Regulatory and innovative mechanisms of bacterial quorum sensing–mediated pathogenicity: a review

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Abstract

Quorum sensing (QS) is a system of bacteria in which cells communicate with each other; it is linked to cell density in the microbiome. The high-density colony population can provide enough small molecular signals to enable a range of cellular activities, gene expression, pathogenicity, and antibiotic resistance that cause damage to the hosts. QS is the basis of chronic illnesses in human due to microbial sporulation, expression of virulence factors, biofilm formation, secretion of enzymes, or production of membrane vesicles. The transfer of antimicrobial resistance genes (ARG) among antibiotic resistant bacteria is a major public health concern. QS-mediated biofilm is a hub for ARG horizontal gene transfer. To develop an innovative approach to prevent microbial pathogenesis, it is essential to understand the role of QS, especially in response to environmental stressors such as exposure to antibiotics. This review provides the latest knowledge on the relationship between QS and pathogenicity and explores the novel approach to control QS via quorum quenching (QQ) using QS inhibitors (QSIs) and QQ enzymes. The state-of-the-art knowledge on the role of QS and the potential of using QQ will help to overcome the threats of rapidly emerging bacterial pathogenesis.

Introduction

Quorum sensing (QS) has been identified as the major contributing factor in several persistent and chronic bacterial illnesses in human (Jin et al., 2021). Pathogenicity is expressed in microorganisms with respect to their virulence. The rise of antibiotic resistance in human and animal pathogens is a significant public health threat, resulting in increased mortality, medical cost, and prolong medical hospitality (Sikdar & Elias, 2020; Whiteley et al., 2017). Many pathogens share common mechanisms to create virulence (Haque et al., 2021). Pathogenic bacteria employ QS to control virulence factor production as well as adapt to the metabolic needs of living in a colony (Dogsa et al., 2021). It is recognized that a considerable percentage of the bacterial genome (4–10%) and proteome (≥ 20%) may be altered by QS during pathogenesis (Camele et al., 2019). It is shown that QS regulates a broad range of activities in microorganisms, including pathogenic gene expression, toxin generation, extracellular polysaccharide synthesis, regulations of bacterial luminescence, factors of virulence, disinfectant resistance, spore development, formation of toxins, biofilm

formation, motility and antibiotic resistance, etc. (Bjarnsholt et al., 2018; Li et al., 2019; Sikdar & Elias, 2020; Tripathi et al., 2021a, b, c, d, e, f).

Pseudomonas aeruginosa is an important pathogen in chronic and burn wounds, and cystic fibrosis lungs in human. *P. aeruginosa* damages the host's tissue by generating a variety of extracellular products, including proteases, that are influenced by a complicated hierarchical QS cascade (Moradali et al., 2017). Similarly, *Staphylococcus aureus* showed pathogenesis due to various virulence factors like toxins, hemolysins, leukocidins, exoenzymes, and surface proteins that reduce the host's immune response (Moradali et al., 2017; Tan et al., 2018). Many of these mechanisms are controlled by the accessory gene regulatory (agr) system that is controlled by QS (Tan et al., 2018). Members of the *Streptococcus* genus are known to employ QS-stimulated autoinducing peptides (AIPs) to control a two-component signaling system that induces a variety of illnesses (Yang et al., 2020). In response, the hosts evolve strategies to fight the agr QS system, such as various oxidants can deactivate the AIP of S. aureus. These oxidants are generated by phagocytes as a possible host defense to inhibit QS signaling in early S. aureus infections, resulting in the suppression of density-dependent virulence factor production. Another major pathogenic bacterium, *Clostridium difficile*, causes diarrhoea via biofilm formation in the human intestine and the production of antibiotic resistant endospores; the toxins produced by the vegetative cells are shown to be governed by QS (Slater et al., 2019).

Bacteria are able to adapt to changing environments (e.g., nutrient availability, temperature, pH and osmolarity, and oxidative stress) and modify the gene expression that is crucial for its acclimation, existence, and expertise. QS enables the bacteria to react to changes in the biotic as well as the abiotic surroundings by gene expression modification (Algburi et al., 2021). Both gram-negative and gram-positive bacteria employ QS, but they produce different types of QS signal molecules (Ameen et al., 2020). Through the synthesis and secretion of signal molecules, bacteria track the activity of the whole bacterial community (Yadav & Chandra, 2019). Figure 1 presents an overview of the functions governed by QS in bacteria. At certain bacterial populations ($> 10^7$ CFU/ml), signal molecule production may be initiated to control bacterial population tolerance and expression of the various genes including pathogenesis (Aravinthan et al., 2015; Balan et al., 2021). The inhibition of QS is known as quorum quenching (QQ); it is an advanced and promising antibacterial technique that prevents bacterial pathogenesis, and eliminates genes associated with the expression of QS virulence factor in human (Balan et al., 2021; Benjamin et al.,

2018; Krzyzek, 2019). A variety of small molecule that inhibit QS signal receptors and LuxI-type QS signal synthases have been discovered, as well as enzymes that degrade autoinducing molecules, such as acyl-homoserine (AHL), that play an essential in QS. Since anti-QS agents have yet to mature clinically, knowledge of microbial QS and QQ gives a new impetus to research to overcome the rising tide of pathogenesis in human (Botelho et al., 2019)

Hence, this review aims to provide an overview of the latest research status of microbial QS in pathogenesis and biofilm production and explore the novel approach of using QQ to combat pathogenesis in human. The information will help to develop new strategy to overcome microbial antibiotic resistance and the emergence of drug-resistible bacteria.

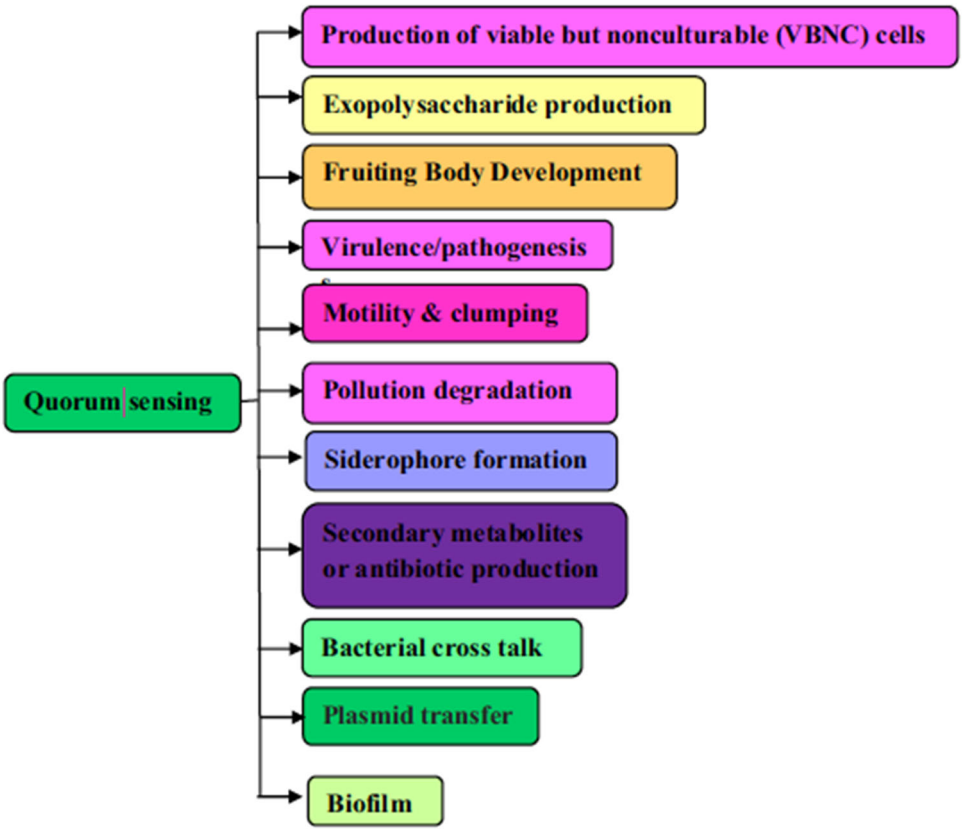

Fig. 1 Different functions govern by quorum sensing in microorganisms adopted from Yadav and Chandra (2017)

