Ji et al.: Efficacy of Salvia-ligustrazine in PIH treatment

The efficacy of Salvia-ligustrazine and Ligustrazine in treating gestational hypertension: A systematic review and meta-analysis

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Data availability: All data generated during the study are presented in the article/Supplementary Material.
ABSTRACT

Pregnancy-induced hypertension syndrome (PIH), a prevalent and critical condition, has garnered increasing attention due to its significant impact on maternal and fetal health outcomes. The conventional treatment approaches rely on magnesium sulfate and various antihypertensive drugs; however, the clinical efficacy of these treatments is limited, highlighting the need to explore alternative avenues for improvement. Recently, a growing number of clinical studies have investigated the use of Salvia-ligustrazine or Ligustrazine in combination with conventional therapy. A comprehensive synthesis and critical analysis of these studies is necessary to evaluate the efficacy and safety of Salvia-ligustrazine or Ligustrazine in treating PIH. We sought all articles published prior to December 2, 2023, from seven databases to identify randomized controlled trials (RCTs) that involved traditional Chinese medicine Salvia-ligustrazine or Ligustrazine in combination with Western medicines for the conventional treatment of PIH, according to predefined inclusion criteria. The studies were assessed using the Cochrane Risk of Bias tool (ROB2.0), and meta-analyses were conducted using Stata 15.0 statistical software. We analyzed 47 RCTs encompassing 4,517 patients. The results demonstrated that combining Salvia-ligustrazine or Ligustrazine with Western medications was more efficacious than using Western medications alone. This combination improved the overall response rate, reduced the incidence of adverse pregnancy outcomes for mothers and infants, and decreased the occurrence of side effects associated with PIH treatment. While we evaluated the efficacy of traditional Chinese medicine injections of Salvia-ligustrazine or Ligustrazine alongside conventional Western treatments, our conclusions must be considered provisional due to potential bias and the limited availability of RCTs.

Keywords: Pregnancy-induced hypertension syndrome (PIH), Salvia-ligustrazine, Ligustrazine, meta-analysis.
INTRODUCTION

PIH is one of the most prevalent obstetric conditions that cause high blood pressure, proteinuria, and other clinical signs that can endanger maternal and infant health and, in severe cases like eclampsia, can lead to coma, seizures, and death(1). Conventional therapy currently consists mainly of magnesium sulfate, with symptomatic therapy, sedation hypotension, etc. But it has low efficacy and side effects. Junxia Sun(2) found that long-term, high-dose use of magnesium sulfate inhibits maternal uterine contractions, prolongs labor, and results in postpartum hemorrhage and that newborns are often born with hypotonia and decreased responsiveness.

Advances in hypertension research have shown that PIH exhibits organ ischemia due to vasospasm resulting in microcirculatory disturbances and blood viscosity(3). According to traditional Chinese medicine (TCM) theory, forming blood stasis leads to the inability to produce new blood(4), therefore Chinese herbs that help to stimulate the circulation and eliminate congested blood, such as Salvia miltiorrhiza, Rhizoma Ligustici Chuanxiong, are commonly used to treat this condition. Salvia-ligustrazine and Ligustrazine (Chuanxiongzine) are active ingredients extracted from the above herbs, which have been employed extensively as injections for the treatment of PIH in the clinical setting in the recent years. The injection promotes circulation and eliminates congestion(5). Several clinical studies in recent years have demonstrated that combined treatment with Chuanxiongzine injection has a significant mitigating effect on PIH compared with conventional treatment, including lowering blood pressure, reducing proteinuria, reducing adverse maternal and infant pregnancy outcomes, promoting coagulation, and reducing the number of drug-induced adverse events.

Current similar meta-analyses of this treatment regimen have only analyzed Chuanxiongzine (6), without Salvia-ligustrazine versus conventional treatment, and with a narrow sample size and only a few outcome indicators, it is not effective in confirming the efficacy of this regimen. Therefore, in order to synthesize more evidence to confirm the role of Salvia-ligustrazine or Ligustrazine in combination with conventional Western drug regimens in the treatment of this disease. We included relevant articles published in recent years in a more comprehensive meta-analysis to confirm the efficacy and safety of this regimen.
MATERIALS AND METHODS

This report was designed and conducted in accordance with the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA) guidelines and is registered for meta-analysis on the PROSPERO website (CRD42024496232).

