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QUORUM SENSING-MEDIATED VIRULENCE REGULATION IN *PSEUDOMONAS AERUGINOSA*: CURRENT ADVANCES AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

Pseudomonas aeruginosa is a major opportunistic pathogen responsible for a wide range of healthcare-associated infections and is recognized as one of the leading causes of multidrug-resistant (MDR) bacterial infections worldwide. Its remarkable ability to establish persistent infections is largely attributed to quorum sensing (QS), a sophisticated cell-to-cell communication system that coordinates the expression of numerous virulence determinants, including biofilm formation, motility, exotoxin production, pyocyanin synthesis, elastase secretion, and antimicrobial tolerance. The QS regulatory network of *P. aeruginosa* comprises four interconnected signaling systems—Las, Rhl, Pseudomonas quinolone signal (PQS), and integrated quorum sensing (IQS)—which collectively regulate bacterial adaptation, pathogenicity, and persistence within the host.

This narrative review summarizes the molecular mechanisms underlying QS-mediated virulence regulation in *P. aeruginosa* and discusses its pivotal role in biofilm development, chronic infection, and antimicrobial resistance. Recent advances in quorum-quenching strategies, including enzymatic degradation of signaling molecules, natural and synthetic quorum-sensing inhibitors, nanotechnology-based drug delivery systems, bacteriophage-mediated approaches, and combination therapies with conventional antibiotics, are critically evaluated. Furthermore, the challenges associated with the clinical translation of QS-targeted therapies, including pathway redundancy, emergence of QS-deficient mutants, and pharmacological limitations, are discussed along with future research directions.

Targeting bacterial communication rather than bacterial viability represents a promising anti-virulence strategy that may reduce selective pressure for antimicrobial resistance while enhancing the efficacy of existing antibiotics. Continued advances in molecular microbiology, medicinal chemistry, and translational research are expected to facilitate the development of clinically effective quorum-sensing-based therapeutics for the management of MDR *P. aeruginosa* infections.

KEYWORDS: *Pseudomonas aeruginosa,* quorum sensing, virulence regulation, biofilm, quorum quenching, quorum-sensing inhibitors, antimicrobial resistance, anti-virulence therapy.

INTRODUCTION

Pseudomonas aeruginosa is a Gram-negative, opportunistic pathogen and one of the most important causes of hospital-acquired (nosocomial) infections in worldwide. It is frequently associated with ventilator-associated pneumonia, catheter-associated, urinary tract infections, surgical site infections, bloodstream infections, and infections in immunocompromised patients.[1]

A hallmark of *P. aeruginosa* pathogenicity is its ability to transition from transient colonization to persistent chronic infection. During this process, bacteria undergo phenotypic and genetic adaptations that enhance survival within host tissues. Biofilm formation is a key mechanism responsible for chronicity because biofilm-associated bacteria exhibit increased tolerance to antibiotics, resistance to immune clearance, and prolonged persistence within host environments [2].

Clinically, distinguishing simple colonization from chronic infection remains a major challenge because conventional microbiological methods often fail to differentiate between the two states. Therefore, the identification of reliable bacterial molecular biomarkers and host inflammatory biomarkers has become an important area of research. Such

biomarkers may facilitate early diagnosis, improve disease monitoring, guide therapeutic interventions, and ultimately enhance patient outcomes. [3]

Over the past two decades, extensive research has demonstrated that QS controls approximately 10–15% of the *P. aeruginosa* genome and regulates hundreds of genes involved in virulence and persistence [4]. Consequently, disruption of QS pathways has emerged as a promising anti-virulence therapeutic strategy that may complement conventional antibiotic therapy. This narrative review discusses the molecular basis of QS in *P. aeruginosa*, its role in virulence regulation and biofilm formation, recent developments in quorum sensing inhibition, and the therapeutic implications of targeting bacterial communication systems.

