

Review

Therapeutic Value of Garlic (*Allium sativum*): A Review

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ABSTRACT

Garlic (*Allium sativum*) is a source of medicine in many ways in human beings in routine life as well as in animals and its leaves, flowers, and cloves have been used in traditional medicine for a long time. Research in recent decades has shown widespread pharmacological and therapeutic effects of *A. sativum* and its organosulfur compounds especially allicin. The most important chemical constituents of this plant are organosulfur compounds such as allicin, diallyl disulphide, S-allylcysteine, and diallyl trisulfide. These chemicals were used for the treatment of inflammation, cancer, blood pressure, atherosclerosis, and hyperlipidemia as praised by several authors. Additionally, extracts of garlic have been used to treat various diseases and have shown anti-viral, anti-bacterial, anti-fungal, anticoagulative and antioxidant effects. However, few adverse effects have been found with garlic are nausea and vomiting when high quantity consumed. To review the therapeutic values of garlic and its importance in human and veterinary practices. Garlic is 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.

Keywords

Allium sativum; Therapeutic values; Antibacterial; Antifungal; Antiviral; Anticancer; Anticoagulative; Antioxidant; Anti-inflammatory.

INTRODUCTION

Traditional medicines occupy a valuable place amongst rural groups of developing countries for the provision of health care inside the absence of an efficient public health care scheme.¹ The use of traditional treatments is common in sub-Saharan Africa, and visits to traditional healers remain a prime live of care for many people because of preference, affordability, limitation of practitioners and modern hospitals.² Moreover, traditional medicines may be the supply of remedy for lots of health complications.^{3,4}

Garlic, *Allium sativum* is a member of the Alliaceae family, has been widely recognized as a valuable spice and a popular medicine for various diseases and physiological disorders. The word garlic was originated from the Celtic word meaning pungent. Garlic is cultivated practically throughout the world and appears to have originated in central Asia and then spread to China, the Near East, and the Mediterranean region before moving west to Central and Southern Europe, Northern Africa (Egypt) and Mexico.⁵⁻⁷ Garlic has played an essential role for over 7,000-years in central

Asia, Africa, Europe, and the Mediterranean region.⁸

Garlic is a bulb growing to 25-70 cm with hermaphrodite flowers where its leaves and cloves have been used in traditional medicine for a long time. Aged garlic is used to make aged garlic extract (AGE), a popular herbal supplement that has been proven to boost the immune system and possibly prevent cancer and cardiovascular disease. Additionally, as garlic ages, it loses its strong flavor, so there is no need to worry about breath odor. Garlic can be used for culinary and medicinal purposes. The culinary use includes spicy flavor that mellows and sweetens considerably with cooking. While its medicinal uses include treatment of whooping cough, lung disease, stomach complaint and disorder resulting from childbirth, cold, sore eyes, and earache as well as help in the prevention of heart disease.^{9,10} A study on Czech revealed that garlic oil especially dehydrated powder could help in reducing the accumulation of cholesterol in the vascular walls of animals.^{11,12}

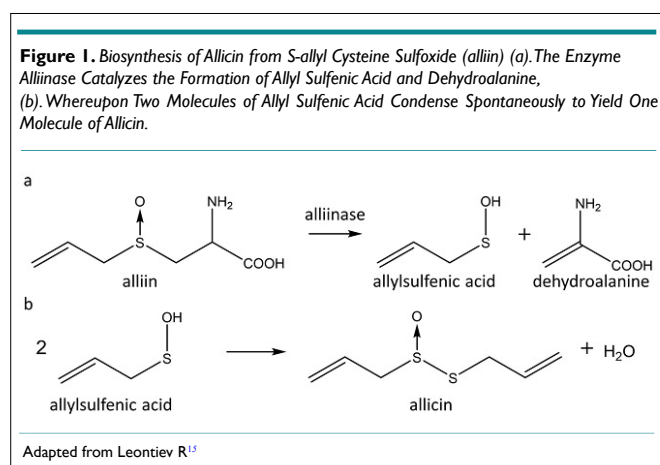
Allicin (diallyl-dithiosulfate) is the most important component of garlic and generally claimed to be responsible for its numerous beneficial effects including antibacterial, antiviral, anti-

fungus and antioxidative effect. Nowadays, the alarming growth of the number of antibiotic-resistant bacteria and difficulties in the treatment of infections has initiated a search for new antibacterial compounds and develop new alternative strategies in combating bacterial infections. Medicinal plants such as garlic, with their long history of use in folk medicine for the treatment of infectious diseases, have become a promising new source of antibacterial agents. Besides, they exhibit a direct antimicrobial activity and/or an indirect activity through synergism with antibiotics that increase their effectiveness.¹³ Hence, this review was prepared with the aim of increasing awareness on the medicinal importance of *A. sativum* in human and veterinary medicine

