International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 1320-1327 www.ijprajournal.com ISSN: 2456-4494

Phytochemical and Anticancer Investigation of Allium Sativum: A Review

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Date of Submission: 28-05-2025 Date of Acceptance: 08-06-2025

ABSTRACT

Garlic (Allium sativum) has long been recognized for its therapeutic potential, particularly in traditional medicine systems. Among its many health benefits, its anticancer properties have become a focal point in modern biomedical research. This review provides a thorough analysis of how garlic and its phytochemical constituents—especially allicin, ajoene, and various organosulfur compounds—may contribute to cancer prevention and treatment. These substances have been shown to exhibit anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic actions in several cancer models. Their activity is linked to interference with cellular signaling pathways involved in oxidative stress, inflammation, programmed cell death, and blood vessel formation. Furthermore, garlic may influence the behavior of key regulatory genes and enhance the body's immune defense mechanisms. While laboratory and animal studies provide compelling support, clinical results are inconsistent, often due to variation in preparation methods, dosages, and participant characteristics. This article also considers the limitations of current studies and offers perspectives on how garlic might be more effectively used in oncology.

Keywords: Allium sativum, garlic, anticancer, allicin, apoptosis, angiogenesis, phytochemicals, cancer prevention, oxidative stress, clinical trials

I. INTRODUCTION

Cancer continues to be one of the most pressing health challenges worldwide, characterized by the uncontrolled proliferation and spread of abnormal cells. It is responsible for a significant number of deaths each year, with the World Health Organization estimating around 10 million fatalities in 2020 alone. Common forms of cancer include lung, breast, colorectal, liver, and stomach cancers. Despite significant advancements in diagnosis and treatment—including the development of immunotherapy, precision medicine, and targeted therapies—the global incidence of cancer remains high. This is especially problematic in low- and middle-income countries where access to quality healthcare and advanced cancer treatments may be limited.

The limitations of conventional therapies, which often come with severe side effects and limited efficacy for certain cancer types, have led to a surge of interest in alternative and complementary therapeutic approaches. Among these, natural products, especially plant-derived compounds, have gained considerable attention due to their multi-targeted actions, relatively low toxicity, and historical use in traditional medicine systems.

Plants have served as a foundation for modern medicine, with over 60% of current anticancer drugs being derived from natural sources, such as herbs, fungi, marine organisms, and bacteria. Garlic (Allium sativum), a widely used culinary and medicinal herb, has emerged as a particularly promising candidate due to its extensive pharmacological profile. It belongs to the Alliaceae family and is known for its therapeutic effects, including antibacterial, antiviral, antihypertensive, lipid-lowering, antioxidant, and anticancer activities.

Historically, garlic has been used across various ancient civilizations. In Egypt, it was given to laborers to enhance strength and productivity. The Greeks and Romans used it for treating infections and gastrointestinal disorders, while in Traditional Chinese Medicine and Ayurveda, it was

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valued for its ability to improve digestion, circulation, and vitality.

Scientific research has since confirmed that garlic contains a wide range of biologically active compounds capable of interacting with numerous molecular targets implicated in cancer development. These include pathways responsible for sustaining proliferative signaling, resisting apoptosis (programmed cell death), inducing angiogenesis (formation of new blood vessels to nourish tumors), enabling metastasis (spread to other parts of the body), and modulating immune responses.

This review compiles and analyzes the existing literature regarding the anticancer effects of garlic, exploring its phytochemical constituents, biological mechanisms, experimental and clinical evidence, safety considerations, and future prospects for its integration into evidence-based oncology.

II. BOTANICAL AND PHYTOCHEMICAL OVERVIEW OF ALLIUM SATIVUM

Botanical Characteristics:

Garlic (Allium sativum) is a hardy perennial plant that reproduces vegetatively through its cloves, which are enclosed within a bulb covered by a papery sheath. The plant typically grows to a height of about 60 centimeters and develops flat, linear leaves and a flowering stalk bearing an umbel of small, white to pinkish flowers. Although garlic is believed to have originated in Central Asia, it is now cultivated globally, with major producers including China, India, South Korea, and the United States. It thrives in well-drained soil and temperate climates and is commonly grown for both culinary and medicinal purposes.

Taxonomic Classification:

- Kingdom: Plantae
- Order: Asparagales
- Family: Amaryllidaceae
- Subfamily: Allioideae
- Genus: Allium
- Species: sativum

Phytochemical Constituents:

Garlic is renowned for its rich and diverse chemical profile, especially its high content of organosulfur compounds. The therapeutic and biological activities of garlic are largely attributed to these sulfur-containing molecules, which are formed when garlic cloves are crushed, chopped, or aged. The exact composition can vary significantly depending on factors such as garlic variety, cultivation conditions, processing methods, and storage.

