Effects of Traditional Chinese Patent Medicine on Essential Hypertension: A Systematic Review

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Effects of Traditional Chinese Patent Medicine on Essential Hypertension

A Systematic Review

Xingjiang Xiong, MD, Pengqian Wang, MD, Yuqing Zhang, MD, and Xiaoke Li, MD

Abstract: Traditional Chinese patent medicine (TCPM) is widely used for essential hypertension (EH) in China. However, there is no critically appraised evidence, such as systematic reviews or meta-analyses, regarding the potential benefits and disadvantages of TCPM to justify their clinical use and recommendation. The aim of this review was to systematically evaluate and meta-analyze the effects of TCPM for EH.

Seven databases, the Cochrane Library, PubMed, EMBASE, the China National Knowledge Infrastructure, the Chinese Scientific Journal Database, the Chinese Biomedical Literature Database, and the Wanfang Database, were searched from their inception to August 2014 for relevant studies that compared one TCPM plus antihypertensive drugs versus antihypertensive drugs alone. The methodological quality of the included trials was assessed using the Cochrane risk-of-bias tool. The primary outcome measures were mortality or progression to severe complications and adverse events. The secondary outcome measures were blood pressure (BP) and quality of life (QOL).

Seventy-three trials, which included 8138 patients, on 17 TCPMs were included. In general, the methodological quality was low. Two trials evaluated the effects of TCPMs on mortality and the progression to severe complications after treatment, and no significant difference was identified compared with antihypertensive drugs alone. No severe adverse events were reported. Thirteen TCPMs used in complementary therapy significantly decreased systolic BP by 3.94 to 13.50 mmHg and diastolic BP by 2.28 to 11.25 mmHg. QOL was significantly improved by TCPM plus antihypertensive drugs compared with antihypertensive drugs alone.

This systematic review provided the first classification of clinical evidence for the effectiveness of TCPM for EH. The usage of TCPMs for EH was supported by evidence of class level III. As a result of the methodological drawbacks of the included studies, more rigorously designed randomized controlled trials that focus on mortality and cardiovascular events during long-term follow-up are warranted before TCPM can be recommended for hypertensive patients. Two TCPMs, Song ling xue mai kang capsules and Yang xue qing nao granules, should be prioritized for further research.

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Abbreviations: AEs = adverse events, BP = blood pressure, CAM = complementary and alternative medicine, CCT = controlled clinical trials, CFDA = China Food and Drug Administration, CI = confidence interval, CNED = Chinese National Essential Drug, CVDs = cardiovascular diseases, DBP = diastolic blood pressure, EH = essential hypertension, PPRC = Pharmacopeia of the People’s Republic of China, QOL = quality of life, RCT = randomized controlled trial, RR = risk ratio, SBP = systolic blood pressure, TCM = traditional Chinese medicine, TCPM = traditional Chinese patent medicine, TPAD = traditional Chinese patent medicine plus antihypertensive drugs, WMD = weighted mean difference.

INTRODUCTION

Hypertension is one of the most important worldwide public-health challenges because of its high frequency and concomitant risks of cardiovascular and kidney disease. Across all World Health Organization regions, approximately 62% of strokes and 49% of myocardial infarctions are caused by high blood pressure (BP). Hypertension has been identified as the fourth leading cause of the global burden of disease. The prevention and effective treatment of essential hypertension (EH) is of utmost importance both in China and the West. However, the effective control of hypertension is far from satisfactory and is limited by the availability, cost, and adverse effects of antihypertensive medications. Therefore, a certain proportion of patients have turned to complementary and alternative medicine (CAM), including traditional Chinese medicine (TCM), in the search for a treatment modality with potential efficacy and few adverse effects. In Western countries, interest in TCM stems from the hope that it might complement Western medicine. This situation is also partially supported by recent studies.

The most significant distinction between China and the West in EH treatment is the application of acupuncture and traditional Chinese patent medicines (TCPMs), which have been considered complementary or adjunctive therapies for symptom management and quality of life (QOL) enhancement along with mainstream care. Although no TCPMs have been listed as an investigational new drug by the US Food and Drug Administration, all TCPMs have resulted in great economic and
clinical benefits in China. For example, yang xue qing nao granules are composed of Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Chinese Angelica Root (Danggui, Radix Angelicae Sinensis), Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis), Mother of Pearl (Zhenzhumu, Concha Margaritiferae), Foetid Cassia Seeds (Juemingzi, Semen Cassiae Torae), Prunella (Xiakucuo, Spica Prunellae Vulgaris), White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae), Szechuan Lovage Root (Chuanxiong, Rhi zoma Ligustici Chuanxiong), Spatholobus (Jixueteng, Caulis Millettiae Seu Spathioli), Corydalis Rhizome (Yanhusuo, Corydalis Rhizome), and Chinese Wild Ginger (Xinxin, Herba Asari Cum Radice). Yang xue qing nao granules have been extensively tested in various types of clinical trials. In 2012, the global market of yang xue qing nao granules was approximately 0.5 billion RMB (equivalent to 81.7 million USD). Several randomized controlled trials (RCTs) and systematic reviews regarding the efficacy of acupuncture for EH have been published in English.\textsuperscript{10–12} However, there is insufficient clinical evidence to support or discourage the use of many commonly used TCPMs in hypertensive patients,\textsuperscript{13–14} especially in conjunction with conventional therapy, despite wide acceptance and authoritative recommendations by the China Food and Drug Administration (CFDA) (available at http://www.sda.gov.cn) and the Pharmacopoeia of the People’s Republic of China (2010 edition) for EH in China.\textsuperscript{15} Therefore, confirmation of the effectiveness of TCPMs as complementary therapies could have a substantial impact on EH management worldwide.