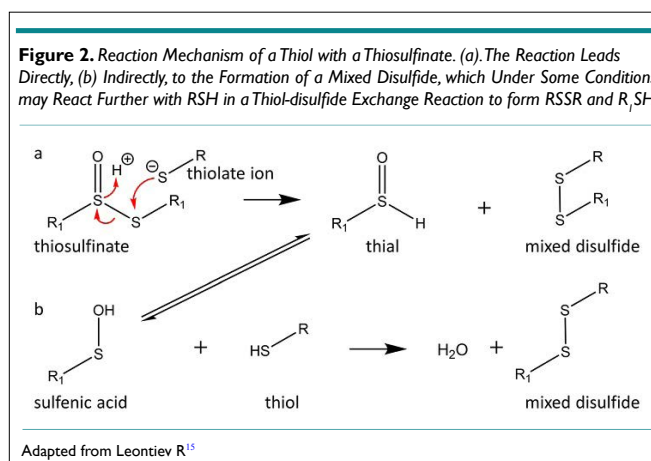
ALLIUM SATIVUM

Biosynthesis

Alliin (allyl 2-propenethiosulfinate or diallyl thiosulfinate) is the principal bioactive compound present in aqueous garlic extract or raw garlic homogenate. It is produced from the non-proteinogenic acid alliin (S-allyl cysteine sulfoxide) upon tissue damage in a reaction that is catalyzed by the enzyme alliinase (Figure 1). Alliinase enzyme is activated when garlic is chopped or crushed and acts on alliin (present in raw garlic) to produce alliin. In addition, structurally analogous thiosulfonates are produced in nature by other *Allium* species.^{4,14}



Allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate, and γ -L-glutamyl-S-alkyl-L-cysteine are other important sulfur-containing compounds present in garlic. The thiosulfonates are condensation products of two sulfenic acids to form disulfide-S-monoxides and can be viewed as 'sulfenic acid anhydrides'. In the laboratory, alliin can be synthesized most effectively by oxidation of diallyl disulfide (DADS) with H_2O_2 in the presence of an organic acid catalyst that is first oxidized to the corresponding peroxy-acid, like performic acid or peracetic acid.¹⁶ The reactivity of thiosulfonates towards thiol-groups is an important component of their antimicrobial activity. The electron-withdrawing effect of the O-atom creates an electrophilic sulfur center which reacts readily with thiols, or more specifically, with thiolate ions (Figure 2), thereby forming an S-allylmercapto adduct.¹⁷



Chemical Constituents of *Allium sativum* and its Nutritional Value

A. sativum contains about 33 sulfur compounds, several enzymes,¹⁷ amino acids, and minerals such as selenium. Studies carried out on the chemical composition of the garlic show that sulfur compounds such as alliin are important constituents of the plant that is responsible for many of its medicinal effects and garlic's pungent odor. Besides, diallyl disulphide (DDS), S-allylcysteine (SAC) and diallyl trisulfide (DTS) are other sulfur compounds that have some roles in the therapeutic effects of the plant. DTS is a chemically stable final transformation product of alliin.^{3,18}

Garlic powder is a simply dehydrated and crushed garlic clove. Besides, the water extract of heat-treated garlic contains mainly alliin. Accordingly, enzymatic activity of alliinase of garlic powder is similar to that of fresh garlic. However, dehydration temperature should not exceed 60 °C, above which alliinase is inactivated.^{3,19} In contrast to fresh garlic and garlic powder, Garlic oil, and steam-distilled garlic do not have significant amounts of alliin or alliin, but instead, contain various products of alliin transformation. Garlic has been analyzed for moisture, carbohydrate, protein, fat, minerals, vitamins, energy, ash, pH, acidity and essential oil contents.^{20,21} Some of the nutritional and chemical properties of garlic bulbs are summarized in Table 1.

