Review Article

Garlic (*Allium sativum* L.): A review of potential therapeutic applications

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Garlic (*Allium sativum* L. fam. Alliaceae), one of the best-researched herbal remedies, is frequently used as a food and a spice. Garlic contains enzymes (e.g., allinase), sulphur-containing compounds, including alliin, and compounds produced enzymatically from alliin (for example, allicin). Conventionally, it has been used to treat infections, wounds, diarrhoea, rheumatism, heart disease, diabetes and many other disorders. Experimental studies have demonstrated that garlic exhibits antibacterial, antihypertensive, cardioprotective, antilipidaemic, anticarcinogenic, immunostimulant and hypoglycaemic properties. Clinically, garlic has been investigated for a variety of indications, namely, hypertension, hypercholesterolaemia, diabetes and for the prevention of arteriosclerosis and cancer. Systematic reviews are available for the possible antilipidaemic, antihypertensive, antithrombotic and chemopreventive effects. Garlic appears to be generally safe although allergic reactions may occur.

Key words: *Allium sativum*, anticarcinogenic, antimicrobial, antioxidant, cardioprotective, garlic

ORIGIN AND HISTORY

A member of the Liliaceae family, garlic (*Allium sativum*) is a cultivated food highly regarded throughout the world. Originally from Central Asia, garlic is one of the earliest of cultivated plants.[1] The name "*Allium sativum*" is derived from the Celtic word "all", meaning burning or stinging, and the Latin "sativum" meaning planted or cultivated. The English word, garlic, is derived from the Anglo-Saxon "gar-leac" or spear plant, referring to its flowering stalk.[2]

Garlic is one of the earliest documented examples of plants employed for treatment of disease and maintenance of health. Garlic was in use at the beginning of recorded history and was found in Egyptian pyramids and ancient Greek temples. Even Bible refers to its use. Medical applications of garlic have been documented in ancient medical texts from Egypt, Greece, Rome, China and India. Garlic was administered to provide strength and increase work capacity for labourers in many cultures. Almost 25 centuries ago, Hippocrates, the Father of Medicine, stated "*let food be thy medicine and let medicine be thy food*". Supporting this statement, Hippocrates prescribed garlic for a variety of conditions. Garlic was given as perhaps one of the earliest "performance enhancing" agents to the original Olympic athletes in Greece.[3]

A bulb of garlic itself represented a whole pharmacy industry due to the broad spectrum of effects at the time when antibiotics and other pharmacy products did not exist. The garlic was given different names that are still in use such as "Russian penicillin", "natural antibiotic", "vegetable viagra", "plant talisman", "rustic's theriac", "snake grass", etc. Presentation of the development of ideas associated with garlic increased the ability of the physicians to respond to the challenges of their professional services in facilitating human life.[4] Modern science is tending to confirm many of the beliefs of ancient cultures regarding garlic, defining mechanisms of action and exploring garlic's potential for disease prevention and treatment. Hence, the objective of this review is to examine the medical uses of garlic and the role that it is considered to play in prevention and treatment of disease.

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CHEMISTRY

Garlic contains at least 33 sulphur compounds, several enzymes, 17 amino acids, and minerals such as selenium. Of all the *Allium* species, garlic contains a higher concentration of sulphur compounds. Garlic's pungent odour and many of its medicinal effects are due to the sulphur compounds. Approximately 1% alliin (S-allyl cysteine sulfoxide) is present in dried, powdered garlic. Allicin (diallyl thiosulfinate or diallyl

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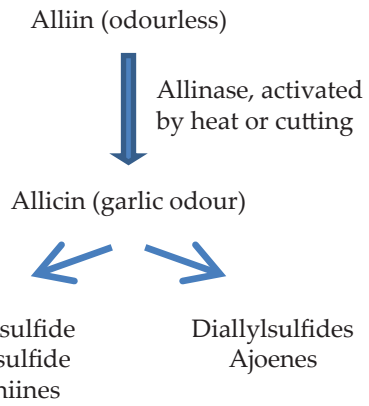
disulfide), which is the most biologically active compound in garlic, does not exist until garlic is crushed or cut. Enzyme allinase, which is activated upon injuring the garlic bulb, metabolises alliin to allicin. Allicin is subsequently metabolised to vinyldithiines. This process requires hours at room temperature and minutes during cooking. Allicin, which has antimicrobial effects against many viruses, bacteria, fungi and parasites, was first chemically isolated in the 1940's. Garlic oil, aged garlic and steam-distilled garlic does not contain significant amounts of alliin or allicin, but instead contain various products of allicin transformation; none appears to have as much physiologic activity as fresh garlic or garlic powder.

POTENTIALLY ACTIVE CHEMICAL CONSTITUENTS

- Sulphur compounds: alliin, allicin, ajoene, diallyl trisulfide, sallylcysteine, vinyldithiines, allylpropyl disulfide, S-allylmercaptocystein and others
- Enzymes: allinase, peroxidases, myrosinase and others
- Amino acids and their glycosides: arginine and others
- Selenium, germanium, tellurium and other trace minerals



Additionally, garlic is also contains a high concentration of selenium, which is responsible, in part, for garlic's antioxidant and cancer-preventive effects. Hence, some growers add selenium to the soil to increase garlic's selenium content.[2]

The myriad of properties in garlic are due the synergistic actions of the different compounds. However, due to garlic's chemical complexity, processing methods produce preparations with differing efficacy and safety. Thiosulfinates such as allicin have been wrongly attributed to be active compounds due to their characteristic odour. Nevertheless, it is not essential for garlic preparations to contain such odorous compounds to be effective, as they decompose and disappear during any processing. Not all of the active constituents of garlic have been identified, and allicin-like transient components are not directly active. However, sufficient investigation proposes that an allicin-free garlic preparation that is standardised with a bioavailable component, such as S-allylcysteine, is active and various effects of garlic may be attributed to it. Additionally, other active components in garlic products, including non-sulphur compounds like saponins, probably account for its essential biological activities. Further studies are needed to confirm their bioavailability and associated activities.[5]

