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Pharmacological Effects of Garlic (*Allium sativum L.*)

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Abstract

Singh VK, Singh DK. Pharmacological Effects of Garlic (Allium sativum L.). ARBS Annu Rev Biomed Sci 2008;10:6-26. Garlic (*Allium sativum L.*) is a bulbous herb used as a food item, spice and medicine in different parts of the world. Its medicinal use is based on traditional experience passed from generation to generation. Researchers from various disciplines are now directing their efforts towards discovering the effects of garlic on human health. Interest in garlic among researchers, particularly those in medical profession, has stemmed from the search for a drug that has a broad-spectrum therapeutic effect with minimal toxicity. Recent studies indicate that garlic extract has antimicrobial activity against many genera of bacteria, fungi and viruses. The role of garlic in preventing cardiovascular disease has been acclaimed by several authors. Chemical constituents of garlic have been investigated for treatment of hyperlipidemia, hypertension, platelet aggregation and blood fibrinolytic activity. Experimental data indicate that garlic may have anticarcinogenic effect. Recent researches in the area of pest control show that garlic has strong insecticidal, nematicidal, rodenticidal and molluscicidal activity. Despite field trials and laboratory experiments on the pesticidal activity of garlic have been conducted, more studies on the way of delivery in environment and mode of action are still recommended for effective control of pest. Adverse effects of oral ingestion and topical exposure of garlic include body odor, allergic reactions, acceleration in the effects of anticoagulants and reduction in the efficacy of anti-AIDS drug Saquinavir.

Keywords: garlic, allicin, alliin, cancer, hyperlipidemia, hypertension, antiplatelet activity, pesticide

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1. Introduction

Garlic, *Allium sativum L.* is a member of the Alliaceae family, has been widely recognized as a valuable spice and a popular remedy for various ailments and physiological disorders. The name garlic may have originated from the Celtic word 'all' meaning pungent. Cultivated practically throughout the world, garlic appears to have originated in central Asia and then spread to China, the Near East, and the Mediterranean region before moving west to Central and Southern Europe, Northern Africa (Egypt) and Mexico (Lutomski, 1987).

As one of the earliest cultivated plants, garlic is mentioned in the Bible and in the literature of Ancient Israel (The Talmud), Egypt (Codex Ebers) and India (Vedas and Purans, Charak Sanghita). Chinese strongly believe that garlic prolongs longevity (Srivastava *et al.*, 1995) and is useful in treating most human diseases, including infections, cancer and heart diseases. In historical writings of India and in literature like Vedas and Purans, garlic is reported to have medicinal as well as nutritive value in food items. Clinical indications of garlic include hemorrhoids, rheumatism, dermatitis, abdominal pain, cough, loss of appetite and loss of weight (Adetumbi & Lau, 1983; Anonymous, 1985; Koch & Lawson, 1996).

The medicinal qualities of garlic were described by Pliny the Elder, Aristophanes, and Galen. Hippocrates, the Father of Medicine, observed that garlic was excellent for curing tumors and is an effective diuretic. Aristotle attributed garlic as a cure for rabies, and the Prophet Mohammad recommended it for treating scorpion stings. In Historia Naturalis by Pliny (Fenwick & Hanley, 1985), garlic was recommended for gastro-intestinal disorders as well as dog and snake bites. Desired medicinal results of garlic are obtained when bulbs are chewed and swallowed or mixed with food and eaten.

Preparations of garlic are available as tablets, capsules, syrup, tinctures and oil. In ointment form, garlic has been used externally for treatment of ring worm; boiled with vinegar and sugar for treatment of asthma; made into an infusion for treatment of epilepsy; pounded with honey for use against rheumatism; and mixed with milk for use as a vermifuge. Garlic is commonly used in Europe and Asia for medicinal benefits in healing wounds, etc. (Bolton *et al.*, 1982; Srivastava *et al.*, 1995). In Germany, sale of garlic preparations competes with sales of leading drugs (Lawson, 1993).

Garlic produces a variety of volatile sulfur-based compounds which are effective as insect repellents and insecticides. Diallyl disulfide is one of such compounds which has a strong odor and acts as a powerful insecticide (Kaufman *et al.*, 1999). Commercial preparations of garlic are certified as insecticide against mites, nematodes and mosquito larvae affecting a variety of crops (Amonkar & Reeves, 1970; Gupta & Sharma, 1993; Gamboa-Leon *et al.*, 2006).

The objective of the present review is to highlight the pharmacological and therapeutic use of garlic in modern medicine and its use as pesticide against certain pest. Garlic chemistry follows in order to reach the aim of this review.

2. Chemistry

Intact garlic cloves contain only a few medicinally active compounds (Block, 1992; Lawson, 1993). The main chemical constituent of intact garlic is the amino acid alliin, an alkyl derivative of cysteine alkyl sulfoxide, which may varies from 0.2 to 2.0% fresh weight (Lutomski *et al.*, 1968; Kabelik, 1970; Michahelles, 1974; Lutomski, 1983a,b; 1987). The efficacy of chemical constituents of garlic chiefly depends on the mode of preparation of its extract. Crushing, chewing or cutting (or exposing dehydrated, pulverized garlic to water) of garlic cloves release the vacular enzyme allinase that rapidly lyses the cytosolic cysteine sulfoxide (Stoll & Seebeck, 1949a,b) to form sulfenic acid (R-SOH) (Block, 1992). Which immediately condenses to form allicin: the compound which produces the odor of fresh-cut garlic? Garlic contains at least 100 sulfur-containing compounds basic to medicinal uses (Lawson, 1993; Cai *et al.*, 1994; Srivastava *et al.*, 1995). Allicin represents 70-80 % of the total thiosulfinates formed (Fig. 1). Other thiosulfinates formed include allyl-ss(o)-methyl (6-16% of total), methyl-ss(o)-allyl (3-9% of total), trans-1-propenyl (0.2-0.4% of total), trans-1-propenyl-ss (o)-methyl+methyl-ss(o)-trans-1-propenyl (0.1-2.5% of total) and methyl-ss(o)methyl (2% of total) thiosulfinates (Lawson *et al.*, 1991b). The formation of allicin (allyl 2-propene thiosulfinate or diallyl thiosulfinate) is complete in 0.2 to 0.5 min at room temperature. Formation of the methyl thiosulfinate takes 1.5 to 5.0 min (Lawson & Hughes, 1992). All possible combinations of 2-propene, 1-propene and methane sulfenic acids result in thiosulfinates (Lawson *et al.*, 1991a,b).