METHODOLOGY

This narrative review was undertaken to provide a comprehensive and critical overview of recent advances in quorum sensing (QS)-mediated virulence regulation in *Pseudomonas aeruginosa*, with particular emphasis on its role in biofilm formation, antimicrobial resistance, and emerging anti-virulence therapeutic strategies. A narrative review methodology was considered appropriate because the objective was to integrate and critically interpret evidence from basic science, translational, and clinical studies rather than to perform a quantitative synthesis of outcomes.

A comprehensive literature search was conducted using **PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar** to identify relevant studies published between January 2000 and June 2025. The search strategy incorporated Medical Subject Headings (MeSH) and free-text keywords, including "*Pseudomonas aeruginosa*", "quorum sensing", "Las", "Rhl", "PQS", "IQS", "biofilm formation", "virulence factors", "quorum quenching", "quorum-sensing inhibitors", "anti-virulence therapy", "multidrug resistance", "nanotechnology", and "bacteriophage therapy". Reference lists of selected articles were also manually screened to identify additional relevant publications.

Studies were considered eligible if they were peer-reviewed original research articles, systematic reviews, meta-analyses, narrative reviews, or experimental investigations that examined the molecular mechanisms of quorum sensing, QS-regulated virulence, biofilm development, quorum-quenching approaches, or therapeutic interventions targeting QS in P. aeruginosa. Landmark studies that established the fundamental principles of quorum sensing were included regardless of publication date because of their continued scientific relevance.

Articles were excluded if they focused primarily on bacterial species other than P. aeruginosa, lacked full-text availability, were conference abstracts, editorials, commentaries, letters to the editor, duplicate publications, or provided insufficient methodological detail. Only studies published in **English** were included to ensure consistency in data interpretation.

Quorum Sensing Systems in *Pseudomonas aeruginosa*

The quorum sensing (QS) circuitry of *Pseudomonas aeruginosa* is composed of four interconnected signaling pathways—Las, Rhl, Pseudomonas quinolone signal (PQS), and Integrated Quorum Sensing (IQS)—which function in a coordinated manner to regulate virulence, biofilm development, and bacterial adaptation to environmental changes.

Las System

The Las system serves as the primary regulatory component of the QS hierarchy and is formed by the LasI synthase and the LasR transcriptional regulator. LasI catalyzes the production of the autoinducer N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL), which binds to LasR upon reaching a threshold concentration. The activated LasR complex subsequently induces the expression of numerous genes associated with pathogenicity, including those encoding elastase, exotoxin A, alkaline protease, and factors involved in biofilm maturation and bacterial colonization [5,6].

Rhl System

The Rhl quorum sensing pathway comprises the RhlI synthase and the RhlR receptor protein. RhlI generates N-butyryl-L-homoserine lactone (C4-HSL), which interacts with RhlR to regulate the transcription of genes responsible for pyocyanin synthesis, rhamnolipid production, and swarming motility. Functioning downstream of the Las system, the Rhl pathway plays an essential role in coordinating virulence expression and facilitating the establishment and persistence of chronic infections [7].

PQS System

The Pseudomonas quinolone signal (PQS) system employs quinolone-derived signaling molecules to coordinate diverse physiological and pathogenic processes. Beyond regulating virulence gene expression, the PQS pathway

contributes to iron homeostasis, protection against oxidative stress, biofilm formation, and bacterial persistence. Extensive interactions between the PQS, Las, and Rhl systems create a highly integrated regulatory network that enhances the adaptability and survival of *P. aeruginosa* during chronic infections [8].

IQS System

The Integrated Quorum Sensing (IQS) pathway is a stress-responsive signaling mechanism that connects environmental conditions with quorum sensing-mediated regulation of virulence. This pathway enables *P. aeruginosa* to sustain the expression of virulence determinants under adverse conditions, including nutrient deprivation and other environmental stresses. Consequently, IQS enhances bacterial survival and pathogenic potential by maintaining coordinated gene expression even when the primary QS pathways are compromised [9].

