Garlic: Nature’s Protection Against Physiological Threats

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Currently reliance on natural products is gaining popularity to combat various physiological threats including oxidative stress, cardiovascular complexities, cancer insurgence, and immune dysfunction. The use of traditional remedies may encounter more frequently due to an array of scientific evidence in their favor. Garlic (Allium sativum) holds a unique position in history and was recognized for its therapeutic potential. Recent advancements in the field of immunonutrition, physiology, and pharmacology further explored its importance as a functional food against various pathologies. Extensive research work has been carried out on the health promoting properties of garlic, often referred to its sulfur containing metabolites i.e. allicin and its derivatives. Garlic in its preparations are effective against health risks and even used as dietary supplements such as age garlic extract (AGE) and garlic oil etc. Its components/formulations can scavenge free radicals and protect membranes from damage and maintains cell integrity. It also provides cardiovascular protection mediated by lowering of cholesterol, blood pressure, anti-platelet activities, and thromboxane formation thus providing protection against atherosclerosis and associated disorders. Besides this, it possesses antimutagenic and antiproliferative properties that are interesting in chemopreventive interventions. Several mechanisms have been reviewed in this context like activation of detoxification phase-I and II enzymes, reactive oxygen species (ROS) generation, and reducing DNA damage etc. Garlic could be useful in preventing the suppression of immune response associated with increased risk of malignancy as it stimulates the proliferation of lymphocytes, macrophage phagocytosis, stimulates the release of interleukin-2, tumor necrosis factor-alpha and interferon-gamma, and enhances natural killer cells. In this paper much emphasis has been placed on garlic’s ability to ameliorate oxidative stress, core role in cardiovascular cure, chemopreventive strategies, and indeed its prospective as immune booster.

Keywords Garlic, aged garlic extract, oxidative stress, hypercholesterolemia, malignancies, immunonutrition

BACKGROUND

Humans for centuries relied on medicinal plants to cure various pathologies and developments in the domain of nutrition during the last few decades and unveiled their therapeutic potentials. In the same era, terms like functional foods, nutraceutical, and pharma foods has taken hold of the nutrition market mainly aiming to provide nutritious and healthy diets (Ramaa et al., 2006; Dattner, 2003; Fong, 2002). Many plants and their components have been extensively researched for their health-promoting benefits that includes anti-oxidant, cardiovascular protection, anti-cancer, anti-microbial, and immunomodulatory agents (Miller et al., 2004; Huffman, 2003).

Changing lifestyle and poor dietary habits often lead to progression and pathogenesis of maladies such as cardiovascular complications, cancer, and immune dysfunction. Recently, concepts of optimum nutrition flourished provided a sound footing for the frequent use of functional food (Amira and Okubadejo, 2007; Shamseer et al., 2006; Tapsell et al., 2006).

Potential health benefits of Allium vegetables, in particular, garlic (Allium sativum), has its origin in antiquity, but still there is a need to unveil the details of these benefits (Galeone et al., 2006). Garlic is one of the most ancient medicinal plants and believed to have originated from central Asia over 6,000 years ago. Garlic-based remedies were functioning in India some 5,000 years ago and its inclusion in Chinese medicine has started 3,000 years ago. As early as 1550 B.C. Egyptians fed garlic to pyramid construction crews to give them extra vigor (Rivlin, 2001). It acquired a reputation in the folklore of many cultures over the centuries as a formidable prophylactic and therapeutic...
medicinal agent. The health benefits of garlic appear to be true today and its use as a dietary supplement is recommended in many countries (Raman et al., 2007; Kik et al., 2001).

During the last decade scientific research and clinical trials to determine the effects of garlic consumption were widely studied and now the medicinal use of garlic is common. Healthful properties of garlic are legion and over a thousand scientific reports enumerated its functional activities which include free radical scavenging activities, immune stimulation, curing cardiovascular diseases, anti-cancer, and anti-infectious properties (Herman-Antosiewicz et al., 2007; Singh et al., 2007; Borek, 2006; Khanum et al., 2004; Colic and Savic, 2001; Harris et al., 2001).

Its potential in combating lifestyle related disorders like hypercholesterolemia, dyslipidemia, and high blood pressure that lead to several cardiovascular pathologies has been the focus of major research interventions (Kojuri et al., 2007; Wojcikowski et al., 2007; Mahmoodi et al., 2006).

In many countries, health claims regarding the potential benefits of garlic or its various preparations has been approved and are now available in the market as dietary supplements and getting a wide range of popularity nowadays in many cultures for their hypolipidemic and procirculatory effects. Garlic and its various preparations are important functional food with diverse health benefits. Evidence also ensures its possible applications in cancer therapy, reactive oxygen species (ROS) associated diseases and certainly in immunonutrition (Butt et al., 2007). This review is also an effort to elucidate the importance of garlic and its constituents as nature’s gift to fight against various physiological threats.

Kingdom Plantae – Plants
Sub-Kingdom Tracheobionta – Vascular plants
Super division Spermatophyta – Seed plants
Division Magnoliophyta – Flowering plants
Class Liliopsida – Monocotyledons
Sub-Class Liliidae –
Order Liliales –
Family Liliaceae – Lily family
Genus Allium L. – onion
Species Allium sativum L. – cultivated garlic

CLASSIFICATION AND CHEMISTRY

Garlic belongs to the family Liliaceae and is cultivated worldwide for the fleshy segments (cloves) of its bulbs. It is rich in sulfur-based compounds, which contribute to its characteristic flavor and taste and even to its beneficial effects (Table 1).

The garlic bulb contains approximately 65% water, 28% carbohydrates (mainly fructans), 2.3% organosulfur compounds, 2% protein (mainly alliinase), 1.2% free amino acids (mainly arginine), and 1.5% fiber. Most biological effects of garlic are attributed to its characteristic organosulfur compounds. Allicin (diallyl thiosulphate), the principle active substance in garlic is responsible for its typical pungent smell. Therapeutic properties of garlic often attributed to allicin and its derivates (Macpherson et al., 2006; Li, 2000; Song and Milner, 2001).

