Significance of Garlic and Its Constituents
in Cancer and Cardiovascular Disease

Garlic and Cardiovascular Disease: A Critical Review[1,2]

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ABSTRACT   Epidemiologic studies show an inverse correlation between garlic consumption and progression of cardiovascular disease. Cardiovascular disease is associated with multiple factors such as raised serum total cholesterol, raised LDL and an increase in LDL oxidation, increased platelet aggregation, hypertension, and smoking. Numerous in vitro studies have confirmed the ability of garlic to reduce these parameters. Thus, garlic has been shown to inhibit enzymes involved in lipid synthesis, decrease platelet aggregation, prevent lipid peroxidation of oxidized erythrocytes and LDL, increase antioxidant status, and inhibit angiotension-converting enzyme. These findings have also been addressed in clinical trials. The studies point to the fact that garlic reduces cholesterol, inhibits platelet aggregation, reduces blood pressure, and increases antioxidant status. Since 1993, 44% of clinical trials have indicated a reduction in total cholesterol, and the most profound effect has been observed in garlic's ability to reduce the ability of platelets to aggregate. Mixed results have been obtained in the area of blood pressure and oxidative-stress reduction. The findings are limited because very few trials have addressed these issues. The negative results obtained in some clinical trials may also have resulted from usage of different garlic preparations, unknown active constituents and their bioavalability, inadequate randomization, selection of inappropriate subjects, and short duration of trials. This review analyzes in vitro and in vivo studies published since 1993 and concludes that although garlic appears to hold promise in reducing parameters associated with cardiovascular disease, more in-depth and appropriate studies are required.   J. Nutr. 136: 736S–740S, 2006.

KEY WORDS: • garlic • hypercholesterolemia • cardiovascular disease • clinical trials

Dietary factors play a key role in the development of some human diseases, including cardiovascular disease. Epidemiologic studies indicate that diets rich in fruits, vegetables, and spices are associated with lower risk of all-cause, cancer, and cardiovascular-disease death (1,2). It has also been suggested that the benefits of fruit and vegetable consumption appear to be primarily related to cardiovascular disease and not cancer (3). These foods contain phytochemicals that have anticancer and antiinflammatory properties, which confer many health benefits. One source of such phytochemicals is garlic, whose role in the prevention and treatment of cardiovascular diseases (and cancer) is best known throughout the world.

Cardiovascular disease

Cardiovascular disease is a complex and multifactorial disease and is characterized by multiple factors. Epidemiologic studies have identified these as elevated serum lipids (cholesterol and triglycerides), increased plasma fibrinogen and coagulation factors, increased platelet activation, alterations in glucose metabolism, and smoking (4). The oxidative modification of LDL by reactive oxygen species (ROS)[4] is also now considered an important mechanism in the development of atherosclerosis, as is the pathogenesis of hypertension (5,6). There is also considerable evidence supporting the involvement of platelets in the development of athersosclerosis. Increased

[4] Abbreviations used: AGE, aged garlic extract; HMG-CoA-reductase, 3-hydroxy-3-methylglutaryl coenzyme A reductase; GSH, reduced glutathione; GSSG, glutathione disulfide reductase; NO, nitric oxide; PAF, platelet-activating factor; ROS, reactive oxygen species; SAC, *S*-allylcysteine; SOD, superoxide dismutase.

platelet activity has been found in smokers as well as in patients suffering from vascular injury, hyperlipidemia, and hypertension. Increased HDL levels are negatively correlated with cardiovascular disease. Normalization of abnormal lipids and lipoproteins, hypertension, inhibition of platelet aggregation, and an increase in antioxidant status are believed to improve cardiovascular disease.

Garlic: the historical perspective

Garlic (*Allium sativum*) is believed to have originated in Central Asia and belongs to the Alliacae family. It is used universally as a flavoring agent, traditional medicine, and a functional food to enhance physical and mental health. The beneficial effects of garlic consumption in treating a wide variety of human diseases and disorders have been known for centuries; thus, garlic has acquired a special position in the folklore of many cultures as a formidable prophylactic and therapeutic medicinal agent. It is even cited in the Egyptian *Codex Ebers,* a 3,500-y-old document, as useful in the treatment of heart disorders, tumors, worms, bites, and other ailments (1). Garlic is also reported to inhibit the pathogenesis of cardiovascular disease and to prevent cancer and other chronic diseases associated with aging (7). Over the last one-quarter century the role of garlic in treating cardiovascular disease has received much attention.

