

82002\_Auto\_Edited.docx

**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 82002

**Manuscript Type:** META-ANALYSIS

**Effectiveness and Safety of Traditional Chinese Medicine Decoction for Diabetic  
Gastroparesis: A Network Meta-Analysis**

TCM Decoction for Diabetic Gastroparesis

yuxin zhang, yanjiao zhang, runyu miao, xinyi fang, jiahua wei, Yu Wei, jiaran lin,  
Jiaxing Tian

## **Abstract**

### **BACKGROUND**

Diabetic gastroparesis (DGP) is a prevalent complication of diabetes that impairs people's quality of life and places a significant financial burden on them. The gastrointestinal symptoms of DGP patients can be improved by several Traditional Chinese Medicine (TCM) decoctions that have been shown to be effective in treating the disease. There are still many unanswered questions regarding the identification of appropriate therapeutic agents for the treatment of DGP in clinical practice.

### **AIM**

To analyze the efficacy of several TCM decoctions in the treatment of DGP using Bayesian network meta-analysis for reference.

### **METHODS**

PubMed, Embase, Cochrane Library, Web of Science, CNKI, CBM, Wanfang, and VIP were searched from inception to September 17, 2022, to collect randomized controlled trials (RCTs) about TCM decoctions for DGP. Clinical effects and symptom scores were the primary outcomes. Additionally, we assessed MOT, SS, GAS, gastric emptying rate, gastric emptying time, and adverse drug events as secondary outcomes.

### **RESULTS**

A total of 67 eligible RCTs involving 4790 DGP patients and 7 TCM decoctions were included. The results of NMA and SUCRA showed that with western medicine (WM) as a common control, the Banxia Xiexin Decoction (BXXD)+WM was most effective in clinical effects and enhancing early satiety scores; the Simo decoction (SMD)+WM was most effective in improving nausea and vomiting scores and anorexia scores, bloating scores; the Chaishao Liujunzi Decoction (CSLJD) was most effective in MOT, the Zhishi Xiaopi decoction (ZSXPD) was most effective in SS and upgrading emptying rate; the

Jianpi Xiaozhi Decoction (JPXZD) was most effective in GAS; the CSLJD+WM was most effective in improving gastric emptying time.

## CONCLUSION

These NMA results suggest that the BXXD+WM and SMD+WM may be one of the potential optimal treatments. Due to various limitations, further large-sample, double-blind, multi-center randomized controlled trials are needed.

**Key Words:** diabetic gastroparesis; traditional Chinese medicine decoction; Network meta-analysis; effectiveness.

zhang Y, zhang Y, miao R, fang X, wei J, Wei Y, lin J, Tian J. Effectiveness and Safety of Traditional Chinese Medicine Decoction for Diabetic Gastroparesis: A Network Meta-Analysis. *World J Diabetes* 2022; In press

**Core Tip:** The gastrointestinal symptoms of diabetic gastroparesis (DGP) patients can be improved by several Traditional Chinese Medicine (TCM) decoctions that have been shown to be effective in treating the disease. <sup>3</sup> The main objective of this study is to analyze the efficacy and safety of several traditional Chinese medicine decoctions in the treatment of DGP using Bayesian network meta-analysis to better guide clinical decision-making. A total of 67 eligible RCTs involving 4790 DGP patients and 7 TCM decoctions were included. These NMA results suggest that combined with qualified TCM decoctions, WM is more effective for DGP patients than WM alone.

## INTRODUCTION

Diabetic gastroparesis (DGP), a complication of diabetes mellitus (DM), is used to describe the upper gastrointestinal (GI) manifestations of diabetes characterized by delayed gastric emptying without mechanical obstruction<sup>[1, 2]</sup>. The International Diabetes Federation (IDF) estimated that approximately 537 million adult people

worldwide were living with diabetes in 2021<sup>[3]</sup>, and DGP is becoming more common as diabetes prevalence increases<sup>[4]</sup>. In the Diabetes Control and Complications Trial study, delayed gastric emptying was usually associated with gastrointestinal symptoms and measures of early and long-term hyperglycemia<sup>[5]</sup>. Anorexia, early postprandial satiety, stomach distension, nausea, and vomiting are the main clinical signs of diabetic gastroparesis<sup>[6-8]</sup>. Because symptoms of gastroparesis resemble those of other gastrointestinal disorders, such as functional dyspepsia and ulcers, diagnostic delay or misdiagnosis of gastroparesis is common in the real world<sup>[9]</sup>. Quality of life is significantly reduced in patients with diabetic gastroparesis impairment, with up to 50% of patients have considerable anxiety or depressive symptoms<sup>[10, 11]</sup>. In addition, studies have shown that the economic burden of gastroparesis remains high several years after diagnosis, and long-term treatment is required to effectively control of symptoms, and reduce the burden of the disease<sup>[12]</sup>. As a result, there is increased interest in figuring out how to use contemporary medical procedures to further enhance the quality of life and long-term prognosis of DGP patients.

