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Garlic for hypertension: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: In the past decade, *garlic* has become one of the most popular complementary therapies for blood pressure (BP) control used by hypertensive patients. Numerous clinical studies have focused on the BP-lowering effect of *garlic*, but results have been inconsistent. Overall, there is a dearth of information available to guide the clinical community on the efficacy of *garlic* in hypertensive patients.

Aim: To systematically review the medical literature to investigate the current evidence of *garlic* for the treatment of hypertension.

Methods: PubMed, the Cochrane Library and EMBASE were searched for appropriate articles from their respective inceptions until August 2014. Randomized, placebo-controlled trials comparing *garlic vs.* a placebo in patients with hypertension were considered. Papers were independently reviewed by two reviewers and were analyzed using Cochrane software Revman 5.2.

Results: A total of seven randomized, placebo-controlled trials were identified. Compared with the placebo, this meta-analysis revealed a significant lowering effect of *garlic* on both systolic BP (WMD: −6.71 mmHg; 95% CI: −12.44 to −0.99; $P = 0.02$) and diastolic BP (WMD: −4.79 mmHg; 95% CI: −6.60 to −2.99; $P < 0.00001$). No serious adverse events were reported in any of the trials.

Conclusion: The present review suggests that *garlic* is an effective and safe approach for hypertension. However, more rigorously designed randomized controlled trials focusing on primary endpoints with long-term follow-up are still warranted before *garlic* can be recommended to treat hypertensive patients.

Introduction

Hypertension affects approximately one billion people, or two-thirds of adults aged 60 years or older worldwide (Go et al. 2013; Mancia et al. 2013). A linear relationship between blood pressure (BP) and risk of cardiovascular events has been identified and, thus, hypertension is the leading risk factor for cardiovascular diseases (CVDs). Currently, the Cochrane systematic review focusing on the first-line drugs for hypertension suggested that antihypertensive agents including thiazides, angiotensin converting enzyme inhibitors, beta-blockers, and calcium channel blockers reduce the risk of mortality, stroke, coronary heart disease (CHD), and/or cardiovascular events (Wright and Musini 2009). Although effective medical treatment has been recommended by various guidelines for the management of patients with high BP, hypertension is not yet adequately controlled (Jaffe et al. 2013; James et al. 2014; Wang and Xiong 2012). In America, approximately half of the hypertensive patients have a controlled BP of ≤140/90 mmHg, and more than 13% (approximately 9 million people) had a systolic blood pressure (SBP) of ≥160 mmHg and/or diastolic blood pressure (DBP) of ≥100 mmHg (Frieden et al. 2014; Guo et al. 2012). In addition, adverse events (AEs) and the complexity of antihypertensive therapy tend to decrease treatment adherence (Bangalore et al. 2011; Wang and Manson 2013). Therefore, it is not surprising that complementary and alternative medicines (CAM) are gaining increasing popularity among patients with CVDs (Tachjian et al. 2010; Vogel et al. 2005), and there is a need to explore the integration of CAM into the treatment of hypertension (Brook et al. 2013; Xiong et al. 2013a).

Garlic, also known as *Allium sativum* L. (*Liliaceae*), is a member of the family *Alliaceae*. It has been used as an important medicinal ailment in many countries for thousands of years (Pittler and Ernst 2007). According to a survey of 10,572 patients with CVDs

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in the 2002 National Health Interview Survey, *garlic* was the second most utilized herbal products (after Echinacea) within the previous 12 months (Yeh et al. 2006). An appreciable amount of scientific reports demonstrated its therapeutic and pharmacological properties. Indeed, raw *garlic* and *garlic*-based preparations exert antihypertensive, anti-atherosclerotic, lipid-lowering, plasma fibrinogen-lowering, fibrinolytic activity-increasing, and other cardiovascular-protective effects (Campbell et al. 2001; Dhawan and Jain 2005; Durak et al. 2004; Rahman 2001; Stevinson et al. 2000; Steiner and Li 2001). It is also considered to be one of the most popular complementary therapies for BP control and is thought to be used by 53.3% of hypertensive patients (Capraz et al. 2007). Biochemically, *garlic* exerts its antihypertensive effects by inhibiting angiotensin-converting enzyme activity (Asdaqa and Inamdarb 2010; Sharifi et al. 2003), reducing the synthesis of vasoconstrictor prostanoids (Al-Qattan et al. 2001), enhancing the concentration and activity of nitric oxide and generation of hydrogen sulfide (Al-Qattan et al. 2006), and reversing arterial remodeling through upregulation of the growth suppressor p27 and the attenuation of ERK 1/2 phosphorylation (Castro et al. 2010) in *in vivo* and *in vitro* experiments. One of the active constituents believed to be responsible for its pharmacological activity is allicin, liberated from alliin (*S*-allylcysteine-*S*-oxide) and the enzyme alliinase.

Indeed, numerous clinical investigations of *garlic* have reported the possible short-term BP-lowering effects on hypertension ranging from case reports and case series to controlled observational studies and randomized controlled trials (RCTs) (Estrada and Young 1993; McMahon and Vargas 1993; Mendis 1988). However, inconsistent and sometimes controversial results have been shown in several other trials (Duda et al. 2008; Simons et al. 1995; Zimmermann and Zimmermann 1990). The possible reason for these discrepancies may be related to different preparations of *garlic* with different biological responses, deficiencies in methodology, variations in the dosage of *garlic* and different treatment durations. As shown in nine published systematic reviews and/or meta-analyses, the effects of *garlic* on BP have been summarized with inconsistent conclusions (Ackermann et al. 2001; Mahdaviroshan et al. 2014; McRae 2005; Reinhart et al. 2008; Ried et al. 2008; Simons et al. 2009; Silagy and Neil 1994; Stabler et al. 2012; Yan and Fan 2011). However, a large number of the clinical trials enrolled in these systematic reviews were conducted in healthy volunteers or patients with hyperlipidemia, or compared hypertensive patients with normal BP patients. Additionally, there was evidence that revealed that the initial BP level is an important factor affecting the BP-lowering efficacy of *garlic* (Qidwai and Ashfaq, 2013); that was, hypertensive subjects with a baseline SBP ≥140 mmHg often showed positive results (De Santos and Grunwald 1993; Holzgartner 1992; Vorberg and Schneider 1990), while normotensive subjects with SBP <140 mmHg showed null results (Al-Wafi and Al-Fartos 2010; Jain et al. 1993; Isaacsohn et al. 1998; Macan et al. 2006; Turner et al. 2004; Williams et al. 2005; Zhang et al. 2001). Although one systematic review evaluated the effect of *garlic* on cardiovascular morbidity and mortality in hypertensive patients, only two trials were included with no definite conclusions (Stabler et al. 2012). Therefore, it is still unknown whether there is robust evidence supporting the clinical effects of *garlic* for hypertensive patients, and whether *garlic* supplementation can be recommended as a routine treatment. The objective of this study was to systematically review the data from RCTs to explore whether *garlic* is an effective and safe alternative approach for the treatment of hypertension.

Methods

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009).

Eligibility criteria

Types of studies

Only randomized, placebo-controlled trials evaluating the effects of *garlic* or *garlic*-based preparations on hypertensive patients were considered.

Types of participants

Unlike the previously published systematic review, all the enrolled participants in this review were diagnosed with hypertension according to established definitions or guidelines. Specifically, participants were eligible if they displayed a SBP ≥140 mmHg and/or DBP ≥ 90 mmHg on at least two occasions whilst off antihypertensive treatment (after a washout period of at least 4 weeks) and/or treatment with antihypertensive medication (James et al. 2014; Mancia et al. 2013). Trials that reported the recruitment of subjects with definite hypertension but without specific diagnostic criteria were also included. If non-hypertensive patients were included in the treatment or control group, the trial was excluded. No restrictions were imposed on sex, age, or ethnic origin of the participants.