- **Allicin**: This compound is produced when the enzyme alliinase acts on the amino acid alliin after garlic is crushed or chopped. Allicin is not present in intact garlic cloves but is rapidly generated upon tissue disruption. Although highly unstable and short-lived, allicin is known for its potent antimicrobial, antifungal, and anticancer properties. It affects cancer cells by inducing oxidative stress, disrupting cellular membranes, inhibiting cell proliferation, and initiating programmed cell death (apoptosis).
- **Ajoene**: Ajoene is a product of allicin transformation during garlic storage or heat processing. It exists in two geometric isomers (E and Z) and exhibits strong anticancer potential by targeting multiple pathways. Ajoene inhibits the ability of cancer cells to adhere, migrate, and invade surrounding tissues. It also interferes with important signal transduction pathways that are essential for tumor survival and progression.
- **Diallyl sulfides (DAS, DADS, DATS)**: These compounds are formed when allicin is decomposed under heat. They are lipid-soluble and have been widely studied for their anticarcinogenic activity. Diallyl disulfide (DADS) and diallyl trisulfide (DATS), in particular, are effective in inhibiting the activity of enzymes that activate pro-carcinogens. They promote apoptosis in cancer cells by modulating mitochondrial membrane potential and activating caspase-dependent pathways. DATS has demonstrated notable anticancer efficacy in experimental models of breast, colon, and lung cancers.
- **S-allyl cysteine (SAC)**: SAC is a stable, water-soluble compound predominantly found in aged garlic extract (AGE). It has excellent bioavailability and has been shown to possess antioxidant, anti-inflammatory, and anticancer properties. SAC can neutralize free radicals, reduce lipid peroxidation, upregulate endogenous antioxidant enzymes, and inhibit tumor angiogenesis. It also downregulates pro-inflammatory mediators and enhances immune surveillance.
- **Other Bioactive Constituents**: In addition to sulfur compounds, garlic contains numerous polyphenols such as quercetin, flavonoids,

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saponins, and trace elements like selenium. These components act synergistically to support the anticancer effects of garlic by reinforcing antioxidant defenses, modulating the immune system, and enhancing DNA repair mechanisms. Selenium, for instance, is essential for the activity of glutathione peroxidase and has been implicated in tumor suppression.

III. MECHANISMS OF ANTICANCER ACTIVITY OF ALLIUM SATIVUM

Garlic and its bioactive constituents exert their anticancer effects through multiple biological mechanisms. These mechanisms involve interactions with diverse molecular targets and signaling pathways that influence the behavior, survival, and proliferation of cancer cells.

3.1 Induction of Apoptosis

Apoptosis, or programmed cell death, is a natural process for removing damaged or unwanted cells. Many cancer cells evade apoptosis, leading to uncontrolled proliferation. Garlic-derived compounds such as allicin, DATS, and ajoene promote apoptosis in cancer cells through both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways. These compounds influence key regulators such as caspases (especially caspase-3, -8, and -9), Bax/Bcl-2 ratio, and cytochrome c release, which are crucial for initiating and executing cell death.

3.2 Cell Cycle Arrest

Garlic compounds can halt the uncontrolled division of cancer cells by inducing cell cycle arrest. For example, DADS and DATS have been shown to inhibit the transition of cells through the G0/G1 and G2/M phases of the cell cycle by modulating the expression of cyclins and cyclin-dependent kinases (CDKs). This action suppresses DNA replication and mitosis, thereby reducing tumor growth.

3.3 Inhibition of Angiogenesis

Tumors rely on the formation of new blood vessels to supply nutrients and oxygen for continued growth—a process known as angiogenesis. Garlic constituents, particularly SAC and DATS, suppress angiogenesis by downregulating vascular endothelial growth factor (VEGF) and its receptor (VEGFR). They also reduce the expression of matrix metalloproteinases (MMPs), which play a role in endothelial cell migration and blood vessel formation.

3.4 Suppression of Metastasis

Metastasis involves the spread of cancer cells to distant organs and is a major cause of cancer mortality. Garlic-derived ajoene and DADS inhibit the migration and invasion of cancer cells by affecting adhesion molecules, cytoskeletal proteins, and extracellular matrix-degrading enzymes such as MMP-2 and MMP-9. These actions limit the ability of cancer cells to invade surrounding tissues and form secondary tumors.

