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Review Article

Quorum sensing inhibitor: an effective strategy to attenuate the virulence and drug resistance of *Pseudomonas aeruginosa*

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Abstract: *Pseudomonas aeruginosa* is a significant contributor to food spoilage and foodborne diseases. The primary strategy for preventing and controlling contamination by *P. aeruginosa* involves the application of antibacterial agents. However, the overuse or abuse of antimicrobial agents has accelerated the development of drug resistance. The control of spoilage and antimicrobial resistance in *P. aeruginosa* has emerged as a major food safety challenge. Numerous studies have established that the pathogenicity and drug resistance of *P. aeruginosa* are regulated by quorum sensing (QS). Therefore, inhibiting the QS system of *P. aeruginosa* is a promising approach to mitigate the pathogenicity and resistance of this pathogen. This review explores various QS systems of *P. aeruginosa* and their roles in bacterial pathogenesis and drug resistance. Additionally, it discusses the potential of small chemical molecules and quorum-quenching enzymes in attenuating the pathogenesis of *P. aeruginosa*, as well as the possibility of using QS inhibitors (QSIs) and antibiotics in future therapeutic approaches for *P. aeruginosa*-associated infections.

Keywords: *Pseudomonas aeruginosa*; quorum sensing; virulence factor; food spoilage; drug resistance

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1 Introduction

According to estimates by the Food and Agriculture Organization of the United Nations, about 13 billion tons of vegetables undergo spoilage and deterioration every year worldwide[1]. Vegetable spoilage is a significant global food safety concern, with microbial contamination being the primary and most severe cause of vegetable losses. A previous study has demonstrated that *Pseudomonas aeruginosa* is one of the main pathogenic bacteria causing vegetable spoilage and deterioration[2]. This pathogen causes water stains, stickiness, discoloration, and decay in vegetables, leading to food poisoning or foodborne diseases, thereby posing a significant threat to vegetable quality and human health[2]. Currently, antimicrobial agents are the primary method for controlling vegetable spoilage caused by *P. aeruginosa*[3]. However, the overuse of antimicrobial agents has significantly contributed to the global spread of multidrug-resistant, pandrug-resistant, and even extensively drug-resistant *P. aeruginosa*[4]. The rapid emergence and evolution of drug-resistant *P. aeruginosa* significantly outpaces the development of novel antimicrobial agents[5]. Therefore, changing control strategies, identifying novel targets, and developing antimicrobial agents with novel anti-virulence mechanisms represent a promising approach to combat the resistance of *P. aeruginosa*. The antimicrobial efficacy of traditional "classical" agents is achieved through the inhibition of the growth of spoilage bacteria or elimination of bacterial cells, thereby facilitating the development of resistance in bacterial cells. In contrast, "non-classical" antibacterial agents, which target the virulence factors of spoilage bacteria without killing cells, offer the advantage of attenuating pathogenicity and reducing drug resistance. This presents a novel strategy for controlling the spoilage caused by *P. aeruginosa*[6].

P. aeruginosa secretes various virulence factors, including protease, elastase, pyocyanin, rhamnolipid, and alginate[7]. Studies have demonstrated that the secretion of these virulence factors is mediated by QS, a transmission network used by bacteria to mediate collective behavior[8,9]. The QS system not only regulates the secretion of virulence factors but also influences biofilm formation and activation of efflux pumps, both of which are key mechanisms that *P. aeruginosa* employs to acquire drug

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resistance[10, 11]. Therefore, inhibiting the QS system has become a promising strategy to reduce the virulence of *P. aeruginosa* and reverse its resistance to antimicrobial agents. The identification of effective and non-toxic QSIs has become a focal point of research in the field of antimicrobial agent development.

2 The QS system of *P. aeruginosa*

The phenomenon of QS was first documented in the 1970s and represents a mechanism by which bacteria communicate within and between species[12]. During bacterial growth, they secrete signaling molecules known as autoinducers (AIs). As the number of bacteria increases, the concentration of secreted AIs also rises continuously. Upon reaching a threshold, AIs bind to their corresponding receptors (for example, the QS receptor of Gram-negative bacteria is LuxR), triggering a cascade of cellular activities, such as motility, adhesion, infection, secretion of virulence factors, and biofilm formation[13] (Fig. 1). Bacterial QS systems can be classified into 4 categories based on the types of AIs: (1) the QS system of Gram-negative bacteria, whose AIs are acyl homoserine lactones (AHLs) (Fig. 1A); (2) the QS system of Gram-positive bacteria, whose AIs are autoinducing peptide (AIP) (Fig. 1B); (3) the QS system common to both Gram-negative and Gram-positive bacteria, whose AIs are autoinducer 2 (AI-2); (4) the QS system among bacterial species, whose AIs are autoinducer 3 (AI-3)[14].

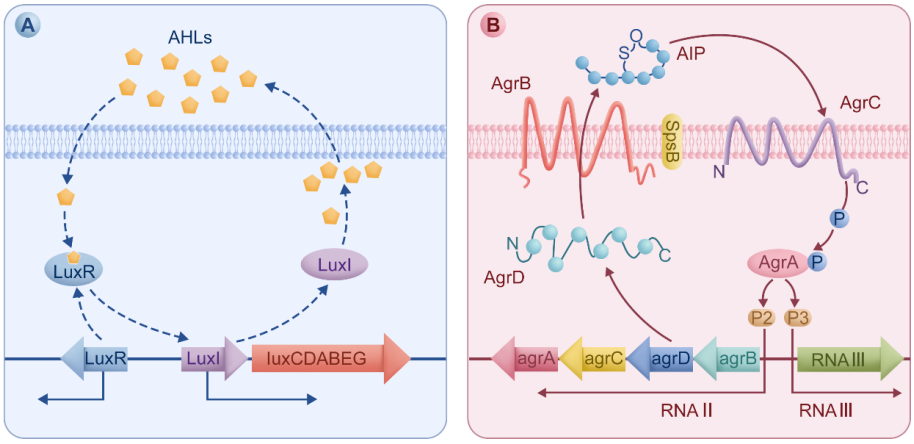


Figure 1 Representative QS systems of Gram-negative (A) and Gram-positive (B) bacteria. For Gram-negative bacteria, the AIs are AHLs, which are encoded by *luxI*. Upon reaching a threshold, AHLs bind to LuxR, subsequently activating the expression of genes involved in the production of virulence factors. For Gram-positive bacteria, the AIs are AIP, which is encoded by *argD*. Upon reaching a threshold, AIP binds to ArgC, subsequently activating the expression of virulence-related genes.

