Berberine for the treatment of hypertension: a systematic review

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Abstract

Background

Hypertension is the highest risk factor for disease globally. When prescription of drug therapy is recommended, patients might decline treatment due to hypertension asymptomatic nature, sometimes turning to alternative therapies. One popular therapy is berberine, a plant alkaloid that has been used in eastern medicine for millennia to treat several ailments, including cardiovascular diseases and their risk factors.

Aims

Through a transparent and pragmatic approach towards searching, synthesising, assessing, and reporting the available clinical evidence, the present review aimed to investigate berberine effect on blood pressure and cardiovascular disease risk. It also intended to provide guidance for clinician when advising their patients, and to highlight gaps in the research along offering suggestions to fill them.

Methods

The review was conducted following the protocol PRISMA-P, and reported according to the related PRISMA statement. The PICO framework was used to define the scope of the review, and to arrive at a database search strategy. The strategy was run on the databases Medline, CINAHL, AMED, Embase, and Cochrane Library through the platforms EBSCOhost and Ovid. Citations were exported to Mendeley citation manger for screening. Relevant studies were selected based on specified inclusion and exclusion criteria. Data from included studies was extracted in the form of a detailed table of characteristics of studies, and summarised in an evidence table. Quality of studies was assessed using the SIGN methodology checklist for controlled trials. The results from the quality assessment were summarised through an adaptation of the Robvis tool software package output. Effect estimates and their precision were calculated with RevMan 5 computer program from the extracted study outcomes.

Results

Five randomised controlled trials and two non-randomised controlled trials were included with 614 participants. All provided data on blood pressure, but none measured cardiovascular events or long-term adverse events. The group of studies was highly heterogeneous in terms of experimental

intervention, comparator intervention, length to follow-up, participants' diagnosis, and setting. The heterogeneity prevented a meaningful meta-analysis. Berberine plus amlodipine was not significantly better than amlodipine alone at reducing systolic and diastolic blood pressure. Compared to metformin, berberine provided a statistically significant moderate reduction effect on systolic blood pressure (-11.87 [-16.64, -7.10] mmHg). A proprietary nutraceutical containing berberine as one of its ingredients was in one study significantly effective at reducing blood pressure compared to placebo (-11.80 [-18.73, -4.87] mmHg systolic, and -11.10 [-15.17, -7.43] mmHg diastolic), and also effective in another study compared to dietary advice (-3.40 [-5.48, -1.32] mmHg for systolic 24h ambulatory blood pressure), although effects could not be reliably attributed to berberine alone. The herbal extract Chunghyul-dan, which contains berberine, showed a significant beneficial moderate effect compared to no treatment on systolic 24h ambulatory blood pressure (-7.34 [-13.14, -1.54] mmHg) in one study, but in another study employing higher dose and longer treatment duration, no effects were detected. Again, the effects could not be attributed to berberine alone. The quality of the body of evidence was low, especially due to lack of trial design details and presence of outcome reporting bias.

Conclusions

The evidence around berberine effect on blood pressure is limited, of low quality, and ultimately inconclusive. Clinicians should be aware that the evidence from randomised trials is not sufficient to establish berberine effectiveness and safety in the treatment of hypertension, and they should balance these findings with the long history of berberine use in the Eastern world. Researchers should aim at improving quality of studies, by raising the standard of designing and reporting them, e.g., by following the CONSORT guidelines, and strive to measure meaningful clinical endpoints, such as cardiovascular events, mortality, and adverse outcomes.

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1. Background

1.1 Description of the condition

High blood pressure, commonly known as hypertension, has long been accepted as a major risk factor for stroke, cardiovascular disease, renal disease, and overall mortality [1]. Blood pressure is a biological continuous variable with a normal distribution across the general population. Hypertension is diagnosed when blood pressure is above an arbitrarily set threshold at the high end of the distribution. The threshold for hypertension is set pragmatically at a level above which the related risk of cardiovascular disease warrants treatment and investigations that would do more good than harm [2].

The National Institute for Health and Care Excellence (NICE) defines hypertension as a blood pressure of 140/90 mmHg (systolic/diastolic) or higher when measured in clinic and either a subsequent daytime ambulatory blood pressure monitoring (ABPM) average or home blood pressure monitoring average of 135/85 mmHg or higher [3]. A clinic blood pressure reading between 120/80 mmHg and 140/90 mmHg is defined as high-normal blood pressure [4].

Hypertension is categorised as primary and secondary hypertension. The latter generally appears earlier in life, independently of family history, has an established cause, such as a renal or endocrine condition, or can be iatrogenic, as in the use of oral contraceptive use [2]. Secondary hypertension should always be suspected in adults under 40 who have hypertension, and should trigger further investigations to establish a possible secondary cause [3]. If the cause can be eliminated, secondary hypertension could resolve without further interventions. In contrast, primary hypertension, also known as essential hypertension, occurs mostly later in life, due to a combination of lifestyle and hereditary factors. In the reminder of this review, the terms hypertension, primary hypertension, and essential hypertension will be used interchangeably.

In the Global Burden of Disease (GBD) 2015 [5], hypertension represented the highest burden among risk factors for disease globally, affecting one in four adults. The GBD also showed that in the UK, hypertension was the third biggest risk factor for disease after tobacco smoking and obesity. At the same time, high blood pressure is the largest single known risk factor for cardiovascular disease and associated disability. The GBD estimated that in 2015 in England there

were 12.5 million people, one in four, affected by hypertension. The latter was responsible for 75,000 deaths in that year.

Current evidence shows that lowering blood pressure reduces the above risks. For example, in an extensive meta-analysis on blood pressure lowering treatment published in the Lancet, Ettehad et al. [5] pooled data from 123 trials dating from 1966 to 2015 which included 613,815 participants. They found that every 10 mmHg reduction in systolic blood pressure resulted in 28% reduction for the risk of heart failure, 27% reduction for stroke, 17% reduction for coronary heart disease, and 13% reduction for all-cause mortality.

Steps have been made towards reducing the English population's blood pressure level. The Health Survey for England 2018 [6] demonstrates that over the last ten years the population's systolic blood pressure has decreased by almost 3 mmHg on average. However, not much progress has been made over the last three years.

1.2 Description of the intervention

When lifestyle and dietary changes do not sufficiently lower a patient's blood pressure to at least the high-normal range, a drug treatment is offered. Generally, patients are less enthusiastic than clinicians about starting an antihypertensive drug regimen, a trend common to therapies that are preventative of a disease rather than intended to treat it. In the UK, as much as 50% of patients at moderate risk of cardiovascular disease have been estimated as likely to decline antihypertensive drugs [7]. When patients decline their doctor's or practice nurse's treatment, they might seek alternative approaches. In their systematic review of Europe citizen's attitude in relation to alternative medicine, Nissen et al. [8] found that the studies they included reported between 54% and 66% of UK healthcare users as supporting the provision of alternative therapies in the National Health Service. Also, they highlighted that citizens wish for more support and knowledge from healthcare professionals about alternative therapies.

Across Europe, herbal medicine is one of the most popular alternative therapies that patients use [9]. Among them is berberine, a yellow coloured isoquinolone alkaloid herbal derivative which has received much attention in its application for the treatment of various conditions, including type 2 diabetes mellitus, hypercholesterolaemia, and hypertension. Plants containing berberine have been used in Chinese and Ayurvedic medicine for over 2500 years for their antimicrobial, antiprotozoal,

and antidiarrheal activity [10]. Berberine is found in varying proportions in roots, rhizomes, stems, and bark of several species of the Ranuncolaceae family, including *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric), C*opti chinensi* (Chinese goldthread), *Coptis trifolia* (American goldthread), and H*ydrastis canadensis* (goldenseal) [11]. Several studies have investigated berberine effects on cardiovascular disease, making berberine one of the most widely studied herbal constituent of the last decades [12]. In recent years, researchers have pooled the growing body of evidence into several narrative reviews of the effects of berberine on various illnesses, including diabetes, dyslipidaemia, dementia, cancer, and hypertension [13–17]. The search carried out for the present review revealed only one systematic review on berberine for the treatment of hypertension [18]. It is somewhat dated and its meta-analysis has some errors which put into question its conclusion on berberine effect on blood pressure. Further insights are given in the Discussion section under Agreements and disagreements with other reviews. It seemed therefore appropriate to conduct a systematic review to clarify the role of berberine in the treatment of hypertension.

2. Objectives

This systematic review aims at evaluating the effectiveness of berberine in reducing blood pressure and cardiovascular events. The 'Population, Intervention, Comparison(s) and Outcome' (PICO) framework, first proposed by Richardson et al. [19], was used to arrive at a review question for which all components would be well defined. The Cochrane Handbook suggests that equal emphasis in defining each PICO component is not necessary [20]. In this review the comparison element was left out to increase sensitivity. The following PICO question was then formulated:

> Does treatment with berberine reduce blood pressure and cardiovascular events in adults with primary hypertension?

From this starting point, the review ultimate aim is to distill for clinicians, and especially primary care doctors and practice nurses who are at the front line of prevention of cardiovascular disease, the evidence available around berberine when used for treatment of hypertension. In particular, the focus is on establishing the quality of evidence around berberine efficacy and safety in lowering blood pressure and in providing long-term benefits through the reduction of cardiovascular events in patients with hypertension. It is hoped that clinicians, should they encounter patients using berberine, will then be better equipped to give advice and support to these patients, and provide treatment that is safe and effective.

3. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21] defines a systematic review as an essential tool to collate evidence comprehensively, accurately, and clearly, to then synthesise and draw conclusions from the whole range of available data. The drafting of this report has followed the PRISMA statement. The PRISMA protocol (PRISMA-P) [22] was fallowed to carry out the review.

3.1 Study eligibility criteria

3.1.1 Types of studies

Studies were included if they were designed as controlled trials, regardless of randomization, blinding, publication status, or language. Observational studies and studies designed as before-after studies, interrupted time-series, and cross sectional studies were excluded. Regardless of the identification of the type of study design given in the related paper, the type of study design was determined through the NICE algorithm for classifying quantitative study designs [23].

3.1.2 Types of participants

Participants had to be human adults aged 18 and above who had primary hypertension. Studies were included if study participants had a mean baseline blood pressure satisfying at least one of the NICE criteria for the diagnosis of hypertension [3]. Therefore, studies were included if the baseline mean blood pressure values of participants in both experimental group and comparator group satisfied at least one of the following criteria:

- Clinic systolic blood pressure (SBP) higher than or equal to 140 mmHg
- Clinic diastolic blood pressure (DBP) higher than or equal to 90 mmHg
- Daytime systolic ABPM higher than or equal to 135 mmHg
- Daytime diastolic ABPM higher than or equal to 85 mmHg
- Home systolic blood pressure monitoring higher than or equal to 135 mmHg
- Home diastolic blood pressure monitoring higher than or equal to 85 mmHg.

Studies were excluded if the condition treated was secondary hypertension.

3.1.3 Types of interventions

Studies were included if the intervention included one of the following:

- Berberine as single independent herbal extract in any form, e.g., berberine hydrochloride, in a given or calculable dose;
- A preparation made through the combination of multiple independent herbal extracts where the actual content of berberine was specified or possible to estimate;
- Decoctions or extract from a mixture of herbs, where at least one of the herbs was a source of berberine, and where the actual content of berberine was specified or possible to estimate.

Any co-intervention in addition to the experimental intervention and comparator interventions were allowed as long as all arms of the trial received the same co-intervention. To ensure a wider scope of analysis, studies with any control intervention were included.

3.1.4 Types of outcome measures

From the eligible studies, it was sought to extract the following outcome measures for all follow-up points after completion of the interventions:

Primary outcomes

- Fatal and non-fatal cardiovascular events of all types
- Systolic and diastolic blood pressure measures of all types

Secondary outcomes

- Death from any cause
- Quality of life
- Adverse events. It was sought to distinguish between two types of adverse events: adverse events considered serious and adverse events considered non-serious. Following the definition in the Yellow Card Scheme [24], adverse events were defined as any harmful medical occurrence that results in death, is life threatening, leads to a congenital

abnormality, results in involved or prolonged inpatient hospitalisation, results in involved persistent or significant disability or incapacity. Adverse events not satisfying these criteria were considered non-serious.

Timing of outcome measurements

No criteria were imposed on the minimum experimental and comparator intervention duration.

3.2 Search methods for identification of studies

The following sources were searched for identification of trials:

- Medline (EBSCOhost) (1946 to 18 April 2020);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text (EBSCOhost) (1937 to 18 April 2020);
- The Allied and Complementary Medicine Database (AMED) (EBSCOhost) (1995 to 18 April 2020);
- Embase (Ovid) (1974 to 18 April 2020);
- Cochrane Central Register of Controlled Trials (CENTRAL) (2020 issue 4).

The keywords used in the searches are reported in Appendix 2. The plants there listed are known sources of berberine. Names were collected through an iterative process during the scoping search, and were found in three reviews [10,11,18].

To increase sensitivity, subject heading searches and keyword searches were used, and subject headings were exploded. Additionally, the only filter used was each database built-in filter for human studies. Reference lists of retrieved papers and reviews on the topic were scrutinised to locate additional relevant citations.

3.3 Data collection and analysis

3.3.1 Selection of studies

All citations retrieved, after having removed duplicate search results directly in EBSCOhost and Ovid platforms, were exported from the search databases to a RIS format file. This was then

imported into the reference management software Mendeley Desktop for Linux, where the whole set of citations was further deduplicated. Mendeley was then used for study selection.

Based on Study eligibility criteria, titles and abstracts of all citations retrieved were screened. The full-text articles of potentially relevant titles and abstracts was sourced, with those not in English or Italian translated with Google Translate [25] into English, and then assessed for eligibility. Reasons for exclusion of papers that did not meet the inclusion criteria were recorded.

3.3.2 Data extraction and management

Standardised forms for data extraction of items of interest from the included papers were developed in LibreOffice Calc spreadsheet computer program. The forms were designed based on the checklist of items to consider in data collection given in the Cochrane Handbook [26]. Data was extracted for the following items:

- Study design
- Characteristics of participants;
- Experimental and comparator interventions;
- Outcomes and timing, and adverse outcomes;
- Results.