The major sulfur-containing compounds in intact garlic are δ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxides (alliin). These compounds act as precursors of several compounds. Usually, when raw garlic is cut or crushed these sulfoxides are converted into thiosulfinates (such as allicin) through enzyme catalyzed reactions. When garlic is extracted with an aqueous solution, the δ-Glutamyl-S-allyl-L-cysteines are converted into S-allylcysteines (SAC) through an enzymatic transformation with δ-glutamyltranspeptidase. These reactions result in the production of intermediates and varieties of compounds as a result. These can be further categorized on the basis of their chemistry and nature (Matsuura, 1997). The complex chemistry of garlic makes it plausible that variations in processing can yield quite different preparations (Amagase, 2006). Highly unstable thiosulfinates, such as allicin, disappear during processing and are quickly transformed into a variety of organosulfur components.

**Thiosulfinate.** When garlic bulbs are disrupted, it results in the formation of thiosulfinates such as allicin through the enzymatic reaction of sulfur-substituted cysteine sulfoxides with alliinase via sulfur-substituted sulfenic acids (highly reactive intermediate). Other thiosulfinates found in garlic are, allylmethyl-, methallyl- and trans-1-propenyl-thiosulfinate and like allicin, they are all unstable (Lawson et al., 1991).

**Organosulfur volatiles.** Allicin usually decomposes to diallyl disulfide (DADS), diallyl sulfide (DAS), diallyl trisulfide (DTS) and sulfur dioxide. The main volatiles that have been identified in disrupted garlic and garlic essential oil include DAS, DADS, diallyl trisulfide, methallyl disulfide, methallyl trisulfide, vinylthiin, and ajoenes. These are also important constituents of steam-distilled garlic oil and oil-soluble extracts of garlic but with varied composition. The main sulfides in garlic oil are DAS (57%), allylmethyl (37%),
Table 1  Important constituents of garlic and various fractions

<table>
<thead>
<tr>
<th>Components and fractions/preparation</th>
<th>Ingredients/Compounds Abbreviation</th>
<th>Chemical Formula/Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiosulfinate and Organosulfur volatiles (Garlic essential oil)</td>
<td>Alicin</td>
<td>CH₂ =CHCH₂-SS(=O)-CH₂CH=CH₂</td>
</tr>
<tr>
<td>Steam-distilled garlic oil, garlic extracts</td>
<td>Diallyl sulfide DAS</td>
<td>CH₂ =CH-CH₂-S-CH₂=CH=CH₂</td>
</tr>
<tr>
<td></td>
<td>Diallyl disulfide DADS</td>
<td>CH₂ =CH-CH₂-S-S-CH₂=CH=CH₂</td>
</tr>
<tr>
<td></td>
<td>Diallyl trisulfide DATS</td>
<td>CH₂ =CH-CH₂-S-S-S-CH₂=CH=CH₂</td>
</tr>
<tr>
<td>Vinyldithiin (Oil macerate of raw garlic)</td>
<td>AllylMethyl sulfide AMS</td>
<td>CH₂ =CH-CH₂-S-CH₃</td>
</tr>
<tr>
<td></td>
<td>AllylMethyl disulfide AMDS</td>
<td>CH₂ =CH-CH₂-S-S-CH₃</td>
</tr>
<tr>
<td></td>
<td>AllylMethyl trisulfide AMTS</td>
<td>CH₂ =CH-CH₂-S-S-S-CH₃</td>
</tr>
<tr>
<td></td>
<td>2-vinyl-4H-1, 3-dithiin</td>
<td>3-vinyl-4H-1, 2-dithiin</td>
</tr>
<tr>
<td>Ajoene (Oil-macerated garlic extract)</td>
<td>E- Ajoene E-4,5,9-tritriadeca-1,7-diene-9-oxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z- Ajoene</td>
<td></td>
</tr>
<tr>
<td>Water-soluble organosulfur compounds (AGE)</td>
<td>S-allyl-L-cysteines SAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S-allylmercaptocysteine SAMC</td>
<td></td>
</tr>
</tbody>
</table>

(Grivets et al., 1992; Lawson et al., 1991; Miething, 1988)

dimethyl (6%), mono-to hexasulfides and a small amount of allyl 1-propenyl and methyl 1-propenyl di-, tri-, and tetra-sulfides (Amagase, 2006; Canizares et al., 2004)

**Vinyldithiins.** These are demonstrated to be thermal-degradation products of allicin. These structures were elucidated to be 2-vinyl-4H-1, 3-dithiin and 3-vinyl-4H-1, 2-dithiin on the basis of spectroscopic analysis. The formation mechanism is a type of Diels-Alder dimerization of thioacrolein derived from the β-elimination of allicin. Vinyldithiins, especially 2-vinyl-4H-1, 3-dithiin are rich in the oil macerate of raw garlic (Lawson and Gardner, 2005)

**Ajoenes.** Their structures are E and Z isomers of 4, 5, 9-trithiadodeca-1-oxide, 6, 11-triene-9-oxide and it is also formed by S-thioallylation of allicin, followed by Cope-type elimination and readdition of 2-propenesulfenic acid. E-4,5,9-tritriadeca-1,7-diene-9-oxide, is another ajoene-type organosulfur compound, present in oil-macerated garlic extract (Yoshida et al., 1999).

**Water-soluble organosulfur compounds.** Aqueous and alcoholic garlic extracts contain mainly S-allyl-L-cysteines (SAC) derived from δ-glutamyl-S-allyl-L-cysteines. SAC and trans-S-1-propenyl-L-cysteine, together with a small amount of S-methyl-L-cysteine are found in garlic extract such as AGE (Kodera et al., 2002).

