

Garlic-Derived Quorum Sensing Inhibitors: A Novel Strategy Against Fungal Resistance

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Abstract: In recent years, the incidence of fungal infections has been rising annually, especially among immunocompromised populations, posing a significant challenge to public health. Although antifungal medications provide some relief, the escalating problem of resistance sharply curtails their effectiveness, presenting an urgent clinical dilemma that demands immediate attention. Research has shown that fungal resistance is closely related to quorum sensing (QS), and QS inhibitors (QSIs) are considered an effective solution to this issue. Garlic, as a natural QSI, has demonstrated significant effects in inhibiting fungal growth, preventing biofilm formation, enhancing immunity, and combating resistance. This study explores the potential of garlic in mitigating fungal drug resistance and identifies its key role in inhibiting the QS mechanism, these findings offer a new perspective for the treatment of fungal infections, especially in addressing the increasingly severe problem of resistance. However, the clinical application of garlic still faces several challenges, such as ensuring the standardization of active ingredient extraction, as well as issues of safety and stability. Future research should focus on the QS mechanism and promote interdisciplinary collaboration to develop more natural, effective, and safe QSI drugs like garlic, while actively conducting clinical trials to validate their efficacy and safety. Additionally, incorporating advanced technologies such as nanotechnology to enhance drug stability and targeting, provide a more comprehensive strategy for the treatment of fungal infections. Overall, Our study provides scientific evidence supporting the potential of garlic as a novel antifungal treatment and lays the groundwork for the development of future natural QSIs for therapeutic use. It offers new insights, particularly for the treatment of immunocompromised populations and drug-resistant fungal strains.

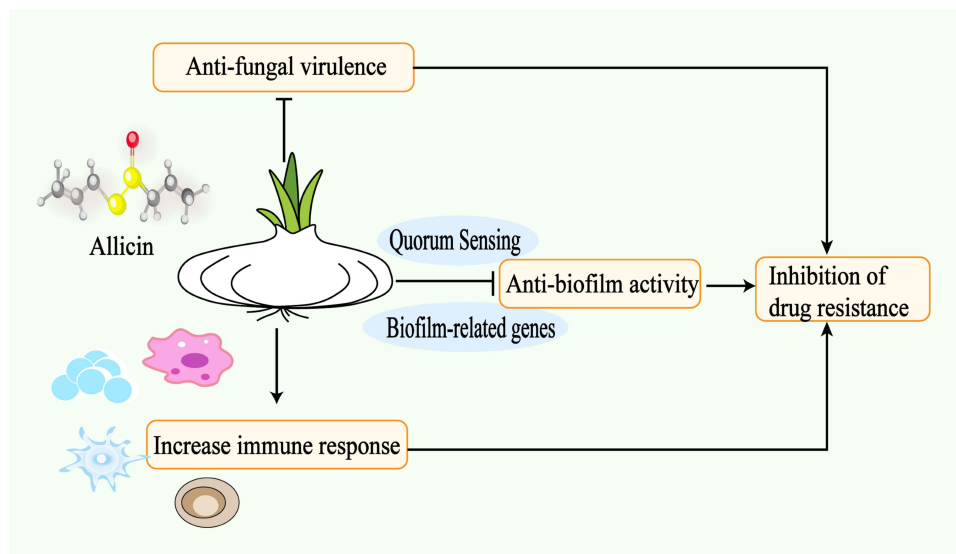
Keywords: fungal infection, drug resistance, garlic, quorum sensing, quorum sensing inhibitors

Introduction

Fungal infections refer to a range of diseases caused by fungi invading the human body. It is estimated that there are between 2.2 and 3.8 million different fungal species in the natural world.¹ While the majority of these are beneficial to humans, a few can cause various diseases and pose severe threats to public health.² Fungal infections are an urgent and often overlooked global health risk.³ Incomplete statistics suggest that approximately one billion people globally are affected by fungal infections, resulting in more than 1.6 million deaths each year,⁴ with the incidence rising annually.⁵ Invasive fungal infections are the predominant cause of these fatalities,⁶ exhibiting mortality rates as high as 90%,⁷ especially among individuals with weakened immune systems. These infections are primarily linked to pathogens such as *Candida*, *Cryptococcus*, and *Aspergillus*.⁸ Currently, there are five principal categories of antifungal drugs:⁹ (1) azoles, (2) echinocandins, (3) polyenes, (4) allylamines, and (5) pyrimidine analogs. Despite these medications can improve symptoms in some patients, they are limited by several factors, including adverse reactions, narrow therapeutic scope, limited targets, and resistance issues among fungi. Particularly, the issue of drug resistance is recognized as an urgent public health crisis that needs immediate attention.¹⁰ There is a crucial need for the development of rapid and sustainable



Graphical Abstract



treatment options, necessitating a focused effort on the research and development of new medications that offer broader potential applications, especially to combat the escalating problem of resistance.

However, developing safe and effective antifungal drugs poses a formidable challenge. This involves addressing widespread epidemics caused by fungal infections, managing the emergence and spread of drug-resistant strains due to medication misuse, and tackling complications arising from host immune deficiencies.^{11,12} Natural compounds and bioactive products, especially those derived from plants, have garnered significant attention in the treatment of infectious diseases, due to their stability, efficiency, broad-spectrum activity, and harmlessness to health.^{13,14} This focus has opened up new perspectives for the development of antifungal drugs.

