Recent Advances on the Nutritional Effects Associated with the Use of Garlic as a Supplement

Historical Perspective on Garlic and Cardiovascular Disease

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ABSTRACT Cardiovascular disease is a complex and multifactorial disease characterized by such factors as high cholesterol, hypertension, reduced fibrinolysis, increase in blood-clotting time and increased platelet aggregation. Dietary therapy is the first step in the treatment of hyperlipidemia; garlic has been used medicinally for centuries and is still included in the traditional medicine of many cultures. Historically, there has been great interest in the role of garlic in reducing cardiovascular risk factors. Evidence from numerous studies points to the fact that garlic can bring about the normalization of plasma lipids, enhancement of fibrinolytic activity, inhibition of platelet aggregation and reduction of blood pressure and glucose. However, some contradictory results have also emerged as a result of methodological shortcomings, the use of different formulations/preparations of garlic and different time scales of the studies. Accordingly, further clinical studies are required in which standardized formulations of garlic with known compositions can be used. Such formulations (e.g., Aged Garlic Extract) are now available and are being investigated. Evidence obtained from these studies indicates that garlic has potential in the prevention and control of cardiovascular disorders and is beneficial when taken as a dietary supplement. J. Nutr. 131: 977S–979S, 2001.

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There are many factors associated with atherosclerosis and cardiovascular disease, by far the greatest killers in modern society. A high fat diet can lead to increases in serum cholesterol and plasma fibrinogen levels and to a decrease in fibrinolytic activity and blood coagulation time. Changes in blood coagulation time are involved in the development of thrombi in atherosclerotic vessels, and elevated serum cholesterol levels contribute significantly to the onset and development of atherosclerosis and cardiovascular disease. Increased levels of LDL are also linked with cardiovascular disease; more specifically, it has been reported that oxidation of LDL particles is likely a key step in the development of atherosclerotic plaques (Luc and Fruchart 1991). Increased levels of HDL are negatively correlated with cardiovascular disease. There is also considerable evidence supporting the involvement of platelets in the development of atherosclerosis. Increased platelet activity has been found in smokers, as well as in patients suffering from vascular injury, hyperlipidemia and hypertension. These circulating platelets can be deposited on the innermost lining of the arteries, thereby forming plaques, which then lead to the thickening of the arterial walls, hence narrowing of the blood vessels. These plaques can aggregate, incorporating cholesterol, lipids and lipoproteins, thus blocking the blood vessels. Alternatively, pieces of plaque may break off and cause a blockage elsewhere in the blood stream. The blockage of the coronary artery results in a heart attack, leading to a myocardial infarction. In addition to hyperlipidemia, obesity, smoking, stress and hypertension are also known to be the risk factors for atherosclerosis (Hulley et al. 1980). Both clinical and epidemiologic studies have shown that hyperlipidemia and hypertension are perhaps the greatest risk factors of atherosclerosis and its complications, such as stroke and myocardial infarction (Hulley et al. 1980). Many studies have demonstrated that normalization of hypertension and abnormal metabolism of lipids and lipoproteins, including cholesterol, improves atherosclerotic coronary artery disease (Kleijnen et al. 1989).

It has been believed for some time that dietary factors play a key role in the development of some human diseases, including cardiovascular disease. Several epidemiologic studies have indicated that certain diets are associated with low risk of cardiovascular disease and that these diets are rich in fruits, herbs and spices; the common spice among them is garlic (Stavric 1994). Considerable anecdotal evidence supports the invaluable role that garlic has in the therapy of many diseases (Bolton et al. 1982). Over the centuries, garlic has acquired a special position in the folklore of many cultures as a formidable prophylactic and therapeutic medicinal agent. It is cited in the Egyptian Codex Ebers, a 35-century-old document, as useful in the treatment of heart disorders, tumors, worms, bites and other ailments. Hippocrates and Pliny the Elder were both promoters of garlic’s medicinal virtues. Charak (ca. 3000 BC), the father of Ayurvedic medicine, claimed that garlic maintains the fluidity of blood and strengthens the heart. The
first-century Indian physician Charaka claimed that garlic acted as a heart tonic and prevented heart disease (Fenwick and Hanley 1985). Over the last 20 years, this important and exciting role of garlic has been and continues to be confirmed by basic and clinical research reports from around the world.

