Br. J. clin. Pharmac. (1989), **28**, 535–544

Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments with emphasis on commercially available preparations.

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1 Claims for beneficial effects on cholesterol levels, fibrinolytic activity, and platelet aggregation are attributed both to fresh garlic and onions (or their extracts) and to commercially available preparations.
2 Regarding fresh garlic, the claims have been confirmed, but so far only at very high dosages.
3 For onions and commercially available supplements contradictory results have been reported.
4 All published trials showed severe methodological shortcomings. Some trials were not randomized and/or not blinded whilst this was possible, and in only one of every three studies more than 25 patients participated in each treatment group. In no trial was prognostic comparability of the treatment and the control groups ascertained. At the moment there is inadequate scientific justification for garlic supplementation.

Keywords garlic onions commercial preparations cardiovascular disease

Introduction

People who take garlic (*Allium sativum*) supplements hope to improve their well-being and to reduce the risk of various diseases. Numerous myths about its medicinal properties have existed for centuries in various cultures. According to some investigators the lower incidence of cardiovascular disease in southern countries may partly be due to consumption of large quantities of garlic (Slater, 1979). Some more specific claims have been made on the beneficial influence of garlic on several risk factors for cardiovascular disease. Garlic is said to lower serum cholesterol, enhance blood fibrinolytic activity, and to inhibit platelet aggregation. Additional claims have been made on its hypoglycaemic effects, antibiotic actions and anticarcinogenic properties. Similar claims have appeared for onions (*Allium cepa*). Thousands of publications have appeared in the last 20 years dealing with research on garlic and onions.

We found 18 controlled trials about the effects on presumed cardiovascular risk indicators in humans. In this article emphasis is put on the results of trials on commercial garlic preparations. Comparing the effects of these preparations to fresh garlic is interesting, especially for those preparations which are (or claim to be) odourless. The typical odour is an unavoidable side effect and substantial amounts of fresh garlic seem to be needed to obtain measurable effects. This review deals critically with methodological problems of these trials. Besides an assessment of the evidence, suggestions for further research are given.

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Biochemical aspects

Alliin ((+)-S-allyl-L-cysteine sulphoxide) is converted by action of the enzyme allinase into allicin (diallyl thiosulphate). This happens when the garlic bulb is crushed. Allicin can be converted (by heat) into diallyldisulphide which in its turn is converted into various sulphide containing substances which cause the typical smell of garlic (di-, tri-, polysulphides). Allicin and diallyldisulphide combine to 4,5,9-trithiadodeca-1,6,11-triene 9-oxide which is called ajoene. In onions the same and related substances are found e.g. cycloalliin (5-methyl-1,4-thiazan-3-carboxylic acid 1-oxide), which is odourless (Augusti & Benaim, 1975). Whitaker (1976) gives a list of compounds of intact onion, of crushed onion and crushed garlic, and a list of compounds identified in steam-distilled onion oil. Additional compounds have been reported by several authors (Ariga *et al.*, 1981; Block & Ahmad, 1984; Bayer *et al.*, 1988). Block & Ahmad (1984) suggest a scheme by which the decomposition of allicin takes place.

Certain actions (on blood lipids, coagulation factors, fibrinolytic activity, blood sugars and antibiotic actions) of onion and garlic are ascribed to specific components listed in Table 1, which is not intended to be complete.

Methods

Experiments were found by a computer search (MEDLINE CD-ROM 1983–1989). Further experiments were found by checking references extensively and by personal communication with authors of experiments. Trials were only reviewed for this article if a control group was included. Only experiments in humans are discussed.

