Prevention of Cardiovascular Diseases by Garlic-Derived Sulfur Compounds

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Summary Lifestyle-related diseases have complex pathogenesis which consists of several different steps. Basic causes of the diseases are attributed to unhealthy lifestyles in dietary habits, physical activity and suffering stress. The unhealthy lifestyles induce risk factors such as hypertension, dyslipidemia, obesity, and hyperglycemia. These risk factors all promote arteriosclerosis leading to serious vascular complications (i.e., thrombotic diseases), myocardial infarction and cerebral infarction. The total number of deaths from these thrombotic diseases almost equals that from cancer in our country. Cancer is also a typical lifestyle-related disease. Food has three different functions: the primary function is to provide enough nutrients to meet the metabolic requirements. The secondary function is the one relating to food preference. The third function is to control our body functions, which help reduction of the risk of diseases. Some of the compounds derived from food, especially phytochemicals in edible plants, vegetables and herbs, have potent functions to control our body functions and contribute to promoting our health. In this review article, we overview the lifestyle-related diseases and food functions involving prevention and amelioration of the diseases by food components especially from edible plants and vegetables. As an example, we will describe the food function of garlic and the prevention of lifestyle-related diseases by its components. Allyl sulfides are characteristic flavor compounds derived from garlic, and these organosulfur compounds are responsible for the food function of garlic.
Key Words life style-related diseases, food function, garlic

1. *Lifestyle-Related Diseases and Food Functions*

The lifestyle-related diseases have a complex pathogenesis, which consists of several different steps. A basic cause of the diseases is attributed to unhealthy lifestyles in dietary habits, physical activity and control of stress. Such unhealthy lifestyles induce risk factors including hypertension, dyslipidemia, obesity, and hyperglycemia. These risk factors promote arteriosclerosis leading to serious vascular complications (i.e., thrombotic diseases), myocardial infarction and cerebral infarction. The total number of deaths from these thrombotic diseases is almost the same number as that of cancer deaths in our country (*1*).

Food has three different functions (*2*). The primary function of food is to provide enough nutrients to meet metabolic requirements. The secondary function is the one relating to food preference. The color, flavor and texture (or mouthfeel) of the food interact with our sensory system including brain function, and control good-tasting. The third function of the food is to control our body functions, and promote our health with reduction of the risk of diseases. Some of the compounds derived from food, especially phytochemicals found in edible plants, vegetables and herbs have potent functions to control our body functions for well-being, and these phytochemicals are supposed to contribute our health.

In this review article, we will describe the food functions of garlic, which we have studied for many years, and found its potent medicinal function to prevent lifestyle-related diseases, like cardiovascular disease (CVD). For the prevention of CVD by medicinal foods, regulation of the platelet function, hyperglycemia, hyperlipidemia, oxidative stresses, and the production of hydrogen sulfide and nitric oxide are thought to be important targets. Allyl sulfides are the characteristic flavor components derived from garlic. Garlic contains a great amount of sulfur as amino acids such as *S*-allyl-L-cysteine sulfoxide (alliin). Upon damage to the cellular structure of garlic, C-S lyase (alliinase) acts on alliin, and converts it into allicin (allylthiosulfinate). Allicin forms several sulfides including diallyl sulfide (DAS), diallyl disulfide (DADS), diallyl trisulfide (DATS), or methyl allyl trisulfide (MATS) by non-enzymatic reaction. These organosulfur compounds are thought to be responsible for the food function of garlic (*3*).

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2. *Anticardiovascular Diseases and Antithrombotic Effects of Garlic*

The incidence of cardiovascular and thrombotic disease has increased recently and these diseases are the leading causes of death, especially in industrialized countries. The basic pathogenesis is attributed to atherosclerosis. The intake of garlic is supposed to lower the mortality and morbidity rates of these diseases through its antithrombotic, lipid-lowering and hypoglycemic effects.

1) Antiplatelet and antithrombotic effects:

Platelets play important roles in haemostasis. Up-regulation of platelet function and sensitivity toward the physiological agonists (aggregation inducers) sometimes induce hypercoagulable states related to the onset of thrombotic diseases. Inhibition of platelet aggregation is the most prominent effect of garlic intake in human subjects (*4*). Methyl allyl trisulfide (MATS) is a potent antiplatelet compound identified in garlic oil (*5*). MATS inhibits platelet aggregation induced by almost all physiological inducers such as collagen, arachidonic acid, epinephrine, thrombin, and ADP. MATS inhibits the hydroperoxydase activity of prostaglandin (PG) endoperoxide synthase and suppresses the subsequent production of thromboxane A2, a strong agonist for platelet aggregation (*6*). Ajoene was discovered as the most potent platelet inhibitor from oil-macerated crushed garlic (*4*). Ajoene inhibits both arachidonic acid metabolism and the signals generated by membrane G-protein (*7*,*8*). Intake of garlic oil enhances fibrinolysis and vascular dilation in both human and animal models (*9*,*10*).