Patients with diabetic gastroparesis are treated with conventional western medicine gastric motility medications such as domperidone, metoclopramide, and mosapride citrate all over the world<sup>[13-16]</sup>. Although these medications help reduce patients' gastrointestinal discomfort and promote increased nutrient intake, they also have some negative side effects and are simple to relapse following drug discontinuation<sup>[17-19]</sup>. Some patients with DGP are also treated with alternative strategies (endoscopy, electrical stimulation, or surgery), but with greater financial burden<sup>[20-23]</sup>. Traditional Chinese medicine (TCM) has a history of more than 2000 years in the treatment of gastrointestinal diseases, which is considered a complementary and alternative therapy for patients with DGP<sup>[24-27]</sup>. It is usually used to improve nausea and vomiting and help relieve abdominal distension. The TCM method is noninvasive and inexpensive and appears to be effective and promising based on clinical practice and some preliminary evidence. A large number of studies have demonstrated the efficacy of TCM decoction in the treatment of DGP<sup>[28-31]</sup>, however, due to the wide variety of

drugs and the lack of randomized controlled trials comparing drugs, it is inconvenient for clinicians to choose drugs, the TCM decoctions with the greatest effectiveness against DGP in adults have not been found.

By combining direct and indirect evidence and evaluating therapies in terms of efficacy or safety, network meta-analysis (NMA) enables simultaneous analysis of multiple interventions within a single study<sup>[32-34]</sup>. To provide a reference for the clinical selection of appropriate drugs suitable for the treatment of DGP, this study reviewed recent randomized controlled trials (RCTs) to compare the efficacy and safety of various TCM decoctions for treatment of DGP.

## **MATERIALS AND METHODS**

To describe our findings, we adhered to the PRISMA extension for network meta-analysis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>[35-38]</sup>. Additionally, our protocol is listed in PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>, identifier CRD42022369187).

### ***Search Strategy***

PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), The China Biology Medicine DVD (CBM), Wanfang, and VIP were searched from inception to September 17, 2022, to collect randomized controlled trials (RCTs) about TCM decoctions for DGP. Search terms were as follows: (Diabetic gastric OR Diabetic gastroparesis OR diabetic stomach paresis OR Diabetic gastropareses) AND (Traditional Chinese Medicine OR Chinese Traditional Medicine OR TCM OR Chinese herb) AND (Clinical Trial OR Intervention Study OR trial OR clinical study). The detailed search strategy was shown in Supplementary File Table S1-S4. To find further eligible research, relevant references from the included papers were looked for. Language, year of publishing, and type of publication were not restricted.

### ***Inclusion and Exclusion Criteria***

The inclusion criteria were as follows:

- 1) Participants: Adults (more than 18 years old) with clinically diagnosed diabetic gastroparesis based on symptomatic assessment.
- 2) Interventions and Comparisons: Patients in the treatment arm who received the Chinese medicine decoction will be included. And the control group was given other prokinetic drugs or decoction.
- 3) Outcomes:
  - ① Primary outcomes: Clinical effects and symptom score (nausea and vomiting, anorexia, early satiety, bloating, and overall gastroparesis symptoms scores).
  - ② Secondary outcomes: motilin (MOT), somatostatin (SS), gastrin (GAS), gastric emptying time, emptying rate, and adverse drug event as secondary outcomes.

The exclusion criteria were as follows:

- 1) Non-RCTs, conference abstracts, case reports, guidelines, letters, animal experiments, and review articles.
- 2) Participants: Gastroparesis caused by any other causes will be excluded.
- 3) Interventions: Studies that involve the use of acupuncture or auric acupuncture are excluded.
- 4) Outcome: data could not be obtained from the original authors due to incorrect data or incomplete outcome measures
- 5) Duplicate published articles.

#### ***Literature Screening and Data Extraction***

Records from databases were managed and screened using EndNote. 20 software. Two researchers (YXZ and YJZ) independently conducted a literature search and data extraction, and the analysis part was discussed and assisted by the third researcher (XYF). The qualified literature was extracted into a data extraction table. Data extraction items included title, first author, publication year, sample size, gender(M/F), mean age, course of dears, intervention, treatment time, and outcomes. We emailed the first or corresponding author to request further information when a research's data were missing or the study procedures were not clearly explained.

### ***Quality Assessment***

Two reviewers (YXZ and YJZ) independently <sup>4</sup> assessed the risk of bias of the included RCTs according to Cochrane Handbook for Systematic Reviews of Interventions<sup>[39, 40]</sup>. <sup>1</sup> Seven aspects of random sequence generation, allocation concealment, subject and personnel blinding, outcome assessment blinding, outcome data incompleteness, selective reporting, and other sources of bias were evaluated. The results of the risk of bias assessment included the low risk of bias, the high risk of bias, and the unclear risk of bias. The outcomes of this examination were categorised as having a "low risk," "high risk," or "unclear risk of bias." Any differences of opinion will be resolved through discussion or agreement with a third reviewer. Review Manager 5.4 will generate a graphical display of the risk of bias assessment.

### ***Grading the Certainty of Evidence for Major Comparisons and Outcomes***

We evaluated the quality of the evidence for systematic reviews and clinical guidelines using the GRADE method <sup>8</sup> (Grading of Recommendations Assessment, Development, and Evaluation)<sup>[41]</sup>. This method was created to rate the overall certainty of a body of information, involving five crucial domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations. These domains included potential confounders that may weaken the relationship and lessen the magnitude of the observed effect, as well as the variables that would enhance the correlation (large effect size, dose-response gradient, and plausible confounding). Each domain was evaluated by two reviewers, and disagreements were settled through discussion. To increase transparency, we recorded every choice we made regarding the certainty of the evidence. GradePro was used to develop finding summary tables (<https://gradepro.org>).