3.3.3 Assessment of risk of bias in the included studies

A standardised form for risk of bias assessment at study level was adapted in LibreOffice Calc from the SIGN methodology checklist for controlled trials [27] and companion notes [28]. This tool has been validated, and provides a balance between methodological rigour and practicality of use [29]. There are several other risk of bias assessment tools. For example, the Rob2 is the tool of choice for Cochrane reviews [30]. This tool is comprehensive but extensive in its practical application. For the scope of this review, the SIGN checklist was deemed more appropriate, providing straightforward questions to assess study design elements that contribute to risk of bias.

3.3.4 Measures of treatment effect

It was planned to group effect measures depending on the type of outcomes reported in the included studies. Also, it was planned to extract both baseline and follow-up outcomes for all groups, and effect estimates in the form of follow-up between-groups comparison or change from baseline between-groups comparison, or both, whichever were given in a study [31]. All statistical analysis were carried out with RevMan 5 [32].

Dichotomous data

It was planned to calculate dichotomous outcomes, e.g., stroke yes/no, as risk ratio (RR) with 95% confidence interval (CI).

Continuous data

It was planned to express continuous outcomes (e.g., SBP) as mean difference (MD) with 95% CI.

4. Results

4.1 Description of studies

4.1.1 Results of the search

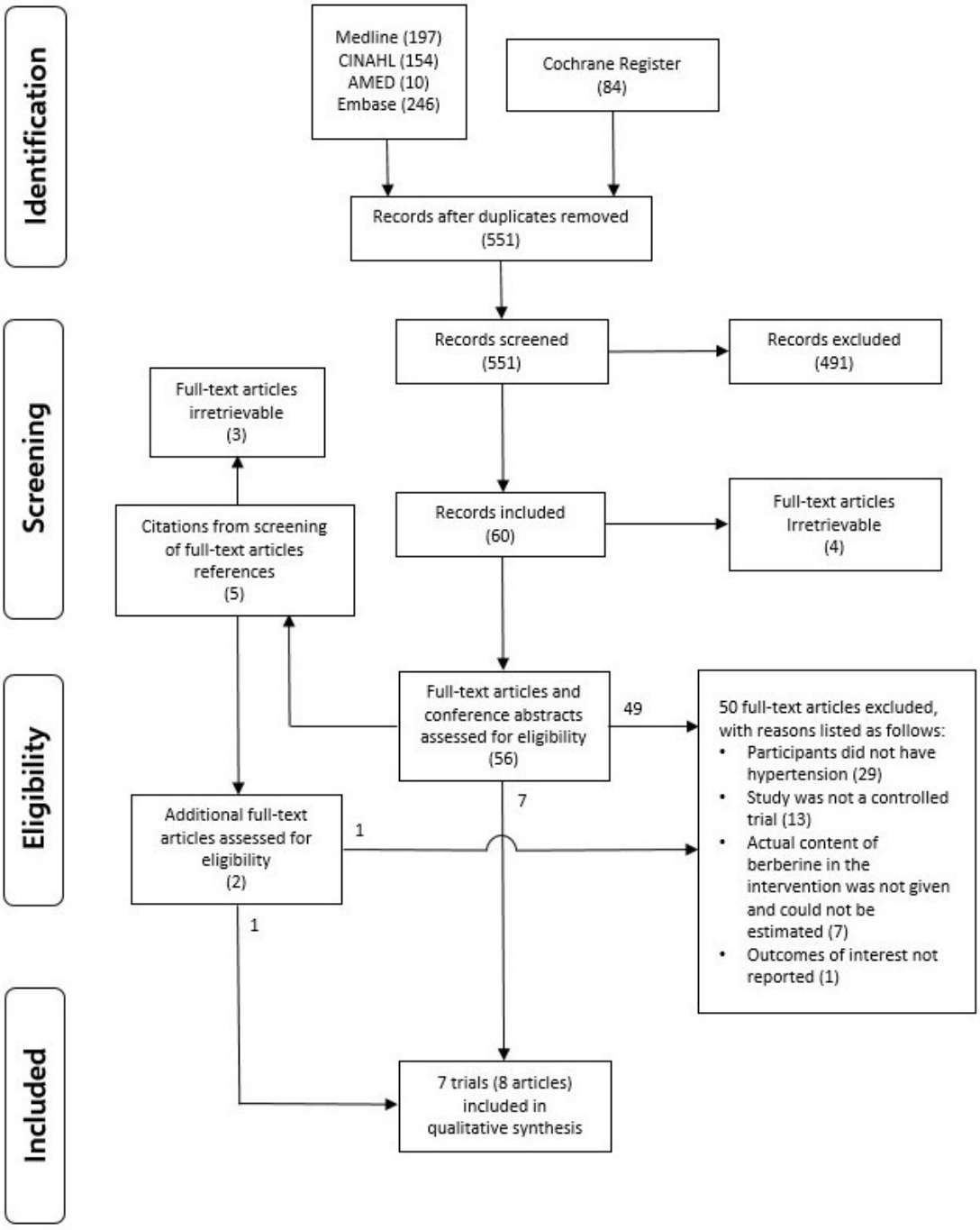
Database searches through the computerised strategy listed in Appendix 2 returned 691 citations. Citation screening is summarised in Figure 1 (PRISMA flow diagram). Removing duplicates left 551 citations to screen. Scanning titles and abstracts left 60 citations to assess for eligibility. Fifty-two were full papers, eight were conference abstracts. Four full-text articles were not retrievable. Scanning of article references retrieved five additional possibly relevant citations. Four were cited in Lan et al. (2015). All were in Chinese, not indexed in the searched databases, of which one full-text article was retrievable. One more citation was in Tabeshpour et al. [17]full-text article was retrievable. Overall, fifty-six articles were in English, two in Chinese. Forty-three papers and seven conference abstracts were excluded. Reasons for exclusion are in Figure 1.

4.1.2 Included studies

Table 1 summarises features of included studies. Appendix 1 - Characteristics of included studies has full details. Seven papers and one conference abstract met the inclusion criteria [33–40]. They corresponded to seven studies, as the conference abstract [39] referred to the same study of one paper [38], the former not providing additional information to the latter.

Six papers were in English, one in Chinese [33]. Three trials were conducted in Italy [34,37,38], two in Korea [36,40], one in China [33], and one in Pakistan [35]. Two trials were not randomised [34,35]. All trials employed a parallel two-arm design.

Figure 1. PRISMA flow diagram of study selection process: berberine for the treatment of hypertension.



Adapted from [41]

The primary aim of five trials was the reduction of blood pressure in individuals with hypertension. In one trial the primary aim was to reduce insulin resistance in individuals newly diagnosed with diabetes [35], and in another trial it was to reduce arterial stiffness in individuals with raised brachial pulse wave velocity (baPWV) [36].

4.1.3 Participants

A total of 614 individuals with hypertension were included in seven trials. Average sample size was 88 (27 [38] to 200 [35]). Among participants, 200 were recruited in Pakistan, 187 in Italy, 164 in China, and 63 in Korea. Mean participant age was 53 (33 [35] to 65 [40]). One study did not report the number of male and female participants [35]. Among 414 participants of six trials, there were 57% men (29% [36] to 85% [38]). Two trials included inpatients [33,40]; one trial included outpatients [36]; four trials did not specify trial setting [34,35,37,38]. All trials were single-centre.

4.1.4 Diagnosis

All participants had hypertension at baseline. All trials enrolled patients who also had one or more comorbidities, i.e., gout [33], hypercholesterolaemia [34], newly diagnosed type 2 diabetes [35], elevated baPWV [36], metabolic syndrome [37], low cardiovascular risk [38], and newly diagnosed stroke [40].

4.1.5 Interventions

There were wide variation in the experimental intervention formulations and doses, in comparator interventions, and in duration of interventions. Four different oral preparations were tested. Only two trials tested berberine without any other component [33,35]. One trial tested a proprietary nutraceutical, i.e., a combination of multiple functional foods, herbal extracts, and supplements [34]. Two trials tested a different version of the same proprietary nutraceutical containing one additional ingredient, orthosiphon staminensi, a purported hypotensor [37,38]. Two trials tested a lyophilised herbal extract of Chinese herbs, known as Chunghyul-dan (Qingxue-dan) [36,40]. These studies did not provide the berberine content of their preparation. However, this was made with a standardised procedure. Content was estimated from a trial which tested Chunghyul-dan made with the same standardised procedure, as this study provided Chunghyul-dan berberine percentage by weight [42].

Control interventions included amlodipine, meformin, a nutraceutical compound, diet, placebo, and observations only. The duration of treatment varied from two weeks to six months.

4.1.6 Outcomes

All included studies reported at least one of blood pressure primary outcomes. No study reported on cardiovascular events, nor on the secondary outcomes death from any cause and quality of life. No study carried out long-term follow-up. Outcomes reported by some studies but not included in this review were not extracted.

All but one study [35] reported some information on adverse events. One study mentioned that interventions were safe [33]; two that there were no adverse events [37,38]; one that two participants withdrew from the experimental group due to dyspepsia and doubling of creatinine kinase level[34]; one that adverse events were absent and there were no statistically significant changes in several measured metabolic parameters [36]; and one that in some participants some symptoms improved, i.e., insomnia, constipation, and pruritus [40].

4.2 Risk of bias in included studies

4.2.1 Overview of risk of bias in included studies

All studies provided limited details about their design and methodology. Figure 2 summarises answers to individual SIGN quality items. Figure 3 summarises the percentage for answers to each item across all studies. These plots were developed in LibreOffice Calc and adapted from the output formats of the Risk-of-bias VISualization (robvis) tool [43], which does not include the SIGN tool as one of its templates. As all studies were single-centre, SIGN tool item 10, relating to multi-centre studies, was excluded. Justifications for all answers are in Appendix 1 - Characteristics of included studies.

Five studies were RCTs, two were non-randomised controlled trial (NRCT) [34,35]. None reported sample size calculation. All studies pre-specified participant inclusion and exclusion criteria. All studies provided insufficient information to establish if they applied intention-to-treat analysis. Overall, all studies were of low quality. Table 1 ‘Quality assessment’ summarises judgment rationales.

4.2.2 Allocation

Only one study reported randomisation method, described as random number tables [33]. No study reported concealment method.

4.2.3 Blinding

One of the study mentioned blinding without other details [37]. The remaining studies either were described as open-label, or they were likely open-label, as blinding was not mentioned or their characteristics suggested non-blinding, e.g., no placebo.

4.2.4 Attrition

Two studies did not report loss to follow-up [33,36]. One study had serious drop-out rate of 30% [40]. In the remaining studies drop-out rate was acceptable.

4.2.5 Other sources of bias

Selective reporting

SIGN quality assessment tool does not include selective reporting, i.e., reporting bias, hence it was assessed separately. Table 1 ‘Outcome measures’ and ‘Effect estimates’ summarises the results reported.

No protocol registrations matching any of the studies were found in either ClinicalTrials.gov or World Health Organization International Standard Randomised Controlled Trial Number registry. Selective reporting judgments were made based on study stated outcomes in method section and reported outcomes in result section of papers.

Three studies carried out at least one statistical comparisons between experimental and comparator group [35,37,40]. These were also studies that, in this review statistical analyses, showed significant effect estimates. The remaining studies reported statistical analyses only within groups [33,34,36,38]. All of these studies but one [34] were also studies that did not show significant effect estimates. Detailed analysis is in Outcome reporting bias.

Source of funding

SIGN quality assessment tool does not include source of funding bias, hence it was also assessed separately. Details are in Table 1 “Source of funding”. One study had high risk of bias, as the experimental intervention manufacturer funded paper preparation [34]. Two papers stated that paper preparation did not require sources of funding [37,38]. The remaining papers left funding unreported.

4.3 Effects of interventions

There was no data on cardiovascular events, death from any cause, and quality of life. All papers reported on blood pressure. No study reported serious adverse events.

4.3.1 Statistical analyses in included studies

No study reported effect estimates and precision. Three studies reported P values for estimates between groups: one compared experimental group follow-up SBP and DBP to those of comparator group [35]; two compared experimental group SBP and DBP change from baseline to those of comparator group [37,40]. All other studies reported only within-group comparisons.

4.3.2 Statistical analyses in the review

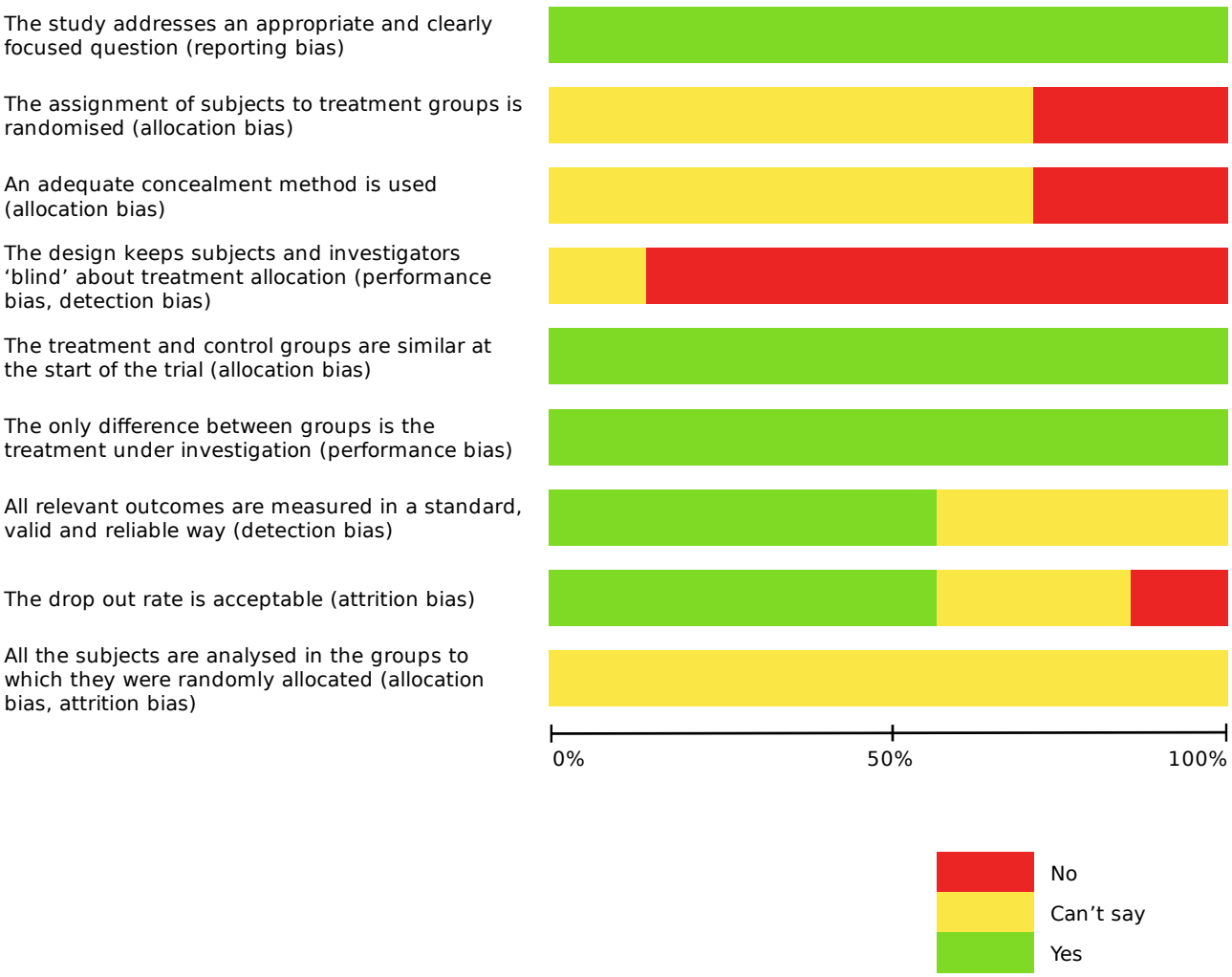
The Consolidated Standards of Reporting Trials (CONSORT) suggests that effect estimates should be calculated through between-groups values, with their precision given as 95% Cis [44]. Follow-up values were used for estimates, or, when reported, change from baseline if the former were unavailable. All studies reported outcomes as mean and standard deviation in mmHg, allowing to calculate effect estimates as mean difference.

