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Garlic: An Updated Review on Multipotential Medicinal Applications

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Abstract

Throughout history, many different cultures have recognized the potential use of garlic for prevention and treatment of different diseases. Recent studies support the effects of garlic and its extracts in a wide range of applications. The main interest of researchers in the medicinal values of garlic is its broad-spectrum therapeutic effect with minimal toxicity. Garlic contains a higher concentration of sulfur compounds which are responsible for its medicinal effects. The chemical constituents of garlic have also been investigated for treatment of cardiovascular disease, cancer, diabetes, blood pressure, atherosclerosis and hyperlipidaemia and highly praised by several authors. However, the exact mechanism of all ingredients and their long-term effects are not fully understood. Further studies are needed to elucidate the pathophysiological mechanisms of action of garlic as well as its efficacy and safety in treatment of various diseases. The aim of this study is to review a variety of experimental and clinical reports, and describe the effectiveness, toxicities and pharmacokinetics, and possible mechanisms of pharmaceutical actions of functionally active compounds isolated from garlic.

Keywords: Garlic, Atherosclerosis, Blood Pressure, Cancer, Diabetes, Hyperlipidaemia.

List of Abbreviations

DADS	Diallyl disulphide
DATS	Diallyl disulphide
SAC	S-Allyl cysteine
AGE	Aged Garlic Extract

INTRODUCTION

Historically, garlic has been revered as part of a healthful diet. The earliest known references indicate that garlic formed part of the daily diet of many Egyptians[1]. It was fed particularly to the working class involved in heavy labor, as in the building of the pyramids. Indeed, a recurring theme throughout early history is that garlic was given to the laboring classes, presumably to maintain and increase their strength, thereby enabling them to work harder and be more productive[2]. Ancient medical texts from Egypt, Greece, Rome, China, and India prescribed garlic for a number of applications including improving performance, reducing infections, and protection against toxins[2]. These medicinal properties, coupled with its savory characteristics, have made garlic a true cultural icon in many parts of the world. Thus, garlic is used traditionally as a flavor enhancer and has been recognized as not only a common food additive but also a potent therapeutic agent.

The whole bulbs of garlic contain alliin, γ-glutamyl-S-allylcysteine, S-methylcysteine sulfoxide, S-trans-1-propenylcysteine sulfoxide, S-2-carboxypropylglutathione and S-allylcysteine. Recently, a novel organosulfur compound, thiacremonone (2,4-dihydroxy-2,5-dimethyl-thiophene-3-one) was isolated and identified from heated garlic . Chemical composition of the preparations obtained by extraction of garlic fractions depends on the extraction conditions: temperature, time and solvent's polarity. The content of organosulfur compounds in garlic bulbs changes during cultivation and storage[3].

Organosulfur compounds have been attributed to the medicinal properties and health benefits of garlic. Several recent studies have shown that these organosulfur compounds have anti-cancer, anti-cardiovascular disease, anti-neurological disease, and anti-liver disease effects, as well as effects for prevention of allergy and arthritis[4]. While these effects are well known, the exact mechanisms of action have not yet been established. In the present paper, the aim of this study is to review data from a variety of experimental and clinical reports and describe the effectiveness and possible mechanisms of action on how garlic showed the medical properties.

Natural products of animals, plants and microbial sources have been used by man for thousands of years either in the pure forms or crude extracts to treat many diseases[5]. Garlic (*Allium sativum* L.) is one of those plants that were seriously investigated over several years and used for centuries to fight infectious diseases. The taxonomic position of garlic and related genera had been a matter of controversy for long period of time. The most recent classification scheme of garlic was class Liliopsida, subclass Liliidae, superorder Liliianae, order Amaryllidales, family Alliaceae, subfamily Allioideae, tribe Allieae and genus *Allium* which is mainly based on the sequences of nuclear ribosomal DNA.

Common Names: Garlic, allium, stinking rose, rustic treacle, nectar of the gods, camphor of the poor, poor man's treacle.

Historical perspective of garlic

Garlic was an important medicine to the ancient Egyptians listed in the medical text *Codex Ebers* (ca. 1550 BC) especially for the working class involved in heavy labor. There is evidence that during the earliest Olympics in Greece, garlic was fed to the athletes for increasing stamina. In ancient Chinese medicine, garlic was prescribed

to aid respiration and digestion, most importantly diarrhea and worm infestation. Three ancient medical traditions in India i.e., Tibbi, Unani and Auryveda, made extensive use of garlic as a central part of the healing efficacy of plants. The leading Indian ancient medical text, *Charaka-Samhita* recommends garlic for the treatment of heart disease and arthritis for over many centuries. A leading physician of the 16th century, Pietro Mattiali of Siena, prescribed garlic for digestive disorders, infestation with worms and renal disorders, as well as to help mother during difficult childbirth . In modern era scientists have been trying to validate many of these properties of garlic, especially in terms of the identity of the active components, their mechanisms of action and exploring the potential benefits as food supplements.

Chemical Constituents of garlic

Among the several functional compounds of garlic, alliin is the most abundant organosulfur compound in whole garlic. It is a derivative of the amino acid cysteine. It is found that fresh garlic contains alliin (6–14 mg/g). 25.65–30.03 mg/g alliin was detected in Korean garlic cloves and 6.7 mg/g in Korean garlic bulbs[6].

