Meta-analysis of the effectiveness of traditional Chinese herbal formula Zhen Wu Decoction for the treatment of hypertension

Xingjiang Xiong, Pengqian Wang, Shengjie Li

ABSTRACT

Objectives: Zhen Wu Decoction (ZWD), a famous classic herbal formula documented in traditional Chinese medicine (TCM), is widely available in China for treating hypertensive patients with kidney yang deficiency and fluid retention syndrome. This systematic review aims to evaluate the effectiveness and safety of ZWD for hypertension.

Methods: Cochrane Central Register of Controlled Trials, PubMed, Embase, the Chinese National Knowledge Infrastructure, the Chinese Scientific Journal Database, the Chinese Biomedical Literature Database, and the Wanfang Database were searched from their inception to November 2014. Randomised controlled trials of ZWD used alone or in combination with antihypertensive drugs against placebo, no intervention or antihypertensive drugs in hypertensive patients were identified. Two assessors independently reviewed each trial. The Cochrane risk of bias assessment tool was used for quality assessment.

Results: Seven trials involving 472 hypertensive patients were identified. Compared with antihypertensive drugs, ZWD showed no significant effects in lowering blood pressure (BP) (n=177; risk ratio (RR) 1.06; 95% CI 0.87 to 1.28; p=0.58); however, ZWD plus antihypertensive drugs (ZPAD) significantly lowered systolic BP (n=177; weighted mean difference (WMD) −14.00 mm Hg, 95% CI −18.84 to −9.16 mm Hg; p<0.00001), diastolic BP (n=80; WMD −9.00 mm Hg, 95% CI −11.35 to −6.65 mm Hg; p<0.00001), and BP (n=215; RR 1.21, 95% CI 1.08 to 1.37; p=0.001). TCM symptoms and syndromes were significantly improved by either ZWD (n=177; RR 1.58, 95% CI 1.28 to 1.95; p<0.0001) or ZPAD (n=215; RR 1.30, 95% CI 1.14 to 1.49; p=0.0001). Adverse effects were not reported.

Conclusions: This systematic review revealed no definite conclusion about the application of ZWD for hypertension due to the poor methodological quality, high risk of bias, and inadequate reporting on clinical data. More rigorously designed trials, especially addressing continuous BP and adverse effects, are warranted.

INTRODUCTION

Hypertension remains one of the major modifiable risk factors associated with cardiovascular morbidity and mortality, affecting more than 60 million individuals in the USA and totalling nearly one billion worldwide.1 2 The primary prevention and management of hypertension and blood pressure (BP) related diseases has become a global public health challenge.3 4 Tremendous progress have been made in the application of renal denervation therapy, combination antihypertensive and lipid-lowering therapies, and evidence-based guideline recommendations for stepwise, multidrug regimens released by the Eighth Joint National Committee (JNC 8) and other authorities.5–7 However, despite the availability of multiple antihypertensive agents with distinct pharmacologic classes and single-pill combination pharmacotherapy, goal BP is not achieved in large numbers of hypertensive patients and the control rates of hypertension among different age groups remain suboptimal.2 8 Therefore, there is an unmet need for new
approaches for the treatment of hypertension. Currently, a revival of interest in complementary and alternative medicine (CAM) for the treatment of hypertension has attracted widespread attention. A large number of systematic reviews and meta-analyses have been performed to summarise the growing number of randomised controlled trials (RCTs) addressing the effectiveness and safety of CAM for hypertension. In 2013, the American Heart Association summarised the BP-lowering efficacy of several commonly used CAM approaches with an evidence-based classification of recommendations for their implementation in clinical practice.

