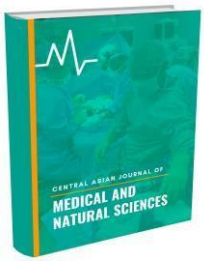

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Article

Quorum Sensing Between Bacterial Communication and Neutralization to Reduce Bacterial Birulence

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Abstract: One of the important means by which bacteria communicate is the quorum sensing(QS) mechanism, which represents the essential point in starting their journey towards controlling the environment in which they exist through the formation of biofilms, the production of virulence factors, the production of internal and external enzymes, movement, reproduction, and spore formation. Therefore, this review sheds light on how bacterial QS occurs, forming genetic coding and the formation of the regulatory and receptor protein molecules responsible for this and their mechanism of action, to develop our strategy in our battle against mutations and resistance that occur in pathogenic bacteria as a result of the use of synthetic antibiotics and the search for natural chemical compounds extracted from plants that are effective in suppressing bacterial QS without affecting their growth, thus reducing the risk of developing resistance later, as well as getting rid of the toxicity of some drugs used in treatment.

Keywords: QS, N-acylhomoserine lactone, Quorum quenching Lactonases Acylases, Autoinducer and plant extracts

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1. Introduction

Since the discovery of quorum sensing in Staphylococcus pneumoniae, which uses a regulatory mechanism controlled by a chemical factor called a competence factor (Tomasz., 1965), Autoinducers were identified in such as Vibrio harveyi and Vibrio fischer; This bacteria has a symbiotic relationship with multiple eukaryotic hosts (Nealson, et al., 1970; Miller.,2001). responsible for the luminescence of some marine fish and squid, the term QS was coined by (Fuqua et al.,1994) to describe a gene regulation process that responds to population density when it reaches the bacterial quorum (When the concentration of extracellular Autoinducers becomes high), the mechanism of QS is similar to the physiology of advanced organisms. It may be one of the foundations from which more advanced intracellular communication processes evolved (March, et al., 2004). Microscopic organisms are found everywhere in the ecosystem, forming a large part of our micro and macro environment, including our bodies, especially the mucous membranes (Wu, et al., 2021). Therefore, they have succeeded in developing several complex systems that adapt

to and control these different environments. To better adapt to these harsh environments, bacteria use protein secretion systems for the medium in which they live (Sana, et al., 2020).

QS is the response to chemical signals produced by bacteria on their own when their density reaches the required quorum, which occurs due to the release of the signal enzyme (or several participating enzymes) that spreads from the cytoplasm to the environmental medium of the bacteria. There are also special receptors in the plasma membrane of the same bacteria or other species to receive those signals when the level of signal molecules reaches the required level responsible for sensing the completion of the quorum and transferring them to the cytoplasm of the cell after the modification processes that occur in those signals to control the process of gene expression (Hense, et al.,2015).

As a result of the vital and effective role played by the bacterial QS system, which has been proven by recent research, this system can be used at the biotechnology level and benefit from the efficiency of bacterial strains and their relationship within their ecosystem in the process of producing antibiotics, the formation of biofilms by both P.aeruginosa and Burkholderia cepacia, in the lungs of patients with cystic fibrosis (CF). (Paul, et al., 2024), the secretion of virulence factors by S.aureus (Miller, 2001), the formation of spores in Bacillus subtilis(Kleerebezem., et al.1997), the reproduction, movement and production of various exotoxins, and the reproduction process in Serratia liquefaciens(Eberl., et al., 1996). Therefore, Understanding the bacterial QS thoroughly is essential for developing strategies to prevent and control the formation of biofilms through the use of biological control measures. (for example, the utilization of compounds that are biologically active) that target biofilms are common in industrial and medical environments and are clearly found in clinical industrial equipment that are closely associated with hospital diseases due to bacterial colonization on medical equipment surfaces (Samrot, et al., 2021), so it is possible to benefit from plant-derived products to obtain more effective formulations and drugs for many bacterial pathogens that are expected to exhibit anti-infective activity (Harris., 2024), as some results indicate that plant extracts containing terpenoids, flavonoids, and phenolic acids act as anti-QS agents by inhibiting the release of Autoinducers (Bouyahya, et al., 2022), thus inhibiting bacterial growth and biofilm formation, which supports their medical use (Adeyemo, et al., 2022), in addition to their importance as natural antibiotics that suppress bacterial QS and biofilm formation, as in Vibrio harvayi bacteria, their residues can be used in bioremediation and energy generation (Dhowlaghar, et al., 2023).