### ***Statistical Analysis***

The generation of this network meta-analysis, forest plot, survey of statistical heterogeneity, and  $I^2$  statistics was performed using the gemtc and jags packages of R (version 4.2.1)<sup>[42]</sup>. Odds ratio (OR) or relative risk (RR) with 95% confidence limits were used to present dichotomous variables. Standardized mean difference for continuous



variables were shown as 95% CrI. Possible heterogeneity was assessed using Chi-square and  $I^2$  tests, statistically significant was defined as  $P < 0.05$ , and the data were compiled using the random-effects model.

To depict the links between different interventions, a network diagram of each outcome was created. To rank various interventions, the surface under the cumulative ranking curve (SUCRA) and a plot of rank probabilities were used<sup>[43-45]</sup>. To obtain an optimal intervention, a multi-dimensional efficacy analysis was conducted to combine the findings from numerous outcomes. STATA 15.0 was used to generate funnel plots to determine the effects of publication bias and small-sample studies.

## **RESULTS**

### ***Literature Screening Result***

The databases yielded 4171 articles in response to our queries. The titles and abstracts of 1453 citations were checked after the deduplicate record was eliminated. The complete text of 279 screened citations was then subjected to a further eligibility analysis. 56 papers that satisfied the criteria after reading the entire text were added to the network meta-analysis<sup>[46-101]</sup>. **Figure 1** depicts the specifics of the literature screening procedure.

### ***Basic Characteristics of Included Studies***

All investigations were carried out between 2005 and 2022, and 4790 patients were included in our meta-analysis, including 2404 in the experimental group (EG) and 2386 in the control group (CG). The average age of participants ranged from 45.1 to 83.5 years. The treatment duration ranged from 0.5 to 3 mo. Among the included trials, 20 RCTs were conducted using Banxia Xiexin Decoction (BXXD)<sup>[46, 50, 51, 55, 57, 58, 61, 63-67, 75, 81, 83, 85, 86, 89, 96, 100]</sup>, and 853 patients as the EG and 844 patients treated with western medicine (WM) as the CG. There were 11 RCTs in which 486 patients in the EG were treated with Xiangsha Liujunzi Decoction (XSLJZD)<sup>[47, 49, 68, 72, 74, 78, 84, 87, 91, 94, 97]</sup>, 6 RCTs in which 360 patients in the EG were treated with simo decoction (SMD)<sup>[73, 82, 90, 98, 101]</sup>, 5 RCTs in which 232 patients in the EG were treated with Zhishi Xiaopi decoction (ZSXPD)<sup>[70, 76, 88, 92, 93]</sup>, and 5 RCTs in which 198 patients in the EG were treated with

Chaishao Liu junzi Decoction (CSLJD)<sup>[53, 60, 62, 77, 95]</sup>. There were 5RCTs with 243 patients in the EG treated with Chaqin Wenden Decoction (CQWD)<sup>[48, 52, 54, 56, 59]</sup>, and 4RCTs with 198 patients in the EG treated with Jianpi Xiaozhi Decoction (JPXZD)<sup>[69, 71, 79, 80]</sup>. Table 1 displays the fundamental features of the RCTs included in the network meta-analysis.

## 6 Risk of Bias Assessment

The Cochrane risk of bias calculation was used to evaluate the bias risk of each included trial. According to the Cochrane Reviewers' Handbook, 28 studies used the random number table method for grouping, while the other studies did not specify their randomization procedure. None of the other papers addressed blinding, only one double-blind trial was rated as low risk<sup>[64]</sup>, and none of the other studies mentioned blinding. There was no selective reporting data in any of the studies or other risks in these studies. However, other risks to the quality of the included studies were not mentioned. Figure 2 displays a summary of the bias risk present in the RCTs. **Table S5** summarizes certainty-of-evidence ratings.

## Results of the Network Meta-Analysis

### Effect of TCM decoctions on clinical effects

53 RCTs in total, encompassing seven different TCM decoctions and twelve different types of interventions, reported the clinical outcomes (WM vs. BXXD ( $n = 10$ ), WM vs. BXXD+WM ( $n = 8$ ), WM vs. XSLJZD ( $n = 6$ ), WM vs. XSLJZD+WM ( $n = 5$ ), WM vs. SMD ( $n = 5$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXPD ( $n = 4$ ), WM vs. ZSXPD +WM ( $n = 1$ ), WM vs. CSLJD ( $n = 3$ ), WM vs. CSLJD+WM ( $n = 1$ ), WM vs. CQWD ( $n = 5$ ), WM vs. JPXZD ( $n = 4$ )) (**Table 1**). The network plot is presented in **Figure 3A**. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in clinical effects, and details are illustrated in **Figure 3B**. Apart from CSLJD+WM, XSLJZD, XSLJZD+WM, and ZSXPD, other TCM decoctions were superior to WM alone. The specifics are displayed in **Table 2**.

Following is the ranking of 13 therapies based on SUCRA probability results (Figure 3C, Table 3): BXXD+WM (75.49%) > SMD+WM (68.1%) > ZSXPD+WM (65.12%) > CSLJD

(64.56%) > ZSXP (61.92%) > JPXZD (61.36%) > CQWD (57.35%) > XSLJZD+WM (56.77%) > BXXD (51.34%) > SMD (42.1%) > XSLJZD (22.32%) > CSLJD+WM (21.53%) > WM (2.03%). The intervention with the highest likelihood of improving clinical results was BXXD+WM.