Allicin features the thiosulfinate functional group, R-S(O)-S-R. The compound is not present in garlic unless tissue damage occurs, and is formed by the action of the enzyme alliinase on alliin[7].The amount of allicin which was known as a major bioactive compound of garlic and garlic preparations is about 2.3–4.6 mg/g in Korean garlic[6]. Commercial garlic preparations are often standardized on the content of sulfur containing constituents, particularly to alliin, or on the allicin yield.

Diallyl sulfide (DAS) is easily transformed from allicin[8]. It is found that garlic oil contains DAS (23 μg/g) by simultaneous distillation extraction, analyzed by FT-Raman spectroscopy[9]. It was found that diethyl ether, ethyl acetate or hexane extract or extracts of garlic were composed of DAS about 10–20, 0–20 or 0–20 μg/g, respectively.

Diallyl trisulfide (DATS) begins its biochemical synthesis with γ-glutamyl-S-alk(en)yl-L-cysteine, which is hydrolyzed and oxidized to produce alliin[7]. Alliin is the odorless precursor of DATS. Processing of garlic (cutting or chewing) generates a vacuolar enzyme (allinase), which acts upon alliin to give rise to allicin and other alkyl alkane-thiosulfinates[7]. Allicin and related thiosulfinates are decomposed to yield various organosulfur compounds including DATS. Kimbaris et al. found that diethyl ether, ethyl acetate or hexane extracts of garlic were composed of DATS about 0–200, 10–220 or 1–180 μg/g, respectively[9].

Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide) is the degradation product of allicin. When incubation temperature was at 40, 60 and 80 °C, the amount of ajoene concentration also increased gradually, with the highest amount of E-ajoene (172.0 μg/g of garlic) and Z-ajoene (476.3 μg/g of garlic) found in Japanese garlic with rice oil at 80 °C, indicating its optimal temperature.

S-allyl cysteine (SAC), a major transformed product from γ-glutamyl-S-allyl-L-cysteine, is the water-soluble organosulfur compounds and its concentration increases through a long-term extraction in an aqueous medium. SAC is detected in the blood, and its blood concentration and pharmacokinetic parameters are well-associated with doses of orally administered SAC in animal studies[4]. Amagase and Milner found that aged garlic contains SAC about 0.45 mg/g found that water extracts of Korean garlic were composed of SAC about 0.36–0.60 mg/g.

Diallyl disulfide (DADS) is an organosulfur compound found in plants of the genus Allium.

Along DATS and diallyl tetrasulfide, it is one of the principal components of the distilled oil of garlic. It is yellowish water in soluble liquid and has a strong garlic odor. It is produced during the decomposition of allicin, which is released during incision of garlic and other plants of the Alliaceae family[4]. DADS has many health benefits from garlic, but it is also an allergen causing garlic allergy. Kimbaris et al. found that diethyl ether, ethyl acetate or hexane extracts of garlic were composed of DADS 80–280, 60–231 or 70–260 μg/g, respectively[9].

Thiacremonone (2,4-dihydroxy-2,5-dimethyl-thiophene-3-one) was isolated and identified as a novel and major organosulfur compound (0.3%) in High-Temperature-High-Pressure (HTHP)-treated garlic[10]. It was recently found that heated Korean garlic contains thiacremonone about 0.7 μg/g[10].

Garlic Dosing

The following doses are recommended: 2 to 5 g of fresh raw garlic; 0.4 to 1.2 g of dried garlic powder; 2 to 5 mg garlic oil; 300 to 1,000 mg of garlic extract (as solid material). Other preparations should correspond to 4 to 12 mg of alliin or approximately 2 to 5 mg of allicin, an active constituent of garlic.

Role of Garlic in Health

Garlic can rightfully be called one of nature's wonderful plants with healing power. It can inhibit and kill bacteria, fungi, lower (blood pressure, blood cholesterol and blood sugar), prevent blood clotting, and contains anti-tumor properties. It can also boost the immune system to fight off potential disease and maintain health[11]. It has the ability to stimulate the lymphatic system which expedites the removal of waste products from the body. It is also considered an effective antioxidant to protect cells against free radical damage. It can help to prevent some forms of cancer, heart disease, strokes and viral infections. Garlic alone can provide us with over two hundred unusual chemicals that have the capability of protecting the human body from a wide variety of diseases. The sulfur containing compounds found in garlic afford the human body with protection by stimulating the production of certain beneficial enzymes.

PHARMACOLGICAL AND THERAPEUTIC PROPERTIES OF GARLIC

Pharmaceutical effect of garlic on cardiovascular disorders

Numerous studies have confirmed the ability of garlic to reduce parameters associated with cardiovascular disease.

A brief description of some of these studies is given below.