The majority of garlic (65%) is water, and the bulk of the dry weight is composed of fructose-containing carbohydrates, followed by sulfur compounds, protein, fiber, and free amino acids (8). It also contains high levels of saponins, phosphorus, potassium, sulfur, zinc, moderate levels of selenium and Vitamins A and C, and low levels of calcium, magnesium, sodium, iron, manganese, and B-complex vitamins; garlic also has a high phenolic content (9). A majority of the compounds present in garlic are water-soluble (97%) with small amounts of oil-soluble compounds also present (0.15–0.7%). Over the years different garlic preparations have been investigated for their prevention and treatment of cardiovascular disease both in vitro and in vivo (clinical trials). The common preparations that have been investigated are raw garlic, garlic powder tablets, oil of steam-distilled garlic, oil of oil-macerated garlic, ether-extracted oil of garlic, and aged garlic extract (AGE). All these preparations differ in their composition (10), which makes comparing studies difficult.

In vitro (preclinical) studies

Numerous in vitro studies have confirmed the ability of garlic to reduce parameters associated with cardiovascular disease. A brief description of some of these studies is given below.

Cholesterol and lipid-lowering effects. Several studies have indicated that garlic and its constituents inhibit key enzymes involved in cholesterol and fatty acid synthesis in cultured rat hepatocytes and human HepG2 cells (11–14). Direct measurements of enzyme activity have indicated that garlic and various constituents inhibit human squalene monooxygenase and HMG-CoA reductase, enzymes involved in cholesterol biosynthesis (11,15). This inhibition of HMG-CoA reductase by garlic has also been confirmed in a recent study (16). It has also been shown that the more water-soluble compounds like S-allylcysteine (SAC) present in aged garlic extract are less cytotoxic and more efficient in inhibiting cholesterol biosynthesis than the lipid-soluble sulfur compounds such as diallyl sulfide (DAS) (13).

Antithrombotic and anti–platelet aggregatory effects. Platelet aggregation and subsequent thrombus formation are signifi-

cantly reduced by garlic and its constituents. Chloroform/acetone extracts of fresh garlic have been shown to inhibit cyclooxygenase activity directly in cell-free assays, with the acetone extract being more effective (17). In this study, the chloroform extract of garlic was a more effective inhibitor of ADP- and platelet-activating factor (PAF)-induced platelet aggregation. The mechanism of inhibition of platelet aggregation by garlic's constituents has also been addressed, and it is thought to work via the inhibition of calcium mobilization (18). Ajone, another garlic derivative, has also been shown to inhibit platelet aggregation in vitro (19). A recent study has also found another garlic component, sodium 2-propenyl thiosulfate, to modulate cyclooxygenase activity in canine platelets, thus preventing their aggregation (20).

Blood coagulation, fibrinolysis and circulatory effects. Fibrinolysis is also enhanced by garlic, resulting in dissolution of clots and thrombi. In vitro studies have demonstrated that aged garlic extract improves circulation and blood properties by preventing lipid peroxidation and hemolysis in oxidized erythrocytes (21). A recent study has confirmed that garlic improves the fluidity of erythrocytes isolated from hypecholesterolemic rats (22). In contrast, garlic oil extracts and the allyl sulfides were unable to protect isolated erythrocytes from *t*-butyl hydroperoxide-induced hemolysis (23).

Blood pressure and vascular tone effects. A garlic extract has been shown to modulate the production and function of both endothelium-derived relaxing factor (NO) and constricting factors (endothelin-1) in isolated rat pulmonary arteries (24). Garlic juice has also been shown to have some beneficial effect on heart rate; however, at higher dosages it exerts undesirable effects (25). γ-Glutamylcysteines are compounds found in garlic, and these may lower blood pressure, as indicated by their ability to inhibit angiotension-converting enzyme in vitro (17).

Effects on endogenous antioxidant defenses. Numerous studies have investigated the antioxidant properties of garlic in various in vitro systems; some of these are outlined below. Garlic has been shown to inhibit the in vitro oxidation of isolated human LDL by scavenging superoxide (ROS) and inhibiting the formation of lipid peroxides (26,27). In vitro studies have shown that AGE prevents the depletion of intracellular glutathione (GSH) when endothelial cells are incubated with oxidized LDL (28). AGE also increases GSH levels in vascular endothelial cells by modulation of the GSH redox cycle and increases glutathione disulfide (GSSG) reductase activity while increasing SOD activity (29).