3.5 Antioxidant and Anti-inflammatory Effects

Chronic inflammation and oxidative stress are key contributors to cancer initiation and progression. Garlic's antioxidant compounds (like SAC and selenium) scavenge reactive oxygen species (ROS) and upregulate endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. Additionally, garlic reduces the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and inhibits the activation of nuclear factor-kappa B (NF-κB), a transcription factor involved in inflammation and cancer promotion.

3.6 Modulation of Detoxification Enzymes

Garlic can enhance the activity of phase I and phase II detoxification enzymes, including cytochrome P450 enzymes and glutathione S-transferase (GST). This activity facilitates the detoxification of carcinogens and reduces DNA damage. Diallyl sulfides are particularly effective in modulating these enzymes and enhancing the body's capacity to neutralize harmful agents.

3.7 Epigenetic Modulation and Gene Expression

Recent studies have shown that garlic compounds can influence gene expression through epigenetic modifications such as DNA methylation and histone acetylation. These changes can upregulate tumor suppressor genes and downregulate oncogenes, altering the cellular environment in a way that suppresses tumor growth and promotes normal cell behavior.

IV. ANTICANCER ACTIVITY: IN VITRO STUDIES

In vitro studies have played a pivotal role in elucidating the anticancer potential of Allium sativum and its constituents. These laboratory-based experiments, conducted on cultured cancer

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cell lines, allow for precise observation of cellular responses to garlic extracts and isolated compounds under controlled conditions. A wide variety of garlic-derived preparations—including fresh garlic extract (FGE), aged garlic extract (AGE), garlic oil, and purified compounds such as allicin, ajoene, and diallyl sulfides—have been tested against numerous cancer cell lines with promising results.

4.1 Effects on Cell Viability and Proliferation

Many studies have demonstrated that garlic compounds reduce the viability and proliferation of cancer cells in a dose- and time-dependent manner. For instance:

- **Allicin** has been shown to inhibit the proliferation of breast (MCF-7), prostate (PC-3), and colon (HT-29) cancer cells by causing oxidative stress and DNA fragmentation.
- **Diallyl trisulfide (DATS)** significantly decreased cell viability in human leukemia (HL-60) cells and induced morphological changes consistent with apoptosis.
- **Aged garlic extract (AGE)** has been found to inhibit the proliferation of gastric and liver cancer cell lines by downregulating key proliferative markers like Ki-67 and cyclin D1.

These results support the hypothesis that garlic components disrupt cellular processes essential for tumor growth.

4.2 Induction of Apoptosis and Cell Cycle Arrest

Apoptosis induction by garlic-derived compounds has been extensively documented in vitro. Several studies have shown:

- In **HeLa cervical cancer cells**, treatment with ajoene resulted in increased caspase-3 activity and PARP cleavage, indicating activation of the intrinsic apoptotic pathway.
- **DADS** caused G2/M phase arrest in colon cancer (Caco-2) and hepatocellular carcinoma (HepG2) cells by inhibiting CDK1 and upregulating the CDK inhibitor p21^WAF1/Cip1.
- **S-allyl cysteine (SAC)** induced apoptosis in prostate cancer cells through the mitochondrial pathway, evidenced by altered Bax/Bcl-2 ratio and release of cytochrome c.

These findings suggest that garlic can effectively trigger programmed cell death and inhibit the unregulated cell cycle progression characteristic of cancer cells.

4.3 Anti-angiogenic and Anti-metastatic Activities

In vitro models of angiogenesis and metastasis have shown that garlic constituents can impair the ability of cancer cells to support new blood vessel formation and to invade surrounding tissues:

- **Ajoene** and **DATS** reduced the migration and invasion of breast (MDA-MB-231) and lung (A549) cancer cells by suppressing matrix metalloproteinases (MMP-2 and MMP-9), which are crucial for extracellular matrix degradation.
- Treatment of endothelial cells with **SAC** reduced capillary-like tube formation and VEGF expression, suggesting an anti-angiogenic effect.
- In prostate and colon cancer cells, **DADS** downregulated CXCR4 and MMPs, reducing chemotactic migration in transwell assays.

These activities are essential for suppressing the growth and spread of tumors.

4.4 Oxidative Stress Modulation and DNA Protection

Cancer cells often exist in a state of oxidative imbalance. Garlic components modulate oxidative stress pathways and protect normal cells from oxidative damage:

- **SAC** increased intracellular levels of glutathione and upregulated antioxidant enzymes such as superoxide dismutase (SOD) and catalase in colorectal cancer cells.
- In hepatoma cells, **DATS** reduced ROS accumulation and lipid peroxidation, thereby stabilizing mitochondrial function.
- Garlic extract pretreatment was shown to reduce DNA fragmentation and comet tail length in DNA damage assays conducted on chemically-induced mutagenic cells.