Types of interventions

RCTs comparing the efficacy of *garlic* or *garlic*-based preparations *vs.* a placebo on hypertension were identified. These studies were excluded: (a) RCTs comparing *garlic* against another non-conventional therapy, or comparing *garlic* plus other non-conventional therapies against conventional medicine; (b) RCTs comparing the effect of *garlic* on hypertensive patients *vs.* normotensive subjects; (c) studies that were not randomized, uncontrolled, and/or animal experiments; (d) studies that reported duplicated results; and (e) trials with no clinical data reported. To ensure all the relevant studies were included, we did not set any specifications for *garlic* preparations, dosage, or treatment duration. If ambiguous or missing information about the outcomes in the original studies were identified, the corresponding authors were contacted by email, fax or telephone.

Types of outcome measures

The primary outcome measures were defined as mortality and cardiovascular events including CHD, myocardial infarction, heart failure, and stroke. The secondary outcome measures were defined as SBP and DBP at the end of the treatment. BP was measured in mmHg. If BP was measured in kPa, it was multiplied by a factor of 7.5 for conversion into mmHg.

Search strategy

We searched the following three electronic databases from their inception until August 17th, 2014 for the identification of studies: PubMed (1995–2014), the Cochrane Library (1996–2014), and EMBASE (1995–2014). In order to minimize selection bias, ongoing registered clinical trials on the Chinese Clinical Trial Register (http://www.chictr.org/) and the international clinical trial registry by U.S. National Institutes of Health (http://clinicaltrials.gov/) were also searched. Keywords for databases searching were: (“*garlic* ” OR “garlicin” OR “*garlic* oil” OR “*garlic* oil macerates” OR “*garlic* extract” OR “*garlic* cloves” OR “*garlic* powder” OR “aged *garlic* extract” OR “*Allium sativum*” OR “alliinase” OR “allicin”) AND (“hypertension” OR “blood pressure” OR “high blood pressure”) AND (“clinical trial” OR “randomized trial” OR “randomized controlled trial”). There were no restrictions on language or publication in the search strategy. Citations of reviews and meta-analyses of *garlic* for the treatment of hypertension were also examined. Experts in the field were contacted to identify any other trials missed in our search.

Data extraction

Studies which complied with the inclusion criteria were examined in detail by two independent reviewers. The data extraction form comprised authors, title, publication year, literature source, sample size, age, sex, diagnosis standard, study design, interventions of each group, chemical compositions of the included *garlic* and *garlic*-based preparations, treatment duration, drop-out, BP data before and after treatment, follow up and AEs.

Quality assessment

Methodological quality was assessed according to the "risk of bias" criteria from the Cochrane Handbook for Systematic Review of Interventions (Higgins and Green 2011). Risks of bias assessment included the following seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential threat to validity. Each domain was judged as low/unclear/high risk of bias. Then, trials were categorized into three levels: low risk of bias (all the items were in low risk of bias), high risk of bias (at least one item was in high risk of bias), unclear risk of bias (at least one item was unclear in regard to risk of bias) (Higgins et al. 2011). Discrepancies were resolved by consultation or consensus with a third party.

Data synthesis

Cochrane Collaboration Review Manager Software (Revman 5.2) was used for statistical analyses. Because BP data before and after treatment is a continuous outcome, it was presented as a weighted mean difference (WMD) with 95% confidence interval (CI). We assessed data by both random effect and fixed effect analyses, but reported the random effect analysis only if the heterogeneity term was statistically significant. The random effect analysis was assessed by the I^2 statistic ($I^2 > 50\%$), and we used $P < 0.10$ as the significance limit. A value of $P < 0.05$ was regarded as statistically significant. Publication bias was explored by funnel plot analysis if the group included more than 10 trials (Higgins and Green 2011).

Results

Trials identification

We identified 213 records on *garlic* after searching the three databases mentioned above. By reading titles and abstracts, we excluded 186 articles that were duplicate records, review articles, case reports, case series, or non-clinical studies. Full-texts of 27 articles were retrieved for further assessment, of which 20 were excluded for reasons listed below: participants did not meet the inclusive criteria ($n = 17$), duplication ($n = 2$), and no control group ($n = 1$). Finally, a total of seven randomized, placebo-controlled trials (Auer et al. 1990; Han et al. 2011; Kandziora 1988; Nakasone et al. 2013; Ried et al. 2010; Ried et al. 2013; Sobenin et al. 2009) from 1988 to 2013 containing 391 hypertensive patients were included (Fig. 1).

Trials characteristics

Basic characteristics of the included trials and subjects are summarized in Table 1. All the trials compared *garlic* with a placebo in hypertensive patients and were written in English. Patients in the treatment group received *garlic* preparations, while participants in the control group received a placebo which was matched with *garlic* in aroma, color and appearance. As presented in Table 1, six different *garlic* preparations were tested in the trials, including dried *garlic* homogenate (Nakasone et al. 2013), aged *garlic* extract (Ried et al. 2010, 2013), processed *garlic* capsule (Han et al. 2011), time-released *garlic* powder tablet (Sobenin et al. 2009), regular *garlic* pill (Kwai) (Sobenin et al. 2009), and *garlic* powder (Kwai) (Auer et al. 1990; Kandziora 1988).

In the trial conducted by Nakasone et al., the dried *garlic* homogenate used was a traditional Japanese *garlic* preparation (Nakasone et al. 2013). It was also known as 'Dentou-ninniku-ranwo™' capsule (Kenkoukazoku Inc., Kagoshima, Japan). In each 500 mg capsule, it was composed by 188 mg of a *garlic* preparation (a powdery mixture of *garlic* homogenate and egg yolk as the active ingredient), 266.5 mg rapeseed oil (as the solvent) and 45.5 mg beeswax (as the stabilizer). Two trials conducted by Ried et al. used Kyolic® (*Garlic* High Potency Everyday Formula 112, Wakunga/Wagner®, Sydney, Australia) as interventions, which contained 240 mg of aged *garlic* extract and 0.6 mg Sallylcysteine in each capsule (Ried et al. 2010, 2013). In the trial by Ried et al. (2010), the daily dosage of four Kyolic® capsules containing 960 mg of aged *garlic* extract and 2.4 mg Sallylcysteine was equivalent to about 2.5 g of fresh *garlic*. In the trial by Ried et al. (2013), one/two/four capsules daily of Kyolic® contained 240/480/960 mg of aged *garlic* extract and 0.6/1.2/2.4 mg *S*-allylcysteine. In the trial conducted by Han et al, processed *garlic* capsules (AGV Products Co., Chia-Yi, Taiwan) were used for hypertensive patients (Han et al. 2011). The processed *garlic* capsules were manufactured as follows: raw was washed then put in a reactor for two weeks; after completion of the enzymatic reaction process, the processed *garlic* was dehulled, lyophilized and then powdered. The active components of Sallylcysteine were determined to be 75.3 mg/100 g and total phenolics were 775 mg/100 g in processed *garlic*. Both two different *garlic* based preparations, namely time-released *garlic* powder tablets (Allicor) and regular *garlic* pills (Kwai), were used in the trial conducted by Sobenin et al. (2009). Among them, one Allicor tablet contained 300 mg *garlic* powder (INAT-Farma, Moscow, Russia), while one Kwai tablet contained 300 mg *garlic* powder (Lichtwer Pharma GmbH, West Berlin, Germany). Kwai (*garlic* powder) was also used in the other two trials (Auer et al. 1990; Kandziora 1988).