In vitro (preclinical) studies have confirmed that garlic has the ability to reduce parameters associated with cardiovascular disease. However, such studies need to be translated into a clinical setting, the results of which are discussed below.

In vivo (clinical) studies A limited number of clinical trials have been conducted with different garlic preparations. In this review an attempt has been made to critically review human trials, which have been conducted since 1993. Only those trials that were conducted for a minimum period of 2 wk and that addressed the following parameters have been included: (a) cholesterol-lowering effects, (b) inhibition of platelet aggregation, (c) lowering of blood pressure, and (d) other cardioprotective properties.

Cholesterol-lowering effects. Since 1993, 25 clinical trials have been published that have investigated the hypolipidemic effects of garlic (30–37). Fourteen of the studies showed that garlic had no effect on lowering cholesterol, but 11 studies showed a reduction in serum cholesterol (**Table 1**). It is interesting to note that of the 14 studies showing no effects, 5 were in normolipidemic subjects, 8 were in moderately

TABLE 1

Summary of clinical trials showing cholesterol-lowering effects of garlic[1]

Cholesterol-lowering effects, n = 11		No effects, n = 14		
Subject profiles				
Hypercholesterolemic subjects	8 (Moderately ↑cholesterol)	5 (Normal subjects)	1 (Familial hypercholesterolemic subject)	
Garlic preparations used in the trials				
6 (GP)	5 (AGE)	9 (GP)	4 (AGE)	1 (GO)

[1] Numbers indicate numbers of trials conducted since 1993. GP = garlic powder, AGE = aged garlic extract, and GO = garlic oil.

hypercholesterolemic subjects, and 1 study was in teenagers with familial hypercholesterolemia (Table 1A). A further breakdown of these 14 studies shows that 9 used garlic powder, 4 used AGE, and 1 used steam-distilled garlic oil. The 11 studies that showed a positive effect on cholesterol reduction were performed in hypercholesterolemic subjects; 5 studies used AGE, and the rest used garlic powder (Table 1B).

It is apparent that garlic is effective in hypercholesterolemic subjects, and it may well be that a reduction in cholesterol will be seen only above a certain threshold. Another factor that may need to be taken into account is the gender of the subjects. Zhang et al. (33) reported that gender might affect the action of garlic on plasma cholesterol and glucose levels of normal subjects. A systematic review of the effectiveness of garlic as an antihyperlipidemic agent was published in 2003 by Alder et al. (38). They included 10 studies and found that in 6 studies garlic was effective in reducing serum cholesterol levels. The average drop in total cholesterol was 9.9%, LDL 11.4%, and triglycerides 9.9%. Earlier metaanalysis has also confirmed that garlic is superior to a placebo in reducing total cholesterol levels (39,40). However, the size of the effect is modest, and the robustness of the effect is open to question.

Inhibition of platelet aggregation. Since 1993, 7 clinical trials have been performed, and all have shown that garlic consumption leads to the inhibition of platelet aggregation (7,30,41). Of these 7 studies, 4 were performed in healthy subjects, and 3 in subjects with coronary artery disease/mild hypercholesterolemia. Two studies involved garlic powder, 1 oil extract, 1 ethyl acetate extract, and 3 studies involved aged garlic extract (**Table 2**). Garlic has a positive response in the inhibition of platelet aggregation in both healthy subjects and subjects with cardiovascular disease.

Lowering of blood pressure. Since 1993, 9 studies have been published on the effects of garlic on blood pressure (30,37, 42,43). Two studies used AGE, 3 used garlic powder, and 1 used garlic in the diet, and all these studies showed a reduction in blood pressure. Three studies utilized Kwai garlic and did not

report any change in the blood pressure (**Table 3**). In support of this, a metaanalysis published in 2001 (40) concluded that garlic has insignificant effects on blood pressure.