NATURAL PROTECTION AGAINST PHYSIOLOGICAL THREATS

Physiological threats like oxidative stress, cardiovascular complexities, cancer insurgence, and immune dysfunction are presently tackled by natural products, which are becoming immensely popular. An increase in the favourable scientific documentation of such traditional remedies has enhanced their utilisation by masses. Garlic holds a unique position in history and was recognised for its therapeutic potential. Current research in the field of immunonutrition, physiology, and pharmacology has documented its importance as a functional food against numerous disorders. The health promoting properties of garlic, along with its sulphur-containing metabolites, i.e., allicin and its derivatives, has been thoroughly investigated recently. Garlic and its preparations are effective against health risks and even used as dietary supplements such as aged garlic extract (AGE) and garlic oil, etc. Garlic constituents/preparations scavenge free radicals, protect membranes from damage and maintain cell integrity. Reduction in cholesterol, blood pressure, anti-platelet activities, and inhibition of thromboxane formation prevents atherosclerosis-related disorders, thus conferring cardioprotective benefits. The antimutagenic and antiproliferative properties provide cancer chemopreventive interventions. Several mechanisms including activation of detoxification phase-I and II enzymes, reactive oxygen species (ROS) generation, and reducing DNA damage, etc., have been implicated. Furthermore, garlic benefits by preventing the suppression of immune response associated with increased risk of malignancy because it stimulates the proliferation of lymphocytes and macrophage phagocytosis, stimulates the release of interleukin-2, tumour necrosis factor-alpha and interferon-gamma, and enhances natural killer cells. The subsequent article stresses garlic's ability to ameliorate oxidative stress, its important role in cardioprotection, chemopreventive properties and immunomodulatory activities.[6]

ANTIMICROBIAL

Louis Pasteur was the first to describe the antibacterial effect of onion and garlic juices. Historically, garlic has been used worldwide to fight bacterial infections. Garlic

inhibits *Aerobacter, Aeromonas, Bacillus, Citrella, Citrobacter, Clostridium, Enterobacter, Escherichia, Klebsiella, Lactobacillus, Leuconostoc, Micrococcus, Mycobacterium, Proteus, Providencia, Pseudomonas, Salmonella, Serratia, Shigella, Staphylococcus, Streptococcus and Vibrio*. Importantly: 1) Garlic demonstrates a broad antibiotic spectrum against gram-positive and gram-negative bacteria. 2) Diarrhoea in humans and animals caused due to enterotoxic *coli* strains and other pathogenic intestinal bacteria are more easily inhibited by garlic than the normal intestinal flora. 3) Even organisms that have developed resistance to antibiotics respond to garlic. 4) Partial or total synergism is achieved by the combination of garlic extracts with antibiotics. 5) Good anti-tuberculosis activity in guinea pigs has been exhibited by a garlic oil preparation. 6) Complete lack of resistance of bacteria to garlic has been found. 7) Toxin production by the bacteria is also prevented.

Anti-*Helicobacter pylori*

Gastric cancer, a leading cancer in the developing world and one of the top two worldwide, is caused due to *Helicobacter pylori*. Individuals with a high intake of Allium vegetables have a lower incidence of stomach cancer. The antimicrobial activity of garlic against *H. pylori* was evaluated as Allium vegetables, particularly garlic, have antibiotic activity. The minimum inhibitory concentration was found to be 40 µg/mL. However, *Staphylococcus aureus*, the control organism, was not inhibited by the garlic extract at this concentration. Hence, *H. pylori* are more susceptible to garlic extract. Testing of 16 clinical isolates of *H. pylori* demonstrated 90% inhibition of the isolates with aqueous garlic extract at 5 mg/mL. Therefore, this outcome may provide a novel strategy for low-cost intervention for stomach cancer with few side effects in populations at high risk, especially in the case of high resistance to antibiotics.

Thiosulfinates play a major role in the antibiotic activity of garlic. Allicin exhibits its antimicrobial activity mainly by immediate and total inhibition of RNA synthesis, although DNA and protein syntheses are also partially inhibited, suggesting that RNA is the primary target of allicin action.

Microbial drug resistance is a growing menace. Despite the progress in the identification for new bacterial targets to attack, bacteria obstinately evolve. This results in a number of bacterial species developing resistance to antibacterial drugs. Hence, alternative techniques need to be evaluated and developed. There have been no reports of resistance to garlic, and it exhibits synergism with antibiotics. Hence, additional dose-response preclinical studies, and eventually clinical studies, should be performed to evaluate the use of an antibiotic/garlic combination for bacteria that are difficult to eradicate. *H. pylori* resistance is a worldwide problem and the cost of eradicating it using standard antibiotic regimen is also high. Thus, this bacterium is another candidate for clinical trials, using garlic either alone or in combination with a less expensive antibiotic regimen.[7]

Tuberculosis

There has been a steady increase in the incidence of *Mycobacterium tuberculosis* (MTB) and especially of multi-drug resistant tuberculosis (MDR-TB). Because present strategies of treatment are inadequate in developing countries, treating MDR-TB infected patients has become a complex task for TB control programs. Thus, in the coming years MDR-TB could become the major form of TB. Dini C *et al*. has reviewed both *in vitro* and *in vivo* studies carried out about anti-tubercular properties of garlic. These researches about the garlic extracts' effectiveness against clinical isolates of MDR-TB are of scientific importance. Thus, it is hoped that the administration of garlic extracts as an alternate therapy by traditional healers could improve TB health management.[8]

