ORIGINAL ARTICLE

A Systematic Review and Metaanalysis on the Effects of Garlic Preparations on Blood Pressure in Individuals With Hypertension

Andres Rohner,[1] Karin Ried,[2] Igor A. Sobenin,[3] Heiner C. Bucher,[1] and Alain J. Nordmann[1]

BACKGROUND
Many patients prefer herbal medications to conventional drugs. Limited trial evidence suggests that garlic preparations reduce high blood pressure (BP).

METHODS
We searched electronic databases through March 2014 to identify all randomized controlled trials that compared a garlic preparation to placebo in hypertensive patients. Trials were required to report BP values at baseline and after a follow-up of at least 4 weeks.

RESULTS
Nine double-blind trials with 482 individuals fulfilled our inclusion criteria. Included trials were rather small, and the quality of the majority of included trials was moderate. Follow-up ranged from 8 to 26 weeks. All trials reported office BP measurements. Systolic BP and diastolic BP (SBP and DBP) were more effectively reduced in individuals treated with garlic preparations than in individuals treated with placebo. However, heterogeneity was high (weighted mean difference (WMD) for SBP was −9.1 mm Hg; 95% confidence interval (CI), −12.7 to −5.4; *P* for heterogeneity = 0.0006; and I^2 = 71%; WMD for BP was −3.8 mm Hg; 95% CI, −6.7 to −1.0; *P* for heterogeneity = 0.00001; I^2 = 80%). When analyses were restricted to higher-quality trials using intention-to-treat analysis or to trials with concealed treatment allocation and standardized and blinded BP measurement, effect sizes for SBP but not for DBP were lower and heterogeneity disappeared.

CONCLUSIONS
Although evidence from this review suggests that garlic preparations may lower BP in hypertensive individuals, the evidence is not strong. A well-conducted and powered trial of longer duration is needed to confirm these findings.

Keywords: blood pressure; garlic; hypertension; metaanalysis.

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Hypertension affects 1 in 3 adults worldwide[1] and contributes to 51% of deaths due to stroke and 45% of deaths due to coronary heart disease.[2]

Low adherence to antihypertensive medication is common and contributes to poor blood pressure (BP) control and adverse outcomes.[3] In the United States, more than 36% of adults treated for hypertension have uncontrolled BP.[4] Low patient adherence to antihypertensive medication is the most significant, modifiable, patient-related barrier to achieving controlled BP.[5]

Since dissatisfaction with conventional antihypertensive treatment is common, use of complementary and alternative treatment for hypertension is increasing.[6] Garlic preparations, as a possible form of complementary alternative medicine, are among the most popular forms of herbal supplements in the United States.[7] The 2002 US National Health Interview Survey showed that 421 of 10,525 (4%) persons with cardiovascular disease in the United States used garlic preparations.[8]

Garlic is claimed to have a moderate BP–reducing effect.[9] A recently published metaanalysis of 11 randomized controlled trials on the effect of garlic on BP concluded that garlic preparations are better than placebo in reducing BP.[10] However, only 4 of the 11 studies exclusively included individuals with hypertension and the metaanalysis did not systematically assess influence of trial quality on effect size.

In this metaanalysis, we included recently published trials to evaluate the effect of garlic on BP in individuals with hypertension and systematically assessed risk of bias.

METHODS

Information sources and search

We searched the electronic databases PubMed, Embase, Cochrane Library, and Web of Science using the search terms "garlic" and "blood pressure" or "hypertension" from their inception through March 2014. Our search was then restricted to articles indexed as randomized clinical trials (for details of the search strategy in PubMed, see Supplementary material). There was no language restriction. We also searched trial

Correspondence: Alain J. Nordmann (alain.nordmann@usb.ch).

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[1]Basel Institute for Clinical Epidemiology and Biostatistics, University of Basel, Switzerland; [2]National Institute of Integrative Medicine, Melbourne, Australia; [3]Russian Cardiology Research and Production Complex, Moscow, Russia.

registries of ongoing trials and contacted authors of identified trials to obtain additional data where necessary.

Study selection

To be eligible, a trial had to be a randomized controlled trial that compared a garlic preparation with placebo or care as usual and included hypertensive patients with baseline BP of systolic blood pressure (SBP) ≥140 mm HG, diastolic blood pressure (DBP) ≥90 mm Hg, or both, irrespective of treatment status. Trials were required to report BP values at baseline and after a follow-up of at least 4 weeks. Two reviewers (A.N., A.R.) independently screened the retrieved database files and the full text of potentially eligible studies for relevance. Disagreement was resolved by consensus.

Data collection and risk-of-bias assessment

Two reviewers independently abstracted data concerning baseline characteristics of included individuals; types and doses of garlic preparations used; presence or absence of antihypertensive treatment at baseline; potential co-interventions; and the number and methods of BP measurements, the patients' position during BP measurements, and the specified outcomes (see below). We assessed risk of bias for each included study at the level of selected outcomes suggested by the Cochrane Collaboration.[11]

Outcomes and data extraction

Two authors (A.N., A.R.) independently extracted published trial data and additional data provided by the original investigators. Our primary endpoints were the values of SBP and DBP at baseline and at the end of follow-up. In addition, we were interested in any clinical outcome data or records of adverse events, if available.

Statistical analysis

We used a random effects model (Review Manager 5.2, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to measure weighted mean differences (WMDs) in SBP and DBP from baseline until the end of follow-up.