Effect estimates could not be calculated for one of two trials that did not report comparator group follow-up values, nor change from baseline values [36]. For the other trial, follow-up measures in comparator group were accurately estimated from a chart in the paper [34].

Figure 2. "Traffic light" plot of SIGN checklist item-level judgments for each study.

Adapted from the output format of the Risk-of-bias VISualization (robvis) tool [43].

Figure 3. Bar plot of the distribution of judgments within each SIGN checklist item.



Adapted from the output format of the Risk-of-bias VISualization (robvis) tool [44].

Table 1. Summary of features of included studies answering the review question: does treatment with berberine reduce blood pressure and cardiovascular events in adults with primary hypertension?

Study ID	Study type	Setting	Number of participants	Participants characteristics	Experimental intervention	Comparator intervention	Length of follow-up	Outcome measures	Effect estimates	Adverse events	Source of funding	Quality assessment (SIGN rating)	Additional comments
Huang 2013 [33] In Chinese. Translated into English with Google Translate	RCT	Lishui City Central Hospital, Zhejiang Province, China	Allocated E=84, C=80 Loss to f/u not described *Inclusion criteria:* mild to moderate hypertension and gout *Exclusion criteria:* endocrine or renal diseases, severe hypertension, history of cardiovascular and cerebrovascular accidents within 6 months, severe heart, liver, and kidney dysfunction, drug allergies	Hospital inpatients 98 males and 66 females Age 42-74 years 61.1 ± 2.8 years	Berberine HCl 300mg oral three times a day in addition to comparator intervention	Amlodipine tablets (Zhejiang Hongyuan Pharmaceutical Chemical Co., Ltd.) 5 mg oral twice a day, plus colchicine 1 mg oral three times a day for patients with acute gout, or allopurinol 50 mg oral twice a day for patients with chronic gout	8 weeks	SBP, DBP	Within both E and C group, follow-up SDB and DBP were significantly lower than baseline values (E: 127.6 ± 12.5mmHg vs 155.8 ± 18.2mmHg p<0.05, 81.5 ± 10.7mmHg vs 99.1 ± 5.4mmHg p<0.05; C: 132.1 ± 18.31mmHg vs 157.3 ± 22.8mmHg p<0.05, 83.5 ± 5.2mmHg vs 99.5 ± 6.1mmHg p<0.05). Calculated mean differences for f/u values (E-C): SBP: -4.50 [-9.32, 0.32] DBP: -2.00[-4.56, 0.56]	Adverse events: not discussed. Paper mentions that intervention was safe	Not stated	Low quality High risk of reporting bias. *Strengths*: moderate group size, randomisation described as random number tables. *Weaknesses*: no placebo, likely open-label, short duration	Between groups comparisons not given Paper reports that at f/u E and C outcomes were not significantly different The study primary aim was to investigate the effect on hypertension of amlodipine combined with berberine
Mazza 2015 [34]	NRCT	Hypertension setting in Italy	Allocated E=66, C=66 At f/u E=64, C=66 C group age and gender matched *Inclusion criteria:* patients with hypertension and hypercholesterolaemia *Exclusion criteria*: severe hypertension, secondary hypertension, diabetes mellitus, neoplastic or hepatic disease, chronic heart or renal failure, positive history or clinical signs of ischemic heart disease, severe obesity, disabling diseases such as dementia or inability to cooperate, pregnancy or breastfeeding, antihypertensive and/or lipid-lowering drug treatment, and organ damage (left ventricular hypertrophy diagnosed by electrocardiogram, carotid plaque or albuminuria) due to hypertension.	Males 54.5% Age 56.0 ± 6.4 years	Armolipid Plus (Rottapharm SpA, a MEDA Company) one tablet oral once daily in the evening before bedtime in addition to comparator intervention Note: ArmoLipid Plus is a food supplement combining natural ingredients containing red yeast rice 200mg (equivalent of 3mg of monacolin K), policosanol 10mg, berberine 500mg, folic acid 0.2mg, astaxanthin 0.5mg, and coenzyme Q10 2mg	Written prescription for a standardised Mediterranean diet regimen, including a high intake of fish, fruits, vegetables, legumes, olive oil, unrefined whole grains and a moderate intake of lean meats and alcohol	2 weeks run-in period, then intervention for 6 months	SBP, DBP. systolic and diastolic day 24h, night 24h, 24h ABPM	For E group, of all blood pressure measures, only the change from baseline of systolic 24h ABPM measurements was statistically significant: (141.6 ± 6.4mmHg at baseline vs. 136.2 ± 4.8mmHg at follow-up; p<0.05). For C group, all the difference measures pre- and post-intervention were not statistically significant. Post-intervention values for C group are not given in the paper It was possible to calculate mean differences between groups after having graphically estimated C group follow-up values. Calculated mean differences for f/u values (E-C): Mean systolic 24h-ABPM: 3.40 [-5.48, -1.32] Mean diastolic 24h-ABPM: 0.90 [-0.28, 2.08]	Adverse events: two participants in E withdrawn from the study due to side effects (one due to a doubling in CK levels and one due to dyspepsia).	Article processing charges for this study were funded by Rottapharm SpA, a MEDA Company, Monza, Italy, manufacturer of the tested nutraceutical compound. High risk of funding bias.	Low quality High risk of allocation, performance, detection, and reporting bias *Strengths*: Low drop out rate *Weaknesses*: no randomisation; no placebo; small to moderate group size	C group outcome values and between-groups comparisons not given in the paper Primary aim of the study was to investigate the effect of nutraceuticals on serum lipid and blood pressure control in subjects with elevated blood pressure and cholesterol levels

Study ID	Study type	Setting	Number of participants	Participants characteristics	Experimental intervention	Comparator intervention	Length of follow-up	Outcome measures	Effect estimates	Adverse events	Source of funding	Quality assessment (SIGN rating)	Additional comments
Memon 2018 [35]	NRCT	Tertiary care hospital, Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro/ Hyderabad, Pakistan, from March 2016 to January 2017	E=100, C=100 C group age and gender matched No loss to f/u. *Inclusion criteria*: subjects with newly diagnosed type 2 DM cases of age ≥25 years taking drug metformin. *Exclusion criteria*: subjects with type 2 DM taking sulfonylurea, herbal drugs, HMG-CoA reductase inhibitors, and multivitamin pills and insulin, subjects with type 2 DM with diabetic complications, and subjects with type 2 DM with concomitant chronic viral hepatic disorders, coronary ischemic heart disease, chronic kidney disease, and pregnancy.	Age E: 33.4 ± 2.96 years, C: 33.26 ± 2.6 years, p=0.81 No significant differences for most measured parameters LDL-C and HDL-C levels where significantly different	Berberine 500mg oral three times a day	Metformin (Glucophage, Merck Pharmaceuticals) 500mg oral three times a day	3 months	SBP and DBP were not stated main outcomes in the study. However, measures are reported for pre- and post-intervention for both groups.	The paper reports between-groups comparison. At follow-up, both SBP and DBP in E group were significantly lower than those in C group (but see note below): 131.4 ± 15.2mmHg vs 143.3 ±19.0mmHg p=0.001, 70.61 ± 13.65mmHg vs 72.57 ± 11.2mmHg p=0.03 Calculated mean differences for f/u values (E-C): SBP: -11.87 [-16.64, -7.10] DBP: -1.96 [-5.42, 1.50] Note: DBP difference between group at f/u is NS. Calculated significant level p=0.27, not p=0.03 as paper reports	Adverse events not discussed in the paper	Not stated	Low quality High risk of allocation, performance, and detection bias *Strengths*: moderate group size, no loss to f/u *Weaknesses*: no randomisation, likely open-label	Primary aim of the study was to determining the effects of berberine on serum methylglyoxal and insulin resistance in newly diagnosed type 2 diabetic patients
Park 2006 [36]	RCT	Outpatients visiting the Cardiovascular Center of Kyung Hee University Kangnam Korean Hospital between November 2003 and October 2004	Allocated E=20, C=15 Loss to follow-up not described *Inclusion criteria*: baPWV higher than 1400cm/s *Exclusion criteria*: use of hormone replacement therapy in the 2 months prior to the study, use of anti-hyperlipidemic agents or steroids within 6 months, and the presence of hepatic or renal diseases	Gender (male vs female) E: 6 vs 14, C: 4 vs 11, p=0.863 Age E: 61.4 ± 9.6 years, C: 63.4 ± 10.5 years p=0.644 No statistically significant differences between groups at baseline in terms of SBP, DBP, and baPWV	Chunghyul-dan (Qingxue-Dan) 600mg oral three times a day. For this review, the content of berberine is calculated as 4% of total preparation using estimate in [43]. Hence, total estimated berberine daily dose was 24mg three times a day	Observations only	8 weeks	SBP and DBP were not primary outcomes of the study, baPWV was the main outcome	For E group SBP and DBP are given at baseline (152.9 ± 22.0 mmHg and 91.3 ± 8.0 mmHg) and follow-up (137.6 ± 13.3 mmHg and 87.2 ± 8.2 mmHg), and the differences were not statistically significant. For C group only baseline SBP and DBP values are given in the paper. Between-groups comparisons of SBP and DBP were not given in the paper, and effect estimates and their precision were also not reported. It was not possible to calculate effect estimates and their precision as mean differences between groups could not be calculated.	There were no clinical adverse effects observed during the 8 weeks of treatment. There were no statistically significant changes in E group baseline and f/u values for the following monitored parameters: AST, ALT, BUN, and CR	Not stated	Low quality High risk of performance, detection, and reporting bias; unclear risk of allocation and attrition bias *Strengths*: none *Weaknesses*: no placebo, small group size, short duration	Primary aim of the study was the effect of Chunghyul-dan (Qingxue-Dan) on arterial stiffness in patients with raised baPWV

Study ID	Study type	Setting	Number of participants	Participants characteristics	Experimental intervention	Comparator intervention	Length of follow-up	Outcome measures	Effect estimates	Adverse events	Source of funding	Quality assessment (SIGN rating)	Additional comments
Rozza 2009 [37]	RCT	Italy	Allocated E=15, C=15 No loss to follow-up *Inclusion criteria*: subjects of both sexes aged 18–75 years and diagnosed with metabolic syndrome *Exclusion criteria*: subjects who were pregnant or breastfeeding women and patients treated with antihypertensive and/or lipid-lowering drugs	Gender (M/F %) E: 67/33, C: 73.3/26.7 Age E: 47.5 ± 10.1 years, C: 45.5 ± 10.8 years, NS At baseline there were no statistically significant differences between all measured parameters, including SBP, and DBP	Armolipid Prev: Armolipid Plus with the addition of orthosiphon staminensi (dose not given) Armoloipid Plus constituents given in the included study above [39] Study does not specify how many tablets of the preparation or how often it was administered	Placebo	2 weeks run-in period, then intervention for 6 months	SDB and DBP were part of the primary outcome measures	The paper reports between-groups comparison of change from 2-week run-in to 6-week follow-up, showing that E group had, compared to C group, a significantly higher SBP reduction (-19.6 ± 9.7mmHg vs -3.6 ± 8.1mmHg; p< 0.0001) and DBP reduction (-13.6 ± 5.5mmHg vs -2.3 ± 5.3mmHg; p< 0.0001). Effect estimates and their precision were not reported. Calculated mean differences for changes from 2-week run-in (E-C): SBP: -16.00 [-22.4, -9.60] DBP: -11.30 [-15.17, -7.43] Calculated mean differences for f/u values (E-C): SBP: -11.80 [-18.73, -4.87] DBP: -11.10 [-14.74, -7.46]	The paper reports no adverse outcomes, but does not give details	No sources of funding were used to assist in the preparation of the paper	Low quality Unclear risk of allocation, performance, detection, and attrition bias *Strengths*: placebo controlled *Weaknesses*: small group size	Primary aim of the study was to investigate reduction of blood pressure in patients with metabolic syndrome treated with nutraceuticals
Trimarco 2012 [38]	RCT	Italy	Allocated E=20, C=10 At f/u E=18 and C=9 *Inclusion criteria*: both genders, aged between 18 and 75 years, with grade 1 essential hypertension and low cardiovascular risk *Exclusion criteria*: pregnant or breastfeeding women and patients treated with antihypertensive and/or lipid lowering drugs	Gender (male/female) E:15/3, C: 8/1 , NS Age E:45.61 ± 12.8 years, C: 47.56 ± 6.0 years, NS At baseline there were no statistically significant differences between all measured parameters, including age, gender, SBP, DBP, and 24h-ABPM	Armolipid Prev Armolipid Prev constituents given in the included study above [37]. Study does not specify how many tablets of the preparation or how often it was administered Dietary advice and placebo for a 2-week run-in period	Armolipid Plus Armoloipid Plus constituents given in the included study above [34] Study does not specify how many tablets of the preparation or how often it was administered Dietary advice and placebo for a 2-week run-in period	4 weeks	24h-ABPM, daytime ABPM, and night-time ABPM were the primary outcome measures	In E group, at 4-week follow-up all measures had significant reduction from baseline, for both systolic and diastolic 24h-ABPM: 130.98 ± 7.2 vs 135.87 ± 8.2mmHg; p = 0.0001; 83.74 ± 3.8 vs 87.34 ± 4.4mmHg, p= 0.0001; daytime: 137.22 ± 8.2 vs 141.82 ± 8.1mmHg, p = 0.002, 89.27 ± 4.5 vs 92.83 ± 4.4mmHg, p= 0.001; night-time: 115.30 ± 8.5 vs 121.46 ± 10.8 mmHg, p = 0.008, 70.31 ± 5.6 vs 74.01 ± 7.5mmHg, p=0.037 In C group, measures at baseline and at 4-week follow-up were not significantly different. Between-groups estimates and effect estimates and their precision were not given. Calculated mean differences for f/u values (E-C): Systolic 24h-ABPM: -0.47 [-7.06, 6.12] Diastolic 24h-ABPM: -3.35 [-9.99, 3.29] Systolic daytime ABPM: -0.99 [-7.60, 5.62] Diastolic daytime ABPM: -3.59 [-9.70, 2.52] Systolic night-time ABPM: -0.70 [-8.83, 7.43] Diastolic night-time ABPM: -2.78 [-11.16, 5.60]	Paper reports that there was a lack of adverse reactions No other details are given	No sources of funding were used to assist in the preparation of the paper	Low quality High risk of performance, reporting, and detection bias Unclear risk of allocation and attrition bias *Strengths*: none *Weaknesses*: small group size, short duration	Primary aim of the study was to investigate the reduction of blood pressure in patients with hypertension treated with a nutraceutical