Overview of quorum sensing in bacteria

QS is initiated via the production and sensing of small extracellular molecules, known as auto-inducers (AIs), that are released in proportion to cell density. In Gram-negative bacteria, autoinducer-l (AI-1) or acyl-homoserine lactone (AHL) is produced encoded by the *LuxI*

gene; the *LuxR* gene is responsible for the transcription activation protein LuxR which is an induction activator (sometimes refers as a transcription regulator) (Boo et al., 2021). AHL is easily absorbed by and expelled from bacterial cells; in the LuxR-LuxI system, it can also circulate in the surrounding environment as a synthetic product (Broniewski et al., 2021). In Gram-negative bacteria, an AHL molecule activates *LuxI*, which codes for the protein synthetase of AHL (Fig. 2). Substrates such as S-adenosylmethionine and an acyl-acyl carrier protein (acyl-ACP) are involved in the synthesis of AHL. The synthesized AHL then binds to the LuxR protein; after dimerization or multimerization, the multimerized product attaches to the target gene's upstream regulatory region, causing the gene's expression to be activated or inhibited. The binding characteristic of AHL and LuxR is strong as various acyl side chain groups regulate AHL characterization. Many Gram-negative bacteria utilize QS to ensure information is transferred between cells of the same species, preventing interference from foreign organisms.

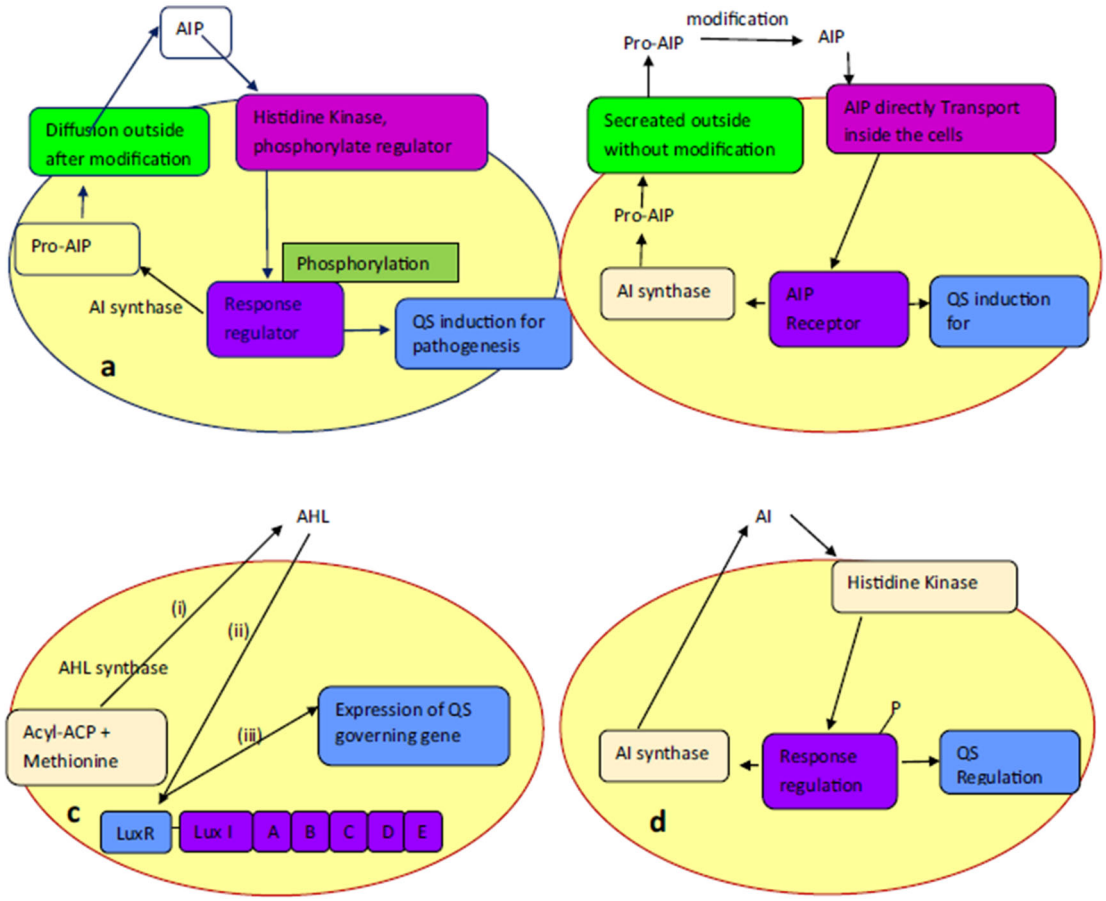

Fig. 2 B Bacterial quorum sensing (QS) in gram positive and gram -negative pathogenic bacteria. **a** Two component signalling in pathogenic bacteria, **b** AIP binding transcriptional factor for induction of QS, **c** LuxI/LuxR type QS in gram-negative bacteria at high AHL

concentration lead to expression of genes, d two-component signaling in gram-positive bacteria.

In Gram-positive bacteria, the auto-inducing molecules are oligopeptides (AIP), about 5–25 amino acids long. A two-component system, including the kinase receptors and cytoplasmic transcription factors, activates their gene expression. The transcription mechanism begins when the oligopeptide signal molecule binds to the cell membrane receptor protein and transmits the intracellular binding promoter with the phosphorylated/dephosphorylated cascade (Miller and Gilmore, 2020). The post-translation changes then activate or inhibit the gene expression. AIPs are specific to species and strains and have been described in *Staphylococcus* spp., *Clostridium* spp., and *Enterococcus* spp., and noted to be responsible for the increase in their pathogenicity and antibiotic resistance (Nakagawa et al., 2020). Additional signalling molecules have been identified, for example, fatty acids used by *Xanthomonas* spp., *Burkholderia* spp., and *Xylella* spp. (Li et al., 2021a, b); ketones by *Vibrio* spp. and *Legionella* spp. (Govarthanan et al., 2013); and epinephrine, nor-epinephrine, and quinolones by *Pseudomonas aeruginosa* (Personnic et al., 2021). A furanosyl borate diester known as AI-2 is used by both Gram-negative and Gram-positive bacteria (Govarthanan et al., 2016).