**GARLIC PREPARATIONS, EFFICACY, AND SAFETY ISSUES**

The health benefits of garlic likely arise from a wide variety of components, possibly working synergistically. A number of studies have demonstrated the health promoting activities of garlic by using different garlic preparations including fresh garlic extract, aged garlic, garlic oil, and a number of organosulfur compounds derived from garlic. The efficacy and safety of these preparations in preparing dietary supplements based on garlic are also contingent on the processing methods employed (Casini et al., 2002; Huang et al., 2001; Siegers et al., 1999).

Although there are many garlic supplements commercially available but they generally fall into one of these four categories, i.e. aged garlic extract (AGE), dehydrated garlic powder, garlic oil, and garlic oil macerate. These formulations perform different pharmacologic functions AGE and garlic oil are most useful garlic preparations. AGE is produced by extraction with water and ageing of organic fresh garlic, at room temperature (37°C), for 20 months. It increases antioxidant levels, well above those of the fresh bulb and converts harsh unstable compounds, such as allicin to stable health-promoting substances. AGE contains mostly stable water-soluble organosulfur compounds which are
mainly responsible for AGE’s health benefits; they include S-
alloy mercaptocysteine (SAMC) and S-alloy cysteine (SAC).
AGE also contains some oil soluble organosulfur compounds,
flavonoids, phenolic acids, and other beneficial nutrients (Ama-
gase et al., 2001; Kasuga et al., 2001). Nowadays, AGE is also
sold as dietary supplement as an alternate source of garlic with
health claims. It is odorless and richer in antioxidants than the
fresh bulb or can be considered as a concentrated form of organic
garlic. AGE has been found to help in preventing atherosclero-
sis, protecting against cardiovascular disparities, improved cir-
culation, and immunity (Matsuura et al., 2006). In preclinical
studies AGE has been shown to prevent various kinds of can-
cer and neurodegenerative disease and have antiaging effects,
improving memory, endurance, and learning and it also has po-
tential as an adjuvant in cancer therapy (Borek, 2001). Garlic
oil also holds some therapeutic potential as it also contain some
sulfur compounds such as DAS, DADS, DATS, and some others
polysulfides.

Consumption of raw garlic is often associated with some
health hazards that include stomach and digestion problems. Al-
ergenic responses should also keep in mind while elaborating
health benefits. Generally, aging and heating or even extraction
of functional components results in varied pharmacological ap-
lications. Concerning efficacy of these formulations, there are
several reports but it is important for clinicians to document
health benefits and consumers/patients should be advised of its
use in safe limits to get its maximum benefits.

**REACTIVE OXYGEN SPECIES AND GARLIC**

Oxygen is required for respiration and the energetic pro-
cesses that enable aerobic life. A cost associated with oxygen
use is free-radical formation, which damages genome stability
and contributes to various processes including aging, degen-
erative diseases, and cancer (Cooke et al., 2003; Mandavilli
et al., 2002). Free radicals or reactive oxygen species (ROS)
have been implicated in mediating various pathological pro-
cesses such as cancer, ischemia, inflammatory diseases, diabetes
and atherosclerosis (Wilson and Demmig-Adams, 2007; Vina
et al., 2006). Increased level of ROS, in inflammation and dur-
ing exposure ionizing radiation, pollutants, exercise and some
medications, requires additional antioxidant protection and ab-
sence results in oxidative stress. ROS are normally neutralized
by cellular antioxidant enzymes and small molecules, such as
glutathione and by vitamins and minerals (Berger, 2005; Ji and
Peterson, 2004).

Garlic has been enumerated in several research investiga-
tions reported to be effective against diseases of which ROS are
considered a major cause. These studies suggested that garlic
may work by reducing ROS or interacting with them to mini-
mize the negative impact on the body. However, the degree of
antioxidative efficacy of various garlic compounds or prepara-
tions differs according to variations in chemical structures and
standardization procedures (Amagase, 2006; Chung, 2006).

The organosulfur compounds of garlic have indeed been
shown to be potent antioxidants and can also stimulate the an-
tioxidants enzymes in liver including glutathione peroxidase
(GPx), glutathione transferase (GST), catalase (CAT), superox-
ide dismutase (SOD) and etc. DAS, DADS, and DAT play dif-
ferential modulatory roles on GSH related antioxidant system in
liver and red blood cells accompanied by increased expression
of GST α, β1, and γc proteins (Sukta, 2002; Wu et al., 2001; 
Yin and Chang, 1998).

Wei and Lau (1998) and Yamasaki and Lau (1997) ob-
served that AGE suppresses hydrogen peroxide (H2O2) and
superoxide anion (O2−) generation and also enhances cellu-
ar antioxidant enzymes thus protecting vascular endothelial
cells from oxidant injury. AGE and SAC inhibits both lactate-
dehydrogenase release and lipid peroxidation induced by H2O2
and antioxidative capabilities of AGE and SAC may be use-
ful in preventing atherosclerosis (Borek, 2001). AGE increases
intracellular glutathione levels, glutathione disulfide reduc-
tase, and SOD activity in pulmonary artery endothelial cells
(PAECS), whereas the level of glutathione disulfide decreased as
enumerated by Borek (2006). AGE inhibits the emission of
low-level chemiluminescence and the early formation of
thiobarbituric acid-reactive substances in a liver microsomal
fraction initiated by t-butyl hydroperoxide thus protecting mem-
branes through preventing lipid peroxidation that also serves
to maintain membrane fluidity (Ogita et al., 2005). Kabasakal
et al. (2005) provided evidence that AGE also protects kid-
ney tissue against induced oxidative stress that includes AGE
(1 mL/kg) restored the reduced GSH levels, decreased free
radicals and MDA, as well as myeloperoxidase activity and
moreover, it restored collagen contents reduced during oxidative
stress.

ROS and oxidative stress are directly related with tumor pro-
motion and Agarwal et al. (2007) suggested protective effects
of garlic oil against Fe-NTA induced hepatic toxicity and it pro-
vided protection against hepatic lipid peroxidation, generation
of hydrogen peroxide, preserved glutathione levels and activi-
ties of antioxidant enzymes. Even beneficial effects of garlic oil
are of significant importance in reducing the oxidative damage
imparted by Tributyltin (TBT) that can be transported through
sea foods as TBT enter into the food chain as a result of marine
pollution (Liu and Xu, 2007).

