

ANTIQUORUM SENSING COMPOUNDS – A NOVEL APPROACH FOR BACTERIAL DISEASE MANAGEMENT

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Abstract– Quorum sensing is a communication system between bacteria for a communication between them, which allows them to coordinate infections based on their population size and bypass host defence mechanisms. This process relies on small, diffusible signalling molecules called autoinducers, their concentration increases with increase in number of bacteria. Through quorum sensing, bacteria regulate various collective behaviors, such as bioluminescence, biofilm formation, survival on plant surfaces, virulence factor production, antimicrobial secondary metabolites, siderophores, plasmid transfer, pigments, and motility. With antibiotic resistance on the rise due to excessive use, there is a growing need for alternative antibacterial strategies. One promising strategy is to use the quorum sensing inhibitors (QSIs) or anti-biofilm agents, which disrupt bacterial communication and prevent disease. These inhibitors work through different mechanisms, such as blocking autoinducer synthesis, interfering with their transport, degrading them with enzymes, sequestering them with monoclonal antibodies, or competing with signals to disrupt quorum sensing pathways. While QSIs have high specificity, making them effective for targeted plant disease management, further research is needed to evaluate their potential toxicity in plants and their broader ecological effects on organisms, populations, and cellular systems.

INTRODUCTION

Bacteria have the ability to monitor their population density and regulate their gene expression accordingly using the cascade of signals through the signal molecules called autoinducers (Fuqua *et al.*, 1994). Nealson *et al.* (1970) reported Quorum sensing (QS) for the first time in *Vibrio fischeri*, a luminous marine gram-negative bacterium. Three major autoinducers (AIs) involved in QS are N-Acylhomoserine lactones (AHLs) (gram-negative bacteria), Oligopeptides/ autoinducing peptides (gram-positive bacteria), Autoinducers 2 (AI-2) (both gram-positive and gram-negative bacteria). Bacteria produce these molecules extracellularly; after reaching some threshold concentration they diffuse passively or are transported actively into the cell and bind to receptor proteins. The synthesis of antimicrobial agents (Bainton *et al.*, 1992), bioluminescence (Nealson and Hastings, 1979), factors associated with virulence (Barber *et al.*, 1997), swarming (Eberl *et al.*, 1996), plasmid conjugal

transfer (Fuqua and Winans 1994), and exopolysaccharide biosynthesis (Beck and Farrand, 1995) are just a few of the collective traits that QS is primarily responsible for coordinating the expression of these traits. Bacteria cause major diseases leading to huge loss of the crop. They have also developed resistance to many antibiotics very quickly and the discovery rate of new antibiotics has reduced drastically, hence there is a need to discover novel ideas for bacterial disease management (Livermore, 2011). Novel concepts and words like quorum quenching, antivirulence, diffusion sensing, mass transfer, and sociomicrobiology were also developed and disseminated as a result of QS-related research (Dong *et al.*, 2001; Parsek and Greenberg 2005; Redfield, 2002; Hense *et al.*, 2007). All of the mechanisms involved in the disruption of QS are called quorum quenching (QQ) (Dong *et al.*, 2001). Since all of the primary steps of the QS pathway- synthesis, diffusion, accumulation, and perception of the QS signals- may be impacted, QQ molecular actors vary in nature (enzymes, chemical

compounds), mode of action (QS-signal cleavage, competitive inhibition, etc.), and targets. Typically, substances that interfere with QS pathways are referred to as QS inhibitors, and the enzymes that deactivate QS signals are known as QQ enzymes. In this article we will understand about the quorum sensing, quorum quenching and role of quorum quenching agents in bacterial disease management.

Quorum sensing (QS)

‘Quorum’ is a Latin word that means “number of members of a group required to be present to carry out an activity legally”. Neelson *et al.* (1970) first described quorum sensing (QS) in the luminous marine gram-negative bacterium *Vibrio fischeri*. When the bacteria are present in marine water due to the shortage of nutrition their number can't reach the level to start the quorum sensing mechanism, when bacteria enter the squid, they can multiply the maximum in number to exhibit quorum sensing.

