

Anticancer potential of garlic bioactive constituents: Allicin, Z-ajoene, and organosulfur compounds

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Abstract

Cancer, a formidable disease with a significant mortality rate, continues to claim the lives of thousands of individuals annually in contemporary society. Conventional cancer therapies are notorious for their substantial adverse effects and lack of specificity. Within the context of neoplastic development, cancer hallmarks represent fundamental biological properties that cancer cells progressively acquire. A promising approach for combating cancer involves the simultaneous targeting of multiple cancer hallmarks. Plant-derived natural compounds stand out as a promising reservoir for the development of novel and more efficacious anticancer therapeutics due to their structural diversity and minimal toxicity profiles.

Garlic (*Allium sativum*) has garnered considerable attention for its established anti-cancer properties over the years. Within garlic, a myriad of bioactive constituents, including organosulfur compounds, flavonoids, and phenolic compounds, exhibit distinct effects on cancer cells.

The objective of this review paper is to furnish a comprehensive elucidation of the mechanisms underpinning the anticancer actions of garlic. The elucidated findings from the studies encompassed within this review not only contribute to a more profound comprehension of the anti-cancer properties of garlic but also serve as a robust foundation upon which researchers and healthcare practitioners can formulate enhanced anticancer pharmaceuticals grounded in natural garlic compounds.

Keywords

allicin, anticancer, natural products, functional food, organosulfur compounds

Introduction

Cancer stands as a highly fatal affliction in contemporary times, resulting in the loss of numerous lives on an annual basis (Chhikara and Parang 2023). In the year 2023, it is

projected that the United States will witness the emergence of 1,958,310 fresh instances of cancer and the unfortunate demise of 609,820 individuals due to this disease (Siegel et al. 2023). The term “Hallmarks of Cancer” pertains to a set of functional capabilities that human cells acquire

during their transition from typical growth phases to neoplastic growth states, particularly skills crucial for the formation of malignant tumors (Hanahan 2022). However, this concept was initially proposed in the year 2000 by Hanahan and Weinberg (Hanahan and Weinberg 2000). These same researchers originally identified six hallmarks, which were subsequently expanded to eight in the year 2011 (Hanahan and Weinberg 2011). The eight hallmarks encompass genomic instability, evasion of growth suppression, sustained proliferation, tissue invasion and metastasis, replicative immortality, altered cellular energetics, resistance to cell death, induction of angiogenesis, and evasion of the immune system (Hanahan and Weinberg 2011). These hallmarks collectively define the essential traits acquired by cells during their transformation from normal to neoplastic states, ultimately contributing to the development of malignant tumors (Hanahan and Weinberg 2011). Targeting several cancer hallmarks is a viable cancer treatment method (Talib et al. 2022). Conventional chemotherapy regimens are plagued by significant side effects arising from their lack of selectivity (Oliveri 2022). Consequently, in the pursuit of more sophisticated therapeutic approaches, a multitude of researchers are turning to nature as a source of novel materials. It is noteworthy that over 60% of contemporary anticancer drugs find their origins in natural products (Newman and Cragg 2012). Throughout history, natural products have served as effective treatments for various human ailments and have garnered considerable attention as potential reservoirs of innovative pharmaceutical agents (Jamshidi-Kia et al. 2017). This attraction is primarily attributed to their characteristic low toxicity and diverse chemical structures (Talib et al. 2022). According to the World Health Organization (WHO), in resource-limited regions, more than three-fourths of communities rely on medicinal plants for their fundamental healthcare needs, primarily due to the fact that over 60% of these populations lack access to and/or affordability of allopathic drugs (Organization 2008).

Among the early cultivated plants known for both culinary and therapeutic purposes, garlic (*Allium sativum* L.) occupies a prominent place. This remarkable plant exhibits a spectrum of pharmacological properties, including antibacterial, antithrombotic, anti-arthritis, hypolipidemic, hypoglycemic, and anti-tumor effects (Mondal et al. 2022). The beneficial effects attributed to *Allium* species are primarily attributed to their volatile organosulfur compounds (Corzo-Martínez et al. 2007). The Bulbs of *A. sativum* have found to contain a diverse array of phytochemicals, with sulfur-containing compounds such as ajoenes (E-ajoene, Z-ajoene), thiosulfonates (allicin), vinyldithiins (2-vinyl-(4H)-1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyl disulfide (DADS), diallyl trisulfide (DATS)), thiocremone, and others, collectively constituting 82% of the total sulfur content in garlic (Al-Snafi 2013).

Indeed, organosulfur compounds have been demonstrated to specifically induce redox stress in cancer cells, leading to apoptosis and cell death (Yu et al. 2012). Notably, Weisberger and Pensky observed in 1958 that diethyl

thiosulfinate from garlic effectively inhibited the development of sarcomas in mice bearing S180 tumors (Weisberger and Pensky 1957). Subsequently, numerous studies have reaffirmed garlic's efficacy in cancer treatment (Fleischauer and Arab 2001). This effectiveness can be attributed to its diverse mechanisms as an antineoplastic agent, including the inhibition of cell growth and proliferation, regulation of carcinogen metabolism, stimulation of apoptosis, and the prevention of angiogenesis, invasion, and migration (Liu et al. 2018).

The primary objective of this review article is to conduct a comprehensive analysis of the potential mechanisms through which garlic and its bioactive constituents manifest their anti-cancer properties by targeting multiple facets of cancer hallmarks.

Garlic as therapeutic agent in cancer hallmarks

Role of garlic in genomic instability

Chromosomal and genomic instability stand out as hallmark characteristics of cancer, inducing alterations in the genetic structure of cancer cells, thereby influencing their behavior and their response to therapeutic interventions (Chen et al. 2022). Mutations can arise from internal factors, referred to as spontaneous mutations, or external environmental factors, such as exposure to ultraviolet light and chemical carcinogens (McTigue et al. 2022). Spontaneous mutations in the human body are typically rare occurrences, owing to the presence of DNA maintenance and repair mechanisms. Conversely, mutations induced by environmental factors can contribute to the development of cancer. Two principal factors that contribute to DNA mutations are heightened sensitivity to mutagenic agents and deficiencies in DNA maintenance and repair mechanisms (Hanahan and Weinberg 2011).

In recent decades, human exposure to genotoxic agents, which induce mutations capable of altering the structure and function of DNA, has witnessed a notable increase. These agents, whether originating from internal processes or external sources, generate reactive oxygen species (ROS) that initiate a cascade of molecular events culminating in genotoxic effects. Consequently, the continued accumulation of DNA damage eventually leads to genomic instability (Aprotosoae et al. 2019).

Numerous studies have been conducted with the aim of identifying and assessing substances possessing Genoprotective capabilities against genotoxic agents. In pursuit of this objective, a wide array of tests has been employed. Among the most utilized models in genetic toxicology are the salmonella mutagenicity test, sister chromatid exchange (SCE), the evaluation of chromosomal aberrations (ChAb), the micronucleus assay (MN), and, more recently, the comet assay (CA). These tests serve as valuable tools for evaluating the Genoprotective potential of various compounds (López-Romero et al. 2018).

Studies investigating the antigenotoxic effects of garlic commenced in the 1990s (Morales-González et al. 2019). Of particular interest is a study that examined five organosulfur compounds derived from garlic: 1-propylmercaptan (PM), dimethyl disulfide (DMDS), diallyl disulfide (DADS), propyl disulfide (PDS), and 2,5-dimethylthiophene (DMT). This research demonstrated the capacity of these compounds to counteract the mutagenicity induced by 4-nitroquinoline-N-oxide in *Salmonella typhimurium* strains TA 98 and TA 100 (Chiu et al. 2016).

Another study explored the effectiveness of pretreating human lung cells with a combination of garlic and vitamin E to mitigate cytotoxicity and genotoxicity induced by lead acetate (Led) and mercury chloride (Mer). This investigation revealed that the DNA damage caused by these substances could be alleviated through the use of garlic and vitamin E (Ali 2018). Furthermore, Medina et al. conducted a study using the *Drosophila melanogaster* genetic model to assess the antigenotoxic effects of garlic after genotoxicity induction by hydrogen peroxide. This research observed moderate antigenotoxic effects associated with garlic (Toledano Medina et al. 2019). These findings collectively underscore the potential Genoprotective properties of garlic and its constituents in various experimental models.

Garlic and its bioactive substances have drawn a lot of interest because of their possible contribution to reducing genomic instability, which is a defining feature of cancer. Numerous ways by which garlic exerts its Genoprotective benefits have been identified by research.

ROS production and oxidative stress inhibition are two important mechanisms. Allicin, one of the sulfur-containing chemicals found in garlic, has been demonstrated to have powerful antioxidant properties that can scavenge ROS and lessen DNA oxidative damage. Garlic may assist in preventing DNA mutations and maintaining genomic integrity by reducing oxidative stress (Hanahan and Weinberg 2011). Garlic has also shown the ability to influence DNA repair processes. According to studies, the chemicals in garlic, especially the organosulfur compounds, may improve the repair of damaged DNA, hence lowering the risk of genomic instability. This method helps to re-

store DNA integrity, which increases the Genoprotective potential of garlic (Chiu et al. 2016). The clinical uses of garlic in treating genomic instability have also been studied recently. For instance, the ability of garlic and vitamin E to lessen the cytotoxicity and genotoxicity caused in human lung cells by heavy metals such as lead acetate and mercury chloride has been investigated (Ali 2018). Such studies underscore the practical relevance of garlic in protecting against genomic instability, particularly in scenarios involving exposure to genotoxic agents. Additionally, research employing genetic models like *Drosophila melanogaster* has shown that garlic has mild antigenotoxic effects after genotoxicity is induced by substances like hydrogen peroxide (Toledano Medina et al. 2019). These findings extend our understanding of garlic's role in counteracting genomic instability in living organisms. In summary, garlic's multifaceted mechanisms, including antioxidant properties, DNA repair enhancement, and its practical applications, position it as a promising candidate for mitigating genomic instability, thereby contributing to cancer prevention and treatment strategies. Further research and clinical studies are warranted to explore the full potential of garlic in this context.

