

## Review

# Effect of garlic on atherosclerosis and its factors

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أثر الثوم على تصلب الشرايين وعوامل الإصابة به  
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**الخلاصة:** من المعتقد أن الأنماط الغذائية في منطقة البحر المتوسط، التي تتميز بارتفاع نسبة استهلاك الفاكهة والخضراوات، ولاسيما الثوم، مفيدة في مختلف أنماط تصلب الشرايين في هذه المنطقة. وهناك اقتناع واسع النطاق بفعالية الثوم، وعديد من مستحضراته، في اتقاء ومعالجة تصلب الشرايين وسائر عوامل الاختطار المرتبطة بالأمراض القلبية الوعائية. وتبحث هذه المقالة الاستعراضية البيّنات المستمدة من الدراسات العلمية المتعددة التي استخدم فيها العديد من مركبات الثوم ومستحضراته، والتي جاءت بنتائج متفاوتة. وهي تؤكد على الحاجة إلى وضع مواصفات معيارية لمنتجات الثوم المتوافرة، للسماح بمقارنة أفضل بين نتائج البحوث، لاستخلاص النتائج حول التأثيرات المفيدة للثوم في تصلب الشرايين.

**ABSTRACT** Dietary patterns in the Mediterranean, characterized by high consumption of fruits and vegetables, especially garlic, are believed to be beneficial to the regional patterns of atherosclerotic disease. Garlic and many of its preparations have been widely recognized as effective in the prevention and treatment of atherosclerosis and other risk factors for cardiovascular disease. This review article examines the evidence from numerous scientific studies that have utilized various formulations of garlic and its preparations with varying results. It highlights the need for standardization of available garlic products to allow for better comparison of research findings in drawing conclusions about the beneficial effects of garlic on atherosclerosis.

## Effet de l'ail sur l'athérosclérose et ses facteurs

**RÉSUMÉ** Les modèles nutritionnels méditerranéens, caractérisés par une forte consommation de fruits et légumes, en particulier de l'ail, sont considérés comme bénéfiques dans la physiologie régionale de la maladie athéroscléreuse. L'efficacité de l'ail et de bon nombre de préparations qui en sont dérivées est depuis longtemps reconnue dans la prévention et le traitement de l'athérosclérose et des maladies cardio-vasculaires. Cet article de synthèse examine les preuves apportées par de nombreuses études scientifiques ayant évalué différentes formulations d'ail et préparations à base d'ail avec des résultats divers. Il en ressort qu'une normalisation des produits à base d'ail existants est une condition préalable à toute comparaison des résultats de la recherche susceptible de permettre de tirer des conclusions quant aux effets bénéfiques de l'ail sur l'athérosclérose.

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## Introduction

Garlic (*Allium sativum*) belongs to the plant family *Liliaceae*, which is a genus of 500 species. It has been in use for many centuries, and was recognized for its therapeutic and medicinal value as far back as the era of ancient Egypt [1]. It is a common ingredient in the preparation of meals in all parts of the world, used for its pungent flavour. The most common use of garlic in the preparation of cooked dishes is in the form of fresh cloves. However, there are many preparations of garlic available, particularly in health food stores, including powdered garlic, tablets and oil capsules. Research work carried out on garlic includes many of these preparations. Thus, whenever appropriate, the form of garlic used in experimental work and/or commercially available preparations will be mentioned in this article.

Dietary factors play a key role in the development of various human diseases, including atherosclerotic disease. Epidemiological studies have shown that diets rich in fruits, herbs and spices are associated with a low risk of cardiovascular disease [2]. Special attention has been drawn to the role of garlic in the Mediterranean diet in the protection of populations against atherosclerosis and heart disease. This is probably related to the lifestyle and, in particular, to the dietary habits of these populations. The Mediterranean diet is characterized by a low intake of saturated animal fats, contrasting with a high but reasonable intake of mono- or polyunsaturated fatty acids and a high consumption of garlic, onions and fresh vegetables [3].