For any claim of therapeutic effects of a specified substance, a randomized, double-blind, placebo-controlled trial is the method of preference to assess specific effects attributable to the experimental intervention. Randomization (and restriction of the test group and/or prestratification if appropriate) takes care of known and unknown confounders which otherwise could influence the prognostic comparability of the test groups. In trials on the effects of garlic or onions, randomization should be no problem. The substance used in the trial, its preparation, its dosage and the way in which it is taken by the patients should be described adequately. Blinding is a major problem in garlic trials because of its characteristic smell. If fresh, cooked or fried garlic is used, blinding the patient is not possible. Only trials of a very short duration can be done with these substances because of problems in controlling the external circumstances for both groups. In several trials garlic was given in this form for weeks or months. Controlling of the patient's diets and other habits for such a long period is an illusion, and differences in uncontrolled factors may account for the results. If capsules or tablets are used, placebo capsules or tablets, indistinguishable from the real ones, should be given. People should be asked if they know in what treatment group they are, to check the blinding. Also compliance must be checked.

Measurements of the effects, especially blood tests of cholesterol levels, fibrinolytic activity and tests of platelet aggregation, should be performed with accepted methods, and physiological variations should be taken into account. For instance, blood fibrinolytic activity may vary with different blood fibrinogen concentrations and other factors.

Statistical analysis in controlled trials should be based on 'between groups comparisons' and differences should be presented with confidence intervals. In most articles presented in this review the reported results and significance levels were based on 'within group comparisons'. Differences between groups with confidence intervals cannot be given because of lack of data in the articles themselves.

Results

The results presented in the tables show the percentage of change from baseline levels for treatment and control groups.

Fresh garlic

Five out of six trials in which fresh garlic or freshly made extracts were used, and in which cholesterol was measured, show a lowering of serum cholesterol. Furthermore, it was shown that garlic increases fibrinolytic activity and inhibits platelet aggregation in all studies reporting these measurements. Unfortunately, the dosages needed to obtain these effects are relatively high. The dosage which was mostly used is approximately (the equivalent of) 0.25 to 1 g of fresh garlic kg^{-1} bodyweight (7 to 28 cloves each day!).

Fresh onions

An increase of fibrinolytic activity was found in all three trials in which onions were used, while

Table 1 Active principles of garlic and onions

Anti-platelet:
Garlic:
alliin (Hanley & Fenwick, 1985)
allicin (Block & Ahmad, 1984)
allyl-1.5-hexadienyl-trisulphide (Block & Ahmad, 1984)
allyl methyl trisulphide (Block & Ahmad, 1984)
S-allyl 2-propene thiosulphinate (Block & Ahmad, 1984)
ajoene (Apitz-Castro *et al.*, 1984)
diallyl disulphide (Ariga *et al.*, 1981)
diallyl trisulphide (Ariga *et al.*, 1981)
1.5-hexadienyl-trisulphide (Apitz-Castro *et al.*, 1983)
methyl allyl trisulphide (Ariga *et al.*, 1981)
2-vinyl-1.3-dithiene (Apitz-Castro *et al.*, 1983)
3-vinyl-1.2-dithiene (Block, 1985)

Onions
adenoside (Kawakishi & Morimitsu, 1988)
alliin (Liakopoulou-Kyriakides, 1985)
1-(methyl sulphinyl)-propyl methyl disulphide (Kawakishi & Morimitsu, 1988)
9,10,13-trihydroxy-11-octadecenoic acid (Üstünes *et al.*, 1985)
9,12,13-trihydroxy-10-octadecenoic acid (Üstünes *et al.*, 1985)
trans-5-ethyl-4,6,7-trithia-2-decene-4-oxide (Bayer *et al.*, 1988)
trans,trans (and trans,cis) 5-ethyl-4,6,7-trithia-2,8-decadiene-4-oxide (Bayer *et al.*, 1988)

Antibiotic
Garlic:
allicin (Hanley & Fenwick, 1985)
ajoene (Yoshida *et al.*, 1987)
diallyl disulphide (Amonkar & Reeves, 1971)
diallyl trisulphide (Amonkar & Reeves, 1971)