These effects contribute to both cancer prevention and therapeutic potential by preserving genomic integrity and enhancing antioxidant defense.

4.5 Gene Expression and Signal Transduction Modulation

Garlic compounds influence a wide range of cellular signaling pathways:

- In **glioblastoma (U87MG) cells**, **allicin** inhibited the PI3K/Akt and MAPK/ERK pathways, both of which are critical for survival and proliferation in many cancers.
- **Ajoene** suppressed the nuclear translocation of NF-κB in pancreatic cancer cells, reducing the

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expression of inflammatory cytokines and anti-apoptotic genes.

- **DATS** was found to increase p53 and p21 expression while reducing cyclin-dependent kinase (CDK) levels, highlighting its effect on tumor suppressor gene activation.

V. SYNERGISTIC EFFECTS AND COMBINATION THERAPIES

Garlic with Chemotherapy or Radiotherapy

Garlic (Allium sativum) has shown considerable potential as an adjuvant therapy alongside conventional treatments like chemotherapy and radiotherapy. Numerous in vitro and in vivo studies support the notion that garlic and its organosulfur compounds, including allicin, diallyl disulfide (DADS), and S-allyl cysteine (SAC), can sensitize tumor cells to chemotherapeutic agents. These compounds act through several mechanisms such as promoting apoptosis, inhibiting angiogenesis, suppressing cell proliferation, and enhancing DNA repair mechanisms.

For instance, garlic compounds can potentiate the efficacy of drugs like cisplatin, doxorubicin, and 5-fluorouracil. DADS has been shown to increase the intracellular accumulation of chemotherapeutic drugs in multidrug-resistant cancer cells by inhibiting P-glycoprotein, a key efflux transporter responsible for drug resistance. Additionally, garlic enhances the production of reactive oxygen species (ROS) in cancer cells, making them more susceptible to oxidative damage during radiotherapy. This dual action helps reduce the required dosage of chemotherapeutic drugs, thereby mitigating associated toxicities.

Preclinical animal models have demonstrated that garlic supplementation can significantly reduce tumor burden when used in combination with chemotherapy. For example, mice bearing Ehrlich ascites carcinoma showed improved survival rates and reduced tumor volume when treated with a combination of garlic extract and cyclophosphamide. In radiotherapy settings, garlic's antioxidant properties help protect normal tissues from radiation-induced damage while selectively sensitizing tumor tissues.

Herb-Drug Interactions and Enhancement of Therapeutic Effects

Despite its potential, garlic's interaction with conventional drugs must be carefully managed. Garlic compounds can modulate cytochrome P450 enzymes, particularly CYP3A4 and CYP2E1, which are involved in the metabolism of many anticancer agents. Such interactions can either potentiate drug effects or reduce drug efficacy. For example, garlic may increase the bioavailability of certain drugs by inhibiting their metabolic degradation, but it may also reduce the plasma concentration of others, such as saquinavir, due to enhanced metabolism.

Moreover, garlic has anticoagulant properties due to its ability to inhibit platelet aggregation. This can increase the risk of bleeding, especially when taken with anticoagulants like warfarin or antiplatelet drugs such as aspirin. Nonetheless, when administered correctly and under medical supervision, garlic may enhance the therapeutic index of chemotherapeutic agents by reducing systemic toxicity and improving efficacy.

VI. FORMULATION AND DELIVERY SYSTEMS

Challenges with Garlic Bioavailability

One of the major hurdles in utilizing garlic as a therapeutic agent is its poor bioavailability. Allicin, the most biologically active compound in fresh garlic, is highly unstable and rapidly degrades into other sulfur-containing compounds upon exposure to air, heat, or acidic environments such as the stomach. This instability significantly limits its therapeutic potential.

Moreover, garlic's hydrophilic nature impairs its ability to cross cellular membranes, leading to reduced absorption and limited systemic availability. The first-pass metabolism in the liver further reduces the effective plasma concentrations of its active components. Additionally, different forms of garlic (raw, boiled, aged, powdered) have varying concentrations of active ingredients, contributing to inconsistent pharmacological outcomes.

Nanotechnology, Encapsulation, and Novel Delivery Systems

To address these challenges, researchers are developing novel delivery systems aimed at enhancing the stability, absorption, and targeted delivery of garlic's bioactive compounds. Nanotechnology-based formulations such as solid lipid nanoparticles (SLNs), liposomes, polymeric nanoparticles, and nanoemulsions have shown promise in improving the bioavailability and therapeutic efficacy of garlic.

