

Therapeutic Uses and Pharmacological Properties of Garlic, Shallot, and Their Biologically Active Compounds

Peyman Mikaili¹, Surush Maadirad², Milad Moloudizargari^{2*}, Shahin Aghajanshakeri², Shadi Sarahroodi³

¹ Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran

² Urmia University, Faculty of Veterinary Medicine, Urmia, Iran

³ Department of Physiology and Pharmacology, School of Medicine, Qom University of Medical Sciences, Qom, Iran

ARTICLE INFO

Article type:
Review article

Article history:
Received: Jan 29, 2013
Accepted: May 30, 2013

Keywords:
Allium hirtifolium
Allium sativum
Garlic
Pharmacological effects
Shallot
Traditional uses

ABSTRACT

Objective(s): Garlic (*Allium sativum* L. family Liliaceae) is well known in Iran and its leaves, flowers, and cloves have been used in traditional medicine for a long time. Research in recent decades has shown widespread pharmacological effects of *A. sativum* and its organosulfur compounds especially Allicin. Studies carried out on the chemical composition of the plant show that the most important constituents of this plant are organosulfur compounds such as allicin, diallyl disulphide, S-allylcysteine, and diallyl trisulfide. Allicin represents one of the most studied among these naturally occurring compounds. In addition to *A. sativum*, these compounds are also present in *A. hirtifolium* (shallot) and have been used to treat various diseases. This article reviews the pharmacological effects and traditional uses of *A. sativum*, *A. hirtifolium*, and their active constituents to show whether or not they can be further used as potential natural sources for the development of novel drugs.

Materials and Methods: For this purpose, the authors went through a vast number of sources and articles and all needed data was gathered. The findings were reviewed and classified on the basis of relevance to the topic and a summary of all effects were reported as tables.

Conclusion: Garlic and shallots are safe and rich sources of biologically active compounds with low toxicity. Further studies are needed to confirm the safety and quality of the plants to be used by clinicians as therapeutic agents.

► Please cite this paper as:

Mikaili P, Maadirad S, Moloudizargari M, Aghajanshakeri Sh, Shadi Sarahroodi. Therapeutic Uses and Pharmacological Properties of Garlic, Shallot, and Their Biologically Active Compounds. Iran J Basic Med Sci; 2013; 16: 1031-1048.

Introduction

Garlic (*Allium sativum* L. family Liliaceae) is originally from Asia but it is also cultivated in China, North Africa (Egypt), Europe and Mexico. It is well known in Iran and various parts of this plant have long been used in traditional folk medicines of Iran and some other cultures. It is also used as a spice and food additive (1, 2). The plant is a bulb growing to 25-70 cm with hermaphrodite flowers (3). Leaves and cloves of *A. sativum* have been used in traditional medicine of Iran and other countries for a long time (4, 5). In pharmacological research, there is a lot of evidence about a wide spectrum of pharmacological effects of *A. sativum* and its active compounds with low toxicity (Table 1) (1). Studies carried out on the chemical composition of the plant show that sulfur compounds such as Allicin are important constituents of the plant (6). Although allicin (diallyl-dithiosulfinate) is the most important alkaloid that is generally claimed to be

responsible for their beneficial effects and numerous studies have been conducted so far (7), it is pointed out that other sulfur compounds such as diallyl disulphide (DDS), S-allylcysteine (SAC) and diallyl trisulfide (DTS) also have some roles in the effects of the plant (Figure 1) (8). In addition to *A. sativum*, allicin, ajoene and other organosulfides are present in *A. hirtifolium* and play important pharmacological roles (Table 2) (9). This article reviews the pharmacological effects and traditional uses of *A. sativum*, *A. hirtifolium*, and their active constituents.

Materials and Methods

Data sources and data extraction

In order to gather the needed information, systematic literature searches were conducted on MEDLINE, EMBASE, and BIOSIS databases. A vast number of papers (more than 200 original articles

*Corresponding author: Milad Moloudizargari, Urmia University, Faculty of Veterinary Medicine, Urmia, Iran. email: miladmoludi@gmail.com

and reviews) were studied during the years 2011-2013 and data extraction was performed methodologically based on previously identified keywords including: *Allium sativum*, garlic, *Allium hirtifolium*, shallot, organosulfur compounds, allicin, and ajoene. The dates of articles used as references ranged from 1973 to 2012. Discrepancies were settled through discussion for a final period of 3 months.

Data presentation

The findings were interpreted and classified on the basis of relevance to the topic and a summary of all effects were reported as tables. Each topic starts with a brief review of the traditional uses of the plant that suits the topic (if present) and then the information is supported by the results of various pharmacological studies conducted in that field. The molecular structures of every active compound present in the studied plants were drawn using the online service (www.emolecules.com). Finally based on the reviewed information a conclusion was reached.

Anti microbial effects

Antibacterial

Allicin and other sulfur compounds are thought to be the major compounds responsible for the antimicrobial effect of garlic. Garlic is effective against a number of gram-negative, gram-positive, and acid-fast bacteria, including *Staphylococcus*, *Salmonella*, *Vibrio*, *Mycobacteria*, and *Proteus* species (7). Aqueous, ethanol and chloroform extracts of garlic inhibited the growth of the pathogenic bacteria, though with varying degrees of susceptibility. The gram positive *Staphylococcus aureus* was more susceptible to the toxic effects of garlic than its gram negative counterparts. It has been shown that the aqueous extract of garlic can be used alongside conventional antibiotics to fight agents of nosocomial infections that are so prevalent in hospitals (5). An *in vitro* study on the effects of aqueous and ethanolic extracts of garlic against specific bacteria such as *Escherichia coli* and *sal. typhi* showed that the aqueous extract had little or no inhibition while the ethanolic extract had a higher inhibitory effect. Allicin in its pure form was found to exhibit antibacterial activity against multidrug-resistant enterotoxigenic strains of *E. coli* (10). In another study, the aqueous extract exhibited antibacterial activity against gram positive (*Bacillus subtilis*, *Staph. aureus*) and Gram negative (*E. coli* and *Klebsiella pneumoniae*) strains, while methanol extract showed antimicrobial activity against all the tested microorganisms except *Stap. aureus* (11).

Garlic ethanolic extract showed maximum activity against *B. subtilis* (12). Allitridi, a proprietary garlic derivative, has been successfully

used to treat systemic bacterial infections (such as *Helicobacter pylori*) in China (13). It was shown in another study that the extract of garlic strongly inhibits *Sal. enteritidis*; however *Staph. aureus* showed less sensitivity (14). It has been shown that Gram-negative diarrheagenic pathogens (*E. coli*, *Shigella sp*, *Salmonella sp*, and *Pro. mirabilis*) from stool samples were highly sensitive to garlic (2). The significant antibacterial activity of garlic extract on streptomycin-resistant strains (Gram-positive *Staph. aureus* and Gram-negative *E. coli*) solely and in synergism with streptomycin has also been proved (15). In a study by Lai and Roy, fresh extracts of *A. sativum* (garlic) and *Nigella sativum* (black cumin) had more antibacterial activity against the isolates of the urinary tract infection, compared to the individual extract or drugs, such as cefalexin, cotrimoxazole, and nalidixic acid (16). Garlic has antibacterial activity against the pig pathogen *Actinobacillus pleuropneumoniae* serotype 9. The main compound that is suggested to be responsible for this effect of garlic is volatile allyl methyl sulfide (AMS) as a lead compound of volatile garlic metabolites (17). Garlic extract was also effective against *Streptococcus mutans* when tested both *in vitro* and *in vivo*. As *Strep. mutans* is one of the primary aetiological organisms in dental caries development (18), garlic extract mouth rinse might be used effectively in the prevention of dental caries (19).

Antifungal

Allicin (diallyl-dithiosulfinate), which is produced by the garlic enzyme alliinase from the alliin, has been shown to have wide-range antifungal specificity. An *in vivo* study showed that antibody-alliinase conjugates and alliin are effective against murine pulmonary aspergillosis (20). One study showed that allicin from garlic has antifungal activity particularly against *Candida albicans* (10). Another *in vitro* study showed both intrinsic antifungal activity of allicin and its synergy with the azoles, in the treatment of candidiasis (21). Studies on the effect of Amphotericin B (AmB) against *C. albicans* showed that allicin enhances significantly the effect of AmB against *Candida albicans*, *Saccharomyces cerevisiae* and against *Aspergillus fumigatus in vitro* and *in vivo* (22, 23). It was found in another study that polymyxin B (PMB), is effective against various yeasts and filamentous fungi when used in combination with allicin. This combination increases the plasma membrane permeability in *Saccharo cerevisiae*. Swollen spherical structure of the yeast disappeared as a result of structural alterations of its vacuole caused by the synergistic activity between PMB and allicin combination (24). A study showed the effects of diallyldisulphide (DADS), one of the components of

garlic, on antioxidant systems in *Candida* species. Changes in antioxidant metabolites and antioxidant activity in the presence of DADS were found in *C. albicans* and *C. tropicalis*. DADS caused a decrease in the activity of all antioxidant enzymes except catalase (25). One study showed that six different mixtures of garlic distilled oils containing diallyl disulfide (DDS) and diallyl trisulfide (DTS), are active against a number of yeasts (*C. albicans*, *C. tropicalis* and *Blastoschizomyces capitatus*) (26). Saponins from *A. sativum* were shown to be effective against *Botrytis cinerea* and *Trichoderma harzianum* (8). Essential oil vapors from *A. sativum* also have inhibitory activity against *Ascosphaera apis* *in vitro* (27). In one study, allicin was shown to be more potent in the growth inhibition of *C. albicans* and also suppression of HWP1 gene expression in comparison with fluconazole, a commonly used antifungal. This compound does not occur in garlic until it is crushed or injured (21, 28). Ajoene, another constituent of garlic, is responsible for many pharmacological activities of this plant specially its antifungal effect (29). This substance is more effective in association with antifungal drugs (sulfametoxazol/ trimethoprim) in the treatment of mice intratracheally infected with *Paracoccidioides brasiliensis* (30). In an *in vitro* study the growth of both *Asper. niger* and *C. albicans* were inhibited by ajoene at <20, ug/ml (31). High zones of inhibition were noted with ethanol extracts of *A. sativum* tested against dermatophytes, saprophytes, and *Candida* species isolated from infected hospitalized patients (32). It has been proven that the blockage of lipid synthesis by aqueous extracts of garlic plays an important role in the anticandidal activity of this plant (33). Alcoholic extracts also have potential anticryptococcal activity against murine disseminated cryptococcosis (34). Another study also showed the sensitivity of *Cryptococcus neoformans* against *A. sativum* (35). A novel antifungal protein, designated allivin, was isolated from *A. sativum* with antifungal activity against *Botrytis cinerea*, *Mycosphaerella arachidicola* and *Phylosporapiricola* (36).