Literature search strategy

Among the databases we searched were PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Database, and VIP Database. Literature was restricted since each database was built through December 2, 2023, and the restricted languages were English and Chinese. The search was conducted with a combination of search terms as subject terms and free terms, and the medical subject terms used were as follows: Hypertension, Pregnancy-Induced, Salvia-ligustrazine, and Ligustrazine. The detailed search strategies are described in Supplementary Text 1.

Study inclusion and exclusion criteria

Inclusion Criteria: (Table 1)

P (participants): People with hypertensive disorders associated with pregnancy. Including gestational hypertension, pre-eclampsia-eclampsia, chronic hypertension, and chronic hypertension with superimposed pre-eclampsia. Subjects were diagnosed according to the Guidelines for the Diagnosis and Treatment of Hypertensive Diseases in Pregnancy (2020 edition)(7).

I (intervention): the treatment group was routinely treated with Salvia-ligustrazine or Ligustrazine combined with Western medicines.

C (control): the control group was only treated with conventional Western medicines, including but not limited to magnesium sulfate, nifedipine, labetalol, and other sedative antihypertensive treatments.

O (outcomes): primary outcome measures: changes in blood pressure (systolic blood pressure, SBP; diastolic blood pressure, DBP), pregnancy outcomes of maternal and infant, overall response rate (ORR); secondary outcome measures: incidence of adverse effects, urine proteins, coagulation indicators (Activated partial thromboplastin time, APTT; Prothrombin time, PT)

S (study design): RCTs
Exclusion criteria:

The exclusion of subjects was as below: 1) Doublet; 2) Non-compliance with the intervention; and 3) No valid data. This signifies that literature lacking outcome indicators distinct from those enumerated under "O(outcome)" will not be included.

Two assessors (RYJ and GQR) checked the literature independently for the aforementioned criteria, and inconsistencies were resolved by negotiation or a third reviewer (ZYZ).

Extraction of data and assessment of study quality

Two reviewers (R.Y.J. and G.Q.R.) separately extracted data identifying the final included articles, which included first author, year of publication, country, interventions and controls, duration of treatment, basic information about the study population, and outcome measures.

The Cochrane Risk of Bias Assessment Tool (ROB 2.0) was used to identify the risk of bias in the selected articles. ROB 2.0 assessed five aspects: bias arising from the random allocation process, bias arising from deviations from established procedures, bias arising from missing outcome data, bias arising from outcome measures, and bias arising from selective reporting of results. For each study, two independent reviewers assessed Rob 2.0 and inconsistencies were handled by a third reviewer (ZYZ). The results of the assessments are presented as the risk of bias plots.

Statistical analysis

The primary outcome indicators were changes in blood pressure, including SBP and DBP, maternal and infant pregnancy outcomes, and ORR while the secondary outcome indicators were urine proteins, coagulation indices (APTT; PT), and occurrence of untoward reaction.

Meta-analysis was performed using stata15.0. Weighted mean differences (WMD) were calculated for continuous data. 95% confidence intervals (CI) were reported when the same scale was used. For dichotomous variables, meta-analysis was performed using RR to indicate effect. Heterogeneity between studies was assessed by the Q test for $X^2$ and $I^2$ statistic. When the heterogeneity across studies is not significant ($I^2<50\%$ and $P>0.1$), meta-analysis is performed using Mantel-Haenszel models. Conversely, a random effects model is employed.

To clarify the extent and sources of heterogeneity among studies, subgroup analyses and regression analyses of Salvia-ligustrazine or Ligustrazine combined with conventional
treatment based on treatment duration were performed. Sensitivity analysis was used to assess the robustness of the meta-analysis results, and the presence of publication bias in the included literature was assessed by funnel plot and statistically tested using the Egger or Begg method (number of studies ≥8). For results with significant publication biases, a cut-and-patch approach was used to assess their effect on results.

RESULTS

Literature search

A 318-article corpus was yielded by the 1st database search, and after removing duplicates and excluding articles not meeting inclusion criteria, 63 articles were carefully reviewed. Finally, 47 studies(5, 8-53) were identified as eligible for meta-analysis. The process of literature screening is depicted in Figure 1.

The characteristics of included studies

The 47 included studies were from China and included 4517 patients, all female, average age of 21 - 42 years. The fundamental attributes of the included studies are presented in Table 1.