Garlic (*Allium sativum* L.), widely utilized in traditional medicine, is frequently selected as a primary treatment for preventing and managing various epidemic diseases.¹⁵ It demonstrates broad-spectrum antibacterial and antifungal properties.¹⁶ Contemporary research indicates that extracts from garlic are effective in inhibiting the growth of a range of fungi, including species from the genera *Candida*, *Torulopsis*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, *Microsporium*, and *Rhodotorula*.¹⁷ Additionally, when combined with other antifungal agents, garlic can significantly enhance the antimicrobial effectiveness of these treatments.¹⁸ The antifungal effects of garlic are primarily attributed to its multiple actions, including inhibiting fungal growth, preventing biofilm formation, boosting immunity, and combating drug resistance, particularly its notable effectiveness against resistant strains.¹⁹ However, the specific mechanisms through which garlic counters fungal resistance and its potential for treating fungal infections still require further research and clarification.

Quorum Sensing (QS), a widely studied microbial communication mechanism, plays a pivotal role in both fungal ecology and the resistance to antifungal drugs. This process affects various aspects of fungal behavior, such as growth, biofilm formation, the expression of virulence factors, and the production of secondary metabolites.^{20–22} It is important to note that reducing gene expression regulated by Quorum Sensing can suppress the formation of fungal biofilms, thereby addressing drug resistance issues. This approach is known as Quorum Sensing Inhibition (QSI).²³ Increasingly, scholars believe that targeting QS is an effective strategy for treating fungal infections.^{24,25} However, synthetic QSIs are limited in clinical application due to their issues with selectivity, cytotoxicity, and instability, prompting more researchers to consider natural products as potential sources for robust and non-toxic new QSIs.²⁶ For example, a study by Vadakkan et al²⁷ showed that while *desmodium gangeticum* root extract does not have direct antimicrobial activity, it

effectively reduces the virulence of *chromobacterium violaceum* by inhibiting QS, confirming that natural products can effectively target QS to suppress microbial infections.

Among various natural products, garlic has attracted significant attention due to its broad-spectrum antifungal effects and potential QS inhibition. A study by Rasmussen et al²⁸ suggested that garlic extract is an “ideal” QSI, as it not only downregulates the expression of virulence factors but also enhances the sensitivity of biofilms to conventional antibiotics. Moreover, garlic’s widespread availability, low toxicity, and cost-effectiveness further enhance its clinical applicability.²⁹ The QS inhibitory effect of garlic could be a key mechanism underlying its antifungal activity, however, no studies have explored this perspective in depth. This study initially discusses the antimicrobial components and pharmacological effects of garlic, as well as its effects on the QS system, before delving deeper into the antifungal mechanisms of garlic and its potential clinical applications. We discovered that garlic, a natural plant, not only inhibits fungal growth effectively but also boosts the body’s immune response. Importantly, it significantly suppresses fungal resistance, a property likely closely linked to garlic’s modulation of the QS system. Therefore, focusing on the QS system to investigate garlic’s therapeutic effects against fungal infections is crucial. Targeting QS offers fresh perspectives on addressing fungal drug resistance, opening new avenues for the treatment of fungal infections.

Heading

Chemical Composition and Antimicrobial Activity of Garlic

Garlic, a shallow-rooted vegetable plant from the *Allium* genus of the Amaryllidaceae family,³⁰ is extensively utilized in both culinary and medicinal contexts,¹⁷ often described as a panacea.³¹ Pharmacological studies have revealed that garlic is rich in multiple bioactive compounds,³² including allicin (diallyl thiosulfinate), garlic phenols, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allyl cysteine (Figure 1). These compounds exhibit a range of biological activities such as antifungal, antioxidant, anti-inflammatory, antiproliferative, antiviral, immunomodulatory, lipid-lowering, and anti-tumor effects.^{33,34}

Garlic is hailed as a “natural broad-spectrum antimicrobial”,¹⁶ with its antimicrobial activity primarily attributed to allicin.³⁵ The chemical structure of allicin is $\text{CH}_2=\text{CH}-\text{CH}_2-\text{S}(=\text{O})-\text{S}-\text{CH}_2-\text{CH}=\text{CH}_2$. Allicin is an active component formed by the decomposition of alliin under the catalysis of alliinase³⁶ (Figure 2). It displays considerable antibacterial, antifungal, antiparasitic, and antiviral properties,³⁷ and also has the capability to effectively alleviate inflammatory responses.³⁸

Studies have shown that fungi are highly susceptible to allicin.³⁹ Both allicin and garlic extracts have been demonstrated to effectively kill various fungi, including *Trichophyton rubrum*,⁴⁰ *Aspergillus versicolor*,⁴¹ *Candida*