Other cardioprotective properties. Oxidative stress can lead to the pathogenesis of cardiovascular disease, and some clinical trials involving garlic have addressed this. Seven studies since 1993 have been identified (**Table 4**). One was performed in patients with essential hypertension, and garlic pears were used. A reduction in blood pressure and a decrease in oxidative stress were reported (42). Four studies (2 in normal subjects, 2 in hypercholetrolemic subjects) used AGE and reported a decrease in oxidative stress (43–46). In contrast, 2 studies utilizing garlic tablets (1 in normal subjects and 1 in hypercholeterolemic subjects) did not show a reduction in oxidative-stress parameters (**Table 4**) (30,47). One of the studies, which showed a reduction in oxidative stress after garlic ingestion, was conducted in our laboratory in healthy smoking and nonsmoking men and women (45). In this study F_2-isoprostanes were measured because their quantification in plasma and urine is a sensitive and specific indicator of oxidative stress in vivo. Dietary supplementation with AGE for 14 d reduced plasma and urine concentrations of F_2-isoprostanes by 29% and 37%, respectively, in nonsmokers and by 35% and 48%, respectively, in smokers (**Fig. 1** A and B). Fourteen days after cessation of dietary supplementation, plasma and urine concentrations of F_2-isoprostanes in both groups returned to values not different from those before ingestion (Fig. 1A and B). It was also observed in this study that the plasma antioxidant capacity of nonsmokers was approximately twice that of smokers. Interestingly, the plasma antioxidant capacity of smokers significantly increased by 53% following supplementation with AGE for 14 d (**Fig. 2**). However, after the 2-wk washout period (day 28), the plasma antioxidant capacity of smokers decreased by 49% and was now similar to that before AGE ingestion; the plasma antioxidant capacity of nonsmokers remained unaffected during this same period (Fig. 2) (45).

The subjects in this study were normolipidemic, and no other changes including those of serum lipids were seen in this study. This underscores the point that multiple questions must be addressed in clinical trials incorporating any new and specific markers. The conclusion from this study was that dietary supplementation with AGE reduces oxidative stress in humans

TABLE 2

Summary of clinical trials showing inhibition of platelet aggregation by garlic[1]

Number of studies showing inhibition of platelet aggregation (7[2])	
Study	Number
Aged garlic extract	3
Garlic powder	2
Ethyl acetate extract	1
Oil extract	1

[1] Numbers indicate number of trials conducted since 1993.
[2] Normal subjects, n = 4; subjects with cardiovascular disease, n = 3.

TABLE 3

Summary of clinical trials showing blood pressure lowering effects of garlic[1]

Blood pressure–lowering effects (6)			No change (3)
3 (Garlic powder)	2 (AGE)	1 (Garlic in diet)	3 (Kwai)

[1] Numbers indicate number of trials conducted since 1993. AGE = aged garlic extract, Kwai = Kwai garlic powder tablets.

TABLE 4

Summary of clinical trials showing antioxidative properties of garlic[1]

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1 (Garlic pearls) Reduced blood pressure and oxidative stress in hypertensive patients

4 (Aged garlic extract) Reduced oxidative stress
    2 (Normal subjects)   2 (Hypercholesterolemic subjects)

2 (Garlic tablets) No changes reported
    1 (Kwai, hypercholesterolemic subject)   1 (Normal subject)

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[1] Numbers indicate number of trials conducted since 1993. Kwai = Kwai garlic powder tablets.

and thus may prevent or delay chronic diseases such as cardiovascular disease.

Other direct cardioprotective effects of garlic in humans have also been reported, such as a decrease in unstable angina (48), an increase in the elastic property of blood vessels (49), and a decrease in peripheral arterial occlusive disease (50). More recently, garlic has been shown to increase peripheral blood flow in healthy subjects (51) while inhibiting the progression of coronary calcification in patients receiving statin therapy (52). However, the number of trials conducted within this area is limited.

