REVIEW ARTICLE

Garlic: A potential source of pharmaceuticals and pesticides: A review

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Abstract

Garlic (*Allium sativum*) holds a unique therapeutic potential as it inhibits invasion of carcinoma, provides cardiovascular protection, lowering of cholesterol, blood pressure, anti-platelet activities, and thromboxane formation. It provides protection against atherosclerosis and associated disorders and helps to decrease serum levels of glucose, insulin, triglycerides, and uric acid, as well as insulin resistance, and reduces cytokine levels. It shows hypolipidemic, anti-platelet, and procirculatory effects, and antimutagenic and antiproliferative properties. It prevents cold and flu symptoms through immune enhancement and exhibits anticancer and chemopreventive activities. The main active component of garlic is alliin (S-allyl cysteine sulfoxide), a potent antioxidant which shows cardioprotective and neuroprotective actions. Diallyl trisulfide, major garlic derivatives, could inhibit the cell proliferation by triggering either cell cycle arrest or apoptosis in a variety of cancer cells. Organosulfur compounds from garlic inhibit the growth of transplanted as well as spontaneous cancers in preclinical animal models without any adverse side effects. Garlic is a good source of anti-invasive, antioxidant, anti-inflammatory, immunomodulatory, chemopreventive, hepatoprotective, antimicrobial, apoptotic, cardioprotective, antidiabetic agents and shows insecticidal effects against lepidopteran, coleopteran, dipteran and homopteran insect pests. Hence, its constituents could be used to develop alternatives to conventional insecticides for control of serious fruit and vegetable pests. Garlic herbal preparations can reduce non-target exposure to hazardous insecticides and curb resistance development in insects. No doubt garlic based different ailments and concoctions can be used to alleviate a variety of health problems. Its various supplements contain a different concentration of organosulfur compounds are available commercially in market.

Key words: *Allium* vegetables, anticancer, hepatoprotective, neuroprotective and pesticidal activity organosulfur compounds

INTRODUCTION

Allium sativum, commonly known as lahsun in Hindi (Garlic in English) belongs to family Alliaceae and plant order liliales.[1] Garlic has been used for centuries as a prophylactic and therapeutic medicinal agent. Plant prefers sunny dry places in relatively arid climate. Garlic is a perinneal, erect, bulbous herb indigenous to Asia but it is commercially grown in many parts of the world. Both cultivated and wild species of garlic are available in different climatic regions. The bulb contains a number of concentric bulblets which have a characteristic strong alliaceous odor and very persistently pungent and acid taste. Other members of the garlic family include *Allium cepa* (onion), *Allium ascalanicum* (shallot), and *Allium porrum* (Leek). Of all the *Allium* species, garlic is the most important because of the presence of sulfur compounds.[2] Garlic (L.) is an important aromatic plant that shows multiple uses [Figure 1]. It is the main singular and combined foodstuff, which is used in traditional medicine of India. *Alliums* has been grown for many centuries for their characteristic, pungent flavor, and medicinal properties. Garlic is one of the important *Alliums* which are used for both culinary and medicinal purpose by many cultures for centuries.[3] It is a rich source of organosulfur compounds which are thought to be responsible for its flavor and aroma, as well as its potential health benefits.[4]

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Received: 27-08-2015
Revised: 06-01-2016
Accepted: 19-01-2016

Figure 1: Green garlic *(Allium sativum)* and aged garlic bulbs

Garlic is used to alleviate a variety of health problems due to its high content of organosulfur compounds and antioxidant activity. The plant contains an array of components which hold immunomodulating properties.[5] Crushing or chopping of garlic releases an enzyme called alliinase that catalyzes the formation of allicin. Different garlic preparations are effective against health risks and even used as dietary supplements such as aged 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, antiplatelet 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.[6] Organosulfur compounds from garlic effectively inhibit the growth of transplanted as well as spontaneous cancers in preclinical animal models without any adverse side effects[7] garlic organosulfide diallyl trisulfide (DATS) inhibits estrogen receptor-α (ER-α) activity in human breast cancer cells. Exposure of MCF7 and T47D cells to DATS resulted in downregulation of ER-α protein, which peaked between 12 and 24 h post-treatment.[7]

Garlic (*A. sativum*) is a good quality functional food which works against various pathologies and holds unique therapeutic potential.[6] Garlic shows health promoting properties due to the presence of sulfur-containing metabolites, i.e., allicin and its derivatives.[6] The main active component is alliin (S-allyl cysteine sulfoxide), a potent antioxidant that also show cardioprotective and neuroprotective actions. In addition, it helps to decrease serum levels of glucose, insulin, triglycerides, and uric acid, as well as insulin resistance, and reduces cytokine levels.[8] Garlic products act on several signaling pathways, including the inflammatory and apoptotic ones, and strongly target cancer.[9] S-allylcysteine (SAC) is a water-soluble garlic derivative which acts on human ovarian cancer cells *in vitro*.[10] SAC treatment significantly reduced the migration of A2780 cells and decreases the protein expression of Wnt5a, p-AKT and c-Jun proteins which are involved in proliferation and metastasis.[10] DATS inhibits matrix metalloproteinase activities and tightening tight junctions[11] and is highly cytotoxic to prostate cancer cells.[12] It inhibits invasion of human bladder carcinoma. Organosulfur compounds, including DATS, diallyl disulfide (DADS), ajoene, and S-allylmercaptocysteine (SAMC), have been found to induce cell cycle arrest when added to cancer cells in cell culture experiments. Their possible inclusion in diets could explore new therapeutic avenues to enhanced immunity against diseases. Garlic supplementation inhibits platelet aggregation and high intakes of garlic and other *Allium* vegetables (e.g., onions and leeks) may help protect against gastric, colorectal cancer (CRC) and relieve from hepatocarcinogenesis.[13]

CULINARY USES

Both green garlic leaves and bulbs or head (spathe) are highly edible and are used for various purposes in vegetables. These are used while immature and tender stage [Figure 1]. These contain milder flavor than the bulbs. Green garlic is highly used in most dishes of various regions, including Asia, South Asia, Middle East, Northern Africa, Europe and parts of South and Central America. Mature garlic imparts a garlic flavor and aroma in food, minus the spiciness. For this purpose, green garlic is often chopped and stir-fried or cooked in soup or hotpot in Southeast Asian mainly in China for preparing cookery. Immature flower stalks are also used in stir-fries. Before using mature garlic bulbs papery, protective layers are removed off before most culinary uses. Garlic flavor varies in intensity and aroma with the aging of bulbs and different cooking methods. Garlic is used with onion, tomato, or ginger for making dishes and fries. The parchment-like skin is much like the skin of onion and is typically removed before using in raw or cooked form. An alternative is to cut the top off the bulb, coat the cloves by dribbling olive oil (or other oil-based seasoning) over them, and roast them in an oven. Garlic softens and can be extracted from the cloves by squeezing the (root) end of the bulb, or individually by squeezing one end of the clove. It is true that garlic is frequently used in cooking, but its use comes with the unwanted accompaniment of "garlic breath." Much as with onions, the chemicals that lead to "garlic breath" are not actually present in unchopped garlic. Garlic is a common flavoring in food and it is also used as a food additive to prevent food poisoning. Few intermediate compounds are formed when the garlic clove is mechanically damaged; or chopping and processing causes enzymes to break down the compound alliin, found in the cloves, to form allicin. Allicin is the major compound that contributes to chopped garlic's aroma. It too is broken down into a range of sulfur-containing organic compounds, several of which contribute to the "garlic breath" effect. During garlic processing and chopping allicin rapidly breaks down to form a variety of organosulfur compounds. Moreover, cooking inactivates alliinase, therefore, garlic should stand for 10 min after chopping or crushing before cooking it. Several garlic supplements/products of household or commercial use are available commercially in the market, and each type provides a different profile of organosulfur compounds depending on how it was processed. Garlic essential oil-based additives, mouth washers, and fumigants and digestives are sold in different brands.[14] There are single products such as garlic essential oil, garlic oil macerate, garlic

powder, and garlic extract sold as single herb category [Table 1]. The manufacturing process is an important consideration when choosing a garlic supplement for household or commercial use. Steroid saponins and sapogenins present in garlic bulbs are used to prepare soft soaps. β-chlorogenin is a characteristic steroid sapogenin from garlic that is used for skin ointment and as a shiner. Both garlic paste and soft garlic preparations are used for flavoring the food items. Garlic products that contain the most safe, effective, stable, and odorless components are the most valuable as dietary supplements. Garlic also contains non sulfur compounds such as steroid saponins. These have characteristic properties, including the production of stable foam when shaken with water, hemolytic activity, and a bitter taste. Garlic preparations differ in their ingredients, effects, toxicities, and trade name. Garlic natural products of therapeutic and dietary use are most preferred items used by nutritionists, physicians, food technologists, food chemists. Raw garlic or half processed garlic pastes are used as pharmaceuticals for maintaining health and act against nutritionally induced acute and chronic diseases.

THERAPEUTIC USES

Garlic is widely recognized for its immense therapeutic potential. Its therapeutical potential has been known for many ages. It is generally used as a therapeutic agent against various diseases such as hyperlipidemia and atherosclerosis related-vascular changes. Fresh garlic juice, aged garlic extract, or volatile oil are used to cut down cholesterol and plasma lipids. Garlic actually may be effective in slowing the development of atherosclerosis and seems to be able to modestly reduce blood pressure. Garlic is used for many conditions related to the cardiovascular functions of heart and blood transport system. It removes of hardening of the arteries, reduce high blood pressure, cut down high cholesterol level, and lower down the risk of coronary heart diseases and even provide safety from heart attack. Garlic and its derivatives can reduce the risk of various types of human cancer.[11] Locals use garlic products to prevent colon cancer, rectal cancer, breast cancer, prostate cancer, and lung cancer. It is also used to treat prostate cancer. The overall activity of garlic is mainly due to the presence of sulfur compounds such as alliin, allicin, ajeone and others.