These TCPMs are composed of >100 herbs, most of which have specific antihypertensive effects both \textit{in vitro} and \textit{in vivo} when tested alone. Pharmacological studies have indicated that most studied TCPMs can be used to lower BP, and the potential mechanisms may be related to improvements in the plasma levels of endothelin, calcitonin gene-related peptide, nitric oxide; the inhibition of sympathetic activity; and the regulation of the renin-angiotensin system.\textsuperscript{16–19} The most commonly used formulations of TCPM for EH include tablets, capsules, pills, granules, and oral liquid. It remains unknown whether there is robust evidence on the clinical effects of TCPM or whether TCPM can be recommended for routine treatment. However, some relevant trials have been reported in China. Thus, the objective of this study was to provide a comprehensive systematic review to summarize and evaluate the evidence regarding the efficacy of TCPM combined with antihypertensive drugs as a complementary therapy for hypertension. To our knowledge, this is the first systematic English-language review of the clinical trials of all TCPMs for the treatment of EH.

METHODS

A methodological evaluation and meta-analysis were conducted in accordance with the recommendations of the Cochrane Collaboration.

Eligibility Criteria

Type of Studies

Only RCTs were eligible for this review, with no restriction on language or publication status. According to the methodological quality of the included RCTs, they were categorized into 3 levels: trials with a clear method of randomization were defined as definite RCTs; trials with an unknown methodology, in which the claimed “RCTs” may not be real “RCTs,” were defined as potential RCTs; and trials that included treatment and control groups, and in which treatment allocation was not necessarily randomized, were defined as controlled clinical trials (CCTs).

Types of Participants

Participants enrolled in the studies of this review had to meet at least one of the current or past guidelines or definitions of EH, which are described as follows: systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg on at least 2 occasions with off-antihypertensive treatment (after a 4-week washout period) and/or treatment with antihypertensive medication, while excluding secondary hypertension.\textsuperscript{1} Trials without a description of the detailed diagnostic criteria but that included patients with definite EH were also included. Because there are many TCM syndromes (also known as zheng or patterns) of EH,\textsuperscript{7,8,9,13,14} no restriction regarding the diagnostic criteria of TCM was utilized. Trials that included patients of any age, sex, or ethnic origin with EH were eligible. There were no restrictions on population characteristics.

Types of Interventions

TCPMs that had been subjected to a relatively strict drug evaluation process, including active constituent identification, a compatibility mechanism study, efficiency and safety evaluation, and RCTs were included. Substantial systemic preclinical or clinical data (regardless of whether they were provided in publications) were available for these selected TCPMs. In our review, only TCPMs listed in the Chinese National Essential Drug (CNED) of 2012 (available at http://www.sda.gov.cn), the Pharmacopoeia of the People’s Republic of China (PPRC) (2010 edition), and commonly used TCPMs in current clinical practice for EH were included in the analysis. Drugs in CNED and PPRC represent the most important therapies listed by the Chinese government, which have been studied extensively and proven to be safe and effective in treatment. More clinical studies reported the use of commonly used TCPMs. In total, 82 TCPMs were identified for further evaluation.

All parallel RCTs of the 82 TCPMs that compared 1 TCPM plus antihypertensive drugs (TPAD) versus antihypertensive drugs alone for EH were eligible. Co-interventions were matched in both the treatment and control groups. Trials were excluded for the following reasons: a multimodal intervention, including TCPM and other complementary and alternative approaches, was used in either the treatment or control groups; a combination of >2 TCPMs was included in the treatment group; head-to-head comparisons of different types of TCPMs were utilized without a standard Western medicine control group; the types and dosages of antihypertensive drugs used in the treatment or control groups were not the same; only biochemical markers, rather than BP, were reported; no data on BP outcome could be extracted; and duplicated publications reported the same results. Trials that evaluated any TCPM formulation (tablets, capsules, or pills) were included regardless of the treatment period length and the treatment dosage.

Types of Outcome Measures

For inclusion, RCTs had to have evaluated at least one of the following outcomes. The primary outcome measures included mortality, progression to severe complications, and adverse events (AEs). Severe complications were defined as coronary heart disease, myocardial infarction, heart failure, cerebral infarction, cerebral hemorrhage, transient ischemic attack, renal failure, and retinopathy. The secondary outcome
measures included SBP, DBP, and QOL after treatment. Trials were excluded if missing information about the outcome measure were found.

Search Strategy

Studies on 82 TCMs were identified through searches of the following 7 electronic databases from their inception until August 17th, 2014: the Cochrane Library (searched in August 2014), PubMed (1959–2014), EMBASE (1980–2014), the Chinese National Knowledge Infrastructure (1979–2014), the Chinese Scientific Journal Database (1989–2014), the Chinese Biomedical Literature Database (1978–2014), and the Wanfang Database (1985–2014). Because TCMPs were invented and are primarily used in China, we conducted a literature search in the 4 main Chinese electronic databases to include the maximum possible number of clinical trials. To include unpublished studies, we also searched the website of the Chinese clinical trial registry (available at http://www.chictr.org/) and the international clinical trial registry maintained by the US National Institutes of Health (available at http://clinicaltrials.gov/).