Anti-parasitic

An ultrastructural study showed that allicin is able to produce morphological changes in the male *Schistosoma mansoni* (37). Another study indicated that Allicin has antiparasitic activity against *Plasmodium falciparum* and *Trypanosoma brucei* (38). It is also effective against some major human intestinal protozoan parasites such as *Entamoeba histolytica* and *Giardia lamblia* (10). Diallyl trisulfide is a chemically stable final transformation product of allicin. The activity of diallyl trisulfide was investigated against several important protozoan parasites *in vitro*. The results

indicated that the compound has the potential to be used in treatment of several human and animal parasitic diseases such as *Trypanosoma sp*, *Ent. histolytica* and *Giar. lamblia* (39). Ajoene isolated from *A. sativum* is an inhibitor of human glutathione reductase and *Trypa. cruzi* trypanothione reductase. The antiparasitic and cytostatic actions of ajoene may at least in part be due to the multiple effects on key enzymes of the antioxidant thiol metabolism (40). Alchinal is a preparation of three different substances including *Echinacea purpurea* and *A. sativum* extracts and cocoa. It has been demonstrated that this preparation significantly decreases the number of adult forms and muscular larvae of *Trichinella spiralis*. It was demonstrated that after Alchinal administration, the number of adult forms and muscular larvae of this parasite was significantly decreased (41). Garlic oil is effective against a wide range of microorganisms including *Plasmodium spp*, *Trypanosoma spp*, *Leishmania spp*, *Giardia spp*, and *Cochlospermum planchonii* (42). Its aqueous extract has been shown to be effective against hymenolepiasis and giardiasis also (43). In an *in vitro* study the ethanol, dichloromethane and water extracts of *A. sativum* were shown to have anthelmintic activity against *Haemonchus contortus* from sheep. The ethanol extract was the most effective in decreasing larval count (44). Another study showed that garlic is effective against nematodes. Aqueous extract from garlic has good activity against *Trichuris muris* and *Angiostrongylus cantonensis* when followed by chloroform extract (45). Garlic is an ingredient of a mixture (Prepared from the extracts of coconut, onion, garlic, fig, date tree, chicory, ananas, and cistrose) tested *in vivo* and *in vitro* for its anthelmintic activity against cestodes (*Hymenolepis diminuta*, *H. microstoma*, and *Taenia taeniaeformis*) and trematodes (*Fasciola hepatica*, *Echinostoma caproni*). In all *in vitro* tests, the target parasites died. In addition, the same composition was effective against the intestinal fluke *Echino caproni*, but not against the liver fluke *F. hepatica* in the final host, while both worms were killed *in vitro* (46). Essential oil of *A. sativum* has paralytic effect on *F. gigantica*. The essential oil produced significant reduction in the frequency and the amplitude of the spontaneous muscular activity of whole fluke at 1 and 3 mg/ml concentrations (1). The extract of *A. sativum* also possesses mosquito larvicidal properties. It is effective against filarial mosquito *Culex quinquefasciatus* (after 24 hr treatment) (47), *Cul. quinquefasciatus* and *Anopheles stephensi* (48). Essential oil from *A. sativum* has acaricidal activity against *Rhipicephalus (Boophilus) microplus (Canestrini)* tick larvae (49). The insecticidal activity of *A. sativum* against larvae of *Aedes albopictus (Skuse)* (50), *Lycoriella ingénué* (51), and *Spodoptera litura* (1000 ppm) has also been shown (11).

Antiviral

A. sativum has been shown to have antiviral activity. In one study the virucidal activity of this plant was attributed to the following contents in this order: ajoene > allicin > allyl methyl > thiosulfinate > methyl allyl thiosulfinate (52). Also Allicin, the main constituent of *A. sativum*, has a variety of antimicrobial activities both *in vitro* and *in vivo*. Among the viruses which are sensitive to garlic extracts are the human *Cytomegalovirus* (HCMV), influenza B virus, *Herpes simplex virus* type 1, *Herpes simplex virus* type 2, *Parainfluenza virus* type 3, *vaccinia virus*, vesicular stomatitis virus, and *human Rhinovirus* type 2 (10). One study showed that Allicin-containing supplements can prevent attacks by the common cold virus (53). The main antimicrobial effect of Allicin is due to its chemical reaction with thiol groups of various enzymes, e.g. alcohol dehydrogenase (10). In an *In vivo* study the administration of garlic in mice models protected them against intranasal inoculation with influenza viruses and enhanced the production of neutralizing antibodies when given the vaccine (7).

Ajoene, isolated from extracts of garlic may inhibit adhesive interaction and fusion of leukocytes (54). In a study investigating the effect of Allitridin (diallyl trisulfide, a compound from *A. sativum* extraction) on the replication of HCMV and the expression of viral immediate-early genes, it was revealed that this substance has anti-HCMV efficacy (55). In another study, it was supposed that the antiviral activity of garlic in humans may be secondary to a direct toxic effect on viruses. It also enhanced NK-cell (Natural killer-cell) activity that destroys virus-infected cells (7).

Cardiovascular effects

Antihypertensive

A statistical study showed that individuals whose blood pressures are on the lower side are more likely to consume more garlic in their diets (56). Various epidemiologic studies have indicated an inverse correlation between garlic consumption and progression of cardiovascular disease (57). The authors are of the opinion that garlic is effective in treatment of mean systolic blood pressure but not d-penicillamine (58).

In one study the aqueous garlic extract (AGE) caused a decrease in blood pressure and bradycardia by direct mechanism not involving the cholinergic pathway, suggesting a likely involvement of peripheral mechanism for hypotension (59). Another study showed that AGE prevents oxidative stress, systolic blood pressure, aortic NAD(P)H oxidase activity and vascular remodeling in rats with metabolic syndrome (60).

It has been also shown that preparations of garlic may be tentatively used as an adjunct agent in treatment of arterial hypertension because of its hypolipemic and antioxidant properties (61). *In vivo* and *in vitro* ischemia reperfusion studies have shown that prophylactic administration of AGE prior to ischemia reperfusion inhibits lipid peroxidation and prevents depletion in glutathione through its compounds that led to functional recovery. Its ability to inhibit neutrophil migration could suppress fibrosis formation. These preventive effects are seen in studied model organs such as kidney and liver with functional recovery. Organ system specific activity such as angiotensin converting enzyme-inhibiting action contributes to a cardioprotective and blood pressure lowering effect of garlic (62). The authors are of the opinion that the blood pressure lowering effect of garlic in rats (two-kidney one-clip model) may be partly mediated through the nitric oxide (NO) pathway, by enhanced NO synthesis (63).

A study on the effects of two garlic sources has the potential to reduce systolic blood pressure. The effect of aged garlic extract was accompanied by a decrease of pulse pressure (PP), suggesting an improvement of the pliability of the artery, although raw garlic (RG) powder did not affect PP. However, harmful effects were observed in the RG group, including a decrease in erythrocytes, an increase in reticulocytes, and generation of papilloma in the forestomach (64). Another study showed that garlic is a potent vasorelaxant and could reduce the atherogenic properties of cholesterol (65).

A small pilot study indicated the potential ability of aged garlic extract to inhibit the rate of progression of coronary calcification (66). In a study garlic appeared to be a good adaptogen to be utilized in patients with coronary artery disease (67). One study indicated that increased intake of garlic has been associated with reduced mortality in cardiovascular patients or reduced incidence of myocardial infarction, stroke, and hypertension (68). Another study showed that garlic may beneficially affect two risk factors for atherosclerosis--hyperlipidemia and hypertension (69).

One survey suggested that allicin lowered intraocular pressure, in part, by dual actions at the neuroeffector junction (70). Oxidative damage by free radicals has been implicated in the pathogenesis of vascular disease in hypertension. Authors concluded that the total antioxidant status can be significantly improved by treatment with garlic (71). An *in vivo* study indicated that garlic blocks hypoxic pulmonary hypertension and demonstrated a combination of endothelium-dependent and -independent mechanisms for the effect in pulmonary arterial rings (72).

An *in vitro* study showed that intravenous administration of garlic extracts produced dose-dependent and reversible hypotensive and bradycardic effects (73).

In One survey the authors are of the opinion that although H₂S (hydrogen sulfide) role in blood pressure regulation and interaction with NO is controversial, H₂S, through its anti-apoptotic, anti-inflammatory and antioxidant effects, has demonstrated significant cardioprotection. As a result, a number of sulfide-donor drugs, including garlic-derived polysulfides such as diallyl disulfide, diallyl trisulfide and S-allyl cysteine, are currently being designed and investigated for the treatment of cardiovascular conditions such as hypertension (74, 75). Stimulation of nitric oxide generation in endothelial cells seems to be the critical preventive mechanism. Cardioprotective effects of dietary garlic are mediated in large part via the generation of H₂S. Garlic-derived organic polysulfides are converted by erythrocytes into hydrogen sulfide which relaxes vascular smooth muscle, induces vasodilation of blood vessels, and significantly reduces blood pressure (76).

Progressive renal damage and hypertension are associated with oxidative and nitrosative stress. On the other hand, S-allylcysteine (SAC), the most abundant organosulfur compound in aged garlic (AG) extract, has antioxidant properties. The effects of SAC and AG on blood pressure, renal damage, and oxidative and nitrosative stress were studied. The data suggested that the antihypertensive and renoprotective effects of SAC and AG are associated with their antioxidant properties and that they may be used to ameliorate hypertension and delay the progression of renal damage (77). Daily treatment with 600 mg of Allicor (garlic powder tablets) has decreasing effects on both systolic and diastolic blood pressures. It has been shown that time-released tablets of Allicor are more effective in the treatment of mild and arterial hypertension than regular garlic additives (78). Allicin within garlic tablets was shown to be the possible responsible substance for the anti-hypertensive effect of the tablets. Other organo-sulfur compounds may also have a role in the hypotensive mechanisms of garlic (6). It was shown in a study that administration of garlic extract decreases systolic and diastolic blood pressure only in hypertensive animals with no such effect in normotensive ones (79). Allyl methyl sulphide (AMS) and diallyl sulphide (DAS), two garlic derivatives, are shown to inhibit migration and angiotensin II-stimulated cell-cycle progression in smooth muscle cells of aorta. As a result, AMS and DAS may serve as effective antioxidant compounds in the arterial structural changes caused by hypertension (80). Hepatopulmonary syndrome is characterized by the presence of portal

hypertension and dilated pulmonary capillaries. In a study, garlic powder and iloprost inhalation demonstrated clinical improvements in the pre- and in the post-transplant period (81).

Administration of moderate doses of garlic along with propranolol has been shown to have beneficial effects in animals with hypertension and myocardial damage (82). Another study indicated that garlic in moderate doses with added hydrochlorothiazide (HCTZ) possesses synergistic cardioprotective and antihypertensive properties against fructose- and isoproterenol-induced toxicities, by increasing the lactate dehydrogenase, creatinine phosphokinase, superoxide dismutase and catalase activities in heart homogenate when used concurrently or separately (83). The influence of garlic on pharmacokinetics of HCTZ was studied. The administration of HCTZ in garlic homogenate pretreated rats was found to decrease the QRS duration, RR interval, QT segment, systolic blood pressure, heart rate, serum potassium level, serum LDH and serum CK-MB activities significantly. It was concluded that careful addition of garlic in moderate doses might result in beneficial effect during treatment of hypertension in patients with myocardial stress as garlic causes substantial fall in excretion of potassium when compared to HCTZ alone treatment in rats (84). One study represented that combination of garlic or its bioactive constituent, S-allyl cysteine sulphoxide, and captopril exerted super-additive (synergistic) interaction with respect to fall in blood pressure and ACE inhibition (85). Another study showed that S-allyl-mercapto-captopril (CPSSA), a conjugate of captopril with allicin, was effective in attenuating systolic and diastolic blood pressures as well as significantly reducing glucose levels (86). A comparable study between the effects of allicin and enalapril on blood pressure (BP) showed similar effects, both of which reduce BP (87).

