Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

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

Na Li[1,2], Junli Zhang[3], Fei Yu[1,2], Fanghang Ye[1,2], Wanying Tan[4], Liyuan Hao[1,2], Shenghao Li[1,2], Jiali Deng[1,2], Xiaoyu Hu[2]

[1]Department of Clinical Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China; [2]Department of Infectious Diseases, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China; [3]Jiangsu Provincial Hospital of Traditional Chinese Medicine, Nanjing, People's Republic of China; [4]Center for Infectious Diseases, West China Hospital, Sichuan University, Chengdu, People's Republic of China

Correspondence: Xiaoyu Hu, Email TCMxiaoyuhu@aliyun.com

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.

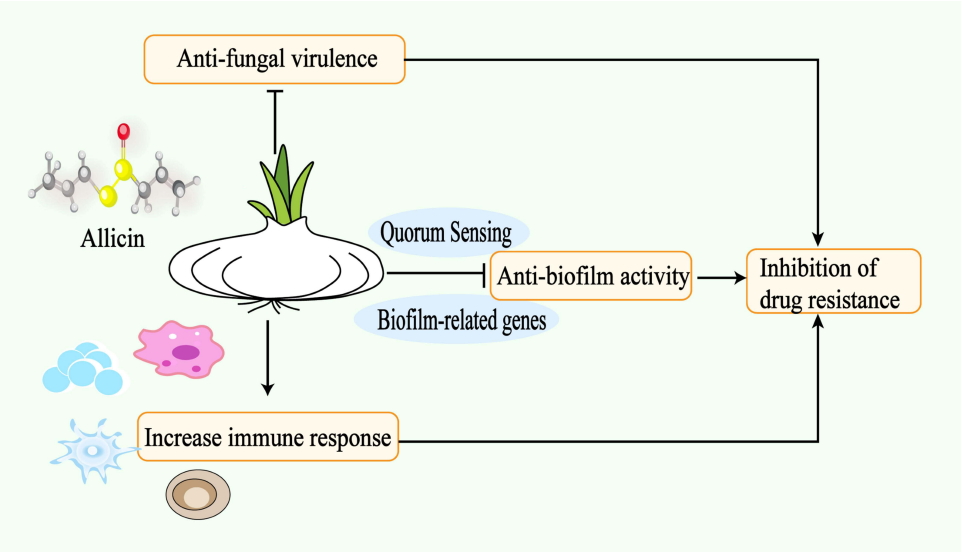
Keywords: fungal infection, drug resistance, garlic, quorum sensing, quorum sensing inhibitors

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

Received: 28 October 2024
Accepted: 11 December 2024
Published: 28 December 2024

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, Microsporum, 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 al[27] 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 al[28] 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 CH2=CH-CH_2-S(=O)-S-CH_2-CH=CH_2. Allicin is an active component formed by the decomposition of alliin under the catalysis of alliinase[36] (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

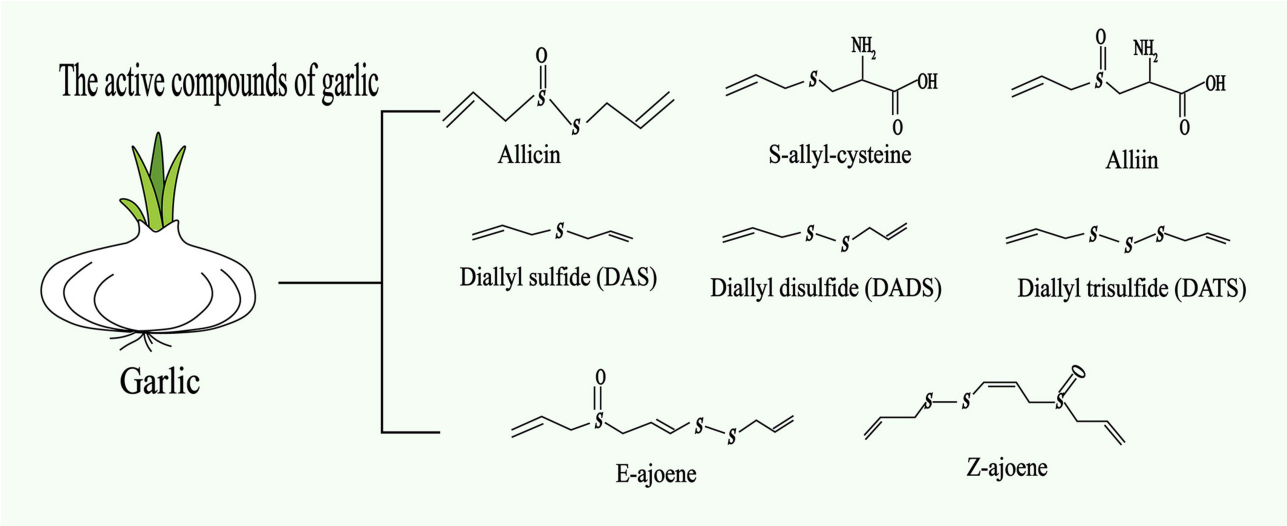


Figure 1 The chemical composition of garlic.