AHL-mediated QS has been studied in different genera of α, β, and γ subclasses of proteobacteria, i.e., *Yersinia*, *Agrobacterium*, *Aeromonas*, *Burkholderia*, *Chromobacterium*, *Citrobacter*, *Enterobacter*, *Hafnia*, *Nitrosomonas*, *Obesumbacterium*, *Pantoea*, *Rahnella*, *Ralstonia*, *Rhizobium*, *Serratia*, *Vibrio*, and *Xenorhabdus* (Li et al., 2021a, b). Most Gram-negative bacteria combine several QS systems to integrate different signals either hierarchically, as *P. aeruginosa* in which four QS systems (Las, Rhl, Iqs, and Pqs) act in a network (Saeki et al., 2020), or in parallel, as in *Vibrio harveyi* where three systems are integrated into one regulatory cascade (Saxena et al., 2019). Some bacteria, such as *Salmonella typhimurium*, have also been found to be QS mediated by autoinducer-3 (AI-3); however, the production pathway of AI-3 is not yet known (Sela et al., 2021). Catecholamine signaling molecules epinephrine and nor-epinephrine are recognized by the AI-3-mediated QS. Moreover, *Xanthomonas campestris* secretes cis-11-methyl-2-dodecenoic acid as well as hydroxy-palmitic acid methyl ester (PAME) by *Ralstonia solanacearum* (Selvam et al., 2017). A list of quorum sensing signaling molecules in microbes is presented in Table 1.

Table 1. List of quorum sensing signaling molecules, responsible gene, and virulence factors of various microbes

Autoinducers	Organisms	Gene	Virulence factors	References
AHL	*Aeromonas hydrophila*, *Agrobacterium*, *Acinetobacter baumannii*, *Erwinia*, *Pseudomonas*, *Vibrio*	*ahyRI*, ***TraR, abaI/R***	Enterotoxin, outer membrane proteins, secretion systems, phospholipases	Tanhay et al. (2020); Lopez-Martín et al. (2021)
PQS	*Pseudomonas aeruginosa*	*aprA*, *toxA*, *LecB*, *lasA*	Exotoxins, protease, alkaline protease, lectin	Andrejko et al. (2019); Passos da Silva et al. (2019); Jurado-Martin et al. (2021), Bogiel et al. (2021)
C4-HSL, C6-HSL	*Serratia liquefaciens*	*swrI/swrR*, *smaI/smaR*, *bsmB/bsmA*	Prodigiosin, protease, lipase, nuclease, hemolysin and biofilm formation	Fekrirad et al. (2020)
N-(3-oxohexanoyl) HSL, *N*-hexanoylHSL, and *N*-(3-oxosep-tanoyl) HSL	*Yersinia pseudotuberculosis*, *Ersinia pestis*	*Hfq*, *yenR/ycoR*	**Coagulase, fibrinolysin plasmalogen activator protease**	Ng et al. (2018)
3-hydroxymyristate (3-OH MAME) or (*R*)-methyl 3-hydroxypalmitate (3-OH PAME)	*Ralstonia solanacearum*	*PhcB/PhcS*	Proteins	Kumar et al. (2016); Ujita et al. (2019)
DSF	*Xanthomonas* sp.	*RpfF*, *RpfC*, and *RpfG*	Toxins, lipases, protease, and siderophores, Biofilm formation	Huedo et al. (2018)
Epinephrine and norepinephrine, AHL	*Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Shigella*, *Yersinia*	*QseC/QseE*, *luxI/R*	Proteolysis, hemolysis, and biofilm formation	Fernando and Santiago (2021)
AIP-1, AIP-2, AIP-3, AIP-4	*Staphylococcus aureus*, *Staphylococcus epidermidis*	*Agr*	Toxins, lipases, protease, and siderophores, biofilm formation	Idrees et al. (2021)
AI	*Clostridium difficile*, *Clostridium botulinum*, *Clostridium chauvoei*	*AgrD*	Toxins, lipases, protease, and siderophores, biofilm formation	Sujeet et al. (2018)
10-amino-acid peptide	*Bacillus subtilis*	*ComQ*, *ComX*, *ComP ComA*, *Rap-Phr*	Exopolysaccharide, collagenase, protease, enterotoxins	Guan et al. (2020)
AI-2 furanosyl borate diester	*Vibrio cholerae*	*hapR*, *flaA*	Encodes Ha protease for establishment of new infection, Exopolysaccharides	Wang et al. (2011), Mylea et al. (2018)
AI-2 furanosyl borate diester that lacks boron	*Salmonella*	*sdiA*	**Virulence-plasmids, toxins, fimbriae and flagella**	Sholpan et al., (2021)

Role of QS in pathogenesis

QS and virulence factors

Multi-drug-resistant micro-organisms is projected to cause 10 million additional deaths per year by 2050, with a total loss of US$100 billion of the world economy (Govarthanan et al., 2018). To understand the significance of QS in microbial pathogenesis and the multidrug resistance phenomena, the full extent of the synchronizing QS systems must be appreciated. An example of the different types of QS circuits in various Gram-positive and -negative bacteria is presented in Fig. 3. QS regulates the synthesis of a variety of virulence factors, causing bacterial pathogenicity and the development of biofilms.

The synthesis and detection of small molecules inside and among pathogenic bacteria have been extensively studied (e.g., Govarthanan et al., 2014; Paramanantham et al., 2018). Table 2 presents a list of genes responsible for QS and function development in pathogenic bacteria. Bacterial infection could be caused by (1) membrane proteins, (2) bacterial toxins that destroy or disrupt signal transmission, (3) polysaccharides capsules, (4) peptidoglycan layer and lipo-polysaccharide, and (5) the formation of biofilms and the synthesis of

siderophores. Bacterial pathogens secrete various enzymes and toxins after colonization in the host that causes severe tissue damage, diffusion, and systemic inflammatory response syndrome. For example, *P. aeruginosa* virulence factors restrict protein synthesis by inactivating elongation factor 2, resulting in cell death (Jurado-Martin et al., 2021). Exoenzyme S allows chronic lung infection by direct tissue destruction, and alkaline protease plays an important role in corneal infection (Chakraborti et al., 2017). Figure 2 presents different types of QS circuits in bacteria. Knowledge of the QS system and pathogenesis in Gram-negative *P. aeruginosa* is well established (Pang et al., 2018; Zhong et al., 2020). Infection of *P. aeruginosa* occurs through a sequence of events that lead to chronic inflammation through biofilm and contributes to numerous virulence factors, including elastases, lipases, rhamnolipids, alginates, and other virulence characteristics (Kathirvel et al., 2020). Three common types of QS systems have been identified in *P. pseudomonas* (Shah et al., 2021). The first system uses signaling molecules N-(3-oxodecanoyl) and N-butanoyl-ı-homoserine to bind to the RhlR receptor, while AHL interacts with the LasR receptor. The second QS system encompasses proteins RhlI and RhlR. RhlI synthase generates C4-HSL; when a complex of signal molecules is present, RhlR acts the transcribers to regulate the gene expression (Chen et al., 2019; Mukherjee et al., 2017). These signals can quickly spread outside bacterial cells. A third QS system is linked to these two AHL-based QS systems, which are involved in processing the *Pseudomonas* quinolone signal (PQS), a third signaling molecule (Yadav & Chandra, 2019). Normally, the AHL-based *LasI* gene is involved in the AHL production process, whereas the *LasR* gene encodes for the receptors in the QS system. During the growth stage of *P. aeruginosa*, the LasI synthase gene produced signaling molecules. Binding of the synthesized signaling molecules to the LasR receptor protein leads to the activation of the transcriptional factors. Interestingly, LasR forms a protein that can bind to DNA, activating multiple gene transcriptions, including the virulence genes (O'Reilly et al., 2018). The QscR protein in *P. aeruginosa* was not well-understood but it was found to control both the LasI and RhlI transcriptions, and the qscR genes play an essential function in the bacterial virulence (Rutherford & Bassler, 2012).