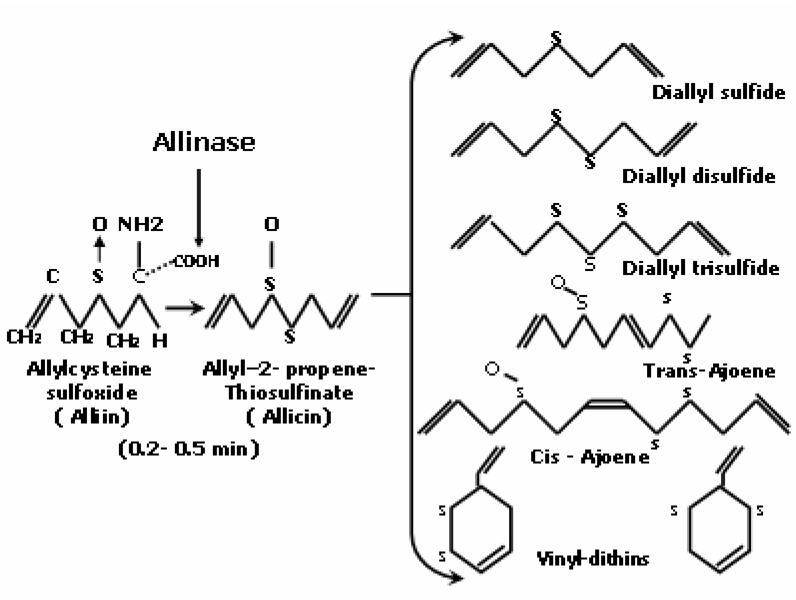

Figure 1. Conversion of alliin to allicin by the enzyme allinase, and of allicin into various sulphur-containing compounds.

The thiosulfinates released from crushed garlic are reactive molecules and undergo a number of transformations, depending on the temperature, pH and solvent conditions. Allyl-s- thiosulfinates (allicin) are the least stable of the eight thiosulfinates (Block, 1992; Lawson & Block, 1997). The half-life of allicin (concentration of 0.1-0.4mg/ml) at room temperature is 10 days in 1mM citric acid (pH 3), 4 days in water, 48 h in methanol or chloroform, 24 h in ethanol, 24 h in hexane and 3 h in ether (Lawson, 1993).

The principal transformation products after incubation of thiosulfinate in water are diallyl trisulfide, diallyl disulfide and allyl methyl trisulfide (Block, 1992). Incubation of allicin or allyl methane thiosulfinate in low polarity solvents (or without solvent) primarily produces 1, 3-vinyldithiin (2-vinyl-4H-, 3-dithiin) (51% of total), 1,2-vinyldithiin (3-vinyl-4H-1,2-dithiin) (19% of total) and lesser amounts of ajoene (E,Z-4,5,9-trithiododeca-1,6,11-trien 9-oxide) (12% of total) and sulfides (18% of total) (Fig. 1). Incubation of pure allicin in methanol yieldes 8% diallyl trisulfide and about equal amounts (20-25% of total) of ajoene and the vinyldithiins (Lawson *et al.*, 1991a; Lawson, 1993). Steam distillation of garlic bulbs yields a garlic oil that consists of diallyl (57% of oil), allyl methyl (37% of oil), and dimethyl (mono to hexa sulfides; 6% of oil of total) (Lawson, 1993). The essential oil content of fresh garlic bulbs is between 0.09 to 0.35 % (Lutomski, 1987).

3. Biological Effects

The biological activity of an extract of garlic depends on the mode of its preparation. The extract prepared at room temperature contains mainly allicin, which has a powerful antibacterial property and a strong smell. Besides allicin, small amounts of several other thiosulfinates and complex sulphinyl components, including the antithrombotic ajoenes, are also present. The enzyme allinase responsible for converting alliin to allicin is inactivated by heat. The water extract of heat-treated garlic mainly contains alliin, which is odour-free. Garlic powder is a simply dehydrated, pulverized garlic clove. The allinase activity of garlic powder is identical to that of fresh garlic. It may be emphasized here that dehydration temperature should not exceed 60 ºC, above which allinase is inactivated (Lawson, 1998). When distilled in steam, garlic yields an oily mass consisting of diallyl, methyl allyl, dimethyl, all originating from the thiosulfinates (Lawson *et al.*, 1991a; Lawson & Hughes, 1992). Garlic oil has been shown to possess biological properties such as antitumor and antioxidant effects (Sumiyoshi & Wargovich, 1989). Another widely studied garlic preparation is aged garlic extract (AGE). When garlic is subjected to cold aging process, organosulphur compounds, such as s-allyl cysteine, s-allyl mercaptocysteine, and several sulphur-containing amino acids, are produced. S-allyl cysteine and s-allyl mercaptocysteine have been shown to be anticarcinogenic and provides protection against liver damage (Srivastava *et al.*, 1995).

Garlic is one of the most investigated medicinal plants. During 1960 to 2007, more than three thousand research papers have been published on the chemistry and biological effects of garlic and garlic preparations. These studies mainly focus on the cardiovascular, anti-microbial and anti-cancer effects of garlic and, to a lesser extent, on the therapeutic indications for the treatment of hypoglycemia, heavy metal poisoning and liver dysfunction and hyperthyroidism (Lawson, 1993; Singh, 1995; Agarwal,

Table 1. Active constituents of garlic and their pharmacological actions.

