BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006502
Article Type:	Research
Date Submitted by the Author:	02-Sep-2014
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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine
Keywords:	essential hypertension, Chinese herbal medicine, Jian Ling Decoction, systematic review

Chinese herbal medicine Jian Ling Decoction for essential hypertension: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Jian Ling Decoction (JLD) is often prescribed for improving hypertension-related symptoms in China. However, it has not been systematically reviewed for the treatment of essential hypertension (EH). This review aims to assess the current clinical evidence of JLD for EH.

Design: Seven electronic databases including PubMed, EMBASE, The Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, and Chinese Biomedical Literature Database were searched up to March 2014. Randomized control trials (RCTs) comparing JLD or combined with antihypertensive drugs versus antihypertensive drugs were included. We assessed the methodological quality, extracted the valid data, and conducted the meta-analysis according to criteria from Cochrane group. Primary outcome was blood pressure (BP) and the secondary was quality of life (QOL).

Results: Ten trials (655 patients) with unclear-to-high risk of bias were identified. Meta-analysis showed that JLD alone showed no more better effect on BP, but positive effect on QOL was found when compared to antihypertensive drugs. Significant reduction on systolic BP and diastolic BP were observed on JLD plus antihypertensive drugs when compared to antihypertensive drugs alone. No serious adverse effect was found.

Conclusion: Some encouraging clinical evidence of JLD as a kind of complementary therapy for EH was found. However, more well-designed trials are needed due to poor

methodological quality and high risk of bias.

KEY WORDS

essential hypertension; Chinese herbal medicine; Jian Ling Decoction; systematic review

ARTICLE SUMMARY

Article focus

Jian Ling Decoction (JLD), a traditional Chinese herbal formula, is often prescribed for patients with essential hypertension (EH).

Key messages

This systematic review indicates that there are some encouraging clinical evidence of JLD as a kind of complementary therapy for EH. However, more well-designed trials are needed.

Strengths and limitations of this study

The strength of this systematic review is its comprehensive, unbiased search of seven electronic databases, especially in four main Chinese databases, without language and publication restrictions. The included trials were small with poor methodological quality and significant heterogeneity.

INTRODUCTION

Hypertension is one of the most important preventable causes of death and one of the commonest conditions treated in primary health care, which represents an important public health challenge because of its high prevalence and concomitant increase in risk of cardiovascular, cerebrovascular and renal diseases [1, 2]. It has been ranked as the leading global risk factor for mortality and as the third leading risk factor for disease burden according to the comparative Risk Assessment Collaborating Group [3, 4]. Currently, about 1 billion patients have been affected [5]. The association between blood pressure (BP) and mortality has been discovered approximately one hundred years ago [6]. Recent studies also confirmed that BP level is closely related to vascular outcomes, and even a minor reduction of BP could reduce cardiovascular events, especially stroke [7, 8]. Therefore, early diagnosis and effective treatment is of great importance for patients with essential hypertension (EH). Nevertheless, despite remarkable achievements on research and development of antihypertensive drugs, the current awareness, curative and control rates of hypertension among different age-groups still far from satisfactory [9, 10]. Additionally, in the light of the undesirable effects of antihypertensive drugs, in the western countries, some patients with EH and other cardiovascular diseases are increasingly using complementary and alternative medicine (CAM) [11-13], including traditional Chinese medicine (TCM), hoping for another adjunctive approach with few adverse effects [14-16].

Chinese herbal medicine (CHM), one of the most common treatment measures, has played an important role for relieving hypertension related signs and symptoms for centuries in East Asia [17, 18]. Recently, more robust evidence from systematic reviews (SRs) suggested the efficacy and safety of CHM for EH [19-26]. In TCM theory, liver yang hyperactivity syndrome (LYHS) and liver-kidney yin deficiency syndrome (LKYDS) are the two most important patterns of EH, which often appear at the same time. They are manifested as headache, vertigo, tinnitus, irritability, insomnia, lassitude in waist and legs, dysphoria with feverish sensation, dry mouth, bright red tongue with less fur, and wiry pulse [14, 17, 21, 27, 28]. Jian Ling Decoction (JLD) is a traditional CHM dispensed by *Zhang Xichun* in *Yi Xue Zhong Zhong Can Xi Lu* (also named as Integrating Chinese and Western Medicine) in 1920s. It contains eight commonly used herbs: Common Yam Rhizome (Shanyao, *Rhizoma Dioscoreae*), Twotooth Achyranthes Root (Niuxi, *Radix Achyranthis Bidentatae*), Red Ochre (Daizheshi, *Ochre Haematitum*), Dragon's Bones (Longgu, *Os Draconis*), Oyster Shell (Muli, *Concha Ostreae*), Rehmannia Root (Dihuang, Radix Rehmanniae), White Peony Root (Baishao, *Radix Paeoniae Alba*), and Platycladi Seed (Baiziren, *Semen Platycladi*). All of these herbs have been recorded in Pharmacopoeia of the People's Republic of China (2010 edition). Both LYHS and LKYDS could be well relieved by JLD [19]. Currently, it is often prescribed for the management of EH by TCM practitioners in China. The pharmacological mechanisms may be related to the reduction of angiotensin II, IL-6, tumor necrosis factor-α (TNF-α), leptin, insulin resistance, blood lipids, etc [29-34]. Clinically, a large number of studies (including

case reports, case series, controlled observational studies, randomized trials, etc) have reported the effect of JLD on EH, including lowering BP, reducing inflammation, reversing cardiovascular risk factors, and improving clinical symptoms and quality of life (QOL) [35-37]. However, there's no comprehensive evaluation of clinical trials on the efficacy and adverse effects of JLD. This review aims to systematically review the published and unpublished randomized controlled trials (RCTs) to evaluate the current evidence of JLD in treating EH.

METHODS

This study was conducted according to the Cochrane practice [38].

Search strategies

RCTs on JLD for treating hypertensive patients were screened *via* the following electronic databases from their respective inceptions up to March 2014: Cochrane Central Register of Controlled Trials (CENTRAL, 1996-2014), PubMed (1959-2014), and EMBASE (1980-2014). In addition, as JLD is mainly prescribed in China, 4 Chinese electronic databases including Chinese National Knowledge Infrastructure (CNKI, 1980-2014), Chinese Scientific Journal Database (VIP, 1989-2014), Chinese Biomedical Literature Database (CBM, 1978-2014), and Wanfang Database (1998-2014) were searched to retrieve the maximum possible number of trials. We

also conducted literature searching in the website of Chinese clinical trial registry (available at: http://www.chictr.org/) and international clinical trial registry by US National Institutes of Health (available at: http://clinicaltrials.gov/) for all the ongoing registered clinical trials and unpublished articles. Bibliographies of studies identified in the systematic search were checked for potentially relevant publications. No restriction on publication status or language was imposed.

Keywords for databases searching were ('hypertension' OR 'essential hypertension' OR 'primary hypertension' OR 'high blood pressure' OR 'blood pressure') AND ('*jian ling* decoction' OR '*jianling* decoction' OR '*jian ling tang*' OR '*jianling tang*' OR '*jianlingtang*') AND ('clinical trial' OR 'randomized controlled trial') (Additional file 1).

Study selection

Types of studies

RCTs about the use of JLD for the treatment of EH were included. Quasi-randomized trials and animal experiments were excluded.

Participants

Trials focused on the patients suffering from EH were included. All patients

should meet the following diagnostic criteria: systolic blood pressure (SBP) ≥ 140 mmHg, and/or, diastolic blood pressure (DBP) ≥ 90 mmHg. Those without description of diagnostic criteria but stated patients with definite EH were also considered. Patients with secondary hypertension should be excluded. There is no restriction on gender, age, or ethnic origin.

Interventions

Studies comparing JLD or combined with antihypertensive drugs versus antihypertensive drugs were included. Studies assessing the combined effect of JLD with other interventions (*e.g.* another CHM, qigong, Tai Chi, acupuncture, moxibustion and massage) were excluded. Interventions in control group include antihypertensive drugs. Studies which used non-conventional medicine or CAM as control groups were excluded as well.

According to the principle of the similarity of TCM formula [39], modified JLD should contain at least 6 out of 8 herbs used in JLD, or, only few herbs could be added into JLD based on TCM syndrome theory. However, the new prescription should contain the following four principal drugs: Twotooth Achyranthes Root (Niuxi, *Radix Achyranthis Bidentatae*), Red Ochre (Daizheshi, *Ochre Haematitum*), Dragon's Bones (Longgu, *Os Draconis*), and Oyster Shell (Muli, *Concha Ostreae*). Duration of treatment was at least 2 weeks.

Outcome measures

Primary outcome measure analyzed for this review was BP. Secondary outcome measures analyzed for this review was QOL.

Data extraction

All articles were read by two independent reviewers (XX and XL). Then, eligible studies were retrieved for further identification according to the above inclusion and exclusion criteria. Duplicated papers were excluded. The data extraction form comprised the items of authors, title, publication year, sample size, age, sex distribution, diagnosis standard, study design, interventions for treatment and control groups, composition of JLD, trial duration, outcome measurements, and adverse effects. If missing information was found, we contacted the primary authors via email, telephone or fax whenever possible. Any disagreement was solved by discussion.

Assessment of methodological quality

The risk of bias of included studies was evaluated independently by two reviewers (XX and YZ) according to the criteria in *Cochrane Handbook for Systematic Review of Interventions Version 5.1.0* (*updated March 2011*) [38]. It included the following seven items: sequence generation (selection bias), allocation

concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessments (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) [38]. Each domain was assessed to be low/unclear/high risk of bias. Then, methodological quality of trials was ranked into three levels: low risk of bias (all items with low risk of bias), high risk of bias (at least one item with high risk of bias), and unclear risk of bias (at least one item with unclear).

Data synthesis

Review Manager, Version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. Values of outcome measures after treatment were retrieved to assess differences between JLD groups and control groups. Weighted mean difference (WMD) was used when continuous data presented, while risk ratio (RR) was used when binary data presented. Subgroups analysis was conducted among different types of comparisons (including JLD *versus* antihypertensive drugs and JLD plus antihypertensive drugs *versus* antihypertensive drugs). If trials with good quality could be got, comparisons between all studies and studies with good quality would be conducted. In a three-group design study that had two treatment groups of JLD and JLD plus antihypertensive drugs, two comparisons were split in the meta-analysis. Heterogeneity was assessed by I^2 statistics [38].

Funnel plots were applied to detect for the publication bias when the number of included studies of any particular outcome was more than ten. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study characteristics

Figure 1 shows the process of study selection. Three hundred and eight potentially relevant articles were extracted in the initial screening of the seven databases. Ten RCTs with a total of 655 participants met the eligibility criteria were included [40-49]. Basic characteristics of included trials were summarized in Table 1. Six diagnostic criteria of EH were specified: two trials [40, 41] used Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDTCM); four trials [42, 44, 46, 47] used WHO-ISH guidelines for the management of hypertension-1999 (WHO -ISH GMH-1999); one trial [43] used WHO-ISH GMH-1985; one trial [45] used Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005); one trial [48] used Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and one trial [49] used Chinese Guidelines for the Management of Hypertension-2010 (CGMH-2010). All were conducted in China and published in Chinese language. Among them, one was three-arm study design (two

intervention groups versus one control group) [44], and others used two-arm study design (one intervention group versus one control group). Clinical efficacy of JLD was observed in all trials. However, the evaluation criteria on BP was different, in which three adopted TCM standards recommended by Chinese government in GCRNDTCM [40-42], and seven used BP values [43-49]. QOL was only tested in one trial [42] (Table 1).

Treatment groups

Types of intervention were classified as JLD (n = 4) and combination therapy (JLD plus antihypertensive drugs, n = 7). The variable prescriptions based on JLD were presented in Table 1. Different compositions of either JLD or modified JLD were presented in Table 2.

Control groups

All patients in control groups were received antihypertensive drugs treatment including felodipine [40-42], nifedipine [43, 47, 49], enalapril [44, 45, 48], and benazepril hydrochloride [46].

Duration of follow-up

The total treatment duration in the studies ranged from three to four weeks. Mostly were four weeks (n = 8). Duration of follow-up was only mentioned in one trial with three months [43].

Methodological quality

As shown in Table 3, four trials reported the method to generate the allocation sequence (random number table) [41, 44, 45, 48]. Information about allocation concealment was provided in two trials [44, 48]. Blinding of participants and personnel was reported in three trials [44, 45, 48]; however, no trial used blinding of outcome assessment. Reporting of drop-out or withdraw was provided for three trials [44, 45, 49]. No trial had a pre-trial estimation of sample size. Selective reporting could not be evaluated as no preregistered protocols could be got.

Outcomes

Primary outcome: BP

JLD *versus* antihypertensive drugs (4 studies):

The clinical efficacy of JLD as monotherapy on BP was assessed in four trials (Table 1) [40-42, 44]. Three trials [40-42] didn't use BP value to evaluate the efficacy

of JLD, but use of evaluation criteria in GCRNDTCM, which was defined as follows: "significant improvement" (DBP decreased by 10 mmHg reaching the normal range, or, DBP hasn't yet returned to normal but reduced by more than 20 mmHg), "improvement" (DBP decreased by less than 10 mmHg but reaching the normal range, or, DBP decreased by 10 to 19 mmHg but not reaching the normal range, or, SBP decreased by more than 30 mmHg), and "no improvement" (not meeting above standards) [50]. These outcomes were converted into binary data for further overall analysis. Both "significant improvement" and "improvement" were classified as "effective", and "no improvement" as "ineffective". Meta-analysis showed that JLD had no significant effect on BP as compared with antihypertensive drugs (n = 170; RR: 0.99; 95% CI: 0.90 to 1.08; $P = 0.79$; Figure 2) with no significant heterogeneity (chi-square = 0.22, $P = 0.90$; $I^2 = 0\%$). Another one trial used BP value to evaluate the efficacy of modified JLD when compared with enalapril [44]. No significant difference was found on both SBP and DBP ($P > 0.05$).

JLD plus antihypertensive drugs *versus* antihypertensive drugs (7 studies):

Seven RCTs evaluated the effect of JLD combined with antihypertensive drugs versus antihypertensive drugs (Table 1) [43-49]. BP value was applied in all these studies. When it comes to SBP, it was significantly reduced in JLD plus antihypertensive drugs group when compared with antihypertensive drugs (n = 485; WMD: -8.37; 95% CI: -9.84 to -6.90; $P < 0.00001$; Figure 3) with no significant

heterogeneity (chi-square = 8.45, $P = 0.21$; $I^2 = 29\%$). When it comes to DBP, significant beneficial effect was also found in JLD plus antihypertensive drugs group (n = 485; WMD: -6.71; 95% CI: -9.32, -4.10; $P < 0.00001$; Figure 4) with significant heterogeneity (chi-square = 9.47, $P < 0.0001$; $I^2 = 80\%$).

Secondary outcome: QOL

Only one trial [42] conducted by Fan et al used the Croog Scale [51] to assess the effectiveness of JLD on QOL in aged hypertension patients. At the end of the trial, JLD showed a statistically significant improvement when compared with felodipine group ($P < 0.05$). The trial demonstrated that long-term use of JLD can improve QOL for hypertensive patients.

Adverse effect

Adverse effect monitoring was only reported in five studies [43-45, 48, 49], while not mentioned in the other trials. Among these, no severe adverse effect was found in two trials [43, 49]. Three trials reported dry cough caused by enalapril in both groups [44, 48]. Two trials reported severe dry cough in antihypertensive drugs groups [44, 45]. All adverse effects were not serious in JLD groups.

Evaluation of publication bias

As the number of included trials in each subgroup was so small, we can't conduct any sufficient additional analysis of publication bias.

DISCUSSION

Summary of evidence

Taking into account the gap between the lack of scientific evidence about the efficacy of JLD and the widespread application by TCM practitioners, the objective of this study was therefore to systematically review the current English and Chinese literatures to evaluate the efficacy and safety of JLD for EH. To our knowledge, this is the first SR of JLD in English.

Ten claimed RCTs with 655 hypertensive patients met the inclusion criteria were included in this review. The result suggested that both SBP and DBP were significantly improved in patients receiving JLD plus antihypertensive drugs therapy although the effect was not significant in JLD alone group. Moreover, JLD was found to be effective in QOL when in comparison with antihypertensive drugs. However, the evidence suggesting JLD represented an effective modality for treating EH was limited by limited number of trials, poor methodological qualities, and the high risk if bias in primary studies.

Limitations

The following limitations should be considered before accepting the findings of this review.

(1) Although there are two randomized, single-blind, controlled trials, the methodology of most included trials was assessed to be generally poor. The main reasons are analyzed as follows:

Firstly, although all studies claimed randomization, only four trials demonstrated the random sequence generation and two trials reported allocation concealment; most of the trials might have selection bias. Secondly, only three trials described blinding of participants and personnel, however, none of them reported blinding of outcome assessment; most of the trials might have both selection bias and detection bias. Thirdly, only three trials reported drop-out or withdraw, which might lead to a high risk of attrition bias. Fourthly, most of the included studies did not mention intention to treat analysis, which might lead to some other bias. Fifthly, no trials had a pre-estimation of sample size. Sixthly, no trial had placebo control, which might downgrade the quality of positive conclusions. Last but not least, due to the variations in study quality, participants, intervention, control, and outcome measures, significant clinical heterogeneity was found, especially in DBP ($I^2 = 80\%$).

(2) Publication bias should also be considered. In this review, all included trials were conducted in China and published in Chinese language. Almost all studies claimed similar beneficial effect or better effect when compared with antihypertensive

drugs alone. No negative conclusions could be found. What is more, a funnel plot checking for possible publication bias for BP can't be conducted due to small number of included studies.

(3) Although one trial had a short-term follow up, most of the studies had no follow up, indicating there was a lack of knowledge for some critical outcomes such as all-caused mortality and progression to severe complications, which was also the most common problem in TCM studies.

(4) Small number of included trials and different subgroup comparisons in this review restricted us from conducting meaningful subgroup analyses to explore effect modifiers such as duration of intervention and types of antihypertensive drugs therapies.

(5) We also assessed the quality of evidence for BP outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach recommended by the Cochrane Collaboration with caution. However, the overall quality of evidence in two subgroup comparison was poor, which can weaken the reliability and validity of recommendation.

(6) As the use of natural products occurs at a very high rate among patients attending a variety of health care settings, the safety of CHM and the potential herb-drug interaction has hence become widely concerned. This review suggested that JLD may be safe for the management of EH. In fact, no parallel double blind randomized placebo-controlled trials indicating the adverse effects of JLD for EH could be found. Due to the insufficient clinical data, it is difficult to draw a definite

conclusion on safety of JLD for EH at present. We, therefore, suggest the adverse effect of JLD need to be monitored rigorously in the future studies.

CONCLUSION

There is some encouraging clinical evidence of JLD as a kind of complementary therapy for EH. However, the findings were limited due to poor methodological qualities and high risk if bias of the current inconclusive studies. More rigorously designed randomized trials using TCM syndrome diagnosis with adequate sample size and long-term follow-up according to the CONSORT Statement [52-54] are warranted for further evaluation.

Additional material

Additional file 1: Search Strategy.

Contributorship statement

XX Conceived and designed the experiments. XX, XL, and YZ performed the experiments and analyzed the data. XX wrote the manuscript.

Competing interests

None.

Funding

XJX was supported by the National Natural Science Foundation Project of China (No. 81403375). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data sharing statement

No additional data available.

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Table 1. Basic characteristics of the included studies.

Table 2. Composition of Chinese herbal medicine Jian Ling Decoction in treatment group.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

Figure 1. PRISMA 2009 Flow Diagram

Figure 2. Forest plot of comparison of JLD versus antihypertensive drugs for the outcome of BP

Figure 3. Forest plot of comparison of JLD plus antihypertensive drugs versus antihypertensive drugs for the outcome of SBP

Figure 4. Forest plot of comparison of JLD plus antihypertensive drugs versus antihypertensive drugs for the outcome of DBP

Table1. Basic characteristics of the included studies.