A body of evidence has accumulated implicating the free rad-
ical generation with subsequent oxidative stress in the biochem-
ical and molecular mechanisms of Cd toxicity. Cytoprotective
potential of DTS in Cd toxicity might be due to its antioxi-
dant and metal chelating properties, which could be useful for
achieving optimum effects in Cd induced renal damage (Pari
et al., 2007).

Among a variety of organosulfur compounds, SAC and
SAMC, showed radical scavenging activity in chemilumines-
cence and 1,1-diphenyl-2-picrylhydrazyl assays, SAC has in
vivo and in vitro antioxidant properties and is able to scavenge
different reactive oxygen or nitrogen species and also ame-
liorate the K2Cr2O7 induced toxicity (Medina-Campos et al.,
2007). SAC decreased CCl₄ induced liver injury by attenuation of oxidative stress, and may be a better therapeutic tool for chronic liver disease associated with oxidative stress (Kodai et al., 2007).

Diallyl tetrasulfide affect the reactive oxygen species generation induced by cadmium, and possesses a novel protective effect on the cytolethality associated with mitochondrial injury, which contributes to the antiapoptotic effect of diallyl tetrasulfide against cadmium (Murugavel et al., 2007). Impaired oxidant/antioxidant balance may play a part in the cyclosporine induced nephrotoxicity, and garlic with high antioxidant power may ameliorate this toxicity and in close proximity to the other studies related with antioxidant vitamins E and C (Durak et al., 2007).

Garlic can scavenge free radicals and is a successful antioxidant, and it has the potency to enhance the activity of the antioxidant enzymes. Garlic in its various preparations also holds a potential to cure maladies related to ROS. Since antioxidative activity is caused by the relative electron status of the materials, in vivo reaction in the whole body should be taken into account when considering the active compounds of garlic and several compounds may play an important role in the antioxidative activity of garlic and its preparations.

AGE is richer in antioxidants than fresh garlic, boosts cellular antioxidants that help in maintaining a healthy immune system, and prevent drug toxicity and enhance peroxidases that eliminate toxic peroxides. Overall, AGE scavenges oxidants, enhances enzymes activity and glutathione levels, and inhibits lipid peroxidation and production of inflammatory prostaglandins (Borek, 2006; Amagase et al., 2001). Garlic oil also holds promise for good health being a free radical scavenger and imparting protection against toxicity of metals and hazardous chemicals. Some other preparation such as aqueous water extract is also effective but reports narrating their potential are limited. In conclusion garlic and its various components/preparations are effective tools in amelioration of oxidative stress and related discrepancies but care should be taken not to use it in excess quantities and opinions and consulting a physician should be taken in account before its use.

**GARLIC AGAINST CARDIOVASCULAR THREATS**

Cardiovascular diseases are the leading cause of morbidity and mortality over the world. High cholesterol, high homocysteine, hypertension, and inflammation are major risk factors for cardiovascular disease and these can be tackled with a healthy diet and physical exercise thus minimizing the chances of being the cause of cardiovascular diseases (Borek, 2006; Lau, 2006).

Management of plasma cholesterol levels continues to be a cardinal issue in cardiovascular disease (CVD) prevention as hypercholesterolemia plays a crucial role in pathogenesis of atherosclerosis and related heart diseases (Singh et al., 2007). Different drugs can be used for its treatment but concerning the length of therapy, natural products may be a suitable substitute and garlic could be important in hypercholesterolemia therapy (Kojuri et al., 2007).

Garlic has been used as a traditional medicine and holds a strong impact on a number of CVD risk factors including high serum lipids, blood pressure, plasma viscosity, and platelet aggregation (Spigelski and Jones, 2001). Garlic supplements have a significant favorable effect on cholesterol, LDL-cholesterol, and HDL-cholesterol, and also beneficial in reducing blood pressure and oxidative stress in hypertensive individuals (Dhawan and Jain, 2004) and these positive influences of garlic are dose dependent. Preventive effects of S-allyl cysteine sulfoxide (SACS) in isoproterenol (ISO)-induced myocardial ischaemia were also evaluated by Sangeetha and Darlin-Quine (2006) and according to their results garlic has the ability to reduce the lipid peroxides because it has a lipid lowering effect. Tapsell et al. (2006) while elaborating the health benefits of herbs reported that consumption of half to one clove of garlic (or equivalent) daily may have a cholesterol-lowering effect of up to 9%. Ackermann et al. (2001) observed that garlic preparations may lead to small reductions (1.2–17.3 mg/dL and 12.4–25.4 mg/dL) in the total cholesterol level after 1 and 3 months respectively.

Garlic also has the ability to inhibit enzymes involved in lipid synthesis, prevent lipid peroxidation of oxidized erythrocytes and LDL, increase antioxidant status, and inhibit the angiotension-converting enzyme (Rahman and Gow, 2006). Garlic extract reduced cholesterol synthesis by up to 75% without evidence of cellular toxicity and inhibition is likely mediated at sterol 4-alpha-methyl oxidase (Singh and Poter, 2006). Inhibition of cholesterol synthesizing may have certain other benefits that include reduction in coronary calcium progression (Achenbach et al., 2002).

Oxidation of LDL results in the production of various metabolites that triggers a cascade of events leading to initiation and progression of atherosclerosis and its inhibitions could be beneficial in CVD’s (Lau, 2006; Albertini et al., 2002). Oxidized LDL also results in endothelial membrane damage that imparts significant changes in other parts of the body as well. Positive antioxidant effect of garlic or its components/preparation against Cu (²⁺) - initiated oxidation of LDL has been reported in many studies as Ide et al.(1997) found clear supportive data that SAC significantly prevent membrane damage, loss of cell viability, and lipid peroxidation in bovine PAECs exposed to oxidized LDL. Water-soluble proteins from garlic also reduced the peroxidative changes in rats due to LDL oxidation. Even allicin-free AGE and SAC have a similar effect against Cu(²⁺)-initiated oxidation of LDL in human subjects consuming AGE (Yin and Chang, 1998).