For the database searches, the following keywords were used in combination: (“clinical trial” OR “randomized trial” OR “randomized controlled trial”) AND (“essential hypertension” OR “primary hypertension” OR “high blood pressure” OR “blood pressure”) AND (“traditional Chinese patent medicine” OR “Chinese patent medicine” OR “song ling xue mai kai capsule”) OR “Pinus armandi Franch benefitting blood vessel capsule” OR “yang xue mai kai granule”) OR “hurting the blood and clearing brain granule”) OR “liu wei dihuang pill”) OR “liu wei dihuang wan”) OR “remannia six formula”) OR “quanned tianma capsule”) OR “total gastrodia capsule”) OR “shanzha jiang ya capsule”) OR “shanzha jiang ya granule”) OR “shu luo niu huang qing granule”) OR “qing xuan jiang ya granule”) OR “qing xuan jiang ya capsule”) OR “xing nao niu huang qing granule”) OR “xing nao jiang ya tablet”) OR “xing nao jiang ya bi feng tablet”) OR “xing nao jiang ya granule”) OR “xing nao jiang ya bi feng granule) OR “erythrocyte and antihypertensive capsule”) OR “zhen xin jiang ya tablet”) OR “calming heart antihypertensive tablet”) OR “jiu ming jiang ya tablet”) OR “chrysanthemum and cassia seed antihypertensive tablet”) OR “fu fang lingyangjiao capsule”) OR “compound cornu saigae tataricae capsule”) OR “fu fang xiaokucuo jiang ya syrupus”) OR “compound prunella antihypertensive syrupus) OR “gao xue ya su jiang pill”) OR “quickly lowering blood pressure pill”) OR “xue ya an ba su gao”) OR “antihypertensive babu plaster”) OR “qiang li niao lii”) OR “enduring and powerful clearing brain pill”) OR “luobuma tea”) OR “apocynum tea”) OR “apocynum venenum leaves granule”) OR “sanqihua granule”) OR “notoginseng flower granule”) OR “xing liu pill”) OR “calming heart pill”) OR “dong qing bu zhi”) OR “holly fill juice”) OR “duzhong granule”) OR “eucommia granule”) OR “feng shi xi tong tablet”) OR “siegesbeckiae and clerodendroa trichotomum tablet”) OR “shanzha jing jiang zhi tablet”) OR “hawthorn lipid-lowering tablet”) OR “guan tong tablet”) OR “dredging coronary artery tablet”) OR “xing niao niu huang qing xin tablet”) OR “calcus bovis calming brain and heart tablet”) OR “kang mai xin oral liquid”) OR “benefitting blood vessel and heart oral liquid”) OR “mai jun an tablet”) OR “calming pulse tablet”) OR “mai luo tong tablet”) OR “promoting blood circulation tablet”) OR “quanned duzhong capsule”) OR “total eucommia capsule”) OR “yan you cha”) OR “yan you tea”) OR “xu xiao niu huang pill”) OR “quick-acting calculus bovis pill”) OR “qiang re xing nao ling tablet”) OR “clearing heat and calming brain tablet”) OR “xing ming yu tea”) OR “clearing heat and improving eyesight tea”) OR “rong shuan capsule”) OR “thrombolysis capsule”) OR “shan hu jia grandule”) OR “hawthorn and chrysanthemum granule”) OR “fu fang an jiang ya granule”) OR “gastrodia granule”) OR “duzhong ping ya capsule”) OR “eucommia antihypertensive tablet”) OR “jia tong yan capsule”) OR “antihypertensive pill”) OR “zhen xin jiang ya granule”) OR “antihypertensive pill”) OR “luo ji jiang ya tablet”) OR “apocynum antihypertensive tablet”) OR “shan zhuang jiang zhi tablet”) OR “shanzha jing jiang zhi tablet”) OR “forced blood pressure”) AND (“traditional Chinese patent medicine”) OR “hypertension”) OR “high blood pressure”) AND (“essential hypertension”) OR “primary hypertension”) OR “clinical trial”) OR “randomized trial”) OR “clinical trial registry”) (available at http://clinicaltrials.gov/).

Furthermore, the reference lists of the identified original articles were manually searched for additional eligible studies. The pharmaceutical companies that manufacture TCMPs were contacted to identify further published and unpublished studies. The literature search was independently conducted by 2 reviewers, and disagreements were settled by discussion between the reviewers or a consultation with a third party.
Data Extraction and Management

Two reviewers independently screened the trials based on the titles and abstracts. The following information was extracted from the eligible trials that met the inclusion criteria: basic characteristics (age, gender, race of participants, and sample size) of the included subjects and basic characteristics (authors, title of study, year of publication, randomization, allocation concealment, blinding, intention to treat analysis, drop-out or withdrawal, diagnosis standard, TCPM name, interventions in the treatment and control groups, outcome measures, treatment duration, and safety reporting) of the included trials. Missing data were obtained from the original authors via email, fax, or telephone when possible. Disagreements were resolved by discussion with a third reviewer.

Risk of Bias in Individual Studies

Two reviewers independently assessed the risk of bias in the included studies using tools from the Cochrane Handbook for Systematic Review of Interventions Version 5.1.0 (updated March 2011). The factors assessed included the following 7 items: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other sources of bias (from Chapter 8: assessing risk of bias in included studies). For each item, the risk of bias was classified as “low,” “unclear,” or “high” according to the previously discussed criteria.

Data Analysis

Data regarding outcomes in the eligible studies were combined in the meta-analysis using the Revman 5.1 software provided by the Cochrane Collaboration. Dichotomous data were presented as the risk ratio (RR), and continuous outcomes were presented as the weighted mean difference (WMD); both measurements were reported with the 95% confidence interval (CI). Statistical heterogeneity between the studies was significant when $I^2 \geq 50\%$. Fixed-effects model was used if there was no significant heterogeneity of the data ($I^2 < 50\%$); random-effects model was used if significant heterogeneity existed. The risk of publication bias was assessed by funnel plot analysis for each meta-analysis if sufficient studies (ie, >10) were identified.

RESULTS

Literature Search

Figure 1 shows a flowchart that depicts the study search and selection process. An initial screening yielded 12,004 potentially relevant citations in accordance with the search strategy. A total of 11,886 articles were screened after 118 duplicates of the same articles included in different databases were removed. According to the inclusion criteria, 11,731 articles were excluded on the basis of the titles and abstracts. These studies were primarily excluded because they were not RCTs. After a full text reading of 155 studies, 82 articles were excluded for the following reasons: the participants did not meet the inclusion criteria (n = 70), duplication (n = 2), no control...
group (n = 3), the intervention included another Chinese herbal formula (n = 5), and no data for extraction (n = 2). Ultimately, 73 studies were included for analysis.21–93

Study Characteristics

The characteristics of the 73 included trials are summarized in Table 1. Of the 82 TCPMs, definite or possible RCTs and CCTs for 17 TCPMs were identified. For the remaining 67 TCPMs, we only identified case reports, case series, and uncontrolled observational studies. Seventy-three trials regarding 17 TCPMs were included, of which 63 and 10 trials were definite or possible RCTs and CCTs, respectively. All trials were conducted in China and published in Chinese journals (from 1994 to 2013).