https://doi.org/10.2147/DDDT.S503302

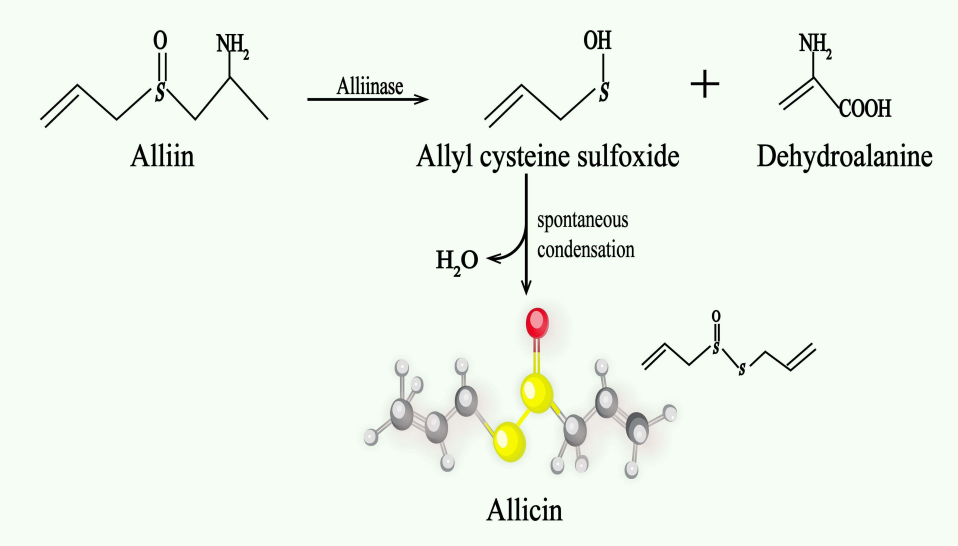


Figure 2 The conversion of alliin to allicin in garlic starts with a sulfur-containing amino acid called alliin. When garlic is minced or crushed, alliin interacts with an enzyme present in garlic known as alliinase. This interaction initiates a chemical reaction that transforms alliin into allicin, 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/(μg·mL−1)	Active Compound	Reference
Candida albicans	0. 35	Garlic oil	[42]
Cryptococcus neoformans	0. 79–3. 13	Allicin	[51]
Trichophyton rubrum	1. 57–6. 25		
Trichophyton mentagrophytes	0. 78–6. 25		
Pseudomonas putida	6. 25	Garlic oil	[45]
Trichophyton rubrum	40	Garlic ethanol extract	[40]
C. glabrata	30–70	Allium sativum agglutinin (ASA)	[52]
C. auris			
Verticillium dahliae	39–195	Allicin	[31]
Sporothrix schenckii	620	Garlic aqueous extract	[43]
	2500	Garlic oil extract	
Aspergillus niger	<400	Garlic aqueous extract	[53]
Aspergillus fumigatus	3600		

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

Already in 1955, Allen[61] observed that in the Puccinia graminis, the density of the population affects the fungal morphology and suppresses spore germination. Kügler and et al[62] 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 identified[74] (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 al[72] 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

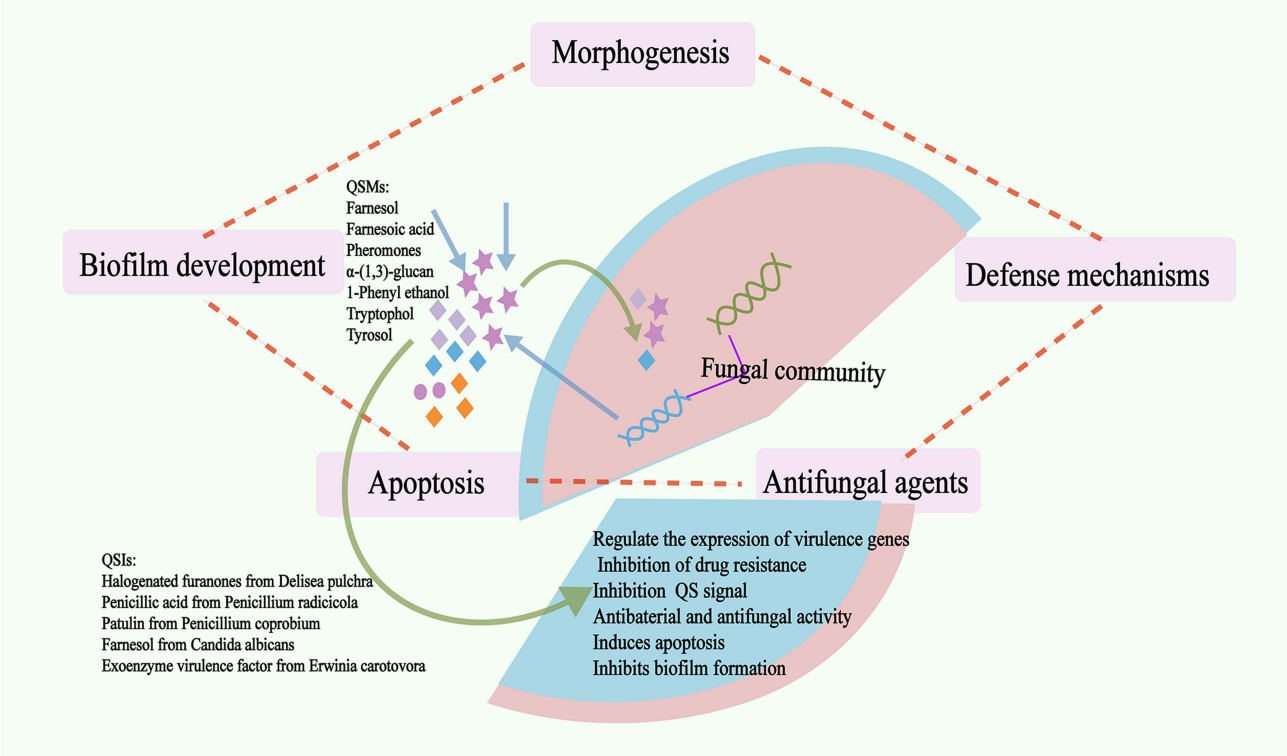


Figure 3 The production of quorum-sensing molecules and quorum-sensing inhibitors and their roles in different cell types.

https://doi.org/10.2147/DDDT.S503302

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 μg/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,