Atherosclerosis is a chronic disease associated with accumulation of lipids in lesions along blood vessels especially LDL cholesterol, leading to the occlusion of blood flow (Le and Walter, 2007). Garlic could be a valuable component of atherosclerosis-preventing diets only in optimal doses. Allicin may also affect atherosclerosis not only by acting as an antioxidant, but also by other mechanisms, such as inhibiting lipoprotein modification and LDL uptake and degradation by...
macrophages (Gonen et al., 2005; Ou et al., 2003)). Hyperlipidemia is a major etiopathological factor for atherosclerosis; therefore, garlic may play an important role in the prevention of atherosclerosis (Thomson et al., 2006). Various heart pathologies are often associated with atherosclerosis/hypercholesterolemia and their prevention or cure render good heart health. The addition of garlic in diets inhibited atherosclerotic changes in the aorta wall, and is related to the homoeostatic activity of antioxidative enzymes and lipid peroxidation (Zalejska-Fiolka et al., 2007).

Homocysteine, a metabolite from methionine, is an independent cardiovascular disease risk factor, which causes thrombosis and oxidative-stress damage (Durand et al., 2001) and often associated with atherosclerosis and a higher risk of coronary heart disease, stroke, and peripheral vascular disease by damaging the inner lining of arteries and promoting blood clotting. Homocysteine has an inverse relationship with folate deficiency and decreased NO production. AGE may at least partly prevent a decrease in bioavailable NO and endothelium-derived hyperpolarizing factor during acute hyperhomocysteinemia (Weiss et al., 2006). Homocysteine in plasma exists in two forms i); free homocysteine and ii) protein bound and amount of total homocysteine is considered as a marker of atherosclerosis. AGE can decrease plasma total homocysteine concentration by 30% without changing the protein-bound/free homocysteine ratio (Yeh and Yeh, 2006).

Increased platelet aggregation plays a significant role in the etiology of cardiovascular disease, and is complex involving multiple mechanisms that includes, increase in free cytoplasmic calcium Ca^{2+}, thromboxane generation, activation of the fibrinogen receptor GPIIb/IIIa, and other modulators such as lipooxygenase metabolites, Kinase C, cAMP, and cGMP and nitric oxide (Chan et al., 2007). The presence of a thrombus in a stenosed coronary artery can lead to acute syndromes such as myocardial infarction and angina (Fuster et al., 1992) and platelet aggregation plays a central role in coronary thrombosis and the cascade of events often relates with platelet aggregation that includes expression of adhesion molecules on the surface of the endothelium, the oxidation of lipoproteins, monocyte invasion of the vessel wall, foam cell formation, smooth muscle phenotypic change, and proliferation and platelet deposition (Ross, 1992).

Garlic possesses the potential to positively alter some of these mechanisms that could have a beneficial impact on human cardiovascular health (Rahman, 2007). Studies suggest that odorless garlic not only activates fibrinolytic activity by accelerating t-PA-mediated plasminogen activation, but also suppresses the coagulation system by downregulating thrombin formation, suggesting a beneficial role in preventing pathological thrombus formation (Fukao et al., 2006). Under diseases states of hypercholesterolemic and atherosclerotic animals usually relaxation mediated by endothelium derived NO is impaired in arteries that leads to endothelial dysfunction. Oxidative stress and increased systemic inflammation may also contribute to this phenomenon. Elimination of certain risk factors and protection of endothelial integrity is effective in maintaining hemostasis. Williams et al. (2005) is of the views that short-term treatment with AGE may improve impaired endothelial function in men with CAD and already treated with aspirin and statin. Garlic extract modulates the production and function of both endothelium-derived relaxing and constricting factors and this may contribute to their protective effect against vasoconstriction (Kim-Park and Ku, 2006; Zahid-Ashraf et al., 2005). Tapsell et al. (2006) reported that 7.2 g of AGE has been associated with antilicoating (in-vivo studies), as well as modest reductions in blood pressure.

Coronary arterial calcification (CAC) has not gained clinical significance but nowadays much interest has been paid. CAC, a marker of plaque formation in human coronary arteries and atherosclerosis has been linked to an increased risk for cardiovascular events such as myocardial infarction, fatal arrhythmia, and congestive heart failure (Raggi et al., 2002; Qunibi et al., 2002). Interventions that are designed to combat the process of calcification may lead to certain improvements. Budoff et al. (2004) evaluated the ability of AGE to inhibit vascular calcification, and indicated the potential ability of AGE to inhibit the rate of progression of coronary calcification as compared to placebo over one year.

SAC derived from garlic possess protection against cardiovascular diseases. Chuah et al. (2007) elucidated that SAC is responsible for this cardioprotection using acute myocardial infarction (AMI) rat models. Their results indicated that SAC significantly lowered mortality and reduced infarct size. Inhibitory action was mediated by increased activity of cystathionine-gamma-lyase (CSE), upregulated its expression and via an H_{2}S related pathway. Garlic extract might have some worth as an angiotensin-converting enzyme (ACE) inhibitor to prevent some vascular complications of diabetes mellitus (Hosseini et al., 2007).

Conjugation of active ingredients of garlic with some drugs of interests has some beneficial impact. Allylmercaptoctaptopril is an example of a conjugate of the ACE inhibitor captopril with allicin. According to Ernsberger et al. (2007) Allylmercaptoctaptopril prevented progressive weight gain, without a detectable effect on food intake, lowered blood pressure, improved cardiac hypertrophy, as indicated by heart weight and ventricular-wall thickness.