Study ID	Study type	Setting	Number of participants	Participants characteristics	Experimental intervention	Comparator intervention	Length of follow-up	Outcome measures	Effect estimates	Adverse events	Source of funding	Quality assessment (SIGN rating)	Additional comments
Yun 2005 [40]	RCT	Department of Cardiovascular and Neurologic Diseases (Stroke Center), Hospital of Oriental Medicine, Kyung Hee Medical Center, Seoul, Korea, from 1 June 2003 to 31 March 2004	Recruited E=20, C=20 At follow-up E=15; C=13 *Inclusion criteria*: subjects hospitalised 10 days after stroke with stage 1 hypertension *Exclusion criteria*: subjects who were taking hypotensors, who had hepatic or renal diseases, or experienced cardiovascular disease within three months	Gender (males, %) E: 8 (53.3), C: 4 (30.8), NS Age E: 64.8 ± 9.59, years C: 65.62 ± 9.77 years, NS At baseline there were no statistically significant differences between all measured parameters, including systolic and diastolic 24h-ABPM	Chunghyul-dan (Qingxue-Dan) 1200mg oral once a day. For this review, the content of berberine is calculated as 4% of total preparation using estimate in [42]. Hence, total estimated berberine daily dose was 48mg once a day	No intervention	2 weeks	Systolic and diastolic 24h-ABPM were part of the primary outcomes	Baseline, f/u, and change from baseline values are given in the paper for both groups The only statistically significant effect was in E group for change from baseline of systolic 24h-ABPM: 141.37 ± 8.96mmHg vs 132.28 ± 9.46mmHg p=0.03, corresponding to mean change from baseline 9.09 ± 8.73mmHg. Estimate is given for SBP changes from baseline between E and C group: 9.09 ± 8.73mmHg vs 1.75 ± 6.90mmHg, p=0.036. Effect estimates and their precision were not given. Calculated mean differences for f/u values (E-C): Systolic 24h-ABPM: -4.99 [-11.81, 1.83] Diastolic 24h-ABPM: 2.06 [-3.27, 7.39] Calculated mean differences for changes from baseline (E-C) Systolic 24h-ABPM: -7.34 [-13.14, -1.54] Diastolic 24h-ABPM: -0.70 [-5.28, 3.88]	Paper reports that no adverse effect was found, and five subjects showed improvement of symptoms (two insomnia, one constipation, and one pruritus)	Not stated	Low quality High risk of attrition, performance, and detection bias Unclear risk of allocation bias *Strengths*: none *Weaknesses*: no placebo, 30% loss to follow up, very short duration	Primary aim of the study was to investigate the effect of Chunghyul-dan (Qingxue-dan) on blood pressure in hospitalised patients just diagnosed with stroke and hypertension

Notes: Mean (M) and standard deviation (SD) are indicated as M ± SD; mean difference (MD) and 95% confidence interval (CI-, CI+) are indicated as MD [CI-, CI+] E: Experimental group; C: Comparator group; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABPM: ambulatory blood pressure monitoring; AST: aspatate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, CR: creatinine; CK: creatinine kinase; DM: Diabetes mellitus; baPWV: brachial artery pulse wave pressure; NS: not statistically significant; f/u: follow-up;

Adapted from ‘Example of an evidence table for intervention studies’ [23].

4.3.3 Meta-analysis

Intervention heterogeneity made a meta-analysis inappropriate for most study groups. Only the two studies on Chunghyul-dan were broadly similar [36,40], and a meta-analysis would have been appropriate. However, one study [36] did not report comparator group follow-up or change from baseline values, also preventing meta-analysis. Therefore, results are presented per intervention and for individual studies.

4.3.4 Berberine as individual ingredient

Amlodipine plus berberine versus amlodipine

One RCT compared amlodipine plus berberine (900mg daily) to amlodipine in individuals with hypertension and gout [33]. Within both groups, follow-up SDB and DBP were significantly lower than the respective baseline values. The study did not report between-groups comparison for either follow-up or change from baseline of SBP and DBP values. Effect estimates were -4.50 [-9.32, 0.32] mmHg for SBP (Figure 4) and -2.00 [-4.56, 0.56] mmHg for DBP (Figure 5), both not statistically significant.

Figure 4. Forest plot comparison: amlodipine plus berberine versus amlodipine; outcome: SBP at follow-up

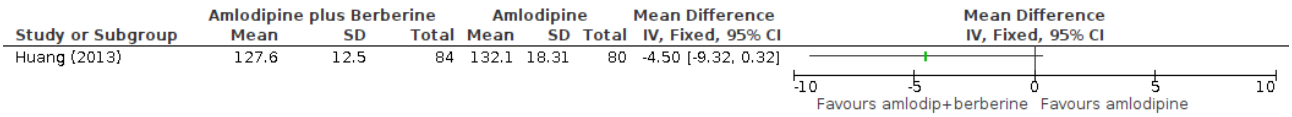
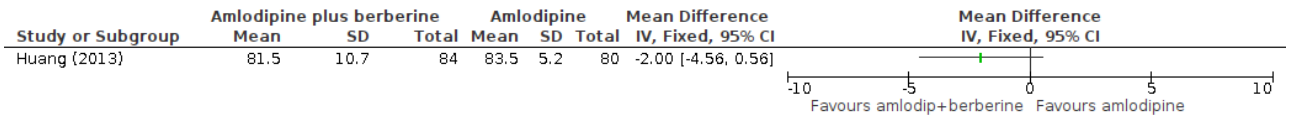


Figure 5. Forest plot comparison: amlodipine plus berberine versus amlodipine; outcome: DBP at follow-up



Berberine versus metformin

One NRCT investigated berberine (1500mg daily) effect on insulin resistance and serum methylglyoxal compared to metformin in newly diagnosed patients with type 2 diabetes [35]. SBP

and DBP were not outcomes of the study. Nonetheless, they were measured at baseline and follow-up. The study reported that follow-up SBP and DBP in experimental group were significantly lower than comparator group values. Effect estimates were -11.87 [-16.64, -7.10] mmHg for SBP (Figure 6), statistically significant, and -1.96 [-5.42, 1.50] mmHg for DBP (Figure 7), not significant. The paper, by miscalculating the P value, mistakenly reported follow-up DBP difference between groups as significant.

Figure 6. Forest plot comparison: berberine versus metformin; outcome: SBP at follow-up

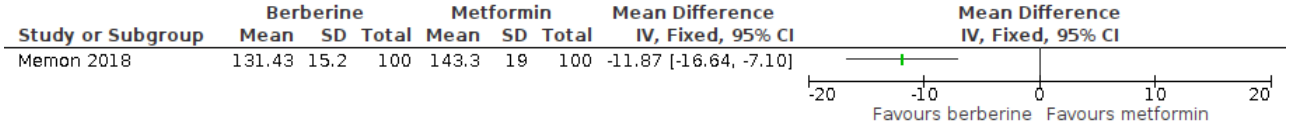
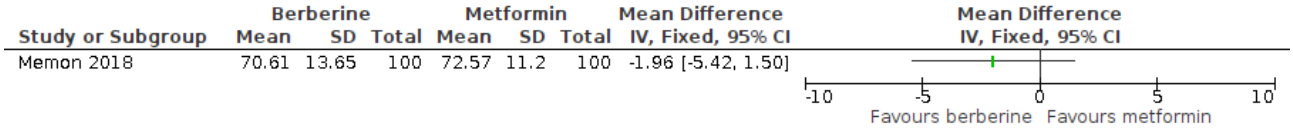


Figure 7. Forest plot comparison: berberine versus metformin; outcome: DBP at follow-up



4.3.5 Proprietary preparations containing berberine

One NRCT compared the nutraceutical Armolipid Plus in addition to dietary advice to dietary advice only [34]. Two RCTs compared the proprietary nutraceutical Armolipid Prev, one to placebo [37], and one to Armolipid Plus [38]. Both nutraceuticals are made by the Italian pharmaceutical company Rottapharm SpA (a MEDA Company). Armolipid Plus combines natural ingredients, i.e., 500mg berberine, red yeast rice (3mg of monacolin K), 10mg policosanol, 0.2 folic acid, 0.5 astaxanthin, and 2mg coenzyme Q10. Armolipid Prev has orthosiphon staminensi added to Armolipid Plus ingredients. The two studies investigating Armolipid Prev did not specify the dose of orthosiphon staminensi. Of the three studies, only one provided actual doses of ingredients [34].

Armolipid Plus plus dietary prescription versus dietary prescription only

In the NRCT investigating Armolipid Plus [34], the experimental intervention included the nutraceutical plus a written prescription for a Mediterranean diet. The comparator intervention included only the dietary prescription.

The study reported that, of all eight outcome measures, i.e., clinic SBP and DBP, and mean systolic and diastolic 24h-, daytime, and night-time ABPM, the only statistically significant change within the experimental group was for systolic 24h-ABPM. There were no statistically significant changes within the comparator group.

The study did not report comparator follow-up values, nor reported between-groups comparisons. However, it reported a chart of comparator group baseline and follow-up mean systolic and diastolic 24h-ABPM. An accurate estimates of actual values was obtained graphically through LibreOffice Draw computer program. The effect estimates were then calculated as -3.40 [-5.48,-1.32] mmHg for systolic 24h-ABPM (Figure 8), statistically significant, and 0.90 [-0.28, 2.08] mmHg for diastolic 24-ABPM (Figure 9), not significant.

Figure 8. Forest plot comparison: Armolipid Plus plus diet versus diet; outcome: systolic 24h-ABPM at follow-up

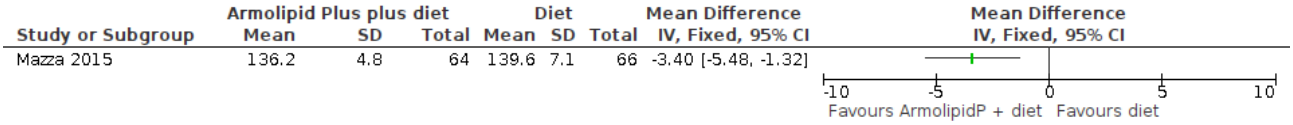
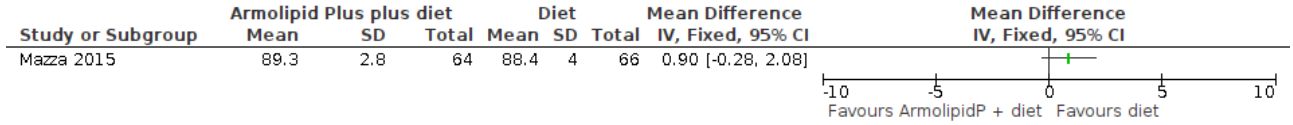


Figure 9. Forest plot comparison: Armolipid Plus plus diet versus diet; outcome: diastolic 24h-ABPM at follow-up



Armolipid Prev versus placebo

The study comparing Armolipid Prev to placebo [37] reported between-groups comparison of change from end of 2-week run-in to end of 6-week follow-up period, showing that experimental group SBP and DBP reduction was significantly higher compared to comparator group.

Effect estimates were calculated for SDB and DBP for both follow-up and change from 2-week run-in. For follow-up, effect estimates were -11.80 [-18.73, -4.87] mmHg for SBP (Figure 10), and -11.10 [-15.17, -7.43] mmHg for DBP (Figure 11), both statistically significant. For change from 2-week run-in, effect estimates were -16.00 [-22.40, -9.60] mmHg for SBP (Figure12), and -11.30 [-14.74, -7.46] mmHg for DBP (Figure 13), both statistically significant.

