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Garlic and Cardiovascular Disorders: A Current Review of Literature

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A B S T R A C T

Garlic, a member of the Allium family, widely used as culinary and medicinal herbs since ancient histories, displays aptly described anti-inflammatory and antioxidant properties. Garlic's therapeutic benefit is showed to be result of its constituent organosulfur compounds. Previous study reported garlic to possess several benefits on cardiovascular health including antihypertensive, anti-atherosclerotic, and antilipidemic activities. This review elaborates the phytochemical composition, pharmacological activities, mechanism of actions, and current clinical evidence of garlic in mitigating cardiovascular disease.

1. Introduction

Garlic is one of the most major root vegetables that has a pungent distinctive flavor and commonly used all over the world not only as a spice, but also as a medicinal herb. The therapeutic effects of garlic (Allium sativum L.) are widely known for millennia[1]. The earliest written literature on medicinal properties of garlic was back to ancient Egyptian culture which listed Garlic usage among working class involved in heavy labour in the medical text Codex Ebers (ca. 1550 BC). Garlic was also listed on Charaka-Samhita, a leading Indian ancient medical textbook, for the treatment of arthritis and heart disease.[2] However, the clinical efficacy of garlic has not been experimentally demonstrated until recently in cause of the emergence of standardized clinical trials and evidence-based medicine. Extracts and isolated compounds of garlic have been thoroughly scrutinized on recent literature for various medicinal effects including antimicrobial, antioxidant, anti-inflammatory, anticarcinogenic, antidiabetic, antihypertensive, reno-protective, and anti-atherosclerotic activities[3].

Fresh garlic contains water, carbohydrates, amino acids, fibres, and hundreds of phytochemicals of organosulfur compounds, such as ajoenes, thiosulfinates, vinyldithiins, and sulfides.[4] Allicin, which is a major thiosulfinates compound in garlic and is a key determinant for garlic's distinctive odor, has inhibitory properties on cancer cell by mechanism of inducing apoptosis.[5] Allicin is an enzymatic product from substrate of allin (S-allyl-Lcysteine sulfoxide) by the alliinase enzyme. Allin itself has potent antioxidant, anti-inflammatory, anti-hypertensive, and antimicrobial effects.[6] Ajoenes, although considerably volatile, are identified to have inhibitory

properties to platelet aggregation, thus promoting clot dissolution and gaining individual protective risk for cardiovascular disorders.[6]

Atherosclerosis-caused-cardiovascular disorders has major role in global burden of the disease and a leading global cause of death.[7] The therapeutic potential of garlic in cardiovascular health emerges to be auspicious given the scale of burden that atherosclerosis puts on current medicine and the demand for novel and safe medications. The therapeutic benefit gains of garlic in prevention and treatment of cardiovascular disorders were tough to demonstrate due to the subtle result, interminable time frame for therapeutic benefit, and intricate pathogenesis of atherosclerosis-related cardiovascular disorders. Garlic-based preparations are considered to have cardioprotective and vasculo-protective effects by its nature, acting through suppressing cholesterol biosynthesis and reducing oxidation of low-density lipoprotein (LDL), thus improving blood lipid profile, improving blood pressure, inhibiting platelet aggregation, and optimizing fibrinolytic activity.[3] Current review discusses the phytochemical composition, pharmacological activities, mechanism of actions, and current clinical evidence of garlic in mitigating cardiovascular disease.

Garlic and its phytochemical composition

Garlic and its derivative products have various bioactive compounds, including polysaccharides, saponins, organosulfur compounds, and phenolic compounds. The main bioactive compounds of garlic products are garlic's organosulfur compounds, including thiosulfonates (alliin and allicin), ajoenes (E/Z-ajoenes), diallyl disulfide (DADS), diallyl trisulfide (DATS), and S-allyl-cysteine (SAC).[8] These sulfur-containing compounds have higher digestibility when consumed in as raw garlic compared to cooked garlic.