Thus, targeting bacterial priming has become a means of protection against pathogens that depend on it because the inhibition process is supposed to hinder the gene expression of pathogenic genes only without affecting the ability to survive (Shi-Hui, et al., 2020).

2. Materials and Methods

QS in Gram-Negative Bacteria:

Many QS systems have been studied in many chromophore-negative bacteria such as Pseudomonas aeruginosaLasI /LasR, Escherichia coli SdiA, Erwinia stewartii EsaI/EsaR, Salmonella typhimurium. /SdiA , Serratia liquefaciens SwrI, the bacterial QS system consists of two types of molecules, which are acyl-homoserine lactones AHLs (Autoinducer-1) and Autoinducer-2 (AI-2) (Kumari,et al., 2008; Tay,.,2013).

1- Acyl-Homoserine Lactones (AHL) QS :

It is one of the most important chemical signals (autoinducer-1) used in Gram-negative bacteria, Cyanobacteria, and Archaea (Sharif, et al., 2008). Its concentration in the environment is proportional to the density of bacteria. The higher the density of bacteria, the more they achieve the quorum. It is characterized by an N-lactone ring shared with an acyl chain of 4-18 carbon atoms. However, the nature of the acyl chain substitution varies according to the individual species, and stability is affected by the length of the acyl chain

(Von Bodman, et al., 2008; Galloway, et al., 2011). After synthesis, AHL molecules become free to move inside the cell or its surroundings (Tay., 2013).

Component Acyl-Homoserine Lactones (AHL) QS:

Two types of regulatory proteins for QS have been identified in Vibrio fischeri(Producer of bioluminescent luciferase enzyme), which are the best examples to illustrate the mechanism of bacterial QS. S-adenosylmethionine (SAM) is the most common class of artificial lipids (AIs) requires an essential substrate to synthesize acyl-homoserine lactones (AHLs). It undergoes metabolic processes that convert it into signals that can be sensed by various types of bacteria (Hanzelka.,1996).

LuxI: AHLs are synthesized by proteins, and LuxR proteins are the regulatory proteins that attach to their respective AHL. Among the 25 species of Gram-negative bacteria that have been identified that use the sensing circuits of the type LuxI/ LuxR, V. fischeri, P.aeruginosa, A. tumefaciens, and Erwinia carotovora are the ones that are the most well-understood system. (Miller.,2001).

When the concentration of AHLs increases, they bind to the regulatory proteins LuxR, leading to the formation of the AHL/LuxR complex, which in turn binds to its specific promoter, known as PluxI, the bioluminescence genes in the bacteria Vibrio fischeri , .There are many different regulatory protein systems in bacteria, such as LasR/LasI and RhlR/RhlI receptors, the QscR receptors in P. aeruginosa, and the SdiA receptor (LuxR homolog) in Escherichia, which can also respond to small molecules produced by the mammalian host (Papenfort., 2016). Sensing bacterial infection using AHL as a signal is responsible for many chronic respiratory infections (CF), such as lung diseases and P. aeruginosa and B. cepacia bacteria, as well as gastrointestinal diseases, are responsible for cystic fibrosis (GI) (Chambers, et al., 2005; Middleton, et al., 2002).

2- Autoinducer-2 (AI-2)

Another group of bacterial QS molecules used by Gram-negative bacteria are believed to play a role in communicating between different species, including those produced by Gram-positive bacteria. (Tay., 2013); Two main steps are involved in the biosynthetic process of AI-2 molecules : first, S-adenosyl-L-homocysteine is broken down by MTAN (also called as Pfs) to S-ribosyl-L-homocysteine (SRH) by removing adenine; second, SRH is subsequently converted to homocysteine and the AI-2 precursor 4,5-dihydroxy-2,3-pentanedione (DPD). An important enzyme in the biosynthetic pathway of type is an LuxS (S-Ribosylhomocysteinase) that is dependent on Fe2+ of type II Autoinducer (AI-2) (Rajan, et al., 2005).

LuxS homologues have been identified in 537 of 1402 sequences, and the most common Autoinducer-2 receptors are LuxP in V. harveyi, a peripheral binding protein with affinity for the membrane-bound kinase sensor LuxQ that initiates a series of transformations that activate transcription, and LsrB in Salmonella typhimurium, Enterobacteriaceae, Rhizobiaceaeand Bacillaceae families. (Pereira, et al., 2009; and 2013).

