Effectiveness of Chinese herbal medicine Zhi Shi Xiao Pi Wan on adult diabetic gastroparesis: a systematic review and meta-analysis [version 1; peer review: awaiting peer review]

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Abstract

Chinese herbal medicine formula Zhi Shi Xiao Pi Wan (ZSPXW) is commonly used for gastrointestinal diseases. Previous research showed ZSPXW also suggested for diabetic gastroparesis (DGP) treatment. The aim of this study is to evaluate the effectiveness and safety of ZSPXW in treating adult DGP. Six databases, including Pubmed, Cochrane Library, EMBASE, China Network Knowledge Infrastructure (CNKI), Wanfang, and Chinese Scientific Journals were searched from their inceptions to November 2021. Only randomized control trials (RCTs) evaluating ZSPXW for adult DGP were included in this review. Two investigators independently evaluated and extracted the data. Total 11 RCTs and 802 participants were included in the review. In these studies, ZSPXW was compared with oral cisapride, domperidone, and mosapride citrate tablets. The outcomes of effective rate, stomach emptying time, stomach emptying rate,
motilin, gastrin, somatostatin, vasoactive intestinal peptide, and
adverse events were analyzed. The effective rate of ZSXPW is higher
than other pharmacotherapies (RR: 1.24, 95% CI [1.16, 1.32]). The
results showed intervention group has better effect on gastric
emptying time used (MD: -0.51, 95% CI [-0.81, -0.21]) and gastric
eating rate (MD: 19.32, 95% CI [12.82, 25.83]) than the comparison
group. The meta-analysis results showed ZSXPW is effective on adult
DGP.

Keywords
Zhi Shi Xiao Pi Wan, Chinese herbal medicine formula, Diabetic
gastroparesis, Systematic review, Meta analysis
Introduction
Diabetes as a significant global challenge to the health and wellbeing of individual, family, and countries. There are a lot of the costs spend on the treatment and prevention of diabetes. A data from International Diabetes Federation (IDF) Atlas 10th edition showed there is a continued global increase in diabetes prevalence. The total number of adults with diabetes is 537 million in year 2021, it is a rise of 16% (74 million) compare with the data in year 2019.1 The unstable glycemia control will cost a lot of money on the treatment and cause diabetes related complications such as diabetic retinopathy, diabetic kidney disease, diabetic neuropathy, etc. They cause the quality of life decrease and may threaten the life of patients.2,3

Diabetes gastroparesis (DGP) is one of the common complications of diabetes. Long-standing type 1 and 2 diabetes mellitus may affect motility and function of the gastrointestinal tract. The symptoms included early satiety, postprandial fullness, nausea, vomiting, belching, and bloating.4,5 The pathogenesis of DGP is still unclear. The causes of DGP include poor glycemia control, sympathetic vagal neuropathy, Cajal interstitial cell abnormalities, and loss of neuronal nitric oxide synthase (nNOS).6,7 A study showed that acute hyperglycemia affects gastric functions including inhibition of antral contractility and delayed gastric emptying.8,9 Another study showed insulin-induced hypoglycemia could happened accelerate of gastric emptying.10 The principal goals for the treatment of DGP are to correct fluid, electrolyte, and nutritional deficiency, and reduce the symptoms. One of the most important targets in DGP management is change of habit. For example, patients are encouraged to eat more often with less amount or a smaller size of food.11

Zhi Shi Xiao Pi Wan (ZSXPW) is a common Chinese herbal medicine formula for gastric diseases. In transitional Chinese medicine clinical application, it can be used while patients have the symptoms of “Food Stagnation” such as poor appetite, stomach bloating, constipation, etc. The main formation of ZSXPW includes Shengjiang (Zingiberis rhizome Recens), Gancao (Glycyrrhiza radix et rhizoma), Maiya (Hordei fructus germinatus), Fuling (Poria), Baizhu (Atractylodes macrocephala rhizoma), Banxia (Pinellia rhizoma), Renshen (Ginseng radix et rhizoma), Houpu (Magnolia officinalis cortex), Zhishi (Aurantii Fructus Immaturus), and Huanglian (Coptidis rhizoma).12,13 A previous study has shown that ZSXPW alleviates the clinical symptoms such as early satiation, postprandial fullness, nausea, etc.13 To date there are only research on the effect of ZSXPW on treatment of DGP. The knowledge concerning the ZSXPW and DGP is necessary for treatment and management. Therefore, to provide evidence based practical information for physicians, this systematic review and meta-analysis of ZSXPW and DGP outcomes conducted.