ANTIOXIDANT

Disorders of aging including cardiovascular, neurodegenerative, and inflammatory diseases and cancer are caused due to the oxidative modification of DNA, proteins and lipids by ROS. This oxidative damage is prevented by extracts of fresh garlic that are aged over a prolonged period to produce AGE. These garlic extracts contain antioxidant phytochemicals like unique water-soluble organosulphur compounds (OSC), lipid-soluble organosulphur components and flavonoids, especially allixin and selenium. Long-term extraction of garlic (up to 20 months) ages the extract, creating antioxidant properties by modifying unstable molecules with antioxidant activity, such as allicin, and increasing stable and highly bioavailable water-soluble OSCs, such as S-allylcysteine and S-allylmercaptocysteine. The antioxidant properties of AGE is achieved by scavenging ROS, increasing the cellular antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and enhancing glutathione levels in the cells. Lipid peroxidation, ischaemic/reperfusion damage and oxidative modification of low-density lipoprotein (LDL) are all ameliorated by AGE. This defends endothelial cells from the injury by the oxidised molecules, which contributes to atherosclerosis. Additionally, the induction of the oxidant-induced transcription factor, nuclear factor (NF)-kappa B, which has clinical significance in human immunodeficiency virus gene expression and atherogenesis, is inhibited by AGE. It also protects DNA against free radical-mediated damage and mutations. It inhibits multi-step carcinogenesis and defends against ionising radiation and UV-induced damage, including protection against some forms of UV-induced immunosuppression. Loss of brain function

in aging is prevented by AGE. This is demonstrated by its capability to increase cognitive functions, memory and longevity in a senescence-accelerated mouse model. The cardiotoxic effects of doxorubicin, an antineoplastic agent used in cancer therapy, are ameliorated by garlic. Liver toxicity caused by carbon tetrachloride (an industrial chemical) and acetaminophen, an analgesic, are mitigated by AGE. Extensive experimental evidence documents the ability of AGE to protect against oxidant-induced disease, acute damage from aging, radiation, chemical exposure and long-term toxic damage. However, additional studies are necessary in humans to support the beneficial health effects attributed to AGE, i.e., reducing the risk of cardiovascular disease, stroke, cancer and aging, including the oxidant-mediated brain cell damage that is implicated in Alzheimer's disease.[9]

CARDIOPROTECTIVE

Antihypertensive

Elevated blood pressure is one of the significant risk factors for stroke and coronary heart disease (CHD) as per epidemiological studies. Considerable interest has been generated towards nutraceuticals and functional foods as potential alternative therapies for treatment of hypertension. This is specifically for pre-hypertensive patients, whose blood pressure is marginally or mildly high but not high enough to warrant the prescription of blood pressure-lowering medications.[10]

Although garlic has been used for prevention and treatment of hypertension, its molecular mechanisms of effects remain to be elucidated. Castro *et al*. demonstrated that allyl methyl sulphide (AMS) and diallyl sulphide (DAS) inhibited aortic smooth muscle cell angiotensin II-stimulated cell-cycle progression and migration. They also found that both OSC inhibited angiotensin II-ROS generation. Thus, their findings suggest that AMS and DAS, compounds derived from garlic, could be effective antioxidants targeted at the arterial remodelling seen in hypertension.[11]

Additionally, it was shown that activation of sodium pump by garlic extract in the kidneys reduces intracellular Na+ concentration and normalizes BP. Even these effects warrant the use of garlic in the treatment of hypertension.[12]

As mentioned earlier ROS has been implicated in the pathogenesis of many diseases including hypertension. Therefore, certain compounds with antioxidative capacity are believed to be protective against such diseases. Hence, certain constituents of garlic known to possess antioxidative properties were investigated on indices of oxidative stress parameters in essential hypertensive (EH) patients. It was observed that there was a significant decline in both systolic (SBP) and diastolic blood pressures (DBP). Furthermore, there was a significant decrease in oxidised LDL (OxLDL) and 8-iso-PGF2alpha levels besides a moderate increase in the total antioxidant status (TOS). These findings suggest that dietary supplementation of garlic may be beneficial in reducing blood pressure and oxidative stress in hypertensive individuals.[13]

Brankovic *et al*, showed that intravenous administration of the garlic extract produced dose-dependent, reversible hypotensive and bradycardic effects in anaesthetised normotensive rats.[14]

Asdaq *et al*. investigated the protective effects of combined therapy of garlic homogenate with hydrochlorothiazide (HCTZ) in animals with hypertension and myocardial damage. The results showed that garlic combined with HCTZ increases the lactate dehydrogenase, creatinine phosphokinase, superoxide dismutase and catalase activities in heart homogenate when used concurrently or separately. There was restoration of normal values in body weight, systolic blood pressure, cholesterol, triglycerides, glucose and histopathological scores in all treated groups. Furthermore, histological disturbances and hypertension were significantly ameliorated in treated animals. Moreover, moderate dose of garlic was more effective than low dose, while a high dose of garlic was least effective in correcting electrocardiographic changes. Thus, garlic in moderate dose with added HCTZ possesses synergistic cardioprotective and antihypertensive properties against fructose- and isoproterenol-induced toxicities.[15]

The combined therapy of fresh garlic homogenate (FGH) 250 mg/kg with captopril (CAP) was more effective in reducing SBP, cholesterol, triglycerides and glucose. Besides Super Oxide Dismutase (SOD), the catalase activities in heart tissue were significantly elevated in rats treated with FGH, SACS (S-allyl cysteine sulphoxide), CAP, FGH+CAP and SACS+CAP. Further, combined therapy of FGH 250 mg/kg with CAP caused significant fall in LDH and Creatine Kinase Myocardial Band (CK-MB) activities in serum and elevation in heart tissue homogenate. Moreover, combination of SACS with CAP exerted super-additive (synergistic) interaction with respect to fall in blood pressure and angiotensin-converting enzyme (ACE) inhibition. This study may represent a beneficial role of concomitant use of garlic or its bioactive constituent, SACS, with captopril.[16]

Ried *et al*. 2010 demonstrated that in patients with uncontrolled hypertension (SBP≥140 mmHg at baseline), SBP was on average 10.2±4.3 mmHg (P=0.03) lower in the garlic group compared with controls over the 12-week treatment period. Changes in blood pressure between the

groups were not significant in patients with SBP 140 mmHg at baseline. Aged garlic extract was generally well tolerated and acceptability of trial treatment was high (92%). This trial suggests that aged garlic extract is superior to placebo in lowering SBP similarly to current first-line medications in patients with treated but uncontrolled hypertension.[17]

