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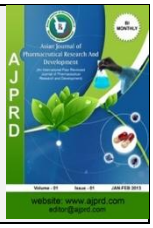

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Review Article

Garlic (*Allium sativum* L.) – A Promising Anti-cancer Drug

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A B S T R A C T

Globally cancer is the leading cause of death. The popular treatments in cancer therapies are radiation, surgery, chemo-therapy, which involves high risk and expensive. The present day, modern cancer therapies are associated with several toxicities and lack of quality of life. Herbal remedies for cancer treatment are found notion to the Oncologists. Garlic known as *Allium sativum* (Family: Liliaceae), is one of the promising drug found to treat cancer patients and also to treat the toxic effects produced by other cancer treatment. By consuming garlic regularly it shows protection to cancer and many ailments. Allicin is a major pharmacological component of garlic, reported to have anti-cancer properties and also used to treat drug-induced toxicity.

Keywords: Oncologists, Garlic, Liliaceae, *Allium sativum*.

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INTRODUCTION

Abnormal cells which grows uncontrollably anywhere in a body is known as cancer cells, malignant cells or tumor cells and these cells can infiltrate normal body tissues. Thecell which grows out of control and invade other tissues cells, and may become cancerous due to the accumulation of defects/mutations in their DNA and damage the DNA which leads to cancer.[1,2] Most of the time cells are able to detect and repair DNA damage. If cells are severely damaged and cannot repair it, it usually undergoes so-called programmed cell death/apoptosis[3]. Etiology of cancer include chronic inflammation, obesity, type 2 diabetes, poor diet, nutritional deficiencies, weak immunity, genetics, drugs, smoking, alcohol use, stress, insomnia, environmental toxins[4] Signs and symptoms of cancer are fever, pain, fatigue, skin changes, weight changes, lumps and tumors, difficulties in bowel function, short of breath, chest pain etc[5]. The anti-cancer drugs act by different mechanism, these are classified as alkylation (temozolomide, procarbazine), cross linking of DNA (cisplatin, oxaliplatin), binding of DNA pairs (actinomycin – D, doxorubicin), inhibit the topoisomerase enzyme (irinotecan, etoposide), and DNA strand cleaving, (bleomycin)[6-10]. Anti-metabolites- an oldest families of anti-cancer drugs, it inhibits the use of metabolite, where the structure is similar to the metabolite that they interfere and presence of anti-metabolites can have toxic effects on the cells such as halting cell growth and cell division, so these are used in chemotherapy of cancer, e.g.; 5 – fluorouracil, 6 –mercaptopurine[11] . Anti-tubulin-it interacts with microtubule dynamic and blocks the division of nucleus, e.g.; taxanes, vinca alkaloids[12-13]. Cancer can be treated by some herbs such as burdock root (*Arctium lappa*) effective at removing the cancer toxins, ginger *(Zingiber officinalis)* its potential to stop or prevent several cancers, aloe vera *(Aloe barbedensis)* a promising plant for treatment of certain types of cancer,turmeric *(Curcuma longa)*causes cancer cell death without harming healthy cells, clove *(Eugenia caryophyllata)* have the ability to improve immune function, garlic *(Allium sativum)* a natural cancer preventing formula[14].

GARLIC

Garlic, *Allium sativum* (Family:Liliaceae), in India popularly known Lasun. It has been associated with humans and their food since ancient times. Commercially it is cultivated and used as food and medicine in all temperate climatic region of the world. Garlic contains sulphur based compound called alliin (S-allylcysteine sulfoxide), present in cell vacuoles. When the cells are broken, it is converted to allicin and finally di-allyl sulphide**.** Both of them are responsible for strong smell and pungent taste of garlic[15]. It is used for culinary spice, sport enthusiasts, energy booster for athletes, cleaning aid[16], reduce the prevalence of cancer[17] and the pharmacological activities includes anti-hyperlipidemic, anti-thrombotic, anti-cancer effects[18], anti-microbial[19], anti-fungal effects[20] and also used for illnesses including heart disease, high blood pressure[21,22].

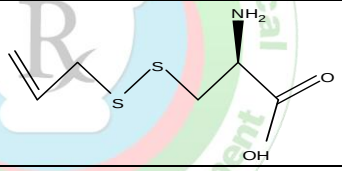
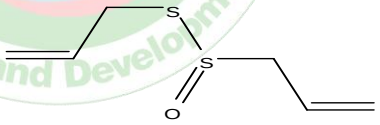
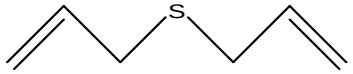
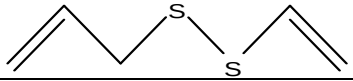
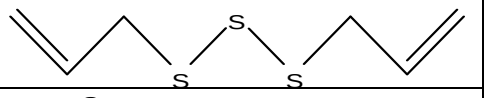
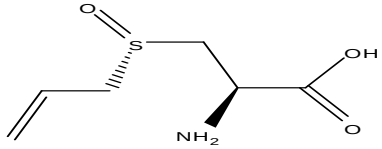
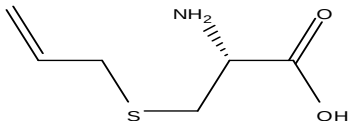
Precautions of garlic utilization