Among various CAM therapies, Chinese herbal medicine (CHM) to treat symptoms related to hypertension for over 2500 years. Previous studies have shown that kidney yang deficiency and fluid retention syndrome is a common syndrome of hypertension, which is usually characterised by aversion to cold, cold limbs, weakness, fatigue, dizziness aggravated by change in body position, tinnitus, thirst without a desire to drink or not being thirsty, chest distress, palpitation, gastric distension, abdominal distension, poor appetite, lumbar heaviness, heaviness in the lower extremities, oedema, daytime sleepiness, dysuria, swollen tongue with greasy fur, and deep-weak-slow pulse. Zhen Wu Decoction (ZWD) is a classical herbal formula invented by a famous TCM physician Zhongjing Zhang in Shang Han Lun almost 1800 years ago. It comprises the floral five commonly used natural herbs: processed aconite (Fu Zi, Radix Lateralis Praeparata Aconiti Carmichaelii), Poria (Fu Ling, Scierotium Poriae Cocos), White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae), White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflorae), and fresh ginger (Sheng Jiang, Rhizoma Zingiberis Officinalis). According to the records by Dr Zhang, kidney yang deficiency and fluid retention syndrome could be significantly improved by ZWD, which happens to be consistent with our studies. Over the past six decades, accumulating data from case reports, cases series, non-controlled trials, and RCTs have generally yielded consistent findings regarding the BP-lowering and symptoms-improving effects of ZWD, either used alone or in combination with antihypertensive drugs, for the management of hypertension. However, no meta-analyses have been conducted to summarise these research studies and many questions about the potential role of ZWD remain unanswered. The purposes of this study are to: (a) evaluate the efficacy of ZWD compared with placebo, no intervention, or antihypertensive drugs; (b) assess the efficacy of ZWD plus antihypertensive drugs (ZPAD) compared with antihypertensive drugs; and (c) estimate the safety of ZWD.

**METHODS**

This study complied with the Preferred Reporting Items for Systematic Review and Meta-analyses Statement (PRISMA).

**Study selection**

Types of studies

All the RCTs reporting the application of ZWD for the treatment of hypertension were involved without limitations on language or publication.

Types of participants

All the participants enrolled in this study had to meet at least one of the current or past diagnostic criteria of hypertension and kidney yang deficiency and fluid retention syndrome. Patients with severe respiratory disease, acute infectious disease, severe heart disease, severe liver disease, or tumour were excluded. If the trials did not elaborate the definitions of hypertension and TCM syndrome but simply stated that the included subjects were hypertensive patients with kidney yang deficiency and fluid retention syndrome, they were also included. No limitations on gender, age, or ethnicity of the participants were set.

Types of interventions

Patients were randomised into either a ZWD group or a control group. RCTs comparing ZWD versus placebo, no intervention, or antihypertensive drugs were included. Trials comparing ZPAD against antihypertensive drugs were also included. The antihypertensive drugs had to be given identically to both groups. If trials included other co-interventions such as another herbal formula, acupuncture, cupping, moxibustion, massage, yoga, qigong, Tai Chi, and aromatherapy, they were excluded. Treatment duration was required to be at least 2 weeks.

Types of outcome measures

The primary outcomes were defined as categorical or continuous BP, and secondary outcomes were TCM symptoms and syndromes. As shown in tables 1 and 2, the efficacy of ZWD on categorical BP and TCM symptoms and syndromes were classified into three grades based on the evaluation criteria from the Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDCM).

**Search strategy**

Electronic searches were conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), and the Wanfang Database from inception through to 17 November 2014. Additionally, two trial registries (http://www.chictr.org/ and http://www.clinicaltrials.gov/) were searched to identify all of
were then further assessed for the eligibility based on the titles and the abstracts. They were screened by two reviewers independently. The eligible studies were screened by two reviewers independently. Data extraction

The eligible studies were screened by two reviewers independently based on the titles and the abstracts. They were then further assessed for the final analysis. Some important information from primary trials were extracted, including first author’s name, country, year of publication, age, gender, number of hypertensive patients, details of interventions for ZWD and control groups, the composition of ZWD or modified ZWD, co-interventions, outcome measures, the duration of treatment, and adverse effects related to ZWD. Disagreements were resolved by discussion between all of the reviewers.

Assessment of risk of bias

Two reviewers independently evaluated the risk of bias of each study using the assessment tool from the Cochrane Handbook. The criteria consisted of the following seven items: (1) sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other sources of bias (from Chapter 8: assessing risk of bias in included studies).

Data analysis

Studies were combined according to the outcome measure, types of interventions, and controls. Meta-analysis was performed using Review Manager (V.5.2 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The weighted mean difference (WMD) with 95% CI was used for continuous BP, while the risk ratio (RR) with 95% CI was adopted in categorical BP and TCM symptoms and syndromes. Heterogeneity was assessed by visual inspection of forest plots, p values, and I² statistics; p<0.10 and I²>50% indicated a substantial level of heterogeneity. Because no significant clinical heterogeneity was identified in this review, a fixed effect model was applied. A value of p<0.05 was considered to be statistically significant.