The species of bacteria that contain luxS genes include but are not restricted to, E. coli, S. typhimurium, Salmonella typhi, Salmonella paratyphi, B. subtilis, Borrelia burgdorferi, Neisseria meningitidis, Haemophilus influenzae, Helicobacter pylori, Yersinia pestis, Campylobacter jejuni, Vibrio cholerae, S. aureus, Clostridium perfringens, Clostridium difficile, Mycobacterium tuberculosis, Enterococcus faecalis, S. pneumoniae, Streptococcus pyogenes, and Klebsiella pneumoniae (Miller., 2001).

3. Results

Autoinducing Peptides (AIP) QS System in Gram-Positive Bacteria:

In Gram-positive bacteria, autoinducers are oligopeptides, which are short peptides that typically range from 8 to 10 amino acids in length or slightly longer. The sensing system of Gram-negative bacteria does not allow AHLs to diffuse in and out of the bacteria as oligopeptides do; instead, they leave the bacteria through specific exporters. They then bind to Autoinducer receptors on the bacterial surface to complete the mechanism (Gebler, et al., 2024); the activity of a DNA-binding transcriptional regulatory protein called a response regulator is influenced by the phosphorylation cascade initiated by membrane-bound histidine kinases, which are used by gram-positive bacteria to communicate with modified signal peptides. The signal peptide is not released directly

across the membrane until it has been processed and changed so that it contains lactone rings, thiolactone rings, lanthionine rings, and isoprenyl groups (Waters and Bassler., 2005; Boban, et al., 2023). QS system uses a two-component adaptation, ComD and ComE, to detect Autoinducers, a series of phosphorylations followed by dephosphorylation (Miller and Bassler, 2001). The arrival of Gram-positive bacteria such as Streptococcus pneumoniae to the competence state is genetically controlled by QS, The activation of this state, known as CSP (competence-stimulating peptide), requires a signal peptide or pheromone, which is composed of 17 amino acids derived from another peptide of 41 amino acids called ComC. to stimulates the transport system ComAB to transfer CSP. The accumulated state of CSP is sensed by the sensor protein histidine kinase ComD, which undergoes autophosphorylation and transfers a phosphorylation group to another protein response regulator ComE (an important regulatory protein responsible for the virulence state), which in turn stimulates the transcription of the ComX gene responsible for the various Com genes. (Yao, et al., 2024; Oh., 2024; Miller.,2001).

It has also studied several QS systems in Gram-positive bacteria B. subtilis ComP/ComA Competence/ Sporulation System and The Staphylococcus aureus AgrC/AgrA. The production of virulence factors like exotoxins or biofilm is controlled by the Virulence System (LaSarre., 2013).

Inhibition of QS

P. aeruginosa has been extensively researched as an example of QS inhibition in bacteria because of its direct involvement in common hospital infection. The formation of the receptor complex was prevented by interference with signal detection and the use of natural or synthetic alternatives or analogs of signal transducers, which resulted in positive results. AHL molecule was one of the important molecules for QS used in these experiments because it consists of two ends, one of which is a lactone ring and the other of a variable-length acyl responsible for binding to the protein regulator LasR. For example, a structural analogue N-decanoyl-L-homoserine lactone (C10-HSL) and N-decanoyl-L-homoserine benzyl ester (C2) were used against P. aeruginosa (Smith and Suga.,2003). They showed significant effects on suppressing the las and rhl genes and thus reducing the production of some biologically active compounds such as rhamnolipid and motility.

For example, several AHL analogues have been synthesized and evaluated for their activity against pathogenic gram-negative bacteria, including the compound D15 (N-(2-(4-(trifluoromethoxy) phenoxy) acetyl)-L-homoserine lactone, in which the acyl chain was replaced, and it showed strong inhibition of QS in P. aeruginosa (Geske et al., 2007). With the availability of 3D data for both LasR and RhlR, synthetic inhibitors were screened by specifically targeting the binding pocket in the receptor structure, thus inhibiting it. (Amara, et al., 2009 ; Ganguly, et al., 2011; Annapoorani,et al., 2012).Therefore, targeting receptors or protein regulators crucial for bacteria's virulence is essential for an inhibitor to fully achieve its therapeutic potential against these pathogens that share similar QS mechanisms.

By deregulating virulence genes (lasA, lasB, chiC, and rhlAB) and decreasing tolerance to Tobramycin (an aminoglycoside antibiotic that interferes with protein synthesis) 4-Nitro-pyridine-Noxide (4-NPO) was evaluated for its effect on virulence of P. aeruginosa in biofilms (Rehman et al., 2018).