Rarely garlic is a source of allergies that can vary from mild to possibly a life threatening issues. On empty stomach, if fresh garlic bulbs are eaten than it may seldom cause nausea, vomiting, heartburn and diarrhea. It is investigated in some human and animal studies that garlic can lower the blood sugar level and increase the insulin level[23]. Pregnant women and the people who are nearly going for surgery and those are using blood thinners like warfarin, garlic is not recommended for them. *Clostridium botulinum* is a bacterium which occasionally contaminates the garlic bulbs. Garlic that is processed in oil foods, if not refrigerated or without any added preservatives or anti-bacterial agents then the bacteria can grow and produce toxins. If garlic is directly applied to skin, it may cause contact dermatitis, chemical burn and bronchial asthma. The people suffering from stomach ulcers, is also not recommended for excess use of garlic because it may worsen the situation or more complicate the situation[24].

Garlic constituents as anti-cancer agents

More than 80% of world's population is dependent on conventional medication for health care as their essential services reported as World Health Organization[25]. Various lethal diseases such as cancer is cured by using plants since long time and it is clear that >60% anti-cancer agents are plant products[26]. Most important *precursor* of bioactive compounds of garlic is allicin, it produce sulfur compounds due to which garlic have its characteristic odor and flavor. It is demonstrated by a number of population studies that a relationship between excess garlic intake and reduction in risk of pancreas, stomach, colon, esophagus and breast cancers[27]. Table 1 illustrates the reported anti - cancer activity of garlic constituents.

Table 1: Major garlic constituents and their reported anti-cancer activity.[28-34]

S. No.	Garlic chemical - compound.	Structure
01.	Alliin	
02.	Diallyl thiosulfinate (allicin)	
03.	Diallyl sulfide (DAS).	
04.	Diallyl disulfide (DADS).	
05.	Diallyltrisulfide (DATS).	
06.	S-allylmercapto-cysteine (SAMC).	
07.	S-allyl cysteine (SAC).	

The high use of cooked or crude garlic intake will reduce the danger of colorectal and stomach cancer which is

demonstrated by an investigation of seven population studies[35]. Direct addition of low-acid components such as lemon juice reduces the garlic anti-cancer properties and it's same with instant boiling of unbroken garlic[36]. Proofs also recommended that in San Francisco Bay area, study was conducted which confirmed that consumption of excess garlic have 54% less danger of pancreatic cancer than those who consume in less amounts[37]. Garlic role in prevention of colorectal cancer was confirmed and all the studies proved that garlic played a positive role in disease reduction. For multiple stages of colorectal cancer, environmental and nutritional factors plays a vital role in its prevention, where in United States third leading cause of death is colorectal cancer and in Australia it a second leading cause[36].

The cancer prevention impacts are not clear by its accurate mechanism even though number of hypotheses is proposed. The numerous metabolizing enzymes which activates the carcinogens and hinder the development of DNA adducts in various targeted tissues adapted by organo-sulfur compounds. Anti-proliferative activity has been described in several tumor cell lines, which is possibly interceded by impelling apoptosis and changes in cell cycle. Thus the best anti-cancer agents are garlic organo-sulfur compounds. For defining the effective dose that does not have the toxicity in humans, clinical trials are required[38].

Mechanism of garlic for its anti-carcinogenic activity:

Garlic and its constituents may include the inhibition of carcinogen activation, the enhancement of detoxification, excretion and protection of DNA from activated carcinogens for possible anti-carcinogenic activity [39-42]. Furthermore, decrease histone deacetylase activity, mitosis in tumor is reducing by DATS, acetylating of H3 and H4 is increased, cell cycle progression is inhibited, and decreased pro-tumor markers[43]. Garlic component have been found to block covalent binding of carcinogens to DNA, enhanced the degradation of carcinogens, have anti-oxidative and free radical scavenging properties, regulate cell proliferation, apoptosis, and immune responses. Garlic-derived natural compound is ajoene, which have been shown to induce apoptosis in human leukemic cells via stimulation of peroxide production, activation of caspase-3-like and caspase-8 activity. Garlic synergizes the effect of a breast cancer suppressor, eicosapentanoic acid, and antagonizes the effect of enhancers of breast cancer, linoleic acid[44].