Table 1. Nutritional Value and Properties of *Allium Sativum*; Values Expressed per 100 g of Raw Garlic (*Allium sativum*)

Properties	Values	Minerals	Values	Vitamins	Values
Energy	119 Kcal	Potassium	446 mg	Thiamine	0.16 mg
Moisture	70%	Phosphorus	134 mg	Riboflavin	0.02 mg
Protein	4.3 g	Magnesium	24.1 mg	Niacin	1.02 mg
Carbohydrate	24.3 g	Sodium	19 mg	Pyridoxine	0.32 mg
Fiber	1.2 g	Calcium	17.8 mg	Folic acid	4.8 µg
Fat	0.23 g	Iron	1.2 mg	Ascorbic acid	14 mg
Alcohol	0 g	Zinc	1.1 mg	Carotenoids	5 µg
Ash	2.3%	Iodine	4.7 µg	Vitamin A	Traces
PH	6.05	Selenium	2 µg	Vitamin E	0.011 µg
Acidity	0.172%				

Source: Pacurar et al²²

Historical Background and Traditional uses of *Allium Sativum*

The ancient Egyptians used garlic to treat diarrhea and its potential medical value was described on the walls of ancient temples and on papyrus dating to 1500 BC. It was used by Greek physicians Hippocrates and Galen to treat intestinal and extra-intestinal diseases; ancient Japanese and Chinese used it to treat headaches, flu, sore throat, and fever. In Africa, particularly in Nigeria, it is used to treat abdominal discomfort, diarrhea, otitis media, and respiratory tract infections.^{6,8}

Garlic is nicknamed as Russian penicillin due to its widespread use as a topical and systemic antimicrobial agent; it is commonly used in many cultures as an excitement and reputation of healing power. Garlic was used to treat common colds, hay fever and asthma in Europe and India.²³ Leaves and cloves of *A. sativum* have been used in traditional medicine of Iran and other countries for a long time.^{24,25} In the pre-antibiotic era, allicin can kill bacteria *via* the gas phase and was used to successfully treat many lung-pathogenic bacteria such as tuberculosis from crushed garlic preparations through breathing in the vapor.²⁶

MEDICINAL IMPORTANCE OF ALLIUM SATIVUM

Therapeutic use of garlic has been recognized as a potential medicinal value for thousands of years to different microorganisms. Antifungal, antiviral, antibacterial, anthelmintic, antiseptic and anti-inflammatory properties of garlic have been well documented. The extracts exhibited a pronounced activity against both gram-negative (*E. coli*, *Salmonella* species, and *Citrobacter* Enterobacter, *Pseudomonas klebsiella*) and gram-positive (*Staphylococcus aureus*, *S. pneumonia* Group A *streptococcus*, and *Bacillus anthrax*) bacteria causing considerable morbidity worldwide.^{4,6,27}

Antimicrobial Activity

Allicin and other sulfur compounds are thought to be the major compounds responsible for the antimicrobial effect of garlic. The antimicrobial properties of garlic were first described by Pasteur in 1958, and since then, many researches had demonstrated its effectiveness and broad-spectrum antimicrobial activity against many species of bacteria, viruses, parasites, protozoan and fungi.^{26,28} Garlic is more effective with the least side effects as compared to commercial antibiotics; as a result, they are used as an alternative remedy for the treatment of various infections.^{29,30} Out of the many medicinal plants, garlic has an antimicrobial property that protects the host from other pathogens highlighting the importance of search for natural antimicrobial drugs.^{28,31} Previously conducted researches confirmed that garlic is not only effective against Gram-positive and Gram-negative bacteria but also possesses antiviral and antifungal activities.^{26,32,33}

Anti-bacterial activity: Garlic has been used for centuries in various societies to combat infectious disease. According to different research findings, garlic has been proven to be effective against a plethora of gram-positive, gram-negative, and acid-fast bacteria. These include *Salmonella*, *Escherichia coli*, *Pseudomonas*, *Proteus*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Salmonella*

spp., *Klebsiella* spp., *Micrococcus* spp., *Clostridium* spp. and *Mycobacterium* spp.^{28,31,33,34}

The gram-positive *Staphylococcus aureus* was more susceptible to the toxic effects of garlic than its gram-negative counterparts. It has been shown that Gram-negative diarrheagenic pathogens (*E. coli*, *Proteus mirabilis*, *Shigella* spp., and *Salmonella* spp.) from stool samples were highly sensitive to garlic.³⁴ It has been shown that the aqueous extract of garlic can be used alongside conventional antibiotics to fight agents of nosocomial infections in hospitals.²⁴ *In vitro* and *in vivo* study of garlic extract was also effective against *Streptococcus mutans* which is primary etiological organisms in dental caries.^{5,9,34}