### *Effect of TCM decoctions on symptom scores*

#### *Nausea and vomiting scores*

A total of 17 RCTs reported nausea and vomiting scores, including five types of TCM decoctions and eight types of interventions (WM vs. BXXD ( $n = 2$ ), WM vs. BXXD+WM ( $n = 3$ ), WM vs. XSLJZD ( $n = 1$ ), WM vs. XSLJZD+WM ( $n = 2$ ), WM vs. SMD ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. CQWD ( $n = 5$ ), WM vs. JPXZD ( $n = 2$ )) (Table 1). The network plot is presented in Figure 4A. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in nausea and vomiting scores, and details are illustrated in Figure 4B. The TCM decoctions were all superior to WM alone, as were the TCM decoctions mixed with WM. Additionally, there were statistically significant variations across various TCM decoctions, such as BXXD vs. BXXD+WM, BXXD vs. CQWD, BXXD vs. JPXZD, BXXD vs. SMD, BXXD vs. SMD+WM, BXXD vs. XSLJZD, BXXD+WM vs. CQWD, BXXD+WM vs. JPXZD, BXXD+WM vs. SMD, BXXD+WM vs. SMD+WM, BXXD+WM vs. XSLJZD, CQWD vs. JPXZD, CQWD vs. SMD, CQWD vs. SMD+WM, CQWD vs. XSLJZD, JPXZD vs. SMD, JPXZD vs. SMD+WM, SMD vs. SMD+WM, SMD vs. XSLJZD, and SMD+WM vs. XSLJZD. Table 2 displays the information.

SMD+WM was most likely the best intervention to raise nausea and vomiting scores, as demonstrated by SUCRA probability values (Figure 4C, Table 3). The ranking of thirteen interventions is as follows: SMD+WM (93.7%) > XSLJZD+WM (75.52%) > BXXD (66.51%) > CQWD (56.35%) > BXXD+WM (44.93%) > JPXZD (42.02%) > XSLJZD (30.55%) > SMD (24.71%) > WM (15.72%).

#### *Anorexia scores*

10 RCTs in total, encompassing four different TCM decoctions and six different types of therapies, reported the anorexia scores (WM vs. BXXD+WM ( $n = 3$ ), WM vs. XSLJZD ( $n$

= 1), WM vs. XSLJZD+WM ( $n = 1$ ), WM vs. SMD ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. CQWD ( $n = 3$ )) (Table 1). The network plot is presented in Figure 4D. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in anorexia scores, and details are illustrated in Figure 4E. Table 2 shows that SMD+WM, XSLJZD+WM, BXXD+WM, CQWD, XSLJZD, and SMD were greater to WM alone, where the difference was statistically significant. In addition, the differences between different interventions, such as BXXD+WM vs. CQWD, BXXD+WM vs. SMD, BXXD+WM vs. SMD+WM, BXXD+WM vs. XSLJZD, BXXD+WM vs. XSLJZD+WM, CQWD vs. SMD, CQWD vs. SMD+WM, CQWD vs. XSLJZD, CQWD vs. XSLJZD+WM, SMD vs. SMD+WM, SMD vs. XSLJZD, SMD vs. XSLJZD+WM, SMD +WM vs. XSLJZD, SMD +WM vs. XSLJZD+WM, and XSLJZD+WM vs. XSLJZD were not significant. SUCRA probability results (Figure 4F, Table 3) indicated that SMD+WM was most likely to succeed in raising anorexia scores. Following is a ranking of the thirteen interventions: SMD+WM (88.74%) > XSLJZD+WM (77.34%) > BXXD+WM (73.55%) > CQWD (43.56%) > XSLJZD (29.37%) > SMD (21.17%) > WM (16.26%).

#### *Early satiety scores*

A total of 13 RCTs reported the early satiety scores, including four types of TCM decoctions and seven types of interventions (WM vs. BXXD ( $n = 1$ ), WM vs. BXXD+WM ( $n = 3$ ), WM vs. XSLJZD+WM ( $n = 2$ ), WM vs. SMD ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. CQWD ( $n = 2$ ), WM vs. JPXZD ( $n = 3$ )) (Table 1). The network plot is presented in Figure 4G. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in early satiety scores, and details are illustrated in Figure 4H. Table 2 shows that BXXD+WM, SMD+WM, CQWD, XSLJZD+WM, BXXD, JPXZD, and SMD were greater to WM alone where difference was statistically significant. In addition, the differences between different interventions, such as BXXD vs. BXXD+WM, BXXD vs. CQWD, BXXD vs. JPXZD, BXXD vs. SMD, BXXD vs. SMD+WM, BXXD+WM vs. CQWD, BXXD+WM vs. JPXZD, BXXD+WM vs. SMD, BXXD+WM vs. SMD+WM, CQWD vs. JPXZD, CQWD vs. SMD, CQWD vs. SMD+WM, JPXZD vs. SMD, JPXZD vs. SMD+WM, SMD vs. SMD+WM were not significant.



SUCRA probability results (Figure 4I, Table 3) showed that BXXD+WM have the most possibility to become the best intervention for improving early satiety scores. The ranking of thirteen interventions is as follows: BXXD+WM (89.88%) > SMD+WM (83.62%) > CQWD (72.67%) > XSLJZD+WM (48.41%) > BXXD (46.12%) > JPXZD (32.36%) > SMD (16.73%) > WM (10.2%).

