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Quorum Sensing as an Antivirulence Strategy in Control of Bacterial Infections

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Abstract. *Quorum sensing (QS) is a bacterial cell-to-cell communication system that plays a central role in regulating virulence, biofilm formation, pathogen adaptation, and infection persistence. The global rise in antimicrobial resistance, driven by conventional antibiotic use, has spurred the development of alternative, non-lethal approaches, including antivirulence strategies. This review aims to examine quorum sensing as an antivirulence target and to evaluate the potential of quorum-sensing inhibition (QSI) to control bacterial infection. A narrative literature review was conducted using scientific publications from 2016 to 2026 retrieved from reputable databases. The review highlights that QS regulates multiple pathogenic determinants, including virulence factor production, control of secretion systems, biofilm development, colonization processes, and bacterial survival within host environments. QSI-based interventions include inhibition of signal molecule synthesis, enzymatic degradation of autoinducers, and receptor competition. Because QSI does not directly affect bacterial viability, it may reduce the selective pressure that drives antimicrobial resistance. Beyond clinical applications in chronic and biofilm-associated infections, QSI also has promising prospects in food safety, environmental management, and medical technologies. However, challenges related to compound stability, in vivo effectiveness, and potential bacterial adaptation require further investigation before broader clinical implementation can be achieved.*

Keywords: *Antimicrobial Resistance; Antivirulence; Biofilm; Quorum Sensing Inhibition; Virulence*

1. Introduction

Antimicrobial resistance (AMR) has been recognized as a serious global public health threat in the 21st century. Antimicrobial resistance occurs when bacteria develop adaptive mechanisms that reduce the effectiveness of previously successful antimicrobial therapies. This crisis is largely driven by the excessive and inappropriate use of antibiotics across healthcare, agriculture, livestock, and food production sectors (Ahmed et al., 2024). As a result, antimicrobial resistance was directly responsible for more than 1.2 million deaths in 2019, and this number is projected to reach approximately 10 million deaths annually by 2050 without effective interventions (Slathia et al., 2026). Continuous antibiotic exposure exerts strong selective pressure, accelerates the emergence of both intrinsic and acquired resistance mechanisms, ultimately reducing treatment efficacy and limiting available therapeutic options (Galgano et al., 2025; Oladeinde et al., 2019).

Besides promoting antimicrobial resistance, conventional antibiotics also disrupt the host microbiota because they are not fully selective toward pathogenic bacteria. Antibiotic-induced dysbiosis impairs colonization resistance, alters immune homeostasis, and promotes

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the expansion of the resistome, thereby increasing susceptibility to opportunistic infections and other microbiota-associated disorders (Dahiya & Nigam, 2023; Fakharian et al., 2023; Khan et al., 2021; Nikmaram et al., 2022). These limitations highlight the need for alternative therapeutic strategies to control bacterial infections while minimizing both the development of resistance and microbiota disruption. Among the proposed alternatives, antivirulence therapy has gained increasing attention because it targets bacterial pathogenicity rather than bacterial viability. By suppressing virulence without directly inhibiting bacterial growth, this strategy is expected to impose lower selective pressure than conventional antibiotics, thereby reducing the likelihood of resistance development (El-Sayed et al., 2026).

One of the most promising antivirulence targets is quorum sensing (QS), a bacterial cell-to-cell communication system that coordinates population density-dependent gene expression, including biofilm formation, toxin production, motility, and the secretion of virulence-associated factors (Solekha et al., 2026). Because multiple virulence determinants are regulated simultaneously through QS, disrupting this signaling network is considered more advantageous than targeting individual virulence factors. Consequently, quorum-sensing inhibition (QSI) has emerged as a promising strategy to attenuate bacterial pathogenicity while minimizing the evolutionary pressure associated with conventional antimicrobial therapy (Konwar et al., 2022; Vadakkan et al., 2026).

Against this background, this review examines the role of QS as an antivirulence strategy for controlling bacterial infections. Specifically, it discusses the regulatory functions of QS in bacterial virulence, the principles of antivirulence therapy, and the potential of QSI as an alternative or complementary approach to conventional antibiotic treatment. This review aims to provide a comprehensive perspective on the potential of QS- and QSI-based interventions for combating bacterial infections in the era of escalating antimicrobial resistance.

