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Garlic — A Diet Therapy For Various Cancers

Diptika Dey[1], PrithaPal[2]*

[1]*Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal-700121, Email: diptikadey2005@gmail.com, Ph- 9330492985*
[2]**Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal-700121, Email: prithap@svu.ac.in, Ph- 8961872389*

***Corresponding author**: Dr. Pritha Pal,*
**Assistant Professor, Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal- 700121, Email: prithap@svu.ac.in, Ph- 8961872389.*

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Abstract

Garlic (*Allium sativum L.*) is the well-known and oldest plants for its medicinal activities. It is a natural source that prevents cancer by slowing the growth of cancer cells, impacting hundreds of proteins involved in cell signaling, repairing the DNA and also decreasing inflammation. Garlic also promotes apoptosis and inhibits many different types of cancer cells. Reports suggest that it has been associated in preventive role in lung, liver, gastric, skin, breast, oral, ovarian, colorectal, prostate and pancreatic cancer. The organosulfur compounds, allicin, diallyl sulfide, diallyl trisulfide present in garlic act as chemotherapeutic agents that prevent carcinogens. Its extract has been reported to reduce proliferation of the cancer cells by increasing endoplasmic reticulum (ER) stress. However, extreme use of garlic may cause gastrointestinal cancer. Diallyl disulfide (DADS) derived from garlic, is oil – soluble compound which has been suggested to suppress the breast cancer, which has also been reported to get suppressed by the intake of raw garlic, the latter being more effective than cooked garlic. Besides the side effects of anti-cancer agents used in therapy of cancer patients have been reported to get reduced by consumption of garlic. The review article mainly deals with the probable anti-cancer properties of garlic and its mechanism of action in treating cancer.

Keywords: Garlic, DADS, Cancer, Allicin, anti-cancer, diet

Introduction

Cancer is a complicated illness defined by unchecked cell division and the spread of aberrant cells into neighboring tissues. The onset, propagation, and development of this disease are all attributed to a variety of dysregulated signaling pathways (Song et al. 2001). The essential signaling proteins for many aspects of cell survival and proliferation include protein kinase B (also known as Akt), phosphatidylinositol 3-kinase (PI3K), mammalian target rapamycin (mTOR), extracellular signal-related kinase (ERK), and mitogen activated protein kinase (MAPK). Reactive oxygen species (ROS), nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-B (NF-B), tumor necrosis factor (TNF), interleukins, B cell lymphoma (Bcl-2), Bcl-2-associated X protein (Bax), caspases, activator protein-1 (AP-1), c-Jun N-terminal kinase (JNK), signal transducer.

Humans have been using garlic for more than a few thousand years as a culinary flavor as well as a food or topical remedy. Raw or cooked garlic has been used as a medicine to cure infections, decrease cholesterol, prevent blood clots, etc. Pasteur was the first to identify garlic's antimicrobial properties in 1858. During World War I and World War II, soldiers frequently used raw garlic paste topically as an anti-infection agent. The anticancer effects of garlic have also been studied recently. Garlic has been used by humans for over a thousand years, not only as a dietary flavoring (De Greef et al. 2021).

In moderate conditions in both temperate and tropical areas, garlic may grow up to 1.2 m tall and is rather simple to cultivate. The garlic bulb is frequently utilized in food and cooking, as well as in medicine. About 4–20 cloves of pure white or light-yellow hue make up each bulb. These cloves are the source of new garlic. Garlic's leaves and stems are usually removed. The temperatures they experience while growing affect how their leaves, cloves, and blossom stalks develop. The plant's primary stem is covered with 1-2 feet long leaves that are spread out along the stalk. The number of little flowers that are possible varies, and they might be greenish-white, pink, or purple (Li et al. 2018). One of the oldest cultivated plants in the world, garlic has a long history of being revered for its medicinal qualities in many different cultures. Garlic has been utilized throughout history as a culinary flavoring, condiment, healing agent, and for its therapeutic properties. Garlic has been mentioned in ancient medical literature from the Babylonians, Egyptians, Greeks, Romans, Chinese, Indians, and Israelites as a treatment for a variety of physiological diseases and illnesses. The Egyptian papyrus known as Codex Ebers, which dates back to 1550 BCE, makes reference to the use of garlic as a remedy for aberrant growths (which probably included malignancies), abscesses, malaise, circulatory disorders, bug and parasite infestations, cardiac issues, cephalea, and snake bites. Garlic was utilized as a remedy for digestive and respiratory diseases in classical Greece (De Greef et al. 2021).