RESULTS

Study identification

Figure 1 shows the process of study selection and identification. A total of 154 potentially relevant articles were initially screened in the seven electronic databases based on our literature searching strategy. After removing 102 duplicates, 52 articles were identified for further analysis. Through screening the titles and abstracts, 28 articles were excluded because they were literature reviews, expert opinions, commentaries, case reports, case series, non-clinical trials, or animal research. The remaining 24 full-text articles were then assessed for eligibility.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Evaluation criteria on the efficacy of categorical blood pressure recommended by GCRNDDTCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three graded criteria</td>
<td>Detailed description</td>
</tr>
<tr>
<td>Significant improvement</td>
<td>A. DBP decreased by 10 mm Hg and reached the normal range</td>
</tr>
<tr>
<td>Improvement</td>
<td>A. DBP decreased by &lt;10 mm Hg but reached the normal range</td>
</tr>
<tr>
<td>No improvement</td>
<td>Not reaching the above standards</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Evaluation criteria on the efficacy of TCM symptoms and syndromes recommended by GCRNDDTCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three graded criteria</td>
<td>Detailed description</td>
</tr>
<tr>
<td>Significant improvement</td>
<td>A. Symptoms and signs were significantly improved</td>
</tr>
<tr>
<td>Improvement</td>
<td>A. Symptoms and signs were improved</td>
</tr>
<tr>
<td>No improvement</td>
<td>A. Symptoms and signs were not improved</td>
</tr>
</tbody>
</table>

GCRNDDTCM, Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; TCM, traditional Chinese medicine.
Of them, 17 articles were excluded for the following reasons: participants did not meet the inclusion criteria (n=11), no control group (n=4), and intervention included other medical therapies (n=2). Ultimately, seven studies were assessed to be eligible in our review.

### Study characteristics

The basic characteristics of the seven included randomised trials are summarised in table 3. A total of 472 hypertensive patients were enrolled, with 248 in the treatment group and 224 in the control group. All of these trials were carried out in China and all the participants involved were Chinese. All studies were of small sample size, ranging from 40 to 80 participants.

Four diagnostic criteria of hypertension were reported: two trials used the Chinese Guidelines for the Management of Hypertension-2004 (CGMH-2004), one trial used the WHO/International Society of Hypertension (ISH) Guidelines for the Management of Hypertension-1999 (WHO/ISH GMH-1999), one trial used the GCRN DTCM, and one trial used the Internal Medicine-2004 (IM-2004). Three trials declared the diagnostic criteria of kidney yang deficiency and fluid retention syndrome by GCRNDTCM.

All the studies used a two-arm design (one treatment group vs one control group). For interventions, patients in the treatment group received either ZWD (n=3) or ZPAD (n=4). The different compositions of ZWD or modified ZWD are presented in table 4. Patients in the control group received antihypertensive drugs, including extended release nifedipine tablets, captopril, hydrochlorothiazide, valsartan, and amlodipine.

The BP outcomes were reported in all of the studies: six trials used categorical BP and one trial used continuous BP. TCM symptoms and syndromes were reported in six trials. The duration of the treatment ranged from 2 weeks to 1 month.

### Risk of bias within studies

As shown in figure 2, the risk of bias in all of the included studies was assessed as high. Although randomisation was declared in all the trials, only one trial described the method to generate the allocation sequence (random number table). Because none of the studies reported how they concealed allocation, the risk of bias was assessed as high. Only one trial reported blinding of participants and personnel, and none of the other studies reported whether double-blinding was done so the risk of bias was evaluated as high. All studies had a low risk of bias for incomplete outcome data. The risk of bias of selective outcome reporting and other sources were assessed as unclear because no protocols or other information could be obtained from the primary authors via email, telephone or fax.
Table 3  Basic characteristics of the included studies