The RCTs included 8138 participants with EH. The age of the hypertensive patients ranged from 23 to 88 years. Standard Western medicine diagnostic criteria for EH was applied in all included trials. Additionally, many trials used TCM diagnostic criteria according to TCM theory. The formulations of the TCPMs included capsules, granules, pills, oral liquid, and tablets. Components of the 17 included TCPMs were depicted in Table 2.21–93 All 73 trials were single-center trials and had parallel designs that compared TPAD and antihypertensive drugs in a control group. The patients in the treatment group were treated with the same type and dosage of antihypertensive drugs under the same standard in the control group. The total treatment duration ranged from 2 weeks to 1 year.

Two trials reported mortality and progression to severe complications after a 1-year follow-up.46,66 BP was assessed in all included trials. The treatment durations of 5 trials was >6 months.42,46,50,66,89 The QOL was reported in 5 trials,63,36,42,76,92 of which 4 trials33,36,42,76 used the Croog Scale.94 and 1 trial92 used the SF-36 Scale.95 The AEs of 33 trials have been described in detail.21–23,28–30,33,35,38–40,43,45–50,53,60–68,71,74,77,79,84,85,88–91

Risk of Bias in Individual Studies

The risk of bias in the included trials was assessed as unclear and high according to the predefined Cochrane criteria. No randomized, double-blind, and placebo-controlled trial was identified. Only 4 trials on Song ling xue mai kang capsules,21,23,28,44 1 trial on Yang xue qing nao granules,51 1 trial on Liu wei dihuang pills,65 2 trials on Xin ke shu,70,71 2 trials on Tianma gouteng granules,76,77 1 trial on Quan tianma capsules,55 1 trial on Zhen ju jiang ya tablets,87 and 1 trial on Quan tianma capsules, Song ling xue mai kang capsules, Tianma gouteng granules, Tianma shouwu tablets, Xin ke shu, and Yang xue qing nao granules. Of the 33 trials, no AEs were reported in 10 trials and with Quan tianma tablets. The AEs of the other 12 TCPMs included orthostatic hypotension, headache, dizziness, facial flushing, palpitations, nasal congestion, drowsiness, rash, pruritus, dry mouth, cough, nausea, abdominal discomfort, diarrhea, constipation, and ankle edema. No serious AEs were identified, and all AEs disappeared without special treatment.

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There were 1087 patients in the TPAD group and 1083 patients in the antihypertensive drugs group. Because significant heterogeneity among the trials on every TCPM existed (chi-square = 28.21, P = 0.003; F = 61%), a random-effects model was applied. A meta-analysis of all 12 TCPMs indicated that there was no significant difference regarding the AEs between TPAD and antihypertensive drugs (RR: 0.57; 95% CI: 0.32–1.00; P = 0.05), with the exception of Xin ke shu (RR: 0.11; 95% CI: 0.04–0.29; P < 0.0001), Yang xue qing nao granules (RR: 0.18; 95% CI: 0.05–0.60; P = 0.005), and Quan tianma capsules (RR: 22.05; 95% CI: 1.34–363.98; P = 0.03) (Figure 2).

Primary Outcomes

Mortality and Progression to Severe Complications

The effects of TCPM on mortality and the progression to severe complications were only reported in 2 trials.46,66 One trial on Yang xue qing nao granules (130 patients) assessed the incidence of mortality and progression to severe complications at 1 year after treatment compared with antihypertensive drugs (with no detailed information regarding the classification of AEs and dosage).46 No deaths or severe complications occurred in the Yang xue qing nao granules group. However, 5 cases of coronary heart disease and 2 cases of transient ischemic attack were identified in the antihypertensive drugs group. A meta-analysis indicated that there was no significant difference between Yang xue qing nao granules and antihypertensive drugs regarding the incidence of coronary heart disease (RR: 0.09; 95% CI: 0.00–1.60; P = 0.10) or a transient ischemic attack (RR: 0.20; 95% CI: 0.01–4.25; P = 0.30).

Another trial also evaluated the effects of quan tianma capsules (500 patients) on the incidence of mortality and the progression to severe complications compared with nifedipine sustained-release tablets (10 mg, bid).66 The meta-analysis indicated that there was no significant difference between quan tianma capsules and nifedipine sustained-release tablets for the incidence of coronary heart disease (RR: 0.84; 95% CI: 0.54–1.29; P = 0.43), myocardial infarction (RR: 0.57; 95% CI: 0.24–1.36; P = 0.21), heart failure (RR: 0.42; 95% CI: 0.11–1.57; P = 0.20), cerebral infarction (RR: 1.04; 95% CI: 0.66–1.62; P = 0.87), cerebral hemorrhage (RR: 0.43; 95% CI: 0.13–1.44; P = 0.17), transient ischemic attack (RR: 1.15; 95% CI: 0.76–1.72; P = 0.51), renal failure (RR: 0.91; 95% CI: 0.42–1.96; P = 0.81), retinopathy (RR: 1.06; 95% CI: 0.49–2.32; P = 0.88), or death (RR: 0.26; 95% CI: 0.06–1.04; P = 0.06).

AEs

AE monitoring was reported in 33 trials on 13 TCPMs,21–23,28–30,33,35,38–40,43,45–50,53,60–68,71,74,77,79,84,85,88–91 whereas it is not mentioned in the remaining 40 trials. The 13 included TCPMs were Liu wei dihuang pills, Niuhuang jiang ya pills, Qiang li tianma duzhong capsules, Quan tianma capsules, Song ling xue mai kang capsules, Tianma gouteng granules, Tianma shouwu tablets, Xin ke shu, and Yang xue qing nao granules. Of the 33 trials, no AEs were reported in 10 trials and with Quan tianma tablets. The AEs of the other 12 TCPMs included orthostatic hypotension, headache, dizziness, facial flushing, palpitations, nasal congestion, drowsiness, rash, pruritus, dry mouth, cough, nausea, abdominal discomfort, diarrhea, constipation, and ankle edema. No serious AEs were identified, and all AEs disappeared without special treatment. There were 1087 patients in the TPAD group and 1083 patients in the antihypertensive drugs group. Because significant heterogeneity among the trials on every TCPM existed (chi-square = 28.21, P = 0.003; F = 61%), a random-effects model was applied. A meta-analysis of all 12 TCPMs indicated that there was no significant difference regarding the AEs between TPAD and antihypertensive drugs (RR: 0.57; 95% CI: 0.32–1.00; P = 0.05), with the exception of Xin ke shu (RR: 0.11; 95% CI: 0.04–0.29; P < 0.0001), Yang xue qing nao granules (RR: 0.18; 95% CI: 0.05–0.60; P = 0.005), and Quan tianma capsules (RR: 22.05; 95% CI: 1.34–363.98; P = 0.03) (Figure 2).
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Secondary Outcomes