Advancements in laboratory techniques in recent years have stimulated an interest in revealing the scientific basis for the beneficial effects of natural substances, including garlic. Garlic contains a number of compounds to which these health benefits have been attributed. The detailed information on

these ingredients is the subject of a separate article. The literature on the health benefits of garlic is vast, including research work on its influence on the cardiovascular system. This article explores relevant experimental work on the efficacy of garlic in influencing factors that contribute to atherosclerosis. Mention is made of atherosclerotic disease patterns in the Eastern Mediterranean Region in relation to local diet and dietary habits.

## Atherosclerosis and dietary aspects

Atherosclerosis is a chronic disease that is caused by damage to the arterial wall from inflammation and fibro-fatty deposits. The disease process also involves several cell types, particularly smooth muscle cells, monocyte-derived macrophages, T-lymphocytes and platelets [4]. Atherosclerosis is considered one of the principal causes of morbidity and mortality worldwide. The development of atherosclerosis, identification of its risk factors and remedies for its complications have been elucidated in recent decades [5].

Dietary therapy is the first step in the treatment of atherosclerosis. This intervention involves the inclusion in the diet of materials such as soluble fibres, soy proteins and garlic, which may lower lipid concentrations to desired targets without the use of drugs [6]. Garlic and onion have been valued in traditional and folk medicine in many cultures to remedy cardiovascular disease and other disorders [7]. In addition to its lipid-lowering effect, garlic is also known for its benefit against the atherosclerotic disease process. There is some evidence to suggest that the use of certain formulations of garlic and/or onion is accompanied by favourable effects on risk factors in normal subjects and in patients with atherosclerotic

disease [7]. However, excessive ingestion of these plants or of their extracts may cause a toxicity problem.

In the Eastern Mediterranean Region, diets are characterized by olive oil, as the dominant fat source, and a high to moderate consumption of garlic, onions, fruit and vegetables. Even though diets differ according to country, common aspects of the Mediterranean diet have been associated with good health and a long life expectancy [3,8–10]. A retrospective study in Jordan showed that hypertension, diabetes mellitus and smoking were the most common risk factors for atherosclerotic patients [8]. Epidemiological studies and intervention trials suggest that the Mediterranean diet lowers the risk of atherosclerosis [9]. A study from Italy showed that Mediterranean countries have a lower rate of atherosclerosis than in Northern Europe and the United States, with the conclusion that diet is an important environmental factor in the atherosclerosis incidence rates in these areas [10].

### **Influence of garlic on atherosclerotic risk factors**

In order to elucidate the role of garlic in the prevention of atherosclerosis, a large number of studies have investigated its effects on serum cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG). Although there is no standardization of garlic preparations, dosages or periods of treatment, most findings suggest that administration of garlic lowers cholesterol and TG levels in patients with increased levels of these lipids.

Garlic juice reduced serum cholesterol and TG in human subjects [11] and helped in preventing the rise of serum cholesterol, thus indicating a cholesterol-lowering property [12,13]. Reduction of serum lipids

by ingestion of fresh garlic preparations may decrease the atherosclerotic process. A direct antiatherogenic effect of garlic was suggested [13].

A systematic review of randomized controlled trials in humans reported that the reduction of total cholesterol and TG with garlic therapy was evident after 1 month and persisted for at least 6 months [14]. Treatment with a standard garlic dose of 900 mg/day produced a reduction in LDL cholesterol after 12 weeks treatment, but no change in HDL or TG [15]. In a placebo-controlled, randomized, double-blind crossover trial, 2-weeks treatment with 600 mg/day garlic tablets did not lower serum lipid and lipoprotein levels. However, there was evidence that lipoprotein oxidation was decreased and that this could contribute to the beneficial effect of garlic against atherosclerosis [16].

