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# Insights into quorum sensing (QS): QS-regulated biofilm and inhibitors

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**Abstract:** In the environment, bacteria can communicate with a known mechanism called quorum sensing (QS). These bacteria will communicate in a group for social interactions like a multi-cellular organism. It provides significant benefits to the bacteria in host colonization, the formation of biofilms, defense against competitors, and adaptation to environmental changes. The bacteria that organize in biofilms are difficult to control and manage, resulting in a higher dosage of antibiotics to clear the infectious biofilms. Also, many QS-controlled activities are involved in virulence and pathogenicity. Hence, understanding the details of quorum sensing mechanisms, its phenotype regulation (biofilm), and QS inhibitors (which attenuate virulence/pathogenicity) may open a new avenue for controlling bacterial infections.

**Keywords:** Quorum sensing; biofilm; inhibitors; virulence; infections

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## INTRODUCTION

Bacteria are a group of microorganisms that can interact with each other and their surroundings via quorum sensing. Quorum sensing is a bacterial cell-to-cell communication process that depends on the release and response to extracellular chemical signaling molecules known as autoinducers[1]. These autoinducers will increase in concentration in a synchronized manner with the density of the bacterial cell population. Thus, detecting a minimum threshold concentration of signaling molecules could stimulate an alteration in gene expression[2, 3]. In other words, QS regulates gene expression as a result of changes in the cell population density. Several types of autoinducers have been identified, and they consist of small peptides, quinolones, and acyl homoserine lactones (AHL). The AHL-based QS system is the most studied among other methods, and AHL molecules are the primary QS signals utilized by Gram-negative bacteria[4]. Briefly, a typical AHL-based QS system comprises two primary proteins: LuxI-type protein (cytoplasmic AHL synthase) and LuxR-type protein (AHL-responsive DNA-binding transcriptional regulator)[5,6]. The bacterial cells generate AHL signals (synthesized by LuxI-type AHL synthase) at a low basal rate, which can penetrate the cell membrane without using a receptor. Once the threshold concentration of AHL signals is achieved, the signs are sensed by LuxR-type transcriptional regulator protein and thereby produce a LuxR/AHL complex that alters gene expression upon binding to *lux* box DNA - a conserved site in the promoter region[6–8].

The AHL is known to be involved in regulating different phenotypes, which is strain-dependent through QS[9,10]. In the natural environment, bacteria can sense the cell population density and regulate a wide range of physiological processes, including expressing essential phenotypes such as bioluminescence, biofilm formation, virulence factor production, swarming motility, chemotaxis, toxin secretion, and antibiotic resistance[1,2,9]. These QS-regulated phenotypes are also essential for bacteria to successfully establish a symbiotic (beneficial or pathogenic) relationship with higher organisms. This review aims to provide insights

into the quorum sensing mechanisms, phenotype regulation (biofilm), and the QS inhibitors in which attenuate bacterial virulence/pathogenicity.

## BACTERIAL QUORUM SENSING AND BIOFILM DEVELOPMENT

The attachment to surfaces is the first step for bacteria forming communities (known as biofilm) that enmeshed in a self-produced polymeric matrix[11,12]. The majority of bacterial infections in humans (more than 80%) involve biofilm development[13]. Notably, biofilm formation is one of the phenotypes which is closely related to QS. The development of biofilm *in vitro* involves five stages. First, the reversible attachment of bacterial cells to the surface will turn into irreversible attachment mediated by exopolymeric material[14,15]. Fibrinogen and fibronectin-binding proteins are usually found to play a role in this attachment process. Next, microcolonies are formed, and this indicates the beginning of biofilm maturation. The mature biofilms engineered varies, from flat, homogenous biofilms to highly structured 3-dimensional biofilms. The matured biofilm contains cells that are packed in clusters with channels in between to allow water and nutrient transportation and waste removal. The architecture of developed biofilm is often influenced by motility, rhamnolipid production, and extracellular polymeric substance matrix production. AHL-based QS has been shown to affect biofilm formation at the maturation stage. Labbate and colleagues (2004)[16] proved that a mutation in *S. liquefaciens* acyl-synthase gene, *swrI* results in thin biofilms that lacked aggregates and filaments as compared to its wildtype's biofilm, which is heterogenous that consist of an aggregation of long filaments of cells. This is further substantiated by work on *Burkholderia cepacia* H111 with mutations in either *cepI* or *cepR*[17]. Both mutants showed defective in biofilm maturation and were only arrested at the microcolony stage of growth compared to the robust biofilms covered with attachment surface formed by the wildtype.