BP

All 73 included trials evaluated the effects of TCPMs on BP in individuals with EH. Fourteen trials used the categorical BP to evaluate the efficacy of 8 TCPMs, the evaluation criteria of which were authoritatively recommended by the CFDA and the Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine. The effects were described as follows: “significant improvement” (DBP decreased by 10 mmHg and reached the normal range or DBP did not return to normal but decreased by more than 20 mmHg), “improvement” (DBP decreased by <10 mmHg but reached the normal range, DBP decreased by 10–19 mmHg but did not reach the normal range, or SBP decreased by >30 mmHg), and “no improvement” (did not meet the previously discussed standards). To permit at least some overall analysis, these outcomes were converted into dichotomous data. Therefore, we grouped together “significant improvement” and “improvement” as “effective” and “no improvement” as “ineffective.” The 8 TCPMs that were included were Liu wei dihuang pills, Niuhuang jiang ya pills, Qi ju dihuang pills, Quan tianma capsules, Song ling xue mai kang capsules, Tianma gouteng granules, Tianma shouwu tablets, and Yang xue qing nao granules. There were 809 patients in the TPAD group and 787 individuals in the antihypertensive drugs group. Fixed-effects model was used because no significant heterogeneity of the trials was identified (chi-square = 5.29, P = 0.62; I² = 0%). A meta-analysis of the 14 trials on the 8 TCPMs identified a significant BP-lowering effect of TPAD (RR: 1.15; 95% CI: 1.10–1.20; P < 0.00001) compared with antihypertensive drugs alone (Figure 3).

Fifty-nine trials used continuous BP to evaluate the treatment effects of 16 TCPMs in hypertensive patients, with the exception of Tianma shouwu tablets. The combined results suggested that 13 TCPMs (13/16, 81.25%) used as complementary therapy to antihypertensive drugs significantly decreased SBP by 3.94–13.50 mmHg; however, the other 3 TCPMs (3/16, 18.75%) decreased SBP by 1.00–5.00 mmHg, with no significant difference compared with antihypertensive drugs alone. The meta-analysis also indicated that 9 TCPMs (9/16, 56.25%) used as complementary therapy to antihypertensive drugs significantly decreased DBP by 2.28–11.25 mmHg; however, the other 7 TCPMs (7/16, 43.75%) decreased DBP by -1.00–9.41 mmHg with no significant difference compared with antihypertensive drugs alone. The detailed effect sizes of TPAD compared with antihypertensive drugs alone are summarized in Table 3. Two TCPMs, Song ling xue mai kang capsules (854 vs 835) and Yang xue qing nao granules (882 vs. 879), had more studies and >1000 patients, respectively.

Quality of Life

Both the Croog and SF-36 scales were used to assess the QOL in 5 trials regarding Song ling xue mai capsules,33,36,42 Tianma gouteng granules,76 and Tian shu capsules.92 All 5 trials reported a significant improvement in the QOL of the TPAD group compared with the antihypertensive drug group at the end of treatment. One trial on Song ling xue mai capsules demonstrated that the Croog Scale increased with the total score (WMD = 26.10; 95% CI: 25.88–26.32; P < 0.00001).

The other 2 trials on song ling xue mai capsules and Yang xue qing nao granules, had more studies and >1000 patients, respectively.
### TABLE 2. Components of the Included TCPMs