Among the included trials, one trial applied a four-armed group design with groups receiving one, two or four capsules daily of aged *garlic* extract (240, 480, or 960 mg containing 0.6, 1.2, or 2.4 mg of *S*-allylcysteine) or a placebo group respectively (Ried et al. 2013). Another trial conducted by Sobenin et al. was also a four-armed group design with groups receiving time-released *garlic* powder tablets of two different doses (600 or 2400 mg/day), regular *garlic* pills (900 mg/day), or a placebo group respectively (Sobenin et al. 2009). Sample sizes ranged from 34 to 90. The duration of treatment ranged from 8 to 12 weeks.

Methodological quality of included trials

All of the included studies were randomized, placebo-controlled trials. The methodological quality of the included studies was assessed by the Cochrane's risks of bias tool. Although randomization was declared in all studies, only four trials reported how the randomization was conducted (Nakasone et al. 2013; Ried et al. 2010, 2013; Sobenin et al. 2009), and allocation concealment was mentioned in 3 trials (Nakasone et al. 2013; Ried et al. 2010, 2013). Four trials were double-blinded (Nakasone et al. 2013; Ried et al. 2010, 2013; Sobenin et al. 2009). Information on withdrawal/dropout and intention-to-treat analysis was declared in five trials (Han et al. 2011; Nakasone et al. 2013; Ried et al. 2010, 2013; Sobenin et al. 2009). The details of risk of biases of the included trials are listed in Table 2.

Outcome measures

Primary outcomes

The primary outcome measures were not reported in all of the trials.

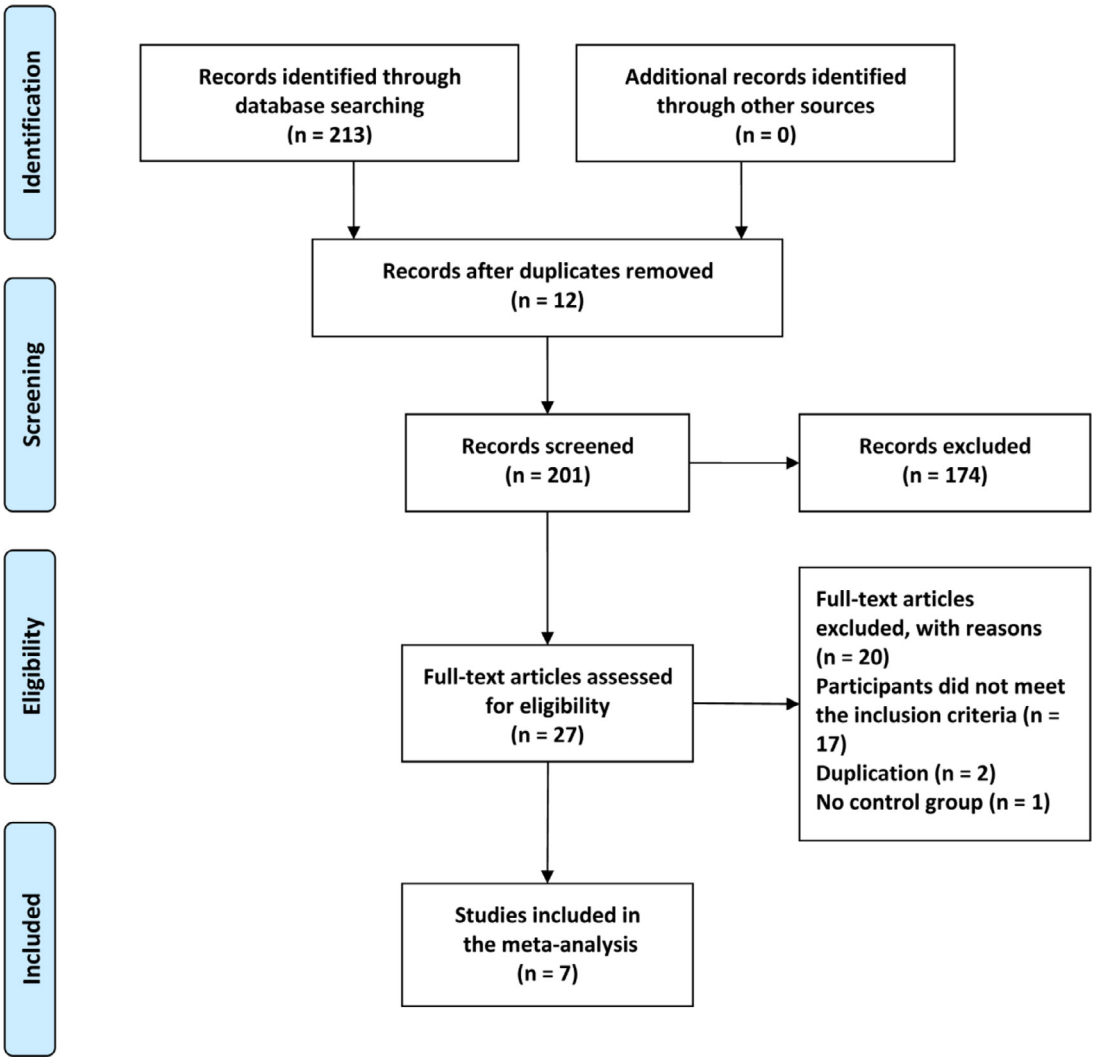

Fig. 1. Flow diagram of study selection and identification.

Secondary outcomes

All of the seven studies were RCTs that reported the BP-lowering effect of *garlic* preparations. Among them, one randomized, placebo-controlled, parallel trial conducted by Han et al. tested the efficacy of processed *garlic* capsules on lowering BP of 44 hypertensive subjects over a period of 8 weeks (Han et al. 2011). Processed *garlic* capsules significantly lowered SBP by an average of 8.77 mmHg after only 2 weeks ($P < 0.01$) and an average of 8.05 mmHg after 8 weeks ($P < 0.01$). In addition, participants exhibited significant reduction in DBP by an average of 4.14 mmHg after treatment ($P < 0.05$). In the placebo group, average reductions of 3.78 mmHg and 4.54 mmHg were also found on SBP ($P > 0.05$) and DBP ($P < 0.05$), respectively. The trial concluded that consuming 1000 mg of processed *garlic* capsules for 8 weeks can significantly lower BP in hypertensive subjects. However, a comparison between groups was not conducted. Furthermore, the standard deviation of BP in placebo group was not reported at the end of treatment.

Another randomized, double-blind, placebo-controlled trial compared the hypotensive action of time-released *garlic* powder tablets and regular *garlic* pills with a placebo in 84 men with mild or moderate arterial hypertension (Sobenin et al. 2009). A significant BP reduction by time-released *garlic* powder tablets (7.0 mmHg of SBP and 3.8 mmHg of DBP) was observed when compared to the placebo after the 8-week treatment ($P < 0.05$). However, detailed information about BP in the placebo group was not reported.

Auer et al. enrolled 47 non-hospitalized patients with mild hypertension to receive either *garlic* powder (600 mg/day) or a matching placebo for 12 weeks (Auer et al. 1990). After treatment, the *garlic* powder significantly lowered supine SBP (from an average of 171 to 152 mmHg), supine DBP (from an average of 102 to 89 mmHg), standing SBP (from an average of 171 to 150 mmHg), standing DBP (from an average of 101 to 90 mmHg), total cholesterol (from an average of 268 to 230 mg/dl), and triglycerides (from an average of 171 to 140 mg/dl). In the placebo group, there were no significant changes on supine SBP (from an average of 161 to 153 mmHg), supine DBP (from an average of 97 to 93 mmHg), standing SBP (from an average of 163 to 153 mmHg), standing DBP (from an average of 94 to 90 mmHg), total cholesterol, or triglycerides (from an average of 200 to 187 mg/dl). The trial suggested a significant BP- and plasma lipids lowering effect of *garlic* powder compared to placebo. However, no detailed information about the standard deviation of SBP and DBP was provided in the placebo group.