Study ID	Sample size (randomized /analyzed) M/F	Age(yrs)	Diagnosis standard	Intervention	Control	Course (week)	Outcome measures
Tong 2013 [40]	60/60 T: 30 C: 30 F/M: NR	40-60 (T/C: NR)	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
He et al. 2012 [41]	60/60 T: 15/15 C: 17/13	T: 54.89 ± 5.34 C: 57.36 ± 6.47	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
Fan 2005 [42]	50/50 T: 14/11 C: 13/12	T: 64.80 ± 7.40 C: 63.70 ± 6.90	WHO -ISHGMH-1999	JLD (1 dose/d)	felodipine (2.5 mg, qd)	4	BP; QOL
Cai 1995 [43]	100/100 T: 35/15 C: 34/16	T: 50-81 C: 47-84	WHO -ISHGMH-1985	modified JLD (1 dose/d) + control	nifedipine (10 mg, tid)	4	BP; adverse effect
Zhang 2004 [44]	90/89 T1: 16/14 T2: 17/13 C: 15/14	T1: 58.23 ± 8.26 T2: 58.45 ± 6.87 C: 59.16 ± 9.28	WHO -ISHGMH-1999	T1: modified JLD (1 dose/d) T2: modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	4	BP; adverse effect
Zhang 2009 [45]	60/57 T: 15/14 C: 12/16	T: 56.41 ± 10.98 C: 58.57 ± 8.21	CGMH-2005	modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Jiang and Cao 2012 [46]	82/82 T: 26/16 C: 23/17	T: 60-75 C: 62-75	WHO -ISHGMH-1999	modified JLD (100 mL/d) + control	benazepril hydrochloride (10 mg, tid)	4	BP
Chu and Xu 2013 [47]	67/67 T: 19/15 C: 17/16	T: 67.00 ± 7.20 C: 68.00 ± 5.90	WHO -ISHGMH-1999	modified JLD (100 mL/d) + control	nifedipine controlled release tablet (30 mg, qd)	4	BP
Liu et al. 2008 [48]	60/60 T: 30 C: 30 F/M: NR	18-70 (T/C: NR)	JNC 7	modified JLD (100 mL/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Li 2013 [49]	60/60 T: 16/14	T: 64.33 ± 7.96 C: 61.20 ± 10.23	CGMH-2010	modified JLD (400 mL/d) +	nifedipine controlled release tablet (30 mg, qd) and	4	BP; adverse effect

C: 17/13	control	irbesartan (150 mg, qd)

Abbreviations: BP: blood pressure; C: control group; CGMH: Chinese Guidelines for the Management of Hypertension; F: female; GCRNDTCM: Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; JLD: Jian Ling Decoction; JNC 7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; M: male; NR: not reported; QOL: quality of life; T: treatment group; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension.

Table 2. Composition of Chinese herbal medicine Jian Ling Decoction in treatment group.

Study ID	Formula	Composition of formula
Tong 2013 [40]	JLD	Platycladi Seed 10 g, White Peony Root 10 g, Rehmannia Root 15 g, Oyster Shell 10 g, Dragon's Bones 10 g, Red Ochre 10 g, Common Yam Rhizome 15 g, and Twotooth Achyranthes Root 20 g.
He et al. 2012 [41]	JLD	Common Yam Rhizome 15 g, Twotooth Achyranthes Root 20 g, Red Ochre 10 g, Oyster Shell 10 g, Dragon's Bones 10 g, Rehmannia Root 15 g, White Peony Root 10 g, and Platycladi Seed 10 g.
Fan 2005 [42]	JLD	Common Yam Rhizome 30 g, Twotooth Achyranthes Root 30 g, Red Ochre 24 g, Oyster Shell 18 g, Dragon's Bones 18 g, Rehmannia Root 18 g, White Peony Root 12 g, and Platycladi Seed 12 g.
Cai 1995 [43]	modified JLD	Twotooth Achyranthes Root 30 g, Common Yam Rhizome 30 g, Sea-ear Shell 30 g, Red Ochre 24 g, Oyster Shell 18 g, Dragon's Bones 18 g, Rehmannia Root 18 g, White Peony Root 12 g, and Platycladi Seed 12 g. Headache plus Puncturevine Caltrop Fruit 10 g; constipation plus Rhubarb 5 g.
Zhang 2004 [44]	modified JLD	Common Yam Rhizome 30 g, Twotooth Achyranthes Root 30 g, Red Ochre 24 g, Oyster Shell 18 g, Dragon's Bones 18 g, Rehmannia Root 18 g, White Peony Root 12 g, and Platycladi Seed 12 g. Headache, dizziness, and irritability plus Tall Gastrodia Tuber 15 g and Sea-ear Shell 30 g; irritability, bitty mouth and red face plus Gloden Thread 10 g and gardenia 10 g; and constipation plus Rhubarb 5 g.
Zhang 2009 [45]	modified JLD	Common Yam Rhizome 30 g, Twotooth Achyranthes Root 30 g, Red Ochre 24 g, Oyster Shell 18 g, Dragon's Bones 18 g, Rehmannia Root 18 g, White Peony Root 12 g, and Platycladi Seed 12 g. excessive accumulation of phlegm-dampness plus Pinellia Tuber 15 g, Indian Buead 15 g, Tangerine Peel 10 g, Bamboo Shavings 10 g, and Liquoric Root 3 g.
Jiang and Cao 2012 [46]	modified JLD	Common Yam Rhizome 30 g, Tortoise Shell 30 g, Twotooth Achyranthes Root 30 g, Red Ochre 20 g, Oyster Shell 20 g, Dragon's Bones 20 g, Rehmannia Root 20 g, White Peony Root 15 g, and Platycladi Seed 15 g.
Chu and Xu 2013 [47]	modified JLD	Rehmannia Root 25 g, Tortoise Shell 25 g, Common Yam Rhizome 30 g, Red Ochre 15 g, Oyster Shell 25 g, Dragon's Bones 25 g, Twotooth Achyranthes Root 25 g, White Peony Root 20 g, and Platycladi Seed 20 g.
Liu et al. 2008 [48]	modified JLD	Common Yam Rhizome 30 g, Rehmannia Root 18 g, Red Ochre 24 g, Oyster Shell 18 g, Dragon's Bones 18 g, Twotooth Achyranthes Root 30 g, White Peony Root 20 g, and Platycladi Seed 20 g.
Li 2013 [49]	modified JLD	Dragon's Bones 30 g, Oyster Shell 30 g, Rehmannia Root 20 g, Red Ochre 20 g, Common Yam Rhizome 30 g, Twotooth Achyranthes Root 30 g, White Peony Root 20 g, Platycladi Seed 15 g, Gambir Plant 30 g, Kudzuvine Root 30 g, Tall Gastrodia Tuber 15 g, Chinese Taxillus Twig 30 g, Eucommia Bark 15 g, and Golden Thread 9 g.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

Included trials	A	B	C	D	E	F	G
Tong 2013 [40]	?	?	?	?	?	?	?
He et al. 2012 [41]	+	?	?	?	?	?	?
Fan 2005 [42]	?	?	?	?	?	?	?
Cai 1995 [43]	?	+	?	?	?	?	?
Zhang 2004 [44]	+	+	+	?	+	?	?
Zhang 2009 [45]	+	?	+	?	+	?	?
Jiang and Cao 2012 [46]	?	?	?	?	?	?	?
Chu and Xu 2013 [47]	?	?	?	?	?	?	?
Liu et al. 2008 [48]	+	+	+	?	?	?	?
Li 2013 [49]	?	?	?	?	+	?	?

Abbreviations: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (participants and personnel); D: Blinding (assessor); E: Incomplete outcome data addressed (ITT analysis); F: Free of selective reporting; G: other potential thereat to validity; +: low risk; -: high risk; ?: unclear.

Figure 1. PRISMA 2009 Flow Diagram

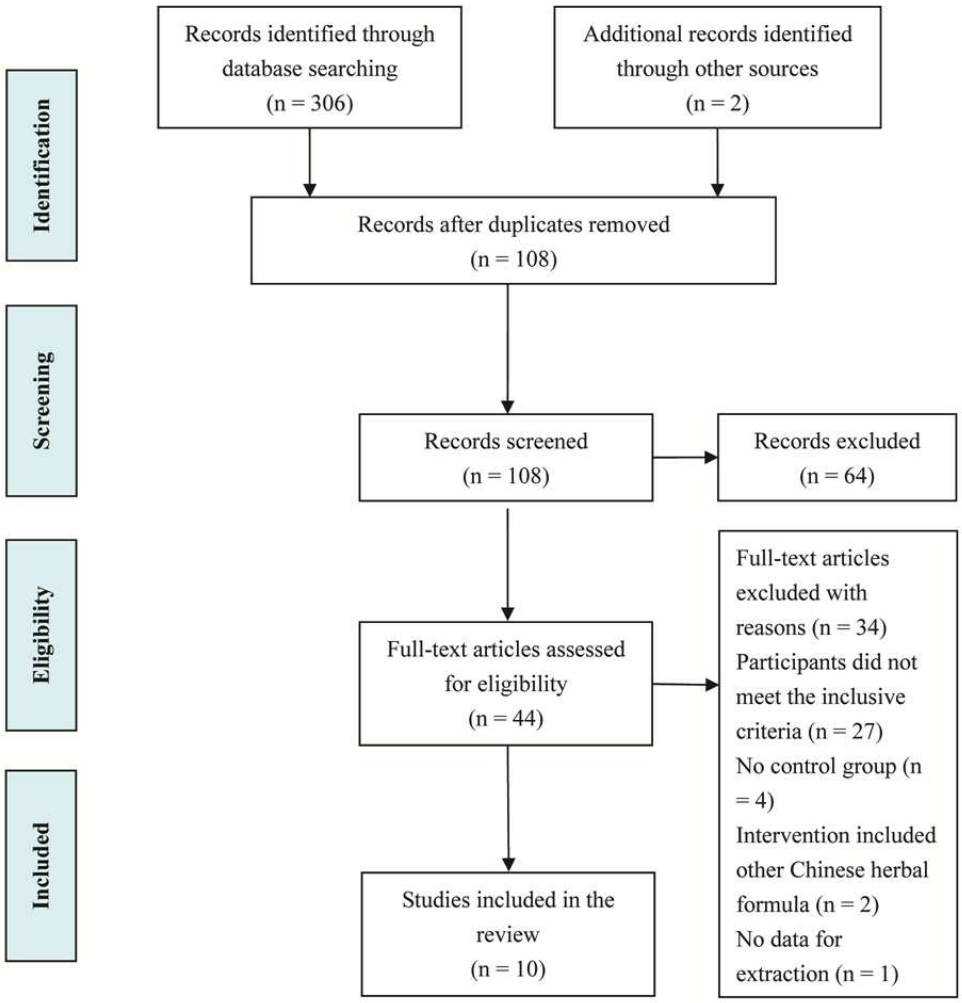


Figure 2. Forest plot of comparison of JLD versus antihypertensive drugs for the outcome of BP

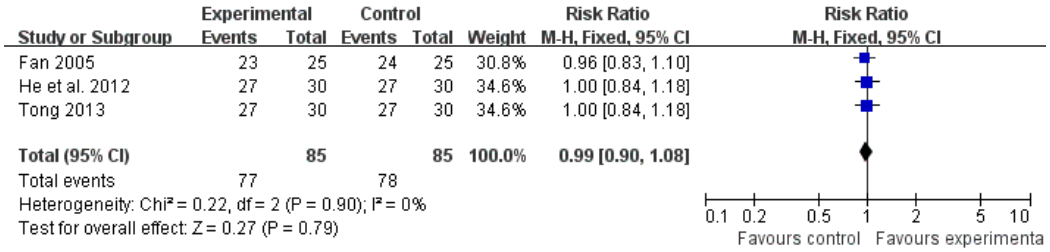


Figure 3. Forest plot of comparison of JLD plus antihypertensive drugs versus antihypertensive drugs for the outcome of SBP

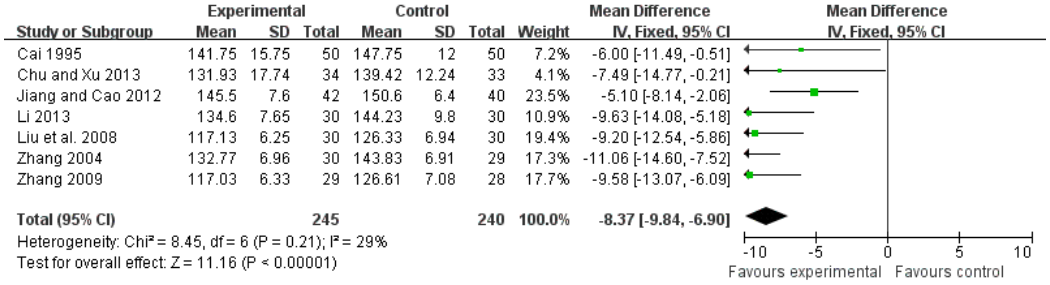
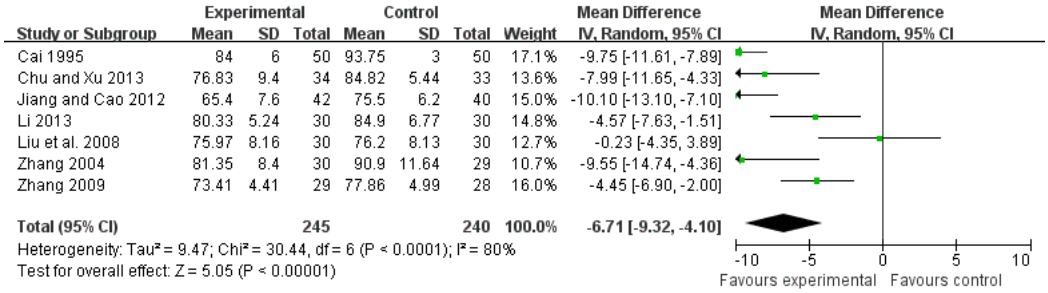


Figure 4. Forest plot of comparison of JLD plus antihypertensive drugs versus antihypertensive drugs for the outcome of DBP



PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P10-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P8-10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P11-12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P12-13

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P12-13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P13-14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P13-14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P15-21
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	P15-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P15-21
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P21-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P24-25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P26-27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P27

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

Additional file 1. Search strategy

CNKI

#1 ‘建瓴汤’ AND ‘血压’

#2 ‘建瓴汤’ AND ‘高血压’

#3 ‘建瓴汤’ AND ‘原发性高血压’

VIP

#1 ‘建瓴汤’ AND ‘血压’

#2 ‘建瓴汤’ AND ‘高血压’

#3 ‘建瓴汤’ AND ‘原发性高血压’

CBM

#1 ‘建瓴汤’ AND ‘血压’

#2 ‘建瓴汤’ AND ‘高血压’

#3 ‘建瓴汤’ AND ‘原发性高血压’

Wanfang Database

#1 ‘建瓴汤’ AND ‘血压’

#2 ‘建瓴汤’ AND ‘高血压’

#3 ‘建瓴汤’ AND ‘原发性高血压’

BMJ Open

Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006502.R1
Article Type:	Research
Date Submitted by the Author:	27-Oct-2014
Complete List of Authors:	Xiong, Xing-jiang; Guang'anmen Hospital, Wang, Pengqian; China Academy of Chinese Medical Sciences, Institute of Basic Research in Clinical Medicine Li, Xiaoke; McLean Hospital, Harvard medical school, Bio-organic and Natural Products Laboratory Zhang, Yuqing; McMaster University, Department of Clinical Epidemiology and Biostatistics
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Cardiovascular medicine
Keywords:	essential hypertension, Chinese herbal medicine, Jian Ling Decoction, systematic review, blood pressure

Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials

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Total word count: 3201.

Number of tables and figures: 3 tables and 2 figures.

Running head: Jian Ling Decoction for essential hypertension.

[*] *BMJ Open* 2014

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ABSTRACT

Objectives: Jian Ling Decoction (JLD) is often prescribed to improve hypertension-related symptoms in China. However, this treatment has not been systematically reviewed for its efficacy against essential hypertension (EH). This review aims to assess the current clinical evidence of JLD in the treatment of EH.

Design: Seven electronic databases including the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), and the Wanfang Database were searched up to March 2014. Randomized control trials (RCTs) comparing JLD or combined with antihypertensive drugs versus antihypertensive drugs were included. We assessed the methodological quality, extracted the valid data, and conducted the meta-analysis according to criteria from the Cochrane group. The primary outcome was categorical or continuous blood pressure (BP), and the secondary outcome was quality of life (QOL).

Results: Ten trials (655 patients) with unclear-to-high risk of bias were identified. Meta-analysis showed that JLD used alone showed no BP reduction effect; however, improvement on QOL was found when compared to antihypertensive drugs. A significant reduction on systolic BP and diastolic BP were observed for JLD plus antihypertensive drugs when compared to antihypertensive drugs alone. No serious adverse effects were reported.

Conclusion: Due to insufficient clinical data, it is difficult to draw a definite

conclusion regarding the effectiveness and safety of JLD for EH, and better trials are needed.

KEY WORDS

essential hypertension; blood pressure; Chinese herbal medicine; Jian Ling Decoction; systematic review

ARTICLE SUMMARY

Article focus

- Jian Ling Decoction (JLD), a traditional Chinese herbal formula, is often prescribed for patients with essential hypertension (EH).

Key messages

- No definitive conclusion regarding the efficacy and safety of JLD for EH could be drawn based on the insufficient clinical data

Strengths and limitations of this study

- The strength of this article is its use of a comprehensive and unbiased literature searching of seven electronic databases without language and publication restrictions.
- The included trials were of small sample size, with poor methodological quality and significant heterogeneity.

INTRODUCTION

Hypertension is one of the most important preventable causes of death and one of the most common conditions treated in primary health care. In addition, hypertension represents an important public health challenge because of its high prevalence and the concomitant increase in the risk of cardiovascular, cerebrovascular and renal diseases.[1,2] This condition has been ranked as the leading global risk factor for mortality and is the third leading risk factor for disease burden according to the comparative Risk Assessment Collaborating Group.[3,4] Currently, about one billion patients have been affected.[5] The association between blood pressure (BP) and mortality was discovered approximately 100 years ago.[6] Recent studies also confirmed that BP is closely related to vascular outcomes, and even a minor reduction in BP could reduce cardiovascular events, especially stroke.[7,8] Therefore, early diagnosis and effective treatment is of great importance for patients with essential hypertension (EH). Nevertheless, despite remarkable achievements in the research and development of antihypertensive drugs, the current awareness, curative and control rates of hypertension among different age groups is still far from satisfactory.[9,10] Additionally, in the light of the adverse effects of antihypertensive drugs and hoping for an adjunctive approach with few adverse effects, patients in Western countries with EH and other cardiovascular diseases increasingly use complementary and alternative medicine (CAM),[11-13] including traditional Chinese medicine (TCM).[14-16]

Chinese herbal medicine (CHM), one of the commonly used TCM therapies, has played an important role in relieving hypertension-related signs and symptoms for centuries in East Asia.[17,18] Recently, more robust evidence from systematic reviews (SRs) has suggested the efficacy and safety of CHM for EH.[19-26] In TCM theory, liver yang hyperactivity syndrome (LYHS) and liver-kidney yin deficiency syndrome (LKYDS) are the two most important patterns of EH, which often appear at the same time.[17] These patterns manifest as headache, vertigo, tinnitus, irritability, insomnia, lassitude in the waist and legs, dysphoria with feverish sensation, dry mouth, bright red tongue with less fur, and a wiry pulse.[14,17,21,27,28] Jian Ling Decoction (JLD) is a traditional CHM invented by *Zhang Xichun* in *Yixue Zhongzhong Canxilu* (Records of Traditional Chinese in Combination with Western Medicine) in the 1920s. It contains the following eight commonly used herbs: Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), Oyster Shell (Muli, Concha Ostreae), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae), and Arbor Vitae Seed (Baiziren, Semen Platycladi). All of these herbs have been recorded in the Pharmacopoeia of the People's Republic of China (2010 edition). Both LYHS and LKYDS can be effectively treated with JLD.[19] Currently, JLD is often prescribed for the management of EH by TCM practitioners in China. It is worth noting that in the context of CAM therapies, add-on designs are very popular for the treatment of hypertension.[14,20-25] JLD is usually used in combination with antihypertensive drugs

to achieve greater improvement in the signs and symptoms of hypertension and to enhance the antihypertensive effect of conventional drugs with less adverse effects. The pharmacological mechanisms of these effects may be related to the reduction in levels of angiotensin II, IL-6, tumor necrosis factor-α (TNF-α), and leptin, as well as insulin resistance and decreased blood lipids.[29-34] Regarding the clinical use of JLD, a large number of studies (including case reports, case series, controlled observational studies, and randomized trials) have reported its effects on EH, including lowering BP, reducing inflammation, reversing cardiovascular risk factors, and improving clinical symptoms and quality of life (QOL).[35-37] However, there has been no comprehensive evaluation of clinical trials on the efficacy and adverse effects of JLD. This review aims to systematically review the published and unpublished randomized controlled trials (RCTs) to evaluate the current evidence for JLD in treating EH.