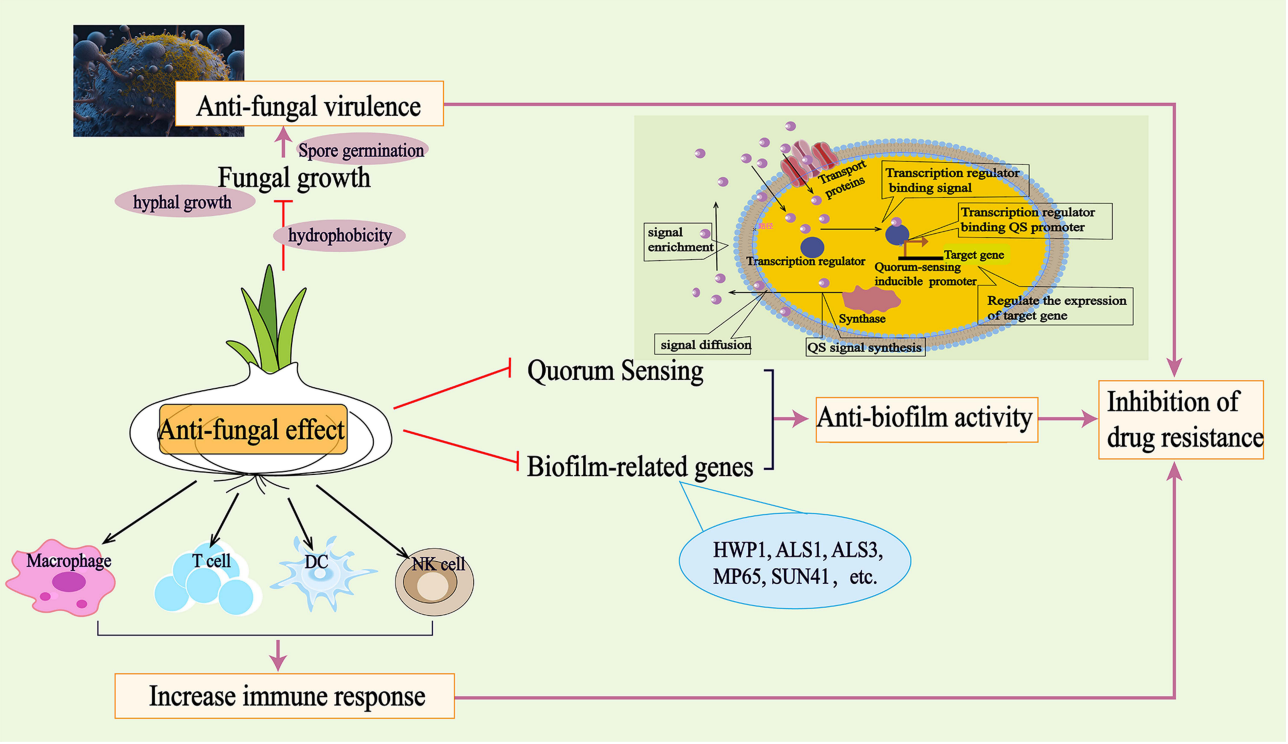


Figure 4 Potential Mechanisms of Garlic in the Treatment of Fungal Infections.

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

Moreover, allicin 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 microbes[88] 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 treatments[91] and contribute to persistent[92] 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 pathogenicity[28] 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 al[110] 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 al[111] 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 γδ-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 infections[124] and has emerged as a major medical challenge.[125]

Choo et al[18] 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 drugs[128] 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 al[132] 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 al[133] 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 al[50] 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 al[134] 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 al[147] 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 al[40] 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 al[148] 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.

Funding

The present study was financially supported by the National Natural Science Foundation of China (No. 81973840), Sichuan Provincial Administration of Traditional Chinese Medicine Major Science and Technology project (2021XYCZ004).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Hawksworth DL, Lücking R. Fungal Diversity Revisited: 2.2 to 3.8 Million Species [J]. *Microbiology Spectrum*. 2017;5(4). doi:10.1128/microbiolspec.FUNK-0052-2016
2. Sun S, Hoy MJ, Heitman J. Fungal pathogens [J]. *Curr Biol*. 2020;30(19). doi:10.1016/j.cub.2020.07.032
3. Almeida F, Rodrigues ML, Coelho C. The Still Underestimated Problem of Fungal Diseases Worldwide [J]. *Front Microbiol*. 2019;10:214. doi:10.3389/fmicb.2019.00214
4. Bongomin F, Gago S, Oladele RO, Denning DW. Global and Multi-National Prevalence of Fungal Diseases-Estimate Precision [J. *J Fungi*. 2017;3(4). doi:10.3390/jof3040057
5. Cui X, Wang L, Y L, Yue C. Development and research progress of anti-drug resistant fungal drugs [J]. *J Infection and Public Health*. 2022;15(9):986–1000. doi:10.1016/j.jiph.2022.08.004
6. Ali GA, Husain A, Salah H, Goravey W. Trichosporon asahii fungemia and COVID-19 co-infection: an emerging fungal pathogen; case report and review of the literature [J]. *IDCases*. 2021;25:e01244. doi:10.1016/j.idcr.2021.e01244
7. Wambaugh MA, Denham ST, Ayala M, Brammer B, Stonhill MA, Brown JC. Synergistic and antagonistic drug interactions in the treatment of systemic fungal infections [J]. *eLife*. 2020;9. doi:10.7554/eLife.54160
8. Robbins N, Wright GD, Cowen LE. Antifungal Drugs: the Current Armamentarium and Development of New Agents [J]. *Microbiology Spectrum*. 2016;4(5). doi:10.1128/microbiolspec.FUNK-0002-2016
9. Fuentefria AM, Pippi B, Dalla Lana DF, Donato KK, De Andrade SF. Antifungals discovery: an insight into new strategies to combat antifungal resistance [J]. *Lett Appl Microbiol*. 2018;66(1):2–13. doi:10.1111/lam.12820
10. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management [J]. *Lancet Infect Dis*. 2017;17(12):e383–e92. doi:10.1016/s1473-3099(17)30316-x
11. Vanzolini T, Magnani M. Old and new strategies in therapy and diagnosis against fungal infections [J]. *Appl Microb Biotech*. 2024;108(1):147. doi:10.1007/s00253-023-12884-8
12. Zhu X, Chen Y, Yu D, Fang W, Liao W, Pan W. Progress in the application of nanoparticles for the treatment of fungal infections: a review [J]. *Mycology*. 2024;15(1):1–16. doi:10.1080/21501203.2023.2285764
13. Adegboye O, A FM, Kupz A, et al. Natural-Product-Based Solutions for Tropical Infectious Diseases [J]. *Clin Microbiol Rev*. 2021;34(4):e0034820. doi:10.1128/cmr.00348-20
14. F PD, Scurtu A, G MI, et al. Antibiotics: conventional Therapy and Natural Compounds with Antibacterial Activity-A Pharmaco-Toxicological Screening [J]. *Antibiotics*. 2021;10(4). doi:10.3390/antibiotics10040401
15. Petrovska BB, Cekovska S. Extracts from the history and medical properties of garlic [J]. *Pharmacogn revi*. 2010;4(7):10.4103/0973–7847.65321.
16. Adetumbi MA, Lau BH. Allium sativum (garlic)--a natural antibiotic [J]. *Med Hypotheses*. 1983;12(3):227–237. doi:10.1016/0306-9877(83)90040-3
17. Batiha G E-S, Magdy Beshbishy A, W LG, et al. Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): a Review [J]. *Nutrients*. 2020;12(3). doi:10.3390/nu12030872
18. Choo S, K CV, H WE, et al. Review: antimicrobial properties of allicin used alone or in combination with other medications [J]. *Folia microbiologica*. 2020;65(3):451–465. doi:10.1007/s12223-020-00786-5
19. Marchese A, Barbieri R, Sanches-Silva A, et al. Antifungal and antibacterial activities of allicin: a review [J]. *Trends Food Sci Technol*. 2016;52:49–56. doi:10.1016/j.tifs.2016.03.010
20. R SA, M CP, A OC, et al. Garlic as an inhibitor of Pseudomonas aeruginosa quorum sensing in cystic fibrosis--a pilot randomized controlled trial [J]. *Pediatric Pulmo*. 2010;45(4):356–362. doi:10.1002/ppul.21193