A meta-analysis of controlled trials on fresh garlic showed that consuming half a clove per day decreased total serum cholesterol levels [17]. In patients with total cholesterol and/or TG values more than 200 mg/dL, garlic tablets lowered cholesterol and TG values by 12% and 17% respectively [18]. Regular administration of garlic tablets for a 6-week period significantly lowered fasting values of TG [19].

Daily doses of 900 mg of garlic powder for 12 weeks in patients with primary hyperlipoproteinaemia caused a significant reduction in total cholesterol, LDL cholesterol and TG, and increased HDL cholesterol [19]. In contrast, a number of controlled studies showed that the lipid-lowering properties of garlic preparations were less evident [20]. A controlled trial and a meta-analysis of the use of garlic powder in the treatment of moderate hyperlipidaemia showed that it was less effective in reducing total cholesterol [21]. A double-blind crossover study on subjects with mild to moderate hypercholesterolaemia revealed that there

was no significant effect of garlic ingestion on plasma cholesterol, LDL cholesterol, HDL cholesterol or TG levels [22]. A lack of efficacy of dried garlic on blood lipids, apolipoproteins and blood coagulation parameters in patients with hyperlipoproteinaemia was also reported [23]. In a double-blind randomized trial, treatment with 900 mg Kwai® (commercial dried garlic powder) in patients with moderate hypercholesterolemia did not affect markers of lipoprotein oxidation, lipoprotein(a) or sub-fractions of LDL cholesterol [24].

Discrepancy in the results of different studies may be due to differences in the concentrations of sulfur-containing compounds in different garlic preparations. Thus, it is critical that different garlic preparations be standardized so that more valid conclusions can be drawn. Additionally, it would be of the utmost value if other experimental factors such as the recruitment of subjects, dietary and lifestyle of subjects, length of study, and methods of analysis among several studies be comparable [14,25].

A meta-analysis of 13 trials showed that garlic tablets significantly reduced total blood cholesterol levels [26]. In contrast, there was no significant reduction in cholesterol level in 6 diet-controlled trials. These results indicate that garlic could be marginally effective in reducing total cholesterol levels. Thus, the cholesterol-lowering influence of garlic needs to be confirmed.

Other preparations, such as garlic protein (the water soluble protein fraction of garlic) and garlic oil, have shown a significant lipid-lowering effect in rats [27]. This effect is believed to be because of reduction in the lipid formation rate by the liver. While garlic oil seemed to be more effective, use of a garlic protein preparation may be more acceptable to humans, as it is palatable and smell-free when incorporated in the diet.

In animal studies, allicin, an active constituent of garlic, showed a beneficial effect

on the serum lipid profile of hyperlipidaemic rabbits [28]. Feeding with ethanol extract of garlic to animals maintained on high fat-high cholesterol diet significantly reduced lipid levels. Breakdown of dietary cholesterol and of fatty acids was increased with treatment involving garlic oil [29]. In avian species, feeding with garlic extract, paste and oil led to a significant decrease in the level of enzymes involved in the cholesterol metabolic pathways: hepatic-hydroxy-3-methylglutaryl-COA reductase (83%), cholesterol 7 alpha-hydroxylase (51%), fatty acid synthase (29%) and in representative pentose-phosphate pathway (39%). This decreased serum cholesterol, LDL cholesterol and TG, but not HDL cholesterol. Thus, the mechanism of hypocholesterolaemic action is at the level of the suppression of cholesterol biosynthesis [30]. In a study of the hypolipidaemic properties of garlic extract, cholesterol was reduced in hypercholesterolaemic rabbits in a comparable way to gemfibrozil, thus revealing an antilipid peroxidative property [31].

The combined administration of fish oil and garlic had a beneficial effect on serum lipid and lipoprotein concentrations in humans. This combination lowered total cholesterol, LDL cholesterol and triacylglycerol concentrations, and influenced the ratios of total cholesterol to HDL cholesterol and that of LDL cholesterol to HDL cholesterol [32]. Desired shifts in TG and lipid sub-fractions were seen in humans after 1 month when combined fish oil and garlic were used. This cholesterol-lowering ability and resultant improvement in risk ratios suggest that garlic is effective against atherosclerosis and possibly protects against the development of coronary artery disease [33].

