



Anticancerous and Antimicrobial Properties of Garlic

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ABSTRACT

Garlic (*Allium sativum*) and its therapeutic effects in prevention and treatment of various diseases has been recognized by several different cultures throughout the history. Of numerous health benefits of garlic, recent studies support its protective effect against different types of cancer risk and a potential inhibition of several pathogens. The anti-tumor and anti-microbial agent present in garlic are widely being recognized for their targets to be used as a potential therapeutics. This review summarizes the molecular mechanism of different garlic compounds and their targets in cancer and antipathogenic activity.

Keywords: Garlic, antitumor, anticancer.

INTRODUCTION

Allium Sativum (Garlic) is a species of genus *Allium*. Garlic is a traditional medicinal plant, originated from central Asia, some parts of southern Europe, Northern Africa and America. Garlic is cultivated and grown asexually by planting the cloves in autumn and harvesting in summers. Depending on the mode of cultivation two subspecies of garlic namely hard neck garlic and soft neck garlic with their hundreds of varieties are found around the world. India is the second largest producer of garlic (5%) followed by china [1]. Several different supplements of garlic are available commercially in raw, powder, oil and aged garlic extract form and each form has different organosulfur profile. Garlic contains dietary fibres several nutrients, minerals and selenium (14.2 µg in 100 g); which produces volatile sulfur compound, importantly thiosulfates responsible for the pungent aroma. Garlic contains more than 30 Organosulfur compounds which are responsible for various physiological effect involved in human health [2]. These compounds are presently being investigated for their role in prevention and treatment of disease as they possesses Anti-microbial (antibacterial, antifungal, antiviral, antiparasitic), Anti-cancer (liver cancer, gastric cancer, colon cancer, prostate cancer, Breast cancer, Bladder cancer, lung cancer, ovarian cancer), activity. The detailed anti-microbial and anti-cancerous mechanisms are discussed further (Figure 1).

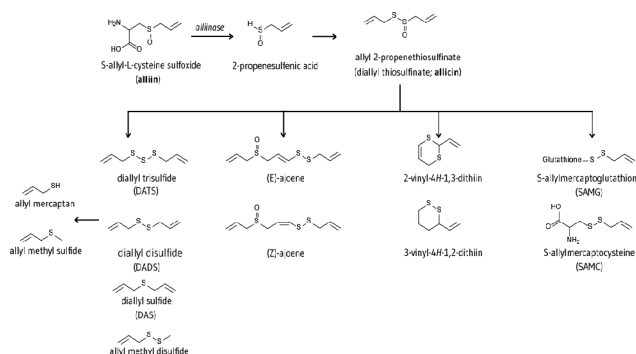


Figure 1. Organosulfur derivatives of Alliin and Garlic product

ANTIMICROBIAL ACTIVITY OF *ALLIUM SATIVUM*

Microbes are unicellular organism essential tools for human health in many ways like ferment foods, sewage treatment, produce fuel, enzymes etc. but they are also pathogens and causative agent of many infectious disease. These causative agents can be broadly classified as pathogenic bacteria, fungi, virus and parasite and many of these pathogens are multi-drug resistant. Plants with medicinal values are now been focused for cure and treatment of these pathogenic infection. *Allium sativum* is well-known antimicrobial activities from ancient time as the sulphur compound present in this can retard the infection from range of highly precarious microorganisms. The mechanistic aspect of antimicrobial activity of various garlic compounds is described below:

Antibacterial activity of Allium sativum

Allium sativum inhibits the growth of several Gram positive (ex. *S. aureus*) and gram negative (ex. *E. coli*) bacteria. Allicin-allyl 2-propenethiosulfate (Allicin) an organosulfur compound from raw garlic targets the SH containing bacterial proteins present in the cell wall of bacteria and modify them into S-allyl derivatives eventually destruct the permeability of cell wall. Allicin also inactivates the sulfur containing enzymes like Alcohol dehydrogenase, Thioredoxin reductase and RNA polymerase ultimately cause DNA and RNA damage of bacterial cell [3]. Allicin also restrain the lipid and fatty acid biosynthesis by inhibiting Acetyl-coA enzyme and changes the viability of bacterial cell [4].

Moreover 3-vinyl-1,2-dithiacyclohex-5-ene and 3-vinyl-1,2-dithiacyclohex-4-ene have also shown the antibacterial activity against a range bacteria by destruction of the structural integrity of cell membranes and protein leakage, leading to cell death [5].