In case standard deviations (SDs) for changes from baseline values were not available in all but 3 trials,[12–14] we calculated missing SDs by imputing values for a correlation coefficient of 0.5 in trials providing baseline and final SDs,[15–17] and conducted sensitivity analyses using the SD values calculated by imputing correlation coefficients of 0.7 and 1.0.[18] When information on SDs of changes of BP values between baseline and end of follow-up and for absolute BP values at the end of follow-up were missing, we imputed the median by use of an SD from the remaining trials.[19] We assessed potential publication bias by creating a funnel plot for the mean differences in SBP and DBP.[20] Heterogeneity among combined study results was assessed using the Cochran Q test and by the degree of inconsistency (I^2).[21] In order to explore potential heterogeneity and to check the robustness of the results, we conducted several prespecified subgroup and sensitivity analyses.

RESULTS

Nine trials with 577 patients fulfilled our inclusion criteria (Figure 1). In 1 additional trial, mean BP values of the 42 participants were normal at the time of study recruitment but slightly hypertensive after a run-in period and start of intervention.[22] Since it remained unclear whether these individuals were truly hypertensive or not, this trial's results were only included in an additional sensitivity analysis.

Four trials included treatment-naive individuals.[12,13,23,24] One trial included both treatment-naive as well as insufficiently controlled individuals taking antihypertensive drugs,[16] and 3 trials included treated hypertensive individuals with insufficiently controlled hypertension (≥140/90 mm Hg).[14,15,17] One trial did not report whether included individuals were treatment naive or insufficiently controlled with antihypertensive drugs.[25]

In 2 of the 9 included trials,[13,17] only a subgroup of included individuals had BP ≥140/90 mm Hg, leaving 482 subjects to be included in the metaanalysis. We included all individuals in the Holzgartner trial[16] since no separate BP values were reported for individuals with and without BP ≥140/90 mm Hg at baseline. Mean age of included individuals ranged from 50 to 70 years. One trial included men only.[12]

Six trials evaluated the effect of garlic preparations specifically in individuals with hypertension, 3 trials in individuals with dyslipidemia.[16,24,25] Six trials had a follow-up of 12 weeks, and the 3 other trials had follow-up periods of 8, 16, and 26 weeks, respectively.[12,24,25]

Characteristics of the included trials are summarized in Tables 1 and 2.

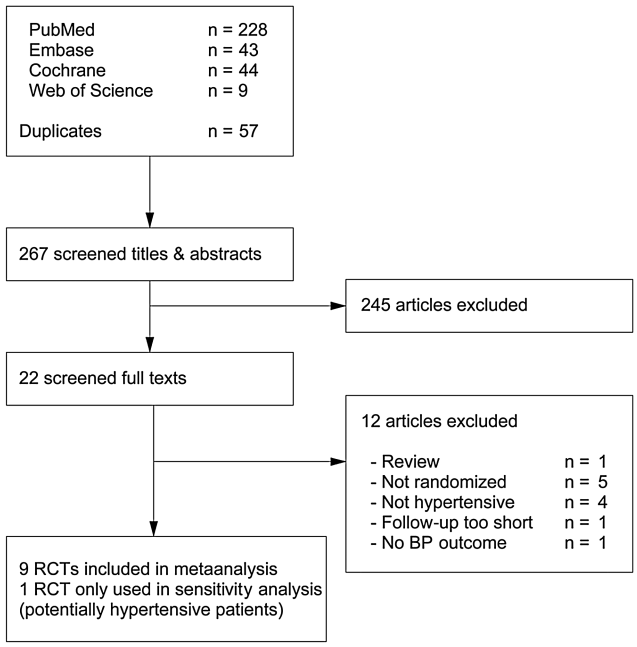


Figure 1. Trial flow. Abbreviations: BP, blood pressure; RCT, randomized controlled trial.