### ***Bloating scores***

Eight different types of interventions and five different TCM decoctions were included in the 20 RCTs that reported the bloating ratings (WM vs. BXXD ( $n = 2$ ), WM vs. BXXD+WM ( $n = 4$ ), WM vs. XSLJZD ( $n = 2$ ), WM vs. XSLJZD+WM ( $n = 2$ ), WM vs. SMD ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. CQWD ( $n = 5$ ), WM vs. JPXZD ( $n = 3$ )) (Table 1). The network plot is presented in Figure 4J. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in bloating scores, and details are illustrated in Figure 4K. Table 2 shows there was statistically significant difference between SMD+WM, BXXD+WM, BXXD, CQWD, JPXZD, XSLJZD+WM, XSLJZD, and SMD, which were superior to WM alone. In addition, there were also statistically significant differences between different interventions, such as BXXD vs. BXXD+WM, BXXD vs. CQWD, BXXD vs. JPXZD, BXXD vs. SMD, BXXD vs. SMD+WM, BXXD vs. XSLJZD, BXXD+WM vs. CQWD, BXXD+WM vs. JPXZD, BXXD+WM vs. SMD, BXXD+WM vs. SMD+WM, BXXD+WM vs. XSLJZD, CQWD vs. JPXZD, CQWD vs. SMD, CQWD vs. SMD+WM, CQWD vs. XSLJZD, JPXZD vs. SMD, JPXZD vs. SMD+WM, SMD vs. SMD+WM, SMD vs. XSLJZD, and SMD+WM vs. XSLJZD.

SUCRA probability results indicate (Figure 4L, Table 3), the possibility of SMD+WM to become the best intervention for improving bloating scores is the most. The ranking of thirteen interventions is as follows: SMD+WM (98.98%) > BXXD+WM (78.56%) > BXXD (71.13%) > CQWD (67.3%) > JPXZD (40.12%) > XSLJZD+WM (38.13%) > XSLJZD (28.76%) > SMD (17.14%) > WM (9.88%).

### ***Effect of TCM decoctions on gastrointestinal hormones***

#### ***MOT***

The MOT was reported in 22 RCTs, using seven different types of TCM decoctions and ten different types of treatments (WM vs. BXXD ( $n = 2$ ), WM vs. BXXD+WM ( $n = 1$ ), WM vs. XSLJZD+WM ( $n = 3$ ), WM vs. SMD ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXPB ( $n = 2$ ), WM vs. CSLJD ( $n = 3$ ), WM vs. CSLJD+WM ( $n = 2$ ), WM vs. CQWD ( $n = 3$ ), WM vs. JPXZD ( $n = 4$ )) (Table 1). The network plot is presented in Figure 5A. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in MOT, and details are illustrated in Figure 5B. According to Table 2, only XSLJZD+WM was superior to WM alone, and the difference was statistically significant. Additionally, there were statistically significant differences between several interventions, including BXXD vs. BXXD+WM, BXXD vs. CSLJD, BXXD vs. CSLJD+WM, BXXD vs. JPXZD, BXXD vs. SMD, BXXD vs. SMD+WM, BXXD+WM vs. CSLJD, BXXD+WM vs. CSLJD+WM, CQWD vs. CSLJD, CQWD vs. CSLJD+WM, CQWD vs. JPXZD, CQWD vs. SMD and CQWD vs. SMD+WM.

As mentioned in SUCRA probability results (Figure 5C, Table 3), the ranking of the thirteen interventions is as follows: CSLJD (97.26%) > CSLJD+WM (92.27%) > JPXZD (73.27%) > SMD+WM (71.2%) > SMD (61.42%) > BXXD+WM (52.91%) > CQWD (37.05%) > XSLJZD+WM (30.21%) > BXXD (24.36%) > WM (9.72%) > ZSXPB (0.33%). CSLJD was the most likely to become the best intervention for improving MOT.

## SS

9 RCTs in total, including five different TCM decoctions and six different types of interventions, reported the SS (WM vs. BXXD ( $n = 2$ ), WM vs. BXXD+WM ( $n = 2$ ), WM vs. XSLJZD+WM ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXPB ( $n = 2$ ), WM vs. CQWD ( $n = 1$ )) (Table 1). The network plot is presented in Figure 5D. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in SS, and details are illustrated in Figure 5E. Table 2 shows that only BXXD was superior to CQWD where the difference was statistically significant.

SUCRA probability results (Figure 5F, Table 3) showed that ZSXPB was mostly likely to become the best intervention to improve on SS. The ranking of thirteen interventions

is as follows: ZSXP (97.79%) > BXXD+WM (63.51%) > SMD+WM (55.6%) > BXXD (49.83%) > XSLJZD+WM (37.57%) > CQWD (33.06%) > WM (12.63%).

### GAS

13 RCTs altogether reported the GAS, with six different TCM decoctions and seven different types of treatments (WM vs. BXXD ( $n = 2$ ), WM vs. BXXD+WM ( $n = 1$ ), WM vs. XSLJZD+WM ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXP ( $n = 2$ ), WM vs. CQWD ( $n = 2$ ), WM vs. JPXZD ( $n = 4$ )) (Table 1). The network plot is presented in Figure 5G. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in GAS, and details are illustrated in Figure 5H. As shown in Table 2, only XSLJZD+WM was superior to WM alone, where the difference was statistically significant.

JPXZD was most likely to emerge as the best intervention for enhancing GAS, according to SUCRA probability results (Figure 5I, Table 3). The ranking of thirteen interventions is as follows: JPXZD (86.17%) > XSLJZD+WM (81.19%) > BXXD+WM (70.43%) > SMD+WM (62.98%) > BXXD (49.06%) > CQWD (28.67%) > ZSXP (18.51%) > WM (2.99%).