Additionally, the maturation of biofilm is influenced by the LuxS-based QS other than the AHL-dependent pathway[18,19]. In *Streptococcus mutans*, the mutation in *luxS* resulted in a mature biofilm with decreased biomass as compared with its wildtype. The final stage of biofilm involved aggregation and detachment, dissolution or dispersal of cells from the biofilm to initiate a new biofilm formation. The dispersed cells showed similarity with planktonic cells, which is non-adherent. This dispersal process allows bacteria to colonize new surfaces and spread its virulence effectively within a closed environment. In this final stage of biofilm formation, the cell dispersal was also found to be QS controlled. In *Rhodobacter sphaeroides*, the mutation in its AHL synthase resulted in hyper-aggregation of cells; but QS's role in this bacteria still remains unknown[20]. Other than that, *yspR* mutant of *Yersinia pseudotuberculosis* resulted in increased swimming motility[15].

The complex formation of biofilm provides a "room" with a hydrated matrix of microbially produced proteins, nucleic acids, and polysaccharides that allows the cells to act less as individual entities but more as collective living systems[14]. Biofilm shields the bacteria by significantly increased in resistance to environmental stresses (pH fluctuation, high salt, and nutrient fluctuation) or microbially harmful particles (antibiotics and biocides). The exciting point arises the criteria for determining the role of QS in biofilm formation[15]. Perhaps it is not surprising that QS indeed plays a major role in biofilm formation, evident by increasing the study of mutant construction experiments that produce pleiotropic phenotypes that affect motility, surface attachment expression, or cell chemistry surface, which is later translated into biofilm formation. However, it would be best if the role of QS could be evaluated by monitoring the signaling process *in situ* in a developing biofilm in the parental strain and determine if the onset of QS corresponds to any observable transition in bacterial biofilm development that relates with other phenotypes such as incline of antimicrobial tolerance.

## USE OF QUORUM SENSING INHIBITORS AS POTENTIAL ANTIPATHOGENS

The pathogenesis portrayed by bacteria is a multi-factorial process regulated by the production of virulence factors, which causes a variety of bacterial infectious diseases[21]. QS could regulate many of the bacterial infectious diseases in humans, animals, and plants. Consequently, QS-regulated biofilm formation plays a vital role in bacterial pathogenesis. This has raised the level of concern in clinical settings and other industrial settings where biofilms pose a significant issue, such as aquaculture, agriculture, wastewater treatment plants, and drinking water processing[22].

The dedication of antibiotics in the early 20$^{th}$ century initiated a new era in treating microbial infections, and they were the most rewarding drug that saves myriad lives[23]. However, antibiotics usage over a long time could cause substantial evolutionary stress on the bacterial population and lead to the emergence of multidrug-resistant strains that possessed defensive mechanisms against these antibiotics[24,25]. Methicillin-resistant *Staphylococcus aureus* (MRSA) [26,27], vancomycin-resistant enterococci (VRE)[28], multi-drug resistant *Salmonella enterica* Subsp. *enterica*[29–31], multidrug-resistant *Mycobacterium tuberculosis*[32], multidrug-resistant *Vibrio parahaemolyticus*[33–42] are some dangerous bacterial species that have emerged due to over usage of antibiotic. The emergence of multidrug-resistant bacteria has caught medical attention, and various approaches are now taken to investigate alternative antimicrobials from different sources (e.g., plants and microorganisms)[24,43–49]. Interestingly, scientists have also considered another approach in recent years by exploring into QS linking to bacterial pathogenicity. The findings into the association of QS and bacterial pathogenicity have been evidently strong as virulence has been greatly reduced in mutants that are defective in QS [21,50,51]. In addition, researchers are actively venture into the investigation of different approaches to interrupt or inhibit QS for the control of bacterial diseases. This inhibition process is generally known as "quorum quenching". Quorum quenching (QQ) can be carried out by the application of enzymatic degradation of autoinducers,

blockage of autoinducer compounds synthesis, and utilization of inhibitor compounds to block the signal detection[52–54]. Therefore, techniques that target the QS pathway could serve as a potential new strategy to attenuate bacterial pathogenicity and inhibition of biofilm formation (Figure 1).