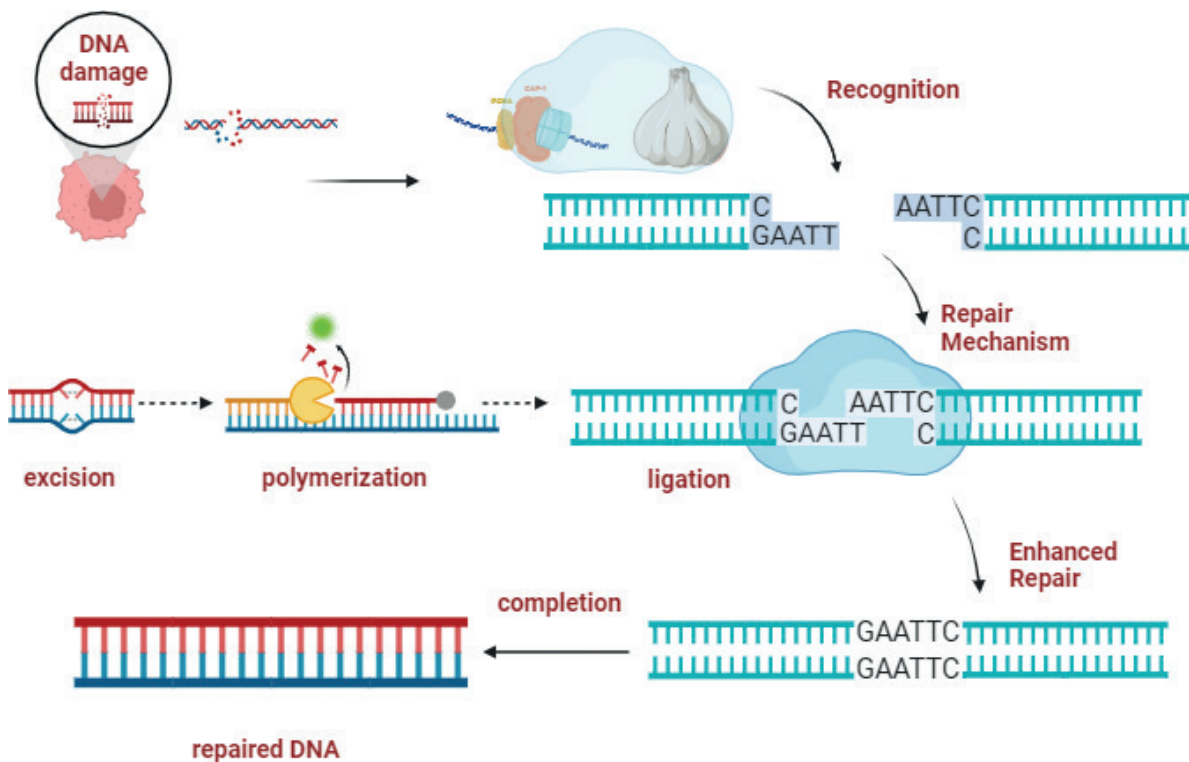
Table 1 gives a thorough summary of the mechanisms that underpin the genoprotective role of garlic, emphasizing the antioxidant qualities of allicin, the enhancement of DNA repair through organosulfur compounds, and potential therapeutic uses like reducing heavy metal-induced cytotoxicity. The table also highlights the current investigation into garlic's possible genoprotective effects in cancer patients and provides evidence of in vivo antigenotoxic effects in genetic models, with an emphasis on new developments in formulations and delivery techniques for increased efficacy.

Replicative immortality: Targeting telomerase and CDKs with garlic compounds

Tumor cells are distinguished by their intrinsic capability for limitless replication, a hallmark feature that underpins

Table 1. Concise summary of garlic's mechanisms and roles in targeting genomic instability.

Mechanism of garlic's genoprotective role	Description and Findings
Antioxidant Properties	Allicin, a sulfur-containing molecule found in garlic, is a powerful antioxidant that can scavenge ROS and prevent DNA oxidative damage (Hanahan and Weinberg 2011).
DNA Repair Enhancement	It has been demonstrated that garlic components, notably organosulfur compounds, improve the repair of damaged DNA, helping to maintain DNA integrity and genomic stability (Chiu et al. 2016).
Clinical Applications	Researchers are investigating into using garlic and vitamin E together to lessen the cytotoxicity and genotoxicity that heavy metals like lead acetate and mercury chloride cause in human lung cells (Ali 2018).
In Vivo Antigenotoxic Effects	Garlic has been shown to exhibit mild antigenotoxic properties in studies utilizing genetic models like <i>Drosophila melanogaster</i> , especially after genotoxicity has been induced by substances like hydrogen peroxide (Toledano Medina et al. 2019).
Recent Clinical Studies	Garlic may have Genoprotective effects in cancer patients and people at risk for cancer, according to ongoing scientific investigations. Initial findings point to positive effects, but further research is required.
Emerging Trends in Garlic Research	Emerging trends in garlic research include the exploration of novel garlic formulations and delivery methods for enhanced Genoprotective effects, as well as the investigation of garlic's role in modulating specific genomic instability-related pathways.



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Figure 1. Enhancement of DNA repair mechanisms by garlic compounds (created by BioRender.com). This diagram illustrates how garlic compounds enhance DNA repair mechanisms: DNA Damage: The process begins with DNA damage, represented as breaks and mutations in the DNA strands. Recognition: The damaged DNA is recognized by cellular repair machinery, signaling the need for repair. Garlic Compounds: Garlic compounds, highlighted in the diagram, play a crucial role at this stage. They are known for their Genoprotective properties. DNA Repair Mechanism: The diagram illustrates the sequential steps of DNA repair, including excision, polymerization, and ligation. Enhanced Repair: Garlic compounds facilitate and enhance the DNA repair process, as indicated by connecting lines and arrows.

their proliferative and invasive potential (Marques et al. 2018). Disrupting this perpetual replication constitutes a promising strategy to impede tumor initiation and progression. Of paramount importance in this context are telomerase and cyclin-dependent kinases (CDKs), both of which play pivotal roles in regulating cellular replication (Bodnar et al. 1998).

In this comprehensive review, our primary focus will be directed towards elucidating the impact of garlic on the process of replicative immortalization by its dual inhibitory effects on telomerase and CDKs.

Telomerase: Telomerase is an important enzyme in cell division. Its primary role lies in the elongation of the ends of chromosomes, which naturally undergo shortening during cell division (Talib 2018).

Henceforth, the activation of this enzyme, telomerase, assumes a pivotal role in facilitating uninterrupted cell division across diverse cancer types, as underscored by (Hanahan and Weinberg 2011). The regulation of replicative immortality is a multifaceted endeavor that encompasses the inhibition of various targets. These encompass not only telomerase but also a spectrum of key molecules,

including mTOR, CDK4/6, CDK 1,2,5,9, Akt, and PI3K, as expounded upon by (Talib 2018).

Garlic's Impact on Telomerase: A research study conducted on gastric cancer SGC-7901 cells unveiled a significant finding: allicin, a bioactive compound found in garlic, exhibited the ability to inhibit telomerase activity in a manner that is both time-dependent and dose-dependent. This discovery underscores the potential of allicin as a telomerase inhibitor with implications for the treatment of gastric cancer (Sun and Wang 2003). In another research investigation, the impact of Z-ajoene, an organosulfur compound derived from garlic, was assessed on the HL-60 cell line. The research findings revealed that a concentration of 10 $\mu\text{mol/L}$ of Z-ajoene administered for a 24-hour period led to a noteworthy reduction in telomerase-associated human telomerase reverse transcriptase (hTERT) and telomerase associated protein 1 (TP1) mRNA levels. This observation highlights the potential of Z-ajoene as a telomerase-modulating agent with potential implications for therapeutic interventions (Ye et al. 2005).

Targeting CDKs in Cell Cycle Progression: Cancer cells employ a strategy of upregulating the expression of

cyclin-dependent kinases (CDKs) to facilitate the progression of the cell cycle. These CDKs play a pivotal role in the process by orchestrating the phosphorylation of cyclins, thereby amplifying the momentum of the cell cycle's forward progression (McTigue et al. 2022).

Garlic's Impact on CDKs and Cell Cycle: S-allylcysteine (SAC), a compound derived from garlic, has been identified as an inhibitor of cell cycle progression. In a study conducted by Sengupta and colleagues, the cell cycle of HepG2 liver cancer cells was examined following treatment with SAC. The research outcomes demonstrated that the application of SAC to HepG2 cells led to an augmentation in the activity of Wee1, a kinase responsible for inhibiting mitosis. Additionally, SAC treatment resulted in the accumulation of cyclin-dependent kinase (CDK) inhibitors, specifically p15, p16, p21, and p27. These findings suggest that SAC exerts its cell cycle inhibitory effects by modulating key regulatory components involved in cell cycle control (Sengupta et al. 2017).

Clinical relevance

Significant therapeutic potential exists for cancer therapies that target replicative immortality. Hope for cancer patients may come from the discovery that chemicals derived from garlic can inhibit telomerase and CDKs.

Mechanisms of action

Complex biochemical pathways play a role in the precise processes by which garlic components inhibit telomerase and CDKs. Here are some broad insights into these mechanisms, while specifics may vary based on the type of cancer cell and the garlic compound:

- Inhibition of telomerase by Garlic Compounds:
 - **Allicin:** Allicin, a bioactive component of garlic, has been shown to suppress telomerase activity. The exact mechanism is still not fully understood; however, it may involve telomerase's enzymatic activity being interfered with or having its capacity to link to telomeres disrupted. This disruption prevents telomeres from lengthening, which lowers the capacity of cancer cells to proliferate. (Omar and Al-Wabel 2010; Shang et al. 2019).
 - **Z-ajoene:** Z-ajoene, a different compound produced from garlic, decreases the levels of TP1 and hTERT mRNA that are associated with telomerase. This implies that Z-ajoene may influence the expression of telomerase components, resulting in a decrease in telomerase activity. To precisely pinpoint the molecular interactions involved in this process, more investigation is required (Ganesan and Xu 2017).
- Inhibition of CDKs by Garlic compounds:
 - **S-allyl cysteine (SAC):** SAC, a substance produced from garlic, slows down the cell cycle by

concentrating on CDKs. It has been observed to increase Wee1, a kinase that prevents mitosis, in its activity. The cell cycle has stopped because of this Wee1 activation. Additionally, SAC therapy causes CDK inhibitors including p15, p16, p21, and p27 to accumulate. These CDK inhibitors prevent the cyclins from being phosphorylated, which then prevents the cell cycle from progressing. They do this by inhibiting the activity of cyclin-CDK complexes (Thomson and Ali 2003).

These mechanisms are complex and may involve multiple molecular interactions within cancer cells. The precise details of how garlic compounds interact with telomerase, CDKs, and associated pathways may vary depending on the specific compound, cell type, and context. Further research is needed to fully elucidate these intricate molecular mechanisms and their potential as therapeutic targets in cancer treatment.

Future work on garlic's effect on replicative immortality and its suppression of telomerase and cyclin-dependent kinases (CDKs) in cancer cells may take the following directions:

- Mechanistic Elucidation: more research into the precise chemical processes by which garlic compounds affect telomerase and CDKs. In-depth research on protein-protein interactions, signaling cascades, and genetic regulation may be required for this (George et al. 2021).
 - Clinical Trials: conducting clinical trials to evaluate the effectiveness and security of chemicals derived from garlic as potential cancer treatments. Different cancer types, stages, and patient demographics could be involved in these trials (Ansary et al. 2020).
 - Combination medications: Examining the beneficial interactions between garlic compounds and common cancer medications including chemotherapy, radiation therapy, or targeted therapies. Combinations may improve therapeutic results while reducing adverse effects (Arijit et al. 2022).
 - Patient Stratification: Identifying biomarkers or patient-specific traits that may predict a patient's receptivity to therapies based on garlic. This customized medicine strategy could assist in customizing treatments for specific individuals (Mathur and Sutton 2017).
 - Drug Development: The creation of new chemicals or derivatives derived from garlic that have improved specificity, bioavailability, and anti-cancer action. Chemical alterations and optimization may be involved (Kaschula et al. 2010).
 - Resistance Mechanisms: Studying potential methods by which cancer cells could become resistant to treatments based on garlic. Understanding resistance mechanisms can help in the creation of methods to get around them (Mansoori et al. 2017).