<table>
<thead>
<tr>
<th>References</th>
<th>Sample size (randomised/analysed) M/F</th>
<th>Age (years)</th>
<th>Diagnosis standard</th>
<th>Baseline SBP (mmHg)</th>
<th>Baseline DBP (mmHg)</th>
<th>Baseline difference</th>
<th>Intervention</th>
<th>Control</th>
<th>Treatment duration</th>
<th>Adverse effects report</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu 2012&lt;sup&gt;35&lt;/sup&gt;</td>
<td>40/40 T: 12/8 C: 13/7</td>
<td>T: 66.72 C: 65.29</td>
<td>CGMH-2004; GCRNDTCM</td>
<td>NR</td>
<td>NR</td>
<td>NSD</td>
<td>ZWD (1 dose/day)</td>
<td>Extended release nifedipine tablets (18 mg, tid) and captopril (12 mg, bid)</td>
<td>15 days</td>
<td>No</td>
<td>(a) BP; (b) TCM symptoms and syndromes</td>
</tr>
<tr>
<td>Li and Shen 2012&lt;sup&gt;36&lt;/sup&gt;</td>
<td>60/60 T: 18/12 C: 19/11</td>
<td>T: 69.53 C: 69.31</td>
<td>WHO/ISH GMH-1999; GCRNDTCM</td>
<td>NR</td>
<td>NR</td>
<td>NSD</td>
<td>ZWD (1 dose/day)</td>
<td>Extended release nifedipine tablets (20 mg, bid) and captopril (10 mg, qd)</td>
<td>2 weeks</td>
<td>No</td>
<td>(a) BP; (b) TCM symptoms and syndromes</td>
</tr>
<tr>
<td>Shen 2004&lt;sup&gt;37&lt;/sup&gt;</td>
<td>77/77 T: 29/16 C: 18/14</td>
<td>T: 64.39 ±8.72 C: 63.28 ±7.62</td>
<td>GCRNDCRM</td>
<td>NR</td>
<td>NR</td>
<td>NSD</td>
<td>Modified ZWD (1 dose/day)</td>
<td>Hydrochlorothiazide (12.5 mg, qd)</td>
<td>2 weeks</td>
<td>No</td>
<td>(a) BP; (b) TCM symptoms and syndromes</td>
</tr>
<tr>
<td>Jiang et al 2013&lt;sup&gt;38&lt;/sup&gt;</td>
<td>80/80 T: 40 C: 40 M/F: NR</td>
<td>21–65</td>
<td>NR</td>
<td>T: 172.00 ±17.00 C: 168.00 ±12.00</td>
<td>T: 96.00 ±10.00 C: 94.00 ±11.00</td>
<td>NSD</td>
<td>T: modified ZWD (1 dose/day) + C</td>
<td>Valsartan (30 mg, qd)</td>
<td>4 weeks</td>
<td>No</td>
<td>(a) BP; (b) DBP</td>
</tr>
<tr>
<td>Li 2009&lt;sup&gt;39&lt;/sup&gt;</td>
<td>76/76 T: 21/19 C: 19/17</td>
<td>T: 66.60 ±8.40 C: 66.30 ±8.60</td>
<td>IM-2004</td>
<td>NR</td>
<td>NR</td>
<td>NSD</td>
<td>T: modified ZWD (1 dose/day) + C</td>
<td>Extended release nifedipine tablets (10 mg, bid)</td>
<td>1 month</td>
<td>No</td>
<td>(a) BP; (b) TCM symptoms and syndromes</td>
</tr>
<tr>
<td>Jiang 2009&lt;sup&gt;40&lt;/sup&gt;</td>
<td>78/78 T: 24/19 C: 19/16</td>
<td>T: 59.30 ±13.50 C: 62.40 ±11.90</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NSD</td>
<td>T: modified ZWD (1 dose/day) + C</td>
<td>Antihypertensive drugs (ACEI, ARB, CCB or indapamide)</td>
<td>1 month</td>
<td>No</td>
<td>(a) BP; (b) TCM symptoms and syndromes</td>
</tr>
<tr>
<td>Zhong 2014&lt;sup&gt;41&lt;/sup&gt;</td>
<td>61/61 T: 19/11 C: 20/11</td>
<td>T: 46–72 C: 48–77</td>
<td>CGMH-2004</td>
<td>NR</td>
<td>NR</td>
<td>NSD</td>
<td>T: modified ZWD (1 dose/day) + C</td>
<td>Amlodipine (5 mg, qd)</td>
<td>4 weeks</td>
<td>No</td>
<td>(a) BP; (b) TCM symptoms and syndromes</td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; bid, twice daily; BP, blood pressure; C, control group; CCB, calcium channel blocker; CGMH, Chinese guidelines for the management of hypertension; DBP, diastolic blood pressure; GCRNDCRM, Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; F, female; IM, internal medicine; M, male; NR, not reported; NSD, no significant difference; SBP, systolic blood pressure; T, treatment group; TCM, traditional Chinese medicine; qd, four times daily; tid, three times daily; WHO/ISH GMH, WHO/International Society for Hypertension Guidelines for the Management of Hypertension; ZWD, Zhen Wu Decoction.
<table>
<thead>
<tr>
<th>References</th>
<th>Formula</th>
<th>Composition of formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu 2012</td>
<td>ZWD</td>
<td>Processed aconite (Fu Zi, Radix Lateralis Praeparata Aconiti Carmichaeli) 20 g, Poria (Fu Ling, Scierotium Poriae Cocos) 15 g, White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae) 10 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 25 g, and fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 8 g</td>
</tr>
<tr>
<td>Li and Shen 2012</td>
<td>ZWD</td>
<td>Processed aconite (Fu Zi, Radix Lateralis Praeparata Aconiti Carmichaeli) 15 g, Poria (Fu Ling, Scierotium Poriae Cocos) 20 g, White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae) 15 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 20 g, and fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 9 g</td>
</tr>
<tr>
<td>Shen 2004</td>
<td>Modified ZWD</td>
<td>Processed aconite (Fu Zi, Radix Lateralis Praeparata Aconiti Carmichaeli) 3–6 g, Poria (Fu Ling, Scierotium Poriae Cocos) 10–18 g, White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae) 10 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 10 g, fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 10 g, Alisma (Ze Xie, Rhizoma Alismatis) 10 g, Baical Skullcap Root (Huang Qin, Radix Scutellariae Baicalensis) 10–30 g, and Achyranthes Root (Niu Xi, Achyranthis Bidentatae Radix) 10 g</td>
