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Focus Review Article

Quorum Sensing Inhibitors: Current Progress of Natural Antimicrobials

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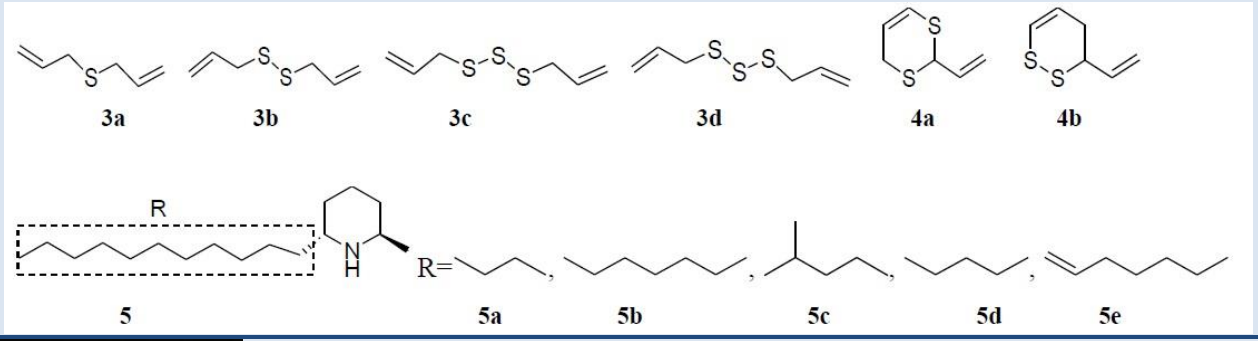
Abstract:

Misuses of antimicrobials in infectious diseases have led to the progress of extensive resistance in the infectious organisms. The unsuccessful of accessible antimicrobials to control infections makes it essential to discover alternatives to currently existing drugs. Their connection to infectious diseases and their natural ability increase antimicrobial resistance in microbes, has led to a platforms for research focused on new techniques to control them. In this affords we studied the pathogenicity in many bacteria was regulated by Quorum sensing (QS). The inhibition of QS system may cause the reduction of virulence and protect against bacterial infections. These bacteria rely on chemical communication (or QS) to coordinate activities necessary for their survival in groups by some course of action. Their dependence on QS has made those signaling systems within bacteria an attractive target for the design of new anti-infective agents. Compounds that can interrupt these processes are known as QS inhibitors. The QS is the key regulator of virulence in various bacteria. Various plants extracts and their chemical constituents were showed their effects on bacterial virulence factors by inhibiting of QS genes and QS-controlled factors and effects on bacterial growth. The anti-QS approach has promise in the fight against infections pathogens, thereby making the bacteria more susceptible to traditional antimicrobials. The QSIs may provide the newest weapon against infections involving drug-resistant bacterial strains. These QSIs come from a variety of sources and have a wide array of structures.

Key words: Quorum sensing inhibition; bacterial communication; antibacterial agents

Graphical Abstract:



Mohammad Asif was born in India. He studied Bachelor of Pharmacy (Pharmaceutical Chemistry) from IFTM, Moradabad, affiliated with Rohilkhand University Bareilly (U.P) in year 2003. Received the M.S. degree in Pharmaceutical Chemistry at Bundelkhand University Jhansi (U.P) in 2006 and the Ph.D degree also in Pharmaceutical Chemistry at Uttarakhand Technical University, Dehradun in year 2015. He focused his doctoral thesis on the Synthesis and biological evaluation of some new pyridazine-3(2H)-one derivatives. His research interests focus on the Medicinal Chemistry, Inorganic Chemistry, Organic Chemistry, Chemistry of Natural Products, Pharmaceutical Analysis and Physical Chemistry.

Introduction

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Recently, microbial quorum sensing (QS) has come out as a new technology, because microbial population occupy a limited space, concentrations of extracellular signalling molecules accumulate, providing stimulus for unique cellular responses and protections from competing microbial communities [1, 2]. The eukaryotic organism produces metabolites that interfere with bacterial communication. *Delisea pulchra* produces a range of metabolites known as halogenated furanones. These compounds exhibit a broad range of biological activities, including antimicrobial activities [3]. Some polyphenolics having a gallic acid moiety (epigallocatechin gallate, ellagic acid and tannic acid) are commonly present in various plant species that inhibited QS communication between bacteria [4-6]. These polyphenolic depositions were correlated with a reduction of bacterial multiplications. The QS and the wide range of biological functions of QS systems is a targets for new antimicrobial agents [7-10]. QS-inhibitors, acting alone or with traditional drugs, could provide the newer generation of antimicrobial agents [11, 12]. The stimulating of QS systems has been responsible for a variety of physiological behavior in the bacteria such as bioluminescence, release of virulence factors, production of antimicrobials and biofilm formation [13-15]. This performance is generally observed to be controlled by cell density, but other conditions such as nutritional and environmental conditions can affect QS activities [16].

The QS system occurs in many bacterial species across both gram-positive and gram-negative bacteria. Bacteria liberate regulatory chemicals, called autoinducers (AIs), into their local environment [17]. As the population increases, concentration of the AIs also increases. At given concentration thresholds, the AIs bind to receptors in nearby bacteria, thereby setting in motion the QS cascade. Three major types of AIs have been identified: acylated homoserine lactones (AHLs) in gram-negative bacteria, auto-inducing peptides (AIPs) in gram-positive and autoinducer-2 (AI-2) molecules in both gram-positive and gram-negative bacteria. The different classes of AIs often target different receptors within the QS systems. AHLs target the LuxR family of transcriptional regulators, with the resulting AHL-LuxR-complex binding a variety of promoters and activating transcription factors [18, 19]. The receptors for AIPs are integral membrane proteins in the bacterial membrane. These proteins contain a protein kinase domain, which upon activation by AIP binding undergoes auto-phosphorylation. The activated receptor phosphorylates a response regulator, which actives the specific genes. The AI-2 signal molecules are more species dependent and target a variety of Lux receptors [20, 21].