Copper is important in altering both lipid and cholesterol metabolism and there have been studies comparing its mechanism of action with that of garlic. In animal stud-

ies, dietary garlic and copper seem to have an influence on the metabolism of lipids and cholesterol. Incorporating garlic or copper into the diet of chickens for 21 days reduced cholesterol levels in the meat produced [34]. A garlic–ginkgo combination showed a reduction in cholesterol values after 1 to 2 months. After a 2-week wash period, cholesterol values returned to the starting values, indicating that the effectiveness was due to continuous long-term garlic therapy [35]. Biochemical studies on the combined effects of garlic and ginger (a spice which is also used in some Mediterranean diets) in albino rats resulted in a significant decrease in serum cholesterol in groups pretreated with either garlic or ginger or with a combination, whereas serum TG, HDL cholesterol and very-LDL cholesterol levels and the atherogenic index were significantly decreased in animals fed with the combination only. This suggests that the combination is much more effective in reducing serum lipids than garlic alone [21].

Male rabbits show increased levels of cholesterol in plasma, aorta and liver, and of total lipids when fed a cholesterol-rich diet. These resultant increased levels were suppressed when garlic powder supplements were incorporated in the diet. Additionally, garlic supplementation increased plasma fibrinolytic activity. Other findings showed that the activity of phospholipase in cell-free supernatants of the aorta and in the liver was increased, while the activity of NADH dehydrogenase in the aorta was decreased suggesting there could be retardation of the development of atherosclerosis. Retardation of the development of atherosclerosis was evidenced by histopathological examination of aorta, liver and heart [36]. Moreover, the possible antiatherogenic effects of dietary garlic were investigated in an experimental model which consists of the de-endothelization by ballooning of the carotis

communis of rats to develop thickening in the blood vessels. In this model, garlic lowered plasma cholesterol and improved peroxide detoxification, which minimizes their role in atherosclerosis initiation; however, it had only little influence on the wound healing reaction and did not significantly inhibit the development of intimal thickening after ballooning [37]. Initiation and progression of atherosclerosis is very much associated with oxidation of LDL cholesterol. When endothelial cells were incubated with S-allylcysteine, the major sulfur-containing compound of aged garlic extract, significant membrane damage was prevented. Additionally, loss of cell viability and lipid peroxidation were reduced. These findings indicate a protection to vascular endothelial cells against injury caused by oxidized LDL cholesterol [38].

The increase in arteriosclerotic plaques in humans in both carotid and femoral arteries was significantly reduced by 5% to 18% with regular intake of high-dose garlic powder. Moreover, this garlic treatment caused a slight regression in plaque development during 48 months. However, there seemed to be an age-related factor, as plaque volume did not change within the 50–80 years age span. The findings of this work suggest not only a preventive property of garlic but also a possible curative role in arteriosclerosis [39]. In contrast, treatment with garlic powder for 3 months in 50 moderately hypercholesterolaemic subjects did not change their total cholesterol level or LDL distribution. However, treatment with garlic may have a greater influence on the diameter of the LDL particle distribution [40].

Treatment with garlic oil for 12 weeks in rats given a high-cholesterol diet neither influenced blood levels of thyroid hormones nor the thyroidal uptake of radioiodine. These findings suggest that the lipid-lowering effect of garlic does not involve



