

REVIEW

Garlic (*Allium sativum* L.) and cardiovascular diseasesGinter E¹, Simko V²*Institute of Preventive and Clinical Medicine, Bratislava, Slovakia. ginter.emil@mail.t-com.sk*

Abstract: Garlic is an important component in the complementary and alternative medicine. Large segments of population believe in and utilize herbal products even when these have not been as thoroughly researched as garlic. Experimental and clinical studies confirm that the ancient experience with beneficial effects of garlic holds validity even in prevention of cardiovascular disorders and other metabolic ills. Most recent data published after year 2000 convincingly point out that garlic and its various forms reduce cardiovascular risk, including abnormal plasma lipids, oxidized low density lipoproteins (LDL), abnormal platelet aggregation and a high blood pressure. Stimulation of nitric oxide generation in endothelial cells seems to be the critical preventive mechanism. Garlic may promote an anti-inflammatory environment by cytokine modulation in human blood. Cardioprotective effects of dietary garlic are mediated in large part via the generation of hydrogen sulfide (H₂S). Garlic-derived organic polysulfides are converted by erythrocytes into hydrogen sulfide which relaxes vascular smooth muscle, induces vasodilation of blood vessels, and significantly reduces blood pressure. There are data on potential ability of garlic to inhibit the rate of progression of coronary calcification. Garlic as a dietary component appears to hold promise to reduce the risk of cardiovascular disease (*Fig. 2, Ref. 46*). Full Text in free PDF www.bmj.sk.

Key words: garlic, cardiovascular diseases, blood pressure, antioxidant effects, platelet aggregation, hydrogen sulfide.

Garlic (G) has been used throughout human history not only as food spice but also for therapeutic benefit. It was a dietary component of ancient Israelites, used in the food of pyramid builders in ancient Egypt, presumably to fend off disease. The contestants prior to the Olympic games in Greece were administered G. Louis Pasteur noted the antibacterial properties of G in the middle of the 19th century. Medics in World War I used G as an antiseptic to prevent gangrene.

G contains a series of potentially beneficial bioactive products of various thiosulfinates. Rat studies in the 20th century reported favorable influence of G on the cardiovascular (CV) system, possibly related to inhibition of hepatic cholesterol synthesis and to reduction of cholesterol in the arterial wall (1). Initially, these reports encountered skepticism, expressing doubt if similar G effects occur in humans. Benefits of G were confirmed by renewed scientific interest in preventive potential of G, triggered in recent decades by the dramatic rise in CV disorders and associated diabetes mellitus in the United States and in other affluent countries. In 2004 more than 20 % of the US population had some form of CV disease and in 2007 about 23 % of people older than 60 had diabetes (2).

This review focuses on recent series of scientific reports that document important beneficial influence of G in CV disorders and diabetes.

Biologic properties of garlic: Recent findings

Research in G has been stimulated by increasing prevalence of CV disorders and diabetes. The adverse factors in these disorders are elevated LDL cholesterol, increased oxidation of LDL, abnormal clumping of blood platelets and impaired immune response, documented by high levels of C-reactive protein and homocystein. These abnormalities are frequently associated with an elevated blood pressure. Oxidation of LDL promotes vascular dysfunction, enhances the production of inflammatory mediators and contributes to the initiation and progression of atherosclerosis. Oxidated LDL particles enhance the production and release of tumor necrosis factor (TNF- α), interleukin (IL)-6, arachidonic acid metabolites and nitric oxide (NO) that are responsible for various human pathologies.

Candidate components of G promoting its beneficial effect include, among others, bioactive allicin and other thiosulfinates, alliin, gamma-glutamylcysteines (S-allyl, S-1-propenyl, S-methyl), S-allylcysteine, gamma-glutamylcysteines, S-allylcysteine and several other compounds.

Effect of garlic on lipid metabolism

Experimental evidence (mostly in rats) indicates that G ingestion lowers blood cholesterol levels and treatment of cells with G inhibits cholesterol synthesis. Cultured hepatoma cells were treated with aqueous G extract and radiolabeled cholesterol was quantified. G extract reduced cholesterol synthesis by up to 75 % without evidence of cellular toxicity (3, 4). These results indi-

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Fig. 1. Mild but statistically significant hypolipemic effect of garlic. According to Alder et al. (5).

cate that compounds containing an allyl-disulfide or allyl-sulfhydryl group are most likely responsible for the inhibition of cholesterol synthesis by G and that this inhibition is likely mediated at sterol 4 alpha-methyl oxidase.

Favorable effect of G was reported also in human studies. In a meta-analysis six of ten studies found G to be effective in decreasing the levels of total cholesterol, LDL and triglyceride (5) (Fig. 1). In another meta-analysis (6) similarly small, but statistically significant declines were observed. No significant changes in HDL levels were observed (7). Other study demonstrated that enteric-coated G powder supplements with 9.6 mg allicin-releasing potential may be useful in mild to moderate hypercholesterolemic patients when combined with a low fat diet (8).