Fibrinolysis:
Garlic:
methane-thiol-3,4-dimethylthiophene (Augusti & Benaim, 1975)
methyl cysteine sulphoxide (Augusti & Benaim, 1975)
propyl allyl disulphide (Augusti & Benaim, 1975)
propyl cysteine sulphoxide (Augusti & Benaim, 1975)

Onions:
cycloalliin (August & Benaim, 1975)

Blood sugar, insulin:
Garlic:
allicin (Hanley & Fenwick, 1985)
diallyl disulphide (Hanley & Fenwick, 1985)

Onions:
allyl propyl disulphide (Augusti & Benaim, 1975)

Blood lipids, cholesterol:
Garlic:
alliin (Kamanna & Chandrasekhara, 1984)
allicin (Kamanna & Chandrasekhara, 1984)
allyl propyl disulphide (Bordia, 1975)
diallyl disulphide (Bordia *et al.*, 1975)
S-methyl-L-cysteine sulphoxide (Kamanna & Chandrasekhara, 1984)

Table 2 Results of trials in which fresh garlic or freshly made extracts were used, as percentage of change compared with baseline

Author, year, randomization	*Number, fat load*	*Preparation, dosage*	*Duration*	*Cholesterol*	*Fibrinolytic activity*	*Coagulation platelets*
Bordia *et al.* (1975), R	10 per group, butter	garlic (d;e), equal to 50 g	once	(+) −6;−7/7	(+) 15;15/−49	(+) 23;22/−13 coagulation time
Bordia *et al.* (1977)	10/10	garlic (d), equal to 1g kg^{-1}	20 days	NM	(+) 96/24	NM
Bhushan *et al.* (1979) R	15/10	garlic (a), 10 g	2 months	(+) −15/0	NM	NM
Sucur (1980) R	200, crossover	garlic (a;f), 15 g; 30 g	25 days	(+) −10;−10/9	NM	NM
Bordia (1981) R	33/29	garlic (d), 0.25 mg kg^{-1} (equal to 30 g)	10 months	(+) −18/0	NM	NM
Chutani & Bordia (1981) R	10;10/10	garlic (a;b), 0.5 g kg^{-1}	1 month	NM	(+) 85;72/3	NM
Arora & Arora (1981)	30, crossover, butter	garlic (d), equal to 50 g; clofibrate, 500 mg	once	(−) 0;1/−1	(+) 3;71/−31	(+) 0;−2/−18, coagulation time
Bordia *et al.* (1982)	20/20, butter	garlic (d), 0.25 mg kg^{-1}	3 weeks	(+) 2/10	(+) 36/−23	(+) −16/31, platelet adhesive index

R = randomized
(+) = beneficial effect
(−) = no effect
NM = not measured
/ = separation of treatment group(s) from control group(s)
; = separation of different treatment groups

a = fresh garlic
b = fried garlic
c = steam distilled extract of garlic
d = ether extract of garlic
e = juice of garlic
f = water-ethanol extract

Table 3 Results of trials in which fresh onions or freshly made extracts were used, as percentage of change compared with baseline

Author, year, randomization	*Number, fat load*	*Preparation, dosage*	*Duration*	*Cholesterol*	*Fibrinolytic activity*	*Coagulation platelets*
Menon *et al.* (1968)	8;14, crossover, breakfast	onions (a;b), 60 g	once	(−) a;b pooled, 3/–2	(+) 50;47/−14;−25	(−) a;b pooled, 0/3, recalcified clotting time
Bordia *et al.* (1975), R	10;10/10, butter	onions (c;d), equal to 50 g	once	(+) −3;−3/7	(+) 16;16/−49	(+) 11;10/−13, coagulation time
Arora & Arora (1981)	30, crossover, butter	onions (c), equal to 50 g; clofibrate 500 mg	once	(−) −2;1/−1	(+) 0;71/−31	(−) −14;−2/−18, coagulation time

R = randomized
(+) = beneficial effect
(−) = no effect
NM = not measured
/ = separation of treatment group(s) from control group(s)
; = separation of different treatment groups

a = boiled onions
b = fried onions
c = ether extract of onions
d = juice of onions

measurements of cholesterol levels and platelet aggregation showed contradictory results.