### Effect of TCM decoctions on gastric emptying

#### gastric emptying time

A total of 23 RCTs reported the gastric emptying time, including six types of TCM decoctions and nine types of interventions (WM vs. BXXD ( $n = 2$ ), WM vs. BXXD+WM ( $n = 4$ ), WM vs. XSLJZD ( $n = 3$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXP +WM ( $n = 1$ ), WM vs. CSLJD ( $n = 3$ ), WM vs. CSLJD+WM ( $n = 2$ ), WM vs. CQWD ( $n = 3$ ), WM vs. JPXZD ( $n = 4$ )) (Table 1). The network plot is presented in Figure 6A. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in gastric emptying time, and details are illustrated in Figure 6B. The superiority of all TCM decoctions over WM alone was statistically significant. Other decoctions' pairwise comparisons were statistically significant as well. The specifics are displayed in Table 2.

CSLJD+WM was found to be the most likely strategy to improve gastric emptying time in the SUCRA probability outcomes (Figure 6C, Table 3). Following is a ranking of the

thirteen interventions: CSLJD+WM (94.08%) > CSLJD (93.89%) > CQWD (77.61%) > BXXD+WM (66.87%) > XSLJZD (47.69%) > ZSXPDP+WM (30.22%) > BXXD (28.03%) > SMD+WM (27.55%) > JPXZD (22.26%) > WM (11.8%).

#### *emptying rate*

There were 9 RCTs in all that reported the emptying rate, five of which used treatments and seven of which used TCM decoctions (WM vs. BXXD ( $n = 2$ ), WM vs. XSLJZD+WM ( $n = 1$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXPDP ( $n = 3$ ), WM vs. CQWD ( $n = 2$ )) (Table 1). The network plot is presented in Figure 6D. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in gastric rate, and details are illustrated in Figure 6E. According to Table 2, only BXXD, CQWD, and SMD+WM outperformed WM alone in a statistically significant way. Additionally, we discovered that BXXD outperformed CQWD, and the difference was statistically significant.

ZSXPDP was the intervention that was most likely to succeed in raising the emptying rate, as shown by the SUCRA probability values (Figure 6F, Table 3). The following is a ranking of the thirteen interventions: ZSXPDP (98.35%) > XSLJZD+WM (72.73%) > SMD+WM (58.18%) > BXXD (47.77%) > CQWD (21.14%) > WM (1.82%).

#### *Adverse drug events*

A total of 19 RCTs reported the adverse drug event, including six types of TCM decoctions and ten types of interventions (WM vs. BXXD ( $n = 1$ ), WM vs. BXXD+WM ( $n = 2$ ), WM vs. XSLJZD ( $n = 2$ ), WM vs. XSLJZD+WM ( $n = 1$ ), WM vs. SMD ( $n = 4$ ), WM vs. SMD+WM ( $n = 1$ ), WM vs. ZSXPDP ( $n = 3$ ), WM vs. CSLJD ( $n = 2$ ), WM vs. CSLJD+WM ( $n = 1$ ), WM vs. CQWD ( $n = 2$ )) (Table 1). The network plot is presented in Figure 7A. Pairwise meta-analyses were conducted to compare TCM decoctions with WM in adverse events, and details are illustrated in Figure 7B. Table 2 shows that only BXXD, XSLJZD+WM, and ZSXPDP are different from WM, and the differences are statistically significant.

BXXD+WM was most likely to develop into the best intervention for enhancing clinical effects, according to SUCRA probability results (Figure 7C, Table 3). Following is a ranking of the thirteen interventions: ZSXPDP (92.72%) > XSLJZD+WM (90.74%) >



CSLJD (84.39%) > CSLJD+WM (59.24%) > CQWD (57.04%) > XSLJZD (41.85%) > SMD+WM (35.65%) > SMD (34.64%) > BXXD+WM (27.85%) > WM (25.41%) > BXXD (0.48%).

### ***Publication Bias***

**Figure 8** displays the results of a comparative adjusted funnel plot for each outcome. Different interventions were identified by different colored points. Clinical effects' funnel plot analysis in **Figure 8A** revealed that the majority of the effects were in the middle and that the left and right were essentially symmetrical, indicating that the included literature's publication bias was minimal. Funnel plot analysis of symptom scores was performed in **Figure 8B**, **Figure 8C**, **Figure 8D**, and **Figure 8E**, and funnel plot analysis of gastrointestinal hormones was performed in **Figure 8F**, **Figure 8 G**, and **Figure 8H**. The results showed that the left and right were not completely symmetrical, and most of them were in the upper part, suggesting that there was a certain publication bias. **Figure 8I**, **Figure 8J**, and **Figure 8K** performed funnel plot analysis of gastric emptying and adverse drug events, and the results showed that the left and right were not completely symmetrical. Most scattered points fell in the middle of the funnel plot and concentrated near the vertical line  $X=0$ , and some scattered points were distributed outside the funnel plot. This suggests that there is a certain publication bias. The reasons for bias may be related to the small sample size, incomplete clinical data, or the lack of blinding methods for data collection and processing.

### **DISCUSSION**

Chinese herbs and TCM decoctions were widely used in the treatment of diabetes and its related complications in ancient China, and a wealth of clinical experience has been accumulated<sup>[102, 103]</sup>. There was no direct comparative study on various TCM decoctions combined with WM. At present, no investigators have performed network meta-analysis on TCM decoctions to treat DGP. Our network meta-analysis overcomes the lack of comparable data in head-to-head trials by offering unified hierarchies of evidence for all TCM decoctions and TCM decoction combined with WM in adults with

diabetic gastroparesis illness. In the present study, the results show the probability of each intervention program on the different possible rankings, at the same time, different intervention programs were also compared.

