

A Review on Anticancer Activities of Garlic (*Allium sativum* L.)

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Abstract: Garlic (*Allium sativum* L.) is amongst the oldest plants cultivated for its utilization as food and medicine. It is an incredible plant with numerous useful impacts such as antithrombotic, antimicrobial, antiarthritic, antitumor, hypoglycemic and hypolipidemic activities. The present review will focus on large preclinical utilization of garlic in the prevention and cure of cancer. Various studies have showed the chemo-preventive action of this agent by means of various garlic mixtures together with garlic oil, garlic extract and various organosulfur compounds. The chemo-preventive action has been ascribed to the existence of these organosulfur compounds in garlic. It is not fully stated that how this is accomplished, yet a number of methods of action have been projected. These comprise its impact on antioxidant properties, inhibition of tumor growth and drug metabolizing enzymes. The majority of these studies were conducted in the animal models. Moreover, current investigations have concentrated on the antimutagenic action of garlic. Newly, it has been noticed that mature garlic extract displays the scavenging activities with the help of two compounds as S-allylmercapto-L-cysteine and S-allylcystine. Furthermore, various organosulfur compounds obtained from garlic, together with S-allylcystine have been found to hinder the intensification of transplantable and tumors induced chemically in animal models. Thus, the use of garlic may give an assurance of protection from cancer advancement.

Key words: Garlic • Cancer • Organosulphur • Anticancer Agents • Diallyl Sulfide • Mutagens

INTRODUCTION

Cancer can influence any race, any age group or societal class or even fetuses and disseminated all around the world causing significant loss of human lives. Environmental factors are the major causes of cancer by acting as carcinogens [1]. Garlic (*Allium sativum* L.) belongs to family Amaryllidaceae and is also called as Poor Man's Treacle. Garlic bulb contains water (65%), carbohydrates (28%), organosulfur compounds (2.3%), proteins (mostly allinase; 2%), amino acids (1.2%) and fiber (1.5%) [2].

Chemical Constituents of Garlic: There are more than two hundred chemical compounds in the Garlic bulb, of which, volatile oil with sulfur containing compounds like Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide), Alliin and Allicin, enzymes like peroxidase, allinase, myrosinase and other compounds like α -phellandrene, β -

phellandrene, linalool, citral and geraniol are important [3]. The garlic carries some biochemically most dynamic compounds having sulfur, specially alliin, allicin diallyl disulphide (DADA) and cycloalliin. Moreover it also contains Vitamins (A, B1 and C) phosphorous, sulfur, sodium, manganese, trace iodine, iron, germanium, selenium, calcium and potassium. In addition garlic contains 17 amino acids with 8 vital amino acids. Several unrevealed garlic substances acquire additional therapeutic agents. Relatively a small number of medically active compounds are found in garlic. On chopping or crushing garlic, a dozen of novel compounds are produced through several chemical reactions [4].

Garlic Organosulfur Compounds: Garlic has an extensive history as a food with novel flavor and aroma all along with some medicinal qualities. Modern scientific study has discovered that large diversity of medicinal and dietary functions of garlic can be ascribed to organosulfur

compounds (OSC) found in or generated from garlic. More than twenty kinds of sulfide compounds from a few sulfur-containing amino acids are produced by garlic with diverse functions such as allicin, diallyl trisulfide and methyl allyl trisulfide, which have shown antithrombotic, anticancer and antibacterial activities [5].

History of Garlic Utilization: Garlic is utilized in cooking by several civilizations and cultures around the world, with most usage in the Middle East, Orient and the Mediterranean cuisine. It is considered to be one of the most primitively cultivated plant along with other growing crops and thought to have cultivated in the Middle East around 5,000 years ago. More over garlic has been used as a medicine for many years in past and now [6].

Garlic Constituents as Anticancer Agents: World Health Organization reported more than 80% of world's population dependent on conventional medication for their essential services of health care [7]. Plants has been used from a long time to cure various lethal diseases such as cancer and it is clear that >60% anticancer agents are plant products [8]. Allicin is most important predecessor of bioactive compounds of garlic, it produce sulfur compounds that give garlic the characteristics odor and flavor. Bioactive compounds are characterized as substances in dietary and food supplement, besides those obligatory to meet fundamental nutritional requirements necessary to elevate the health status [9]. A number of population studies demonstrated a relationship between excess garlic intake and reduction in risks of pancreas, colon, stomach, esophagus and breast cancers. An investigation from seven population studies demonstrated that the high use of cooked or crude garlic will reduce the danger of colorectal and stomach cancer [10]. Researchers have shown that about 60 seconds of quick microwaving before crushing or chopping resulted in reduction of anticancer properties of garlic. Instant boiling of unbroken garlic also reduces these properties, the same as with direct addition of an extremely low-acid component such as lemon juice [11].