Sharma *et al.* (1977) found in a small trial that an aqueous extract of onions had hypoglycaemic effects. Other parameters have to our knowledge not been tested in humans with control groups. For further details of the studies in which fresh garlic and onions were used and for the results of uncontrolled human studies and of interesting animal studies, we refer to other reviews (Lau *et al.*, 1983; Fenwick & Hanley, 1986; Ernst, 1987; Kendler, 1987). A serious side effect – the odour – invariably occurs at effective dosages of garlic, which will be unacceptable for most people.

Commercially available preparations

What about the commercially available (deodourized) products? In studies with rats and pullets deodourized garlic was shown to retain active components (Qureshi *et al.*, 1983; Lau *et al.*, 1987). There were only seven controlled studies in humans.

Augusti & Benaim (1975) compared the effects of a commercially produced steam distilled extract of onions with self-prepared ether extracts and to purified cyclo-alliin on blood fibrinolysis. The steam-distilled oil yielded 0.28g kg^{-1} of raw onion. The dosage was 125 mg per subject (healthy volunteers) given once. The ether-extractable oil yielded 1 g kg^{-1} of raw onion. Cyclo-alliin (yield 0.2 g kg^{-1}) was given in a dose of 0.125 g. A number of sulphur-containing components was present in both extracts, as was shown by gas chromatography. Measurements were performed before and 2 h after the products had been taken. This study, which was not randomized and not blinded and in which six patients in each group participated, showed that all three substances increased the fibrinolytic activity compared with controls.

Agarwal *et al.* (1977) assessed the effect of 0.25 g synthesized cyclo-alliin (equal to 1.2 kg of extracted onions) or placebo (lactose) on fibrinolytic activity and platelet aggregating activity in 18 male volunteers in a randomized double-blind cross-over trial. Measurements were performed before and 1.5 h after the medication was taken. They found an increased fibrinolytic activity and no effect on platelet aggregability.

Lutomski (1984) tested in a double-blind randomized study the effect of six garlic pills a day (Ilja Rogoff garlic pills with rutin, one pill contains 50 mg 'bulb. allii sat sicc.' and other substances) against undefined placebos in 102 patients aged 45–60 years complaining of decreased operating capacity, joy of life and physical well-being. After 12 weeks full data were available of 82 patients, 44 on garlic and 38 on placebo. Lipids, fibrinolytic activity, psychologic tests, pulse, and glucose showed no differences. Positive effects were measured for subjective symptoms (headache, sleep, dizziness, digestion, joy of life, physical well-being, operating capacity) and blood pressure. For all subjective symptoms 52% of patients using garlic showed improvement, compared to 35% of the patients using placebo. Data on blood pressure were only given for patients with initial high pressures (22 using garlic, 14 on placebo). Improvement was found in 17 patients on garlic and eight patients on placebo. It was not mentioned whether compliance or blinding was checked.

Ernst *et al.* (1985) treated 20 hypercholesterolaemic patients in an open study with a hypocaloric diet. Ten patients also received 21 g garlic powder (Kwai Tabs) equivalent to 64 g fresh garlic a day for 4 weeks. They found lower cholesterol and triglyceride levels in the patients treated with garlic.

Luley *et al.* (1986) assessed the effects of a commercial dried garlic preparation in patients with primary hyperlipoproteinemia types IIa, IIb and IV in two randomized double-blind cross-over studies. Garlic and placebo treatment were given for 6 weeks each. Dried garlic was administered in a dosage of 600 mg a day to 34 patients in the first study, and in a dosage of 1350 mg a day to 51 patients in the second study. The higher dose corresponds to 5 g of fresh garlic. Compliance was estimated 86% by tablet counts. Neither dosage showed any effect on many lipid parameters and coagulation parameters. The use of the relatively low dosages compared to those administered in other studies, and a possible loss of the active principle due to the drying process might explain the negative results according to Luley *et al.* We would like to add that a carry-over effect might explain the negative results since no wash-out period was mentioned. Some of the patients in the second study reported complaints of a bad smell.