Mechanism of quorum sensing

The quorum sensing mechanism differs significantly between gram-negative and gram-positive bacteria. In a nutshell, signaling molecules called autoinducers are produced inside the bacterial cell, due to the concentration gradient they are transported out of the cell either passively (G-negative bacteria) or actively using transport proteins located in the cell membrane (G-positive bacteria). Once the bacteria reach enough cell number the concentration of autoinducers outside

the cell will be higher than that inside the cell, due to which these autoinducers are transported back into the cell. Inside the cell, they bind to the receptor proteins, which trigger the gene expression (Figure 1) (Waters and Bassler, 2005).

Autoinducers

Autoinducers are tiny chemicals produced by bacteria that can be used to determine population density. Their type and mechanism differ between gram-negative and gram-positive bacteria (Xavier and Bassler, 2003). Three main classifications can be used to broadly categorize these signaling molecules; (1) Nacyl homoserine lactones (AHLs), which are the molecules having homoserine lactone ring and alterable length of acyl side chain and produced by gram-negative bacteria to track their population density in QS mediated control of gene expression. The signals are synthesized by members of the LuxI family of proteins; (2) Oligopeptides/ Autoinducing peptides (AIPs), they consist of 5-34 amino acid residues, generally modified post-translationally. They are involved in intercellular communication in gram-negative bacteria. They are transported by dedicated channels (transport protein) out of the cell and finally sensed by other cells through membrane-located receptors that are part of two component regulatory systems; (3) Autoinducer-2 (AI-2), generated for interspecies communication in both Gram-positive and Gram-negative bacteria. It has been chemically identified as a furanosylborate diester synthesized by members of the LuxS family of proteins (Xavier and Bassler, 2003; Zhang *et al.*, 2002; Choudhary and Schmidt Dannert, 2010).

Quorum sensing system in Gram-negative bacteria

Gram-negative bacteria use small molecules called autoinducers (AHLs) for quorum sensing signaling. These molecules are produced and secreted out by the cells. Once these molecules reach threshold concentration outside the cell they are diffused into the cell and bind to the regulator/ activator protein to form the AHL-activator complex, which in turn triggers the gene expression required for the QS-dependent character (Figure 2) (Sharma *et al.*, 2024).

Quorum sensing system in Gram-positive bacteria

Gram-positive bacteria employ oligopeptides for intercellular communication as autoinducers. These oligopeptides are produced after processing of the

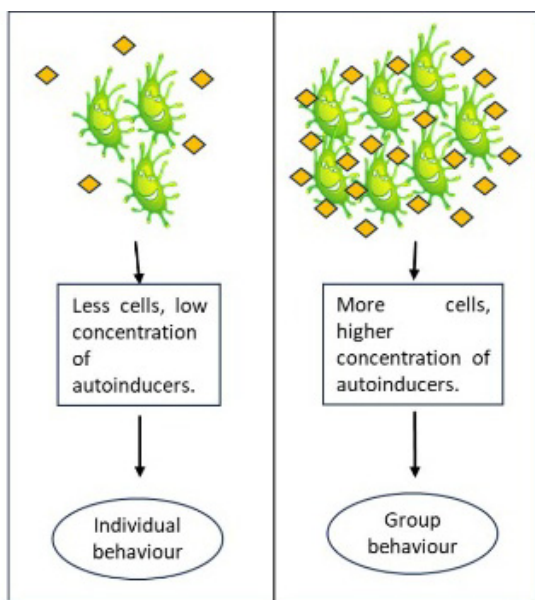


Fig. 1. Quorum sensing mechanism in bacteria

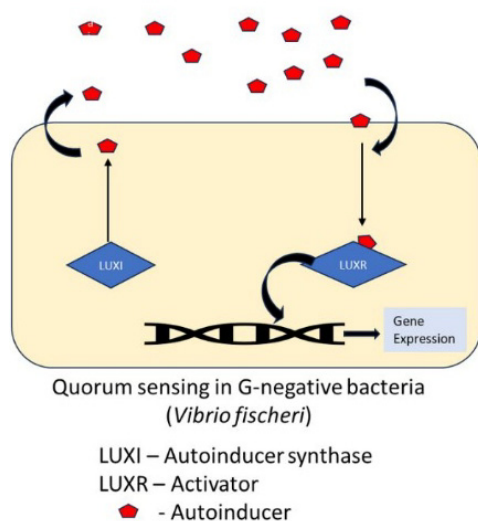


Fig. 2. Quorum sensing system in G-negative bacteria

prepropeptides. Once produced they are transported out of the cell through the membrane located transport protein. After the threshold concentration is reached, they are sensed by the histidine kinases located on the cell membrane. Histidine kinases get excited and release a phosphate group which binds to the cytoplasmic response regulator. This complex binds to the operon and triggers the gene expression (Figure 3) (Monnet and Gardan, 2015).