For thousands of years medicinal properties of garlic have been known. It has been listed in Roman and Greek writings as a treatment for a number of diseases like infections, hypertension and interestingly tumors, even though garlic continued to be utilized as an anti-hypertensive and an antibiotic agent. The European Prospective Investigation into Cancer and Nutrition (EPIC) is an enduring international study involving women and men from 10 different countries. The

investigations were performed to investigate the impacts of garlic utilization on cancer, which revealed that the higher consumption of garlic and onion were related with reduction in danger of intestinal cancer [12]. In an alternative study, the utilization of allium vegetables particularly garlic and onion minimize the danger of stomach cancer [13]. In another study, higher ingestion of allium vegetables, especially scallions and garlic were linked with about 50% decrease in risk of prostate cancer [14]. Proofs also recommended that improved garlic utilization might decrease pancreatic cancer risk. In the San Francisco Bay area, a study was conducted, which confirmed that the people who consumed garlic in excess have 54% less risk of pancreatic cancer then those who consume it in less amounts [15].

The effect of garlic ingestion on gastric cancer has been assessed by three randomized trials. One study includes more than 5,000 Chinese ladies and men at elevated risk of stomach cancer. The researchers compared the impacts of taking a mixture of 200 mg man made allitridum (garlic extract used as a medicine in China for over 3,000 years) plus 100 micrograms selenium on daily basis in comparison with taking placebo only (inactive substance used as control). The allitridum-selenium mixture was given in the similar way as an active drug and the trial was being tested for five years. The results confirmed that the risk of combined tumors was reduced by 33% and stomach cancer risk was reduced by 52% in the group that was receiving the allitridum-selenium mixture then the other group that only received placebo [16].

Cell cultures and animals studies conducted in several laboratory investigations suggested that garlic might help in reducing tumor growth. Garlic is capable of allowing cancer cell death normally, the process called as apoptosis shown in cell culture studies. Substances found in the garlic appear to be capable to act as antioxidants observed in other cell culture studies. Besides this, few other studies have recommended that garlic can also act against *Helicobacter pylori* (a bacterium) considered as a main cause of stomach cancer [15]. The other studies in laboratory animals have suggested that it might also help to protect against skin, colon, breast, liver and other types of cancers [16]. A study conducted in Chinese population having stomach cancer revealed that garlic extract obtained from mature bulbs and garlic oil obtained by steam-distillation did not avert this disease [17]. However some investigations on garlic are encouraging, it is very difficult to conclude the accurate role of a specific food

against cancer. It is significantly harder, when the food under investigation is frequently used in little amount like garlic. Additional studies proposed garlic as agent to makes blood less prone to form clots that may facilitate in avoiding heart stroke. On the other hand, no reliable clinical evidence is found for garlic activity in preventing the heart stroke or attack. There are diverse proofs on garlic to control high blood pressure [18].

In Unites States the third leading cause of death is colorectal cancer (CRC) and in Australia it is second leading cause of death. For multiple stages of CRC, environmental factors play important role and nutritional involvement has been said to play a vital role in its prevention. The objective of the study was to review thoroughly the scientific indications about the effects of garlic on CRC from all the studies conducted in previous decades and garlic role in prevention or reduction of colorectal cancer was confirmed. All the studies confirmed that garlic played a positive role in disease reduction [10].

The anticarcinogenic impact of *Allium* vegetables including garlic is ascribed to organosulfur compounds (OSC), which are extremely efficient in boosting defense against cancer in animal models instigated by a number of different chemical carcinogens. Later studies have demonstrated that certain OSC analogues found in nature can repress propagation of cancer cells *in vivo* and in culture. The OSC-induced changes in the propagation of cancer cells are often linked with perturbations in cell cycle sequence and stimulation of G2/M phase detain. The OSC have also been verified to prompt apoptosis through the basic pathway by changing the ratio of the Bcl-2 family of proteins both in *in vivo* models and cell cultures. Anti-angiogenic activity of OSC derived from garlic has also been acknowledged [19].