Risk of bias of the included studies

Figure 2 shows the results of the risk of bias assessment of the 47 included trials. There was a possible risk in 23 studies(5, 10, 11, 13, 14, 20-22, 25, 27-29, 36, 38, 41-46, 48, 50, 51) for missing random assignment, missing subgroup concealment or missing blinding, and a low risk in the remaining 24 studies(8, 9, 12, 15-19, 23, 24, 26, 30-35, 37, 39, 40, 47, 49, 52, 53). The potential for bias was minimal in all studies regarding missing outcome data, missing outcome measures and selective reporting. Overall, the included literature was at low risk of bias.

Meta-analysis results

Main Outcome Indicators

Changes in blood pressure: SBP, DBP

There were 12 studies(5, 24, 34, 36, 40, 44, 47, 48, 50-53) and 17 studies(11, 16, 20-23, 25, 26, 28, 29, 33, 35, 37, 39, 42, 46, 49) respectively reported changes in blood pressure with conventional treatment using Salvia-ligustrazine or Chuanxiongzine combined. Both SBP and DBP changes were analyzed by random effects meta-analysis ($I^2$=85.0%, P<0.001); ($I^2$=83.2.0%, P<0.001). Results of the meta-analysis indicate that combining with Salvia-
ligustrazine injection substantially decreased SBP (WMD=-10.73; 95%CI: -13.12 to -8.33; P<0.001) and DBP (WMD=-8.79; 95%CI: -10.78 to -6.80; P<0.001) in patients compared with conventional treatment; treatment with Chuanxiongzine injection significantly reduced SBP (WMD=-11.73; 95%CI: -14.12 to -9.34; P<0.001) and DBP (WMD=-8.25; 95%CI: -9.66 to -6.84; P<0.001) in patients (Figure 3, Figure 4).

Pregnancy outcome-mother

There are 6 studies (24, 27, 32, 34, 52, 53) that reported pregnancy outcomes with Salvia-ligustrazine in combination with conventional therapy. Heterogeneity test analysis of Salvia-ligustrazine treatment showed no significant heterogeneity among the included literature (I²=0.0%, P=0.843). Accordingly, a fixed effects model was employed to aggregate the findings. This showed that the Salvia-ligustrazine combination reduced the risk of multiple pregnancy outcomes compared with conventional treatment. [Cesarean (RR=0.64; 95%CI:0.52 to 0.77; P<0.001), Postpartum eclampsia (RR=0.41; 95%CI:0.12 to 1.38; P=0.151), Placental abruption (RR=0.50; 95%CI:0.19 to 1.30; P=0.154), Postpartum hemorrhage (RR=0.25; 95%CI:0.12 to 0.53; P<0.001), Others (RR=0.63; 95%CI:0.29 to 1.34; P=0.229)] However, there was no significant difference in the incidence of postpartum eclampsia, placental abruption, and other outcomes with TCM combination therapy compared with Western medicine therapy alone. Due to the small sample size involved in Salvia-ligustrazine Combination Therapy, this may occur. (Figure 5)

There are 21 studies (8, 9, 12, 14, 15, 17-20, 23, 25, 26, 28, 29, 33, 35, 37-39, 45, 49) that reported pregnancy outcomes with Chuanxiongzine in combination with conventional therapy. The heterogeneity test analysis was nonsignificant (I²=0.0%, P=0.978), so a fixed effects model was constructed to summarize the results. This showed that the combination of Chuanxiongzine was able to reduce the risk of a variety of maternal pregnancy outcomes compared with conventional Western drug therapy. [Cesarean (RR=0.53; 95%CI:0.43 to 0.65; P<0.001), Postpartum hemorrhage (RR=0.29; 95%CI:0.22 to 0.40; P<0.001), Placental abruption (RR=0.28; 95%CI:0.16 to 0.50; P<0.001), Postpartum eclampsia (RR=0.39; 95%CI:0.16 to 0.95; P=0.038), uterine inertia (RR=0.31; 95%CI:0.18 to 0.52; P<0.001) (Figure 6)