METHODS

This study was conducted according to the Cochrane practice.[38]

Search strategies

RCTs of JLD for the treatment of hypertensive patients were screened through the following electronic databases from their respective inceptions to March 2014: Cochrane Central Register of Controlled Trials (CENTRAL, 1996-2014), PubMed

(1959-2014), and EMBASE (1980-2014). In addition, as JLD is mainly prescribed in China, four Chinese electronic databases including the Chinese National Knowledge Infrastructure (CNKI, 1980-2014), Chinese Scientific Journal Database (VIP, 1989-2014), Chinese Biomedical Literature Database (CBM, 1978-2014), and Wanfang Database (1998-2014) were searched to retrieve the maximum possible number of trials. We also conducted a literature search of the website of the Chinese clinical trial registry (available at http://www.chictr.org/) and international clinical trial registry hosted by the US National Institutes of Health (available at http://clinicaltrials.gov/) for all of the relevant ongoing registered clinical trials and unpublished articles. The bibliographies of the studies identified in the systematic search were reviewed for potentially relevant additional publications. No restriction on publication status or language was imposed.

The keywords for databases searching were listed as follows: ("hypertension" OR "essential hypertension" OR "primary hypertension" OR "high blood pressure" OR "blood pressure") AND ("*jian ling* decoction" OR "*jianling* decoction" OR "*jian ling tang"* OR "*jianling tang"* OR "*jianlingtang"*) AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial").

Study selection

Types of studies

RCTs on the use of JLD for the treatment of EH were included. Quasi-randomized trials and animal experiments were excluded.

Types of participants

Trials focused on the patients suffering from EH were included. All of the participants who were enrolled in the trials were required to meet at least one of the current or past definitions of EH.[2] Trials without a description of the detailed diagnostic criteria but which reported patients with definite EH were also included . Patients with secondary hypertension were excluded. There was no restriction on gender, age, or ethnic origin of the participants.

Types of interventions

Only studies that tested JLD used alone versus antihypertensive drugs, or JLD combined with antihypertensive drugs versus antihypertensive drugs were included. However, trials assessing the combined effect of JLD with other interventions (*e.g.,* another CHM, qigong, Tai Chi, acupuncture, moxibustion and massage) were excluded given that the therapeutic effect of JLD could not be distinguished. Interventions in the control group included antihypertensive drugs. Studies that used non-conventional medicine or CAM as control groups were also excluded. The duration of treatment was required to be at least two weeks.

According to the principle of similarity of the TCM formula,[39] modified JLD should contain at least six out of eight herbs used in JLD, and only a few herbs could be added into the JLD based on TCM syndrome theory. However, the resulting prescription should contain the following four principal drugs: Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), and Oyster Shell (Muli, Concha Ostreae).

Types of outcome measures

The primary outcome analyzed for this meta-analysis was categorical or continuous BP, and secondary outcome was QOL.

Data extraction

All of the articles were read by two independent reviewers. Then, the eligible studies were retrieved for further identification according to the above inclusion and exclusion criteria. Duplicate papers were excluded. The data extraction form comprised the authors, title, publication year, sample size, age, sex distribution, diagnosis standard, study design, interventions in the treatment and control groups, the composition of JLD or modified JLD, trial duration, outcome measures, and adverse effects. If missing or unclear information regarding the original study was found, we contacted the primary authors via email, telephone or fax whenever

possible. Any disagreement was resolved by discussion between the reviewers.

Methodological quality

The risk of bias of the included studies was independently evaluated by two reviewers according to the criteria in the Cochrane Handbook for Systematic Review of Interventions Version 5.1.0 (updated March 2011).[38] The following seven items were included: (a) sequence generation (selection bias); (b) allocation concealment (selection bias); (c) blinding of participants and personnel (performance bias); (d) blinding of outcome assessments (detection bias); (e) incomplete outcome data (attrition bias); (f) selective reporting (reporting bias); and (g) other sources of bias (from Chapter 8: assessing risk of bias in included studies).[38] Each domain was assessed as a "high", "unclear", or "low" risk of bias based on the above criteria. Then, the methodological quality of the trials was ranked into three levels: low risk of bias (all items with low risk of bias), high risk of bias (at least one item with high risk of bias), or unclear risk of bias (at least one item with an unclear domain).

Data synthesis

Review Manager, Version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. The values of the outcome measures after treatment were retrieved to assess differences between the JLD and control groups.

The weighted mean difference (WMD) was used for continuous data, while the risk ratio (RR) was used for binary data. Subgroups analysis was conducted among different types of comparisons (including JLD *versus* antihypertensive drugs and JLD plus antihypertensive drugs *versus* antihypertensive drugs). If high quality trials could be found, comparisons between all of the studies and studies with high quality would be conducted. In a three-group design study that had two treatment groups of JLD and JLD plus antihypertensive drugs, the two comparisons were split in the meta-analysis. Heterogeneity was assessed by I^2 statistics.[38] Funnel plots were applied to detect for publication bias when the number of included studies of any particular outcome was more than ten. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study characteristics

Figure 1 shows the process of study selection. Three hundred eight potentially relevant articles were extracted in the initial screening of the seven databases. Ten RCTs, with a total of 655 participants, met the eligibility criteria and were included.[40-49] The basic characteristics of included trials are summarized in Table 1. Six diagnostic criteria of EH were specified: two trials[40,41] used the Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDTCM); four trials[42,44,46,47] used the WHO-ISH guidelines for the management of

hypertension-1999 (WHO -ISH GMH-1999); one trial[43] used the WHO-ISH GMH-1985; one trial[45] used the Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005); one trial[48] used the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and one trial[49] used the Chinese Guidelines for the Management of Hypertension-2010 (CGMH-2010). All of the studies were conducted in China and published in Chinese language. One trial was a three-arm design (two intervention groups versus one control group),[44] and the others used a two-arm study design (one intervention group versus one control group). The clinical efficacy of JLD was observed in all of the trials. However, the evaluation criteria on BP was different: three trials used the categorical BP recommended by Chinese government in GCRNDTCM,[40-42] and seven used continuous BP.[43-49] QOL was only tested in one trial.[42]

Treatment groups

The types of intervention were classified as JLD (n = 4) or combination therapy (JLD plus antihypertensive drugs, n = 7). The variable prescriptions based on JLD are presented in Table 1. Different compositions of either JLD or modified JLD are presented in Table 2.

Control groups

All of the patients in the control groups received antihypertensive drug treatment, including felodipine,[40-42] nifedipine,[43,47,49] enalapril,[44,45,48] and benazepril hydrochloride.[46]

Treatment duration

The total treatment duration in the trials ranged from three to four weeks, with most being four weeks (n = 8). The duration of follow-up was only mentioned in one trial, being three months.[43]

Methodological quality

As shown in Table 3, four trials reported the method used to generate the allocation sequence (random number table).[41,44,45,48] Information regarding allocation concealment was provided in two trials.[44,48] Blinding of participants and personnel was reported in three trials;[44,45,48] however, no trial used blinding of outcome assessment. Drop-out and withdrawal data were provided for three trials.[44,45,49] No trial had a pre-trial estimation of sample size. Selective reporting could not be evaluated as no preregistered protocols could be obtained from the primary authors.

Outcome measures

Primary outcome: BP

JLD *versus* antihypertensive drugs (4 studies)

The clinical efficacy of JLD as monotherapy for BP was assessed in four trials.[40-42,44] Three trials[40-42] did not use continuous BP to evaluate the efficacy of JLD, but used categorical BP, the evaluation criteria of which has been authoritatively recommended by China Food and Drug Administration (available at http://www.sda.gov.cn). It was defined as follows: "significant improvement" (DBP decreased by 10 mmHg, reaching the normal range, or DBP not returning to normal but reduced by more than 20 mmHg), "improvement" (DBP decreased by less than 10 mmHg but reaching the normal range, DBP decreased by 10 to 19 mmHg but not reaching the normal range, or SBP decreased by more than 30 mmHg), and "no improvement" (not meeting the above standards).[50] These outcomes were converted into binary data for further overall analysis. Both "significant improvement" and "improvement" were classified as "effective", and "no improvement" was classified as "ineffective". The meta-analysis showed that JLD had no BP reduction effect compared with antihypertensive drugs (n = 170; RR: 0.99; 95% CI: 0.90 to 1.08; P = 0.79; Figure 2a), with no significant heterogeneity (chi-square = 0.22, P = 0.90; I^2 = 0%). Another trial used continuous BP to evaluate the efficacy of modified JLD when compared with enalapril.[44] No significant difference was found for either SBP or DBP

($P > 0.05$).

JLD plus antihypertensive drugs *versus* antihypertensive drugs (7 studies)

Seven RCTs evaluated the effect of JLD combined with antihypertensive drugs versus antihypertensive drugs.[43-49] Continuous BP was measured in all of these studies. SBP was significantly reduced in the JLD plus antihypertensive drugs group when compared with antihypertensive drugs (n = 485; WMD: -8.37 mmHg; 95% CI: -9.84 to -6.90; $P < 0.00001$; Figure 2b), with no significant heterogeneity (chi-square = 8.45, $P = 0.21$; $I^2 = 29\%$). For DBP, a significant beneficial effect was also found in the JLD plus antihypertensive drugs group (n = 485; WMD: -6.71 mmHg; 95% CI: -9.32, -4.10; $P < 0.00001$; Figure 2c), with significant heterogeneity (chi-square = 9.47, $P < 0.0001$; $I^2 = 80\%$).

Secondary outcome: QOL

Only one trial,[42] conducted by Fan et al, used the Croog Scale[51] to assess the effectiveness of JLD on QOL in aged hypertension patients. At the end of the trial, QOL was significantly improved by JLD when compared with the felodipine group ($P < 0.05$). The trial demonstrated that long-term use of JLD might improve QOL for hypertensive patients.

Adverse effects

Adverse effect monitoring was only reported in five studies [43-45, 48, 49] and was not mentioned in the other five trials. Among the former, no severe adverse effects were reported in two trials.[43,49] Three trials reported dry cough caused by enalapril in both the JLD and antihypertensive drugs groups.[44,45,48] Two trials reported severe dry cough in the antihypertensive drugs groups.[44,45] None of the adverse effects were serious in the JLD groups.

Evaluation of publication bias

As the number of included trials was so small, it was not possible to conduct a sufficient additional analysis of publication bias.

DISCUSSION

Summary of evidence

Taking into account the gap between the lack of scientific evidence regarding the efficacy of JLD and the widespread application by TCM practitioners, the objective of this study was to systematically review the current English and Chinese literature to evaluate the efficacy and safety of JLD for EH. To our knowledge, this is the first SR

of JLD in English.

Ten claimed RCTs, with a total of 655 hypertensive patients, met the inclusion criteria and were included in this review. The results suggested that both SBP and DBP were significantly improved in patients receiving JLD plus antihypertensive drugs therapy, although the effect was not significant in the JLD alone group. Moreover, JLD was found to be effective in terms of improving QOL when compared with antihypertensive drugs. However, the evidence for JLD as an effective modality for treating EH was restricted by a limited number of trials, small sample sizes, poor methodological quality, and a high risk of bias in primary studies.

Limitations

The following limitations should be considered before accepting the findings of this review.

(1) Although there were two randomized, single-blind, controlled trials, the methodology of most of the included trials was assessed to be generally poor. The main reasons are analyzed as follows:

Firstly, although all studies claimed randomization, only four trials demonstrated the random sequence generation, and two trials reported allocation concealment; therefore, selection bias may exist. Secondly, only three trials described the blinding of the participants and personnel; however, no trials reported the blinding of outcome assessment. Therefore, both selection bias and detection bias might have occurred.

Thirdly, only three trials reported drop-out or withdraw statistics, suggesting a high risk of attrition bias. Fourthly, most of the included studies did not mention intention to treat analysis, which may lead to some other bias. Fifthly, no trials had a pre-estimation of sample size. Sixthly, no trial had a placebo control, which might decrease the quality of positive conclusions.

(2) As shown in Figure 2c, heterogeneity is another critical issue that should be considered, which may be associated with variations in study quality, participants, JLD compositions, and antihypertensive drugs.

(3) Limited number of included trials and different interventions in both the JLD and antihypertensive drugs groups restricted us from conducting meaningful subgroup analyses to explore effect modifiers such as duration of intervention and types of antihypertensive drug therapies.

(4) Publication bias should also be considered. In this review, all of the included trials were conducted in China and published in Chinese. Almost all studies claimed a similar beneficial effect or a better effect when compared with antihypertensive drugs alone. No negative conclusions were found. What is more, a funnel plot checking for possible publication bias for BP could not be conducted due to the small number of included studies.

(5) Although one trial had a short-term follow up, most of the studies had no follow up, indicating a lack of knowledge for some critical outcomes, such as all-cause mortality and progression to severe complications due to high BP, which is the most common problem for TCM studies in general.

(6) As the use of natural products is very common among patients in a variety of health care settings, the safety of CHM and potential herb-drug interactions has hence become a concern. This review suggested that JLD may be safe for the management of EH. In fact, no parallel double blind randomized placebo-controlled trials indicating the adverse effects of JLD for EH could be found. Due to the insufficient clinical data, it is difficult to draw a definitive conclusion regarding the safety of JLD for EH at present. We therefore suggest that the adverse effects of JLD need to be monitored rigorously in future studies.

CONCLUSION

Due to the insufficient clinical data, poor methodological design, and high risk of bias, it is difficult to draw a definite conclusion regarding the effectiveness and safety of JLD for EH. More rigorously designed trials according to the CONSORT Statement are needed.[52-54]

Funding

XJX was supported by the National Natural Science Foundation Project of China (No. 81403375). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None.

Contributors

XX conceived the idea for the study and designed the method of this systematic review and meta-analysis including the inclusion and exclusion criteria. XX also performed data collection and extraction, conducted the statistical analysis, and wrote the first draft of the article. PW, XL, and YZ searched the articles and assessed their methodological quality. Disagreement was resolved by discussion between XX, PW, XL, and YZ. PW performed the major revision, interpreted the results, and made comments. All of the authors approved the final version of the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data available.

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Table 1. Basic characteristics of the included studies.

Table 2. Herbal medicines in the included studies.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

FIGURE LEGENDS

Figure 1.

Flow diagram of study selection and identification.

Figure 2.

Effect of JLD on BP. (a) JLD *versus* AD and (b) JPAD *versus* AD.

AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.

Table1. Basic characteristics of the included studies.

Study ID	Sample size (randomized /analyzed) M/F	Age(yrs)	Diagnosis standard	Intervention	Control	Course (week)	Outcome measures
Tong 2013 [40]	60/60 T: 30 C: 30 F/M: NR	40-60 (T/C: NR)	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
He et al. 2012 [41]	60/60 T: 15/15 C: 17/13	T: 54.89 ± 5.34 C: 57.36 ± 6.47	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
Fan 2005 [42]	50/50 T: 14/11 C: 13/12	T: 64.80 ± 7.40 C: 63.70 ± 6.90	WHO -ISH GMH-1999	JLD (1 dose/d)	felodipine (2.5 mg, qd)	4	BP; QOL
Cai 1995 [43]	100/100 T: 35/15 C: 34/16	T: 50-81 C: 47-84	WHO -ISH GMH-1985	modified JLD (1 dose/d) + control	nifedipine (10 mg, tid)	4	BP; adverse effect
Zhang 2004 [44]	90/89 T1: 16/14 T2: 17/13 C: 15/14	T1: 58.23 ± 8.26 T2: 58.45 ± 6.87 C: 59.16 ± 9.28	WHO -ISH GMH-1999	T1: modified JLD (1 dose/d) T2: modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	4	BP; adverse effect
Zhang 2009 [45]	60/57 T: 15/14 C: 12/16	T: 56.41 ± 10.98 C: 58.57 ± 8.21	CGMH-2005	modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Jiang and Cao 2012 [46]	82/82 T: 26/16 C: 23/17	T: 60-75 C: 62-75	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	benazepril hydrochloride (10 mg, tid)	4	BP
Chu and Xu 2013 [47]	67/67 T: 19/15 C: 17/16	T: 67.00 ± 7.20 C: 68.00 ± 5.90	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	nifedipine controlled release tablet (30 mg, qd)	4	BP
Liu et al. 2008 [48]	60/60 T: 30 C: 30 F/M: NR	18-70 (T/C: NR)	JNC 7	modified JLD (100 ml/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Li 2013 [49]	60/60 T: 16/14 C: 17/13	T: 64.33 ± 7.96 C: 61.20 ± 10.23	CGMH-2010	modified JLD (400 ml/d) + control	nifedipine controlled release tablet (30 mg, qd) and irbesartan (150 mg, qd)	4	BP; adverse effect

Abbreviations: BP: blood pressure; C: control group; CGMH: Chinese Guidelines for the Management of Hypertension; F: female; GCRNDTCM: Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; JLD: Jian Ling Decoction; JNC 7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; M: male; NR: not reported; QOL: quality of life; T: treatment group; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension.

Table 2. Herbal medicines in the included studies.

Study ID	Formula	Composition of formula
Tong 2013 [40]	JLD	Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Hematite (Daizheshi, Haematitum) 10 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, and Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g.
He et al. 2012 [41]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g, Hematite (Daizheshi, Haematitum) 10 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g.
Fan 2005 [42]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g.
Cai 1995 [43]	modified JLD	Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Abalone Shell (Shijueming, Haliotidis Concha) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache plus Puncturevine Caltrop Fruit (Cijili, Tribulus terrestris Linn) 10 g; constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2004 [44]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache, dizziness, and irritability plus Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g and Abalone Shell (Shijueming, Haliotidis Concha) 30 g; irritability, bitty mouth and red face plus Coptis Rhizome (Huanglian, Rhizoma Coptidis) 10 g and Gardenia (Zhizi, Fructus Gardeniae Jasminoidis) 10 g; and constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2009 [45]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Jiang and Cao	modified	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Fresh Water Turtle Shell (Guijia, Plastrum

2012 [46]	JLD	Testudinis) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 20 g, Oyster Shell (Muli, Concha Ostreae) 20 g, Fossilized Mammal Bones (Longgu, Os Draconis) 20 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 15 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g.
Chu and Xu 2013 [47]	modified JLD	Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 25 g, Fresh Water Turtle Shell (Guijia, Plastrum Testudinis) 25 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Hematite (Daizheshi, Haematitum) 15 g, Oyster Shell (Muli, Concha Ostreae) 25 g, Fossilized Mammal Bones (Longgu, Os Draconis) 25 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 25 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g.
Liu et al. 2008 [48]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Li 2013 [49]	modified JLD	Fossilized Mammal Bones (Longgu, Os Draconis) 30 g, Oyster Shell (Muli, Concha Ostreae) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, Hematite (Daizheshi, Haematitum) 20 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g, Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis) 30 g, Pueraria (Gegen, Radix Puerariae) 30 g, Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g, Chinese Taxillus Twig (Sangjisheng, Herba Taxilli) 30 g, Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis) 15 g, and Coptis Rhizome (Huanglian, Rhizoma Coptidis) 9 g.

Abbreviations: JLD: Jian Ling Decoction.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

Included trials	A	B	C	D	E	F	G
Tong 2013 [40]	?	?	?	?	+	?	?
He et al. 2012 [41]	+	?	?	?	+	?	?
Fan 2005 [42]	?	?	?	?	+	?	?
Cai 1995 [43]	?	+	?	?	+	?	?
Zhang 2004 [44]	+	+	+	?	+	?	?
Zhang 2009 [45]	+	?	+	?	+	?	?
Jiang and Cao 2012 [46]	?	?	?	?	+	?	?
Chu and Xu 2013 [47]	?	?	?	?	+	?	?
Liu et al. 2008 [48]	+	+	+	?	+	?	?
Li 2013 [49]	?	?	?	?	+	?	?