21. Hemmati J, Nazari M, Abolhasani FS, Ahmadi A, Asghari B. In vitro investigation of relationship between quorum-sensing system genes, biofilm forming ability, and drug resistance in clinical isolates of Pseudomonas aeruginosa [J]. *BMC Microbiol*. 2024;24(1):99. doi:10.1186/s12866-024-03249-w
22. Barriuso J, Hogan DA, Keshavarz T, J MM. Role of quorum sensing and chemical communication in fungal biotechnology and pathogenesis [J]. *FEMS Microbiol Rev*. 2018;42(5):627–638. doi:10.1093/femsre/fuy022
23. Padder SA, Prasad R, Shah AH. Quorum sensing: a less known mode of communication among fungi [J]. *Microbiol Res*. 2018;210. doi:10.1016/j.micres.2018.03.007
24. Wongsuk T, Pumeesat P, Luplertlop N. Fungal quorum sensing molecules: role in fungal morphogenesis and pathogenicity [J]. *J Basic Microbiol*. 2016;56(5). doi:10.1002/jobm.201500759
25. Madhani HD. Quorum sensing in fungi: q&A [J]. *PLoS Pathogens*. 2011;7(10):e1002301. doi:10.1371/journal.ppat.1002301
26. Zhou L, Zhang Y, Ge Y, Zhu X, Pan J. Regulatory Mechanisms and Promising Applications of Quorum Sensing-Inhibiting Agents in Control of Bacterial Biofilm Formation [J]. *Front Microbiol*. 2020;11:589640. doi:10.3389/fmicb.2020.589640
27. Vadakkan K, Vijayanand S, Hemapriya J, Gunasekaran R. Quorum quenching attenuation of rhizobacteria Chromobacterium violaceum virulence by Desmodium gangeticum root extract [J]. *Rhizosphere*. 2022;22:100490. doi:10.1016/j.rhisph.2022.100490
28. B RT, Bjarnsholt T, E SM, et al. Screening for quorum-sensing inhibitors (QSI) by use of a novel genetic system, the QSI selector [J]. *J Bacteriol*. 2005;187(5):1799–1814. doi:10.1128/jb.187.5.1799-1814.2005
29. Verma T, Aggarwal A, Dey P, et al. Medicinal and therapeutic properties of garlic, garlic essential oil, and garlic-based snack food: an updated review [J]. *Frontiers in Nutrition*. 2023;10. doi:10.3389/fnut.2023.1120377
30. Alam K, Hoq O. Medicinal plant Allium sativum. *A Review*. 2016;4(6):72–79.
31. Hayat S, Cheng Z, Ahmad H, Ali M, Chen X, Wang M. Garlic, from Remedy to Stimulant: evaluation of Antifungal Potential Reveals Diversity in Phytoalexin Allicin Content among Garlic Cultivars; Allicin Containing Aqueous Garlic Extracts Trigger Antioxidants in Cucumber [J]. *Front Plant Sci*. 2016;7. doi:10.3389/fpls.2016.01235
32. Shang A, Y CS, Xu X Y GR, et al. Bioactive Compounds and Biological Functions of Garlic (Allium sativum L.) [J]. *Foods*. 2019;8(7). doi:10.3390/foods8070246
33. Netzel ME. Garlic: much More Than a Common Spice [J]. *Foods*. 2020;9(11). doi:10.3390/foods9111544
34. Chidike Ezeorba TP, Ezugwu AL, Chukwuma IF, Anaduaka EG, Udenigwe CC. Health-promoting properties of bioactive proteins and peptides of garlic (Allium sativum) [J]. *Food Chem*. 2024;435. doi:10.1016/j.foodchem.2023.137632
35. Cavallito C, Buck J, Suter CA. the Antibacterial Principle of Allium sativum. II. Determination of the Chemical Structure [J]. *J AM CHEM SOC*. 1944;66(11):1952–1954. doi:10.1021/ja01239a049
36. Gs Ellmore RF. Alliin lyase localization in bundle sheaths of the garlic clove (Allium sativum) [J]. *American J Boan*. 1994;81(1):89–94.
37. Ankri S, Mirelman D. Antimicrobial properties of allicin from garlic [J]. *Microb Infect*. 1999;1(2):125–129. doi:10.1016/s1286-4579(99)80003-3
38. Dai J, Chen Y, Jiang F. Allicin reduces inflammation by regulating ROS/NLRP3 and autophagy in the context of A. fumigatus infection in mice [J]. *Gene*. 2020;762:145042. doi:10.1016/j.gene.2020.145042
39. Curtis H, Noll U, Störmann J, Slusarenko AJ. Broad-spectrum activity of the volatile phytoanticipin allicin in extracts of garlic (Allium sativum L.) against plant pathogenic bacteria, fungi and Oomycetes [J]. *Physiol Mol Plant Pathol*. 2004;65(2). doi:10.1016/j.pmpp.2004.11.006