Method
The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021283873).

Study selection criteria
This systematic review was designed to evaluate the effectiveness and safety of Chinese herbal medicine formula ZSXPW for DGP. No limits on language and publication type were placed on study selection. The participants included studies were adult DGP patients aged 18 years old and above. The included studies were RCTs comparing oral ZSXPW in any preparation forms as the recommended treatment for DGP. If ZSXPW used with other Chinese herbs only the studies using ZSXPW as main formula and other herbs as additional modification were included.

The included studies needed to report at least one of the outcomes, which were effectiveness of the treatment or stomach empty rate; secondary outcomes were the level of Motilin (MOT), gastrin (GAS), somatostatin (SS), vasoactive intestinal peptide (VIP), and adverse events (AEs). Studies with incomplete information were excluded.

Search strategy
The references were searched in six databases, including Pubmed, Cochrane Library, EMBASE, China Network Knowledge Infrastructure (CNKI), Wanfang Database, and Chinese Scientific Journals Database. Abstracts and full texts were read by two members (CJW and PT) independently according to the selection criteria. The disagreement was solved by the third member (RT).

Methodological assessment
Two members assessed the methodological quality of included studies independently by using the risk of bias tools. Disagreements were solved through discussion with the third member. Each subject was assessed as low, unclear, or high risk, with reasons and proof to support the judgements.

Data extraction
Two members independently undertook data extraction via a standardized data collection form. The information such as 1st author, year of publication, study design, sample size, comparator group, study setting, outcome measured,
methodology for statistical data analysis, and publication characteristic were extracted and recorded. Any divergence on data extraction were judged by the two reviewers (CJW and PT). The third reviewer checked the final results of the data extraction and provided arbitration for further disagreements.

Risk of bias assessment
The Cochrane Handbook for Systematic Reviews of Interventions was used for assessment of the quality of randomized studies. Any discrepancies in the assessment of risk of bias were resolved by discussion and an arbiter was consulted if necessary.

Statistical analysis
Review Manager 5.4 (RevMan 5.4) software was used to perform meta-analysis. Studies were grouped for analysis according to their comparisons and outcome. Dichotomous data were expressed as risk ratio (RR) and continuous data were expressed as mean difference (MD), both with 95% confidence intervals (CI). Subgroup analysis was performed based on the type of pharmacotherapy medicine used on the compare group and treatment duration. Publication bias was assessed using a funnel plot.

Results
In total 976 studies were found from six databases, 80 duplicated and 875 studies were excluded after screening the titles and abstracts. Ten studies were further excluded for the reason of not being proper RCTs, not standard pharmacotherapy used in control group, intervention group not ZSXPW, etc. Eleven studies were included for meta-analysis after full text reading. All trials were conducted in China. The flow chart of literature retrieval and screening is shown in Figure 1.