P. aeruginosa, classified as a Gram-negative bacterium, primarily utilizes a QS system comprising *las*, *rhl*, and *pqs*[15]. LasI is responsible for the synthesis of the signal molecule N-(3-Oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) (Fig. 2), which binds to the receptor LasR, thereby regulating the synthesis of virulence factors, such as elastase and biofilm (Fig. 3). N-butyryl-L-Homoserine lactone (C4-HSL) (Fig. 2), another signal molecule synthesized by RhlI, binds to the receptor RhlR and activates the expression of genes responsible for the synthesis of rhamnolipids and hydrogen cyanide (Fig. 3). The *Pseudomonas* quinolone signal (PQS) system is the third QS system of *P. aeruginosa*, serving as a link between *las* and *rhl*. PQS (Fig. 2) is encoded by the cluster genes *pqsABCDEH* and binds to the receptor PqsR to activate the expressions of genes associated with the production of pyocyanin, hydrogen cyanide, and iron carriers (Fig. 3). Among these 3 QS systems, the *las* system is the primary regulator, exerting a direct effect on *rhl* and *pqs* systems (Fig. 3)[16]. However, under certain conditions, the *rhl* and *pqs* systems can also be activated independently, even in the absence of the *las* system[15]. Furthermore, the *rhl* system exerts a negative regulatory effect on the *pqs* system; however, the underlying mechanism remains unclear[17] (Fig. 3). Recently, a novel fourth QS system referred to as the IQS system has been identified (Fig. 3), characterized by its signaling molecule 2-(2-hydroxyphenyl)-thiazole-4-carbaldehyde[18] (Fig. 2). However, the signal cascade of the IQS system and its regulatory effect on gene expression are not yet fully understood.

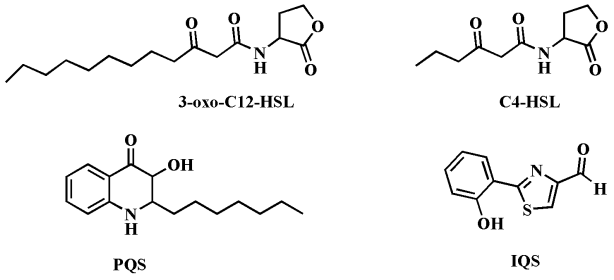


Figure 2 Structures of *P. aeruginosa* QS signals.

3 Virulence factors secreted by *P. aeruginosa*

3.1 Protease and elastase

Protease and elastase are key extracellular enzymes secreted by *P. aeruginosa*, playing crucial roles in protein degradation and food spoilage[19]. Upon entering the human body, these enzymes promote the *P. aeruginosa* infection by disrupting the physical barriers of host cells, degrading immunoglobulin and fibrin, and inhibiting the connections between epithelial cells. This leads to a range of clinical manifestations, such as eye infections, respiratory damage, urinary system infections, and even sepsis[20-22]. Protease, a zinc metalloprotease encoded by the gene *lasA*, primarily degrades host complement proteins and fibrin (Table 1). It can interfere with flagella receptor signaling by binding to host Toll-like receptor 5, thereby enabling bacterial cells of *P. aeruginosa* to evade immune testing[23]. Elastase, encoded by the *lasB* gene (Table 1), is secreted through the type II secretion system. It plays a critical role in degrading the matrix proteins of connective tissue,