Table 2 A microbial resistance mechanism for enhanced pathogenesis and QS inhibition strategies of microbes to block the pathogenesis

Microbial resistance mechanisms		**QS system inhibition strategies, i.e., QQ**		
Mechanisms	**Actions**	**Mechanisms**	**Actions**	**Effects**
Changes in antibiotics structure	Failure of antibiotic action	**a. Production of auto inducer inhibition**		
		TNRHNPHHLHHV	Inhibit LuxS	Inhibit the synthesis of AI-2
Presence of efflux pump	Antibiotics are discharged outside the microbial cells	MT-DADMe-ImmA	Pico molar inhibitor	Inhibit the synthesis of AI-2
Changes in drug targeting genes	Failure of antibiotic action	(2-nitrophenyl) methanol derivatives and FabI derivatives	Inhibits auto inducer biosynthesis molecular enzymes	Inhibit the production of autoinducers
various strategy for cellular adaptation	Various proteins and enzymes are secreted to cope with the stressed conditions	**b. Degradation of auto inducer**		
Biofilm formation	Stop or reduce the penetration of antibiotics	Activation of *aiiA* gene in *Bacillus* sp. *240B1*	*aiiA* gene encodes enzyme responsible for AHL degradation	AHL degraded
Diversity in biofilm	Due to heterogeneity various microbes are grown inside biofilm and showed nutrient diversity led to more and more adaptation	AHL lactonase (AidB)	Hydrolyzing the ester bond of the HSL ring	Degrade AHL
		Addition of ATP and LsrK	Phosphorylation and degradation of AI-2	Reduced QS action
		Imidazole	Degrade AI-2	Inhibit AI-2 function
		c. Inhibition of binding to receptors		
		Extract of medicinal herbs	MHE as a competitive agent	Inhibit QS
		Flavonoids compounds	Reduce autoinducers concentration	Inhibit QS
		D-galactose	Inhibitor of AI-2	Inhibit AI-2 activity
		Haloquinone analogs	Block endogenous Wnt-driven transcription	Inhibit Wnt/β-catenin signaling
		2H-pyran-3(6H)-one derivatives	As an inhibitor	Inhibit signaling pathway
		Alkyl-quinoxalin-2(1H)-one derivatives	Reduced QS	Reduced or inhibits production of autoinducers
		N-(3-oxododecanoyl) homoserine lactone derivatives	Block the QS molecule binding place	Stop biofilm formation and increase the antibiotic sensitivity

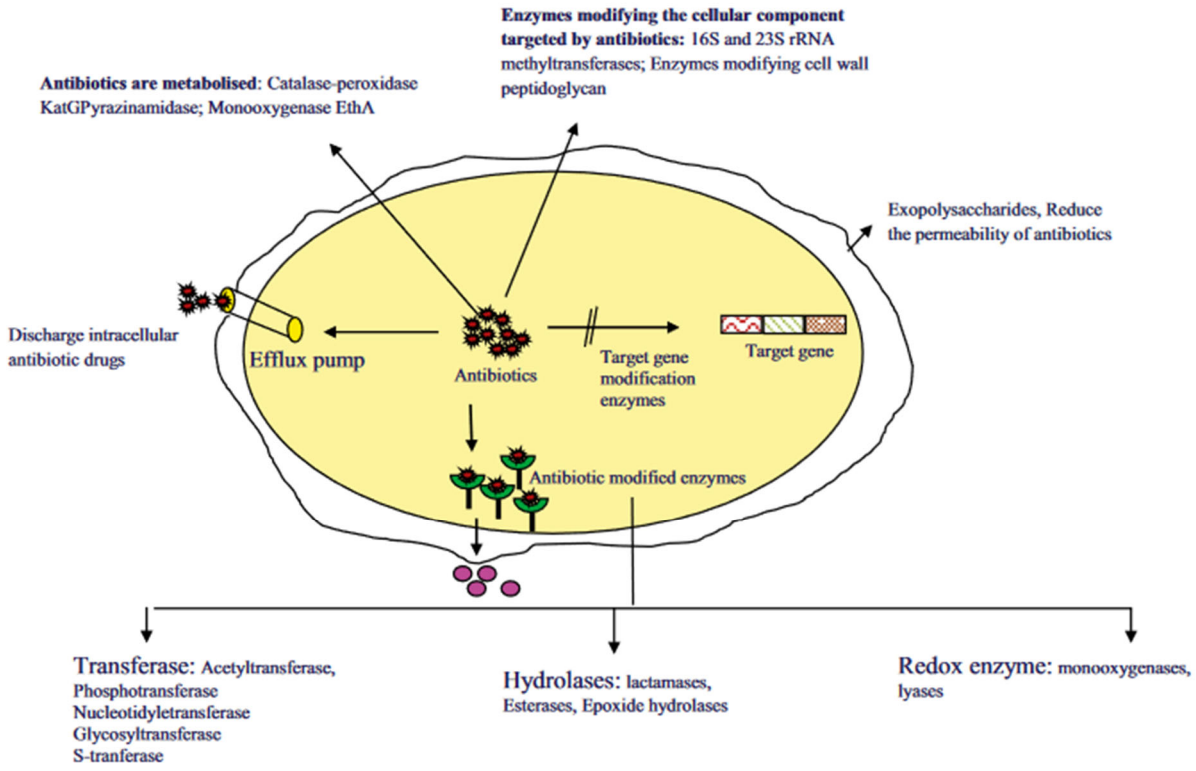

Fig. 3 Common mechanisms of microbial resistance to enhanced pathogenesis.

The pathogenicity of pathogenic Gram-positive bacteria Staphylococcus aureus is controlled by the Agr QS system. The Agr QS framework molecular analysis reveals that the chromosome region comprises two distinct transcripts, RNAII and RNAIII. The transcript of RNAII consists of four genes of *AgrBDCA* which are part of the coding process for the production of the API and the activation of the regulator circuits. In the Agr operon, *AgrB* encodes for a membrane endopeptidase, which generates the API; *AgrD* synthesized precursor peptide of the API; a histidine kinase is the gene product of *AgrC*, which becomes activated after API binds with the receptor, while *AgrA* regulates the transcription of transcripts RNAII and RNAIII. In the RNAIII transcript production, the RNA regulating molecules function as the main Agr QS controllers by upregulating extracellular virulence and decreasing cell surface protein regulation. In addition, δ-haemolysin, a small amphibian peptide, contains the transcript RNAIII and supports the production of biofilms. The other important feature of the S. aureus QS circuit is the competitive interactions between the AIP specialities. Four distinct forms of S. aureus AIPs have been identified in the same strain due to the hyper-variable actions of the *agrD* and *agrB* genes (Shivaprasad et al., 2021). The

related hypervariability occurred in the *agrC* gene segment encoding the AIP receptor sensing domain. The *agrC* cognate sensor senses a special AIP and the noncognate AIP binding leads to QS inhibition (Sholpan et al., 2021).