Conflicting message and variable results: why? In-vitro studies strongly suggest that garlic has the ability to reduce
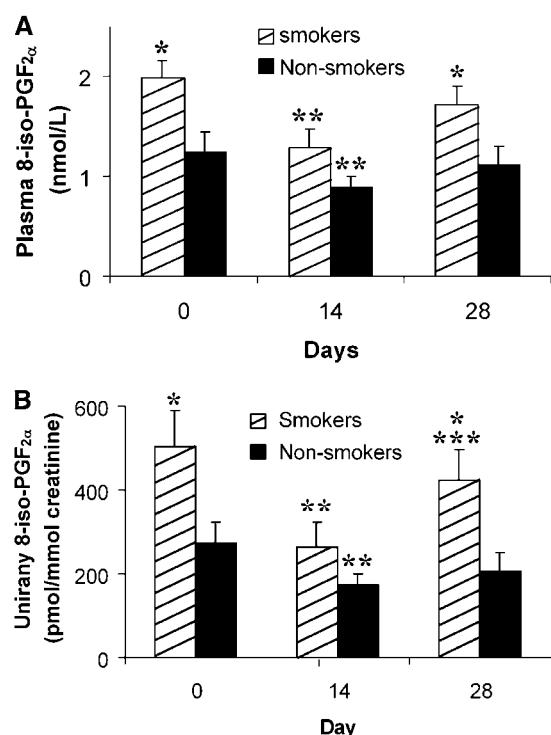
FIGURE 1 Plasma and urine concentrations of 8-iso-PGF$_{2\alpha}$ in smoking and nonsmoking subjects before and after aged-garlic consumption. (A) Plasma total concentration of 8-iso-PGF$_{2\alpha}$. Significant difference is indicated by asterisks: (*$P < 0.05$) from control (nonsmokers) and (**$P < 0.05$) from day 0. (B) Urine concentration of 8-iso-PGF$_{2\alpha}$. Significant difference is indicated by asterisks: (*$P < 0.05$) from control (nonsmokers), (**$P < 0.05$) from day 0, and (***$P < 0.05$) from day 14. Values are means ± SEM ($n = 10$).
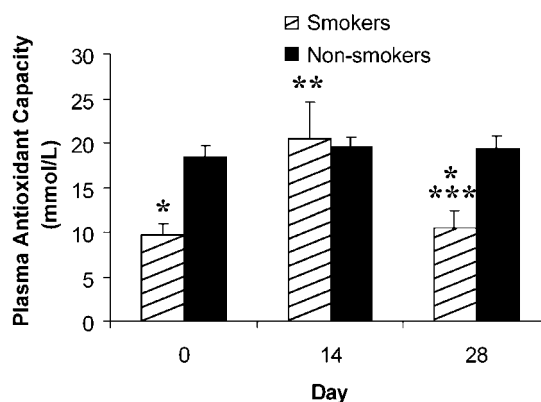
FIGURE 2 Antioxidant capacity of plasma in nonsmokers and smokers before and after aged garlic extract consumption. Antioxidant capacity is expressed as ascorbate equivalent antioxidant units (μmol/L). Values are means ± SEM ($n = 10$). Significant difference is indicated by asterisks: (*$P < 0.05$) from control (nonsmokers), (**$P < 0.05$) from day 0, and (***$P < 0.05$) from day 14.[2]
[1] Taken from (7) and (45). [2] Taken from (7).

parameters associated with cardiovascular disease. This has prompted a number of clinical studies, some of which give conflicting messages. The reasons for these are outlined below. (a) A limited number of trials have been performed; some have been of short durations including inadequate randomization and blinding procedures. (b) Different garlic preparations have different properties. Raw garlic's composition is variable, and some toxicity has been reported. Allicin has some antioxidant properties, but it has not been detected in serum or urine after ingestion of raw garlic, and it has also been reported to oxidize LDL. Garlic powder must be prepared at a suitable temperature and is associated with some toxicity. No major studies on the efficacy of garlic oils have been reported (10). The composition of AGE is such that it has increased sulfur compounds with the loss of allicin. (c) There is also substantial variability in the contents of garlic preparations, with inadequate definitions of the biologically active and available constituents and their dissolution properties. This makes it difficult to ascertain the consistency of garlic's effect in these trials. (d) In some trials there are a lack of intention-to-treat analyses and incomplete reporting of data. (e) Some trials have not addressed the right questions (normolipidemic versus hyperlipidemic subjects?). The appropriate cardiovascular endpoints need to be defined. Would we expect a reduction in serum cholesterol of normolipidemic subjects? Do we really want this?

The way forward: future research It is important that standardized preparations of garlic are used in clinical trials and the bioavailability of the active constituents is established. It is also important to ask the right questions: are we looking at the prevention or treatment of cardiovascular disease by garlic? One also needs to conduct well-designed randomized trials that are of sufficient duration so morbidity and mortality outcomes, as well as lipid and thrombotic outcomes, can be addressed. It is also perhaps more important to investigate whether garlic taken as dietary supplement can either delay or prevent cardiovascular disease in a healthy population. It may well be that if garlic is taken before the onset of cardiovascular disease, the outcome will be different. This is supported by some epidemiologic evidence (1). Finally, it is important that new biomarkers and methodologies in cardiovascular disease are incorporated into the clinical trials, and if a positive effect is observed, the mechanism of action on the disease parameters must be established. Cardiovascular disease is complex and multifactorial, and garlic

has multiple properties that may reduce cardiovascular disease; hence, multiple questions must be addressed in clinical trials.

DISCUSSION

In summary, evidence from clinical trials points toward garlic having a role to play in either preventing or delaying cardiovascular disease. However, more research is still required to convince health workers, consumers, and regulatory bodies.

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