40. Robles-Martínez M, C GJF, J P-VF, Montejano-Carrizales JM, Pérez E, Patiño-Herrera R. Antimycotic Activity Potentiation of Allium sativum Extract and Silver Nanoparticles against Trichophyton rubrum [J]. *Chem. Biodivers*. 2019;16(4):e1800525. doi:10.1002/cbdv.201800525
41. Kocić-Tanackov S, Dimić G, Lević J, et al. Effects of onion (Allium cepa L.) and garlic (Allium sativum L.) essential oils on the Aspergillus versicolor growth and sterigmatocystin production [J]. *Journal of Food Science*. 2012;77(5). doi:10.1111/j.1750-3841.2012.02662.x
42. R LW, S SQ, Q DH, et al. Antifungal activity, kinetics and molecular mechanism of action of garlic oil against Candida albicans [J]. *Sci Rep*. 2016;6. doi:10.1038/srep22805
43. Burian JP, Sacramento LVS, Carlos IZ. Fungal infection control by garlic extracts (Allium sativum L.) and modulation of peritoneal macrophages activity in murine model of sporotrichosis [J]. *Brazilian Jf Bi*. 2017;77(4):848–855. doi:10.1590/1519-6984.03716
44. Wang Y, Wei K, Han X, et al. The Antifungal Effect of Garlic Essential Oil on Phytophthora nicotianae and the Inhibitory Component Involved [J]. *Biomolecules*. 2019;9(10). doi:10.3390/biom9100632
45. Li WR, Shi QS, Liang Q, Huang XM, Chen YB. Antifungal effect and mechanism of garlic oil on Penicillium funiculosum [J]. *Appl Microb Biotech*. 2014;98(19):8337–8346. doi:10.1007/s00253-014-5919-9
46. Pârvu M, A MC, E PA, et al. Allium sativum Extract Chemical Composition, Antioxidant Activity and Antifungal Effect against Meyerozyma guilliermondii and Rhodotorula mucilaginosa Causing Onychomycosis [J]. *Molecules*. 2019;24(21). doi:10.3390/molecules24213958
47. Aala F, Yusuf UK, Jamal F, Rezaie S. Antimicrobial effects of allicin and ketoconazole on trichophyton rubrum under in vitro condition [J]. *Brazilian j Microbi*. 2012;43(2):786–792. doi:10.1590/s1517-83822012000200044
48. Bakhshi M, Taheri JB, Shabestari SB, Tanik A, Pahlevan R. Comparison of therapeutic effect of aqueous extract of garlic and nystatin mouthwash in denture stomatitis [J]. *Gerodontology*. 2012;29(2):e680–4. doi:10.1111/j.1741-2358.2011.00544.x
49. Ismaiel AA, Rabie GH, Kenawey SE, Abd El-Aal MA. Efficacy of aqueous garlic extract on growth, aflatoxin B1 production, and cyto-morphological aberrations of Aspergillus flavus, causing human ophthalmic infection: topical treatment of A. flavus keratitis [J]. *Brazilian j Microbi*. 2012;43(4):1355–1364. doi:10.1590/s1517-838220120004000017
50. Schier C, Foerster Née Reiter J, Heupel M, et al. Allicin as a Volatile or Nebulisable Antimycotic for the Treatment of Pulmonary Mycoses: in Vitro Studies Using a Lung Flow Test Rig [J]. *Int J Mol Sci*. 2022;23(12). doi:10.3390/ijms23126607
51. Yamada Y, Azuma KJAA. Evaluation of the in vitro antifungal activity of allicin [J]. *Chemotherapy*. 1977;11(4):743–749.
52. Sharma S, Raj K, Riyaz M, Singh DD. Antimicrobial Studies on Garlic Lectin [J]. *Probiotics Antimicrob Proteins*. 2023;15(6):1501–1512. doi:10.1007/s12602-022-10001-1
53. Pai ST, Platt MW. Antifungal effects of Allium sativum (garlic) extract against the Aspergillus species involved in otomycosis [J]. *Lett Appl Microbiol*. 1995;20(1):14–18. doi:10.1111/j.1472-765x.1995.tb00397.x
54. Fuqua WC, Winans SC, Greenberg EP. Quorum sensing in bacteria: the LuxR-LuxI family of cell density-responsive transcriptional regulators [J]. *J Bacteriol*. 1994;176(2):269–275. doi:10.1128/jb.176.2.269-275.1994
55. Albuquerque P, M NA, Nieves E, et al. Quorum sensing-mediated, cell density-dependent regulation of growth and virulence in Cryptococcus neoformans. *mBio*. 2013;5(1):e00986–13. doi:10.1128/mBio.00986-13