The fourth trial, conducted by Kandziora in 1988, included 40 hypertensive patients who were randomized to receive either *garlic* powder (600 mg/day) plus the diuretic group or a matching placebo plus the diuretic group. After 12 weeks, the group consuming *garlic*

Table 1
Basic characteristics of the included studies.

References	Sample size (randomized/analyzed) M/F	Age (years)	Diagnosis standard	Intervention	Control	Treatment duration	Main outcomes	Adverse effects report	Main findings from original study
Nakasone et al. (2013)	Prehypertension 34/32 T: 15 C: 17 Hypertension 47/40 T: 19 C: 21 F/M: NR	Prehypertension T: 53.0 ± 12.0 C: 47.0 ± 16.0 Hypertension T: 54.0 ± 8.0 C: 53.0 ± 9.0	JSHGMH 2004	Dried *garlic* homogenate (300 mg/day)	Placebo	12 weeks	Prehypertension: (1) SBP: $P > 0.05$ (2) DBP: $P > 0.05$ Hypertension: (1) SBP: $P < 0.05$ (2) DBP: $P < 0.05$	Y	*Garlic* homogenate diet was well tolerated, and had a clinically relevant hypotensive effect in adults with mild hypertension, but not in those with prehypertension
Ried et al. (2010)	50/46 T: 23 C: 23 F/M: NR	T: 66.0 ± 9.0 C: 66.0 ± 9.0	NR	Aged *garlic* extract (960 mg/day) + AD	Placebo + AD	12 weeks	SBP and DBP: $P > 0.05$	Y	Aged *garlic* extract is superior to placebo in lowering SBP similarly to current first line medications in patients with treated but uncontrolled hypertension
Ried et al. (2013)	84/79 T1: 12/9 T2: 12/8 T3: 9/10 C: 9/10	T1: 70.1 ± 12.4 T2: 67.5 ± 11.8 T3: 70.4 ± 13.1 C: 71.5 ± 10.9	NR	T1: aged *garlic* extract (240 mg/day) + AD T2: aged *garlic* extract (480 mg/day) + AD T3: aged *garlic* extract (960 mg/day) + AD	Placebo + AD	12 weeks	(1) SBP T1 VS C: $P > 0.05$ T2 VS C: $P < 0.01$ T3 VS C: $P < 0.05$ (2) DBP T1 VS C: $P > 0.05$ T2 VS C: $P > 0.05$ T3 VS C: $P > 0.05$	Y	It suggests aged *garlic* extract to be an effective and tolerable treatment in uncontrolled hypertension, and may be considered as a safe adjunct treatment to conventional antihypertensive therapy.
Han, et al. 2011	46/44 T: 16/6 C: 17/5	20-60 T/C: NR	NR	Processed *garlic* capsule (1000 mg/day)	Placebo	8 weeks	(1) SBP T: significantly reduced ($P < 0.01$) C: NSD T VS C: NR (2) DBP T: significantly reduced ($P < 0.05$) C: significantly reduced ($P < 0.05$) T VS C: NR	N	Daily consumption of processed *garlic* produces a statistically significant reduction in SBP that can be sustained for 8 weeks
Sobenin et al. (2009)	90/84 T1: 30 T2: 18 T3: 16 C: 20 F/M: NR	T1: 51.5 ± 2.1 T2: 50.9 ± 2.4 T3: 52.2 ± 2.5 C: 52.7 ± 2.5	NR	T1: time-released *garlic* powder tablets (600 mg/day) T2: time-released *garlic* powder tablets (2400 mg/day) T3: regular *garlic* pills (Kwai) (900 mg/day)	Placebo	8 weeks	(1) SBP T1 VS C: $P < 0.001$ T2 VS C: $P < 0.001$ T3 VS C: $P < 0.05$ T1 VS T2, T1 VS T3, and T2 VS T3: $P > 0.05$ (2) DBP T1 VS C: $P < 0.001$ T2 VS C: $P < 0.001$ T3 VS C: $P > 0.05$ T1 VS T2: $P > 0.05$	Y	It showed that time-released *garlic* powder tablets are more effective for the treatment of mild and moderate arterial hypertension than regular *garlic* supplements

(*continued on next page*)

Table 1 (*continued*)

References	Sample size (randomized/analyzed) M/F	Age (years)	Diagnosis standard	Intervention	Control	Treatment duration	Main outcomes	Adverse effects report	Main findings from original study
Auer et al. (1990)	47/47 T: 11/13 C: 10/13	T: 58.0 ± 7.0 C: 57.0 ± 6.0	NR	*Garlic* powder (Kwai) (600 mg/day)	Placebo	12 weeks	(1) SBP T: supine and standing SBP (significantly reduced, $P < 0.05$) C: supine and standing SBP (NSD) T VS C: NR (2) DBP T: supine and standing DBP (significantly reduced, $P < 0.01$) C: supine and standing DBP (NSD) T VS C: NR	Y	*Garlic* powder significantly lowered BP and plasma lipids after 12 weeks treatment. However, no significant change occurred in the placebo group
Kandziora (1988)	40/40 T: 20 C: 20 F/M: NR	NR	NR	*Garlic* powder (Kwai) (600 mg/day) + diuretic	Placebo + diuretic	12 weeks	(1) SBP T: supine and standing SBP (significantly reduced, $P < 0.05$) C: supine and standing SBP (NSD) T VS C: NR (2) DBP T: supine and standing DBP (significantly reduced, $P < 0.05$) C: supine and standing DBP (NSD) T VS C: NR	N	*Garlic* powder in combination with hydrochlorothiazide-triamterene generated a 10–11 mmHg reduction in SBP and a 6–8 mmHg reduction in DBP compared to placebo

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; AD, antihypertensive drugs (ACEI, ARB, CCB, BB, or diuretics); ARB, angiotensin II receptor antagonists; BB, beta-blockers; BP, blood pressure; C, control group; CCB, calcium channel blockers; DBP, diastolic blood pressure; F, female; JSHGMH 2004, Japanese Society of Hypertension guidelines for the management of hypertension 2004; M, male; N, no; NR, not reported; SBP, systolic blood pressure; T, treatment group; VS, *versus*; Y, yes.