Effect of Garlic on Cholesterol

Experimental evidence indicates that garlic ingestion lowers blood cholesterol levels and inhibits cholesterol synthesis. Zeng and his colleagues deduced from 26 studies that hypercholesterolemic patients treated with garlic (garlic powder and aged garlic extract) had a mean serum TC and TG concentration, that were 0.28 (95% CI, −0.45, −0.11) mmol/l (P = 0.001) and 0.13 (95% CI, −0.20, −0.06) mmol/l (P b 0.001) lower than that of patients treated with placebo, respectively[12]. Several experimental studies have indicated that garlic and its constituents inhibit key enzymes involved in cholesterol and fatty acid synthesis in cultured rat hepatocytes and human HepG2 cells[13]. Cultured hepatoma cells were treated with aqueous garlic extract and radiolabeled cholesterol was quantified.

Garlic extract reduced cholesterol synthesis by up to 75% without evidence of cellular toxicity. These results indicate that compounds containing an allyl-disulfide or allyl-sulfhydryl group are most likely responsible for the inhibition of cholesterol synthesis by garlic and that this inhibition is likely mediated at sterol 4 alpha-methyl oxidase.

Effect of garlic on blood pressure

In patients with uncontrolled hypertension (SBP N/= 140 mm Hg at baseline), systolic blood pressure was on average 10.2 +/− 4.3 mm Hg (P = 0.03) lower in the garlic group who consumed four capsules of aged garlic extract (960 mg containing 2.4 mg SAC) daily for 12 weeks compared with controls over the 12-week treatment period. Garlic reduces blood pressure (BP) in two-kidney, one-clip (2K-1C) rats through enhancement of nitric oxide (NO) synthesis in invivo and in vitro as well as in human[14]. Garlic appears to exert this effect by modulating the activity of several mechanisms that are vital in BP homeostasis in favor of hypotension. The drinking water was replaced with an L-Arg solution (10 mg/ml; average intake of 300 mg/day) from 7 to 14 days. A day after surgery, there was a significant reduction of mean blood pressure in the L-Arg-treated group compared to control (129 ± 7 vs 168 ± 6 mm Hg)[15]. It was also reported that extract of garlic (2.86 g/kg) increased NO production by 30–40% from 15 to 60 min after administration[16]. Elevating evidence indicates that hydrogen sulfide (H_2S) plays a cell signaling role similar to NO and CO. In vivo and in vitro cardiovascular effects of H_2S include decreased blood pressure and cardioprotection against ischemic damage and vasorelaxation. A recent study by Benavides et al. suggests that H_2S may underlie the beneficial effects that garlic exerts on the cardio-vascular system. Garlic and garlic-derived organic polysulfides, including DATS and DADS induced H_2S production in a thiol-dependent manner[17].Garlic-mediated and H_2S-mediated vascular smooth muscle relaxation indicate that both were based on NO signaling pathways.

Effects of garlic on platelet aggregation

Platelet aggregation and subsequent thrombus formation are significantly reduced by garlic and its constituents. All constituents displayed a biphasic pattern of inhibition that was only significant for SEC at 0.78 μmol/l, SMC at 3.125 and 6.25 μmol/l, SPC at 0.78, 3.125 and 6.25 μmol/l, and BC at 0.78, 3.125 and 25 μmol/l. Aqueous garlic extracts (final concentration, 1 mg/ml) inhibited human platelet aggregation[18]. DATS inhibited platelet aggregation and $Ca(2^+)$ mobilization in a concentration-dependent manner without increasing intracellular cyclic AMP and cyclic GMP. DT at high concentrations partially blocked the binding of IP(3) to its receptor. The mechanism of inhibition of platelet aggregation by garlic's constituents has also been addressed, and it is thought to work via the inhibition of calcium mobilization. A recent study has also found another garlic component, sodium 2-propenyl thiosulfate, to modulate cyclooxygenase activity in canine platelets, thus preventing their aggregation[19].

"is shown in table 1. *Anti Platelet Effect of Garlic in Human"*

Pharmaceutical effect of garlic on neurological diseases

Recent studies have demonstrated beneficial effects of AGE and one of its active ingredients SAC in Alzheimer disease models[26]. The therapeutic effects of SAC were also assessed in various models of neurodegenerative diseases including stroke, ischemia/reperfusion, Alzheimer's disease, and Parkinson's disease[27].The molecular mechanisms of these effects may include protecting neurons against oxidative/nitrosative (reactive oxygen/nitrogen species) stress, mitochondrial damage, and subsequent cell death[28]. SAC also reduces edema formation in the ischemic rat brain through the inhibition of LPO and produces neuroprotective effects on the Aβ-induced oxidative damage, and learning deficits.

Thiacremonone also inhibited LPS-induced memory impairment, glial activation, pro-inflammatory mediator expression, and amyloidogenesis in in vitro and in vivo via the inactivation of NF-κB via blocking of phosphorylation of IκBα in mice brain as well as cultured astrocytes and microglial BV-2 cells. These results indicated that thiacremonone inhibited neuroinflammation and amyloidogenesis through inhibition of NF-κB activity, which controls the genes involved in not only inflammation but also amyloidogenesis. Therefore, organosulfur compound in garlic could be applied for intervention of inflammation-related neurodegenerative disease including Alzheimer's disease, stroke, and Parkinson's disease.