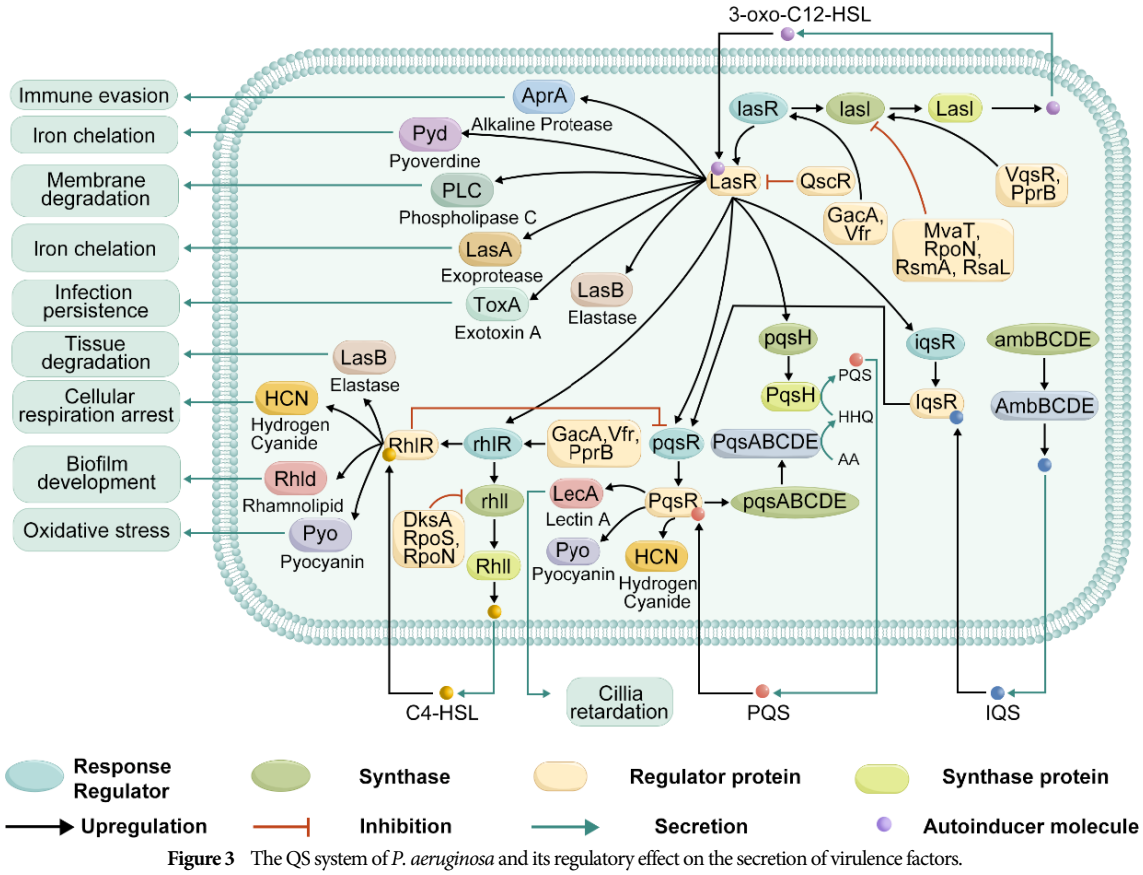


Figure 3 The QS system of *P. aeruginosa* and its regulatory effect on the secretion of virulence factors.

Table 1 The QS system of *P. aeruginosa* and its regulatory effect on the secretion of virulence factors

Genes	Virulence factors	Effect on host	Effect on *P. aeruginosa*	References
lasA	Protease	Disruption of host complement proteins	Host immune evasion	[23]
lasB	Elastase	Degradation of matrix proteins	Iron acquisition	[24]
phzABCDEFG, phzM	Pyocyanin	Inhibit epidermal cell growth and cause oxidative stress	Drug resistance and enhanced colonization	[25, 26]
rhlA, rhlB	Rhamnolipid	Neutrophil necrosis	Immune evasion and enhanced infection	[41]
lpxD	Lipopolysaccharide	Inflammation and immune rejection response	Drug resistance	[45, 46]
PA3540-3551	Alginate	Affect cell-to-cell communication	Drug resistance and enhanced colonization	[47]

disrupting the connections between basal lateral cells, and increasing the damage to tissue cells by *P. aeruginosa*[24] (Table 1). Therefore, inhibiting the secretion of protease and elastase represents an important strategy to prevent food spoilage and reduce foodborne diseases caused by *P. aeruginosa*.

3.2 Pyocyanin

Pyocyanin, another key virulence factor secreted by *P. aeruginosa*, inhibit epidermal cell growth, disrupt cellular redox homeostasis, and causes neutrophils death. It also trigger inflammation, which can lead to sepsis[25] (Table 1). Additionally, pyocyanin stimulates the release of extracellular DNA, facilitates biofilm formation, and consequently increases bacterial resistance to antibiotics[26] (Table 1). Pyocyanin is a toxic secondary metabolite with redox activity that increases the resistance of *P. aeruginosa* to antimicrobial agents by activating the redox-sensing transcription factor SoxR, which induces the expression of efflux pump genes *mexGHI-opmD*[27] (Fig. 4). Moreover, pyocyanin stimulates the expression of a second efflux pump operon, *mexEF-oprN*, further promoting antimicrobial resistance and invasion of host cells[28]. Increasing evidence indicates that efflux is a primary mechanism by which *P. aeruginosa* acquires resistance to both pyocyanin and antimicrobial agents[29]. In the presence of pyocyanin, the efflux activity of *P. aeruginosa* is upregulated, which significantly increases its resistance to antibiotics. In contrast, the exocytosis and drug resistance of *P. aeruginosa* are significantly reduced following the knockout of the gene encoding pyocyanin[30]. Therefore, the inhibition of pyocyanin synthesis is a crucial strategy for mitigating the drug resistance of *P. aeruginosa*. Pyocyanin represents a promising target for therapeutic interventions aimed at addressing the drug resistance of *P. aeruginosa*.

The synthesis of pyocyanin begins with chorismic acid, which serves as its precursor. Chorismic acid is converted to phenazine-1-carboxylic acid through the action of dual gene clusters *phz1* and *phz2* (Table 1). This intermediate is subsequently converted into pyocyanin catalyzed by the enzymes of PhzM and PhzS[32] (Fig. 5). Pyocyanin synthesis is also mediated by *las*, *rhl*, and *pqs* systems[33,34], as well as the two-component regulatory system GacA-GacS[35], global regulatory factor Vfr[36]. Knockout of the aforementioned genes results in a significant reduction in pyocyanin secretion[32]. Furthermore, the synthesis of pyocyanin is

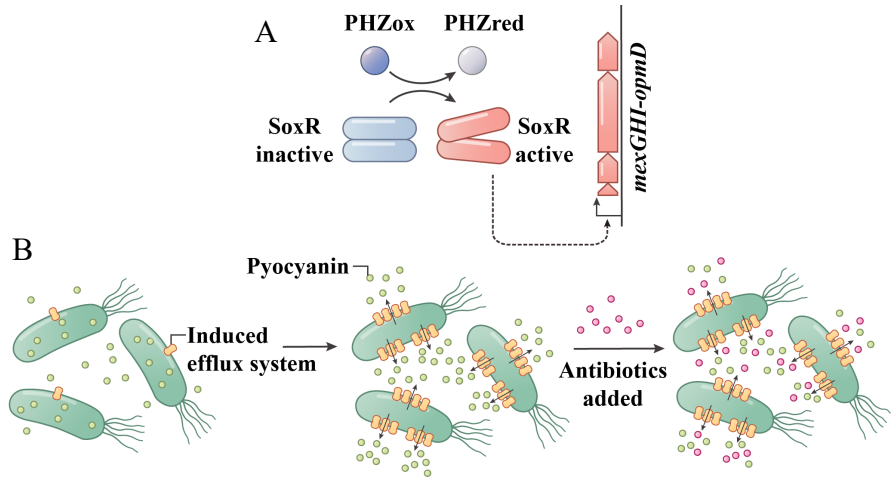


Figure 4 The expression of efflux pump induced by pyocyanin. (A) Pyocyanin activates SoxR and induces the expression of MexGHI-OpmD, (B) Pyocyanin activates efflux pumps and facilitates the efflux of pyocyanin and antibiotics. PHZox, oxidized pyocyanin. PHZred, reduced pyocyanin[31].