(a) SBP and (b) DBP

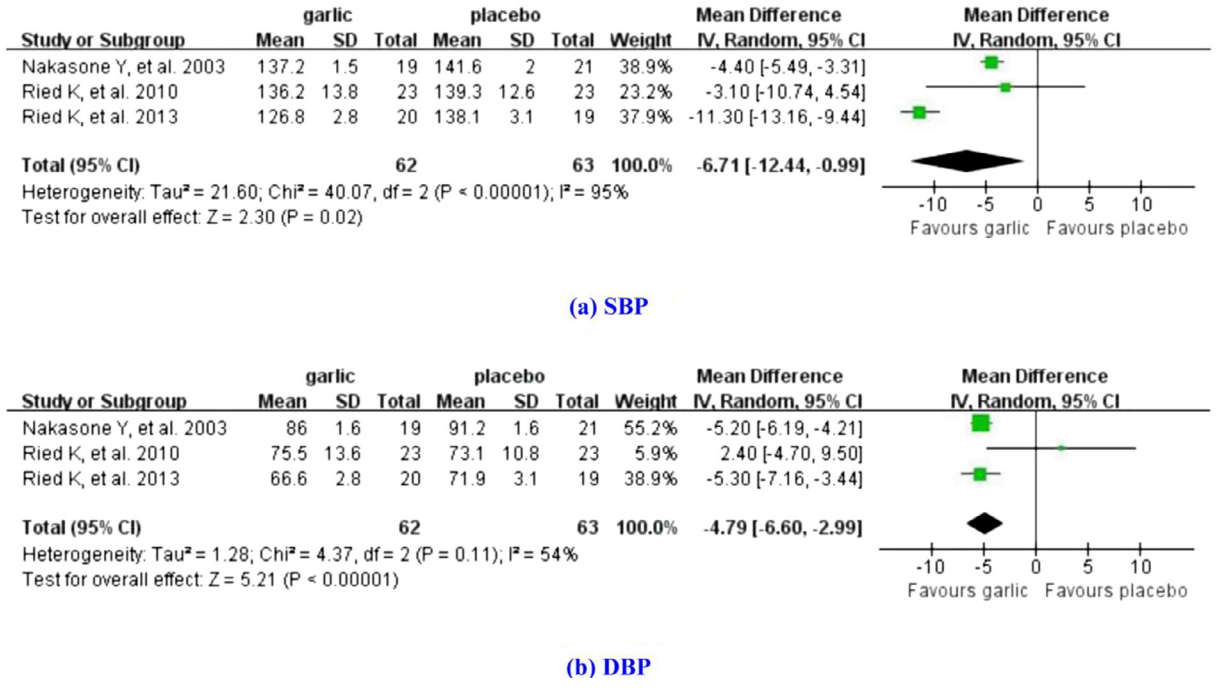

Fig. 2. Forest plot of comparison of *garlic vs.* the placebo for the outcome of BP. (a) SBP and (b) DBP.

Table 2
Methodological quality of the included studies.

References	A	B	C	D	E	F	G
Nakasone et al. (2003)	+	+	+	+	+	+	+
Ried et al. (2010)	+	+	+	+	+	+	+
Ried et al. (2013)	+	+	+	+	+	+	+
Han et al. (2011)	?	?	?	?	+	?	?
Sobenin et al. (2009)	+	?	+	+	+	+	+
Auer et al. (1990)	?	?	?	?	?	?	–
Kandziora (1988)	?	?	?	?	?	?	?

Abbreviations: A, adequate sequence generation; B, concealment of allocation; C, blinding (participants and personnel); D, blinding (assessor); E, incomplete outcome data addressed (ITT analysis); F, free of selective reporting; G, other potential threat to validity; +, low risk; –, high risk; ?, unclear.

plus the diuretic showed a statistically significant reduction in supine SBP (from an average of 178 to 162 mmHg), supine DBP (from an average of 100 to 85 mmHg), standing SBP (from an average of 174 to 158 mmHg), and standing DBP (from an average of 99 to 83 mmHg). In the placebo plus diuretic group, no significant reduction on supine SBP (from an average of 178 to 173 mmHg), supine DBP (from an average of 100 to 91 mmHg), standing SBP (from an average of 175 to 169 mmHg), or standing DBP (from an average of 98 to 90 mmHg) were observed. However, as the number of hypertensive patients randomized into each treatment group was unclear in the original paper, the data were not used in our analysis. The original author was contacted for the missing data by email, however, the data were not available.

Therefore, BP data from the remaining three trials could be included in the meta-analysis (Nakasone et al. 2013; Ried et al. 2010, 2013). Among them, one randomized, placebo-controlled, dose-response trial conducted by Ried et al. adopted three treatment groups; however, only the aged *garlic* extract (480 mg) group was included in our analysis because it demonstrated a significant reduction in BP when compared to the other three groups (Ried et al. 2013). There were 62 patients in the *garlic* preparation group and 63 in the placebo group. Because a statistically significant heterogeneity was identified, a random effect was used in this review. Compared with the placebo, this meta-analysis revealed a significant lowering effect of *garlic* preparation on both SBP (WMD: −6.71 mmHg; 95% CI: −12.44 to −0.99; $P = 0.02$) and DBP (WMD: −4.79 mmHg; 95% CI: −6.60 to −2.99; $P < 0.00001$) (Fig. 2).

Adverse events

Symptoms and signs of AEs from *garlic* preparations were reported in five trials (Auer et al. 1990; Nakasone et al. 2013; Ried et al. 2010, 2013; Sobenin et al. 2009). Two trials demonstrated no AEs of *garlic* preparations (Auer et al. 1990; Sobenin et al. 2009). In the remaining three trials, the nine most frequently reported AEs were gastric distress, belching, reflux, flatulence, constipation, diarrhea, headache, *garlic* taste, and difficulty swallowing the capsules (Nakasone et al. 2013; Ried et al. 2010, 2013). Among them, the most commonly reported AE or complaint associated with the *garlic* therapy was gastrointestinal discomforts. Taking *garlic* preparations in the morning rather than evening, taking the *garlic* with food, sucking on mints, and splitting the daily dosage could alleviate the AEs. All of the reported AEs were not severe and well-tolerated. Meta-analysis showed that there was no significant difference in the frequency of AEs between *garlic* preparations and placebo (RR: 1.64; 95% CI, 0.82 to 3.28; $P = 0.16$) (Fig. 3).

Publication bias

Because the number of included trials was less than 10, we could not perform any meaningful analysis for publication bias.

Discussion

Summary of evidence

Hypertension is an important risk factor of morbidity and mortality worldwide. A major concern is that the treatment of hypertension in a large number of hypertensive patients is unsatisfactory, and compliance with antihypertensive agents is usually poor

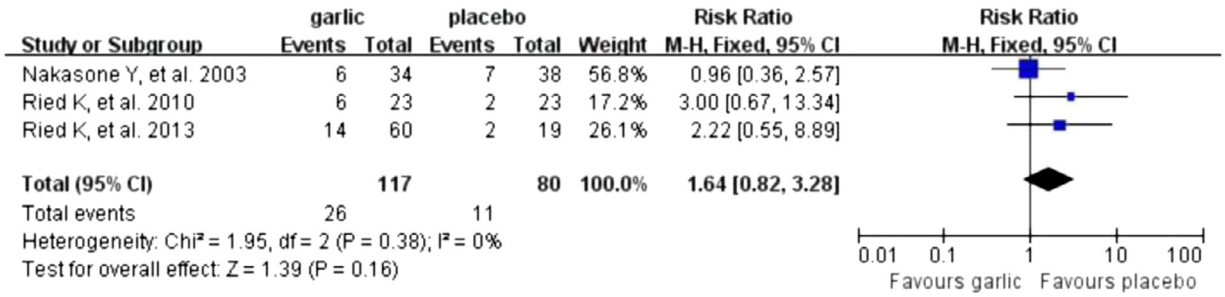

Fig. 3. Forest plot of the reported adverse effects.

(James et al. 2014; Mancia et al. 2013; Xiong et al. 2013b). Therefore, CAM approaches are widely utilized by patients with hypertension (Osamor and Owumi 2010; Xiong et al. 2014a). Currently, CAM approaches that have been supported by clinical studies and meta-analyses for BP-lowering and symptom-improving effects include yoga (Blom et al. 2014), tai chi (Wang et al. 2013b), qigong (Xiong et al. 2015), acupuncture (Flachskampf et al. 2007), moxibustion (Xiong et al. 2014d), massage (Xiong et al. 2014b), and natural herbal products (Wang et al. 2013a; Xiong et al. 2014c).

How about the role of *garlic* in the treatment of hypertension? We aimed to provide the latest systematic review and meta-analysis to summarize the existing evidence of *garlic* as an antihypertensive agent. Unlike previous meta-analyses (Ackermann et al. 2001; Mahdaviroshan et al. 2014; McRae, 2005; Reinhart et al. 2008; Ried et al. 2008; Silagy and Neil 1994; Simons et al. 2009; Stabler et al. 2012; Yan and Fan 2011), this article only focused on patients with hypertension, while normotensive subjects were excluded.