Animal studies have suggested that garlic reduces blood pressure, but primary studies in humans and non-systematic reviews have reported mixed results. Ried *et al*. 2008 conducted a systematic review and meta-analysis from 1994 of studies investigating the effect of garlic preparations on blood pressure. Randomised controlled trials with true placebo groups, using garlic-only preparations, reporting mean SBP and/or DBP and standard deviations were included in the meta-analysis. Eleven of 25 studies included in the systematic review were suitable for meta-analysis. Meta-analysis of all studies showed a mean decrease of 4.6±2.8 mm Hg for SBP in the garlic group compared with placebo (P=0.001), while the mean decrease in the hypertensive subgroup was 8.4±2.8 mm Hg for SBP (P<0.001) and 7.3±1.5 mm Hg for DBP (P<0.001). Thus, meta-analysis suggests that garlic preparations are superior to placebo in reducing blood pressure in individuals with hypertension.[18]

In another meta-analysis conducted by Reinhart *et al*., 10 trials were included; three of these had patients with elevated SBP. Garlic reduced SBP by 16.3 mmHg and DBP by 9.3 mmHg compared with placebo in patients with elevated SBP. However, the use of garlic did not reduce SBP or DBP in patients without elevated SBP. There was only a minor degree of heterogeneity in the analyses and publication bias did not appear to influence the results. This meta-analysis suggests that garlic is associated with blood pressure reductions in patients with an elevated SBP although not in those without elevated SBP. Future research should focus on the impact of garlic on clinical events and the assessment of the long-term risk of harm.[19]

Anti-atherosclerotic

Several risk factors for heart disease have been identified in prospective epidemiologic studies, and most can be the target of risk reduction interventions. Atherosclerotic cardiovascular disease (ASCVD) is the most widely recognized risk factor. There has been a tremendous growth in the understanding of the pathogenesis and aetiology of coronary ASCVD. Although garlic has been used conventionally in treating ASCVD, no studies on its ability to inhibit the atherosclerotic process have been reported. Incremental benefits have been reported from a pilot study of patients with coronary artery calcification who were concurrently administered garlic and statins. The implications of this study must be put in context of the potential importance of early atherosclerosis detection and prevention.[20]

Hypercholesterolaemia, which is a major risk factor for atherosclerosis, has been acknowledged since many decades. Thus, reduction of cholesterol can significantly decrease the risk for cardiovascular diseases. Evidence from recent years suggests that oxidation of LDL contributes majorly in the initiation and progression of atherosclerosis. Oxidized LDL, but not native LDL, promotes vascular dysfunction by exerting direct cytotoxicity toward endothelial cells. It increases chemotactic properties for monocytes by transforming macrophages to foam cells via scavenger receptors. In addition, it enhances the proliferation of various cell types, e.g., endothelial cells, monocytes and smooth muscle cells; all of these events are recognised as contributing to atherogenesis. Experimental evidence by Lau *et al*. shows that several garlic compounds can effectively suppress LDL oxidation *in vitro*. Besides, short-term supplementation of garlic in human subjects has demonstrated an increased resistance of LDL to oxidation. These data suggest that suppressed LDL oxidation may be one of the powerful mechanisms accounting for the anti-atherosclerotic properties of garlic.[21]

Expression of CD36 scavenger receptors on macrophages is involved in OxLDL uptake and foam cell formation during atherosclerotic lesion development. *In vitro* and *in vivo* experiments have demonstrated that the atherosclerotic risk factor homocysteine (Hcy) induces macrophage CD36 expression as well as OxLDL uptake. However, Morihara *et al*. observed that AGE inhibits CD36 expression and OxLDL uptake in human macrophages by modulating the PPARγ pathway. Thus the study suggests that the extract could be useful for the prevention of atherosclerotic lesions.[22] Moreover, Lei *et al*. suggest that diallyl disulfide (DADS) and diallyl trisulphide (DATS) protect endothelial nitric oxide synthetase (eNOS) activity against OxLDL insult. This protection can be attributed partly to their mediation of phosphatidylinositol 3-kinase/protein kinase B signalling and prevention of eNOS degradation.[23]

Garlic along with its water-soluble allyl sulphur-containing compound, S-Allyl-L-cysteine Sulfoxide (ACSO), has shown antioxidant and anti-inflammatory activities, inhibiting the development of atherosclerosis. Apparently, ACSO inhibited pro-inflammatory cytokine-induced adhesion of monocytes to endothelial cells by inhibiting the mitogen-activated protein kinase signalling and related intercellular cell adhesion molecule-1 expression. It also maintains mitochondrial membrane potential and suppresses the overproduction of superoxide anion in endothelial cells. Hence, these findings may provide new

insights into ACSO on controlling TNF-alpha-mediated inflammation and vascular disease.[24]

Previous studies demonstrated that aged garlic extract reduces multiple cardiovascular risk factors. However, this study by Budoff *et al*, was designed to evaluate whether aged garlic extract therapy with concurrent supplements (AGE+S) favourably affects inflammatory markers, oxidation biomarkers, vascular function and progression of atherosclerosis as compared with placebo. All patients underwent coronary artery calcium scanning (CAC), temperature rebound (TR) as an index of vascular reactivity using Digital Thermal Monitoring (DTM), and measurement of lipid profile, autoantibodies to malondialdehyde (MDA)-LDL, apoB-immune complexes, oxidised phospholipids (OxPL) on apolipoprotein B-100 (OxPL/apoB), lipoprotein (a) [Lp (a)], C-reactive protein (CRP), and Hcy were measured at baseline and 12 months. CAC progression was defined as an increase in CAC>15% per year and an increase in TR above baseline was considered a favourable response.

It was observed that at 1 year, CAC progression was significantly lower and TR significantly higher in the AGE+S compared with the placebo group after adjustment of cardiovascular risk factors (P<0.05). Total cholesterol, LDL-C, Hcy, IgG/IgM autoantibodies to MDA-LDL and apoB-immune complexes were decreased, whereas HDL, OxPL/apoB, and Lp (a) were significantly increased in AGE+S compared with placebo. Therefore, AGE+S are associated with a favourable improvement in oxidative biomarkers, vascular function and reduced progression of atherosclerosis.[25]