Abbreviations: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (participants and personnel); D: Blinding (assessor); E: Incomplete outcome data addressed (ITT analysis); F: Free of selective reporting; G: other potential thereat to validity; +: low risk; -: high risk; ?: unclear.

F

Figure legends

Figure 1. Flow diagram of study selection and identification.

Figure 2. Effect of JLD on BP. (a) JLD *versus* AD and (b) JPAD *versus* AD.

Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials

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Total word count: 3201.

Number of tables and figures: 3 tables and 2 figures.

Running head: Jian Ling Decoction for essential hypertension.

[*] *BMJ Open* 2014

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ABSTRACT

Objectives: Jian Ling Decoction (JLD) is often prescribed to improve hypertension-related symptoms in China. However, this treatment has not been systematically reviewed for its efficacy against essential hypertension (EH). This review aims to assess the current clinical evidence of JLD in the treatment of EH.

Design: Seven electronic databases including the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), and the Wanfang Database were searched up to March 2014. Randomized control trials (RCTs) comparing JLD or combined with antihypertensive drugs versus antihypertensive drugs were included. We assessed the methodological quality, extracted the valid data, and conducted the meta-analysis according to criteria from the Cochrane group. The primary outcome was categorical or continuous blood pressure (BP), and the secondary outcome was quality of life (QOL).

Results: Ten trials (655 patients) with unclear-to-high risk of bias were identified. Meta-analysis showed that JLD used alone showed no BP reduction effect; however, improvement on QOL was found when compared to antihypertensive drugs. A significant reduction on systolic BP and diastolic BP were observed for JLD plus antihypertensive drugs when compared to antihypertensive drugs alone. No serious adverse effects were reported.

Conclusion: Due to insufficient clinical data, it is difficult to draw a definite

conclusion regarding the effectiveness and safety of JLD for EH, and better trials are needed.

KEY WORDS

essential hypertension; blood pressure; Chinese herbal medicine; Jian Ling Decoction; systematic review

ARTICLE SUMMARY

Article focus

- Jian Ling Decoction (JLD), a traditional Chinese herbal formula, is often prescribed for patients with essential hypertension (EH).

Key messages

- No definitive conclusion regarding the efficacy and safety of JLD for EH could be drawn based on the insufficient clinical data

Strengths and limitations of this study

- The strength of this article is its use of a comprehensive and unbiased literature searching of seven electronic databases without language and publication restrictions.
- The included trials were of small sample size, with poor methodological quality and significant heterogeneity.

INTRODUCTION

Hypertension is one of the most important preventable causes of death and one of the most common conditions treated in primary health care. In addition, hypertension represents an important public health challenge because of its high prevalence and the concomitant increase in the risk of cardiovascular, cerebrovascular and renal diseases.[1,2] This condition has been ranked as the leading global risk factor for mortality and is the third leading risk factor for disease burden according to the comparative Risk Assessment Collaborating Group.[3,4] Currently, about one billion patients have been affected.[5] The association between blood pressure (BP) and mortality was discovered approximately 100 years ago.[6] Recent studies also confirmed that BP is closely related to vascular outcomes, and even a minor reduction in BP could reduce cardiovascular events, especially stroke.[7,8] Therefore, early diagnosis and effective treatment is of great importance for patients with essential hypertension (EH). Nevertheless, despite remarkable achievements in the research and development of antihypertensive drugs, the current awareness, curative and control rates of hypertension among different age groups is still far from satisfactory.[9,10] Additionally, in the light of the adverse effects of antihypertensive drugs and hoping for an adjunctive approach with few adverse effects, patients in Western countries with EH and other cardiovascular diseases increasingly use complementary and alternative medicine (CAM),[11-13] including traditional Chinese medicine (TCM).[14-16]

Chinese herbal medicine (CHM), one of the commonly used TCM therapies, has played an important role in relieving hypertension-related signs and symptoms for centuries in East Asia.[17,18] Recently, more robust evidence from systematic reviews (SRs) has suggested the efficacy and safety of CHM for EH.[19-26] In TCM theory, liver yang hyperactivity syndrome (LYHS) and liver-kidney yin deficiency syndrome (LKYDS) are the two most important patterns of EH, which often appear at the same time.[17] These patterns manifest as headache, vertigo, tinnitus, irritability, insomnia, lassitude in the waist and legs, dysphoria with feverish sensation, dry mouth, bright red tongue with less fur, and a wiry pulse.[14,17,21,27,28] Jian Ling Decoction (JLD) is a traditional CHM invented by *Zhang Xichun* in *Yixue Zhongzhong Canxilu* (Records of Traditional Chinese in Combination with Western Medicine) in the 1920s. It contains the following eight commonly used herbs: Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), Oyster Shell (Muli, Concha Ostreae), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae), and Arbor Vitae Seed (Baiziren, Semen Platycladi). All of these herbs have been recorded in the Pharmacopoeia of the People's Republic of China (2010 edition). Both LYHS and LKYDS can be effectively treated with JLD.[19] Currently, JLD is often prescribed for the management of EH by TCM practitioners in China. It is worth noting that in the context of CAM therapies, add-on designs are very popular for the treatment of hypertension.[14,20-25] JLD is usually used in combination with antihypertensive drugs

to achieve greater improvement in the signs and symptoms of hypertension and to enhance the antihypertensive effect of conventional drugs with less adverse effects. The pharmacological mechanisms of these effects may be related to the reduction in levels of angiotensin II, IL-6, tumor necrosis factor-α (TNF-α), and leptin, as well as insulin resistance and decreased blood lipids.[29-34] Regarding the clinical use of JLD, a large number of studies (including case reports, case series, controlled observational studies, and randomized trials) have reported its effects on EH, including lowering BP, reducing inflammation, reversing cardiovascular risk factors, and improving clinical symptoms and quality of life (QOL).[35-37] However, there has been no comprehensive evaluation of clinical trials on the efficacy and adverse effects of JLD. This review aims to systematically review the published and unpublished randomized controlled trials (RCTs) to evaluate the current evidence for JLD in treating EH.

METHODS

This study was conducted according to the Cochrane practice.[38]

Search strategies

RCTs of JLD for the treatment of hypertensive patients were screened through the following electronic databases from their respective inceptions to March 2014: Cochrane Central Register of Controlled Trials (CENTRAL, 1996-2014), PubMed

(1959-2014), and EMBASE (1980-2014). In addition, as JLD is mainly prescribed in China, four Chinese electronic databases including the Chinese National Knowledge Infrastructure (CNKI, 1980-2014), Chinese Scientific Journal Database (VIP, 1989-2014), Chinese Biomedical Literature Database (CBM, 1978-2014), and Wanfang Database (1998-2014) were searched to retrieve the maximum possible number of trials. We also conducted a literature search of the website of the Chinese clinical trial registry (available at http://www.chictr.org/) and international clinical trial registry hosted by the US National Institutes of Health (available at http://clinicaltrials.gov/) for all of the relevant ongoing registered clinical trials and unpublished articles. The bibliographies of the studies identified in the systematic search were reviewed for potentially relevant additional publications. No restriction on publication status or language was imposed.

The keywords for databases searching were listed as follows: ("hypertension" OR "essential hypertension" OR "primary hypertension" OR "high blood pressure" OR "blood pressure") AND ("*jian ling* decoction" OR "*jianling* decoction" OR "*jian ling tang*" OR "*jianling tang*" OR "*jianlingtang*") AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial").

Study selection

Types of studies

RCTs on the use of JLD for the treatment of EH were included. Quasi-randomized trials and animal experiments were excluded.

Types of participants

Trials focused on the patients suffering from EH were included. All of the participants who were enrolled in the trials were required to meet at least one of the current or past definitions of EH.[2] Trials without a description of the detailed diagnostic criteria but which reported patients with definite EH were also included . Patients with secondary hypertension were excluded. There was no restriction on gender, age, or ethnic origin of the participants.

Types of interventions

Only studies that tested JLD used alone versus antihypertensive drugs, or JLD combined with antihypertensive drugs versus antihypertensive drugs were included. However, trials assessing the combined effect of JLD with other interventions (*e.g.,* another CHM, qigong, Tai Chi, acupuncture, moxibustion and massage) were excluded given that the therapeutic effect of JLD could not be distinguished. Interventions in the control group included antihypertensive drugs. Studies that used non-conventional medicine or CAM as control groups were also excluded. The duration of treatment was required to be at least two weeks.

According to the principle of similarity of the TCM formula,[39] modified JLD should contain at least six out of eight herbs used in JLD, and only a few herbs could be added into the JLD based on TCM syndrome theory. However, the resulting prescription should contain the following four principal drugs: Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), and Oyster Shell (Muli, Concha Ostreae).

Types of outcome measures

The primary outcome analyzed for this meta-analysis was categorical or continuous BP, and secondary outcome was QOL.

Data extraction

All of the articles were read by two independent reviewers. Then, the eligible studies were retrieved for further identification according to the above inclusion and exclusion criteria. Duplicate papers were excluded. The data extraction form comprised the authors, title, publication year, sample size, age, sex distribution, diagnosis standard, study design, interventions in the treatment and control groups, the composition of JLD or modified JLD, trial duration, outcome measures, and adverse effects. If missing or unclear information regarding the original study was found, we contacted the primary authors via email, telephone or fax whenever

possible. Any disagreement was resolved by discussion between the reviewers.

Methodological quality

The risk of bias of the included studies was independently evaluated by two reviewers according to the criteria in the Cochrane Handbook for Systematic Review of Interventions Version 5.1.0 (updated March 2011).[38] The following seven items were included: (a) sequence generation (selection bias); (b) allocation concealment (selection bias); (c) blinding of participants and personnel (performance bias); (d) blinding of outcome assessments (detection bias); (e) incomplete outcome data (attrition bias); (f) selective reporting (reporting bias); and (g) other sources of bias (from Chapter 8: assessing risk of bias in included studies).[38] Each domain was assessed as a "high", "unclear", or "low" risk of bias based on the above criteria. Then, the methodological quality of the trials was ranked into three levels: low risk of bias (all items with low risk of bias), high risk of bias (at least one item with high risk of bias), or unclear risk of bias (at least one item with an unclear domain).

Data synthesis

Review Manager, Version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. The values of the outcome measures after treatment were retrieved to assess differences between the JLD and control groups.

The weighted mean difference (WMD) was used for continuous data, while the risk ratio (RR) was used for binary data. Subgroups analysis was conducted among different types of comparisons (including JLD *versus* antihypertensive drugs and JLD plus antihypertensive drugs *versus* antihypertensive drugs). If high quality trials could be found, comparisons between all of the studies and studies with high quality would be conducted. In a three-group design study that had two treatment groups of JLD and JLD plus antihypertensive drugs, the two comparisons were split in the meta-analysis. Heterogeneity was assessed by I^2 statistics.[38] Funnel plots were applied to detect for publication bias when the number of included studies of any particular outcome was more than ten. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study characteristics

Figure 1 shows the process of study selection. Three hundred eight potentially relevant articles were extracted in the initial screening of the seven databases. Ten RCTs, with a total of 655 participants, met the eligibility criteria and were included.[40-49] The basic characteristics of included trials are summarized in Table 1. Six diagnostic criteria of EH were specified: two trials[40,41] used the Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDTCM); four trials[42,44,46,47] used the WHO-ISH guidelines for the management of

hypertension-1999 (WHO -ISH GMH-1999); one trial[43] used the WHO-ISH GMH-1985; one trial[45] used the Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005); one trial[48] used the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and one trial[49] used the Chinese Guidelines for the Management of Hypertension-2010 (CGMH-2010). All of the studies were conducted in China and published in Chinese language. One trial was a three-arm design (two intervention groups versus one control group),[44] and the others used a two-arm study design (one intervention group versus one control group). The clinical efficacy of JLD was observed in all of the trials. However, the evaluation criteria on BP was different: three trials used the categorical BP recommended by Chinese government in GCRNDTCM,[40-42] and seven used continuous BP.[43-49] QOL was only tested in one trial.[42]

Treatment groups

The types of intervention were classified as JLD (n = 4) or combination therapy (JLD plus antihypertensive drugs, n = 7). The variable prescriptions based on JLD are presented in Table 1. Different compositions of either JLD or modified JLD are presented in Table 2.

Control groups

All of the patients in the control groups received antihypertensive drug treatment, including felodipine,[40-42] nifedipine,[43,47,49] enalapril,[44,45,48] and benazepril hydrochloride.[46]

Treatment duration

The total treatment duration in the trials ranged from three to four weeks, with most being four weeks (n = 8). The duration of follow-up was only mentioned in one trial, being three months.[43]

Methodological quality

As shown in Table 3, four trials reported the method used to generate the allocation sequence (random number table).[41,44,45,48] Information regarding allocation concealment was provided in two trials.[44,48] Blinding of participants and personnel was reported in three trials;[44,45,48] however, no trial used blinding of outcome assessment. Drop-out and withdrawal data were provided for three trials.[44,45,49] No trial had a pre-trial estimation of sample size. Selective reporting could not be evaluated as no preregistered protocols could be obtained from the primary authors.

Outcome measures

Primary outcome: BP

JLD *versus* antihypertensive drugs (4 studies)

The clinical efficacy of JLD as monotherapy for BP was assessed in four trials.[40-42,44] Three trials[40-42] did not use continuous BP to evaluate the efficacy of JLD, but used categorical BP, the evaluation criteria of which has been authoritatively recommended by China Food and Drug Administration (available at http://www.sda.gov.cn). It was defined as follows: "significant improvement" (DBP decreased by 10 mmHg, reaching the normal range, or DBP not returning to normal but reduced by more than 20 mmHg), "improvement" (DBP decreased by less than 10 mmHg but reaching the normal range, DBP decreased by 10 to 19 mmHg but not reaching the normal range, or SBP decreased by more than 30 mmHg), and "no improvement" (not meeting the above standards).[50] These outcomes were converted into binary data for further overall analysis. Both "significant improvement" and "improvement" were classified as "effective", and "no improvement" was classified as "ineffective". The meta-analysis showed that JLD had no BP reduction effect compared with antihypertensive drugs (n = 170; RR: 0.99; 95% CI: 0.90 to 1.08; P = 0.79; Figure 2a), with no significant heterogeneity (chi-square = 0.22, P = 0.90; I^2 = 0%). Another trial used continuous BP to evaluate the efficacy of modified JLD when compared with enalapril.[44] No significant difference was found for either SBP or DBP

($P > 0.05$).

JLD plus antihypertensive drugs *versus* antihypertensive drugs (7 studies)

Seven RCTs evaluated the effect of JLD combined with antihypertensive drugs versus antihypertensive drugs.[43-49] Continuous BP was measured in all of these studies. SBP was significantly reduced in the JLD plus antihypertensive drugs group when compared with antihypertensive drugs (n = 485; WMD: -8.37 mmHg; 95% CI: -9.84 to -6.90; $P < 0.00001$; Figure 2b), with no significant heterogeneity (chi-square = 8.45, $P = 0.21$; $I^2 = 29\%$). For DBP, a significant beneficial effect was also found in the JLD plus antihypertensive drugs group (n = 485; WMD: -6.71 mmHg; 95% CI: -9.32, -4.10; $P < 0.00001$; Figure 2c), with significant heterogeneity (chi-square = 9.47, $P < 0.0001$; $I^2 = 80\%$).

Secondary outcome: QOL

Only one trial,[42] conducted by Fan et al, used the Croog Scale[51] to assess the effectiveness of JLD on QOL in aged hypertension patients. At the end of the trial, QOL was significantly improved by JLD when compared with the felodipine group ($P < 0.05$). The trial demonstrated that long-term use of JLD might improve QOL for hypertensive patients.

Adverse effects

Adverse effect monitoring was only reported in five studies [43-45, 48, 49] and was not mentioned in the other five trials. Among the former, no severe adverse effects were reported in two trials.[43,49] Three trials reported dry cough caused by enalapril in both the JLD and antihypertensive drugs groups.[44,45,48] Two trials reported severe dry cough in the antihypertensive drugs groups.[44,45] None of the adverse effects were serious in the JLD groups.

Evaluation of publication bias

As the number of included trials was so small, it was not possible to conduct a sufficient additional analysis of publication bias.

DISCUSSION

Summary of evidence

Taking into account the gap between the lack of scientific evidence regarding the efficacy of JLD and the widespread application by TCM practitioners, the objective of this study was to systematically review the current English and Chinese literature to evaluate the efficacy and safety of JLD for EH. To our knowledge, this is the first SR

of JLD in English.

Ten claimed RCTs, with a total of 655 hypertensive patients, met the inclusion criteria and were included in this review. The results suggested that both SBP and DBP were significantly improved in patients receiving JLD plus antihypertensive drugs therapy, although the effect was not significant in the JLD alone group. Moreover, JLD was found to be effective in terms of improving QOL when compared with antihypertensive drugs. However, the evidence for JLD as an effective modality for treating EH was restricted by a limited number of trials, small sample sizes, poor methodological quality, and a high risk of bias in primary studies.

Limitations

The following limitations should be considered before accepting the findings of this review.

(1) Although there were two randomized, single-blind, controlled trials, the methodology of most of the included trials was assessed to be generally poor. The main reasons are analyzed as follows:

Firstly, although all studies claimed randomization, only four trials demonstrated the random sequence generation, and two trials reported allocation concealment; therefore, selection bias may exist. Secondly, only three trials described the blinding of the participants and personnel; however, no trials reported the blinding of outcome assessment. Therefore, both selection bias and detection bias might have occurred.

Thirdly, only three trials reported drop-out or withdraw statistics, suggesting a high risk of attrition bias. Fourthly, most of the included studies did not mention intention to treat analysis, which may lead to some other bias. Fifthly, no trials had a pre-estimation of sample size. Sixthly, no trial had a placebo control, which might decrease the quality of positive conclusions.

(2) As shown in Figure 2c, heterogeneity is another critical issue that should be considered, which may be associated with variations in study quality, participants, JLD compositions, and antihypertensive drugs.

(3) Limited number of included trials and different interventions in both the JLD and antihypertensive drugs groups restricted us from conducting meaningful subgroup analyses to explore effect modifiers such as duration of intervention and types of antihypertensive drug therapies.

(4) Publication bias should also be considered. In this review, all of the included trials were conducted in China and published in Chinese. Almost all studies claimed a similar beneficial effect or a better effect when compared with antihypertensive drugs alone. No negative conclusions were found. What is more, a funnel plot checking for possible publication bias for BP could not be conducted due to the small number of included studies.

(5) Although one trial had a short-term follow up, most of the studies had no follow up, indicating a lack of knowledge for some critical outcomes, such as all-cause mortality and progression to severe complications due to high BP, which is the most common problem for TCM studies in general.

(6) As the use of natural products is very common among patients in a variety of health care settings, the safety of CHM and potential herb-drug interactions has hence become a concern. This review suggested that JLD may be safe for the management of EH. In fact, no parallel double blind randomized placebo-controlled trials indicating the adverse effects of JLD for EH could be found. Due to the insufficient clinical data, it is difficult to draw a definitive conclusion regarding the safety of JLD for EH at present. We therefore suggest that the adverse effects of JLD need to be monitored rigorously in future studies.

CONCLUSION

Due to the insufficient clinical data, poor methodological design, and high risk of bias, it is difficult to draw a definite conclusion regarding the effectiveness and safety of JLD for EH. More rigorously designed trials according to the CONSORT Statement are needed.[52-54]

Funding

XJX was supported by the National Natural Science Foundation Project of China (No. 81403375). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None.

Contributors

XX conceived the idea for the study and designed the method of this systematic review and meta-analysis including the inclusion and exclusion criteria. XX also performed data collection and extraction, conducted the statistical analysis, and wrote the first draft of the article. PW, XL, and YZ searched the articles and assessed their methodological quality. Disagreement was resolved by discussion between XX, PW, XL, and YZ. PW performed the major revision, interpreted the results, and made comments. All of the authors approved the final version of the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data available.