There are many different edible forms of garlic available on the market, including fresh garlic, garlic extract, garlic oil, dried oil macerate, temperature-aged garlic bulbs, and garlic powder. The pill, oil, and powder forms of garlic are nonetheless utilized for medicinal reasons. The extraction of active compounds from a variety of fruits or vegetables is now being pursued using extremely effective techniques. The extraction technique and the kind of solvent have been proven in the literature to have an impact on the quantity of bioactive components and biological characteristics in both fruit and vegetables. Garlic is one example of the bioactive chemicals that have been extracted from plants and are employed in the pharmaceutical, culinary, and cosmetic sectors. Weighing, volume measurement, mixing, dilution, and other factors can affect how well isolation and extraction work. The composition of garlic is 60–65% water, 28–30% carbohydrates, 2.3% organosulfur compounds, 2-6% proteins, 1.2% amino acids, and 1.5% fiber, phenols, fatty acids, and trace minerals. The makeup of various garlic types might, however, change dramatically. Additionally, the soil and general meteorological and climatic circumstances have a significant impact on the composition of garlic bulbs. Different bioactive component categories, including organic sulfides, saponins, phenolic compounds, and polysaccharides, are mostly responsible for garlic's medicinal effects. A number of active chemicals, including allicin (AC), alliin, S-allyl cysteine (SAC), diallyl disulfide (DADS), diallyl trisulfide (DATS), diallyl sulfide (DAS), and ajoene, have been shown to be included in the group of sulfur compounds found in garlic (Bar et al. 2022).

Numerous bioactive substances found in garlic are responsible for many of its medicinal and therapeutic advantages. Garlic contains organic sulfides, saponins, phenolic compounds, and polysaccharides, among other bioactive substances. Water, fats, fiber, proteins, vitamins, and minerals are other components. Garlic has a wide range of health advantages, including anti-inflammatory, antiangiogenic, antidiabetic, antiarthritic, antihyperglycemic, anticoagulant, antispasmodic, antihistaminic, antibacterial, antiviral, antifungal, and antiparasitic activities, according to a number of recent research. Other beneficial benefits of garlic include suppression of osteoarthritis and osteoporosis, reduction of oxidative stress, lowering of hyperlipidemia and hypertension, promotion of prostanoids synthesis, acceleration of immunological enhancement, and protection of cardiac and hepatic functions. Garlic has been linked negatively to a number of cancer types in epidemiological research, with the majority of the effects cited being attributable to garlic. Previous reviews on the anticancer potential of garlic had a number of drawbacks. The majority of past articles give a concise summary of the anticancer activity of garlic and its different phytocompounds. A small number of papers concentrated on particular anticancer pathways, such as anti-inflammatory and immunomodulatory activity, as well as autophagy, or the antineoplastic effects of garlic components in tumors of the gastrointestinal tract. Other writers exclusively cited old garlic or a certain OSC. A critical assessment of the anti-cancer properties of garlic, garlic products, extracts, and phytochemicals has not been carried out in a systematic manner, despite

the existence of numerous and emerging publications based on experimental and clinical findings (De Greef et al. 2021).