A total of seven different types of TCM decoctions (BXXD, XSLJZD, SMD, ZSXP, CSLJD, CQWD, and JPXZD) were included in this study, and all the TCM decoctions included in this study have the effects of regulating the spleen and stomach and regulating the movement of Qi<sup>[104, 105]</sup>. Numerous articles and reviews have covered the molecular mechanisms used to explain how these TCM decoctions' active components regulate gastrointestinal motility<sup>[106, 107]</sup>. BXXD is a famous Chinese herbal medicine prescription, which contains seven kinds of herbal medicines, and is composed of Rhizoma Pinelliae, Radix Scutellariae, Rhizoma Zingiberis, Panax ginseng, Coptis chinensis, Fructus jujube and Radix glycyrrhizae<sup>[108]</sup>. BXXD can treat diabetic gastroparesis by inhibiting the apoptosis of gastric interstitial cells of Cajal (ICC), regulating the proportion of intestinal flora, inhibiting the release of inflammatory factors, regulating gastrointestinal hormones, reducing blood glucose and improving insulin resistance<sup>[109, 110]</sup>. XSLJZD contains <sup>5</sup> eight commonly used herbs Panax ginseng, Rhizoma atracylodes macrocephalus, Poria, Radix glycyrrhiza, Pericarpium citri reticulata, Pinellia tuber, Fructus amomi, and Radix Aucklandiae<sup>[111]</sup>. Moreover, XSLJZD has a bidirectional effect of excitation or inhibition of the gastrointestinal tract, which can promote the secretion of digestive juice and accelerate gastric emptying through gastrointestinal peristalsis<sup>[112-114]</sup>. SMD is mainly composed of Radix costumae, Aconitum Fructus, Fructus aurantii, and areca nut, which is the classic representative of traditional Chinese medicine used in gastrointestinal motility disorders<sup>[115, 116]</sup>. ZSXP is composed of Codonopsis, bitter orange, Atractylodes, Poria, Pinellia, Salvia miltiorrhiza, malt, and so on<sup>[117]</sup>. Combined with WM, ZSXP can effectively improve the level of gastrointestinal hormones and gastrointestinal function of patients, with fewer adverse reactions and drug safety, which is worthy of promotion<sup>[118, 119]</sup>. CSLJD is composed of Bupleurum, Paeony, Panax ginseng, Atractylodes atracylodes, Tangerine peel, Rhizoma Pinelliae, Poria cocos, glycyrrhiza Radix, etc. It can down-regulate the

levels of inflammatory factors TNF- $\alpha$  and IFN- $\gamma$ , and increase the contents of IL-1 $\beta$  and IL-10, indicating that it can regulate the inflammatory response of the intestine and play a good therapeutic effect<sup>[120, 121]</sup>. CQWD including Radix bupleurum, Scutellaria baicalensis, Rhizoma Pinelliae, bamboo mushroom, Citrus aurantium, Tangerine peel, Poria cocos, and glycyrrhiza radix, has been shown to reduce blood glucose, increase gastrointestinal excitability and relieve gastrointestinal spasm by altering the number of intestinal flora<sup>[122]</sup>. JPXZD is composed of Astragalus membranaceus, Atractylodes rhizoma, Rhizoma polygonatum, Codonopsis ginseng, Xiangfu Rhizoma, Atractylodes rhizoma, Bupleurum, turmeric rhizoma, Tujin rhizoma, Chuanxiong Rhizoma, and Rhizoma rhizoma rhizoma. This decoction can improve the plasma levels of SS and GAS, thereby reducing the inhibition of gastrointestinal motility and promoting the recovery of gastrointestinal motility<sup>[123]</sup>.

In order to select the best interventions based on TCM decoctions and <sup>1</sup> better guide clinical decision-making based on TCM, we conducted a detailed literature review to make the included literature more comprehensive and our results more credible. The inclusion and exclusion criteria for this study were very strict. The use of TCM decoction alone or in conjunction with TCM and WM for all of the study's interventions lessened the effects of potential heterogeneity and improved the reliability of the findings. The results of NMA and SUCRA showed that BXXD+WM was the most effective in improving the clinical effect and early satiety score with WM as the common control; the SMD+WM was most effective in improving nausea and vomiting scores and anorexia scores, bloating scores; the CSLJD was most effective for MOT, the ZSXPD was most effective in SS and increased emptying rate; the JPXZD was most effective in GAS; the CSLJD+WM was most effective in improving gastric emptying rate. The clinical recommendation of TCM decoction requires a series of multifaceted evaluation methods. In this study, clinical effects and symptom ratings were utilized in this study as the main outcome measures for a thorough review. The results show that BXXD+WM and SMD+WM are probably the two most effective therapies, followed by CSLJD, ZSXPD, JPXZD, CSLJD+WM, ZSXPD+WM and CQWD, XSLJZD+WM, BXXD

and SMD. Conclusions may vary depending on the main objectives and outcome indicators of the study. Previous meta-analysis studies have shown that oral ZSXPB is effective in the treatment of adult DGP and has less adverse effects<sup>[124]</sup>, which is consistent with the results of our study.