- Prevention and Early Intervention: Examining the potential of garlic components for cancer prevention and early detection in people who are at high risk or who have the earliest stages of the disease (Pandey et al. 2023).
- In Vivo Models: Expanding study employing animal models to replicate the intricate tumor microenvironment and systemic effects of garlic components more accurately. In Vivo Models. Insights regarding in vivo efficacy and safety may result from this (Mukherjee et al. 2022).
- Long-Term Outcomes: Examining the long-term outcomes of cancer survivors receiving garlic-based therapy, including possible implications on cancer recurrence and general health (Lee et al. 2021).
- Global Impact: Examining how to make garlic-based medicines available and inexpensive on a global scale, particularly in areas with few healthcare resources (Labont 2011).

These directions indicate several ways to develop our knowledge of garlic's potential application in cancer

treatment and its effects on replicative immortality. Innovative therapies and methods for enhancing the prognosis of cancer patients may result from research in these fields.

Tumor dysregulated metabolism

Cancer cells enact alterations in metabolic pathways to facilitate the generation of essential nutrients and enzymes necessary for their sustained proliferation and viability. These metabolic adaptations encompass processes such as aerobic glycolysis, diminished oxidative phosphorylation, and augmented synthesis of biosynthetic intermediates. To accommodate the heightened requirements associated with these metabolic transformations, cancer cells upregulate the expression of enzymes responsible for catalyzing these metabolic modifications, along with plasma membrane transporters that facilitate the uptake and transport of vital nutrients (Kalyanaraman 2017).

Cancer cells implement modifications in metabolic pathways to promote the production of vital nutrients and enzymes crucial for their ongoing growth and survival.

Table 2. Key aspects of replicative immortality and garlic's impact on telomerase and CDKs in cancer.

Aspect	Findings/information	Research methodology	References
Replicative immortality	- Cancer cells exhibit inherent replicative immortality, a key driver of their growth and invasion.	N/A	(Marques et al. 2018)
	- Telomerase and cyclin-dependent kinases (CDKs) are critical regulators of cellular replication.	N/A	(Bodnar et al. 1998)
	- Garlic's impact on replicative immortality, particularly through dual inhibition of telomerase and CDKs, is the primary focus of this review.	N/A	
Telomerase	- Telomerase, an enzyme responsible for chromosome end elongation, facilitates continuous cell division in various cancer types.	N/A	(Hanahan and Weinberg 2011)
	- Replicative immortality regulation involves targeting multiple molecules, including mTOR, CDK4/6, CDK 1,2,5,9, Akt, and PI3K.	N/A	(Talib 2018)
Garlic's Impact on Telomerase	- Allicin, a garlic-derived compound, exhibits time-dependent and dose-dependent inhibition of telomerase activity in gastric cancer SGC-7901 cells.	In vitro assay using SGC-7901 cells	(Sun and Wang 2003)
	- Z-ajoene, another garlic-derived compound, leads to significant reductions in telomerase-associated hTERT and TP1 mRNA levels after a 24-hour treatment in the HL-60 cell line.	In vitro assay using HL-60 cells	(Ye et al. 2005)
CDKs and Cell Cycle Progression	- Cancer cells upregulate cyclin-dependent kinases (CDKs) to promote cell cycle progression.	N/A	(McTigue et al. 2022)
Garlic's Impact on CDKs and Cell Cycle	- S-allylcysteine (SAC), derived from garlic, inhibits cell cycle progression.	In vitro assay using HepG2 cells	(Sengupta et al. 2017)
	- SAC treatment of HepG2 liver cancer cells increases Wee1 kinase activity and leads to the accumulation of CDK inhibitors p15, p16, p21, and p27.	In vitro assay using HepG2 cells	

Table 3. This table provides a summary of the impact of different garlic compounds on specific cancer hallmarks.

Garlic compound	Impact on cancer hallmarks	References
Allicin	- Inhibition of telomerase activity - Potential telomerase inhibitor for gastric cancer	(Sun and Wang 2003)
Z-ajoene	- Reduction in telomerase-associated hTERT and TP1 mRNA levels	(Brandt et al. 2005)
S-allylcysteine (SAC)	- Inhibition of cell cycle progression - Enhancement of Wee1 activity - Accumulation of CDK inhibitors p15, p16, p21, and p27	(Arunima et al. 2013)

These metabolic adjustments involve procedures like aerobic glycolysis, where cancer cells prioritize the utilization of glycolysis even when oxygen is available, resulting in elevated lactate synthesis. Moreover, there is a decline in oxidative phosphorylation, which leads to diminished energy generation via the mitochondrial electron transport chain (Schiliro and Firestein 2021).

An additional characteristic of the metabolism of cancer cells is the increased synthesis of biosynthetic intermediates. This includes a rise in the production of the amino acids, lipids, and nucleotides necessary for the creation of membranes, the replication of DNA, and the synthesis of proteins, respectively. Together, these metabolic changes promote the quick division and development of cancer cells (Martínez-Reyes and Chandel 2021).

Cancer cells upregulate the production of the enzymes needed to catalyze these metabolic processes in order to meet the increased needs associated with them. Hexokinase 2 (HK2), for instance, is frequently overexpressed in cancer cells to promote glycolysis. Similar to this, transporters such as GLUT1 make it easier to absorb glucose, and monocarboxylate transporters (MCTs) help to export the lactate created during glycolysis (Elia and Haigis 2021).

These metabolic changes are essential for the development of cancer. In addition to giving cancer cells a quick source of energy, increased glycolysis also causes lactate to build up, which can provide an acidic microenvironment that encourages tumor spread and immune evasion. Furthermore, altered lipid and nucleotide synthesis pathways provide evidence for the increased demands for membrane synthesis and DNA replication seen in cancer cells that divide quickly (Hsu and Sabatini 2008).

Understanding the metabolic modifications made by cancer cells has important therapeutic ramifications. As a fresh approach to cancer treatment, researchers are actively investigating methods to disrupt these metabolic advantages. For instance, inhibitors aimed at important enzymes like hexokinase 2 (HK2) and transporters like GLUT1 seek to obstruct glucose absorption and glycolysis, hence limiting the availability of energy and metabolic intermediates and inhibiting the proliferation of cancer cells (Elia and Haigis 2021). These promising therapeutic

modalities are now being investigated in preclinical and clinical settings.

It's crucial to understand that tumor dysregulated metabolism does not function independently. It interacts with other characteristics of cancer, including DNA repair, immune evasion, and angiogenesis. For instance, enhanced glycolysis can encourage angiogenesis by supplying endothelial cell migration and proliferation with energy and metabolic intermediates (Semenza 2003). Creating comprehensive cancer therapy requires an understanding of these linkages.

In the last few years, there have been tremendous improvements in our knowledge of cancer metabolism, including the discovery of brand-new metabolic targets and the creation of ground-breaking treatments. The discipline is still being shaped by promising research on the use of metabolic inhibitors, immunotherapies, and combination medicines (Cantor and Sabatini 2012).

It is crucial to comprehend these metabolic modifications made by cancer cells because they have consequences for both understanding the biology of cancer and developing effective treatments. For the development of innovative anticancer therapies, targeting certain enzymes and transporters involved in these metabolic pathways is a current field of research. For example, inhibitors of HK2 or GLUT1 attempt to disrupt the metabolic advantage of cancer cells and prevent their proliferation (Kalyanaraman 2017).

Tumor-promoting inflammation

It has been noted that there is a clear connection between inflammation and cancer initiation. (Greten and Grivennikov 2019) Some of the Potential linkers that play a crucial role in this relationship are cytokines (interleukins, TNF- α , TGF- β , chemokines), transcription factors (NF- κ B, STAT3, HIF-1- α) and factors that affect repair mechanisms (Chakraborty et al. 2020; Jennifer Kay et al. 2019). In addition to fostering a microenvironment favorable to tumor growth, chronic inflammation, which is frequently brought on by recurrent infections or environmental factors, also contributes to genomic instability and affects other key characteristics of cancer, such as angiogenesis and immune system. For the purpose of creating targeted

Table 4. Summary of tumor dysregulated metabolism: Key points and references.

Aspect	Key points	References
Tumor dysregulated metabolism	- Cancer cells alter the metabolic processes that produce nutrients and enzymes. - Aerobic glycolysis, decreased oxidative phosphorylation, and increased biosynthetic intermediate production are examples of adaptations.	(Kalyanaraman 2017) (Schiliro and Firestein 2021)
Impact on cancer progression	- Rapid growth, invasion, and immune evasion are supported by altered metabolism.	(Hsu and Sabatini 2008)
Therapeutic implications	- Current study examines how to interfere with metabolic advantages by targeting certain enzymes and transporters. - Both preclinical and clinical investigations have shown promise for inhibitors of important enzymes and transporters.	(Elia and Haigis 2021) (Elia and Haigis 2021)
Interplay with other hallmarks	- DNA repair, immunological evasion, and dysregulated metabolism all interact.	(Semenza 2003)
Recent advances	- improvements in our understanding of metabolic targets and novel treatments.	(Cantor and Sabatini 2012)

This table provides a concise summary of the key points related to tumor dysregulated metabolism in cancer. It highlights the impact of metabolic adaptations, their implications for cancer progression, therapeutic strategies, interplay with other hallmarks, and recent advances, along with corresponding references for further exploration.

medicines intended to block various inflammatory pathways, it is crucial to comprehend the complex function that inflammation plays in cancer (Casey et al. 2015).

- **Clinical implications of inflammation in cancer:**

1. **Diagnosis and prognosis:**

The presence and degree of inflammation in a tumor's microenvironment can have an enormous effect on a patient's prognosis and cancer diagnosis. Chronic inflammation or elevated inflammatory markers may act as prognostic markers, affecting patient outcomes and survival rates. Inflammation frequently plays a crucial role in the development of tumors like pancreatic and liver cancer, where it is recognized as a diagnostic and prognostic factor (Greten and Grivennikov 2019).

2. **Treatment strategies:**

The way a patient reacts to cancer treatment can be impacted by inflammation. The inflammatory environment surrounding the tumor may have an impact on chemotherapy, immunotherapy, and targeted therapies. Customized therapeutic methods are possible when the role of inflammation in modifying treatment responses is understood. Emerging approaches, like incorporating anti-inflammatory drugs with traditional therapies, have promising opportunities for enhancing therapeutic outcomes (Greten and Grivennikov 2019).