Anti-thrombotic

Ischaemic heart disease (IHD) is multifactorial with a complex aetiology. Conventional risk factors including serum lipids account for less than one-half of future IHD events. Novel risk factors such as haemostatic and thrombotic factors responsible for the development and progression of IHD have been explored. Although dietary modification is conventionally recommended as the first-line therapy in the prevention of IHD, there is only sparse information regarding the effect of diet along with nutrients has on haemostasis and thrombosis. Vegetarians may have a lower concentration of certain markers of haemostasis compared with non-vegetarians as per cross-sectional studies. Besides, certain fruits, vegetables such as soy, garlic, and purple grapes may have antithrombotic effects, which may in part be due to the phytochemicals in these foods. Although it is suggested that a plant-based diet with sufficient n-3 fatty acids, certain fruits and vegetables may have a favourable impact on haemostasis and thrombosis, the evidence is neither sufficient nor conclusive. Clearly, much remains to be done in this area of investigation.[26]

Multiple complex mechanisms are involved in increased platelet aggregation, which plays a significant role in the aetiology of cardiovascular disease. There is a transient increase in free cytoplasmic calcium (Ca[2+]), thromboxane A2 generation, and the activation of the fibrinogen receptor GPIIb/IIIa on platelet activation. Lipoxygenase metabolites, protein kinase C, cyclic adenosine monophosphate (cAMP), cyclic guanine monophosphate (cGMP) and nitric oxide (NO) too are involved in this process. Garlic prevents inhibition of platelet aggregation by inhibiting cyclooxygenase activity and thus thromboxane A2 formation. It does so by suppressing mobilisation of intraplatelet Ca2+, increasing levels of cAMP and cGMP. Garlic also displays significant antioxidant properties and stimulates nitric oxide synthase (NOS), leading to an increase in platelet-derived NO. It can also interact directly with the GPIIb/IIIa receptors, thus reducing the ability of platelets to bind to fibrinogen. Thus, garlic by inhibiting platelet aggregation via multiple mechanisms may have a role in preventing cardiovascular disease.[27]

Lipid Lowering

Hyperlipidaemia constitutes a major aetiopathological factor for atherosclerosis. Although best known for its lipid lowering effects and antiatherogenic effects, the mechanism by which lipid soluble OSC from garlic reduce plasma lipids has not been fully investigated. Mathew *et al*. had shown that the hepatic activity of beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis and the incorporation of radiolabeled (1, 2 14C) acetate into hepatic free and esterified cholesterol, was significantly decreased in rats treated with garlic-derived OSC. The investigators attribute the antiatherogenic effect of the OSC to the formation of protein internal disulphide. This inactivates thiol (-SH) group enzymes such as HMG-CoA reductase and the multienzyme complex of fatty acid synthesis. The anticarcinogenic effects of these compounds may also be due to inhibitory reactions on enzymes that activate carcinogens.[28]

In a study conducted by Kwon *et al*., the garlic-supplemented group exhibited significantly lower Cholesteryl ester transfer protein (CETP) activity, the total cholesterol, TG, LDL-C, VLDL-C, and atherogenic index, whereas the HDL-C concentration was significantly higher (P<0.05). Atherosclerotic lesion area in the aorta arch was also significantly lower in the garlic group (P<0.05). In the morphological examination, garlic supplement also lowered the aortic and hepatic cholesterol, and triglycerides. As such, the inhibition of CETP activity may delay the progression

of atherosclerosis, thereby supporting the atherogenicity of CETP and the inhibitory activity of garlic supplementation against CETP.[29]

A placebo-controlled, double-blind, randomised pilot study was conducted to determine whether the atherosclerotic plaque burden detected by electron beam tomography (EBT) will change at a different rate under the influence of AGE as compared with placebo. It was found that the mean change of the calcium score (volumetric method) for the AGE group was 7.5% over 1 year. The placebo group demonstrated an average increase in calcium scores of 22.2%, significantly greater than the treated cohort (P=0.046). This small pilot study indicates the potential ability of AGE to inhibit the rate of progression of coronary calcification as compared with placebo over 1 year. Should these findings be extended and confirmed in larger studies, garlic may prove useful for patients who are at high risk of future cardiovascular events.[30]

A prospective 4-year clinical trial with primary endpoint "arteriosclerotic plaque volume", displayed a 9% to 18% reduction and 3% regression in plaque volume. Moreover, it caused a decrease in LDL level by 4%, increase in HDL concentration by 8% and lowering in blood pressure by 7%. The reduction of arterial blood pressure is due to an additional opening of K(Ca) ion channels in the membrane of vascular smooth muscle cells that effects its hyperpolarisation. This membrane hyperpolarisation closes about 20% of the L-type Ca2+ channels, consequence of which is vasodilatation. In human coronary arteries, the increase in vascular diameter by 4% is closely associated with an improvement of coronary perfusion by 18%. These pleiotropic effects of garlic result in a reduction of relative cardiovascular risk for infarction and stroke by more than 50%.[31]

ANTIDIABETIC

Diabetes mellitus is a common endocrine disorder characterised by hyperglycaemia leading to long-term complications affecting the eyes, nerves, blood vessels, skin and kidneys. Increased glycation of proteins and accumulation of advanced glycation end-products (AGEPs) have been implicated in the pathogenesis of diabetic complications. Glycation together with AGEP formation is also accompanied by formation of free radicals via autoxidation of glucose and glycated proteins. Compounds with combined antiglycation and antioxidant properties may offer therapeutic potential. Recent studies suggest that AGE suppresses production of AGEPs *in vitro* and formation of glycation-derived free radicals. S-Allylcysteine, a key component of aged garlic, is a potent antioxidant and can inhibit AGEP formation. Aged garlic extract and S-allylcysteine deserve more attention, thus should be investigated to see whether they can reduce AGEPs *in vivo*.[32]