**Early work.** The cardiovascular effects of garlic have been documented in several older publications (May 1926, Schlesinger 1926, Taubmann 1934); however, it was essentially rediscovered in the late 1960s and 1970s when it became the subject of extensive scientific research. Because people who regularly eat larger amounts of garlic and onions have lower lipid and cholesterol levels than people who refrain from eating these vegetables (Sainani et al. 1976), much of the earlier work investigated the effectiveness of raw garlic. In the late 1970s, a number of studies were conducted in which raw garlic was given orally for 2–3 mo to healthy subjects and patients with ischemic heart disease. These studies demonstrated significant reductions in blood cholesterol and triglyceride levels after garlic ingestion (Agarwal 1996). The only problem with these studies was that the dosages required to obtain these effects were relatively high (7–28 cloves/d). One of the main problems with these studies may be that the percentage of active constituents in fresh garlic can vary by a factor of 10 (Newall et al. 1995). The debate on fresh garlic is still very much alive, and some conflicting data are evident. Chutani and Bordia (1981) investigated the effect of fried vs. raw garlic on fibrinolytic activity in humans and found that both raw and fried garlic enhanced fibrinolytic activity within hours of ingestion and that frying preserved this fibrinolytic activity. Fourteen years later, Ali (1995) examined the effect of aqueous extract of raw garlic and boiled garlic on cyclooxygenase activity in rabbit tissues. It was concluded that raw garlic inhibits cyclooxygenase activity, whereas boiled garlic does not. Another study by Ali and Thomson (1995) reported that subjects who ate 3 g of fresh garlic daily for 16 wk had a 21% decrease in cholesterol levels, although no significant decrease was seen before 4 wk. A significant reduction in serum thromboxane was also reported in that study. Because the composition of raw garlic differs and large amounts are required for it to be effective, historically, it has been difficult to convince the general population to consume garlic regularly. Standard garlic preparations that can be incorporated into studies under control conditions should be developed.

The last decade has seen the vast majority of work in the garlic area; since then, various commercial preparations of garlic have appeared on the market.

**Work with garlic preparations.** Several clinical trials using commercially available garlic preparations were conducted in the 1980s and early 1990s; most of these used dried garlic powder (Kwai). The majority of these studies demonstrated the lipid-lowering effects of garlic; some also showed a significant decrease in serum triglyceride levels (Reuter et al. 1996). It was also shown that garlic reduced blood pressure, increased fibrinolytic activity and inhibited platelet aggregation (Reuter et al. 1996). However, in contrast, recent studies with Kwai garlic powder have shown no significant effect on cardiovascular variables (Issacson et al. 1998).

**Studies showing no effect of garlic.** Over the last 3 years, 5 clinical trials of garlic’s effect on cardiovascular disease have been reported; all of these studies showed garlic to be ineffective. Morris et al. (1995) investigated the effects of garlic extract on platelet aggregation in a randomized, placebo-controlled, double-blind trial. They investigated the effects of feeding garlic to healthy men on platelet aggregation, serum thromboxane and lyso-platelet activating factor as well as the effect on platelet aggregation in vitro. No significant differences were observed except that the in vitro aggregation of platelets with collagen decreased linearly with increasing amounts of garlic extract, but the concentrations were higher than those attainable in vivo (Morris et al. 1995). Similarly, Simons et al. (1995) investigated the effects of garlic powder (Kwai) on plasma lipids and lipoproteins in subjects with mild-to-moderate hypercholesterolemia. This was a double-blind, placebo-controlled, randomized crossover study in which the subjects were asked to take 300 mg of garlic powder tablets three times per day. This study found no demonstrable effect of garlic on lipids and lipoproteins and also found no effect on the oxidizability of LDL (Simons et al. 1995). Another study in which the garlic powder was standardized to allicin was reported by Neil et al (1996). This was a double-blind, randomized, 6-mo parallel trial in which the effect of 900 mg/d of dried garlic powder (standardized to 1.3% allicin) in reducing cholesterol was investigated. The results of this study confirmed earlier work that this form of dried garlic powder was less effective in reducing total cholesterol than had been suggested by previous meta-analyses (Neil et al. 1996). Two trials reported this year, one with garlic powder and the other with garlic oil, again failed to demonstrate any significant reduction in serum lipids. Isaacsom et al. (1996) conducted a randomized, placebo-controlled trial in which they investigated the effect of 900 mg/d of dried garlic powder (Kwai) on serum cholesterol levels. Their conclusion was that at this dosage for 12 wk, garlic powder was ineffective in lowering cholesterol levels in patients with hypercholesterolemia. Steam-distilled garlic oil preparation (5 mg twice per day for 12 wk) was used in a double-blind, randomized, placebo-controlled trial by Berthold et al. (1998). The conclusion of this study was that this commercial garlic oil preparation had no influence on serum lipoproteins, cholesterol absorption or cholesterol synthesis.