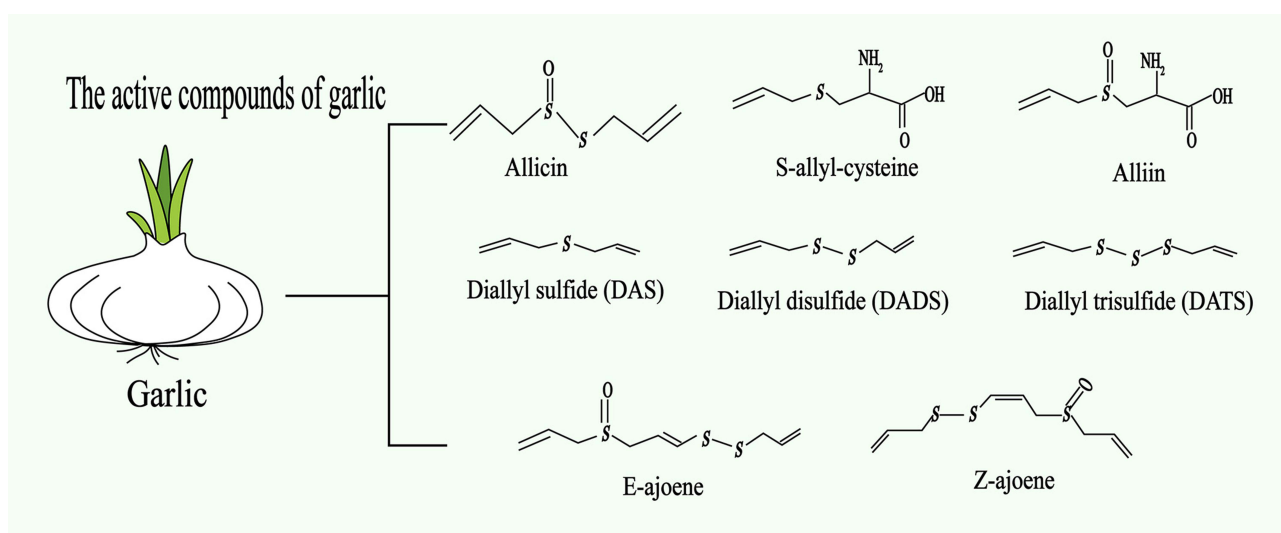


Figure 1 The chemical composition of garlic.

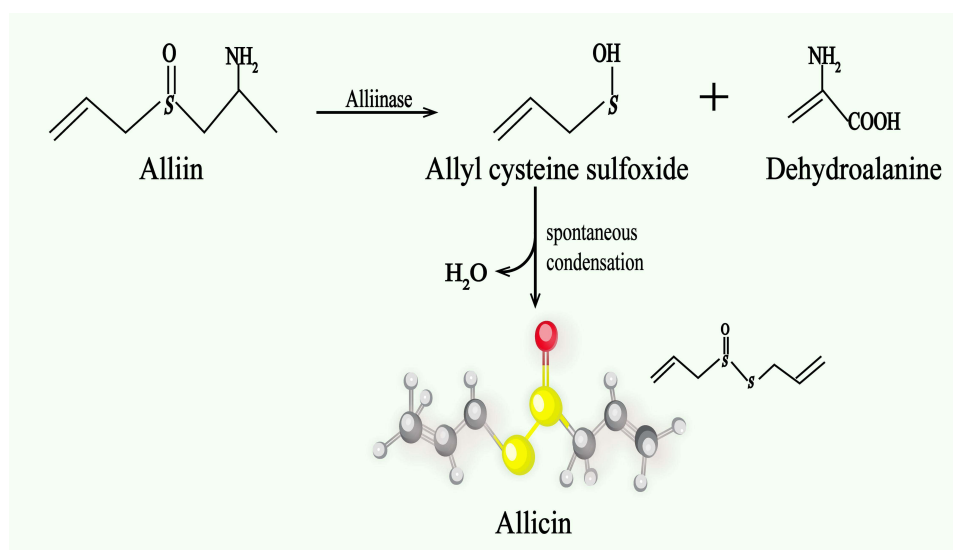


Figure 2 The conversion of alliin to allicin in garlic starts with a sulfur-containing amino acid called alliin. When garlic is minced or crushed, alliin interacts with an enzyme present in garlic known as alliinase. This interaction initiates a chemical reaction that transforms alliin into allicin, a compound that not only suppresses fungal growth but also demonstrates antibacterial and anti-inflammatory properties.

albicans,⁴² *Sporothrix schenckii*,⁴³ *Phytophthora capsici*,³¹ *Phytophthora nicotianae*,⁴⁴ *Penicillium funiculosum*⁴⁵ and *Meyerozyma guilliermondii*⁴⁶ (Table 1). Garlic is now extensively employed in the management of a variety of fungal-related diseases such as skin fungal infections,⁴⁷ denture stomatitis (DS),⁴⁸ *Fusarium keratitis*,⁴⁹ and fungal pulmonary diseases.⁵⁰

A New Strategy for Treating Fungal Infections: QS in Fungal Species

QS was first introduced and defined by Fuqua and others in 1994 in bacteria,⁵⁴ QS is a widespread cell-to-cell communication mechanism that is prevalent among various microbes, characterized by the release of signaling molecules known as Quorum Sensing Molecules (QSMs). These molecules coordinate microbial metabolism and gene expression in a synchronous manner.⁵⁵ QS is involved in a variety of biological behaviors, including virulence factor production, motility, symbiosis, adhesion, the development of antibiotic resistance, sporulation, and biofilm creation.^{56,57} The role of QS in bacteria is widely acknowledged by researchers,⁵⁸ and it has been recognized as a potential therapeutic target for