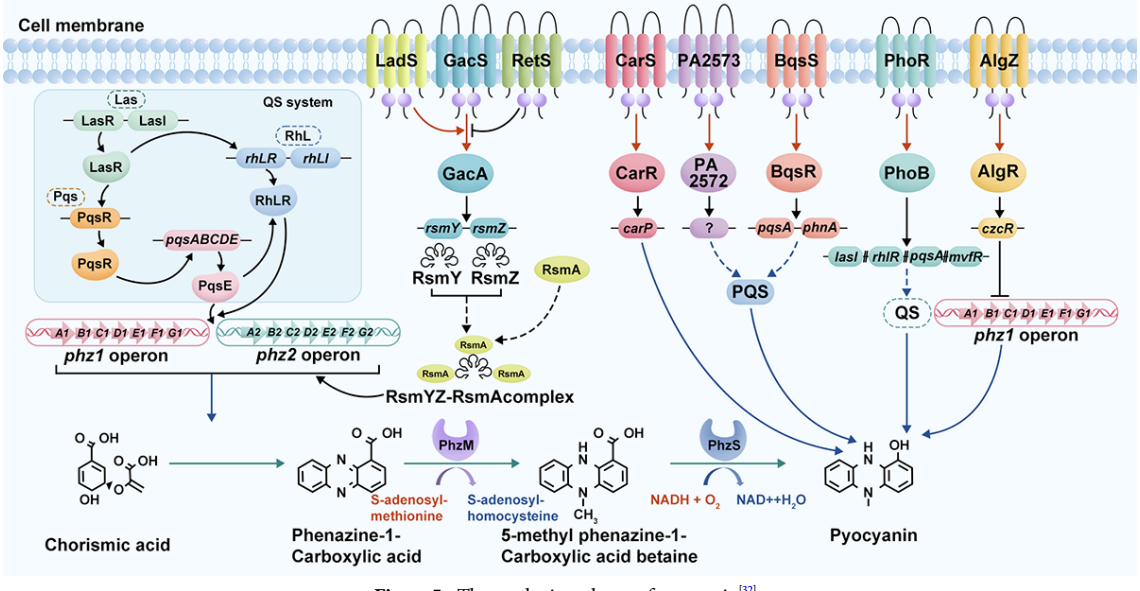


Figure 5 The synthetic pathway of pyocyanin[32].

influenced by other regulators. For example, at high Ca^{2+} concentrations, the two-component regulatory system CarSR not only regulates Ca^{2+} homeostasis but also controls pyocyanin synthesis by modulating the transcription of *carO* and *carP*[37]. Methyl-accepting chemotaxis protein PA2573 and Fe^{2+} sensing protein BqsSR serve as key regulators of pyocyanin synthesis via the PQS signaling pathway[32,38]. Under conditions of phosphate scarcity, PhoB plays a crucial role in regulating pyocyanin synthesis by activating the QS system[39]. Therefore, the regulatory network of pyocyanin synthesis is exceptionally complex.

3.3 Rhamnolipid

Rhamnolipid, one of the most important virulence factors secreted by *P. aeruginosa*, is directly encoded by the *rhlA* and *rhlB* genes and is globally regulated by the *rhl* system[40] (Table 1). Rhamnolipid, categorized as surfactants, promote the diffusion of *P. aeruginosa* in tissue cells while inhibiting the function of immune cells. This process results in neutrophil necrosis and aids bacterial cells in evading clearance by host immune mechanisms[41] (Table 1). In addition, a study conducted by Daver *et al.* demonstrated that rhamnolipid affects the biofilm architecture of *P. aeruginosa*[42]. Biofilms produced by mutants deficient in rhamnolipid synthesis fail to maintain the noncolonized channels that typically surround macrocolonies[42]. Upon biofilm maturation, the secreted rhamnolipid maintains open channels among bacterial cells within the biofilm matrix, thereby facilitating biofilm lysis and the subsequent release of daughter cells[43]. Under conditions of limited Fe^{2+} availability, *P. aeruginosa* maintains the structural integrity of mature biofilms by increasing the synthesis of rhamnolipids[44]. Therefore, rhamnolipid is crucial in the dissemination, infection, and biofilm formation of *P. aeruginosa*.

3.4 Lipopolysaccharide and alginate

Lipopolysaccharide is a key component of the outer membrane of *P. aeruginosa* cells, comprising lipid A, core oligosaccharides, and highly variable O-antigen polysaccharides. It exhibits immunogenic properties and plays a central role in triggering inflammatory and immune rejection responses[45] (Table 1). Lipopolysaccharide confers Gram-negative bacteria with a low outer membrane permeability. This decreased permeability, in conjunction with the activity of efflux pumps, prevents the entry of antimicrobial agents within bacterial cells[46]. Therefore, lipopolysaccharide is closely associated with the drug resistance of *P. aeruginosa*, making it an important target for the development

of novel drugs aimed at combating this pathogen (Table 1). Alginate, another important virulence factor secreted by *P. aeruginosa*, is encoded by the *PA3540-3551* gene cluster (Table 1). Alginate is a linear, polyanionic encapsulated extracellular polysaccharide composed of mannuronic acid and guluronic acid monomers[47]. Although alginate is not an important component of biofilms, it plays a crucial role in influencing their formation, structure, and functionality[47]. Overexpression of alginate leads to biofilms with a highly structured architecture, significantly increasing their resistance to tobramycin[47] (Table 1). Therefore, alginate serves as a key factor in the development of drug resistance in *P. aeruginosa*.