The recent data from the clinical trials outlined above contradict some of the results reported earlier. This could be due to several factors, including a lack of consistency among studies in relation to dosage, standardization of garlic preparations and period of treatment. Although many of these studies using garlic powder claimed the potential of allicin, it is recognized that allicin is unstable and is not absorbed on ingestion; studies on the fate of allicin are rare (Lawson et al. 1992). In addition, garlic preparations that are produced by heat or solvent extraction processes are stated to contain allin but to be devoid of allinase; hence no allicin may be formed. Garlic oil macerates and steam-distillation products are rich in secondary metabolites such as ajoene. However, it is unclear to what extent these secondary compounds are formed in the body after the ingestion of garlic and whether their actions can be compared with those of fresh garlic (Newall et al. 1995). In contrast to the above studies, there have also been some recent clinical trials showing garlic to be cardioprotective. These studies have incorporated a different garlic proprietary, commercially available product, which is particularly rich in 5-allyl cysteine, a water-soluble, sulfur-containing amino acid; however, it also contains other compounds.

**Studies showing garlic to be cardioprotective.** Aged garlic extract (Kyolic) was found to be effective in lowering serum cholesterol and triglycerides in hyperlipidemic patients in a randomized study conducted by Lau et al (1987). Subjects took four 1-mL capsules containing 250 µL dry weight of the active garlic components. More recently, Steiner et al. (1996) reported the results of a double-blind, cross-over trial in moderately hypercholesterolemic men in which the authors compared the effect of aged garlic extract and placebo administration on blood lipids. Aged garlic extract (7.2 g) was...
given as a dietary supplement for 6 mo. In that study, reductions of 6% in total cholesterol, 4% in LDL and 5.5% in systolic blood pressure were obtained. Because oxygen radical injury and lipid peroxidation have been suggested as major causes of various diseases including atherosclerosis, Ide et al. (1997) reported that aged garlic extract inhibits oxidative modification of low density lipoprotein (LDL), hence slowing down or preventing atherosclerosis. In support of these findings, Bordia et al. (1996) investigated the effect of garlic on platelet aggregation in healthy subjects and patients with coronary artery disease. They found that long-term administration of a low dosage of garlic led to inhibition of platelet aggregation. The modulation of lipid profiles by garlic in combination with fish oil has also been reported by Morcos (1997), using a single-blind, placebo-controlled crossover study involving 40 subjects. After 1 mo, decreases of 11% in cholesterol, 34% in triglycerides, 10% in LDL and 19% in cholesterol/HDL ratio were observed.

Overall, the studies to date give a conflicting message, which can be confusing for consumers and health care professionals. These differences are probably due to the following: 1) the amount of active constituents in raw garlic can vary; 2) because different garlic preparations have been used, there is a need to establish active constituents; and 3) standardized commercial preparations must be used such that bioavailability, toxicity and tolerance data are available.

Most of the published studies have been performed in subjects in whom cardiovascular disease is apparent. It is perhaps more important to investigate whether garlic taken as a dietary supplement can either delay or prevent cardiovascular disease. Such studies are now being performed and published. One of the early studies was conducted by Legnani et al. (1993) in which the authors investigated the acute and chronic effects of dried garlic powder on platelet aggregation in apparently healthy subjects. At a dose of 900 mg/d, a significant reduction in platelet aggregation occurred. More recently, Effendy et al. (1997) investigated the effect of aged garlic extract, "Kyolic," on the development of experimental atherosclerosis in rabbits. Their conclusion was that Kyolic treatment reduced fatty streak development, vessel wall cholesterol accumulation and the development of fibro-fatty plaques in neointimas of cholesterol-fed rabbits, thus providing protection against the onset of atherosclerosis.

We also recently conducted a clinical trial in our laboratory and asked the question, "Is aged garlic extract a cardioprotective agent?" This trial was conducted in apparently healthy subjects who took 5 mL/d of aged garlic extract for 3 mo. Blood samples were taken at the beginning and the end of the study. There was a significant reduction in platelet aggregation and also a significant reduction in the circulating levels of thromboxane B2 at the end of the aged garlic extract ingestion. No significant differences were found in the circulating levels of 6-keto PGF1α; therefore, we concluded that aged garlic extract when taken as a dietary supplement can act as a cardioprotective agent.

Summary

Despite conflicting studies, possibly due to the use of different preparations and different experimental protocols, the historical perspective on garlic points toward its positive role in either preventing or delaying cardiovascular disease, i.e., reducing serum lipids, blood pressure and platelet aggregation. However, further controlled human studies with standardized preparations and known and established active constituents are required to establish the true usefulness of this remarkable herb in reducing or preventing cardiovascular disease.

LITERATURE CITED