Figure 10. Forest plot comparison: Armolipid Prev versus placebo; outcome: SBP at follow-up

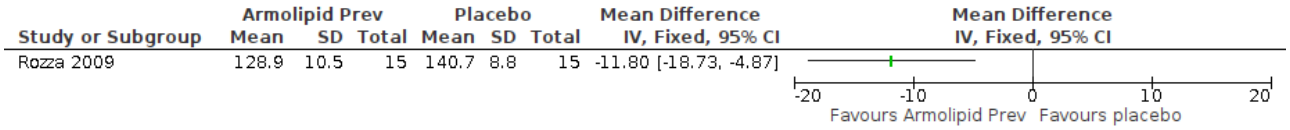


Figure 11. Forest plot comparison: Armolipid Prev versus placebo; outcome: DBP at follow-up

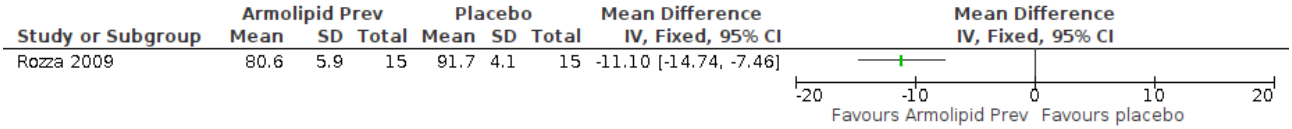


Figure 12. Forest plot comparison: Armolipid Prev versus placebo; outcome: SBP change from 2-week run-in to follow-up

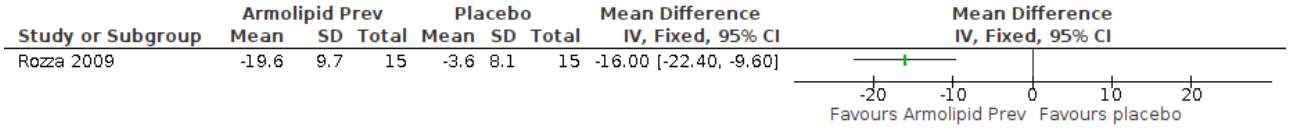
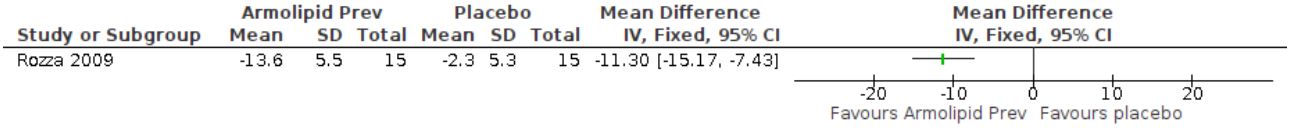


Figure 13. Forest plot comparison: Armolipid Prev versus placebo; outcome: DBP change from 2-week run-in to follow-up



Armolipid Prev versus Armolipid Plus

The study comparing Armolipid Prev (experimental intervention) to Armolipid Plus (comparator intervention) did not report between-groups comparisons [38]. The study provided a significant P value for the comparison within experimental group between baseline and follow-up of both systolic and diastolic 24h-, daytime, and night-time ABPM. Comparison in comparator group were reported as not significant, with actual P values unreported. Effect estimates are given in Figure 14 to Figure 19, all below 4 mmHg in magnitude and not statistically significant.

The difference between the interventions was the presence in the experimental group of orthosiphon staminensi, which purported action as hypotensor was the object of the study investigation. Hence,

this study alone does not provide insights on berberine effect, as both interventions contained equal doses of berberine. However, this study provides insights when combined to results of the study comparing Armolipid Prev to placebo [37]. Details are in the Discussion under Proprietary preparations containing berberine.

Figure 14. Forest plot comparison: Armolipid Prev versus Armolipid Plus; outcome: 24h ambulatory SBP at follow-up

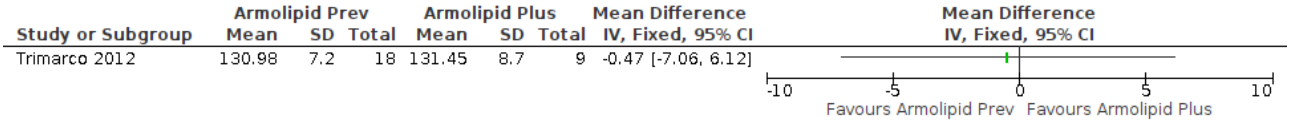


Figure 15. Forest plot comparison: Armolipid Prev versus Armolipid Plus; outcome: 24h ambulatory DBP at follow-up

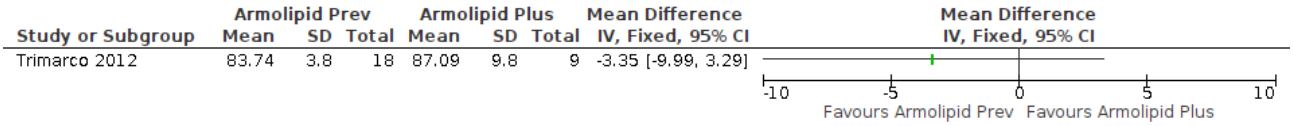


Figure 16. Forest plot comparison: Armolipid Prev versus Armolipid Plus; outcome: daytime ambulatory SBP at follow-up

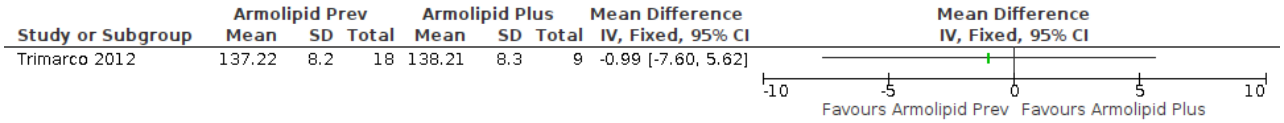


Figure 17. Forest plot comparison: Armolipid Prev versus Armolipid Plus; outcome: daytime ambulatory DBP at follow-up

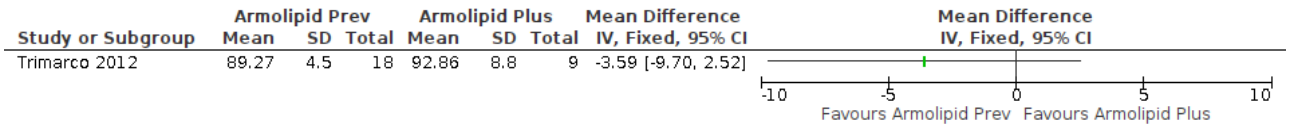


Figure 18. Forest plot comparison: Armolipid Prev versus Armolipid Plus; outcome: night-time ambulatory SBP at follow-up

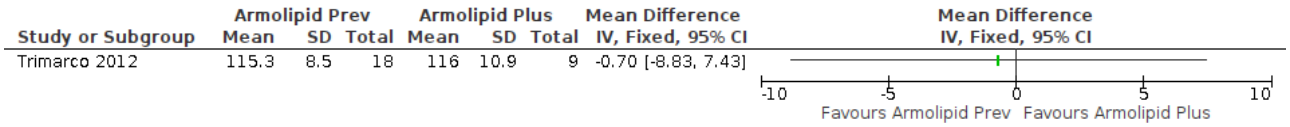
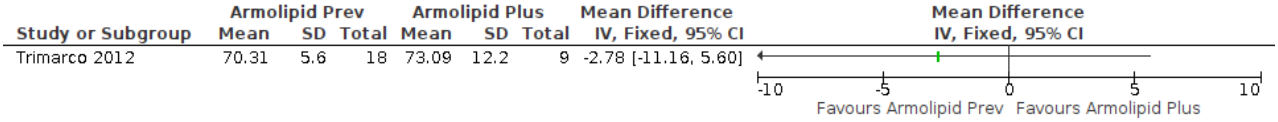


Figure 19. Forest plot comparison: Armolipid Prev versus Armolipid Plus; outcome: night-time ambulatory DBP at follow-up



4.3.6 Chunghyul-dan

Chunghyul-dan versus no intervention

Two RCTs compared the herbal extract Chunghyul-dan to no intervention, one providing 72mg of berberine daily [36], the other 48mg [40]. In the first trial, experimental group SBP and DBP values were given at both baseline and follow-up [36]. These were reported as not significantly different. Effect estimates could not be calculated as comparator group follow-up SBP and DBP values were not given.

The second trial primary outcomes were systolic and diastolic 24h-ABPM [40]. Experimental group follow-up systolic value was reported as significantly lower than baseline. There was no significant difference between comparator group corresponding values. Diastolic values were not significantly different between baseline and follow-up within both groups. The study also reported that experimental group changes from baseline of systolic 24h-ABPM was significantly higher than in comparator group, but not of diastolic 24h-ABPM. Between-groups comparisons for follow-up values were not given. Effect estimates were calculated for both follow-up values and change from baseline for all outcomes. For follow-up, effects estimates were -4.99 [-11.81, 1.83] mmHg for both systolic 24h-ABPM, and 2.06 [-3.27, 7.39] mmHg for diastolic 24h-ABPM (Figure 20 and Figure 21), both not statistically significant. For change from baseline, effect estimates were -7.34 [-13.14, -1.54] mmHg (Figure 22) for systolic 24h-ABPM, statistically significant, and -0.70 [-5.28, 3.88] mmHg for diastolic 24h-ABPM (Figure 23), not significant.

Figure 20. Forest plot comparison: Chunghyul-dan versus no intervention; outcome: 24h ambulatory SBP at follow-up

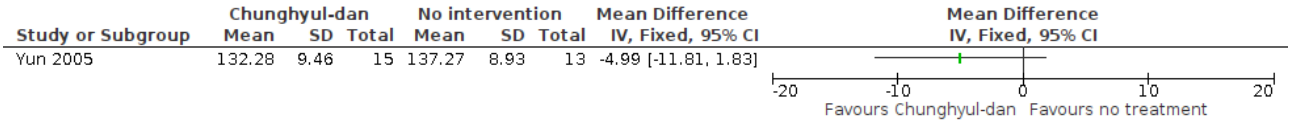


Figure 21. Forest plot comparison: Chunghyul-dan versus no intervention; outcome: 24h ambulatory DBP at follow-up

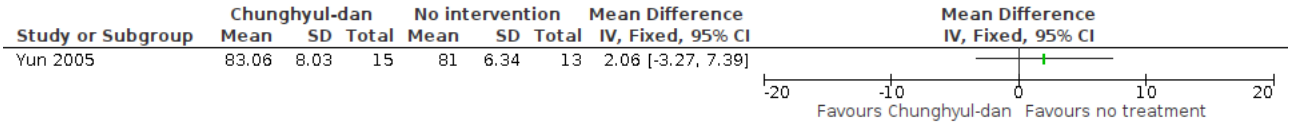


Figure 22. Forest plot comparison: Chunghyul-dan versus no intervention; outcome: 24h ambulatory SBP change from baseline to follow-up

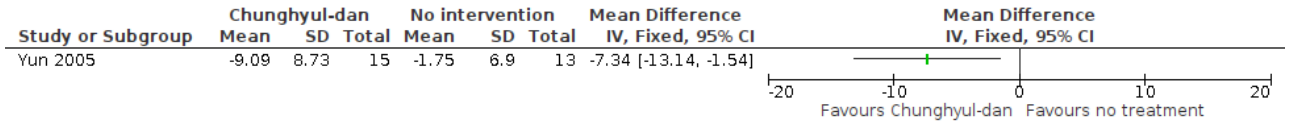
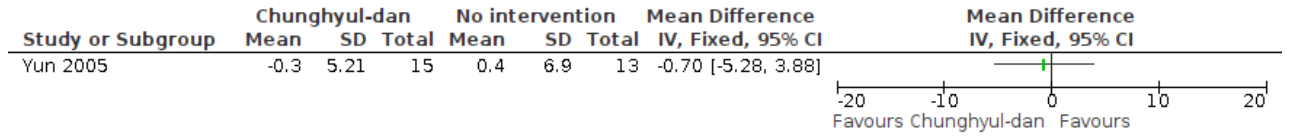


Figure 23. Forest plot comparison: Chunghyul-dan versus no intervention; outcome: 24h ambulatory DBP change from baseline to follow-up



5. Discussion

5.1 Summary of main results

Even if literature reviews have suggested that berberine could be beneficial in hypertension, the evidence base presented here highlights a lack of high quality, long-term, high-powered controlled trials investigating berberine as hypertension treatment. Seven trials with 614 participants are included in this review. The mean duration of treatment was 2.6 months. Effect estimates were mixed, with most trials showing non-significant effects. Results from some trials were inconsistent.

Trials demonstrated unclear or high risk of bias, due to missing details around randomisation and blinding, and to outcome reporting bias. Individual interventions are discussed below.

5.1.1 Berberine as individual ingredient

Compared with metformin, there was a significant moderate to large effect estimate in favour of berberine (1500mg daily) on SBP (-11.87 mmHg). The study that compared the two regimens aimed at establishing berberine effect on insulin resistance in patients with type 2 diabetes [35]. Metformin own blood pressure effect cannot be excluded, and could lead to overestimate or underestimate berberine effect. However, an extended meta-analysis of 21 RCTs with 1667 patients with type 2 diabetes and hypertension showed that metformin did not significantly affect SBP or DBP [45]. Hence, the estimated effect is likely due to berberine alone. The trial comparing berberine (900mg daily) plus amlodipine to amlodipine only [33] did not show significant effect estimates.

The two studies had comparable group sizes, hence similar power of detecting effects. Lack of effect in the second study could have been due to the two experimental components interacting towards reducing effects. Or perhaps a dose effect was present; either 900mg of berberine daily had reduced effect compared to 1500ng daily, or 900mg was below berberine pharmacological action threshold, and 1500mg was above it. Another possibility is that, as the second study participants received also treatment for gout, the combination might have reduced effects.

5.1.2 Proprietary preparations containing berberine

The proprietary nutraceutical compound Armolipid Plus (berberine 500mg daily) in combination with diet was superior to diet alone [34]. The only statistically significant effect was on systolic 24h-ABPM, albeit small (-3.40 mmHg). Armolipid Plus contains additional ingredients, making it difficult to isolate berberine effect. The added ingredients are considered important in plasma lipids and glucose control, and not considered hypotensors [46]. However, Askarpour et al. [47] investigated policosanol effect on blood pressure. Their meta-analysis included 19 RCTs with 2426 participants with mainly hypercholesterolaemia, with hypertension present in two trials. They showed that an average of 12mg of policosanol daily, compared to placebo, significantly reduced SBP (-3.42 mmHg). As Armolipid Plus contains a comparable policosanol dose (10mg), the effect on systolic 24h-ABPM could be due to policosanol rather than berberine. Caution should be taken here as 24h-ABPM cannot immediately be compared against clinic SBP.