In human intestinal and non-intestinal infections, hemolysin, phospholipase, and toxin secretion from pathogenic Gram-positive *Bacillus* bacteria can rapidly cause serious diarrheal disease. Extracellular and intracellular Bacillus spp. virulence factors are regulated by QS of more than 200 genes. *B. subtillis* employs the *ComQXPA* circuit, the four-protein QS system in which ComQ is an isoprenyl trans- ferase, ComX as a signaling peptide, and ComP as a histidine kinase. The ComX system synthesizes 55 remaining isoprene and isoprenyl transferase, modified by ComQ. A transcription factor termed PlcR is also required for QS in Bacillus cereus, which controls the production of most *B. cereus* virulence factors (Rutherford & Bassler, 2012). AI-3 is involved in the pathogenic process of enterohemorrhagic *Escherichia coli* (EHEC) and *Shigella castellani*. In addition to gastroenteritis, EHEC can cause fever, meningitis, and septicaemia. For transcription of virulence genes, EHEC relies on three signals: a bacteria-produced aromatic AI (AI-3) and two host-produced hormones (epinephrine/norepinephrine). *Vibrio* spp. are also responsible for many outbreaks of gastroenteritis; they secrete various extracellular toxins, metalloprotease, components of pathogenicity, secretion of type III, and the formation of siderophore that are regulated by QS (Soto-Aceves et al., 2021a, b). *Serratia marcescens* is another well-known human pathogen. Various human infections caused by *S. marcescens* might be due to virulence secretions such as nuclease, protease, lipase, chitinase, gelatinase, hemolysine, and siderophores which are governed by QS (Santhakumari & Ravi, 2019). The presence of autoinducers like AHL in the sputum, plasma, and urine of the diseased person confirmed the correlation between QS and pathogenesis (Erickson et al., 2002; Garance et al., 2020). Studies showed that 3OC12-HSL was present in a majority (54–78%) of sputum samples, while C4-HSL was detected in only 26% of samples. QS gene which highly transcribed in human infections also showed the role of QS in pathogenesis (Rutherford & Bassler, 2012).

QS and biofilm formation

Apart from virulence factors, the development of biofilms on biotic or abiotic surfaces by the bacterial community also plays an essential part in their pathogenicity. Biofilms are

the only mechanism that supports the connection of bacteria to and growth on biological or non-biological surfaces. Acute infections contain planktonic bacteria which are usually treated with antibiotics, but their effective treatment requires a precise and rapid diagnosis. However, when the bacteria create a biofilm, the infection sometimes becomes untreatable and becomes a chronic disease (Shivaprasad et al., 2021). Proteins, nucleic acid, and carbohydrates are essential components of biofilm. For example, low amino glycoside antibiotic levels in *P. aeruginosa* have been found to cause bacterial biofilm development (Pang et al., 2018). The biofilm is separately enclosed by the self-secreted three-dimensional extracellular polymeric substance (EPS) matrix that consists of hydrated polysaccharides, proteins, nucleic acids, and lipids. Pathogenic bacteria develop resistance and tolerance towards convectional antibiotics through QS-assisted biofilm formation (Uruen et al., 2021). Biofilm formation, virulence factors, and antibiotic resistance is strictly controlled under QS, and the QS-mediated virulence factors can change the equilibrium of host defense system (Sholpan et al., 2021).

Quorum sensing–mediated antibiotic resistance mechanisms of pathogens

Multi-drug resistance of pathogens can be attributed to a number of key pathways, including chemical modification due to the passivation of antibiotic, systemic efflux pump, antibiotic removal, targeted gene modification, and biofilm formation (Table 2 and Fig. 3). The chemicals' modification resistance mechanism involves the secretion of enzymes that alter the antibiotic chemical composition, which leads to the inactivation of antibiotics. Many of these enzymes can metabolize antibiotics, degrade the antibiotic, or derivatize the antibiotic chemical groups (Ana et al., 2020; Zhao et al., 2020). Drug efflux pump also acts as QS-mediated resistant mechanism of pathogens in which microorganisms remove antibiotics. Various efflux systems such as lipophilic and hydrophilic efflux systems have been reported in pathogens as an adoptive feature against antibiotics governed by QS (Alav et al., 2021; Du et al., 2018). Bacteria selectively or non-selectively removed the proteins, and foreign materials, including antibiotics and their metabolic products. For example, antibiotic sensitivity in Bacteroides fragilis ATCC25285 tested in the presence and absence of C6-HSL and C8-HSL autoinducers found that synthesis of AHL upregulated the expression of efflux pump gene bmeB (Sholpan et al., 2021). Similarly, several researchers showed that the MexAB-OprM multi-drug resistance pump can be upregulated, causing multiple-antibiotic

resistance in bacteria (Cao et al., 2019; Pesingi et al., 2019). The expression level of the efflux pump also affects the QS system itself. Further activation of the QS system can facilitate high efflux pump expression, maintain QS system control over the synthesis of the toxin infection factor and expression of the efflux pumps, and improve infectiveness or bacterial invasiveness (Minagawa et al., 2012). The change or modification in antibiotic targeting genes is an essential mechanism in antimicrobial resistant pathogens. Bacteria have developed resistant mechanisms by preventing a binding site of the antibiotic and modifying the target to lead to antibiotic molecular affinity (Zhao et al., 2020). Research has shown that the development of biofilm is a significant, systematic,
and complicated process for drug super-resistant *Staphylococcus aureus* (Zhao et al., 2020). *Acinetobacter baumannii* accounts for 9.4% of all Gram-negative pathogens and 22.6% of intensive care unit isolates found in Indian hospitals (Peng et al., 2018). QS-mediated biofilm formation is one of the key reasons for pathogenesis and multidrug resistant in *A. baumannii* (Saipriya et al., 2020).

One of the main components of cell adhesion infections that protect cells against environmental stress is the biofilm matrix. The biofilm-forming properties of pathogens improve their survival in hospital settings, including resistance to antibiotics and biocides, and increase risk of nosocomial infection (Andersen et al., 2017). The ability to inhibit QS has become a promising tool to reduce infection. Peng et al. (2018) showed that rutin could substantially reduce QS by inhibiting AI-2 secretion, which inhibited the development of biofilms and decreased *E. coli* APEC-078 expression of the virulence genes. Biofilm formation in *Acinetobacter* spp. is also under the control of QS (Shahid et al., 2019); the gene *abaI* is responsible for the formation of auto-inducer, and a mutation in abaI reduced the formation of biofilm. These findings identified the function of auto-inducer in biofilm formation, which led to the development of numerous pathogenic properties in clinical isolates, including antibiotic resistance.

Regulation of bacterial biofilm formation by QS

The QS system plays a major regulatory role in the formation of biofilms. A biofilm is an exclusive structure produced by bacteria which adhere to inert oractive materials' surface to adjust to the environment. Biofilms are aggregates in which cells are protected within a matrix of extracellular polymer molecules generated themselves. EPS consists of components excluding cells such as proteins, polysaccharides, nucleic acids, lipid substances, dead

bacterial cells, and other water hydrated polymers up to 85 to 95% of the water (Wu et al., 2020). It is spatially structured and has new biological characteristics and enhanced environmental adaptability. Biofilm supports heat, cold, other physical stresses, environmental hazards, pH, and bacterial oxygen tolerance (Tripathi et al., 2021a, b, c; Yadav & Chandra, 2017). Recent studies showed that most bacterial infections in humans are biofilm based and one of the principal reasons why clinical bacterial infections are difficult to cure is due the development of biofilms (Khatoon et al., 2018; Tripathi et al., 2021d, e, f; Yadav & Chandra, 2018).

QS mediated exopolysaccharide secretion and biofilm formation that enhance bacterial resistance towards antibiotics through penetration control mechanisms, nutritional restriction mechanisms, and phenotypical mechanisms for antibiotic resistance. During pathogenesis, bacterial extracellular adhesive matrix (glycocalyx) formation occurs due to QS, and bacteria micro-colonized the mucosa and adhered permanently to human cells which led to biofilm formation (Wang et al., 2021). Virulence factors, such exo-enzymes and toxins, can harm the host cells to provide nutrients for the biofilm to enable it to develop and mature (Wu et al., 2020). In biofilm formation, all bacterial populations activate their virulence genes, and the body's immune systems may not have the time to counteract before harm is done. Antibiotics could be administered as the next line of defense against the pathogens. However, polysaccharides in the biofilm can prevent the entry of some antibiotic materials by reducing permeability (Limoli et al., 2015). Several reports showed that nutrient levels and microbial metabolites were not equal in different areas of the biofilm; this led to heterogeneity inconsistent bacterial growth status in different biofilm areas, creating heterogeneity of resistance bacterial cells in biofilms (Yadav & Chandra, 2019). Stress factors including temperature fluctuations, pH, and the concentration of certain non-biofilm substances also influenced cell activity to control physical and metabolic activities and growth efficiency and create a resistance state to antibiotics (Yu et al., 2021). However, the pathways used to transmit the cells by inter-species or intra-species interactions in biofilms during chronic diseases continue to be unclear.