Antiatherosclerotic

One study by Wang and Ng (1999) showed that garlic compounds possess anti-atherosclerotic activity (88). Also numerous animal studies have reported that garlic can have protective effect against atherosclerosis (89). Sulfur-containing volatiles from garlic are the principal compounds responsible for such property and the most abundant volatile compound is diallyl disulfide followed by diallyl trisulfide (90). These active constituent(s) of garlic responsible for its anti-atherogenic action are shown to be mostly present in the oily fraction of the plant (91). Among these constituents, allicin is another compound that plays an important role in anti-atherosclerotic activity of garlic. It is produced upon crushing of the garlic clove. A pure allicin preparation may affect

atherosclerosis not only by acting as an antioxidant, but also by other mechanisms, such as lipoprotein modification and inhibition of LDL uptake and degradation by macrophages (92). In a study, 112 patients (47 men and 65 women) 40 to 60 years of age were examined. 56 patients had ischemic heart disease and/or equal disorders. Another 56 patients were free of any signs of atherosclerosis, but had one or more cardiovascular pathology risk factor. Six month therapy using allicin results in moderate hypolipidemic and antioxidative effect. A dosage of 600 mg per day decreases ten-year chance of fatal cardiovascular complications in patients with clinical signs of atherosclerosis, whereas in patients who have no signs of atherosclerosis the complications are decreased with dosage of 300 mg per day (93). Another survey indicated that garlic indirectly affects atherosclerosis by reduction of hyperlipidemia. Moreover, in animal models, garlic causes direct antiatherogenic (preventive) and anti-atherosclerotic (causing regression) effects at the level of artery wall. It was suggested in one study that garlic powder also manifests direct anti-atherogenic-related action not only *in vitro* but also *in vivo* (94). Garlic's direct effect on atherosclerosis may be explained by its capacity to reduce lipid content in arterial cells and to prevent intracellular lipid accumulation. This effect, in turn, is accompanied by other atherosclerotic manifestations, i.e., stimulation of cell proliferation and extracellular matrix synthesis (95). A study demonstrated that garlic reduces the atherogenic properties of cholesterol (65). As cited above, suppressed LDL oxidation may be one of the powerful mechanisms accounting for the anti-atherosclerotic properties of garlic (96, 97). In one study, intake of high-dose garlic powder dragees significantly reduced the increase in arteriosclerotic plaque volume by 5-18% or even caused a slight regression within the observational period of 48 months (98).

Fish oil and garlic combinations can serve as good dietary supplements with anti-atherosclerotic properties (99). Other possible mechanisms for lipid lowering and anti-atherogenic effects of garlic include inhibition of the hepatic activities of lipogenic and cholesterogenic enzymes that are thought to be the origin for dyslipidemias, increased excretion of cholesterol and suppression of LDL-oxidation (100). In an *in vitro* study, the potential anti-atherosclerotic property of moderate and high doses of garlic homogenate (GH) was significantly attenuated by propranolol and hydrochlorothiazide. However, GH anti-hyperlipidemic activity was augmented by captopril (101). Another study indicated that (egg yolk-enriched garlic powder) EGP inhibits copper-induced LDL oxidation in a dose-dependent manner that might be ascribed, in

part, to the biodistribution of garlic compounds and egg yolk interaction. This finding suggests that EGP might be useful in the prevention of atherosclerosis (102).

Antithrombotic

Garlic extracts and several garlic constituents demonstrated significant antithrombotic actions both *in vitro* and *in vivo*. Allicin and adenosine are the most potent antiplatelet constituents of garlic (103). A study suggested that odorless garlic not only activates fibrinolytic action by accelerating (tissue-type plasminogen activator) t-PA-mediated plasminogen activation, but also suppresses the coagulation system by down regulating thrombin formation, suggesting a beneficial role in preventing pathological thrombus formation in such cardiovascular disorders (104). A study mentioned that aqueous extract of garlic inhibits platelet aggregation induced by several aggregation agents, including arachidonate in a dose-dependent manner (105).

Another survey indicated that garlic extracts act through inhibition of the ADP (adenosine diphosphate) pathway. Their mechanisms of action are comparable to that of the clinically used drug clopidogrel. The pharmacologically active component of the extracts appears to be lipophilic rather than hydrophilic (106). One study mentioned that the aromatic thiosulfonate derived from garlic is a very effective inhibitor of platelet aggregation (107). Diallyl trisulfide (DATS) is one of the major constituents in garlic oil and has demonstrated various pharmacological activities, such as antithrombotic (108). DAT-rich garlic oil showed anticoagulant action due to inhibition and/or inactivation of thrombin, in an animal study. In addition DAT-rich garlic oil benefits blood anticoagulation factors, which might further prevent the development of thrombus formation. However, the intake of garlic oil at high dose significantly increased plasma fibrinogen concentration ($P < 0.05$) and affected the levels of several hematological parameters such as erythrocyte count, hemoglobin and platelets ($P < 0.05$). Supplementation of garlic oil at 5 mg/kg BW had anticoagulation effect in this study (109). It was shown in a survey that diallyl disulphide (DADS) and DATS - are usual constituents of garlic oil, with antiplatelet activity. They also inhibit platelet thromboxane formation. In this respect DATS is more potent than DADS (110). The antiplatelet activity of methyl allyltrisulfide (MATS), a component commonly present in steam-distilled garlic oil, has also been demonstrated. MATS inhibits arachidonic acid cascade at the reaction site with PGH synthase (111). In a study allicin and thiosulfates were considered as responsible compounds for the

(*in-vitro* antiaggregatory activity) IVAA response. It was also shown that the loss of activity, and the partial loss of antithrombotic effect in crushed-cooked garlic may be compensated by increasing the amount consumed (112). Authors mentioned that sulfur compounds' contribution to the health promotion in allium species are produced via enzymic and thermal reactions. Potent antithrombotic agents which have been identified as allyl trisulfides, dithiols, and ajoene in garlic are thermochemically transformed forms of allicin (allyl 2-propenethiosulfinate) (113). A study showed that allicin had the strongest antiplatelet activity at 0.4 mM inhibiting aggregation by 89% (114). Ajoene is another potent antiplatelet compound isolated from alcoholic extracts of garlic. It is suggested that ajoene may be potentially useful for the acute prevention of thrombus formation induced by severe vascular damage, mainly in arterial sites with low local shear rates (115, 116). One study indicated that the antiaggregatory effect of ajoene is causally related to its direct interaction with the putative fibrinogen receptors (117). Another survey demonstrated that the antithrombotic potential of ajoene is substantially increased in the presence of physiologically and pharmacologically active antiplatelet agents (118). In a study, ajoene inhibited platelet aggregation induced by arachidonic acid, adrenaline collagen, adenosine diphosphate and calcium ionophore. The nature of the inhibition was irreversible (119). It has been suggested that supplements of garlic could adversely affect coagulation when taken alone or in combination with antiplatelet medications (120). In a study coadministration of aged garlic extract and cilostazol did not enhance the antiplatelet activity compared with individual drugs (121). Another study suggested that aged garlic extract is relatively safe and poses no serious hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy (122).

Spolarich and Andrews mentioned that patients undergoing routine dental and dental hygiene procedures do not need to discontinue the use of anticoagulant and antiplatelet medications (such as aspirin). However, alterations in drug use may be required for those patients undergoing invasive surgical procedures. It is recommended that herbal supplements, such as garlic, must be discontinued 2 weeks prior to receiving invasive surgical procedures (123).

Blood factors

One survey mentioned that garlic has antihyperlipidemic, hypocholesterolaemic and hypo triacylglyceride activities (124). The hypoglycemic and hypolipidaemic effects of garlic have been shown in sucrose fed rabbits also (125). In one study, raw and boiled garlic improved plasma lipid metabolism and plasma antioxidant activity in rats.

Thus, dietary garlic was effective in reducing the oxidant stress, which was indicated by an increase of antioxidant activity and a decrease of lipids in the rats' blood (126).

In another study, garlic powder significantly ($P < 0.05$) lowered the animal's blood lipid levels (127). Garlic has been shown to have applications as a hypoglycemic agent (128). A study suggested a new mechanism for the hypolipidemic effect of fresh garlic. Long-term dietary supplementation of fresh garlic may exert a lipid-lowering effect partly through reducing intestinal MTP (microsomal triglyceride transfer protein) gene expression, thus suppressing the assembly and secretion of chylomicrons from intestine to the blood circulation (129). Short-term garlic therapy in adults with mild to moderate hypercholesterolemia does not affect lipid levels (130). In a study the water soluble protein fraction of garlic was investigated for its effect on hyperlipidemia induced by alcohol (3.76 g/kg body wt/day). It showed hypolipidemic action mainly due to an increase in cholesterol degradation to bile acids and neutral sterols and mobilization of triacyl glycerols in treated rats. Garlic protein (500 mg/kg body wt/day) showed significant hypolipidemic action comparable with a standard dose of gugu-lipid (50 mg/kg body wt/day) (131). One study in 1984 showed that garlic oil has hypolipidemic effects in ethanol-fed rats (132). In another study, the water soluble proteins and the essential oil of garlic were investigated for their hypolipidemic effect on hyperlipidemia induced by cholesterol containing diet in albino rats. Both garlic protein (16% of diet) and garlic oil (100 mg/kg body weight/day) exhibited significant lipid lowering effects (133). A survey mentioned that garlic methanol-extracts behave as hypolipidemic drugs, increasing the activity of peroxisomal fatty acyl-coenzyme A oxidase and of total carnitine acetyl-coenzyme A transferase in primary cultures of rat hepatocytes (134). In an *in vivo* study, garlic demonstrated a reduction of lipid plaques in the arteries of hypercholesterolemic animals. It decreased accumulation of cholesterol in vascular walls, and had other positive interventions (135).

In one study, the glutathione reductase activity that was lowered in hypercholesterolemic conditions, methemoglobin concentration that was significantly increased in hypercholesterolemic rats and significant fall in hepatic total thiols in hypercholesterolemia were partially corrected by garlic. Similarly, the lowered activities of hepatic antioxidant enzymes in hypercholesterolemic rats were effectively countered by this plant (136).

Garlic treatment significantly diminished total-cholesterol, LDL-cholesterol and triglycerides, but not HDL-cholesterol in chronic nephrotic syndrome

(NS). These data indicate that garlic treatment ameliorates hyperlipidemia and renal damage in chronic NS which is unrelated to proteinuria or antioxidant enzymes (137). In a survey, hepatic triglyceride content that was significantly higher in high-fat fed rats was effectively countered by inclusion of the hypolipidemic spice agents such as garlic in the diet (138).

One study mentioned that garlic's organosulfur compounds (such as diallyl trisulfide) display hypolipidemic effects by inhibiting fatty acid and cholesterol synthesis (139).

Diallyl disulfide, an active principle of garlic (*A. sativum*), is known for its antihyperlipidemic properties (140). Water-soluble organosulfur compounds, S-allyl cysteine (SAC), S-propyl cysteine (SPC) and S-ethyl cysteine (SEC), were studied. The results indicated that SAC, SEC, and SPC inhibit lipid biosynthesis in cultured rat hepatocytes, and further suggested that these S-alk(en)yl cysteines of garlic impair triglyceride synthesis in part due to decreased *de novo* fatty acid synthesis resulting from inhibition of fatty acids (141). Allicin (diallyl disulphide-oxide) exerts various beneficial biological effects such as antihyperlipidemic (142) and hypoglycaemic actions (143). Dietary garlic also reduces the cholesterol gallstone incidence by 15-39 % (144). Action of long-acting garlic powder tablets (Allicor) have been investigated on blood factors. The results show that allicor lowers total cholesterol, LDLP cholesterol, raises HDLP cholesterol and therefore can be recommended for correction of lipid content in patients with moderate hyperlipidemia (145). A comparative study on the beneficial effects of garlic amla (*Emblca Officinalis Gaertn*) and onion (*A. cepa L*) on hyperlipidemia showed that the order of the curative effects of the vegetables is as follows: garlic > amla > onion (146).

Anticancer effects

A study mentioned that phytoalexins have been identified in at least 75 plants including garlic. Preclinical evidence has suggested that these compounds possess anticancer properties including an inhibition of cell proliferation, invasion and metastasis, hormonal stimulation, and stimulatory effects on expression of metabolizing enzymes (147). Diallyl sulfide (DAS), diallyl disulfide (DADS) and diallyl trisulfide (DATS) derived from garlic have been shown to exhibit anticancer activities (148). The cytotoxicity caused by DATS is mediated by generation of ROS (reactive oxygen species) and subsequent activation of the ROS-dependent caspase pathway in U937 leukemia cells (108). DATS has been shown to induce apoptosis in many human cancer cell lines *in vitro* and also affords significant protection against cancer in animal tumor models *in vivo* i.e. colorectal cancer (149). Another suggested that DADS treatment may inhibit

tumor cell motility and invasion and therefore, act as a dietary source to decrease the risk of cancer metastasis (150).