Active component of garlic	Anti-biotic	Anti-fungal	Hyper-lipidemia	Anti-platelet aggregation	Anti-cancer	As a pesticide
alliin			+	+		
allicin	+	+	+	+	+	+
allixin					+	
adenosine				+	+	
Allyl1,5-hexadienyl trisulphide				+	+	
Allyl methyl trisulphide				+	+	
s-allyl2-pro pene thiosul phinate				+		
ajoene	+	+		+	+	+
Diallyl disulfide	+		+	+	+	+
1,5-hexa dianyl trisulfide				+		
Methyl allyl trisulfide				+		
2-vinyl 1,3- dithiene				+		
3-vinyl 1,3- dithiene				+		
S-allyl merc aptocysteine					+	
Se-methyl selenocysteine					+	
Allyl propyl disulfide			+			
Sodium 2-propenyl thiosulphinate				+		
s-methyl1- cysteine sulfoxide			+			

1996; Augusti, 1996; Block, 1998; Tahiliani & Kar, 2003; Mohamed *et al.*, 2006; Eidi *et al.*, 2006; Murugavel *et al.*, 2007). Reuter & Sendl (1995), Srivastava *et al.* (1995), Augusti (1996), Ross (1999), Warber (1999), Harris *et al.* (2001), Morbidoni *et al.* (2001), Ichikawa *et al.* (2003), Stephen (2005), Ariga & Seki (2006) and Nies *et al.* (2006) have reviewed the pharmacology and medicinal application of garlic isolated compounds for the treatment of a number of diseases (Table 1).

3.1. Antimicrobial activities

Garlic has a reputation as a cure for a variety of bacterial and fungal diseases. Louis Pasteur (1858) and Lehmann (1930) provided the first modern scientific evidences for medicinal and anti-bacterial use of garlic extract. Garlic has been observed to possess antiviral, antibacterial and antifungal activities (Cavallito & Bailey, 1944; Cavallito *et al.*, 1944; Johnson & Vaughn, 1969; Nagai, 1973; Appleton & Tansey, 1975; Tansey & Appleton, 1975; Tynecka & Gos, 1975; Sharma *et al.*, 1977; Yamada & Azuma, 1977; Amer *et al.*, 1980; Caporaso *et al.*, 1983; Elnima *et al.*, 1983; Lau *et al.*, 1983; Tutakne *et al.*, 1983; Adetumbi *et al.*, 1986; Yoshida *et al.*, 1987; Srivastava *et al.*, 1995; Lee *et al.*, 2003; Kim *et al.*, 2004; Konaklieva & Plotkin, 2006). Cavallito & Bailey (1944) had demonstrated that garlic juice diluted to one part in 125,000 inhibits the bacterial growth of *Staphylococcus*, *Streptococcus*, *Vibrio* (including *V. cholerae*) and *Bacillus* (including *Bacillus typhosus*, *B. dysenteriae* and *B. enteritidis*). Johnson & Vaughn (1969) reported that 10 % extract of dehydrated garlic bulb demonstrated antibactericidal action against *Salmonella typhimurium* and *Escherichia coli* within 2 to 6 h exposure. Crude extract of garlic has proven to be quite effective against both gram-negative and gram-positive bacteria. Bacterial cultures resistant to the commonly used antibiotic chloramphenicol appear sensitive to garlic. Jezpwa *et al.* (1966), Adetumbi & Lau (1983), Khan *et al.* (1985), Hughes & Lawson (1991), Ahsan & Islam (1996), Tsao *et al.* (2003) and Zhou (2003) observed that preparation of fresh garlic and vacuum dried powdered garlic preparations were effective against *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus haematyticus*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Escherichia coli*, *Salmonella enteritidis*, *Bacillus subtilis*, *B. megaterium*, *B. pumitus*, *B. mycoides*, *B. thuringiensis*, *Sarcina lutea*, and *Serratia marcescens.* Al-Waili Saloom *et al.* (2007) investigated that heating, storage and ultraviolet exposure of fresh garlic juice significantly inhibited its antimicrobial activity against common human pathogens. Hughes & Lawson (1991) observed allicin, methyl allylthiosulfinates and allylmethylsulfinates, constituents in aqueous garlic clove and powder homogenate, had *in vitro* anti-bacterial activities while polar compound alliin did not. Allicin and allyl-methyl plus methyl-allyl thiosulfinate have shown inhibition of the *in vitro* growth of *Helicobacter pylori*, the bacterium responsible for serious gastric diseases as ulcer and even gastric cancer (Canizares *et al.*, 2004a,b). Sasaki & Kita (2003) reported the antibacterial activity of garlic powder against *Bacillus anthracis*. A 1% water solution of garlic powder in the test tube method killed *B. anthracis* within 3 h of treatment at room temperature. Barki & Douglas (2005) and Groppo *et al.* (2007) observed that garlic extract inhibits the growth of oral pathogens and certain proteases and thus it may have therapeutic value, particularly for periodontitis.

Anti-fungal activity of garlic extract has been demonstrated in 40 species of zoopathogenic fungi, retarding the growth in 8 of 15 genera tested (Appleton & Tansey, 1975; Shadkchan *et al.*, 2004; Ledezma & Apitz-Castro, 2006). In a comparison of the fungistatic activity of garlic extract with nystatin, griseofulvin and amphotericin B, garlic had a broad-spectrum activity against 17 strains of fungi, including the dermatophytes, yeasts, *Aspergillus* and *Penicillium*. Garlic was more effective than nystatin in retarding growth of the fungi (Srivastava, 1984). Barone & Tansey (1977) and Yamada & Azuma (1977) demonstrated that allicin in aqueous extract of garlic bulbs was the major anticandida constituent. Aqueous extract of garlic is inhibitory and lethal to numerous strains of *Cryptococcus neoformans* (Fromtling & Bulmer, 1978). In China, garlic is used frequently to treat fatal form of *Cryptococcal meningitis* (Abdullah *et al.*, 1988). Singh & Singh (1997) observed that water extract of garlic inhibits the growth of certain fungi that can cause meningitis. An aqueous extract of garlic has been demonstrated to inhibit the growth of several zoopathogenic fungi such as *Candida albicans*, commonly involved in vaginitis, *Histoplasma capsulatum*, a fungus that produces a disease similar to tuberculosis and fungi that cause athletics' foot and ringworm (Srivastava *et al.*, 1995). Yoshida *et al.* (1987), in studying the antifungal activity of different purified fractions of garlic against *Aspergillus niger* and *Candida albicans*, have observed that ajoene has stronger activity than allicin. Adetumbi & Lau (1986) have reported that an aqueous extract of dehydrated garlic preparation inhibits the growth of the dimorphic fungus *Coccidioides immitis* and inhibits *in vitro* fungal spore germination. Adetumbi *et al.* (1986) and Lemar *et al.* (2002) reported that reduction of *Candida albicans* growth by the aqueous garlic extract is due to the inhibition of nucleic acid, protein and lipid syntheses. Stephen (2005) reported that the breakdown products of allicin, the main parent antifungal compound in garlic, have a common mode of action against antimicrobial, anticancer and anticholesterol properties. Some of the breakdown products of allicin cross cell membranes and combine with sulfur-containing molecular groups in amino acids and proteins, thus interfering with cell metabolism. Human cells are not poisoned by allicin derivatives as they contain glutathione, a sulfur-containing amino acid that combines with the allicin derivative, thus preventing cell damage (Stephen, 2005). Allicin synergized the fungicidal activity of Cu^{2+} ions against various strains of fungus (Ogita *et al.*, 2006). Allicin treatment caused Cu^{2+} solubilization complexation with a plasma membrane protein.