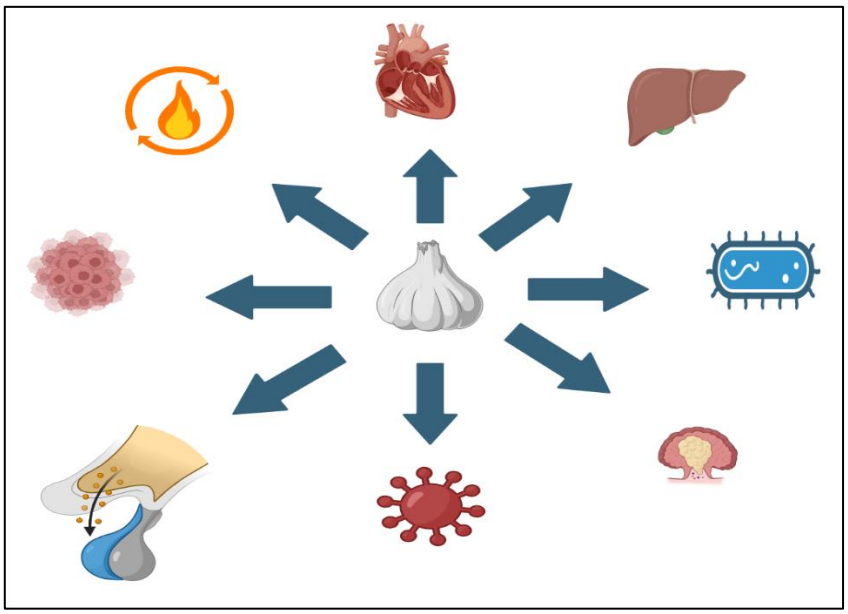

Fig 1. Figure showing the effects of garlic on various of organs of human body

Preventing Breast Cancer

majority of cancer-related fatalities among women are caused by breast cancer (BC), which affects over 2.1 million individuals worldwide each year. Genetic predisposition, food, age, family history, reproductive variables, lifestyle, and hormones are only a few of the risk factors that affect BC occurrence. The hormone receptor (HR) and the human epidermal growth factor receptor 2 (HER2) are significantly altered differently in distinct BC tumors, which is then adds to their complexity and high degree of variability. The subtypes of BC include basal-like/triple-negative BC (TNBC), luminal cell-like BCs (luminal A and luminal B), which express receptors (estrogen receptors (ERs) and progesterone receptors), and HER2+ BC. Less aggressive than luminal B BC (HR+/HER2+) cancers, luminal A BC (HR+/HER2-) tumors often develop slowly.

DADS and DATS's effects on Breast Cancer

Consuming Allium vegetables is substantially linked to a lower chance of developing BC, according to epidemiological research. A high consumption of garlic and onions may have protective benefits against BC, according to population-based research. Furthermore, a case-control research study conducted at a hospital on 285 women found a negative correlation between eating Allium vegetables, especially garlic and leeks, and developing BC. As part of nutritional treatment, dietary recommendations for BC patients are encouraged to consume more garlic and cruciferous vegetables. These plants, notably garlic, contain highly reactive sulfur compounds that interact with cellular macromolecules, indicating that they are effective inhibitors of phospholipase A2 and MAPKs, cytochrome P450, and glutathione-s-transferases that may lower the chance of developing cancer. Major allyl sulfur compounds such as DADS and DATS have been shown to have anticancer properties by inhibiting tumor vascularization, tumor metastasis, and cancer cell proliferation, all of which appear to be redox-controlled. Additionally, DADS and DATS disrupt the cell signaling pathways that control cancer cell mitosis and cell death. Additionally, DADS synergistically enhances the effects of eicosatetraenoic acid and antagonizes the effects of linoleic acid in BC (Fig.1). Due to these characteristics, allyl sulfur compounds are recommended for consideration as possible natural inhibitors.