Laboratory studies and experimental animals have demonstrated that the solid indication of OSCs in garlic might influence cancer cells by promoting the early mitotic arrest followed by apoptotic cell death devoid of disturbing healthy cells [5]. The capacity of OSCs to hamper cancer cell propagation and feasibility strongly relates with the length of sulfur chain. Recent records supports a method of mitotic arrest of cancer cells because of changes in the microtubule network, probably as a result of the elevated reactivity of sulfur atoms against thiol groups of diverse cellular macromolecules controlling the crucial regulatory functions. Collectively, these results showed a guaranteeing potential for the utilization of sulfur compounds derived from garlic in chemotherapy and chemoprevention [20].

Indications support the defensive effect of garlic in colorectal, bosom and stomach tumor in people. The protecting properties appear to be associated with the occurrence of organosulfur, mainly derivatives of allyl that have also been revealed to hinder carcinogenesis in esophagus, colon, lungs, mammary glands and stomach of animals [20]. Garlic has been utilized for thousands of years as a therapeutic and prophylactic medicinal agent. Significantly, garlic has been recommended to have both cancer defensive potential as well as considerable upgrading effect on the immune system. Studies tending to immune-modulatory impacts of garlic uncover contradictory data as to anti- and pro-inflammatory responses relying upon the specific experimental setups and garlic preparation utilized i.e. extract of garlic vs pure chemical garlic compounds. The chemistry of the main organosulfur compounds of garlic sum up the recent comprehension and suggest the link between the immune modulating activity of garlic and the avoidance of cancer. Researchers hypothesize that garlic rather evokes anti oxidative and anti inflammatory responses that help organisms towards suppression of a developing tumor [21].

Aged garlic extract (AGE) is extensively used as a dietary supplement and is asserted to encourage human health through anti-inflammatory/anti-oxidant activities by means of neuroprotective, hypolipidemic and antiplatelet effects [2]. Two most important compounds in old garlic S-allylmercapto-L-cysteine and S-allylcysteine had the utmost radical scavenging activities. Moreover, a number of garlic-derived organosulfur compounds including S-allylcysteine have been found to reverse the development of transplantable and chemically induced tumors in several animal models [22].

One of the most common brain malignancies is Glioblastoma multiforme (GBM) and has an extremely poor prognosis. Current indication proposed treatment failure and adverse prognosis of GBM, which may be the result of presence of cancer stem cells (CSC) in GBM and the uncommon subpopulation of CSC which is resistant to chemotherapy. A compound derived from garlic is Z-ajoene that has revealed a range of biological activities such as anti-proliferative effects on various cancers. In the article, researchers showed that Z-ajoene particularly hinders the growth of population of GBM CSC. CSC sphere-forming hindrance was accomplished at a concentration that did not possess a cytotoxic effect in standard cell culture conditions [23].

Table 1: List of chemicals from garlic, experimental inhibition of cancer by garlic and antimutagenic activity of garlic constituents.

Chemicals	Carcinogen and Mutagens	Organ/Species	Citations
Fresh garlic extract	DMBA (7,12dimethylbenz(a) anthracene)	Buccal pouch/Hamster	[27]
Garlic oil	DMBA/PMA (phorbol myristate acetate)	Skin/Mouse	[28]
Diallyl sulfide (DAS)	DMH (1,2-dimethyl hydrazine), NMBA (N-nitrosomethyl benzylamine), BP (benzo[a] pyrene), DMBA	Esophagus, Colon /Rat Lungs, Forestomach Skin/Mouse	[29]
Allyl methyl sulfide	BP	Forestomach/Mouse	[30]
Diallyl trisulfide (DATS)	BP	Forestomach/Mouse	[31]
Allyl methyl trisulfide	BP	Forestomach/Mouse	[32]
Methanol extract of garlic	AFB1 (aflatoxin B1)	Liver/Rat	[32]
Fresh garlic powder	DEN (diethyl nitrosamine)	Liver/Rat	[32]
S-methyl cysteine (SMC)	DEN	Liver/Rat	[33]
Methanolic garlic extract	AFB1 (aflatoxin B1)	<i>Salmonella</i> TA98	[34]
Aqueous garlic extract	AFB1	<i>Salmonella</i> TA100 88	[35]
Aqueous garlic extract	4-NQO (4-nitroquinoline -1-oxide)	<i>E. coli</i>	[36]
Aqueous garlic extract	Gamma rays, Hydrogen peroxide Cumene hydroperoxide, t-butyl hydroperoxide	<i>Salmonella</i> TA102	[36]
S-allyl cysteine (SAC)	DMBA	Buccal pouch/Hamster	[36]
Diallyl sulfide	PhIP (2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine)	Colon/ Rat	[37]
Garlic powder	PhIP	Colon/ Rat	[38]

One of the major active constituents of garlic is Diallyl sulfide (DAS), which is the major factor for growth reversion of *in vitro* cancer cells and advances *in vivo* immune responses in trial settings. The study involved investigations of the anti-cancer effects of DAS in HeLa human cervical cancer cells and to examine the fundamental mechanisms *in vitro*. Apoptosis and cytotoxicity in human cervical cancers were investigated by viability assay, morphological changes, comet assay, DAPI staining, confocal microscopy examination and Western blotting. Therefore, the study revealed that DAS considerably retrain the growth and instigates apoptosis of HeLa human cervical cancer cells *in vitro* [24].