2) Cardioprotective effect of garlic and onion through the production of hydrogen sulfide and nitric oxide:

Human erythrocytes convert garlic-derived organic polysulfides into hydrogen sulfide (H_2S) (*10*). H_2S is an important endogenous vascular cell signaling molecule having potent cardioprotective effects. H_2S protects the heart via antioxidant, antiapoptotic and anti-inflammatory actions. H_2S production is dependent on cytosolic glutathione concentration and on the reduced thiol groups locating on the surface of the erythrocyte membrane (*10*). H_2S production from organic polysulfides is facilitated by allyl substituents and by increasing numbers of tethering-sulfur atoms. Allyl-substituted polysulfides undergo nucleophilic substitution at the alpha carbon of the allyl substituent forming a hydropolysulfide (RSnH), a key intermediate in the formation of H_2S. Organic polysulfides (R-Sn-R′; $n>2$) also undergo nucleophilic substitution at a sulfur atom, yielding RSnH and H_2S. Intact aorta rings metabolize garlic-derived organic polysulfides to liberate H_2S. The vasodilating activity of garlic compounds was synchronous with H_2S production, and their potency to mediate vascular smooth muscle relaxation increases with H_2S yield, indicating that H_2S mediates the vasodilation with garlic (*10*).

Nitric oxide (NO) produced by endothelial nitric oxide synthase (eNOS) plays important roles in the maintenance of vascular functions. Dysregulation of NO production has been implicated in the development of atherosclerosis and in the pathogenesis of cardiovascular disorders such as essential hypertension, reperfusion injury and myocardial dysfunction. Oxidized-LDL (oxLDL) elicits endothelial dysfunction to promote arteriosclerosis by decreasing NO production. The oxLDL inhibits eNOS activity and production of NO. eNOS activity is highly regulated by post-translational modifications including phosphorylation and protein-protein interactions. Phosphorylation of eNOS at Ser^{1177} by protein kinase B (PKB) as well as the complex formation of eNOS with caveolin-1 and heat shock protein 90 is involved in the activation. oxLDL inhibits the eNOS phosphorylation by PKB leading to a decrease in NO production. Diallyl disulfide (DADS) and diallyl trisulfide (DATS) protect the inactivation of eNOS caused by ox-LDL insult (*11*); i.e., DADS and DATS reverse the suppression of eNOS Ser^{1177} phosphorylation by ox-LDL by enhancing the interaction of eNOS with caveolin-1 in the membrane. In addition, DADS and DATS suppress the degradation of the cellular eNOS protein content by ox-LDL. DATS protects vascular endothelium from hyperglycemia-induced injury by reducing mitochondrial oxidative stress (*12*); it also protects the ischemic myocardium by preservation of endogenous H_2S and increasing NOS bioavailability (*13*).

3) Antioxidative and antiglycative effects of organosulfur compounds:

In diabetes mellitus, hyperglycemia leads to an increase in oxidative stress. This increase is due to the overproduction of free radicals and to the decrease in the efficacy of the antioxidant defense system. The increased oxidative stress in diabetes is sometimes closely related to vascular complications such as diabetes nephropathy. DATS reduces the oxidative stress induced by a culture of cardiomyocytes under high-glucose conditions (*14*). In this culture system, DATS activated PI3K/Akt signaling and the nuclear translocation of Nrf2 followed by the upregulation of heme oxigenase 1 (HO-1). The PI3K/Akt-dependent activation of Nrf2 and the upregulation of HO-1 was also observed in streptozotocin-induced diabetic model rats in vivo.

DAS and DADS protect the oxidation and glycation of LDL. LDL and plasma which had been already partially oxidized and glycated were prepared from patients with type 2 diabetes. DAS and DADS showed significant oxidative-delaying effects in both partially oxidized LDL and plasma samples. These results suggest that DAS and DATS protect against further oxidation and glycation of LDL or plasma. These antioxidative and antiglycative effects might benefit patients with diabetes-related vascular diseases (*15*).

4) Lipid-lowering effect:

Hypercholesterolemia is an important risk factor of CVD. Lipid-lowering and cholesterol-lowering effects of garlic were demonstrated by numerous studies in both humans and laboratory animals. A meta-analysis including twenty-nine trials conducted to determine the impact of garlic on total cholesterol (TC), triglyceride (TG), LDL-C and HDL-C (*16*) revealed that garlic intake significantly reduces TC and TG, but exhibits no significant effect on LDL-C or HDL-C. The more recent meta-analysis which is the most comprehensive to date, found garlic (garlic preparations were used for longer than 2 mo) to be effective in reducing TC and LDL-C in individuals with elevated total cholesterol levels (>200 mg/dL). An 8% reduction in TC is of clinical relevance and is associated with a 38% reduction in risk of coronary events at 50 y of age. HDL-C improved only slightly, and TG was not influenced significantly (*17*).

Taken together, garlic may prevent thrombus formation during CVD through different mechanisms involving antiplatelet, vasodilative, lipid-lowering, and anti-atherosclerotic effects.

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