The cloves of garlic and rhizomes of ginger, extracted with 95% ethanol, suggested to have antibacterial activity against multi-drug clinical pathogens and can be used for prevention of drug resistant microbial diseases. *Pseudomonas aeruginosa* was the most sensitive germ to the mixture. Garlic also suggested as a treatment for multi-drug resistant tuberculosis. Besides, allicin in its pure form was found to exhibit antibacterial activity against multidrug-resistant enterotoxigenic strains of *E. coli*.^{33,35} 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 than cefalexin, cotrimoxazole, and nalidixic acid. Garlic, allyl methyl sulfide, has antibacterial activity against the pig pathogen *Actinobacillus pleuropneumoniae* serotype 9.^{9,24}

Anti-viral activity: Garlic and its sulfur constituents verified antiviral activity against Coxsackievirus species, Herpes simplex virus types 1 and 2, Influenza B, Para-influenza virus type 3, Vaccinia virus, Vesicular stomatitis virus, Human immunodeficiency virus type 1 and Human rhinovirus type 2. The order of compounds found in garlic for virucidal activity was, ajoene>allicin>allyl methyl thiosulfate>methyl allyl thiosulfate; no activity was found for the polar fractions, alliin, deoxy alliin, diallyl disulfide, or diallyl trisulfide. According to different research findings, garlic is an effectual treatment for both the influenza B virus and herpes simplex virus. Two independent researchers in Japan and Romania have found that garlic is able to protect living organisms from the influenza virus and enhanced the production of neutralizing antibodies when given the vaccine.^{24,36,37}

Ajoene, isolated from extracts of garlic may inhibit adhesive interaction and fusion of leukocytes. In a study investigating the effect of allitridin (diallyl trisulfide) on the replication of human cytomegalovirus (HCMV) and the expression of viral immediate-early genes, it was revealed that this substance has anti-HCMV efficacy.³⁸ 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 the NK-cell (Natural killer-cell) activity that destroys virus-infected cells.²⁴ On, a double-blind placebo-controlled study has shown significant protection from the common cold virus and used for prevention, treatment and reduction of reinfection benefits from taking allimax powder capsules once daily.^{4,11,39}

Anti-fungal activity: Different dilutions of extracts of *A. sativum* have been shown to possess fungistatic and fungicidal activity *in vitro* and *in vivo*. Ajoene is an active compound found in garlic which plays a great role as a topical antifungal agent. Garlic has been shown to inhibit the growth of fungal diseases as equally as the drug ketoconazole, when tested on the fungi *Malassezia furfur*, *Candida albicans*, *Aspergillus*, *Cryptococcus* and other *Candida* species.^{11,40} A report from a Chinese medical journal delineates the use of intravenous garlic to treat a potentially fatal fungal brain infection called *Cryptococcus meningitis*. Studies on the effect of amphotericin B (AmB) against *Candida albicans* showed that allicin enhances significantly the effect of AmB against *Candida albicans*, *Saccharomyces cerevisiae* and against *Aspergillus fumigatus in vitro* and *in vivo*.^{24,40}

An *in vivo* study showed that antibody-allylase conjugates and allyl are effective against murine pulmonary aspergillosis.⁴¹ An *in vitro* study showed both intrinsic antifungal activity of allicin and its synergy with the azoles group of drugs, in the treatment of candidiasis.⁴² One study showed that six different mixtures of garlic distilled oils containing DDS and DTS are active against a number of yeasts (*C. albicans*, *C. tropicalis*, and *Blasotrichomyces capitatus*).³⁰ Saponins from *A. sativum* were shown to be effective against *Botrytis cinerea* and *Trichoderma harzianum*.⁴³ Another antifungal protein, allivin, was isolated from *A. sativum* with antifungal activity against *Botrytis cinerea*, *Mycosphaerella arachidicola* and *Phytophthora apiricola*.²⁴

According to the study made in mice, liquid garlic extract was having a substantial effect in reducing the *Candida* colonies in mice through stimulating the body's own defenses to enhance the phagocytic activity of the cells. Garlic oil can be used to treat ringworm, skin parasites and warts if it is applied externally. Lesions that were caused by skin fungi in rabbits and guinea pigs were treated with external applications of garlic extract and began to heal after seven days.^{4,24}