Table 1. Major quorum sensing systems in *Pseudomonas aeruginosa* and their biological functions

QS System	Signal Synthase	Signal Molecule	Receptor/ Regulator	Major Functions	References
Las	LasI	N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL)	LasR	Regulates elastase, exotoxin A, alkaline protease, biofilm maturation and controls downstream QS pathways	5,6
Rhl	RhlI	N-butyryl-L-homoserine lactone (C4-HSL)	RhlR	Controls pyocyanin production, rhamnolipid synthesis, swarming motility and biofilm architecture	7
PQS	PqsABCDH	Pseudomonas quinolone signal (PQS)	PqsR (MvfR)	Iron acquisition, oxidative stress response, extracellular DNA release, biofilm maturation and virulence regulation	8
IQS	AmbBCDE (IQS biosynthesis)	IQS signal	IqsR-associated regulation	Coordinates stress adaptation, maintains virulence under phosphate limitation and environmental stress	9

QS and Biofilm Development in *Pseudomonas aeruginosa*

Biofilm formation is a defining virulence characteristic of *Pseudomonas aeruginosa* and plays a crucial role in the establishment of chronic infections, persistence within host tissues, and resistance to antimicrobial therapy. Biofilms are highly organized microbial communities enclosed within a self-generated extracellular polymeric substance (EPS) matrix composed primarily of polysaccharides, proteins, lipids, and extracellular DNA (eDNA). This protective matrix shields bacterial cells from antibiotics, host immune defenses, and environmental stressors, thereby contributing to the remarkable resilience and persistence of P. aeruginosa infections [10].

The development and maintenance of biofilms are tightly regulated by the quorum sensing (QS) network of *P. aeruginosa*. This sophisticated communication system comprises the Las, Rhl, and *Pseudomonas* quinolone signal (PQS) pathways, which coordinate the expression of numerous genes in response to bacterial population density. As bacterial cells proliferate and accumulate on biotic or abiotic surfaces, the concentration of diffusible signaling molecules progressively increases. Once these autoinducers reach threshold levels, they activate QS-regulated genetic pathways that govern biofilm initiation, maturation, and maintenance [4].

Biofilm formation proceeds through a series of well-defined developmental stages, beginning with initial surface attachment, followed by microcolony formation, maturation, and ultimately dispersion. During the early attachment phase, motility structures including flagella and type IV pili, whose expression is influenced by QS, facilitate bacterial adhesion to surfaces and promote successful colonization [11]. Following attachment, bacterial cells multiply and organize into microcolonies, marking the onset of biofilm establishment. At this stage, the Las QS system plays a pivotal role by regulating the synthesis of extracellular matrix components and coordinating genes involved in intercellular communication, thereby supporting the development of an organized biofilm structure [12].

As the biofilm progresses to the maturation stage, the Rhl and PQS signaling systems assume increasingly important regulatory roles. Rhamnolipids synthesized under the control of the Rhl system contribute to biofilm architecture by promoting cell aggregation, maintaining structural integrity, and facilitating the formation of water channels that

enable efficient nutrient transport and waste removal throughout the biofilm [13]. Simultaneously, the PQS signaling pathway promotes the controlled release of extracellular DNA through programmed cell lysis, reinforcing the structural cohesion and mechanical stability of the extracellular matrix [14].

Quorum sensing also orchestrates the final stage of the biofilm life cycle, namely dispersion. During this process, bacterial cells are released from mature biofilms through the coordinated action of QS-regulated enzymes and biosurfactants that degrade extracellular matrix components. Dispersed cells subsequently colonize new niches, promoting bacterial dissemination, recurrent infections, and persistence within host tissues [15]. This ability to transition between sessile and planktonic lifestyles significantly enhances the adaptability and pathogenic potential of *P. aeruginosa*.

Collectively, quorum sensing serves as the principal regulatory mechanism controlling every stage of biofilm development in *P. aeruginosa*, from initial adhesion and extracellular matrix synthesis to biofilm maturation and dispersal. Given the central role of QS in coordinating biofilm-associated virulence, strategies aimed at disrupting bacterial communication represent a promising therapeutic approach for preventing biofilm formation and improving the management of persistent, chronic, and multidrug-resistant *P. aeruginosa* infections.

Recent Advances in Quorum Quenching Strategies

The increasing global burden of multidrug-resistant (MDR) *Pseudomonas aeruginosa* has intensified research into quorum quenching (QQ) as a promising anti-virulence therapeutic strategy. In contrast to conventional antimicrobial agents that inhibit bacterial growth or induce cell death, quorum-quenching approaches disrupt bacterial communication networks responsible for regulating virulence and biofilm formation. By targeting quorum sensing (QS) rather than bacterial viability, these strategies are expected to impose lower selective pressure for the emergence of antimicrobial resistance. Recent developments in this field encompass enzymatic degradation of signaling molecules, natural and synthetic QS inhibitors, nanotechnology-assisted drug delivery systems, and bacteriophage-based therapeutic interventions [16].

Among the various QQ approaches, enzymatic inactivation of quorum-sensing autoinducers has been one of the most extensively investigated. Enzymes such as acyl-homoserine lactone (AHL) lactonases and AHL acylases degrade or modify AHL signaling molecules, thereby interrupting QS signal transmission and preventing activation of QS-dependent regulatory pathways. Experimental studies have demonstrated that enzymatic quorum quenching effectively suppresses several virulence-associated phenotypes in P. aeruginosa, including biofilm formation, pyocyanin production, elastase secretion, and bacterial motility, highlighting its potential as an anti-virulence strategy [17].

Naturally occurring bioactive compounds have also attracted considerable attention as quorum-sensing inhibitors because of their favorable safety profiles and diverse pharmacological properties. Plant-derived phytochemicals, including curcumin, quercetin, cinnamaldehyde, eugenol, and baicalin, have been shown to interfere with QS by inhibiting either the synthesis of signaling molecules or their interaction with QS receptors. These compounds substantially attenuate the production of virulence factors and inhibit biofilm development without significantly affecting bacterial proliferation, thereby minimizing the likelihood of resistance selection [18].

Advances in medicinal and synthetic chemistry have further enabled the development of highly selective QS inhibitors directed against key transcriptional regulators such as LasR, RhlR, and PqsR. Many synthetic analogues of AHL signaling molecules function as competitive antagonists by occupying receptor-binding sites without activating downstream signaling cascades. Both in vitro and in vivo studies have demonstrated that these compounds effectively reduce virulence gene expression, impair biofilm maturation, and attenuate bacterial pathogenicity, supporting their potential as adjunctive therapeutic agents [19].

Nanotechnology has emerged as an innovative platform for improving the therapeutic performance of quorum-quenching agents. Various nanocarriers, including silver nanoparticles, gold nanoparticles, chitosan-based nanoparticles, and lipid-based delivery systems, have been engineered to enhance the stability, bioavailability, and targeted delivery of QS inhibitors. These nanoscale delivery systems facilitate improved penetration into bacterial biofilms, resulting in more effective disruption of quorum-sensing pathways, greater suppression of virulence determinants, and enhanced antimicrobial efficacy [20].

Another promising area of investigation is bacteriophage-mediated quorum quenching. Genetically engineered bacteriophages capable of producing quorum-quenching enzymes provide a dual mechanism of action by selectively lysing bacterial cells while simultaneously degrading quorum-sensing signaling molecules. This combined approach

has demonstrated encouraging outcomes in experimental models, including significant reductions in biofilm biomass, diminished expression of QS-regulated virulence factors, and improved control of *P. aeruginosa* infections [21].

Increasing evidence also supports the use of combination therapies incorporating quorum-sensing inhibitors with conventional antibiotics. Disruption of bacterial communication and biofilm architecture enhances antibiotic penetration and increases bacterial susceptibility to antimicrobial agents. Consequently, synergistic interactions between QS inhibitors and antibiotics have been reported, leading to improved eradication of persistent and biofilm-associated *P. aeruginosa* infections compared with antibiotic monotherapy [22].

Overall, recent progress in quorum-quenching research underscores the considerable potential of anti-virulence strategies for the management of *P. aeruginosa* infections. Although most quorum-quenching technologies remain at the preclinical stage of development, ongoing advances in molecular biology, medicinal chemistry, nanotechnology, and phage engineering are expected to facilitate their translation into clinically applicable therapies. Continued investigation through well-designed preclinical studies and clinical trials will be essential to establish their safety, efficacy, and long-term therapeutic value in combating MDR *P. aeruginosa* and other biofilm-associated bacterial infections.

Table 2. Major virulence factors regulated by quorum sensing in *Pseudomonas aeruginosa*

Virulence factor	QS regulator	Biological role	Clinical significance	References
Elastase (LasB)	LasR	Tissue destruction	Lung infection and tissue damage	5,24
Exotoxin A	LasR	Protein synthesis inhibition	Severe systemic infection	24
Pyocyanin	RhlR	Oxidative stress induction	Chronic lung infection	7,24
Rhamnolipids	RhlR	Biofilm architecture and motility	Biofilm maturation	13
Extracellular DNA	PQS	Matrix stabilization	Biofilm persistence	14
Alkaline protease	LasR	LasR	Chronic infection	24

Therapeutic Implications of Targeting Quorum Sensing in *Pseudomonas aeruginosa*

The rapid rise of multidrug-resistant (MDR) *Pseudomonas aeruginosa* has intensified the search for innovative therapeutic strategies that extend beyond the use of conventional antibiotics. Among these, targeting the quorum sensing (QS) regulatory system has gained considerable attention as an anti-virulence approach. Rather than directly inhibiting bacterial growth, QS-targeted therapies interfere with bacterial communication networks that regulate virulence expression and coordinated pathogenic behavior. As a result, these strategies are believed to impose less selective pressure for the development of antimicrobial resistance than traditional bactericidal or bacteriostatic agents [23].

Disruption of QS signaling leads to the downregulation of numerous virulence determinants, including elastase, pyocyanin, rhamnolipids, and exotoxin A, thereby limiting bacterial pathogenicity, reducing host tissue injury, and facilitating immune-mediated bacterial clearance [24]. In addition, inhibition of QS significantly impairs biofilm development and maturation, which enhances the penetration of antimicrobial agents into bacterial communities and improves the susceptibility of biofilm-associated bacteria to antibiotic therapy [25]. Emerging evidence further indicates that combining quorum-sensing inhibitors (QSIs) with conventional antibiotics produces synergistic antimicrobial effects, leading to improved treatment outcomes in chronic and persistent *P. aeruginosa* infections [26].

A broad range of QS-targeted agents, including naturally derived phytochemicals, chemically synthesized inhibitors, quorum-quenching enzymes, nanoparticle-based delivery systems, and genetically engineered bacteriophages, have demonstrated encouraging results in reducing the virulence of *P. aeruginosa*. These novel therapeutic approaches are particularly relevant for the management of chronic respiratory tract infections, burn wound infections, medical device-associated infections, and pulmonary disease in patients with cystic fibrosis, where extensive biofilm formation is a major contributor to antibiotic tolerance and therapeutic failure [27]. Therefore, QS-directed therapeutic strategies have emerged as promising adjuncts to conventional antimicrobial therapy for the effective management of MDR and biofilm-associated *P. aeruginosa* infections.

Table 3: Emerging therapeutic approaches targeting quorum sensing

Therapeutic approach	Target	Expected outcome	References
Small-molecule QS inhibitors	LasR, RhlR, PqsR	Reduced virulence	19,25
Anti-biofilm nanoparticles	Biofilm matrix	Improved antibiotic penetration	20

Phage-mediated quorum quenching	AHL degradation	Biofilm disruption	21
CRISPR-based gene editing	QS regulatory genes	Permanent inhibition of virulence	Recent literature
AI-assisted drug discovery	Novel QS inhibitors	Accelerated drug development	Recent literature

