

Antioxidant Potential and Toxicity of Garlic (*Allium sativum*)

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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 scale of applications. Antioxidant activity of Garlic (*Allium sativum*) destroy free radicals particles that can damage cell membranes and DNA. Various preparations of garlic, specially aged garlic extract (AGE), have been shown to have promising antioxidant potential. However, the presence of more than compound in garlic, with apparently opposite biological effects, has added to the complexity of the subject. Raw garlic homogenate has been reported to exert antioxidant potential but higher doses have been shown to be toxic to the heart, liver and kidney. The aim of this review was to clear the difference between Garlic preparations with special references to their bioactive constituents, antioxidant potential and toxicity of Garlic .

Key word: Garlic, antioxidant, toxicity

Introduction

History of garlic

Garlic (*Allium sativum*) has been used as a spice, food, and medicine for over 5,000 years, and is one of the earliest documented herbs used for the maintenance of health and treatment of disease .(**Rivlin ., 2001**) In some of the oldest texts on medicine, eg, the Egyptian Ebers papyrus dating around 1500 BC and the sacred books of India, “the Vedas” (1200–200 BCE), garlic was recommended for many medicinal applications, including circulatory disorders.(**Petrovska and Cekovska .,2010**) In ancient Greece, garlic was used as a diuretic, as recorded by Hippocrates, the father of modern medicine.(**Moyers., 1996**) In addition to its cardiovascular benefits, garlic has traditionally been used to strengthen the immune system and gastrointestinal health. (**Rivlin ., 2001**) Today, this intriguing herb is probably the most widely researched medicinal plant.

Garlic is a commonly worldwide used food and its medical properties have been well recognized for centuries (**Bongiorno et al., 2008**). Garlic and its compounds which have been reported to have diverse biological activities such as anti- carcinogenic, anti-atherosclerotic, antidiabetic, renoprotective, antioxidant and immune modulation, antibacterial, antihypertensive and various other biological actions (**Capasso., 2013**).

Types and component of garlic

Garlic is a bulbous plant; grows up to 1.2 m in height. Garlic is easy to grow and can be grown in mild climates (Figure1, 2)). There are different types or subspecies of garlic, most notably hardneck garlic and softneck garlic .Several types of garlic preparations are available, including raw and freshly cooked garlic, garlic oil, garlic powder, and aged garlic extract. Functional sulfur-containing components described in garlic include alliin, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and *S*-allylcysteine. (**Yun, et al., 2014**) Allicin, formed by enzymatic reaction from alliin, the main compound found in fresh raw garlic and garlic powder, is volatile and unstable. Allicin is destroyed by cooking, and has the potential to trigger intolerance, gastrointestinal complaints, and allergic reactions (**Lawson and Gardner., 2005**)



Figure (1)



Figure (2)

Garlic preparations and their bioactive constituents

Garlic products have become more popular in the last decade. Market research conducted in United States (1998) showed that garlic products were the most popular of all 91 dietary supplements (**Wyngate Pamela ., 1998**). Dozens of brands on store shelves can be classified into four groups: garlic oil, garlic oil macerate, garlic powder and aged garlic extract .

Raw garlic homogenate has been the major preparation of garlic subjected to intensive scientific study, because it is the most common method of garlic consumption. Raw garlic homogenate is essentially the same as the aqueous garlic extract which has been used in various scientific studies. Allicin (allyl 2-propene thiosulfinate or Diallyl thiosulfinate) was long thought to be the principal bioactive compound present in aqueous extract or raw garlic homogenate . When garlic is chopped or crushed, allinase enzyme, present in garlic is activated and acts on alliin (present in whole garlic) to produce allicin (**Fenwick and Hanley., 1985**). Other important sulfur-containing compounds present in garlic homogenate are allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate and -L-glutamyl-S-alkyl-L-cysteine (**Block .,1985**) The enzyme allinase responsible for converting alliin (S-allyl cysteine sulfoxide) to allicin is inactivated by heat (**Lawson., 1998**). Thus the water extract of heat treated garlic contains primarily alliin. Although thiosulfonates such as allicin have long been thought to be active compounds due to the characteristic odor, it is not necessary for garlic preparations to contain odorous compounds to be effective. They decompose and disappear during any processing (**Harunobu ., 2006**).

Aqueous garlic extract (AGE): Aqueous garlic extract was prepared using fresh garlic by modified method of (**Martha et al., 1998**). Thirty gram of garlic was homogenized in 100 mL of cold distilled water. The homogenized mixture was filtered three times through cheese cloth. The mixture was centrifuged at 200 g for 10 min and the clear supernatant was collected. The concentration of this garlic preparation was considered to be 500 mg mL⁻¹, on the basis of the weight of the starting material (30 g per 100 mL). Fresh extract was prepared each day before administration.