Anti-Cancer Activity

Among the most prominent and favorable effects of garlic is its effect on the inhibition of the growth of cancer cells. Diallyl trisulphide (DATS) is one of the components of garlic that has a great effect on fighting cancer cells. The cytotoxicity caused by DATS is mediated by the generation of reactive oxygen species (ROS) and subsequent activation of the ROS-dependent caspase pathway in U937 leukemia cells. The action of garlic has been attributed to stimulating immune effector cells including T-cell and natural killer cells.^{21,44} Numerous epidemiological, clinical and laboratory studies have demonstrated that garlic has a great role in cancer prevention especially in relation to digestive tract cancers. Different studies on humans have shown that regular intake of garlic reduces the risk of esophageal, stomach and colon cancer. This was thought to be due to the antioxidant effect of allicin in reducing the formation of carcinogenic compounds in the gastrointestinal tract.^{27,45}

Garlic has also a variety of anti-tumor effects, includ-

ing tumor cell growth inhibition and chemopreventive effects. In rodents, garlic and its constituents have been reported to inhibit the development of chemically induced tumors in the liver, colon prostate, bladder, mammary gland, esophagus, lung, skin, and stomach in both rodent and human studies.^{36,46,47} DATS an organosulfur compound isolated from garlic has been shown anticancer activity both in *in vitro* and *in vivo* investigations. The cytotoxicity of DATS toward prostate epithelial cells reduced as opposed to PC-3 cancer cells.⁴⁸

The toxic effect of garlic indirectly plays an important role in the death of cancer cells. Another key role in the prevention of cancers is garlic's effect on the immune system. Macrophage activity, NK as well as the cytokine tumor necrosis factor (TNF), were all shown to have increased activity after administration of garlic and this resulted in an increase in antitumor response.⁴ Colorectal cancer is the third leading cause of cancer death in the world. In this respect, normal garlic cannot be administered and would need to be introduced as part of a strict diet. The garlic and low meat diet, however, show a decrease in colorectal tumor growth.^{6,11}

According to different research findings, aged garlic extract such as S-allyl cysteine, and S-allylmercapto-L-cysteine exhibited radical scavenging activity. In addition, S-allyl cysteine and some organosulfur compounds derived from garlic have been found to retard the growth of chemically induced and transplantable tumors in several animal models. Therefore, the consumption of garlic may provide some kind of protection from cancer development.^{6,24}

Anti-Helminthic Activity

Development of anthelmintic resistance in helminths reported in a number of countries gives a clear indication that control programs based exclusively on their use are not sustainable. The development of integrated programs to control helminths is vital, but such control programs require viable alternatives to the use of anthelmintic.^{49,50} Medicinal plants such as garlic have been used to treat parasitic infections in man and animals. A study showed that allicin is able to produce morphological changes in the male *Schistosoma mansoni*.⁵¹ The alcoholic extract of bulb of *A. sativum* has also shown moderate *in vitro* anthelmintic activity against human *Ascaris lumbricoides*. Garlic has been reported to be effective in the exposure of dysentery and possess anthelmintic activity against *Entamoeba histolytica* and *Giardia lamblia*.^{4,52}

Diallyl trisulfide has *in vitro* activity against several important protozoan parasites. The results indicated that the compound has the potential to be used in the treatment of several human and animal parasitic diseases such as *Trypanosoma species*, *Entamoeba histolytica* and *Giardia lamblia*.^{11,53,54} Garlic oil is effective against a wide range of protozoan parasites including *Plasmodium species*, *Trypanosoma species*, *Leishmania species*, *Giardia species*, and *Cochlospermum planchonii*. Its aqueous extract has also been shown to be effective against hymenolepiasis and giardiasis. In an *in vitro* study, the extracts of *A. sativum* were shown to have anthelmintic

activity against *Haemonchus contortus* from sheep by decreasing larval count. The ethanol extract was the most effective in decreasing larval count. In another study, aqueous extract from garlic has good activity against nematodes such as *Trichuris muris* and *Angiostrongylus cantonensis* when followed by chloroform extract.^{6,22,55}

Garlic with a mixture of the different extracts was 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 only against *Echino. Caproni* (intestinal fluke), while both worms were killed *in vitro*. The essential oil of *A. sativum* has a paralytic effect on *F. gigantica*.⁵⁶ The extract of *A. sativum* also possesses mosquito larvicidal properties. It is effective against filarial mosquito *Culex quinquefasciatus* (24-hour post-treatment), *Culex quinquefasciatus* and *Anopheles stephensi*.^{7,57} Essential oil from *A. sativum* has acaricidal activity against *Rhipicephalus (Boophilus) Microplus (Canestrini)* tick larvae.⁵⁸ *A. sativum* has also been an insecticidal activity against larvae of *Aedes albopictus (Skuse)*, *Lycoriella ingénue*, and *Spodoptera litura* at 1000 ppm.^{59,60}