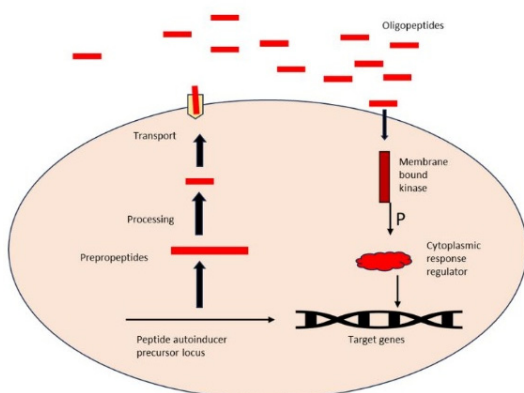


Fig. 3. Quorum sensing system in G-positive bacteria

Use of quorum sensing in bacteria

The QS circuit is utilized by bacteria for a variety of metabolic processes, which can be broadly categorized as follows: (1) cell maintenance and proliferation (production of exoenzymes, synthesis of siderophores, sporulation, acid resistance, etc.); (2) cell behaviors (formation and dispersal of

biofilms, motility, adhesion, etc.); and (3) horizontal gene transfer (plasmid conjugation, competence, etc.). (4) Interactions with the host and other microorganisms (host colonization factors, bioluminescence, antibiotics, exopolysaccharide synthesis, and virulence factors) (Grandclement *et al.*, 2015).

Antiquorum sensing (AQS)

Antiquorum sensing is the method for controlling bacterial infections by interfering with their communication mechanism, also known as quorum quenching and the agents involved in this mechanism are called antiquorum sensing agents/ quorum quenching agents/ quorum sensing inhibitors. Low molecular weight, chemical stability with a high degree of selectivity for the QS regulator, and no adverse effects on bacterial growth are the characteristics of the ideal AQS agent (Asfour, 2018).

Givskov *et al.* (1996) first reported the antiquorum sensing activity of the secondary metabolites produced by a marine macro alga *Delisea pulchra*, these secondary metabolites showed inhibition of the swarming motility of *Serratia lequefaciens*, these metabolites were identified as halogenated furanones which are structurally similar to AHLs and have strong biological activity. They bind competitively to SwrR (regulator) protein and inhibit quorum sensing.

Mechanism of antiquorum sensing

By observing the action mechanism of quorum sensing, one can think of interrupting the mechanism at any point of time from the production of autoinducers to binding them to regulators to stop the quorum sensing. QS can be stopped by stopping the biosynthesis of AHLs, their transport, degradation, sequestration with antibodies, and competition by similar structured molecules.

Inhibition of AIs synthesis

These agents target the precursors of AHL synthesis and bind with acyl-ACP (Acyl Carrier Protein) and SAM (S-Adenosyl methionine). Sinefungin is a general inhibitor of SAM-dependent methyltransferases that has both antimicrobial and antiviral properties (Galati *et al.*, 2021). Hoang and Schweizer (1999) reported that triclosan is also a good AHL synthesis inhibitor that target the enoyl-ACP reductase activity. Another AHL antagonist identified by Chung *et al.* (2011) (named J8-C8) is an

acyl-ACP carrier competitive inhibitor.

Synthesis of AHLs

AHLs are produced after a combination of the precursors (Acyl-ACP and SAM) in the presence of AHL synthase enzyme. Acyl-ACP is a by-product of the fatty acid metabolic pathway produced after the action of the acetyl-CoA enzyme. SAM is produced when ATP binds with methionine in the presence of methionine adenosyl transferase enzyme (Figure 4) (Papenfort and Bassler, 2016). AHLs produced by different bacteria have different shape based on the metabolites they produce (Table 1).