"is shown in table 2. *Effect on neurological diseases of garlic"*

Pharmaceutical Effects of Garlic on Arthritis

Consumption of alliums (garlic, leeks, and onions) (P = 0.029) showed the strongest protective association with hip osteoarthritis (OA)[33]. They suggested that diallyl disulfide, a compound found in garlic and other alliums, represses the expression of matrix-degrading proteases in chondrocyte like cells, providing a potential mechanism of action[33]. DAS (48.9 mg/kg) significantly inhibited the increase of IL-1β generation and COX-2 gene expression through inactivation of NF-κB induced by monosodium urate crystals in a rat model and in synovial cells and

chondrocytes. A 1–10 mg/kg dose of thiacremonone also suppressed the carrageenan and mycobacterium butyricum-induced inflammatory and arthritic responses as well as expression of iNOS and COX-2, in addition to NF-κB DNA-binding activity.

Natural Immunity Booster

With the arrival of frightening viral diseases strengthening the body's ability to fight off infection has become even more important. Garlic has abundant sulfur containing amino acids and other compounds that seem to initiate increased activity in the immune system[34]. It is one of the impressive conductors of the body's immune system; which stimulates immune function by making macrophages or killer cells more active. In light of the enormous pressures, which our immune systems sustain, supplemental nutrients like garlic are clearly needed. Its remarkable content of germanium alone offers excellent immune stimulation. In addition to germanium, garlic contains thiamine, sulfur, niacin, phosphorous, and selenium[35].

In aged subjects, the administration of 600 mg garlic powder per day for 3 months induced significant ($p<0.01$) increases in the percentage of phagocytosing peripheral granulocytes and monocytes when tested *ex vivo* for their ability to engulf *Escherichia coli* bacteria. Another human study was conducted with an unrefined garlic extract (5 to 10 g/day) which was given to HIV/AIDS patients. For the seven patients who completed the 12 weeks study, there was a major increase in the natural killer cells activity from a seriously low mean value[36].

A double blind placebo controlled survey using a 100% allicin yielding supplement has reported that allicin can reduce the occurrence of the common cold and recovered from symptoms[37].

Anticancer effect

Of the many favorable actions of garlic, inhibition of the growth of cancer is perhaps the most prominent. It has several synergistic effects that either prevent or possibly may fight cancer. The action of garlic has been attributed to stimulate immune effector cells including T-cell and natural killer cells. Human population studies have shown that, regular intake of garlic reduces the risk of oesophageal, 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 gastro-intestinal tract.

Men in the higher of two intake categories of total *Allium* vegetables (>10.0 g/day) had a statistically significant lower risk of prostate cancer than those in the lowest category (<2.2 g/day). Similar comparisons between categories showed reductions in risk for men in the highest intake categories for garlic specifically. The reduced risk of prostate cancer was independent of body size, intake of other foods and total calorie intake and was more pronounced for men with localized prostate cancer than with advanced prostate cancer[38]. Prostate specific antigen serum markers had significant decreases during short term ingestion, but returned to baseline after 4 weeks.

A very important epidemiological study for Americans has been published in which the intake of 127 foods (including 44 vegetables and fruits) was determined in 41,387 women (ages 55 to 69) followed by a five year monitoring of colon cancer incidence. The most striking result of this "Iowa Women's Health Study" was the finding that garlic was the only food which showed a statistically significant association with decreased colon cancer risk.

Prevents diabetes

A number of animal studies support the effectiveness of garlic in reducing blood glucose in streptozotocin-induced as well as alloxan-induced diabetes mellitus in mice. A study was conducted to evaluate oral administration of garlic extract for 14 days on the level of serum glucose, total cholesterol, triglycerides, urea and uric acid, in normal and streptozotocin-induced diabetic mice. The result of the study showed significant decrease ($p<0.05$) in serum glucose, total cholesterol, triglycerides, urea, uric acid, aspartate amino transferase and alanine amino transferase levels, while increased serum insulin in diabetic mice, but not in normal mice. From a comparison study made between the action of garlic extract and glibenclamide, it was shown that the antidiabetic effect of the garlic was more effective than the glibenclamide.

Dermatologic applications

A study examined 43 persons for their topical use of two different garlic extracts for wart and corn treatment. Of these persons, 15 volunteers utilized a water extract of garlic, while 23 volunteers applied lipid extract to appropriate areas twice a day. Five controls applied only a neutral solvent. All lipid extract volunteers experienced complete resolution of wart and 80% of corn within one to two weeks. The water extract seemed to be less potent, with complete dissolution of smaller warts and corns, and only partial dissolution of larger ones. Controls showed no improvement from baseline.

Antimicrobial Effect

The antimicrobial properties of garlic were first described by Pasteur (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[39]. Garlic is more effective with least side effects as compared to commercial antibiotics; as a result, they are used as an alternative remedy for treatment of various infections. Out of the many medicinal plants, garlic has an antimicrobial property which protects the host from other pathogens highlighting the importance of search for natural antimicrobial drugs[40].

Antiviral Effect

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. The order of compounds found in garlic for virucidal activity was, ajoene > allicin > allyl methyl thiosulfanate > methyl allyl thiosulfanate; no

activity was found for the polar fractions, alliin, deoxyalliin, diallyl disulfide, or diallyl trisulfide. Two independent researchers in Japan and Romania have found that garlic is able to protect living organisms from the influenza virus[41]. As conducted by The Garlic Centre, published in Advances in Therapy, this is the first serious work to show prevention, treatment and reduction of reinfection benefits from taking Allimax Powder capsules once daily[37].