Modulation of activity by garlic organo-sulfur compounds of phase I and phase II metabolizing enzymes:

Biotransformation of xenobiotics are important, to protect all living organisms from environmental toxic effects. Xenobiotic metabolizing enzymes are usually classified as phase I and phase II enzymes, in mammalian system. Phase I reaction starts the drug metabolism, generally by functional group modifications. Conjugation with endogenous compounds involves in phase II reactions, thus facilitating excretion from body[45].

Modulations of activity of phase I metabolizing enzymes:

Specific CYP450 enzymes which play a key role in catalyzing the microsomal biotransformation of many xenobiotic compounds as its activities increased or decreased [46, 47] can be directly beneficial by decreasing metabolism and/or increasing excretion of some carcinogens as well as by circumventing the DNA damage. By selectively enhancing or suppressing the levels of cytochrome P450 genes or proteins, garlic active components have been found to exert their chemo preventive effect [48, 49].

For the activation of numerous carcinogenic chemicals CYP2E1 is responsible[50]. Diallyl sulfide as a substrate have revealed that the sulfur atom on diallyl sulfide is oxidized by CYP2E1 to diallyl sulfone (DASO), then subsequently to diallyl sulfoxide ($DASO_2$) by CYP2E1 enzymes kinetics studies. Then the final metabolite was an epoxide, which is generated by oxidation of the terminal double bond of $DASO_2$, CYP2E1 enzyme is irreversibly bonded and lead to the autocatalytic destruction of the enzyme [51, 52]. Diallyl sulfide (DAS), diallyl disulfide (DADS), and allyl mercaptan (AM) suppressed hepatic CYP2E1 protein expression and N-nitroso-di-methyl-amine de-methylase (NDMA) activity in a time and NADPH- dependent manner[53] while alkyl sulfides such as di-propyl sulfide (DPS), di-propyl disulfide (DPDS), and propyl methyl sulfide (PMS) did not inhibit the hepatic CYP2E1 protein expression, indicates that alkenyl group on the organo-sulfur compounds may be critical for inhibiting the CYP2E1 enzyme[54].

Modulation of activity of phase II metabolizing enzymes:

By inhibiting carcinogen activation and enhancing detoxification of activated carcinogenic intermediates through the induction of phase II enzymes where garlic constituents functions as a double-edge sword in the prevention of chemically induced cancers[54-57], such phase II enzymes are glutathione S- transferase (GST), epoxide hydrolyses (EH), quinone reductase (QR), and UDP glucuronosyl transferase (UGT)[58]. On GST enzymes, the study has been specially emphasis on the effects of the garlic organo-sulfur compounds. Glutathione s- transferase enzymes are the detoxification enzymes, which catalyze the conjugation of wide variety of electrophiles and carcinogens with glutathione (GSH) [57]. Diallyl sulfide (DAS), allyl methyl disulfide (AMDS), allyl methyl trisulfide (AMTS), diallyl disulfide (DADS), diallyltrisulfide (DATS), and S-allyl cysteine (SAC) compared to their corresponding saturated compounds in which propyl groups were substituted for the allyl groups were found to be an inducer of GST, which catalyzing the conjugation of a wide variety of electrophiles and carcinogens with glutathione (GSH) in the fore stomach, small-bowel mucosa, liver, colon and lung of the mice[57,58-61]. The most active structure than mono and di-sulfur compounds were DATS possessing triple sulfur bonds (-S-S-S) in its structure, for the induction of detoxifying enzymes while the saturated analogs were almost without inhibitory activity, and indicating the importance of the allyl group on the sulfides.

By up-regulation of the GST-α, GST-π, and GST-μ, exert anti-tumor properties by organo-sulfur compounds [56, 62-67]. Increasing the activity of GST as well as other detoxifying enzymes such as epoxide hydrolyses (EH), quinone reductase (QR), and UDP-glucuronosyl transferase (UGT) by lipid-soluble organo-sulfur compounds. Thus, its reasonable conclusion is the induction of phase II enzymes,

especially GST, represents another potential mechanism to explain OSC-mediated prevention of chemically induced cancers.

Inhibition of post-translation modification of oncogenic Ras:

By oral administration of DADS (8.25, 16.5, and 33 µmol, 3 times per week beginning the day of tumor cell injection), but not with its saturated analogue di-propyl disulfide, suppressed growth of H- ras oncogene transformed tumor xenografts, without causing weight loss or any other side effects in nude mice, which have been revealed by studies from Prof. Shivendra V singh laboratory [68, 69].