thyroid hormones [41]. It also reduced the accumulation of collagen through greater mobilization of lipids and/or decreased biosynthesis and maturation of collagen [42]. Garlic protein has been shown to be an effective lipid-lowering agent. This hypolipidaemic action is a result of an increased breakdown of cholesterol to bile acids and neutral sterols, in addition to increased mobilization of tri-acylglycerols in rats [43]. In another animal study with albino rats, treatment with garlic protein extract had no significant influence on the sub-fraction composition or oxidative rate of LDL cholesterol, suggesting a delay of the initiation of atherosclerosis [44]. Garlic stems reduced plasma lipids by inhibiting hepatic cholesterol and triglycerol synthesis. The cholesterol-lowering effect of garlic is caused by decreased hepatic synthesis of cholesterol and the triglycerol-lowering is due to inhibited fatty acid synthesis in *in vitro* work on rat hepatocytes (liver cells) [45]. In pigs, treatment with the methanol fraction of garlic bulbs for 4 weeks suppressed 3-hydroxy-3-methylglutaryl coenzyme A reductase and cholesterol 7- $\alpha$ -hydroxylase, which play a role in initiation of atherosclerosis. Modest increases in serum TG were associated with significantly increased hepatic lipogenic activities [46].

The lipid-lowering potential of garlic powder, standardized to 1.3% alliin, has been studied. Allicin is the main biologically active component of freshly-crushed garlic cloves, produced by interaction of the amino acid alliin with the enzyme alliinase. In 7 out of 8 studies, including over 500 patients, a daily dose of 0.6 g to 0.9 g garlic powder reduced plasma cholesterol and TG levels by 5% to 20%. The metabolic mechanisms of these reductions are not known [47]. Garlic powder at a dose of 900 mg/day for 4 months showed a significant decrease in

total cholesterol, TG and blood pressure [48]. In contrast to these results, a multi-centre randomized placebo-controlled trial showed that treatment with garlic powder (900 mg/day) for 12 weeks was not effective in lowering cholesterol levels in patients with hypercholesterolaemia [11].

Treatment with garlic extract significantly decreased circulating TG and LDL cholesterol levels in rats. Intra-arterial cholesterol level was also decreased and resulted in a normalization of atherosclerotic lesions in rats [49]. A study of the effect of garlic powder extract on the lipid content of cultured human aortic cells indicated that it prevented accumulation of free cholesterol, TG and cholesteryl esters in smooth muscle cells *in vitro*. Lipid synthesis in normal and atherosclerotic cells was inhibited by garlic powder extract treatment. The extract also inhibited the activity of acyl-CoA cholesterol acyltransferase activity that participates in the cholesteryl ester formation, while it stimulated cholesteryl ester hydrolase which degrades cholesteryl esters. This may explain how garlic powder extract lowers lipid levels in atherosclerotic cells. The inhibition of the uptake of modified LDL cholesterol and degradation of lipoprotein-derived cholesteryl esters suggest the possible mechanisms for prevention of lipid accumulation in aortic cells caused by atherosclerosis [50]. When smooth muscle cells from atherosclerotic plaques of human aorta were incubated for 24 hours with an aqueous extract of garlic powder, the levels of cholesteryl esters and free cholesterol in these cultured cells were reduced and their proliferative activity was inhibited. Cholesterol accumulated much less in the cultured cells of patients with coronary atherosclerosis when they received a dose of 300 mg of garlic powder. Thus, it seems that garlic powder may possess an anti-atherogenic action both *in vitro* and *in vivo*

[51]. The effect of garlic powder extract on lipid content in normal and atherosclerotic human aortic cells was studied *in vitro*. The possible mechanism of action of the extract is by prevention of lipid accumulation in aortic cells [52].

The antioxidant effect of aqueous garlic extract may be due to inhibition of the Cu (2+)-initiated oxidation of LDL cholesterol [53]. Water-soluble garlic extracts lowered blood cholesterol through reduction of its synthesis by the liver [54]. It influenced the rate of peroxidation and reduced production of lipids in injured liver. Also, it altered peroxidation towards a more reductive condition, in a manner that is similar to the effect of vitamin E, and inhibited TG accumulation in the liver [55]. Odourless, water-soluble fractions of garlic (polar fractions) inhibited cholesterol and fatty acid in liver cells of chickens [56]. Significant prevention in the rise of serum cholesterol and TG levels caused by an atherogenic diet in cats and rats was achieved by oral administration of a petroleum ether extract of garlic, which also provided protection against atherosclerosis [57].