Garlic contains flavor volatiles which are of high medical and therapeutic importance. Garlic and its active compounds were found effective in reducing cardiovascular and metabolic risk by normalizing abnormal plasma lipids, oxidized low-density lipoproteins (LDLs), abnormal platelet aggregation, high blood pressure, and cardiac injury. Garlic has the potential to protect the heart against myocardial infarction; garlic

Table 1: Multiple uses of various plant parts of Garlic (*Allium sativum*) for treatment of different diseases

Medicinal	Preparation/ailment	Treatment
Leaves	Hot concoction	Common cold
Leaves	Tea	Reduce serum total cholesterol and triglyceride levels
Bulbs green	Crushed paste	Reduce platelet aggregation, hyperlipidemia
Leaves	Oil	Blood-thinning
Bulb	Sticky juice	Adhesive in mending glass and porcelain
Bulb	Solvent extract (w/v)	Nematicide and insecticide for cabbage root fly and red mite in poultry
Folk medicine	Crushed bulbs and dry stem	Relieving pain, defense against malaria, flu, cold and, sneezing deterring animals such as birds, insects, and worms from eating the plant
Cherokee	Hot syrup	Expectorant for coughs and croup
Bulb	Luke warm paste	Antiseptic to prevent gangrene
Garlic+cinnamon	Bulb and bark	Fish and meat preservative, and antimicrobial
Spiritual and religious	Total plant	Both good and evil
Europe	Bulbs	White magic
Central European	Total garlic plant could be worn, hung in windows, or rubbed on chimneys and keyholes	Powerful ward against demons, werewolves, and vampires
Muslims	Green and raw garlic	Good for prayer
Hinduism	Green and raw garlic	Garlic is thought to stimulate and warm the body and to increase one's desires
Jain	Green and raw garlic	Religion avoid eating garlic and onion on a daily basis
Buddhist traditions	Green and raw garlic	Increase drives to the detriment of meditation practice

essential oil shows anti-atherosclerotic effect.[15] It also decreases the doxorubicin-induced cardiotoxicity, arrhythmia, hypertrophy, and ischemia-reperfusion injury. Garlic contains many functional groups that may act as cardiac endogenous antioxidants and do reduction of lipid peroxidation. Other mechanisms, such as regulating ion channels, modulating Akt signaling pathways, histone deacetylase inhibition, and cytochrome P450 inhibition, could be responsible for the cardioprotective effect of garlic. Garlic showed positive effects on an enlarged prostate benign prostatic hyperplasia (BPH), diabetes, osteoarthritis, hay fever (allergic rhinitis), traveler's diarrhea, high blood pressure late in pregnancy (pre-eclampsia), cold, and flu. It is also used for toning up immune system, preventing tick bites, and preventing and treating bacterial and fungal infections [Table 2].

Garlic exerts beneficial effects against a wide spectrum of diseases, including cancer and diabetes. It provides relief from microbial infections, as well as immunological and cardiovascular disorders. It is actively used for the treatment of fever, coughs, headache, stomach ache, sinus congestion, rheumatism, hemorrhoids, asthma, gout, shortness of breath, bronchitis low blood pressure, low blood sugar, high blood sugar, and snakebites. It is also used for fighting stress and fatigue, and treatment of cancer and liver related diseases.[13,16] Garlic oil is used for the treatment of skin fungal infections warts, and corns. Garlic ointment is topically used for control of fungal infections like ringworm, jock itch, and athlete's foot. The smelly secondary metabolites from garlic serve two important functions serve as defense against predators, parasites, and diseases.

DATS is a major organosulfur component of garlic (*A. sativum* L.) that inhibits cell proliferation by triggering either cell cycle arrest or apoptosis, but the exact mechanisms of its action in human bladder cancer cells is still remain

Table 2: Nutritional value of garlic (*Allium sativum*) and its components

Garlic, raw	Nutritional value per 100 g (3.5 oz)	Metabolic functions
Nutrient	Types	Energy provider
Carbohydrates	33.06 g	Play key roles in the immune system, fertilization, preventing pathogenesis, blood clotting and development
Sugars	1 g	Sugar good for human health
Dietary fiber	2.1 g	Production of healthful compounds, increase bulk, soften stool, and shorten transit time through the intestinal tract
Fat	0.5 g	Membrane synthsis, tissue
Protein	6.36 g	Build body tissues
Vitamins		
Thiamine B1	17% (0.2 mg)	Synthesis of acetylcholine, carbohydrate metabolsim
Riboflavin (B2)	(9%) (0.11 g)	Forms the coenzyme FAD
Niacin (B3)	5% (0.7 g)	Forms the coenzyme NAD
Pantothenic acid (B5)	12% (0.596)	Forms conezymes involved in amino acid metabolism
Vitamin B6	96% (1.235 mg)	Coenzyme in many chemical reactions
Folate (B9)	1% (3 µg)	Induce DNA synthesis
Vitamin C	38% (31.2 mg)	Promotes protein synthesis
Trace metals		
Calcium	18% (181 mg)	Matrix component of bone tissue, cofactors of coagulation enzyme
Iron	13% (1.7 mg)	Constituent of hemoglobin
Magnesium	7% (25 mg)	Activates ATPase
Manganese	80% (1.672)	Cofactor of kinases and isocitric decarboxylase
Phosphorus	22% (153 mg)	Contituent of lipids, proteins, nucleic acids, sugar phosphates
Sodium	1% (17 mg)	Membrane transporter
Zinc	12% (1.16 mg)	Co-factor of enzyme
Selenium	14.2 µg	Cofactor of glutathione peroxidase
Sulfur	16%	Antimicrobial

µg: Micrograms, mg: Milligrams, IU: International units. Percentages are roughly approximated, Garlic bulbs contain approximately 84.09% water, 13.38% organic matter, and 1.53% inorganic matter, while the leaves are 87.14% water, 11.27% organic matter, and 1.59% inorganic matter. This percentage varies from variety to variety and climatic conditions.

unknown.[17] Presumably proapoptotic activity of DATS is regulated by a caspase-dependent cascade through the activation of both intrinsic and extrinsic signaling pathways, which is mediated through the blocking of PI3K/Akt and the activation of the JNK pathway.[17] There is a lot of variation among garlic products sold for medicinal purposes. Garlic's distinctive odor depends on the method of preparation. However, the amount of allicin provides, it commercial value as it is unstable, and changes into a different chemical rather quickly. Some manufacturers take advantage of this by aging garlic to make it odorless. Some odorless garlic preparations and products may contain very little, or no allicin it depends on garlic processing. The amount of allicin and its effectiveness of the product are two important parameters of herbal care products. In dietary methods crushing the fresh clove release more allicin, hence delayed processing remove out burning taste. Some products have a coating (enteric coating) to protect them against attack by stomach acids [Table 1].

PHARMACEUTICAL USES

Garlic shows many health benefits, it is best selling vegetable and a cheaper medicine available as herbal supplements throughout the world. Garlic contains four major compounds, i.e., DADS, allyl methyl sulfide, allyl mercaptan, and allyl methyl disulfide. Of these, allyl methyl sulfide is the compound that takes the longest for the body to break down. It is absorbed in the gastrointestinal tract and passes into the bloodstream, then passes on to other organs in the body for excretion, specifically the skin, kidneys and lungs. Due to the presence of functionally active organosulfur compounds such as allin, DADS, SAMC, and S-trityl-l-cysteine garlic has received great attention from a large number of pharmaceutical companies because of its broad spectrum disease curing potential. Garlic derived organosulfur compounds are able to prevent the development of cancer, cardiovascular, neurological, and liver diseases as well as allergy and arthritis.[18] Dietary garlic shows protective effects[19] and is a well-known herbal remedy for removing nephrotoxicity lipid lowering, platelet, fibrinolytic and vascular effects.[20] Green garlic is strong antidiabetic and cardiovascular agent that restores the insulin level and cut down extra concentration of lipids from the body. Garlic contains organosulfur compounds which are used to prevent and treat chronic diseases such as cancer and cardiovascular disease.[3] *Allium* vegetables reduce the risk of prostate cancer,[21] but higher intake of *Allium* vegetables reduces risk for CRC.[22] Moreoften, simple aqueous extract of garlic contains allicin which is highly anticancerous[23] and antimicrobial agent. Green garlic is hepatoprotective, exhibits anticancer, and chemopreventive activities. It contains organosulfur compounds which showed immunomodulation and anti-inflammatory effects and showed prevention of cancer and its proliferation. Garlic exhibits hypolipidemic, antiplatelet, and procirculatory effects. It prevents cold and flu symptoms through immune enhancement. Dietary consumption of garlic mainly aged garlic gives therapeutic potency[24] (AGE) because it attributes a wide variety of biological activities. AGE also has hepatoprotective, neuroprotective, and antioxidative activities, whereas other preparations may stimulate oxidation.[25] Important biological effects of garlic may be due to conversion of compounds that are formed during AGE's long-term extraction process [Table 2]. Dietary use of garlic restores immune function and prevents cancer. Garlic and its components possess following pharmaceutical activities.