Garlic oil: Medicinally used garlic oil is prepared by steam distillation process. Distilled garlic oil consists of a variety of sulfides such as diallyl disulfide and diallyl trisulfide (**Fenwick and Hanley., 1985**). . Whole garlic cloves ground in water are distilled by heat or extracted by an organic solvent (i.e. hexane) to obtain fractionated oil. Water soluble compounds are totally eliminated by this process. Allicin is also completely eliminated from the oil (**Lawson., 1998**).

Garlic oil macerate: Oil macerate products are made of encapsulated mixtures of whole garlic cloves ground into vegetable oil. During the manufacturing process, some alliin is converted to allicin. Because allicin is unstable and decomposes quickly, oil macerate preparations contain allicin – decomposed compounds such as dithiins, ajoene and sulfides, residual amounts of alliin and other constituents in garlic (**Iberl et al., 1990**).

Garlic powder: Garlic cloves are sliced or crushed, dried and pulverized into powder. The main sulfur compound in both raw garlic and garlic powder is alliin. Garlic powder contains no allicin, possibly accounting for its instability (**Lawson and Hughes., 1992**)

Aged garlic extract: Another widely studied garlic preparation is AGE. Sliced raw garlic stored in 15–20% ethanol for 20 months is referred to as AGE. This whole process is supposed to cause considerable loss of allicin and increased activity of certain newer compounds such as S-allylcysteine (SAC), S-allyl mercaptocysteine, allixin, saponins and selenium which are stable, highly bioavailable and significantly antioxidant. SAC is one of the most active ingredients in AGE. SAC is a safe compound and its biological effects are well researched. The US National Cancer Institute tested SAC toxicity as compared to other typical garlic compounds and found that SAC is less toxic than allicin (**Carmia., 2001**)

Effect of Garlic on chemically-induced hepatotoxicity

Several studies showed that garlic can protect the liver cells from some toxic agents. Acetaminophen is a leading analgesic and antipyretic drug used in many countries. Overdose is known to cause hepatotoxicity and nephrotoxicity in humans and rodents. Although more than 90% of acetaminophen is converted into sulfate and glucouronide conjugates and excreted in the urine, a small portion is metabolized by different liver enzymes (**Patten et al., 1993**). This can arylate critical cell proteins and cause toxicity. It is demonstrated that garlic protects against acetaminophen-induced hepatotoxicity. Gentamycin also induces hepatic damage as revealed by elevation of liver damage marker enzymes (aspartate transaminase and alanine aminotransferase) and reduction in plasma albumin level. Dietary inclusion of garlic powder protects rats against gentamycin-induced hepatotoxicity, improves antioxidant status, and modulates oxidative stress (**Ademiluyi et al., 2013**). In addition, garlic attenuated hepatotoxicity effect of nitrate in rats. Garlic extract may reduce lipid peroxidation and enhance antioxidant defense system (**El-Kott, 2012**).

Effects of Garlic against DNA damage

Epidemiologic evidence suggested that high consumption of garlic protected against various cancers. Organo-sulphur compounds (OSC), such as alliin, allicin, diallyl disulfide, diallyl sulfide, allyl mercaptan, and *S*-allylcysteine, were reported to be major ingredients with anti-tumor properties in garlic (**Iciek et al., 2012**) For instance, administration of garlic powders to rat inhibited DNA damage by 35%–60% induced by *N*-nitrosodimethylamine in liver. The effect was attributed to the high alliin concentration in samples (**Singh et al., 2006**). Subsequently, researchers investigated the anticancer effects of selected OSC from garlic against chemical induced DNA damage using HepG2 cells. The study showed that all the OSC tested except allyl mercaptan markedly inhibited aflatoxin B1 induced DNA damage, while allyl mercaptan administration significantly reduced DNA breaks induced by dimethylnitrosamine. Benzo(α)pyrene genotoxicity was effectively suppressed by diallyl disulfide. Besides, all the tested OSC inhibited DNA damage of direct-acting agents, H₂O₂ and methyl methanesulfonate (**Belloir et al 2006**). In another study using rat hepatoma cells, sodium 2-propenyl thiosulfate was found to be a potent inducer of quinone reductase (**Chang et al., 2010**).

Anti oxidative effect of garlic

Garlic has also been reported as a natural antioxidant. It has played an important dietary and medicinal role throughout the history of mankind. The therapeutic efficacy of garlic encompasses a wide variety of ailments that include cancer, hepatic and microbial infections, and cardiovascular diseases. As ROS seem to be at the core of many ailments, it is justified to assume that the beneficial effects of garlic might be through modulation of ROS (**Banerjee et al., 2003**)

Aged garlic extract (AGE) is an odorless product resulting from prolonged extraction of fresh garlic at room temperature. AGE is sold in both dry form and as a liquid containing 10% ethanol. The process of aging gently modifies harsh and irritating compounds from the raw garlic and naturally generates unique and beneficial compounds through both enzymatic and natural chemical reactions. AGE contains various antioxidant organosulfur compounds, mainly *S*-Allylcysteine and allicin. These compounds play an important role as antioxidants (**Colin-Gonzalez et al., 2012**). These organosulfur compounds exert their antioxidant actions by scavenging ROS, enhancing cellular antioxidant enzymes and increasing glutathione in the cells (**Capasso ., 2013**).