Cardiovascular protection is also important in people already with some other chronic diseases such as diabetic mellitus and cancer because often these maladies accompanied by high cholesterol, hypertension and changes in homeostasis of the body. Ethanolic extract of garlic was found to lower lipids such as total cholesterol and triglycerides and it also tends to improve enzymes associated with membrane damage and transportation in diabetes mellitus (Eidi et al., 2006). AGE decreases homocysteine, lowers blood pressure, and increases microcirculation, which is important in diabetes, where microvascular changes increase heart disease and dementia risks (Borek, 2006).

Alternative therapeutic approaches with complementary therapies are becoming increasingly popular among patients. It is important for healthcare providers to be familiar with the
safety and efficacy of these agents to facilitate optimal outcomes for patients with dyslipidemia (Nies et al., 2006). People consuming garlic and other supplements are at a lower risk because a greater degree of supplement use is associated with more favorable concentrations of serum homocysteine, C-reactive protein, high-density lipoprotein cholesterol, and triglycerides, as well as a lower risk of prevalent elevated blood pressure and diabetes (Block et al., 2007). Some contradictions still hinder its utilization to control hyperlipidemia but generally it is believed that garlic consumption alone can decrease serum lipids, but it cannot be used as the main therapeutic agent for Hyperlipidemia (Mahmoodi et al., 2006). Overall, garlic possesses plasma lipid-lowering and plasma anticoagulant and antioxidant properties and improves impaired endothelial function (Gorinstein et al., 2007) that in turn yields improved cardiovascular health.

**MALIGNANCIES AND GARLIC**

It has been estimated that 30–40% of all kinds of cancer can be prevented with a healthy lifestyle and dietary measures. The relevance of nutrition on the cancer process is evident, some components result in cancer progression and some play an important role in chemopreventive strategies (Divisi et al., 2006). However, mechanisms behind their actions remain to be explored and accumulated knowledge should be used by public health authorities to develop recommendations and activities to promote healthy dietary habits (Gonzalez, 2006). Generally, chemopreventive agents can be divided into two groups (anti-mutagenic and anti proliferative) on the basis of the mechanism through which they exert anticancer effects (Steele, 2003).

Of the many beneficial actions of garlic, inhibition of the growth of cancer is perhaps the most remarkable (Matsura et al., 2006). Several in vivo and in vitro studies have brought to light several mechanisms of action of garlic and its components which can be associated with elicitation of their anticarcinogenic activity noted in a wide range of experimental systems (Table 2).

During the mid twentieth century, use of garlic in the treatment of tumors has been narrated for the first time when Weisberger and Pensky (1958) suggested that garlic could inhibit the growth of malignant cells and prevents growth of sarcoma 180 ascites tumor. Since that time, garlic has been demonstrated in many epidemiological studies to be associated with reduced risk of several cancers. During the last decade antitumor activity have been explored against Gastrointestinal tract cancer; Colon cancer; Prostate cancer; Mammary carcinoma; Hepatocellular carcinoma; Lungs cancer; and Sarcoma and Squamous cell carcinoma of the skin and esophagus (Ban et al., 2007; Howard et al., 2007; Kim et al., 2007; Zhang et al., 2007; Kalra et al., 2006; Milner, 2006).

Galeone et al. (2006) provided evidence using multivariate odd ratios that garlic is inversely associated with the risk of several common cancers. Chemopreventive benefits are often associated with its sulfur compounds or preparations such as AGE shown to inhibit early and late stages of carcinogenesis (Fleischauer and Arab, 2001; Schaffer et al., 1996). Various modes of action for its anticancer properties have been proposed falling in two major categories—anti-mutagenic and anti proliferative properties.

**Antimutagenic Properties**

Antimutagens reduce the formation of mutagens or carcinogens thereby preventing DNA damage. For instance, ROS scavenging and modifications in carcinogen metabolism (through suppression of phase I enzymes or enhancement of phase II detoxifying enzymes) represent antimutagenic effects (Manson, 2003). Administration of garlic significantly increase the level of many detoxification enzymes including GST, acid soluble sulfhydryl (-SH) cytochrome b5, and cytochrome P450 in murine liver. Garlic extracts, along with several principal sulfur constituents induces a positive impact on phase II detoxification enzymes like GST and quinone reductase in mammalian tissues (Rose et al., 2005; Dion and Milner, 1997; Liu et al., 1992). Similar impact for garlic powder was observed in rat liver and mammary tissues (Singh and Singh, 1999). Cytochrome P450s (CYPs) play an important role in procarcinogen activation and their inhibition could result in a decreased formation of toxic metabolites and thus indirectly inhibiting carcinogenesis, and diallyl sulfone isolated components from garlic preparations act as inhibitors of various CYPs (Zhou et al., 2007).

Some OSC induce the expression of NAD(P)H: quinone oxireductase an enzyme required in the detoxification of activated quinone metabolite of Benzo[a]pyrene (Singh et al., 1998). DADS can increase tissue activities of phase II detoxification enzymes quinone reductase and GST in some gastrointestinal organs of the body thus providing them protection against GIT cancers (Monday and Monday, 1999). Garlic, OSC or its formulations enhance the activities of gene expression of GST reducing hepatic lipid peroxidation (Tsai et al., 2006; Khanum et al., 1998).

Oil-soluble sulfur compounds containing dehydrated garlic powder decreased the p-Nitrophenol hydroxylase activity and the level of cytochrome P450 2E1 protein in the hepatic microsomes and induced cytochrome P450 1A1/2 protein suggesting that DAS suppresses vitamin C-induced mutagenesis or tumorigenesis, in part, through inhibition of the cytochrome P-450 2E1 isoform responsible for activation of this carcinogen (Amagase, 2006). Arora et al. (2005) arrived at similar conclusions that regulation of p21/ras protein expression is important in curing skin cancer. These regulatory enzymes and proteins play a significant role in the prevention and inhibition of cancer growth and mechanism and modulating these could leave a beneficial impact.