ANTIDIABETIC AND CARDIOVASCULAR

Garlic is a common ingredient in Mediterranean cuisine and it is an important part of the Mediterranean diet. It is widely used in Asian countries for dietary purposes as aged or processed garlic for the treatment of cardiovascular and diabetic patients.[26,27] It contains fructooligosaccharides which have potential benefits on health.[28] Home made green garlic preparations possess potential to prevent cardiovascular disease, and hence it is used as a good protective ailment by Mediterranean people who have a noted lower mortality rate due to cardiovascular diseases.[29] Garlic shows multiple protective effects and improves functioning of cardiovascular system.[30-32] It removes off atherosclerosis and does reduction of serum lipids.[29] It shows inhibition of platelet aggregation and enhancement of fibrinolysis. Wild garlic (Allium ursinum) has been reported to contain similar amounts of sulfur-containing compounds[33] (thiosulfinates and ajoenes) as garlic, and to exert similar effects on cyclooxygenase, 5-lipoxygenase, angiotensin converting enzyme, and platelet aggregation.[34] Effect of DADS on insulin-like growth factor signaling molecules involved in cell survival and proliferation of human prostate cancer cells *in vitro* and *in silico* approach through docking analysis.[35]

LIPID-LOWERING EFFECTS

Garlic products showed positive effects on lipid metabolism in cholesterol-fed rats[36] and cut down lipid contents in experimental animals.[37-39] Possibly it may occur via inhibition of 3-hydroxy-3-methyl-glutaryl-CoA reductase or other enzymes.[40-43] More specifically, garlic-derived organosulfur diallyl di- and trisulfide compounds inhibit cholesterol biosynthesis in primary rat hepatocyte cultures.[44,45] Moreover, garlic ingredients increase loss of bile salts in feces and mobilization of tissue lipids into circulation.[46] Garlic does lowering of blood lipids, blood sugar, and fibrinogen and induces fibrinolytic activity in patients with coronary artery diseases. Garlic essential oil shows profound effect on postprandial hyperlipidemia and does prevention of atherosclerosis.[47]

Wild garlic (*A. ursinum*) causes decrease hepatocyte cholesterol synthesis *in vitro*.[48] Aged garlic extract and its

constituents inhibit Cu^{2+}-induced oxidative modification of LDL.[49] Aged garlic extract and its constituent SAC have been found to protect vascular endothelial cells from injury caused by oxidized LDL.[50] Moreoften, aged garlic extract, "Kyolic," and essential oil[51,52] showed anti-atherosclerosis-related effects.[53] Garlic products affect lipid content in normal and atherosclerotic human aortic cells.[54] Garlic products show long term effect on the development of plaque formation in the carotid branches of both femoral arteries[55] and lower down blood lipid level in cholesterol-fed rabbits.[56] Daily supplementation of aged garlic extracts lower down lipoprotein oxidation susceptibility,[57] and protects against LDL malfunction.[58,59] Garlic contains oil-soluble organosulfur compounds which effect on doxorubicin-induced lipid peroxidation.[60] Garlic extracts cut down vascular tissue lipids, fatty streak formation, and atherosclerotic plaque size.[50,56] Garlic supplementation in diet shows significant lowering in hypercholesterolemia in patients.[57]

PLATELET EFFECTS

Garlic both dietary as well as herbal medicine improve platelet function and stop its aggregation and overcoagulation.[61] Similar anti-platelet properties are also found in cooked blanched garlic leaves[62] against platelet aggregation.[63] Aged garlic extract inhibits platelet activation by increasing intracellular cAMP and reducing the interaction of glycoprotein IIb/IIIa receptor with fibrinogen[64] Wild garlic (*A. ursinum* L.) contains galactolipid and a phytosterol which exert anti-aggregatory effects.[65] Dietary supplements of garlic show anticoagulant activity and stop platelet aggregation and increase the bleeding time.[66,67] Garlic-derived DADS inhibits proliferation and transdifferentiation of lung fibroblasts through induction of cyclooxygenase and synthesis of prostaglandin.[68] Garlic is used to cure cardiovascular diseases[69] and causes inhibition of platelet activation by lachrymatory factor synthase.[70] Plant polyphenols are also used for prevention of heart disease.[71] Garlic derived allicin shows cardiovascular benefits and antioxidant properties.[72] It also shows significant anti-atherosclerotic potential and unique vascular protective properties.[73] Both processing and cooking conditions of *Allium* sp. induced antiplatelet activity and thiosulfinate content.[74]

Garlic and its derived compound ajoene have demonstrated inhibition of platelet aggregation *in vitro* as well as in experimental animals.[75] Garlic inhibits cyclooxygenase activity[76] and arachidonic acid metabolism in human blood platelets.[77] Ajoene, the antiplatelet compound derived from garlic, specifically inhibits platelet release reaction by affecting the plasma membrane internal microviscosity.[78] Ajoene and thromboxane[79] act as strong platelet inhibitor.[80,81] Morespecifically, orally administered inclusion complex of garlic oil[80] and boiled aqueous extract of garlic affect platelet aggregation in man [Table 3][81]

Use of garlic in diet causes reduction of platelet-dependent thrombus formation[82,83] and inhibit platelet aggregation in hypercholesterolemic men[84] and provide relief to coronary artery disease patients[85-89] Green garlic cease effect of cerebrovascular risk factors but low dietary dosage has no such effects.[90] Raw garlic causes dose-dependent inhibition of cyclooxygenase in human placenta villi[91] and inhibit platelet cyclooxygenase in vitro.[92] Raw garlic also reduces serum thromboxane B2 in animal and human Bordia[93-94] but boiling garlic prior to before administration appears to reduce or abolish this effect.[95]

FIBRINOLYTIC EFFECTS

Raw garlic and its essential oil show serum fibrinolytic activity and anti-clotting effects that could become a solution of cardiovascular diseases[96] for patients suffering from coronary artery disease.[46] The long-term use of garlic causes significant improvement in ischemic heart diseases. Both raw garlic and fried garlic improve microhemovascular system[97] and increase fibrinolytic activity in patients if continued therapy is provided [Table 3].[98]

VASCULAR EFFECTS

Garlic shows endothelium mediated vasorelaxant response in isolated rat aorta which tone up heart physiology.[99] Garlic may act on the nitric oxide system and exert effects on the elastic properties of vasculature.[99] It restores systemic blood pressure[100a,b] and shows protective effect in aorta of the elderly patients.[101] However, potent activation of nitric oxide synthase by garlic may be highly useful in multiple therapeutic applications.[102] Both allicin and ajoene, compounds derived from garlic, induce nitric oxide synthase system[103] that prevents hypertension.[104] Garlic does pulmonary vasorelaxation due to presence of allicin[105] and prostaglandins.[106] Similarly, aqueous garlic extract shows benefical effect on the blood vascular system of streptozotocin-diabetic rats.[107] It may be endothelium-dependent and -independent.[108] Garlic powder put positive effect on cutaneous microcirculation of diseased[100a] and healthy persons.[100b] Similarly, dried ethanol-water extract of garlic shows acute effect on the microhaemovascular system of the skin[100] and restore function of conjunctival vessels [Table 3].[101]

ANTICANCER ACTIVITY

Due to the presence of multi-components, garlic is a pioneer food which could be used in complementary therapy for clinical cancer treatment. Garlic shows many health benefits and it increases the life quality and expectancy of cancer patients.[3] It is best selling vegetable and a cheaper medicine available as herbal supplements throughout the world. Higher intake

Table 3: Biological activity of chemical constituents isolated from garlic (*Allium sativum*) and its associating species

Garlic component	Characteristics/attributes	Biological activity
	Chemo-preventive and anticancer	
Allicin	A sulfur-containing compound found in garlic generates hot sensation	Found in raw garlic opens thermo-transient receptor potential channels that are responsible for the burning sense of heat in foods
Allicin derivatives	Major contributors to the characteristic odor of garlic	Anti-mutagenic and anti-proliferative properties
Alliin	A sulfur-containing compound found in garlic	Flavor and aroma, as well as its potential health benefits, Prevents LPS-induced inflammation in 3T3-L1 adipocytes
Vinyldithiins	A sulfur-containing compound found in garlic	Strong antioxidant, control several signaling pathways, including the inflammatory and apoptotic ones, inhibit matrix metalloproteinase activities and tightening tight junctions
Proteins, minerals, saponins, flavonoids, enzymes, B vitamins	Non sulfur compounds	Anticarcinogenic
Allixin mainly phytoalexin	A nonsulfur, with a γ-pyrone skeleton structure	Antioxidant, show antimicrobial antitumor promoting effects, inhibition of aflatoxin B2 DNA binding, and neurotrophic effects, cancer prevention
Allicin	Organosulfur compound	Growth inhibitors of cancer cells, Strong odor a stinking rose, repellent action
Allyl methyl sulfide	After food intake garlic's strong-smelling sulfur compounds are metabolized, forming allyl methyl sulfide	Abundant sulfur compounds in garlic responsible for turning garlic green or blue during pickling and cooking. Act as mosquito repellent
DAS	A garlic-derived organosulfur compound is used to prevent growth of pancreatic cancer cells	Prevents tumor progression and promotes apoptosis in ectopic glioblastoma xenograft, prevent growth of pancreatic cancer cells, promotes cell-cycle arrest through the p53 expression. It also triggers induction of apoptosis via caspase- and mitochondria-dependent signaling pathways in human cervical cancer Ca Ski cells. It is found more toxic to prostate cancer cells PC-3, human retina pigment epithelial cells (ARPE-19) and HCT116 cells It induces apoptosis in MCF7 human breast cancer cells
DATS	Cytotoxic to prostate cancer cells	Highly cytotoxic to prostate cancer cells, inhibits cell proliferation by triggering either cell cycle arrest or apoptosis, shows proapoptotic activity regulated by a caspase-dependent cascade through the activation of both intrinsic and extrinsic signaling pathways, or mediated through the blocking of PI3K/Akt and the activation of the JNK pathway
Diallylpolysulfides	Organosulfur compound	Diallylpolysulfides induce growth arrest and apoptosis in cells
DATTS	Organosulfur compound	Induce mitotic arrest to apoptosis
gamma-glutamylcysteines, Allylcysteine sulfoxide (alliin)	Organosulfur compound	Generate hot odor
Allyl sulfides	Organosulfur compound	Inhibit cell growth of skin cancer cells through induction of DNA damage mediated G2/M arrest and apoptosis
SAC	Organosulfur compound	Acts on human ovarian cancer cells in

(Contd...)