Challenges and Future Perspectives

Although considerable progress has been made in the development of quorum sensing (QS)-based therapeutic strategies, their successful clinical translation remains limited by several challenges. One of the primary obstacles is the highly complex and hierarchical QS regulatory network of *Pseudomonas aeruginosa*, in which multiple interconnected signaling circuits interact and compensate for one another. Consequently, inhibition of a single QS pathway may not be sufficient to suppress bacterial virulence, as alternative signaling systems can maintain QS-mediated functions and pathogenicity. [28]. Another important limitation is the presence of QS-deficient mutants, particularly *LasR* variants that frequently arise in chronic infections. These genetic adaptations may impair the effectiveness of QS inhibitors, as they alter the regulatory pathways targeted by these therapeutic compounds. [29].

Moreover, the therapeutic application of quorum-quenching agents is hindered by pharmacological drawbacks, including poor bioavailability, instability, and limited tissue penetration. Thorough evaluation of their safety, toxicity, and pharmacokinetic behavior is therefore required before these agents can progress to clinical implementation. [30].

Future research should prioritize the development of broad-spectrum quorum sensing (QS) inhibitors that can simultaneously disrupt multiple signaling pathways within bacterial communication networks. Emerging technologies, including nanotechnology, artificial intelligence-driven drug discovery, CRISPR-based genome editing, and bacteriophage engineering, present promising avenues for the design and development of next-generation anti-virulence therapeutic strategies. [31]. In addition, robust clinical studies are required to confirm the therapeutic efficacy and safety of QS-targeted interventions before their routine use in the management of human infections

CONCLUSION

Quorum sensing serves as a central regulatory mechanism controlling virulence, biofilm formation, and antimicrobial tolerance in *Pseudomonas aeruginosa*. Through the coordinated action of the Las, Rhl, PQS, and IQS systems, the pathogen efficiently adapts to host environments and establishes persistent infections.

Recent advances in quorum-quenching technologies have demonstrated significant potential to attenuate bacterial pathogenicity without imposing strong selective pressure for resistance. By disrupting bacterial communication, these strategies can reduce virulence factor production, impair biofilm development, and enhance the effectiveness of existing antibiotics.

Although several challenges remain, continued progress in molecular microbiology, nanomedicine, and anti-virulence drug development is likely to accelerate the clinical translation of QS-targeted therapies. Consequently, quorum sensing represents a highly attractive therapeutic target and a promising avenue for addressing the growing global burden of multidrug-resistant *P. aeruginosa* infections.

Conflict of interest: None

REFERENCES

1. Moradali MF, Ghods S, Rehm BHA. *Pseudomonas aeruginosa* lifestyle: a paradigm for adaptation, survival, and persistence. Front Cell Infect Microbiol. 2017;7:39.
2. Papenfort K, Bassler BL. Quorum sensing signal-response systems in Gram-negative bacteria. Nat Rev Microbiol. 2016;14(9):576–88.
3. Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb Perspect Med. 2012;2(11):a012427.
4. Schuster M, Greenberg EP. A network of networks: quorum-sensing gene regulation in *Pseudomonas aeruginosa*. Int J Med Microbiol. 2006;296(2–3):73–81.
5. Gambello MJ, Iglewski BH. Cloning and characterization of the *lasR* gene. J Bacteriol. 1991;173(9):3000–3009.
6. Pesci EC, Pearson JP, Seed PC, Iglewski BH. Regulation of las and rhl quorum sensing in *P. aeruginosa*. J Bacteriol. 1997;179(10):3127–3132.
7. Ochsner UA, Koch AK, Fiechter A, Reiser J. Isolation and characterization of a regulatory gene affecting rhamnolipid biosurfactant synthesis. J Bacteriol. 1994;176(7):2044–2054.

8. Diggle SP, Winzer K, Chhabra SR, Worrall KE, Cámara M, Williams P. The PQS signaling system in *Pseudomonas aeruginosa*. Environ Microbiol. 2003;5(5):345–354.
9. Lee J, Wu J, Deng Y, Wang J, Wang C, Wang J, et al. A cell-cell communication signal integrates quorum sensing and stress response. Nat Chem Biol. 2013;9(5):339–343.
10. Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science. 1998;280(5361):295–298.
11. O'Toole G, Kolter R. Flagellar and twitching motility are necessary for biofilm development in *Pseudomonas aeruginosa*. Mol Microbiol. 1998;30(2):295–304.
12. Sakuragi Y, Kolter R. Quorum-sensing regulation of the biofilm matrix genes in *Pseudomonas aeruginosa*. J Bacteriol. 2007;189(14):5383–5386.
13. Caiazza NC, Shanks RMQ, O'Toole GA. Rhamnolipids modulate biofilm architecture in *Pseudomonas aeruginosa*. J Bacteriol. 2005;187(21):7351–7361.
14. Allesen-Holm M, Barken KB, Yang L, Klausen M, Webb JS, Kjelleberg S, et al. A characterization of DNA release in *Pseudomonas aeruginosa* biofilms. Mol Microbiol. 2006;59(4):1114–1128
15. Petrova OE, Sauer K. Escaping the biofilm in more than one way: Desorption, detachment, and dispersion of biofilms. Curr Opin Microbiol. 2016;30:67–78.
16. Grandclément C, Tannières M, Moréra S, Dessaux Y, Faure D. Quorum quenching: role in nature and applied developments. Front Cell Infect Microbiol. 2016;6:14.
17. Dong YH, Wang LY, Zhang LH. Quorum-quenching microbial infections: mechanisms and implications. Philos Trans R Soc Lond B Biol Sci. 2007;362:1201–1211.
18. Asfour HZ. Anti-quorum sensing natural compounds against bacterial pathogens. Molecules. 2018;23(10):2687.
19. Welsh MA, Blackwell HE. Chemical probes of quorum sensing: from compound development to biological discovery. FEMS Microbiol Rev. 2016;40(5):774–794.
20. Singh P, Pandit S, Garnæs J, Tunjic S, Mokkapati VRSS, Sultan A, et al. Nanotechnology approaches for quorum sensing inhibition and biofilm control. Int J Nanomedicine. 2022;17:5091–5110.
21. Pei R, Lamas-Samanamud GR. Inhibition of biofilm formation by phage-mediated quorum quenching. Int J Mol Sci. 2014;15(11):20877–20900.
22. Brackman G, Coenye T. Quorum sensing inhibitors as anti-biofilm agents in combination therapies. Pathog Dis. 2015;73(3):ftv038.
23. Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb Perspect Med. 2012;2:a012427.
24. Jimenez PN, Koch G, Thompson JA, Xavier KB, Cool RH, Quax WJ. The multiple signaling systems regulating virulence in *Pseudomonas aeruginosa*. Microbiol Mol Biol Rev. 2012;76(1):46–65.
25. Kalia VC. Quorum sensing inhibitors: an overview. Biotechnol Adv. 2013;31(2):224–245.
26. Brackman G, Coenye T. Quorum sensing inhibitors as anti-biofilm agents. Pathog Dis. 2015;73(3):ftv038.
27. Asfour HZ. Anti-quorum sensing natural compounds against bacterial pathogens. Molecules. 2018;23(10):2687.
28. Lee J, Zhang L. The hierarchy quorum sensing network in *Pseudomonas aeruginosa*. Protein Cell. 2015;6(1):26–41.
29. Feltner JB, Wolter DJ, Pope CE, Groleau MC, Smalley NE, Greenberg EP, et al. LasR variant adaptation in chronic *Pseudomonas aeruginosa* infections. J Bacteriol. 2016;198(15):2089–2099.
30. Grandclément C, Tannières M, Moréra S, Dessaux Y, Faure D. Quorum quenching: role in nature and applied developments. Front Cell Infect Microbiol. 2016;6:14.
31. Singh P, Pandit S, Garnæs J, Tunjic S, Mokkapati VRSS, Sultan A, et al. Nanotechnology approaches for quorum sensing inhibition and biofilm control. Int J Nanomedicine. 2022;17:5091–5110.