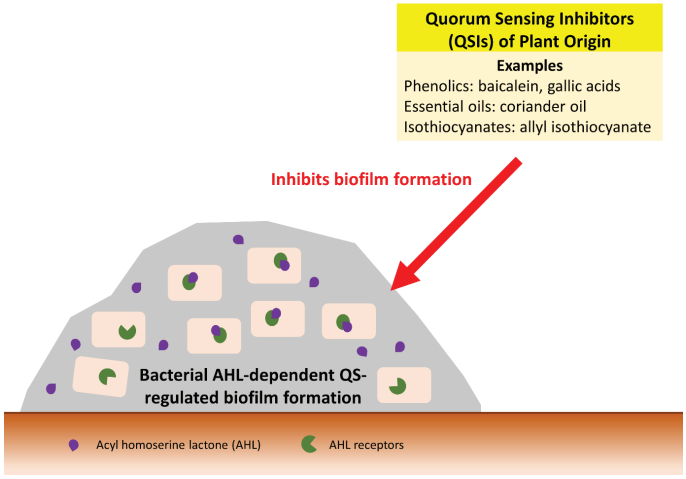


**Figure 1.** Application of QS inhibitors against biofilm formation.

Halogenated furanone compounds or known as fimbrolides are intensively studied as a group of QS inhibitors[23]. They are isolated from red microalga *Delisea pulchra*, an alga that can produce secondary metabolites that are made up of more than 30 types of furanones. Previous studies had shown that these secondary metabolites could interfere with the AHL-based QS communication circuit. A study performed by Janssens and colleagues (2008)[55] showed that brominated furanones could prevent biofilm formation of *Salmonella* serovar *Typhimurium* at non-growth inhibiting concentrations. Brominated furanones were also found to meddle with the biofilm formation of several other bacterial species including *E. coli*, *B. subtilis*, *P. aeruginosa* and *Streptococcus* species. Another study performed by Givskov and colleagues (1996)[56] evident that 100 µg/mL of furanone extracted from *D. pulchra* could inhibit swarming abilities of *Serratia liquefaciens*. Moreover, Defoirdt *et al.* (2006)[57] also showed that furanone can inhibit bioluminescence of *Vibrio harveyi* strain JMH597 at a concentration of 100 mg/L. However, drawbacks of halogenated furanones are too reactive and could cause toxicity towards human cells.

Thus, researchers exert into finding potential quorum sensing inhibitors (QSIs) from various natural sources. It has been proposed that a potential QSI should fulfill specific criteria[22]: (i) small molecule with high efficiency in reducing QS regulated genes, (ii) high degree of specificity with no adverse effect, (iii) chemically stable and resist to host metabolic system, (iv) longer than AHLs to prevent bacteria resistance, (v) do not affect the host microbiome, and (vi) show no toxicity effects towards the host. To date, numerous naturally occurring QSI is presently well established and grouped into various categories. Besides, several QQ enzymes have been discovered from prokaryotes and animal sources. One of the QQ enzymes is AHL-acylase that cleaves acyl side chain. Acylase produces by *Streptomyces* sp. is similar to acylase I produce by porcine kidney, where both cleaves the acyl chain longer than six carbons[58,59]. Some other QQ enzymes are AHL lactonases that produced by *Bacillus* spp.[60] and mammalian paraoxonases[61] that function to hydrolyze AHL lactone ring. However, researchers have been focusing on exploring potential QSIs from plant extract because it has been anticipated that plant sources are safer for human consumption. These natural compounds are known as secondary metabolites (or phytochemicals), and many classes of these phytochemicals demonstrated their potential as antimicrobials or synergists of other products[62]. Recent studies have promoted the potential of these phytochemicals as potential QSIs. As a result, the active compounds have been extracted from plants and their QS inhibition activity has been evaluated by numerous studies (Table 1). Further toxicology study should be performed on these extracted compounds to validate their safety as biopharmaceutical agents.