Multi drug resistant *Mycobacterium tuberculosis* (MTB) causes the highest burden of bacterial disease known as tuberculosis which grows within the macrophages. Garlic extract have shown macrophages related inhibition of TB better than the standard drugs like Rifampicin and Isoniazid, making it a noble phytochemical for the treatment of TB [6].

Antifungal activity of Allium sativum

Ajoena from garlic rigorously damage the morphological thickness of hyphae and destruct the cell wall, eventually damage the cell organelles. It is a latent antifungal agent of garlic extract against fungal pathogens like *Aspergillus niger*, *Candida albicans*, *Candida glabrata*, *C. tropicalis*, *Trichophyton mentagrophytes*, *Tricosporon beigelii* and *T. rubrum* etc. [7]. Allicin is also an important antifungal compound as it directly down regulate the expression of SIR2 gene responsible for growth and development of hyphae in *C. albicans* [8].

Antiviral activity of Allium sativum

Diallyl trisulfide a compound from garlic has been reported of having Anti-Human CytoMegaloVirus (HCMV). HCMV is a herpesvirus infect human for lifelong. Mechanistically DATS effect the replication of HCMV by suppressing the expression of viral immediate-early genes transcription ultimately hinders the viral replication and infection [9]. Also DATS exhibits prophylactic effect on non-lethal Murine Cytomegalovirus (MCMV) hepatitis by significantly decreasing the DNA load via reducing Alanine Aminotransferase (ALT) level in the plasma [10]. Garlic has also shown Infectious Bronchitis Virus (IBV) and anti influenza activity but further studies are needed.

Antiparasitic activity of Allium sativum

Garlic has been elucidated to kill *Trypanosoma* sp. and *Leishmania* sp. parasites, Antiparasitic activity of garlic by binding and inactivating the sulphur containing substances like trypanothione reductase essential for the survival of the parasite, through disulfide bond formation between SH groups of compounds and sulfur-containing secondary metabolites present in garlic extract [11]. Moreover garlic kill pathogens like *E. papillata* via specific changes in miRNA by downregulating the *E. papillata*-induced increases in the expression of the miRNAs miR-1959, miR-203, and miR-21, and it upregulating the expression of the 11 miRNA species [12].

ANTI-CANCER ACTIVITY OF *ALLIUM SATIVUM*

Cancer is a group of disease characterizes by growth of abnormal cells called neoplasms. Cancer is the second leading cause of death globally as it accounts for 9.6 million deaths in 2018 globally. Though cancer can affect almost any part of the body, but lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer reported worldwide. Treatment option for cancer is limited includes surgery, chemotherapy, radiotherapy and medicinal which are also not successful benchmarks moreover these therapies have severe side effect. Organosulfur compounds present garlic has been researched in cancer therapy since decade which strongly suggests the natural prevention and treatment of a range of cancers. Below us summaries the critical mechanisms involve in various cancers by organosulfur garlic compound.

Hepatocellular carcinoma (HCC) or liver cancer

Liver cancer can either arise within the liver cells (Primary liver cancer) or it can pass by cancer cells streaming in blood through metastasis. HCC arise due to high alcohol abuse, chronic infection like Hepatitis B and C, Hemochromatosis and Cirrhosis. Allicin has been reported to arrest the cell cycle at S-phase by suppressing the expression of p53 gene via PI3K/mTOR pathway

[13]. Allicin also up regulate AMPK-TSC2 signaling pathway to suppress the mTORC1 activity through inducing a disorder of energy metabolism in cancer cells [14]. It also directly increase apoptosis by decreasing Bcl-x1 and Bcl-2 and increase the activity of caspase-3 and caspase-9 [15]. Moreover S-Allyl Mercaptocystein (SAMC) a derivative of garlic directly interact with Wnt-pathway co-receptor LRP6 ultimately decreasing the level of B-catenin in the cell hence downregulate the proliferation and metastasis of HCC cells [16]. SAC another organosulfure compound suppresses the expression of proliferation marker Ki-67 and PCNA. Increase the expression of E-cadherin [17].

Gastric cancer

Gastric cancer is the third leading cause of cancer related death worldwide. Gastric cancer begins within the inner lining of stomach and grows into tumor. Allicin has been reported to induce apoptosis through p38 mitogen activated protein kinase/ caspase 3 signalling pathway [18]. DATS another compound from garlic can activates kinases such as p38 and JNK/MAPK and inhibit Nrf2/Akt pathway [19]. DATS provokes intracellular ROS generation and loss of mitochondrial membrane potential hence induce apoptosis through ROS-mediated activation of AMP-activated protein kinase [20]. SAMC is another compound from garlic significantly induces apoptosis via JNK and P38 pathway. And inhibit cell proliferation and activates PI3K/AKT signaling pathway [21].