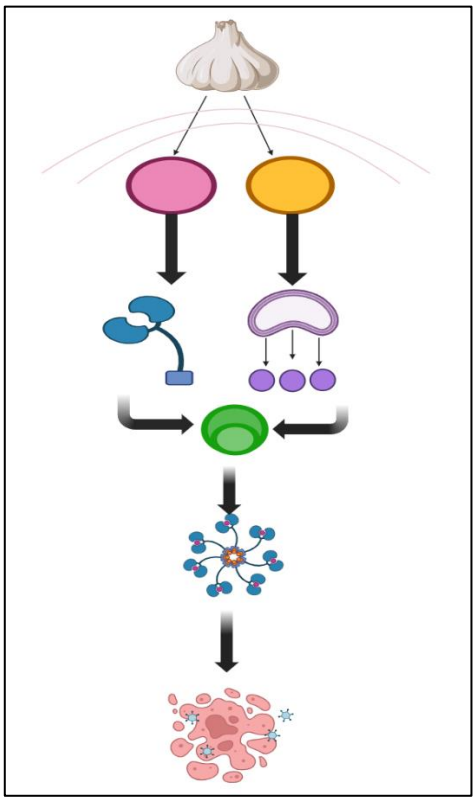

Fig 2. Representation of DADS and DATS's effects on Breast Cancer

Allyl sulfur compounds' effects on treatment resistance caused by BC stem cells

A particular subset of cells known as BC stem cells (BCSCs) has the potential to self-renew, differentiate, and become tumorigenic, all of which promote the development of BC. Due to their ability to confer drug resistance, BCSCs have been emphasized as prospective targets for BC treatment. Through targeting the CD44/pyruvate kinase M2/AMP-activated protein kinase signaling pathways, DADS has been shown in experiments on BCSCs in a xenograft model to decrease the proliferation, metastasis, and stemness of these cells as well as glucose metabolism. The expression of FOXQ1, which negatively regulates Dachshund homolog 1 (DACH1) expression by interacting with the DACH1 promoter region, is decreased when TNBC stem cells are exposed to DATS. DATS also decreases tumor sphere development and capacity to form tumors, which promotes BC development. The development of BCSCs and the expression of CSC markers (CD44, ALDH1A1, Nanog, and Oct4) have made BCSCs stand out as promising targets for BC treatment. Recent research has shown that Fork head box Q1 is the target of DATS, which reduces the expression of EMT markers in BCSC. DATS treatment makes BCSCs more sensitive to chemotherapeutics by reducing the expression of FOXQ1, which contributes to the development of stem cell-like characteristics and enhanced EMT during cancer metastasis. According to the combined findings of these research, BCSC-driven drug resistance can be attacked using DADS and DATS (Malla et al. 2022).

Preventing Colorectal Cancer

Animals have been given extracts or chemicals from garlic to prevent cancer. In mice, DAS prevented the development of invasive colon cancer brought on by 1,2-dimethylhydrazine, while in rats, DADS prevented the development of invasive colon cancer brought on by azoxymethane. In xenograft mice models, DADS and DATS slowed the formation of tumors. Using animal models of chemically produced uterine, prostate, or mammary malignancies, similar outcomes have been described. Garlic, its allyl sulfur components, or both, had a considerable impact on animal studies of carcinogen-induced colonic tumor development, according to a comprehensive study. The majority of popular meals include some selenium, which is associated to antioxidants and may be exchanged for sulfur in organic molecules. Selenium is present in modest levels in natural garlic. Cancer chemoprevention studies have indicated that organo-selenium compounds are more effective than the comparable sulfur counter parts. This result underlines the requirement to pinpoint the garlic compounds that are actually responsible for the animals' chemoprevention. It appears likely that clinical trials

utilizing garlic preparations won't advance until that is accomplished and the substance can be delivered in a suitable quantity.
Whether the high micromolar doses of active substances required to inhibit the proliferation and death of cancer line cells are attainable in vivo is another important topic in interpreting the preclinical in-vivo investigations. Animal pharmacokinetic data are insufficient to provide a response to this query. The issue is that allicin's primary metabolites are extremely unstable, and until recently, there were no techniques for analyzing them. DATS may be detected by gas chromatography-mass spectrometry, and in rats, a dosage of 10 mg intravenously results in a serum concentration of around 30 mol/l. Oral administration has not been used in any research. Rats have a high bioavailability of water-soluble allicin metabolites, more than 85%. But there was a considerable first pass impact, and feeding was affected Rats given 9–27 mg of stable DATS metabolites only produced blood levels of around 7 mol/l. Other bodily tissues had lower concentrations than the serum did. Allicin's metabolites have not been the subject of any known human pharmacokinetic research. Therefore, it is unclear if sufficient concentrations of allicin metabolites can produce concentrations in rats (or people) comparable with those that have been utilized to establish mechanistic effects in cell culture (Alpers et al. 2009).