Compared to placebo, Armolipid Prev (berberine 500mg daily) showed a significant moderate effect on SDB (-11.80 mmHg) and DBP (-11.10 mmHg). The effects on blood pressure were attributed to orthosiphon staminensi, the component added to Armolipid Plus to make Armolipid Prev [37]. However, in the study that compared Armolipid Prev against Armolipid Plus [38], effects on systolic and diastolic 24h-ABPM were not significant. Even if 24h-ABPM cannot immediately be compared against clinic SBP and DBP, the insights from these studies suggest an inconsistent effect from orthosiphon staminensi, leaving berberine and the other constituents as potential hypotensors.

5.1.3 Chunghyul-dan

Compared to no intervention, the effect of a 2-week intervention with the herbal extract Chunghyul-dan (berberine 48mg daily) estimated from the results of one study [40] was a significant moderate effect on systolic 24h-ABPM change from baseline (-7.34 mmHg). The effect estimates and precision from the other study providing 74mg of berberine daily from Chunghyul-dan and making a similar comparison over an 8-week intervention could not be calculated due to the lack of comparator group follow-up measures [36]. However, the study reported non significant changes within the experimental group.

These results seem inconsistent, as the second study showed no significant effect from a treatment dose 50% higher and a length of treatment four times longer than the trial showing a moderate effect. Also, the studies had comparable group sizes, hence both potentially able to discern similar effect. However, participants were selected from different populations. The study with favourable outcomes, with lower treatment dose and shorter intervention, recruited inpatients with hypertension admitted for stroke. The other study recruited outpatients with elevated baPWV and hypertension. Perhaps the effect was higher in the former because inpatients showed higher treatment adherence, possibly due to higher supervision and a more serious diagnosis (stroke) with actual symptoms, which might have increased participants' motivation to follow protocol. Moreover, the study with beneficial results had a 30% drop-out rate, potentially introducing attrition bias. Also, its results are inconsistent with other included trials which for much higher berberine doses showed no significant effect. Hence, perhaps another constituent of Chunghyul-dan provided the hypotensive action.

5.2 Overall completeness and applicability of the evidence

5.2.1 Participants

Participants' age and gender of the included trials were representative of patients with hypertension. Participants were selected in broadly similar proportions from Pakistan, Italy, and China, and to a lesser extent from Korea. This makes the evidence generally applicable to different populations and ethnicity.

All participants had hypertension. However, most trials excluded participants with severe hypertension, i.e., higher than 180 mmHg. Hence, the result of this review might not apply to this group of people. Also, all studies recruited participants who either had a hypertension diagnosis that occurred concomitantly with one another diagnosis, i.e., gout, hypercholesterolaemia, stroke, and low cardiovascular risk, or who did not necessarily have a formal diagnosis of hypertension but who had one other diagnosis, i.e., diabetes, metabolic syndrome, elevated baPWV, and who, at baseline assessment, resulted nonetheless to have hypertension. The results of this review might not apply to people affected only by hypertension.

5.2.2 Interventions

Only two studies investigated berberine as individual ingredient of known dose [33,35]. The other studies investigated berberine in combination with other therapeutic agents, making it problematic to isolate berberine contribution to effects.

The two studies investigating Chunghyul-dan failed to report the content of the individual active substances contained in their preparations [36,40], including berberine content, which for this review had to be estimated, with a unknown degree of imprecision, through a different study. However, this limitation might just reflect the stance that western medical research has in relation to treatment of diseases compared to the approach of Chinese and Ayurveda medicine. While the former often focuses on isolating the effect of individual therapeutic agents, the latter take the holistic approach of employing treatments made of whole and unrefined ingredients expected to act synergistically [48].

The length of interventions varied from two weeks to six months. The variation adds to the heterogeneity of the evidence. It also cannot shine any light on the effect of long-term use of berberine, both on intended and adverse outcomes.

5.2.3 Outcomes

The primary goal of hypertension treatment is to prevent cardiovascular events. These were part of the primary outcomes of this review. The included trials did not report on cardiovascular event clinical endpoint, as all trials had a short-term follow-up. In any case, due to the relatively small sample sizes, these trials would have had little power to discriminate significant between-groups differences in the rate of the relatively rare cardiovascular events without a considerably long follow-up and increased costs.

Other outcomes from the included trials are primary outcomes of this review, namely, clinic SBP and DBP, and 24h-ABPM. However, blood pressure is a surrogate outcome. Temple defined the latter as “a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives” [49]. In a major RCT, the large Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [50], doxazosin and chlorthalidone had comparable effects on blood pressure, but the risk of one of the clinical endpoint, namely, congestive heart failure, for patients on doxazosin was twice that of those on chlorthalidone. This suggested that some non-blood pressure related effect were present in one or both treatments in either direction. Hence, even if blood pressure is widely accepted as a reliable surrogate outcome for establishing the long-term cardiovascular benefit of hypotensors, inferring the effect of the latter on the basis of their action on blood pressure alone does not always adequately indicate what their effect would be on meaningful clinical endpoints. Measuring these endpoints is therefore key in understanding true efficacy of a drug, and certainly its long-term safety.

5.2.4 Adverse outcomes

The reporting of adverse events was inadequate. Only one study [36] measured several metabolic parameters and reported on statistical significance for their changes from baseline to follow-up. All other studies either did not report on safety, or at most mentioned that there were no adverse outcomes, or that interventions were safe. Studies were of short duration, hence no information can be drawn regarding long-term berberine undesired effects. The evidence from this review does not allow to establish the overall safety of berberine, albeit there is some indication that short term use is generally safe.

5.3 Quality of the evidence

5.3.1 Overall quality of studies

All included trials were of low quality, in terms of design, reporting, and methodology. Two trials were not randomised, hence of intrinsically poorer quality in terms of allocation bias. All studies provided very limited or no description of design, randomisation, and allocation concealment. Baseline data was generally well reported, and intervention groups were similar within all trials. No study reported details on intention-to-treat analysis. Hence, all included trials were deemed to have unclear risk of allocation bias.

Most trials were designed or were likely to be designed as open-label, even when the addition of a placebo to the control arm could have been a viable option.

5.3.2 Outcome reporting bias

The overall body of evidence in this review shows a degree of outcome reporting bias, a problem often under-recognised by reviewers of RCTs [51]. No study used the CONSORT standards for reporting effect estimates [44]. Where the effect estimates calculated for this review showed, through comparison of between-groups outcomes, statistically significant beneficial effects of experimental interventions for some studies [34,35,37,40], those same studies but one [34] also reported the statistical significance of between-groups comparisons. Where, instead, the analyses showed not statistically significant effect estimates for the other studies [33,36,38], those studies did not report between-groups comparisons. They reported only on the statistical significance between baseline and follow-up value within groups, often showing significance for the experimental group. Hence, there seems to be an association between significance or non-significance of between-groups comparisons and the reporting or not reporting of them, as shown in Table 2. Moreover, all studies reported statistically analyses only through P values, which inferiority have long ago be highlighted compared to the use of CIs [52].

Table 2. Outcome reporting bias analysis.

Study ID	Effect estimate statistically significant	Between-groups statistical analyses reported	Within-group difference between baseline and follow-up values	Within-group statistical analyses reported
Huang 2013	No	No	Significant for E and C	Yes

Study ID	Effect estimate statistically significant	Between-groups statistical analyses reported	Within-group difference between baseline and follow-up values	Within-group statistical analyses reported
Huang 2013 [33]				
Mazza 2015 [34]	Yes for systolic 24h-ABPM No for diastolic 24h-ABPM	No No	Significant for E	Yes
Memon 2018 [35]	Yes for SBP No for DBP	Yes Yes (wrongly states significant)	Significant for E	Yes
Park 2006 [36]	Missing data for C did not allow for analysis	No	Not significant for E, no data for C	Yes
Rozza 2009 [37]	Yes for change from baseline (larger effect estimate) Yes for follow-up (smaller effect estimate)	Yes No	Significant for E	Yes
Trimarco 2012 [38]	No	No	Significant for E	Yes
Yun 2005 [40]	Yes for change from baseline No for follow-up	Yes No	Significant for E, not significant for C	Yes

Note: E: Experimental group; C: Comparator group.

5.4 Limitation and potential biases of the review process

Chinese medical literature databases were not searched for this review. It is recognised that a review on a herbal medicine with a long history of use in China would warrant a search of Chinese databases. Indeed, the Chinese biomedical literature is large and growing, but often not available through databases in the English language. In their comparison between two systematic reviews answering the same question around diagnosing rheumatoid arthritis, one employing a search of databases in English and Chinese, the other searching only those in English, Cohen, Korevaar, Wang, Spijker, & Bossuyt (2015) found that both reviews arrived at the same answer, with the same effect. However, the reviews compared were not on Chinese herbal medicine. Indeed, they still concluded that limiting systematic reviews to English only is common in systematic reviews and could result in biased effect estimates and reduce generalisability.

5.5 Agreements and disagreements with other reviews

The search for this review revealed only one existing systematic review and meta-analysis on berberine for hypertension [18]. However, the study quality assessment and data pooling methods therein were found to be of low quality. Four papers in Chinese are included in the meta-analysis; the full-text was retrievable for one of them [33], translated, and included in this review; three papers were not retrievable (Zhong et al., 1997; Han et al., 1999; Sun et al., 2013; all cited in [19]).

In terms of quality assessment, in the meta-analysis the paper also included in this review [41] was given a Jadad score [54] of 4 (high quality). The Jadad score arrived at here was only 2 (low quality). This was based on randomisation being mentioned and described as random number tables, but double-blinding not being mentioned and attrition not being discussed. The study also resulted of poor quality through the SIGN tool used for this review. The authors of the meta-analysis did not mention having sought additional information from the author to justify a higher score. The other three studies were given a score of 2, 3, and 3, respectively, hence of low to average quality.

For their meta-analysis, the authors pooled data from the two studies comparing amlodipine plus berberine versus amlodipine ([41]; Sun et al., 2013, cited in [19]). While it was not possible to retrieve Sun et al.'s paper, its data reported in [19] suggests that either Sun et al. conducted a study on a subgroup of the other study [41], or there was a data extraction error in the meta-analysis. If the first hypothesis is true, the meta-analysis has a unit-of-analysis error, which occurs when in a meta-analysis information from a treatment arm is used more than once [55]. Consequently, a significant effect estimate was obtained for both SBP and DBP from a single study that showed non-significant effects.

The same type of error occurred also in pooling the other two studies (Zhong et al., 1997; Han et al., 1999; all cited in [19]), the first comparing berberine to nitrendipine, the second with metropolol given at different doses in two comparator groups. Again, Han et al.'s experimental group is included twice in the same meta-analysis when pooling the comparisons with the two comparator groups. The correct approach would have been to first combine the two comparator groups results to arrive at one statistic, and then pool the data with the other study [56]. In this case, as Han et al.'s experiment favoured the comparator groups, effects were actually underestimated. Overall, the meta-analysis conclusion that berberine is effective in reducing blood pressure does not seem

justifiable on the basis of the analyses it reports. Nonetheless, this work is widely cited to highlight berberine benefit. For example, in a narrative review on berberine for hypertension [57], berberine is reported as providing a significant benefit based on the said meta-analysis results. A similar conclusion is given in a review of berberine in metabolic syndrome [17].

6. Conclusions

6.1 Implications for practice

Hypertension is a condition affecting a large part of the world population, and widely accepted as a risk factor for developing cardiovascular disease. When lifestyle interventions fail to control blood pressure, drugs are offered to patients, who can be reluctant to take medications for an asymptomatic condition. Often patients turn to alternative therapies, perceived as safer and less prone to side effects. Berberine is one such therapy, having been used for millennia in Chinese and Ayurveda medicine, and in the last few years become more known in the western world.

This systematic review reveals that the evidence from clinical trials that investigated berberine effect on blood pressure, rate of cardiovascular events, and rate of adverse events, is of limited quantity and quality. The risk of bias of the limited number of relevant trials is high, especially around study design and reporting of outcomes. Some evidence points to varying degrees of beneficial effect of berberine at reducing blood pressure, albeit with inconsistencies across studies. The results did not demonstrate harm from the interventions, but caution needs to be taken before arriving at firm conclusions, as reporting of adverse events was limited, and no long-term data was available. Also, existing reviews have some flaws, and care is needed before using their results for clinical decision making.

Based solely on the evidence above, which comes in the form of Western medicine research methods, it cannot be suggested with a reasonable degree of confidence that berberine is effective or safe in the treatment of hypertension. However, this suggestion needs to be balanced with the extensive anecdotal evidence and the professional expertise originating from the ancient tradition of Eastern medicine, holding berberine as effective and safe hypertension treatment for a considerable fraction of the world population.

6.2 Implications for research

This review includes only seven trial. Most trials' group size was small, duration was short, and related papers lacked details around trial design. Papers often omitted results on primary outcomes, or reported results without following widely accepted reporting standards.

A significant gap in the evidence is the lack of data around clinical endpoints, such as cardiovascular events. Adding these would increase the weight of the evidence, avoiding reliance on surrogate outcomes.

Given the methodological limitations demonstrated by the trials, there are some considerations for future trials. First, they should be adequately powered to allow for greater precision and estimate of long-term relatively rare events. Second, long-term follow-up should be considered to estimate clinically significant endpoints. And, finally, design and reporting of trials should follow the standards of the CONSORT statement.