</tr>
<tr>
<td>Jiang et al 2013</td>
<td>Modified ZWD</td>
<td>Processed aconite (Fu Zi, Radix Lateralis Praeparata Aconiti Carmichaeli) 30 g, Poria (Fu Ling, Scierotium Poriae Cocos) 30 g, White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae) 30 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 12 g, fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 20 g, Astragalus (Huang Qi, Radix Astraalagi Membranacei) 40 g, Hirsute Shiny Bugleweed Herb (Ze Lan, Herba Lycopi) 15 g, Salvia Root (Dan Shen, Radix Salviae Miltiorrhizae) 15 g, and Achyranthes Root (Niu Xi, Achyranthis Bidentatae Radix) 15 g</td>
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<tr>
<td></td>
<td></td>
<td>Polyborus Sclerotium (Zhu Ling, Sclerotium Polypori Umbellati) 20 g, Cassia twig (Gui Zhi, Ramulus Cinnamomi Cassiae) 10 g, and Betel Husk (Da Fu Pi, Pericarpium Arecae Catechu) 20 g were added. If lassitude, aversion to cold, and soreness of waist and knee were found, Cuscuta Seed (Tu Si Zi, Cuscutae Semen) 20 g and Aerial Parts of Epimedium (Yin Yang Huo, Herba Epimedi) 20 g were added.</td>
</tr>
<tr>
<td>Li 2009</td>
<td>Modified ZWD</td>
<td>Processed aconite (Fu Zi, Radix Lateralis Praeparatus Aconiti Carmichaeli) 6 g, Poria (Fu Ling, Scierotium Poriae Cocos) 12 g, White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae) 9 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 6 g, fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 3 tablets, Astragalus (Huang Qi, Radix Astraalagi Membranacei) 30 g, Earthworm (Di Long, Lumbiricus) 9 g, Eucomma Bark (Du Zhong, Cortex Eucommiae Ulmoidis) 12 g, Chinese Taxillus Twig (Sang Ji Sheng, Herba Taxilli) 12 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 15 g, fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 6 g, Poria (Fu Ling, Scierotium Poriae Cocos) 25 g, and fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 6 g</td>
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<td></td>
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<td>Hirsute Shiny Bugleweed Herb (Ze Lan, Herba Lycopi) 15 g, Salvia Root (Dan Shen, Radix Salviae Miltiorrhizae) 15 g, and Achyranthes Root (Niu Xi, Achyranthis Bidentatae Radix) 9 g</td>
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<td>Polyborus Sclerotium (Zhu Ling, Sclerotium Polypori Umbellati) 20 g, Cassia twig (Gui Zhi, Ramulus Cinnamomi Cassiae) 10 g, and Betel Husk (Da Fu Pi, Pericarpium Arecae Catechu) 20 g were added. If lassitude, aversion to cold, and soreness of waist and knee were found, Cuscuta Seed (Tu Si Zi, Cuscutae Semen) 20 g and Aerial Parts of Epimedium (Yin Yang Huo, Herba Epimedi) 20 g were added.</td>
</tr>
<tr>
<td>Jiang 2009</td>
<td>Modified ZWD</td>
<td>Processed aconite (Fu Zi, Radix Lateralis Praeparatus Aconiti Carmichaeli) 15 g, Poria (Fu Ling, Scierotium Poriae Cocos) 15 g, White Atractylodes Rhizome (Bai Zhu, Rhizoma Atractylodis Macrocephalae) 15 g, White Peony Root (Bai Shao, Radix Albus Paeoniae Lactiflora) 10 g, fresh ginger (Sheng Jiang, Rhizoma Zingiberis Recens) 10 g, Cassia twig (Gui Zhi, Ramulus Cinnamomi Cassiae) 12 g, and Liquorice Root (Gan Cao, Radix Glycyrrhizae) 10 g</td>
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<td>If insomnia was found, Spiny Jujube Kernel (Suan Zao Ren, Ziziphi Spinosi Semen) was added. If chest tightness was found, Bulb of Chinese Chive (Xie Bai, Bulbus Allii) was added.</td>
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<tr>
<td></td>
<td></td>
<td>If palpitation was found, Spiny Jujube Kernel (Suan Zao Ren, Ziziphi Spinosi Semen) was added. If significant edema was found, Polyporus Sclerotium (Zhu Ling, Sclerotium Polypori Umbellati) 20 g, Cuscuta Seed (Tu Si Zi, Cuscutae Semen) 20 g and Aerial Parts of Epimedium (Yin Yang Huo, Herba Epimedi) 20 g were added.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If chest tightness was found, Bulb of Chinese Chive (Xie Bai, Bulbus Allii) was added. If palpitation was found, Spiny Jujube Kernel (Suan Zao Ren, Ziziphi Spinosi Semen) was added.</td>
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<td></td>
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<td>If lassitude, aversion to cold, and soreness of waist and knee were found, Cuscuta Seed (Tu Si Zi, Cuscutae Semen) 20 g and Aerial Parts of Epimedium (Yin Yang Huo, Herba Epimedi) 20 g were added.</td>
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</tr>
</tbody>
</table>
Outcome measures