Recently, S-allylcysteine (SAC) has been identified as a potent compound derived from garlic. This substance has *in vitro* chemo-preventive activity. It may also be a promising candidate for prostate cancer treatment (151). Allicin (diallyl thiosulfinate), the best-known biologically active component in freshly crushed garlic extract, is effective on cell proliferation of colon cancer cells (152). A study indicated that the anticancer action of aged black garlic extract may be partly due to its antioxidant and immunomodulative effects (153).

Anti-inflammatory effect

Garlic extracts have been shown to exert anti-inflammatory effects (154). In one study, garlic treatment significantly attenuated inflammation and injury of the liver induced by *Eimeria papillata* infections (155). The anti-inflammatory activity exhibited by garlic oil is mainly through inhibiting the assembly-disassembly processes of the cytoskeleton (156).

Other authors have shown the preventive effect and possible toxicity of garlic oil and its organosulfur compounds in endotoxin-induced systemic inflammation and intestinal damage (157). A lead compound derived from allicin is shown to be a good starting point for the development of anti-inflammatory drugs with fewer side effects (158).

One study indicated that thiacecremonone, a sulfur compound isolated from garlic, inhibits neuroinflammation and amyloidogenesis through inhibition of NF- κ B activity, and thus could be applied for intervention in inflammation-related neurodegenerative diseases including Alzheimer's disease (159).

Immunomodulatory effect

Immunomodulation is among innumerable biological activities of *A. sativum*. Aged garlic extract has been shown to have superior immunomodulatory properties over raw garlic extract (160). This effect of garlic is attributed to the transformed organosulfur compounds (161). Aged garlic fructans have recently been shown to possess immunomodulatory activities *in vitro* (160). Garlic extract is concentration-dependently effective on the proliferation of interleukin (IL)-2 and interferon (INF)- γ gene expression of stimulated lymphocytes (162). Garlic extracts reduced macrophage infection through induction of nitric oxide (NO) production *In vitro* (163).

A study demonstrated that immune-mediated liver damage in mice can be prevented by allicin, probably because of its immunomodulatory effects on T cells and adhesion molecules and inhibition of NF-kappaB activation (164). Another observation indicated that allicin exerts an inhibitory

immunomodulatory effect on intestinal epithelial cells and it may have the potential to attenuate intestinal inflammation (165). Allicin exerted an *in vitro* immunomodulatory effect on certain functions of the peripheral blood cells (166).

Toxicology

Tattelman mentioned that garlic appears to have no effect on drug metabolism, but patients taking anticoagulants should be cautious. It seems prudent to stop taking high dosages of garlic seven to 10 days before surgery because garlic can prolong bleeding time (167).

One study indicated that garlic application usually results in local inflammation, but, if applied under a pressure bandage, or if there is poor wound care or a secondary infection, it can cause a severe dermal reaction and a deep chemical burn (168). Data of a study showed that a high garlic dose induced liver toxicity and a pro-oxidative status characterized by increased malondialdehyde and decreased antioxidant enzyme activities as catalase, peroxidase, and superoxide dismutase (169). Another study suggested that garlic with high dose has the potential ability to induce liver damage (170).

A parallel study also highlighted the potential ability of a high dose of garlic to induce morphological changes in the liver and kidneys (171). Administration of high doses of garlic (500 mg/kg) results in profound changes in lung and liver tissues of rats. Intraperitoneal administration of the high dose of garlic is more damaging to lung and liver tissue of rats than oral administration (172). It is also shown that the adverse effect of high doses of garlic oil might further influence the hemostatic balance (109).

High doses of diallyl disulfide may further complicate the metabolic disturbances in diabetes (173). High dose of garlic oil worsened intestinal mucosal damage accompanied by elevated peripheral proinflammatory cytokines in another study (157).

Active compounds

It has been shown that sulfur compounds such as allicin are important constituents of garlic (6). Although allicin (diallyl-dithiosulfinate) is the most important alkaloid that is generally claimed to be responsible for most of the beneficial effects of the plant (7); however, it is pointed out that other sulfur compounds such as diallyl disulphide (DDS),

S-allylcysteine (SAC) and diallyl trisulfide (DTS) also have some roles in the pharmacological effects of the plant (88). SAC is the most abundant organosulfur compound found in aged garlic extract (77). It has also been shown that allicin (diallyl-dithiosulfinate) does not occur in garlic until it is crushed or injured (28). Among the active compounds present in the plant, DTS and DDS are the most active against yeasts (26) and ajoene is the main compound responsible for the antiviral activity of garlic (52).

Drug interaction and pharmacokinetics

One study indicated that those who use traditional/complementary/alternate medicines (TCAMs) in addition to antiretroviral (ARV) treatment may be at risk of experiencing clinically significant pharmacokinetic (PK) interactions, particularly between the TCAMs and the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Mechanisms of PK interactions include alterations to the normal functioning of drug efflux transporters, such as P-gp and/or CYP isoenzymes, such a CYP3A4 that mediate the absorption and elimination of drugs in the small intestine and liver. Specific mechanisms include inhibition and activation of these proteins and induction via the pregnane X receptor. Garlic exhibited potentially significant interactions, each with a PI or NNRTI (174). *In vivo* absorption changes are possible between aged garlic extract and cardiovascular, antidiabetic and antiviral drugs, but the magnitude of the changes depends on the most profound process involved (influx, efflux, passive diffusion) in compound's permeability (175). In a study, pharmacokinetic interaction of garlic and atorvastatin in dyslipidemic rats was shown (176). Another study indicated that the bioavailability and half-life of propranolol was significantly enhanced by 2- and 3-folds, respectively, in animals pretreated with garlic (250 mg/kg) (82). It has been also shown that herbs such as garlic with the potential to significantly modulate the activity of drug-metabolizing enzymes (notably cytochrome p450 isozymes) and/or the drug transporter P-glycoprotein participate in potential pharmacokinetic interactions with anticancer drugs (177).

Table 1. Pharmacological effects of *Allium sativum*

System	Effect	Preparation	Reference	
Antibacterial	<i>Staphylococcus aureus</i>	Aqueous, ethanol, chloroform extract	EL-mahmood, 2009 (5)	
	<i>Escherichia coli, Salmonella typhi</i>	Aqueous and ethanolic extract	Ankri and Mirelman, 1999 (10)	
	<i>Bacillus subtilis, Kelebsiella pneumoniae</i>	Aqueous, methanol and ethanol extract	Meriga et al, 2012; Pundir et al, 2010 (11, 12)	
	<i>Helicobacter pylori</i>	Extract	Liu et al, 2010 (13)	
	<i>Sal enteritidis</i>	Extract	Benkeblia, 2004 (14)	
	<i>Shigella sp, Proteus mirabilis</i>	Extract	Eja et al, 2007 (2)	
Antiviral	<i>Actinobacillus pleuro pneumonia serotype 9</i>	Extract	Becker et al, 2012 (17)	
	<i>Streptococcus mutan</i>	Extract	Loesche, 1986 (18)	
	<i>Human cytomegalo virus (HCMV), Influenza B, Herpes simplex virus type 1-2, Parainfluenza virus type 3, vaccine virus, Vesicular stomatitis virus, Human rhino virus type 2</i>	Not mentioned	Ankri and Mirelman, 1999 (10)	
Antifungal	<i>Candidia albicans, C. tropicalis, Blastoschizomyces capitatus</i>	Extract	Avato et al, 2000 (26)	
	<i>Botr. cinerea, Trichoderma harzianum</i>	Extract	Lanzotti et al, 2012 (8)	
	<i>Ascosphaera apis</i>	Essential oil vapors	Kloucek et al, 2012 (27)	
	<i>Paracoccidioides brasiliensis</i>	Extract	Thomaz et al, 2008 (30)	
	<i>Aspergillus niger</i>	Extract	Matsuura and Nakagawa, 1987 (31)	
	<i>Dermatophytes, saprophytes</i>	Ethanol extract	Shamim et al, 2004 (32)	
	<i>Cryptococcal</i>	Alcoholic extract	Khan and Katiyar, 2000	
	<i>Botr. cinerea, Mycosphaerella arachidicola, Physalospora piricola</i>	Extract	Wang and Ng, 2001 (34)	
	Anti-parasitic	<i>Trypanosoma sp, Entamoeba hirtolytica, Giardia lamblia</i>	Extract	Lun et al, 1994 (39)
		<i>Trypa. Cruzi</i>	Extract	Gallwitz et al, 1999 (40)
<i>Plasmodium spp, Giardia spp, Leishmania spp, Cochlospermum planchomi</i>		Extract	Anthony et al, 2005 (42)	
<i>Hymenolepiasis, Giardiasis</i>		Aqueous extract	Soffar and Mokhtar, 1991 (43)	
<i>Haemonchus contortus</i>		Ethanol, dichloro methane and water extract	Ahmed et al, 2012 (44)	
Cardiovascular	Hypotensive via increasing nitric oxide synthesis	Extract	Al-Qattan et al, 2006 (63)	
	Hypotensive (endothelial dependent and independent)	Not mentioned	Fallon et al, 1998 (72)	
	Induces vasodilation with H ₂ S	Extract	Ginter and Simko, 2010 (76)	
	Angiotensin converting enzyme-inhibiting activity	Aqueous extract	Sener et al, 2007 (62)	
	Stimulation of nitric oxide generation in endothelial cells	Garlic derived polysulfides	Ginter and Simko, 2010 (76)	
	Bradycardia	Aqueous extract	Nwokocha et al, 2011(59)	
	Hepatopulmonary syndrome	Garlic powder	Theveno et al, 2009 (81)	
	Decreases systolic blood pressure	Aged garlic	Harauma and Moriguchi, 2006 (64)	
	Vasorelaxant	Not mentioned	Zahid Ashraf et al, 2005 (65)	
	Coronary artery disease	Extract	Verma et al, 2005 (67)	
Blood	Reduce myocardial infarction, Shoke	Not mentioned	Yang et al, 2011 (68)	
	Anti-thrombotic	Extract and derived	Choi and Park, 2012 (108)	
	Anti-atherosclerotic	Volatiles derived	Calvo-Gómez et al, 2004 (90)	
	hypolipemic effect	Capsule of garlic preparation	Duda et al, 2008 (61)	
	Hypolipidemia,	Extract	Kuda et al, 2004 (124)	
	Hypocholesterolaemic,			
	Hypotriacylglyceride			
	Hypoglycemic	Extract	Sengupta et al, 2004 (128)	
	Hypolipidemic	Organosulfur compound	Lii et al, 2012 (139)	
	Immune system	Immunomodulation	Extract	Chandrashekar and Venkatesh, 2012 (160)
All	Anti-inflammatory	Extract	Ben et al, 2012	
	Antioxidant properties	Organo sulfur compound in aged garlic	Cruz et al, 2007 (77)	

Allium hirtifolium**Antimicrobial**

It has been shown that the alcoholic and aqueous extracts of shallot (*A. hirtifolium*) have good antifungal activity against *Aspergillus fumigatus*, *Asper. flavus*, *Asper. niger*, *Penicillium gryseogenum*, *Alternaria*, *Microsporium canis* and *Trichophyton mentagrophytes* in comparison with the miconazole (178). A comparative study between Persian shallot aqueous extract and chlorhexidine on salivary bacterial counts indicated that shallot extract has more persistent inhibitory action than chlorhexidine mouth rinse lasting up to 24 hr (179).