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with yin deficiency and yang hyperactivity syndrome. *Zhong Yi Yao Dao Bao* 2012; 18: 50-51.

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Table 1. Basic characteristics of the included studies.

Table 2. Herbal medicines in the included studies.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

FIGURE LEGENDS

Figure 1.

Flow diagram of study selection and identification.

Figure 2.

Effect of JLD on BP. (a) JLD *versus* AD and (b) JPAD *versus* AD.

AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.

Table1. Basic characteristics of the included studies.

Study ID	Sample size (randomized /analyzed) M/F	Age(yrs)	Diagnosis standard	Intervention	Control	Course (week)	Outcome measures
Tong 2013 [40]	60/60 T: 30 C: 30 F/M: NR	40-60 (T/C: NR)	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
He et al. 2012 [41]	60/60 T: 15/15 C: 17/13	T: 54.89 ± 5.34 C: 57.36 ± 6.47	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
Fan 2005 [42]	50/50 T: 14/11 C: 13/12	T: 64.80 ± 7.40 C: 63.70 ± 6.90	WHO -ISH GMH-1999	JLD (1 dose/d)	felodipine (2.5 mg, qd)	4	BP; QOL
Cai 1995 [43]	100/100 T: 35/15 C: 34/16	T: 50-81 C: 47-84	WHO -ISH GMH-1985	modified JLD (1 dose/d) + control	nifedipine (10 mg, tid)	4	BP; adverse effect
Zhang 2004 [44]	90/89 T1: 16/14 T2: 17/13 C: 15/14	T1: 58.23 ± 8.26 T2: 58.45 ± 6.87 C: 59.16 ± 9.28	WHO -ISH GMH-1999	T1: modified JLD (1 dose/d) T2: modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	4	BP; adverse effect
Zhang 2009 [45]	60/57 T: 15/14 C: 12/16	T: 56.41 ± 10.98 C: 58.57 ± 8.21	CGMH-2005	modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Jiang and Cao 2012 [46]	82/82 T: 26/16 C: 23/17	T: 60-75 C: 62-75	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	benazepril hydrochloride (10 mg, tid)	4	BP
Chu and Xu 2013 [47]	67/67 T: 19/15 C: 17/16	T: 67.00 ± 7.20 C: 68.00 ± 5.90	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	nifedipine controlled release tablet (30 mg, qd)	4	BP
Liu et al. 2008 [48]	60/60 T: 30 C: 30 F/M: NR	18-70 (T/C: NR)	JNC 7	modified JLD (100 ml/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Li 2013 [49]	60/60 T: 16/14 C: 17/13	T: 64.33 ± 7.96 C: 61.20 ± 10.23	CGMH-2010	modified JLD (400 ml/d) + control	nifedipine controlled release tablet (30 mg, qd) and irbesartan (150 mg, qd)	4	BP; adverse effect

Abbreviations: BP: blood pressure; C: control group; CGMH: Chinese Guidelines for the Management of Hypertension; F: female; GCRNDTCM: Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; JLD: Jian Ling Decoction; JNC 7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; M: male; NR: not reported; QOL: quality of life; T: treatment group; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension.

Table 2. Herbal medicines in the included studies.

Study ID	Formula	Composition of formula
Tong 2013 [40]	JLD	Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Hematite (Daizheshi, Haematitum) 10 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, and Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g.
He et al. 2012 [41]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g, Hematite (Daizheshi, Haematitum) 10 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g.
Fan 2005 [42]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g.
Cai 1995 [43]	modified JLD	Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Abalone Shell (Shijueming, Haliotidis Concha) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache plus Puncturevine Caltrop Fruit (Cijili, Tribulus terrestris Linn) 10 g; constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2004 [44]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache, dizziness, and irritability plus Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g and Abalone Shell (Shijueming, Haliotidis Concha) 30 g; irritability, bitty mouth and red face plus Coptis Rhizome (Huanglian, Rhizoma Coptidis) 10 g and Gardenia (Zhizi, Fructus Gardeniae Jasminoidis) 10 g; and constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2009 [45]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Jiang and Cao	modified	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Fresh Water Turtle Shell (Guijia, Plastrum

2012 [46]	JLD	Testudinis) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 20 g, Oyster Shell (Muli, Concha Ostreae) 20 g, Fossilized Mammal Bones (Longgu, Os Draconis) 20 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 15 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g.
Chu and Xu 2013 [47]	modified JLD	Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 25 g, Fresh Water Turtle Shell (Guijia, Plastrum Testudinis) 25 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Hematite (Daizheshi, Haematitum) 15 g, Oyster Shell (Muli, Concha Ostreae) 25 g, Fossilized Mammal Bones (Longgu, Os Draconis) 25 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 25 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g.
Liu et al. 2008 [48]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Li 2013 [49]	modified JLD	Fossilized Mammal Bones (Longgu, Os Draconis) 30 g, Oyster Shell (Muli, Concha Ostreae) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, Hematite (Daizheshi, Haematitum) 20 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g, Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis) 30 g, Pueraria (Gegen, Radix Puerariae) 30 g, Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g, Chinese Taxillus Twig (Sangjisheng, Herba Taxilli) 30 g, Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis) 15 g, and Coptis Rhizome (Huanglian, Rhizoma Coptidis) 9 g.

Abbreviations: JLD: Jian Ling Decoction.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

Included trials	A	B	C	D	E	F	G
Tong 2013 [40]	?	?	?	?	+	?	?
He et al. 2012 [41]	+	?	?	?	+	?	?
Fan 2005 [42]	?	?	?	?	+	?	?
Cai 1995 [43]	?	+	?	?	+	?	?
Zhang 2004 [44]	+	+	+	?	+	?	?
Zhang 2009 [45]	+	?	+	?	+	?	?
Jiang and Cao 2012 [46]	?	?	?	?	+	?	?
Chu and Xu 2013 [47]	?	?	?	?	+	?	?
Liu et al. 2008 [48]	+	+	+	?	+	?	?
Li 2013 [49]	?	?	?	?	+	?	?

Abbreviations: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (participants and personnel); D: Blinding (assessor); E: Incomplete outcome data addressed (ITT analysis); F: Free of selective reporting; G: other potential thereat to validity; +: low risk; -: high risk; ?: unclear.

Figure 1. Flow diagram of study selection and identification.

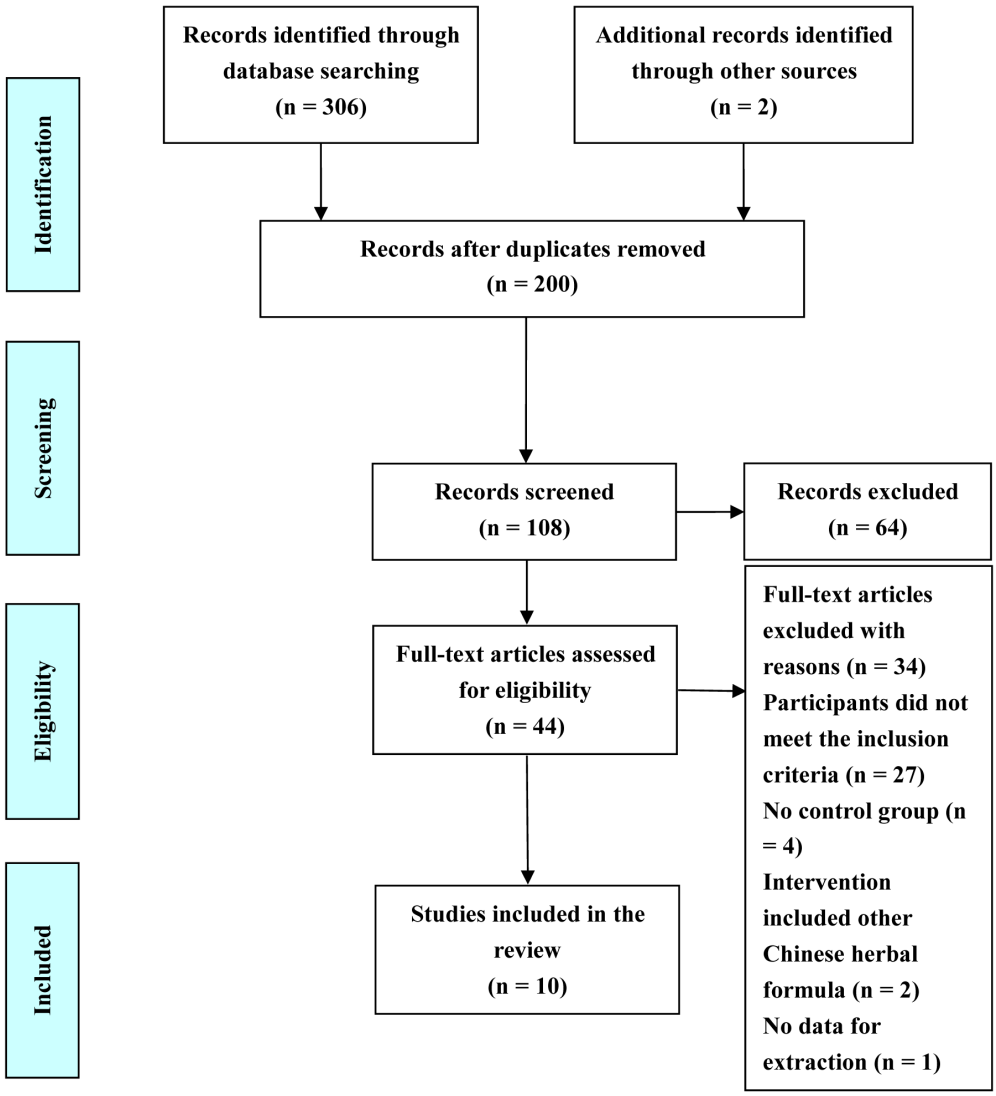
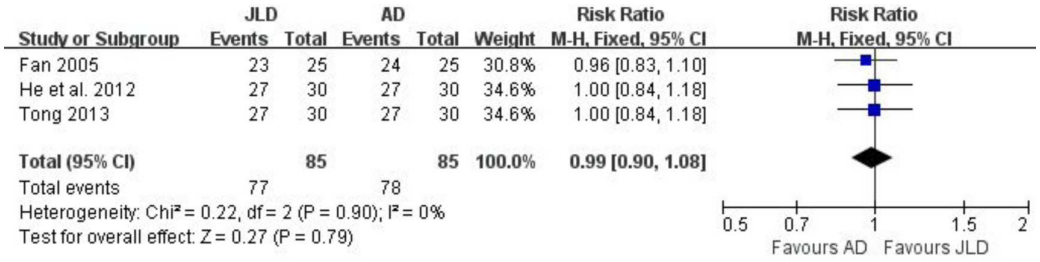
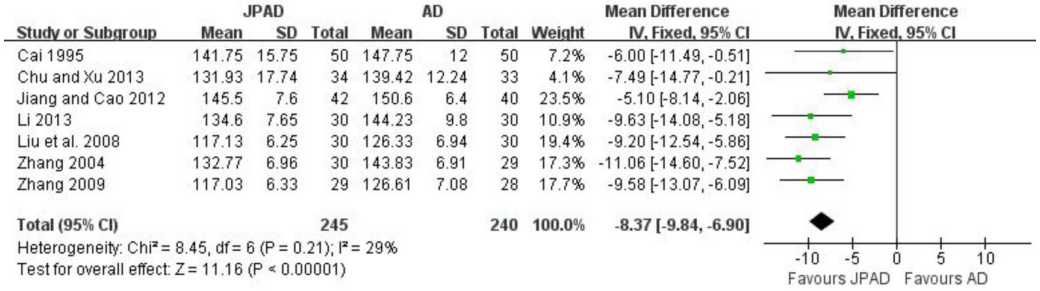


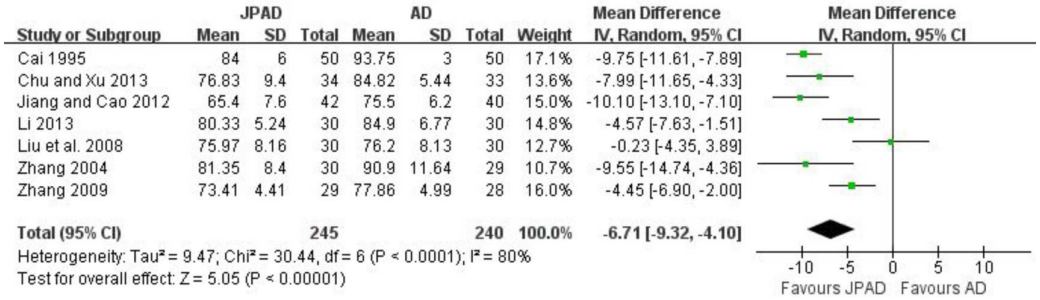
Figure 2. Effect of JLD on BP. (a) JLD *versus* AD and (b) JPAD *versus* AD.



(a) JLD *versus* AD: BP



(b) JPAD *versus* AD: SBP (mmHg)



(b) JPAD *versus* AD: DBP (mmHg)

AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P9-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P11-12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P12-13

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P12-13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P13-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P16-17
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	P16-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P19-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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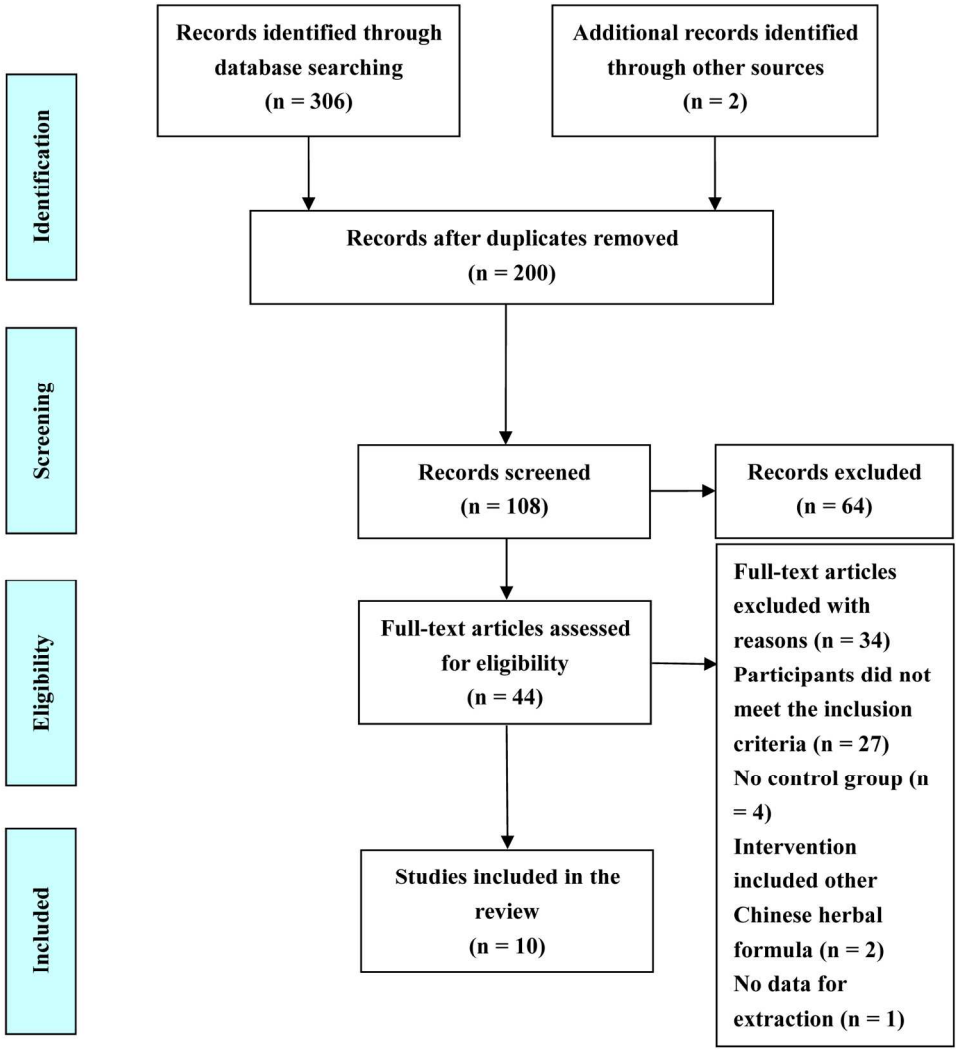

Fig 1 Flow diagram of study selection and identification.
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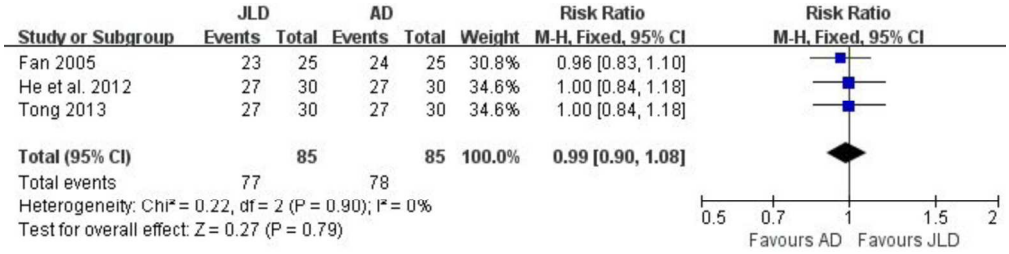
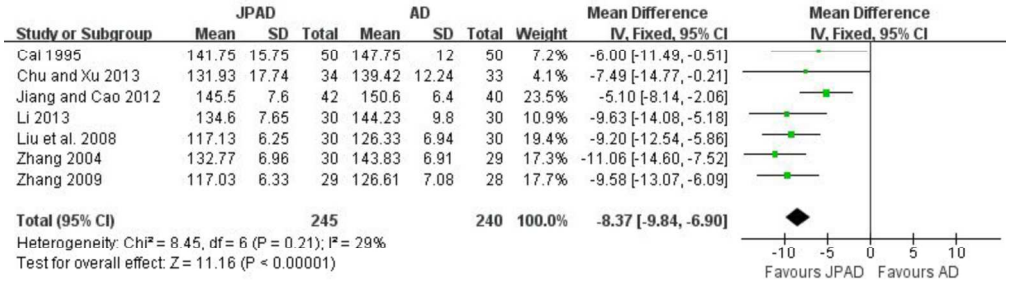
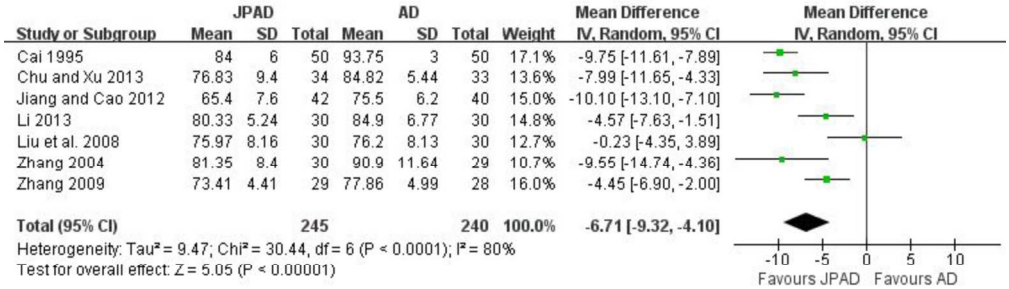


(a) JLD *versus* AD: BP



(b) JPAD *versus* AD: SBP (mmHg)



(b) JPAD *versus* AD: DBP (mmHg)

Figure 2. Effect of JLD on BP. (a) JLD versus AD and (b) JPAD versus AD. AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.
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BMJ Open

Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-006502.R2
Article Type:	Research
Date Submitted by the Author:	10-Nov-2014
Complete List of Authors:	Xiong, Xing-jiang; Guang'anmen Hospital, Wang, Pengqian; China Academy of Chinese Medical Sciences, Institute of Basic Research in Clinical Medicine Li, Xiaoke; McLean Hospital, Harvard medical school, Bio-organic and Natural Products Laboratory Zhang, Yuqing; McMaster University, Department of Clinical Epidemiology and Biostatistics
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Cardiovascular medicine
Keywords:	essential hypertension, Chinese herbal medicine, Jian Ling Decoction, systematic review, blood pressure

Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials

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Total word count: 3200.

Number of tables and figures: 3 tables and 2 figures.