56. Maha Swetha BR, Saravanan M, Piruthivraj P. Emerging trends in the inhibition of bacterial molecular communication: an overview [J]. *Microb Pathogenesis*. 2024;186:106495. doi:10.1016/j.micpath.2023.106495
57. Miller MB, Bassler BLJARIM Quorum sensing in bacteria. 2001, 55: 165–199.
58. Raina S, Odell M, Keshavarz T. Quorum sensing as a method for improving sclerotiorin production in Penicillium sclerotiorum [J]. *J Biotech*. 2010;148(2–3):91–98. doi:10.1016/j.jbiotec.2010.04.009
59. Vadakkan K, Sathishkumar K, O MV, et al. Critical review on plant-derived quorum sensing signaling inhibitors in pseudomonas aeruginosa [J]. *Bioorg Chem*. 2024;151:107649. doi:10.1016/j.bioorg.2024.107649
60. Vadakkan K, Sathishkumar K, Kuttiyachan Urumbil S, Ponnenkunnathu Govindankutty S, Kumar Ngangbam A, Devi Nongmaithem B. A review of chemical signaling mechanisms underlying quorum sensing and its inhibition in Staphylococcus aureus [J]. *Bioorg Chem*. 2024;148. doi:10.1016/j.bioorg.2024.107465
61. Allen PJ. Properties of a Volatile Fraction from Uredospores of Puccinia graminis var. tritici Affecting Their Germination and Development. I. *Plant Phys*. 1957;32(5). doi:10.1104/pp.32.5.385
62. Kügler S, Schurtz Sebghati T, Groppe Eissenberg L, Goldman WE. Phenotypic variation and intracellular parasitism by Histoplasma *Capsulatum* [J]. *Proc Natl Acad Sci USA*. 2000;97(16):8794–8798. doi:10.1073/pnas.97.16.8794
63. Sifri CD. Healthcare epidemiology: quorum sensing: bacteria talk sense [J]. *Clinical Infectious Disea*. 2008;47(8):1070–1076. doi:10.1086/592072
64. Chen H, Fujita M, Feng Q, Clardy J, Fink GR. Tyrosol is a quorum-sensing molecule in Candida albicans [J]. *Proc Natl Acad Sci USA*. 2004;101(14). doi:10.1073/pnas.0401416101
65. Avbelj M, Zupan J, Raspor P. Quorum-sensing in yeast and its potential in wine making [J]. *Appl Microb Biotech*. 2016;100(18). doi:10.1007/s00253-016-7758-3
66. Fischer MS, Jonkers W, Glass NL. Integration of Self and Non-self Recognition Modulates Asexual Cell-to-Cell Communication in Neurospora crassa [J]. *Genetics*. 2019;211(4). doi:10.1534/genetics.118.301780
67. Berrocal A, Oviedo C, Nickerson KW, Navarrete J. Quorum sensing activity and control of yeast-mycelium dimorphism in Ophiostoma floccosum [J]. *Biotechnol. Lett*. 2014;36(7). doi:10.1007/s10529-014-1514-5
68. Tian X, Ding H, Ke W, Wang L. Quorum Sensing in Fungal Species [J]. *Annual Rev Microbi*. 2021;75. doi:10.1146/annurev-micro-060321-045510
69. Zawrotniak M, Wojtalik K, Rapala-Kozik M. Farnesol, a Quorum-Sensing Molecule of Candida Albicans Triggers the Release of Neutrophil Extracellular Traps [J]. *Cells*. 2019;8(12). doi:10.3390/cells8121611
70. Chen H, Fink GR. Feedback control of morphogenesis in fungi by aromatic alcohols [J]. *Genes Dev*. 2006;20(9). doi:10.1101/gad.1411806
71. Han TL, Tumanov S, Cannon RD, Villas-Boas SG. Metabolic response of Candida albicans to phenylethyl alcohol under hyphae-inducing conditions [J]. *PLoS One*. 2013;8(8). doi:10.1371/journal.pone.0071364
72. Albuquerque P, Casadevall A. Quorum sensing in fungi--a review [J]. *Med Mycol*. 2012;50(4):337–345. doi:10.3109/13693786.2011.652201
73. Kovács R, Majoros L. Fungal Quorum-Sensing Molecules: a Review of Their Antifungal Effect against Candida Biofilms [J]. *J Fungi*. 2020;6(3). doi:10.3390/jof6030099
74. Shchepin R, Hornby JM, Burger E, Niessen T, Dussault P, Nickerson KW. Quorum sensing in Candida albicans: probing farnesol's mode of action with 40 natural and synthetic farnesol analogs [J]. *Chem Biol*. 2003;10(8):743–750. doi:10.1016/s1074-5521(03)00158-3
75. Paluch E, Rewak-Soroczyńska J, Jędrusik I, Mazurkiewicz E, Jermakow K. Prevention of biofilm formation by quorum quenching [J]. *Appl Microb Biotech*. 2020;104(5):1871–1881. doi:10.1007/s00253-020-10349-w
76. Zhu X, J CW, Bhatt K, et al. Innovative microbial disease biocontrol strategies mediated by quorum quenching and their multifaceted applications: a review [J]. *Front Plant Sci*. 2022;13. doi:10.3389/fpls.2022.1063393
77. Grandclément C, Tannières M, Moréra S, Dessaux Y, Faure D. Quorum quenching: role in nature and applied developments [J]. *FEMS Microbiol Rev*. 2016;40(1). doi:10.1093/femsre/fuv038
78. Borlinghaus J, Albrecht F, Gruhlke MC, Nwachukwu ID, Slusarenko AJ. Allicin: chemistry and biological properties [J]. *Molecules*. 2014;19(8):12591–12618. doi:10.3390/molecules190812591
79. Miron T, Rabinkov A, Mirelman D, Wilchek M, Weiner L. The mode of action of allicin: its ready permeability through phospholipid membranes may contribute to its biological activity [J]. *BBA*. 2000;1463(1):20–30. doi:10.1016/s0005-2736(99)00174-1
80. Borlinghaus J, Foerster Née Reiter J, Kappler U, et al. Allicin, the Odor of Freshly Crushed Garlic: a Review of Recent Progress in Understanding Allicin's Effects on Cells [J]. *Molecules*. 2021;26(6). doi:10.3390/molecules26061505
81. Chen C, Liu C, Cai J, et al. Broad-spectrum antimicrobial activity, chemical composition and mechanism of action of garlic (Allium sativum) extracts [J]. *FOOD CONTROL*. 2018;86:117–125. doi:10.1016/j.foodcont.2017.11.015
82. Ghannoum MA. Studies on the anticandidal mode of action of Allium sativum (garlic) [J]. *J Gen Microbiol*. 1988;134(11):2917–2924. doi:10.1099/00221287-134-11-2917
83. Kyung KH. Antimicrobial properties of allium species [J]. *Curr Opin Biotechnol*. 2012;23(2):142–147. doi:10.1016/j.copbio.2011.08.004
84. Low CF, Chong PP, Yong PV, Lim CS, Ahmad Z, Othman F. Inhibition of hyphae formation and SIR2 expression in Candida albicans treated with fresh Allium sativum (garlic) extract [J]. *J Appl Microbiol*. 2008;105(6):2169–2177. doi:10.1111/j.1365-2672.2008.03912.x
85. Khodavandi A, Alizadeh F, S HN, et al. Expression analysis of SIR2 and SAPs1-4 gene expression in Candida albicans treated with allicin compared to fluconazole [J]. *Tropical Biomed*. 2011;28(3):589–598.
86. Zhao G, Rusche LN. Genetic Analysis of Sirtuin Deacetylases in Hyphal Growth of Candida albicans [J]. *mSphere*. 2021;6(3). doi:10.1128/mSphere.00053-21
87. Aala F, Yusuf UK, Nulit R, Rezaie S. Inhibitory effect of allicin and garlic extracts on growth of cultured hyphae [J]. *Iran J Basic Med Sci*. 2014;17(3):150–154.
88. Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases [J]. *Nat Rev Microbiol*. 2004;2(2):95–108. doi:10.1038/nrmicro821
89. Jamal M, Ahmad W, Andleeb S, et al. Bacterial biofilm and associated infections [J]. *J Chinese Med Asso*. 2018;81(1):7–11. doi:10.1016/j.jcma.2017.07.012