Primary outcomes: BP

**ZWD versus antihypertensive drugs (three studies)**

Three trials tested ZWD with antihypertensive drugs for categorical BP. The meta-analysis showed no significant difference between ZWD and antihypertensive drugs in their effect on BP reduction (n=177; RR 1.06, 95% CI 0.87 to 1.28; p=0.58, figure 3A), with no significant heterogeneity ($\chi^2=2.64; p=0.27; I^2=24\%$).

**ZPAD versus antihypertensive drugs (four studies)**

Four trials evaluated the effect of ZPAD versus antihypertensive drugs. Among them, one trial used continuous BP and the other three trials used categorical BP. ZPAD significantly lowered systolic BP (n=80; WMD -14.00 mm Hg, 95% CI -18.84 to -9.16 mm Hg; p<0.00001, figure 3B), diastolic BP (n=80; WMD -8.00 mm Hg, 95% CI -11.35 to -4.65 mm Hg; p<0.00001, figure 3C), and BP (n=215; RR 1.21, 95% CI 1.08 to 1.37; p=0.001, figure 3D), with no significant heterogeneity ($\chi^2=0.76; p=0.49; I^2=0\%$).

Secondary outcomes: TCM symptoms and syndromes

**ZWD versus antihypertensive drugs (three studies)**

Three trials assessed the effect of ZWD on TCM symptoms compared with antihypertensive drugs. The combined effects of these three independent trial results suggested that TCM symptoms were significantly improved by ZWD (n=177; RR 1.58, 95% CI 1.28 to 1.95; p<0.0001, figure 4A), with no significant heterogeneity ($\chi^2=1.50; p=0.47; I^2=0\%$).

**ZPAD versus antihypertensive drugs (three studies)**

Three trials compared the effect of ZPAD versus antihypertensive drugs on TCM symptoms and syndromes. A remarkable improvement in TCM symptoms and syndromes with ZPAD was identified (n=215; RR 1.30, 95% CI 1.14 to 1.49; p=0.0001, figure 4B) compared to use of antihypertensive drugs alone, with no significant heterogeneity ($\chi^2=0.94; p=0.62; I^2=0\%$).

**Adverse effects**

Adverse effects monitoring was not reported in all the included trials.