Table 1 Inhibitory Effects of Active Ingredients of Garlic on Different Fungi (Partial Overview)

Fungal Species	MIC/($\mu\text{g}\cdot\text{mL}^{-1}$)	Active Compound	Reference
<i>Candida albicans</i>	0.35	Garlic oil	[42]
<i>Cryptococcus neoformans</i>	0.79–3.13	Allicin	[51]
<i>Trichophyton rubrum</i>	1.57–6.25		
<i>Trichophyton mentagrophytes</i>	0.78–6.25		
<i>Pseudomonas putida</i>	6.25	Garlic oil	[45]
<i>Trichophyton rubrum</i>	40	Garlic ethanol extract	[40]
<i>C. glabrata</i>	30–70	<i>Allium sativum</i> agglutinin (ASA)	[52]
<i>C. auris</i>			
<i>Verticillium dahliae</i>	39–195	Allicin	[31]
<i>Sporothrix schenckii</i>	620	Garlic aqueous extract	[43]
	2500	Garlic oil extract	
<i>Aspergillus niger</i>	<400	Garlic aqueous extract	[53]
<i>Aspergillus fumigatus</i>	3600		

bacterial infections such as *Pseudomonas aeruginosa*⁵⁹ and *Staphylococcus aureus*.⁶⁰ However, its role in fungi remains poorly understood.

Already in 1955, Allen⁶¹ observed that in the *Puccinia graminis*, the density of the population affects the fungal morphology and suppresses spore germination. Kügler and et al⁶² were the first to associate fungi with the term “quorum sensing”, unveiling the QS phenomenon in fungi. The signaling mechanism is remarkably similar to that of bacteria and primarily involves four steps:⁶³ (1) the generation of signaling molecules; (2) secretion of signal molecules; (3) recognition by receptors when the concentration of signal molecules reaches a threshold; (4) initiation of target gene expression. Studies have demonstrated that a range of fungi, including *Candida albicans*,⁶⁴ *Cryptococcus neoformans*,⁵⁵ *Saccharomyces cerevisiae*,⁶⁵ *Neurospora crassa*,⁶⁶ and *Ophiostoma floccosum*,⁶⁷ are influenced by quorum sensing mechanisms.

Fungi regulate various crucial biological processes such as pathogenicity, resistance, morphological development, and secondary metabolism through the production of QSMs, which are influenced by community density.⁶⁸ At present, the quorum sensing system in fungi has confirmed several QSMs such as farnesol,⁶⁹ aromatic alcohols,⁷⁰ tyrosol,⁶⁴ tryptophol,²³ and phenylethanol.⁷¹ These molecules are pivotal in regulating the formation of fungal mycelia, morphogenesis, and biofilms,^{72,73} with farnesol being the earliest identified⁷⁴ (Figure 3). According to research by Wongsuk et al, QSMs not only influence spore germination but also initiate programmed cell death or apoptosis, playing a role in fungal pathogenicity.²⁴

Albuquerque et al⁷² argue that targeting QS could enhance the development of antifungal therapies. Quorum quenching (QQ) disrupts the QS systems among microbes, significantly reducing or even completely suppressing the production of microbial virulence factors, including biofilm formation.⁷⁵ QSIs that exhibit QQ properties are increasingly being discovered and have emerged as a key area in microbial management.⁷⁶ QSIs offer an effective solution to alleviate microbial resistance compared to traditional antimicrobial drugs. QSIs operate through three main mechanisms:⁷⁷ First, blocking the synthesis of QS signaling molecules; Second, inhibiting the intercellular exchange and transport of QS signals; and third, suppressing the detection and response to QS signals. Although extensive research has been conducted