Pathogenesis through horizontal gene transfer control by QS

Several bacteria have developed pathogenesis due to horizontal gene transfer (HGT), which is governed by QS. Plasmids and chromosome gene mutations are responsible for HGT and are the result of changes in the virulence site and modulation of the binding site of the essential enzyme (Zhang et al., 2021). The horizontal transmission of intra- or inter-species pathogenic genes in bacterial colonies helps to cause disease in even non-pathogenic bacteria (Hegstad et al., 2020; Lerminiaux and Cameron, 2019). Methicillin-resistant *Staphylococcus aureus* is immune to most antibiotics. They transfer the genetic material, from pathogenic strain to non-pathogenetic strain (Hegstad et al., 2020; Lerminiaux and Cameron, 2019). HGTmay result in adaptation or loss of antibiotic resistance. The mobile genetic element produces the vital protein to pathogenicity and host adaptability. QS is responsible for bacterial communication, while some deactivate the molecules for virulence or fordominance other species (Bhardwaj et al., 2013). HGT occurs during the formation of biofilms. It produces stronger bacteria that control the host cells. Inter- or intra-kingdom interactions of bacteria by QS are involved in symbiotic interaction (Li et al., 2019). QS molecule affects the physiology of high eukaryotes by affecting their hosts' immune defense, hormonal status, and growth factor (Zhong & He, 2021).

Regulation of the secretion system of pathogenic bacteria by QS

Pathogenic bacteria secrete proteins and auto-inducers through the cell membrane to invade microorganisms or host cells, evade the host's immunity, and cause harm to their tissue. The secreted proteins can be infectious, toxic molecules can be created by host cells, and adherence can also be promoted. Microorganisms use several secretary systems for protein transport and eight secretary systems were recognized, i.e., T1, T2, T3, T4, T5, T6, T7, and T9 (Prajapati et al., 2021). The difference in Gram-positive and Gram-negative bacteria is the reason for these variances (Zhao et al., 2020). Type I secretion system (T1SS) is common in Gram-negative bacteria. It includes three structural elements: ABC transport, fusion protein, and factors of the external membrane.

To date, the Has system for *Serratia marcescens* and *Pseudomonas aeruginosa* and hemolysin systems for *Vibrio cholerae*, *Neisseria meningitidis*, and *E. coli* are the two best studied systems; both systems control the expression and secretion of T1SS substrates (Zhao et al., 2020). In P. aeruginosa, QS controls T1SS via alkaline protease AprA

activation of its effectors. In Gram-negative bacteria, the type II secretion system (T2SS) secretes folding proteins from periplasm (Zhao et al., 2020). T2SS secretes vast quantities of exo-proteins to secure nutrient. The Xcp in *P. aeruginosa*
secretion of the elastase and exotoxin as virulence factors is controlled by QS (Chaturvedi et al., 2020a, b). The type II secretion system for biofilm development of *Vibrio cholerae* is also controlled by QS (Silva and Benitez, 2016). Type IV secretion systems are commonly adopted in both Gram-negative and Gram-positive bacteria (Grohmann et al., 2018).

Secretion of toxins is the stress response or virulence factor of bacteria involving QS (Balan et al., 2021). Toxins are especially helpful in identifying evolutionary roles established to control and destroy the activity of other bacteria, such as bacteriocin and pyocyanin. By knowing the number of microorganisms in the community mediated by QS, bacteria experience ecological competence. The density ofthe self-cell is a key element to regulate toxic effects (Shivaprasad et al., 2021). QS regulations guarantee that there are sufficient toxin or growth products in a population of the same genotype. QS knowledge is also able to forecast the level of pathogenesis. The diverse capacities of microbial communities ensure that population density experience is not limited to itself, but the genotype can produce even unique signals from other cells, and the molecules of the signal are highly specific.

Quorum quenching: a novel approach to control pathogenesis

QQ is the process that takes place when the QS mechanism of a bacterium is disturbed. This prevents information exchanges between bacteria and decreases the risk factor expression. The QQ molecules influence key phases of the QS route, including synthesis, diffusion, and the detection of part of the QS signal (Selvam et al., 2017). Therefore, the use of QQ to reduce pathogenesis and bacterial antibiotic resistance is an extremely desirable technique to treat diseases caused by bacteria and their multi antibiotic-resistant properties. Figure 4 presents the mechanism of QS and QQ during pathogenesis. In recent years, QQ has opened up new avenues to overcome and resolve microbial pathogenesis (Mion et al., 2019; Hemmati et al., 2020; Zhao et al., 2020). The mode of action of QQ molecules can be competitive, inhibiting, or preventing QS signaling (Shah et al., 2021). QQ can be accomplished in two forms: (1) degradation of signal molecules that reduces or stops the auto-inducer production, and (2) blockage of signal molecules or binding of the receptor. Detail of QQ molecules and their mechanisms are shown in Table 1.

Degradation of signal molecule (auto-inducers)

Several enzymes are used to destroy QS signal (Soheili et al., 2019). The decay of signal molecules decreases the accumulation of signal molecules, and pathogenic bacteria are unable to transmit the pathogenic genes, thereby losing the capacity of host infection. A number of bacterial species have identified to produce QQ enzymes as follows: (i) Firmicutes—*Bacillus* and *Oceanobacillus*, *Arthrobacteria*; (ii) Actinobacteria—*Streptomyces*; (iii) Proteobacteria—*Acintrobacteria*, *Agrobacterium tumefacienes*, and *Alteromonas*, *Comomonas*, *Halomonas*, *Hyphomonas*, *Klebsiella pneumoniae*, *P. aeruginosa*, *Ralstonia*, *Stappia*, and *Variovorax paradoxus*; and (iv) Cyanobacteria—*Anabaena* (Soheili et al., 2019). Jing et al. (2020) showed that quercetin could suppress the development of P. aeruginosa biofilms and the LasIR system via the *vfr* gene. PqsD is an enzyme present in *P. aeruginosa* helpful in intercellular communication. 2-Nitrophenyl is a PqsD-inhibitor that inhibits intercellular communication with P. aeruginosa and offers novel therapy possibilities for PqsD as anti-infectious medicines (Soheili et al., 2019). Enoyl-ACP reductase which promotes acyl chain length of AHL, in which an ester constitutes, is the principal signal molecule of Gram-negative bacteria.