Anti-Inflammatory Activity

Garlic extracts have been shown to exert anti-inflammatory effects.⁶¹ In one study, garlic treatment significantly attenuated inflammation and injury of the liver induced by *Eimeria papillata* infections.⁵³ The anti-inflammatory activity exhibited by garlic oil is mainly through inhibiting the assembly-disassembly processes of the cytoskeleton.⁶²

Cytokines involved in inflammatory bowel disease (IBD) direct a predominantly cell-mediated T-helper-1 (Th1) immune response. Several compounds isolated from *A. sativum* modulate leukocyte cell proliferation and cytokine production. To investigate the possible therapeutic effects of garlic in the treatment of patients with IBD, whole blood and peripheral blood mononuclear cells (PBMCs) should be assessed. In the presence of various concentrations of garlic extract, *in vitro*, the effect of garlic extract on leukocyte cytokine production was determined using multiparameter flow cytometry. Accordingly, inflammation associated with IBD can be treated with garlic extract by inhibiting Th1 and inflammatory cytokines while upregulating IL-10 production. An *in vivo* animal model study needs to be undertaken to determine the significance of these *in vitro* findings.^{4,62,63}

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.⁶⁴ 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.⁶⁵

Anti-Oxidative Activity

Whole garlic knob and aged garlic extract exhibit direct antioxidant effects and enhance the serum levels of two antioxidant

enzymes, catalase, and glutathione peroxidase.¹⁸ Garlic extract, allicin is efficiently scavenged exogenously generated hydroxyl radicals in a dose-dependent fashion, but their effectiveness was reduced by about 10% by heating to 100 °C for 20 min. The sulfur compounds such as S-allyl cysteine, found in fresh garlic appear to be nearly 1000 times more potent as antioxidants than crude, aged garlic extract. Garlic (both the homogenate of 10% in physiological saline solution and its supernatant) was able to reduce the radicals present in cigarette smoke.⁶⁶

In vivo, antioxidant effects of several garlic organosulfur compounds have been studied. In one study, two lipophilic organosulfur compounds, diallyl sulfide (DAS) and diallyl disulfide (DADS) and two hydrophilic organosulfur compounds, s-ethyl cysteine (SEC) and n-acetylcysteine (NAC), protected against lipid-related oxidations by activating associated antioxidant enzymes. The *in vivo* antioxidant effects of four test organosulfur compounds against lipid-associated oxidations have been studied by the researcher reported that these antioxidant effects were due to the activation and modification of several enzymes such as 3-hydroxy-3 methylglutaryl-CoA reductase, glutathione-s-transferase and catalase.^{11,67}

Anti-Coagulant/Fibrinolytic Activity

Garlic and other species in the genus *Allium* have played an important role as a prophylactic and therapeutic agent over centuries. Of these, the usefulness of garlic in preventing disease of the cardiovascular system is widely recognized. There are several reports on anticoagulants.⁶⁸ In a study, blood anticoagulant substance was isolated from garlic and its physical and chemical properties were also studied. A half milligram of garlic extracts completely inhibited one milliliter of blood from coagulating. The inhibiting effect of garlic extract on blood clotting was almost the same as that of potassium oxalate.^{3,4,11}

MECHANISMS OF ACTION AND SYNERGISTIC EFFECT OF ALLIUM SATIVUM

It is widely accepted that plant extracts, because of complex nature, possess multiple mechanisms of action. Garlic extracts and their main components may exhibit activity by: (i) inhibiting bacterial growth or viability, (ii) targeting bacterial virulence factors or (iii) potentiating the effectiveness of antibiotics as resistance modifying agents. The inhibition of bacterial growth occurs through several mechanisms: disruption of membrane function and structure (including the efflux system), interruption of deoxyribonucleic acid/ribonucleic acid (DNA/RNA) synthesis and function, interference with intermediary metabolism and induction of coagulation of cytoplasmic constituents (Table 2).^{13,69,70}

Synergistic interaction between two agents, in which one agent enhances the effect of the other and together they act more efficiently than as individual agents. The mechanism of synergistic action is explained by (a) modification of active sites on bacterial cell, (b) inhibition of enzymes, which catalyze degradation or modification of antibiotics, (c) increase of membrane permeabil-