A balanced view has to include reports on the absence of G effect of various preparations on plasma lipids in subjects who were healthy or with only mildly elevated cholesterol (9-11). In contrast, other authors repeatedly confirmed a cholesterol-lowering effect of G (12, 13). This was most pronounced in type 2 diabetes (14), in patients with hypertension (15) and elevated cholesterol (16). Negative results obtained in some clinical trials may have resulted from using different garlic preparations with unknown active constituents and their bioavailability.

In balance, favorable reports on G suggest that this herb may be considered as a potential adjunct to preventive diets and medications used for lipid disorders.

Garlic and blood pressure

The general public holds a belief that G has beneficial effects on high blood pressure and that it may prove useful for patients who are at high risk of future CV events. In contrast to some other popular beliefs, this opinion regarding G is consistent with clinical studies. Medical reports documenting hypotensive effect of G repeatedly appear in the literature (most recently see 10, 16, 17). A systematic review and meta-analysis published in 2008 has a prominent place (18). The authors analyzed 25 studies published between 1955 and October 2007 and found that G preparations were superior to placebo in reducing blood pressure in individuals with hypertension ($p < 0.001$). The mean decrease in the hypertensive patients was 8.4 mmHg for systolic

blood pressure (SBP) and 7.3 mmHg for diastolic blood pressure (DBP). They conclude that the effect of G preparations on blood pressure are comparable to the hypotensive effects of many commonly-prescribed blood pressure drugs. These findings may have implications at a population level, where a reduction of 4 to 5 mmHg in SBP and 2 to 3 mmHg in DBP has been estimated to reduce the risk of cardiovascular morbidity and mortality by 8–20 % (18).

However, the mechanism of hypotensive effect of G has in large part remained a mystery. Cardiovascular research has largely been focused on two endogenously produced gaseous signaling molecules, nitric oxide (NO) and carbon monoxide (CO). Very recently, a third endogenously produced gaseous signaling molecule, hydrogen sulfide (H_2S), has emerged as a potentially important mediator of G cardioprotective effects. Benavides et al (19) reveal that the antihypertensive effect of dietary G is mediated in large part via the generation of hydrogen sulfide. They demonstrated that G-derived organic polysulfides are converted by erythrocytes into hydrogen sulfide gas (H_2S). After discovery that H_2S is a powerful gaseous signaling molecule, H_2S has been shown to relax vascular smooth muscle, induce vasodilation of isolated blood vessels and reduce blood pressure (20, 21).

Antioxidative effects of garlic

Oxidative stress is caused by an imbalance between the production of reactive oxygen and the ability to detoxify the reactive intermediates or to repair the resulting damage.

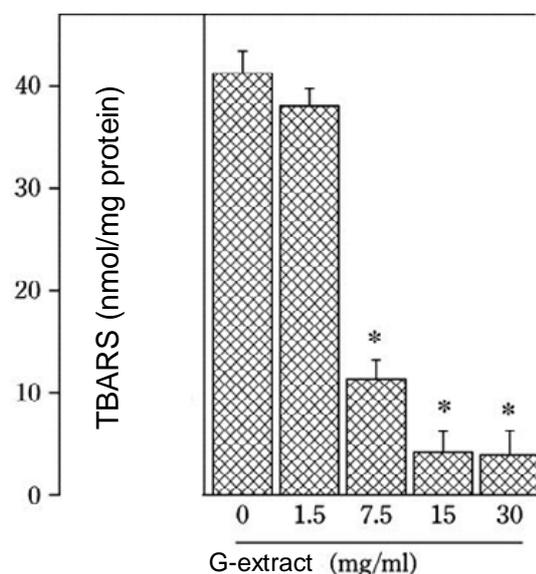


Fig. 2. The effect of garlic extract on LDL oxidation. The extent of lipid oxidation was determined by measuring thiobarbituric acid reactive substances (TBARS). Bars represent means \pm SEM and asterisks denote significant difference compared with control without garlic. According to Lau (22).

Main carrier of plasma cholesterol are the LDL particles. These are prone to oxidation to form ox-LDL. Oxidation alters the structure and metabolism of LDL. Macrophage cells preferentially take up ox-LDL, become loaded with lipids and convert into foam cells which accumulate in fatty streaks at the endothelial lining of the arteries. Endothelial cell function is impaired by an increased release of inflammatory cytokines. These contribute to inflammation and mobilization of white cells to sites of injury. Increased expression of adhesion proteins enhances the ability of leukocytes to stick to and traverse arterial endothelium.

There are 3 major antioxidant organosulfur compounds of garlic oil: diallyl sulfide, diallyl disulfide and diallyl trisulfide. They can effectively suppress LDL oxidation in vitro (22, 23, 26, 27, 28, 29) (Fig. 2). Several clinical studies found that administration of G resulted in an increased resistance of LDL to oxidation (15, 22, 24, 25). Suppressed LDL oxidation may be one of the most important mechanisms accounting for the antiatherosclerotic properties of G.