Pregnancy outcome-fetus

Six articles (24, 27, 32, 34, 52, 53) reported on fetal pregnancy outcomes with Salvia-ligustrazine in combination with conventional therapy. Its heterogeneity test was
nonsignificant ($I^2=0.0\%$, $P=0.976$). A fixed-effects model is employed. The finding indicated that combined Salvia-ligustrazine treatment was able to reduce the risk of multiple fetal pregnancy outcomes compared with Western medicine treatment alone. [Neonatal asphyxia (RR=0.25; 95%CI:0.07 to 0.87; $P=0.030$), Fetal distress (RR=0.29; 95%CI:0.13 to 0.65; $P=0.003$), others (RR=0.45; 95%CI:0.22 to 0.93; $P=0.031$), Prematurity (RR=0.33; 95%CI:0.11 to 0.99; $P=0.047$)] (Figure 7)

22 articles (9, 11-13, 15, 18-20, 23, 25, 26, 28, 29, 31, 33, 35, 37-39, 45, 46, 49) report on fetal pregnancy outcomes with Chuanxiongzine in combination with conventional therapy. ($I^2=0.0\%$, $P=1.000$), The results were integrated via a fixed-effect model. The findings revealed that combined Ligustrazine treatment could reduce the risk of multiple fetal pregnancies compared to conventional Western medicine. [Fetal distress (RR=0.33; 95%CI:0.22 to 0.50; $P<0.001$), Neonatal asphyxia (RR=0.30; 95%CI:0.21 to 0.42; $P<0.001$), prematurity (RR=0.28; 95%CI:0.17 to 0.46; $P=0.001$), Neonatal death (RR=0.37; 95%CI:0.21 to 0.65; $P=0.001$), others (RR=0.47; 95%CI:0.31 to 0.72; $P<0.001$)] (Figure 8)

**Overall Response Rate**

8 (5, 27, 34, 36, 40, 47, 50, 53) and 17 studies (8, 9, 11, 14-16, 19, 20, 22, 25, 28, 30, 33, 37, 38, 43, 52) reported the ORR of conventional Western medicine combined with Salvia-ligustrazine or Ligustrazine treatment respectively, and their heterogeneity test analysis showed no significance ($I^2=0.0\%$, $P=0.998$), results showed that Salvia-ligustrazine or Ligustrazine combination treatment significantly increased the overall response rate compared to conventional Western medicine treatment. [Salvia, Ligustrazine (RR=1.21; 95%CI:0.17 to 1.25; $P=0.001$), Ligustrazine (RR=1.21; 95%CI:1.16 to 1.26; $P=0.001$)] (Figure 9)

**Secondary outcome indicators**

**Urine protein**

6 (5, 24, 34, 48, 52, 53) and 8 (21, 22, 28, 31, 38, 39, 46, 49) reported changes in 24-hour urine protein with conventional treatment combined with Salvia-ligustrazine or Ligustrazine, respectively. A random effects model ($I^2=95.3\%$, $P<0.001$) was applied. Meta-analysis revealed that combined treatment with Salvia-ligustrazine or Ligustrazine both reduced patients' 24-hour urine protein levels. (WMD=-0.30; 95%CI: -0.47 to -0.13; $P<0.001$), (WMD=-0.68; 95%CI: -1.00 to -0.37; $P<0.001$) (Figure 10)
Coagulation function (APTT, PT)

Changes in APTT and PT values of conventional treatment combined with Chinese medicine injections were reported in 8(28, 30, 31, 35, 39, 41, 47, 53) and 9 cases(28, 30, 31, 35, 39, 41, 45, 47, 53), respectively, which were meta-analyzed with a random-effects model ($I^2=89.8\%, \, P<0.001$), ($I^2=94.4\%, \, P<0.001$). The meta-analysis showed that combined treatment with Salvia-ligustrazine or Ligustrazine increased both the APTT and PT values in the blood of the patients. (WMD=3.23; 95%CI: 2.31 to 4.14; $P<0.001$), (WMD=1.79; 95%CI: -1.10 to 2.48; $P<0.001$) (Figure 11) (Figure 12)

Untoward reaction

10 articles(14, 17, 18, 21, 24, 29, 30, 37, 42, 53) reported adverse events of conventional treatment combined with Salvia-ligustrazine or Ligustrazine. Adverse events included headache, dizziness, chest tightness, and impaired liver and kidney function. ($I^2=14.5\%, \, P=0.310$). The findings indicated that compared with conventional treatment, combined Chinese medicine injections reduced the number of adverse reactions in patients. (WMD=0.64; 95%CI: 0.46 to 0.89; $P=0.008$) (Figure 13)