Table 2. Mechanism of Action and Pharmacological Effects of *Allium Sativum*

Effect	Pathogen	MOA	Preparation
Antibacterial	<i>Staphylococcus aureus</i>	Inhibition of bacteria growth	Aqueous, ethanol, chloroform extract
	<i>Escherichia coli</i> , <i>Salmonella typhi</i>	Higher inhibitory effect with Ethanolic extract and potentiating antibiotics effect	Aqueous and ethanolic extract
	<i>Bacillus subtilis</i> , <i>Klebsiella pneumonia</i>	Inhibition of bacteria growth with Ethanolic extract	Aqueous, methanol and ethanol extract
	<i>Helicobacter pylori</i>		Extract
	<i>Salmonella enteritidis</i>	Higher inhibitory effect	Extract
	<i>Shigella spp.</i> , <i>Proteus mirabilis</i>		Extract
	<i>Actinobacillus pleuropneumonia serotype 9</i>		Extract
	<i>Streptococcus mutan</i>	Inhibition of bacteria growth	Extract
Antiviral	Human cytomegalovirus, Influenza B, Herpes simplex virus type 1-2, Parainfluenza virus type 3, vaccine virus, Vesicular stomatitis virus, Human rhinovirus type 2	Boost antibody production	Not mentioned
Antifungal	<i>Candidia albicans</i> , <i>C. tropicalis</i> , <i>Blastoschizomyces capitatus</i>	Inhibition by Changing antioxidant metabolites	Extract, DADS
	<i>Botrytis cinerea</i> , <i>Trichoderma harzianum</i>		Extract
	<i>Ascosphaera apis</i>	Inhibition of fungal growth	Essential oil vapors
	<i>Paracoccidioides brasiliensis</i>		Extract
	<i>Aspergillus niger</i>	Potentiating antibiotics effect	Extract, Ajoene
	Dermatophytes, Saprophytes, <i>Candidia</i>	Blockage of lipid synthesis	Ethanol extract
	<i>Cryptococcal spp.</i> , <i>Botr. cinerea</i> , <i>Mycosphaerella arachidicola</i> , <i>Physalospar apiricola</i>	Inhibition of fungal growth	Alcoholic extract
Antiparasitic	<i>Trypanosoma spp.</i> , <i>Entamoeba hirtolytica</i> , <i>Giardia lamblia</i>	Inhibition of glutathione reductase	Extract
	<i>Schistosoma mansoni</i>	Enhances morphological changes	Extract
	<i>Trypanosoma cruzi</i> , <i>T. brucei</i> , <i>Plasmodium spp.</i> , <i>Giardia spp.</i>	Inhibition of Trypanothione reductase.	Extract
	<i>Leishmania spp.</i> , <i>Cochlospermum planchomi</i>	Inhibition of glutathione reductase	Extract
	Hymenolepiasis, Giardiasis	Muscular paralysis of the parasite	Aqueous extract
	<i>Haemonchus contortus</i>	Muscular paralysis of the parasite	Ethanol, dichloromethane and water extract
Other	Anti-inflammatory effect	Inhibition of assembly-disassembly processes of the cytoskeleton	Extract
	Antioxidant properties	Protection against free radical damage in the body	Organosulfur compound in garlic
	Anti-coagulant/ antithrombotic effect	Suppresses the coagulation system and inhibition of platelet aggregation	Extract
	Anti-tumor/cancer	Enhances immune effector cells, growth inhibition, and chemopreventive effects	Extract

Source: Mikaili et al²⁴

ity and (d) inhibition of efflux pumps.⁷¹

Alliin, an antibacterial compound from garlic (*A. sativum*), potentiated the action of cefazolin (4 to 128-fold) and oxacillin (32 to 64-fold), against *Staphylococcus spp.* and cefoperazone (8 to 16-fold) against *P. aeruginosa*.⁷² The significant antibacterial activity of garlic extract on streptomycin-resistant strains (*Staph. aureus* and *E. coli*) solely and in synergism with streptomycin has also been proved.⁷³ It was found in another study that polymyxin B (PMB), is effective against various yeasts and filamentous fungi when used in combination with alliin. This combination increases the plasma membrane permeability in *Saccharomyces cerevisiae*. The synergistic activity between PMB and alliin combinations resulted in the disappearance of the swollen spherical structure of the yeast as a result of structural alterations of its vacuole.⁷⁴ In addition, the synergism between ciprofloxacin and garlic extract has antibacterial activity against multi-drug clinical patho-