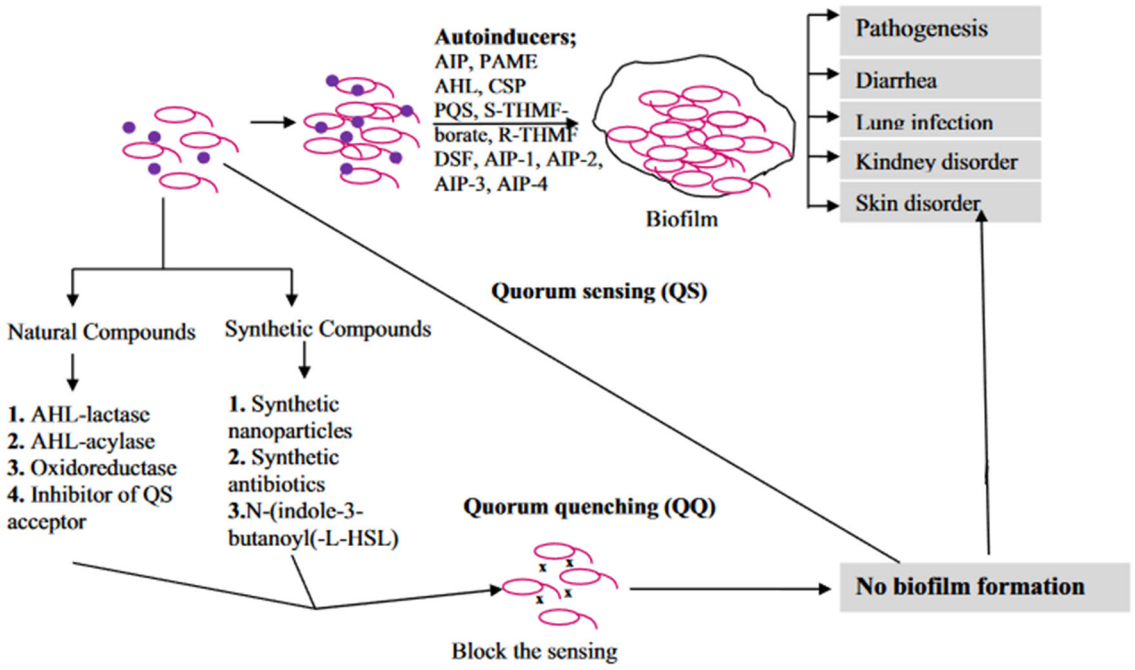

Fig. 4 Schematic diagram demonstrating the mechanism of QS and QQ during pathogenesis.

AHL-degrading enzyme was encoded with *aiiA* gene in Bacillus sp. (Pereyra et al., 2019). AidB from Bosea sp. strain F3-2 has been shown to secrete a new type of AHL lactonase that degraded AHL ester bond to reduce the pathogenicity of *P. aeruginosa* and *Pectobacterium carotovorum* (Zhao et al., 2020). AidB is also a thermo-tolerant enzyme that maintains its catalytic activity at a temperature of 80 °C after 30 min. Hence, it is the strongest candidate to control antibiotic-resistant pathogenesis (Cui et al., 2020). Zhang et al. (2019) reported that a recombinant strain (BbMomL) can degrade the exogenous signal molecule C6-HSL signal molecules produced by pathogen *Clostridium botulinum*. BbMomL has shown a wide variety of actions that inhibit Gram-positive and Gram-negative parthenogenesis and fungal growth. In addition, *P. aeruginosa* secretion and pathogenicity have been greatly reduced by recombinant strain BbMomL. Cui et al. (2020) has shown that Lactobacillus crustorum extracts ZHG 2–1, which can degrade AHL. The inactivation of the signaling molecule or its denaturation can be accomplished through a number of pathways and is the simplest solution for the use of QS to avoid bacterial resistance. Some micro-organisms can metabolize AI-2 and thus impede QS activity. After phosphorylation, AI-2 molecules are more hydrophilic and cannot cross the cell membranes and function as a QS signal. In *E. coli* and *Salmonella typhimurium*, phosphorylation AI-2 blocked QS responses (Zhao et al., 2020). The furan analog of AI-2, which reduces *E. coli* potency in the inhibition of AI-2 activities, has been verified to be exogenous imidazole (Yu et al., 2018). The AHL lactonase AiiK is expressed in the surface layer of *Lactobacillus casei* MCJ1 (Dong et al., 2020). LcAiiK showed significant AHL lactonase activity causing degradation of the auto-inducer, and excellent QQ capacities against A. hydrophila AH-1 and AH-4, attenuating rather than eliminating their QS activities. As a result, the LcAiiK can be used as an anti-pathogenic or anti-cancer medication, a biocontrol agent that inhibits pathogenic bacteria's AHL-mediated QS.

Inhibition of receptor binding

Based on the function and composition of small chemical substances that inhibit QS, QQ molecules may be classified into two groups. One group is a community of chemical products with structures as QS molecules. These chemicals interact with the receptor signal and contribute to cause a reduction in the receptor concentration. The most popular QQ enzyme in many bacteria is lactonase and acylase. The less common QQ enzyme is oxide-reductase and its mode of action can change the hydrolyzing behavior in AHL. The changed

AHL remains functionally active but cannot bind to its receptors, causing a disorder in the activation of QS-mediated gene expression. The second group of QQ molecules is enzyme inhibitors that can obstruct the synthesis of essential molecules in the QS system. Triclosan inhibits enoyl-ACP reductase, a vital intermediate in AHL biosynthesis, and closantel is a powerful inhibitor of the two-component system's histidine kinase sensor. AHL-lactonases secreted by bacterial species hydrolyze the homoserine lactone ring of AHLs. Streptomyces sp. and P. aeruginosa PAO1 secreted AHL-acylase, which degraded AHL signal by hydrolyzing the amide AHL connection and producing subsequent fatty acids and homoserines. Further, paraoxonase found in human epithelial cells is the enzyme that showed QQ activity (Soheili et al., 2019).

QS signal analogues can be secreted by many organisms that combine competitively with bacterial quorum sensors, disrupted quorum sensor systems, and greatly reduced pathogenicity. The discovery of QS in mammals reveals the impact of innate immunity against super bugs. Research confirmed the use of gallium; amino quinoline acts as QQ molecules to regulate biofilm through QQ and iron metabolism inhibition (Kaur et al., 2020; Kelson et al., 2013) in *S. Marcescens* and *P. aeruginosa*. The host innate defense and enzymes can be utilized to combat harmful antibiotic bacteria that use QS as a communications technique. QQ can be divided into inhibitors of signal supply and signal response. Antagonistic receptor binding medicines may be signal response inhibitors. It can be an analog of the signaling molecule. The inhibitors of signal supply can stop signal generation. It has been documented that some extracts of plants are inhibitors of quorum sensing. Quorum quenchers hinder the development of biofilms by disrupting the adhesion of the cell. Brominated furanone, metallo-beta-lactamase enzymes are secreted by resistant bacteria towards some common antibiotics (e.g., penicillin and cephalosporin); the enzymes worked as QQ molecules which mitigate the QS activity and biofilm formation. Metalloenzyme interacts with aptamers of organisms and inactivated the response. This finding shows that aptamer can be used to work with conventional antibiotics (Shirani et al., 2016). Non-halogenated chemicals such as 2(5H) [(1R)-1-hydroxypropyl]-furanone, 5-hydroxy-3–4-methylfuran-2(5H) Kojic acid and -one (5R) dihydroxy-5-[1S-1,2-dihydroxyethyl]-3.4-[1S-1,2-dihydroxyethyl]furan-2(5H) acted as QQ molecules to regulate the development of biofilms (Nakagawa et al., 2020). Additional substrates, such as phenolic aldehyde, d-tyrosine, and vanillin, behave like a QQ molecule to reduce the production of microbial biofilms on the solid surface via EPS

inhibition (Balan et al., 2021). Enzymes such as acylases, laptonases, and paraoxotasis also function like QQ enzymes that reduce the development of biofilms in *Rhodococcus* sp. and *Bacillus thuringiensis* (Nakagawa et al., 2020).