Garlic's smell and flavor are caused by the Allicin [S-(2-propenyl)-2-propene-1-sulfinothioate], the most biologically active organosulfur compounds.[9] Allicin is an enzymatic end-product of Alliin (S-allyl-L-cysteine sulfoxide) which is accounting for over 70% of the total thiosulfinates in crushed garlic.[10] When allicin or diallylisulfide interacts with cysteine in the presence of S-ally-mercaptocysteine, Allyl mercaptan is formed and being the responsible odorant molecule that causes garlic breath.[4] Allicin is a lipid-soluble sulfur molecule that is quickly destroyed by cooking and can cause intolerance, allergic reactions, and gastrointestinal problems in sensitive people.[11]

β-resorcylic acid os the most abundant phenolic component, followed by pyrogallol, gallic acid, rutin, protocatechuic acid, and quercetin.[12] Quercetin, the main flavonoid extracted from garlic, is discovered to interact with various drugs, including vitamin E and C.[13] Furthermore, garlic polysaccharides have been shown to include 85% fructose, 14% glucose, and 1% galactose.

Pharmacokinetics of Garlic Preparations

Garlic might be eaten raw, or it might be processed into oil and extract powder. Crushing, slicing, freeze-drying, heating, soaking, maceration, and steam distillation of garlic products altered the chemical composition and, as a result, in the content of bioactive chemicals found in garlic.[14] The impact of different garlic product manufacturing methods on the bioactive components of garlic have been investigated. It was discovered that after thermal treatment during garlic processing, thirties components of garlic changed.[15] During the thermal processing of garlic, the polysaccharide dissolved and the quantity of reducing sugar increased. Increasing the temperature and decreasing the humidity leads to the accumulation of polyphenols and total flavonoids in garlic.[16]

Ingestion of garlic preparations leads to distinctive pharmacokinetic profile. A previous study found N-acetyl-S-allyl cysteine (NASAC) in human urine following garlic administration, which was produced by the N-acetyl transferase enzyme converting SAC into the N-acetylated metabolite.[17] Previous studies found diallyl disulfide (DADS), allyl methyl sulfide (AMS), diallyl sulfide (DAS), allyl methyl disulfide (AMDS), dimethyl sulfide, acetone, and diallyl

trisulfide (DATS) in the breath of participants after ingesting 38 g of raw garlic. The maximal concentrations of DADS, DAS, DATS, and AMDS were observed to be reached peak concentration in 2 to 3 hours.

Allicin stability was tested in simulated gastric fluid (SGF), blood, stimulated intestinal fluid (SIF), and various solvents such as water, methanol, and ethyl acetate at pH 1.2 and 7.5, and it was found that allicin influenced the SGF and SIF, respectively.[18] It suggested that Allicin decomposed at room temperature and was more stable in methanol than in ethyl acetate. Furthermore, following incubation at 37°C for 5 hours, almost 90% of the allicin remained in the SIF (pH 7.5) and SGF (pH 1.2), but only a little quantity could be found in the blood after 5 minutes. One day after garlic extracts ingestion, 62-80 percent of allicin remained, with no increment of allicin breakdown products such as DADS.[17] The alliin peak time (Tmax) was less than 10 minutes and was eliminated from the blood after 6 hours, whereas the allicin peak time (Tmax) was 30–60 minutes and the mean total fecal and urine excretion was 85.5 percent after 72 hours. The results were resulted from pharmacokinetics testing in rats utilizing 35 S-labeled alliin, vinyl dithiins, and allicin. Allicin is a bright yellow oily liquid with a characteristic garlic odor and is extremely unstable, therefore it decomposes quickly even at room temperature.[19] Previous research has found that allicin is quickly degraded by temperature to produce ajoenes ((E)- and (Z)-4, 5, 9-trithiadodeca-1, 6, 11-triene-9-oxides) and vinyldithiins, which are far more stable than allicin.[20] These breakdown products are widely identified from garlic extracts in oil, aqueous, and chloroform, and are discovered as (E) and (Z) isomers, with (E)-ajoene being detected in double concentrations.[21]