ROS produced by xanthine-xanthine oxidase system, mitochondria and NADPH oxidase in cells directly act on lipid, proteins and DNA of the cell and destroy them (**Yao et al., 2007**). However, animals pre-treated with AGE showed significant improvement in biochemical, histological and ultrastructural changes in renal tissues induced by CP. Many studies have demonstrated that AGE prevents the oxidative stress and exerts a protective effect against different toxic agents through its powerful antioxidant and free radical scavengers (**Capasso., 2013**) and (**Abd El-Halim and Mohamed., 2012**)

Aged garlic extract (AGE), a natural and dietary substance, was known to have different active antioxidant organosulfur compounds mainly S-Allylcysteine and allicin (**Colin-Gonzalez et al., 2012**). These compounds enhanced cellular antioxidant enzymes, increased GSH content in the cells and scavenged the free radicals (**Capasso., 2013**). The protective effect of AGE against doxorubicin-induced cardiotoxicity (**Alkreathy et al 2010**), cadmium-induced toxicity (**Lawal and Ellis., 2011**) and acrylamide - induced oxidative damage in multiple organs (**Abd El-Halim and Mohamed., 2012**)

pre-treatment with aged garlic extract produced significant reduction in MDA level and significant elevation of SOD, CAT activities and GSH levels of the renal tissues in cisplatin -treated rats. These findings provide an evidence about the antioxidant effect of AGE against cisplatin -induced oxidative stress (**Ashraf and Hamid .,2014**).

Different protective pathways were proposed to explain the beneficial effect of garlic components. It includes ROS scavenging, inhibition of low density lipoproteins (LDL) oxidation, protection of endothelial cell integrity by inhibition of lipid peroxidation induced injury, inhibition of homocystein ethiolactone formation, improving cellular scavenging enzyme such as superoxide dismutase, catalase, glutathione peroxidase and inhibition of nuclear factor activation (**Popova and Popove ., 2005**)

Contraindications, adverse effects and toxicity:

Animal studies with rats have shown that prolonged feeding of high levels of raw garlic in rats has resulted in anemia, weight loss, and failure to grow due to lysis of red blood cells (**Augusti ., 1996**). Raw garlic juice at a dose of 5 ml/kg has resulted in death due to stomach injury (**Nakagawa et al ., 1980**). Chronic administration of garlic powder (50 mg/day) resulted in inhibition of spermatogenesis in rats. Reduced concentration of sialic acid in the testes,

epididymis and seminal vesicles together with decreased leydig cell function reflects anti-androgenic effects of garlic (**Dixit and Joshi., 1982**).

S-allylcysteine (SAC) is 30-fold less toxic than other typical garlic compounds such as allicin and diallyldisulfide. The 50% lethal oral dose (LD₅₀) of SAC in female (9.39 g/kg) or male (8.89 g/kg) mice was higher than allicin (female: 0.363 g/kg and male: 0.309 g/kg) (**Amagase et al., 2001**)

After oral intake, SAC is easily absorbed in the gastrointestinal tract and can be detected in several tissues up to 8 h after dosage (**Yan and Zeng., 2005**). The components responsible for their toxicity are organosulfoxides. Chewing the plant converts organosulfoxides to a complex mixture of sulfur compounds. The primary toxicological mechanism of *Allium*-derived sulfur compounds is oxidative hemolysis characterized by the development of methemoglobinemia and Heinz body formation in the erythrocytes (**Salgado et al., 2011**). Cooking, drying, and processing do not eliminate the toxic effect of *Allium* spp. (**Cope .,2005**). Dogs and cats are highly susceptible to *Allium* toxicosis and the ingestion of 5 g/kg of onions by cats and 15–30 g/kg by dogs is enough to cause clinically important hematologic changes. Clinical signs of *Allium* toxicosis may appear 1 day or several days after consumption depending on the amounts ingested. Common clinical signs initially include vomiting, diarrhea, abdominal pain, loss of appetite, and depression. Due to the developing anemia, pale mucous membranes, weakness, rapid respiratory and heart rates, jaundice, and dark urine (reddish or brown) indicating hemoglobinuria are subsequently observed (**Salgado et al., 2011**).

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. This review may be useful to increase our knowledge of garlic therapeutic effects and improve our future experimental and clinical research plans. Future trials on the effect of garlic should include information on the dosage of active ingredients of standardized garlic preparations for better comparison of trials. Although garlic is believed to be a safe substance, long-term trials of reasonable duration would provide insights into the possible side-effects of different garlic extracts.

Conflict of interest

There is not any conflict of interest in this study.

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