Figure 1. PRISMA flow chart of study selection process.
Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication year, Country</th>
<th>Number of participants</th>
<th>Gender (M/F)</th>
<th>Participant’s age (Mean SD, Range)</th>
<th>Duration of diabetes (Mean SD, Range)</th>
<th>Treatment duration</th>
<th>Intervention</th>
<th>Control</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao Xue Qing</td>
<td>2003, China</td>
<td>I: 46 C: 46</td>
<td>I: 28/18 C: 30/16</td>
<td>I: 20 – 70 C: 18 – 72</td>
<td>I: 5 – 22 C: 5 – 24</td>
<td>30 days</td>
<td>Modification Zhishixiaopi decoction, 200ml/time, 3 times/day, before meal</td>
<td>Cisapride tablets, 10mg, 3 times/day, before meal</td>
<td>None</td>
</tr>
<tr>
<td>Wu Zhen Dong</td>
<td>2005, China</td>
<td>I: 28 C: 24</td>
<td>I: 16/12 C: 10/14</td>
<td>I: 65.5, 40 – 73 C: 64.1, 42 – 72</td>
<td>None</td>
<td>4 weeks</td>
<td>Basic treatment for diabetes, modification Zhishixiaopi decoction, 200ml/time, 3 times/day, before meal</td>
<td>Basic treatment for diabetes, cisapride tablet 20mg, 3 times/day, before meal</td>
<td>None</td>
</tr>
<tr>
<td>Dong Wen Ling</td>
<td>2009, China</td>
<td>I: 32 C: 32</td>
<td>I: 9/23 C: 7/25</td>
<td>I: 59.6, 41 – 76 C: 55.7, 39 – 77</td>
<td>I: 2 – 15 C: 1.5 – 15</td>
<td>1 month</td>
<td>Modification Zhishixiaopi decoction, 250ml/time, 2 times/day, after meal</td>
<td>Domperidone tablets 10mg/time, 3 times/day, before meal</td>
<td>None</td>
</tr>
<tr>
<td>Yang Li Hong</td>
<td>2010, China</td>
<td>I: 30 C: 30</td>
<td>I: 20/10 C: 19/11</td>
<td>I: 56.73 ± 14.14, 33 ~ 74 C: 56.76 ± 14.21, 34 ~ 75</td>
<td>I: 7.57 ± 2.48 C: 7.85 ± 2.74</td>
<td>4 weeks</td>
<td>Basic treatment for diabetes, modification of Zhishixiaopi decoction, 200ml/time, 2 times/day</td>
<td>Basic treatment for diabetes, mosapride 5mg, 3 times/day, before meal</td>
<td>I: None C: Breast tenderness 4, galactorrhea 1</td>
</tr>
<tr>
<td>Zhao Yun Yan</td>
<td>2010, China</td>
<td>I: 36 C: 32 5 dropouts</td>
<td>I: 15/18 C: 13/17</td>
<td>I: 63.20 ± 6.93, 52 ~ 75 C: 61.90 ± 6.41, 48 ~ 73</td>
<td>I: 16.30 ± 7.52 C: 18.10 ± 7.94</td>
<td>4 weeks</td>
<td>Modification Zhishixiaopi decoction, 200ml/time, 2 times/day, after meal</td>
<td>Domperidone tablets 10mg, 3 times/day, before meal</td>
<td>I: None C: Breast tenderness 2, galactorrhea 1</td>
</tr>
<tr>
<td>Deng Han Jun</td>
<td>2012, China</td>
<td>I: 32 C: 32</td>
<td>I: 20/12 C: 21/11</td>
<td>I: 49.2 ~ 76.6 C: 48.6 ~ 76.2</td>
<td>I: 6.8 ~ 11.6 C: 6.5 ~ 11.4</td>
<td>60 days</td>
<td>Modification Zhishixiaopi decoction, 150ml/time, 3 times/day, after meal</td>
<td>Cisapride tablets 10mg, 3 times/day, before meal</td>
<td>None</td>
</tr>
<tr>
<td>Lu Xue Ying</td>
<td>2012, China</td>
<td>I: 59 C: 59</td>
<td>I: 34/25 C: 31/28</td>