Cardiovascular disease is associated with multiple factors such as raised serum total cholesterol, raised LDL, an increase in LDL oxidation, increased platelet aggregation, hypertension, diabetes and smoking. Numerous *in vitro* studies have confirmed the ability of garlic to reduce these parameters. Thus, garlic has been shown to inhibit enzymes involved in lipid synthesis, decrease platelet aggregation, prevent lipid peroxidation of oxidised erythrocytes and LDL, increase antioxidant status, control diabetes, besides inhibiting ACE. Many of these findings have also been evaluated in clinical trials. These studies point to the fact that garlic reduces cholesterol, inhibits platelet aggregation, reduces blood pressure and increases antioxidant status. Since 1993, 44% of clinical trials have indicated a reduction in total cholesterol, and the most profound effect has been observed in garlic's ability to reduce the ability of platelets to aggregate. Mixed results have been obtained in the area of blood pressure and oxidative stress reduction. The findings are limited because very few trials have addressed these issues. The negative results obtained in some clinical trials may also have resulted from usage of different garlic preparations, unknown active constituents and their bioavailability. Additional reasons could include inadequate randomisation, selection of inappropriate subjects and short duration of trials. Moreover, garlic consumption and progression of cardiovascular disease is inversely correlated as per epidemiologic studies. Thus, analyses of these *in vitro* and *in vivo* studies published since 1993 suggests that although garlic appears to hold promise in reducing parameters associated with cardiovascular disease, more in-depth appropriate studies are required.[33]

CANCER CHEMOPREVENTIVE

To increase the use of phytochemical supplements as chemoprevention or adjuvant drugs in cancer treatment, it is necessary to verify their biological effects and correlative mechanisms. Substantial evidence documents the anticarcinogenic potential of Allium vegetables with their constituents, viz., allylsulfides and flavonoids. Higher intake of Allium products is associated with reduced risk of several types of cancers as per epidemiological studies. These epidemiological findings are well correlated with laboratory investigations. OSC present in Allium vegetables are considered to be responsible for the beneficial effects of these herbs.[34] Both water- and lipid-soluble allyl sulphur compounds are effective in blocking a myriad of chemically induced tumours. Probably, block in nitrosamine formation and metabolism could partly account for the protection

from these compounds. Garlic along with its constituents can alter several phase I and II enzymes as evidenced by the blockages in the initiation as well as promotion phases of the carcinogenicity of various compounds, including polycyclic hydrocarbons. Their ability to block experimentally-induced tumours in a variety of sites including skin, mammary and colon, suggests a general mechanism of action. Some protection against carcinogenesis is provided by changes in DNA repair and in immunocompetence. Certain, but not all, allyl sulphur compounds too can effectively slow tumour proliferation and induce apoptosis. Anti-tumourigenic properties of garlic may also be attributed to changes in cellular thiol and phosphorylation stains.[35]

In recent years, it has be demonstrated that certain naturally occurring OSC analogues can inhibit proliferation of cancer cells in culture and *in vivo*. These are frequently associated with perturbations in cell cycle progression and induction of G2/M phase arrest. They induce apoptosis via the intrinsic pathway by altering the ratio of the Bcl-2 family of proteins both in cell culture and in *in vivo* models. Garlic-derived OSC exhibits anti-angiogenic activity also.[36]

Colorectal Cancer

The incidence rates of both large as well as small bowel cancer are low in India, and rectal cancer is more common than colon cancer. The incidence rates of colon cancer in eight population registries vary from 3.7 to 0.7/100,000 among men and 3 to 0.4/100,000 among women. For rectal cancer the incidence rates range from 5.5 to 1.6/100,000 among men and 2.8 to 0/100,000 among women.[37] Colorectal cancer (CRC) is the 3rd leading cause of cancer death in the United States and the 2nd leading cause of cancer death in Australia. Environmental factors play important roles in the multiple-stage process of CRC and nutritional intervention has been identified as playing a major role in its prevention. Hence, a systematic review of the scientific evidence from all studies conducted over the last decade that examined effects of garlic on CRC was performed. One randomised controlled trial demonstrated a statistically significant 29% reduction in both size and number of colon adenomas in CRC patients taking aged garlic extract. Five of eight case control/cohort studies suggested a protective effect of high intake of raw/cooked garlic. In addition, two of these eight studies suggested a protective effect for distal colon. A published meta-analysis of these studies confirmed this inverse association, with a 30% reduction in relative risk. Eleven animal studies demonstrated a significant anticarcinogenic effect of garlic and/or its active constituents. Therefore, there is consistent scientific evidence derived from RCT of animal studies reporting protective effects of garlic on CRC despite great heterogeneity of measures of intakes among human epidemiological studies.[38]

Prostate Cancer

A study was performed to investigate the dose-dependent effect of diallyl disulfide (DADS) on an androgen-dependent prostate cancer cell line. Various concentrations of DADS ranging from 25 to 100 microM were given to LNCaP cells. The activity of lactate dehydrogenase (LDH), prostatic acid phosphatase (PAcP) and the level of prostate specific antigen were studied. Results from the study suggest that DADS reduced the secretory activity of LNCaP cells with the gradual increase in dosage. DADS acts as a good antiproliferative agent, as confirmed by proliferation assay. DADS also induced apoptosis and nuclear segmentation in the higher doses.[39]

Liu *et al*. found that SAC, S-allylcysteine, a potent compound present in garlic, suppressed the proliferation of PC-3 cells and led to cell cycle arrest at the G0/G1 phases, as well as inducing cell apoptosis. This was accompanied by the decreased expression of Bcl-2 and increased expression of Bax and caspase 8. This study demonstrated the chemopreventive activity of SAC *in vitro*, and that SAC may be a promising candidate for prostate cancer treatment.[40]

Breast Cancer

Nkrumah-Elie *et al*. revealed mechanisms involved in DATS inhibition of BaP-induced carcinogenesis. This includes inhibition of cell proliferation, regulation of cell cycle, attenuation of ROS formation and inhibition of DNA damage. Thus, the investigators suggest that at the doses evaluated, DATS could be an effective attenuator of BaP-induced breast carcinogenesis *in vitro*.[41]

Gastric Cancer

In a study by Lee *et al*., the effect of DADS was investigated in terms of the proliferation of gastric adenocarcinoma cell line at various concentrations. It was observed that the percentage of live gastric adenocarcinoma cells was decreased to 23% of that in the control group after 400 μM DADS treatment for 48 h. The Annexin V positive/PI negative (apoptosis portion) area increased from low concentration of DADS to high concentration. When comparing among the DADS treatment groups, the amount of ROS production increased in a dose-dependent manner. The percentage of sub-diploid DNA content increased from 8.71% at 50 μM to 25.74% at 400 μM DADS treatment group. The expressions of Fas, caspase-3 and Bax were increased and that of Bcl-2 was decreased in a dose-dependent manner.[42]