Nagai (1973) reported *in vivo* antiviral effect of garlic in mice against intranasally-inoculated influenza virus. The garlic extract also enhances the production of neutralizing antibody if inoculated with the influenza vaccine (Nagai, 1973). Investigation on *in vitro* activity of garlic against selected viruses, including herpes simplex virus type[1] and type[2], parainfluenza virus type[3], vaccinia virus, vesicular stomatitis virus and human rhinovirus type[2], demonstrated that certain garlic constituents - (viz.) ajoene, allicin, allyl methyl thiosulfinate, methyl allyl thiosulfinate - are potent virucides (Weber *et al.*, 1992). Josling (2001), on the basis of his study on 146 volunteers, reported that an allicin containing garlic supplement can prevent the infection of common cold virus. Diallyl trisulfide in garlic bulb has anti-human cytomegalovirus (anti-HCMV) activity and the mechanism is associated with suppression of ie gene transcription (Zhen *et al.*, 2006).

3.2. Garlic and cardiovascular diseases

The medicinal effect of garlic and garlic extracts on cardiovascular diseases has been widely studied. Preparations of garlic and chemical constituents of garlic have been investigated for possible effects on cardiovascular diseases such as hyperlipidemia, hypertension, platelet aggregation and blood fibrinolytic activity (Kendler, 1987; Lawson *et al.*, 1992; Isensee *et al.*, 1993; Isaacsolin *et al.*, 1998; Koscielny *et al.*, 1999; Mantawy & Mahoud, 2002; Gardner *et al.*, 2003; Siegel *et al.*, 2004).

3.2.1. Hypocholesterolaemic action

Most of the studies on the effects of garlic on blood lipids in patients with cardiovascular disorders have been carried out in India. Intake of high-fat meals causes a significant increase in serum triglyceride and cholesterol levels (Groot & Scheck, 1984). Observations suggest that use of garlic (and onion as well) prevents the hypercholesterolemia induced by high-fat meal (Jain & Andleigh, 1969; Bordia & Bansal, 1973; Sainani *et al.*, 1979; Mirhadi & Singh, 1991; Elkayam *et al.*, 2003). Augusti (1977) and Bhushan *et al.* (1979) reported that eating of 10 g fresh garlic per day for 2 months significantly decreases (15%-28.5%) serum cholesterol levels among hypercholesterolemic patient. Sainani *et al.* (1979) compared vegetarians, with different eating habits with regards to the use of onions and garlic. Group I consumed onion and garlic in liberal amounts (50 g garlic and 600 g onion per week); Group II consumed small amount of onion and garlic (10 g garlic and 200 g onion per week), and Group III totally abstained from the use of garlic and onion. The level of cholesterol, triglyceride, phospholipid and ß- lipoproteins were the lowest in the individuals consuming liberal amounts of garlic and onion. These results indicate that routine consumption of onion and garlic in the diet has a beneficial effect in maintaining the serum lipids at low or normal levels.

Total serum cholesterol is an important factor in the development of ischemic heart disease (IHD). Cholesterol present in the ß-lipoprotein (LDL, Low density lipoprotein) and pre-ß-lipoprotein (VLDL, Very low density lipoprotein) fractions finds its way into the arterial wall, whereas ∝-lipoprotein (HDL, High density lipoprotein) cholesterol helps to reduce the serum cholesterol level. Increase in HDL/LDL ratio is a preventive effect of the development of IHD. Jain (1977) and Bordia (1981) observed that consumption of 0.25 mg/kg garlic oil caused a steady decrease in LDL+VLDL levels with concomitant increase in HDL levels. Ernst *et al.* (1985), Orekhov *et al.* (1995), Efendy *et al.* (1997) and Ide *et al.* (1997) have observed that the aged garlic extract, aqueous extract from garlic powder, and its constituents lower serum cholesterol level and inhibit the oxidative modification of LDL, and thus is presumed to have a protective effect against atherosclerosis.

Gebhardt (1993) reported the multiple inhibitory effects of garlic extracts at several different steps in cholesterol biosynthesis pathway in human Hep G_2 cells. According to him, defined compounds (allicin) present in water soluble extracts of garlic inhibit the biosynthesis of cholesterol in hepatocytes, thus contributing to the reduction of serum cholesterol. Garlic derived components are capable of combining with the sulphydryl (-SH) group (Augusti & Mathew, 1974; Block, 1985). Reduced conversion of acetate into cholesterol has been observed both *in vivo* and *in vitro* (Chang & Johnson, 1980; Saxena *et al.*, 1980). As -SH groups are involved in several metabolic pathways, it may be inferred that garlic besides inhibiting lipid synthesis (Eilat *et al.*, 1996) would affect other metabolic activities as well (Srivastava *et al.*, 1995). Larner (1995) proposed the tellurium hypothesis of hypocholesterolaemic action of garlic. Accordingly, tellurium compounds found in high concentration in fresh garlic bulb may contribute to hypocholesterolaemic action by inhibiting squalene epoxidase, the penultimate enzyme in the synthetic pathway of cholesterol. Oxidation of LDL plays an important role in the initiation and progression of atherosclerosis. Yamaji *et al.* (2004) suggested that use of egg-yolk-enriched garlic powder (EGP) has antiatherogenic effect. EGP inhibits copper-induced LDL oxidation in a dose-dependent manner. Use of EGP significantly suppressed the production of peroxides in HL 60 cells and protects endothelial cells from hydrogen peroxide-induced cell injury. Sumioka *et al.* (2006) reported that Monascus garlic fermented extract (MGFE) attenuates hyperlipidemia suggesting that it is a potent agent for preventing arteriosclerotic diseases. Intake of enteric-coated garlic powder (equal to 400 mg garlic, 1mg allicin) twice daily has significantly reduced total cholesterol, LDL-cholesterol and triglyceride and increased HDL-cholesterol (Kojuri *et al.*, 2007).