In this meta-analysis, we included seven randomized, placebo-controlled trials. Although no conclusion could be made about *garlic* for the primary outcomes, mortality or cardiovascular events, our results demonstrated that *garlic* has a statistically significant and clinically meaningful effect on SBP (decreased by 6.71 mmHg) and DBP (decreased by 4.79 mmHg) compared to the placebo. A recent meta-analysis of 147 randomized trials totaling 958,000 people revealed that a reduction of SBP by 10 mmHg or DBP by 5 mmHg by any of the main classes of antihypertensive drugs reduces CHD events (fatal and non-fatal) by about a quarter and stroke by about a third, regardless of the presence of vascular disease and of BP before treatment and with no increase in non-vascular mortality (Law et al. 2009). Therefore, great economical and clinical benefit could be achieved with the significant BP-lowering effect of *garlic*. Importantly, the treatment duration of the included studies ranged from 8 to 12 weeks, and the maximum BP-lowering effects had been exerted at the end of the treatment. Finally, use of *garlic* seemed safe and well-tolerated by hypertensive patients. Collectively, these findings suggest that *garlic* represents an effective and safe modality for treating hypertension.

Limitations

Before recommending the findings of this review to clinicians, a number of potential limitations should be considered. First, some important primary endpoints have not been reported, such as morbidity and mortality with long-term follow-up. Second, there was insufficient reporting of the methodology in some of the included trials, thereby preventing us to comment on the quality of the methods. Third, the main limitation of our review is the heterogeneity of the clinical assessment due to variations in participants as well as the vastly different *garlic* preparations. As described in the "Trials characteristics" section, six different *garlic*-based preparations were evaluated in these seven included trials of this review. Not all of these included *garlic* preparations were assumed to be identical in the composition and biological activity they possessed. All of them were manufactured in five different regions, including Japan, Australia, Taiwan, Russia and Germany. What's more, the chemical compositions of the 6 included *garlic*-based preparations were also different, which might lead to the discrepancies in the BP-lowering effect. Additionally, these discrepancies in chemical composition and pharmacological effects of various *garlic* preparations may be due to several other factors, including a lack of consistency among studies in relation to growth environment, storage environment, manufacturing process, dosage, standardization of *garlic* preparations, and treatment duration. Therefore, all of these deficiencies have weakened the clinical evidence of *garlic* preparations for hypertension. Future trials should place more emphasis to the selection of standard *garlic* preparations and reporting of trials according to the CONSORT Statement (Gagnier et al. 2006; Moher et al. 2010).

Conclusion

The present meta-analysis suggests that *garlic* is an effective and safe approach for the management of hypertension, which may be an alternative therapy in patients with a history of AEs related to antihypertensive drugs. However, evidence suggesting that *garlic* is an effective modality for treating hypertension remains insufficient and limited. Further insights into this topic are needed; more randomized, double-blinded, placebo-controlled trials implementing a comprehensive reporting of primary endpoints with long-term follow-up will provide stronger evidence of the *garlic* for hypertension.

Conflict of interests

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phymed.2014.12.013.

References

Ackermann, R.T., Mulrow, C.D., Ramirez, G., Gardner, C.D., Morbidoni, L., Lawrence, V.A., 2001. Garlic shows promise for improving some cardiovascular risk factors. Arch. Intern. Med. 161 (6), 813–824.

Al-Qattan, K.K., Khan, I., Alnaqeeb, M.A., Ali, M., 2001. Thromboxane-B2, prostaglandin-E2 and hypertension in the rat 2-kidney 1-clip model: a possible mechanism of the garlic induced hypotension. Prostag. Leukotr. Ess. 64 (1), 5–10.

Al-Qattan, K.K., Thomson, M., Al-Mutawa'a, S., Al-Hajeri, D., Drobiova, H., Ali, M., 2006. Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. J. Nutr. 136 (3s), 774s–776s.

Al-Wafi, H.A.M., Al-Fartos, A.J.M., 2010. Effect of garlic (*Allium sativum*) on blood pressure in patient volunteers. J. Basrah. Res. 36, 80–84.

Asdaqa, S.M., Inamdarb, M.N., 2010. Potential of *garlic* and its active constituent, S-allyl cysteine, as antihypertensive and cardioprotective in presence of captopril. Phytomedicine. 17 (13), 1016–1026.

Auer, W., Eiber, A., Hertkorn, E., Hoehfeld, E., Koehrle, U., Lorenz, A., Mader, F., Merx, W., Otto, G., Schmid-Otto, B., Taubenheim, H., 1990. Hypertension and hyperlipidaemia: garlic helps in mild cases. Br. J. Clin. Pract. 69 (Suppl.), 3–6.

Bangalore, S., Kumar, S., Kjeldsen, S.E., Makani, H., Grossman, E., Wetterslev, J., Gupta, A.K., Sever, P.S., Gluud, C., Messerli, F.H., 2011. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. Lancet Oncol. 12 (1), 65–82.

Blom, K., Baker, B., How, M., Dai, M., Irvine, J., Abbey, S., et al., 2014. Hypertension analysis of stress reduction using mindfulness meditation and yoga: results from the harmony randomized controlled trial. Am. J. Hypertens. 27 (1), 122–129.

Brook, R.D., Appel, L.J., Rubenfire, M., Ogedegbe, G., Bisognano, J.D., Elliott, W.J., Fuchs, F.D., Hughes, J.W., Lackland, D.T., Staffileno, B.A., Townsend, R.R., Rajagopalan, S., American Heart Association Professional Education Committee of the Council for High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity, 2013. Beyond medications and diet: alternative approaches to lowering blood pressure. Hypertension 61 (6), 1360–1383.

Campbell, J.H., Efendy, J.L., Smith, N.J., Campbell, G.R., 2001. Molecular basis by which *garlic* suppresses atherosclerosis. J. Nutr. 131 (3s), 1006s–1009s.

Capraz, M., Dilek, M., Akpolat, T., 2007. Garlic, hypertension and patient education. Int. J. Cardiol. 121 (1), 130–131.

Castro, C., Lorenzo, G.A., González, A., Cruzado, M., 2010. Garlic components inhibit angiotensin II-induced cell-cycle progression and migration: involvement of cell-cycle inhibitor $p27^{Kip1}$ and mitogen-activated protein kinase. Mol. Nutr. Food. Res. 54 (6), 781–787.

De Santos, A.O.S., Grunwald, J., 1993. Effect of garlic powder tablets on blood lipids, blood pressure and well being: a placebo controlled double-blind study. Br. J. Clin. Res. 4, 37–44.

Dhawan, V., Jain, S., 2005. Garlic supplementation prevents oxidative DNA damage in essential hypertension. Mol. Cell. Biochem. 275 (1–2), 85–94.

Duda, G., Sulibursk a, J., Pupek-Musialik, D., 2008. Effects of short-term garlic supplementation on lipid metabolism and antioxidant status in hypertensive adults. Pharmacol. Rep. 60 (2), 163–170.

Durak, I., Kavutcu, M., Aytaç, B., Avci, A., Devrim, E., Ozbek, H., Oztürk, H.S., 2004. Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. J. Nutr. Biochem. 15 (6), 373–377.

Estrada, C.A., Young, M.J., 1993. Patient preferences for novel therapy: an N-of-1 trial of garlic in the treatment for hypertension. J. Gen. Intern. Med. 8 (11), 619–621.

Flachskampf, F.A., Gallasch, J., Gefeller, O., Gan, J.X., Mao, J.T., Pfahlberg, A.B., et al., 2007. Randomized trial of acupuncture to lower blood pressure. Circulation 115 (24), 3121–3129.