Antibacterial Effect

Garlic extract inhibits the growth of Gram positive and Gram negative bacteria, such as *Staphylococcus, Streptococcus, Micrococcus*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Lactobacillus*, *Pseudomonas*, *Shigella, Salmonella, Proteus*, and *Helicobacter pylori[42].* Its antibacterial activity is mainly due to the presence of allicin, but it can be unstable, breaking down within 16 h at 23°C[43]. However, the use of a water-based extract of allicin stabilizes the allicin molecule due to the hydrogen bonding of water to the reactive oxygen atom in allicin or there may be water soluble components in crushed garlic that destabilize the molecule.

Antifungal Effect

Ajoene is an active compound found in garlic which plays a great role as topical antifungal agent and Garlic has been shown to inhibit 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. A report from a Chinese medical journal delineates the use of intravenous garlic to treat a potentially fatal and rare fungal infection of the brain called *Cryptococcus meningitis*. In the report, the Chinese compared the effectiveness of the garlic with standard medical treatment which involved a very toxic antibiotic called Amphotericin-B. The study revealed that, intravenous garlic was more effective than the drug and was not toxic regardless of its dosage.

A study found that *Candida* colonies were substantially reduced in mice that had been treated using liquid garlic extract. 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[44].

Antiparasitic Effect

Many herbalists worldwide recommend garlic as a treatment for intestinal parasites. In some cultures, children infested with helminthes are treated with enemas containing crushed garlic. One of the traditional Chinese medical treatments for intestinal diseases is an alcoholic extract of crushed garlic cloves. Allicin exhibits anti-parasitic activity against major human intestinal parasites such as *Entamoeba histolytica, Ascaris lumbricoides* and *Giardia lamblia. Entamoeba histolytica,* the human intestinal protozoan parasite, is very sensitive to allicin, as only 30 µg/ml of allicin totally inhibits the growth of amoeba cultures. Moreover, researchers have found that at lower concentrations (5 µg/ml), allicin inhibited 90% the virulence of trophozoites of *E. histolytica* as determined by their inability to destroy mono-layers of tissue-cultured mammalian cells *in vitro*.

Role of garlic against multi-drug resistant bacteria

Garlic is active against microorganisms that are resistant to antibiotics and the combination of garlic extracts with antibiotics leads to partial and total synergism. The emergence of multi-drug resistant strains of Gram negative (*Pseudomonas*, *Klebsiella*, *Entero-bacter*, *Acinetobacter*, *Salmonella* species, etc) and Gram positive (*Staphylococcus*, *Enterococcus*, *Strepto-coccus* species, etc) bacteria is troubling for human and animals. The emergence of epidemic methicillin resistant *Staphylococcus aureus* (MRSA) resistant to mupirocin has led many authors to suggest that the use of mupirocin should be controlled more strictly, especially as there is a lack of alternative agents. Consequently, garlic is an alternative agent for the treatment of MRSA and in a great demand.

Role of garlic against multi-drug resistant tuberculosis (MDR-TB)

Scientific evidence from randomized clinical trials supports the use of garlic and enhances access for MDR-TB infected people, through the public health system

The anti-tuberculosis activity *in vivo* of garlic oil preparation was demonstrated in a study of guinea pigs which were given an intra-peritoneal dose of 0.5 mg/kg. However, when garlic oil was used, a reduced causative process was noted in the organs involved, indicating that garlic oil administration causes less marked lesions in the viscera of the animals inoculated with tubercle bacilli. The high potential of garlic extract was revealed to inhibit the growth of *Mycobacterium tuberculosis* $H_{37}R_v$ and *M. tuberculosis* TRC-C1193, susceptible and resistant to isoniazid (first-line anti-tuberculosis medication), respectively. The minimum inhibitory concentration (MIC) of garlic was between 80 and 160 µg/ml for the susceptible strain and 100 and 200 µg/ml for the resistant strain.

Antioxidant Effect

Whole garlic and aged garlic extract exhibit direct antioxidant effects and enhance the serum levels of two antioxidant enzymes, catalase and glutathione peroxidase.

Garlic extract, allicin is efficiently scavenged exogenously generated hydroxyl radicals in a dose dependent fashion, but their effectiveness was reduced about 10% by heating to 100°C for 20 min. Other garlic constituents, such as S-allyl cysteine, also confirmed significant antioxidant effects. The sulfur compounds found in fresh garlic appear to be nearly 1000 times more potent as antioxidants than crude, aged garlic extract.

Pharmaceutical effect of garlic on liver diseases

Preclinical studies have shown that garlic ameliorates alcohol-induced oxidative stress inhibits induction of cytochrome P450 (CYP) and prevents fatty liver and liver cirrhosis[45]. Garlic is also shown to reduce the ethanol-induced increase in the lipid peroxidation and to increase the levels of antioxidants such as glutathione (GSH), ascorbic acid, catatase (CAT), and glutathione reductase

(GR) in the rat liver. Treatment of SAMC attenuated non-alcoholic fatty liver disease (NAFLD)-induced liver injury, fat accumulation, collagen formation and free fatty acids through reduction of MAP kinase pathways and the NF-κB and AP-1 activity[46].