Oral Cancer

Oral cancer is prevalent worldwide. An increase in the osteopontin (OPN) plasma level is correlated with the progression of oral cancer. Therefore, the study by Pai *et al*. investigated whether SAC consumption would help prevent tumour growth and progression, including the

EMT (epithelial-mesenchymal transition), in a mouse xenograft model of oral cancer. The results displayed that SAC dose-dependently inhibited the growth of oral cancer in tumour-bearing mice. Results from the histopathological and immunohistochemical staining too suggested that SAC inhibits the tumour growth and progression of oral cancer *in vivo*. There was a suppression of carcinogenesis factors such as N-methylpurine DNA glycosylase and OPN. These results show that SAC has potential as an agent against tumour growth and the progression of oral cancer in a mouse xenograft model.[43]

Hepatic Cancer

Iciek *et al*. determined the mechanism of biological action of garlic-derived sulphur compounds in human hepatoma (HepG2) cells. Diallyl trisulfide (DATS), a sulfane sulphur-containing compound, showed the highest biological activity in HepG2 cells. This compound increased the H_2O_2 formation, lowered the thiol level, produced the strongest inhibition of cell proliferation and the greatest induction of caspase 3 activity in HepG2 cells. DATS did not alter the activity of sulphur transferases and reduced sulfane sulphur level in HepG2 cells. It appears that sulfane sulphur containing DATS can be bioreduced in cancer cells to hydroperthiol that leads to H_2O_2 generation, thereby influencing transmission of signals regulating cell proliferation and apoptosis.[44]

Leukaemias

Ajoene, a chemical constituent from garlic, was shown to inhibit proliferation and induce apoptosis of several human leukaemia CD34-negative cells. Additionally, ajoene induces 30% apoptosis in myeloblasts from chronic myeloid leukaemia patients in blast crisis. More significantly, ajoene greatly improved the apoptotic effect of the two chemotherapeutic drugs: cytarabine and fludarabine, in human CD34-positive resistant myeloid leukaemia cells through enhancing their bcl-2 inhibitory and caspase-3 activation activities. The anti-proliferation activity of ajoene is associated with a block in the G2/M phase of cell cycle in human myeloid leukaemia cells. Because acute myeloid leukaemia (AML) is a heterogeneous malignant disease in which disease progression at the level of CD34-positive cells has a major impact on resistance to chemotherapy and relapse, the inability to undergo apoptosis is a crucial mechanism of multi-drug resistance in AML patients. The recent findings of the potent enhancing activity of ajoene on chemotherapy-induced apoptosis in CD34-positive resistant human myeloid leukaemia cells suggest a novel promising role for the treatment of refractory and/or relapsed AML patients as well as elderly AML patients. Further studies are warranted to evaluate similar enhancing effect for ajoene in blast cells from AML patients in primary cultures before its introduction in pilot clinical study.[45]

Anticancer Toxicity

Almost all clinically used antitumuor drugs exhibit toxic side effects affecting heart function. Because of cardiotoxicity during anticancer chemotherapy, effective doses of cytostatics have to be curtailed, which may worsen antitumuor efficacy. Massive stimulation of ROS is responsible for the cardiotoxicity induced by cytostatics of the anthracycline group in particular. Hence, certain phytochemicals with high antioxidant potential, when co-administered with antitumuor agents, could ameliorate the adverse effects of chemotherapy and lower the risk of heart failure. Foods such as grapes, garlic, tomato, spinach and beet root exhibit such properties. Results of data from limited studies suggest that dietary intervention with antioxidants found in edible plants may be a safe and effective way of mitigating the toxicity of anticancer chemotherapy and preventing heart failure.[46]

The anticarcinogenic effect of active ingredients in garlic has been provided by animal and *in vitro* studies. Nineteen studies reported relative risk estimates for garlic consumption and cancer incidence. A protective effect of high intake of raw and/or cooked garlic has been suggested by site-specific case-control studies of stomach as well as CRC. Inverse association for CRC has been confirmed by cohort studies. Few cohort and case-control studies for other sites of cancer exist. A preventive effect of garlic consumption in stomach and CRC is nevertheless suggested from available evidence. The study limitations warrant the need for more definitive research and improved nutritional epidemiologic analyses of dietary data.[47]

NEUROPROTECTIVE

High cholesterol, high Hcy, hypertension and inflammation, all risk factors for cardiovascular disease, also increase the risk of dementia, including its most common form, Alzheimer's disease (AD). High cholesterol is also associated with elevated beta-amyloid (Abeta), the hallmark of AD. Aging with associated oxidative damage is a major factor in both cardiovascular disease and dementia. The antioxidant property of AGE scavenges oxidants, increases superoxide dismutase, catalase, glutathione peroxidase, glutathione levels, besides suppressing lipid peroxidation and inflammatory prostaglandins. Inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase by AGE reduces cholesterol synthesis. These effects retard arterial plaque formation. AGE decreases Hcy, lowers blood pressure and increases microcirculation, which is important not only in diabetes management but also reduces dementia risks. AGE also may help prevent cognitive decline by

protecting neurons from Abeta neurotoxicity and apoptosis. This prevents ischaemia- or reperfusion-related neuronal death, thus improves learning and memory retention. Evidence supports the beneficial health effects attributed to AGE in helping prevent cardiovascular, cerebrovascular diseases, lowering the risk of dementia and AD. However, additional studies are warranted in humans.[48]

NEPHROPROTECTIVE

Progressive renal damage along with hypertension are associated with oxidative and nitrosative stress. On the other hand, S-allylcysteine (SAC), the most abundant ODC in AGE, has antioxidant properties. The effects of SAC and AGE on blood pressure, renal damage, oxidative and nitrosative stress were studied in nephrectomised rats treated with SAC (200 mg/kg ip) and AG (1.2 mL/kg ip) every other day for 30 days. SAC and AGE reduced hypertension, renal damage, the abundance of inducible NOS, besides increasing SOD activity. Thus, data suggest that the antihypertensive as well as renoprotective effects of SAC and AGE are associated with their antioxidant properties. Hence, they may be used to ameliorate hypertension and delay the progression of renal damage.[49]