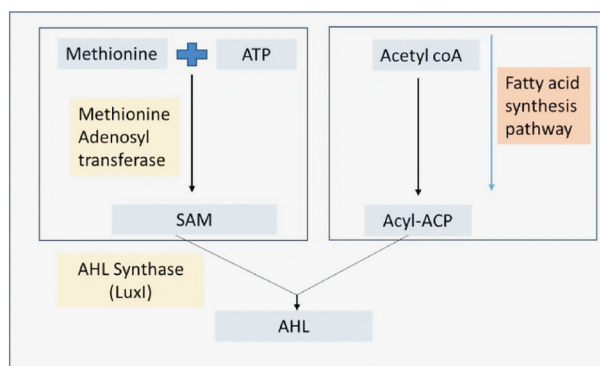


Fig. 4. Biosynthesis pathway of AHLs

Inhibition of AI Transport

In *Escherichia coli* QS (for biofilm formation) is mediated by secretion and transport of autoinducer 2 (AI2). The uptake of AI2 is done by the ABC transporter protein (ATP Binding Cassette protein). Inside the cell, in presence of AI2 Kinase (LsrK), the AI2 gets phosphorylated to form Phospho-AI2, which triggers the gene expression. Phospho-AI2 degrades overnight to form phosphoglycolic acid (PG). If LsrK is added externally it does the

phosphorylation of AI2 outside the cell converting it to phospho-AI2, which cannot be detected by the ABC transporter located in the cell membrane. Hence, stopping QS. Phosphoglycolic acid was later found not to have any effect on QS (Roy *et al.*, 2010).

Degradation of AIs using Enzymes

Autoinducers can be exposed to enzymes like acylases, lactonases, and oxidases, in which the acylases hydrolyses the amide bond in acyl side chain, lactonases hydrolyze the HSL (homoserine lactone) ring and oxidases and reductases don't hydrolyze the AHL, but modify it by reducing the hydroxyl or carbonyl group from the acyl side chain (Verma *et al.*, 2021).

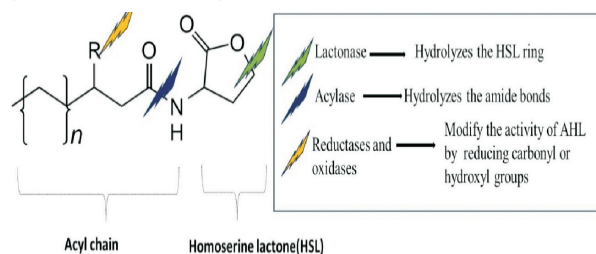


Fig. 5. Action of different enzymes on the AHLs.

Plant pathogenic bacteria can be exposed to these enzymes by biotization, mutagenesis, and genetically engineered plants (Verma *et al.*, 2021).

Biotization

It is the process of introducing non-native organisms (here organisms producing AHL degrading enzymes) into plants. Microbes along with producing the AHL degrading enzymes occupy the intercellular spaces, inhibiting the colonization by the later-entered pathogen (Figure 6) (Alagarasan *et al.*, 2017). They also help in the acquisition of

Table 1. Some important phytopathogenic bacteria and autoinducer molecules produced by them

Bacteria	Autoinducers produced	Reference
<i>Pseudomonas syringae</i>	3-oxo-hexanoyl homoserine lactone	Quiñones <i>et al.</i> , 2004
<i>Ralstonia solanacearum</i>	3-hydroxy palmitic acid methyl ester (3OH-PAME)	Achari and Ganesh, 2015
<i>Agrobacterium tumefaciens</i>	3-oxo-octanoylhomoserine lactone (OC8HSL)	Haudecoeur and Faure, 2010
<i>Xanthomonas oryzae</i> pv. <i>oryzae</i>	cis-11-2-methyl-dodecenoic acid	Singh <i>et al.</i> , 2022
<i>Erwinia amylovora</i>	N-(3-oxo-hexanoyl)-homoserine lactone	Venturi <i>et al.</i> , 2004
<i>Dickey</i> sp.	N-3-oxohexanoyl-homoserine lactone (3OC6-HSL), N-3-oxo-octanoyl-homoserine lactone (3OC8-HSL), N-hexanoyl-homoserine lactone (C6-HSL), and N-decanoyl-homoserine lactone (C10-HSL)	Liu <i>et al.</i> , 2022
<i>Pectobacterium carotovorum</i>	N-3-oxo-octanoyl-l-homoserine lactones	Crépin <i>et al.</i> , 2012