<table>
<thead>
<tr>
<th>TCPMs</th>
<th>Components</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Song ling xue mai kang capsules</td>
<td>Fresh Pine Needles (Xiansongye, Pinus armandi Franch), Pueraria (Gegen, Radix Puerariae), and Pearl (Zhenzhu, Margarita)</td>
<td>21–44</td>
</tr>
<tr>
<td>Yang xue qing nao granules</td>
<td>Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Chinese Angelica Root (Danggui, Angelicae Sinensis), Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis), Mother of Pearl (Zhenzhumu, Concha Margaratiferae), Foetid Cassia Seeds (Juejingzi, Semen Cassiae Torae), Prunella (Xiaokuao, Spica Prunellae Vulgaris), White Peony Root (Baishao, Radix Albus Paconiae Lactiflorae), Szechuan Lovage Root (Chuanxiong, Rhizoma Ligustici Chuanxiong), Spatholobus (Jixu, Caulis Spatholobi), Corydalis Rhizome (Yanhusuo, Corydalis Rhizome), and Chinese Wild Ginger (Xixin, Herba Asari Cum Radice)</td>
<td>45–54</td>
</tr>
<tr>
<td>Liu wei dihuang pills</td>
<td>Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Cornus Fruit (Shanzhuyu, Corni Fructus), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Poria (Fuling, Scirpium Poriae Cocos), Alisma (Zexie, Rhizoma Alismatis), and Cortex of the Peony Tree Rote (Danpi, Cortex Radicis Moutan)</td>
<td>55–65</td>
</tr>
<tr>
<td>Quan tianma capsules</td>
<td>Gastrodia (Tianma, Gastrodiae Rhizoma), Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis), Wild Chrysanthemum Flower (Yejuhua, Flos Chrysanthemi Indici), leaves of the Peony Tree (Peony Root (Baishao, Radix Albus Paconiae Lactiflorae), Borneol (Bingpian, Borneolum), Foetid Cassia Seeds (Juejingzi, Semen Cassiae Torae), Chinese Motherwort (Yimucao, Herba Leonuri Heterophylli), Poria (Fuling, Scirpium Poriae Cocos), and Flowery Knotweed Stem (Shouwuteng, Polygony Multi florii Caulis)</td>
<td>66–68</td>
</tr>
<tr>
<td>xin ke shu</td>
<td>Salvia Root (Danshen, Radix Salviae Miltiorrhizae), Pueraria (Gegen, Radix Puerariae), Notoginseng Root (Sanqi, Notoginseng Radix), Cestaegus Fruit (Shanzha, Cestaegus Fructus), and Costus Root (Muxiang, Radix Aucklandiae Lappae)</td>
<td>69–72</td>
</tr>
<tr>
<td>Qing niao jiang ya tablets</td>
<td>Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Prunella (Xiaokuao, Spica Prunellae Vulgaris), Pagoda Tree Flower (Huaimi, Flos Immaturus Sophorae Japonice), Magnette (Cishi, Magnettum), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Chinese Angelica Root (Danggui, Angelicae Sinensis), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Salvia Root (Danshen, Radix Salviae Miltiorrhizae), Leech (Shuizhi, Hirudo seu Whitmania), Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis), Foetid Cassia Seeds (Juejingzi, Semen Cassiae Torae), Earthworm (Dilong, Lumbricus), and Mother of Pearl (Zhenzhumu, Concha Margaratiferae)</td>
<td>73–75</td>
</tr>
<tr>
<td>Tianna gouteng granules</td>
<td>Gastrodia (Tianma, Gastrodiae Rhizoma), Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis), Abalone Shell (Shijueying, Hollandia Concha), Eucommia Bark (Duzhong, Cortex Eucommiae Rhizoma), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Chinese Taxisillus Twig (Sangshi, Herba Taxillii), Gardenia (Zhizi, Fructus Gardeniae Japonica), Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Chinese Motherwort (Yimucao, Herba Leonuri Heterophylli), Poria (Fuling, Scirpium Poriae Cocos), and Flowery Knotweed Stem (Shouwuteng, Polygony Multi florii Caulis)</td>
<td>76–78</td>
</tr>
<tr>
<td>Qiang li tianma duzhong capsules</td>
<td>Gastrodia (Tianma, Gastrodiae Rhizoma), Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Chinese viscum herb (Hujiusheng, Herba Visci), Ningpo Figwort Root (Xuanshen, Radix Scrophulariae Ning poensis), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Chinese Angelica Root (Danggui, Angelicae Sinensis), Processed aconite (Fuzi, Radix Lateralis Praeparatus Aconitae Carminacae), Prepared Wild Aconite (Caowu, Radix Aconiti Kusnezoffii Preparata), Nototoperygium Root (Qinghuo, Nototoperygium Rhizoma), Pusen Angelica Root (Rhuo, Radix Angelicae Pubescens), and Straw Wege (Gaoben, Radix Et Rhizoma Ligustici Chinensis)</td>
<td>79–81</td>
</tr>
<tr>
<td>Qi ji dihuang pills</td>
<td>Chinese Wolfberry Fruit (Gouqizi, Fructus Lycii Chinensis), Chrysanthemum Flower (Juhua, Flos Chrysanthemi Morifolii), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), Cornus Fruit (Shanzhuyu, Corni Fructus), Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Poria (Fuling, Scirpium Poriae Cocos), Alisma (Zexie, Rhizoma Alismatis), and Cortex of the Peony Tree Rote (Danpi, Cortex Radicis Moutan)</td>
<td>82–83</td>
</tr>
<tr>
<td>niuhuang jiang ya pills</td>
<td>extracts from Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Codonopsis Root (Dangshen, Radix Codonopisits Pilosulae), Baical Skullcap Root (Huangqin, Radix Scutellariae Baicalensis), Szechuan Lovage Root (Chuanxiong, Rhizoma Ligustici Chuanxiang), White Peony Root (Baishao, Radix Albus Paconiae Lactiflorae), Borneol (Bingpian, Borneolum), Foetid Cassia Seeds (Juejingzi, Semen Cassiae Torae), Chinese Nardostachys Rhizome (Gansong, Radix Et Rhizoma Nardostachydis), Tumeric Tuber (Yujin, Tuber Curcumae), Field Mint (Bohe, Herba Menthae Haplocalycis), Cattle (Niu huang, Calculus Bovis), Antelope Horn (Lingyangjiao, Cornu Saigae Tataricae), Eucommia Bark (Duzhong, Cortex Eucommiae Rhizoma), and Pearl (Zhenzhu, Margarita)</td>
<td>84–86</td>
</tr>
<tr>
<td>Zhen ju jiang ya tablets</td>
<td>Wild Chrysanthemum Flower (Yehuahua, Flos Chrysanthemi Indici), Pearl (Zhenzhu, Margarita), clonidine hydrochloride, hydroxychlorothiazide, and rutin</td>
<td>87</td>
</tr>
<tr>
<td>Qiang li ding xuan tablets</td>
<td>Gastrodia (Tianma, Gastrodiae Rhizoma), Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis), Wild Chrysanthemum Flower (Yehuahua, Flos Chrysanthemi Indici), leaves of Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis), and Szechuan Lovage Root (Chuanxiong, Rhizoma Ligustici Chuanxiang)</td>
<td>88</td>
</tr>
</tbody>
</table>
DISCUSSION

Summary of Evidence

The previous decade has witnessed an unprecedented expansion of the field of antihypertensive treatment and drug discovery and development. Thus, Western medicine became the dominant medical treatment worldwide. However, it has been increasingly realized that Western medicine may sometimes fail to treat cardiovascular diseases (CVDs), especially in patients with a history of conventional medicine-related AEs, whereas CAM is becoming increasingly popular and frequently used among patients with CVDs. As a result of the different theoretical systems and control methods, Western physicians often find CAM difficult to understand. TCM has continued to hold an important position in primary healthcare both in China and other Asian countries. Additionally, there is one important characteristic of China’s national medical system that facilitates CAM, that is, integrative medicine, which combines TCM and Western medicine together in the clinic and is responsible for health care. Therefore, as an adjunctive treatment to antihypertensive drugs, TCPM is a popular natural product for EH. Because of its health-enhancing qualities, TCPM has been developed and used in China for >30 years. Currently, there are 82 TCPMs approved by the CFDA for the treatment to antihypertensive drugs, AEs are adverse events, TCPM = traditional Chinese patent medicine.