Subgroup analysis

For each major outcome measure (SBP, DBP, ORR), we conducted subgroup analyses based on the duration of the treatment (up to 7 days; over 14 days; 7-14 days). (Figure 14-16) The results showed that all three treatment durations had a significant effect on the improvement of the indices as long as they were treated with the program ($P<0.01$). Furthermore, in our regression analysis, we found that changes in SBP may be influenced by different treatment durations. ($P=0.042 < 0.05$)

Sensitivity analysis

Analyses of the sensitivity of the key outcome indicators indicated that the findings were fundamentally reliable. (Figure S1-9)

Publication bias

Primary outcome measures were tested for publication bias by means of funnel plots, Egger's test or Begg's test. The data indicated that the biases in the publication of blood pressure changes and pregnancy outcome indicators in mothers and infants treated with combined Salvia-ligustrazine was not significant ($P>0.05$). In contrast, there was a notable publication
bias (P<0.01) for total efficiency, and our conclusions did not change after we supplemented the eight publications using the cut-and-patch method. In addition, there was a publication bias in the maternal and infant pregnancy outcome indicators of combined Chuanxiongzine treatment (P<0.05), and the conclusions did not change after the cut-and-patch method was used to supplement the 0 literature, which further validated what we found.

**DISCUSSION**

PIH represents a considerable threat to the health of both mothers and infants. In severe cases, it may precipitate placental abruption, eclampsia, cardiovascular and cerebrovascular accidents, as well as other adverse pregnancy outcomes(54). The conventional therapeutic agents employed in such cases are magnesium sulfate and sedative antihypertensive drugs. However, the results obtained are often unsatisfactory and accompanied by a variety of adverse effects, underscoring the urgent need to improve the treatment. Salvia-liguistrazine and ligustrazine may be a suitable pharmacological option for the management of PIH. The aforementioned clinical application has yielded favorable outcomes, thereby facilitating more efficacious treatment regimens for patients diagnosed with PIH.

Based on meta-analysis, evidence suggests that the combination of Salvia-liguistrazine or Ligustrazine injection with conventional treatment is superior to the use of Labetalol, Nifedipine, etc. alone in terms of reducing blood pressure, improving coagulation function, enhancing clinical efficacy, and improving maternal and infant pregnancy outcomes. Pharmacological studies have shown that Salvia miltiorrhiza acts against myocardial ischemia, atherosclerosis and thrombosis(55). Ligustrazine is an alkaloid, the main active substance extracted from the rhizome of Artemisia *Ligusticum chuanxiong Hort*, family Umbelliferae, which is widely used clinically for a variety of diseases. Pharmacological reviews have established that Chuanxiongzine has antithrombotic, Anti-ischemia-reperfusion injury, and cardiovascular and cerebrovascular system protection effects. Ligustrazine may have vasodilatory effects through activation of the adenylate cyclase (AC)/PKA cascade and inhibition of voltage-dependent L-type Ca^{2+} channels(56). Xu et al.(57) found that Ligustrazine may improve vascular endothelial cell dysfunction through an increase in mitochondrial biosynthesis.

The results showed that treatment with Ligustrazine injection combined with antispasmodic drugs such as magnesium sulfate or diazepam substantially cut the number of eclamptic episodes and the severity of eclampsia. Ligustrazine protects the brain and nerves through
antioxidant and anti-apoptotic pathways, according to pharmacological studies. Zhu Xiaoqin found that Ligustrazine inhibited the production of glutamate (Glu) in the brain and promoted the production of gamma-aminobutyric acid (GABA) in the brain, thus reducing neuronal excitability and inhibiting epilepsy. However, eclampsia was not improved by Salvia-liguistazine.

It was found that injection of Salvia-liguistazine or Ligustrazine in combination with conventional Western medicine treatment reduced side effects such as dizziness, nausea, and liver and kidney dysfunction. Ligustrazine has been found to have biological activities such as protection of liver and kidney function, detoxification, antipyretic, and immune enhancement. Cui et al found that Ligustrazine reduced cochlear ototoxicity by decreasing hearing threshold changes and reducing the expression of heat shock protein 70 and caspase-3 proteins. Ligustrazine enhanced phagocytosis of murine peritoneal macrophages, promoted T-lymphocyte esterase positivity, and increased serum hemolysin content, according to Daohong Zhang.