While previous reviews have discussed quorum sensing inhibition or antivirulence therapy separately (Davares et al., 2022; Dehbanipour & Ghalavand, 2022; Li et al., 2022), this review provides a comprehensive synthesis of both natural and synthetic QSI strategies, systematically compares the three principal mechanisms of quorum sensing inhibition, and integrates current evidence on their applications in human health, food safety, and environmental biotechnology. By combining mechanistic, translational, and application-oriented perspectives, this review provides a broader framework for understanding QSI as a sustainable antivirulence strategy against antimicrobial resistance.

Furthermore, the development of QSI-based antivirulence strategies aligns with broader global health and sustainability goals. By supporting the development of innovative therapeutic approaches with reduced reliance on conventional antibiotics, QSI-based interventions contribute to Sustainable Development Goals (SDGs), particularly SDG 3.4 (promoting health through prevention and treatment), SDG 3.8 (access to safe, effective, quality and affordable essential medicines), and SDG 12.4 (environmentally sound management of chemicals) (United Nations, 2015). Therefore, advancing QSI-based therapeutics may contribute not only to mitigating antimicrobial resistance but also to promoting more sustainable healthcare practices.

2. Methods

This study employed a narrative literature review with a structured literature search to examine the development of antivirulence therapy, quorum sensing (QS), quorum-sensing

inhibition (QSI), and their implications for bacterial virulence, biofilm formation, pathogen adaptation, bacterial persistence, and antimicrobial resistance. Only publications published between 2016 and 2026 were included to ensure the use of recent scientific evidence.

Literature was retrieved from PubMed, Scopus, Web of Science, ScienceDirect, SpringerLink, and Google Scholar using combinations of the following keywords: "antivirulence therapy," "anti-virulence strategy," "non-lethal antimicrobial," "quorum sensing," "quorum sensing inhibition," "quorum quenching," "QS inhibitor," "QS interference," "signal synthesis inhibition," "autoinducer degradation," "enzymatic quorum quenching," "receptor antagonism," "bacterial virulence," "biofilm formation," "pathogen adaptation," "bacterial persistence," and "antimicrobial resistance." Boolean operators (AND/OR) were applied to optimize the search strategy.

Eligible literature included experimental (in vitro and/or in vivo) studies, clinical studies, and review articles used as conceptual references that addressed QS, QSI, antivirulence therapy, or antimicrobial resistance. Only full-text articles published in English or Indonesian between 2016 and 2026 were included. Editorials, commentaries, opinion articles, duplicate publications, irrelevant studies, and articles without accessible full texts were excluded.

The retrieved articles were screened through title, abstract, and full-text evaluation according to the predefined eligibility criteria. Reference management and duplicate removal were performed using Mendeley. Subsequently, the selected studies were synthesized using a thematic-comparative approach by grouping evidence into five major themes: (1) concepts and development of antivirulence therapy; (2) mechanisms of quorum-sensing inhibition; (3) effects on bacterial virulence and biofilm formation; (4) roles in pathogen adaptation and persistence; and (5) implications for antimicrobial resistance and potential clinical applications.

3. Results and Discussion

3.1. Basic Concepts of Quorum Sensing

3.1.1. Definition and General Principles of Quorum Sensing

Quorum sensing (QS) is a bacterial cell-to-cell communication system that coordinates population density-dependent gene expression through the production, release, and detection of signaling molecules known as autoinducers (AIs) (Bao et al., 2025). As bacterial populations increase, AIs accumulate in the extracellular environment until a threshold concentration is reached, triggering the activation or repression of QS-responsive genes involved in diverse physiological processes and bacterial virulence (Sonbol et al., 2022; M. Xu et al., 2023).

Through this coordinated regulation, QS controls multiple pathogenicity-associated traits, including biofilm formation (Markowska et al., 2024), toxin and enzyme production (Tang et al., 2026; Vidal et al., 2015), and siderophore synthesis (Naga et al., 2024). Because QS simultaneously regulates numerous virulence determinants, it has emerged as an attractive target for antivirulence strategies aimed at attenuating bacterial pathogenicity without directly affecting bacterial viability (Falà et al., 2022).

3.1.2. Quorum-Sensing Signal Molecules

Bacteria employ distinct QS signaling molecules according to their phylogenetic characteristics (Figure 1). Gram-negative bacteria primarily utilize N-acyl-homoserine lactones (AHLs), Gram-positive bacteria rely on autoinducing peptides (AIPs), whereas

autoinducer-2 (AI-2) functions as an interspecies signaling molecule shared by diverse bacterial taxa. Despite differences in signal molecules and perception mechanisms, these QS systems ultimately coordinate population density-dependent gene expression associated with bacterial adaptation, virulence, and pathogenicity.