Table 1: Summary of AE profiles of the TCPM trials

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu wei dihuang pill</td>
<td>1</td>
<td>49</td>
<td>48</td>
<td>3.4%</td>
</tr>
<tr>
<td>Niuhuang jiang ya pill</td>
<td>15</td>
<td>75</td>
<td>70</td>
<td>14.7%</td>
</tr>
<tr>
<td>Qiang li ding xuan tablet</td>
<td>7</td>
<td>48</td>
<td>12</td>
<td>12.6%</td>
</tr>
<tr>
<td>Qiang li tianma duzhong</td>
<td>1</td>
<td>39</td>
<td>2</td>
<td>4.4%</td>
</tr>
<tr>
<td>Qiang gan jiang ya capsule</td>
<td>0</td>
<td>40</td>
<td>4</td>
<td>3.2%</td>
</tr>
<tr>
<td>Qiang niao jiang ya tablet</td>
<td>10</td>
<td>39</td>
<td>0</td>
<td>3.3%</td>
</tr>
<tr>
<td>Quan tianma capsule</td>
<td>1</td>
<td>36</td>
<td>0</td>
<td>2.7%</td>
</tr>
<tr>
<td>Song ling xue mai kang</td>
<td>14</td>
<td>249</td>
<td>16</td>
<td>13.8%</td>
</tr>
<tr>
<td>Tianma gouteng granule</td>
<td>12</td>
<td>48</td>
<td>12</td>
<td>13.8%</td>
</tr>
<tr>
<td>Tianma shouwu tablet</td>
<td>2</td>
<td>40</td>
<td>4</td>
<td>7.1%</td>
</tr>
<tr>
<td>Xin ke shu</td>
<td>4</td>
<td>149</td>
<td>38</td>
<td>120</td>
</tr>
<tr>
<td>Yang xue qing nao granule</td>
<td>3</td>
<td>275</td>
<td>17</td>
<td>276</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1087</td>
<td>1083</td>
<td>100.0%</td>
<td>0.57 [0.32, 1.00]</td>
</tr>
<tr>
<td>Total events</td>
<td>70</td>
<td>126</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 3. Forest plot of the trials that compared TPAD with antihypertensive drugs for BP. AD = antihypertensive drugs, BP = blood pressure, TPAD = traditional Chinese patent medicine plus antihypertensive drugs.
TABLE 3. Effect sizes of TPAD Compared with Antihypertensive Drugs

<table>
<thead>
<tr>
<th>TCMP</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Song ling xue mai kang capsules</td>
<td>19</td>
<td>1689</td>
<td>WMD: −7.30 (−8.56, −6.04); P &lt; 0.00001</td>
<td>WMD: −6.74 (−8.32, −5.16); P &lt; 0.00001</td>
</tr>
<tr>
<td>Yang xue qing nao granules</td>
<td>8</td>
<td>1761</td>
<td>WMD: −8.11 (−11.96, −4.27); P &lt; 0.00001</td>
<td>WMD: −4.91 (−7.42, −2.40); P &lt; 0.00001</td>
</tr>
<tr>
<td>Liu wei dihuang pills</td>
<td>9</td>
<td>833</td>
<td>WMD: −7.76 (−10.01, −5.50); P &lt; 0.00001</td>
<td>WMD: −6.61 (−7.60, −5.62); P &lt; 0.00001</td>
</tr>
<tr>
<td>Quan tianma capsules</td>
<td>2</td>
<td>600</td>
<td>WMD: −3.94 (−5.21, −2.68); P &lt; 0.00001</td>
<td>WMD: −3.89 (−4.90, −2.87); P &lt; 0.00001</td>
</tr>
<tr>
<td>Xin ke shu</td>
<td>4</td>
<td>371</td>
<td>WMD: −8.68 (−15.35, −2.02); P = 0.01</td>
<td>WMD: −1.96 (−5.12, 1.21); P = 0.23</td>
</tr>
<tr>
<td>Qing nao jiang ya tablets</td>
<td>3</td>
<td>324</td>
<td>WMD: −7.19 (−8.86, −5.52); P &lt; 0.00001</td>
<td>WMD: −9.41 (−21.07, 2.25); P = 0.11</td>
</tr>
<tr>
<td>Tianma gouteng granules</td>
<td>2</td>
<td>157</td>
<td>WMD: −4.91 (−7.23, −2.60); P &lt; 0.0001</td>
<td>WMD: −2.92 (−7.81, 1.98); P = 0.24</td>
</tr>
<tr>
<td>Qiang li tianma duzhong capsules</td>
<td>3</td>
<td>214</td>
<td>WMD: −2.34 (−4.91, 0.23); P = 0.07</td>
<td>WMD: −2.28 (−3.96, −0.60); P = 0.008</td>
</tr>
<tr>
<td>Qi ju dihuang pills</td>
<td>1</td>
<td>80</td>
<td>WMD: −5.00 (−20.44, 10.44); P = 0.53</td>
<td>WMD: −1.00 (−3.23, 1.23); P = 0.38</td>
</tr>
<tr>
<td>Niu huang jiang ya pills</td>
<td>2</td>
<td>130</td>
<td>WMD: −7.13 (−10.17, −4.09); P &lt; 0.00001</td>
<td>WMD: −6.61 (−13.47, 0.25); P = 0.06</td>
</tr>
<tr>
<td>Zhen ju jiang ya tablets</td>
<td>1</td>
<td>150</td>
<td>WMD: −6.68 (−9.02, −4.34); P &lt; 0.00001</td>
<td>WMD: −5.94 (−7.69, −4.19); P &lt; 0.00001</td>
</tr>
<tr>
<td>Qiang li ding xuan tablets</td>
<td>1</td>
<td>96</td>
<td>WMD: −9.40 (−13.32, −5.58); P &lt; 0.00001</td>
<td>WMD: −9.30 (−11.61, −6.99); P &lt; 0.00001</td>
</tr>
<tr>
<td>Qiang gan jiang ya capsules</td>
<td>1</td>
<td>80</td>
<td>WMD: −9.70 (−11.15, −8.25); P &lt; 0.00001</td>
<td>WMD: −3.50 (−5.41, −1.59); P = 0.0003</td>
</tr>
<tr>
<td>Qiang xuan jiang ya tablets</td>
<td>1</td>
<td>61</td>
<td>WMD: −1.00 (−4.17, 2.17); P = 0.54</td>
<td>WMD: 1.00 (−1.93, 3.93); P = 0.50</td>
</tr>
<tr>
<td>Tian shu capsules</td>
<td>3</td>
<td>60</td>
<td>WMD: −5.87 (−9.20, −2.54); P &lt; 0.00001</td>
<td>WMD: −1.87 (−4.27, 0.53); P = 0.13</td>
</tr>
<tr>
<td>Cornu saigae tataricae capsules</td>
<td>1</td>
<td>60</td>
<td>WMD: −13.50 (−18.06, −8.94); P &lt; 0.00001</td>
<td>WMD: −11.25 (−14.98, −7.52); P &lt; 0.00001</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure, No. = number, SBP = systolic blood pressure, TCMP = traditional Chinese patent medicine, TPAD = traditional Chinese patent medicine plus antihypertensive drugs, WMD = weighted mean difference.