In summary, the combination of traditional therapy with Salvia-liguistazine or Ligustrazine injection represents a viable strategy for enhancing efficacy while minimizing adverse effects in patients diagnosed with PIH. That aligns with the findings of pharmacological studies on Salvia and Chuanxiong species. Firstly, evidence indicates that the therapy is more efficacious in lowering blood pressure. Secondly, this therapy diminishes the likelihood of adverse pregnancy outcomes, including eclampsia, placental abruption, postpartum hemorrhage, and so forth. Furthermore, it has fewer adverse effects. The regression analysis demonstrated that both herbal injections exhibited favorable therapeutic effects after approximately one to two weeks of continuous treatment, with no significant difference between them. A prolonged treatment duration did not lead to a statistically significant enhancement of the clinical outcomes. In our regression analyses, we found that SBP values appear to be affected by the duration of treatment. Specifically, our findings suggest that treatment lasting more than seven days may be more efficacious than treatment lasting up to seven days.

However, it should be noted that the study has certain limitations. The overall heterogeneity of the articles was relatively low, yet the heterogeneity of ORR and pregnancy outcomes among outcome indicators was considerable. Despite performing a thorough heterogeneity analysis, we were unable to identify the source of the heterogeneity. We speculate that the unclear randomization process of the majority of the included studies may have resulted in
the omission of crucial information regarding blinding, case-shedding, and other factors. This may have contributed to the observed heterogeneity in the present study. RCTs are rare and the study was geographically limited, being almost entirely from China and necessitating the conduct of additional high-quality trials to provide supporting evidence for our findings.

CONCLUSION

In conclusion, the available evidence supports the hypothesis that the combination of Chinese herbal injections, specifically Salvia-ligustrazine or Ligustrazine, is more effective in treating PIH than Western medicine alone. It is associated with a higher overall response rate and a lower number of adverse pregnancy outcomes. Meanwhile, combination injection treatment with Salvia-ligustrazine or Ligustrazine has superior safety characteristics and longer-term benefits. Nevertheless, further well-designed studies are required to substantiate these findings.

ACKNOWLEDGMENTS

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TABLES AND FIGURES

**Table 1. PICOS**

<table>
<thead>
<tr>
<th><strong>P (participants)</strong></th>
<th>People with hypertensive disorders associated with pregnancy</th>
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<tr>
<td><strong>I (intervention)</strong></td>
<td>Salvia-liguistrazine or Ligustrazine combined with Western medicines</td>
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<tr>
<td><strong>C (control)</strong></td>
<td>Only conventional Western medicines</td>
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<td><strong>O (outcomes)</strong></td>
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<td></td>
<td><strong>secondary</strong> Incidence of adverse effects; Urine proteins, APTT, PT</td>
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<td><strong>S (study design)</strong></td>
<td>RCTs</td>
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SBP: systolic blood pressure; DBP: diastolic blood pressure; ORR: overall response rate; APTT: Activated partial thromboplastin time; PT: Prothrombin time; RCTs: Randomized controlled trials
Figure 1. Flowchart of searching and screening for the studies
Figure 2. The risk of bias assessment
**Figure 3. Forest plot of SBP.** The systolic blood pressure (SBP) changes in PIH patients treated with Salvia-ligustrazine or Ligustazine injection combined with conventional treatment.
Figure 4. Forest plot of DBP. The diastolic blood pressure (DBP) changes.

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<th>Study ID</th>
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- Salvia–ligustrazine
  - Chen R et al. (2019) | -5.55 (-7.39, -3.71) | 4.13 |
  - Guo XL (2023) | -10.59 (-11.84, -9.34) | 4.38 |
  - Hao YQ et al. (2023) | -7.00 (-10.06, -3.94) | 3.45 |
  - Huang YM (2020) | -10.40 (-14.78, -6.02) | 2.72 |
  - Xue LL et al. (2023) | -11.48 (-13.47, -9.49) | 4.60 |
  - Song YH (2019) | -3.55 (-6.38, -0.72) | 3.58 |
  - Wang QY et al. (2018) | -8.00 (-12.70, -3.30) | 2.57 |
  - Wei MP et al. (2023) | -11.02 (-14.21, -7.83) | 3.38 |
  - Xiao PP et al. (2021) | -8.37 (-12.62, -4.12) | 2.79 |
  - Qin LL et al. (2018) | -13.91 (-19.64, -8.18) | 2.11 |
  - Zhang HJ (2020) | -14.30 (-18.11, -10.49) | 3.03 |
  - Jia AL et al. (2022) | -3.93 (-6.46, -1.40) | 3.75 |
  - Subtotal (I² = 84.1%, p = 0.000) | -8.79 (-10.78, -6.80) | 39.94 |
  - Overall (I² = 83.2%, p = 0.000) | -8.45 (-9.57, -7.32) | 100.00 |