<td>I: 56.42 ± 4.96, 45 ~ 72 C: 54.63 ± 4.48, 33 ~ 67</td>
<td>I: 6.81 ± 2.57 C: 5.97 ± 2.75</td>
<td>4 weeks</td>
<td>Modification Zhishixiaopi decoction, 200ml/time, 2 times/day</td>
<td>Domperidone tablets 10mg, 3 times/day</td>
<td>None</td>
</tr>
<tr>
<td>Guo Xiao</td>
<td>2015, China</td>
<td>I: 24 C: 25</td>
<td>I: 14/10 C: 14/11</td>
<td>I: 57.9 ± 4.72 C: 59.2 ± 6.41</td>
<td>I: 5.27 ± 5.17 C: 5.91 ± 5.42</td>
<td>2 weeks</td>
<td>Modification Zhishixiaopi decoction, 200ml/time, 2 times/day, after meal</td>
<td>Mosapride citrate tablets 5mg, 3 times/day, before meal</td>
<td>None</td>
</tr>
<tr>
<td>First author</td>
<td>Publication year, Country</td>
<td>Number of participants</td>
<td>Gender (M/F)</td>
<td>Participant’s age (Mean SD, Range)</td>
<td>Duration of diabetes (Mean SD, Range)</td>
<td>Treatment duration</td>
<td>Intervention</td>
<td>Control</td>
<td>Adverse events</td>
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<tr>
<td>Liu Ning Zhou</td>
<td>2017, China</td>
<td>I: 32 C: 34</td>
<td>I: 19/13 C: 20/14</td>
<td>I: 42.67 ± 6.52, 31 – 65 C: 44.55 ± 5.78, 33 – 65</td>
<td>I: 16.02 ± 7.12 months C: 15.61 ± 6.66 months</td>
<td>4 weeks</td>
<td>Basic treatment for diabetes, domperidone tablets 10mg (3 times / day, before meal) modification Zhishixiaopi decoction (2 times / day)</td>
<td>Basic treatment for diabetes, domperidone tablets 10mg, 3 times / day, before meal</td>
<td>None</td>
</tr>
<tr>
<td>Xu Bao Shi</td>
<td>2020, China</td>
<td>I: 35 C: 35</td>
<td>I: 18/17 C: 19/16</td>
<td>I: 54.05 ± 6.73, 37 – 75 C: 54.12 ± 6.91, 38 – 76</td>
<td>None</td>
<td>1 month</td>
<td>Modification Zhishixiaopi decoction, 200ml / time, 2 times / day</td>
<td>Mosapride citrate tablets 5mg, 3 times / day, before meal</td>
<td>I: Palpitation 1, diarrhea 1, dizzy 1 C: Palpitation 2, hypokalemia 1, diarrhea 2, dizzy 3</td>
</tr>
<tr>
<td>Yang Fei</td>
<td>2020, China</td>
<td>I: 51 C: 50</td>
<td>None</td>
<td>I: 54.58 ± 4.06 C: 54.32 ± 4.01</td>
<td>I: 17.13 months C: 17.76 months</td>
<td>1 month</td>
<td>Modification Zhishixiaopi decoction, 200ml / time, 2 times / day</td>
<td>Mosapride citrate tablets</td>
<td>I: Galactorrhea 1, hypersomnia 2, breast tenderness 1, dryness mouth 1 C: Galactorrhea 1, hypersomnia 1, breast tenderness 1, mouth dryness 1</td>
</tr>
</tbody>
</table>
Included studies characteristics
All 11 studies used the modification of ZSXPW as treatment, the modifications are based on the original formula of ZSXPW. The preparation of ZSXPW was in decoctions form. The modification of ZSXPW decoction used in 11 trials, cisapride was used in 3 trials, domperidone used in 4 trials, and mosapride citrate used in 4 trials. Table 1 lists the detail information of all included studies. The treatment duration in range of 14 days to 60 days.