Lau *et al.* (1987) found in a randomized study that a liquid garlic extract (Kyolic) was effective in lowering serum cholesterol and triglycerides in hyperlipidaemic patients. Sixteen patients (initial cholesterol 220–440 mg dl^{-1}, conversion factor to mmol l^{-1} is 0.026) took four 1 ml capsules containing 250 mg ml^{-1} dry weight of the active garlic components and 16 patients took an indistinguishable placebo for 6 months. Fourteen patients were lacto-ovo vegetarians, 10 were occasional meat eaters and eight were

regular meat eaters. It was not stated whether the patients and investigators were blinded. Five patients withdrew, one taking garlic and four taking placebo, because of minor discomforts. After 6 months mean serum cholesterol had changed from 306 to 262 mg dl^{-1} and from 302 to 292 mg dl^{-1} in the garlic and placebo group respectively. Data on triglycerides, HDL, LDL etc. were only shown for the patients taking garlic. In normolipidaemic patients (fourteen subjects receiving garlic or placebo) 'data . . . are not shown since no significant changes were noted'.

Sitprija *et al.* (1987) studied the effect of 350 mg of garlic (spray dried method) or an undefined placebo twice daily in a double-blind randomized study in forty non-insulin dependent diabetic patients. Blood glucose and serum immunoreactive insulin responses to an oral glucose load were measured before and 1 month after treatment. Blood total cholesterol, high density lipoprotein and triglyceride levels were also measured. Thirty-three patients completed the study. No differences, and no side effects of garlic were observed. It was not mentioned whether compliance or blinding was checked.

Discussion and conclusion

Commercial garlic preparations are often manufactured with heat application in at least some stage of the process. Besides heat, drying and pulvering, the essential oil is often extracted by steam distillation using ether or methanol. At least one company (Wakunaga, Kyolic) uses a so-called 'cold aging process' which means that the garlic bulbs are stored for some 20 months. In this manner components that cause the bad smell are converted or vapourized. Whether active substances are left after the processing and storage is of course the crucial question. The exact composition of commercial garlic preparations is mostly unknown and surely there are

Table 4 Results of trials in which commercially available preparations were used, as percentage of change compared with baseline

Author, year, randomization	*Number, fat load*	*Preparation, dosage*	*Duration*	*Cholesterol*	*Fibrinolytic activity*	*Coagulation platelets*
Onions						
Augusti & Benaim (1975)	6/6	steam dist.	once	NM	(+) 87/7	NM
		ether dist.; 2 preparations	once	NM	(+) 68;50/13;15	NM
		cycloalliin	once	NM	(+) 42/13	NM
Agarwal *et al.* (1977), R	18 crossover	cycloalliin	once	NM	(+) 77/7	(−) no difference
Garlic Lutomski (1984), R	44/38	Ilja Rogoff	12 weeks	(−) no diff.	(−) no diff.	NM
Ernst *et al.* (1985)	10/10	Kwai tabs	4 weeks	(+) −22/−12	NM	NM
Luley *et al.* (1986), R	34;51 crossover	dried garlic	6 weeks	(−) no diff.	NM	(−) no diff.
Lau *et al.* 1987, R	16/16	Kyolic	6 months	(+) −14/−3	NM	NM
Sitprija *et al.* (1987), R	20/20	spray dried garlic	1 month	(−) 5/1	NM	NM

R = randomized
(+) = beneficial effect
(−) = no effect
NM = not measured
/ = separation of treatment group(s) from control group(s)
; = separation of different treatment groups

many preparations on the market in which active compounds like ajoene and the cyclic anti-thrombotic compounds cannot be isolated (Block, 1985). Most reports mention the laboratory methods used, but the contents of the preparations of garlic or onions are not described (except in the studies in which cyclo-alliin was used). One should bear in mind that the dose of the different components in garlic may vary to a great extent in different regions and years, which might influence the composition of garlic preparations.

