that the clinical symptoms of the subjects after treatment were significantly improved compared with that before treatment, and the test group was significantly improved compared with the control group (P<0.05).

### 3.7. Quality of life

Two studies [42,44] have statistically analyzed the quality of life of subjects before and after treatment. One study [42] used the Health Questionnaire (SF-36), and the other [44] used the IBS Quality of Life Scale (IBS-QOL). Both evaluation methods rated higher scores as better quality of life. The assessment criteria in the 2 studies were different, so a descriptive analysis was conducted to analyze the results. In one study [42], the difference in the quality of life scores between the two groups before treatment was not statistically significant (P>0.05); after the treatment, the quality of life scores of patients in the test group was higher than those in the control group, and the difference was statistically significant (P<0.05). Another study [44] showed that all quality of life scores, except the health concerns and sexual behavior (e.g., anxiety, conduct disorder, food avoidance), increased after treatment than before treatment, the difference was statistically significant (P<0.05), and the change was more significant in the test group than in the control group (P<0.05). Both studies assessed subjects' anxiety (mental health) and social functioning, and the results showed that patients in the test group had higher anxiety (mental health) and social functioning scores than the control group after treatment, and the differences were statistically significant (P<0.05).
3.8. Biochemical indicators

A study [42] examined the immunological indicators of the subjects before and after treatment, which revealed that the differences in IgA, IgG, and IgM between the two groups after treatment were not statistically significant (P>0.05). The values of CD3+, CD4+, and CD4+/CD8+ in the serum of patients in both groups after treatment were higher than those before treatment, while CD8+ content was lower than before treatment with statistically significant differences (P<0.05), and the change in the test group was more significant than in the control group (P<0.05). Another study [44] tested the brain gut peptide indicators of the subjects before and after treatment, and the results showed that the NPY levels of the two groups of patients significantly increased after treatment, while the CGRP and VIP levels significantly decreased. The difference was statistically significant (P<0.05), and the change in the test group was more significant than in the control group (P<0.05). By the descriptive analysis, modified Sijunzi Decoction combined with Tongxie Yaofang may be superior to conventional Western medical treatment in improving immunological disorders in IBS-D. However, due to the small number of the included RCTs reporting subject immunological indicators, more RCTs are still needed to verify whether there are differences in their changes between the two groups.

3.9. Adverse effects and recurrence rate

Three studies [33,42,44] mentioned the absence of adverse effects. Two [39,44] mentioned recurrences in subjects. The incidence of secondary diarrhea (recurrence after cessation of treated diarrhea) was counted and found to be 4% in the test group and 18% in the control group [39]. The incidence of secondary diarrhea was significantly lower and statistically significant in the test group compared to the control group (P=0.025). In subjects observed during the 8-week follow-up period, the recurrence rate was 22.22% in the test group and 42.31% in the control group [44]. The recurrence rate of the test group was lower than that of the control group, and the difference was statistically significant (P<0.05).

4. Discussion

This study included 14 RCTs [31-44] for meta-analysis. The results showed that the clinical efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D was significantly better than conventional Western medicine treatment. In terms of clinical symptom improvement, the meta-analysis on 3 RCTs [33,37,38] revealed that modified Sijunzi Decoction combined with Tongxie Yaofang was significantly more effective than conventional Western medical treatment for improving daily bowel movement frequency. The descriptive analysis on 6 RCTs [32,34,37,42-44] showed that modified Sijunzi Decoction combined with Tongxie Yaofang significantly outperformed conventional Western medical treatment for lowering clinical symptom scores. Improvement in patients' quality of life is an essential indicator in assessing efficacy. From the descriptive analysis, it can be tentatively concluded that modified Sijunzi Decoction combined with Tongxie Yaofang is superior to conventional Western medicine in improving patients' emotional well-being and quality of life. However, more RCTs with the same evaluation criteria and large sample sizes are needed for verification. According to the descriptive analysis, modified Sijunzi Decoction combined with Tongxie Yaofang may have an advantage over conventional Western medical treatment in improving immunological disorders in IBS-D. The recurrence rate of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D was significantly lower than that of conventional Western medical treatment, indicating that the long-term efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D may be better than that of conventional Western medical treatment. However, due to the small sample size, the long-term efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D and the adverse effects are unclear. In conclusion, this study showed that the clinical efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D was significantly better than that of conventional Western medical treatment, especially in ameliorating symptoms.

In the indicator analysis process and results, this study has some limitations: (1) the overall quality of the study is not satisfactory. The overall quality of our study was limited by the small number of included studies, the small sample size, and the small number of RCTs that elaborated on the randomization method, whether blinding masking was implemented, and allocation concealment. (2) The data source is single. The RCTs included in this study were only from a small geographical area in China, which was not conducive to clarifying and promoting the efficacy of the modified Sijunzi
Decoction combined with Tongxie Yaofang in the treatment of IBS-D. (3) The study is somewhat superficial. Only 2 [42,44] of the included RCTs examined biochemical indicators before and after treatment, 2 [42,44] measured subjects' quality of life before and after treatment, only 3 RCTs [33,42,44] mentioned adverse effects, and 2 [39,44] mentioned recurrence rate. This study has the following strengths: At present, there is no meta-analysis study on the treatment of IBS-D with modified Sijunzi Decoction combined with Tongxie Yaofang abroad, and this study is the first of its kind, and is beneficial to expanding research on TCM in foreign countries.

Future directions: (1) Extensive RCTs are warranted to expand the geographical scope to clarify further and promote the efficacy of the modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D. (2) More outcome indicators should be included, such as biochemical indicators and brain-gut peptide indicators, in order to understand the changes of indicators during the treatment of IBS-D with modified Sijunzi Decoction combined with Tongxie Yaofang and explore the possible internal mechanism of modified Sijunzi Decoction combined with Tongxie Yaofang in treating IBS-D. (3) Additional observation is required on the adverse effects and follow-up results to analyze the safety and long-term efficacy of modified Sijunzi Decoction combined with Tongxie Yaofang in the treatment of IBS-D.

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