Table 1. Characteristics of included trials

Study (First Author, Year)	Inclusion criteria	Number of participants at baseline	Follow–up (w)	Average age (SD)	Proportion of males%	Number/proportion of patients with hypertension	Method of BP measurement	BP–medication at baseline	Co-intervention	Intervention: garlic preparations	Recruitment place
J. Kandziora, 1988	DBP–values between 95 and 104 mm Hg after 2 weeks under triamterene/ hydrochlorothiazide only	40	12	NM	NM	40; 100%	Place of BP measurement not described. Supine and standing after 0, 2, 4, 8, 12 weeks; 2 measurements every time	Triamteren/ hydrochlorothiazide, dose unknown	Triamteren/ hydrochlorothiazide	Triamterene/ hydorchlorothiazide and 600 mg *Kwai* vs. triamteren/ hydrochlorothiazide and placebo	NM
G. Vorberg, 1990	Values of serum cholesterol between 230 and 350 mg/dl	40	16	50 (NM)	42.5	Not reported	BP measurements at office. Supine and upright, before beginning, after washout and at 2, 4, 8, 12, 16 weeks after baseline	Unclear	None	900 mg of a garlic preparation vs. placebo	Patients in a general practice
W. Auer, 1990	DBP between 95 and 104 mm Hg on 2 control measurements, with 14 d between each	47	12	57.5 (6.5)	45	47; 100%	BP measurements at office. Supine and standing at −2, 0, 4, 8, 12 weeks	None	None	600 mg *Kwai* vs. placebo	11 general practice areas
H. Holzgartner, 1992	Primary type IIa, IIb, or IV hyperlipoproteinemia according to Frederickson	98	12	57 (11.8)	40.4	37; 38%	Place and method of BP measurement not described	Antihypertensive drugs, β-receptor blockers, Ca-antagonists	Step 1 diet	900 mg garlic powder *(Sapec/ Kwai)* vs.600 mg bezafibrate	NM
OS. De Santos, 1993	Total cholesterol >6.5 mmol/l	52	26	52 (NM)	38	Not reported	Place and method of BP measurements not described. Measured at baseline and monthly thereafter	None	Low-fat/low-cholesterol diet	900 mg of garlic powder vs. placebo	Single general practice
I. Sobenin, 2009	SBP 150–160, DBP 90–115 after 8 weeks placebo run in phase	90	8	52 (2.3)	100	90; 100%	Place of BP measurements not described. Morning BP, right and left arm, supine, sitting, standing every 4 weeks	Unclear	Low-salt diet, dietary and behavior recommendations	600 mg *Allicor* or 2,400 mg *Allicor* or 900 mg *Kwai* vs. placebo	NM
K. Ried, 2010	Uncontrolled hypertension, SBP ≥140 mm Hg; DBP ≥90 mm Hg; 20–80 years old, seen by general practitioner in the previous 12 months	50	12	66 (9)	68	20; 40%[a]	Office measurements by trained research nurse with automated sphygmomanometer while in sitting position. The arm with higher reading was used. Mean of 3 readings at inter vals of 30 seconds. Measurements at 0, 4, 8, 12 weeks	ACE inhibitors, A2 receptor antagonists, β–receptor blockers, Ca–antagonists, diuretics	None	4 capsules of *Kyolic* (960 mg of AGE/ 2.4 mg SAC) vs. placebo	Two general practices
Y. Nakasone, 2013	20–70 years old, prehypertensive (130–139; 85–89 mm Hg) or mildly hypertensive (140–159; 90–99 mm Hg)	81	12	54 (9)	55	47; 58%[a]	Office measurements, automated sphygmomanometer. Sitting position. Left arm, repeated measurements at 2-minute intervals, until variance of 2 successive measurements ≤5 mm Hg. Mean values of 2 such measurements were then used. Measurements at 0, 4, 8, 12 weeks	None	None	2× 500-mg capsules: 188 mg of crushed garlic mixed with egg yolk (80:20), 266.5 mg of rapeseed oil (as solvent), and 45.5 mg of beeswax (as stabilizer) vs. placebo: dextrin, rapeseed oil, beeswax	NM
K. Ried, 2013	Uncontrolled hypertension, SBP ≥140 mm Hg on established plan of prescription of antihypertensive medication for at least 2 months	79	12	70 (12)	53	79; 100%	Office measurements by trained research nurse with automated sphygmomanometer. Sitting position. The arm with higher reading was used, mean of 3 readings at intervals of 30 seconds. Measurements at 0, 4, 8, 12 weeks	ACE inhibitors, A2 receptor antagonists, β-receptor blockers, Ca-antagonists, diuretics	None	One, two, or four capsules of *Kyolic* (240, 480, 960 mg of AGE/0.6, 1.2, 2.4 mg SAC) vs. placebo	Two metropolitan general practices
I. Sobenin, 2008[b]	*Plasma cholesterol level of 5.8–7 mmol/l, LDL cholesterol level 3.5–4.6 mmol/l, HDL cholesterol 0.65–1.95 mmol/l. No intake of lipid-lowering drugs for at least 3 months prior to the recruitment. No diseases demanding continuous administration of β–receptor blockers, Ca–antagonists, nitrates, sugar-lowering drugs, diuretics*	*42*	*12*	*51.7 (2.2)*	*100*	*Not reported*	*Place and method of BP measurement not described*	*Unclear for ACE inhibitors*	*8 weeks of hypolipidemic diet before randomization*	*600 mg Allicor vs. placebo*	*NM*

Abbreviations: ACE, angiotensin converting enzyme; AGE, aged garlic extract; BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density cholesterol; LDL, low-density cholesterol; NM, not mentioned; SAC, S-allylcysteine; SBP, systolic blood pressure; SD, standard deviation.

aOnly hypertensive subgroup included in this metaanalysis.

bTrial only included in sensitivity analysis.