3.2.2. Hypotensive effect

High blood pressure is one of the major risk factors of atherosclerosis (Srivastava *et al.*, 1995). The hypotensive effect of garlic was recognized by Loeper & Debray (1921). Damrau (1941) gave two Allimin tablets containing 4.75 g of garlic concentrate (equivalent to about 0.31 g of desiccated garlic and 2.375 g of desiccated parsley) to 26 hypertensive patients three times daily for three days. Blood pressure reduction was observed in 85% of the patients: the average decline in systolic and diastolic blood pressure was 12.3 mm Hg and 6.5 mm Hg, respectively. He also reported that headache was relieved in 14 of the 17 patients complaining of the symptom, and dizziness was cured in 12 of 13 patients and improvement was observed in remaining patient.

For centuries garlic has been used against hypertension in China and Japan and is recognized officially for this treatment by the Japanese food and drug administration (Bolton *et al.*, 1982). Piotrowski (1948), Papayannopoulos (1969), Srinivasan (1969) and Anonymous (1986) have also demonstrated garlic's antihypertensive effect. Pectov (1979) cited several studies on hypotensive effect of garlic from the Soviet Union and Bulgaria. Aqel *et al.* (1991) suggested that hypotensive action of garlic juice may be due to a direct relaxant effect on smooth muscles. Although components of garlic do exert pharmacological and therapeutic effects on hypertension (Srivastava *et al.*, 1995), the nature of the garlic component responsible is not known. Andrianova *et al.* (2002) observed that allicor treatment of 600 mg/day produced reduction in both systolic and diastolic blood pressure.

3.2.3. Antiplatelet aggregation activity

More recent literature suggests possible beneficial effects of garlic and its extract in preventing atherosclerotic disease. Reuter *et al.* (1974) and Lutomski (1987) demonstrated that adenosine, a compound in high concentration (0.056%) in garlic, inhibits aggregation of platelet and improves blood flow in the coronary vessels. Investigations have shown that garlic oil could inhibit platelet aggregation (Mohammad *et al.*, 1980; Mohammad & Woodward, 1986; Srivastava & Justesen, 1989) and ether extract of garlic juice taken with a fatty diet could decrease cholesterol and fibrinogen and increase fibrinolytic activity and blood coagulation time. Garlic can lead to a decrease in thrombocyte aggregation in blood (Bordia *et al.*, 1977; Srivastava, 1984, 1986; Harenberg *et al.*, 1988; Jung *et al.*, 1989; Kiesewetter *et al.*, 1991; Lawson, 1993; Srivastava & Tyagi, 1993; MacDonald *et al.*, 2004). Srivastava & Mustafa (1993) reported that several mechanisms are involved in garlic-induced inhibition of platelet aggregation. These effects are the modification of platelet membrane properties, inhibition of calcium mobilization, and inhibition of several steps of the arachidonic acid cascade in platelets. In fact, a direct inhibitory effect of garlic extracts and its components on the enzymes of the arachidonic acid cascade have been reported (Srivastava, 1984; Srivastava & Justesen, 1989; Makheja & Bailey, 1990; Wagner *et al.*, 1991). Day *et al.* (1976) reported that several biochemical agents such as adenosine diphosphate (ADP), collagen, epinephrine, arachidonate and especially thromboxane-A elevate platelet aggregation. Bordia *et al.* (1978) observed that garlic caused a dose dependent inhibition of platelet aggregation induced by ADP, epinephrine and collagen. Both aqueous and organic extracts of garlic inhibit platelet aggregation induced by arachidonic acid, ADP, adrenaline, collagen, calcium ionophore A23187 and thrombin (Apitz-castro *et al.*, 1983; Srivastava, 1984; Srivastava & Justesen, 1989).

Makheja & Bailey (1990) reported that adenosine is one of the most important ingredients of garlic bulb. About half of the anti-platelet activity of garlic has been attributed to adenosine. They also reported that adenosine and allicin present in garlic inhibited platelet aggregation without altering arachidonic acid (AA) metabolism in platelets. Lawson *et al.* (1992) reported the antiaggregatory activity of different garlic preparations. In platelet rich plasma most of the antiaggregatory activity of garlic clove homogenates was due to adenosine; however, in whole blood the antiaggregatory activity was due to allicin and other thiosulfinates. Garlic powder tablets were equally as active as clove homogenates, whereas steam distilled oils and oil macerates only 35% and 12%, respectively. In steam distilled oils most of the activity was due to diallyl trisulfide. For the oil macerates, most of the activity was due largely to the vinyldithiins. Polysulfides, such as diallyl trisulfide (Srivastava & Mustafa, 1993) and dimethyl trisulfide (Makheja & Bailey, 1990), are shown to be antiaggregatory and altered AA metabolism. Inhibition of platelet aggregation ultimately decreases atherosclerosis and thrombosis (Mirhadi & Singh, 1991). Kiesewetter *et al.* (1991) observed that intake of 800 mg of garlic powder over a period of 4 weeks caused disappearance of thrombocyte aggregation, increased microcirculation of the skin by 47.6% and decreased plasma viscosity by 3.2%; decreases in diastolic blood pressure by 9.5% and blood glucose concentration by 11.6% were also observed. Jung *et al.* (1990) investigated that single intake of 900 mg garlic powder (corresponds to 2700 mg fresh garlic) by healthy subjects caused no change in blood pressure and heart rate. Jung *et al.* (1991) reported that five hours after intake of 900mg garlic powder caused a significant increase in capillary skin perfusion by 55%. It causes minimal vasodilation and significant reduction in haematocrit and plasma viscosity. Apitz-Castro *et al.* (1983) reported that methanol extract of garlic and some pure fractions inhibited platelet aggregation. The antiplatelet property of garlic is especially due to one of its components (E) and (Z)-ajoene, which perturbs membrane by lodging itself deep between the two monolayers of plasma membranes of the intact platelets. Jain & Apitz-Castro (1987) reported that ajoene did not alter AA metabolism in intact platelets. It is of interest to note that ajoene was shown to potentiate synergistically the antiaggregatory effects of prostacyclin, forskolin, indomethacin and dipyridamole (Apitz-castro *et al.*, 1986). Chang *et al.* (2004) identified sodium 2-propanyl thiosulfinate (2PTS) from boiled garlic, which significantly inhibits ADP-induced platelet aggregation at 0.1 mM in human platelets. In contrast, the maximal aggregation percentage returned to normal level at 1mM of alk (en) yl thiosulfinate in human platelets, suggesting that 2PTS has the potential to promote immune function and prevents cardiovascular diseases. Cavagnaro *et al.* (2007) suggest that processing of garlic and the conditions used for cooking can markedly influence its effectiveness as a platelet inhibitor. They are of the opinion that crushing garlic before moderate cooking can reduce the loss of antiplatelet activity.