Effect sizes of TPAD Compared with Antihypertensive Drugs

The table shows the effect sizes of traditional Chinese patent medicine (TPAD) compared with antihypertensive drugs for systolic blood pressure (SBP) and diastolic blood pressure (DBP). The effect sizes are presented as weighted mean differences (WMD) along with their 95% confidence intervals and p-values. The table includes data from 19 studies with a total of 1689 participants, showing significant reductions in SBP and DBP with TPAD compared to antihypertensive drugs. The p-values for most comparisons are less than 0.0001, indicating strong statistical significance.

Methodologies. Only 10 trials reported methods for randomization. Allocation concealment was not mentioned in any of the trials. Therefore, the “alleged” trials may not actually represent real RCTs, which could weaken the strength of the clinical evidence and lead to a potential selection bias. No trials were double-blinded. Only 1 trial reported the blinding of participants and personnel. Blinding of the outcome assessment was not mentioned. This would directly lead to performance and detection biases. Additionally, there was a lack of placebo control use. All trials included in the review used an “A + B versus B” design, in which patients with EH are randomized to receive treatment (A) combined with treatment (B) versus treatment (B) alone. This type of add-on design is quite popular in TCM studies in which TCM therapy is added to conventional therapy. Nevertheless, without a rigorous control for a placebo effect, this approach may exaggerate the effects of TCM and is prone to generate false-positive results and significant systemic errors in the assessment of outcomes. We understood that such
bias is a common problem in all TCM studies. Perhaps certain physical features associated with TCPMs, such as aromas, colors, and appearances, limited clinical placebo use. Unfortunately, none of the RCTs utilized a placebo control in the trials. Only a few trials reported drop-outs or withdrawals. Most of the trials did not report details of the intention-to-treat analysis. No trials had a pre-trial estimation of sample size. Thus, whether a sample size met the requirements of a given trial remains unknown.

Second, publication bias is another major cause of bias that should also be considered. We have made efforts to avoid language and location biases; however, only trials conducted in China and published in Chinese could be included for further analysis after comprehensive searches. Therefore, we cannot completely rule out the potential publication bias.

Furthermore, other systematic reviews regarding CAM have encountered similar problems. Recently, through huge investments in scientific research and the economical exploitation of TCM, the Chinese government has undertaken enormous efforts to modernize TCM and aims to prove the efficacy of the treatment of EH.

capsules and Yang xue qing nao granules, which were evaluated have encountered similar problems. Recently, through huge investments in scientific research and the economical exploitation of TCM, the Chinese government has undertaken enormous efforts to modernize TCM and aims to prove the efficacy of TCM according to international standards. However, in our review, only 1 of the 73 selected articles declared their sources of funding.

Overall, the results of the trials included in this systematic review are likely to be biased by many factors because of the poor methodological qualities of these studies. The reported beneficial effect of TCPM in lowering BP in hypertensive patients should be interpreted cautiously. Additionally, 2 TCPMs, Song ling xue mai kang capsules and Yang xue qing nao granules, had more studies and greater patient numbers (>1000 patients) and may be worthy of further research.

CONCLUSIONS

In summary, this systematic review provided the first limited piece of clinical evidence regarding the effectiveness of TCPMs as a complementary therapy in improving mortality, the progression to severe complications, AEs, BP, and QOL. According to the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence, the usage of TCPMs for EH was supported by evidence of class level III. However, because of the negative results on primary outcomes, insufficient clinical data, poor methodological quality, small sample sizes, limited numbers of each trial, and the high heterogeneity of the studies, the current evidence is insufficient to support a recommendation for wide TCPM use.

Therefore, future studies should overcome the limitations of the trials included in this systematic review. The following methodological issues should be cautiously addressed: adequate generation of allocation sequences and the concealment of allocation; appropriate methods of double-blinding (blinding of participants and personnel and blinding of outcome assessment); wider use of placebo controls; strict reporting regarding drop-outs and the use of intention-to-treat analysis; a specifically focus on mortality and cardiovascular events with long-term follow-up; and comprehensive reporting of the trials according to the recommendations of the CONSORT Statement. We also suggest that Song ling xue mai kang capsules and Yang xue qing nao granules, which were evaluated to be with the evidence of class level III, should be prioritized for further research. We hope that this systematic review will pave the way for the generation of evidence-based TCPMs for the treatment of EH.

ACKNOWLEDGMENTS

None.

REFERENCES


Zhao GX. Clinical observation of the combination of Losartan and song ling xue mai kang capsule on 76 cases of patients with essential hypertension. Med Inform. 2011;24:4926–4927.


He ZM, Liang YR. Discussion on the effect of valsartan combined with song ling xue mai kang capsule on essential hypertension. Pract J Cardiac Cereb Pneumal Vasc Dis. 2006;14:968–969.


Xu LR, Gao XW, Chen JX. Effect of song ling xue mai kang capsule on 34 cases of elderly patients with hypertension of liver yang hyperactivity syndrome. Fujian J Tradit Chin Med. 2010;41:45.


Li LQ. Effect of song xue qing nao granule combined with calcium channel blockers on hypertension. J Jiangxi Med Coll. 2006;46:188.