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Appendix 1 – Characteristics of included studies

Huang 2013

Method	Randomised controlled trial. Randomisation method not specified.
Study setting	Lishui City Central Hospital, Zhejiang Province, China.
Participants	N=164, randomised: E=84, C=80. Loss to follow-up not discussed in the paper. Patients admitted to hospital from January 2010 to January 2011. Inclusion criteria: mild to moderate hypertension (diagnostic criteria not specified), and gout (BUA for males not less than 420μmol/L, for female not less than 360μmol/L). Exclusion criteria: endocrine or renal diseases, severe hypertension, history of cardiovascular and cerebrovascular accidents within 6 months, severe heart, liver, and kidney dysfunction, drug allergies. Among the 164 patients, 98 were male and 66 were female; aged 42-74 years, with an average age of (61.1±2.8) years. No significant differences between groups at baseline for BUA, SBP, and DBP, and all other measured parameters.
Interventions	E: oral berberine hydrochloride 300mg three times a day in addition to C group intervention. C: oral amlodipine tablets (Zhejiang Hongyuan Pharmaceutical Chemical Co., Ltd.) 5 mg twice a day, oral colchicine 1 mg three times a day if patients with acute gout, or oral allopurinol 50 mg twice a day if patients had chronic gout Both intervention lasted 8 weeks.
Outcomes	Within both groups, follow up SBP and DBP were significantly lower than baseline values (E: 127.6 ± 12.5mmHg vs 155.8 ± 18.2mmHg $p<0.05$, 81.5

	± 10.7mmHg vs 99.1 ± 5.4mmHg p<0.05; C: 132.1 ± 18.31mmHg vs 157.3 ± 22.8mmHg p<0.05, 83.5 ± 5.2mmHg vs 99.5 ± 6.1mmHg p<0.05). However, the between groups comparison of follow-up SBP and DBP showed no statistically significant differences. Author does mention this in the result section, but in the conclusion only the statistically significant difference between baseline and follow-up within the E group is highlighted. It was not possible to compare changes from baseline between groups as this were not reported in the paper. Adverse events: not discussed. Author mentions that intervention was safe.
Publication details	Study in Chinese.
Notes	E: Experimental group, C: Comparator group, BUA: Blood Uric Acid, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Study quality assessment

Question	Author's answer	Support for answer
1. The study addresses an appropriate and clearly focused question (reporting bias)	Yes	The study specifies that the aim was to investigate the effect on hypertension of amlodipine combined with berberine.
2. The assignment of subjects to treatment groups is randomised (allocation bias)	Can't say	Insufficient information available to permit a judgement.
3. An adequate concealment method is used (allocation bias).	Can't say	Insufficient information available to permit a judgement.
4. The design keeps subjects and investigators 'blind' about treatment allocation (performance bias, detection bias)	No	No placebo is given to comparator group, likely to be open label study.

5. The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	No statistically significant differences at baseline between groups in respect to gender, age, BUA, SBP, and DBP.
6. The only difference between groups is the treatment under investigation (performance bias)	Yes	No other interventions are mentioned.
7. All relevant outcomes are measured in a standard, valid and reliable way (detection bias)	Can't say	Insufficient information available to permit a judgement.
8. The drop out rate is acceptable (attrition bias)	Can't say	Insufficient information available to permit a judgement.
9. All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can't say	Insufficient information available to permit a judgement.

Mazza 2015

Method	Non-randomised controlled trial.
Study setting	Hypertension setting in Italy.
Participants	N=132, allocated E=66, C=66; at follow-up E=64 (one dropped out due to doubling of CK, one due to dyspepsia), C=66. C group age and gender matched. Age 56.0 ± 6.4 (mean ± SD), men 54.5%. Inclusion criteria: SBP equal to or higher than 140 mmHg or DBP equal to or higher than 90 mmHg, confirmed hypertension with 24 hour ABPM using a 2430 oscillometric device (TM-2430, Takeda, Japan) applied to the non-dominant arm, TC higher than 200 mg/dl or LDL-C higher than 150 mg/dl. Exclusion criteria: clinic SBP equal to or higher than 180 mmHg or DBP equal to or higher than 110 mmHg), secondary hypertension, diabetes

	mellitus, presence of neoplastic or hepatic disease, chronic heart or renal failure, positive history or clinical signs of ischemic heart disease, severe obesity (BMI equal to or higher than 35 kg/m$^{2)}$, disabling diseases such as dementia or inability to cooperate, pregnancy or breastfeeding, antihypertensive and/or lipid-lowering drug treatment, and organ damage (left ventricular hypertrophy diagnosed by electrocardiogram, carotid plaque or albuminuria) due to hypertension. No significant differences between groups at baseline for SBP, and DBP. Only PP (SBP-DBP) was significantly higher in E group. All other measures differences were not statistically significant.
Interventions	E: Armolipid Plus (Rottapharm SpA, a MEDA Company), one tablet, once daily in the evening before bedtime, for 6 months, in addition to a specific dietary regimen as in group C. C: written prescription for a standardised Mediterranean diet regimen, including a high intake of fish, fruits, vegetables, legumes, olive oil, unrefined whole grains and a moderate intake of lean meats and alcohol. Note: ArmoLipid Plus is a food supplement combining natural ingredients containing red yeast rice (equivalent of 3 mg of monacolin K), 10 mg of policosanol, 500 mg of berberine, 0.2 mg of folic acid, 0.5 mg of astaxanthin and 2 mg of coenzyme Q10. 2-week run in period when baseline values were taken. Then 6-months intervention.
Outcomes	SBP, DBP. systolic and diastolic day 24h, night 24h, 24h ABPM. For E group, of all blood pressure measures, only the change from baseline of 24h ABPM measurements was statistically significant: (141.6 ± 6.4mmHg at baseline vs. 136.2 ± 4.8mmHg at follow-up; $p<0.05$). For C group, all the difference measures pre- and post-intervention were not statistically significant. Post-intervention values for C group are not given in

	the paper, only bar charts are shown, from which precise numerical value cannot be extracted. No comparison between groups given in the study. It was not possible to compare post-intervention outcomes between groups, or compare changes from baseline between groups due to the lack of reporting of outcome measures in C group. High risk of reporting bias. Adverse events: two participants in E withdrawn from the study due to side effects (one due to a doubling in CK levels and one due to dyspepsia). Otherwise, all safety parameters measured had no significant changes among E and C.
Publication details	Study in English. Article processing charges for this study were funded by Rottapharm SpA, a MEDA Company, Monza, Italy, manufacturer of the tested nutraceutical compound.
Notes	E: experimental group, C: comparator group, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, BMI: body mass index, ABPM: ambulatory blood pressure monitoring, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, CK: creatinine kinase.

Study quality assessment

Question	Author's answer	Support for answer
1. The study addresses an appropriate and clearly focused question (reporting bias)	Yes	The aim was clearly stated as investigating the effect of nutraceuticals on serum lipid and blood pressure control in hypertensive and hypercholesterolaemic subjects.
2. The assignment of subjects to treatment groups is randomised	No	Non-randomised controlled trial. Age and gender matched comparator group.

	(allocation bias)		
3.	An adequate concealment method is used (allocation bias).	No	Non-randomised controlled trial.
4.	The design keeps subjects and investigators ‘blind’ about treatment allocation (performance bias, detection bias)	No	Non-randomised controlled trial.
5.	The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	No significant differences between groups at baseline for SBP, and DBP. Only PP (SBP-DBP) was significantly higher in E group. All other measures differences were not statistically significamt.
6.	The only difference between groups is the treatment under investigation (performance bias)	Yes	No other interventions are mentioned.
7.	All relevant outcomes are measured in a standard, valid and reliable way (detection bias)	Yes	All blood pressures measure techniques are described in details, and reflect standard accepted practice.
8.	The drop out rate is acceptable (attrition bias)	Yes	Two participants withdrew from E group.
9.	All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can’t say	Insufficient information available to permit a judgement.

Memon 2018

Method	Non-randomised controlled trial.

Study setting	Tertiary care hospital, Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro/Hyderabad, Pakistan, from March 2016 to January 2017.
Participants	N=200, E=100, C=100. C group age and gender matched. No loss to follow-up. Inclusion criteria: subjects with newly diagnosed type 2 DM cases of age ≥25 years taking drug metformin. Exclusion criteria: subjects with type 2 DM taking sulfonylurea, herbal drugs, HMG-CoA reductase inhibitors, and multivitamin pills and insulin, subjects with type 2 DM with diabetic complications, and subjects with type 2 DM with concomitant chronic viral hepatic disorders, coronary ischemic heart disease, chronic kidney disease, and pregnancy. No significant differences for most measured parameters. LDL-C and HDL-C levels where significantly different. Age E: 33.4 ± 2.96years, C: 33.26 ± 2.6years, p=0.81; body weight E: 64.37 ± 11.6kg, C: 60.8 ± 8.95kg, p=0.09; LDL-C E: 109.2 ± 16.4mg/dl, C: 181.9 ± 43.07mg/dl, p=0.0001; HDL-C E: 33.65 ± 11.36mg/dl, C: 34.5 ± 0.47mg/dl, p=0.04.
Interventions	E: berberine 500 mg three times a day. C: metformin (Glucophage, Merck Pharmaceuticals) 500 mg three times a day. Intervention lasted for 3 months.
Outcomes	SBP and DBP were not stated main outcomes in the study. However, measures are reported for pre- and post-intervention for both groups. The authors also carried out between groups comparison. Paper reports that, at follow-up, both SBP and DBP were significantly lower than those in C group (but see note below): 131.4 ± 15.2mmHg vs 143.3 ±19.0mmHg p=0.001, 70.61 ± 13.65mmHg vs 72.57 ± 11.2mmHg p=0.03. It was not possible to compare changes from baseline between groups.

	Adverse events not discussed in the paper. Note: DBP difference at f/u is NS. Calculated significant level p=0.27, not p=0.03 as paper reports.
Publication details	Study in English.
Notes	E: experimental group, C: comparator group, SBP: systolic blood pressure, DBP: diastolic blood pressure, DM: diabetes mellitus.

Study quality assessment

Question	Author's answer	Support for answer
1. The study addresses an appropriate and clearly focused question (reporting bias)	Yes	The aim was clearly stated as determining the effects of berberine therapy on serum methylglyoxal and insulin resistance in newly diagnosed type 2 diabetic patients.
2. The assignment of subjects to treatment groups is randomised (allocation bias)	No	Non-randomised controlled trial. Age and gender matched comparator group.
3. An adequate concealment method is used (allocation bias).	No	Non-randomised controlled trial.
4. The design keeps subjects and investigators 'blind' about treatment allocation (performance bias, detection bias)	No	Non-randomised controlled trial.
5. The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	No significant differences for most measured parameters. Body weight and cholesterol levels where significantly different.

6. The only difference between groups is the treatment under investigation (performance bias)	Yes	No other interventions are mentioned.
7. All relevant outcomes are measured in a standard, valid and reliable way (detection bias)	Can't say	Insufficient information available to permit a judgement.
8. The drop out rate is acceptable (attrition bias)	Yes	No loss to follow-up.
9. All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can't say	Insufficient information available to permit a judgement.

Park 2006

Method	Randomised controlled trial.
Study setting	Outpatients visiting the Cardiovascular Center of Kyung Hee University Kangnam Korean Hospital between November 2003 and October 2004.
Participants	N=35, E=20, C=15. Loss to follow-up not described. Inclusion criteria: baPWV higher than 1400 cm/sec. Exclusion criteria: use of hormone replacement therapy in the 2 months prior to the study, use of anti-hyperlipidemic agents or steroids within 6 months, or the presence of hepatic or renal diseases. No statistically significant differences between groups at baseline in terms of age, gender, SBP, DBP, and baPWV. Age E: 61.4 ± 9.6years, C: 63.4 ± 10.5year p=0.644; gender (male vs female) E: 6 vs 14, C: 4 vs 11 p=0.863
Interventions	E: CHD 600mg three times a day. For this review, the content of berberine is

	calculated as 4% of total preparation using estimate in [58]. Hence, total estimated berberine daily dose was 24mg three times a day. C: Observations only. Interventions lasted for 8 weeks.
Outcomes	SBP and DBP were not primary outcomes of the study, baPWV was the main outcome. For E group SBP and DBP are given at baseline (152.9 ± 22.0 mmHg and 91.3 ± 8.0 mmHg) and follow-up (137.6 ± 13.3 mmHg and 87.2 ± 8.2 mmHg), and the differences were not statistically significant. For C group only baseline SBP and DBP values are given in the paper. This represent a high risk of reporting bias. Between-groups comparisons of SBP and DBP were not given in the paper. Because of the lack of reporting of SBP and DBP values for C group at follow-up, for this review it was not possible to calculate between-groups comparison of post-intervention values of SBP and DBP or comparison of changes from baseline. While baPWV was not an outcome of interest for this review, it is worth noting that values for baPWV are given at baseline and follow-up for both groups. The paper highlights that, in E group, follow-up value was significant lower than baseline, but not for C group. However, for this review, between-groups comparison of follow-up values were calculated, and showed no statistically significant difference. As this was not an outcome of interest of this review, the actual calculations are not reported. There were no clinical adverse effects observed during the 8 weeks of treatment. There were no statistically significant changes in E group pre- and post-intervention values for the following monitored parameters: AST, ALT, BUN, and CR.
Publication details	Study in English.

Notes	E: experimental group, C: comparator group, SBP: systolic blood pressure, DBP: diastolic blood pressure, baPWV: brachial-ankle pulse wave velocity, CHD: chunghyul-dan, AST: aspatate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, CR: creatinine

Study quality assessment

Question	Author's answer	Support for answer
1. The study addresses an appropriate and clearly focused question (reporting bias)	Yes	Aim of the study was the effect of Chunghyul-dan (CHD) (Qingxue-Dan) on arterial stiffness in patients with raised baPWV.
2. The assignment of subjects to treatment groups is randomised (allocation bias)	Can't say	Insufficient information available to permit a judgement.
3. An adequate concealment method is used (allocation bias).	Can't say	Insufficient information available to permit a judgement.
4. The design keeps subjects and investigators 'blind' about treatment allocation (performance bias, detection bias)	No	Blinding not mentioned. There was no placebo in comparator group. Very likely to be open label study.
5. The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	Participants similar in all measured parameters: age, gender, SBP, DBP, baPWV,
6. The only difference between groups is the treatment under investigation (performance bias)	Yes	Yes, no other intervention is described.
7. All relevant outcomes are measured in a standard, valid and	Can't say	SBP, DBP, and baPWV said to be measured per usual way as measured at

	reliable way (detection bias)		the trial hospital.
8.	The drop out rate is acceptable (attrition bias)	Can't say	Insufficient information available to permit a judgement.
9.	All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can't say	Insufficient information available to permit a judgement.