Participants
In total there were 804 participants with DGP involved in 11 RCTs, 5 participants drop out. All participants aged between 20 to 76 years old. Ten studies mentioned the gender of participants, there were 377 male participants and 321 female participants. The participants were divided into 6 groups ZSXPW group (n = 253), ZSXPW with domperidone group (n = 32), ZSXPW with mosapride citrate group (n = 110), domperidone group (n =157), mosapride citrate group (n = 140), and cisapride group (n = 102).

Outcomes
The primary outcome measures of clinical effect were report in 10 trials,15–23,25 2 trials reported time used on stomach emptying,20,23 and 3 trials reported the stomach emptying rate.18,19,22 The secondary outcomes were reported in 5 trials, which included motilin, gastrin, somastostatin, and vasoactive intestinal peptide rate.19,21,22,24,25 Adverse events were reported in 4 trials.18,19,23,25

Risk of bias assessment
All trials announced randomization, four studies were assessed as “low risk” since they used random number for randomization,19,22,24,25 other studies didn’t report the method for randomization. However, no details were found in random allocation concealment, blinding of participants, personnel, and outcome assessors.

Clinical effectiveness
There were 10 trials reported the clinical effective rate of the treatment. The clinical effect rate judged according to the stomach function rate and symptoms after treatment as shown in Figure 2. The analysis results show ZSXPW is more effective than another pharmacotherapy (RR: 1.24, 95% CI [1.16, 1.32], I² = 0%, P < 0.0001). The 3 trials were evaluated the clinical effectiveness of ZSXPW with cisapride,15,16,20 the results showed the clinical effectiveness of ZSXPW is 1.25 times more effective (3 trials, n = 208, RR: 1.25, 95% CI [1.09, 1.43], I² = 0%, P = 0.001). 4 trials evaluated the clinical effectiveness of ZSXPW with domperidone,17,19,21,23 the analysis results showed the clinical effectiveness of ZSXPW is 1.23 times more effective (4 trials, n = 314, RR: 1.23, 95% CI [1.12, 1.36], I² = 0%, P < 0.0001). 1 trial compared ZSXPW decoction to mosapride citrate, the result showed ZSXPW is more effective in clinical application (1 trial, n = 60, RR: 1.26, 95% CI [1.02,1.55]).18 2 trials showed the combination of ZSXPW and mosapride citrate is more effective than single used mosapride citrate (2 trials, n = 150, RR: 1.21, 95% CI [1.08, 1.37], I² = 0%, P = 0.002).22,25

Time used for gastric emptying
Two trials reported the time used for gastric emptying,20,23 The result showed patients in ZSXPW group spend less time on gastric emptying (2 trials, n = 130, MD: -0.51, 95% CI [-0.81, -0.21], I² = 84%, P = 0.0008). The used time for stomach emptying was shown in Figure 3.

Gastric emptying rate
Gastric emptying rate was reported by 3 trials.18,19,22 The results showed patients with ZSXPW had a higher gastric emptying rate than the control group (3 trials, n = 172, MD: 19.32, 95% CI [12.82, 25.83], I² = 0%, P < 0.00001). The gastric emptying rate was shown in Figure 3.

Sub-outcomes
Motilin
There were 5 studies reported the motilin rate and 3 trials compared combination of ZSXPW with mosapride citrate to mosapride citrate single used. Two trials showed the motilin rate is lower in ZSXPW group22,24 and 1 trial showed the motilin rate is lower in control group.25 The total result showed the motilin rate is lower in control groups (3 trials, n = 220, MD: 0.40, 95% CI [-6.32, 7.12], P = 0.91). Two trials compared ZSXPW to domperidone.19,21 One trial showed the motilin rate is lower in ZSXPW group,19 another trial showed the motilin rate is lower in control group.22 The total result showed control group had lesser motilin rate (2 trials, n = 182, MD: 25.56, 95% CI [10.37, 40.76], P = 0.0010). The total rate of motilin is less in control group (5 trials, n = 401, MD: 4.52, 95% CI [-1.63,10.66], P = 0.15). The motilin rate was shown in Figure 4.
Five studies reported the somatostatin rate and 3 trials compared combination of ZSXPW with mosapride citrate to mosapride citrate single used. One trial showed the somatostatin rate is lower in ZSXPW group,25 and 2 trials showed the somatostatin rate is lower in control group.22,24 The total result showed the somatostatin rate is lower in ZSXPW groups, and the difference was statistically significant (3 trials, n = 220, MD: -27.05, 95% CI: [-28.05, -26.04], P < 0.00001). Two trials compared ZSXPW to domperidone. Both trials showed the somatostatin rate is lower in ZSXPW group.19,21 The total result showed ZSXPW group had lesser motilin rate and the difference was statistically significant (2 trials, n = 181, MD: -43.17, 95% CI [-49.80, -36.54], P < 0.00001). The total rate of somatostatin rate is less in ZSXPW group (5 trials, n = 401, MD: -27.41, 95% CI [-28.40, -26.41], P < 0.00001). The somatostatin rate was shown in Figure 4.

Figure 2. Forest plot of clinical effect.
Gastrin

There were five studies reported the Gastrin rate and 3 trials compared combination of ZSXPW with mosapride citrate to mosapride citrate single used. Two trials showed the motilin rate is lower in ZSXPW group22,24 and 1 trial showed the motilin rate is lower in control group.25 The total result showed the motilin rate is lower in control groups (3 trials, n = 220, MD: 7.78, 95% CI [6.76, 8.81], P < 0.00001). The 2 trials compared ZSXPW to domperidone. Both trials showed the motilin rate is lower in control group.19,21 The result showed control group had lesser motilin rate (2 trials, n = 182, MD: 11.62, 95% CI [5.10, 18.15], P = 0.0005). The total rate of gastrin is lower in control group (5 trials, n = 401, MD: 7.87, 95% CI [6.86, 8.89], P < 0.00001). The gastrin rate was shown in Figure 4.