In Gram-negative bacteria, AHLs are the predominant QS signaling molecules. Structural variations in AHLs, including acyl side-chain length, substitutions at the third carbon, and the degree of saturation, determine signal specificity and regulatory responses. Upon reaching a threshold concentration, AHLs bind LuxR-family transcriptional regulators to activate or repress QS-responsive genes, while positive feedback through LuxI further amplifies signal production via autoinduction (Cai & Zhang, 2024).

In contrast, Gram-positive bacteria employ peptide-based AIPs that are detected through membrane-associated two-component regulatory systems consisting of histidine kinase receptors and cytoplasmic response regulators. Because AIPs cannot freely diffuse across the cell membrane, they require dedicated export and sensing mechanisms. Activation of this signaling cascade subsequently regulates genes involved in bacterial physiology and virulence (Williams, 2025). The major quorum sensing signaling systems in Gram-negative bacteria, Gram-positive bacteria, and interspecies AI-2 communication are illustrated in Figure 1.

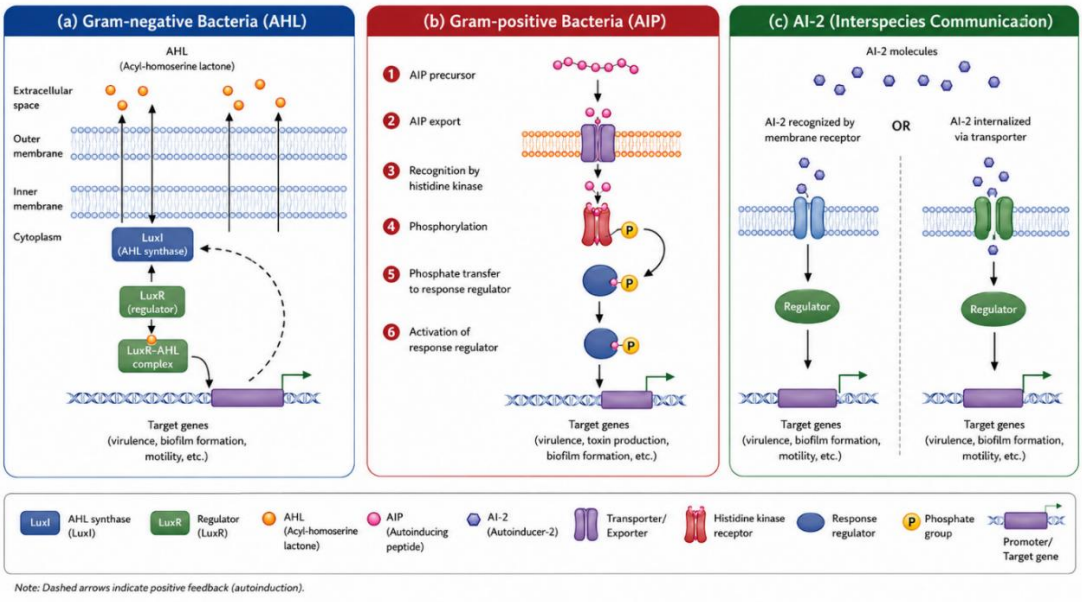

Figure 1. Major quorum sensing signaling systems in bacteria: (a) AHL-mediated signaling in Gram-negative bacteria, (b) AIP-mediated signaling in Gram-positive bacteria, and (c) AI-2-mediated interspecies communication. Dashed arrows indicate positive feedback (autoinduction) (Cai & Zhang, 2024; Williams, 2025; L. Zhang et al., 2020).

Unlike the species-specific AHL and AIP systems, AI-2 is widely distributed among both Gram-negative and Gram-positive bacteria and is recognized as a key mediator of interspecies communication. Depending on the bacterial species, AI-2 may be detected by membrane receptors or internalized through specialized transporters such as the Lsr system before modulating downstream gene expression (L. Zhang et al., 2020). Although AI-2 has also been proposed to function as an environmental cue or metabolic byproduct, its

widespread distribution highlights an essential role in coordinating interactions within polymicrobial communities (Guo et al., 2026; X. Liu et al., 2022).

3.2. The Role of Quorum Sensing in Regulating Bacterial Virulence

QS functions not only as a bacterial communication system but also as a global regulatory network that coordinates the expression of multiple virulence determinants in a population density-dependent manner. Through this regulatory mechanism, QS orchestrates biofilm formation, virulence factor production, pathogen adaptation, and bacterial persistence, thereby promoting successful host colonization and infection.