For instance, allicin-loaded nanoparticles have demonstrated superior anticancer effects in vitro compared to free allicin, with better cellular uptake and prolonged retention time. Chitosan-

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based microencapsulation techniques protect garlic compounds from degradation in the gastrointestinal tract and allow for controlled release. Additionally, phytosome technology enhances the solubility and membrane permeability of garlic extracts.

These advanced formulations not only increase the bioavailability of garlic compounds but also facilitate targeted drug delivery, reducing off-target effects and improving the therapeutic index. Co-encapsulation of garlic extracts with chemotherapeutic agents is another emerging strategy that offers synergistic effects and minimizes drug resistance.

VII. SAFETY, TOXICITY, AND DOSAGE

Safe Consumption Levels

Garlic is widely regarded as safe when consumed in dietary amounts. Clinical trials and epidemiological studies suggest that daily doses of 1–3 grams of raw garlic or 300–900 mg of standardized garlic extract are generally well-tolerated. Aged garlic extract (AGE), which is odorless and more stable, is often used in clinical studies due to its standardized composition and reduced gastrointestinal side effects.

Reported Adverse Effects

Although garlic is safe for most individuals, high doses or prolonged use can cause adverse effects. Gastrointestinal symptoms such as nausea, bloating, and flatulence are common. Dermatitis and allergic reactions have also been reported, especially in individuals with sensitivity to sulfur-containing compounds. Garlic's antithrombotic activity can increase the risk of bleeding, particularly in patients on anticoagulants or undergoing surgery.

Some reports have linked excessive garlic consumption to hepatotoxicity and hemolytic anemia in animal models, although these effects are typically associated with extremely high doses not encountered in standard therapeutic use. It is crucial to follow standardized dosing guidelines and consult healthcare providers before initiating garlic supplementation, especially in cancer patients who are already undergoing intensive therapy.

Toxicological Studies

Toxicological assessments in animal models indicate that garlic has a high safety margin. Acute toxicity studies have reported LD50 values exceeding 5000 mg/kg for garlic extracts, indicating low toxicity. Sub-chronic and chronic toxicity studies have not shown significant alterations in hematological or biochemical parameters at therapeutic doses.

Histopathological analyses generally reveal no major organ damage, although extremely high doses may cause mild liver inflammation. These findings support the safety of garlic for long-term use, provided it is administered within recommended dosage ranges.

VIII. GAPS IN RESEARCH AND FUTURE PERSPECTIVES

Limitations in Current Research

Despite substantial preclinical evidence, the clinical translation of garlic as an anticancer agent remains limited. Most human studies are small-scale, lack control groups, or use non-standardized garlic preparations, making it difficult to draw definitive conclusions. Additionally, variability in extraction methods, dosage, and treatment duration contributes to inconsistent outcomes.

Mechanistic studies, though abundant, often focus on isolated compounds rather than whole extracts, which may overlook synergistic interactions. The bioavailability of active components in human subjects has also not been adequately addressed.

Suggestions for Future Study

Future research should prioritize well-designed, randomized controlled trials using standardized garlic preparations. These studies should focus on:

- Specific cancer types (e.g., colorectal, breast, prostate)
- Pharmacokinetics and pharmacodynamics
- Long-term safety and efficacy
- Interactions with chemotherapeutic agents

Multi-omics approaches, including genomics, proteomics, and metabolomics, can be employed to elucidate the molecular pathways influenced by garlic. Investigations into garlic's impact on the tumor microenvironment, cancer stem cells, and immune modulation are also warranted.

Standardization of Extracts

Standardization remains a major bottleneck in garlic research. The therapeutic efficacy of garlic depends heavily on the concentration and stability of its bioactive constituents, particularly allicin and DADS.

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Variability in cultivation, harvesting, and processing methods leads to inconsistent chemical profiles.

Developing standardized extraction protocols and quantifiable markers is essential to ensure reproducibility. Regulatory frameworks should mandate the inclusion of pharmacopoeial standards in garlic-based therapeutic products. Collaborations between researchers, clinicians, and industry stakeholders will be critical in achieving this goal.

IX. CONCLUSION

Garlic holds considerable promise as a complementary anticancer agent due to its broad-spectrum biological activities, including antioxidative, anti-inflammatory, and pro-apoptotic effects. It can potentiate the efficacy of chemotherapeutic and radiotherapeutic treatments while reducing adverse effects and improving patient outcomes.

However, its clinical utility is constrained by issues related to bioavailability, standardization, and potential drug interactions. Advanced formulation strategies and rigorous clinical research are required to overcome these limitations. Safety data support its use within recommended dosages, although caution is advised in specific patient populations.

With continued research and technological innovation, garlic could be integrated into standardized cancer treatment protocols as a safe, effective, and affordable adjunct therapy.

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