The results of the experiments with fresh garlic are consistent: garlic causes an increase of fibrinolytic activity, it inhibits platelet aggregation and it also lowers cholesterol levels. The dosages needed are for most western people unacceptably high: at least 7 cloves of garlic each day. We did not find experiments in which low dosages (for instance one clove a day) were used. In several (cross-over) experiments four or five different preparations were given once in the same week. At each following day, initial levels of cholesterol and fibrinolytic activity had returned to baseline levels. Therefore, it seems that the effects only last for several hours after intake. Bordia (1981) and Lau *et al.* (1987) in longer term studies reported an initial raise of cholesterol levels (Bordia used an ether extract of garlic and Lau *et al.* used Kyolic) and a decrease below baseline levels after several months of garlic intake. Fresh garlic may cause dermatitis, gastrointestinal problems and allergic reactions.

Fresh onions also appear to cause an increase of fibrinolytic activity but regarding the other parameters contradictory results have been reported.

When commercially available preparations were tested, contradictory results have been reported too. Besides a bad smell, no side effects of commercial preparations were reported.

It is easy to criticize a study on methodological shortcomings. In practice, however, it is often not possible to conduct an impeccable trial. When fresh garlic is used, blinding of the patient is not possible. This may result in differences in external circumstances. The risk of measurement bias is limited when only laboratory parameters are assessed. The results of these unblinded trials may be biased, but they show a remarkable consistency.

Only eleven out of eighteen trials were randomized, five in which fresh garlic was used, one in which onions were used and five in which commercial preparations were used, but not one described how the randomization was executed. From the randomized studies using commercial preparations four out of five were blinded. The number of people in the studies was limited. In only six studies more than 25 patients participated in each treatment group. In no article was it mentioned whether the placebo was tested for indistinguishability and whether blinding was checked when appropriate. Compliance was checked in two studies. Proper randomization, sufficient numbers of patients, checking of the placebo, compliance and blinding are factors that must be controlled whenever possible. It can be concluded that all trials of the effects of garlic and onions on factors associated with cardiovascular disease show several major methodological shortcomings.

Several of the active components such as allicin, ajoene and cycloalliin (found in onions) can be synthesized. Many components of garlic and onion have been identified, and supplementation with isolated components of garlic may give no side effects, while causing beneficial effects. Unfortunately, the components that cause the bad smell may also be the active ones i.e. sulphides, with one or two exceptions like cycloalliin.

If a substance is effective in lowering serum cholesterol and if it inhibits platelet aggregation it does not necessarily follow that it is good for general health. It is doubtful whether healthy people need a change of their fibrinolytic activity, or inhibition of their platelet aggregation. Even lowering cholesterol levels is no guarantee for beneficial effects (Committee of Principal Investigators, 1978). Trials with endpoints that are more relevant than mere laboratory measurements are necessary before claiming that garlic improves health. For instance, morbidity and mortality rates could be assessed. These trials are, of course, expensive and time consuming and there should be good reasons to start them. It is not probable that these trials will be done in the near future. In that case we suggest that the proper dose and duration of intake are assessed, and that the preparations of garlic and onions are standardized. Their effects should be compared to those of other drugs with similar action, before large scale trials are being considered. Side effects should also be taken into account.

For this moment there is inadequate scientific justification for garlic supplementation.

This article was supported by a grant of the Dutch Ministry of Welfare, Public Health and Cultural Affairs.

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(Received 9 May 1989, accepted 13 July 1989)