Vasoactive intestinal peptide

Three studies reported the vasoactive intestinal peptide rate.19,21,24 The results showed control group had lesser vasoactive intestinal peptide rate (3 trials, n = 151, MD: -7.66, 95% CI [-9.91, -5.40], P < 0.00001). The vasoactive intestinal peptide rate was shown in Figure 4.

Adverse event

Four studies reported adverse events happened during the research.18,19,24,25 The adverse events include breast tenderness, galactorrhea, palpitation, diarrhea, dizzy, hypokalemia, diarrhea, hypersonmia, and mouth dryness. The analysis result showed ZSXPW group had less adverse events than control group and the difference was statistically significant (4 trials, RR: 0.42, 95% CI [0.20, 0.89], P = 0.02). The adverse events related to ZSXPW treatment was shown in Figure 5.

Publication bias

Two studies were assessed as “low risk” for “random sequence generation” since the random number used for randomization,19,22 other studies were assessed as “unclear” since they only mention about random without the method. All studies were “unclear risk” for allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. All studies were “low risk” incomplete outcome data because of no dropouts happened and one studies mention about dropout.19 All studies assessed as “low risk” for selective reporting and other bias. The funnel plot about publication bias was shown in Figure 6.

Discussion

The results of this review showed ZSXPW is effective on the treatment of DGP. The clinical effect, stomach emptying time, and stomach emptying rate (P < 0.05). The main compound of Ban Xia is Alkaloid. Study showed Ban Xia can relieve the sensation of vomit and nausea by inhibiting the vomiting center and vagus nerve.26 Ren Shen, Fu Ling, Bai Zhu, and Gan Cao is a combination of Si Jun Zi Tang (SJZT), which is a commonly used herbal medicine formula in clinical application. SJZT has the effects improving the immune function of the intestinal mucosa and repairing the damaged intestinal mucosa. This might relate to the increase of CD4+ cells and the reduction of the proportion of CD3+ and CD8+T cells.27
(a) Motilin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>IV, Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo Xie 2015</td>
<td>326.52</td>
<td>47.12</td>
<td>279.35</td>
<td>&lt;0.0001</td>
<td>10.44-28.87</td>
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<tr>
<td>Xu Bo Sh 2020</td>
<td>319.72</td>
<td>75.63</td>
<td>244.09</td>
<td>&lt;0.0001</td>
<td>13.64-28.70</td>
</tr>
<tr>
<td>Yang Fei 2020</td>
<td>327.65</td>
<td>23.18</td>
<td>304.48</td>
<td>0.0001</td>
<td>13.11-28.70</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>110</td>
<td>90.63</td>
<td>199.37</td>
<td>0.0001</td>
<td>4.32-7.12</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.12 (P = 0.90)

(b) Somatostatin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>IV, Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo Xie 2015</td>
<td>54.17</td>
<td>74</td>
<td>39.32</td>
<td>&lt;0.0001</td>
<td>13.03-14.57</td>
</tr>
<tr>
<td>Yang Fei 2020</td>
<td>12.85</td>
<td>3.12</td>
<td>9.73</td>
<td>0.005</td>
<td>3.17-16.88</td>
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<tr>
<td>Xiao Sh 2020</td>
<td>87.15</td>
<td>10.03</td>
<td>77.12</td>
<td>0.005</td>
<td>11.19-16.87</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>110</td>
<td>90.63</td>
<td>199.37</td>
<td>0.0001</td>
<td>4.32-7.12</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.33 (P = 0.001)

(c) Gastrin

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>IV, Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo Xie 2015</td>
<td>92.42</td>
<td>23.22</td>
<td>69.22</td>
<td>&lt;0.0001</td>
<td>25.77-118.7</td>
</tr>
<tr>
<td>Yang Fei 2020</td>
<td>66.42</td>
<td>3.54</td>
<td>62.88</td>
<td>0.0001</td>
<td>5.18-118.7</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>110</td>
<td>90.63</td>
<td>199.37</td>
<td>0.0001</td>
<td>4.32-7.12</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 1.26 (P = 0.002)

(d) Vasoactive Intestinal Peptide

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>IV, Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guo Xie 2015</td>
<td>21.37</td>
<td>7.46</td>
<td>13.91</td>
<td>&lt;0.0001</td>
<td>3.32-18.5</td>
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<td>Xiao Sh 2020</td>
<td>21.98</td>
<td>7.45</td>
<td>14.53</td>
<td>0.0001</td>
<td>3.32-18.5</td>
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<tr>
<td>Total (95% CI)</td>
<td>127</td>
<td>124.68</td>
<td>199.37</td>
<td>0.0001</td>
<td>4.64-7.46</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 6.66 (P = 0.0001)

Figure 4. a-Motilin rate; b-Somatostatin rate; c-Gastrin rate; d-Vasoactive intestinal peptide.