Dietary garlic can suppress the production of DNA-adducts by DMBA and nitroso compounds (Liu et al., 1992). Utilization of AGE results in protection as a mechanism of its action and includes disabling DNA-damaging free radicals, increasing glutathione levels, blocking carcinogen binding to DNA,
increasing the disposal of carcinogens that enter the body (Borek, 2001; Amagase and Milner, 1993). Prostate cancer, third in death causalities, can be cured with the use of AGE. AGE acts on several fronts inhibiting polyamines needed for cell division, increasing breakdown of testosterone, and reducing prostate specific antigen (PSA) levels (Pinto et al., 1997). Kim et al. (2007) elaborated that DATS results in excessive production of reactive oxygen species that results in prostate tumor suppression while Wu et al. (2005) summarized the same arguments but for DADS in the treatment of lung cancer.

Topical application of garlic and its preparations results in the prevention of cancer, usually the alteration of carcinogen metabolism, inhibition of cell division, and inhibition of lipoxygenase and cyclooxygenase. Garlic compounds also result in blockage in the initiation and promotion phases of the carcinogenicity of various compounds including polycyclic hydrocarbons (Borek, 2006; Sengupta et al., 2004). Antimutagenic properties of garlic are mainly achieved through its ability to reduce Phase-I enzymes and enhancing the activities of Phase-II enzymes.

### Antiproliferative and Induction of Apoptosis

Chemopreventive agents may exert antiproliferative effects via induction of cell cycle arrest or apoptosis, inhibition of angiogenesis, induction of terminal differentiation, and inhibition of oncogene activity or DNA synthesis (Manson, 2003). Garlic extracts along with organosulfur constituents influence cell cycle arrest and apoptosis in numerous in vitro cancer cell models (Rose et al., 2005). Changes in cellular thiol and phosphorylation may account for some of these antitumorigenic properties. Milner (2001) suggested garlic and its constituents can suppress carcinogen formation, carcinogen bioactivation, and tumor proliferation. Garlic extracts induce lymphocyte proliferation triggered by potent T-cells mitogen. Proliferation of lymphocytes...
by increasing IL-2 and IL-4 production depends on the type and dilutions of extracts used (Colic and Savic, 2000).

Organosulfur compounds (OSC) from garlic can suppress proliferation of cancer cells in culture and in vivo. The OSC-induced changes in the proliferation of cancer cells are frequently associated with perturbations in cell cycle progression and induction of G2/M phase arrest. Garlic compounds induced apoptosis in glioblastoma cells due to the production of ROS and activation of stress kinases and cysteine proteases (Das et al., 2007). The OSC induces apoptosis via the intrinsic pathway by altering the ratio of the Bcl-2 family of proteins both in cell culture (Herman-Antosiewicz et al., 2007). Chu et al. (2006) demonstrated that water soluble components of garlic like SAC also result in decreased production of Bcl-2 proteins and increased caspase-3 activities to cure prostate cancer. Activation of natural killer cells (NK) and T lymphocytes as well as level of IL 2 was pronounced in the prevention of oral pre-cancer and hepatocarcinogenesis induced by 4-nitroquinoline 1-oxide and diethylnitrosamine respectively with the help of garlic powder (Kweon et al., 2003; Tang et al., 1997).

Histone acetylation, a molecular mechanism implicated in the regulation of gene expression, could account for the antiproliferating effects of DADS in colon tumor cells (Druesne-Pecollo et al., 2006). Arunkumar et al. (2007) while studying the influence of DADS gave similar remarks that histone acetylation play a significant role in the induction of apoptosis of malignant cells.

Z-ajoene another OSC has potent anti-cancer activity as it inhibits telomerase activity and blocks G2/M phase (Ye et al., 2005). Correlation of sulfur atoms number in OSC with their capacity in apoptosis induction has also been explored that support the role of redox-sensitive “sulfhydryl switches” in maintaining intracellular redox milieu (Jakubıková and Sedláková, 2006).

Studies suggested that garlic has been bestowed a dual potential being antimutagenic and antiproliferative and can become an important component of chemopreventive strategies. Garlic holds antimutagenic and antiproliferative actions on human cancers. The mechanism of its action also involves modifications in pathways of signal transduction and regulation of nuclear factors involved in cellular proliferation (Pinto and Rivlin, 2001).

**GARLIC IN IMMUNONUTRITION**

Diet is a pivotal link with human health and foods rich in phytochemicals often associated with proper functionality of immune system. Immunonutrition term employs the intake of certain nutrients that play an important part in bringing a balance to the human immune system. Immune responses are influenced by intrinsic and extrinsic factors but diet plays a crucial role in regulation and proper functionality of immune system (Lin and Karin, 2007). The immune system is an incredibly intricate arrangement that prevents infections and diseases by moderating malignant and foreign cells (Bourgeon et al., 2007). Human beings have spent ages searching for immunity boosters—almost as long as human history. Garlic and garlic supplements are consumed in many cultures as immune boosters in addition to proclaimed beneficial effects (Amagase et al., 2001). Immunonutrition often based on the principle to have a diet that can improve the immune system, maintains homeostasis of the body, and helps to fight against foreign and malignant cells. Several compounds and classes have been identified playing an important role in proper functionality of immune system (Barta et al., 2006).

Garlic use as reported in literature is centuries old and many civilizations banked on its potential to cure various maladies and even Egyptians fed to its crews to give them strength (Milner, 2001). Garlic possesses several lines of actions; on the one hand works as an immune stimulant but on the other hand under circumstances performs the function of an immune suppressant.

The immunostimulating effects of garlic and its components/preparations include increase in the total white blood cell (WBC) count and enhanced bone-marrow cellularity (Kuttan, 2000). The OSC in garlic scavenge oxidizing agents inhibiting the oxidation of fatty acids, thereby preventing the formation of pro-inflammatory messengers, via interaction with sulphur-containing enzymes (Wilson and Demmig-Adams, 2007). Consumption of garlic resulted in stimulated synthesis of NO and, in turn, IFN-alpha in humans, which could be beneficial in viral or proliferative diseases (Bhattacharyya et al., 2007).