The antioxidative property of garlic has been previously ascribed mainly to its four major chemical components, i.e. allinin, SAC, DADS, and allicin[47]. In addition, have viewed that the oxidative stress is mainly due to NO produced by the stimulated iNOS. The inhibitory effect of garlic is mainly attributed to the impaired action of iNOS[48]. Our data also showed that thiacremonone reduced acute hepatic injury through inactivation of NF-κB and STAT3 by inhibition of pro-inflammatory cytokine production (unpublished data). Taken together, all these observations indicate the usefulness of garlic in the prevention of liver diseases.

Pharmaceutical effect of garlic on allergy

Several studies suggested anti-allergic properties for garlic extract reported that in their rodent basophile cell line model, addition of garlic extract reduced histamine release (anti-histamine effect). They showed suppression of IgE-mediated antigen-specific skin reaction in murine model too and concluded that garlic extract could beneficially balance, or modify the function of mast cells, basophile, and activated T lymphocyte factors, which all play a leading role in allergic cascade reactions and inflammation[49].

Reduces stress

Among the many uses of garlic, it appears to have the fortunate capacity for protecting against the negative effects of stress that affects the autonomic nervous and neuroendocrine system. Rats that were trained with endurance exercises to physical fatigue enjoyed improved parameters of aerobic glucose metabolism, attenuated oxidative stress, and vasodilations, when given garlic at a dosage of 2.86 g/kg for 30 min before exercise. In rats exposed to psychologically stressful situations, aged garlic extracts significantly prevented the decreases in spleen weight seen in control animals. Additionally, the garlic significantly prevented the reduction of hemolytic plaque forming cells in spleen cells.

Moreover, garlic was able to block the lipopolysaccharide induced immune cytokine and plasma corticosterone and catecholamine changes following cold water immersion stress. Given the extreme chronic stress many people now face in their daily life, garlic may prove useful to counter the negative impact of this stress on human physiology.

PHARMACOKINETICS

There have been many reports on the pharmacokinetics of garlic and its constituents. The oil-soluble organosulfur compounds in garlic, including allicin, ajoene, and vinyldithiins are not found in blood or urine, even after consumption of a large amount of garlic. Therefore, they are likely not the active compounds. Allicin, perfused into isolated rat livers, showed a remarkable first-pass effect and is metabolized to DADS and allyl mercaptan, whereas ajoenes and vinyldithiins were recovered in the effluent. Allicin disappeared very rapidly when incubated with liver homogenate. The maximum concentration of radiolabeled DADS in the liver of mice occurred 90 min after intraperitoneal administration[50]. DADS, like allicin, was not detected in human blood or urine from 1 to 24 h after oral ingestion of 25 g of crushed raw garlic. The instability and/or metabolism of such compounds likely contributes to the inconsistent results found in the clinical cholesterol studies using garlic oil and garlic powder products. Metabolites of garlic constituents, such as N-acetyl-S-(2-carboxypropyl)-cysteine, N-acetylcysteine, and hexahydrohippuric acid have been detected in human urine after ingestion of garlic. At present, SAC is the only reliable human compliance marker used for studies involving garlic consumption because it is detectable and increases quantitatively in the blood after oral intake of garlic capsules. The pharmacokinetic studies of SAC demonstrated rapid absorption and almost 100% bioavailability after oral administration. The absorbed SAC seems to be metabolized to N-acetyl-SAC in urine of rats, dogs, and humans by N-acetyltransferase, which is mainly found in liver and kidneyHowever, it is assumed that the bioavailability of these sulfur containing compounds will play an important role in determining the biological response to various garlic preparations.

TOXICITY AND SAFETY

Adverse effects that have been documented in humans include a burning sensation in the mouth and gastrointestinal tract, nausea, diarrhoea, vomiting and body odor. The allergenic potential of garlic is well recognized, and the allergens have been identified as DADS, allylpropyl sulfide and allicin. Raw garlic juice (0.5 ml) caused significant damage to the epithelial mucosal membrane after2 h in rats. Enteric-coated garlic products are designed to deliver allicin (1–5 mg, depending on the product label claim) directly into the intestinal tract. When three kinds of commercially available enteric-coated garlic preparations, i.e., Garlicin, Garlique, and Garlinase 4000, were used at dosages of 133, 108 and 60.5 mg/rat, respectively, each caused severe damage to the duodenal mucosa after 2 h of exposure[4]. According to their study, enteric-coated garlic powder products, which are designed to generate allicin in the delicate intestine, may be hazardous to the intestinal tract[4].

The safety of garlic extracts has been well established by the following studies 1) acute and subacute toxicity tests 2) chronic toxicity test 3) mutagenicity tests 4) general toxicity tests 5) teratogenicity tests (Segments I, II, and III) 6) toxicity test conducted by the U.S. Food and Drug Administration; and 7) clinical studies conducted on N1000 subjects. The United States National Cancer Institute tested toxicity of typical garlic compounds. In humans, daily doses of up to 60 g of fresh garlic and 120 mg of essential oil of garlic, over a period of three months, did not result in any serious disorders. The U.S. National Cancer Institute (NCI) investigated the toxicity of SAC when compared with other garlic compounds and found that SAC has less toxicity than allicin and DADS.