In terms of safety, 18 studies reported the occurrence of adverse reactions, all of which were mild, mainly manifested as diarrhea, fatigue, dizziness, drowsy, *etc.* No drug was stopped because of adverse reactions or adverse events, and the adverse reactions or adverse events <sup>3</sup> in the observation group were less than those in the control group, indicating that TCM decoctions combined with WM in the treatment of DGP are safe.

### **Limitations**

However, there are some limitations to our study. First off, the included RCTs had poor overall quality, and the majority of them did not provide detailed information on blinding, allocation concealment, selective reporting, and procedure registration. These restrictions might increase the chance of bias. Second, there were few direct comparisons between various combination therapies, and the majority of the study groups included in this analysis were indirect comparisons. Additionally, the accuracy of the results will be somewhat constrained because all of the studies that made up this study were carried out in China. The findings of this meta-analysis should be interpreted carefully given these restrictions. The standard of clinical research as a whole has to be raised as a result of these constraints. It is advised that clinical trials be carried out precisely following the most recent CONSORT recommendations to enhance the reporting quality of RCTs<sup>[125]</sup>.

### **Future directions**

TCM combined with WM effectively improves the total effective rate, cure rate, and gastric emptying function in DGP patients without increasing the risk of adverse reactions, and the curative effect is safe and reliable. These findings underpin the clinical use of TCM combined with WM in the treatment of DGP. The results of this review may help develop novel treatment strategies for DGP in the future.

## **CONCLUSION**

In conclusion, the results of our meta-analysis suggest that qualified TCM decoction combined with WM is more effective than WM alone in treating patients with DGP. The BXXD+WM was the most effective in improving early satiety scores, and the SMD+WM was most effective in improving nausea and vomiting scores, anorexia scores, and bloating scores. The safety of these TCM decoctions needs to be further observed. Nevertheless, this finding still needs to be further verified, and due to various limitations, further high-quality, large-sample, double-blind, multi-center RCTs are needed.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Diabetes-related gastroparesis (DGP) has a negative impact on the quality of life of patients. Although conventional western medicine gastric motility drugs like domperidone and metoclopramide can alleviate gastrointestinal pain, they also have some unfavorable side effects, and patients are easy to relapse after drug withdrawal.

### ***Research motivation***

The gastrointestinal symptoms in DGP patients can be improved by several Traditional Chinese Medicine (TCM) decoctions, which have been shown to be effective in treating the disease.

### ***Research objectives***

The goal of this study is to analyze the efficacy of several TCM decoctions in the treatment of DGP based on Bayesian network meta-analysis.

### ***Research methods***

PubMed, Embase, Cochrane Library, Web of Science, CNKI, CBM, Wanfang, and VIP were searched from the databases' inception to September 17, 2022 to gather

randomized controlled trials (RCTs) about TCM decoctions for DGP. The main outcomes were symptom scores and clinical effects. The secondary outcomes included MOT, SS, GAS, gastric emptying rate, gastric emptying time, and adverse medication events.

### ***Research results***

NMA and SUCRA studies demonstrated that, using western medicine (WM) as a common control, the Banxia Xiexin Decoction (BXXD)+WM was the most effective in the improvement of early satiety scores; the Simo decoction (SMD)+WM was the most effective in improving nausea and vomiting scores, anorexia scores, and bloating scores; the Chaishao Liujunzi Decoction (CSLJD) was the most effective for MOT; the Zhishi Xiaopi Decoction (ZSXPD) was the most effective for improving SS and emptying rate; the Jianpi Xiaozhi Decoction (JPXZD) was the most effective for GAS; and the CSLJD+WM was the most effective in improving gastric emptying time.

### ***Research conclusions***

TCM decoction combined with WM is more effective than WM alone in treating patients with DGP.

### ***Research perspectives***

These NMA findings may aid in the development of DGP treatments and, as a consequence, enhance treatment effectiveness and patient wellbeing.

7

## **ACKNOWLEDGEMENTS**

We would like to thank the researchers and study participants for their contributions.



7%

SIMILARITY INDEX

### PRIMARY SOURCES

- 1

[www.frontiersin.org](http://www.frontiersin.org)  
Internet

199 words — 3%
- 2

Do, D.. "3D deformation models for the automated manufacture of composite components", Composites Part A, 200609  
Crossref

93 words — 1%
- 3

[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)  
Internet

55 words — 1%
- 4

Yuchen He, Hongyi He, Xiaoxiao Li, Guanghua Lei, Dongxing Xie, Yilun Wang. "Intra-articular magnesium plus bupivacaine is the most effective and safe for post-operative analgesic option following knee arthroscopy: a network meta-analysis", Arthroscopy: The Journal of Arthroscopic & Related Surgery, 2022  
Crossref

22 words — < 1%
- 5

Tian, Jia-Xing. "Xiangshaliujunzi Decoction for the treatment of diabetic gastroparesis: A systematic review", World Journal of Gastroenterology, 2014.  
Crossref

20 words — < 1%
- 6

[link.springer.com](http://link.springer.com)  
Internet

17 words — < 1%

---

7 Hao Gou, Ya Wang, Yan Liu, Cai Peng, Weijia He, Xiangjuan Sun. "Efficacy of vitamin D supplementation on child and adolescent overweight/obesity: a systematic review and meta-analysis of randomized controlled trials", European Journal of Pediatrics, 2022  
Crossref 14 words — < 1%

---

8 open.alberta.ca  
Internet 14 words — < 1%

---

9 pubmed.ncbi.nlm.nih.gov  
Internet 12 words — < 1%

---

---

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS