

# Garlic for peripheral arterial occlusive disease (Review)

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## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	2
METHODS . . . . .	3
RESULTS . . . . .	4
DISCUSSION . . . . .	4
AUTHORS' CONCLUSIONS . . . . .	4
ACKNOWLEDGEMENTS . . . . .	4
REFERENCES . . . . .	5
CHARACTERISTICS OF STUDIES . . . . .	5
DATA AND ANALYSES . . . . .	8
Analysis 1.1. Comparison 1 Garlic versus placebo, Outcome 1 Pain-free walking distance. . . . .	8
APPENDICES . . . . .	8
WHAT'S NEW . . . . .	9
HISTORY . . . . .	9
CONTRIBUTIONS OF AUTHORS . . . . .	9
DECLARATIONS OF INTEREST . . . . .	10
SOURCES OF SUPPORT . . . . .	10
INDEX TERMS . . . . .	10

[Intervention Review]

# Garlic for peripheral arterial occlusive disease

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## ABSTRACT

### Background

Commercially available preparations of garlic have been reported to have beneficial effects on some of the risk factors associated with atherosclerosis.

### Objectives

To assess the effects of garlic (both dried and non-powdered preparations) for the treatment of peripheral arterial occlusive disease.

### Search methods

We searched the Cochrane Peripheral Vascular Diseases Group trials register, the Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, Issue 4, 2007, AMED, EMBASE, Science Citation Index, abstracts of relevant symposia and reference lists of relevant articles up to November 2007. We also contacted pharmaceutical companies, investigators and experts in garlic therapies.

### Selection criteria

Randomised trials of garlic therapy in patients with lower limb atherosclerosis were included. The main outcomes were objective measures of progression of underlying atherosclerosis (e.g. ankle pressure measurements, treadmill testing) and subjective measures (e.g. symptom progression).

### Data collection and analysis

Two review authors (RJ and JK) independently extracted data and assessed trial quality. One author (RJ) contacted investigators to obtain information needed for the review that could not be found in published reports.

### Main results

One eligible trial with 78 participants was found. Both men and women (aged 40 to 75) were included. The follow-up period was short, 12 weeks only.

After twelve weeks of treatment, pain-free walking distance increased from 161 to 207 metres in the group receiving garlic and from 172 to 203 metres in the placebo group. This was not a statistically significant difference. There was no difference in change of systolic or diastolic blood pressure, heart rate, ankle and brachial pressures. No severe side effects were observed and nine patients taking garlic (28%) and four patients taking placebo (12%) complained of a noticeable garlic smell.

One further trial was excluded from the review because it did not include any clinical measurements.

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1

## Authors' conclusions

One small trial of short duration found no statistically significant effect of garlic on walking distance.

## PLAIN LANGUAGE SUMMARY

### Garlic for peripheral arterial occlusive disease affecting the legs

The most common symptom of peripheral arterial occlusive disease is intermittent claudication, discomfort in the legs that is triggered by exercise and relieved with rest. The underlying cause is atherosclerosis. Risk factors associated with the development of peripheral arterial disease include cigarette smoking, raised blood cholesterol and other fats (lipids), high blood pressure and diabetes. Garlic has been used as a medicinal therapy since ancient times. The main active ingredient is an unstable odorous sulphurous compound called allicin so that active ingredients may be lost in processing, and with different types of preparation. Commercially available preparations of garlic are reported to have beneficial effects on some of the risk factors for vascular disease. With fresh garlic, at least seven cloves of garlic per day are needed. Apart from the odour, garlic has only minor gastrointestinal side effects.

The review authors made a thorough search of the medical literature and found one controlled trial in which 78 participants with peripheral arterial occlusive disease were randomized to receive garlic or a placebo medication. The dose of garlic was two coated tablets of 200 mg oral standardised garlic powder twice daily. Both men and women, aged 40 to 75 years, were included although sixteen did not keep to their treatment.

After twelve weeks of treatment, pain-free walking distance increased similarly whether receiving garlic or placebo. Similarly there was no difference in the changes in blood pressure, heart rate and pressure differences between the ankle and brachial pressures. No severe side effects were observed although more people taking garlic (28%) than placebo (12%) complained of a noticeable garlic smell. Peripheral arterial occlusive disease is a long-term (chronic) condition and any improvements in symptoms would require longer-term treatment and follow up than in this study.

## BACKGROUND

Peripheral arterial occlusive disease primarily affects the major arteries of the lower limb. The most common symptom in early occlusive disease is intermittent claudication - discomfort in the legs induced by exercise and relieved by rest. Numerous risk factors have been associated with the development of peripheral arterial disease, including cigarette smoking, raised blood lipids, hypertension and diabetes.

The medicinal use of garlic can be traced back to Egyptian times. The primary active component of garlic is an unstable odorous sulphurous compound called allicin. Meta-analysis of commercially available preparations of garlic have been reported to have beneficial effects on some of the risk factors associated with atherosclerosis such as serum cholesterol (Silagy 1994; Warshafsky 1993). With fresh garlic, the dosages needed to inhibit platelet aggregation or lower cholesterol levels are unacceptably high; at least seven cloves of garlic per day (Kleijnen 1989).

Garlic is an acceptable therapy to the general population and, apart

from the odour, has only minor gastrointestinal side effects. Trials with endpoints more meaningful and relevant than laboratory endpoints, however, are necessary before claiming that garlic improves health. Many trials have been carried out to assess its efficacy in the treatment and risk reduction of coronary atherosclerosis, but few trials have been carried out in people with peripheral vascular disease.

The purpose of this review is to assess the efficacy of garlic therapy in improving the morbidity associated with peripheral arterial occlusive disease. The relevant trials of garlic have been considered. As one of the difficulties in showing the effectiveness of garlic is that active ingredients may be lost in processing, the type of preparation (i.e. fresh, powdered or non-powdered) has been taken into consideration.

## OBJECTIVES

To establish the effectiveness of garlic in the treatment of peripheral arterial occlusive diseases.

We wished to test the following hypotheses:

- a) That commercially prepared garlic preparations have a beneficial effect on the morbidity associated with peripheral arterial occlusive disease;
- b) That the magnitude of the effects observed with dried garlic is greater than with non-powder preparations in the treatment of peripheral arterial occlusive disease.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We assessed randomised controlled trials of garlic versus placebo for the treatment of peripheral arterial occlusive disease. As there are currently only a few trials in this area, any trials identified in future that either use alternation (e.g. allocation by date of birth or days of the week) or that have not been analysed on an intention-to-treat basis (as long as all randomised patients were accounted for) will be included. Blinding of participants is a particular problem in garlic trials because of its characteristic smell.

#### Types of participants

People with peripheral arterial occlusive disease were included. Most participants had intermittent claudication (diagnosed either by questionnaire or clinically), but those with critical limb ischaemia and asymptomatic disease identified by testing (angiography, ankle pressures, etc.) were also eligible.

People with aortic disease and no peripheral arterial disease were excluded.

#### Types of interventions

Any trial of garlic therapy for the treatment of peripheral arterial occlusive disease was considered. Since one of the difficulties in showing the effectiveness of garlic is that active ingredients may be lost in processing, the type of preparation (i.e. fresh, powdered or non-powdered) was taken into consideration.

#### Types of outcome measures

Two main outcome measures were considered: objective measures of progression of underlying atherosclerosis (e.g. ankle pressure measurements, treadmill testing, angiography); and subjective measures (e.g. symptom progression).

### Search methods for identification of studies

We searched the trials register of the Cochrane Peripheral Vascular Diseases (PVD) Review Group (last searched 8 November 2007) and the Cochrane Central Register of Controlled Trials CENTRAL in *The Cochrane Library*, (last searched Issue 4, 2007) for reports of randomised controlled trials of garlic for the treatment of lower limb atherosclerosis. We used the search strategy developed by the Cochrane PVD Group to search these databases.

The trials register of the PVD Group has been constructed from regular electronic searches of MEDLINE (January 1966 to date), EMBASE (January 1980 to date), and through hand-searching relevant journals and conference proceedings. The full list of journals that have been handsearched, as well as the search strategies for the electronic databases are described in the 'Search strategies for the identification of studies' section within the editorial information about the Cochrane PVD Group in *The Cochrane Library* (<http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/PVD/frame.html>). See Appendix 1 for the strategy used to search CENTRAL.

Additional search strategies used to identify studies included: searches of AMED (Allied and Alternative Medicine Database), EMBASE and ISI WoS Science Citation Index using the terms 'garlic' and ('peripheral arterial occlusive disease' or 'intermittent claudicat\*' or 'lower limb atherosclerosis'); direct contact with principal investigators of trials; searching abstracts of relevant symposia as published in journals and through colleagues who attended; handsearching of other relevant medical journals; contact with experts in garlic therapies; direct contact with pharmaceutical companies listed as manufacturing garlic; cross referencing the bibliographies of identified trials. The most recent searches were carried out in November 2007.

### Data collection and analysis

#### Selection of trials

Ruth Jepson selected trials for possible inclusion in the review and sought additional information from the principal investigators of all trials.

#### Assessment of methodological quality

Ruth Jepson and Jos Kleijnen independently assessed the methodological quality of trials using a standard scoring sheet developed by the Cochrane PVD Review Group. Any discrepancies were considered by Gill Leng until a consensus decision could be made.

#### Data extraction

For the one included trial, information was collected about the method of randomisation, blinding and whether an intention-to-

treat analysis could possibly be done. Ruth Jepson and Jos Kleijnen extracted data independently to ensure quality control. Self-designed forms were used for the data extraction in accordance with Cochrane guidelines.

### Statistical analysis

If more trials become available in the future, the heterogeneity between trial results will be tested. Such tests will be subjective, by clinical judgement of differences in patient populations, interventions and outcome assessments, and objective, using appropriate statistical tests. Depending on the results of the heterogeneity assessments, part of the outcomes may be pooled statistically using relevant techniques.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Only one trial ([Keisewetter 1993](#)) was identified that fulfilled the criteria for inclusion in the review. Summary details of this trial are given in the 'Characteristics of included studies' table. The trial was relatively small with only 80 patients being randomised and 16 of these did not show sufficient compliance. The duration of the trial was 12 weeks. Further details were requested from the principal author, but no reply was received.

One further trial ([Koscielny 1999](#)) was excluded because it only measured arteriosclerotic effects and not clinical symptoms. In addition, the subject population was described as 'probationers', and it was not clear if these were healthy volunteers or people with pre-existing disease.

### Risk of bias in included studies

The one included study ([Keisewetter 1993](#)) was randomised, double-blinded and placebo-controlled. There was no mention of the method of randomisation, nor the concealment of allocation (score B). Inclusion and exclusion criteria were adequate, but the trial was of short duration (only 12 weeks). No intention-to-treat analysis was used for the sixteen patients who did not complete the study.

### Effects of interventions

The weighted mean difference and a fixed-effect model were used to test the significance of the results. The mean difference between the two groups at the end of treatment was analysed rather than the mean change within the two groups before and after treatment. After twelve weeks of treatment, pain-free walking distance increased from 161 to 207 metres in the garlic group and from 172 to 203 metres in the placebo group. There was no difference in change of systolic or diastolic blood pressure, heart rate, ankle and brachial pressures. No severe side effects were observed but nine patients taking garlic (28%) and four patients taking placebo complained of a noticeable garlic smell (12%). No studies were found comparing dried garlic with non-powder preparations.

## DISCUSSION

The only included study was small and of short duration (12 weeks). Although no statistically significant improvement was found overall, the authors of the trial report that there was a significant increase in walking distance, but this only occurred in the last weeks of therapy. Peripheral arterial occlusive disease is a chronic condition, and any subjective or objective improvement in outcomes would require longer term therapy and follow up.

## AUTHORS' CONCLUSIONS

### Implications for practice

One small trial of short duration found no statistically significant effect on walking distance. Thus, at this stage, garlic as a therapy for the treatment of peripheral arterial occlusive disease cannot be recommended.

### Implications for research

Further trials of garlic therapy for the treatment of peripheral arterial occlusive disease are required to determine its effectiveness. These trials should be large and of reasonable duration.

## ACKNOWLEDGEMENTS

We would like to thank Claire Allen (Consumer Representative, Complementary & Alternative Medicine Field) for her very useful comments on the review. We would also like to thank the Cochrane Consumer Network for supplying the Plain Language Summary.

## REFERENCES

### References to studies included in this review

#### **Keisewetter 1993** *{published data only}*

Keisewetter H, Jung F, Jung EM, Blume J, Mrowietz C, Birk A, et al. Effects of garlic coated tablets in peripheral arterial occlusive disease. *Clinical Investigator* 1993;**71**(5):383–6.

### References to studies excluded from this review

#### **Koscielny 1999** *{published data only}*

Koscielny J, Klussendorf D, Latza R, Schmitt R, Radtke H, Siegal G, et al. The antiatherosclerotic effect of *Allium sativum*. *Atherosclerosis* 1999;**144**(1):237–49.

### Additional references

#### **Kleijnen 1989**

Kleijnen J, Knipschild P, Ter Riet G. Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments with emphasis on commercially available preparations. *British Journal of Clinical Pharmacology* 1989;**28**(5):535–44.

#### **Silagy 1994**

Silagy C, Neil A. Garlic as a lipid lowering agent - a meta-analysis. *Journal of the Royal College of Physicians of London* 1994;**28**(1):39–45.

#### **Warshafsky 1993**

Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. A meta-analysis. *Annals of Internal Medicine* 1993;**119**(7 Pt 1):599–605.

\* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Keisewetter 1993

Methods	Study design: Randomised, placebo controlled, double-blind single centre trial Method of randomisation: not stated. Exclusions post-randomisation: Not stated. Losses to follow up: 8 patients in each group (out of a total of 78 patients)	
Participants	Participants: men and women aged 40 to 75 years. Country: Germany. Inclusion criteria: femoral and/or tibial type PAOD; angiographically-localised stenosis or occlusion of the superficial femoral artery free vascular system of the popliteal artery (stenosis under 60% was excluded); mean stable PFWD between 80 and 300 metres; Doppler pressure values over peripheral arteries at rest greater than 50 mm Hg, and haematocrit values up to 47% Exclusion criteria: arterial occlusion of the pelvic type in the lower extremities (or stenosis over 60%) ; endangiitis obliterans; nonvascular walking impediment; operations within the preceding 3 months; history of a cerebral infarction with gait disturbances; severe cerebral insufficiency; polyneuropathy; cardiac infarction within the past 6 weeks; unstable angina pectoris, crescendo angina, angina CCS stage III; cardiac insufficiency stage II or IV; haemodynamically relevant valvular heart defect*; arrhythmia Lown IVb and V; higher degree SA and AV blocks; heart rate at rest below 50 per min or over 100 per min; chronic venous insufficiency; inadequately compensated severe internal diseases; cerebral spasms; intake of anticoagulants, rheological or vasoactive drugs, analgesics and antiphlogistic intake not discontinued for at least 4 weeks prior to the study; readjustment or correction of therapy with cardiac glycosides, diuretics, antidiabetics, antiarrhythmics, calcium antagonists; Doppler pressure values over peripheral arteries below 50 mm Hg	
Interventions	Treatment: 2 x 2 coated tablets of 200 mg oral standardised garlic powder (Kwai, Sapec) Control: Placebo tablets. Duration of trial: 12 weeks.	
Outcomes	Primary: PFWD. Secondary: Diastolic blood pressure, cholesterol concentrations, rheological parameters, side effects	
Notes	Original article states 'hemodynamically relevant valvular nearby defect'	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

PAOD: peripheral arterial occlusive disease

PFWD: pain-free walking distance



### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Koscielny 1999	Only measured anti-atherosclerotic effects such as plaque volume. Did not include any clinical measurements such as walking distances. Also, not clear who the study population was (only described as 'probationers')

## DATA AND ANALYSES

### Comparison 1. Garlic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Pain-free walking distance</a>	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

#### Analysis 1.1. Comparison 1 Garlic versus placebo, Outcome 1 Pain-free walking distance.

Review: Garlic for peripheral arterial occlusive disease

Comparison: 1 Garlic versus placebo

Outcome: 1 Pain-free walking distance

Study or subgroup	garlic		placebo		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
Keisewetter 1993	32	207.1 (85)	32	203.1 (72.8)		4.00 [ -34.78, 42.78 ]

-100 -50 0 50 100  
garlic placebo

## APPENDICES

### Appendix I. CENTRAL search strategy

#1 MeSH descriptor Intermittent Claudication explode all trees  
 #2 intermitt\* near claudic\*  
 #3 peripher\* near arter\* near occlus\*  
 #4 critic\* near limb\* near isch\*  
 #5 (#1 OR #2 OR #3 OR #4)  
 #6 MeSH descriptor Garlic explode all trees  
 #7 MeSH descriptor Allium explode all trees  
 #8 garlic\*  
 #9 allium\*  
 #10 (#6 OR #7 OR #8 OR #9)  
 #11 (#5 AND #10)

## WHAT'S NEW

Last assessed as up-to-date: 7 November 2007.

Date	Event	Description
12 May 2008	Amended	Converted to new review format.

## HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 3, 1997

Date	Event	Description
14 November 2007	New search has been performed	No new trials found. Conclusions remain unchanged.
21 November 2006	New search has been performed	Added Plain Language Summary. No new trials found.
11 July 2005	New search has been performed	No new trials found. Review updated without change.
26 May 2004	New search has been performed	Review updated without change. No new studies found.
4 April 2003	New search has been performed	One new study excluded, no change to conclusions.

## CONTRIBUTIONS OF AUTHORS

Ruth Jepson: selected trials for inclusion; sought additional information from the principal investigators of all trials; assessed trials for quality; extracted data; wrote text; revised review (April 2003).

Jos Kleijnen: assessed trials for quality; extracted data.

Gillian Leng: resolved disagreements between RJ and JK regarding trial quality.

The Peripheral Vascular Diseases Review Group assisted with searching for trials for this review.

## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT

### Internal sources

- The University of Edinburgh, UK.

### External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Phytotherapy; \*Plants, Medicinal; Arterial Occlusive Diseases [\*drug therapy]; Garlic [\*therapeutic use]

### MeSH check words

Female; Humans; Male