Inhibition of cell cycle progression:

Signal transduction pathways were activated by cellular stresses, referred to as checkpoints, to ensure the completion of phase specific events and protects against genomic instability, or in cases where damage is too severe, which switch the cell fate to programmed cell death[70, 71]. According to studies that garlic-derived OSC can suppress growth of cancer cells of different anatomical locations in association with cell cycle arrest, mainly in G2/M phase of cell cycle. In human colon cancer cells, the DADS-mediated G2/M phase cell cycle arrest was accompanied by reduction in complex formation between Cdk1 and cyclin B1, by decrease in the kinase activity of the Cdk1/cyclin B1 complex and a decrease in Cdc25C protein level[72]. DATS was much more effective than either DADS or DAS in causing G2/M phase cell cycle arrest and further shows the subtle change in OSC structure (the oligo-sulfide chain length) could have a significant impact on its biological activity, have been revealed by thorough investigation of mechanism of DATS-induced G2/M phase cell cycle arrest using PC-3 and DU145 human prostate cancer cells as a model was used[73].

Histone modification:

Cancer cell proliferation through modification of histone acetylating and thus, regulation of gene expression was affected by OSC[74].

Induction of programmed cell death:

Programmed cell death is also known as apoptosis, a form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area, which is tightly controlled process whose dysregulation leads to numerous pathological conditions including cancer, whereas apoptosis is a valid target in cancer therapy and prevention [75, 76]. Number of key elements in cellular signal transduction pathways linked to the apoptosis process is modulated by garlic-derived OSC as shown in studies.

In execution of apoptosis, the intrinsic and mitochondria-mediated pathway was included, which involves loss of mitochondrial membrane potential and release of apoptogenic molecules from mitochondria to the cytosol[77, 78], whose activation is regulated by the Bcl-2 family: anti-apoptotic (Bcl-2 and Bcl-xL) and proapoptotic (Bax and Bak) proteins[79]. To trigger apoptosis by modulating the levels of Bcl-2 proteins are believed by garlic-derived OSC.

DATS mechanism for anti-cancer effects:

Induction of G2/M cell cycle arrest and apoptosis in cancer cells is due to diallyltrisulfide (DATS) which is a garlic chemical constituent by altering the levels of G3/M regulatory proteins of cell cycle and apoptotic proteins. Reactive oxygen species production is induced by DATS which in turn induces DNA damage which results in H2AX (also known as γH2AX) phosphorylation predominantly by ataxia tetangiectasia mutated protein kinase serine/threonine kinase. Also results in activation of p53, p21 and regulatory proteins of G2/M phase cdc 2 cyclin B, cdc25c. DATS treatment may activate the caspase-mediated apoptosis by inducing the endoplasmic reticulum stress related molecules like CHOP/GADD153 and BIP/GRP78. DATS may also increase the levels of calcium, down-regulated the expression level of Bcl-xl-B-cell of lymphoma extra-large, increased the hyper phosphorylation of B-cell of lymphoma 2 and ratio of Bax /Bcl2 inducing apoptosis. DATS decreased the mitochondrial membrane potential and triggered the release of mitochondrial molecules like Apoptotic inducing factors, cytochrome c, endonuclease G and HtrA2 mitochondrial serine protease. Further activation of apoptosis molecules like Apaf1(apoptotic protease activity factor 1), caspase-9, caspase-3 and cleavage of poly ADP ribose polymerase inducing caspase dependent apoptosis by releasing cytochrome c. Caspase independent apoptosis by apoptosis inducing factors and endonuclease G is induces by DATS and N-acetyl cysteine blocks the DATS –induced reactive oxygen species production, cell cycle arrest and apoptosis in cancer cells[80,81].

Table 2: How much garlic may be useful in cancer prevention[82]:

Types of garlic	Amount of garlic
Fresh garlic	2-5g, approx. 1 clove
Dried garlic powder	0.4 -1.5g
Garlic oil	2 – 5 mg
Garlic extract	300 – 1000 mg
Other formulations	2 – 5 mg of allicin

CONCLUSION:

A survey of literature strongly indicates that garlic and its chemical compounds which elicit a wide range of biological activities associated with anti-carcinogenesis and cancer prevention merits more focused attention. In Asian countries it was recognized for its medicinal properties and also used for flavoring of food. Now scientists have revealed many health protective effects of garlic including prevention of cancer. It has become quite evident that the white bulb of garlic, though not a panacea for cancer, is packed with cancer chemo-preventive substances and should prove to be not just a flavoring agent but also a natural cancer preventive formula. This beneficial plant part therefore is worthy of serious consideration for further investigation and clinical trials with respect to prevention and treatment of human cancer. Research over past years had confirmed that garlic derived organo-sulfur compounds appear to target multiple targets like cell cycle machinery, intrinsic pathway of apoptotic cell death and angiogenic pathway, which may contribute to their anti-cancer activities. Alliin, ajoene and allicin is a bioactive constituent of garlic which acts as new and efficient anti-

cancer agents which may know use in diet, considered to be compulsory to sustain good health.

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