Figure 5. Adverse events related to ZSXPW treatment.
Motilin is less in control group (P > 0.05) and Somatostatin is less in ZSXPW group (P < 0.05). The result showed that ZSXPW might can improve the contraction of the gastrointestinal tract and accelerate gastric emptying. ZSXPW may have the better effects on stomach emptying because of the effect of improving cholinergic nerve, improving gastric electrical activity, increase motilin rate, and decrease gastrin rate.28,29 In a study showed the neuroprotective effect of ZSXPW against autophagy-induced damage and apoptosis occurs mainly through the block able of mTOR signaling pathway.13 Zhi Shi is the main herbs in ZSXPW, and the main compound is p-synephrine.30 Studies showed that Zhi Shi has the effect on small intestine electric activity, smooth muscle contraction, antispasmodic, stimulate intestine increase intestinal peristalsis, and improve small intestine emptying activity.31,32 The active compounds of Bai Zhu are sesquiterpenoids, polysaccharides and polyacetylenes. Bai Zhu can be used to promote the gastrointestinal motility, which mainly mediated by cholinergic receptors and α receptors.33

Vasoactive intestinal peptide is less in the ZSXPW group, while gastrin is more in the control group (P < 0.05). These results showed that ZSXPW can improve digestion by stimulating the smooth muscle and accelerating the digestion activity. The major compounds of Hou Pu are polyphenolic neolignans, magnolol, and honokiol.34–36 Hou Pu showed the effect of treating gastrointestinal disorder by the antispasmodic effect and relaxing gastrointestinal tract smooth muscle.37,38

The adverse events which appeared in all studies included breast tenderness, galactorrhea, palpitation, etc. The analysis results showed ZSXPW had less adverse events than the control group (P<0.05). Studies have been done to determine the safety issues of herbs in ZSXPW and the results showed they are safe in clinical application in the certain dosage.39–45

Strengths and limitations
This review included the most recent clinical research following methodology recommended by the Cochrane Handbook.46 This review focus on ZSXPW treating adult DGP to recommended pharmacotherapy. The outcome measures included clinical effectiveness, time used for stomach empty, and stomach emptying rate

However, the review results didn’t include the control of blood glucose, only with the clinical effectiveness and stomach emptying function as the main outcome. The included studies were all conducted in China and published in Chinese language although all the majority databases had been searched. The long-term effects of ZSXPW were uncertain due to the lack of follow-up phase. Lack of the studies to determine the effect of ZSXPW to motilin, gastrin, somatostatin, and vasoactive intestinal peptide.

Conclusion
Oral ZSXPW has an effect on adult DGP treatment and had less adverse effects. More RCTs following rigorous methodology and using internally well-accepted outcome measures are needed to further define the effectiveness of ZSXPW.
**Data availability statement**

**Underlying data**

All data underlying the results are available as part of the article and no additional source data are required.

**Extended data**


This project contains the following extended data:

- Table 1: Characteristics of included studies
- Figure 1: PRISMA Flow chart of study selection process.
- Figure 2. Forest plot of clinical effect. (a) All studies; (b) 1.2.1 ZSXPW group compare with cisapride group; 1.2.2 ZSXPW group compare with domperidone group; 1.2.3 ZSXPW plus mosapride citrate compare with mosapride citrate.
- Figure 3: (a) Used time for stomach emptying. (b) Stomach emptying rate.
- Figure 4: (a) Motilin rate (b) Somatostatin rate (c) Gastrin rate (d) Vasoactive intestinal peptide
- Figure 5: Adverse events related to ZSXPW treatment
- Figure 6: Funnel plot: ZSXPW compare with cisapride; domperidone; mosapride citrate; ZSXPW plus mosapride citrate combination compare with mosapride citrate tablet.

**Reporting guidelines**


Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**References**


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