3.2.1. Regulation of Biofilm Formation

Biofilm formation is a major virulence strategy that enhances bacterial colonization, persistence, and tolerance to antibiotics and host immune defenses. Within biofilms, bacterial cells are embedded in an extracellular polymeric substance (EPS) matrix that provides structural protection while creating heterogeneous microenvironments that promote metabolic diversity and bacterial survival (X. Zhang et al., 2025).

QS plays a central role in coordinating biofilm development by regulating bacterial adhesion, EPS production, biofilm maturation, and cell dispersal. Through this coordinated regulation, QS facilitates the transition between planktonic and biofilm lifestyles, thereby promoting persistent infection and reducing susceptibility to antimicrobial therapy. Consequently, disruption of QS has emerged as a promising strategy for preventing biofilm formation and attenuating bacterial virulence (Sedarat et al., 2023).

3.2.2. Virulence Factor Production

QS plays a central role in regulating the expression and secretion of bacterial virulence factors, enabling pathogens to coordinate their pathogenic potential according to population density and environmental conditions (Shen et al., 2023). This regulation is largely mediated through bacterial secretion systems, which translocate toxins, enzymes, and other effector molecules into the extracellular environment or directly into host cells.

In Gram-positive bacteria such as *Staphylococcus aureus*, increasing concentrations of autoinducing peptides (AIPs) activate the Agr two-component system, inducing the production of major toxins, including hemolysins and phenol-soluble modulins (PSMs), while repressing adhesion-associated proteins. This regulatory switch facilitates the transition from bacterial colonization to invasive infection (Butrico & Cassat, 2020).

Similarly, in Gram-negative bacteria such as *Pseudomonas aeruginosa*, AHL-mediated QS regulates the production of extracellular proteases, including elastase (LasB) and protease IV (PIV), which contribute to tissue damage during corneal and pulmonary infections (Oh et al., 2017). Collectively, QS enables bacteria to synchronize virulence factor production, thereby enhancing host adaptation and infection success.

3.2.3. Quorum Sensing and Pathogen Adaptation

Beyond regulating virulence factor production, QS facilitates bacterial adaptation throughout the infection process by coordinating colonization, persistence, and stress responses. QS modulates the expression of adhesion- and secretion-related genes, allowing pathogens to adapt their virulence programs according to spatiotemporal changes within the host environment (Peña-Díaz et al., 2023).

QS also contributes to bacterial persistence by promoting phenotypic heterogeneity within bacterial populations. Under adverse conditions, a subpopulation of cells can enter a dormant persister state characterized by increased tolerance to antimicrobial therapy while maintaining the capacity to express virulence-associated traits. This mechanism contributes to chronic infection and disease recurrence (Personnic et al., 2021).

In addition, QS enhances bacterial adaptation to hostile host environments, including oxidative stress, pH fluctuations, and nutrient limitation (Kang et al., 2024; Podkowik et al., 2024; Zhuang et al., 2023). Through these coordinated responses, QS optimizes bacterial survival and persistence, reinforcing its importance as a promising target for antivirulence therapy.

3.3. The Concept of Antivirulence and Quorum-Sensing Inhibition (QSI)

3.3.1. Antivirulence Strategies: Concept and Advantages

Antivirulence therapy has emerged as an alternative therapeutic strategy that attenuates bacterial pathogenicity without directly inhibiting bacterial growth or viability. Instead of eliminating bacteria, this approach targets virulence determinants, including adhesins, toxins, secretion systems, QS, two-component regulatory systems, and other virulence-associated pathways required for host colonization, immune evasion, nutrient acquisition, and tissue damage (Chebotar et al., 2025; Lau et al., 2023). By preserving bacterial viability, antivirulence therapy is expected to impose lower selective pressure than conventional antibiotics, thereby reducing the likelihood of antimicrobial resistance development while minimizing disruption of the host microbiota (Lau et al., 2023).

The concept of antivirulence has already been translated into clinical practice through toxin-neutralizing strategies. One representative example is bezlotoxumab, a Food and Drug Administration (FDA)-approved monoclonal antibody that neutralizes *Clostridioides difficile* toxin B (TcdB), demonstrating the clinical feasibility of antivirulence therapy (Thandavaram et al., 2022). Building on this concept, QSI has become one of the most extensively investigated antivirulence strategies because it simultaneously disrupts the regulation of multiple virulence factors through interference with bacterial cell-to-cell communication.