Table 1: Anti Platelet Effect of Garlic in Human"

Preparation	Doses	Duration	Effect	References
Garlic tablet	225 mg/d	5 y & 9 m	PA	[20]
Garlic oil	9.9 g/d	4 h	No significance	[21]
AGE	7.2 g/d	6 w	PA	[22]
AGE	5 ml/d	13 w	PA	[23]
SEC	(In vitro) 0.78 μM	5 min	PA	[24]
SMC	(In vitro) 3.125–6.25 μM	5 min	PA	[24]
SPC	(In vitro) 0.78–6.25 μM	5 min	PA	[24]
BC	(In vitro) 0.78–25 μM	5 min	PA	[24]
AGE	(In vitro) 80 mg/ml	10 min	PA	[24]
Aqueous garlic extract	(In vitro)1 mg/ml	15 min	PA	[18]
Diallyl trisulfide	(In vitro) 10 μg/ml	5 min	PA	[25]

a)SEC, S-ethylcysteine; b)SMC, methyl-L-cysteine; c)SPC, S-1-proponyl-L-cysteine; d)BC, β-chlorogenin; e)PA, Platelet aggregation.

Table 2: Effect on neurological diseases of garlic

Components	Diseases	Doses	Duration	Effects	References
DADS	Alzheimer's diseases	20 mg/kg	4 months	Anti-amyloidogenic, anti-inflammatory and anti-tangle effects	[26]
SAC	Alzheimer's diseases	20 mg/kg	4 months	Anti-amyloidogenic, anti-inflammatory and anti-tangle effects	[26]
SAC	Alzheimer's diseases	30 mg/kg	15 days	Cognitive and neurobehavioral improvement	[31]
Thiacremonone	Alzheimer's diseases	1, 3, and 10 mg/kg	1 month	Memory improvement, glial inactivation, and anti-amyloidogenesis	[30]
SAC	Ischemia	300 mg/kg	30 min before MCAO	Reduction of infarct size	[31]
DAS	Ischemia	100, 150, and 200 mg/kg	7 days before MCAO	Increase in Bcl-2 and decrease in caspase-3	[32]
AGE	Ischemia	1.2 ml/kg	30 min before MCAO	Reduction of SOD, GPX, and EC-SOD activities	[32]
SAC	Parkinson's diseases	120 mg/kg	5 days	Reduction of TNF-α, iNOS, and GFAP expression	[28]

a)MCAO, Middle cerebral artery occlusion; b)GPX, Glutathione peroxidase; c)SOD, Superoxide dismutase; d)EC-SOD, Extracellular superoxide dismutase.

CONCLUSION

Garlic, from crushed to capsules, is consumed throughout the world. This review paper demonstrated some of the benefits of garlic for its potential uses in preventing and curing different diseases, and acting as antioxidant for many radicals. Fresh and powdered garlic are popular for food flavor and should continue to be used. Today, with the ever-growing resistant organisms, taking of garlic extract remains a powerful antimicrobial agent. Clearly more studies are needed to refine the use and improvement of the efficacy of this important medicinal plant.

REFERENCES

1. Block, E., Sci Am.1985, 252(3), 114–119.
2. Rivlin, R. S., J Nutr.2001, 131(3s), 951S–954S.
3. Lawson, L. D., Wang, Z. J., Hughes, B. G., et al. J Nat Prod.1991, 136–444.
4. Amagase, H., J Nutr.2006, 136(3 Suppl.), 716S–725S.
5. Parekh, J, Chanda, S., Afr. J. Biotechnol.*2007,* 6(6),766-770.
6. Yoo, M., Lee, S., Seog, H., & Shin, D., Food Sci Biotechnol. 2010,19(6), 1619–1626.
7. Block, E., Sci Am.1985, 252(3),114–119.
8. Sengupta, A., Ghosh, S., Bhattacharjee, S., & Das, S., Asian Pac J Cancer Prev.2004, 5(2),126–132.
9. Kimbaris, A.C., Siatis, N. G., Daferera, D. J., Tarantilis, P. A., Pappas, C. S., & Polissiou M. G., Ultrason Sonochem.2006, 13(1), 54–60.
10. Hwang, I. G., Woo, K. S., Kim, T. M., Kim, D. J., Yang, M. H., & Jeong, H. S., Korean J Food Sci Technol.2006,38, 342–347.
11. Abdullah TH, Kandil O, Elkadi A, Carter J, J Natl Med Assoc.1988, 80,439-445.
12. Zeng, T., Guo, F. F., Zhang, C. L., Song, F. Y., Zhao, X. L., & Xie, K. Q., J Sci Food Agric.2012, 92(9), 1892–1902.
13. Gebhardt R. Lipids.1993, 28(7), 613–619.
14. Sobenin, I. A., Nedosugova, L. V., Filatova, L. V., Balabolkin, M. I., Gorchakova, T. V., & Orekhov, A. N., Acta Diabetol.2008, 45(1), 1–6.
15. Kim-Park, S., & Ku, D.D., Clin Exp Pharmacol Physiol.2000, 27(10), 780-786.
16. Morihara, N., Sumioka, I., Moriguchi, T., Uda, N., & Kyo, E., Life Sci.2002, 71(5), 509–517.
17. Calvert, J. W., Coetzee, W. A., & Lefer, D. J., Antioxid Redox Signal.2010, 12(10), 1203–1217.
18. Pierre, S., Crosbie, L., & Duttaro, A. K., Platelets.2005, 16(8), 469–473.
19. Chang, H. S., Yamato, O., Yamasaki, M., & Maede, Y., Prostaglandins Leukot Essent Fatty Acids.2005, 72(5), 351–355.