Table 3: *(Contd...)*

Garlic component	Characteristics/attributes	Biological activity
	Chemo-preventive and anticancer	
SAMC	Organosulfur compound	Induce cell cycle arrests and reduces the risk of various types of human cancer
S-alkenylmercaptocysteine	Organosulfur compound	Induce apoptosis in pancreatic cells
Garlicnins B (1), C (1), and D	Sulfur containing compounds	Highly toxic to cancer cells
SAMC	Active organosulfur compounds	Highly toxic to cancer cells
SAC	Active organosulfur compounds	Suppresses proliferation and induces apoptosis in human ovarian cancer cells in vitro. reduced the migration of A2780 cells and decreases the protein expression of Wnt5a, p-AKT and c-Jun proteins which are involved in proliferation and metastasis
Polysulfanes	Sulfur containing compounds	Possess antimicrobial, chemopreventive and anticancer properties

SAC: S-allylcysteine, SAMC: S-allylmercaptocysteine, DATTS: Diallyltetrasulfide, DAS: Diallyl sulfide

of *Allium* vegetables reduces risk for CRC.[22] Garlic contains organosulfur compounds which are used to prevent and treat chronic diseases, such as cancer and cardiovascular disease.[3] Thiacremonone (2, 4-dihydroxy-2, 5-dimethyl-thiophene-3-one is sulfur compound generated from high-temperature-high-pressure-treated garlic.[108] It shows inhibition of NF-kappaB and cancer cell growth with IC (50) values about 100 µg/mL in colon cancer cells.[108] Peroxiredoxin 6 is a member of peroxidases, and has glutathione peroxidase and calcium-independent phospholipase A2 activities. DATS, a garlic-derived organosulfur compound is used to prevent growth of pancreatic cancer cells.[109] Similarly, S-Allylmercaptocysteine is known to exhibit anti-cancer effects.[110] while S-benzyl-cysteine a structural analog of SAC, is one of the major water-soluble compounds in aged garlic extract. Aged black garlic contains diallyl trisulfide which induces aopotic pathway in pancreatic cancer cells.[111] Allicin also inhibit oncogenesis.[112] SBC exerts cytotoxic activity involving activation of mitochondrial-dependent apoptosis through p53 and Bax/Bcl-2 pathways in human gastric cancer SGC-7901 cells [Table 3].[113]

Green garlic contains S-benzyl-cysteine that mediate cell cycle arrest and induce apoptosis by involving activation of mitochondrial-dependent caspase cascade through the p53 pathway in human gastric cancer SGC-7901 cells[114] while its green tea shows good therepeutic potential against lung cancer. Garlic is an important functional food[114] whose dietary consumption is found highly protective in lung cancer[115] and lowers down cancer risk[116] Black garlic extracts (BGE) check proliferation of lung cancer[117] while green garlic possesses enough potential to control CRC and other types of carcinoma.[118] Garlic oil inhibits the proliferation of AsPC-1, PANC-1, and Mia PaCa-2 cells and induced programmed cell death, cell cycle arrest, and show pro-apoptosis effects on AsPC-1 cells in a dose and time dependent manner *in vitro*.[119] Garlic oil shows preventive and therapeutic potential in human pancreatic carcinoma cells.[120] Allyl mixed sulfides inhibit cell growth of skin cancer cells through induction of DNA damage mediated G2/M arrest and apoptosis.[121] Both allicin and allyl-mixed disulfides with proteins and small thiol molecules affect microbial growth mainly bacteria.[121] Green garlic in diet is best nutruceuticals for controlling invasive cervical cancer [Table 3].[122,123]

DATS is found more toxic to prostate cancer cells PC-3[68] and human retina pigment epithelial cells (ARPE-19) and HCT116 cells.[124] Cyclic sulfoxides garlicnins B2, B3, B4, C2, and C3 form are toxic to cancer cells.[125] Garlic, silver bullets are used for carcinoma surveillance in upper endoscopy for Barrett's esophagus.[126] Multi-targeted DATS prevents tumor progression and promotes apoptosis in ectopic glioblastoma xenografts in SCID mice via HDAC inhibition.[10] Garlic constituent DATS induced apoptosis in MCF7 human breast cancer cells.[126,127] Alliin, isolated from garlic (*A. sativum*) prevents LPS-induced inflammation in 3T3-L1 adipocytes. SAC, derived from garlic suppresses proliferation and induces apoptosis in human ovarian cancer cells *in vitro*.[127] Sodium 2-propenyl thiosulfate derived from garlic induces phase II detoxification enzymes in rat hepatoma H4IIE cells[128] while conjugates of daidzein-alliinase are used as a targeted pro-drug enzyme system against ovarian carcinoma.[129] *Allium* vegetables reduce risk for gastric cancer and adenocarcinoma[130-132] and inhibit occurrence of disease[133] in follow-up nutritional cohort[134] Garlic contains vitamin, minerals, and special supplements that lower down risk of hematologic malignancies and lifestyle diseases such as cancer.[135,136] However, dietary supplements containing multivitamins, folic acid showed strong anticancer effects in breast cancer survivors[Table 2].[21] These lower down oxidative stress and induce apoptotic mechanisms in acute promyelocytic leukemia.[137] Garlic shows cardioprotective effects[138,139] and is used as a complementary and alternative medicines treatment of breast cancer.[140,141] It shows potential beneficial effects in oncohematology.[142]

IMMUNOMODULATION AND ANTI-INFLAMMATORY EFFECTS

Garlic contains organosulfur compounds that elicit anti-inflammatory and anti-oxidative responses and control an emerging tumor.[143] Garlic compounds showed immunomodulation and anti-inflammatory effects[143] and combat various physiological threats including oxidative stress, cardiovascular complexities, cancer insurgence, and immune dysfunction. 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. Garlic possesses ability to ameliorate oxidative stress, core role in cardiovascular cure, chemopreventive and as an immune booster.[140] Garlic contains garlicnins B (1), C (1), and D, that regulate macrophage activation.[144] Purified protein fraction from garlic modulates cellular immune responses against transplanted tumors in Balb/c mice model[145] while organosulfur compounds showed multiple potential chemotherapeutic effects against cancer [Table 3].[146]

CHEMOPREVENTIVE/ANTITUMOR EFFECTS

Diet-derived phytochemicals from garlic reduce the risk of prostate cancer[147,148] and show onco-cardiological prevention.[149] These also reduce the risk of invasive cervical[127,150] and ovarian carcinoma.[133] DATS induces Bcl-2 and caspase-3-dependent apoptosis via downregulation of Akt phosphorylation in human T24 bladder cancer cells.[125] DATS does transcriptional repression and inhibition of nuclear translocation of androgen receptor in human prostate cancer cells.[151] Garlic and its derived products possess enough potential for prevention of CRC and other conditions.[133] DATS inhibits ER-α activity in human breast cancer cells.[152] Garlic powder supplemented diet shows chemopreventive effects in diethylnitrosamine-induced rat hepatocarcinogenesis.[152] S-allyl-L-cysteines possess free radicals scavenging capacity and show anti-cancer and anti-cardiovascular activity. In addition, S-allylmercapto-L-cysteine, demonstrates hepato-protective effect *in vivo*[153] and *in vitro* cancer-preventive effect in human prostate carcinoma cells [Table 3].[154]

ANTI-OXIDANT ACTIVITY

Garlic chemical constituents showed very multiple therapeutic efficacy and are proved useful for preventing diseases associated with reactive oxygen species (ROS).[155,156] Aged garlic extract scavenges superoxide radicals and induces apoptosis in cancer cells.[157,158] DATS does inhibition of cell proliferation and migration in cancer cells and acts as chemopreventive drug.[159] DATS also increases ROS production in primary CRC cells.[160] Diallyl tetrasulfide acts independently of ROS and tubulin represents one of its major cellular targets.[160] It induces production of ROS in normal cells similar to cancer cells in a time and dose-dependent manner.[161] This is the main reason that both garlic and its derivatives are used as a conventional drug in many countries for the clinical treatment of cancer [Table 3].[161]

HEPATOPROTECTIVE

Garlic oil removes hepatocarcinogenesis by modulating the metabolic activation and detoxification enzymes.[162] Garlic-derived allicin enhances chemotherapeutic response and ameliorates tamoxifen-induced liver injury in experimental animals[162] and shows protective effects on NDEA-induced rats hepatotoxicity.[163] Water-soluble garlic derivatives show anticancer responses against human bladder carcinoma[164] and other lifestyle diseases[165] Dietary garlic supplements reduces precancerosis in patients[166] and inhibit early stages of malignancy malignant melanoma and tissue invasion.[167,168] These also prevent the development of cancer, cardiovascular, neurological, and liver diseases as well as allergy and arthritis.[18] Sodium 2-propenyl thiosulfate derived from garlic induces phase II detoxification enzymes in rat hepatoma H4IIE cells [Table 3].[169]

ANTI-INVASIVE AND ANTIPROLIFERATIVE EFFECT

DADS show anti-invasive activity through tightening of tight junctions and show inhibition of matrix metalloproteinase activities in LNCaP prostate cancer cells.[170] Natural tetrasulfides also show antiproliferative effect of in human breast cancer cells that are mediated through the inhibition of the cell division cycle 25 phosphatases.[170,171] Garlic reduces the risk of colorectal polyps[172] and accelerates red blood cell turnover and splenic erythropoietic gene expression in mice.[173] Boiled garlic does inhibition of 1, 2-dimethylhydrazine-induced mucin-depleted foci and O^6-methylguanine DNA adducts in the rat colorectum.[174] Allicin shows antitumoral activity in murine lymphoma L5178Y.[175] While DATS-induce apoptosis of human CNE2 cells [Table 3].[176]