One of the QSIs consists of phenolic products or polyphenols, which constitute one of the most abundant and omnipresent as plant secondary metabolites (phytochemicals)[63]. Phenolics are considered potential QSIs because they are used to treat ailments such as diabetes, cancer, or inflammatory diseases besides having antimicrobial properties. Jagani and colleagues (2009)[64] proved that naturally occurring phenolics could act against biofouling of *P. aeruginosa*. Another study conducted by Vandeputte and colleagues (2010)[65] showed that catechin extracted from *Combretam albiflorum* reduces elastase, pyocyanin, and biofilm formation *P. aeruginosa* PAO1. They had selected eight types of phenolics, anarcadic acid, polyanarcadic acid, salicyclic acid, polysalicyclic acid, polyphenol, catechin, epigallocatechin, and tannic acid; all eight compounds showed significant reduction towards *P. aeruginosa* biofilm formation. Flavonoids extracted from citrus species such as quercetin and naringenin hinder the biofilm formation of *E. coli* O157:H7 and *V. harveyi* BB120[66,67]. Another subclass of phenolics, furocoumarins, shows QSI abilities in which purified furocoumarins — dihydroxybergamottin and

berggamottin inhibit autoinducer activities *V. harveyi*[68]. Girennavar and colleagues (2008)[69] further substantiated that furocoumarins from grapefruit juice inhibited more than 95% of autoinducer-1 and autoinducer-2 activities in *V. harveyi*. Other than that, ferulic acid and gallic acid (grouped under subclass of phenolic acids) were found to block bacterial motility, adhesion, and biofilm formation of *E. coli*, *P. aeruginosa*, *S. aureus*, and *Listeria monocytogens*[70]. A study carried out by Plyuta and colleagues (2013)[71] showed that the usage of 200 µg/mL of gallic acid reduced the biofilm formation of *P. aeruginosa* PAO1 to 30 %. Gallic acid has been proven as a potential QSI. Gallic acid at a concentration of 1mM resulted in an 80% reduction of biofilm formation by Eikenella corrodens as demonstrated in the experiment Matsunaga *et al.* (2010)[72]. As for ferulic acid, application at a concentration lower than eight µg/mL found to forbid S. aureus' biofilm formation[73].

Other groups of phytochemicals such as isothiocyanates and essential oils could serve as potential QSIs. Isothiocyanates are products formed during glucosinolate hydrolysis, and they are considered the most critical biological active products in plants[74]. One of the aliphatic isothiocyanates, allylisothiocyanate, interfered with the adhesion-related genes in *S. aureus* in work done by Lee *et al.* (2013)[75]. This compound demonstrated to reduce the *Pseudomonas sp.* planktonic cell growth and the number of cells adhered to the *Brassica nigra*. Likewise, essential oils have proven to be potential QSIs as they are complex mixtures of volatile compounds synthesized from several plant organs[76]. The QS activities of *P. aeruginosa*, *Proteus mirabilis,* and *S. marcescens* — swarming, production of extracellular polymeric substances and biofilm formation were inhibited upon exposing to methanolic extracts of *Cuminum cynimum*, where one of the components is methyl eugenol — an essential oil with an aromatic ring[77]. This plant-based QSIs may not function as bactericidal compounds; however, the infection process could be interrupted by interfering the bacterial QS and this eventually leads to elimination of pathogens by the host immune system.