- **Cancer types:**

In their microenvironments, many cancer forms display varied degrees of inflammation. Due to factors including nutrition and gut bacteria, gastrointestinal malignancies like colorectal cancer are significantly linked to chronic inflammation. In these situations, controlling inflammation becomes crucial to complete cancer management (Brennan and Garrett 2016).

- **Examples and case studies:**

The substantial effect of inflammation on cancer can be effectively illustrated by specific case studies and instances. The complex relationship between inflammation and the development of cancer is demonstrated, for example, by the fact that chronic inflammation in people with viral hepatitis can result in the formation of hepatocellular carcinoma. These incidents emphasize the value of early action to reduce the risk of cancer caused by inflammation (Russo et al. 2022).

- **Emerging therapies:**

Research is still being done on innovative cancer treatments that target inflammation. Utilizing the immune response against inflammatory components in the tumor microenvironment is the goal of clinical trials examining immunomodulatory drugs such checkpoint inhibitors and cytokine treatments. These treatments represent a promising new area in the fight against malignancies brought on by inflammation (Hou et al. 2021).

- **Prevention and lifestyle:**

Diet, exercise, and obesity are examples of lifestyle factors that can affect cancer risk and inflammation. Promoting better lifestyles may reduce the risks of cancer caused by inflammation. Choosing a diet high in anti-inflamma-

tory foods, including garlic, and leading an active lifestyle can support attempts to avoid cancer (Anand et al. 2008).

- **Future research directions:**

Cancer research that is focusing on inflammation continues to raise interesting questions. The development of targeted therapeutics and the mechanisms underlying inflammation-driven oncogenesis should be the focus of future study. New opportunities for early identification, individualized treatment, and prevention should become available as we get a better knowledge of the complex link between inflammation and cancer (Greten and Grivennikov 2019).

Angiogenesis

Angiogenesis, the growth of new blood vessels, is essential for the development, progression, and metastasis of tumors (Carmeliet and Jain 2011). It is a complex biological process regulated by many factors, with Vascular endothelial growth factor (VEGF) considered as a key regulator (Yang et al. 2020). The study of angiogenesis has important clinical repercussions for the treatment of cancer. The level of angiogenesis within a tumor affects prognosis and response to treatment across a variety of cancer types (Pang and Poon 2006). Increased angiogenesis in tumors is associated with more aggressive phenotypes and worse outcomes. Anti-angiogenic medicines that particularly target the blood arteries supplying tumors have been developed as a result of this knowledge (Abdalla et al. 2018). Anti-angiogenic medications, like bevacizumab, have been introduced into cancer treatment plans and have shown the ability to slow the growth of tumors and lengthen patient survival (Vasudev and Reynolds 2014).

Anti-angiogenic treatments try to prevent tumors from growing new blood vessels. The main targets of these therapies are VEGF and its receptors (Lopes-Coelho et al. 2021). They function by obstructing the signals that stimulate angiogenesis, which ultimately reduces the tumor's blood supply and inhibits its growth (Gupta and Qin 2003). To increase the efficacy of these therapies, they are frequently combined with more conventional medical procedures like radiation and chemotherapy (Bayat Mokhtari et al. 2017).

Novel treatment targets and strategies have been discovered in the angiogenesis and cancer sector recently. To increase the effectiveness of anti-angiogenic therapy even more, researchers are experimenting with novel medication combinations and delivery systems. Current research is also examining the function of angiogenesis inhibitors in uncommon and treatment-resistant tumors (Lopes-Coelho et al. 2021).

Angiogenesis and a number of cancer characteristics, including immune evasion and tissue invasion, are strongly related (Aguilar-Cazares et al. 2019). It may result in the development of an immunosuppressive tumor microenvironment, which makes it more difficult for the immune system to identify and eradicate cancer cells (Labani-Motlagh et al. 2020). Additionally, tumor cells can penetrate neighboring tissues and potentially spread to distant areas

through the process of angiogenesis, which increases the overall aggressiveness of cancer (Lugano et al. 2020).

The development of new medications that target various components of the angiogenic process as well as improving patient selection for anti-angiogenic therapy are likely to be the main areas of future study in the subject of angiogenesis and cancer (Vasudev and Reynolds 2014). Understanding the function of angiogenesis in particular cancer subtypes and how it interacts with other characteristics may also result in more individualized and efficient treatment plans (Rajabi and Mousa 2017). Another intriguing area of research is looking into the possibilities of combination medicines that simultaneously target angiogenesis and other important cancer processes (Comunanza and Bussolino 2017).

Cell migration and tumor metastasis

The crucial and dangerous feature of tumor growth is cell migration. It entails the spread of cancer cells from the initial tumor site to the tissues in the area, where they then infiltrate the blood vessels and organs nearby (Hanahan and Weinberg 2011).

- Mechanism of metastasis:

The spread of cancer cells to distant locations in the body is known as metastasis, and it is a complex process controlled by a number of different mechanisms. The extracellular matrix's metalloproteinase activity is a critical factor in metastasis. These enzymes are crucial in the breakdown of the extracellular matrix's structural elements, which helps cancer cells escape from the original tumor and invade nearby tissues (Lin et al. 2002).

The destruction of cell-cell adhesion, particularly the integrity of tight and gap junctions, is a crucial component of metastasis. The cohesive structure of tissues is maintained in large part by these junctions. Cancer cells are less able to adhere to surrounding cells due to the loss of tight and gap junctions, which allows them to migrate and invade distant anatomical regions (Talib et al. 2022).

Clinical relevance of the mechanisms underlying cell migration and metastasis cannot be overstated. Because it results in the development of secondary tumors in important organs, metastasis is frequently the main factor in cancer-related fatalities (Liu et al. 2017). Targeted medicines aimed at preventing cell migration and metastasis have been developed as a result of the identification of specific molecules and pathways involved in these processes (Stuelten et al. 2018). Potential treatments to stop the spread of metastatic disease include therapeutic methods that block the activity of metalloproteinases and encourage the restoration of cell-cell adhesion (Cabral-Pacheco et al. 2020).

Targeting cell migration and metastases requires a variety of treatment modalities. One of these is the creation of medications that block metalloproteinases and stop the breakdown of the extracellular matrix (Winer et al. 2018). In order to decrease the mobility of cancer cells and hinder their capacity to spread, techniques to restore and improve cell-cell adhesion are also being investigated (van Zijl et al. 2011).

Angiogenesis and immune evasion are two additional characteristics of cancer that are tightly linked to cell migration and metastasis. Angiogenesis, the growth of new blood vessels, is essential for providing oxygen and nutrition to metastatic cancers (Saman et al. 2020). Furthermore, the immune system's capacity to identify and destroy cancer cells can be thwarted by the immunosuppressive environment that metastatic tumors produce (Simiczyjew et al. 2020).

The specific mechanisms driving cell migration and metastasis are likely to be the focus of future study in this area. This information will help in the creation of more specialized and efficient treatments to stop or slow metastasis (Fontebasso and Dubinett 2015). Additionally, a deeper comprehension of the interactions between cell migration and other cancer-related characteristics will help in the creation of thorough treatment plans that take into account the complex nature of tumor progression (Quail and Joyce 2013).

Immune evasion

Immune evasion is a distinguishing trait of cancer cells that describes their extraordinary ability to manipulate and elude the host immune system. This phenomenon is defined by cancer's capacity to have a significant impact on immune system operations, allowing it to get past the body's built-in defenses.

Suppressing the efficacy of immune cells is one method used by cancer cells to accomplish immune escape. Immune cells' ability to function can be inhibited by cancer cells by preventing their entry into the tumor microenvironment. This reduces the capacity of the immune system to identify and get rid of the malignant cells within the tumor (Talib et al. 2022).

Cancer cells can actively secrete immunosuppressive chemicals and signaling factors in addition to altering checkpoint mechanisms. These chemicals alter the tumor's surrounding environment in an immunosuppressive manner, making it more difficult for the immune system to mount a successful antitumor response. Examples of these immunosuppressive cells that limit the function of cytotoxic T lymphocytes (CTLs) and other immune cells include regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (Quail and Joyce 2013; Zamanian et al. 2021).

The clinical consequences of comprehending immune evasion mechanisms are profound. Immune evasion is a significant barrier to the effectiveness of immunotherapy, a potential method of cancer treatment that tries to use the immune system's ability to target and eliminate cancer cells (Kim and Cho 2022). Immunotherapeutic medications developed to combat immune evasion include immune checkpoint inhibitors, which prevent the interaction of checkpoint proteins. To develop strategies to improve the efficacy of immunotherapy, a fuller understanding of these systems is necessary (Zhou et al. 2022).

Immunotherapy, especially immune checkpoint inhibitors like anti-PD-1 and anti-PD-L1 antibodies, has

revolutionized the way that cancer is treated (Wojtkiewicz et al. 2021). These medicines improve the immune system's ability to identify and combat cancer cells by obstructing the cancer cells immune evasion strategies (Gonzalez et al. 2018). In order to improve patient outcomes and broaden the variety of malignancies that can be treated, current and future research efforts are concentrated on strengthening existing immunotherapies and investigating novel methods to circumvent immune evasion (Sahu and Suryawanshi 2021).

Combination therapies are being researched as a possible strategy to increase the clinical effects of immunotherapy. These medications simultaneously target several immune evasion mechanisms, such as inhibiting checkpoint pathways and neutralizing immunosuppressive substances (Varayathu et al. 2021).

Immune evasion and other cancer-related characteristics are closely related. For instance, immune evasion might further encourage angiogenesis, which helps the formation of blood vessels that feed the tumor. This creates an immunosuppressive tumor microenvironment. Developing thorough cancer treatment plans requires an understanding of these intricate interconnections (Kim and Cho 2022).

Sustained proliferative signaling

To support their continuous cell division and proliferation, cancer cells frequently rearrange the expression of signals that promote growth (Hanahan and Weinberg 2011). Hypoxia-inducible factor-1 (HIF-1), NF- κ B, PI3K/AKT, insulin-like growth factor receptor (IGF-1R), cyclin-dependent kinases (CDKs), and estrogen receptor signaling are important signaling pathways implicated in this sustained proliferative signaling. It is crucial to block these signaling pathways to stop cancer cells from replicating indefinitely (Yaswen et al.).

It is crucial to comprehend the clinical effects of persistent proliferative signaling in cancer. The diagnosis, prognosis, and therapy options for cancer are influenced by these signaling pathways. For instance, inhibiting IGF-1R signaling, which is important in the development of breast and prostate cancer, has shown potential as a treatment (Abeshouse et al. 2015). Personalized treatment strategies can be determined by identifying the distinct signaling pathways that are active in a patient's cancer.