3.5 Biofilms

Biofilms are systematic, highly organized microbial communities formed by bacteria and embedded in extracellular matrix composed of polysaccharides, nucleic acids, proteins, and lipids[48]. Exopolysaccharides are the predominant component of biofilms constituting more than 90% of the total extracellular matrix[49]. The high levels of exopolysaccharides act as a thick protective layer, allowing bacteria within the capsule to evade the body's immune surveillance and antimicrobial agents, thereby promoting resistance of *P. aeruginosa* to antibacterial agents. The presence of bacteria within biofilms significantly enhances their resistance to antimicrobial agents, exhibiting a resistance level that is 100 to1000-fold higher than that of planktonic bacteria. This augmented resistance contributes to high morbidity and mortality associated with infections caused by *P. aeruginosa*[50]. Upon biofilm maturation, the bacteria in the biofilms undergo degradation and release, which causes recurrent infection and long-term non-resolving conditions[51]. Studies indicate that over 80% of microbial infections are attributable to biofilm formation[52].

Biofilm formation encompasses 5 stages: adhesion, attachment, micro-colony formation, macrocolony formation, and dispersion[53,54] (Fig. 6). Biofilm formation is influenced not only by intrinsic genetic factors but also by extrinsic environmental conditions, such as nutrient availability, temperature, and pH levels. This complex process is mainly regulated by 4 signaling pathways: cAMP/Vfr signaling pathway, Gac/Rsm signaling pathway, QS system, and c-di-GMP signaling pathway. The cAMP/Vfr and Gac/Rsm signaling pathways play crucial roles in regulating the adhesion process during the early stages of the biofilm formation, whereas the QS system is responsible for maintaining biofilm architecture, facilitating the secretion of virulence factors, and promoting the formation of persisting bacteria populations[55]. Furthermore, the c-di-GMP signaling pathway regulates extracellular polysaccharide synthesis, macrocolony and architecture formation, and biofilm maturation[56]. Therefore, inhibiting these 4 signaling pathways represents an important strategy for blocking the formation of *P. aeruginosa* biofilms.

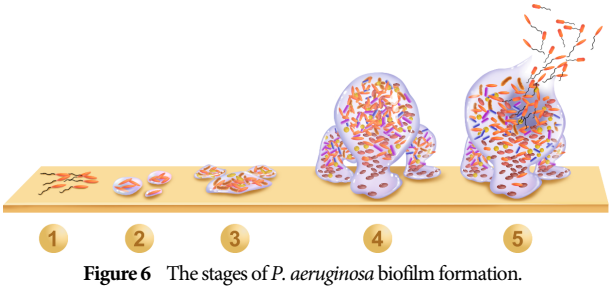


Figure 6 The stages of *P. aeruginosa* biofilm formation.

4 Quorum sensing inhibitors (QSIs)

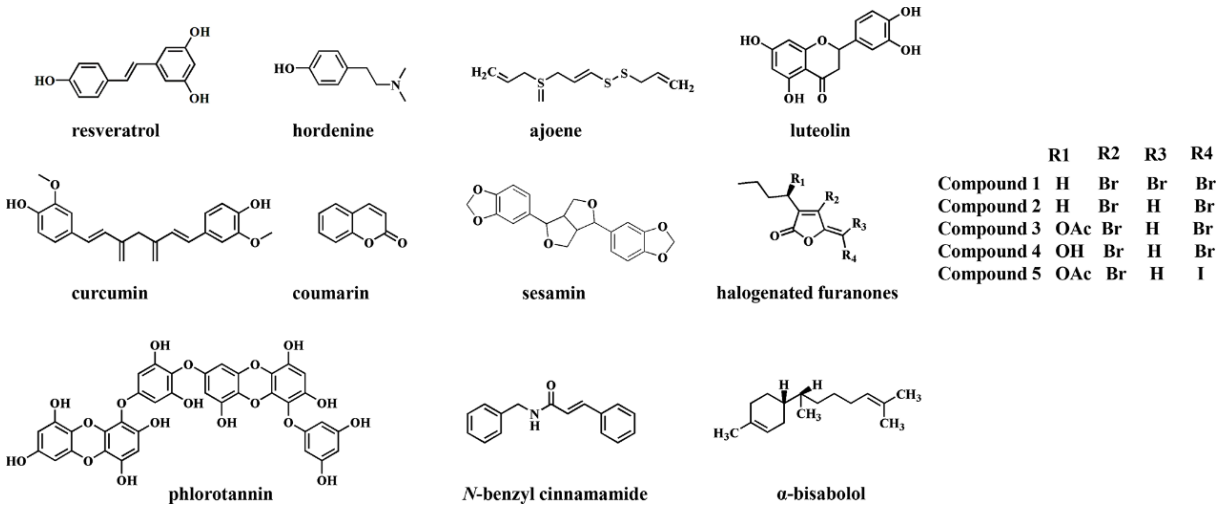
Given the ability to regulate the synthesis of virulence factors, including protease, pyocyanin, and biofilms, QS has emerged as an important target for inhibiting the virulence and pathogenicity of *P. aeruginosa*. The exploration of new and effective QSIs has become a research hotspot for the prevention and control of spoilage, pathogenicity, and drug resistance associated with *P. aeruginosa*. QSIs can eliminate pathogenic bacteria by inhibiting the synthesis of virulence factors, utilizing self-immunity mechanisms to target pathogens, or enhancing the effectiveness of traditional antimicrobial agents[57]. This approach does not cause selective pressure on bacterial populations, thereby naturally reducing their resistance to conventional antibiotics[6]. QSIs can be primarily categorized into 2 types: small molecule QSIs and degrading enzymes.