NOTE: Weights are from random effects analysis
Figure 5. Forest plot of Salvia-ligustrazine on pregnancy outcomes for mothers.
Figure 6. Forest plot of Ligustrazine on pregnancy outcomes for mothers
Figure 7. Forest plot of Salvia-ligustrazine on pregnancy outcomes for the fetus
**Figure 8. Forest plot of Ligustrazine on pregnancy outcomes for the fetus**
<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2018)</td>
<td>1.17 (1.00, 1.37)</td>
<td>3.72</td>
</tr>
<tr>
<td>Chen S Xing (2002)</td>
<td>1.18 (1.05, 1.32)</td>
<td>6.57</td>
</tr>
<tr>
<td>Cheng H J (2019)</td>
<td>1.21 (1.02, 1.44)</td>
<td>4.04</td>
</tr>
<tr>
<td>Ding N et al. (2019)</td>
<td>1.24 (1.02, 1.50)</td>
<td>3.61</td>
</tr>
<tr>
<td>Huang Y F et al. (2017)</td>
<td>1.18 (1.01, 1.38)</td>
<td>4.14</td>
</tr>
<tr>
<td>Li M L (2018)</td>
<td>1.22 (1.01, 1.47)</td>
<td>3.40</td>
</tr>
<tr>
<td>Liu Y X (2019)</td>
<td>1.38 (1.14, 1.66)</td>
<td>3.40</td>
</tr>
<tr>
<td>Xue L et al. (2023)</td>
<td>1.33 (1.11, 1.60)</td>
<td>3.83</td>
</tr>
<tr>
<td>Peng W J et al. (2012)</td>
<td>1.10 (0.94, 1.29)</td>
<td>2.55</td>
</tr>
<tr>
<td>Quan G H (2015)</td>
<td>1.13 (0.96, 1.33)</td>
<td>2.64</td>
</tr>
<tr>
<td>Shi G L et al. (2017)</td>
<td>1.22 (1.03, 1.44)</td>
<td>3.93</td>
</tr>
<tr>
<td>Guo Z Y (2019)</td>
<td>1.17 (1.01, 1.36)</td>
<td>4.36</td>
</tr>
<tr>
<td>Liao Y T et al. (2004)</td>
<td>1.18 (1.04, 1.34)</td>
<td>5.48</td>
</tr>
<tr>
<td>Liu X F (2015)</td>
<td>1.23 (1.00, 1.51)</td>
<td>2.76</td>
</tr>
<tr>
<td>Wang X F et al. (2020)</td>
<td>1.21 (1.01, 1.46)</td>
<td>3.55</td>
</tr>
<tr>
<td>Xu F D (2014)</td>
<td>1.23 (1.04, 1.46)</td>
<td>4.99</td>
</tr>
<tr>
<td>Zhang P (2014)</td>
<td>1.23 (0.99, 1.54)</td>
<td>2.80</td>
</tr>
<tr>
<td>Subtotal (I²-squared = 0.0%, p = 0.988)</td>
<td>1.21 (1.16, 1.26)</td>
<td>65.78</td>
</tr>
<tr>
<td>Salvia-liguistrarine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen R et al. (2019)</td>
<td>1.14 (1.00, 1.29)</td>
<td>5.31</td>
</tr>
<tr>
<td>Hao Y Q et al. (2023)</td>
<td>1.15 (1.00, 1.31)</td>
<td>4.99</td>
</tr>
<tr>
<td>Song Y H (2019)</td>
<td>1.17 (1.02, 1.36)</td>
<td>4.25</td>
</tr>
<tr>
<td>Wang Q Y et al. (2018)</td>
<td>1.27 (1.00, 1.60)</td>
<td>3.19</td>
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<tr>
<td>Wei M P et al. (2023)</td>
<td>1.21 (1.02, 1.43)</td>
<td>3.61</td>
</tr>
<tr>
<td>Xiao P P et al. (2021)</td>
<td>1.21 (1.01, 1.44)</td>
<td>3.61</td>
</tr>
<tr>
<td>Zhang H J (2020)</td>
<td>1.26 (1.08, 1.47)</td>
<td>4.46</td>
</tr>
<tr>
<td>Zhao W Q et al. (2018)</td>
<td>1.31 (1.10, 1.56)</td>
<td>4.78</td>
</tr>
<tr>
<td>Subtotal (I²-squared = 0.0%, p = 0.900)</td>
<td>1.21 (1.14, 1.28)</td>
<td>34.22</td>
</tr>
<tr>
<td>Overall (I²-squared = 0.0%, p = 0.998)</td>
<td>1.21 (1.17, 1.25)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 9. Forest plot of overall response rate
### Figure 10. Forest plot of urine protein