IMMUNOMODULATORY

Using various kinds of models, the effects of AGE on immune functions were examined. AGE significantly decreased the antigen-specific ear swelling, suppressed the growth of Sarcoma-180 (allogenic) and LL/2 lung carcinoma (syngenic) cells transplanted into mice. Simultaneously, there was an increase in natural killer (NK) and killer activities of spleen cells in Sarcoma-180-bearing mice. AGE significantly prevented the decrease in spleen weight. These studies strongly suggest that AGE could be a promising candidate as an immune modifier, which maintains the homeostasis of immune functions. More studies are warranted to evaluate when it is most beneficial.[50]

As compared with Bacillus Calmette-Guerin (BCG), the approved immunotherapy for human bladder cancer, garlic is effective when added to the diet. On elucidating the mechanism of this antitumuor effect, it was found that garlic detoxifies carcinogens by stimulation of cytochrome P (450) enzymes, antioxidant activity or sulphur compound binding. Evidence suggests a direct toxic effect of garlic to sarcoma, gastric, colon, bladder and prostate cancer cells in tissue culture. However, these effects cannot explain the inhibition of growth of transplanted cancer in animal models. The most likely explanation of this effect is immune stimulation. There are many similarities in the effects of garlic and BCG immunotherapy. Both stimulate proliferation of lymphocytes and macrophage phagocytosis. They induce the infiltration of macrophages and lymphocytes in transplanted tumours. Both produce splenic hypertrophy; stimulate release of interleukin-2, tumour necrosis factor-alpha and interferon-gamma. They also enhance natural killer cell, killer cell and lymphokine-activated killer cell activity. These activities represent effective stimulation of the immune response. Studies suggest that garlic may be useful in preventing the suppression of immune response that is associated with increased risk of malignancy. Studies recommend that maintenance of immune stimulation could significantly decrease the risk of cancer. The hypothesis that the immune stimulation and other beneficial effects of garlic are able to reduce the incidence of cancer should be confirmed clinically.[51]

AGING

Increase in the individual life expectancy has led to a concurrent increase in age-related chronic diseases of the cardiovascular, brain and immune systems. This leads to loss of autonomy, dependence, and high social costs for individuals and society. Free-radical reactions are now known to be associated with aging and age-related diseases. Hence, research in ongoing to arrest aging and rejuvenate the human body. Epidemiological evidence since the past 20 years has increased not only the popularity but usage of herbs and natural products as well. Garlic, which has been used throughout the history of civilisation for treating a wide variety of ailments including aging, has been investigated extensively over the last 10–15 years. Its strong antioxidant properties can prevent cardiovascular disease, inhibit platelet aggregation, thrombus formation, prevent cancer, diseases associated with cerebral aging, arthritis, cataract formation, rejuvenate skin, improve blood circulation and energy levels. Thus, the evidence of garlic's antioxidant properties may either prevent or delay chronic diseases associated with aging.[52]

CONTRAINDICATIONS, ADVERSE EFFECTS, INTERACTIONS

The ingestion of one to two cloves of raw garlic per day is considered safe in adults. The most common side effect of ingested garlic is breath and body odour. Consumption of excessive amounts of raw garlic, especially on an empty stomach, can cause gastrointestinal upset, flatulence and changes in the intestinal flora. There have been reports of allergic dermatitis, burns and blisters from topical application of raw garlic. Garlic appears to have no effect on drug metabolism, although recent studies in healthy volunteers show conflicting results related to garlic's effect on protease inhibitor pharmacokinetics. It has been

suggested that patients taking anticoagulants use caution when taking garlic because of its antithrombotic properties. It seems prudent to stop taking high dosages of garlic 7 to 10 days before surgery because garlic can prolong bleeding time and has been associated (in one case report) with spontaneous spinal epidural haematoma.

DOSAGE

The effective dosage of garlic has not been determined. Dosages generally recommended in the literature for adults are 4 g (one to two cloves) of raw garlic per day, one 300-mg dried garlic powder tablet (standardised to 1.3% alliin or 0.6% allicin yield) two to three times per day, or 7.2 g of AGE per day.[53]

DISCUSSION AND CONCLUSION

Since the past 15–20 years studies has primarily focused in the fields of cardiovascular and cancer research. Most studies pertaining to the cardiovascular research have been related to atherosclerosis, serum cholesterol, LDL, HDL and triglycerides. Findings suggest that garlic decreases cholesterol and triglycerides levels in patients with increased levels of these lipids. However, the studies were not consistent in relation to the dosage, standardisation of garlic preparations and period of treatment. Reduction of serum lipids by garlic ingestion could probably retard the atherosclerosis process. Besides these, extensive research both *in vitro* and *in vivo* systems has been pertaining to its antithrombotic actions. Recent findings on the identification of potent enzyme inhibiting activities of adenosine deaminase and cyclic AMP phosphodiesterase in garlic extracts are interesting. This could have a significant role in the pharmacological actions in the body. Presence of such enzyme inhibitors in garlic may perhaps explain several clinical effects in the body, including the antithrombotic, vasodilatory and anticancer actions. Garlic plays a significant role in the reduction of deaths caused by malignant diseases as per epidemiological studies. Hence, numerous investigators have examined garlic with its constituents for their antitumuor and cytotoxic actions both *in vitro* as well as in laboratory animals.[54] The data from these investigations suggest that garlic contains several potentially important agents that possess antitumuor and anticarcinogenic properties. In summary, the epidemiological, clinical and laboratory data have proved that garlic contains many biologically as well as pharmacologically important compounds. These are beneficial to human health for cardiovascular, neoplastic and several other diseases. Numerous studies are in progress all over the world to develop effective and odourless garlic preparations as well as to isolate the active principles that may be therapeutically useful.

Garlic is the plant necessary in everyday life from the past until the present days. It contains active compounds that are responsible for its effect on almost every part of the human body. Garlic is an excellent tonic for the human organism. It has been used for medical treatment of everything, from ancient civilisations to date. Not withstanding its confirmed action, in the past it was avoided, even banned, only because of its sharp and unpleasant smell.

From all of the above-mentioned data, it can be concluded that administration of garlic should not be avoided; on the contrary, its intake should be as much as possible since it underlies human health.

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