Table 2. Blood pressure changes in included trials

Study (First Author, Year)	Intervention vs. comparison	N	Follow-up (wk)	SBP at baseline (mm Hg)	SD	SBP at end of follow-up (mm Hg)	SD	Change of SBP (mm Hg)	SD	DBP at baseline (mm Hg)	SD	DBP at end of follow-up (mmHg)	SD	Change of DBP (mm Hg)	SD
J. Kandziora, 1988	600 mg *Kwai* and Tr-HCT	20	12	178.0	8.0	162.0	9.0	–16.0	8.5[a]	100.0	4.0	85.0	4.0	–15.0	4.0[a]
	Placebo and Tr-HCT	20	12	178.0	8.0	173.0	6.0	–5.0	7.2[a]	100.0	3.0	91.0	6.0	–9.0	5.2[a]
G. Vorberg, 1990	900 mg *Kwai*	20	16	144.0	10.6	138.0	4.0	–6.0	9.3[a]	91.0	4.0	87.0	4.0	–4.0	4.0[a]
	Placebo	20	16	143.5	10.0	146.0	6.5	2.5	8.8[a]	87.5	6.0	90.0	4.0	2.5	5.3[a]
W. Auer, 1990	600 mg *Kwai*	24	12	171.0	24.5	152.0	24.5	–19.0	24.5[a]	101.0	14.7	89.0	4.6[a]	–12.0	4.8[a]
	Placebo	23	12	161.0	14.4	152.0	19.2	–9.0	17.3[a]	97.0	9.6	94.0	9.6	–3.0	9.6[a]
H. Holzgartner, 1992	900 mg *Kwai*	47	12	143.4	15.4	135.4	14.6	–8.0	15.0[a]	82.8	10.5	78.6	9.3	–4.2	10.0[a]
	600 mg bezafibrate	47	12	140.6	18.7	137.2	15.9	–3.4	17.5[a]	82.4	9.5	78.4	9.2	–4.0	9.4[a]
OS. De Santos, 1993	900 mg garlic powder equivalent to *Kwai*	25	26	143.0	21.0	120.0	13.1b	–23.0	13.0[a]	89.0	11.0	80.0	4.6[b]	–9.0	4.8[a]
	Placebo	27	26	144.0	17.0	145.0	11.7b	1.0	12.2[a]	89.0	11.0	90.0	8.3[b]	1.0	8.2[a]
I. Sobenin, 2009	600 mg *Allicor*, 2,400 mg *Allicor*, 900 mg *Kwai*	64	8	154.0	12.3	147.0	12.8	–7.0	4.6	95.7	3.8	92.9	4.4	–2.8	3.0
	Placebo	20	8	149.8	12.6	149.9	11.7	0.1	5.2	94.4	6.1	93.0	6.1	–1.4	5.5
K. Ried, 2010	960 mg of AGE (*Kyolic)* and allocated medication	8	12	151.2	7.7	136.0	8.0	–15.2	7.9[a]	87.3	7.8	91.9	8.3	4.6	8.1[a]
	Placebo	12	12	152.8	9.3	145.4	3.5	–7.4	8.1[a]	88.6	8.0	84.0	8.3	–4.6	8.2[a]
Y. Nakasone, 2013	188 mg garlic powder contained in garlic homogenate diet	23	12	141.8	5.6	137.0	7.8	–4.8	10.0	90.9	6.9	87.0	7.1	–3.9	6.5
	Placebo	24	12	141.8	5.6	140.4	7.6	–1.4	6.3	91.6	5.8	90.7	6.5	–0.9	4.6
K. Ried, 2013	240–960 mg of AGE *(Kyolic)* and allocated medication	39	12	149.3	13.0	130.0	12.8	–19.3	25.6	75.7	12.4	68.6	11.6	–7.2	25.0
	Placebo	19	12	148.6	13.1	135.9	12.8	–12.7	18.3	76.0	12.2	70.2	12.0	–5.8	17.4
I. Sobenin, 2008[c]	*600 mg Allicor*	*23*	*12*	*143.4*	*7.2*	*136.8*	*5.8*	*–6.6*	*6.6*[a]	*88.8*	*4.3*	*83.8*	*3.4*	*–5.0*	*3.9*[a]
	Placebo	*19*	*12*	*140.3*	*7.8*	*139.4*	*6.5*	*–0.9*	*7.3*[a]	*87.9*	*4.8*	*85.9*	*4.4*	*–2.0*	*4.6*[a]

Abbreviations: AGE, aged garlic extract; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation; Tr-HCT, triamterene/hydrochlorothiazide.
[a]Not indicated but calculated (correlation coefficient, 0.5).
[b]Not indicated but calculated by imputing median values.
[c]Trial only included in sensitivity analysis.

Types of garlic preparations used

All trials reported the dose of the garlic preparation used (Table 1). Six trials used only dried garlic powder (4 trials using Kwai),[15,16,23,25] and 1 trial used garlic powder of unknown origin that was described to be equivalent with Kwai.[24] One trial[12] compared 3 groups using garlic preparations (2 groups using 600 mg and 2,400 mg of time-released garlic powder (Allicor) daily, and 1 group used 900 mg of garlic powder (Kwai) daily) with a placebo group. For the purpose of this analysis, we pooled the data of all 3 garlic preparations and compared them with placebo. In another trial,[13] crushed garlic was kneaded and pulverized together with egg yolk in a weight ratio of 80:20. This mixture was described as garlic homogenate (a traditional Japanese garlic preparation). Two trials by the same author used aged garlic extract (Kyolic).[14,17] One of these trials was a dose-response trial that compared 3 doses of aged garlic extract (240 mg, 480 mg, and 960 mg daily) with placebo. For the purpose of this analysis, we pooled the data of the groups receiving 480 and 960 mg/day and compared them with the placebo group[14] since there was no difference in BP between the groups receiving placebo or 240 mg aged garlic extract.

Types of BP measurement devices used for outcome assessment

All trials reported office BP measurements. Four trials did not describe which type of BP measurement device was used or whether a mean of repeated measurements or a single value was recorded.[16,23–25] Two trials did not describe the device used but mentioned performance of repeated measurements.[12,15] One trial reported 2 BP measurements in the supine and standing position;[15] another trial exclusively relied on a mean of 12 BP measurements (second and third BP measurement in both arms in standing, sitting, and supine positions).[12]

We used sitting BP measurements where available and supine BP measurements when only supine and standing BP measurements were reported. Three trials used automated sphygmomanometer and calculated the mean of repeated measurements in the sitting position.[13,14,17]

Risk-of-bias assessment

Results for the risk-of-bias assessments are presented in Table 3. The sequence generation for randomization was adequate in 5 trials[12–14,16,17] and unclear in 4 trials.[15,23–25] Concealment of group allocation was unclear in 5 trials[15,16,23–25] and adequate in 4 trials.[12–14,17] Risk-of-performance bias was considered to be low in all trials. Detection bias was considered to be low in 4 trials[12–14,17] and unclear in 5 trials.[15,16,23–25] Four trials conducted an intention-to-treat-analysis.[13,14,17,25] No trial explicitly reported industry funding; however, in 2 trials, at least 1 study author could be identified as an employee of the company producing the garlic preparation under investigation.[13,24] Since study protocols were not available for all but 2 trials,[14,17] we rated the risk of selective reporting bias

Table 3. Risk-of-bias review of included studies

Study (First Author, Year)	Risk-of-selection bias: random sequence generation	Risk-of-selection bias: concealment of allocation	Risk-of-performance bias: blinding of patients and health care providers	Risk-of-detection bias: blinding of outcome assessment personnel	Risk-of-attrition bias: incomplete outcome data	Risk-of-reporting bias: selective reporting	Risk of other biases
J. Kandziora, 1988	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Funding not mentioned
G. Vorberg, 1990	Unclear	Unclear	Low	Unclear	Low[a]	Unclear	Funding not mentioned
W. Auer, 1990	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Funding not mentioned
H. Holzgartner, 1992	Low	Unclear	Low	Unclear	Low	Unclear	Low
O.S. De Santos, 1993	Unclear	Unclear	Low	Unclear	high	Unclear	Industry funding
I. Sobenin, 2009	Low	Low	Low	Low	Low	Unclear	Low
K. Ried, 2010	Low	Low	Low	Low	Low[a]	Low	Low
Y. Nakasone, 2013	Low	Low	Low	Low	Low[a]	Unclear	Industry unding
K. Ried, 2013	Low	Low	Low	Low	Low[a]	Low	Low
I. Sobenin, 2008[b]	*Low*	*Low*	*Low*	*Low*	*Unclear*	*Unclear*	*Low*

Unclear, insufficient information about the process to permit judgment of low risk or high risk; industry funding, at least 1 author affiliated with company that produces garlic preparations.

[a]Intention-to-treat analysis.

[b]Trial only included in sensitivity analysis.

for these trials as unclear. The relatively small number of included trials precluded a sensitive exploration of publication bias (Figure 2).

Changes in SBP and DBP

SBP was more effectively reduced in individuals treated with garlic preparations than in individuals treated with placebo (WMD, −9.1 mm Hg; 95% CI, −12.7 to −5.4; *P* for heterogeneity = 0.0006; I^2 = 71%). Similarly, DBP was more effectively reduced in individuals treated with garlic preparations than in individuals treated with placebo (WMD, −3.8 mm Hg; 95% CI, −6.7 to −1; *P* for heterogeneity = 0.00001; I^2 = 80%) (Figure 3).

The observed heterogeneity for changes in SBP was reduced by restricting analyses to higher-quality trials. Changes in SBP were less pronounced but still in favor of individuals allocated to garlic preparations when analyses were restricted to trials using intention-to-treat analysis,[13,14,17,25] concealed treatment allocation, blinded outcome assessment, and automated BP measurement devices;[13,14,17] to trials without necessity to impute SDs for changes in mean BP differences;[12–14] to trials not explicitly mentioning industry support;[12,14–17,23,25] and to trials using aged extract rather than other garlic preparations (Table 4).[14,17]

Various sensitivity analyses could not elucidate further reasons for the high inconsistency of observed changes in DBP. Only when analysis was restricted to trials without imputed SDs for the mean difference in BP changes did heterogeneity disappeared (Table 4).

Sensitivity analyses using correlation coefficients of 0.7 and 1.0 for SD values calculated by imputing or adding the trial where it was unclear whether included individuals were truly hypertensive or not[22] did not result in substantial changes of BP differences or heterogeneity.

Adverse events

Seven of 9 trials reported on adverse events. No trial reported any serious adverse events. One trial reported 1 death not considered to be related to the garlic treatment.[24] Two trials reported that there was no difference in adverse events between garlic preparations and placebo.[13,23] In 1 trial that compared a garlic preparation with bezafibrate,[16] 11 of 47 individuals randomized to garlic and 7 of 47 individuals randomized to bezafibrate reported minor side effects (sensation of repletion, lack of appetite, headaches and vertigo, palpitations, myalgia, tiredness). In 2 trials 24% and 23% of individuals taking garlic preparations experienced bloating, flatulence, and reflux compared with 8% and 2% of individuals in the placebo group.[14,17]

Only 3 trials reported dropouts in the garlic groups due to adverse events in 5 of 105 (5%) individuals; all events were related to gastrointestinal symptoms (bloating, discomfort/mild pain).[14,17,24]

DISCUSSION

In this metaanalysis, we observed a statistically significant reduction in SBP and DBP in hypertensive individuals treated with garlic preparations; however, heterogeneity was high. When we restricted analyses to higher-quality trials, effects were less pronounced but remained significant, with low heterogeneity for SBP but not for DBP. The observed differences are clinically important, and side effects associated with garlic preparations were rare and mild.

Our study did have strengths. We carried out a comprehensive literature search for randomized controlled trials comparing garlic preparations with placebo or care as usual in hypertensive individuals with a minimal follow-up of 4 weeks. The results of our metaanalysis remained robust across various subgroup and sensitivity analyses, including differences in trial quality and types of garlic preparations used.

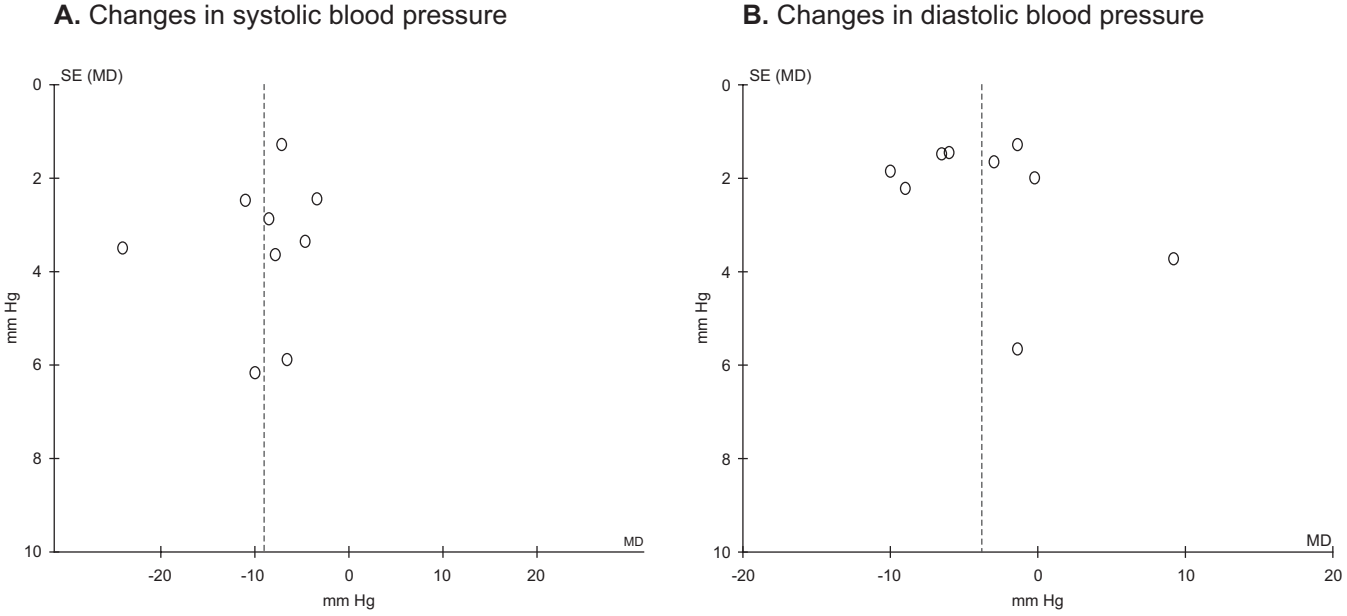


Figure 2. Funnel plots for changes in systolic and diastolic BP. (**A**) Changes in systolic blood pressure. (**B**) Changes in diastolic blood pressure. Abbreviations: MD, mean difference; SE, standard error.

Table 4. Comparison of subgroups[e]

Type of BP	WMD (95% CI)	Test for heterogeneity	Inconsistency	WMD (95% CI)	Test for heterogeneity	Inconsistency
	ITT analysis (13, 14, 17, 25)			No ITT analysis or unclear		
SBP (mm Hg)	-6.1 (–9.2 to –2.9)	$P = 0.54$	$I^2 = 0\%$	–11.2 (–17.3 to –5.2)	$P = 0.0001$	$I^2 = 83\%$
DBP (mm Hg)	–1.2 (–6.8 to 4.4)	$P = 0.001$	$I^2 = 81\%$	–5.2 (–8.9 to –1.5)	$P < 0.0001$	$I^2 = 84\%$
	Dried garlic preparations (12, 15, 16, 23–25))			Not dried garlic preparations		
SBP (mm Hg)	–10.6 (–15.4 to – 5.8)	$P = 0.004$	$I^2 = 78\%$	–5 (–8.7 to –1.2)	$P = 0.58$	$I^2 = 0\%$
DBP (mm Hg)	–5.4 (–8.4 to –2.4)	$P = 0.00001$	$I^2 = 80\%$	1.5 (–6.9 to 9.8)	$P = 0.01$	$I^2 = 78\%$
	Aged garlic (14, 17)			Not aged garlic extract		
SBP (mm Hg)	–7.5(–13.5 to –1.4)	$P = 0.86$	$I^2 = 0\%$	–9.5 (–13.8 to –5.2)	$P = 0.0001$	$I^2 = 78\%$
DBP (mm Hg)	4.8 (–5.5 to 15)	$P = 0.12$	$I^2 = 59\%$	–5.1 (–7.7 to –2.5)	$P = 0.00002$	$I^2 = 78\%$
	Industry funded (13, 24)			Not industry funded or unclear		
SBP (mm Hg)	–13.6 (–33.7 to 6.6)	$P < 0.00001$	$I^2 = 96\%$	–7.7 (–9.6 to –5.9)	$P = 0.8$	$I^2 = 0\%$
DBP (mm Hg)	–6.5 (–13.3 to 0.4)	$P = 0.005$	$I^2 = 87\%$	–2.9 (–6.3 to 0.4)	$P < 0.00001$	$I^2 = 80\%$
	SBP >160 mm Hg (15, 23)			SBP <160 mm Hg		
SBP (mm Hg)	–10.9 (–15.4 to –6.3)	$P = 0.88$	$I^2 = 0\%$	–8.7 (–13.1 to –4.3)	$P = 0.0002$	$I^2 = 77\%$
DBP (mm Hg)	–7 (–9.8 to –4.2)	$P = 0.26$	$I^2 = 21\%$	–2.6 (–6.1 to 0.9)	$P < 0.00001$	$I^2 = 82\%$
	Adequate concealment, blinded outcome assessment, and automated BP measurement (13, 14, 17)			No adequate concealment, blinded outcome assessment, or automated BP measurement		
SBP (mm Hg)	–5 (–8.7 to –1.2)	$P = 0.58$	$I^2 = 0\%$	–10.6 (–15.4 to –5.8)	$P = 0.0004$	$I^2 = 78\%$
DBP (mm Hg)	1.5 (–6.9 to 9.8)	$P = 0.01$	$I^2 = 78\%$	–5.4 (–8.4 to –2.4)	$P = 0.0001$	$I^2 = 80\%$
SBP (mm Hg) DBP (mm Hg)	No SD for BP difference imputed (14, 15, 17)			SD for BP difference imputed		
	–6.3(–8.5 to 4.1)	$P = 0.41$	$I^2 = 0\%$	–2 (–3.9 to –0.03)	$P = 0.74$	$I^2 = 0\%$
	–11(–16.3 to 5.7)	$P = 0.002$	$I^2 = 74\%$	–4.5(–8.4 to 0.6)	$P = 0.00001$	$I^2 = 84\%$

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; ITT, intention to treat; SBP, systolic blood pressure SD, standard deviation; WMD, weighted mean difference.

Our analysis did have several limitations. The overall estimates for both SBP and DBP were highly heterogeneous with relatively large effect sizes and large CIs. All included trials were of small sample size. Empirical evidence suggests that effect sizes from small trials tend to be larger than those of highly powered trials.[19] In addition, we were forced to impute SDs for the changes in BP for 6 of 9 trials.

The overall quality of the majority of included trials was moderate. Only a few trials conducted an intention-to-treat analysis, used adequate methods for concealed treatment allocation, and standardized BP measurements with automated sphygmomanometers. Summary estimates from trials that used more adequate methods were considerably lower, which is of concern. In addition, we were unable to explain the observed inconsistency for the results of changes in DBP despite various sensitivity analyses performed. Only when analysis was restricted to trials without imputed SDs for the mean difference in BP changes did heterogeneity disappear.

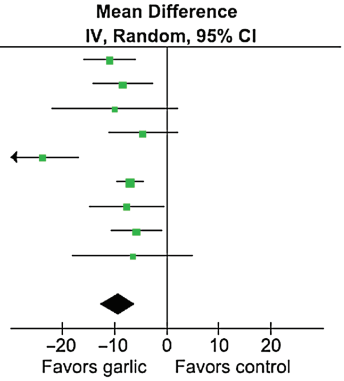
Dosages and type of garlic preparations used in included trials were heterogeneous. Most trials used garlic powder dosages of 600–2,400 mg/day, providing 3.6–13.6 mg of allicin. In comparison, fresh garlic cloves (approximately 2 g) each yield 5–9 mg of allicin.[26] It must be noted that different garlic preparations have variable effectiveness on BP. For example, ingestion of heat-treated garlic may yield only minimal allicin compounds.[27,28] Thus, the different garlic preparation methods used in the trials may have contributed to the heterogeneous study findings and preclude an appropriate analysis of a dose relationship. Finally, the duration of intervention in all trials was relatively short, with a mean of 13.5 weeks. It has yet to be determined whether the observed differences in BP in these short intervention trials last in the long term due to potential regression dilution bias.[29]

Information about how garlic could influence BP originates primarily from animal or *in vitro* models; however, the exact mechanism remains to be elucidated. Possible mechanisms are inhibition of the angiotensin-converting enzyme,[30] an increase in the concentration and activity of an array of vasodilatory agents including nitrous oxide (NO),[31] and stimulation of erythrocytes to produce hydrogen sulfide, which acts as a signaling molecule by opening K-ATP channels in smooth muscle cells and thus inducing depolarization and blood vessel dilatation.[32] In particular, S-allylcysteine

A. Mean changes in systolic blood pressure

Study or Subgroup	Garlic Mean	Garlic SD	Garlic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kandziora 1988	−16	8.5	20	−5	7.2	20	13.5%	−11.00 [−15.88, −6.12]	1988
Vorberg and Schneider 1990	−6	9.3	20	2.5	8.8	20	12.4%	−8.50 [−14.11, −2.89]	1990
Auer et al. 1990	−19	24.5	24	−9	17.3	23	5.6%	−10.00 [−22.09, 2.09]	1990
Holzgartner et al. 1992	−8	15	47	−3.4	17.5	47	11.0%	−4.60 [−11.19, 1.99]	1992
De Santos and Grünwald 1993	−23	13	25	1	12.2	27	10.6%	−24.00 [−30.87, −17.13]	1993
Sobenin et al. 2009	−7	4.6	64	0.1	5.2	20	16.9%	−7.10 [−9.64, −4.56]	2009
Ried (hypert) et al. 2010	−15.2	7.9	8	−7.4	8.1	12	10.3%	−7.80 [−14.94, −0.66]	2010
Nakasone et al. 2013	−6.6	10	23	−0.7	6.3	24	13.6%	−5.90 [−10.70, −1.10]	2013
Ried et al. 2013	−19.3	25.6	39	−12.7	18.3	19	6.0%	−6.60 [−18.10, 4.90]	2013
Total (95% CI)			**270**			**212**	**100.0%**	**−9.36 [−12.77, −5.95]**	