The concentration of G extract used in some of these clinical studies was equivalent to an adult eating about two medium-sized cloves of G per day. In Italy, Korea and China, per capita consumption is as high as 8-12 cloves per day. To maximize the health benefits, G should be crushed at room temperature and allowed to sit for about 15 minutes. That triggers an enzyme reaction that boosts the organosulfur compounds in G.

Garlic-powder pills claim to solve the problem, but the data on these supplements has been mixed. It is still not clear if the beneficial compounds found in G remain potent once it has been processed into a pill. Very often aged garlic extract (AGE) and its major compound, S-allylcysteine are used in human studies. There is substantial variability in the contents of G preparations, with inadequate definitions of the biologically active and available constituents and their dissolution properties. This makes it difficult to ascertain the consistency of G effect in these trials (12).

Over the counter G preparations in the US include odor-less garlic capsules where 500 mg equals 1,200 mg fresh G. One clove of G represents about 2,500 mg fresh G. Garlic oil is sold in pills containing 2 mg, equivalent to 1,000 mg fresh G. Obviously, natural G in the market is much less expensive.

Further protective effects of garlic: anti-inflammatory activity and inhibition of platelet aggregation

Although the molecular mechanism responsible for the development of atherosclerosis is not completely understood, it is clear that the immune system plays a key role in the development of the atherosclerotic plaque. The development of atherosclerotic lesions is a complex endothelial dysfunction induced by elevated and modified LDL and ox-LDL, free radicals, toxins, hypertension and other factors. This dysfunction of the endothelium leads to a compensatory inflammatory response characterized by disruption in normal function of the endothelial cells. Endothelial cells are part of a complex system that regulates vasodilation and vasoconstriction, growth of vascular smooth muscle cells and inflammation. The earliest event in atherogen-

esis is endothelial dysfunction, manifested by deficiencies in the production of nitric oxide (NO) and prostacyclin (30, 31).

Many recently published reports show that G possesses plasma anticoagulant and antioxidant properties and improves impaired endothelial function (32). G may promote an anti-inflammatory environment by cytokine modulation in human blood that leads to an overall inhibition of NF-kappaB activity in the surrounding tissue (33). G extract and its major component, S-allyl cysteine differentially regulate NO production by inhibiting inducible nitric oxide synthase (iNOS) in macrophages while increasing NO in endothelial cells. Thus, this selective regulation may contribute to the anti-inflammatory effect of G (34).

G-derived organosulfur compounds have been found to inhibit the activity of the inflammatory enzymes, cyclooxygenase and lipoxygenase (35) and to decrease the expression of iNOS in inflammatory macrophages (34, 36, 37). A variety of G-derived organosulfur compounds have been found to inhibit platelet aggregation (38, 39). Fibrinolytic activity of G may then inhibit platelet aggregation, preventing thrombotic events.

Some G compounds inhibit arterial smooth muscle cell proliferation and migration of vascular smooth muscle cells (40, 41). A pilot study indicated the potential ability of G to inhibit the rate of progression of coronary calcification, as compared to placebo over 1 year (42, 43).

Physicochemical analyses of G used various extraction procedures to separate and identify biologically active components (44). Aged G has more potent immunomodulatory effect than raw G. This is related to transformed organosulfur compounds. Examination of changes in G protein fractions during its aging identified protein fractions in garlic lecithins of the aged extract that are potentially responsible for immunomodulation (45). From a practical point of view, it is important to realize that the antioxidant property of G are preserved during most culinary procedures (boiling, microwaving, frying, baking) (46).

Finally, a warning note. Potential for side effects confirms biological activity of G. G users should be aware of possible side effects in subjects who have predisposition to bleeding, who take anticoagulants, NSAID medications potentially damaging the stomach, patients who have tendency to abnormally low blood pressure or diabetics who take insulin and are prone to hypoglycemia.

Conclusion

There is wide spread opinion among general public that G has beneficial effects on health. In contrast to many other popular beliefs, this notion on G is confirmed by multiple well controlled clinical reports published in recent years. Epidemiologic studies, mostly after 2008 show an inverse correlation between G consumption and progression of cardiovascular disease. In experiments, G inhibits enzymes involved in lipid synthesis, decreases platelet aggregation, prevents oxidation of LDL and increases antioxidant status. Clinical trials had similar results: G reduced blood pressure, lowered cholesterol and oxo-LDL levels, inhibited platelet aggregation, increased antioxidant status

and had prominent antiinflammatory effects. There are three major antioxidant organosulfur compounds in G: diallyl sulfide, diallyl disulfide and diallyl trisulfide. Cardioprotective effects of dietary G are mediated in large part via the generation of hydrogen sulfide (H₂S). G-derived organic polysulfides are converted by erythrocytes into gaseous signaling molecule H₂S. H₂S has been shown to relax vascular smooth muscle, induce vasodilation of isolated blood vessels, and reduce blood pressure. G appears to hold promise in reducing risk of cardiovascular diseases. Recent studies indicate potential ability of G to inhibit the rate of progression of coronary calcification. More research has to be performed to fully evaluate the benefits of this important herb.

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Received June 24, 2009.

Accepted May 3, 2010.