Garlic extract and its fractions showed cytotoxic effect on malignant and nonmalignant cell lines.[177] Garlic provides great protection against physiological threats[6] and lower downs risk of gastric cancer.[178,179] Diallyl sulfide (DAS) from garlic induces growth inhibition and apoptosis of anaplastic thyroid cancer cells by mitochondrial signaling pathway[180] while allyl sulfur compounds cause cellular detoxification of carcinogens and is used in cancer therapy.[181,182] DATS

inhibits phorbol ester-induced tumor promotion, activation of AP-1, and expression of COX-2 in mouse skin by blocking JNK and Akt signaling.[183] Garlic contains phytochemicals that counteract the cardiotoxic side effects of cancer chemotherapy [Table 3].[182]

CHEMOPREVENTIVE/ANTITUMOR EFFECTS

Diet-derived phytochemicals from garlic reduce the risk of prostate cancer[144,146] and show onco-cardiological prevention[184] These also reduce the risk of invasive cervical[68,182] and ovarian carcinoma.[134] DATS induces Bcl-2 and caspase-3-dependent apoptosis via downregulation of Akt phosphorylation in human T24 bladder cancer cells.[121] DATS does transcriptional repression and inhibition of nuclear translocation of androgen receptor in human prostate cancer cells.[153] Garlic and its derived products possess enough potential for prevention of CRC and other conditions.[119] DATS inhibits ER-α activity in human breast cancer cells [Table 3].[7]

Garlic powder supplemented diet shows chemopreventive effects in diethylnitrosamine-induced rat hepatocarcinogenesis.[155] It also shows chemoprotection toward cyclophosphamide toxicity in mice.[185] Garlic protects against Adriamycin-induced alterations in the oxido-reductive status of mouse red blood cells[186] and methylcholanthrene-induced carcinogenesis in the uterine cervix of mice.[187] Garlic also shows prevention of 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis[188] and shows protective effects against bromobenzene toxicity to precision cut rat liver slices[189,190] DADS shows prevention of chemically induced skin tumor development[191] and hamster cheek pouch carcinogenesis.[192] Onion and garlic oils extracts inhibit tumor promotion in experimental animals.[193] Garlic extracts showed antitumor-promoting activity while vegetables prevent cancer.[194,195] DAS, a flavor component of garlic, inhibits dimethylhydrazine-induced colon cancer[194] while organosulfur compounds from garlic and onions protect from benzo[a]pyrene-induced neoplasia and glutathione S-transferase activity in the mouse [Table 3].[196]

Garlic derivatives such as ajoene, induces apoptosis in human promyelo leukemic cells, accompanied by generation of ROS and activation of nuclear factor kappa B[102] and show antiproliferative effects. Garlic-derived compound SAMC is associated with microtubule depolymerization and c-Jun NH(2)-terminal kinase 1 activation.[197,198] These components also show induction of apoptosis in breast cancer cell lines, and did attenuation of cell migration and induction of cell death in rat sarcoma cells.[199,200] The garlic-derived organosulfur component ajoene decreases basal cell carcinoma tumor size by inducing apoptosis.[201] Z-ajoene, a natural compound purified from garlic shows antimitotic and microtubule-interaction properties.[201] A protein fraction from aged garlic extract enhances cytotoxicity and proliferation of human lymphocytes mediated by interleukin-2 and concanavalin A.[202] More specifically, garlic preparation were found active against human tumor cell proliferation[203] and show antitumor[204] and anti-cancer effects effects of cancer,[205] Morespecifically, *Allium* vegetables play important role in the prevention of cancer [Table 3].[206]

ANTIMICROBIAL ACTIVITY

Herbal extracts of garlic and its products showed antibacterial activity against multidrug resistant *Escherichia coli* and *Streptococcus mutans*.[207] These enhance antimicrobial activity of antibiotics[207] and stop viability of *Staphylococcus epidermidis*.[21] Garlic essential oil shows antibacterial activity[208-210] while extract also found active against periodontal pathogens.[211] Monodispersed garlic oil microspheres in water using the emulsion technique work as potential antimicrobials.[211] Allicin shows inhibitory effect on the growth of *Babesia* and *Theileria equi* parasites) while crude garlic shows activity against *Bifidobacterium* species[212] and periodontal pathogens. Garlic shows inhibitory effect against oral bacteria,[213] and clinical strains of *Staphylococcus, Escherichia, Proteus, Pseudomonas and Klebsiella,*[214] Garlic extracts and sulfur compounds are known to destroy thiol groups in bacterial enzymes. Garlic preparations have been shown to exhibit antibacterial activity against *Helicobacter pylori, Shigella dysenteriae, Shigella flexneri, Shigella sonnei,* and *E. coli*.[215] Fresh garlic kill certain bacteria such as *E. coli,* antibiotic-resistant *Staphylococcus aureus*, and *Salmonella enteritidis*. Garlic exerts anti-pathogen activity against mycobacteria, *H. pylori*, and fungi and *Histoplasma capsulatum*.[216] Thiosulfinates, particularly allicin, are thought to play an important role in the antimicrobial activity of garlic.[217,218] Allicin-derived compounds, including DATS and ajoene, also have some antimicrobial activity *in vitro*, although generally less than allicin.[219,220] Oral garlic preparations showed significant antibacterial activity in humans.[221-223] Crude extract of bulbs show antimycobacterial and antibacterial activity.[224,225] Allicin is highly antimicrobial and work as an antiseptic candidate molecule but it is extremely unstable and toxic. Allicin may act via inhibition of thiol-containing and other enzyme systems, DNA, RNA and protein synthesis.[226] Ajoene alone possesses antibacterial activity against both Gram-positive and Gram-negative bacterial species and inhibits yeast growth. More specifically, Sulfur compounds in garlic are known to destroy thiol groups in bacterial enzymes.[227] Garlic oil shows potent antimicrobial activity on a unit weight basis [Table 3].[228,229]

Garlic extracts showed broad spectrum antifungal properties[228] against *Penicillium funiculosum*[229] endophytic fungus *Trichoderma brevicompactum*.[230] Volatile sulfur compounds from *A. sativum* show post-harvest control of gray mold in table grapes[231] and inhibit the growth of

cultured hyphae.[232] Aqueous garlic extract (AGE) against clinical yeast isolates and alter the structure and integrity of the outer surface of yeast cells as well as decrease their total lipid content.[233] Garlic was also shown to increase phosphatidylserines while decreasing phosphatidylcholines. Oxygen consumption of yeast cells was also reduced by garlic. The anti-candidal activity of AGE was antagonized by thiols including L-cysteine, glutathione, and 2-mercaptoethanol. AGE effects macromolecular synthesis of *Candida albicans* mainly protein, nucleic acid and lipid synthesis.[234] (Garlic) inhibits lipid synthesis by *C. albicans* [Table 3].[235]

Allium species contain active ingredients[236] such as allicin which show antimicrobial activity[224] Garlic contains ajoene, a sulfur-containing compound shows inhibition of microbial growth[13] Garlic extract shows inhibition of *Mycobacterium tuberculosis*[237] and *Mycobacterium avium*,[238] garlic extract shows antimycobacterial synergism to antituberculosis drugs.[239,240] Garlic oil, garlic powder, and their diallyl constituents were found active against *H. pylori.*[241,242] Aqueous garlic extract was found fungicidal and fungistatic effects on medically important yeast-like fungi.[243] Garlic shows antifungal activity in human urine and serum.[243] Garlic oil sulfides and garlic powder showed antimicrobial properties against human enteric bacteria.[104] Garlic compound SAC[244] and allicin[245] shows growth inhibition in *H. capsulatum.*[246,247] Steroid saponins isolated from the garlic bulb, eruboside-B exhibited antifungal activity against *C. albicans*.[248] Garlic shows *in vitro* antimycobacterial activity as well as anti-bacterial activity of various extracts rich in contains sulfur compounds like allicin, ajoene, allyl methyl trisulfide, DATS, diallyl disulfide.[231] Garlic oil demonstrated significant antibacterial activity, particularly against methicillin-resistant *S. aureus*.[14] Garlic also shows anticandidal mode of action[249] and protect from influenza B, herpes simplex and coxsackie virus infection.[250] Garlic extracts have a strong antifungal effect and inhibit the formation of mycotoxins like the aflatoxin of *Aspergillus parasiticus*. Garlic contains allicin that displayed significant *in vitro* fungicidal and fungistatic activity against three different isolates of *Cryptococcus neoformans* [Table 3].[251,252]

ANTI-VIRAL EFFECTS

Garlic extracts have an antiviral effect against human cytomegalovirus, influenza B, herpes simplex virus Type 1, herpes simplex virus Type 2, parainfluenza virus Type 3, *Vaccinia virus*, vesicular stomatitis virus and human rhinovirus Type 2.[253] Allicin is safe and shows antifungal prophylactic[254] reported the efficacy of allicin and its various transformation products against Herpes simplex virus 1 and 2, vesicular stomatitis virus, *V. virus* and parainfluenza virus.[255] Allitridin works against human cytomegalovirus *in vitro*.[256] Garlic extract and compounds showed anti-viral activity against human cytomegalovirus *in vitro.*[257] Garlic derived DATS found active against leukemic cells[258] while Z-ajoene, targets glioblastoma multiforme cancer stem cell.[240] produces terpenes with fungistatic properties in response to infection with *Sclerotium cepivorum.*[259] Garlic extracts show antiviral activity against several viruses, including influenza B virus, herpes simplex virus Type 1, herpes simplex virus Type 2, parainfluenza virus Type 3, *V. virus*, vesicular stomatitis virus, human rhinovirus Type 2,[260] and cytomegalovirus.[256] Ajoene, found in oil-macerates of garlic, possesses a high level of antiviral activity followed by allicin, allyl methyl thiosulfinate and methyl allyl thiosulfinate[217] Allicin is the key component which shows antimicrobial activity. Allicin has also been found to be effective as an anti fungal, antibacterial, antiviral and anti parasitic agent.[218,259] Allitridin inhibits human cytomegalovirus replication *in vitro* [Table 3].[259]