3.3.2. General Mechanism of Quorum-Sensing Inhibition (QSI)

As illustrated in Figure 2, QSI interferes with bacterial communication through three principal mechanisms: inhibition of signal-molecule biosynthesis, enzymatic inactivation of extracellular autoinducers (quorum quenching), and disruption of signal recognition by receptor competition. Although these strategies target different stages of QS signaling, they share the common objective of attenuating virulence without directly inhibiting bacterial growth.

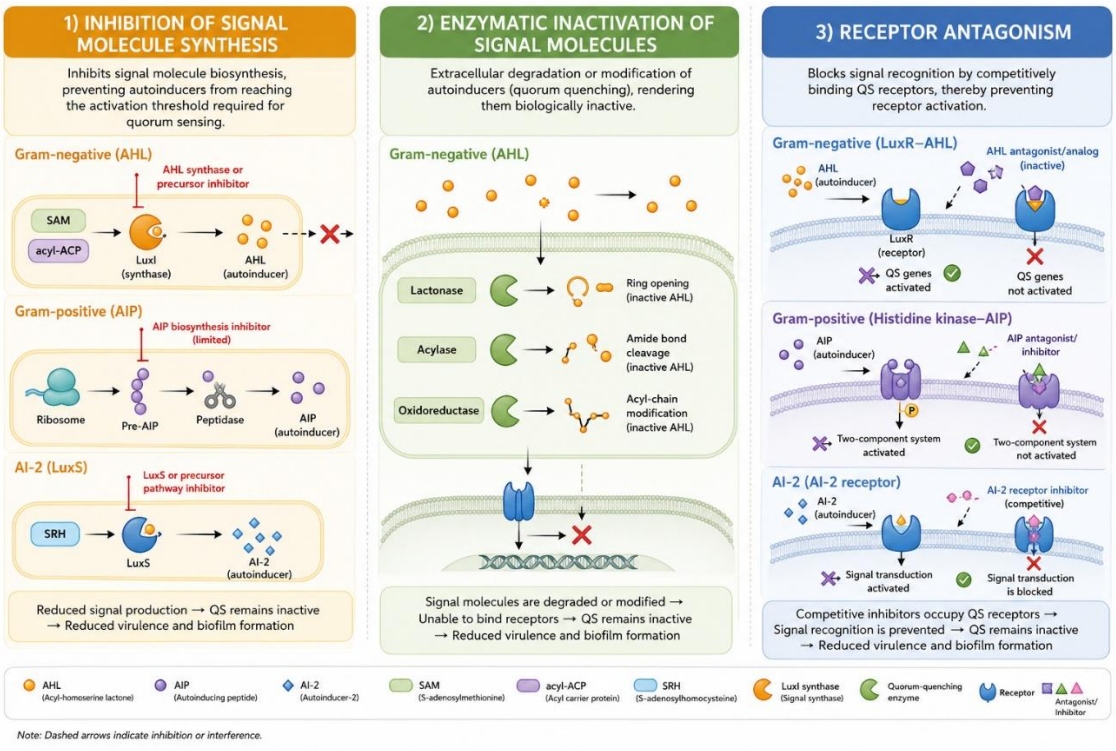

Figure 2. General mechanisms of quorum-sensing inhibition (QSI). (Abbas et al., 2020; Hetta et al., 2024; Li et al., 2022; Naga et al., 2023; Rodríguez-Urretavizcaya et al., 2024; D. Wang et al., 2023; Woods et al., 2024)

3.3.2.1. Inhibition of Signal Molecule Production

Signal synthesis inhibition prevents autoinducer accumulation before the activation threshold is reached (Figure 2). In Gram-negative bacteria, LuxI-family synthases are attractive targets because they are absent in mammalian cells, allowing selective inhibition of AHL biosynthesis. Compounds such as sinefungin and *S*-adenosyl homocysteine analogs have been reported to suppress AHL production, whereas disruption of the bacterial methyl cycle further reduces signal synthesis. In contrast, inhibition of AIP biosynthesis remains less explored because peptide maturation is closely associated with essential cellular processes. Likewise, inhibition of LuxS-mediated AI-2 synthesis has been shown to reduce biofilm formation, motility, and bacterial colonization (Li et al., 2022).