3.3. Anticancer potential

Garlic is one of the most ancient spice plants reputed to have an effect on cancer. As recorded around 1550 B.C. in the Ebers Papyrus, garlic was applied externally for the treatment of tumors by ancient Egyptians and internally by Hippocrates and Indian physicians (Hartwell, 1967, 1968).

Interestingly, China provides an ideal "Field Laboratory" for epidemiological studies of cancer incidence. Stomach cancer was found to rank higher for males and females in cancer mortality (Wang *et al.*, 1985; Lau *et al.*, 1990) than other cancer incidence in China (Mei *et al.* 1982). They suggested that consumption of garlic may have inhibited nitrate reduction by bacteria. Subsequently, the lower gastric nitrite (a nitrosamine precursor) concentration may reduce the risk of developing stomach cancer. You *et al.* (1989) identified that cigarette smoking, use of salty foods and moldy grains are associated with increased risk of stomach cancer. A significant reduction of stomach cancer risk was found to be associated with increasing consumption of garlic, scallicens and Chinese chives (You *et al.*, 1988). Galeone *et al.* (2006) investigated the role of allium's vegetables in the etiology of various neoplasms. They analyzed the relation between frequency of onion and garlic use and cancer at several sites of Italian and Swiss case-control studies. They reported an inverse relationship between the frequency of use of garlic and the risk of several common cancers. Abdullah *et al.* (1988) observed that natural killer-cells of raw garlic and aged group destroyed 139% and 159% more tumor cells than those from the control group. Aged garlic extract is a good chemopreventive agent for colorectal cancer. Aged garlic extract could prevent tumour formation by inhibiting angiogenesis through suppression of endothelial cell mortality, proliferation and tube formation (Matsuura *et al.*, 2006).

Aflatoxins are naturally occurring toxic metabolites produced by *Aspergillus flavus* and related fungi. Among the 16 or more toxic compounds secreted by these fungi, aflatoxin B_1 (AFB_1) is most potent in causing mutations in various microorganisms as well as mammalian and human cells. It is both toxic and hepato-carcinogenic to a variety of animals and humans in Asia and Africa (Stolooff, 1976; Wong & Hsieh, 1976; Perkin *et al.*, 1988). Tadi *et al.* (1991a,b) reported that two organosulfur compounds of garlic, ajoene and dially sulfide affected AFB_1 metabolism and DNA binding by inhibiting phase I enzymes and, therefore, act as potential cancer chemopreventive agents.

Garlic is one of the best natural sources of germanium. It is of interest to note that this trace metal has also been reported to prevent and cure cancer. Garlic is also an excellent source of selenium, which has potential therapeutic value in cancer treatment (Bolton *et al.*, 1982; Lawson, 1993). Se-methyl selenocysteine is the major seleno-compound in garlic bulb. Epidemiological studies have indicated a negative relationship between selenium intake and the incidence of certain cancers. Blood or plasma levels of selenium are usually lower in patients with cancer than those without this disorder. In mammary tumour model, se-methyl selenocysteine was shown to be most effective seleno-compound so far in reduction of tumours (Whanger, 2004).

Although garlic has been shown to be chemopreventive against cancer, its mode of action is not fully understood. Several mechanisms have been suggested. A potential carcinogen may exert its effects by producing nuclear damage. Wargovich & Goldberg (1985) studied the effect of a sulfide and disulfide component of garlic on several chemical carcinogens. DMH (1,2-dimethyhydrazine) and NMBA (N-nitroso methyl benzylamine) are procarcinogens, which are metabolized in the liver to carcinogenic metabolites, an effect mediated by their binding to the nucleus. Pre-administration of diallyl sulfide prevented nuclear damage induced by DMH and NMBA. These observations suggest that diallyl sulfide might inhibit the conversion of procarcinogens to ultimate carcinogens, an important factor of the initiation phase of carcinogenesis. Chung *et al.* (2002) observed that garlic juice reduced endogenous formation of carcinogens N-nitrosodimethylamine (NDMA) in young human. Recently, Singh *et al.* (2006) have reported that consumption of garlic powder induced a 35-60% reduction in DNA damage induced by NDMA in rat.

Glutathione-s-transferase (GST) is an important enzyme that conjugates electrophils and assists in the detoxification of many carcinogens. Compounds that increase GST activity have been found to inhibit carcinogen induced neoplasia (Wattenberg, 1983; Sparnin *et al.*, 1988). Oral administration of methyl trisulfide and diallyl disulfide stimulated glutathione-s-transferase activity, which increased with time and showed a time lag of 18 h or more (Sparnin *et al.*, 1986; Sumiyoshi & Wargovich, 1989). These studies suggest that stimulation of glutathione-s-transferase activity in the liver and other target organs of carcinogens by garlic derived organosulphur compounds may be responsible for their protective effects in chemical carcinogenesis and on different stages of carcinogenesis.