Running head: Jian Ling Decoction for essential hypertension.

[*] *BMJ Open* 2014

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ABSTRACT

Objectives: Jian Ling Decoction (JLD) is often prescribed to improve hypertension-related symptoms in China. However, this treatment has not been systematically reviewed for its efficacy against essential hypertension (EH). This review aims to assess the current clinical evidence of JLD in the treatment of EH.

Design: Seven electronic databases including the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), and the Wanfang Database were searched up to March 2014. Randomized control trials (RCTs) comparing JLD or combined with antihypertensive drugs versus antihypertensive drugs were included. We assessed the methodological quality, extracted the valid data, and conducted the meta-analysis according to criteria from the Cochrane group. The primary outcome was categorical or continuous blood pressure (BP), and the secondary outcome was quality of life (QOL).

Results: Ten trials (655 patients) with unclear-to-high risk of bias were identified. Meta-analysis showed that JLD used alone showed no BP reduction effect; however, improvement on QOL was found when compared to antihypertensive drugs. A significant reduction on systolic BP and diastolic BP were observed for JLD plus antihypertensive drugs when compared to antihypertensive drugs alone. No serious adverse effects were reported.

Conclusion: Due to insufficient clinical data, it is difficult to draw a definite

conclusion regarding the effectiveness and safety of JLD for EH, and better trials are needed.

KEY WORDS

essential hypertension; blood pressure; Chinese herbal medicine; Jian Ling Decoction; systematic review

ARTICLE SUMMARY

Article focus

- Jian Ling Decoction (JLD), a traditional Chinese herbal formula, is often prescribed for patients with essential hypertension (EH).

Key messages

- No definitive conclusion regarding the efficacy and safety of JLD for EH could be drawn based on the insufficient clinical data

Strengths and limitations of this study

- The strength of this article is its use of a comprehensive and unbiased literature searching of seven electronic databases without language and publication restrictions.
- The included trials were of small sample size, with poor methodological quality and significant heterogeneity.

INTRODUCTION

Hypertension is one of the most important preventable causes of death and one of the most common conditions treated in primary health care. In addition, hypertension represents an important public health challenge because of its high prevalence and the concomitant increase in the risk of cardiovascular, cerebrovascular and renal diseases.[1,2] This condition has been ranked as the leading global risk factor for mortality and is the third leading risk factor for disease burden according to the comparative Risk Assessment Collaborating Group.[3,4] Currently, about one billion patients have been affected.[5] The association between blood pressure (BP) and mortality was discovered approximately 100 years ago.[6] Recent studies also confirmed that BP is closely related to vascular outcomes, and even a minor reduction in BP could reduce cardiovascular events, especially stroke.[7,8] Therefore, early diagnosis and effective treatment is of great importance for patients with essential hypertension (EH). Nevertheless, despite remarkable achievements in the research and development of antihypertensive drugs, the current awareness, curative and control rates of hypertension among different age groups is still far from satisfactory.[9,10] Additionally, in the light of the adverse effects of antihypertensive drugs and hoping for an adjunctive approach with few adverse effects, patients in Western countries with EH and other cardiovascular diseases increasingly use complementary and alternative medicine (CAM),[11-13] including traditional Chinese medicine (TCM).[14-16]

Chinese herbal medicine (CHM), one of the commonly used TCM therapies, has played an important role in relieving hypertension-related signs and symptoms for centuries in East Asia.[17,18] Recently, more robust evidence from systematic reviews (SRs) has suggested the efficacy and safety of CHM for EH.[19-26] In TCM theory, liver yang hyperactivity syndrome (LYHS) and liver-kidney yin deficiency syndrome (LKYDS) are the two most important patterns of EH, which often appear at the same time.[17] These patterns manifest as headache, vertigo, tinnitus, irritability, insomnia, lassitude in the waist and legs, dysphoria with feverish sensation, dry mouth, bright red tongue with less fur, and a wiry pulse.[14,17,21,27,28] Jian Ling Decoction (JLD) is a traditional CHM invented by *Zhang Xichun* in *Yixue Zhongzhong Canxilu* (Records of Traditional Chinese in Combination with Western Medicine) in the 1920s. It contains the following eight commonly used herbs: Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), Oyster Shell (Muli, Concha Ostreae), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae), and Arbor Vitae Seed (Baiziren, Semen Platycladi). All of these herbs have been recorded in the Pharmacopoeia of the People's Republic of China (2010 edition). Both LYHS and LKYDS can be effectively treated with JLD.[19] Currently, JLD is often prescribed for the management of EH by TCM practitioners in China. It is worth noting that in the context of CAM therapies, add-on designs are very popular for the treatment of hypertension.[14,20-25] JLD is usually used in combination with antihypertensive drugs

to achieve greater improvement in the signs and symptoms of hypertension and to enhance the antihypertensive effect of conventional drugs with less adverse effects. The pharmacological mechanisms of these effects may be related to the reduction in levels of angiotensin II, IL-6, tumor necrosis factor-α (TNF-α), and leptin, as well as insulin resistance and decreased blood lipids.[29-34] Regarding the clinical use of JLD, a large number of studies (including case reports, case series, controlled observational studies, and randomized trials) have reported its effects on EH, including lowering BP, reducing inflammation, reversing cardiovascular risk factors, and improving clinical symptoms and quality of life (QOL).[35-37] However, there has been no comprehensive evaluation of clinical trials on the efficacy and adverse effects of JLD. This review aims to systematically review the published and unpublished randomized controlled trials (RCTs) to evaluate the current evidence for JLD in treating EH.

METHODS

This study was conducted according to the Cochrane practice.[38]

Search strategies

RCTs of JLD for the treatment of hypertensive patients were screened through the following electronic databases from their respective inceptions to March 2014: Cochrane Central Register of Controlled Trials (CENTRAL, 1996-2014), PubMed

(1959-2014), and EMBASE (1980-2014). In addition, as JLD is mainly prescribed in China, four Chinese electronic databases including the Chinese National Knowledge Infrastructure (CNKI, 1980-2014), Chinese Scientific Journal Database (VIP, 1989-2014), Chinese Biomedical Literature Database (CBM, 1978-2014), and Wanfang Database (1998-2014) were searched to retrieve the maximum possible number of trials. We also conducted a literature search of the website of the Chinese clinical trial registry (available at http://www.chictr.org/) and international clinical trial registry hosted by the US National Institutes of Health (available at http://clinicaltrials.gov/) for all of the relevant ongoing registered clinical trials and unpublished articles. The bibliographies of the studies identified in the systematic search were reviewed for potentially relevant additional publications. No restriction on publication status or language was imposed.

The keywords for databases searching were listed as follows: ("hypertension" OR "essential hypertension" OR "primary hypertension" OR "high blood pressure" OR "blood pressure") AND ("*jian ling* decoction" OR "*jianling* decoction" OR "*jian ling tang"* OR "*jianling tang"* OR "*jianlingtang"*) AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial").

Study selection

Types of studies

RCTs on the use of JLD for the treatment of EH were included. Quasi-randomized trials and animal experiments were excluded.

Types of participants

Trials focused on the patients suffering from EH were included. All of the participants who were enrolled in the trials were required to meet at least one of the current or past definitions of EH.[2] Trials without a description of the detailed diagnostic criteria but which reported patients with definite EH were also included . Patients with secondary hypertension were excluded. There was no restriction on gender, age, or ethnic origin of the participants.

Types of interventions

Only studies that tested JLD used alone versus antihypertensive drugs, or JLD combined with antihypertensive drugs versus antihypertensive drugs were included. However, trials assessing the combined effect of JLD with other interventions (*e.g.,* another CHM, qigong, Tai Chi, acupuncture, moxibustion and massage) were excluded given that the therapeutic effect of JLD could not be distinguished. Interventions in the control group included antihypertensive drugs. Studies that used non-conventional medicine or CAM as control groups were also excluded. The duration of treatment was required to be at least two weeks.

According to the principle of similarity of the TCM formula,[39] modified JLD should contain at least six out of eight herbs used in JLD, and only a few herbs could be added into the JLD based on TCM syndrome theory. However, the resulting prescription should contain the following four principal drugs: Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), and Oyster Shell (Muli, Concha Ostreae).

Types of outcome measures

The primary outcome analyzed for this meta-analysis was categorical or continuous BP, and secondary outcome was QOL.

Data extraction

All of the articles were read by two independent reviewers. Then, the eligible studies were retrieved for further identification according to the above inclusion and exclusion criteria. Duplicate papers were excluded. The data extraction form comprised the authors, title, publication year, sample size, age, sex distribution, diagnosis standard, study design, interventions in the treatment and control groups, the composition of JLD or modified JLD, trial duration, outcome measures, and adverse effects. If missing or unclear information regarding the original study was found, we contacted the primary authors via email, telephone or fax whenever

possible. Any disagreement was resolved by discussion between the reviewers.

Methodological quality

The risk of bias of the included studies was independently evaluated by two reviewers according to the criteria in the Cochrane Handbook for Systematic Review of Interventions Version 5.1.0 (updated March 2011).[38] The following seven items were included: (a) sequence generation (selection bias); (b) allocation concealment (selection bias); (c) blinding of participants and personnel (performance bias); (d) blinding of outcome assessments (detection bias); (e) incomplete outcome data (attrition bias); (f) selective reporting (reporting bias); and (g) other sources of bias (from Chapter 8: assessing risk of bias in included studies).[38] Each domain was assessed as a "high", "unclear", or "low" risk of bias based on the above criteria. Then, the methodological quality of the trials was ranked into three levels: low risk of bias (all items with low risk of bias), high risk of bias (at least one item with high risk of bias), or unclear risk of bias (at least one item with an unclear domain).

Data synthesis

Review Manager, Version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. The values of the outcome measures after treatment were retrieved to assess differences between the JLD and control groups.

The weighted mean difference (WMD) was used for continuous data, while the risk ratio (RR) was used for binary data. Subgroups analysis was conducted among different types of comparisons (including JLD *versus* antihypertensive drugs and JLD plus antihypertensive drugs *versus* antihypertensive drugs). If high quality trials could be found, comparisons between all of the studies and studies with high quality would be conducted. In a three-group design study that had two treatment groups of JLD and JLD plus antihypertensive drugs, the two comparisons were split in the meta-analysis. Heterogeneity was assessed by I^2 statistics.[38] Funnel plots were applied to detect for publication bias when the number of included studies of any particular outcome was more than ten. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study characteristics

Figure 1 shows the process of study selection. We identified 308 potentially relevant articles in the initial screening of the seven databases. Ten RCTs, with a total of 655 participants, met the eligibility criteria and were included.[40-49] The basic characteristics of included trials are summarized in Table 1. Six diagnostic criteria of EH were specified: two trials[40,41] used the Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDTCM); four trials[42,44,46,47] used the WHO-ISH guidelines for the management of hypertension-1999 (WHO -ISH

GMH-1999); one trial[43] used the WHO-ISH GMH-1985; one trial[45] used the Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005); one trial[48] used the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and one trial[49] used the Chinese Guidelines for the Management of Hypertension-2010 (CGMH-2010). All of the studies were conducted in China and published in Chinese language. One trial was a three-arm design (two intervention groups versus one control group),[44] and the others used a two-arm study design (one intervention group versus one control group). The clinical efficacy of JLD was observed in all of the trials. However, the evaluation criteria on BP was different: three trials used the categorical BP recommended by Chinese government in GCRNDTCM,[40-42] and seven used continuous BP.[43-49] QOL was only tested in one trial.[42]

Treatment groups

The types of intervention were classified as JLD (n = 4) or combination therapy (JLD plus antihypertensive drugs, n = 7). The variable prescriptions based on JLD are presented in Table 1. Different compositions of either JLD or modified JLD are presented in Table 2.

Control groups

All of the patients in the control groups received antihypertensive drug treatment, including felodipine,[40-42] nifedipine,[43,47,49] enalapril,[44,45,48] and benazepril hydrochloride.[46]

Treatment duration

The total treatment duration in the trials ranged from three to four weeks, with most being four weeks (n = 8). The duration of follow-up was only mentioned in one trial, being three months.[43]

Methodological quality

As shown in Table 3, four trials reported the method used to generate the allocation sequence (random number table).[41,44,45,48] Information regarding allocation concealment was provided in two trials.[44,48] Blinding of participants and personnel was reported in three trials;[44,45,48] however, no trial used blinding of outcome assessment. Drop-out and withdrawal data were provided for three trials.[44,45,49] No trial had a pre-trial estimation of sample size. Selective reporting could not be evaluated as no preregistered protocols could be obtained from the primary authors.

Outcome measures

Primary outcome: BP

JLD *versus* antihypertensive drugs (4 studies)

The clinical efficacy of JLD as monotherapy for BP was assessed in four trials.[40-42,44] Three trials[40-42] did not use continuous BP to evaluate the efficacy of JLD, but used categorical BP, the evaluation criteria of which has been authoritatively recommended by China Food and Drug Administration (available at http://www.sda.gov.cn). It was defined as follows: "significant improvement" (DBP decreased by 10 mmHg, reaching the normal range, or DBP not returning to normal but reduced by more than 20 mmHg), "improvement" (DBP decreased by less than 10 mmHg but reaching the normal range, DBP decreased by 10 to 19 mmHg but not reaching the normal range, or SBP decreased by more than 30 mmHg), and "no improvement" (not meeting the above standards).[50] These outcomes were converted into binary data for further overall analysis. Both "significant improvement" and "improvement" were classified as "effective", and "no improvement" was classified as "ineffective". The meta-analysis showed that JLD had no BP reduction effect compared with antihypertensive drugs (n = 170; RR: 0.99; 95% CI: 0.90 to 1.08; P = 0.79; Figure 2a), with no significant heterogeneity (chi-square = 0.22, P = 0.90; I^2 = 0%). Another trial used continuous BP to evaluate the efficacy of modified JLD when compared with enalapril.[44] No significant difference was found for either SBP or DBP (P > 0.05).

JLD plus antihypertensive drugs *versus* antihypertensive drugs (7 studies)

Seven RCTs evaluated the effect of JLD combined with antihypertensive drugs versus antihypertensive drugs.[43-49] Continuous BP was measured in all of these studies. SBP was significantly reduced in the JLD plus antihypertensive drugs group when compared with antihypertensive drugs (n = 485; WMD: -8.37 mmHg; 95% CI: -9.84 to -6.90; $P < 0.00001$; Figure 2b), with no significant heterogeneity (chi-square = 8.45, $P = 0.21$; $I^2 = 29\%$). For DBP, a significant beneficial effect was also found in the JLD plus antihypertensive drugs group (n = 485; WMD: -6.71 mmHg; 95% CI: -9.32, -4.10; $P < 0.00001$; Figure 2c), with significant heterogeneity (chi-square = 9.47, $P < 0.0001$; $I^2 = 80\%$).

Secondary outcome: QOL

Only one trial,[42] conducted by Fan et al, used the Croog Scale[51] to assess the effectiveness of JLD on QOL in aged hypertension patients. At the end of the trial, QOL was significantly improved by JLD when compared with the felodipine group ($P < 0.05$). The trial demonstrated that long-term use of JLD might improve QOL for hypertensive patients.

Adverse effects

Adverse effect monitoring was only reported in five studies [43-45, 48, 49] and was not mentioned in the other five trials. Among the former, no severe adverse effects were reported in two trials.[43,49] Three trials reported dry cough caused by enalapril in both the JLD and antihypertensive drugs groups.[44,45,48] Two trials reported severe dry cough in the antihypertensive drugs groups.[44,45] None of the adverse effects were serious in the JLD groups.

Evaluation of publication bias

As the number of included trials was so small, it was not possible to conduct a sufficient additional analysis of publication bias.

DISCUSSION

Summary of evidence

Taking into account the gap between the lack of scientific evidence regarding the efficacy of JLD and the widespread application by TCM practitioners, the objective of this study was to systematically review the current English and Chinese literature to evaluate the efficacy and safety of JLD for EH. To our knowledge, this is the first SR of JLD in English.

Ten claimed RCTs, with a total of 655 hypertensive patients, met the inclusion criteria and were included in this review. The results suggested that both SBP and DBP were significantly improved in patients receiving JLD plus antihypertensive drugs therapy, although the effect was not significant in the JLD alone group. Moreover, JLD was found to be effective in terms of improving QOL when compared with antihypertensive drugs. However, the evidence for JLD as an effective modality for treating EH was restricted by a limited number of trials, small sample sizes, poor methodological quality, and a high risk of bias in primary studies.

Limitations

The following limitations should be considered before accepting the findings of this review.

(1) Although there were two randomized, single-blind, controlled trials, the methodology of most of the included trials was assessed to be generally poor. The main reasons are analyzed as follows:

Firstly, although all studies claimed randomization, only four trials demonstrated the random sequence generation, and two trials reported allocation concealment; therefore, selection bias may exist. Secondly, only three trials described the blinding of the participants and personnel; however, no trials reported the blinding of outcome assessment. Therefore, both selection bias and detection bias might have occurred. Thirdly, only three trials reported drop-out or withdraw statistics, suggesting a high

risk of attrition bias. Fourthly, most of the included studies did not mention intention to treat analysis, which may lead to some other bias. Fifthly, no trials had a pre-estimation of sample size. Sixthly, no trial had a placebo control, which might decrease the quality of positive conclusions.

(2) As shown in Figure 2c, heterogeneity is another critical issue that should be considered, which may be associated with variations in study quality, participants, JLD compositions, and antihypertensive drugs.

(3) Limited number of included trials and different interventions in both the JLD and antihypertensive drugs groups restricted us from conducting meaningful subgroup analyses to explore effect modifiers such as duration of intervention and types of antihypertensive drug therapies.

(4) Publication bias should also be considered. In this review, all of the included trials were conducted in China and published in Chinese. Almost all studies claimed a similar beneficial effect or a better effect when compared with antihypertensive drugs alone. No negative conclusions were found. What is more, a funnel plot checking for possible publication bias for BP could not be conducted due to the small number of included studies.

(5) Although one trial had a short-term follow up, most of the studies had no follow up, indicating a lack of knowledge for some critical outcomes, such as all-cause mortality and progression to severe complications due to high BP, which is the most common problem for TCM studies in general.

(6) As the use of natural products is very common among patients in a variety of

health care settings, the safety of CHM and potential herb-drug interactions has hence become a concern. This review suggested that JLD may be safe for the management of EH. In fact, no parallel double blind randomized placebo-controlled trials indicating the adverse effects of JLD for EH could be found. Due to the insufficient clinical data, it is difficult to draw a definitive conclusion regarding the safety of JLD for EH at present. We therefore suggest that the adverse effects of JLD need to be monitored rigorously in future studies.

CONCLUSION

Due to the insufficient clinical data, poor methodological design, and high risk of bias, it is difficult to draw a definite conclusion regarding the effectiveness and safety of JLD for EH. More rigorously designed trials reported according to the CONSORT Statement are needed.[52-54]

Funding

XJX was supported by the National Natural Science Foundation Project of China (No. 81403375). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None.

Contributors

XX conceived the idea for the study and designed the method of this systematic review and meta-analysis including the inclusion and exclusion criteria. XX also performed data collection and extraction, conducted the statistical analysis, and wrote the first draft of the article. PW, XL, and YZ searched the articles and assessed their methodological quality. Disagreement was resolved by discussion between XX, PW, XL, and YZ. PW performed the major revision, interpreted the results, and made comments. All of the authors approved the final version of the manuscript.

Acknowledgements

The author would like to thank Cheryl C. from American Journal Experts (AJE) in revising the English language of the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data available.

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Table 1. Basic characteristics of the included studies.

Table 2. Herbal medicines in the included studies.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

FIGURE LEGENDS

Figure 1.

Flow diagram of study selection and identification.

Figure 2.

Effect of JLD on BP. (a) JLD *versus* AD and (b) JPAD *versus* AD.

AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.

Table1. Basic characteristics of the included studies.