3.3.2.2. Enzymatic Inactivation of Signal Molecules

Quorum-quenching enzymes mainly target AHL molecules through hydrolysis or structural modification (Table 1). Lactonases possess the broadest substrate spectrum and remain the most extensively investigated QQ enzymes, whereas acylases exhibit greater substrate specificity. In contrast, oxidoreductases reduce signaling efficiency by chemically modifying AHL molecules without complete degradation.

Table 1. Major quorum-quenching enzymes targeting AHL molecules.

Enzyme	Mechanism	Target	Representative sources	Biological effect	References
Lactonase	Opens lactone ring	AHL	*Bacillus spp.*	Reduced biofilm formation and virulence	(Raafat et al., 2019; Tomy & Yasarla, 2025)
Acylase	Cleaves the amide bond	AHL	*Pseudomonas spp.*	Reduced QS activation	(Bravo et al., 2025; Tomy & Yasarla, 2025)
Oxidoreductase	Modifies the acyl chain	AHL	Various bacteria	Reduced receptor binding	(Tomy & Yasarla, 2025)

3.3.2.3. Receptor Competition

Receptor competition is among the most extensively investigated QSI strategies because it directly blocks signal perception without affecting bacterial viability. Both synthetic and natural inhibitors have demonstrated the ability to attenuate QS-regulated virulence in Gram-negative, Gram-positive, and AI-2-mediated systems (Table 2), highlighting receptor-targeting approaches as promising candidates for future antivirulence therapy.

Table 2. Representative receptor-targeting quorum-sensing inhibitors.

Type of Receptor	Target receptor	Representative inhibitor	Target organism	Main effect	References
AHL Receptors in Gram-Negative	LuxR	mBTL	*P. aeruginosa*	Reduced pyocyanin and biofilm formation	(Rodríguez-Urretavizcaya et al., 2024)
	LuxR	Sitagliptin	*P. aeruginosa*	Reduced biofilm formation	(Abbas et al., 2020)
	RhlR	o-Vanillin	*P. aeruginosa*	Reduced virulence	(Woods et al., 2024)
Histidine Kinase Receptors in Gram-Positive	Agr	RIP	*S. aureus*	Reduced toxin	(Ciulla et al., 2018)
	Agr	Hamamelitannin	*S. aureus*	Increased antibiotic susceptibility	(Brackman et al., 2016)
AI-2 Signaling Receptor	LuxP/LuxQ	Small molecules	*V. harveyi*	Reduced AI-2 signaling	(Jiang et al., 2018)
	LsrK	4171-0375	Various bacteria	Reduced AI-2 signaling	(Shi et al., 2023; Y. Xu et al., 2023)

3.4. Sources and Examples of Quorum-Sensing Inhibitors (QSI)

3.4.1. Natural Compounds as QSI

Natural products represent one of the richest sources of QSI. Bioactive compounds derived from plants, microorganisms, fermented foods, and breast milk interfere with QS through diverse mechanisms, including inhibition of signal production, degradation of autoinducers, and disruption of signal recognition (Table 3). Despite their diverse molecular targets, these natural QSI consistently attenuate bacterial virulence by reducing biofilm formation, motility, toxin production, and bacterial colonization without directly inhibiting bacterial growth, highlighting their potential as sustainable antivirulence agents.

Table 3. Natural quorum-sensing inhibitors from different biological sources.

Source	Representative compound/agent	Target organism	QSI mechanism	Major antivirulence effects	References
Plants	Curcumin	*B. cereus* D8	AI-2 interference	Reduced Biofilm	(L. Wang et al., 2025)
	Eugenol	*E. coli* (UPEC)	LuxS inhibition	Reduced Biofilm and Motility	(Morgaan et al., 2023)
	Carvacrol	*E. coli* (UPEC)	LuxS inhibition	Reduced Virulence	(Morgaan et al., 2023)
	Cinnamaldehyde	*E. coli* (UPEC)	QS inhibition	Reduced Biofilm	(Morgaan et al., 2023)
Microorganisms	AidC enzyme from bacteria *Chryseobacterium sp.* StRB126	*P. aeruginosa*	AHL degradation	Reduced Biofilm	(Khatun et al., 2023)
	Lactobacillus spp.	*Salmonella Heidelberg*	QS interference	Reduced Colonization	(Okamoto et al., 2018)
Fermented foods	LAB metabolites	*C. violaceum*	QS inhibition	Reduced Violacein	(Darai & Pelyuntha, 2025)
	LAB metabolites	*V. harveyi*	AI-2 inhibition	Reduced AI-2 signaling	(Kostoglou & Giaouris, 2025)
Breast milk	Human Milk Oligosaccharides (HMOs)	Various pathogens	Biofilm modulation	Reduced Colonization	(Bhowmik et al., 2022)

3.4.2. Synthetic Compounds and Engineering Approaches

Compared with natural compounds, synthetic QSI provide greater opportunities for structural optimization, stability, and target specificity (Table 4). Advances in rational molecular design and drug repurposing have expanded the repertoire of receptor-targeting QSI, supporting their development as promising candidates for future clinical translation.