Oxygen radicals may play a role in tumor promotion. Various anti-oxidants, trace radicals, scavengers, stimulation of super oxide dismutase, glutathine peroxidase inhibitors of cyclooxigenase and lipooxygenase enzymes were found to modulate the oxidative stress and the formation of molecular species involved in tumor promotion. Perchellet *et al.* (1986) demonstrated garlic oil stimulated glutathione peroxidase activity, and inhibited the decrease in the intracellular ratio of reduced to oxidize glutathione produced by TPA in epidermal cells. Garlic oil was also found to inhibit lipooxigenase enzymes, which is involved in TPA-stimulated arachidonic acid metabolism (Block *et al.*, 1988). Li *et al.* (1995) investigated the effect of aged garlic extract (AGE) and two of its components, s-allylcysteine (SAC) and s-allyl mercaptocysteine (SAMC), on human breast cancer cells MCF-7 and MCF-7-s. They observed an anti-proliferative response to SAC and SAMC and an alteration in glutathione level without significant concurrent changes in the glutathione metabolizing enzymes. Xiao *et al.* (2003) found that SAMC exerts anti proliferative effects by binding directly to tubulin and disrupting the microtubule assembly, thus arresting cells in mitosis and triggering JNK_1 and caspase-3 signaling pathways that lead to apoptosis.

Xu *et al.* (2004) reported a novel aspect into the understanding of the molecular mechanism of potential antitumor action of ajoene. Ajoene-treated leukemia cell line HL60 cells were arrested in G(2)/M phase and total amount of cytosolic proteasome increased. Proteasome plays a key role in the regulation of many cellular processes. Oommen *et al.* (2004) found that allicin inhibited the growth of cancer cells of murine and human origin. Allicin induced the formation of apoptotic bodies, nuclear condensation and a typical DNA ladder in cancer cells. They have observed that allicin activate the caspases-3,-8 and –9 and cleavage of poly (ADP-ribose) polymerase. Xiao *et al.* (2006) have observed that diallyl trisulfide found in garlic bulb induces apoptosis in PC-3 human prostate cancer cell by induction of protein Bax and Bak. Chu *et al.* (2006) studied the effect of garlic derivatives S-allylcysteine and S-allylmercaptocysteine on the inhibition of cancer cell invasion through restoration of E-cadherin expression. They suggest that these compounds might be potential therapeutic agents for suppressing androgen-independent prostate cancer.

It seems that garlic derived organosulfur compounds could have effects on different stages of carcinogenesis. It is now recognized that a wide range of human cancer, perhaps as many as 80-90% is attributed to environmental factors (Doll, 1977; Doll & Peto, 1987). Garlic has been shown to inhibit growth of transplantable tumors and to reduce the incidence of certain spontaneously occurring tumors. Components of garlic also inhibit the activity of diverse chemical carcinogens during both the initiation and promotion phases of carcinogenesis (Lau *et al.*, 1990; Tadi *et al.*, 1990; 1991a,b; Milner, 1996).

Kodera *et al.* (1989) isolated a new allixin (phytoalexin) synthesized by garlic. Being a phenolic compound, it is an effective inhibitor of phospholipid metabolism stimulated *in vitro* by the tumor promoter. Yamasaki *et al.* (1991) observed that allixin plays an important role in cancer prevention. Lau *et al.* (1991) and Patya *et al.* (2004) studied the effect of organosulphur compounds of garlic on the growth of animal tumors. According to Patya *et al.* (2004), allicin exhibits immune-stimulatory and antitumor properties. Immune stimulatory effect of allicin is mediated by redox-sensitive signaling such as activation of p2(ras). The antitumor effect of allicin is related to its immune-stimulatory properties. Allicin inhibits the apoptosis of macrophages in depleted nutritional state through the mitogen-activated protein kinase/extra cellular signal-regulated kinase pathway (Cho *et al.*, 2006). Druesne *et al.* (2006) observed that diallyl disulfide (DADS) found in garlic bulb inhibits colon tumor cell proliferation. They suggest that 200 µM of DADS increases histone acetylation, CDKN1A mRNA and p21 (waf1) protein levels and induces G2/M cells cycle arrest in tumor cells. Agarwal *et al.* (2007) observed that pretreatment of rats with 50-100 mg garlic oil/kg body weight for a week significantly protects free radical injury and cancer in kidneys induced by ferric nitrilotriacetate (Fe-NTA). This is due to the inhibition of hepatic tumour markers viz., ornithine decarboxylase activity and DNA synthesis. It is therefore obvious that the organosulphur compounds of garlic extend their protective anti-cancer effects in three ways: (i) a direct inhibition of tumor cell metabolism; (ii) inhibition of the initiation and/or promotion phases of carcinogenesis; and (iii) modulation of the host response by augmenting macrophages and T-lymphocytes function.

3.4. Garlic as a pesticide

Effective pesticides have been developed from garlic extracts. Field trials carried out on mosquito breeding sites at Bombay (now Mumbai, India) have shown that garlic oil is very effective on several species of mosquitoes. Amonkar & Reeves (1970) studied the toxic effect of crude methanolic extract and garlic oil against 3rd stage of larvae of *Culex peus*, *C. tarsalis*, *Aedes aegypti*, *A. trisoriatus*, *A. sirensis* and 3rd and 4th stage larvae of highly insecticide resistant strains of *A. nigromaculis*. They reported that partially purified oil fraction was more toxic than the crude extract. Later, the larvicidal principles of garlic oil have been isolated and identified as diallyl disulfide and diallyl trisulfide (Amonkar & Banerji, 1971). Allicin inhibited malaria infection by inhibiting cysteine protease, which processed circumsporozoite protein (CSP) of *Plasmodium sporozoites* for invasion of host cells (Coppi *et al.*, 2006). These compounds were fatal to *Culex pipiens quinquefasciatus*. Nakagawa *et al.* (1980) reported that raw garlic juice at a dose 5 ml/kg body weight caused death of rats due to stomach injury. Gupta & Sharma (1993) have observed that root-dip treatment for tomato seedlings in 25 ppm allicin for 5 min is effective against nematode *Meloidogyne incognita*. Concentration of 200 and 100 ppm allicin as bare-root dips for 30 min killed 83% and 87% of *M. incognita* of tomato seedlings, respectively. Gareth *et al.* (2006) reported that the insecticidal activity of garlic juice in two dipterian pests *Delia radicum* (LC_{50} - 0.4%) and *Musca domestica* (LC_{50}- 2.2%). They reported that garlic juice is effective against all the life stages of both insects.