## BIOTECHNOLOGICAL IMPLICATIONS OF STUDYING QS

As the number of bacteria that employ QS systems continues to bloom, the research into QS could span a wide variety of potential applications, mostly controlling bacteria growth and activities by interfering with the signaling pathways[78]. QS cross talk is also another exciting implication as bacteria always exist in the mixed-species population, such as biofilms in nature. This could cause an outbreak of infectious diseases or further health complications[79]. The study into QS paved the way for discovering various QSIs that is feasible as a treatment for bacterial infections in all living organisms. Given the growing numbers of multidrug-resistant strains, the rational strategy is to control these bacteria's outbreak by manipulating QS properties. Nowadays, scientists are exploiting the possible benefits of understanding the bacterial QS system. Ultimately, this could significantly contribute to many fields, such as improving the water treatment process, preventing bacterial diseases in aquaculture systems, and treating human infections[80].

Another interesting fact of QS is that eukaryotes can recognize bacterial QS molecules. This cross-kingdom interaction alters the physiological adaptation in colonized eukaryotes that modify their defense system, immune responses, hormonal responses, or growth responses[81]. Besides creating a pathogenic relationship with higher organisms, the interesting interaction is signaling molecules (AHLs); reported to mediate root growth through biosynthesis of phytohormones. Indole-3-acetic acid (IAA), or known as auxin, is a crucial phytohormone that enhances different developmental processes in plants. IAA production is widely spread among plant-associated bacteria. They can play a critical role in promoting plants' growth and development, especially root elongation[82]. Plant growth-promoting bacteria (PGPB) have been extensively studied as potential bio-fertilizers due to increasing pollution by over-usage of chemical fertilizers[83]. Biosynthesis of IAA by microbial strain is considered one of the essential criteria to be selected as an efficient PGPB. To date, there is an increasing number of reports stating that QS facilitates the PGPB in enhancing plant growth. As previously reported, treatment of *Arabidopsis thaliana* roots with 1–10 µM of C4- and C6-HSL increased the ratio of IAA/cytosine that led to promoted root growth[84]. In their study, they found out that the introduction of C6-HSL did not induce the systemic resistance and priming effect of *A. thaliana*. They further stated that short-chain AHLs might play a better role in promoting plant growth due to the hydrophobicity of long-chain AHLs. A study substantiates this fact revealed that C6-HSL was transported to the leaves of yam beans and barley leaves but not the C10-HSL[85]. Various studies also showed that Rhizobium mutants that were unable to produce AHLs were unable to nodulate legume plants compared to the wildtype strain[86]. These also further support the idea that AHLs could be participating in beneficial plant-bacteria interactions. Thus far, the QS studies could lead us into a different dimension in searching the potential of QS bacteria to contribute beneficially.

## CONCLUSION

It is undeniable that QS plays an essential part in the physiological processes of bacteria. Nonetheless, further studies are still required to characterize the function and pathway-related to QS fully. The occurrence of antibiotic resistance and infections reflects the downside of utilizing antibiotics to treat biofilm linked continual bacterial infections. The application of QSIs has exhibited promising results against biofilm formation; however, the utilization of QSIs as an approach to the battle against multidrug-resistant bacteria entails additional investigation. Future work needs to reveal if QSI compounds can be developed as antipathogenic treatment and their successful bacterial eradication mechanisms.

**Table 1.** Examples of QS inhibitors (QSIs) from plant origin and its effect on QS activity.

| Phytochemical Group | QSIs (Phytochemicals) | Effect on QS Activity | References |
|---|---|---|---|
| Phenolics | Ascorbic acids | Reduction in autoinducer-2 activities, spore production, and enterotoxin production in *Clostridium perfringens* | [87] |
| | Baicalein, Hamamelitannin | Inhibition of biofilm formation increased permeability of vancomycin and reduced production of staphylococcal enterotoxin in *S. aureus* | [88, 89] |
| | Curcumin | Attenuation of virulence in *P. aeruginosa* | [90] |
| | Ellagic acids | Inhibit biofilm production in *E. corrodens*; reduction of AHLs production in *E. carotovora*. | [91] |
| | Epigallocatechin gallate, Catechin | Interference with biofilm formation of *E. coli* and *P. putida*. Reduction in extracellular polymeric substance of *Staphylococcus* sp. | [65, 92, 93] |
| | Ferulic acids | Inhibition of biofilm in *P. aeruginosa*, interference to the motility of *P. fluorescens* and *B. cereus* | [94, 95] |
| | Gallic acids | Inhibition of biofilm in *S. mutans* | [96] |
| | Giganteone A | Reduction of QS-related activity in *E. coli* biosensors | [97] |