In One study *A. hirtifolium* exhibited significant anti-trichomonas activity due to its components such as allicin, ajoene and other organosulfides, comparable to metronidazole (9).

Anticancer

One study showed that components of *A. hirtifolium* can dose-dependently inhibit proliferation of tumor cell lines. Therefore, *A. hirtifolium* might be a candidate for tumor suppression (180).

Clinical trials (garlic)

By a simple search in the literature it could be figured out that garlic has been used clinically to elicit desirable pharmacological and therapeutic effects. For instance, the use of garlic along with iloprost improved both the pre and post-transplant period in patients with hepatopulmonary syndrome (81). It has also been shown that daily administration of allicin may decrease the occurrence of fatal cardiovascular complications in atherosclerotic patients (93). Although garlic has the potential to be used clinically in the treatment of some disorders, care should be taken regarding its usage with other medications due to possible drug interactions that might arise as a result (174).

Table 2. Pharmacological effects of *Allium hirtifolium*

System	Effect	Reference
Antibacterial	Antibacterial: <i>Staphylococcus spp</i> , <i>Salmonella spp</i> , <i>Nitro spp</i> , <i>Mycobacteria spp</i> , <i>Proteus spp</i> <i>Escherichia coli</i>	Tariq <i>et al</i> , 1988 (7)
Antiviral	<i>Common cold virus</i>	Ankri and Mirelman, 1999 (10) Josling, 2001 (53)
Antifungal	<i>Candida albicans (Candidiasis)</i> <i>Saccharomyces cerevisia</i> <i>Aspergillus fumigatus</i>	Ankri and Mirelman, 1999 (10) Khodavandi <i>et al</i> , 2010 (21) An <i>et al</i> , 2009; Ogita <i>et al</i> , 2006 (23)
Antiparasitic	<i>Schistosoma mansoni</i> (male) <i>Plasmodium falciparum</i> , <i>Trypanosoma brucei brucei</i>	Lima <i>et al</i> , 2011 (37)
Cardiovascular	<i>Entamoeba histolytica</i> , <i>Giardia lamblia</i> Hypotensive intraocular pressure	Ankri and Mirelman, 1999 (10) Chu <i>et al</i> , 1993 (70)
	Hypotensive Anti-Atherosclerotic Antithrombotic or Anti-aggregatory	Younis <i>et al</i> , 2010 (86) Gonen <i>et al</i> , 2005 (92) Cavagnaro <i>et al</i> , 2007 (112)
Blood	Hypolipidaemic Hypoglycaemic	Sela <i>et al</i> , 2004 (142) Mathew and Augusti, 1973 (143)
Immune system	Immunomodulatory	Bruck <i>et al</i> , 2005 (164)
CNS	Neuro protection	Zhu <i>et al</i> , 2012 (182)
Respiratory system	Pulmonary oedema	Krumm <i>et al</i> , 2012 (183)
Other	Anticancer Anti-inflammatory Antidiabetic	Bar-chen <i>et al</i> , 2010 (152) Krishna and Yadav, 2012 (158) Younis <i>et al</i> , 2010 (86)


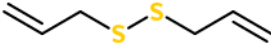
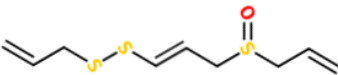
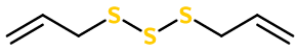
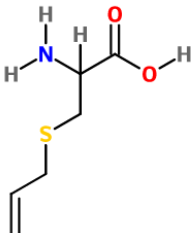
Compound	Molecular structure	Description
Allicin		This compound does not occur in garlic until it is crushed or injured (Londhe <i>et al</i> , 2011) (28)
DDS		Active against yeasts (Avato <i>et al</i> , 2000) (26).
Ajoene		The most active antiviral compound present in garlic (Weber <i>et al</i> , 1992) (52)
DTS		Active against yeasts (Avato <i>et al</i> , 2000) (26)
SAC		The most abundant organosulfur compound found in aged garlic extract (Cruz <i>et al</i> , 2007) (77)

Figure 1. Molecular structure of important organosulfur compounds from *Allium sativum* and *Allium hirtifolium*

Discussion

Our aim in preparing this paper was to show the traditional usage and previously confirmed pharmacological effects of garlic along with shallots as two of the most well-known medicinal plants in Iran and to illustrate their potential to be used as novel sources for development of new drugs based on the most recent associated studies. As it is shown in this study, garlic has a wide range of pharmacological effects including antimicrobial, cardiovascular, anti-inflammatory, anticancer, and immunomodulatory activity among many other effects. Organosulfur compounds present in garlic and shallots are the most important contents responsible for most of their pharmacological effects. Among these biologically active compounds, allicin, allyl methyl sulfide, DTS, and ajoene have been shown to be the main responsible compounds for the antifungal, antibacterial, antiprotozoal, and antiviral effects of garlic, respectively. It is evident from this study that *A. sativum* may exert toxicity only at high doses and that there have been few reports of intoxications following the ingestion of garlic.

However, care should be taken by scientists and clinicians regarding usage of this plant for therapeutic purposes until adequate studies confirm the safety and quality of the plant.

Conclusion

Finally based on this information, this review provides the evidence for other researchers to introduce garlic and shallots and their sole active compounds as safe and effective therapeutic sources in the future.

References

1. Singh TU, Kumar D, Tandan SK, Mishra SK. Inhibitory effect of essential oils of *Allium sativum* and *Piper longum* on spontaneous muscular activity of liver fluke, *Fasciola gigantica*. *Exp Parasitol* 2009; 123:302-308.
2. Eja ME, Asikong BE, Abriba C, Arikpo GE, Anwan EE, Enyi-Idoh KH. A comparative assessment of the antimicrobial effects of Garlic (*Allium sativum*) and Antibiotics on diarrheagenic organisms. *Southeast Asian J Trop Med Public Health* 2007; 38:2.
3. PDR for Herbal Medicines. Montvale: Medical Economics Company, Inc; 2000.
4. Mikaili P, Mehdioghli R. Garlic Pharmacology. National Library and Archives Organisation of Iran. 2010. ISBN: 9789647780704. (In Persian).

5. EL-mahmood MA. Efficacy of crude extracts of garlic (*Allium sativum* Linn.) against nosocomial *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. *J Med Plants Res* 2009; 3:179-185.
6. McRae MP. A review of studies of garlic (*Allium sativum*) on serum lipids and blood pressure before and after 1994: does the amount of allicin released from garlic powder tablets play a role? *J Chiropr Med* 2005; 4:82-90.
7. Tariq HA, Kandil O, Elkadi A, Carter J. Garlic revisited: therapeutic for the major diseases of our times? *J Natl Med Assoc* 1988; 80:439-445.
8. Lanzotti V, Barile E, Antignani V, Bonanomi G, Scala F. Antifungal saponins from bulbs of garlic, *Allium sativum* L. var. Voghiera. *Phytochemistry* 2012; 78:126-34.
9. Azimi H, Fallah-Tafti M, Karimi-Darimiyan M, Abdollahi M. A comprehensive review of vaginitis phytotherapy. *Pak J Biol Sci* 2011; 14:960-966.
10. Ankri S, Mirelman D. Antimicrobial properties of allicin from garlic. *Microbes Infect* 1999; 2:125-129.
11. Meriga B, Mopuri R, MuraliKrishna T. Insecticidal, antimicrobial and antioxidant activities of bulb extracts of *Allium sativum*. *Asian Pac J Trop Med* 2012; 5:391-395.
12. Pundir RK, Jain P, sharma CH. Antimicrobial activity of ethanolic extracts of *syzygium aromaticum* and *Allium sativum* against food associated bacteria and fungi. *Ethnobotan Leaflets* 2010; 14:344-360.
13. Liu S, Sun Y, Li W, Yu H, Li X, Liu Z, et al. The antibacterial mode of action of allitridi for its potential use as a therapeutic agent against *Helicobacter pylori* infection. *FEMS Microbiol Lett* 2010; 303:183-189.
14. Benkeblia N. Antimicrobial activity of essential oil extracts of various onions (*Allium cepa*) and garlic (*Allium sativum*). *Lebensm.-Wiss. u.-Technol* 2004; 37:263-268.
15. Palaksha MN, Ahmed M, Das S. Antibacterial activity of garlic extract on streptomycin-resistant *Staphylococcus aureus* and *Escherichia coli* solely and in synergism with streptomycin. *J Nat Sci Biol Med* 2010; 1:12-5.
16. Lai PK, Roy J. Antimicrobial and chemopreventive properties of herbs and spices. *Curr Med Chem* 2004; 11:1451-1460.
17. Becker PM, van Wikselaar PG, Mul MF, Pol A, Engel B, Wijdenes JW, et al. Actinobacillus pleuropneumoniae is impaired by the garlic volatile allyl methyl sulfide (AMS) *in vitro* and in-feed garlic alleviates pleuropneumonia in a pig model. *Vet Microbiol* 2012; 154:316-324.
18. Loesche WJ. Role of *Streptococcus mutans* in human dental decay. *Microbiol Rev* 1986; 50:323-580.
19. Chavan SD, Shetty NL, Kanuri M. Comparative evaluation of garlic extract mouthwash and chlorhexidine mouthwash on salivary *Streptococcus mutans* count - an *in vitro* study. *Oral Health Prev Dent* 2010; 8:369-374.
20. Appel E, Vallon-Eberhard A, Rabinkov A, Brenner O, Shin I, Sasson K, et al. Therapy of murine pulmonary aspergillosis with antibody-alliinase conjugates and alliin. *Antimicrob Agents Chemother* 2010; 54:898-906.
21. Khodavandi A, Alizadeh F, Aala F, Sekawi Z, Chong PP. *In vitro* investigation of antifungal activity of allicin alone and in combination with azoles against *Candida* species. *Mycopathologia* 2010; 169:287-295.
22. An M, Shen H, Cao Y, Zhang J, Cai Y, Wang R, et al. Allicin enhances the oxidative. *Int J Antimicrob Agents* 2009; 33:258-263.
23. Ogita A, Fujita K, Taniguchi M, Tanaka T. Enhancement of the fungicidal activity of amphotericin B by allicin, an allyl-sulfur compound from garlic, against the yeast *Saccharomyces cerevisiae* as a model system. *Planta Med* 2006; 72:1247-1250.
24. Ogita A, Nagao Y, Fujita K, Tanaka T. Amplification of vacuole-targeting fungicidal activity of antibacterial antibiotic polymyxin B by allicin, an allyl sulfur compound from garlic. *J Antibiot* 2007; 60:511-518.
25. Yousuf S, Ahmad A, Khan A, Manzoor N, Khan LA. Effect of diallyldisulphide on an antioxidant enzyme system in *Candida* species. *Can J Microbiol* 2010; 56:816-821.
26. Avato P, Tursil E, Vitali C, Miccolis V, Candido V. Allylsulfide constituents of garlic volatile oil as antimicrobial agents. *Phytomedicine* 2000; 7:239-243.
27. Kloucek P, Smid J, Flesar J, Havlik J, Titera D, Rada V, et al. *In vitro* inhibitory activity of essential oil vapors against *Ascosphaera apis*. *Nat Prod Commun* 2012; 7:253-256.
28. Londhe VP, Gavasane AT, Nipate SS, Bandawane DD, Chaudhari PD. Role of garlic (*Allium sativum*) in various diseases: An overview. *J Pharm Res Opin* 2011; 1:129 - 134.
29. Ledezma E, Apitz-Castro R. Ajoene the main active compound of garlic (*Allium sativum*): a new antifungal agent. *Rev Iberoam Micol* 2006; 23:75-80.
30. Thomaz L, Apitz-Castro R, Marques AF, Travassos LR, Taborde CP. Experimental paracoccidioidomycosis: alternative therapy with ajoene, compound from *Allium sativum*, associated with sulfamethoxazole/trimethoprim. *Med Mycol* 2008; 46:113-118.
31. Yoshida S, Kasuga Sh, Hayashi N, Ushiroguchi T, Matsuura H, Nakagawa Sh. Antifungal activity of ajoene derived from garlic. *Appl Environ Microbiol* 1987; 53:615-617.
32. Shamim S, Ahmed SW, Azhar I. Antifungal activity of *Allium*, *Aloe*, and *Solanum* species. *Pharm Biol* 2004; 42:491-498.
33. Adetumbi M, Javor GT, Lau BHS. *Allium sativum* (Garlic) inhibits lipid synthesis by *Candida albicans*. *Antimicrob Agents Chemother* 1986; 30:499-501.
34. Khan ZK, Katiyar R. Potent antifungal activity of garlic (*Allium sativum*) against experimental murine disseminated cryptococcosis. *Pharm Biol* 2000; 38:87-100.
35. Davis LE, Shen JK, Cai Y. Antifungal activity in human cerebrospinal fluid and plasma after intravenous administration of *Allium sativum*. *Antimicrob Agents Chemother* 1990; 34:651 -653.