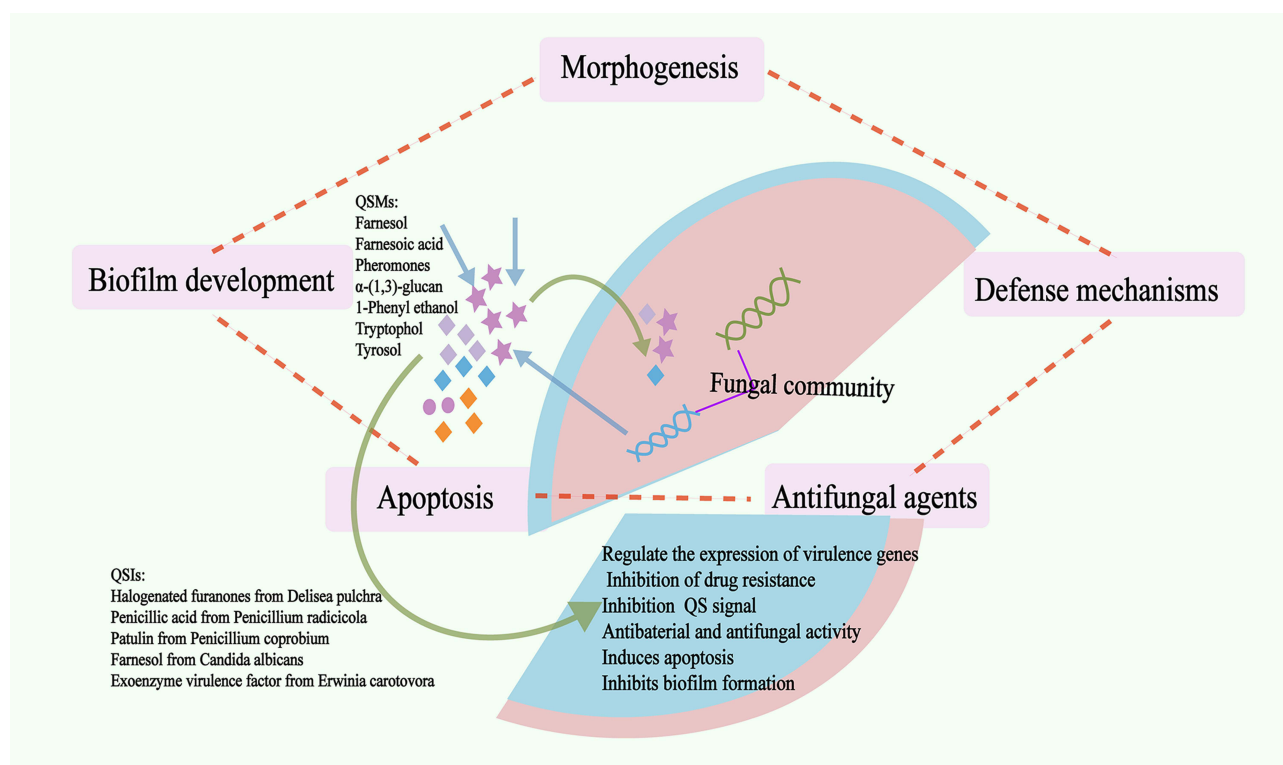


Figure 3 The production of quorum-sensing molecules and quorum-sensing inhibitors and their roles in different cell types.

on QSIs, the stability and effectiveness of artificially synthesized QSIs are suboptimal. Moreover, their potential toxicity restricts their application. Therefore, seeking potent, natural, and non-toxic new QSIs from natural products appears to be a promising direction for future efforts.

Potential Mechanisms of Garlic in Treating Fungal Infections

QS is a mechanism by which microbes coordinate behavior through the production and detection of signaling molecules. It plays a role in many critical biological processes, including biofilm maturation, immune evasion, and drug tolerance, providing microbial populations with enhanced survival rates.²⁰ Garlic, a natural compound with dual roles in food and medicine, is recognized as an ideal QSI.²⁸ It combats various fungal species by inhibiting fungal growth, exhibiting anti-biofilm properties, boosting immune responses, and reducing the development of resistance, thus effectively curbing fungal infections (Figure 4). The crucial aspect of garlic's anti-resistance properties is its QSI effect.

Anti-Fungal Growth

Garlic has demonstrated antifungal properties against a range of fungal genera. Research by Yamada et al has shown that allicin, a compound in garlic, is effective in vitro against genera such as *Candida*, *Cryptococcus*, *Trichophyton*, *Epidermophyton*, and *Microsporum*, with inhibitory concentrations ranging from approximately 1.57 to 6.25 $\mu\text{g}/\text{mL}$.⁵¹ Allicin, the primary antimicrobial agent found in garlic, displays biological activity across microbial, plant, and mammalian cells. It acts in a dose-dependent fashion to inhibit fungal growth or directly kill cells.⁷⁸

Allicin is highly hydrophobic, allowing it to rapidly diffuse across various phospholipid membranes.⁷⁹ This property allows allicin to easily traverse cell membranes, be taken up by exposed cells, and directly interact with molecules within the organism.⁸⁰ When pathogenic microorganisms come into contact with allicin, it alters their cell membrane permeability, which disrupts the structural integrity of the cells and ultimately leads to cell death.⁸¹ Allicin's primary mechanism for inhibiting microbial growth involves its molecules penetrating the cell membrane, where its oxygen atoms react with the thiol groups in cysteine or deactivate thiol-based enzymes within the pathogens.⁸² Furthermore,