Antihypertensive effect of garlic

Antihypertensive medication non-adherence is frequently associated with mild to severe adverse outcomes. It is the most common obstacle in hypertension patients to achieve controlled blood pressure. Thus, lower adherence to antihypertensive agent making the standard medication is not always effective. As standard antihypertensive medication is often unsuccessful, the use of complementary and alternative hypertension treatment is increasing.[22]

It is known that many compounds derived from garlic have beneficial effects on lowering blood pressure. Garlic extracts' antihypertensive action is due to the presence of numerous active sulfur compounds, which have been proven to trigger endothelium-constricting and -relaxing factors, lowering blood pressure. The vasodilation effect of garlic is from the enhanced synthesis of nitric oxide and hydrogen sulfide.[23] Substrate from garlic has several mechanisms of action lowering the blood pressure, such as inhibit the angiotensin-converting enzyme by the gamma-glutamylcysteine isolated from garlic, reduce of vasoconstrictor prostanoids synthesis, up-regulation of the growth suppressor p27 and depletion of ERK1/2 phosphorylation, and down-regulation of angiotensin II receptor.[24] Moreover, garlic substrate has effects on reducing the risk of plasma viscosity, arterial occlusive disorders, unstable angina, and increasing the elasticity of blood vessel and perfusion of capillaries.[25]

Anti-atherosclerotic and vasculo-protective properties of garlic

Atherosclerosis treatment plans should aim to prevent the progression of preexisting atherosclerotic lesions as well as the development of new ones. The direct anti-atherosclerotic activity of garlic-based preparations was the most exciting feature. It was proved to be independent factors for the major reduction in cardiovascular event accidents. Garlic's components had the ability to affect two major intracellular enzymes involved in cholesterol metabolism. Garlic extract also suppressed cellular proliferation and the formation of connective tissue matrix components, exhibited antioxidant properties, and reduced LDL oxidation susceptibility.[26,27] In vivo study on cholesterol-fed rabbits showed garlic-based treatments prevented neointimal thickening.[28] After a

single dose, a garlic-based preparation inhibited cholesterol buildup in cultured cells treated with serum from atherosclerosis patients, reducing serum atherogenic potency.[26–28] The production of modified atherogenic LDL, such as oxidized LDL, glycosylated LDL, or desialylated LDL, was required for atherogenesis.[29] In blood plasma, garlic components and derivatives had been found to decrease these modified atherogenic LDL.[30,31] As a result, utilizing garlic-based preparations may reduce the pool o atherogenic modified LDL and hence lessen cholesterol accumulation in the arterial walls.

Inflammation was recognized to play a part in the development of atherosclerosis. The inflammatory pathway was demonstrated to be a major physiological response to modified LDL, presumably initiating alterations in lipid metabolism.[32] The expression and secretion of atherosclerosis related pro-inflammatory cytokine such as TNF, IL-1, VCAM, ICAM-1, and HLA-DR were all known to be inhibited by garlic components.[32,33] As a result, they might have a positive effect on artery wall cells.

A randomized, double-blind, placebo-controlled clinical trial in Germany showed reduced growth (by 5%–18%) and even a modest regression of plaques using B-mode ultrasonography measurements of plaque volume in patients taking high-dose garlic powder during the 48-month follow-up period.[34] Another clinical trial in 211 asymptomatic men aged 40–74 years explore the effects of time-released garlic dust tablets (Allicor) on the advancement of carotid atherosclerosis. The trials showed a significant decrease of cIMT by 47% during 12-months follow-up period.[35] A randomized placebo-controlled trial in individuals with coronary heart disease looked at garlic powder pills as a complement to standard medical treatment.[36] After 3 months of follow-up in this trial, the study group showed a 0.009 mm drop in cIMT, while the placebo group showed a 0.040 mm increase in cIMT. There were no differences in lipid profile between the two groups.