The importance of persistent proliferative signals is illustrated by specific examples. The overabundance of estrogen receptors promotes unchecked cell proliferation in breast cancer. By blocking this signaling system, targeted treatments like tamoxifen and aromatase inhibitors have successfully improved patient outcomes (Lukong 2017).

Antigrowth signaling evasion

Cancer cells use a variety of complex tactics in their unrelenting quest for unrestricted proliferation, one of which centers upon their effective evasion of antigrowth signals. These signals, which are crucial for preserving the balance between cell division and growth, frequently depend on

the stability of tumor suppressor genes (Talib 2018). Tumor suppressor genes like BRCA1 and BRCA2, adenomatous polyposis coli, phosphatase and tensin homolog (PTEN), retinoblastoma (RB), and Wilms tumor 1 (WT1) are frequently at the forefront of mutations and inactivation within the genomic landscape of cancer (Yaswen et al.).

Cancer cells have diverse mechanisms to evade anti-growth signals. In addition to gene mutations, oncogene overexpression, and rewiring of signaling networks, it covers a maze of genetic and molecular changes. Cancer cells essentially take advantage of these abnormalities in genetics to tip the scales in favor of unrestrained cell division (Sever and Brugge 2015).

Clinically, the evasion of antigrowth signals has a significant impact on how cancer develops. It has a significant impact on the course of the disease, the prognosis of the patient, and the range of potential treatments. The development of individualized treatment plans, where the detection of active signaling pathways in a patient's cancer can direct therapeutic decisions, depends critically on our understanding of how cancer cells evade these important checkpoints (Krzyszczczyk et al. 2018).

Specific instances and examples demonstrate the real-world effects of antigrowth signals evasion to illuminate its effects. For instance, the development of targeted medicines like Poly (ADP-ribose) polymerase PARP inhibitors is necessary since the absence of functioning BRCA1 or BRCA2 genes in breast and ovarian cancer increases an individual's risk of developing cancer. These incidents serve as a reminder of the serious clinical ramifications that mutations in tumor suppressor genes can have (Gobet and Gilkes 2017).

A developing area of therapeutic innovation focuses on stopping the evasion of antigrowth signals in cancer. Scientists and medical professionals are continuously investigating methods to activate tumor suppressor genes, block oncogenes, or deactivate signaling pathways that promote unregulated proliferation. Dismantling the processes that enable cancer to resist the normal growth restraints would give sufferers new hope (Amin et al. 2015).

Cancer progression is characterized by antigrowth signaling evasion, which has clinical ramifications that affect cancer diagnosis, prognosis, and treatment options. Designing customized treatments that focus on the active signaling pathways in a patient's cancer requires an understanding of how cancer cells avoid antigrowth signals. Examples highlight the real-world therapeutic effects of tumor suppressor gene mutations, such as the creation of PARP medicines for malignancies with BRCA1 or BRCA2 mutations. Additionally, ongoing research projects constitute a developing frontier in therapeutic innovation as they aim to activate tumor suppressor genes, block oncogenes, and deactivate signaling pathways implicated in uncontrolled cell proliferation (Amin et al. 2015).

There is still much to learn about the relationship between garlic's bioactive components and the evasion of antigrowth signals. Garlic's multi-targeted strategy for influencing different cancer hallmarks raises the possibility that it may have consequences for preventing or dealing with

antigrowth signaling evasion. The capacity of garlic components to affect various aspects of cancer markers highlights its promise in comprehensive cancer care, even though the precise mechanisms are still being clarified. This link fits with our main goal, which is to examine how garlic attacks various aspects of cancer hallmarks. Future studies may also reveal more information about the interaction between garlic and antigrowth signaling evasion, potentially assisting in the creation of fresh anticancer tactics (Shirzad et al. 2011).

Resistance to apoptosis: targeting anti-growth signaling pathways.

By encouraging the synthesis of anti-apoptotic proteins and blocking or evading apoptosis through a variety of methods, cancer cells frequently display resistance to apoptosis, the normal process of programmed cell death. Changes to critical genes' activity and crucial pathways may be involved in this resistance.

Although there are numerous ways for cancer cells to prevent apoptosis, one noteworthy pathway entails the alteration of the p53 tumor suppressor gene and the overexpression of antiapoptotic regulators including Bcl-2 and Bcl-xL. Additionally, they upregulate proapoptotic proteins like Bax, Bim, and Puma, downregulate survival signals like Igf1/2, and block signals in the extrinsic ligand-induced death pathway (Hanahan and Weinberg 2011).

Garlic's role in targeting signaling pathways: balancing proliferative and anti-growth signaling

Anti-growth signaling pathways can be disregarded by cancer cells, allowing for unchecked expansion. TP53

and RB1 are two examples of tumor suppressor genes that are crucial for controlling cell growth and avoiding unchecked proliferation. These genes' normal function is disrupted by mutations or changes, allowing cancer cells to avoid anti-growth signals (Levine and Oren 2009).

Growth factor receptors or their production are frequently overexpressed in cancer cells. Due to this dysregulation, growth factor signaling pathways such as the PI3K/Akt and MAPK/ERK pathways are constantly stimulated, resulting in prolonged cell proliferation (Sliwkowski 2001).

According to research, garlic and its bioactive ingredients influence a number of these signaling pathways, which helps to reduce the growth and multiplication of cancer cells:

- **diallyl trisulfide (DATS):** Growth inhibition results from the diallyl trisulfide (DATS) treatment's enhancement of p53 translocation into the nucleus via ROS (Jiang et al. 2017). It stimulates the SAPK/JNK and p38 pathways while inhibiting the stress-activated protein kinase extracellular signal-regulated kinase (ERK)/MAPK pathway. Additionally, it stops colorectal tumor growth by activating the NF- κ B signaling system (Saud et al. 2016). Aside from that, DATS inhibits Cdk1 activity during G2-M cell-cycle arrest, which is connected to a temporal rise in cyclin B1 protein levels, a decline in Cdk1-cyclin B1 complex formation, Cdk1 inactivation through hyperphosphorylation, and a drop in Cdc25C protein levels (Knowles and Milner 2000).
- **S-allyl mercaptocysteine (SAMC):** increases p53 and p21 expression and limits the development of breast cancer cells by causing apoptosis and G0/G1 phase cell cycle arrest (Zhang et al. 2014).
- **Se-methyl-L-selenocysteine (MseC):** a garlic organoselenium compound reduces the growth of

Table 5. This table summarizes the mechanisms of anti-growth signaling evasion in cancer cells and the impacts of various garlic compounds, providing a clear and concise overview.

Mechanisms of anti-growth signaling evasion and garlic compounds	Cancer cell mechanism	Garlic compound impact	References
Anti-Apoptotic Proteins	- Promotion of anti-apoptotic proteins	- Impact on key pathways including p53 and Bcl-2/Bcl-xL	(Hanahan and Weinberg 2011)
Tumor Suppressor Gene Alteration	- Disruption of tumor suppressor genes (TP53, RB1)	- Modulation of signaling pathways impacted by gene alterations	(Oren and Rotter 2010)
Growth Factor Dysregulation	- Overproduction of growth factors and receptors	- Targeting of signaling pathways, including PI3K/Akt and MAPK/ERK	(Yarden and Sliwkowski 2001)
Diallyl Trisulfide (DATS)	- Promotion of p53 translocation and ROS mediation	- Inhibition of ERK/MAPK pathway and activation of SAPK/JNK and p38, NF- κ B modulation, Cdk1 inhibition	(Casey et al. 2015; Knowles and Milner 2000; Liu et al. 2017)
S-allyl Mercaptocysteine (SAMC)	- Induction of apoptosis and cell cycle arrest	- Increased p53 and p21 expression	(Asyifah et al. 2014)
Se-methyl-L-selenocysteine (MseC)	- Modulation of protein levels in growth factor pathways	- Protein level changes in ERK1/2, PI3K/Akt, p38, and JNK	(Tung et al. 2015)
Allicin	- Suppression of cervical carcinoma cell growth	- Downregulation of Nrf2, heme oxygenase 1, and PI3K/Akt signaling	(Gong et al. 2020; Zhang and Yang 2019)
Ze-ajoene	- Inhibition of colon cancer cell growth	- Decreased expression of catenin, c-Myc, and cyclin D1, modulation of Wnt/-catenin pathway	(Li et al. 2020)

colo205 cells by regulating the levels of the proteins ERK1/2 and PI3K/Akt and elevating the levels of p38 and JNK (Tung et al. 2015).

- **Allicin:** reduces the expression of heme oxygenase 1 and nuclear factor erythroid 2-related factor 2 (Nrf2), which inhibits the proliferation of cervical squamous cell carcinoma cells (SiHa). Additionally, it blocks the PI3K/Akt signaling pathway (phosphoinositide 3-kinase/protein kinase B) (Zhang and Yang 2019). In Hep 3B (p53 mutation) cell lines, alliin induces apoptosis through p53-mediated autophagy activation (Chu et al. 2013).
- **Z-ajoene:** By reducing the levels of catenin, c-Myc, and cyclin D1 expression in SW480 cells, another sulfur-containing component of garlic reduces the proliferation of colon cancer cells. Additionally, it raises catenin's level of Ser45 phosphorylation, which affects casein kinase 1 (CK1) activity and blocks the Wnt/-catenin signaling pathway (Li et al. 2020).

These studies demonstrate the potential of garlic and its components in balancing proliferative and anti-growth signals in signaling pathways, ultimately suppressing the growth and proliferation of cancer cells. The influence of garlic on these pathways offers a promising direction for additional study and the creation of brand-new cancer therapies.

Role of garlic in induction of apoptosis

The creation of treatments that support the efficient destruction of cancer cells through apoptosis has been a cornerstone and objective of clinical oncology for more than three decades. The members of the Bcl-2 family are essential for controlling apoptosis. Cancer cells may have imbalances in the expression or activity of Bcl-2 family members that are pro- and anti-apoptotic, which can disturb the apoptotic equilibrium and encourage cell survival (Strasser et al. 2011).

Caspases are a prime example of a crucial apoptotic signaling pathway component that can become mutated or altered, preventing cancer cells from going through with cell death (Fulda and Debatin 2006). The diverse intracellular second messengers known as calcium ions (Ca²⁺) control a variety of intricate cellular processes, including cell death.

Ca²⁺/calpain activation happens, for instance, when chemicals derived from garlic, such as DAS, DADS, and DATS, cause apoptosis in glioblastoma and neuroblastoma cells. The release of pro-apoptotic molecules like cytochrome c and Apaf-1, which activate caspase-9 and then caspase-3 and ultimately lead to apoptosis, are all triggered by an increase in the concentration of Ca²⁺ in the mitochondria ([Ca²⁺] mit). Thus, caspase-dependent apoptosis takes place (Das et al. 2007; Nakagawa et al. 2020).