The ethanolic garlic extract, ajoene, has been shown to prevent fat digestion by human gastric lipase, *in vitro*. This enzyme has been shown to be inhibited by hydrophobic disulfides, since it is a sulfhydryl enzyme. The inactivation of human gastric lipase by ajoene is consistent with the fact that it is reactive towards the sulfhydryl compounds and also agrees with the reported property of garlic to lower the level of tri-acylglycerol in blood. These findings can help explain the belief that garlic has a blood-thinning effect [58].

Human atherosclerotic lesions may involve inducible nitric oxide synthase, the enzyme that enhances production of the harmful peroxynitrite. Work with activated macrophages showed that allicin and ajoene

are beneficial against the development of atherosclerosis and provide evidence that they reduce the accumulation of nitrite in a dose-dependent manner [59].

Protection against *in vitro* oxidation of LDL cholesterol with daily supplementation of aged garlic extract was reported [60,61]. In moderately hypercholesterolaemic men, aged garlic extract resulted in a reduction in total serum cholesterol, LDL cholesterol, decrease in systolic blood pressure and a modest reduction of diastolic blood pressure, indicating that this dietary supplementation is beneficial for both lipid profile and blood pressure [62]. Kyolic, an aged garlic extract, lowered blood cholesterol levels in humans and experimental animals. Thus, it may be potent in protecting against atherosclerosis. Treatment with kyolic was shown to reduce many manifestations of atherosclerosis in cholesterol-fed rabbits, such as formation of fatty streaks, cholesterol accumulation in vascular wall and development of fibro-fatty deposits [63]. An important role in the initiation and development of atherosclerosis is played by oxidation of LDL cholesterol. Aged garlic extract has been reported to protect endothelial cells from oxidized LDL-cholesterol-induced injury. Also, aged garlic extract reduced the levels of nitric oxide and peroxides in macrophages, suggesting that it has a protective ability against the cytotoxicity caused by oxidized LDL cholesterol and nitric oxide and, thus, it may be of value in prevention of atherosclerosis and cardiovascular diseases [64].

Garlic oil with its active principle, diallyl disulfide, had a hypolipidaemic effect in rats fed on high sucrose and alcohol diets. This oil increased the hydrolysis of triacyl-glycerols and lipase activity, and reduced the biosynthesis of triglycerols. It also reduced total lipids, cholesterol and TG and increased adipose tissue TG lipase activity

in rats maintained on high fat-high cholesterol diet [65]. Garlic oil greatly inhibited lipid peroxidation and chemiluminescence of mouse liver mitochondria, thus showing effectiveness against the initiation and rate of development of atherosclerosis [66]. However, a commercial preparation of garlic oil did not have an effect on cholesterol absorption, cholesterol synthesis or serum lipoproteins in a randomized controlled trial [67]. These variable findings may be attributed to the difference in composition of sulfur components and their quantities in commercially-available garlic oil, as well as to the method of its preparation.

## Conclusion

Experimental work to determine the influence of garlic and many of its preparations on risk factors of cardiovascular disease

is very vast. This review article shows a wealth of scientific literature, which involved laboratory animals and humans and included *in vivo* as well as *in vitro* studies. Most research findings support the proposal that garlic consumption has a significant protective effect against atherosclerosis. While there is a bulk of evidence showing beneficial effects of garlic, there are contrasting studies that show no effect. Thus, to reach a decisive conclusion, standardization of garlic and its products is needed and the application of evidence-based analysis of research findings is a must. The Mediterranean diet, with its high to moderate garlic consumption, has proven to be beneficial in minimizing the risk factors of atherosclerotic disease in the Region. Therefore, it is recommended that such a diet be preserved and promoted.

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