Study ID	Sample size (randomized /analyzed) M/F	Age(yrs)	Diagnosis standard	Intervention	Control	Course (week)	Outcome measures
Tong 2013 [40]	60/60 T: 30 C: 30 F/M: NR	40-60 (T/C: NR)	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
He et al. 2012 [41]	60/60 T: 15/15 C: 17/13	T: 54.89 ± 5.34 C: 57.36 ± 6.47	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
Fan 2005 [42]	50/50 T: 14/11 C: 13/12	T: 64.80 ± 7.40 C: 63.70 ± 6.90	WHO -ISH GMH-1999	JLD (1 dose/d)	felodipine (2.5 mg, qd)	4	BP; QOL
Cai 1995 [43]	100/100 T: 35/15 C: 34/16	T: 50-81 C: 47-84	WHO -ISH GMH-1985	modified JLD (1 dose/d) + control	nifedipine (10 mg, tid)	4	BP; adverse effect
Zhang 2004 [44]	90/89 T1: 16/14 T2: 17/13 C: 15/14	T1: 58.23 ± 8.26 T2: 58.45 ± 6.87 C: 59.16 ± 9.28	WHO -ISH GMH-1999	T1: modified JLD (1 dose/d) T2: modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	4	BP; adverse effect
Zhang 2009 [45]	60/57 T: 15/14 C: 12/16	T: 56.41 ± 10.98 C: 58.57 ± 8.21	CGMH-2005	modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Jiang and Cao 2012 [46]	82/82 T: 26/16 C: 23/17	T: 60-75 C: 62-75	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	benazepril hydrochloride (10 mg, tid)	4	BP
Chu and Xu 2013 [47]	67/67 T: 19/15 C: 17/16	T: 67.00 ± 7.20 C: 68.00 ± 5.90	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	nifedipine controlled release tablet (30 mg, qd)	4	BP
Liu et al. 2008 [48]	60/60 T: 30 C: 30 F/M: NR	18-70 (T/C: NR)	JNC 7	modified JLD (100 ml/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Li 2013 [49]	60/60 T: 16/14 C: 17/13	T: 64.33 ± 7.96 C: 61.20 ± 10.23	CGMH-2010	modified JLD (400 ml/d) + control	nifedipine controlled release tablet (30 mg, qd) and irbesartan (150 mg, qd)	4	BP; adverse effect

Abbreviations: BP: blood pressure; C: control group; CGMH: Chinese Guidelines for the Management of Hypertension; F: female; GCRNDTCM: Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; JLD: Jian Ling Decoction; JNC 7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; M: male; NR: not reported; QOL: quality of life; T: treatment group; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension.

Table 2. Herbal medicines in the included studies.

Study ID	Formula	Composition of formula
Tong 2013 [40]	JLD	Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Hematite (Daizheshi, Haematitum) 10 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, and Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g.
He et al. 2012 [41]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g, Hematite (Daizheshi, Haematitum) 10 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g.
Fan 2005 [42]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g.
Cai 1995 [43]	modified JLD	Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Abalone Shell (Shijueming, Haliotidis Concha) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache plus Puncturevine Caltrop Fruit (Cijili, Tribulus terrestris Linn) 10 g; constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2004 [44]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache, dizziness, and irritability plus Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g and Abalone Shell (Shijueming, Haliotidis Concha) 30 g; irritability, bitty mouth and red face plus Coptis Rhizome (Huanglian, Rhizoma Coptidis) 10 g and Gardenia (Zhizi, Fructus Gardeniae Jasminoidis) 10 g; and constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2009 [45]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Jiang and Cao	modified	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Fresh Water Turtle Shell (Guijia, Plastrum

2012 [46]	JLD	Testudinis) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 20 g, Oyster Shell (Muli, Concha Ostreae) 20 g, Fossilized Mammal Bones (Longgu, Os Draconis) 20 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 15 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g.
Chu and Xu 2013 [47]	modified JLD	Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 25 g, Fresh Water Turtle Shell (Guijia, Plastrum Testudinis) 25 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Hematite (Daizheshi, Haematitum) 15 g, Oyster Shell (Muli, Concha Ostreae) 25 g, Fossilized Mammal Bones (Longgu, Os Draconis) 25 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 25 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g.
Liu et al. 2008 [48]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Li 2013 [49]	modified JLD	Fossilized Mammal Bones (Longgu, Os Draconis) 30 g, Oyster Shell (Muli, Concha Ostreae) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, Hematite (Daizheshi, Haematitum) 20 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g, Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis) 30 g, Pueraria (Gegen, Radix Puerariae) 30 g, Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g, Chinese Taxillus Twig (Sangjisheng, Herba Taxilli) 30 g, Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis) 15 g, and Coptis Rhizome (Huanglian, Rhizoma Coptidis) 9 g.

Abbreviations: JLD: Jian Ling Decoction.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

Included trials	A	B	C	D	E	F	G
Tong 2013 [40]	?	?	?	?	+	?	?
He et al. 2012 [41]	+	?	?	?	+	?	?
Fan 2005 [42]	?	?	?	?	+	?	?
Cai 1995 [43]	?	+	?	?	+	?	?
Zhang 2004 [44]	+	+	+	?	+	?	?
Zhang 2009 [45]	+	?	+	?	+	?	?
Jiang and Cao 2012 [46]	?	?	?	?	+	?	?
Chu and Xu 2013 [47]	?	?	?	?	+	?	?
Liu et al. 2008 [48]	+	+	+	?	+	?	?
Li 2013 [49]	?	?	?	?	+	?	?

Abbreviations: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (participants and personnel); D: Blinding (assessor); E: Incomplete outcome data addressed (ITT analysis); F: Free of selective reporting; G: other potential thereat to validity; +: low risk; -: high risk; ?: unclear.

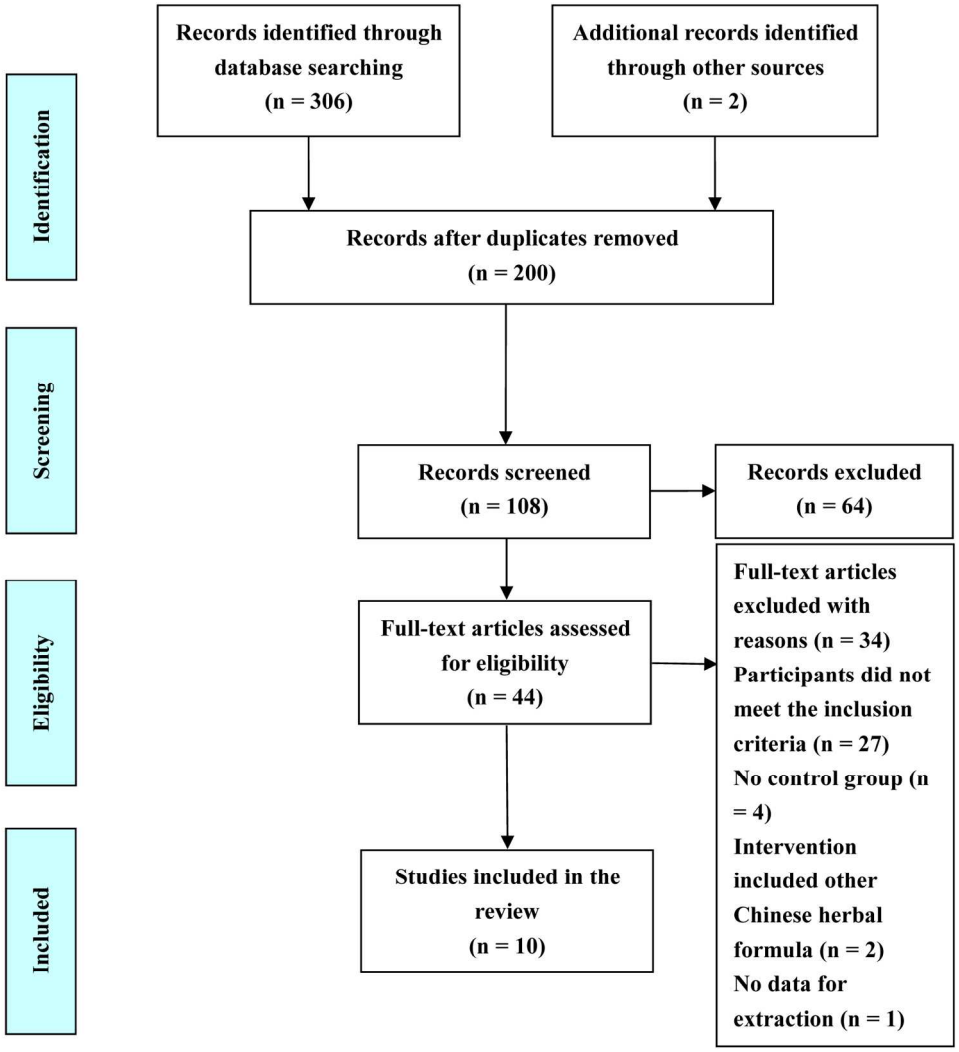
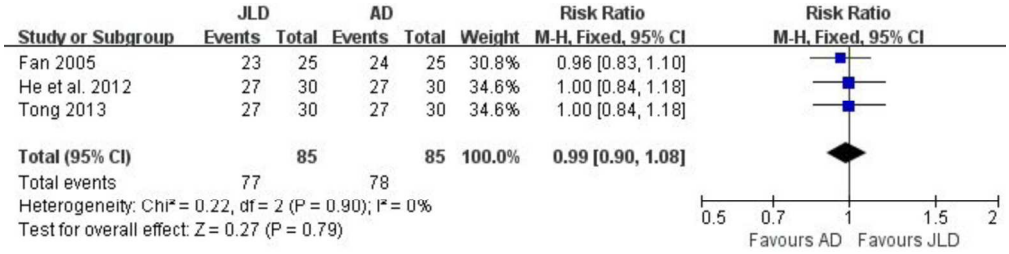
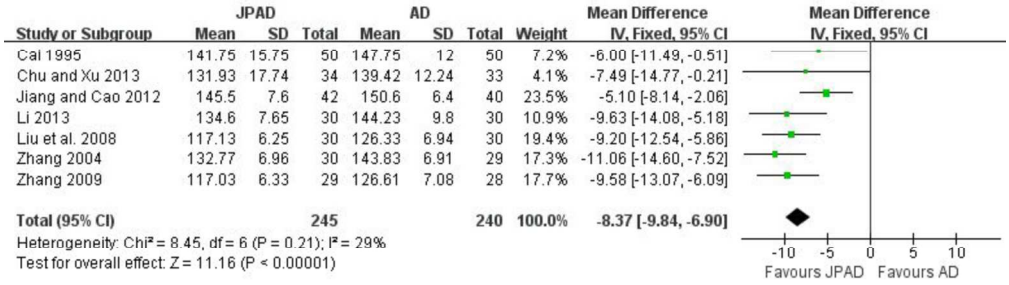


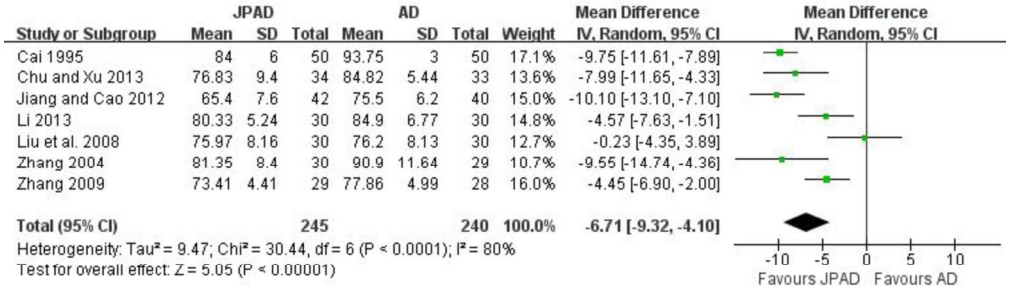
Fig 1 Flow diagram of study selection and identification.
159x171mm (300 x 300 DPI)



(a) JLD *versus* AD: BP



(b) JPAD *versus* AD: SBP (mmHg)



(b) JPAD *versus* AD: DBP (mmHg)

Figure 2. Effect of JLD on BP. (a) JLD versus AD and (b) JPAD versus AD. AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.
145x156mm (300 x 300 DPI)

Chinese herbal medicine Jian Ling Decoction for essential hypertension: A systematic review and meta-analysis of randomized controlled trials

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Total word count: 3200.

Number of tables and figures: 3 tables and 2 figures.

Running head: Jian Ling Decoction for essential hypertension.

[*] *BMJ Open* 2014

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ABSTRACT

Objectives: Jian Ling Decoction (JLD) is often prescribed to improve hypertension-related symptoms in China. However, this treatment has not been systematically reviewed for its efficacy against essential hypertension (EH). This review aims to assess the current clinical evidence of JLD in the treatment of EH.

Design: Seven electronic databases including the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), and the Wanfang Database were searched up to March 2014. Randomized control trials (RCTs) comparing JLD or combined with antihypertensive drugs versus antihypertensive drugs were included. We assessed the methodological quality, extracted the valid data, and conducted the meta-analysis according to criteria from the Cochrane group. The primary outcome was categorical or continuous blood pressure (BP), and the secondary outcome was quality of life (QOL).

Results: Ten trials (655 patients) with unclear-to-high risk of bias were identified. Meta-analysis showed that JLD used alone showed no BP reduction effect; however, improvement on QOL was found when compared to antihypertensive drugs. A significant reduction on systolic BP and diastolic BP were observed for JLD plus antihypertensive drugs when compared to antihypertensive drugs alone. No serious adverse effects were reported.

Conclusion: Due to insufficient clinical data, it is difficult to draw a definite

conclusion regarding the effectiveness and safety of JLD for EH, and better trials are needed.

KEY WORDS

essential hypertension; blood pressure; Chinese herbal medicine; Jian Ling Decoction; systematic review

ARTICLE SUMMARY

Article focus

- Jian Ling Decoction (JLD), a traditional Chinese herbal formula, is often prescribed for patients with essential hypertension (EH).

Key messages

- No definitive conclusion regarding the efficacy and safety of JLD for EH could be drawn based on the insufficient clinical data

Strengths and limitations of this study

- The strength of this article is its use of a comprehensive and unbiased literature searching of seven electronic databases without language and publication restrictions.
- The included trials were of small sample size, with poor methodological quality and significant heterogeneity.

INTRODUCTION

Hypertension is one of the most important preventable causes of death and one of the most common conditions treated in primary health care. In addition, hypertension represents an important public health challenge because of its high prevalence and the concomitant increase in the risk of cardiovascular, cerebrovascular and renal diseases.[1,2] This condition has been ranked as the leading global risk factor for mortality and is the third leading risk factor for disease burden according to the comparative Risk Assessment Collaborating Group.[3,4] Currently, about one billion patients have been affected.[5] The association between blood pressure (BP) and mortality was discovered approximately 100 years ago.[6] Recent studies also confirmed that BP is closely related to vascular outcomes, and even a minor reduction in BP could reduce cardiovascular events, especially stroke.[7,8] Therefore, early diagnosis and effective treatment is of great importance for patients with essential hypertension (EH). Nevertheless, despite remarkable achievements in the research and development of antihypertensive drugs, the current awareness, curative and control rates of hypertension among different age groups is still far from satisfactory.[9,10] Additionally, in the light of the adverse effects of antihypertensive drugs and hoping for an adjunctive approach with few adverse effects, patients in Western countries with EH and other cardiovascular diseases increasingly use complementary and alternative medicine (CAM),[11-13] including traditional Chinese medicine (TCM).[14-16]

Chinese herbal medicine (CHM), one of the commonly used TCM therapies, has played an important role in relieving hypertension-related signs and symptoms for centuries in East Asia.[17,18] Recently, more robust evidence from systematic reviews (SRs) has suggested the efficacy and safety of CHM for EH.[19-26] In TCM theory, liver yang hyperactivity syndrome (LYHS) and liver-kidney yin deficiency syndrome (LKYDS) are the two most important patterns of EH, which often appear at the same time.[17] These patterns manifest as headache, vertigo, tinnitus, irritability, insomnia, lassitude in the waist and legs, dysphoria with feverish sensation, dry mouth, bright red tongue with less fur, and a wiry pulse.[14,17,21,27,28] Jian Ling Decoction (JLD) is a traditional CHM invented by *Zhang Xichun* in *Yixue Zhongzhong Canxilu* (Records of Traditional Chinese in Combination with Western Medicine) in the 1920s. It contains the following eight commonly used herbs: Dioscorea Root (Shanyao, Dioscoreae Rhizoma), Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), Oyster Shell (Muli, Concha Ostreae), Rehmannia (Dihuang, Radix Rehmanniae Glutinosae), White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae), and Arbor Vitae Seed (Baiziren, Semen Platycladi). All of these herbs have been recorded in the Pharmacopoeia of the People's Republic of China (2010 edition). Both LYHS and LKYDS can be effectively treated with JLD.[19] Currently, JLD is often prescribed for the management of EH by TCM practitioners in China. It is worth noting that in the context of CAM therapies, add-on designs are very popular for the treatment of hypertension.[14,20-25] JLD is usually used in combination with antihypertensive drugs

to achieve greater improvement in the signs and symptoms of hypertension and to enhance the antihypertensive effect of conventional drugs with less adverse effects. The pharmacological mechanisms of these effects may be related to the reduction in levels of angiotensin II, IL-6, tumor necrosis factor-α (TNF-α), and leptin, as well as insulin resistance and decreased blood lipids.[29-34] Regarding the clinical use of JLD, a large number of studies (including case reports, case series, controlled observational studies, and randomized trials) have reported its effects on EH, including lowering BP, reducing inflammation, reversing cardiovascular risk factors, and improving clinical symptoms and quality of life (QOL).[35-37] However, there has been no comprehensive evaluation of clinical trials on the efficacy and adverse effects of JLD. This review aims to systematically review the published and unpublished randomized controlled trials (RCTs) to evaluate the current evidence for JLD in treating EH.

METHODS

This study was conducted according to the Cochrane practice.[38]

Search strategies

RCTs of JLD for the treatment of hypertensive patients were screened through the following electronic databases from their respective inceptions to March 2014: Cochrane Central Register of Controlled Trials (CENTRAL, 1996-2014), PubMed

(1959-2014), and EMBASE (1980-2014). In addition, as JLD is mainly prescribed in China, four Chinese electronic databases including the Chinese National Knowledge Infrastructure (CNKI, 1980-2014), Chinese Scientific Journal Database (VIP, 1989-2014), Chinese Biomedical Literature Database (CBM, 1978-2014), and Wanfang Database (1998-2014) were searched to retrieve the maximum possible number of trials. We also conducted a literature search of the website of the Chinese clinical trial registry (available at http://www.chictr.org/) and international clinical trial registry hosted by the US National Institutes of Health (available at http://clinicaltrials.gov/) for all of the relevant ongoing registered clinical trials and unpublished articles. The bibliographies of the studies identified in the systematic search were reviewed for potentially relevant additional publications. No restriction on publication status or language was imposed.

The keywords for databases searching were listed as follows: ("hypertension" OR "essential hypertension" OR "primary hypertension" OR "high blood pressure" OR "blood pressure") AND ("*jian ling* decoction" OR "*jianling* decoction" OR "*jian ling tang"* OR "*jianling tang"* OR "*jianlingtang"*) AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial").

Study selection

Types of studies

RCTs on the use of JLD for the treatment of EH were included. Quasi-randomized trials and animal experiments were excluded.

Types of participants

Trials focused on the patients suffering from EH were included. All of the participants who were enrolled in the trials were required to meet at least one of the current or past definitions of EH.[2] Trials without a description of the detailed diagnostic criteria but which reported patients with definite EH were also included . Patients with secondary hypertension were excluded. There was no restriction on gender, age, or ethnic origin of the participants.

Types of interventions

Only studies that tested JLD used alone versus antihypertensive drugs, or JLD combined with antihypertensive drugs versus antihypertensive drugs were included. However, trials assessing the combined effect of JLD with other interventions (*e.g.,* another CHM, qigong, Tai Chi, acupuncture, moxibustion and massage) were excluded given that the therapeutic effect of JLD could not be distinguished. Interventions in the control group included antihypertensive drugs. Studies that used non-conventional medicine or CAM as control groups were also excluded. The duration of treatment was required to be at least two weeks.

According to the principle of similarity of the TCM formula,[39] modified JLD should contain at least six out of eight herbs used in JLD, and only a few herbs could be added into the JLD based on TCM syndrome theory. However, the resulting prescription should contain the following four principal drugs: Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix), Hematite (Daizheshi, Haematitum), Fossilized Mammal Bones (Longgu, Os Draconis), and Oyster Shell (Muli, Concha Ostreae).