**DISCUSSION**

Summary of evidence

This meta-analysis provides a quantitative synthesis of the clinical efficacy of ZWD for the treatment of hypertension by integrating outcomes from seven clinical trials.
trials involving 472 participants. Two categories for outcomes of BP and TCM symptoms and syndromes were performed. Results from the meta-analysis revealed that: (a) ZWD showed no additional BP-lowering effect compared to antihypertensive agents; (b) ZWD could significantly enhance the BP-lowering effect of conventional antihypertensive agents; (c) ZWD either used alone or in combination with antihypertensive agents could improve the TCM symptoms and syndromes in patients with hypertension; (d) as no included trials reported the occurrence or absence of adverse effects, the safety of ZWD for the treatment of hypertension remains unclear. However, the overall estimated results should be interpreted cautiously considering the high risk of bias and the limited number of trials included.

Limitations
This review had the following limitations. Cochrane risk of bias criteria was used to evaluate the methodology of the included trials. Poor methodological design was commonly seen in the clinical trials of CAM. Despite a comprehensive and unbiased literature search of seven electronic databases without language and publication restrictions, no randomised, double-blind, placebo-controlled trials could be identified. In this review, all the trials had flaws in terms of random sequence.

Figure 3  Effect of Zhen Wu Decoction (ZWD) and Zhen Wu Decoction plus antihypertensive drugs (ZPAD) on blood pressure (BP). (A) ZWD versus AD: BP; (B) ZPAD versus AD: SBP; (C) ZPAD versus AD: DBP; and (D) ZPAD versus AD: BP, AD, antihypertensive drugs; DBP, diastolic blood pressure; SBP, systolic blood pressures.

(A) ZWD vs. AD: BP

(B) ZPAD vs. AD: SBP

(C) ZPAD vs. AD: DBP

(D) ZPAD vs. AD: BP
generation, allocation concealment, double-blinding, and reporting. Therefore, we could not rule out the potential for selection, performance and/or detection bias completely. Additionally, inadequate reporting on dropout or withdrawal, the small sample size, and the limited number of included studies were also identified in this review, which might weaken the strength of the positive conclusions. Similar poor methodological quality of primary studies was also confronted in other systematic reviews and meta-analyses of CHM for hypertension.\textsuperscript{12, 13, 16, 19, 43–46} It has been one of the major challenges for CAM researchers to establish its place in the evidence-based treatment of hypertension.\textsuperscript{28, 47–49}

Another limitation of this review is the inadequate reporting on BP outcomes. Although the efficacy of ZWD on BP was reported in all the included trials, continuous BP was reported in only one trial\textsuperscript{38} and categorical BP was used in the other six trials. Without a detailed BP reduction value, it is impossible to recommend this conclusion for researchers worldwide. Indeed there are some difficulties in evaluating the efficacy of TCM by continuous BP because the application of categorical BP was authoritatively recommended by the China Food and Drug Administration (available at http://www.sda.gov.cn).\textsuperscript{47–49} However, continuous BP could be reported in further studies simultaneously.

Last but not least, inadequate reporting on adverse effects was identified in this review. CHM is becoming increasingly popular among patients with cardiovascular diseases worldwide,\textsuperscript{50–52} but recently concerns have emerged over its safety and potential interaction with conventional western medicine.\textsuperscript{53–55} As no information about adverse effects could be obtained, it was not possible to carry out a systematic review on these effects. We hope that the adverse effects of ZWD or ZPAD will be monitored and reported in detail in the future.

**CONCLUSION**

This systematic review revealed no definite conclusion about the application of ZWD for the treatment of hypertension due to the poor methodological quality, high risk of bias, and inadequate reporting on clinical data. More rigorously designed RCTs, especially addressing continuous BP and adverse effects, are warranted.

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**Contributors** XX conceived the idea, designed the study and interpreted the data. PW and SL conducted the literature searches, and evaluated the risk of bias of each study. XX performed the analysis, having full access to all of the data in this study, and taking responsibility for the integrity and accuracy of the data analysis. He also drafted the paper, which was revised by PW and SL.

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**Figure 4** Effect of Zhen Wu Decoction (ZWD) and Zhen Wu Decoction plus antihypertensive drugs (ZPAD) on traditional Chinese medicine symptoms and syndromes. (A) ZWD versus AD; (B) ZPAD versus AD. AD, antihypertensive drugs.
REFERENCES