36. Wang HX, Ng TB. Purification of allivin, a novel antifungal protein from bulbs of the round-cloved garlic. *Life Sci* 2001; 70:357-365.
37. Lima CM, Freitas FI, Morais LC, Cavalcanti MG, Silva LF, Padilha RJ, et al. Ultrastructural study on the morphological changes to male worms of *Schistosoma mansoni* after in vitro exposure to allicin. *Rev Soc Bras Med Trop* 2011; 44:327-330.
38. Waag T, Gelhaus C, Rath J, Stich A, Leippe M, Schirmeister T. Allicin and derivatives are cysteine protease inhibitors with antiparasitic activity. *Bioorg Med Chem Lett* 2010; 20:5541-5543.
39. Lun ZR, Burri C, Menzinger M, Kaminsky R. Antiparasitic activity of diallyl trisulfide (Dasuanu) on human and animal pathogenic protozoa (*Trypanosoma sp.*, *Entamoeba histolytica* and *Giardia lamblia*) in vitro. *Ann Soc Belg Med Trop* 1994; 74:51-59.
40. Gallwitz H, Bonse S, Martinez-Cruz A, Schlichting I, Schumacher K, Krauth-Siegel RL. Ajoene is an inhibitor and subversive substrate of human glutathione reductase and *Trypanosoma cruzi* trypanothione reductase: crystallographic, kinetic, and spectroscopic studies. *J Med Chem* 1999; 42:364-72.
41. Bany J, Zdanowska D, Zdanowski R, Skopińska-Rózewska E. The effect of herbal remedy on the development of *Trichinella spiralis* infection in mice. *Pol J Vet Sci* 2003; 6:6-8.
42. Anthony JP, Fyfe L, Smith H. Plant active components - a resource for antiparasitic agents? *Trends Parasitol* 2005; 21:462-468.
43. Soffar SA, Mokhtar GM. Evaluation of the antiparasitic effect of aqueous garlic (*Allium sativum*) extract in *hymenolepiasis nana* and *giardiasis*. *J Egypt Soc Parasitol* 1991; 21:497-502.
44. Ahmed M, Laing MD, Nsahlai IV. In vitro anthelmintic activity of crude extracts of selected medicinal plants against *Haemonchus contortus* from sheep. *J Helminthol* 2012; 26: 1-6.
45. Klimpel S, Abdel-Ghaffar F, Al-Rasheid KA, Aksu G, Fischer K, Strassen B, et al. The effects of different plant extracts on nematodes. *Parasitol Res* 2011; 108:1047-1054.
46. Abdel-Ghaffar F, Semmler M, Al-Rasheid KA, Strassen B, Fischer K, Aksu G, et al. The effects of different plant extracts on intestinal cestodes and on trematodes. *Parasitol Res* 2011; 108:979-984.
47. Kalu IG, Ofoegbu U, Eroegbusi J, Nwachukwa CU, Ibeh B. Larvicidal activities of ethanol extract of *Allium sativum* (garlic bulb) against the filarial vector, *Culex quinquefasciatus*. *J Med Plants Res* 2010; 4:496-498.
48. Singha S, Chandra G. Mosquito larvicidal activity of some common spices and vegetable waste on *Culex quinquefasciatus* and *Anopheles stephensi*. *Asian Pac J Trop Med* 2011; 4:288-293.
49. Martinez-Velazquez M, Rosario-Cruz R, Castillo-Herrera G, Flores-Fernandez JM, Alvarez AH, Lugo-Cervantes E. Acaricidal effect of essential oils from *Lippia graveolens* (Lamiales: Verbenaceae), *Rosmarinus officinalis* (Lamiales: Lamiaceae), and *Allium sativum* (Liliales: Liliaceae) against *Rhipicephalus (Boophilus) microplus* (Acari: Ixodidae). *J Med Entomol* 2011; 48:822-827.
50. Tedeschi P, Leis M, Pezzi M, Civolani S, Maietti A, Brandolini V. Insecticidal activity and fungitoxicity of plant extracts and components of horseradish (*Armoracia rusticana*) and garlic (*Allium sativum*). *J Environ Sci Health* 2011; 46:486-490.
51. Park IK, Choi KS, Kim DH, Choi IH, Kim LS, Bak WC, et al. Fumigant activity of plant essential oils and components from horseradish (*Armoracia rusticana*), anise (*Pimpinella anisum*) and garlic (*Allium sativum*) oils against *Lycoriella ingenua* (Diptera: Sciaridae). *Pest Manag Sci* 2006; 62:723-728.
52. Weber ND, Andersen DO, North JA, Murray BK, Lawson LD, Hughes BG. In vitro virucidal effects of *Allium sativum* (garlic) extract and compounds. *Planta Med* 1992; 58:417-423.
53. Josling P. Preventing the common cold with a garlic supplement: a double-blind placebo-controlled survey. *Adv Ther* 2001; 18:189-193.
54. Tatarintsev AV, Vrzhets PV, Ershov DE, Shchegolev AA, Turgiev AS, Karamov EV, et al. The ajoene blockade of integrin-dependent processes in an HIV-infected cell system. *Vestn Ross Akad Med Nauk* 1992; 6-10.
55. Zhen H, Fang F, Ye DY, Shu SN, Zhou YF, Dong YS, et al. Experimental study on the action of allitridin against human cytomegalovirus in vitro: Inhibitory effects on immediate-early genes. *Antiviral Res* 2006; 72:68-74.
56. Qidwai W, Qureshi R, Hasan SN, Azam SI. Effect of dietary garlic (*Allium Sativum*) on the blood pressure in humans--a pilot study. *J Pak Med Assoc* 2000; 50:204-207.
57. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. *J Nutr* 2006; 136:736S-740S.
58. Kianoush S, Balali-Mood M, Mousavi SR, Moradi V, Sadeghi M, Dadpour B, et al. Comparison of therapeutic effects of garlic and d-Penicillamine in patients with chronic occupational lead poisoning. *Basic Clin Pharmacol Toxicol* 2012; 110:476-481.
59. Nwokocha CR, Ozolua RI, Owu DU, Nwokocha MI, Ugwu AC. Antihypertensive properties of *Allium sativum* (garlic) on normotensive and two kidney one clip hypertensive rats. *Niger J Physiol Sci* 2011; 26:213-218.
60. Vazquez-Prieto MA, González RE, Renna NF, Galmarini CR, Miatello RM. Aqueous garlic extracts prevent oxidative stress and vascular remodeling in an experimental model of metabolic syndrome. *J Agric Food Chem* 2010; 58:6630-6635.
61. Duda G, Suliburska J, Pupek-Musialik D. Effects of short-term garlic supplementation on lipid metabolism and antioxidant status in hypertensive adults. *Pharmacol Rep* 2008; 60:163-170.
62. Sener G, Sakarcan A, Yegen BC. Role of garlic in the prevention of ischemia-reperfusion injury. *Mol Nutr Food Res* 2007; 51:1345-1352.
63. Al-Qattan KK, Thomson M, Al-Mutawa'a S, Al-Hajeri D, Drobiova H, Ali M. Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. *J Nutr* 2006; 136:774S-776S.
64. Harauma A, Moriguchi T. Aged garlic extract improves blood pressure in spontaneously hypertensive rats more safely than raw garlic. *J Nutr* 2006; 136:769S-773S.
65. Zahid Ashraf M, Hussain ME, Fahim M. Antiatherosclerotic effects of dietary supplementations