<table>
<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2018)</td>
<td>-0.52 (-0.68, -0.36)</td>
<td>8.18</td>
</tr>
<tr>
<td>Huang Y F et al. (2017)</td>
<td>-0.95 (-1.10, -0.80)</td>
<td>8.25</td>
</tr>
<tr>
<td>Lai J Q (2019)</td>
<td>-2.24 (-3.22, -1.26)</td>
<td>2.77</td>
</tr>
<tr>
<td>Li Y H et al. (2022)</td>
<td>-0.91 (-1.02, -0.80)</td>
<td>8.40</td>
</tr>
<tr>
<td>Li Z Y (2019)</td>
<td>-0.55 (-0.71, -0.39)</td>
<td>8.15</td>
</tr>
<tr>
<td>Xu H Y (2017)</td>
<td>0.08 (-0.07, 0.23)</td>
<td>8.23</td>
</tr>
<tr>
<td>Guo Z Y (2019)</td>
<td>-1.05 (-1.45, -0.65)</td>
<td>6.35</td>
</tr>
<tr>
<td>Yu L et al. (2021)</td>
<td>-0.20 (-0.60, 0.20)</td>
<td>6.35</td>
</tr>
<tr>
<td>Subtotal (I² = 95.4%, p = 0.000)</td>
<td>-0.68 (-1.00, -0.37)</td>
<td>56.69</td>
</tr>
</tbody>
</table>

### Salvia–ligustrazine

<table>
<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen R et al. (2019)</td>
<td>-0.08 (-0.17, 0.01)</td>
<td>8.47</td>
</tr>
<tr>
<td>Hao Y Q et al. (2023)</td>
<td>-0.38 (-0.70, -0.06)</td>
<td>7.07</td>
</tr>
<tr>
<td>Xue L et al. (2023)</td>
<td>-0.58 (-0.71, -0.45)</td>
<td>8.30</td>
</tr>
<tr>
<td>Wang Q Y et al. (2018)</td>
<td>-0.57 (-1.51, 0.37)</td>
<td>2.94</td>
</tr>
<tr>
<td>Qin L et al. (2018)</td>
<td>-0.27 (-0.34, -0.20)</td>
<td>8.55</td>
</tr>
<tr>
<td>Jia A L et al. (2022)</td>
<td>-0.18 (-0.37, 0.01)</td>
<td>7.98</td>
</tr>
<tr>
<td>Subtotal (I² = 86.9%, p = 0.000)</td>
<td>-0.30 (-0.47, -0.13)</td>
<td>43.31</td>
</tr>
<tr>
<td>Overall (I² = 95.3%, p = 0.000)</td>
<td>-0.51 (-0.71, -0.31)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Figure 11. Forest plot of activated partial thromboplastin time
Figure 12. Forest plot of prothrombin time
Figure 13. Forest plot of untoward reaction
Figure 14. Forest plot of treatment duration subgroup analysis of SBP (systolic blood pressure)
Figure 15. Forest plot of treatment duration subgroup analysis of DBP (diastolic blood pressure)
Figure 16. Forest plot of treatment duration subgroup analysis of overall response rate

SUPPLEMENTARY DATA

Supplementary table is available at the following link: