

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/79686>

Please be advised that this information was generated on 2020-11-26 and may be subject to change.

A systematic review on the influence of trial quality on the effect of garlic on blood pressure

S. Simons^{1*}, H. Wollersheim², T. Thien³

Departments of ¹Pulmonary Diseases and ³General Internal Medicine, and ²Scientific Institute on Quality of Healthcare, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, the Netherlands, *corresponding author: tel.: +31 (0)24-361 45 79, fax: +31 (0)24-361 03 24, e-mail: S.Simons@long.umcn.nl

ABSTRACT

Background: Garlic is a widely used herbal product for hypertension. Previous meta-analyses on the effect of garlic on blood pressure (BP) have been contradictory however. We hypothesised that methodological deficiencies may have contributed to this disagreement. We therefore evaluated whether trials reporting on the effect of garlic on BP had sufficient methodological qualities and a proper description of BP determination.

Methods: MEDLINE, EMBASE, AMED, the COCHRANE library, IBIDS and CINAHL were systematically searched for trials reporting on the effect of garlic on BP. Both the methodological quality and the quality of blood pressure measurement were appraised using predefined quality scores.

Results: 32 Studies were identified. Of these studies, 13 were included previously by other meta-analyses. The methodological quality of the studies was poor. Only four trials had adequate allocation concealment, no single trial reported an intention-to-treat analysis and blinding of the evaluators was done in three trials only. Moreover, half of the studies did not report any data on BP measurement. No trials reported on the arm level. Body position was described most often. All trials fulfilling a predefined cutoff point were conducted in normotensive subjects.

Conclusion: The effect of garlic on blood pressure cannot be ascertained. Previous meta-analyses have been based on trials with inadequate study designs, methodological deficiencies and with too little information about blood pressure measurement. In our view, use of garlic cannot be recommended as antihypertensive advice for hypertensive patients in daily practice.

KEYWORDS

Blood pressure, hypertension, garlic, systematic review, quality analysis

INTRODUCTION

For the treatment of hypertension, non-pharmacological therapeutic advice is the initial therapeutic approach in patients with an increased cardiovascular risk.¹ A number of such lifestyle recommendations clearly reduce blood pressure, e.g. weight reduction and regular physical activity.¹ Food supplementation could provide another, less strenuous non-pharmacological intervention.

Garlic is the second most used herb taken by patients with cardiovascular disease.² Moreover, garlic might lower blood pressure via the conversion of garlic-derived organic polysulphides into hydrogen sulphide by the red blood cell leading to vasorelaxation.³ It could therefore be a potential target as an antihypertensive food supplement.

Indeed, several trials suggest possible short-term effects of garlic on cardiovascular risk factors.⁴ The effects of garlic on blood pressure specifically have been summarised in three systematic reviews.⁴⁻⁶ However, the results were contradictory. This phenomenon has been evaluated previously by Linde *et al.*⁷ In their analysis on discordant conclusions of systematic reviews in complementary medicine, they concluded that these differences were mostly due to differences in inclusion and exclusion criteria. We wondered whether this could also be explained by the different approaches to appraise trial quality,⁸ because trials in complementary medicine have low methodological quality⁹ and because these deficiencies may translate into biased findings in systematic reviews.¹⁰

Besides, none of these reviews⁴⁻⁶ looked at the quality of blood pressure measurement. Recently, Wood *et al.* demonstrated that bias in intervention effects is only seen in trials using subjective outcomes, i.e. physician assessed disease outcome.¹¹ During blood pressure measurements many errors can occur resulting in varying blood pressures making it amenable to faulty outcomes.¹² Thus when addressing the bias in blood pressure trials introduced by methodological deficiencies, proper blood pressure measurements seem to be an additional quality criterion. We therefore conducted an analysis of the methodological quality of trials reporting on the effect of garlic on blood pressure using multiple strict quality criteria. The present study aims to answer the following four questions:

- Does garlic lower blood pressure in humans?
- What is the methodological quality of human trials measuring the effect of garlic on blood pressure?
- What information about criteria for blood pressure measurements is presented in these garlic studies?
- Did the inclusion of methodologically poor studies affect the conclusions of previous systematic reviews?

METHODS

Literature search

MEDLINE (1966-2008), EMBASE (1980-2008), CINAHL (1982-2008), IBIDS (2008), AMED (1985-2008) and the COCHRANE library were searched from March 2008 until May 2008 using search strategies mentioned in *table 1*. The search was last updated in January 2009 by two reviewers independently. References from garlic reviews and eligible trials were searched for additional articles.

Selection criteria

Studies in adults measuring the effect of garlic on blood pressure were considered eligible. Inclusion was limited to studies lasting more than eight weeks and with more than 20 participants. In crossover trials each parallel arm had to last more than eight weeks. Trials were selected independently by two reviewers on the basis of abstracts.

Data extraction

Two reviewers identified eligible trials. Data extraction and quality assessment were done by two reviewers. When results of a scoring card (see: quality analysis) deviated more than one point, a third independent reviewer was consulted. Differences were resolved by consensus. In case of different conclusions, consensus could always be reached.

Quality analysis

Both the methodological quality and the quality of blood pressure measurement were assessed using two different scoring systems.

Methodological quality was assessed using a scoring card derived from the Cochrane checklist 'the assessment of a randomised trial'.¹³ The card consisted of nine items mentioned in *table 2*. A trial had to describe each item specifically. Moreover, both the number as well as the reasons for dropping out had to be recorded. Trial arms had to be similar in age, sex, blood pressure and modifying factors (smoking, diabetes, hypercholesterolaemia, overweight, alcohol, cardiovascular comorbidity; at least four mentioned). Each study could score a maximum of nine points.

Table 2. Methodological quality of the selected trials (*n*=32) using the nine quality criteria*

Cochrane criterion	Number of studies fulfilling criterion
Allocation concealment	4
Randomisation	28
Patients blinded	24
Researchers blinded	24
Evaluators blinded	3
Comparable groups	10
Adequate lost-to-follow-up analysis	15
Intention-to-treat analysis	0
Groups receiving same treatment	27

*Dutch Cochrane Centre: checklist for bias assessing of randomised controlled trials. www.cochrane.nl. Accessed 21 July 2008.

Table 1. Search strategy for each search engine

Medline	((((blood pressure) OR (blood pressure determination) OR (hypertension)) OR ('Blood Pressure Determination' ^{Mesh} OR 'Blood Pressure' ^{Mesh} OR 'Hypertension' ^{Mesh})) AND ((vinyl dithiin) OR (thiosulfonates) OR (diallyl derivative) OR (s-allyl cysteine) OR (kyolic) OR (kwai) OR (knoblauch) OR (garlic oil) OR (garlic extract) OR (dipropyl disulfide) OR (dipropyl disulfide) OR (diallyl disulfide) OR (diallyl disulfide) OR (allyl mercaptan) OR (alliinase) OR (allicin) OR (alisat) OR (ajoene) OR (ajo) OR (allium sativum) OR (garlic) OR ('Garlic' ^{Mesh})) AND ((Humans ^{Mesh}) AND (adult ^{Mesh:noxp} OR middle age ^{Mesh} OR (middle age ^{Mesh} OR aged ^{Mesh}) OR aged ^{Mesh} OR aged, 80 and over ^{Mesh}))
EMBASE	('human-' / all SUBHEADINGS in DEM,DER,DRM,DRR) and ('blood-pressure' / all SUBHEADINGS in DEM,DER,DRM,DRR) and ('garlic-' / all SUBHEADINGS in DEM,DER,DRM,DRR)
CINAHL	('Blood-Pressure' / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) and ('Garlic-' / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE)
IBIDS	+garlic +'blood pressure'
Cochrane library	Garlic and blood pressure

Roche *et al.*¹⁴ have reported on the quality of the blood pressure measurement in medical literature. During a preliminary data analysis, however, it became clear that no single study sufficiently fulfilled the criteria used in that study. Therefore, from the list used by Roche *et al.*, five essential criteria were formulated based on a prioritisation procedure (table 3). The methodology section of each trial was screened for the description of blood pressure measurement by two reviewers independently. A study could score a maximum of five points if each criterion was written specifically.

Table 3. Criteria for the judgement of the quality of the blood pressure measurement reported in the included trials (n=32)

Quality criterion	Number of studies fulfilling criterion
Blood pressure device and accuracy mentioned (yes/no)	6
Body position reported (yes/no)	13
Measurement with arm at heart level (yes/no)	0
Rest period before measurement (yes/no; at least 5 minutes)	7
Number of readings reported (yes/no; at least 2)	9

Comparison with earlier systematic reviews

We hypothesised that conclusions drawn by previous authors were based on differences in inclusion and exclusion criteria due to differences in evaluating trial quality. Methodological weaknesses were identified in the two earlier meta-analyses^{5,6} by examining if the trials included by these authors lacked our quality criteria. Because one previous review⁴ did not use a quality assessment this review was not included in the analysis.

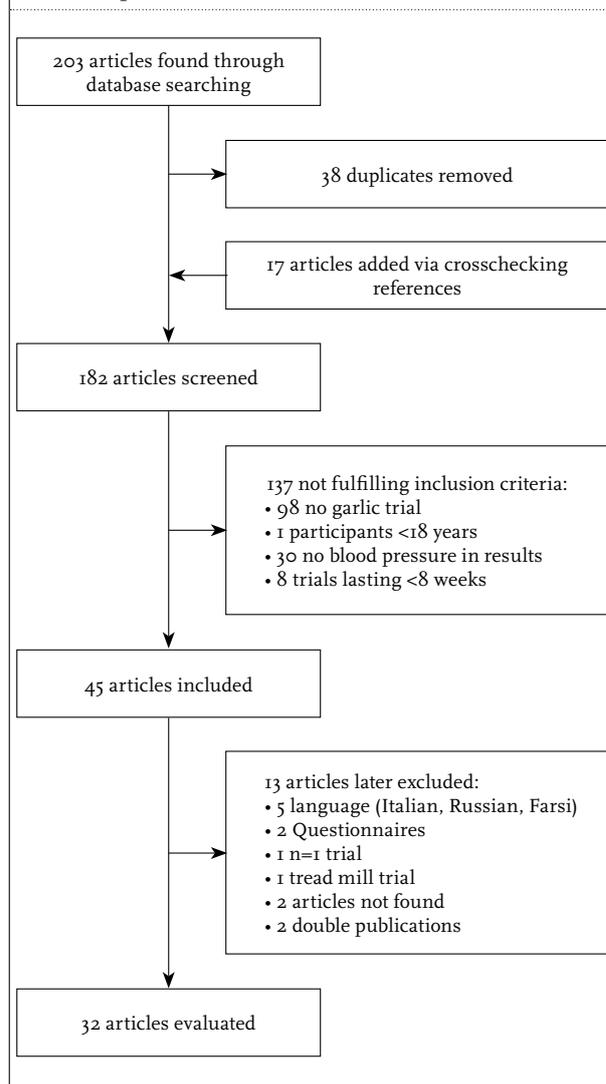
RESULTS

Figure 1 shows the selection process. Of the 203 trials found through the initial database search, 165 possible garlic trials were identified. The crosschecking of references and reviews revealed another 17 trials. A total of 137 studies did not meet the inclusion criteria. Another 13 trials were excluded for various reasons mentioned in figure 1. The remaining 32 trials were further analysed.¹⁵⁻⁴⁶

Study description

Table 4 describes the trials reporting on the effect of garlic on blood pressure. Sample size ranged from 23²⁴ to 862¹⁸ subjects and trials lasted from 8^{23,29,46} to 156¹⁷ weeks. Fifteen trials had blood pressure as a primary objective^{16,19-23,26,30-32,36-37,41,43,45} and 16 trials comprised of hypertensive patients.^{16,18-24,26-27,31-32,34-35,41,44}

Figure 1. Flow diagram of the process of selecting clinical trials examining the effect of garlic ingestion on blood pressure



Different study designs were used; 21 double-blind, randomised, placebo-controlled, parallel trials;^{15-17,20-21,25,27-28,30,32-39,42-45} two randomised placebo-controlled crossover trials;^{40,41} one single-blind, placebo-controlled trial;⁴⁶ one double-blind, randomised trial against an active component;³² six uncontrolled before-after trials;^{18,22-24,26,29} one controlled before-after trial.¹⁹ Only one trial was *a priori* set up in a randomised placebo-controlled fashion to test solely whether garlic lowers blood pressure in a hypertensive population.¹⁶ Some trials lacked important data. Fourteen trials did not report any numerical blood pressure data. Two studies reported no demographic data,^{17,37} 14 studies^{24,28-30,35,36-39,41-42,44-46} did not explicitly exclude patients on hypertensive medication and in two trials such medication was allowed.^{27,33}

Table 4. Summary of the 32 clinical trials of more than eight weeks examining the effect of garlic ingestion on blood pressure

Author (publication year) [reference number]	Sample size	Primary objective	Blood pressure	Intervention (total daily intake in grams)	Control group (total daily intake in grams)	Co-interventions	Trial length (in weeks)
Adler et al. (1997) ¹⁵	50	LP	N	GP (0.9)	PL	Primrose oil	12
Auer et al. (1990) ¹⁶	47	LP + BP	H	GP (0.6)	PL	NG	12
Bordia et al. (1989) ¹⁷	432	reinfarction	NND	GO (NND)	PL	NG	156
Brewitt et al. (1991) ¹⁸	862	LP	H	GP (6-12)	No placebo group	NG	26
Cheng et al. (2006) ¹⁹	79	LP + BP	H	GP (0.012) + diuretic	Diuretic	Diuretic	52
Czerny et al. (1996) ²⁰	100	LP + BP	H	GO (0.4) + lecithin	PL	NG	14
De A Santos et al. (1993) ²¹	60	LP + BP	N + H	GP (0.9)	PL	DA	24
De A Santos et al. (1995) ²²	80	LP + BP	N + H	GP (1.8)	GO (0.006)	NG	16
Dhawan et al. (2004) ²³	40	LP + BP	N + H	Garlic pearls (0.4)	Garlic pearls (0.4)	NG	8
Durak et al. (2004) ²⁴	23	LP	N + H	Garlic extract (10)	No control group	NG	16
Gardner et al. (2001) ²⁵	53	LP	N	GP (0.3-1.0)	PL	DA	12
Grünwald et al. (1992) ²⁶	48	LP + BP	N + H	GP (0.6)	No placebo group	NG	18
Holzgartner et al. (1992) ²⁷	98	LP	N + H	GP (0.9)	Bezafibrate (0.6)	NG	12
Isaacsohn et al. (1998) ²⁸	50	LP	N	GP (0.9)	PL	DA	12
Jabbari et al. (2005) ²⁹	50	LP	N	Raw garlic (1)	Raw garlic (1)	NG	8*
Jain et al. (1993) ³⁰	42	LP + BP	N	GP (0.9)	PL	NG	12
Kandziora (1988) ³¹	40	BP	H	GP (0.6)	Diuretic-reserpin combination	Lifestyle advice	12
Kandziora (1988) ³²	40	BP	H	GP (0.6) + diuretic	PL + diuretic	Low salt diet	12
Kiesewetter et al. (1993) ³³	80	Pain-free walking distance	NND	GP (0.8)	PL	Physiotherapy	12
Lutomski (1984) ³⁴	102	NG	N + H	GP (0.3) + rutin	PL	NG	12
Macan et al. (2006) ³⁵	52	Warfarin safety	N + H	Garlic solution (0.008)	PL	NG	12
Mansell et al. (1996) ³⁶	60	BP	NND	GP (0.9)	PL	NG	12
McMahon et al. (1992) ³⁷	42	BP	NND	GP (0.9)	PL	NG	12
Mrozikiewicz et al. (1988) ³⁸	NND	NG	NND	GP (0.9/1.8) or GO (3)	PL	NG	12
Saradeth et al. (1994) ³⁹	72	LP	N	GP (0.6)	PL	NG	15
Simons et al. (1995) ⁴⁰	31	LP	N	GP (0.9)	Lactose	NG	12*
Steiner et al. (1996) ⁴¹	52	LP + BP	N + H	GP (2.4)	PL	DA	24*
Superko et al. (2000) ⁴²	50	LP	N	GP (0.9)	PL	DA	12
Turner et al. (2004) ⁴³	75	LP + BP	N	GP (0.92)	PL	NG	12
Vorberg et al. (1990) ⁴⁴	40	NG	N + H	GP (0.9)	PL	NG	16
Zhang et al. (2000) ⁴⁵	36	BP	N	GO (0.012)	PL	NG	16
Ziaei et al. (2001) ⁴⁶	100	LP	N	GP (0.8)	PL	NG	8

BP = blood pressure; DA = dietary advice with adequate instruction; GO = garlic oil; GP = garlic powder; H = hypertensive; LP = lipids; N = normotensive; NND = no numerical data available; NG = data not given; PL = placebo. *Crossover studies; only the first parallel arm.

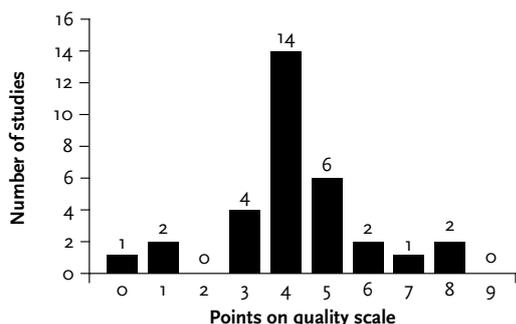
Methodological quality

Figure 2 shows how well studies performed on the methodology scale. No trials scored maximum. The median score was four points (range 0-8). Eleven trials scored five or more points.^{21,25,27-28,30,33,35,40,43-45} Trials scored low for intention-to-treat analysis, allocation concealment (i.e., shielding those who admit participants to a study from knowing the upcoming assignments) and for the blinding of evaluators. This is shown in table 2. Randomisation^{15-17,19-22,25,27-46} and providing the same treatment among treatment arms^{15-17,19-23,28-46} were fairly well described in the selected studies.

Blood pressure measurement

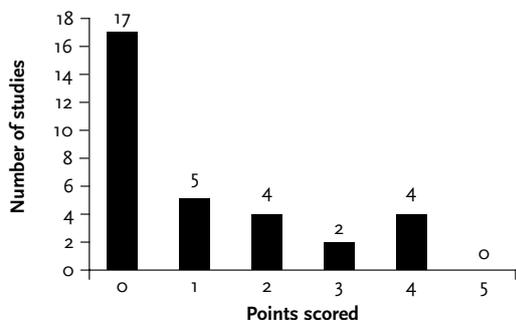
Figure 3 depicts the spread of scores on reporting the five blood pressure criteria. Scoring was poor. Half of the trials did not report any criterion^{17-21,24,26-27,29,34-39,42,46} and only six trials scored three points or more.^{23,25,30,40,43,45} A subdivision of the scoring system is shown in table 3. Information about the five criteria was scarce; no trial reported arm height during measurement and less than a quarter described the blood pressure device^{25,30,40,41,43,45} or the resting period.^{23,25,30,33,40,43,45} Body position was most often cited.^{15,16,22-23,25,28,30-33,40,43-44}

Figure 2. Spread of quality scores on the methodology of the selected clinical trials (n=32)



No points indicates a high suspicion of bias. The quality criteria are mentioned in table 2.

Figure 3. Spread of scores of the quality of blood pressure measurement as reported in the selected clinical trials (n=32)



The 5 criteria are depicted in table 3.

Comparison with earlier meta-analysis

Of the 32 studies, 13 have been studied by either Ried *et al.*⁶ or Silagy and Neil.⁵ The latter also included one study lasting less than eight weeks.⁴⁷ The quality of these studies is summarised in table 5. All trials lack proper allocation concealment, blinding of evaluators and intention-to-treat analysis. Moreover, there was little information about the quality of blood pressure measurement. None of the trials provided information about arm height. Only two trials^{30,40} mentioned resting period, the device used, body position of the patient and number of readings.

Trials with highest scores in both our quality assessments are summarised in table 6. For clarity cutoff points of 5 and 3 were used for the methodology score and the blood pressure score respectively. Garlic did not lower blood pressure in any selected trial. However, none of these trials were performed in hypertensive subjects.

DISCUSSION

Our main conclusion is that the hypotensive effect of garlic cannot be ascertained, because conclusions from previous meta-analyses have been based on trials with inadequate study designs, with methodological defects and with insufficient information on blood pressure measurement. Moreover, trials with the best methodology were performed in normotensive subjects.

This study shows that designs of trials on the effect of garlic on blood pressure have important flaws. Few trials used only hypertensive subjects. Only one trial was set up in a randomised, placebo-controlled, double-blind fashion to evaluate the effect of garlic on blood pressure in a hypertensive population. Although other study designs may be used, these are prone to the introduction of bias. Moreover, it may be questionable, but not entirely ruled out, that effects found in normotensive subjects can be extrapolated to hypertensive patients.

Secondly, the methodological quality was poor. No trials reported intention-to-treat analysis and only a minority had an adequate allocation concealment and blinding of evaluators. This is in agreement with two previous systematic reviews on the effect of garlic on blood pressure.^{4,5} Using another methodology scale, Silagy and Neil scored for randomisation, intention-to-treat analysis and for blinding of the evaluators.⁵ None of their eight included trials^{16,21,27,30,31-32,44,47} scored positive on all points and they therefore concluded that 'quality assessment of the trials was generally poor'. These trials also scored weak in our rating scales (table 5). Another systematic review by Ackermann *et al.*⁴ did not perform a systematic quality analysis. However, they do provide some overview of trial quality mainly corroborating with our findings. Ackermann *et al.*⁴ refrained from carrying out a meta-analysis because 'about half of the studies did not present numerical data, multiple blood pressure measurements were used and few studies had *a priori* hypotheses related to blood pressure.'

In trials on complementary medicine in general, others have also reported low methodological quality.^{7,48} Linde *et al.*⁷ reviewed trials on homeopathy, acupuncture and herbal medicine, garlic not included. They concluded that most trials had inadequate allocation concealment, poor randomisation procedures and gave little information about dropouts. In a more comprehensive review, Gagnier *et al.*⁴⁸ analysed 1321 English trials on herbal medicine, garlic included. They concluded that trials in herbal medicine provided less than half of the necessary information in their reports. Of the ten herbs studied, garlic trials scored second worst. Allocation concealment, randomisation and

Table 5. Quality analysis of the 14 included trials in the meta-analyses performed by Ried *et al.*⁶ or by Silagy and Neil⁵

Author (year) [reference]	Included by Ried (R) or Silagy (S)	Total points quality scale (max. 9)	Lacking items	Total points blood pressure scale (max. 5)	Lacking items
Adler (1997) ¹⁵	R	4	AC, PB, EB, CG, IT	1	DM, AH, RP, NR
Auer (1990) ¹⁶	R + S	4	AC, EB, CG, D, IT	1	DM, AH, RP, NR
De A Santos (1993) ²¹	S	6	AC, EB, IT	0	DM, AH, BP, RP, NR,
Holzgartner (1992) ²⁷	R + S	5	AC, EB, IT, ST	0	DM, AH, BP, RP, NR
Jain (1993) ³⁰	R + S	5	AC, EB, D, IT	4	AH
Kandziora (1988) ³¹	S	4	AC, PB, EB, D, ITT	2	DM, AH, RP
Kandziora (1988) ³²	R + S	4	AC, EB, D, IT	2	DM, AH, RP
Kiesewetter [*] (1991) ⁴⁷	S	4	AC, EB, CG, D, IT	0	DM, AH, BP, RP, NR
Kiesewetter (1993) ³³	R	5	AC, EB, D, IT	2	DM, AH, NR
Saradeth (1994) ³⁹	R	4	AC, EB, CG, D, IT	0	DM, AH, BP, RP, NR
Simons (1995) ⁴⁰	R	5	AC, EB, CG, IT	4	AH
Steiner (1996) ⁴¹	R	4	AC, EB, CG, D, IT	1	BP, AH, RP, NR
Vorberg (1990) ⁴⁴	R + S	5	AC, EB, CG, IT	1	DM, AH, RP, NR
Zhang (2000) ⁴⁵	R	6	AC, EB, D, IT	3	BP, AH

AC = allocation concealment; PB = patient blinding; EB = evaluators blinding; D = dropouts; CG = comparable groups; IT = intention-to-treat analysis; ST = same treatment of groups; DM = device mentioned; AH = arm at heart level; BP = body position; RP = resting period; NR = number of reading. ^{*}Not included in our systematic review because of a treatment period of less than eight weeks.

Table 6. Summary of the five clinical trials on the effect of garlic on blood pressure with the highest methodological quality score and highest score for the quality in reporting blood pressure measurements

Author (year) [reference]	Blood pressure a primary goal	Hypertensive population	Methodological quality [*]	Blood pressure quality ^{**}	Garlic effective in lowering blood pressure
Gardner (2001) ²⁵	No	No	7	4	No
Jain (1993) ³⁰	No	No	5	4	No
Simons (1995) ⁴⁰	No	No	5	4	No
Turner (2004) ⁴³	Yes	No	8	4	No
Zhang (2000) ⁴⁵	Yes	No	6	3	No

^{*}Score based on the criteria proposed by the Dutch Cochrane society. No points indicates a high suspicion of bias. A cutoff value of five points or more was chosen. ^{**}Blood pressure quality was scored on reporting on exact device, body position, arm at heart level, resting period and number of readings reported. A maximum of five point could be obtained. A cutoff value of three points was chosen.

blinding of the evaluators, as in the present study, were poorly described.

Our conclusion on the methodological quality contrasts with the work by Ried *et al.*⁶ however. In their systematic review they also used guidelines by the Cochrane Collaboration for assessing trial quality. They concluded on the basis of their analysis that trial quality of their included trials was 'generally high'. However, they only provided information about blinding, randomisation and blood pressure as a primary outcome. Our analysis shows that what trials mostly lack is an adequate allocation concealment, blinding of the evaluators and proper use of an intention-to-treat analysis. It has been shown that inadequate allocation concealment or blinding may lead

to exaggerated treatment effects.^{10,50,51} When taking into account all nine quality criteria, the performance of the included garlic trials is, at least, equivocal.

The third conclusion that can be drawn from our results is that trials provide insufficient information about the technique used to measure blood pressure. The absence of proper information about blood pressure measurements is worrying since factors such as arm position may influence blood pressure measurements by up to 10 mmHg.¹² The fact that only 15 studies had blood pressure as a primary outcome might explain this absence. One could argue it is not the blood pressure per se that counts but rather the difference between the measurements. However, incorrect

blood pressure measurements would inherently lead to data pollution of normotensive and hypertensive subjects making conclusions impossible. Besides, none of the studies included in the present review described that blood pressure was measured similarly every time.

To our knowledge, the present study is the first review that systematically assessed blood pressure measurement in garlic trials. Of the three previous systematic reviews on garlic and blood pressure, only Ried *et al.*⁶ provide data about blood pressure measurements, but they do not draw the conclusion that the information was insufficient. Roche *et al.*¹⁴ have reviewed the reporting of blood pressure measurements in leading English medical journals. In their analysis of 116 papers, device accuracy and validation or reporting of arm level was also poorly described; device accuracy was only reported in 3% and arm level in 5%. As in the present study, both body position and number of readings were best reported. Also in a review of Brazilian medical literature, Holanda *et al.*⁴⁹ showed articles lacked important data; in only half of the studies the type of sphygmomanometer or the number of readings were mentioned and only a quarter described the body position.

Did the inclusion of these garlic trials affect the conclusions of previous meta-analyses? In our view the absence of a proper methodology may have indeed affected outcome. Both Schulz *et al.* and Moher *et al.* have shown that inadequate allocation concealment and lack of blinding may lead to exaggerated results.^{50,51} In the present study it was shown that garlic trials scored poorly in both criteria. Biased results in trials may also affect results of systematic reviews.¹⁰ According to the criteria put forward in the present study, only five trials provide sufficient quality data (table 6).^{25,30,40,43,45} These studies do not show an effect of garlic on blood pressure. We refrained from conducting a meta-analysis, however, because all trials were performed on normotensive subjects. In our view these trials are not suitable to answer the only clinically relevant question whether garlic lowers blood pressure in hypertensive patients.

Our analysis has several limitations. Our scoring systems inherently had some subjective elements. We minimised this effect by using two independent evaluators and a standardised checklist. Second, the absence of reporting procedures in the garlic trials does not necessarily imply these procedures were not done. Our criteria might have been biased towards precisely written studies. It is our opinion, though, that transparency is a key element in conducting trials. In such a way, clear writing might in itself be a quality criterion. Deficient reporting generally embodies imperfect methodologies.¹⁰ Thirdly, the applicability of scores to appraise the methodological

quality has been challenged by others,^{8,10} arguing that high scores do not necessarily represent valid trials. They propose that relevant methodological aspects should be assessed individually.¹⁰ We therefore used both, because in our view an overall composite score nevertheless gives a pragmatic and visual tool for a global quality assessment.

CONCLUSION

It is our view that garlic cannot be recommended to lower blood pressure in the daily practice of physicians working in the field of hypertension treatment, given the low methodological quality, the lack of information about blood pressure measurement and the absence of methodological sound trials in hypertensive patients.

ACKNOWLEDGEMENTS

We would like to thank Professor J. Lenders and Dr J. Deinum for their assistance in prioritising quality criteria for blood pressure measurement.

REFERENCES

1. Dutch Guideline Cardiovascular Risk Management 2006. Utrecht: Dutch Institute for Health Care Improvement CBO, 2006.
2. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol.* 2006;98:673-80.
3. Benavides GA, Squadrito GL, Mills RW, et al. Hydrogen sulfide mediates the vasoactivity of garlic. *Proc Natl Acad Sci USA.* 2007;104:17977-82.
4. Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA. Garlic shows promise for improving some cardiovascular risk factors. *Arch Intern Med.* 2001;161:813-24.
5. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. *J Hypertens.* 1994;12:463-8.
6. Ried K, Frank OR, Stocks NP, Fakler P, Sullivan T. Effect of garlic on blood pressure: a systematic review and meta-analysis. *BMC Cardiovasc Disord.* 2008;8:13.
7. Linde K, Willich SN. How objective are systematic reviews? Differences between reviews on complementary medicine. *J R Soc Med.* 2003;96:17-22.
8. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA.* 1999;282:1054-60.
9. Linde K, Jonas WB, Melchart D, Willich S. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int J Epidemiol.* 2001;30:526-31.
10. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ.* 2001;323:42-6.
11. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ.* 2008;336:601-5.
12. McAlister FA, Straus SE. Evidence based treatment of hypertension. Measurement of blood pressure: an evidence based review. *BMJ.* 2001;322:908-11.
13. Dutch Cochrane Centre. The assessment of a randomized controlled trial. Updated 2009 Jan 17; cited 2009 Feb 2. www.cochrane.nl.

14. Roche V, O'Malley K, O'Brien E. How 'scientific' is blood pressure measurement in leading medical journals? *J Hypertens.* 1990;8:1167-8.
15. Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipids and lipoprotein concentrations in hypercholesterolemic men. *Am J Clin Nutr.* 1997;65:445-50.
16. Auer W, Eiber A, Hertkorn E, et al. Hypertension and hyperlipidaemia: garlic helps in mild cases. *Br J Clin Pract Suppl.* 1990;69:3-6.
17. Bordia A. Knoblauch and koronare Herzkrankheit: Wirkungen einer dreijährigen Behandlung mit Knoblauchextrakt auf die Reinfarkt- und Mortalitätsrate. *Dtsch Apoth Ztg.* 1989;129:16-7.
18. Brewitt B, Lehmann B. Lipidregulierung durch standardisierte Naturarzneimittel: multizentrische Lanzeitstudie an 1209 Patienten. *Kassenarzt.* 1991;5:47-55.
19. Cheng W, Ke Y, Shi Z, et al. Clinical study on effect of garlic in stabilizing the carotid artery atherosclerotic plaque in patients with primary hypertension and coronary artery disease. *Chin J Integr Med.* 2006;12:166-70.
20. Czerny B, Samochowiec J. Klinische Untersuchungen mit einem Knoblauch-Lezithin-Präparat. *Ärztzeitschr Naturheilverf.* 1996;37:126-36.
21. De A Santos OS, Grünwald J. Effect of garlic powder tablets on blood lipids and blood pressure- a six month placebo controlled, double blind trial. *Br J Clin Res.* 1993;4:37-44.
22. De A Santos OS, Johns RA. Effects of garlic powder and garlic oil preparations on blood lipids, blood pressure and well-being. *Br J Clin Res.* 1995;6:91-100.
23. Dhawan V, Jain S. Effect of garlic supplementation on oxidized low density lipoproteins and lipid peroxidation in patients of essential hypertension. *Mol Cell Biochem.* 2004;266:109-15.
24. Durak I, Kavutcu M, Aytaç B, et al. Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. *J Nutr Biochem.* 2004;15:373-7.
25. Gardner CD, Chatterjee LM, Carlson JJ. The effect of a garlic preparation on plasma lipid levels in moderately hypercholesterolemic adults. *Atherosclerosis.* 2001;154:213-20.
26. Grünwald J, Heede J, Koch H, et al. Effects of garlic powder tablets on blood lipids and blood pressure-the Danish multicentre Kwai study. *Eur J Clin Res.* 1992;3:179-86.
27. Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. *Arzneimittel-Forschung.* 1992;42:1473-7.
28. Isaacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. *Arch Intern Med.* 1998;158:1189-94.
29. Jabbari A, Argani H, Ghorbanihaghjo A, Mahdavi R. Comparison between swallowing and chewing of garlic on levels of serum lipids, cyclosporine, creatinine and lipid peroxidation in Renal Transplant Recipients. *Lipids Health Dis.* 2005;4:11.
30. Jain AK, Vargas R, Gotzkowsky S, McMahon FG. Can garlic reduce levels of serum lipids? A controlled clinical study. *Am J Med.* 1993;94:632-5.
31. Kandziora J. Antihypertensive Wirksamkeit und Verträglichkeit eines Knoblauch-Präparates. *Ärztliche Forschung.* 1988;35:1-8.
32. Kandziora J. Blutdruck- und lipidsenkende Wirkung eines Knoblauch-Präparates in Kombination mit einem Diuretikum. *Ärztliche Forschung.* 1988;35:3-8.
33. Kiesewetter H, Jung F, Jung EM, et al. Effects of garlic coated tablets in peripheral arterial occlusive disease. *Clin Investig.* 1993;71:383-6.
34. Lutomski J. Klinische Untersuchungen zur therapeutischen Wirksamkeit von ilja Rogoff Knoblauchpillen mit Rutin. *Z Phytother.* 1984;5:938-42.
35. Macan H, Uykimpang R, Alconcel M, et al. Aged garlic extract may be safe for patients on warfarin therapy. *J Nutr.* 2006;136:S793-4.
36. Mansell P, Reckless JPD, Leatherdale B. The effect of dried garlic powder tablets on serum lipids in non-insulin dependent diabetic patients. *Eur J Clin Res.* 1996;8:25-6.
37. McMahon FG, Jain A, Vargas R, Kadowitz P, McNamara D. Clinical effects of a garlic powder preparation on various cardiovascular risk factors. *Eur J Clin Res.* 1992;3:8-9.
38. Mrozikiewicz A, Lutomski J. Wirkungseffekte einiger Knoblauchpräparate. *Dtsch Apoth Ztg.* 1989;129:16.
39. Saradeth T, Seidl S, Resch K, Ernst E. Does garlic alter the lipid pattern in normal volunteers? *Phytomedicine.* 1994;1:183-5.
40. Simons LA, Balasubramaniam S, Konigsmark M, Parfitt A, Simons J, Peters W. In the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis.* 1995;113:219-25.
41. Steiner M, Khan AH, Holbert D, Lin RI. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. *Am J Clin Nutr.* 1996;64:866-70.
42. Superko HR, Krauss RM. Garlic powder, effect on plasma lipids, postprandial lipemia, low-density lipoprotein particle size, high-density lipoprotein subclass distribution and lipoprotein(a). *J Am Coll Cardiol.* 2000;35:321-6.
43. Turner B, Mølgaard C, Marckmann P. 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.* 2004;92:701-6.
44. Vorberg G, Schneider B. Therapy with garlic: results of a placebo-controlled, double-blind study. *Br J Clin Pract Suppl.* 1990;69:7-11.
45. Zhang XH, Lowe D, Giles P, et al. A randomized trial of the effects of garlic oil upon coronary heart disease risk factors in trained male runners. *Blood Coagul Fibrinolysis.* 2000;11:67-74.
46. Ziaei S, Hantoshzadeh S, Rezasoltani P, Lamyian M. The effect of garlic tablet on plasma lipids and platelet aggregation in nulliparous pregnant at high risk of preeclampsia. *Eur J Obstet Gynecol Reprod Biol.* 2001;99:201-6.
47. Kiesewetter H, Jung F, Pindur G, Jung EM, Mrowietz C, Wenzel E. Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors. *Int J Clin Pharmacol Ther Toxicol.* 1991;29:151-5.
48. Gagnier JJ, DeMelo J, Boon H, Rochon P, Bombardier C. Quality of reporting of randomized controlled trials of herbal medicine interventions. *Am J Med.* 2006;119:800.e1-11.
49. Holanda HEM, Mion JD, Pierin AMG. Medida da pressão arterial: critérios em-pregados em artigos científicos de periódicos brasileiros. *Arq Bras Cardiol.* 1997;68:433-6.
50. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* 1995;273:408-12.
51. Moher D, Pham B, Jones A, et al. Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet.* 1997;352:609-13.