- of garlic and turmeric Restoration of endothelial function in rats. *Life Sci* 2005; 77:837-857.
66. Budoff MJ, Takasu J, Flores FR, Niihara Y, Lu B, Lau BH, *et al.* Inhibiting progression of coronary calcification using Aged Garlic Extract in patients receiving statin therapy: a preliminary study. *Prev Med* 2004; 39:985-991.
67. Verma SK, Rajeevan v, Jain P, Bordia A. Effect of garlic (*Allium sativum*) oil on exercise tolerance in patients with coronary artery disease. *J Physiol Pharmacol* 2005; 49:115-118.
68. Yang Y, Chan SW, Hu M, Walden R, Tomlinson B. Effects of some common food constituents on cardiovascular disease. *ISRN Cardiol* 2011; 397136.
69. Ali M, Al-Qattan KK, Al-Enezi F, Khanafer RM, Mustafa T. Effect of allicin from garlic powder on serum lipids and blood pressure in rats fed with a high cholesterol diet. *Prostaglandins Leukot Essent Fatty Acids* 2000; 62:253-259.
70. Chu TC, Ogidighen M, Han JC, Potter DE. Allicin-induced hypotension in rabbit eyes. *J Ocul Pharmacol* 1993; 9:201-209.
71. Drobiova H, Thomson M, Al-Qattan K, Peltonen-Shalaby R, Al-Amin Z, Ali M. Garlic increases antioxidant levels in diabetic and hypertensive rats determined by a modified peroxidase method. *Evid Based Complement Alternat Med* 2011; 703049.
72. Fallon MB, Abrams GA, Abdel-Razek TT, Dai J, Chen SJ, Chen YF, *et al.* Garlic prevents hypoxic pulmonary hypertension in rats. *Am J Physiol* 1998; 275: L283-287.
73. Brankovic S, Radenkovic M, Kitic D, Veljkovic S, Ivetic V, Pavlovic D, *et al.* Comparison of the hypotensive and bradycardic activity of ginkgo, garlic, and onion extracts. *Clin Exp Hypertens* 2011; 33:95-99.
74. Gu X, Zhu YZ. Therapeutic applications of organosulfur compounds as novel hydrogen sulfide. *Expert Rev Clin Pharmacol* 2011; 4:123-133.
75. Lavu M, Bhushan S, Lefer DJ. Hydrogen sulfide-mediated cardioprotection: mechanisms and therapeutic potential. *Clin Sci* 2011; 120:219-229.
76. Ginter E, Simko V. Garlic (*Allium sativum* L.) and cardiovascular diseases. *Bratisl Lek Listy* 2010; 111:452-456.
77. Cruz C, Correa-Rotter R, Sánchez-González DJ, Hernández-Pando R, Maldonado PD, Martínez-Martínez CM, *et al.* Renoprotective and antihypertensive effects of S-allylcysteine in 5/6 nephrectomized rats. *Am J Physiol Renal Physiol* 2007; 293:F1691-1698.
78. Sobenin IA, Andrianova IV, Fomchenkov IV, Gorchakova TV, Orekhov AN. Time-released garlic powder tablets lower systolic and diastolic blood pressure in men with mild and moderate arterial hypertension. *Hypertens Res* 2009; 32: 433-437.
79. Durak I, Kavutcu M, Aytac B, Avci A, Devrim E, Ozbek H, Oztürk HS. Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. *J Nutr Biochem* 2004; 15:373-377.
80. Castro C, Lorenzo AG, González A, Cruzado M. Garlic components inhibit angiotensin II-induced cell-cycle progression and migration: Involvement of cell-cycle inhibitor p27 (Kip1) and mitogen-activated protein kinase. *Mol Nutr Food Res* 2010; 54:781-787.
81. Thevenot T, Pastor CM, Cervoni JP, Jacquelinet C, Nguyen-Khac E, Richou C, *et al.* Hepatopulmonary syndrome. *Gastroenterol Clin Biol* 2009; 33:565-579.
82. Asdaq SM, Inamdar MN. Pharmacodynamic and Pharmacokinetic Interactions of Propranolol with Garlic (*Allium sativum*) in Rats. *Evid Based Complement Alternat Med* 2011; 824042.
83. Asdaq SM, Inamdar MN. The potential benefits of a garlic and hydrochlorothiazide combination as antihypertensive and cardioprotective in rats. *J Nat Med* 2011; 65:81-88.
84. Asdaq SM, Inamdar MN. The potential for interaction of hydrochlorothiazide with garlic in rats. *Chem Biol Interact* 2009; 181:472-479.
85. Asdaq SM, Inamdar MN. Potential of garlic and its active constituent, S-allyl cysteine, as antihypertensive and cardioprotective in presence of captopril. *Phytomedicine* 2010; 17:1016-1026.
86. Younis F, Mirelman D, Rabinkov A, Rosenthal T. S-allyl-mercapto-captopril: a novel compound in the treatment of Cohen-Rosenthal diabetic hypertensive rats. *J Clin Hypertens (Greenwich)* 2010; 12:451-455.
87. Elkayam A, Mirelman D, Peleg E, Wilchek M, Miron T, Rabinkov A, *et al.* The effects of allicin and enalapril in fructose-induced hyperinsulinemic hyperlipidemic hypertensive rats. *Am J Hypertens* 2001; 14:377-381.
88. Wang HX, Ng TB. Natural products with hypoglycemic, hypotensive, hypocholesterolemic antiatherosclerotic and antithrombotic activities. *Life Sci* 1999; 65:2663-2677.
89. Espirito Santo SM, van Vlijmen BJ, van Duyvenvoorde W, Offerman EH, Havekes LM, Arnault I, *et al.* Absence of an atheroprotective effect of the garlic powder printanor in APOE*3-Leiden transgenic mice. *Atherosclerosis* 2004; 177:291-297.
90. Calvo-Gómez O, Morales-López J, López MG. Solid-phase microextraction-gas chromatographic-mass spectrometric analysis of garlic oil obtained by hydrodistillation. *J Chromatogr A* 2004; 1036:91-93.
91. Jain RC, Konar DB. Effect of garlic oil in experimental cholesterol atherosclerosis. *Atherosclerosis* 1978; 29:125-129.
92. Gonen A, Harats D, Rabinkov A, Miron T, Mirelman D, Wilchek M, *et al.* The antiatherogenic effect of allicin: possible mode of action. *Pathobiology* 2005; 72:325-334.
93. Gromnatskiĭ NI, Sereditskaia ZhE, Lazareva NV, Sereditskiĭ AV, Annenkova GV. Effects of garlic allicor tablets on lipid metabolism and risk of fatal cardiovascular complications in patients with atherogenic dyslipoproteinemia. *Vopr Pitan* 2007; 76:60-64.
94. Orekhov AN, Tertov VV, Sobenin IA, Pivovarova EM. Direct anti-atherosclerosis-related effects of garlic. *Ann Med* 1995; 27:63-65.
95. Orekhov AN, Grünwald J. Effects of garlic on atherosclerosis. *Nutrition* 1997; 13:656-663.
96. Lau BH. Suppression of LDL oxidation by garlic. *J Nutr* 2001; 131:985S-988S.
97. Phelps S, Harris WS. Garlic supplementation and lipoprotein oxidation susceptibility. *Lipids* 1993; 28:475-477.
98. Koscielny J, Klüssendorf D, Latza R, Schmitt R, Radtke H, Siegel G, *et al.* The antiatherosclerotic effect

- of *Allium sativum*. Atherosclerosis 1999; 144:237-249.
99. Morcos NC. Modulation of lipid profile by fish oil and garlic combination. J Natl Med Assoc 1997; 89:673-678.
100. Mathew B, Biju R. Neuroprotective effects of garlic: a review. Libyan J Med 2008; 3:23-33.
101. Asdaq SM, Inamdar MN, Asad M. Effect of conventional antihypertensive drugs on hypolipidemic action of garlic in rats. Indian J Exp Biol 2009; 47:176-181.
102. Yamaji K, Sarker KP, Abeyama K, Maruyama I. Anti-atherogenic effects of an egg yolk-enriched garlic supplement. Int J Food Sci Nutr 2004; 55:61-66.
103. Agarwal K. Therapeutic actions of garlic constituents. Med Res Rev 1996; 16:111-124.
104. Fukao H, Yoshida H, Tazawa Y, Hada T. Antithrombotic effects of odorless garlic powder both in vitro and in vivo. Biosci Biotechnol Biochem 2007; 71:84-90.
105. Srivastava KC. Aqueous extracts of onion, garlic and ginger inhibit platelet aggregation and alter arachidonic acid metabolism. Biomed Biochim Acta 1984; 43:S335-346.
106. Hiyasat B, Sabha D, Grotzinger K, Kempfert J, Rauwald JW, Mohr FW, et al. Antiplatelet activity of *Allium ursinum* and *Allium sativum*. Pharmacology 2009; 83:197-204.
107. MacDonald JA, Marchand ME, Langler RF. Improving upon the *in vitro* biological activity of antithrombotic disulfides. Blood Coagul Fibrinolysis 2004; 15:447-450.
108. Choi YH, Park HS. Apoptosis induction of U937 human leukemia cells by diallyl trisulfide induces through generation of reactive oxygen species. J Biomed Sci 2012; 19:50.
109. Chan KC, Yin MC, Chao WJ. Effect of diallyl trisulfide-rich garlic oil on blood coagulation and plasma activity of anticoagulation factors in rats. Food Chem Toxicol 2007; 45:502-507.
110. Bordia A, Verma SK, Srivastava KC. Effect of garlic (*Allium sativum*) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 1998; 58:257-263.
111. Ariga T, Tsuj K, Seki T, Moritomo T, Yamamoto JI. Antithrombotic and antineoplastic effects of phyto-organosulfur compounds. Biofactors 2000; 13:251-255.
112. Cavagnaro PF, Camargo A, Galmarini CR, Simon PW. Effect of cooking on garlic (*Allium sativum* L.) antiplatelet activity and thiosulfates content. J Agric Food Chem 2007; 55:1280-1288.
113. Nishimura H, Takahashi T, WijayaCH, Satoh A, Ariga T. Thermochemical transformation of sulfur compounds in Japanese domestic *Allium*, *Allium victorialis* L. Biofactors 2000; 13: 257-263.
114. Briggs WH, Xiao H, Parkin KL, Shen C, Goldman IL. Differential inhibition of human platelet aggregation by selected *Allium* thiosulfates. J Agric Food Chem 2000; 48:5731-5735.
115. Apitz-Castro R, Badimon JJ, Badimon L. A garlic derivative, ajoene, inhibits platelet deposition on severely damaged vessel wall in an *in vivo* porcine experimental model. Thromb Res 1994; 75:243-249.
116. Mousa SA. Antithrombotic effects of naturally derived products on coagulation and platelet Function. Methods Mol Biol 2010; 663:229-240.
117. Apitz-Castro R, Escalante J, Vargas R, Jain MK. Ajoene, the antiplatelet principle of garlic, synergistically potentiates the antiaggregatory action of prostacyclin, forskolin, indomethacin and dypiridamole on human platelets. Thromb Res 1986; 42:303-311.
118. Apitz-Castro R, Ledezma E, Escalante J, Jain MK. The molecular basis of the antiplatelet action of ajoene: direct interaction with the fibrinogen receptor. Biochem Biophys Res Commun 1986; 141:145-150.
119. Srivastava KC, Tyagi OD. Effects of a garlic-derived principle (ajoene) on aggregation and arachidonic acid metabolism in human blood platelets. Prostaglandins Leukot Essent Fatty Acids 1993; 49:587-595.
120. Stanger MJ, Thompson LA, Young AJ, Lieberman HR. Anticoagulant activity of select dietary supplements. Nutr Rev 2012; 70:107-117.
121. Mateen AA, Rani PU, Naidu MU, Chandrashekar E. Pharmacodynamic interaction study of *Allium sativum* (garlic) with cilostazol in patients with type II diabetes mellitus. Indian J Pharmacol 2011; 43:270-274.
122. Macan H, Uykipang R, Alconcel M, Takasu J, Razon R, Amagase H, et al. Aged garlic extract may be safe for patients on warfarin therapy. J Nutr 2006; 136:793S-795S.
123. Spolarich AE, Andrews L. An examination of the bleeding complications associated with herbal supplements antiplatelet and anticoagulant medications. J Dent Hyg 2007; 81:67.
124. Kuda T, Iwai A, Yano T. Effect of red pepper *Capsicum annuum* var. *conoides* and garlic *Allium sativum* on plasma lipid levels and cecal microflora in mice fed beef tallow. Food Chem Toxicol 2004; 42:1695-1700.
125. Zacharias NT, Sebastian KL, Philip B, Augusti KT. Hypoglycemic and hypolipidaemic effects of garlic in sucrose fed rabbits. Indian J Physiol Pharmacol 1980; 24:151-154.
126. Gorinstein S, Leontowicz H, Leontowicz M, Drzewiecki J, Najman K, Katrich E, et al. Raw and boiled garlic enhances plasma antioxidant activity and improves plasma lipid metabolism in cholesterol-fed rats. Life Sci 2006; 78:655-663.
127. Kuo CF, Jao YC, Yang P. Downregulation of hepatic lipoprotein assembly in rats by fermented products of *Monascus pilosus*. Nutrition 2008; 24:477-483.
128. Sengupta A, Ghosh S, Bhattacharjee S. *Allium* vegetables in cancer prevention: an overview. Asian Pac J Cancer Prev 2004; 5:237-245.
129. Lin MC, Wang EJ, Lee C, Chin KT, Liu D, Chiu JF, et al. Garlic inhibits microsomal triglyceride transfer protein gene expression in human liver and intestinal cell lines and in rat intestine. J Nutr 2002; 132:1165-1168.
130. Peleg A, Hershovici T, Lipa R, Anbar R, Redler M, Beigel Y. Effect of garlic on lipid profile and psychopathologic parameters in people with mild to moderate hypercholesterolemia. Isr Med Assoc J 2003; 5:637-640.