In *P. aeruginosa*, the QS-signaling network consists of three main interconnected regulatory systems, i.e., Las, Rhl, and Pqs, which synthesize and respond to the autoinducers N-(3-oxododecanoyl)-ʟ-homoserine lactone (3-oxo-C12-HSL), N-butanoyl-ʟ-homoserine lactone (C4-HSL), and the 2-alkyl-4(1H)-quinolones (AQs) *Pseudomonas* quinolone signal (PQS), or its immediate precursor 2-heptyl-4-hydroxyquinoline, respectively. Qing et al. (2020) extracted medicinal herb extract from medicinal plants that suppressed the PQS, partially suppressed the RhlR/rhlI QS system, and partially suppressed the lasR/lasI QS systems. Truchado et al. (2012) found that the flavonoids of *Citrus sinensis* demonstrated QQ properties, which decreased the QS signals secreted for biofilm formation in *Yersinia enterocolitica*. Other research revealed that ᴅ-galactose blocked AI-2 activities that could impede the formation of biofilms by periodontal pathogens (Shirani et al., 2016).

QS molecules also help establish a symbiotic association cross-kingdom. The QS molecule modifies high eukaryotic morphology by affecting their host reproductive, hormonal, and growth factors. A halobiont living ecosystem is formed by different bacteria and their signaling. Neem, garlic, aloe vera, and tulsi contain tannins and flavonoids; these medicinal plants are highly effective against *K. pneumoniae*, *S. aureus*, and *E. coli* (Harjai et al., 2010; Seghal et al., 2017). Various natural chemicals or compounds have been considered effective against the development of biofilms. Zeaxanthin, a carotenoid, was effective against the bacteria P. aeruginosa. Piper leaf extract against pathogenic developing biofilms has also been proven efficient (Srinivasan et al., 2017). BlcC enzyme secreted by *A. tumefaciens* worked as QQ molecules (Catharine & Turlough, 2009). Despite that several bacterial, fungal, plant, and animal metabolites have found antagonistic action on QS, only a few active molecules are isolated and identified. Many studies have therefore synthesized the QS signal analogs to oppose pathogenic bacterial QS signals. Five different haloquinones having different methoxy and hydroxyl groups have been tested. Two of these could be successful Wnt/β-catenin signaling regulators (Soheili et al., 2019). Moreover, several researchers have used N-(3-oxododecanoyl) as QS inhibitors. The LasR antagonist interacts with the LasR N-terminal binding field that blocks the location of QS binding. Research on signal molecule synthesis inhibitors showed that the LuxS compound responsible for the AI-2 signal could be inhibited by a chemically modified peptide in Vibrio harveyi BB170 (Zhao et al.,

2020). After three selection rounds, the TNRHNPHHLHV synthetic peptide was found to inhibit LuxS enzymes. Population quenchers can thus be employed in addition to antibiotics to decrease microorganism resistance to enhance bactericidal effectiveness of antibiotics and microbiological disease prevention and management.

Target antibodies for QS blockage

AHL and AI-2 activation may cause programmed cell death by influencing the immune system of the host. Antibodies XYD-11G2 were shown to catalyse 3-oxo-C12-HSL signaling hydrolysis, thereby impeding Gram-negative bacteria synthesis of pyocyanin (Miller and Gilmore, 2020) . AP4-24H11 monoclonal antibody was shown to inhibit *Staphylococcus* aureus QS signal by interfering with AIP IV (Saeki et al., 2020). Another in vivo investigation has shown that the AP4-24H11 antibody may dramatically diminish tissue necrosis in the infected model (Nakagawa et al., 2020). While monoclonal antibodies have been found to inhibit the QS signaling of harmful bacteria (Personnic et al., 2021), however, they are still in the early stages of their use to treat bacterial disorders.

Future outlook

Since 1990, QS has increasingly gained attention as an emerging field of study in microbial research, but the associated QS regulation in microbial resistance remains uncertain. Studies have shown that bacteria acquire resistance to quorum sensing inhibitors (QSIs) (Koul et al., 2016) where QSI affects pathogenicity without interfering with bacterial growth (Chu et al., 2014). The richness of the pathways for bacterial resistance brought significant research challenges; therefore, studying the development and regulation of major microorganism resistance mechanisms to control bacterial disorders is of high functional importance. Studies have shown that the QS system participates in biofilm formation and drug efflux pump controls efflux pump gene expression in *P. aeruginosa* and many other pathogens. However, further research is still needed to develop and regulate antibiotic resistance mechanisms for more clinically relevant pathogens. Therefore, the progress and breakthrough in QS analysis would probably lead to new vitality in microbial resistance study.

QQ is a novel strategy in combating QS in pathogenic bacteria. QQ molecules can reduce the barrier effect of biofilm and prevent bacterial alterations in biofilms to reduce bacterial biofilm antibiotic resistance. Researchers have found medicinal plants containing

spectrum of secondary metabolites present in extracts, which include phenolics, quinones, flavonoids, alkaloids, terpenoids, and polyacetylenes which suppressed the QS activities. However, most anti-QS medicines are still in the preclinical stage and there is a need to invest in this promising technology to fully explore its clinical usage and transition from the bench to the clinic scale.

Several researchers also immobilized QQ enzymes to overcome free enzyme limitation. QS and QQ genes from *Agrobacterium tumefaciens* were found to synchronize virulence expression in *A. tumefaciens* (Saeki et al., 2020). *A. tumefaciens* can secrete 3-oxo-C8-HSL, and its level is modulated by two attM and aiiB lactonases (Personnic et al., 2021). Moreover, the AHL-based QS and QQ actions of *Acinetobacter* and *Burkholderia*, as rhizosphere bacteria, reduced pollutants to vegetables by controlling the entire bacterial rhizosphere culture. Therefore, the QQ technology has good potential to be applied to field beyond human medicine, for example, to tackle the emerging problem of microplastic-associated pathogens and antimicrobial resistance in the environment (Kaur et al., 2021), where QS plays an important role in biofilm and cluster formation that promote antimicrobial-resistance gene transfer.

There are many prospects and challenges for QS study in the area of antibiotic sensitivity. Future quorum detection research should concentrate on the following areas: (1) given the incompleteness of regulatory pathways relating to QS, similar studies by molecular biology should further be strengthened; (2) since the microbial pathogenesis mechanism is complex, effort should concentrate on improving applicable bacterial QS science; (3) due to the inadequacy of current QQ screening, new and effective QQ technologies must be developed.

Concluding remarks

The study of QS in microorganism is complicated. Biofilm development through inter- and intra-cell communication, which involves signals and signal transfer processes, may lead to the adaptation to stress or changing environments of bacteria. AHL-and AIP dependent gene expression is responsible for cell–cell communication in bacteria to lead virulence. Knowledge of bacterial QS systems provide an understanding to the inter- and intra-species communication and adaptation under stress or antibiotic treatment. The control of bacterial

QS by target substances is an efficient way of regulating bacterial virulence factors and the development of biofilms. In the antibiotic resistance arm race, QQ is an innovative non-antibiotic treatment targeting QS that presents a new and novel way to suppress the production of harmful genes, prevent infections, and minimize the likelihood of bacterial cell drug resistance. However, further research is needed to develop QQ and anti-QS drugs for clinical applications. Future, studies should be concentrated on QS regulatory systems, which are essential for pathogenesis and antibiotic resistance. If QQ is to be used to treat human illnesses, it will likely be in the context of combination treatments with traditional antimicrobials.

Authors contribution

ST, DP, and MG—review and revision; RC—supervision and conceptualization, SY—supervision, conceptualization, data curation, investigation, and writing—original draft.

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Declarations

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

The authors declare no competing interests.

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