Ajoene, the major bioactive compound derived from garlic, showed a potent leishmanicidal activity in *in vitro* against *Leishmania mexicana* and *L. donovani* (Ledezma *et al.*, 2002). The 50% inhibitory concentration (IC_{50}) for lysis was about 2 μM. They reported that leishmanicidal activity of ajoene is due to the morphological alteration of the mitochondrial membrane and nuclear envelope, as well as the formation of large autophagic vacuoles. Gamboa-Leon *et al.* (2006) suggest that garlic extract has mild protective effect against *Leishmania donovani*. This might be due to unspecific enhancement of interferon-gamma secretions. The homopteran sucking insect *Lipaphis erysimi* (mustard aphid) causes severe damage to various crops. This pest not only affects plants but it also transmits single-stranded RNA luteoviruses while feeding, which cause disease and damage in the crop. The mannose-binding garlic leaf lectin has been found to be a potent control agent of *L. erysimi* on one hand and on the other symbionin mediated luteovirus transmission (Banerjee *et al.*, 2004).

Singh & Singh (1993) reported that the water extract of garlic bulb is a potential source of molluscicide against *Lymnaea acuminata* and *Indoplanorbis exustus*. These snails are the intermediate host of liver fluke *Fasciola hepatica* and *F. gigantica*, which causes 94% fascioliasis in the buffalo's population of northern India (Singh & Agarwal, 1981; Singh & Agarwal, 1983). Singh & Singh (1995) characterized that allicin is the main molluscicidal component of garlic. The toxicity of allicin (LC_{50} - 3.64 mg/l) at 96 h exposure is 4.1, 4.2 and 2.5 times higher with respect to synthetic molluscicides (phorate, carbaryl and formothion, respectively) (Singh & Agarwal, 1983). There was a progressive increase in the toxicity (8.67 fold) of garlic bulb extract against *Lymnaea acuminata* in the pre-harvest (2 to 5 months) period while in the post-harvest period (5 to 11 months) it was 5.5 fold (Singh & Singh, 1996a). Significant increase in toxicity of pre-harvest garlic is due to increase in level of alliin. Increase in molluscicidal activity of garlic in post harvest period is due to some changes in the chemical composition of garlic bulb (Lawson *et al.*, 1991b). Singh & Singh (1996b) demonstrated that the treatment of snail with sublethal concentrations of allicin caused a significant inhibition of acetylcholinesterase (AChE), lactic dehydrogenase (LDH) and alkaline phosphatase (ALP) activity in the nervous tissue of *Lymnaea acuminata*. Kinetic studies demonstrated that the inhibition of AChE by allicin was uncompetitive whereas inhibition of LDH and ALP was competitive (Singh & Singh, 1996b). Inhibition of this enzyme by allicin in the nervous tissue of snail *L. acuminata* may be the cause of the molluscicidal action of garlic.

Singh & Singh (1997), Singh *et al.* (1998), Singh & Singh (2000a,b), Singh & Singh (2001a,b) and Tripathi & Singh (2001) have reported that combinations of garlic bulb powder with *Cedrus deodara* oil, *Annona squamosa* seed, *Lawsonia inermis* seed, *Punica granatum* bark, *Canna indica* root powder, piperonyl butoxide and MGK-264 are very effective molluscicide. These combinations were effective in reducing the fecundity, hatchability and survival of young snails (Singh & Singh, 2004). Singh & Singh (2000b) have clearly demonstrated that these effects of garlic powder were due to inhibition of certain enzymes and alteration in brain biogenic amine levels in the nervous tissue of *L. acuminata*. Mantawy & Mahmoud (2002) observed that glucose and glycogen levels and phenol oxidase activity in snail *Biomphalaria alexandrina* were significantly decreased after 2 and 7 day of feeding on garlic, which ultimately reduced the fecundity of snails. Spraying of garlic powder (24h LC_{50} - 7.24%) singly and in combination with *Cedrus deodara* (24h LC_{50}- 4.18%) were toxic, as well as effective in controlling the reproductive capacity of the giant African snail *Achatina fulica* (Rao & Singh, 2000, 2002; Rao *et al.*, 2003). Allicin, the active molluscicidal component of garlic (Singh & Singh, 1995), is effective in killing snails as well as making them sterile (Singh & Singh, 2000a).

3.5. Adverse effects

Apart from the valuable medicinal properties garlic may also act toxically when overdosed. Repeated or excessive garlic ingestion produces toxic effects (Rose *et al.*, 1990; Fehri *et al.*, 1991). The most apparent problem with using garlic in human medicine is its strong odor (Morbidoni *et al.*, 2001). A problem of clinical importance is that some people are allergic to sulfur based compounds. There were several reported allergic reactions to garlic; namely, contact dermatitis, asthma, rhinitis, conjunctivitis, urticaria, anaphylaxis and angioedema (Gaddoni *et al.*, 1994; Rauterberg, 1995; Kanerva *et al.*, 1996; Armentia & Vega, 1997; Roberge *et al.*, 1997; Morbidoni *et al.*, 2001). Consumption of garlic enhances the pharmacological effects of anticoagulants (Warfarin, fluindione) and reduces the efficacy of antiAIDS drug Saquinavir (Borrelli *et al.*, 2007).

4. Conclusion

The foregoing account emphasizes the fact that garlic is a nature's boon to mankind. A single clove of garlic has the potential of curing a man from a large number of diseases by inhibiting the population of different strains of bacteria, fungi, harmful viruses, insects and snails. Garlic's cardiovascular, antibiotic and perhaps anticancer effects are well-accepted world over because of the wealth of scientific literature supporting these effects. Use of garlic in the prevention of heart disease has been advocated by prominent researchers. Instead of several clinical tests, garlic is not yet widely recognized by medical authorities. More research should be undertaken in future to determine its efficacy as a cardiovascular preventive agent with respect to other natural product on one hand and modern drugs on the other. Anticarcinogenic components of garlic deserve urgent attention by scientist. Use of garlic as a pesticide is one of the recent concepts for eco-friendly and effective control of pest. Garlic requires investigation mainly in its mode of action in pest body and the way of delivery in the environment to ensure more effective control with less effort. Therefore, garlic deserves more attention by agriculturists and public health specialists. More investigations are still required in experimental, clinical as well as in epidemiological field to explore its full potential in the welfare of mankind.

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