Effects of Diallyl Disulfide on Colorectal Cancer

In the United States, colorectal cancer ranks third in terms of cancer-related mortality for both males and females. The development and course of several cancers, including those of the colon, have been shown to be significantly influenced by inflammation. A higher risk of colorectal cancer exists in those with intestinal inflammatory diseases including Crohn's disease and ulcerative colitis. By controlling the expression of genes related in cell proliferation, apoptosis, and metastasis, the proinflammatory transcription factor NF-B is theorized to encourage carcinogenesis. In patients with inflammatory bowel illness, NF-B is constitutively active, which may help to explain why these people have a higher risk of developing colorectal cancer. Although NF-B has emerged as a promising target for cancer treatment, it has been difficult to create drugs that can inhibit its activation due to the intricacy of NF-B regulation. The inhibitor of NF-B (I-B) is degraded as part of the canonical route, and then NF-B is nucleus translocated and gene transcription is activated. Numerous substances have been demonstrated to indirectly decrease NF-B by affecting important regulatory components of the IKK complex's kinase subunits, which are part of the normal route for the degradation of IBs.

Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase that is made up of two homologous proteins, GSK-3 and GSK-3, which are produced by two very similar but distinct genes. GSK-3 is more thoroughly understood than GSK-3 and, depending on the cellular setting, can both repress and promote tumor growth. GSK-3 is often thought of as a tumor suppressor largely because of its function in the signaling cascade, where it phosphorylates -catenin and causes its ubiquitin-mediated degradation, blocking its nuclear translocation and subsequent transcription of proto-oncogenes. The NF-B signaling cascade is activated by GSK-3, which increases the transcriptional activity of NF-B in the nucleus. However, new research has shown that GSK-3 can also cause cancer. GSK-3 inhibition reduces proliferation and triggers apoptosis in cells, according to studies.

At least one interventional research found small advantages of garlic in avoiding the recurrence of colorectal adenoma, supporting epidemiologic evidence that suggests the use of garlic prevents colorectal cancer. We tested the impact of one of the sulfur-containing components, DADS, in a mouse model of colitis-induced colorectal cancer in order to further examine the anti-inflammatory action of garlic and its capacity to prevent the disease. In mice given azoxymethane (AOM) and dextran sulfate sodium (DSS), we discovered that adding DADS to their diets dramatically decreased the development of colon tumors. In these animals, the DSS-induced inflammation was treated by the anti-inflammatory actions of DADS. In human colorectal cancer cells, DADS also prevented NF-B activation and nuclear translocation, which we were able to show was reliant on GSK-3 inhibition (Saud et al. 2016).

Preventing Liver Cancer

The large population-based case-control research in China that found an inverse link between raw garlic consumption and liver cancer is the first of its kind to be reported in the medical literature. When known risk variables and possible confounders were taken into account, regular use of raw garlic (more than twice per

week) revealed an inverse correlation, suggesting that raw garlic may have a preventative impact. Low raw garlic consumption and HBV infection or excessive alcohol use were also found to have potential additive interactions. The adjusted odds ratio and its 95% confidence interval for eating raw garlic were 0.77 (95% CI: 0.62-0.96), which indicates that eating raw garlic twice or more a week may have a preventative impact on liver cancer. Epidemiologic research on the relationship between eating garlic and the risk of developing other malignancies has produced conflicting results. Several additional studies revealed a null connection whereas several indicated a protective effect (You et al. 1989, Setiawan et al. 2005, Buiatti et al. 1989, Takezaki et al. 1999, Lazarevic et al. 2010, Yassibas et al. 2012, Fleischauer et al. 2000, Ngo et al. 2007, Chen et al. 2009, Challier et al. 1998, Jin et al. 2013, Zheng et al. 1992, Hsing et al. 2002, Key et al. 1997, Mazdak et al. 2012, Salem et al. 2011).