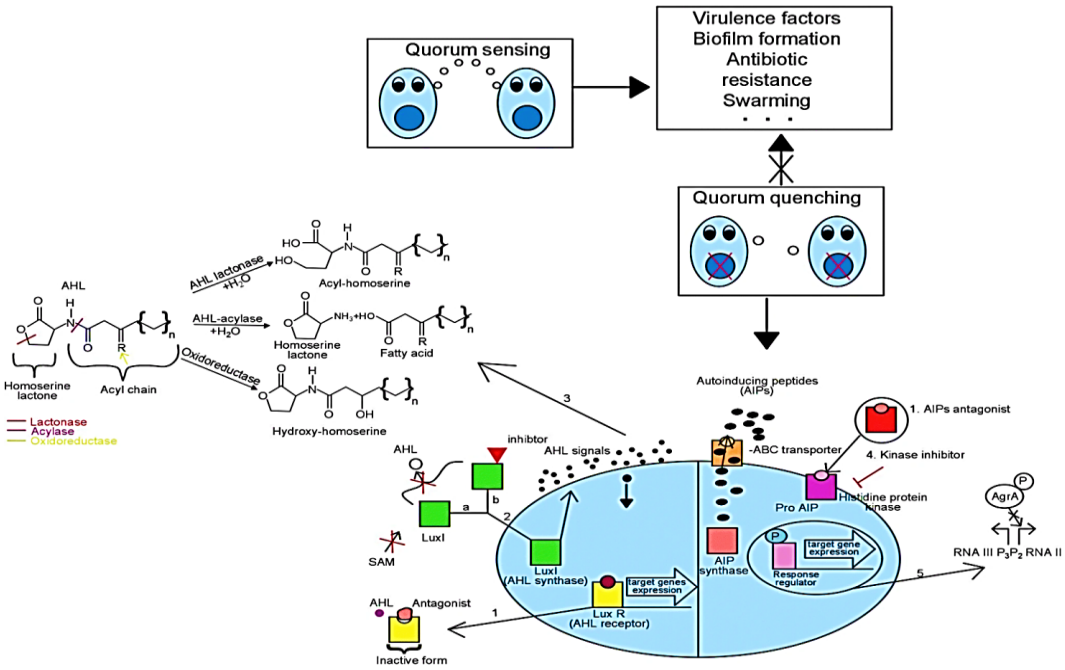
QS Quenching

The expression of genes responsible for virulence can be stopped by suppressing bacterial quorum completion to control pathogens. The use of enzyme systems as effective agents for degrading or inactivating quorum-sensing molecules has been increased. Many enzymes affect AHL, namely acylases, lactones, oxidoreductases, and paraoxonases. Acylases AiiD, produced by Ralstonia and AiiA, produced by Bacillus, degrades amide bonds in AHL molecules, releasing lactone, homoserine, and fatty acyl chains. In contrast, lactonase targets degrading the ester bond in the lactone ring, and the oxidoreductase enzyme degrades the quorum-sensing molecule and converts it to an inactive form. All of these enzymes have proven effective against P. aeruginosa bacteria. (Dong and Zhang., 2000 ;Reimmann, et al., 2002 ;Uroz, et al., 2005; Chen, et al., 2013).

Other mechanisms inhibit the synthesis of signalling molecules, such as kinase inhibitors in Gram-positive bacteria. Savrin, a small molecule inhibitor, has been shown to interfere with AgrA (a transcription regulator of the QS-involved agr operon), thus inhibiting virulence factors (Sully et al., 2014).

4. Discussion

The QS molecule N-acyl homoserine lactone (A) and the quorum quenching enzymes (B) have the potential to degrade a linkage. (Chen, et al., 2013).



Inhibition by Natural Compounds

Plant extracts act as inhibitors of bacterial QS because they are complex molecules produced naturally by plants and have diverse medicinal and therapeutic properties. These include secondary metabolites such as phenols, terpenoids, flavones, quinones, catechins and alkaloids, which are similar to those found in acyl-homoserine lactones (QS signals) (Al-Hussaini., 2009) or may be in the form of saponin glycosides, anthraquinones, sesquiterpenoids and other compounds capable of inhibiting biofilm formation in Gram-negative bacteria, including P. aeruginosa, at a certain concentration because non-inhibitory concentrations may cause biofilm growth. Among these extracts that have been used are vanillin, 4-hydroxybenzoic and gallic acids, which reducing the production of virulence factors and disrupting the expression of LasR and RhlR genes (Adonizio et al., 2008; Tai and Yeo, 2013). Because plants grow in different and diverse environments that contain types of bacteria, they have developed adaptive mechanisms that protect them from bacterial infections, such as by producing various complex chemical compounds that target quorum-sensing molecules or competitive molecules, thus reducing the virulence of pathogens, Inhibiting signaling molecules synthesized by LuxI synthase is one of the three mechanisms that phytochemicals typically target Gram-negative bacterial QS systems through, to interfere with signal reception, it is possible to inhibit AHL-producing enzymes activity, secrete signal-degrading enzymes, and target the LuxR signal receptor with signal blockers or signal mimetic. Competition (structurally similar to AHLs) and non-competition are both possible (will bind to the site on the receptor other than the AHL binding site) molecules that have the potential to hinder AHL's binding to its corresponding LuxR receptor. (Koh et al., 2013; Nazzaro et al., 2013).