Frieden, T.R., Coleman, S.M., Wright, J.S., 2014. Protocol-based treatment of hypertension: a critical step on the pathway to progress. J. Am. Med. Assoc. 311 (1), 21–22.

Gagnier, J.J., Boon, H., Rochon, P., Moher, D., Barnes, J., Bombardier, C., 2006. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Arch. Intern. Med. 144 (5), 364–367.

Go, A.S., Mozaffarian, D., Roger, V.L., Benjamin, E.J., Berry, J.D., Borden, W.B., Bravata, D.M., Dai, S., Ford, E.S., Fox, C.S., Franco, S., Fullerton, H.J., Gillespie, C., Hailpern, S.M., Heit, J.A., Howard, V.J., Huffman, M.D., Kissela, B.M., Kittner, S.J., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Magid, D., Marcus, G.M., Marelli, A., Matchar, D.B., McGuire, D.K., Mohler, E.R., Moy, C.S., Mussolino, M.E., Nichol, G., Paynter, N.P., Schreiner, P.J., Sorlie, P.D., Stein, J., Turan, T.N., Virani, S.S., Wong, N.D., Woo, D., Turner, M.B., American Heart Association Statistics Committee and Stroke Statistics Subcommittee, 2013. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 127 (1), e6–e245.

Guo, F., He, D., Zhang, W., Walton, R.G., 2012. Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010. J. Am. Coll. Cardiol. 60 (7), 599–606.

Han, C.H., Liu, J.C., Chen, K.H., Lin, Y.S., Chen, C.T., Fan, C.T., Lee, H.L., Liu, D.Z., Hou, W.C., 2011. Antihypertensive activities of processed garlic on spontaneously hypertensive rats and hypertensive humans. Bot. Stud. 52, 277–283.

Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., Cochrane Bias Methods Group, Cochrane Statistical Methods Group, 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br. Med. J. 343, d5928.

Higgins, J.P.T., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration. http://handbook.cochrane.org/.

Holzgartner, H., Schmidt, U., Kuhn, U., 1992. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. Arzneimittelforschung 42, 1473–1477.

Isaacsohn, J.L., Moser, M., Stein, E.A., Dudley, K., Davey, J.A., Liskov, E., Black, H.R., 1998. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch. Intern. Med. 158 (11), 1189–1194.

Jaffe, M.G., Lee, G.A., Young, J.D., Sidney, S., Go, A.S., 2013. Improved blood pressure control associated with a large-scale hypertension program. J. Am. Med. Assoc. 310 (7), 699–705.

Jain, A.K., Vargas, R., Gotzkowsky, S., McMahon, F.G., 1993. Can garlic reduce levels of serum lipids? A controlled clinical study. Am. J. Med. 94 (6), 632–635.

James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., Dennison-Himmelfarb, C., Handler, J., Lackland, D.T., LeFevre, M.L., MacKenzie, T.D., Ogedegbe, O., Smith, S.C., Svetkey, L.P., Taler, S.J., Townsend, R.R., Wright, J.T., Narva, A.S., Ortiz, E., 2014. Evidence-based guideline for the management of high blood pressure in adults report from the panel members appointed to the Eighth Joint National Committee (JNC 8). J. Am. Med. Assoc. 311 (5), 507–520.

Kandziora, J., 1988. The blood pressure lowering and lipid lowering effect of a garlic preparation in combination with a diuretic. Arztl. Forsch. 35, 1–8.

Law, M.R., Morris, J.K., Wald, N.J., 2009. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Br. Med. J. 338, b1665.

Macan, H., Uykimpang, R., Alconcel, M., Takasu, J., Razon, R., Amagase, H., Niihara, Y., 2006. Aged garlic extract may be safe for patients on warfarin therapy. J. Nutr. 136 (s3), s793–s795.

Mahdaviroshan, M., Nasrollahzadeh, J., Khodadadi, E., 2014. Effects of garlic supplementation on blood pressure. J. Paramedical. Sci. 5, 92–98.

Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Böhm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D.E., Jaarsma, T., Kirchhof, P., Kjeldsen, S.E., Laurent, S., Manolis, A.J., Nilsson, P.M., Ruilope, L.M., Schmieder, R.E., Sirnes, P.A., Sleight, P., Viigimaa, M., Waeber, B., Zannad, F., Redon, J., Dominiczak, A., Narkiewicz, K., Nilsson, P.M., Burnier, M., Viigimaa, M., Ambrosioni, E., Caufield, M., Coca, A., Olsen, M.H., Schmieder, R.E., Tsioufis, C., Borne, P., Zamorano, J.L., Achenbach, S., Baumgartner, H., Bax, J.J., Bueno, H., Dean, V., Deaton, C., Erol, C., Fagard, R., Ferrari, R., Hasdai, D., Hoes, A.W., Kirchhof, P., Knuuti, J., Kolh, P., Lancellotti, P., Linhart, A., Nihoyannopoulos, P., Piepoli, M.F., Ponikowski, P., Sirnes, P.A., Tamargo, J.L., Tendera, M., Torbicki, A., Wijns, W., Windecker, S., Clement, D.L., Coca, A., Gillebert, T.C., Tendera, M., Rosei, E.A., Ambrosioni, E., Anker, S.D., Bauersachs, J., Hitij, J.B., Caulfield, M., De Buyzere, M., De Geest, S., Derumeaux, G.A., Erdine, S., Farsang, C., Funck-Brentano, C., Gerc, V., Germano, G., Gielen, S., Haller, H., Hoes, A.W., Jordan, J., Kahan, T., Komajda, M., Lovic, D., Mahrholdt, H., Olsen, M.H., Ostergren, J., Parati, G., Perk, J., Polonia, J., Popescu, B.A., Reiner, Z., Rydén, L., Sirenko, Y., Stanton, A., Struijker-Boudier, H., Tsioufis, C., Borne, P., Vlachopoulos, C., Volpe, M., Wood, D.A., 2013. ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur. Heart J. 34 (28), 2159–2219.

McMahon, F.G., Vargas, R., 1993. Can garlic lower blood pressure? A pilot study. Pharmacotherapy 13 (4), 406–407.

McRae, M.P., 2005. A review of studies of garlic (*Allium sativum*) on serum lipids and blood pressure before and after 1994: does the amount of allicin released from garlic powder tablets play a role?. J. Chiropr. Med. 4 (4), 182–190.

Mendis, S., 1988. Garlic oil in mild and moderate hypertension. Pak. Heart J. 21, 26–28.

Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gøtzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M., Altman, D.G., Consolidated Standards of Reporting Trials Group, 2010. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trial. J. Clin. Epidemiol. 63 (8), 1–37.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann. Intern. Med. 151 (4), 264–269.

Nakasone, Y., Nakamuray, Y., Yamamoto, T., Yamaguchi, H., 2013. Effect of a traditional Japanese garlic preparation on blood pressure in prehypertensive and mildly hypertensive adults. Exp. Ther. Med. 5 (2), 399–405.

Osamor, P.E., Owumi, B.E., 2010. Complementary and alternative medicine in the management of hypertension in an urban Nigerian community. BMC Complement. Altern. Med. 10 (e36), 1–9.

Pittler, M.H., Ernst, E., 2007. Clinical effectiveness of garlic (*Allium sativum*). Mol. Nutr. Food Res. 51 (11), 1382–1385.

Qidwai, W., Ashfaq, T., 2013. Role of garlic usage in cardiovascular disease prevention: an evidence-based approach. Evid. Based Complement. Alternat. Med 2013, e125649 1–9.