ANTIPARASITIC

Garlic extract shows antiparasitic effects against hymenolepiasis nana and giardiasis[260] and gastrointestinal parasites mainly cestodes and on trematodes,[261] *Blastocystis hominis* and African trypanosomes[262] and intestinal flagellates of poultry animals.[263] Garlic has been found to be effective against gastrointestinal parasites of humans and animals. Garlic-induced death of protozoans such as *Entamoeba histolytica, Hymenolepsis nana,* and *Giardia lamblia.*[264] Ajoene cream found effective against *Tinea pedis* (athlete's foot) as 1% terbinafine (Lamisil) cream.[265] Allicin shows inhibitory effect of on the growth of *Babesia* and *T. equi* parasites [Table 3].[266]

GLYCEMIC EFFECTS

White vegetable including garlic and onion makes to the carbohydrate and nutrient composition of the diet and their functionality in satiety and metabolic control within usual meals. These contribute the energy and nutrient content of the diet and glycemia and satiety.[267] These also effect of food composition of mixed food on glycemic index.[268] Effect of methanolic extract of (AS) in delaying cataract in STZ-induced diabetic rats,[269] antidiabetic effect of garlic oil but not DADS in rats with streptozotocin-induced diabetes.[270] Garlic antidiabetic agent provides better diabetic control in Type 2 diabetes.[271] Garlic dietary supplements are used as anti-diabetic agent to cure Type 2 diabetes patients[272] with obesity.[273] Garlic either used in salads or taken as medicine could manage Type 2 diabetes mellitus[274] and is said to be an anti-glycant culinary herbs.[275] It shows efficacy on carbohydrate metabolism[275] and finish cataract in STZ-induced diabetic rats.[271] Garlic oil also showed anti-diabetic[276,277] and decrease cardiovascular risk factors.[278]

GENITOURINARY EFFECTS

Garlic supplemented diet attenuates gentamicin nephrotoxicity ın rats and does amelioration of lead-induced changes in ovary

of mice.[279] Aqueous extract alleviates liver fibrosis and renal dysfunction in bile-duct-ligated rats.[280] Allyl sulfides found in garlic essential oil on intracellular Ca_2 levels in renal tubular cells.[281] SAC prevents cisplatin-induced nephrotoxicity and oxidative stress,[282] Ethanolic extract of garlic for attenuation of gentamicin-induced nephrotoxicity in Wistar rats, while aqueous extract of bulbs shows nephroprotection by attenuating vascular endothelial growth factor and extracellular signal-regulated kinase-1 expression in diabetic rats.[282] Hexane extract of aged black garlic reduces cell proliferation and attenuates the expression of ICAM-1 and VCAM-1 in TNF-α-activated human endometrial stromal cells.[281] Aged garlic extract showed renoprotective effect in streptozotocin-induced diabetic rats and its effect of allyl sulfides from garlic essential oil on intracellular ca2+ levels in renal tubular cells[281] effect of SAC, a sulfur containing amino acid on iron metabolism in streptozotocin-induced diabetic rats.[282] Green garlic extract shows *in vivo* radioprotective activity.[283] Raw garlic consumption shows effect on male reproductive functions and effect male fertility.[284] Thiol-reactive compounds from garlic inhibit the epithelial sodium channel[285] and down-regulates the expression of angiotensin II AT(1) receptor in adrenal and renal tissues of streptozotocin-induced diabetic rats.[286] Chronic garlic ingestion for 70 days has been associated with suppression of spermatogenesis in rats. Allicin acts as an oxidant in the blood when it is mixed with blood *in vitro* almost all allicin disappears within a few minutes [Table 3].[283]

PESTICIDAL ACTIVITY

Garlic (L. (Asparagales: Alliaceae) essential oil is used for control of arthropod pests[287] mainly Japanese termite, *Reticulitermes speratus* Kolbe at very low concentration 3.5 µL/L of volatile garlic oil in fumigation assay.[288] DATS is more toxic, than DADS, eugenol, DAS, and beta-caryophyllene.[288] Its essential oil was found active against 6th instars and adults of the darkling beetle, *Alphitobius diaperinus* (Panzer) (Coleoptera: Tenebrionidae) and effects level of AChE activity. Allyl isothiocyanate trans-anethole, DADS and p-anisaldehyde isolated from garlic oil exhibited very high insecticidal potential against larvae of *Lycoriella ingénue* (Dufour) at very low LC (50) values 0.15, 0.20, 0.87 and 1.47 µL L(-1).[289] Similarly, allyl isothiocyanate, isolated from *A. sativum* essential oil exhibited toxicity against third instars of the Japanese beetle *Popillia japonica* Newman, European chafer *Rhizotrogus majalis* (Razoumowsky), oriental beetle *Anomala orientalis* (Waterhouse), and northern masked chafer *Cyclocephala borealis* arrow.[290] Essential oil and its constituents were found effective against scarab larvae, Trichoplusia ni Hübner (Lepidoptera: Noctuidae) larvae with LC (50) 3.3 µL/ mL.[291]

Moreover, natural organic sulfur compounds possess considerable practical potential against fruit and vegetable insect pests. Various natural polysulfanes, such as DATS and diallyltetrasulfide (DATTS) from garlic, are mostly harmless to humans, higher animals and plants, but these were found active against a wide range of agricultural pests.[292] Two of the major constituents of the essential oil of garlic, *A. sativum* L., methyl allyl disulfide and DATS, were found active against *Sitophilus zeamais* Motschulsky and *Tribolium castaneum* (Herbst). These compounds show contact toxicity, fumigant toxicity, and antifeedant activity. The contact and fumigant toxicities of DATS were greater than that of methyl allyl disulfide to the adults of these two species of insects. These two compounds were also more toxic to *T. castaneum* adults than to *S. zeamais* adults. Older *T. castaneum* larvae were more susceptible to the contact toxicity of the two compounds, whereas younger larvae were more susceptible to the fumigant toxicity of these compounds.[293] Both compounds cut down egg hatching of *T. castaneum* and subsequent emergence of progeny. Methyl allyl disulfide significantly decreased the growth rate, food consumption, and food utilization of adults of both insect species, with feeding deterrence indices of 44% at 6.08 mg/g food for *S. zeamais* and 1.52 mg/g food for *T. castaneum*. A feeding deterrence of 85% was seen in *T. castaneum* adults at a much lower concentration of 0.75 mg/g food [Table 3].[294]

Ingestion of garlic provides protection against bloodsucking pests such as mosquitoes. However, it *Aedes aegypti* (Linnaeus) (Diptera: Culicidae) did not feed on the treated subjects because garlic components may act as surface repellent for mosquito as skin may exudates some volatiles. Similarly, polysulfanes were found active against *Botrytis cinerea*, which show low ecotoxicity. It could be used for agronomically important plant pathogens.[293] Moreover, wheat-garlic intercropping successfully control aphid *Sitobion avenae* (Fabricius) in wheat fields.[295] Similarly, *Allium* scheonparum L. when interplanted with roses showed effectiveness by releasing of nonhost masking odors and protect roses against the Japanese beetle, *P. japonica* Newman.[296]

GARLIC ESSENTIAL OIL COATED NANOPARTICLES

Polyethylene glycol (PEG) coated nanoparticles loaded with garlic essential oil showed insecticidal activity against adult *Tribolium castaneum*. These PEG coating nanoparticles loaded with garlic essential oil were found highly effective to control the store-product pests.[297]

GARLIC LECTINS

Garlic lectins were also found promising candidate molecules which are used for the protection against chewing (lepidopteran) as well as sap sucking (homopteran) insect pests.[298] Lectins show its effect right from sensory receptors of mouth parts by disrupting the membrane integrity and food detection ability. Subsequently, these enter into the gut

lumen and interact with midgut glycosylated proteins such as alkaline phosphatase, aminopeptidase-N, cadherin-like proteins, polycalins, sucrase, symbionin and others. These proteins play a critical role in life cycle of insect directly or indirectly.[299] Lectins interfere with gut enzymes/proteins and cause physiological disorders leading to the death of insects. These are further transported across the insect gut, accumulated in various body parts (like hemolymph and ovary) and interact with intracellular proteins such as symbionin and cytochrome p450. Lectins bind with cytochrome p450 that involve in ecdysone synthesis and may interfere in the development of insects, which results in growth retardation and pre-mature death.[300] Similarly, garlic lectin gene (*A. sativum* leaf agglutinin [ASAL]) holds great promise in conferring protection against chewing (lepidopteran) and sap-sucking (homopteran) insect pests. Lectin transgenics exhibited enhanced resistance (1-2 score) against brown hoppers, and minimal plant damage was obtained with no growth penalty or phenotypic abnormalities.[301] ASAL, a novel lectin isolated from leaves of garlic (*A. sativum*) was found toxic to hemipteran pests. Green leafhopper (GLH) mediated resistance to infection by RTBV/RTSV in ASAL expressing transgenic rice plant.[302]

Similarly, mannose binding leaf agglutinin (ASAL) has been shown to be antifeedant and insecticidal against sap-sucking insects.[303] Insecticidal proteins, namely, *Bacillus thuringiensis* delta-endotoxin (Bt) and mannose-binding lectins from, exhibited detrimental effect on the growth and development of the insect, where *A. sativum* bulb lectin showed the highest mortality of all, in particular. The same bulb lectin not only affected the growth and fecundity of the insect but also imparted drastic changes in the color, weight, and size, even on the second generation of the insects when these were reared on artificial diet supplemented with a sublethal dose of the lectin. Therefore, lectins are proved highly useful and can be used to control important crop pests.[304] Similarly, *A. sativum* leaf lectin gene (asal), coding for mannose binding homodimeric protein (ASAL) from garlic plants, introduced into elite indica rice cultivars was found susceptible to sap-sucking insects, viz., brown planthopper (BPH), GLH and white backed planthopper (WBPH). ASAL also shows potent entomotoxicon BPH, GLH, and WBPH insects and causes significant decrease in the survival, development and fecundity of the insects. The stable transgenic lines, expressing ASAL, showed explicit resistance against major sap-sucking pests.[305]