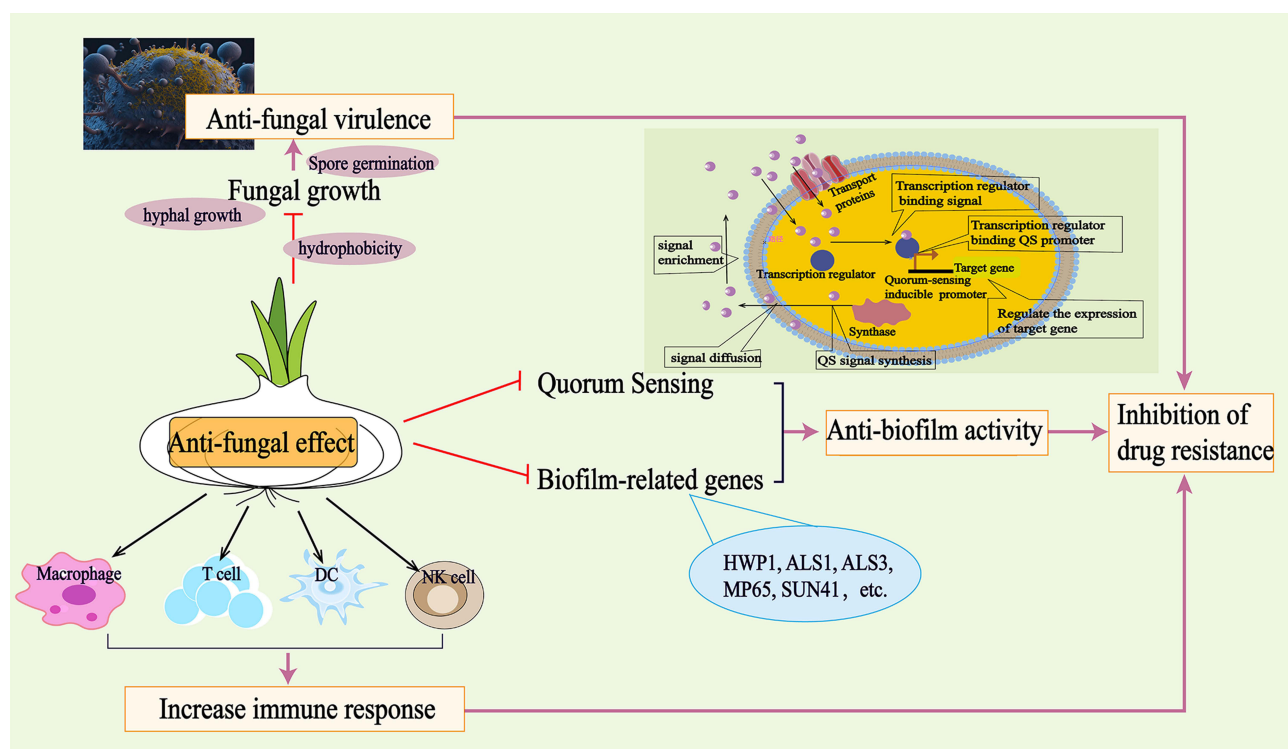


Figure 4 Potential Mechanisms of Garlic in the Treatment of Fungal Infections.

allicin's S-(O)-S groups react with -SH group-containing proteins in pathogens, forming mixed disulfides that inhibit microbial growth.⁸³

Moreover, allicin inhibits spore germination and mycelial growth under both in vivo and in vitro conditions.³⁹ Extracts from fresh garlic reduce the expression of SIR2 in *Candida albicans*,^{84,85} a gene essential for its mycelial growth.⁸⁶ Allicin's ability to inhibit the development of *Candida albicans* mycelia matches or surpasses that of fluconazole.⁸⁵ Studies have shown that *Trichophyton rubrum* treated with allicin or garlic extract exhibits cytoplasmic disintegration/degradation, with damage to the cell walls and membranes, leading to mycelial fragmentation.⁸⁷

Anti-Biofilm Activity

Garlic's anti-biofilm activity is widely acknowledged, with its effectiveness likely stemming from the disruption of quorum sensing mechanisms. Biofilms are resilient communities of microbes⁸⁸ that strongly adhere to microbial surfaces and each other, shielding the microbes from antibiotics and the immune system.^{89,90} They are a principal factor in the development of antibiotic resistance during microbial infection treatments⁹¹ and contribute to persistent⁹² and recurrent infections.⁹³ Interrupting any phase of the biofilm formation process, whether attachment, maturation, or dispersal, can significantly diminish microbial virulence.⁹⁴

Biofilms are primarily composed of microbial cells and the extracellular polymeric substances (EPS) they secrete.⁹⁵ EPS includes extracellular polysaccharides that provide cohesion and adhesion sites, proteins that serve as carbon and energy sources, and extracellular DNA (eDNA) that facilitates the dissemination of resistance genes.⁹⁶ The secretion of EPS encourages individual bacteria to exhibit behaviors that either aid or harm nearby cells, and influences the evolutionary dynamics of the biofilm to balance individual and community interests.⁹⁷ EPS forms the biofilm matrix, which protects microorganisms from the host's immune system and antifungal agents, playing a crucial role in the development of resistance.⁹⁸ According to the research by Xavier et al,⁹⁹ EPS secretion typically increases in mixed bacterial populations, strengthening the biofilm's structure and stability. Therefore, inhibiting EPS secretion can effectively prevent the formation of biofilms.¹⁰⁰

The secretion of EPS is regulated by QS, which enables microorganisms to toggle EPS production on or off.¹⁰¹ QS is pivotal in biofilm formation,^{102,103} and pathogenic bacteria within biofilms can leverage QS to activate virulence factors, both of which contribute to the development of resistance.¹⁰⁴ QQ can inhibit microbial biofilm formation by disrupting QS signals, thereby decreasing the potential for resistance development.¹⁰⁵ As a quorum-sensing inhibitor, garlic not only effectively diminishes microbial pathogenicity²⁸ but also inhibits biofilm formation to combat microbial resistance.¹⁰⁶ The anti-biofilm efficacy of garlic has been demonstrated in several microorganisms, including *Candida albicans*,¹⁰⁷ *Escherichia coli*,¹⁰⁸ and *Proteus mirabilis*.¹⁰⁹ Garlic has shown positive antibacterial effects through QSI in vitro, in animal models, and in clinical trials.²⁰ This points to a promising new therapeutic approach for tackling antibiotic resistance. Research by Li et al¹¹⁰ has demonstrated that garlic can increase the sensitivity of multiple drug-resistant strains, including *Candida albicans* and methicillin-resistant *Staphylococcus aureus* (MRSA), to antibiotics.