Rahman, K., 2001. Historical perspective on garlic and cardiovascular disease. J. Nutr. 131 (3s), 977s–979s.

Reinhart, K.M., Coleman, C.I., Teevan, C., Vachhani, P., White, C.M., 2008. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. Ann. Pharmacother. 42 (12), 1766–1771.

Ried, K., Frank, O.R., Stocks, N.P., 2010. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. Maturitas 67 (2), 144–150.

Ried, K., Frank, O.R., Stocks, N.P., 2013. Aged garlic extract reduces blood pressure in hypertensives: a dose–response trial. Eur. J. Clin. Nutr. 67 (1), 64–70.

Ried, K., Frank, O.R., Stocks, N.P., Fakler, P., Sullivan, T., 2008. Effect of garlic on blood pressure: a systematic review and meta-analysis. BMC Cardiovasc. Disord. 8, 13.

Sharifi, A.M., Darabi, R., Akbarloo, N., 2003. Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rat. J. Ethnopharmacol. 86 (2–3), 219–224.

Silagy, C.A., Neil, H.A., 1994. A meta-analysis of the effect of garlic on blood pressure. J. Hypertens. 12 (4), 463–468.

Simons, L.A., Balasubramanian, S., Konigsmark, M., Parfitt, A., Simons, J., Peters, W., 1995. On the effects of garlic on plasma lipids and lipoproteins in mild hypercholesterolemia. Atherosclerosis 113 (2), 219–225.

Simons, S., Wollersheim, H., Thien, T., 2009. A systematic review on the influence of trial quality on the effect of garlic on blood pressure. Neth. J. Med. 67 (6), 212–219.

Sobenin, I.A., Andrianova, I.V., Fomchenkov, I.V., Gorchakova, T.V., Orekhov, A.N., 2009. Time-released garlic powder tablets lower systolic and diastolic blood pressure in men with mild and moderate arterial hypertension. Hypertens. Res. 32 (6), 433–437.

Stabler, S.N., Tejani, A.M., Huynh, F., Fowkes, C., 2012. Garlic for the prevention of cardiovascular morbidity and mortality in hypertensive patients. Cochrane Database Syst. Rev. 8, CD007653.

Steiner, M., Li, W., 2001. Aged garlic extract, a modulator of cardiovascular risk factors: a dose-finding study on the effects of AGE on platelet functions. J. Nutr. 131 (3s), 980s–984s.

Stevinson, C., Pittler, M.H., Ernst, E., 2000. Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials. Arch. Intern. Med. 133 (6), 420–429.
Tachjian, A., Maria, V., Jahangir, A., 2010. Use of herbal products and potential interactions in patients with cardiovascular diseases. J. Am. Coll. Cardiol. 55 (6), 515–525.
Turner, B., Mølgaard, C., Marckmann, P., 2004. Effect of garlic (*Allium sativum*) powder tablets on serum lipids, blood pressure and arterial stiffness in normo-lipidaemic volunteers: a randomised, double-blind, placebo-controlled trial. Br. J. Nutr. 92 (4), 701–706.
Vogel, J.H., Bolling, S.F., Costello, R.B., Guarneri, E.M., Krucoff, M.W., Longhurst, J.C., Olshansky, B., Pelletier, K.R., Tracy, C.M., Vogel, R.A., Abrams, J., Anderson, J.L., Bates, E.R., Brodie, B.R., Grines, C.L., Danias, P.G., Gregoratos, G., Hlatky, M.A., Hochman, J.S., Kaul, S., Lichtenberg, R.C., Lindner, J.R., O'Rourke, R.A., Pohost, G.M., Schofield, R.S., Shubrooks, S.J., Tracy, C.M., Winters, W.L., American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine), 2005. Integrating complementary medicine into cardiovascular medicine. J. Am. Coll. Cardiol. 46 (1), 184–221.
Vorberg, G., Schneider, B., 1990. Therapy with garlic: results of a placebo-controlled, double-blind study. Br. J. Clin. Pract. 69, 7–11.
Wang, A., Manson, J.E., 2013. Hypertension: do calcium-channel blockers increase breast cancer risk?. Nat. Rev. Cardiol. 10 (11), 621–622.
Wang, J., Feng, B., Xiong, X.J., 2013. Chinese herbal medicine for the treatment of obesity-related hypertension. Evid. Based Complement. Alternat. Med. 2013 (2013), e757540 1–11.
Wang, J., Feng, B., Yang, X.C., Liu, W., Teng, F., Li, S., Xiong, X.J., 2013. Tai Chi for essential hypertension. Evid. Based Complement. Alternat. Med. 2013 (2013), e215254 1–10.
Wang, J., Xiong, X.J., 2012. Control strategy on hypertension in Chinese medicine. Evid. Based Complement. Alternat. Med. 2012 (2012), e284847 1–6.
Williams, M.J., Sutherland, W.H., McCormick, M.P., Yeoman, D.J., Jong, S.A., 2005. Aged garlic extract improves endothelial function in men with coronary artery disease. Phytother. Res. 19 (4), 314–319.
Wright, J.M., Musini, V.M., 2009. First-line drugs for hypertension. Cochrane Database Syst. Rev. 13 (3), CD001841.
Xiong, X.J., Borrelli, F., Ferreira, A.S., Ashfaq, T., Feng, B., 2014a. Herbal medicines for cardiovascular diseases. Evid. Based Complement. Alternat. Med. 2014 (2014), e809741 1–2.
Xiong, X.J., Li, S.J., Zhang, Y.Q., 2014b. Massage therapy for essential hypertension: a systematic review. J. Hum. Hypertens. doi:10.1038/jhh.2014.52.
Xiong, X.J., Liu, W., Yang, X.C., Feng, B., Zhang, Y.Q., Li, X.K., Wang, J., 2014c. *Ginkgo biloba* extract for essential hypertension: a systemic review. Phytomedicine 21 (10), 1131–1136.
Xiong, X.J., Liu, W., Yang, X.C., Feng, B., Wang, J., 2014d. Moxibustion for essential hypertension. Complement. Ther. Med. 22 (1), 187–195.
Xiong, X.J., Wang, P.Q., Li, X.K., Zhang, Y.Q., 2015. Qigong for hypertension: A systematic review. Medicine 94 (1), e352, 1–14.
Xiong, X.J., Yang, X.C., Liu, Y.M., Zhang, Y., Wang, P.Q., Wang, J., 2013a. Chinese herbal formulas for treating hypertension in traditional Chinese medicine: perspective of modern science. Hypertens. Res. 36 (7), 570–579.
Xiong, X.J., Yang, X.C., Liu, W., Chu, F.Y., Wang, P.Q., Wang, J., 2013b. Trends in the treatment of hypertension from the perspective of traditional Chinese medicine. Evid. Based Complement. Alternat. Med. 2013 (2013), e275279 1–13.
Yan, J.H., Fan, Z.J., 2011. Meta-analysis of the effect of garlic on blood pressure. Int. J. Cardiol. 152 (s1), s84–s85.
Yeh, G.Y., Davis, Rs.B., Phillips, R.S., 2006. Use of complementary therapies in patients with cardiovascular disease. Am. J. Cardiol. 98 (5), 673–680.
Zhang, X.H., Lowe, D., Giles, P., Fell, S., Board, A.R., Baughan, J.A., Connock, M.J., Maslin, D.J., 2001. A randomized trial of the effects of garlic oil upon coronary heart disease risk factors in trained male runners. Blood. Coagul. Fibrinol. 12 (1), 67–74.
Zimmermann, W., Zimmermann, B., 1990. Reduction in elevated blood lipids in hospitalised patients by a standardised garlic preparation. Br. J. Clin. Pract. 44 (s69), 20s–23s.