Additionally, chemicals derived from garlic have proven to be effective at triggering apoptosis. For instance, DADS reduced proliferation by triggering apoptosis through an intrinsic signaling mechanism linked to upregulated ex-

pression of Bax, Bad, caspase-3, and caspase-9 and down-regulated expression of Bcl-2 (Talluri et al. 2017). By influencing NF- κ B, Thiocremone decreased the expression of the anti-apoptotic proteins Bcl-2, cIAP1/2, XIAP, and the cell cycle-regulating gene cyclin D1, while increasing the expression of the apoptotic regulatory proteins Bax, cleaved caspases 3, and cleaved PARP (Ban et al. 2007).

Additionally, combination therapy using alliin and 5-fluorouracil (5-FU), two substances derived from garlic, have demonstrated encouraging anticancer efficacy. These therapies shown their potential for improved cancer therapy by increasing ROS levels, lowering mitochondrial membrane potential, activating caspase-3 and PARP, and decreasing Bcl-2 expression (Zou et al. 2016).

Their multimodal approach to treating cancer relies heavily on the facilitation of apoptosis by garlic components. Sustained proliferative signaling and angiogenesis are two additional cancer hallmarks that are closely related to this process. Understanding these links helps to clarify the broad significance of garlic components in the treatment of cancer (Xiao et al. 2003).

Sustained proliferative signaling

The ability of cancer cells to constantly stimulate cell division and proliferation is characterized by the sustained proliferative signaling signature. Cancer frequently exhibits dysregulation of important signaling pathways, including TP53 and RB1. These pathways' changes or mutations can interfere with the systems that normally regulate cell development. Through their impact on the activation of apoptosis, garlic components interact with various signaling pathways to stop unchecked proliferation (Feitelson et al. 2015).

Angiogenesis

The process of angiogenesis, the creation of new blood vessels, is essential for the growth and spread of malignancies. Inducing apoptosis and angiogenesis go hand in hand because controlling the balance between cell survival and death has an impact on the angiogenic switch. Garlic compounds increase apoptosis, which has a direct effect on cancer cells, but they also have a secondary impact on angiogenesis by changing the pro-survival signaling pathways that are involved in both processes (Saman et al. 2020).

Investigating the interaction between persistent proliferative signaling, angiogenesis, and apoptotic induction highlights the holistic approach of garlic chemicals in cancer treatment. These chemicals offer a viable method to battle the complexity of cancer and improve treatment outcomes by concurrently tackling several disease hallmarks.

Role of garlic in replicative immortality

Cancer is characterized by replicative immortality, which is the unchecked capacity for cancer cells to divide end-

lessly. Due to the Hayflick limit, which restricts the number of times they may divide, normal human cells have a short lifespan. Cancerous cells can, however, get beyond this restriction and continue to multiply unabatedly. The preservation of telomeres, which are protective caps at the ends of chromosomes, is largely responsible for this ability. With each cell division, telomeres naturally shorten, which finally causes cellular senescence or death. Cancer cells turn on processes that either retain or lengthen their telomeres to combat this. This characteristic significantly contributes to the unchecked growth of malignancies and their ability to metastasize (Hanahan and Weinberg 2011).

According to research, garlic and its bioactive components may help fight cancer cells' ability to replicate indefinitely. It has been discovered that garlic extracts, such as diallyl trisulfide (DATS), affect telomerase activity. Telomerase is an enzyme that increases the length of telomeres by attaching repeating DNA sequences to the ends of chromosomes. A potential method to reduce cancer cells' capacity for replicative immortality is to inhibit the activity of the enzyme telomerase (Zeng et al. 2012).

Garlic components have also been related to the control of several pathways involved in replicative immortality. For example, some research indicates that garlic may affect the expression of crucial genes involved in telomere maintenance (Mármol et al. 2017).

Research on garlic's impact on replicative immortality is ongoing, and while the precise mechanisms are not yet fully understood, it provides encouraging insights into the potential of garlic to combat this characteristic of cancer. To develop tailored therapeutics using this knowledge, more research is required to better understand how garlic components affect replicative immortality.

Role of garlic in tumor dysregulated metabolism

One of the main characteristics of cancer is tumor dysregulated metabolism, in which cancer cells alter metabolic pathways to create the nutrients and enzymes necessary for their unabated proliferation and survival. Changes in procedures like aerobic glycolysis, the Krebs cycle, and oxidative phosphorylation are examples of this characteristic (Kalyanaraman 2017). Diallyl disulfide (DADS), one of the bioactive components of garlic, has been researched for its potential to inhibit aerobic glycolysis in cancer cells. Research on DADS-treated MGC-803 human gastric cancer cells produced several interesting findings. The therapy reduced lactate production, upregulated AMP-activated protein kinase alpha1 (AMPK) expression and increased the amount of glucose in the medium. Since AMPK1 is frequently overexpressed in many cancer cells, inhibiting it causes apoptosis, which makes DADS a possible choice for addressing abnormal glucose metabolism in cancer cells (Zhang et al. 2020).

Additionally, the effects of DADS on the glucose metabolism of breast cancer stem cells (BCSCs) have been investigated. It was shown that DADS preferentially targets pyruvate kinase isoform M2 (PKM2), a crucial enzyme

involved in glycolysis, to block glucose metabolism in BCSCs. This inhibition demonstrates the ability of garlic components to interfere with the metabolic processes of cancer cells (Zhang et al. 2020).

The effects of allicin, a different sulfur-containing component of garlic, on post-translational thiol-modification in human Jurkat T-cells have been studied. Enolase-1 (ENO1), an enzyme in the glycolytic pathway that changes 2-phosphoglycerate into phosphoenolpyruvate, was S-thioallylated by allicin. Enolase activity was reduced as a result of this change, suggesting that allicin, a chemical found in garlic, may interfere with important enzymes involved in the metabolism of cancer cells (Martin C. H. Gruhlke et al. 2019).

Research is currently being done to determine the precise processes by which garlic components interfere with cancer cell proliferation and dysregulated metabolism in tumors. However, a few proposed pathways and ways that garlic compounds might function include as follows:

- **Key enzyme inhibition:** It has been demonstrated that chemicals in garlic, such as diallyl disulfide (DADS) and allicin, inhibit the activity of important enzymes in metabolic pathways. For instance, AMP-activated protein kinase alpha1 (AMPK1), which is involved in glycolysis, has been discovered to be inhibited by DADS. Garlic chemicals can interfere with the metabolic processes that cancer cells rely on to produce energy by blocking these enzymes (Song et al. 2021).
- **Changes in glucose metabolism:** According to certain research, garlic components may influence how cancer cells use glucose. For instance, it has been demonstrated that DADS increases the medium's glucose concentration while reducing lactate generation. The Warburg effect, a metabolic change frequently seen in cancer cells that depend on glycolysis for energy production, is interfered with by this change in glucose metabolism (Liberti and Locasale 2016).
- **Targeting cancer stem cells:** The effects of garlic components, such as DADS, on cancer stem cells have also been studied. These cells frequently play a role in the development and upkeep of tumors. DADS has been reported to block pyruvate kinase isoform M2 (PKM2), which in turn prevents glucose metabolism in breast cancer stem cells. Garlic chemicals have the ability to slow tumor development and progression by interfering with the metabolic processes in cancer stem cells (Mitra et al. 2022).
- **Modification of enzyme activity:** Allicin, another component of garlic, has been found to alter the activity of glycolysis-related enzymes. Enolase-1 (ENO1) was specifically S-thioallylated by allicin, which reduced the enzyme's activity. The ability of the cancer cell to efficiently digest glucose is compromised by this interference with crucial glycolysis enzymes (M. C. H. Gruhlke et al. 2019).

Reduction of Survival Signals: Garlic chemicals may also block insulin-like growth factor 1 and 2 (Igf1/2),

which are survival signals in cancer cells. Garlic components can encourage apoptosis (programmed cell death) and prevent unchecked cell development by decreasing these signals (Chen et al. 2017).

Role of garlic in Tumor-promoting inflammation

Rudolf Virchow made the first allusion to a potential link between inflammation and tumor in the 19th century after observing inflammatory mediators (leukocytes) in the tumor microenvironment (Coussens and Werb 2002). Before or after tumor initiation, inflammation can take place in the tumor microenvironment. Inflammation supports all stages of tumor growth and aids in the development of cancer in tumor-promoting inflammation. Early stages of tumor formation may see the effects of inflammation, or later phases such as metastasis or late stages may not see any effects (Greten and Grivennikov 2019).

DNA damage is one possible factor that connects cancer and inflammation. Numerous mechanisms, including DNA repair and tolerance pathways, cell cycle arrest mechanisms, as well as intra- and extracellular signaling pathways, may mediate the relationship between DNA damage and inflammation. DNA repair and the response to oxidative stress are highly coordinated in healthy cells. DNA repair mechanisms are crucial for cellular survival because they prevent mutations by repairing DNA damage (Kay et al. 2019).

Tumorigenesis, proliferation, and migration may be influenced by factors that interfere with these systems by preventing repair or initiating the damage. Oxygen and nitrogen species (RONS) are produced during inflammation to combat infections and support tissue repair. On the other hand, these organisms have the ability to interact with DNA bases, damage them, interfere with repair processes, and reduce the efficiency of those processes. Nitric oxide has a function in repair disruption as it has the potential to disrupt DNA repair processes and result in mistakes (Kay et al. 2019).

Additionally, some cytokines, such as IL-22, activate the DNA damage response (DDR) gene to reduce genotoxicity, which is a contributing factor in inflammation (Gronke et al. 2019). Since inflammation and the development of tumors are strongly correlated, inflammation is being examined as a potential target for improving anti-cancer treatment (Zhao et al. 2021).

A study comparing the chemoprotective properties of spirulina and garlic against hepatocellular cancer was carried out in 2022 on male rats. This study demonstrated that garlic has a hepatoprotective effect due to its antioxidant activity, as it caused a significant decrease in the activity of malondialdehyde (MDA), an oxidative stress marker, compared to that in the HCC group, and as it sequenced elevated levels of superoxide dismutase (SOD) and catalase (CAT) (Zhao et al. 2021).

SOD catalyzes the disproportionation of two superoxide species to yield H₂O and O₂, and CAT enhances the

conversion of H₂O₂ to H₂O by assisting antioxidant enzymes (Vásquez-Garzón et al. 2009). Garlic's ability to reduce the expression of genes linked to cancer growth and inflammation is the second component that contributes to its hepatoprotective effects. According to their findings, garlic has the ability to reduce the production of the genes for TGF-1, nitric oxide synthase, tumor necrosis factor, and interleukin-6 (Abouzed et al. 2022).