90. Mah TF, A OG. Mechanisms of biofilm resistance to antimicrobial agents [J]. *Trends in Microbiology*. 2001;9(1):34–39. doi:10.1016/s0966-842x(00)01913-2
91. Nakamoto M, Kunimura K, Suzuki JI, Kodera Y. Antimicrobial properties of hydrophobic compounds in garlic: allicin, vinyldithiin, ajoene and diallyl polysulfides [J]. *Exp Ther Med*. 2020;19(2):1550–1553. doi:10.3892/etm.2019.8388
92. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections [J]. *Science*. 1999;284(5418):1318–1322. doi:10.1126/science.284.5418.1318
93. Abdelhamid AG, Yousef AE. Combating Bacterial Biofilms: current and Emerging Antibiofilm Strategies for Treating Persistent Infections [J]. *Antibiotics*. 2023;12(6). doi:10.3390/antibiotics12061005
94. Rabin N, Zheng Y, Opoku-Temeng C, Du Y, Bonsu E, Sintim HO. Biofilm formation mechanisms and targets for developing antibiofilm agents [J]. *Future Medicinal*. 2015;7(4):493–512. doi:10.4155/fmc.15.6
95. Aparna MS, Yadav S. Biofilms: microbes and disease [J]. *Brazilian J Infect*. 2008;12(6):526–530. doi:10.1590/s1413-86702008000600016
96. Davey ME, A OG. Microbial biofilms: from ecology to molecular genetics [J]. *Microb molecular biology revi*. 2000;64(4):847–867. doi:10.1128/mmbr.64.4.847-867.2000
97. Rainey PB, Rainey K. Evolution of cooperation and conflict in experimental bacterial populations [J]. *Nature*. 2003;425(6953):72–74. doi:10.1038/nature01906
98. Borghi E, Borgo F, Morace G. Fungal Biofilms: update on Resistance [J]. *Adv Exp Med Biol*. 2016;931:37–47. doi:10.1007/5584_2016_7
99. Xavier JB, Foster KR. Cooperation and conflict in microbial biofilms [J]. *Proc Natl Acad Sci USA*. 2007;104(3):876–881. doi:10.1073/pnas.0607651104
100. Dieltjens L, Appermans K, Lissens M, et al. Inhibiting bacterial cooperation is an evolutionarily robust anti-biofilm strategy [J]. *Nat Commun*. 2020;11(1):107. doi:10.1038/s41467-019-13660-x
101. Nadell CD, Xavier JB, Levin SA, Foster KR. The evolution of quorum sensing in bacterial biofilms [J]. *PLoS biol*. 2008;6(1):e14h. doi:10.1371/journal.pbio.0060014
102. Parsek MR, Greenberg EP. Sociomicrobiology: the connections between quorum sensing and biofilms [J]. *Trends in Microbiology*. 2005;13(1):27–33. doi:10.1016/j.tim.2004.11.007
103. Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control [J]. *Cold Spring Harbor Perspec Medi*. 2012;2(11). doi:10.1101/cshperspect.a012427
104. Saxena P, Joshi Y, Rawat K, Bisht R. Biofilms: architecture, Resistance, Quorum Sensing and Control Mechanisms [J]. *Indian J Microbi*. 2019;59(1):3–12. doi:10.1007/s12088-018-0757-6
105. Juszczuk-Kubiak E. Molecular Aspects of the Functioning of Pathogenic Bacteria Biofilm Based on Quorum Sensing (QS) Signal-Response System and Innovative Non-Antibiotic Strategies for Their Elimination [J]. *Int J Mol Sci*. 2024;25(5). doi:10.3390/ijms25052655
106. Ashrit P, Sadanandan B, Shetty K, Vaniyamparambath V. Polymicrobial Biofilm Dynamics of Multidrug-Resistant Candida albicans and Ampicillin-Resistant Escherichia coli and Antimicrobial Inhibition by Aqueous Garlic Extract [J]. *Antibiotics*. 2022;11(5). doi:10.3390/antibiotics11050573
107. Zainal M, Mohamad Zain N, Mohd Amin I, Ahmad VN. The antimicrobial and antibiofilm properties of allicin against Candida albicans and Staphylococcus aureus - A therapeutic potential for denture stomatitis [J]. *Saudi Dental j*. 2021;33(2):105–111. doi:10.1016/j.sdentj.2020.01.008
108. Yang X, Sha K, Xu G, et al. Subinhibitory Concentrations of Allicin Decrease Uropathogenic Escherichia coli (UPEC) Biofilm Formation, Adhesion Ability, and Swimming Motility [J]. *Int J Mol Sci*. 2016;17(7). doi:10.3390/ijms17070979
109. Ranjbar-Omid M, Arzanlou M, Amani M, Shokri Al-Hashem SK, Amir Mozafari N, Peeri Doghaheh H. Allicin from garlic inhibits the biofilm formation and urease activity of Proteus mirabilis in vitro [J]. *FEMS Microbiol Lett*. 2015;362(9). doi:10.1093/femsle/fnv049
110. Li G, Ma X, Deng L, et al. Fresh Garlic Extract Enhances the Antimicrobial Activities of Antibiotics on Resistant Strains in Vitro [J]. *Jundishapur J Microbiol*. 2015;8(5):e14814. doi:10.5812/jjm.14814
111. Yan-Jing W Y-H X. The inhibitory effects of allicin on biofilm formation of Candida albicans [J]. *Mycosystema*. 2020;39(2):343–351. doi:10.13346/j.mycosystema.190437
112. Wangsanut T, Pongpom M. Human-Fungal Pathogen Interactions from the Perspective of Immunoproteomics Analyses [J]. *Int J Mol Sci*. 2024;25(6). doi:10.3390/ijms25063531
113. Casadevall A. Immunity to Invasive Fungal Diseases [J]. *Ann Rev Immunol*. 2022;40:121–141. doi:10.1146/annurev-immunol-101220-034306
114. Loh JT, Lam KP. Fungal infections: immune defense, immunotherapies and vaccines [J]. *Adv Drug Delivery Rev*. 2023;196:114775. doi:10.1016/j.addr.2023.114775
115. Drummond RA, Lionakis MS. Organ-specific mechanisms linking innate and adaptive antifungal immunity [J]. *Semin Cell Dev Biol*. 2019;89:78–90. doi:10.1016/j.semcdb.2018.01.008
116. Moutia M, Habti N, Badou A. In Vitro and In Vivo Immunomodulator Activities of Allium sativum L [J]. *Evid Based Complem Alternative Medi*. 2018;2018:4984659. doi:10.1155/2018/4984659
117. Morioka N, Sze LL, Morton DL, Irie RF. A protein fraction from aged garlic extract enhances cytotoxicity and proliferation of human lymphocytes mediated by interleukin-2 and concanavalin A [J]. *Cancer immun mmunothe*. 1993;37(5):316–322. doi:10.1007/bf01518454
118. Arreola R, Quintero-Fabián S, I L-R-R, et al. Immunomodulation and anti-inflammatory effects of garlic compounds [J]. *J Immunol Res*. 2015;2015:401630. doi:10.1155/2015/401630
119. Percival SS. Aged Garlic Extract Modifies Human Immunity [J]. *J Nutr*. 2016;146(2):433s–6. doi:10.3945/jn.115.210427
120. Lau BH, Yamasaki T, Gridley DS. Garlic compounds modulate macrophage and T-lymphocyte functions [J]. *Molecular Biothe*. 1991;3(2):103–107.
121. Zamani AH, Mohammad M, Hasan AM. Effect of garlic consumption on the argyrophilic nucleolar organiser regions (AgNORs) in splenocytes and thymocytes of rats [J]. *Food Agr Immunol*. 2011;22(4):345–353. doi:10.1080/09540105.2011.581271
122. Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance [J]. *Clin Microbiol Rev*. 1999;12(4):501–517. doi:10.1128/cmr.12.4.501
123. C FM, Alastruey-Izquierdo A, Berman J, et al. Tackling the emerging threat of antifungal resistance to human health [J]. *Nat Rev Microbiol*. 2022;20(9):557–571. doi:10.1038/s41579-022-00720-1