| Phytochemical Group | QSIs (Phytochemicals) | QS Activity | References |
|---|---|---|---|
| Phenolics | Gingerone | Reduction in swarming and biofilm-forming capacity in *P. aeruginosa* PAO1 | [98] |
| | *Glycyrrhiza glabra* flavonoids | Interference of motility and reduction in biofilm formation in *Acinetobacter baumannii* | [99] |
| | Malabaricone C | Reduction in pyocyanin production and biofilm formation in *P. aeruginosa* | [100] |
| | Rosamarinic acid | Influence the protease and elastase production, biofilm formation, and virulence factors of *P. aeruginosa* | [101] |
| | Salicylic acids | Reduction of AHL production, interference towards twitching and swimming motility of *P. aeruginosa* | [102] |
| | Tea polyphenols (*Camellia sinensis* L.) | Reduction of proteolytic activity, elastase, swarming motility, and biofilm formation in *P. aeruginosa* | [103] |
| | Pyrizine-2-carboxylic acid | Inhibition of biofilm formation in multidrug-resistant *V. cholerae* | [104] |
| | Proanthocyanidins | Reduction in production of QS-regulated virulence determinants in *P. aeruginosa* | [105] |

| Phytochemical Group | QSIs (Phytochemicals) | QS Activity | References |
|---|---|---|---|
| Essential Oils | Cinnamon oil, Ferula oil, Dorema oil | Interference of QS related phenotypes; production of pyocyanin, alginate, and rhamnolipid in *P. aeruginosa* | [106, 107] |
| | Cinnamon bark oil | Modification of permeability of outer membrane and inhibition of bacterial QS-activity in *E. coli* | [108] |
| | Clove oil | Reduction of violacein production in *C. violaceum* and interference of swarming ability of *P. aeruginosa* | [109] |
| | Coriander oil | Inhibition of biofilm formation and lipid peroxidation in *Campylobacter coli* and *C. jejuni* | [110] |
| | Linalool | Inhibition of biofilm formation and alteration of the adhesion of *A. baumannii* | [111] |
| | Oregano oil | Inhibition of violacein production by *C. violaceum* | [112] |
| | Rose oil, Geranium oil, lavender oil, Rosemary oil | Reduction in violacein pigmentation in *C. violaceum* and AHLs production in *E. coli* | [113] |
| | Thyme oil | Reduction of flagella gene expression in *C. violaceum* and interference of biofilm formation in *P. fluorescens* KM121 | [114, 115] |

| Phytochemical Group | QSIs (Phytochemicals) | QS Activity | References |
|---|---|---|---|
| Isothiocyanates | Allicin, Ajoene | Renders *P. aeruginosa* sensitive towards tobramycin; inhibition of biofilm | [116, 117] |
| | Allyl isothiocyanate | Interference of adhesion and motility, inhibition of biofilm formation in *E. coli*, *S. aureus*, *L. monocytogenes,* and *P. aeruginosa* | [75, 118-120] |
| | Iberin | Interference of rhamnolipid production and gene expression of *lasB* and *rhlA* in *P. aeruginosa* | [121, 122] |
| | Sulforaphane, Erucin | Antagonists of transcriptional activator of LasR and inhibition of biofilm formation in *P. aeruginosa* | [123] |
| Stilbenoids | Resveratrol, Piceatannol, Oxyresveratrol | Reduction of violacein in *C. violaceum* CV026; Decreased in production of pyocyanin and swarming motility in *P. aeruginosa* PAO1 | [124] |

## Author Contributions

The literature search, data extraction, and manuscript writing were performed by TW-S, LJW-F, LLN-S, and VL. At the same time, K-GC provided vital guidance, insight, and technical support to complete the project.

## Conflict of Interest

The authors declared that research and writing were conducted in the absence of financial and non-financial interest. The funders do not participate or influence any of the experimental design, research, or writing work. This research was completed in the absence of any commercial or financial relationships construed as a potential conflict of interest.

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