Additionally, allicin, a compound in garlic, can exert anti-biofilm effects by downregulating genes associated with biofilm formation. Research by Xiong et al¹¹¹ demonstrated that allicin reduces the expression of key biofilm-related genes in *Candida albicans*, including HWP1, ALS1, ALS3, MP65, and SUN41, effectively inhibiting biofilm formation. Furthermore, the earlier allicin is introduced, the more significant its biofilm-inhibiting effects. In conclusion, garlic exhibits significant anti-biofilm effects through its QSI activity and gene regulatory mechanisms. This effectiveness has been validated in fungi, indicating substantial potential for the clinical treatment of fungal infections.

Enhancing Immune Response

Immunity plays a vital role in protecting humans against fungal diseases.¹¹² When the immune system is significantly compromised, fungi, as opportunistic pathogens, can cause severe infections, especially invasive fungal infections.¹¹³ Enhancing immune responses is critical in the treatment of fungal infections.^{114,115} Garlic, recognized for stabilizing the immune system, typically exerts beneficial effects on immune functions.^{116,117} It primarily boosts immunity by activating various immune cells, including macrophages, lymphocytes, natural killer (NK) cells, dendritic cells, and eosinophils.¹¹⁸

The existing research indicates that Aged Garlic Extract (AGE) promotes the proliferation of $\gamma\delta$ -T cells and NK cells, thereby improving the host's immune cell function;¹¹⁹ specifically, the protein component F4 within AGE has been identified as an effective immune booster;¹¹⁷ other chemical components in garlic also help enhance the functions of macrophages and T lymphocytes.¹²⁰ Additionally, experimental research by Zamani et al has demonstrated that a water-soluble extract of garlic enhances the proliferation of lymphocytes in the thymus and spleen of rats.¹²¹ This further confirms the potential of garlic to modulate immune responses.

Suppressing Resistance

In recent years, the extensive use of antifungal drugs has significantly heightened resistance among fungi.¹²² This resistance manifests as increased minimum inhibitory concentrations (MICs), which results in reduced drug efficacy and an inability to effectively suppress infections.¹²³ It represents one of the primary causes of persistent fungal infections¹²⁴ and has emerged as a major medical challenge.¹²⁵

Choo et al¹⁸ have identified that using allicin in combination with other antimicrobial drugs offers a potent strategy to combat increasing antimicrobial resistance. When allicin is paired with azole compounds such as fluconazole or ketoconazole, it generates a synergistic effect that lowers the MICs of fungal strains, thereby reducing their resistance.¹²⁶ This demonstrates that the active ingredients in garlic are effective in curbing fungal resistance. The inhibitory effect is multifaceted (Figure 4): 1. Allicin can directly influence fungal growth, reducing their exposure and selective pressure, thus lowering the likelihood of resistance development. 2. Allicin boosts the body's immune response, which in turn aids in more effective combat against infections, indirectly mitigating the emergence of resistance. According to Bicer et al,¹²⁷ exosomes that possess immunomodulatory characteristics can counteract fungal resistance. 3. Most importantly, allicin significantly inhibits fungal biofilms. The effectiveness of garlic in inhibiting biofilm formation is now widely recognized and is likely achieved through QQ mechanisms. Biofilm formation alters the sensitivity of fungi to antifungal drugs¹²⁸ and is considered an ideal target for antifungal therapy, offering a promising solution to the problem of drug resistance.^{129,130} EPS, a major component of biofilms, is considered crucial in the development of drug resistance.¹³¹ Notably, QS, an intercellular communication system, regulates EPS secretion and activates virulence, thereby contributing to resistance.^{101,104} Thus, garlic's ability to inhibit QS may be key to overcoming fungal drug resistance.

From Bench to Bedside: The Antifungal Effects of Garlic

Garlic and its derivatives have demonstrated impressive antifungal effects in both laboratory research and clinical applications. These effects not only inhibit fungal growth but also aid in preventing the development of fungal resistance.

Laboratory studies have shown that the active compounds in garlic can inhibit fungal infections at multiple levels, including spore germination, biofilm growth, cell wall synthesis, metabolism, and oxidative stress. Additionally, these compounds exhibit synergistic effects when combined with antifungal drugs. For example, Schier et al¹³² found that both allicin solution and vapor can inhibit the germination of Mucorales fungi, with half-maximal effective concentrations (EC50) being 25–72 times lower than those for fungal spores. Allicin also demonstrated synergistic effects with amphotericin B (ampB), and in direct contact, allicin was even more effective than ampB at inhibiting spore germination. Research by Yang et al¹³³ demonstrated that allicin effectively inhibits the growth of *T. asahii* planktonic cells and biofilm cells significantly; In vivo, allicin increased the average survival time of mice with systemic trichosporonosis and decreased the fungal burden in their tissues; Electron microscopy revealed that allicin causes significant morphological damage to *T. asahii* cells, including structural disorganization and irregular plasma membranes. These findings indicate that allicin disrupts fungal processes on multiple levels, including the cell membrane, cell wall, glucose metabolism, and oxidative stress response.