Kwal JS et al conducted a meta-analysis that included nine trials that measured systolic blood pressure and ten trials that measured diastolic blood pressure.[37] In patients treated with garlic, both systolic and diastolic blood pressure were reduced by 4.3 and 2.4 mmHg, respectively, according to the study. Another meta-analysis of 9 randomized placebo-controlled trials that tested garlic preparation in 482 hypertension patients over a period of 8–26 weeks found a difference in systolic and diastolic blood pressure of 9.1 mm Hg and 3.8 mm Hg, respectively.[38] Majority of current evidence supported the hypothesis that garlic could moderately lower arterial blood pressure in hypertensive individuals.

Antilipidemic effect of garlic

Hyperlipidemia is one of the modifiable risk factors of CVD. Furthermore, one of the basic current therapeutic strategies for reducing the risk of CVD is to normalize the blood lipid profile. Studies showed that garlic-substrate has many pathways to reduce the risk of CVD, including as a potential lipid-lowering agent.

The antilipidemic effect of garlic has been studied by several groups. A clinical study by Sudipta et al. showed the comparison of garlic homogenate (500mg/kg body weight), atorvastatin (7.2 mg/kg/day) and ezetimibe (0.9 mg/kg/day) treatment in high fat diet-fed rats. The result revealed that garlic homogenate was proved to significantly cut down all the lipid parameters; reduce total cholesterol (TC) 16%, triglyceride (TG) (23%), low-density lipoporotein (LDL) 44%, very lowdensity lipoprotein (VLDL) 8% and increase high density lipoprotein (HDL) 21%, after 12 weeks of treatment. Additionally, the garlic homogenate can augment the hypolipidemic effect of atorvastatin and ezetimibe.[39] There are some mechanisms of action of garlic substrate in lowering lipid concentration, one of them is the inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase by diallyl disulfide.[40] The main active constituent of aged garlic extract, S-allyl cysteine, was also validated as an antioxidant and hypolipidemic agent in rats, causing significant reductions in TG, TC, AST, ALT, malondialdehyde, glutathione peroxidase enzyme

activity, total glutathione, and oxidized glutathione in rat serum.[41]

Some studies and meta-analysis showed the beneficial effect of garlic as a lipid-lowering agent, but some showed an insignificant effect. A positive summary result was from a meta-analysis that reviewed 29 randomized, placebo-controlled trials of garlic which showed that garlic can lower the level of total cholesterol and triglyceride, but had no effect on HDL and LDL. Meanwhile, a meta-analysis which was conducted in 2009 reviewed 13 randomized controlled trials and didn't show any substantial difference compared with the placebo group. The result did not assist the beneficial effect of garlic in lowering the level of lipid in serum.[42] Other studies focused to describe the effective dosage of garlic to have the optimum effect. A study from Javad and the co-author showed 400 mg (contains 1 mg allicin) of enteric-coated garlic powder tablet twice a day can cut down 12% TC, 17% LDL-cholesterol, increase almost 16% HDL-cholesterol, and insignificant effect on TGA serum.[43] Another study from Sobenin et al. showed subjects with hyperlipidemia were received 600 mg daily of garlic powder tablet proved to reduce 7.6% TC, 12% LDL-cholesterol, and increase 11.5% HDL-cholesterol.44 Hence, other control studies had the same garlic extract tested but had different result, delivery contradicting results.

2. Conclusion

This review discussed on the chemical ingredients and pharmacological actions of garlic and its derivate product. The primary ingredients extracted from garlic extracts are sulfur-containing compounds such as alliin, allicin, ajoenes, vinyldithiins, and sulfides. Garlic extracts and isolated chemicals have been shown to have a variety of biological functions, including antilipidemic, direct anti-atherosclerotic, and antihypertensive effects. The considerable variety of studies in terms of patient characteristics, doses, and garlic-containing medicinal formulations makes accurate evaluation of garlic's anti-atherosclerotic potential tricky. The evidence suggests that garlic preparations can be utilized as a complementary therapy for patients with atherosclerosis-related cardiovascular diseases and as a preventative intervention. Pre-emptive consideration should be exercised while utilizing garlic as a therapy to treat cardiovascular diseases.

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