4.1 Small molecule QSIs

4.1.1 Plant-derived small molecule QSIs

Terrestrial plants serve as important sources of QSIs. For example, resveratrol (Fig. 7), a phenolic compound abundantly found in *Polygonum cuspidatum*, grapes, *Senna obtusifolia*, and peanuts, exhibits potent inhibitory activity against the QS systems of *Chromobacterium violaceum* and *P. aeruginosa*[58]. Hordenine, present in sprouted barley, effectively inhibits the production of virulence factors and biofilm formation in *P. aeruginosa* and *Serratia marcescens* by suppressing their QS systems[34,59]. The plant infection model indicated that hordenine exposure could notably attenuate the pathogenicity of *S. marcescens* in tomato plants[56]. Ajoene, present in onions and cruciferous plants, exerts a strong inhibitory effect on the virulence factors and biofilm formation of *P. aeruginosa*[60]. Luteolin, a flavonoid found in citrus fruits, inhibits the synthesis of extracellular polysaccharides, pyocyanin, alginate and biofilm formation in *P. aeruginosa* by competitively binding to the transcriptional regulator LasR[61]. Curcumin, a natural product derived from *Curcuma longa*, effectively inhibits biofilm formation and the production of virulence factors in *P. aeruginosa* by inhibiting the LasI/LasR QS systems[62]. Coumarin, a broad-spectrum QSI, can effectively reduce infections in aquatic products caused by pathogenic bacteria[63]. Additionally, sesamin demonstrates a significant inhibitory effect on LasR-mediated QS in *P. aeruginosa*[64]. Volatile compounds from plants are also an important source of QSIs. For example, hexanal can effectively inhibit the synthesis of AHLs and the formation of biofilms in *Pseudomonas* spp., thereby reducing the infection of pathogens on vegetables[65]. The application of geraniol could reduce the spoilage of fruits and vegetables induced by *Pseudomonas* spp. by suppressing its QS system[66].

In addition to terrestrial plants, the ocean has been an important source of medicine and food for humans since ancient times. Since the initial discovery of halogenated furanone (QSIs) (Fig. 7) from *Delisea pulchra*, reported by Manefield in 1999, researchers have isolated and identified a wide array of structurally diverse natural QSIs from marine organisms[67,68]. For example, phlorotannin, a seaweed polyphenol isolated from *Sargassum fusiformes*, demonstrates excellent inhibitory activity against the QS systems of *Chromobacterium violaceum*, *P. aeruginosa*, and *Vibrio harzianum*[69]. Additionally, *N*-benzyl cinnamamide, isolated from red seaweed *Gracilaria fisheri*, effectively inhibits biofilm formation in *V. harveyi* by targeting its AI-2 QS system[70]. Furthermore, the natural compound α-bisabolol, isolated from the



	R1	R2	R3	R4
Compound 1	H	Br	Br	Br
Compound 2	H	Br	H	Br
Compound 3	OAc	Br	H	Br
Compound 4	OH	Br	H	Br
Compound 5	OAc	Br	H	I

Figure 7 Plant-derived small molecule QSIs.

brown macroalga *Padina gymnospora*, can mitigate biofilm formation and the secretion of QS-mediated virulence factors in *S. marcescens*[71].

4.1.2 *Animal-derived small molecule QSIs*

The literature review reveals a scarcity of reports on animal-derived small molecule QSIs compared to their plant-derived counterparts. To date, only 3 animal-derived small-molecule QSIs have been reported. Solenopsin A (Fig. 8), a venom alkaloid isolated from the fire ant *Solenopsis invicta*, inhibits the synthesis of virulence factors, such as pyocyanin, by disrupting the *rhl* QS system[72]. Additionally, 10 brominated alkaloids were isolated from *Flustra foliacea*, with 2 of these alkaloids (Fig. 8) demonstrating effective inhibition of the synthesis of signal molecules in *P. aeruginosa*[73]. The secondary metabolites manoalide, manoalide monoacetate, and secomanoalide, derived from sponges, exh ibit potent inhibitory activity against the QS system in *P. aeruginosa*[74].

4.1.3 *Microorganism-derived small molecule QSIs*

Microorganisms represent a rich source of active small molecule compounds, with many traditional antibiotics isolated from their secondary metabolites, such as penicillin, streptomycin, oxytetracycline, erythromycin, etc. Recognizing the crucial role of microorganisms in the development of novel drugs, researchers have increasingly focused on exploring small-molecule QSIs derived from microorganisms, yielding some QSIs with significant bioactivity. For example, *ω*-hydroxyrhein, rhein, and emodin (Fig. 9), isolated from the guttates of *Penicillium restrictum*, effectively inhibit the QS system of *Staphylococcus aureus*[75]. Penicillic acid and patulin (Fig. 9), secreted by *Penicillium* sp., can inhibit the expression of QS-related genes in *P. aeruginosa*[76]. Equisetin, produced by *Fusarium* sp., significantly inhibits biofilm formation in *P. aeruginosa* by suppressing its *las, rhl*, and *pqs* systems[77]. New *α*-pyridones isolated from the extracts of a marine algae-derived *Streptomyces* sp. exhibit inhibitory effect on the *las* system of *P. aeruginosa*[78]. The long-chain fatty aldehyde pentadecanal, secreted by the Antarctic marine bacterium *Pseudoalteromonas haloplanktis*, inhibits biofilm formation in *Staphylococcus epidermidis* by disrupting the AI-2 QS system[79]. Cladodionen, isolated from *Cladosporium* sp. Z148, exhibits a suppressive effect on elastase activity in *P. aeruginosa*[80]. Additionally, the cyclic dipeptide cyclo (Trp-Ser), produced by the marine bacterium *Rheinheimera aquimaris*, significantly reduces the production of virulence factors and biofilm formation in *P. aeruginosa* by inhibiting its LasR receptor[81].

4.1.4 *Chemosynthetic small molecule QSIs*

Although plants, animals, and microorganisms are vital sources of small molecule QSIs, they often present certain limitations, such as low compound yields, challenges in separation and purification, and potential resource wastage[82]. Consequently, chemical synthesis has emerged as the primary strategy for obtaining small molecule QSIs. Currently, the synthesis of small molecule QSIs is mainly achieved through various methods, the first of which involves the structural modification of signaling molecules of C4-HSL, 3-oxo-C12-HSL, and PQS. These structural analogs (Fig. 10, compounds 1-13) can competitively bind to the receptors and inhibit the binding of signaling molecules to their corresponding receptor proteins, thereby exerting QS inhibitory activity[83-85].

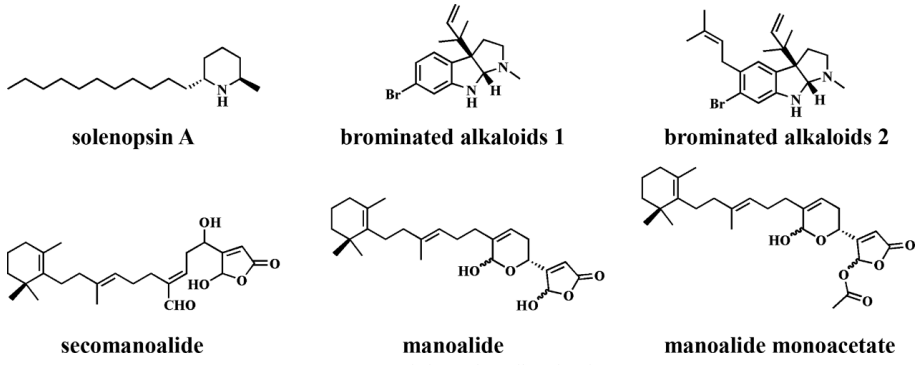


Figure 8 Animal-derived small molecule QSIs.

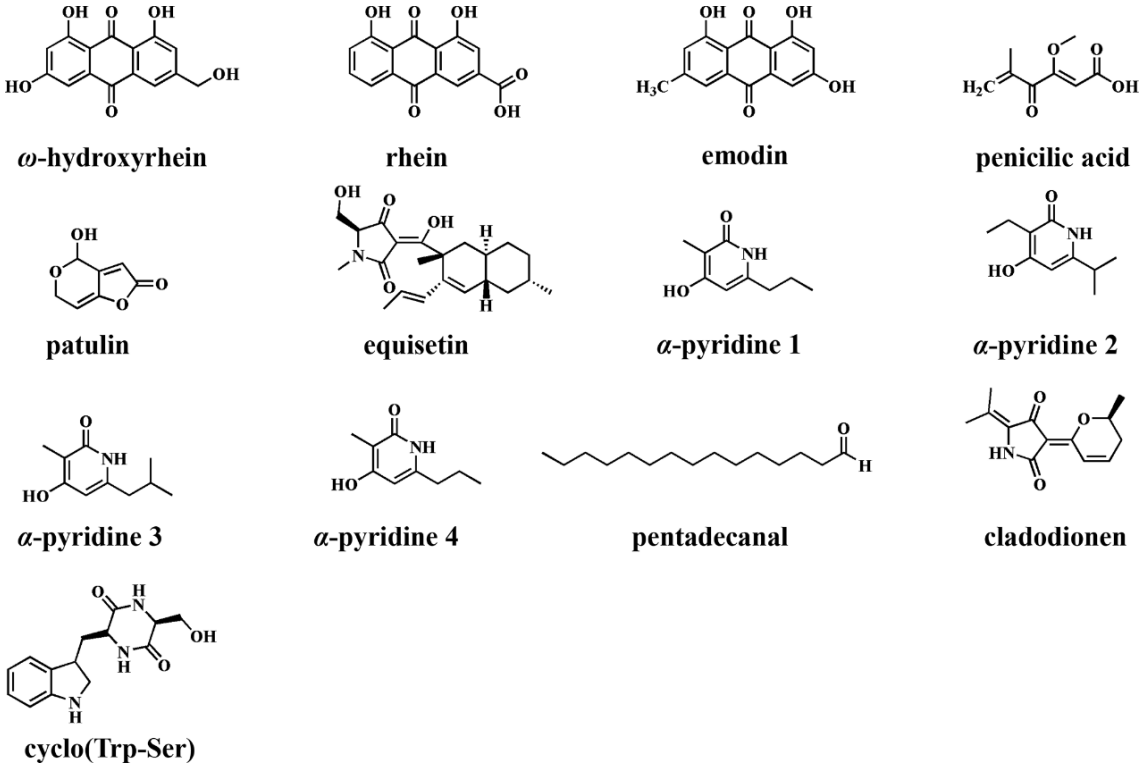


Figure 9 Microorganism-derived small molecule QSIs.

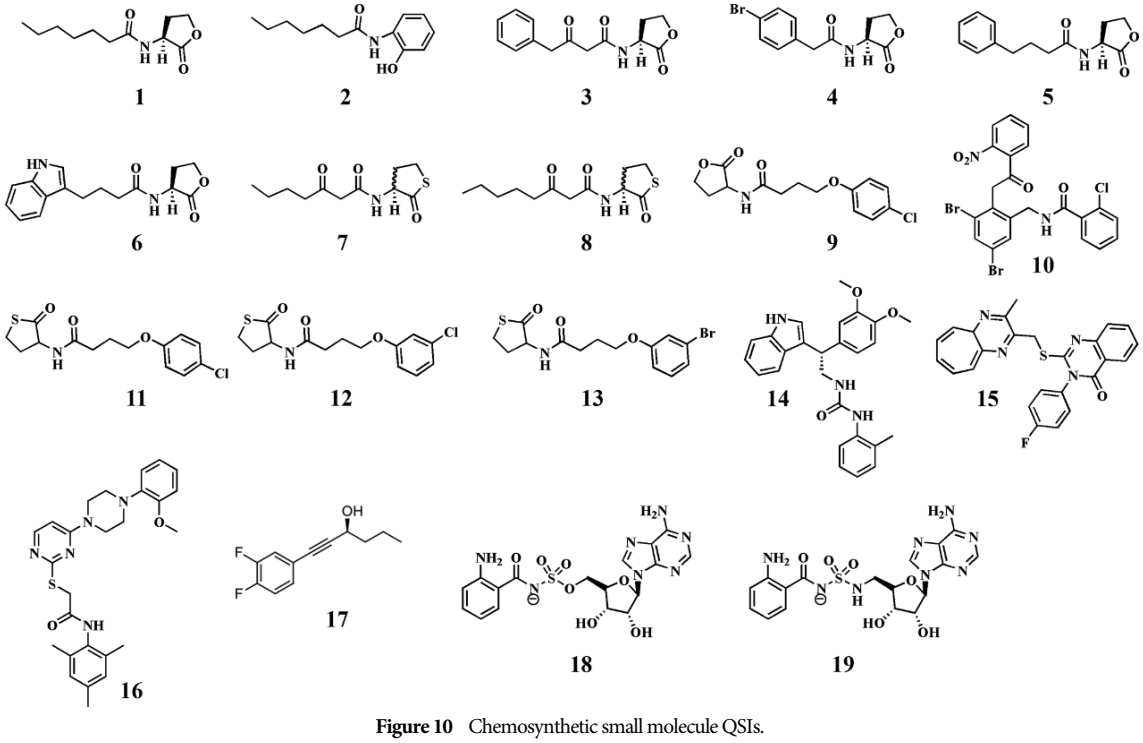


Figure 10 Chemosynthetic small molecule QSIs.

Another approach involves the synthesis of QSIs that can inhibit the activity of specific QS receptor proteins. For example, Vetrivel *et al.* designed and synthesized 12 compounds targeting LasR through computer simulation. Among these, 3 compounds (Fig. 10, compounds 14-16) demonstrated effective inhibition of LasR activity and exhibited significant potential for drug development[86]. Nam *et al.* optimized and synthesized 55 compounds using 4-gingerol as the lead compound, targeting RhlR in their drug design[87]. Among these, alkynyl ketone 30 (Fig. 10, compound 17) effectively inhibited the production of virulence factors and attenuated the lethality of *P. aeruginosa* to yellow mealworm larvae by suppressing the activities of both RhlR and PqsR[87]. Ji *et al.* designed and synthesized a series of sulfonyladenine derivatives utilizing sulfonyladenine as a substrate, targeting PqsA as the protein of interest. Among these compounds, anthranilyl-AMS and anthranilyl-MSN were found to significantly inhibit PqsA activity and the synthesis of signaling molecules, such as 2-heptyl-4-hydroxyquinoline (HHQ) and PQS.

This inhibition ultimately resulted in a reduced secretion of virulence factors, such as pyocyanin[88].

4.1.5 *Degrading enzymes*

During the metabolic process of various microorganisms, a variety of hydrolases is produced, some of which effectively degrade the QS-related effectors of *P. aeruginosa*, eventually leading to the disruption of the QS system. These hydrolases can be classified into 4 distinct classes based on their degradation patterns. The first class comprises AHL lactonases, which specifically hydrolyze the lactone ring of AHLs, resulting in the inactivation of the signaling molecules. The second class consists of lactone-ring decarboxylases. The third and fourth classes include AHL acyltransferase and AHL acyl side chain deaminases, respectively[89-91]. Some microorganisms secrete hydrolytic enzymes that do not target the degradation of signal molecules but instead act on enzymes responsible for their synthesis, thereby blocking their production. For example, the ATP-dependent Lon enzyme can effectively degrade LasI and RhlI, leading to the inhibition of 3-oxo-C12-HSL and C4-HSL synthesis. This action ultimately results in the inactivation of the QS system in *P. aeruginosa*[92].

5 Conclusion and future work

P. aeruginosa is a primary pathogen responsible for causing vegetable spoilage and foodborne diseases. The abuse of antimicrobial agents has intensified the drug resistance of this bacterium. Addressing the issue of drug resistance in *P. aeruginosa* and restoring its antimicrobial susceptibility has emerged as a major global food safety concern in the 21st century. The traditional approach of developing "classical" antimicrobial agents aimed at killing spoilage bacteria has inadvertently led to the evolution of these bacteria and increased resistance to such agents. In contrast, "non-classical" antimicrobial agents that target the virulence factors of spoilage bacteria can weaken virulence and reduce drug resistance by inhibiting the synthesis of virulence factors without killing bacteria. This strategy introduces a novel solution for combating the drug resistance exhibited by *P. aeruginosa*. This review summarizes the QS system, virulence factors, and their association with food spoilage and foodborne diseases. Additionally, it examines various types of QSIs. This review provides a theoretical reference for the development of anti-virulence drugs and strategies to prevent and treat drug resistance in *P. aeruginosa*.

However, there are also many challenges in the development of QSIs. Firstly, bacteria have evolved resistance to QSIs while the research on QSIs has been slowing down year by year[93]. Therefore, the reduction of resistance of bacteria to QSIs should be taken into account when searching for novel QSIs. A first strategy might consist of using QS disrupting technique with a broad activity. AHL lactonase, for instance, is active towards a wide range of AHLs. AHL lactonase has the ability to hydrolyze both short and long chain AHLs with similar efficiency, but shows no or little residue activity to other chemicals, including non-acyl lactones and aromatic carboxylic acid esters, avoiding the fitness and resistance to QSIs[94]. Secondly, most QSIs, especially those derived from plants, commonly suffer from the drawback of high dosage and weak activity. For example, the isoflavones isolated from soybean can significantly inhibit the QS system of P. aeruginosa, but the concentration used is 1 mg/mL[95]. Thirdly, most of the QSIs are toxic to human cells to some extent, which limits their application in food[96]. Furanone C-30, a brominated derivative of natural furanone compounds, is a potent inhibitor of the QS system of *P. aeruginosa*[97]. However, their cytotoxic in cell lines renders them unsuitable for use in food and medicine. Therefore, developing efficient and non-toxic QSIs is expected to become a research hotspot for new antibacterial agents in the future. Finally, most QSIs have a narrow spectrum and are effective against only one or two bacterial strains[96]. All of these issues must be addressed in order to fabricate more effective, less toxic QSIs, which will foster potential value in the long run for drug resistance prevention and treatment approach towards *P. aeruginosa*. Further research will enable us to utilize QSIs more effectively and address constraint issues.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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