Another garlic derivative sulfur compound Diallyl disulfide (DADS) has been revealed in several studies to have protecting impacts on colon carcinogenesis in rodent models. On the other hand, molecular mechanism of action of DADS is still not clear. This study was intended to authenticate the DADS anti-proliferative activity and to monitor for differently DADS induced expressed genes in human colon cancer cells with the aim to investigate its promising anticancer mechanisms. The study revealed that a new gene and 49 notorious genes were involved in the DADS anti-proliferative effects. These genes were associated to cell proliferation, apoptosis and extracellular matrix proteins and transduction. In conclusion, DADS demonstrate anti-proliferative effects on colon cancer HT-29 cells and two cDNA libraries, DHUG and DHDG genes were found to involve in this procedure. Additional studies on the description and identification of these genes possibly will permit a better understanding about the protective roles

of DADS in colon carcinogenesis [25]. As a result, the utilization of garlic may give some kind of protection from cancer development.

The studies by various researchers confirmed the inhibitory activities of different chemical constituents of garlic against various carcinogens and mutagens, which revealed that garlic played a major role in cancer control and elimination (Table 1). These garlic compounds cause inhabitation against various carcinogenic compounds and control various cancers like buccal pouch, colon, skin, liver, forestomach and lung cancers in model animals like rat, mouse and hamster etc (Table 1).

The accurate mechanisms of the cancer prevention impacts are not clear, even though a number of hypotheses are proposed. Organosulfur compounds adapt the activity of numerous metabolizing enzymes that activate carcinogens and hinder the development of DNA adducts in various targeted tissues. In several tumor cell lines antiproliferative activity has been described, which is possibly interceded by impelling of apoptosis and changes in the cell cycle. Thus the garlic organosulfur compounds are best anticancer agents. For defining the effective dose that does not cause toxicity in humans, clinical trials are required [26].

Safety Considerations in Garlic Utilization: Garlic is rarely a source of allergies that can vary from a mild irritation to possibly life threatening issues. It can seldom cause nausea, vomiting, diarrhea and heartburn if fresh garlic bulb is eaten on empty stomach. It can also lower the level of blood sugar and increase the insulin level investigated in some human and animal studies. Garlic has been shown to meddle with numerous prescribed

medicines, particularly the HIV drug saquinavir (brand names Fortovase and Invirase). Garlic is capable of lowering the serum levels of saquinavir to a great extent (50%) [39]. Garlic is not recommended to use by pregnant women, people nearly going for surgery and the people using the blood thinners like warfarin (brand name Coumadin).

Garlic bulbs are occasionally contaminated with bacterium *Clostridium botulinum* (causative agent of botulinum). The bacterium can grow and produce toxin in garlic processed in oil goods, not refrigerated or without any preservative or antibacterial agent. Furthermore, contact dermatitis, bronchial asthma and chemical burns can occur if garlic is applied to the skin. Excess garlic use is also not recommended to the people having stomach ulcers, as it can worsen the situation or may cause more complications [40].

CONCLUSIONS

Garlic is still used globally for the treatment of various kinds of diseases together with cancer as a natural remedy. The present review described the work of various researches providing pharmacological evidence of garlic as an anti-carcinogenic agent. A lot of sulfur compounds identified and extracted from the garlic revealed to have anti-carcinogenic activities. As described in the present review, the anti-carcinogenic activities of garlic involves several aspects such as effects on free radical scavenging activities, antioxidant, drug metabolizing enzymes, inhibition of tumor instigation and effects on cell cycle and stimulation of apoptosis in the cancer cells. Significant improvement has been made in last few years on the mechanisms by which the garlic and its organosulfur compounds repress initiation and growth of cancer. It is concluded from this review article that the active compounds of garlic like Alliin, Ajoene and Allicin acts as new and efficient anticancer agents. It is recommended to use garlic in the diet, considered to be compulsory to sustain good health.

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