Bruck et al. (2005) examined the ability of allicin to prevent immune-mediated, concanavalin A (Con A)-induced liver damage in mice and demonstrated that immune-mediated liver damage can be prevented because of its immunomodulatory effects on T cells and adhesion molecules and inhibition of NF-kappaB activation. In vitro studies showed that allicin inhibited TNF-alpha-mediated T cell adhesion to extracellular matrix components and to endothelial cells. Allicin also inhibited TNF-alpha-mediated intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression on human vascular endothelial cells (Truchlinski et al., 2006). Allicin (20–100 µM) inhibits the SDF-1alpha (CXCL12)-induced T cell migration through fibronectin (FN), and that this inhibition is mediated by the down-regulation of (i) the reorganization of cortical actin and the subsequent T cell polarization, and (ii) T cell adhesion to FN (Sela et al., 2004).

Studies suggested that allicin may be used therapeutically with chronic inflammatory diseases. Cytokines involved in inflammatory bowel disease (IBD) direct a predominantly cell-mediated T-helper-1 (Th1) immune response. Treatment with garlic extract may help to resolve inflammation associated with IBD by inhibiting Th1 and inflammatory cytokines while regulating IL-10 production (Hodge et al., 2002). The inhibitory effect of diallyl sulphide (DAS) and diallyl disulphide (DADS) against meticillin-resistant Staphylococcus aureus (MRSA) infection was studied by Tsoo et al. (2007) and they finally concluded that DAS and DADS could provide multiple protective functions against MRSA infection. Garlic (Allium sativum) extract has been known to have inhibitory activity on various...
pathogenic bacteria, viruses, and fungi (Fani et al., 2007). A 10- to 14-kDa fraction was identified as responsible for the in vitro effect of the whole extract and may lead to the identification of novel immunomodulating drugs and therapeutic alternatives for the treatment of leishmaniasis (Gamboa-León et al., 2007). Overall, immunomodulating action of the allicin and others OSC applied results in the improvement in cellular immune parameters (Truchlinski et al., 2006).

Kim et al. (2001) demonstrated that garlic extract and one of its components S-allyl cysteine (SAC), inhibited nitric oxide production through suppression of iNOS mRNA and protein expression in LPS and IF gamma stimulated murine macrophage cell line RAW264. Garlic stimulates the proliferation of lymphocytes and macrophage phagocytosis, induces the infiltration of macrophages and lymphocytes in transplanted tumors, induces splenic hypertrophy, stimulates and modulates cytokines production, and brings and enhances activities of the natural killer cell and the lymphokine-activated killer cell. These activities result in effective stimulation of the immune response. These effects, particularly the pattern of cytokine release, suggest that garlic and its aged extract (AGE), stimulates a Th1 cellular immune response that is characteristic of effective antitumor immunotherapies. Garlic thus protects against the suppression of immunity by chemotherapy and ultraviolet radiation. AGE could be a promising candidate as an immune modifier, which maintains the homeostasis of immune functions and is highly effective and even effective when added to the diet (Kyo et al., 2001; Lamm and Riggs, 2001; Kyo et al., 1998).

Reactive oxygen species formation or respiratory burst by the neutrophils helps to remove the invaded pathogens and these actions often result in inflammation that is an integral part of the immune system. Garlic seems to be very potent in attenuating the free radical generation from rat neutrophils, which could be beneficial in the inflammation-associated pathological conditions (Sankaranarayanan et al., 2007).

ROS are involved in signal transduction pathways leading to nuclear factor kappa B (NF-κB) activation that has been implicated in the regulation of gene transcription. Geng et al. (1997) determined the effects of SAC on NF-κB activation in human T lymphocytes (Jurkat cells) induced by the tumor necrosis factor alpha and H2O2. SAC consistently inhibited NF-κB activation induced by both tumor necrosis factor alpha and H2O2 in nuclear extracts. The results suggest that SAC might act through antioxidant mechanisms to block NF-κB activation in Jurkat cells. The inhibitory effect of DATS on LPS-induced iNOS expression is likely attributed to its antioxidant potential to inhibit NF-kappaB activation (Liu et al., 2006). In summary, garlic may indeed promote an anti-inflammatory environment by cytokine modulation in human blood that leads to an overall inhibition of NF-kappaB activity in the other organs and tissue.

Garlic exerting immunomodulatory properties may find relevant clinical applications as garlic and its extracts enhanced the innate and/or specific cell immunity and improve host resistance (Dorhoi et al., 2006) and administering AGE to patients with advanced cancer improved NK cell activity (Ishikawa et al., 2006). Inclusion of garlic and its products in diets specially designed to provide immunonutrition in patients suffering from cancer and other maladies could impart a beneficial impact. Care should be taken so that allergic responses if present may be avoided. Nevertheless, the potential health benefits of garlic have supported its centuries old use as an immune booster.

CONCLUSIONS

Scientific investigations in the field of nutrition led to the discovery of phenomena credited for prevalence and pathogenesis of various health disparities. Significance of natural products revitalized nowadays to alleviate such maladies. Functional food and related therapies are often patterned with phytochemicals; studying the influence of each compound on human health can provide better insight regarding these nutraceutical agents. Garlic holds a promising position as it contains organosulfur compounds which possess worthwhile health benefits. Its components/preparations are effective against oxidative stress rendering protection against membrane damage. Likewise cholesterol lowering, antiplatelet aggregation, antithrombus, and decreasing homocysteine level are also its possible targets resulting in reduced risks of atherosclerosis and allied cardiovascular complexities. Whilst its effectiveness against malignancies, its antimutagenic and antiproliferative properties has been proveds its inclusion in nutritional support programs ensures greater concerns. Furthermore the health benefits of garlic explain its function in immunonutrition especially to maintain homeostasis of body, regulating cytokines metabolisms, and brings balance to the immune cells. No doubt, an array of evidence has been presented in its favor but some ambiguous statements necessitates the demand for further research before claiming its vitality.

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