124. Pemán J, Cantón E, Espinel-Ingroff A. Antifungal drug resistance mechanisms [J]. *Exp Rev Anti-Infective Ther*. 2009;7(4):453–460. doi:10.1586/eri.09.18
125. Revie NM, Iyer KR, Robbins N, Cowen LE. Antifungal drug resistance: evolution, mechanisms and impact [J]. *Curr Opin Microbiol*. 2018;45:70–76. doi:10.1016/j.mib.2018.02.005
126. Khodavandi A, Alizadeh F, Aala F, Sekawi Z, Chong PP. In vitro investigation of antifungal activity of allicin alone and in combination with azoles against Candida species [J]. *Mycopathologia*. 2010;169(4):287–295. doi:10.1007/s11046-009-9251-3
127. Bicer M. Exploring therapeutic avenues: mesenchymal stem/stromal cells and exosomes in confronting enigmatic biofilm-producing fungi [J]. *Arch. Microbiol*. 2023;206(1):11. doi:10.1007/s00203-023-03744-0
128. Sherry L, Kean R, Mckloud E, et al. Biofilms Formed by Isolates from Recurrent Vulvovaginal Candidiasis Patients Are Heterogeneous and Insensitive to Fluconazole [J]. *Antimicrob. Agents Chemot*. 2017;61(9). doi:10.1128/aac.01065-17
129. Mehta D, Saini V, Bajaj A. Recent developments in membrane targeting antifungal agents to mitigate antifungal resistance [J]. *RSC Medicinal Chem*. 2023;14(9):1603–1628. doi:10.1039/d3md00151b
130. Zhou Y, Reynolds TB. Innovations in Antifungal Drug Discovery among Cell Envelope Synthesis Enzymes through Structural Insights [J. *J Fungi*. 2024;10(3). doi:10.3390/jof10030171
131. Almatroudi A. Investigating Biofilms: advanced Methods for Comprehending Microbial Behavior and Antibiotic Resistance [J]. *Front Biosci*. 2024;29(4):133. doi:10.31083/j.fbl2904133
132. Schier C, Gruhlke MCH, Reucher G, Slusarenko AJ, Rink L. Combating Black Fungus: using Allicin as a Potent Antifungal Agent against Mucorales [J]. *Int J Mol Sci*. 2023;24(24). doi:10.3390/ijms242417519
133. Yang X, Bai S, Wu J, et al. Antifungal Activity and Potential Action Mechanism of Allicin against Trichosporon asahii [J]. *Microbiology Spectrum*. 2023;11(3):e0090723. doi:10.1128/spectrum.00907-23
134. J WC, Grando D, K FC, et al. The effects of oral garlic on vaginal candida colony counts: a randomised placebo controlled double-blind trial [J]. *BJOG*. 2014;121(4):498–506. doi:10.1111/1471-0528.12518
135. Said MM, Watson C, Grando D. Garlic alters the expression of putative virulence factor genes SIR2 and ECE1 in vulvovaginal C. albicans isolates [J]. *Sci Rep*. 2020;10(1):3615. doi:10.1038/s41598-020-60178-0
136. Karkowska-Kuleta J, Rapala-Kozik M, Kozik A. Fungi pathogenic to humans: molecular bases of virulence of Candida albicans, Cryptococcus neoformans and Aspergillus fumigatus [J]. *Acta Biochim Pol*. 2009;56(2):211–224.
137. Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges human health and food security [J]. *Science*. 2018;360(6390):739–742. doi:10.1126/science.aap7999
138. Chong PP, Chin VK, Wong WF, Madhavan P, Yong VC, Looi CY. Transcriptomic and Genomic Approaches for Unravelling Candida albicans Biofilm Formation and Drug Resistance-An Update [J]. *Genes*. 2018;9(11). doi:10.3390/genes9110540
139. Lee J, Wu J, Deng Y, et al. A cell-cell communication signal integrates quorum sensing and stress response [J]. *Nature Chemical Biology*. 2013;9(5):339–343. doi:10.1038/nchembio.1225
140. Defoirdt T. Quorum-Sensing Systems as Targets for Antivirulence Therapy [J]. *Trends in Microbiology*. 2018;26(4):313–328. doi:10.1016/j.tim.2017.10.005
141. Jakobsen TH, Tolker-Nielsen T, Givskov M. Bacterial Biofilm Control by Perturbation of Bacterial Signaling Processes [J]. *Int J Mol Sci*. 2017;18(9). doi:10.3390/ijms18091970
142. Tang N, Yuan S, Luo Y, et al. Nanoparticle-Based Photodynamic Inhibition of Candida albicans Biofilms with Interfering Quorum Sensing [J]. *ACS omega*. 2023;8(4):4357–4368. doi:10.1021/acsomega.2c07740
143. Amagase H, Petesch BL, Matsuura H, Kasuga S, Itakura Y. Intake of garlic and its bioactive components [J]. *J Nutr*. 2001;131(3s):955s–62s. doi:10.1093/jn/131.3.955S
144. Amagase H. Clarifying the real bioactive constituents of garlic [J]. *J Nutr*. 2006;136(3 Suppl):716s–25s. doi:10.1093/jn/136.3.716S
145. Vadakkan K, Rumjit NP, Ngangbam AK, Vijayanand S, Nedumpillil NK. Novel advancements in the sustainable green synthesis approach of silver nanoparticles (AgNPs) for antibacterial therapeutic applications [J]. *Coord. Chem. Rev*. 2024;499:215528. doi:10.1016/j.ccr.2023.215528
146. Ibrahim E, Zhang M, Zhang Y, et al. Green-Synthesization of Silver Nanoparticles Using Endophytic Bacteria Isolated from Garlic and Its Antifungal Activity against Wheat Fusarium Head Blight Pathogen Fusarium Graminearum [J]. *Nanomater*. 2020;10(2). doi:10.3390/nano10020219
147. Vijayakumar S, Malaikozhundan B, Saravanakumar K, Durán-Lara EF, Wang MH, Vaseeharan B. Garlic clove extract assisted silver nanoparticle - Antibacterial, antibiofilm, antihelminthic, anti-inflammatory, anticancer and ecotoxicity assessment [J]. *J Photochem Photobiol B Biol*. 2019;198:111558. doi:10.1016/j.jphotobiol.2019.111558
148. Tomšik A, Šarić L, Bertoni S, et al. Encapsulations of wild garlic (Allium ursinum L.) extract using spray congealing technology [J]. *Food Research Int*. 2019;119:941–950. doi:10.1016/j.foodres.2018.10.081