Recently, an increasing number of researchers have explored the potential application of garlic in treating various fungal infections in clinical studies. For example, Schier et al⁵⁰ simulated airflow conditions in the human lung in vitro and discovered that allicin can inhibit fungal spore germination through direct contact or vapor transmission. These findings suggest that allicin could be a promising candidate for treating fungal infections in the lungs and upper respiratory tract. Watson et al¹³⁴ have used garlic tablets to treat vulvovaginal candidiasis (VVC), with some patients

experiencing significant improvement. Their in-depth research revealed that treatment with fresh garlic extract and pure allicin led to the downregulation of the SIR2 gene expression in all strains, and pure allicin treatment also inhibited ECE1 expression. These findings suggest that garlic and its derivatives may alleviate VVC symptoms by downregulating key virulence genes.¹³⁵

Summary and Discussion

Over the past few decades, the risk of fungal infections has significantly increased due to the widespread use of antimicrobial drugs, the routine application of immunosuppressive therapy following organ transplants, and cancer treatments involving radiation and chemotherapy.¹³⁶ Furthermore, fungal resistance has significantly escalated on a global scale.¹³⁷ However, current antifungal therapies are limited and have not effectively tackled the issue of resistance.¹³⁸ This poses severe challenges to antifungal treatment, making it a critical clinical problem that urgently needs to be addressed.

Targeting quorum sensing is considered a highly promising therapeutic strategy. QS is a communication mechanism among microorganisms, where a single microbe can possess multiple QS systems and produce various QS signal molecules to coordinate or regulate their biological functions.¹³⁹ QS regulates the production and expression of fungal virulence factors, biofilm formation, and drug resistance.^{21,140,141} Disrupting QS can inhibit hyphal formation, reduce the expression of fungal virulence factors, and prevent biofilm formation, effectively decreasing resistance.¹⁴² However, the development of QSI drugs still faces significant challenges.

Garlic is considered an “ideal” natural QSI drug and has been widely used to treat infectious diseases for centuries due to its medicinal properties. Both laboratory and clinical studies have demonstrated garlic’s significant antifungal efficacy. This antimicrobial effect is achieved through various mechanisms, including inhibiting fungal growth, exhibiting anti-biofilm activity, enhancing immune responses, and reducing resistance. Most notably, garlic’s ability to combat resistance offers an effective solution to this issue, with the core mechanism being the inhibition of the QS system.

Additionally, garlic’s chemical composition is complex, and its processing methods can influence the efficacy and safety of its active components.^{143,144} Therefore, finding effective ways to preserve garlic’s antifungal properties has become a crucial area of research. Currently, scientists are actively investigating how to combine garlic’s active components with modern technology to enhance its antimicrobial efficacy. Silver nanoparticles (AgNPs) are a rapid, environmentally friendly, and sustainable synthesis method that exhibits exceptional antibacterial properties.¹⁴⁵ Notably, when used in combination with garlic extract.¹⁴⁶ For example, A study by Vijayakumar et al¹⁴⁷ revealed that using garlic clove extract with silver nanoparticles (G-AgNPs) significantly enhanced antibacterial and anti-biofilm activities against key clinical pathogens, including MRSA and *Pseudomonas aeruginosa*. Robles-Martínez et al¹⁴⁰ discovered that the combination of allicin and G-AgNPs effectively inhibited the growth of *Trichophyton rubrum*. Remarkably, even at a low concentration of 0.4 µg/mL, allicin was able to completely inhibit the growth of this fungus. Additionally, Tomsik et al¹⁴⁸ utilized spray congealing technology to encapsulate wild garlic extract, significantly enhancing the solubility, bioavailability, and stability of garlic’s active components without compromising their antimicrobial properties. These findings underscore the potential of garlic in the antimicrobial field, particularly when combined with modern technology, which can greatly enhance its effects. Building on the research of Vijayakumar,¹⁴⁷ Tomsik,¹⁴⁸ and others, developing more straightforward and cost-effective methods to improve garlic’s bioavailability seems to be a promising direction for future efforts.

In conclusion, QS is a critical target in fungal infections, closely related to biofilm formation and the development of drug resistance. Targeting QS can effectively address the challenge of fungal resistance. Garlic, a natural QSI, has been widely recognized for its therapeutic effects on fungal infections. It effectively inhibits fungal resistance, and its mechanism of action is closely related to QS. These discoveries provide novel and valuable insights into the treatment and prognosis of fungal infections. However, the clinical application of garlic still faces some challenges. Firstly, there may be variability in the potency of bioactive compounds, the composition of garlic extracts can differ significantly between batches, and different application methods may influence their clinical efficacy. In addition, although natural QSIs are generally considered to have low toxicity, their potential toxicity with long-term use remains to be further assessed. Therefore, optimizing the activity, stability, and safety of natural QSIs, as well as ensuring their consistency in clinical applications, are critical issues that need to be addressed in future research. Future studies should focus on the following directions: 1) Investigating the specific mechanisms through which garlic modulates QS; 2) Conducting

clinical trials to evaluate the effectiveness and safety of garlic in treating various refractory fungal infections; 3) Optimizing garlic-derived formulations by utilizing modern technologies such as AgNPs and spray-drying techniques to improve drug release efficiency and enhance antifungal activity; 4) Promoting interdisciplinary collaboration across fields such as biology, chemistry, and medicine to explore and develop more efficient QSIs, providing new strategies and broader applications for antifungal therapy.

Consent for Publication

All authors have consented to the publication.

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Disclosure

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