20. Manoharan, A., Gemmell, R., & Hartwell, T., Am J Hematol.2006; 81(9): 676–683.
21. Wojcikowski, K., Myers, S., & Brooks, L., Platelets.2007, 18(1), 29–34.
22. Steiner, M., & Li, W., J Nutr.2001, 131(3s), 980S–984S.
23. Rahman, K., & Billington, D., J Nutr.2000, 130(11), 2662–2665.
24. Allison, G. L., Lowe, G. M., & Rahman, K., J Nutr.2006; 136(3 Suppl): 782S–788S.
25. Qi, R., Liao, F., Inoue, K., Yatomi, Y., Sato, K., & Ozaki, Y., Biochem Pharmacol.2000, 60(10), 1475–1483.
26. Chauhan, N.B.,J Ethnopharmacol.108(6), 385–394.
27. Ashafaq,M., Khan, M. M., Shadab Raza, S., Ahmad, A., Khuwaja, G., Javed, H., et al. Nutr Res.2012, 32(2), 133–143.
28. Garcia,E., Villeda-Hernandez, J., Pedraza-Chaverri, J., Maldonado, P. D., & Santamaria, A., Phytomedicine.2010, 18(1), 65–73.
29. Javed, H., Khan, M. M., Khan, A., Vaibhav, K., Ahmad, A., Khuwaja, G., et al. Brain Res.2011, 1389, 133–142.
30. Lin, G. H., Lee, Y. J., Choi, D. Y., Han, S. B., Jung, J. K., & Hwang,B. Y., J Alzheimers Dis.2012, 29(3), 659–676.
31. Kim, J. M., Chang, N., Kim, W. K., & Chun, H. S., Biosci Biotechnol Biochem.2006, 70(8), 1969–1971.
32. Aguilera, P., Chanez-Cardenas, M. E., Ortiz-Plata, A., Leon-Aparicio, D., Barrera, D., Espinoza-Rojo, M. V., et al. Phytomedicine.2010, 17(3–4), 241–247.
33. Williams, F. M., Skinner, J., Spector, T. D., Cassidy, A., Clark, I. M., Davidson, R. M., et al. BMC Musculoskelet Disord.2010, 11, 280.
34. Lau, BH., Nutr. Res.1991, 7,139-149.
35. Morioka, N, Sze, LL, Morton, DL, Irie, RF., Cancer Immunol. Immunother. 1993,37, 316-322.
36. Abdullah, TH, Kandil, O, Elkadi, A, Carter, J., J Natl Med Assoc.1988, 80,439-445.
37. Josling, P., Adv. Ther.2001,18,189-193.
38. Hsing, AW, Chokkalingam, AP, Gao, YT, Madigan, MP, Deng, J, Gridley, G, Fraumeni, JF Jr. Am. J. Med. 2002;94(21):1648-1651.
39. Jaber, MA, Afr. J. Biotechnol.2007, 6(6),771-776.
40. Bajpai, M, Pande, A, Tewari, SK, Prakash, D., Int. J. Food Sci. Nutr.2005, 56(4),287-291.
41. Tsai,Y, Cole, LL, Davis, LE, Lockwood, SJ, Simmons, V, Wild, GC., Planta Med.1985; 8:460-461.
42. Tsao, SM, Yin, MC., J. Med. Microbiol.2001,50, 646-649.
43. Hahn, G, Koch, HP, Lawson, LD, Baltimore Williams and Wilkins.1996,Pp1- 24.
44. Sabitha, P, Adhikari, PM, Shenoy, SM., Trop Doct. 2005,35(2),99-100.
45. Zeng, T., Guo, F. F., Zhang, C. L., Zhao, S., Dou, D. D., Gao, X. C., et al. Chem Biol Interact.2008,176(2-3),234–242.
46. Xiao, J., Ching, Y. P., Liong, E. C., Nanji, A. A., Fung, M. L., & Tipoe, G. L., Eur J Nutr.2013, 52(1), 179–191.
47. Chung, L. Y., J Med Food.2006, 9(2), 205–213.
48. Gu, G., Du, Y., Hu, H., & Jin, C., Carbohydr Res.2003; 338(15): 1603–1607.
49. Zare A., Farzaneh P., Pourpak Z., Zahedi F., Moin M., Shahabi S., et al. Iran J Allergy Asthma Immunol. 2008, 7(3), 133–141.
50. Pushpendran, C. K., Devasagayam, T. P., Chintalwar, G. J., Banerji, A., & Eapen, J., Experientia.1980, 36(8), 1000–1001.