TRANSGENIC CROPS

Different transgenic crop plants, developed with δ-endotoxins of *Bacillus thuringiensis* (Bt) and mannose-specific plant lectins, exhibited significant protection against chewing and sucking insects. Cry1Ac, the fusion-protein showed enhanced (8-fold and 30-fold) insecticidal activity against two major lepidopteran pests.[306] δ-Endotoxins produced by *Bacillus thuringiensis* (Bt) have been used as bio-pesticides for the control of lepidopteran insect pests. Garlic (L.) leaf agglutinin (ASAL), being toxic to several sap-sucking pests and some lepidopteran pests, may be a good candidate for pyramiding with δ-endotoxins in transgenic plants for enhancing the range of resistance to insect pests. Binding of fusion-protein to the additional receptors in the midgut cells of insects is attributable to its enhanced entomotoxic effect.[306] *Bacillus thuringiensis* (Bt) Cry proteins has resulted in the synthesis of various novel toxin proteins with enhanced insecticidal activity and specificity towards different insect pests. A fusion protein consisting of the DI-DII domains of Cry1Ac and garlic lectin (ASAL) has been designed *in silico* by replacing the DIII domain of Cry1Ac with ASAL. There is a need to design and develop customized fusion molecules for improved pest management in crop plants.[307] A synthetic gene (cry-asal) encoding the fusion-protein having 488 amino acids, comprising DI and DII domains from Bt Cry1Ac and agglutinin (ASAL), was cloned and expressed in *E. coli*. Fusion-protein exhibited significant 8-fold and 30-fold protection against chewing and sucking insects mainly lepidopteran pests than Cry1Ac. This synthetic gene, appears to be promising and might serve as a potential candidate for engineering crop plants against major insect pests.[307] ASAL can be safely employed with Cry1Ac for developing transgenic crops for wider insect resistance.[307,308] Transgenic rice lines containing delayed the development of insects BPH, GLH and white backed planthopper (WBPH) as compared to the parental transgenics. Reducing insect survival, fecundity, feeding ability under infested conditions, pyramided lines were found superior to the parental transgenics in their seed yield potential. Moreoften, two lectin genes incorporated into rice exhibit enhanced resistance against major sucking pests.[309] Similarly, introduction of coding sequence of *A sativum* leaf agglutinin, ASAL, in rice cultivar IR64 give rise sustainable resistance against homopteran sucking pests mainly plant hoppers. In plant bioassay of GLH and BPH performed on these T(2) progenies exhibited radical reduction in survivability and fecundity compared with the untransformed control plants.[310]

PHYTOCHEMISTRY

Garlic (*A. sativum*) bulbs contain a large amount of carbohydrates, glycosides, and proteins. These also contain alkaloids, saponins, reducing sugars, oils, and steroids in medium concentrations. Both green garlic and raw dry garlic contain flavonoids and acidic compounds in low amounts. Both green and aged garlic contain many sulfur-containing compounds which provide it a characteristic flavor. These sulfur-containing compounds are diallyl sulfate, alliin, ajoene, allicin. From garlic two categories of compounds oil- and water-soluble are isolated. Oil-soluble compounds are sulfides such as DAS, DADS, DATS and allyl methyl trisulfide, dithiins, and ajoene while water-soluble compounds are cysteine derivatives.[9] These are S-allyl cysteine (SAC),

SAMC and S-methyl cysteine, and gamma-glutamyl cysteine derivatives [Figure 2]. Oil-soluble sulfur compounds possess characteristic odor, whereas water-soluble compounds are odorless.[309] Moreover, water-soluble compounds are more stable and safer than oil-soluble compounds.[310] DADS, the major organosulfur component of processed garlic is very effective in chemoprevention of several types of cancers [Table 3].[311]

Intact garlic contains water-soluble organosulfur compounds such as γ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxides (alliin) as major sulfur-containing compounds. Both found in higher concentration. S-allyl-L-cysteines derive from γ-glutamyl-S-allyl-L-cysteines [Figure 2]. In aged garlic extract, both S-Allyl-L-cysteine and trans-S-1-propenyl-L-cysteine in ample amount while S-methyl-L-cysteine found in a small amount.[312] Alliin is the primary odorless, sulfur-containing amino acid, a known precursor of allicin,[313] methiin, (+)-S-(trans-1-propenyl)-L-cysteine sulfoxide, and cycloalliin.[312] Transformation of cysteine sulfoxides to sulfenic acid [Figure 1] takes place in the presence of alliinase. This enzyme acts at pH optimum of 6.5 using S-methyl-L-cysteine as substrate molecule.[314] After its formation sulfenic acids spontaneously react with each other to form unstable compounds called thiosulfinates. This reaction occurs in cytoplasm in the presence of enzyme alliinase inside vacuole, via sulfur-substituted sulfenic acids [Figure 2].

Other thiosulfinates, such as allylmethyl-, methylallyl-, and trans-1-propenyl-thiosulfinate, are also formed during garlic homogenization. These are also unstable like allicin.[34] In addition, pyridoxal phosphate stimulates alliinase activity as a cofactor.[34] Thiosulfinates are formed during processing or chopping or crushing of garlic very rapidly within 10-60 s but these are not formed below pH 3.6, which is the usual pH range in the stomach [Table 3].[34]

Garlic root bulbs are rich in sulfur compounds such as allicin that breaks down *in vitro* to form a variety of fat-soluble organosulfur compounds [Figure 2]. Allicin is highly temperature sensitive and decompose in to DATS, DADS, and DAS sulfur dioxide if it is kept at 20°C for 20 h.[122] This decomposition also takes place in the presence of oil or organic solvents. Alliin is water-soluble compound which is absorbed inside the body but never converted to allicin in the body and metabolized to various organosulfur compounds such as DADS by liver enzymes.[6,122] Allicin easily reacts with amino acids and proteins, creating a -SH group, and cannot circulate in the blood stream[6,122] that is why it is not detected in the blood sample after the ingesting raw garlic or pure allicin.[122] Allicin is an irritating, acidic, and oxidizing compounds being used as a therapeutic agent. Garlic also contains a variety of components, including nonsulfur compounds, work synergistically to provide various health benefits. Processed garlic contains a wider variety of organosulfur volatiles than the intact garlic clove [Table 3].

Garlic also contains water-soluble compounds such as SAC. SAC are formed from gamma-glutamylcysteine during long-term incubation of crushed garlic in aqueous solutions, as in the manufacture of aged garlic extracts. Few nonvolatile sulfur containing precursors also found in intact garlic. These are γ-Glutamyl-*S*-allyl-L-cysteines which are converted into *S*-allyl-cysteines (SAC) through an enzymatic transformation with γ-glutamyltranspeptidase when garlic is extracted with an aqueous solution.[10] SAC, a major transformed product from γ-glutamyl-S-allyl-L-cysteine, is a well-known chemical marker which is scientifically reasonable and well justified. Moreover, sulfides having an allyl group provide characteristic smell and taste after ingesting garlic. These are detected in the blood samples in orally administered experimental animals [Table 3].

GARLIC OIL

Garlic essential oil contains important sulfur compounds such as DAS, DADS, DATS, methylallyl disulfide, methylallyl trisulfide, 2-vinyl-4H-1, 3-dithiin, 3-vinyl-4H-1, 2-dithiin, and (E, Z)-ajoenes [Figure 2]. DAS, DADS, and DATS are major volatile components of garlic oil.[115] Some other chemical constituents such as allylmethyl (37%), and dimethyl (6%) mono- to hexasulfides allyl 1-propenyl and methyl 1-propenyl di-, tri-, and tetrasulfides found in trace amounts in garlic. DATS is the most abundant in fresh garlic oil but in commercially available garlic-oil presence of DADS percentage decide its activity and price.[11,12] DASs and vinyldithiins are the major organosulfur components of garlic oil and oil-macerate preparations. Vinyldithiins, especially 2-vinyl-4H-1, 3-dithiin, are rich in the oil macerate of raw garlic.[310] Garlic contains ajoene a much potent antithrombotic agent.[11] It is formed by S-thioallylation of allicin, followed by Cope-type elimination and re-addition of 2-propenesulfenic acid. Another ajoene-type organosulfur compound, E-4,5,9-tritriadeca-1,7-diene-9-oxide, is also isolated from oil-macerated garlic extract [Table 3].[11]

Garlic also contains non sulfur compounds such as steroid saponins and sapogenins that could be considered reliable chemical markers for the identification of garlic and garlic preparations, except for garlic oil. β-chlorogenin is a characteristic steroid sapogenin of garlic. Two categories of saponins i.e., triterpenoid saponins and steroid saponins, based on the molecular structure of aglycone.[4] Important steroid saponins isolated from the garlic bulb are eruboside-B, proto-eruboside-B.[4] Other steroid saponins are furostanol and spirostanol saponins. Garlic includes allixin and organo-selenium compounds which show synergistic action better that organosulfur compounds. Garlic supplement products are very popular among consumers because of its multiple uses. In the present time, so many herbal supplements of house hold use are available in the market. Many of them are the most popular herbal supplement included in the single herb category. There are dozens of brands of garlic products