Table 4. Synthetic compounds as quorum-sensing inhibitors.

Compound	Class	Target	Mechanism	Major findings	References
mBTL	AHL analog	Las/Rhl	Receptor antagonism	Reduced Pyocyanin and Biofilm Formation	(Rodríguez-Urretavizcaya et al., 2024)
Sitagliptin	Drug repurposing	LasR	Receptor inhibition	Reduced Biofilm Formation	(Abbas et al., 2020)

3.5. Potential of Quorum Sensing Applications as an Antivirulence Strategy

3.5.1. Applications in Human Health

Because QS regulates biofilm formation, virulence factor production, and bacterial persistence, it has emerged as a promising therapeutic target for managing difficult-to-treat bacterial infections. QS disruption not only attenuates bacterial pathogenicity but also enhances susceptibility to conventional antimicrobial therapy.

In chronic and biofilm-associated infections, including *P. aeruginosa* infections in patients with cystic fibrosis, QS contributes to persistent colonization and increased antibiotic tolerance. Consequently, QSI has been shown to reduce bacterial virulence, inhibit biofilm formation, and improve the efficacy of antibiotic treatment (H. Y. Liu et al., 2024). Furthermore, combining QSI with conventional antibiotics enhances biofilm susceptibility. It may reduce the antibiotic dose required to achieve therapeutic efficacy, highlighting QSI's potential as an adjuvant to antimicrobial therapy (J. Wang et al., 2024).

Beyond its therapeutic potential, QSI may also serve as a prophylactic strategy to prevent bacterial infections before extensive colonization, biofilm maturation, and virulence activation occur (Lu et al., 2022). Early disruption of QS signaling could suppress the coordinated expression of virulence factors during the initial stages of infection, thereby limiting disease establishment without directly affecting bacterial viability. This preventive approach may be particularly beneficial for high-risk populations, including immunocompromised individuals, patients with cystic fibrosis who are prone to recurrent *Pseudomonas aeruginosa* infections (Fong et al., 2019), and surgical patients at risk of device-associated or postoperative infections (Cavallo et al., 2024). From a translational perspective, evaluating prophylactic QSI will require clinical trials with preventive endpoints, such as reduced infection incidence, delayed biofilm establishment, or decreased recurrence rates, rather than conventional therapeutic endpoints alone (Alum et al., 2025; Hernández-Huerta et al., 2025).

3.5.2. Applications in Non-Clinical Fields

Beyond human health, QSI has broad applications in food safety, environmental biotechnology, and industrial biofilm control. In the food industry, fermentation-derived

microorganisms and their metabolites inhibit QS-regulated biofilm formation and virulence, thereby improving food quality and shelf life. In wastewater treatment, quorum-quenching (QQ) bacteria have been applied to reduce biofouling and extracellular polymer accumulation, improving membrane performance and treatment efficiency (R. Wang et al., 2025). Similarly, anti-QS materials and surface coatings represent promising strategies for preventing microbial colonization in industrial pipelines, filtration systems, and water distribution networks without relying on bactericidal agents (Ganaraja & Mulky, 2024).

3.6. Challenges and Future Research Directions

3.6.1. Current Challenges in QSI Development

Despite its considerable potential, the clinical translation of QSI remains challenging. Many QSI candidates demonstrate promising activity in vitro but exhibit reduced efficacy in complex biological systems due to limitations in stability, bioavailability, and host-associated interactions. Moreover, the lack of standardized methods for evaluating QSI activity complicates comparisons across studies, as different assays use diverse endpoints, including biofilm inhibition, virulence factor production, reporter gene expression, and quantification of quorum-sensing signals (Lu et al., 2022; Luís & Domingues, 2025; J. W. Zhang et al., 2023). This lack of methodological consistency hinders the identification of the most promising candidates for further development.