Another study examined the effects of the organic sulfides contained in garlic—DADS, DATS, and DTS—on the gene expression profiling of human hepatocellular carcinoma cells (HepG2), which are cells that produce liver tumors. This study found that DTS decreased the expression of pro-inflammatory cytokines in macrophages, and among 33 inflammatory markers, IL-1, IL-2, IL-6, IL-12, TNF-, and Eotaxin were six that underwent significant alteration. We may argue that garlic administration may be helpful in controlling liver cell cancer based on the two studies stated above and the evidence that shows the majority of HCC cases are caused by liver inflammation (Lv et al. 2021). A randomized study on breast cancer-bearing female mice was carried out in 2022 to demonstrate the effects of garlic consumption and endurance training on the levels of pro- and anti-inflammatory cytokines in the serum. The results showed that eight weeks of garlic administration and endurance training decreased serum levels of IL-6, IL-8, and IL-17, increased levels of IL-10, and inhibited NF- κ B, which prevented the transcription of the genes for TNF-, IL-12, IL-8, IL-6, IL-1B, and IL-17 cytokines, which are essential pro-inflammatory mediators. The effect of allicin, a garlic extract, on glioblastoma multiforme (GBM) with human cytomegalovirus (HCMV) infection was demonstrated in a separate investigation. The release of IL-6 and IFN- γ was found to have significantly decreased. They recommend allicin as a cutting-edge treatment option for GBM (Enayatjazi et al. 2022).

Garlic and its bioactive components, such as allicin and diallyl trisulfide (DATS), work through complex pathways to reduce inflammation. For instance, allicin can prevent nuclear factor-kappa B (NF- κ B), a crucial regulator of inflammatory reactions, from becoming activated. Allicin dampens the entire inflammatory cascade by inhibiting NF- κ B activation, which in turn decreases the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules (Shang et al. 2019).

DATS, a different component of garlic, affects mitogen-activated protein kinases (MAPKs) like p38, JNK, and ERK1/2 to target inflammatory mediators. This interference disrupts the inflammatory signaling pathways and prevents the generation of inflammatory cytokines (You et al. 2013).

The anti-inflammatory effects of garlic have significant clinical significance, particularly when it comes to cancer. Tumor genesis and progression are intimately linked to inflammation. Garlic may affect cancer formation, progression, and therapeutic response by reducing inflammation. The use of garlic or garlic supplements in cancer treatment plans to control the inflammatory tumor microenvironment is gaining popularity (Schäfer and Kaschula 2014).

Table 6. Garlic's role in targeting tumor-promoting inflammation.

Key point	Description
Inflammation and Tumor Development	Inflammation within the tumor microenvironment can support all stages of tumor formation and progression, and it may be present at any stage.
DNA Damage and Inflammation	DNA damage and inflammation are intricately linked. Factors that interfere with DNA repair mechanisms or trigger damage can contribute to tumorigenesis.
Cytokines and DNA Damage Response	Some cytokines, like IL-22, can stimulate the DNA damage response (DDR) genes to mitigate genotoxicity caused by inflammation.
Garlic's Anti-Inflammatory Effect	Garlic exhibits an anti-inflammatory effect by reducing oxidative stress, modulating antioxidant enzymes, and downregulating genes associated with inflammation and cancer development.
Study on Hepatocellular Carcinoma (HCC)	A study showed garlic's hepatoprotective effect against HCC, attributed to its antioxidant activity and gene expression downregulation (TNF- α , IL-6, nitric oxide synthase, TGF- β 1).
Impact of Diallyl Tetrasulfide (DTS)	Research on DTS suggests it inhibits the expression of pro-inflammatory cytokines in macrophages, potentially regulating liver cell cancer.
Breast Cancer Study	A study involving garlic consumption and endurance training reduced pro-inflammatory cytokines (IL-6, IL-8, IL-17) and inhibited NF- κ B, which regulates gene transcription of pro-inflammatory cytokines.
Impact of Allicin on GBM	Allicin, an extract of garlic, showed promise in reducing the release of pro-inflammatory cytokines (IL-6 and IFN- β) in glioblastoma multiforme (GBM), making it a potential therapeutic option.

This table provides an overview of how garlic targets tumor-promoting inflammation and its associated effects.

Role of garlic in angiogenesis inhibition

According to Adair and Montani (2010), angiogenesis is a difficult process that creates new blood vessels from pre-existing ones in order to provide the tissues with enough oxygen and blood (Adair and Montani 2010). It is regarded as an essential mechanism for the development and spread of tumors (Carmeliet and Jain 2011). Additionally, because it serves as a pathway for metastatic cells to travel to other organs, neovascularization is a necessary condition for the spread of cancer cells (Aventurado et al. 2020). Tumors can only grow to a maximum size of 1–2 mm without being stimulated to generate new blood vessels, and they are unable to metastasize (Dijkgraaf and Boerman 2009).

One important regulator of this biological process is VEGF.

Angiogenesis takes an appealing emphasis in cancer therapy because of its critical role in tumor growth (Yang et al. 2020). Veterini et al. found that allicin, a chemical found in garlic, had anti-angiogenic properties through their computer investigation. This is explained by its capacity to inhibit breast cancer cells' production of vascular endothelial growth factor receptor-2 (VEGFR-2) (Veterini et al. 2021). Additionally, through preventing VEGF and subsequently angiogenesis, the combination of garlic and lemon aqueous extracts had a suppressive effect on EMT6/P breast cancer cells in BALB/c mice (Talib 2017).

In a 2015 *in vivo* investigation, it was found that Diallyl trisulfide, a component of garlic, inhibits the migration, invasion, and angiogenesis of human colon cancer HT-29 cells as well as the formation of mice xenograft tumors. DATS was found to dramatically reduce VEGF in HT29 cells and human umbilical vein endothelial cells (HUVEC) in this study. Which suggests that VEGF is crucial to DATS's anti-angiogenic impact. Additionally, the chorioallantois membrane (CAM) tests showed that DATS decreased the number of blood vessels and hindered tubule formation in HUVEC. Additionally, it was

shown that HT-29 cell tumor xenografts had far less blood vessels than normal, which explains how DATS's ability to block angiogenesis may have contributed to the reduction in proliferation. They came to the conclusion that DATS is a strong angiogenesis inhibitor and is thought to have promise for the treatment of human colon cancer and other conditions dependent on angiogenesis (Lai et al. 2015).

Role of garlic in preventing tissue Invasion and Metastasis

Organosulfur compounds found in garlic, especially diallyl disulfide (DADS), are the main compounds responsible for its carcinogenic activity. The exact molecular mechanism of cell migration inhibition is not completely understood yet. The inhibition of metalloproteinases expression in the extracellular matrix is supposed to be a mechanism of cell migration inhibition (Lin et al. 2002), the down-regulation of the expression of PI3K, Ras, MEKK3, MKK7, ERK1/2, JNK1/2, and p38, are thought to inhibit the expression of MMP-2, -7, and -9 which are involved in the metastasis and invasion of cancer. In addition, the inhibition of proteins found in tight junctions can be a way of cell motility and invasion inhibition.

The DADS compounds found in garlic can lower the levels of claudin proteins which are an important elements in tight junctions responsible for paracellular transport, this lowering can increase the tightness of junctions that inhibit motility and invasion (Shin et al. 2010). The up-regulation of transcription factor 3 (ATF3) mRNA is thought to have a role in metastasis inhibition, where it can induce genes responsible for some proteins like maspin and plasminogen activator inhibitor (PAI-1), and repress genes responsible for metastatic elements like metastasis-associated protein MTA-1 and b-catenin (Bottone Jr et al. 2005).

Diallyl trisulfide (DATS) compounds also have an inhibitory effect of metastasis through modulation of MMP9 and E-cadherin protein expressions. DATS showed an increment in E-cadherin expression level and a decrement

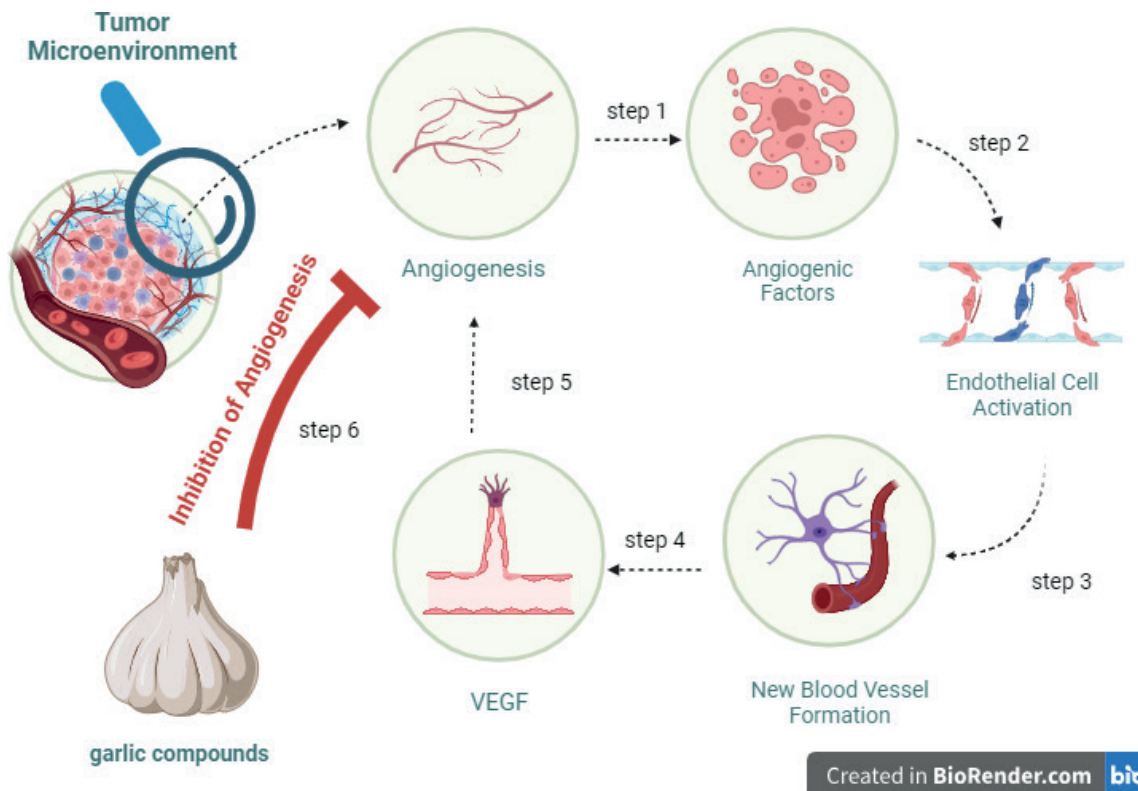


Figure 2. Angiogenesis processes and garlic compound interference (created by: BioRender.com). Fig. 2 provides an overview of the intricate process of angiogenesis within the tumor microenvironment and demonstrates how garlic compounds interfere with this critical pathway. Tumor Microenvironment: On the left, the tumor microenvironment is depicted as the origin of angiogenesis.

in MMP-9 expression level, which will modulate the cell migration.(Jiang et al. 2017)

Alllicin was thought to prevent metastasis in MCF-7 (an ER- α positive breast cancer cell line) through altering the function of vascular cell adhesion molecule-1 (VCAM-1), that has an important role in cell migration and metastasis. Alllicin has inhibited TNF- α -induced VCAM-1 protein expression and the suggested mechanism is that alllicin strongly suppressed TNF- α -induced activation of ERK $\frac{1}{2}$ and NF- κ B signaling pathways(Lee et al. 2015).