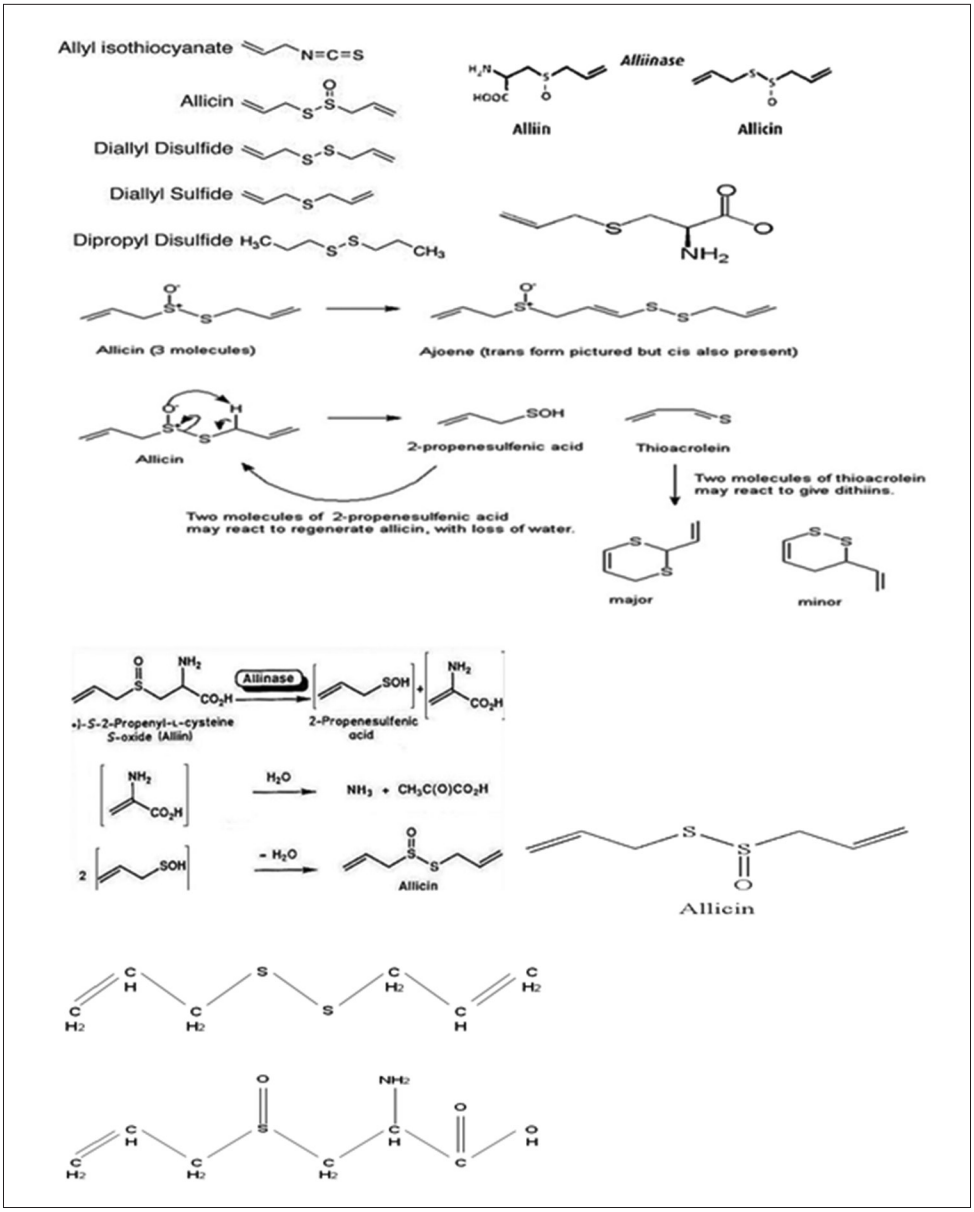

Figure 2: Various chemical compounds isolated from garlic *(Allium sativum)*

on store shelves that provide a convenient way to obtain the health benefits of garlic. Few important products are garlic essential oil, garlic oil macerate, garlic powder, and garlic extract [Table 2]. Garlic essential oil is available in the form of additive, mouthwashsr, and fumigant and digestive. The manufacturing process is an important consideration when choosing a garlic supplement for household or commercial use. Steroid saponins and sapogenins present in garlic bulbs are mixed in soft soaps. β-chlorogenin is a characteristic steroid sapogenin from garlic that is used for skin ointment and as a shiner. Both garlic paste and soft garlic preparations are used for flavoring the food items. The various forms also differ in their ingredients, effects, and toxicities. Garlic products that contain the most safe, effective, stable, and odorless components are the most valuable as dietary supplements. Garlic also contains non-sulfur compounds such as steroid saponins. These have characteristic properties, including the production of stable foam when shaken with water, hemolytic activity, and a bitter taste [Table 3].

ADVERSE EFFECTS OF GARLIC

Over dose of crude garlic extract and its derived pure compounds cause multiple adverse clinical effects such as inflammation and dermatoses.[315] S-alk(en)yl cysteines of garlic inhibit cholesterol synthesis by deactivating HMG-CoA reductase in cultured rat hepatocytes[316] and control smooth muscle cell proliferation in vascular disease.[317] Garlic-derived compounds are good antioxidants and its dietary supplementation lower down oxidized LDLs and are of high clinical and therapeutic use.[318,319] Low doses of diallyl disulfide, a compound derived from garlic, increase tissue activities of quinone reductase, and glutathione

transferase in the gastrointestinal tract of the rat.[320] Low and regular dose of garlic products restore cell cycle dysregulation and are good for cancer therapy.[321,322] These also show good anticoagulant activity.[323]

Garlic shows occupational effects such as allergic responses and asthma in field workers due to exposure of dust and garlic powder.[324-327] Regular exposure of garlic and its organosulfur compounds impose contact dermatitis[328] and black spots or black burning.[329] A much longer topical exposure to garlic causes blackish skin burns, lesions, and blisters mainly in farmers and wagers. Dietary oral ingestion of garlic and garlic supplements imposes hot breath and body odor.[330] In first time, users garlic consumption imposes gastrointestinal symptoms displayed as heartburn, abdominal pain, nausea, vomiting, flatulence, and diarrhea.[331] Over consumption of garlic seriously affects fertility in males.[332] Very high oral garlic supplementation or oral ingestion causes uncontrolled bleeding in surgery patients.[333] Allicin and its degraded compounds show strong adverse reaction hence an appropriate extraction process should be used to eliminate these undesirable compounds. Garlic consumption affects milking behavior in mothers.[334] It alters the odor and flavor of breast milk that seriously affects behavior of infant.[334] Excessive oral intake of garlic extract (1.5 g daily) effects lactation in women and increase the perceived intensity of breast milk odor.[334] Green synthesis of biocompatible gold nanocrystals[335] and sulfur containing compounds were found potential anticarcinogenic agent against major gastric cancers [Table 3].[336]

CONCLUSION

It is pioneer food of that is used in complementary therapy in clinical cancer treatment and increase the quality of life cancer patients. Garlic synthesizes series of sulfur compounds which show multiple biological activities. Garlic components are nutritionally and therapeutically highly useful. These are highly demanded by nutritionists, physicians, food technologists, and food chemists. Garlic organosulfur compounds show cardiovascular, antineoplastic, lipid-lowering effects, anti-platelet, hepatoprotective, antioxidant, antiproliferative, anticancer, and antimicrobial activity. These also cut down blood pressure and show immunomodulation and anti-inflammatory effects in cancer chemoprevention. Allicin a sulfur compound from garlic is an important ingredient that has great therapeutic use. Alliin prevents LPS-induced inflammation in 3T3-L1 adipocytes while SAC suppresses proliferation and induces apoptosis in human ovarian cancer cells *in vitro*. DADS, the major organosulfur component of processed garlic was found highly effective in chemoprevention of several types of cancers by significantly enhancing the immune system. *A. sativum* (L.) is rich in antioxidants which help destroy free radicals particles that can damage cell membranes and DNA, and may contribute to the aging process as well as the development of a number of conditions including heart disease and cancer. Natural polysulfanes including DATS and DATTS from garlic possess antimicrobial, chemopreventive, and anticancer properties. *Allium* vegetables, especially garlic intake, are related to decreased risk of prostate and pancreatic cancer. Garlic inclusion in diet does immunomodulation and boost up immune system, by activation and suppression of immune specialized cells, interfering in several pathways that eventually led to improvement in immune responses and defense system. Garlic oil suppressed the hematological disorders induced by chemotherapy and radiotherapy in tumor-bearing mice. Garlic could not only induce apoptosis Type II programed cell death but also autophagy in cancer cells. ABGE may be effective in the prevention and treatment of colon cancer in humans.

Organosulfur compounds from garlic removes off oxidants and induce free radical scavenging and anti-inflammatory activities. These potentially work as therapeutic drugs cardiovascular, neurological and liver diseases as well as allergy and arthritis. These inhibit oncogenesis and type of cancer insurgence. Major volatile components of garlic oil show a very high potency in inducing antioxidant enzyme expression. Aged garlic extracts show ameliorating effects against Aβ-induced neurotoxicity and cognitive impairment. Although there are adverse reports on toxicities and pharmacokinetics of these compounds, hence over use of garlic imposes adverse effects which are generally mild and uncommon. Garlic appears to have no effect on drug metabolism, but patients taking anticoagulants should be cautious. Therefore, overuse use of garlic should be avoided. For safe use of garlic products should be investigated for toxicity and allergic reactions. It is harmful for pregnant women. Today as herbal medicine garlic is attracting public health authorities, pharmaceutical industries because of its larger use in prevention and treatment of so many diseases and disorders. Garlic is used as a basic resource material for modern pharmaceuticals which are thought to be powerful instrument in maintaining public health and act against nutritionally induced acute and chronic diseases. No doubt garlic and its derived herbal products are providing optimal health and quality of life.

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Source of Support: Nil. **Conflict of Interest:** None declared.