gens such as enterotoxigenic strains of *E. coli* and mycobacterium.^{29,75}

DRUG INTERACTION AND PHARMACOKINETICS OF GARLIC

Glutathione is a compound necessary for the liver to facilitate the detoxification of substances. Organo-sulfur compounds found in garlic showed to prevent glutathione depletion. Patients who experience increases in reactive oxygen-induced stress on liver function may be protected by garlic ingestion.⁶⁷ It was found in *E. coli* cultures that aged garlic extract, S-allyl cysteine, diallyl sulfide, and diallyl disulfide do not interfere with the antibiotic activity of gentamycin but may improve gentamycin-induced nephrotoxicity.²³ Aged garlic has also been shown to reverse the oxidant effects of nicotine toxicity in rat studies. More researches are required in future garlic may be a unique choice to help minimize

the toxic effects of therapeutic drugs.^{3,8}

One study indicated that those who use traditional/complementary/alternative medicines (TCAMs) in addition to antiretroviral (ARV) treatment may be at risk of experiencing clinically significant pharmacokinetic interactions, particularly between the traditional complementary alternative medicines and the protease inhibitors as well as non-nucleoside reverse transcriptase inhibitors (NNRTIs). Mechanisms of pharmacokinetic interactions include alterations to the normal functioning of drug efflux transporters, such as P-gp and/or Cytochromes P450 (CYP) isoenzymes, such as CYP3A4 that mediates the absorption and elimination of drugs in the small intestine and liver. Specific mechanisms of action include inhibition and activation of these proteins and induction *via* the pregnane X receptor also known as the steroid and xenobiotic sensing nuclear receptor (SXR). Garlic exhibited potentially significant interactions, each with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.^{24,37}

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.⁷⁶ In a study, there was some pharmacokinetic interaction of garlic and atorvastatin in dyslipidemic rats was shown. 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.^{8,37}

ADVERSE EFFECT OF GARLIC

Nausea, vomiting and breath odor are major adverse effects especially when raw forms of the herb are used and care should be taken in consuming high quantities. Although garlic generally poses little in terms of safety issues, there are isolated cases of topical garlic burns and anaphylaxis.^{67,77}

According to Tattelman, garlic should be taken with great caution in patients taking anticoagulants. It seems prudent to stop taking high dosages of garlic seven to ten days before surgery because garlic can prolong bleeding time.⁷⁸ 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 also induces a severe dermal reaction. 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. Another study suggested that garlic with a high dose has the potential ability to induce liver damage.^{77,79}

A parallel study also highlighted the potential ability of a high dose of garlic to induce morphological changes in the liver and kidneys.⁶⁶ Another study also shows intraperitoneal (IP) administration of high doses of garlic (500 mg/kg) results in profound changes in lung and liver tissues of rats than oral adminis-

tration. It is also shown that the adverse effect of high doses of garlic oil might further influence the hemostatic balance.^{64,68}

CONCLUSION

A recent increase in the popularity of alternative medicine and natural products has renewed interest in garlic and their derivatives as potential natural remedies. Garlic, from crushed to capsules, and is consumed throughout the world. Garlic has a lot of benefits and potential uses in preventing and curing different diseases. Fresh and powdered garlic are popular for food flavor and should continue to be used. Nowadays, the problem of bacterial resistance is growing, and the outlook for the use of antibacterial drugs in the future is still uncertain. Even though pharmacological industries have produced a number of new antibiotics in the last few decades, resistance to these drugs by bacteria has increased. Garlic is a valuable source of new and biologically active molecules possessing antibacterial properties through direct action against bacteria or synergism with antibiotics. Garlic's antifungal, antibiotic and perhaps anticancer effects are well-accepted world over because of the many scientific literature supporting these effects. Garlic also has hepatoprotective, antioxidant, and anthelmintic effects as well as unidentified anti-malarial substances. In conclusion, a detailed study regarding the phytochemical assessment and pharmacological effect of garlic and more attention as well as researches regarding the anticoagulant, anti-inflammatory, immunomodulatory and wound-healing action. Besides, advances being made in analytical techniques, sophisticated bioassays, and biotechnological exploitation should provide the means by which these important plants continue to play a key role in the benefit of man and animals' health. Finally, medicinal plants are in danger due to marketing and using them for different activities, so every citizen should give care and conservation in their natural habitat, this can be achieved through public education to increase the awareness of the community about potential uses of medicinal plants.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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