Rozza 2009

Method	Randomised controlled trial.
Study setting	Italy. No other details given in the paper.
Participants	N=30, E=15, C=15. No loss to follow-up. Inclusion criteria: subjects of both sexes aged 18–75 years and with a diagnosis of metabolic syndrome established according to the NCEP ATP-III criteria [17], i.e., subjects with at least subjects with at least three of these factors: waist measurement higher than 102cm for men and higher than 88cm for women, fasting glycaemia equal to or higher than 100mg/dL, arterial blood pressure equal to or higher than 130/85mmHg, trigliceride equal to or higher than 150mg/dL; HDL-C less than 40mg/dL for men or less than 50mg/dL for women. Exclusion criteria: subjects who were pregnant or breastfeeding women and patients treated with antihypertensive and/or lipid-lowering drugs. At baseline there were no statistically significant differences between all measured parameters, including age, gender, SBP, and DBP. Age E: 47.5 ± 10.1years, C: 45.5 ± 10.8years, NS; sex (M/F%) E: 67/33; C: 73.3/26.7.
Interventions	E: A patented combination of policosanol, red yeast rice extract, berberine, folic acid and coenzyme Q10 with the addition of Orthosiphon Staminensi

	(Armolipid Prev, Rottapharm, Monza, Italy). The paper does not specify actual content in mg of the individual components of Armolipid Prev. However, Armolipid Prev is made up of Armolipid Plus with the addition of Orthosiphon Staminensi. Armolipid Plus content is given in the included study by Mazza et al. (2015) as red yeast rice (equivalent of 3 mg of monacolin K), 10 mg of policosanol, 500 mg of berberine, 0.2 mg of folic acid, 0.5 mg of astaxanthin and 2 mg of coenzyme Q10. C: placebo. There was a 2-week run-in period when both groups received dietary advice and placebo. Then the interventions as above run for 6 weeks.
Outcomes	SDB and DBP were part of the primary outcomes measures. Measures are given in the paper at baseline, after 2-week run-in period, and at 6-week folllow-up. The authors did a between group comparison of change from 2-week run-in to 6-week follow-up, showing that E group had, compared to C group, a significant higher SBP reduction (-19.6 ± 9.7 vs -3.6 ± 8.1 mmHg; p< 0.0001) and DBP reduction (-13.6 ± 5.5 vs -2.3 ± 5.3mmHg; p< 0.0001). Between groups comparison of follow-up values were made for this review. The paper reports no adverse outcomes, but does not give details.
Publication details	Study in English.
Notes	E: experimental group, C: comparator group, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL-C: high density lipoprotein cholesterol, NS: non-significant.

Study quality assessment

Question	Author's answer	Support for answer
1. The study addresses an appropriate and clearly focused	Yes	There was clear focus on investigating reduction of blood pressure in patients

question (reporting bias)		with metabolic syndrome treated with nutraceuticals.
2. The assignment of subjects to treatment groups is randomised (allocation bias)	Can't say	Insufficient information available to permit a judgement.
3. An adequate concealment method is used (allocation bias).	Can't say	Insufficient information available to permit a judgement.
4. The design keeps subjects and investigators 'blind' about treatment allocation (performance bias, detection bias)	Can't say	Double-blinding mentioned. Insufficient information available to permit a judgement.
5. The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	At baseline there were no statistically significant differences between all measured parameters, including age, gender, SBP, and DBP.
6. The only difference between groups is the treatment under investigation (performance bias)	Yes	Yes, no other intervention is described.
7. All relevant outcomes are measured in a standard, valid and reliable way (detection bias)	Yes	Systolic and diastolic blood pressure were measured by standard sphygmomanometer after 5 minutes in the supine position, according to the guidelines of the European Society of Cardiology and the European Society of Hypertension [4]. Three blood pressure measurements were obtained in the sitting position at 2-minute intervals. The averages of these measurements were used for the analysis.

8. The drop out rate is acceptable (attrition bias)	Yes	No loss to follow-up.
9. All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can't say	Insufficient information available to permit a judgement.

Trimarco 2012

Method	Randomised controlled trial.
Study setting	Italy. No other details given in the paper.
Participants	N=30, recruited E=20, C=10. Analyses done for E=18 and C=9, as at follow-up 2 in E group and 1 in C group were lost due to invalid 24h ABPM values (the 24h ABPM was considered valid if at least 80% of reading were valid, and there were not more than 2 consecutive hours without a valid reading). Hence, the analysed sample consisted of 27 patients (23 men; mean age=46.26, SD=10.9 years). Inclusion criteria: both genders, aged between 18 and 75 years, with high-normal hypertension (SBP=130-139mmHg and/or DBP=85-89mmHg) or grade 1 hypertension (SBP=140-159mmHg and/or DBP 90-99mmHg) and low cardiovascular risk, so that there was no indication to immediate antihypertensive treatment according to the European guidelines management of essential hypertension [4]. Exclusion criteria: pregnant or breastfeeding women and patients treated with antihypertensive and/or lipid lowering drugs. At baseline there were no statistically significant differences between all measured parameters, including age, gender, SBP, DBP, and 24h-ABPM.
Interventions	E: A patented combination of policosanol, red yeast rice extract, berberine, folic acid and coenzyme Q10 with the addition of Orthosiphon Staminensi (Armolipid Prev, Rottapharm, Monza, Italy). The paper does not specify

	actual content in mg of the individual components of Armolipid Prev. However, Armolipid Prev is made up of Armolipid Plus with the addition of Orthosiphon Staminensi. Armolipid Plus content is given in the included study by Mazza et al. (2015) as red yeast rice (equivalent of 3 mg of monacolin K), 10 mg of policosanol, 500 mg of berberine, 0.2 mg of folic acid, 0.5 mg of astaxanthin and 2 mg of coenzyme Q10. C: Armolipid Plus. There was a 2-week run-in period when both groups received dietary advice and placebo. Then the interventions as above run for 4 weeks.
Outcomes	24h-ABPM, daytime ABPM, and night-time ABPM were the primary outcome measures. In E group, at 4-week follow-up all measures had significant reduction from baseline, for both systolic and diastolic. 24h-ABPM: 130.98 ± 7.2 vs 135.87 ± 8.2mmHg; p = 0.0001; 83.74 ± 3.8 vs 87.34 ± 4.4mmHg, p= 0.0001; daytime: 137.22 ± 8.2 vs 141.82 ± 8.1mmHg, p = 0.002, 89.27 ± 4.5 vs 92.83 ± 4.4mmHg, p= 0.001; night-time: 115.30 ± 8.5 vs 121.46 ± 10.8 mmHg, p = 0.008, 70.31 ± 5.6 vs 74.01 ± 7.5mmHg, p= 0.037. In C group, measures at baseline and at 4-week follow-up were not significantly different. No between groups comparisons are given in the paper. Between groups comparison of values at follow-up were carried out for this review. It was not possible to do between groups comparison of changes from baseline. Adverse outcomes: authors state that there was a lack of adverse reactions. No other details are given.
Publication details	Study in English.
Notes	E: experimental group, C: comparator group, SBP: systolic blood pressure, DBP: diastolic blood pressure, ABPM: ambulatory blood pressure monitoring.

Study quality assessment		
Question	Author's answer	Support for answer
1. The study addresses an appropriate and clearly focused question (reporting bias)	Yes	There was clear focus on investigating reduction of blood pressure in patients with hypertension treated with a nutraceutical.
2. The assignment of subjects to treatment groups is randomised (allocation bias)	Can't say	Insufficient information available to permit a judgement.
3. An adequate concealment method is used (allocation bias).	Can't say	Insufficient information available to permit a judgement.
4. The design keeps subjects and investigators 'blind' about treatment allocation (performance bias, detection bias)	No	Blinding not mentioned.
5. The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	At baseline there were no statistically significant differences between all measured parameters, including age, gender, SBP, DBP, and 24h-ABPM.
6. The only difference between groups is the treatment under investigation (performance bias)	Yes	Yes, no other intervention is described.
7. All relevant outcomes are measured in a standard, valid and reliable way (detection bias)	Yes	ABPM devices (Spacelabs model 90207, Rendmond, WA, USA) were used with the appropriately sized cuff and bladder. The units were programmed to take measurements at 15-minute intervals during the day and

		the evening (8:00am to 11:00pm) and at 20-minute intervals during the night (11:00pm to 8:00am) throughout the 24-hour period. With this device, the first BP measurement appears on the device's display screen, but all subsequent measures are blinded.
8. The drop out rate is acceptable (attrition bias)	Yes	At follow-up 2 in E group and 1 in C group were lost due to invalid 24h ABPM values.
9. All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can't say	Insufficient information available to permit a judgement.

Yun 2005

Method	Randomised controlled trial.
Study setting	Department of Cardiovascular and Neurologic Diseases (Stroke Center), Hospital of Oriental Medicine, Kyung Hee Medical Center, Seoul, Korea, from 1 June 2003 to 31 March 2004.
Participants	N=40, recruited E=20, C=20. At follow-up E=15, C=13. From C group 5 subjects dropped out due to unexpected early discharge and 2 due to data errors; from E group 3 subjects dropped out due to unexpected early discharge and 2 due to data errors. The final analysis was performed on the remaining 28. Inclusion criteria: subjects hospitalised 10 days after stroke with stage 1 hypertension defined in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood

	Pressure, i.e., sitting SBP between 140–159 mmHg or DBP between 90–99 mmHg. White coat hypertension was excluded (SBP below 125 mmHg or DBP below 80 mmHg) by 2. The diagnosis of stroke was made when neurologic4h-ABPM. The diagnosis of stroke was made when neurological deficits were accompanied by corresponding abnormal computed tomography or magnetic resonance imaging findings of the brain. Exclusion criteria: subjects who were taking hypotensors, who had hepatic or renal diseases, or experienced cardiovascular disease within three months. At baseline there were no statistically significant differences between all measured parameters, including age, gender, 24h-ABPMSBP, and DBP.
Interventions	E: Chunghyul-dan (Qingxue-dan) 1200mg once a day. For this review, the content of berberine is calculated as 4% of total preparation using estimate in (Chung, Ryu, Chung, & Kim, 2016). Hence, total estimated berberine daily dose was 48mg once a day. C: No intervention. Intervention lasted for 2 weeks.
Outcomes	Systolic and diastolic 24h-ABPM were part of the primary outcomes. Pre-interventions, post-interventions, and change from baseline values are given in the paper for both groups. E group change from baseline of systolic 24h-ABPM, from 141.37 ± 8.96 mmHg to 132.28 ± 9.46 mmHg (P = 0.03), was statistically significant, as was the corresponding mean change from baseline of 9.09 ± 8.73 mmHg. No other between-groups comparison are not given in the paper. These were calculated for this review, for both follow-up and change from baseline. Adverse outcomes: authors report that no adverse effect was found, and 5 subjects showed improvement of symptoms (two insomnia, one constipation, and one pruritus).
Publication	Study in English.

details			
Notes	E: experimental group, C: comparator group, SBP: systolic blood pressure, DBP: diastolic blood pressure, ABPM: ambulatory blood pressure monitoring.		
Study quality assessment			
Question		Author's answer	Support for answer
1.	The study addresses an appropriate and clearly focused question (reporting bias)	Yes	There was clear focus on investigating the effect of Chunghyul-dan (Qingxue-dan) on blood pressure in hospitalised patients just diagnosed with stroke and hypertension.
2.	The assignment of subjects to treatment groups is randomised (allocation bias)	Can't say	Insufficient information available to permit a judgement.
3.	An adequate concealment method is used (allocation bias).	Can't say	Insufficient information available to permit a judgement.
4.	The design keeps subjects and investigators 'blind' about treatment allocation (performance bias, detection bias)	No	Authors mention in the paper that placebo was not used, as it was impossible to provide a placebo of same smell, colour, taste and weight as the experimental intervention.
5.	The treatment and control groups are similar at the start of the trial (allocation bias)	Yes	At baseline there were no statistically significant differences between all measured parameters, including age, gender, 24h-ABPMSBP, and DBP.
6.	The only difference between groups is the treatment under	Yes	Yes, no other intervention is described.

	investigation (performance bias)		
7.	All relevant outcomes are measured in a standard, valid and reliable way (detection bias)	Yes	Manual blood pressure was measured using mercury sphygmomanometer four times a day. We used mean values of these data before recruitment. When the subjects met the inclusion criteria, ambulatory blood pressure was monitored using non-invasive oscillometric devices TM-2421 (A&D Company, Japan). The recorders were programmed to start 8:00 am and measure blood pressure at 30-minute intervals for 24 hours. All participants were instructed to carry out their usual daily activities including physiotherapy.
8.	The drop out rate is acceptable (attrition bias)	No	At follow-up, E group lost 35% of subjects, C group lost 25%, largely due to early discharge. There is high risk of attrition bias.
9.	All the subjects are analysed in the groups to which they were randomly allocated (attrition bias)	Can’t say	Insufficient information available to permit a judgement.

Appendix 2 – Search strategy

Boolean phrase for Medline, CINAHL, and AMED in EBSCOHost

((TX Berberine) OR (TX Barberry) OR (TX Chitra) OR (TX Coptis) OR (TX Daruhaldi) OR (TX Daruharidra) OR (TX Goldenseal) OR (TX Goldthread) OR (TX Huang Bai) OR (TX Huang Bo) OR (TX Huang Lian) OR (TX Huangbai) OR (TX Huanglian) OR (TX Hydrastis) OR (TX Kashmal) OR (TX Mahonia) OR (TX Oregon Grape) OR (TX Phellodendron) OR (TX Tree Turmeric)) AND ((TX Elevated Blood Pressure) OR (TX High Blood Pressure) OR (TX Htn) OR (TX Hypertension) OR (TX Hypertensive)).

Limiters - Human

Boolean phrase for Embase in Ovid

(Berberine OR Barberry OR Chitra OR Coptis OR Daruhaldi OR Daruharidra OR Goldenseal OR Goldthread OR Huang Bai OR Huang Bo OR Huang Lian OR Huangbai OR Huanglian OR Hydrastis OR Kashmal OR Mahonia OR Oregon Grape OR Phellodendron OR Tree Turmeric) AND (Elevated Blood Pressure OR High Blood Pressure OR Htn OR Hypertension OR Hypertensive).AF

Limiters – Human