Angiogenesis Pathway: A branching pathway illustrates the sequential steps in angiogenesis. It starts with the release of angiogenic factors from cells within the tumor microenvironment. These factors trigger endothelial cell activation, leading to the formation of new blood vessels, a process facilitated by VEGF.

Garlic Compound Interference: Running alongside the angiogenesis pathway, garlic compounds intervene in the process. They disrupt angiogenesis at various stages, ultimately inhibiting the formation of new blood vessels.

Inhibition of Angiogenesis: Garlic compounds interfere with the angiogenesis process, making it a potential therapeutic approach to hinder tumor growth and metastasis.

Role of garlic in tumor associated immune evasion

Tumor cells use a variety of techniques to elude immune monitoring, which might hinder the body's built-in can-

cer protection. These evasion strategies involve modifying immune checkpoint pathways, producing immunosuppressive cells, and preventing the invasion of essential immune components (Talib et al. 2022).

• Cancer cells' immunosuppressive mechanisms

Cancer cells use a variety of strategies to evade the immune system's close attention. These tactics involve modifying immunological checkpoint pathways, creating immunosuppressive cells, and weakening the immune components required for a successful antitumor response. For instance, cancer cells might hinder essential immune cells from penetrating the tumor microenvironment, which would decrease the immune system's capacity to identify and eradicate cancerous cells (Talib et al. 2022).

• The Immunomodulatory Potential of Garlic

Numerous studies demonstrating garlic's capacity to elicit immunological responses have established its immunomodulatory potential. It increases the production of cytokines including interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma) as well as T-lymphocyte blastogenesis, natural killer (NK) cells, dendritic cell activity, phagocytosis, and cytokines like tumor necrosis factor-alpha and interferon-gamma. According to Venkatesh (2018), the organosulfur compounds, immunomodulatory proteins (mainly lectins), other water-soluble fructans, and fructosyl arginine present in garlic are responsible for these immunomodulatory effects (Venkatesh 2018).

• Impact on T-Lymphocytes and Infiltration

Garlic is effective at increasing the infiltration of T-lymphocytes into the tumor microenvironment, with a focus on CD8+ cytolytic T-cells, according to studies (Ebrahimi et al. 2013). The increased presence of these CD8+ cells within tumors has a promising immunomodulatory effect as they play a crucial role in tumor rejection. Additionally, altering the CD4/CD8 ratio can be a successful immunomodulatory approach for malignancies (Hilders et al. 1994).

• Stimulation of IFN- γ Production

Garlic's immunomodulatory effects include a notable rise in splenocyte IFN- production in addition to boosting lymphocyte infiltration (Tabari and Ebrahimpour 2014). IFN- is an important cytokine that is involved in immune responses and has been linked to anticancer properties. Garlic may have an anticancer effect via increasing IFN-production, which can counteract immune system dysfunction and tumor resistance.

T-cell levels reduce during tumor progression, which assures that these cells contribute to tumor rejection, studies

showed that the presence of T-helper (CD4+) and cytolytic (CD8+) cells are required for tumor rejection. Lymphocytes that migrate into the tumor site (tumor infiltrating lymphocytes) represent an enriched group of cells having a specific effect to the tumor (Hilders et al. 1994). Then, any treatment that can modulate the infiltrating T-lymphocytes, as well as the CD4/CD8 ratio assumed to be a good immunomodulatory agents in tumors.

As a result, garlic is a good candidate for preventing tumor-associated immune evasion due to its immunomodulatory effects. It has the potential to improve the results of cancer therapy and strengthen the immune response against cancer due to its capacity to increase lymphocyte infiltration and activate IFN-production.

Conclusion

A traditional food and medicine for millennia, garlic presents a potential approach to the treatment of several

Table 7. Garlic compounds and their concentrations in targeting cancer hallmarks.

Cancer hallmark	Concentration used	Garlic compound	Type of cells	Outcomes	Reference
Genomic Instability	100–400 $\mu\text{mol/l}$ of garlic		Human liver	improved cell viability by preventing the synthesis of reactive oxygen species and the cellular loss of glutathione.	(Chiu et al. 2016)
			cancer cells (HepG2)		
	300 $\mu\text{g/mL}$ of garlic + 26,800 $\mu\text{g/mL}$ of vitamin E		Human lung cells (WI-38)	p53 and Bcl2-expressions were reduced, whereas Bax-expression was augmented.	(Ali 2018)
	0.25, 1, and 2 mg/mL of garlic		<i>Drosophila melanogaster</i>	Garlic caused extension of lifespan in <i>D. melanogaster</i>	
Replicative immortality	0.016, 0.05, and 0.1 mg/mL	Allicin	Gastric cancer adenocarcinoma cells (SGC-7901)	Allicin inhibited telomerase activity in a dose-dependent and time-dependent manner	(Li Sun and Xu Wang 2003)
			Human leukemia cell line (HL-60)	Reduction in TP1 mRNA and telomerase hTERT levels was observed after 24 hr treatment.	(Ye et al. 2005)
	10 $\mu\text{mol/L}$	Z-ajoene	Human liver	A remarkable drop in the expression of cyclinD1, D2, D3 and E.	(Sengupta et al. 2017)
	10–100 μM	Allicin	cancer cells (HepG2)	reduced cell growth and increased apoptosis	(Chu et al. 2013)
			Cervical cancer cells (SiHa)		
Proliferative signaling	25–200 μM	Allicin	Lung cancer cells (A549)	decreased cell migration and proliferation	(Chu et al. 2013)
Resistance to apoptosis	5–40 μM	DADS	Colorectal cancer cells (HT-29)	induced cell cycle arrest and apoptosis	(Talluri et al. 2017)
Tumor promoting inflammation.	10–50 μM	Allicin	Glioblastoma cells (U87MG)	reduced release of pro-inflammatory cytokines	(Enayatjazi et al. 2022)
Angiogenesis	10–20 μM	DATS	Human colon cancer cells (HT-29)	inhibited angiogenesis and reduced tumor growth	(Lai et al. 2015)
Immune evasion	2–6 μM	SAMC	Breast carcinoma cells (MDA-MB-231)	Induced apoptosis and cell cycle arrest	(Zhang et al. 2014)
Induction of apoptosis	10–20 μM (DAS); 1–20 μM (DADS); 1–10 μM (DATS)	DAS,	Colon cancer cells (HT-29), human umbilical vein endothelial cells (HUVEC), and mouse xenograft models	Inhibited angiogenesis and reduced tumor growth	(Chu et al. 2013; Lai et al. 2015; Zhang et al. 2020)
		DADS,			
		DATS,			
Preventing metastasis	10–20 μM	Allicin	Glioblastoma cells (GBM)	reduced production of inflammatory cytokines	(Enayatjazi et al. 2022)
Tumor dysregulated metabolism	20–100 μM (MGC-803); 50 μM (Breast cancer stem cells)	DADS	Human gastric cancer cells (MGC-803), breast cancer stem cells	Suppressed glycolysis and glucose metabolism	(Zhang et al. 2020)

This table provides an overview of various garlic compounds and the concentrations used to target different cancer hallmarks. These compounds have been studied in various cellular models, and the outcomes of their application are summarized. The reference column cites the sources for more detailed information on each study.

Table 8. Roles of garlic compounds in cancer control.

Aspects of cancer control	Role of garlic
Tumor Associated Evasion	Enhances intra-tumor CD8+ lymphocyte infiltration and IFN- γ production (Ebrahimi et al. 2013; Venkatesh 2018).
Angiogenesis Inhibition	Inhibits angiogenesis by targeting VEGF and inflammatory mediators (Lai et al. 2015; Talib 2017; Veterini et al. 2021).
Tumor-Promoting Inflammation	Mitigates inflammation by downregulating pro-inflammatory cytokines (Abouzed et al. 2022; Zhao et al. 2021).
Tumor Dysregulated Metabolism	Modifies metabolic pathways to hinder cancer cell proliferation (Zhang et al. 2020).
Replicative Immortality	Inhibits telomerase and cyclin-dependent kinases, disrupting replicative immortality.
Induction of Apoptosis	Promotes cancer cell death and apoptosis through various pathways (Fulda and Debatin 2006; Zou et al. 2016)
Preventing Tissue Invasion and Metastasis	Restricts metastasis and cell migration by regulating critical proteins (Ebrahimi et al. 2013; Jennifer Kay et al. 2019).

The several functions of garlic in cancer prevention are detailed in this table, which focuses on various markers of cancer initiation and progression. The sources illustrate the scientific evidence in favor of garlic components' possible medicinal uses.

cancers. Garlic's varied role in cancer prevention has been thoroughly examined, indicating its potential as a potent anticancer agent.

Phytoconstituents with anti-cancer properties: Among the many phytochemicals found in garlic, allicin, SAC, SAMC, DAS, DADS, and DATS have all shown significant anti-cancer effects in a variety of cancer models. Their mechanisms of action include angiogenic pathway modulation, cell cycle arrest, and induction of cancer cell death.

Breast and colon cancer prevention: By preventing angiogenesis and inflammation, garlic shows noteworthy effectiveness in the treatment of breast and colon cancer. Garlic chemicals interfere with the mechanisms that promote cancer progression by blocking VEGF and important inflammatory mediators. Garlic components also control proteins involved in cell motility, tight junctions, and transcription factors, which reduce metastasis and cell migration. Garlic also increases CD8+ lymphocyte intra-tumor infiltration and stimulates splenic IFN- γ production, which reduces its potential for tumor immune evasion.

Replicative immortality is prevented: The ability of garlic to suppress telomerase and cyclin-dependent kinases (CDKs) has been demonstrated. Garlic is an attractive possibility for obstructing this essential characteristic of

cancer because these enzymes play critical roles in the replicative immortality of cancer cells.

Molecular protection and metabolic dysregulation: Compounds produced from garlic have been found to be powerful regulators of the metabolism of cancer cells. Garlic also has Genoprotective qualities since it reduces DNA damage brought on by genotoxic substances. Garlic demonstrates its capacity to repair DNA damage when combined with vitamin E.

Changing important genes and signaling networks: The anticancer effects of garlic and its active metabolites are mediated through modulation of multiple genes and existing signaling networks. These include the Wnt/-catenin signaling network, the JNK signaling pathway, the PI3K/Akt and p38 MAPK signaling pathways, the Chk1/CDC25C/cyclin B1 signaling pathway, p53-mediated autophagy, the ERK signaling pathway, the NF-B signaling pathway, and the NF-B signaling pathway.

In conclusion, garlic's diverse range of cancer-management potential makes it an important natural resource in the fight against cancer. It holds significant promise for improved cancer treatment tactics thanks to its variety of modes of action, making it a promising choice for future study and therapeutic development.

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