Heterogeneity: Tau² = 16.18; Chi² = 24.42, df = 8 (P = 0.002); I² = 67%
Test for overall effect: Z = 5.38 (P < 0.00001)



B. Mean changes in diastolic blood pressure

Study or Subgroup	Garlic Mean	Garlic SD	Garlic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kandziora 1988	−15	4	20	−9	5.2	20	13.1%	−6.00 [−8.88, −3.12]	1988
Vorberg and Schneider 1990	−4	4	20	2.5	5.3	20	13.1%	−6.50 [−9.41, −3.59]	1990
Auer et al. 1990	−12	4.8	24	−3	9.6	23	11.2%	−9.00 [−13.37, −4.63]	1990
Holzgartner et al. 1992	−4.2	10	47	−4	9.4	47	11.8%	−0.20 [−4.12, 3.72]	1992
De Santos and Grünwald 1993	−9	4.8	25	1	8.2	27	12.2%	−10.00 [−13.62, −6.38]	1993
Sobenin et al. 2009	−2.8	3	64	−1.4	5.5	20	13.6%	−1.40 [−3.92, 1.12]	2009
Ried (hypert) et al. 2010	4.6	8.1	8	−4.6	8.2	12	7.7%	9.20 [1.92, 16.48]	2010
Ried et al. 2013	−7.2	25	39	−5.8	17.4	19	4.6%	−1.40 [−12.48, 9.68]	2013
Nakasone et al. 2013	−3.9	6.5	23	−0.9	4.6	24	12.7%	−3.00 [−6.23, 0.23]	2013
Total (95% CI)			**270**			**212**	**100.0%**	**−3.82 [−6.69, −0.96]**	

Heterogeneity: Tau² = 14.11; Chi² = 40.87, df = 8 (P < 0.00001); I² = 80%
Test for overall effect: Z = 2.62 (P = 0.009)

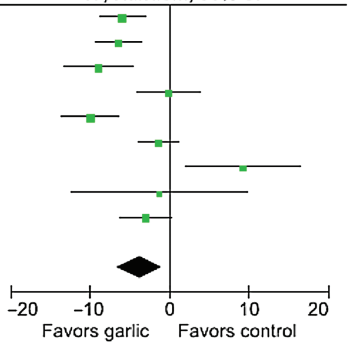


Figure 3. Mean changes in systolic and diastolic blood pressure. (**A**) Mean changes in systolic blood pressure. (**B**) Mean changes in diastolic blood pressure. Abbreviations: CI, confidence interval; df, degrees of freedom; I^2 = inconsistency; SD, standard deviation.

seems to increase NO production within endothelial cells and thus enhances the elasticity of blood vessels.[28]

Previous metaanalyses in which the effect of garlic preparations on BP was evaluated all included both individuals with and without hypertension. Also, they included fewer individuals with hypertension and none of them systematically assessed the effect of trial quality on interpretation of findings. The metaanalysis by Silagy *et al.*[33] included 415 normo- and hypertensive individuals from 7 randomized controlled trials, with only 3 trials including hypertensive individuals, the metaanalysis by Reinhart *et al.*,[34] which included 410 individuals from 10 randomized controlled trials with only 3 trials including individuals with elevated SBP (n = 139), and the metaanalysis by Ried *et al.*,[10] which included 11 randomized controlled trials with only 4 trials including hypertensive individuals (n = 231). In all of these metaanalyses, SBP and DBP were lowered more efficiently in individuals treated with garlic in the hypertensive population. Thus, the beneficial effect of garlic preparations on BP control in hypertensive individuals observed in previous subgroup metaanalyses is substantiated by our metaanalysis.

Based on short-term evidence, the BP-lowering effect of garlic preparations seems comparable to the effect of the 5 main classes of BP-lowering drugs (diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers). In a metaanalysis of 354 short-term randomized placebo-controlled trials of these 5 BP-lowering drugs in fixed dose, the 5 main classes of BP-lowering drugs produced similar reductions in BP, with a standard dose of a drug on average lowering SBP by 9.1 mm Hg and DBP by 5.5 mm Hg, which is similar to the BP-lowering effects of garlic preparations observed in this study.[35]

Although no serious side effects have been reported for garlic preparations, garlic odor is the most common[36] and may limit the acceptability of some garlic preparations.

Implications for further research and clinical practice

More research is required to understand the mechanisms for the BP-lowering effect of garlic preparations. Current evidence on the effectiveness of garlic preparations in lowering BP is in hypertensive individuals and is primarily based on short-term evidence from small randomized controlled

trials. Many of these trials suffer from methodological shortcomings. More than 25 years after publication of the first randomized controlled trial that compared a garlic preparation with a placebo for the treatment of hypertension,[15] we still do not know whether garlic preparations lower BP in the long term. There is an urgent need for an adequately powered randomized controlled trial using standardized BP measurements with automated sphygmomanometers for blinded outcome assessment of BP response in hypertensive individuals treated with garlic preparations.

CONCLUSIONS

Garlic preparations look promising as an herbal medication for reducing high BP. However, considering current trials to be short term, a well-conducted, sufficiently powered long-term trial is needed to assess the BP-lowering capacities of a standardized form of a garlic preparation. As of now, there is insufficient evidence to have confidence that garlic preparations are an effective alternative or complementary/adjunct herbal medication to conventional antihypertensive drugs.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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