Some research teams looked at allium vegetables like leeks, garlic, and onions in these investigations. The majority of earlier research had limited sample numbers and insufficient confounding factor adjustments. Garlic may be processed in a variety of ways, including extracts, cooked food, and raw food. Garlic preparation may affect its bioavailability and anti-carcinogenic action (Gonzalez et al. 2012, Dorant et al. 1996, McCullough et al. 2012, Dorant et al. 1995, Yu et al. 2012, Brasky et al. 2011). In order to study the impact of the elements as a whole—most of which are the metabolites of allicin, which is prevalent in fresh garlic—we first gathered information on raw garlic consumption frequency. The second difference is that, in contrast to other regions where garlic is frequently cooked, residents in these study regions of China typically consume raw garlic cloves uncooked. In the Northern Jiangsu Province's Ganyu and Tongshan Districts, where people have a propensity of eating raw garlic straight, this is most prevalent. We were able to analyze the relationship between raw garlic consumption and liver cancer with a sizable sample size thanks to this region's very unique dietary custom (Takezaki et al. 1999).

In addition to the main impact of raw garlic consumption on the emergence of liver cancer, possible effect measure alterations between garlic consumption and other risk variables were examined on both additive and multiplicative scales. Raw garlic consumption with HBsAg status and high alcohol use have been found to deviate from additivity. This may point to a potential biological connection between the molecular processes underpinning garlic's protection against liver damage brought on by such exposures, as suggested in several animal studies. In stratified analyses, inverse relationships between consumption of raw garlic and liver cancer were seen, particularly in individuals from Tongshan, men, HBsAg-negative participants, regular drinkers, those who could have been exposed to aflatoxin, and those who did not have any of these factors (El-Mofty et al. 1994, Guyonnet et al. 2002).

Allicin Triggers Human Liver Cancer Cells

Crushed garlic has a significant amount of allicin. Allicin is a significant bioactive component of crushed garlic even though it is rapidly converted into other substances including diallyl disulfide, diallyl trisulfide, and diallyl sulfide and is sensitive to heat and light. Hepatocellular carcinoma has one of Taiwan's top 10 cancer-related mortality rates, which is relatively high. Allicin's impact on the development of human liver cancer cells has not been investigated, despite the fact that multiple-research have demonstrated the anti-cancer effects of garlic and its constituents. We concentrated on allicin-induced autophagic cell death in human liver cancer HepG2 cells in this investigation. According to our findings, allicin decreased the viability of human hepatocellular carcinoma cell lines and promoted p53-mediated autophagy. Using Western blotting, we discovered that allicin boosted the expression of the AMPK/TSC2 and Beclin-1 signaling pathways while decreasing the levels of cytoplasmic p53, the PI3K/mTOR signaling pathway, and Bcl-2 in Hep G2 cells. Confocal laser microscopy was also used to show the colocalization of LC3-II with Mito Tracker-Red (labeled mitochondria), which led to the destruction of mitochondria caused by allicin. As a new chem-preventive agent for the prevention of liver cancer, allicin from garlic has significant promise (Chu et al. 2012).

Conclusion

Garlic is a multipurpose vegetable with a high phytochemical content that has been utilized for millennia for its special nutritional, flavoring, and therapeutic properties. Garlic has a long history of medicinal use, including the treatment of asthma, diarrhea, constipation, infectious diseases, hypertension, and fever in addition to its antiseptic properties. Garlic was first used in Egypt thousands of years ago for its anticancer qualities.

Conflict of interest

The authors declare no conflict of interest related to the study.

Author Contributions

Acquisition and interpretation of data is done by Diptika Dey. Conception, design and revising of the article are done by Dr. Pritha Pal.

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