In recent years, it has been shown that halogenated furanone, a class of secondary receptors extracted from the red algae Delisea pulchra, holds great promise as an anti-pollution products and inhibitor of biofilms, proliferation and aggregation of several bacteria without affecting their growth rate, such as Salmonella enterica, Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis, Staphylococcus epidermidis, and Streptococcus spp (Janssens, et al., 2008).

The effectiveness of some plant extracts

Among the plant extracts studied is the compound allicin (extracted from garlic), which has been shown to inhibit the QS systems rhl and pqs in P. aeruginosa (Xu, et al., 2019). Among the plant inhibitors that have been studied are catechins from the leaves of green tea Camellia sinensis(Paluch, et al., 2020). Another study, through the identification of phytochemical components such as saponins, phytosterols and volatile oils extracted from the Moringa aquaticus plant, has shown QS inhibitory activity in Chromobacterium violaceum (Jonnalagadda, et al., 2016). In another study on clove oil, its menthol content, and its effect on QS inhibition in P. aeruginosa and Aeromonas hydrophila (Husain, et al., 2015). The methanolic extract of Punica granatum, which contains proportions of chlorogenic acid, rutin, epicatechin, gallic acid and caffeic acid, has shown anti-QS activity in P. aeruginosa by inhibiting movement and aggregation and reducing virulence factors such as the production of Pyocyanin (Hamrita, et al., 2022), curcumin, capsaicin, resveratrol and phloridzin, which are phenolic compounds, showed similar anti-biofilm and QS activity in foodborne bacteria such as Chromobacterium violaceum ATCC 12472, Chromobacterium violaceum 026 and Serratia marcescens MG1,Aeromonas hydrophila IOC/FDA 110-36 and Salmonella Montevideo 163 (Santos, et al., 2021). Tannic acid and Quercetin, major compounds extracted from Alnus japonica, were identified as having anti-biofilm activity by suppressing the icaA and icaD adhesion genes in Staphylococcus aureus (Lee, et al., 2013). Gingerol (a phenolic compound of ginger) was found to interfere with and inhibit different QS receptors (LasR and PhzR) in P. aeruginosa (Shukla, et al., 2021). Biofilms and QS, especially in bacteria associated with chronic infections, inflammations and foodborne pathogens, especially the ESKAPE group (Enterococcus spp., Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa, and Enterobacter spp.) were affected by Eugenol, a major component of the essential oils of Indian clove and cinnamon (Ribeiro, et al., 2024). Finally, Terpinen-4-ol, one of tea tree oil's active terpene monooxygenase components, showed antibacterial activity against P. aeruginosa (Bose, et al., 2020). Many studies have shown the role of chemical compounds extracted from plants and their effect on QS of bacteria, especially pathogenic ones, such as epicatechin in green tea, essential fatty acids in flax and olive oil, and piperine in black pepper. Berberine in Berberis, apigenin in parsley and chamomile,1,8-cineole in eucalyptus, luteolin in beans and broccoli, quercetinin onions, carvone in mint, and sesquiterpenes in aromatic plants (Moradi, et al., 2020) .

5. Conclusion

Controlling the pathogenesis caused by various can be achieved by using bacterial quorum sensing types of bacteria and to eliminate resistant bacterial strains that have developed as a result of the use of antibiotics through:

1- A broad study of non-pathogenic bacteria present in the environment or living in a symbiotic relationship with some plants to identify their ability to inhibit the sensing of bacterial quorum completion of pathogenic species.

2- It is extracting active ingredients from plants that are widespread in our environment, especially those that have received sufficient attention in previous studies, especially some herbs in desert plants.

3- Using natural materials or combining them with other industrial materials, the results can be used to inhibit the formation of cell membranes in non-pathogenic bacteria, causing many industrial problems, to develop sustainable and more effective compounds.

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