Types of outcome measures

The primary outcome analyzed for this meta-analysis was categorical or continuous BP, and secondary outcome was QOL.

Data extraction

All of the articles were read by two independent reviewers. Then, the eligible studies were retrieved for further identification according to the above inclusion and exclusion criteria. Duplicate papers were excluded. The data extraction form comprised the authors, title, publication year, sample size, age, sex distribution, diagnosis standard, study design, interventions in the treatment and control groups, the composition of JLD or modified JLD, trial duration, outcome measures, and adverse effects. If missing or unclear information regarding the original study was found, we contacted the primary authors via email, telephone or fax whenever

possible. Any disagreement was resolved by discussion between the reviewers.

Methodological quality

The risk of bias of the included studies was independently evaluated by two reviewers according to the criteria in the Cochrane Handbook for Systematic Review of Interventions Version 5.1.0 (updated March 2011).[38] The following seven items were included: (a) sequence generation (selection bias); (b) allocation concealment (selection bias); (c) blinding of participants and personnel (performance bias); (d) blinding of outcome assessments (detection bias); (e) incomplete outcome data (attrition bias); (f) selective reporting (reporting bias); and (g) other sources of bias (from Chapter 8: assessing risk of bias in included studies).[38] Each domain was assessed as a "high", "unclear", or "low" risk of bias based on the above criteria. Then, the methodological quality of the trials was ranked into three levels: low risk of bias (all items with low risk of bias), high risk of bias (at least one item with high risk of bias), or unclear risk of bias (at least one item with an unclear domain).

Data synthesis

Review Manager, Version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. The values of the outcome measures after treatment were retrieved to assess differences between the JLD and control groups.

The weighted mean difference (WMD) was used for continuous data, while the risk ratio (RR) was used for binary data. Subgroups analysis was conducted among different types of comparisons (including JLD *versus* antihypertensive drugs and JLD plus antihypertensive drugs *versus* antihypertensive drugs). If high quality trials could be found, comparisons between all of the studies and studies with high quality would be conducted. In a three-group design study that had two treatment groups of JLD and JLD plus antihypertensive drugs, the two comparisons were split in the meta-analysis. Heterogeneity was assessed by I^2 statistics.[38] Funnel plots were applied to detect for publication bias when the number of included studies of any particular outcome was more than ten. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study characteristics

Figure 1 shows the process of study selection. We identified 308 potentially relevant articles in the initial screening of the seven databases. Ten RCTs, with a total of 655 participants, met the eligibility criteria and were included.[40-49] The basic characteristics of included trials are summarized in Table 1. Six diagnostic criteria of EH were specified: two trials[40,41] used the Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine (GCRNDTCM); four trials[42,44,46,47] used the WHO-ISH guidelines for the management of hypertension-1999 (WHO -ISH

GMH-1999); one trial[43] used the WHO-ISH GMH-1985; one trial[45] used the Chinese Guidelines for the Management of Hypertension-2005 (CGMH-2005); one trial[48] used the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and one trial[49] used the Chinese Guidelines for the Management of Hypertension-2010 (CGMH-2010). All of the studies were conducted in China and published in Chinese language. One trial was a three-arm design (two intervention groups versus one control group),[44] and the others used a two-arm study design (one intervention group versus one control group). The clinical efficacy of JLD was observed in all of the trials. However, the evaluation criteria on BP was different: three trials used the categorical BP recommended by Chinese government in GCRNDTCM,[40-42] and seven used continuous BP.[43-49] QOL was only tested in one trial.[42]

Treatment groups

The types of intervention were classified as JLD (n = 4) or combination therapy (JLD plus antihypertensive drugs, n = 7). The variable prescriptions based on JLD are presented in Table 1. Different compositions of either JLD or modified JLD are presented in Table 2.

Control groups

All of the patients in the control groups received antihypertensive drug treatment, including felodipine,[40-42] nifedipine,[43,47,49] enalapril,[44,45,48] and benazepril hydrochloride.[46]

Treatment duration

The total treatment duration in the trials ranged from three to four weeks, with most being four weeks (n = 8). The duration of follow-up was only mentioned in one trial, being three months.[43]

Methodological quality

As shown in Table 3, four trials reported the method used to generate the allocation sequence (random number table).[41,44,45,48] Information regarding allocation concealment was provided in two trials.[44,48] Blinding of participants and personnel was reported in three trials;[44,45,48] however, no trial used blinding of outcome assessment. Drop-out and withdrawal data were provided for three trials.[44,45,49] No trial had a pre-trial estimation of sample size. Selective reporting could not be evaluated as no preregistered protocols could be obtained from the primary authors.

Outcome measures

Primary outcome: BP

JLD *versus* antihypertensive drugs (4 studies)

The clinical efficacy of JLD as monotherapy for BP was assessed in four trials.[40-42,44] Three trials[40-42] did not use continuous BP to evaluate the efficacy of JLD, but used categorical BP, the evaluation criteria of which has been authoritatively recommended by China Food and Drug Administration (available at http://www.sda.gov.cn). It was defined as follows: "significant improvement" (DBP decreased by 10 mmHg, reaching the normal range, or DBP not returning to normal but reduced by more than 20 mmHg), "improvement" (DBP decreased by less than 10 mmHg but reaching the normal range, DBP decreased by 10 to 19 mmHg but not reaching the normal range, or SBP decreased by more than 30 mmHg), and "no improvement" (not meeting the above standards).[50] These outcomes were converted into binary data for further overall analysis. Both "significant improvement" and "improvement" were classified as "effective", and "no improvement" was classified as "ineffective". The meta-analysis showed that JLD had no BP reduction effect compared with antihypertensive drugs (n = 170; RR: 0.99; 95% CI: 0.90 to 1.08; P = 0.79; Figure 2a), with no significant heterogeneity (chi-square = 0.22, P = 0.90; I^2 = 0%). Another trial used continuous BP to evaluate the efficacy of modified JLD when compared with enalapril.[44] No significant difference was found for either SBP or DBP (P > 0.05).

JLD plus antihypertensive drugs *versus* antihypertensive drugs (7 studies)

Seven RCTs evaluated the effect of JLD combined with antihypertensive drugs versus antihypertensive drugs.[43-49] Continuous BP was measured in all of these studies. SBP was significantly reduced in the JLD plus antihypertensive drugs group when compared with antihypertensive drugs (n = 485; WMD: -8.37 mmHg; 95% CI: -9.84 to -6.90; $P < 0.00001$; Figure 2b), with no significant heterogeneity (chi-square = 8.45, $P = 0.21$; $I^2 = 29\%$). For DBP, a significant beneficial effect was also found in the JLD plus antihypertensive drugs group (n = 485; WMD: -6.71 mmHg; 95% CI: -9.32, -4.10; $P < 0.00001$; Figure 2c), with significant heterogeneity (chi-square = 9.47, $P < 0.0001$; $I^2 = 80\%$).

Secondary outcome: QOL

Only one trial,[42] conducted by Fan et al, used the Croog Scale[51] to assess the effectiveness of JLD on QOL in aged hypertension patients. At the end of the trial, QOL was significantly improved by JLD when compared with the felodipine group ($P < 0.05$). The trial demonstrated that long-term use of JLD might improve QOL for hypertensive patients.

Adverse effects

Adverse effect monitoring was only reported in five studies [43-45, 48, 49] and was not mentioned in the other five trials. Among the former, no severe adverse effects were reported in two trials.[43,49] Three trials reported dry cough caused by enalapril in both the JLD and antihypertensive drugs groups.[44,45,48] Two trials reported severe dry cough in the antihypertensive drugs groups.[44,45] None of the adverse effects were serious in the JLD groups.

Evaluation of publication bias

As the number of included trials was so small, it was not possible to conduct a sufficient additional analysis of publication bias.

DISCUSSION

Summary of evidence

Taking into account the gap between the lack of scientific evidence regarding the efficacy of JLD and the widespread application by TCM practitioners, the objective of this study was to systematically review the current English and Chinese literature to evaluate the efficacy and safety of JLD for EH. To our knowledge, this is the first SR of JLD in English.

Ten claimed RCTs, with a total of 655 hypertensive patients, met the inclusion criteria and were included in this review. The results suggested that both SBP and DBP were significantly improved in patients receiving JLD plus antihypertensive drugs therapy, although the effect was not significant in the JLD alone group. Moreover, JLD was found to be effective in terms of improving QOL when compared with antihypertensive drugs. However, the evidence for JLD as an effective modality for treating EH was restricted by a limited number of trials, small sample sizes, poor methodological quality, and a high risk of bias in primary studies.

Limitations

The following limitations should be considered before accepting the findings of this review.

(1) Although there were two randomized, single-blind, controlled trials, the methodology of most of the included trials was assessed to be generally poor. The main reasons are analyzed as follows:

Firstly, although all studies claimed randomization, only four trials demonstrated the random sequence generation, and two trials reported allocation concealment; therefore, selection bias may exist. Secondly, only three trials described the blinding of the participants and personnel; however, no trials reported the blinding of outcome assessment. Therefore, both selection bias and detection bias might have occurred. Thirdly, only three trials reported drop-out or withdraw statistics, suggesting a high

risk of attrition bias. Fourthly, most of the included studies did not mention intention to treat analysis, which may lead to some other bias. Fifthly, no trials had a pre-estimation of sample size. Sixthly, no trial had a placebo control, which might decrease the quality of positive conclusions.

(2) As shown in Figure 2c, heterogeneity is another critical issue that should be considered, which may be associated with variations in study quality, participants, JLD compositions, and antihypertensive drugs.

(3) Limited number of included trials and different interventions in both the JLD and antihypertensive drugs groups restricted us from conducting meaningful subgroup analyses to explore effect modifiers such as duration of intervention and types of antihypertensive drug therapies.

(4) Publication bias should also be considered. In this review, all of the included trials were conducted in China and published in Chinese. Almost all studies claimed a similar beneficial effect or a better effect when compared with antihypertensive drugs alone. No negative conclusions were found. What is more, a funnel plot checking for possible publication bias for BP could not be conducted due to the small number of included studies.

(5) Although one trial had a short-term follow up, most of the studies had no follow up, indicating a lack of knowledge for some critical outcomes, such as all-cause mortality and progression to severe complications due to high BP, which is the most common problem for TCM studies in general.

(6) As the use of natural products is very common among patients in a variety of

health care settings, the safety of CHM and potential herb-drug interactions has hence become a concern. This review suggested that JLD may be safe for the management of EH. In fact, no parallel double blind randomized placebo-controlled trials indicating the adverse effects of JLD for EH could be found. Due to the insufficient clinical data, it is difficult to draw a definitive conclusion regarding the safety of JLD for EH at present. We therefore suggest that the adverse effects of JLD need to be monitored rigorously in future studies.

CONCLUSION

Due to the insufficient clinical data, poor methodological design, and high risk of bias, it is difficult to draw a definite conclusion regarding the effectiveness and safety of JLD for EH. More rigorously designed trials reported according to the CONSORT Statement are needed.[52-54]

Funding

XJX was supported by the National Natural Science Foundation Project of China (No. 81403375). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

None.

Contributors

XX conceived the idea for the study and designed the method of this systematic review and meta-analysis including the inclusion and exclusion criteria. XX also performed data collection and extraction, conducted the statistical analysis, and wrote the first draft of the article. PW, XL, and YZ searched the articles and assessed their methodological quality. Disagreement was resolved by discussion between XX, PW, XL, and YZ. PW performed the major revision, interpreted the results, and made comments. All of the authors approved the final version of the manuscript.

Acknowledgements

The author would like to thank Cheryl C. from American Journal Experts (AJE) in revising the English language of the manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data available.

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Table 1. Basic characteristics of the included studies.

Table 2. Herbal medicines in the included studies.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

FIGURE LEGENDS

Figure 1.

Flow diagram of study selection and identification.

Figure 2.

Effect of JLD on BP. (a) JLD *versus* AD and (b) JPAD *versus* AD.

AD: antihypertensive drugs; BP: blood pressure; DBP: diastolic blood pressure; JLD: Jian Ling Decoction; JPAD: Jian Ling Decoction plus antihypertensive drugs; SBP: systolic blood pressure.

Table1. Basic characteristics of the included studies.

Study ID	Sample size (randomized /analyzed) M/F	Age(yrs)	Diagnosis standard	Intervention	Control	Course (week)	Outcome measures
Tong 2013 [40]	60/60 T: 30 C: 30 F/M: NR	40-60 (T/C: NR)	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
He et al. 2012 [41]	60/60 T: 15/15 C: 17/13	T: 54.89 ± 5.34 C: 57.36 ± 6.47	GCRNDTCM	JLD (1 dose/d)	felodipine (5 mg, qd)	4	BP
Fan 2005 [42]	50/50 T: 14/11 C: 13/12	T: 64.80 ± 7.40 C: 63.70 ± 6.90	WHO -ISH GMH-1999	JLD (1 dose/d)	felodipine (2.5 mg, qd)	4	BP; QOL
Cai 1995 [43]	100/100 T: 35/15 C: 34/16	T: 50-81 C: 47-84	WHO -ISH GMH-1985	modified JLD (1 dose/d) + control	nifedipine (10 mg, tid)	4	BP; adverse effect
Zhang 2004 [44]	90/89 T1: 16/14 T2: 17/13 C: 15/14	T1: 58.23 ± 8.26 T2: 58.45 ± 6.87 C: 59.16 ± 9.28	WHO -ISH GMH-1999	T1: modified JLD (1 dose/d) T2: modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	4	BP; adverse effect
Zhang 2009 [45]	60/57 T: 15/14 C: 12/16	T: 56.41 ± 10.98 C: 58.57 ± 8.21	CGMH-2005	modified JLD (1 dose/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Jiang and Cao 2012 [46]	82/82 T: 26/16 C: 23/17	T: 60-75 C: 62-75	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	benazepril hydrochloride (10 mg, tid)	4	BP
Chu and Xu 2013 [47]	67/67 T: 19/15 C: 17/16	T: 67.00 ± 7.20 C: 68.00 ± 5.90	WHO -ISH GMH-1999	modified JLD (100 ml/d) + control	nifedipine controlled release tablet (30 mg, qd)	4	BP
Liu et al. 2008 [48]	60/60 T: 30 C: 30 F/M: NR	18-70 (T/C: NR)	JNC 7	modified JLD (100 ml/d) + control	enalapril (10 mg, bid)	3	BP; adverse effect
Li 2013 [49]	60/60 T: 16/14 C: 17/13	T: 64.33 ± 7.96 C: 61.20 ± 10.23	CGMH-2010	modified JLD (400 ml/d) + control	nifedipine controlled release tablet (30 mg, qd) and irbesartan (150 mg, qd)	4	BP; adverse effect

Abbreviations: BP: blood pressure; C: control group; CGMH: Chinese Guidelines for the Management of Hypertension; F: female; GCRNDTCM: Guidelines of Clinical Research of New Drugs of Traditional Chinese Medicine; JLD: Jian Ling Decoction; JNC 7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; M: male; NR: not reported; QOL: quality of life; T: treatment group; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension.

Table 2. Herbal medicines in the included studies.

Study ID	Formula	Composition of formula
Tong 2013 [40]	JLD	Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Hematite (Daizheshi, Haematitum) 10 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, and Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g.
He et al. 2012 [41]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 15 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 20 g, Hematite (Daizheshi, Haematitum) 10 g, Oyster Shell (Muli, Concha Ostreae) 10 g, Fossilized Mammal Bones (Longgu, Os Draconis) 10 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 15 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 10 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 10 g.
Fan 2005 [42]	JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g.
Cai 1995 [43]	modified JLD	Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Abalone Shell (Shijueming, Haliotidis Concha) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache plus Puncturevine Caltrop Fruit (Cijili, Tribulus terrestris Linn) 10 g; constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2004 [44]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Headache, dizziness, and irritability plus Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g and Abalone Shell (Shijueming, Haliotidis Concha) 30 g; irritability, bitty mouth and red face plus Coptis Rhizome (Huanglian, Rhizoma Coptidis) 10 g and Gardenia (Zhizi, Fructus Gardeniae Jasminoidis) 10 g; and constipation plus Rhubarb Root and Rhizome (Daihuang, Radix Et Rhizoma Rhei) 5 g.
Zhang 2009 [45]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 12 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 12 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Jiang and Cao	modified	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Fresh Water Turtle Shell (Guijia, Plastrum

2012 [46]	JLD	Testudinis) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, Hematite (Daizheshi, Haematitum) 20 g, Oyster Shell (Muli, Concha Ostreae) 20 g, Fossilized Mammal Bones (Longgu, Os Draconis) 20 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 15 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g.
Chu and Xu 2013 [47]	modified JLD	Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 25 g, Fresh Water Turtle Shell (Guijia, Plastrum Testudinis) 25 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Hematite (Daizheshi, Haematitum) 15 g, Oyster Shell (Muli, Concha Ostreae) 25 g, Fossilized Mammal Bones (Longgu, Os Draconis) 25 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 25 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g.
Liu et al. 2008 [48]	modified JLD	Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 18 g, Hematite (Daizheshi, Haematitum) 24 g, Oyster Shell (Muli, Concha Ostreae) 18 g, Fossilized Mammal Bones (Longgu, Os Draconis) 18 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, and Arbor Vitae Seed (Baiziren, Semen Platycladi) 20 g. Excessive accumulation of phlegm-dampness plus Pinellia Rhizome (Banxia, Rhizoma Pinelliae Tematae) 15 g, Sclerotium of Tuckahoe (Fuling, Scierotium Poriae Cocos) 15 g, Tangerine Peel (Chenpi, Pericarpium Citri Reticulatae) 10 g, Bamboo Shavings (Zhuru, Bambusae Caulis in Taeniam) 10 g, and Liquoric Root (Gancao, Radix Glycyrrhizae) 3 g.
Li 2013 [49]	modified JLD	Fossilized Mammal Bones (Longgu, Os Draconis) 30 g, Oyster Shell (Muli, Concha Ostreae) 30 g, Rehmannia (Dihuang, Radix Rehmanniae Glutinosae) 20 g, Hematite (Daizheshi, Haematitum) 20 g, Dioscorea Root (Shanyao, Dioscoreae Rhizoma) 30 g, Achyranthes Root (Niuxi, Achyranthis Bidentatae Radix) 30 g, White Peony Root (Baishao, Radix Albus Paeoniae Lactiflorae) 20 g, Arbor Vitae Seed (Baiziren, Semen Platycladi) 15 g, Gambir Vine Stems and Thorns (Gouteng, Ramulus Uncariae Cum Uncis) 30 g, Pueraria (Gegen, Radix Puerariae) 30 g, Gastrodia (Tianma, Gastrodiae Rhizoma) 15 g, Chinese Taxillus Twig (Sangjisheng, Herba Taxilli) 30 g, Eucommia Bark (Duzhong, Cortex Eucommiae Ulmoidis) 15 g, and Coptis Rhizome (Huanglian, Rhizoma Coptidis) 9 g.

Abbreviations: JLD: Jian Ling Decoction.

Table 3. Methodological quality of included studies based on the Cochrane handbook.

Included trials	A	B	C	D	E	F	G
Tong 2013 [40]	?	?	?	?	+	?	?
He et al. 2012 [41]	+	?	?	?	+	?	?
Fan 2005 [42]	?	?	?	?	+	?	?
Cai 1995 [43]	?	+	?	?	+	?	?
Zhang 2004 [44]	+	+	+	?	+	?	?
Zhang 2009 [45]	+	?	+	?	+	?	?
Jiang and Cao 2012 [46]	?	?	?	?	+	?	?
Chu and Xu 2013 [47]	?	?	?	?	+	?	?
Liu et al. 2008 [48]	+	+	+	?	+	?	?
Li 2013 [49]	?	?	?	?	+	?	?

Abbreviations: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (participants and personnel); D: Blinding (assessor); E: Incomplete outcome data addressed (ITT analysis); F: Free of selective reporting; G: other potential thereat to validity; +: low risk; -: high risk; ?: unclear.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P9-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P11-12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P12-13

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P12-13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P13-15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P16-17
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	P16-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P19-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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