Another important challenge is achieving sufficient concentrations of QSI compounds at infection sites in vivo, where tissue distribution, metabolic degradation, and limited penetration into biofilms may substantially reduce therapeutic efficacy (Alum et al., 2025; Touati et al., 2025). In addition, bacterial adaptation through regulatory rewiring or compensatory mechanisms may reduce long-term therapeutic effectiveness, although selective pressure remains lower than that associated with conventional antibiotics (Y. Liu et al., 2018). Furthermore, some pathogens may partially compensate for QS inhibition by activating QS-independent regulatory pathways involved in virulence and stress adaptation, highlighting the complexity of bacterial regulatory networks (Popoff & Brüggemann, 2022).

3.6.2. Strategies for Clinical Translation of QSI-Based Therapeutics

Although numerous natural and synthetic QSI compounds have demonstrated promising antivirulence activity, only a limited number have progressed toward clinically viable therapeutics. One of the major barriers is the formulation of QSI compounds into pharmaceutical products that maintain stability, bioavailability, and biological activity under physiological conditions. Many natural QSI compounds exhibit poor aqueous solubility, rapid metabolism, chemical instability, or limited tissue penetration, thereby reducing their therapeutic performance (Abdulrazzaq & Dawood, 2026).

To overcome these limitations, advanced formulation strategies have been proposed, including nanoparticle-based delivery systems (Mitchell et al., 2020), liposomes (Hallan et al., 2020), polymeric carriers (Zieba et al., 2020), hydrogels (H. Yu et al., 2024), and microencapsulation techniques (Yu et al., 2025). These approaches may improve compound stability, protect bioactive molecules from premature degradation, enhance controlled release, and increase penetration into bacterial biofilms. In addition, combination therapy between QSI and conventional antibiotics has emerged as a promising strategy because disruption of bacterial communication can restore antibiotic susceptibility, enhance biofilm eradication, and reduce the antibiotic dosage required for effective treatment (Ansari et al., 2026).

Despite their promising antivirulence potential, natural QSI compounds should not be assumed to be inherently safe. Natural products may exhibit variable potency, limited selectivity, and off-target biological activities depending on their chemical composition, source, and extraction methods. In addition, variability in the concentration of bioactive constituents may affect both therapeutic efficacy and safety (Alum et al., 2025). Therefore, comprehensive toxicological evaluation, pharmacokinetic characterization, dose optimization, and assessment of potential interactions with host tissues, the resident microbiota, and conventional antibiotics remain essential before natural QSI compounds can be translated into clinically applicable therapeutics (Abdulrazzaq & Dawood, 2026).

From a regulatory perspective, QSI-based therapeutics also present unique challenges because they attenuate bacterial virulence rather than directly inhibit bacterial growth. Consequently, conventional efficacy endpoints used for antibiotic approval may not adequately reflect the clinical benefits of QSI. Future clinical translation will therefore require standardized evaluation methods, well-defined clinical endpoints, robust pharmacokinetic data, and regulatory frameworks specifically designed for antivirulence therapeutics (Alum et al., 2025).

3.6.3. Future Research Directions

Future research should prioritize the discovery of more stable and selective QSI, optimization of delivery systems, and validation in clinically relevant in vivo models. Continued exploration of natural products, particularly from biodiversity-rich regions, may accelerate the discovery of novel antivirulence agents with improved efficacy and safety profiles. Furthermore, multidisciplinary collaboration integrating microbiology, medicinal chemistry, pharmaceutical sciences, biomaterials, and clinical research will be essential to facilitate the successful translation of QSI-based therapeutics from laboratory research to clinical application. Future studies should also establish standardized protocols for evaluating QSI efficacy and safety to facilitate comparison across studies and accelerate clinical translation.

Conclusions

Quorum sensing (QS) is a central regulatory system that coordinates bacterial virulence by controlling biofilm formation, virulence factor production, colonization, pathogen adaptation, and infection persistence. Consequently, disrupting QS has emerged as a promising antivirulence strategy capable of attenuating bacterial pathogenicity without directly compromising bacterial viability. Among the available approaches, quorum-sensing inhibition (QSI), including inhibition of signal molecule synthesis, autoinducer degradation, and receptor antagonism, offers significant potential to reduce bacterial virulence while imposing lower selective pressure for antimicrobial resistance than conventional antibacterial therapies. Although further studies are required to optimize compound stability, delivery systems, and clinical efficacy, QSI represents a promising complementary strategy for the sustainable management of bacterial infections in the era of escalating antimicrobial resistance.

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Conflicts of Interest

The authors declare no conflict of interest.

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