131. Rajasree CR, Rajamohan T, Augusti KT. Biochemical effects of garlic protein on lipid metabolism in alcohol fed rats. *Indian J Exp Biol* 1999; 37:243-247.
132. Bobboi A, Augusti KT, Joseph PK. Hypolipidemic effects of onion oil and garlic oil in ethanol-fed rats. *Indian J Biochem Biophys* 1984; 21:211-213.
133. Mathew BC, Daniel RS, Augusti KT. Hypolipidemic effect of garlic protein substituted for casein in diet of rats compared to those of garlic oil. *Indian J Exp Biol* 1996; 34:337-340.
134. Orellana A, Kawada ME, Morales MN, Vargas L, Bronfman M. Induction of peroxisomal fatty acyl-coenzyme A oxidase and total carnitine acetyl-coenzyme A transferase in primary cultures of rat hepatocytes by garlic extracts. *Toxicol Lett* 1992; 60:11-17.
135. Sovová M, Sova P. Pharmaceutical importance of *Allium sativum* L. 5. Hypolipemic effects *in vitro* and *in vivo*. *Česka Slov Farm* 2004; 53:117-123.
136. Kempaiah RK, Srinivasan K. Antioxidant status of red blood cells and liver in hypercholesterolemic rats fed hypolipidemic spices. *Int J Vitam Nutr Res* 2004; 74:199-208.
137. Pedraza-Chaverrí J, Medina-Campos ON, Granados-Silvestre MA, Maldonado PD, Olivares-Corichi IM, Hernández-Pando R. Garlic ameliorates hyperlipidemia in chronic aminonucleoside nephrosis. *Mol Cell Biochem* 2000; 211:69-77.
138. Kempaiah RK, Srinivasan K. Beneficial influence of dietary curcumin, capsaicin and garlic on erythrocyte integrity in high-fat fed rats. *J Nutr Biochem* 2006; 17:471-478.
139. Lii CK, Huang CY, Chen HW, Chow MY, Lin YR, Huang CS, *et al*. Diallyl trisulfide suppresses the adipogenesis of 3T3-L1 preadipocytes through ERK activation. *Food Chem Toxicol* 2012; 50:478-484.
140. Rai SK, Sharma M, Tiwari M. Inhibitory effect of novel diallyldisulfide analogs on HMG-CoA reductase expression in hypercholesterolemic rats: CREB as a potential upstream target. *Life Sci* 2009; 85:211-219.
141. Liu L, Yeh YY. Water-soluble organosulfur compounds of garlic inhibit fatty acid and triglyceride syntheses in cultured rat hepatocytes. *Lipids* 2001; 36:395-400.
142. Sela U, Ganor S, Hecht I, Brill A, Miron T, Rabinkov A, *et al*. Allicin inhibits SDF-1 α -induced T cell interactions with fibronectin and endothelial cells by down-regulating cytoskeleton rearrangement, Pyk-2 phosphorylation and VLA-4 expression. *Immunology* 2004; 111:391-399.
143. Mathew PT, Augusti KT. Studies on the effect of allicin (diallyl disulphide-oxide) on alloxan diabetes I. Hypoglycaemic action and enhancement of serum insulin effect and glycogen Synthesis. *Indian J Biochem Biophys* 1973; 10:209-212.
144. Vidyashankar S, Sambaiah K, Srinivasan K. Dietary garlic and onion reduce the incidence of atherogenic diet-induced cholesterol gallstones in experimental mice. *Br J Nutr* 2009; 101: 1621-1629.
145. Andrianova IV, Demidova OM, Medvedeva LA, Latyshev OA. Correction of hyperlipidemia with Allicor. *Klin Med (Mosk)* 2004; 82:56-58.
146. Augusti KT, Arathy SL, Asha R, Ramakrishnan J, Zaira J, Lekha V, *et al*. A comparative study on the beneficial effects of garlic (*Allium sativum* Linn) amla (*Embllica officinalis* Gaertn) and onion (*Allium cepa* Linn) on the hyperlipidemia induced by butter fat and beef fat in rats. *Indian J Exp Biol* 2001; 39:760-766.
147. Romagnolo DF, Davis CD, Milner JA. Phytoalexins in cancer prevention. *Front Biosci* 2012; 17: 2035-2058.
148. Lai KC, Kuo CL, Ho HC, Yang JS, Ma CY, Lu HF, *et al*. Diallyl sulfide, diallyl disulfide and diallyl trisulfide affect drug resistant gene expression in colo 205 human colon cancer cells *in vitro* and *in vivo*. *Phytomedicine* 2012; 19:625-630.
149. Yu CS, Huang AC, Lai KC, Huang YP, Lin MW, Yang JS, *et al*. Diallyl trisulfide induces apoptosis in human primary colorectal cancer cells. *Oncol Rep* 2012; 28:949-954.
150. Park HS, Kim GY, Choi IW, Kim ND, Hwang HJ, Choi YW, *et al*. Inhibition of matrix metalloproteinase activities and tightening of tight junctions by diallyl disulfide in AGS human gastric carcinoma cells. *J Food Sci* 2011; 76:T105-111.
151. Liu Z, Li M, Chen K, Yang J, Chen R, Wang T, *et al*. S-allylcysteine induces cell cycle arrest and apoptosis in androgen-independent human prostate cancer cells. *Mol Med Report* 2012; 5:439-443.
152. Bar-Chen W, Golan T, Peri I, Ludmer Z, Schwartz B. Allicin purified from fresh garlic cloves induces apoptosis in colon cancer cells via Nrf2. *Nutr Cancer* 2010; 62:947-957.
153. Wang X, Jiao F, Wang QW, Wang J, Yang K, Hu RR *et al*. Aged black garlic extract induces inhibition of gastric cancer cell growth *in vitro* and *in vivo*. *Mol Med Report* 2012; 5:66-72.
154. Ban JO, Lee DH, Kim EJ, Kang JW, Kim MS, Cho MC, *et al*. Antiobesity effects of a sulfur compound thiocresonone mediated via down-regulation of serum triglyceride and glucose levels and lipid accumulation in the liver of db/db mice. *Phytother Res* 2012; 10:3729.
155. Dkhil MA, Abdel-Baki AS, Wunderlich F, Sies H, Al-Quraishy S. Anticoccidial and antiinflammatory activity of garlic in murine *Eimeria papillata* infections. *Vet Parasitol* 2011; 175:66-72.
156. Shih PC, Kuo CH, Juang JY, Liu CH, Hsu L, Liu CT. Effects of garlic oil on the migration of neutrophil-like cell studied by using a chemotactic gradient Labchip. *J Biomed Biotechnol* 2010; 31:9059.
157. Chiang YH, Jen LN, Su HY, Lii CK, Sheen LY, Liu CT. Effects of garlic oil and two of its major organosulfur compounds, diallyl disulfide and diallyl trisulfide, on intestinal damage in rats injected with endotoxin. *Toxicol Appl Pharmacol* 2006; 213:46-54.
158. Krishna A, Yadav A. Lead compound design for TPR/COX dual inhibition. *J Mol Model* 2012; 18:4397-4408.
159. Lin GH, Lee YJ, Choi DY, Han SB, Jung JK, Hwang BY, *et al*. Anti-amyloidogenic effect of thiocresonone through anti-inflammation *in vitro* and *in vivo* models. *J Alzheimers Dis* 2012; 29:659-676.
160. Chandrashekar PM, Venkatesh YP. Fructans from aged garlic extract produce a delayed immunoadjuvant response to ovalbumin antigen in BALB/c mice. *Immunopharmacol Immunotoxicol* 2012; 34:174-180.
161. Chandrashekar PM, Prashanth KV, Venkatesh YP. Isolation, structural elucidation and

- immunomodulatory activity of fructans from aged garlic extract. *Phytochemistry* 2011; 72:255-264.
162. Hanieh H, Narabara K, Tanaka Y, Gu Z, Abe A, Kondo Y. Immunomodulatory effects of Alliums and Ipomoea batata extracts on lymphocytes and macrophages functions in White Leghorn chickens: *in vitro* study. *Anim Sci J* 2012; 83:68-76.
163. Gamboa-León MR, Aranda-González I, Mut-Martín M, García-Miss MR, Dumonteil E. *In vivo* and *in vitro* control of *Leishmania mexicana* due to garlic-induced NO production. *Scand J Immunol* 2007; 66:508-514.
164. Bruck R, Aeed H, Brazovsky E, Noor T, Hershkovitz R. Allicin, the active component of garlic, prevents immune-mediated, concanavalin A-induced hepatic injury in mice. *Liver Int* 2005; 25:613-621.
165. Lang A, Lahav M, Sakhnini E, Barshack I, Fidler HH, Avidan B, et al. Allicin inhibits spontaneous and TNF-alpha induced secretion of proinflammatory cytokines and chemokines from intestinal epithelial cells. *Clin Nutr* 2004; 23:1199-1208.
166. Salman H, Bergman M, Bessler H, Punsky I, Djaldetti M. Effect of a garlic derivative (alliin) on peripheral blood cell immune responses. *Int J Immunopharmacol* 1999; 21:589-597.
167. Tattelman E. Health effects of garlic. *Am Fam Physician* 2005; 72:103-106.
168. Friedman T, Shalom A, Westreich M. Self-inflicted garlic burns: our experience and literature review. *Int J Dermatol* 2006; 45:1161-1163.
169. Hamlaoui-Gasmi S, Mokni M, Limam N, N'guessan P, Carrier A, Limam F, et al. Grape seed and skin extract mitigates garlic-induced oxidative stress in rat liver. *Can J Physiol Pharmacol* 2012; 90:547-556.
170. Rana SV, Pal R, Vaiphei K, Singh K. Garlic hepatotoxicity: safe dose of garlic. *Trop Gastroenterol* 2006; 27:26-30.
171. Banerjee SK, Maulik M, Manchanda SC, Dinda AK, Das TK, Maulik SK. Garlic-induced alteration in rat liver and kidney morphology and associated changes in endogenous antioxidant status. *Food Chem Toxicol* 2001; 39:793-797.
172. Alnaqeeb MA, Thomson M, Bordia T, Ali M. Histopathological effects of garlic on liver and lung of rats. *Toxicol Lett* 1996; 85:157-164.
173. Liu CT, Wong PL, Lii CK, Hse H, Sheen LY. Antidiabetic effect of garlic oil but not diallyl disulfide in rats with streptozotocin-induced diabetes. *Food Chem Toxicol* 2006; 44:1377-1384.
174. Müller AC, Kanfer I. Potential pharmacokinetic interactions between antiretrovirals and medicinal plants used as complementary and African traditional medicines. *Biopharm Drug Dispos* 2011; 32:458-470.
175. Berginc K, Žakelj S, Kristl A. *In vitro* interactions between aged garlic extract and drugs used for the treatment of cardiovascular and diabetic patients. *Eur J Nutr* 2010; 49:373-384.
176. Reddy GD, Reddy AG, Rao GS, Kumar MV. Pharmacokinetic interaction of garlic and atorvastatin in dyslipidemic rats. *Indian J Pharmacol* 2012; 44:246-252.
177. Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004; 22:2489-2503.
178. Fateh R, Kashani MJN, Motevallian M, Falahati M, Yazdanparast A. *In vitro* antifungal activity of *Allium hirtifolium* in comparison with the miconazole. *Med J Islam Repub Iran* 2010; 24:1.
179. Amin M, Jahangirnezhad M, Rasaei N, Pipelzadeh MH, Rafiee M. Evaluation of the effect of Persian shallot (*Allium hirtifolium*, boiss) aqueous extract on mouth bacterial count compared with chlorhexidine mouth rinse. *Afr J Microbiol Res* 2012; 6:5809-5813.
180. Ghodrati Azadi H, Ghaffari SM, Riazi GH, Ahmadian S, Vahedi F. Antiproliferative activity of chloroformic extract of Persian Shallot, *Allium hirtifolium*, on tumor cell lines. *Cytotechnology* 2008; 56:179-185.
181. Sela U, Ganor S, Hecht I, Brill A, Miron T, Rabinkov A, et al. Allicin inhibits SDF-1alpha-induced T cell interactions with fibronectin and endothelial cells by down-regulating cytoskeleton rearrangement, Pyk-2 phosphorylation and VLA-4 expression. *Immunology* 2004; 111:391-399.
182. Zhu Z, Mao S, Zhu W. Effects of ruminal infusion of garlic oil on fermentation dynamics, fatty acid profile and abundance of bacteria involved in biohydrogenation in rumen of goats. *Asian-Aust J Anim Sci* 2012; 25:962-970.
183. Krumm P, Giraldez T, Alvarez de la Rosa D, Clauss WG, Fronius M, Althaus M. Thiol-reactive compounds from garlic inhibit the epithelial sodium channel (ENaC). *Bioorg Med Chem* 2012; 20:3979-3984.