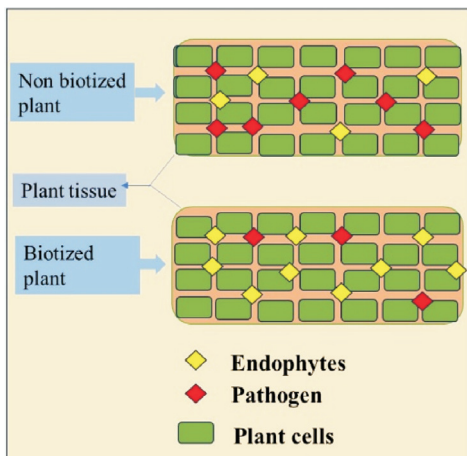


Fig. 6. Endophytes colonizing intercellular spaces in biotized plant tissue.

transition metals by producing siderophores thus increasing the immunity of the plants (Fones and Preston, 2013).

Mutagenesis

In *Agrobacterium tumefaciens*, conjugal transfer of Ti plasmid is governed by QS. In *A. tumefaciens* the AHL lactonase is encoded by *attM* which in normal conditions gets suppressed by the negative transcription factor *attJ*. By knocking out the *attJ* gene by Tn5 (transposon) mutagenesis AHL lactonase is produced degrading the AHL, hence QS (Zhang *et al.*, 2002).

Genetically engineered plants

Plants can also be genetically transformed by engineering them with *aiiA* gene (autoinducer inactivation gene) from *Bacillus spp.* which encodes for lactonase enzymes. Rogayah *et al.* (2016) introduced the *aiiA* gene into *Carica papaya* from *Bacillus cereus* against the pathogen *Erwinia mallotivora*.

Sequestration of AIs using antibodies

These anti-AHLs are antibodies that bind to the autoinducers, these autoinducer-antibody complexes will not be detected and transported by the carrier protein present on the cell membrane. Kaufmann *et al.* (2011) reported that RS2-1G9 produced by substituting the homoserine lactone moiety with a lactam group efficiently suppressed QS signaling in *Pseudomonas aeruginosa* as well as conferred protection upon mammalian cells via neutralization of 3-oxo-C12-HSL *in vitro*. Park *et al.* (2007) replaced hydrolytically labile thiolactone

present in AIP produced by *Staphylococcus aureus* with a more stable lactone moiety, which quenched QS in the same bacteria. Further efforts have been made on the synthesis of QQ catalytic antibodies which resemble the transition-state structure of AHL-ring hydrolysis leading to attenuation of bacterial virulence (Marin *et al.*, 2007).

QS Signal Competition (QS Mimicry)

The signal analogues compete with the signal molecules and bind to the receptors. Rasmussen *et al.* (2000) used an AHL analogue (halogenated furanone compound) produced by a marine macroalga *Delisea pulchra* against *Erwinia carotovora* to inhibit the exoenzyme production (an AHL-regulated process). These compounds can also be produced by replacing the homoserine lactone ring with other cyclic compounds like cyclopentyl, cyclohexanone, thiolactone, *etc.*, (Morohoshi *et al.*, 2007).

CONCLUSION AND RESEARCH GAP

Antibiotics work by killing bacteria or slowing their growth, which often leads to the emergence of resistant strains. In contrast, quorum-quenching (QQ) strategies don't pose a direct life-or-death threat to bacteria. Instead, they weaken bacterial virulence by disrupting quorum sensing—the communication system bacteria use to coordinate their actions. QQ mechanisms target different aspects of this process, such as blocking signal production, breaking down signals, interfering with signal transport, or competing with natural signals. This approach holds great promise for both fundamental research and biotechnological applications. Notably, QQ endophytes could be harnessed as an effective, sustainable strategy for managing plant diseases. Despite the potential of quorum-quenching (QQ) strategies, several challenges still need to be addressed. These include the effective targeting and delivery of QQ enzymes or molecules, assessing their potential toxicity in plants, and understanding their unintended effects at various biological levels—from individual cells to entire populations. Advancements in assay techniques, along with cutting-edge analytical imaging systems, will play a crucial role in uncovering bacterial behavior and development, ultimately helping refine QQ-based approaches for practical applications.

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Conflict of interest

The authors declare that there is no potential conflict of interest.

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