Bladder cancer

Bladder cancer occurs in the inner lining of bladder with a common symptom of hematuria and painful urination. Bladder cancer commonly occurs due to tobacco, chemicals, parasitic infection and also with age. Garlic extract has reported to have cancer preventive activity especially in bladder cancer, oral administration of GE can significantly target the Protein Kinase A (PKA) signaling pathway and decrease the level of PKA in serum, and also upregulate the expression of AKAP12 and RDX genes [21]. It also downregulate the expression of RAB13 gene. DATS a garlic extract arrest the cancer cell proliferation at G2/M-phase by down-regulation of cyclin B1 and up-regulation of p21WAF1 through the activation of ATM and CHK2 [22]. Also GE impedes the migration of cancer cells *via* inhibition of MMP-9 expression followed by decreased binding activities of AP-1, Sp-1, and NF- κ B motifs [23].

Breast cancer

Breast cancer occurs in the milk producing ducts of breast, it is the most common cancer reported in women though it can occur in men also. A breast lumps and abnormal thickening is the very first sign of breast cancer. In human breast cancer SAMC can potentially arrest the cancer cells at G0/G1 phase by up regulation of p53 and p21 gene [23]. SAMC also up regulate the expression of Bax and decrease the expression of BCL2 and BCLX and successively activate Caspase 9 and Caspase 3 which all around triggers the mitochondrial apoptotic pathway in cancer cells [24]. Another compound from garlic DADS inhibit the proliferation of breast cancer cell by inhibiting Extracellular Signal-Regulated Kinase (ERK) and also induce apoptosis by activating SAPK/JNK and p38 pathways [25]. DATS inhibits Estrogen Receptor- α (ER- β) activity in human breast cancer cells resulted in downregulation of ER- α protein which ultimately decrease nuclear levels of ER- α protein, ER- α mRNA suppression, and inhibition of ERE2e1bluciferase reporter activity and ultimately induce apoptosis [26].

Colon cancer

Colorectal cancer occurs in the inner lining of colon its cause is not clear, but it has only 8% survival rate. DADS prevent the colorectal tumorigenesis by suppressing the nuclear localization activity of NF κ B. A process mainly involving GSK-3 β inhibition and consequential reduction in NF κ B nuclear localization [27]. SAMC in combination with rapamycin enhance the anticancer activity by downregulation of autophagosome cargo p62, p62 played a negative-regulatory role between Nrf2 and autophagy.

Ovarian cancer

The cause of ovarian cancer is not completely clear, some research evidences suggest it arise due to mutation. SAC treatment of ovarian cancer result in reexpression of tumor suppressor gene CDKN1A [28]. Further SAC arrest the cell cycle at G1/S phase [29]. SAC decreases global DNA methylation and also the levels of 5-methylcytosine, DNMT activity, messenger RNA (mRNA) and protein levels of DNMT1 [30].

Prostate cancer

Prostate cancer is generally inheritate from one generation to the other. But it has no proper treatment. DADS treatment induced phosphorylation of Mitogen-Activated Protein Kinases (MAPKs) in prostate cancer cells, including extracellular-signal regulating kinase (ERK), p38 MAPK and c-Jun N-terminal kinase (JNK) [31]. DADS also induce apoptosis by modulation of Bcl-2 and activation of JNK and the inhibition of PI3K/Akt [32]. Apart from DADS, DATS is also a cancer chemopreventive constituent of garlic, inhibits phosphorylation of STAT3 in prostate cancer cells [33]. Also SAC suppresses the proliferation of cell cycle arrest at the G0/G1 phases and decreased expression of Bcl-2 and increased expression of Bax and caspase 8 [34].

Thyroid cancer

Thyroid cancer arises due to the reactivation of telomeric activity by enzyme called telomerase. SAMC has been reported to induces apoptosis by cell cycle arrest at G2/M phase. And it inhibit the activity of telomerase. Moreover DIALLYL TRISULFIDE

(DATS) another oragnosulfure compound from garlic cause cell arrest at G0/G1 phase ultimately results in apoptosis through mitochondrial apoptotic pathway via activation of p38, JNK, ERK members of MAPK family [35].

CONCLUSION

These studies suggest that garlic and its bioactive compounds exerts potential targets as an antimicrobial and anticancer therapeutic. 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.

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