Target areas for antiqourum sensing activity

The drug to target the QS system of bacteria is generally divided in three main target areas:

- destruction of the signal molecule,
- inhibition of signal production, and
- Inhibition of the signal receptor.

However, the last two target approaches involve, drug molecules interrupt some step in the natural QS-signaling pathway. Recently, few examples of QSIs which inhibit QS-signal molecule production have been reported in various bacterial strains. These QSIs may be similar in structure to the natural ligand or different, either binding directly to the signal-binding pocket or elsewhere on the receptors, in either case preventing the resulting QS-signal [22, 23]. The QSIs can come in a wide variety of chemical structures and be obtained from different sources. The recent advances of anti-QS activity is new and promising antimicrobial agents [24, 25].

Unexploited potential for antimicrobial activity

Plants should be a great source of antimicrobial agents. In fact, about 75% of the antibiotics are derived from the natural source like actinomycetes, a specific group of Gram-positive bacteria [26]. Antibiotic-producing microbes possess genes which protect them from the toxic effects of these compounds. It is very easy for one microbe to acquire antibiotic resistance from another through plasmid transfer or transposons. Plants are genetically dissimilar from the organisms they are trying to eradicate. Thus, there is little chance for a microbe to gain resistance from a plant. Plants can produce a multitude of diverse antimicrobial compounds such as simple phenolics, polyphenolics, catechins, quinones, flavanones, alkaloids, and terpenoids. Like microbial antibiotics, these compounds are targeted at killing the pathogen and work via a non-species specific mechanism such as disrupting microbial cell membranes. However, plants have another way of dealing with microbes-targeting a cell's communication system [27]. One form of intercellular communication in bacteria is known as QS [28]. Breakdown of QS system causes an attenuation of microbial pathogenicity [29, 30]. The discovery of anti-QS agents in plants provides us with yet another type of antimicrobial agents.

Functions of quorum sensing

A classic approach to solving problems is to break a system under consideration down into functional

elements. For many organisms of interest within biotechnology, the role of QS is complicated and unobvious. The QS is believed to regulate competence development, sporulation, antibiotic synthesis, virulence factor induction, cell differentiation, and nutrient flux along with other physiological events in pathogenic bacterial infections [31-33]. The QS was linked through proteomic analysis to increased pathogenic competence in tubercular strains of *P. aeruginosa* [34]. As biofilms age, cellular differentiation and death enhance nutrient sequestration and allow for biofilm sustenance when nutrients become scarce [35,36]. Many human or plant pathogens exist as biofilms in their hosts, but occupy a different modality both pre- and postinfection. QS is thought to regulate this transition. For example, in the human pathogen *V. cholera* quorum signalling enables the cells to negotiate the acidic human gut environment without compromising their ability to infect. Biofilms formed by *V. cholerae* protect the cells from stomach bile and low pH [36,37]. In addition to regulating intraspecies survival and differentiation in bacterial communities, QS also relates interspecies information between symbionts and competitors [38, 39]. Acyl-homoserine lactone (AHL) signals from *P. aeruginosa* can enter mammalian cells and activate artificial transcription factors, although it is yet unclear which native eukaryotic proteins may be transcribed through this mechanism [40, 41].

Quorum sensing a novel target

Quorum sensing (QS) is a population-dependent phenomenon and its ability to sense the size of a bacterial population mediated through small signaling molecules or autoinducers (AIs) [28]. These AI molecules are constantly produced and received at a basal level by bacterial cells. With high population density, there is a excess of signaling AI molecules in their environment. These signals diffuse back into the cell where they facilitate the regulation of gene expression. QS-systems are everywhere among bacteria, and have found to regulate diverse functions such as luminescence, biofilm formation, antibiotic and virulence factor generation, pigment production, plant-microbe interactions, and motility [43]. Although there are different QS systems [44], the most widely considered model is based on the Lux system of *Vibrio fisheri* and *V. harvey*i. This QS phenomenon involves a three component-system: a freely diffusible signal, a synthetase to make this signal, and a regulator that interacts in conjunction with the signal to regulate gene expression. The main signaling molecules produced by Gram-negative bacteria are AHLs. They differ in the length of their side chains and substitution, based on the organism that produces those [45]. In *V. fisheri*, LuxI produces an AHL signaling molecule which binds to LuxR at a definite concentration. This concentration is reached only when adequate bacteria are present to produce satisfactory amounts of AHL. The *V. fischeri* LuxR-AHL-complex can then bind to the operator and up regulate transcription of the luciferase genes [46-49]. The AHLs bind to LuxR (product of *luxR*) at a certain concentration and activate transcription of *luxI* and the luciferase genes [44]. AHL-mediated QS-systems based on the LuxI/R model have been described in human pathogens like *P. aeruginosa*, *Yersinia pseudotuberculosis*, and *E. coli*, as well as plant associated bacteria like *Rhizobium leguminosarum*, *Ralstonia solanacearum*, and *Erwinia carotovora* [50]. In all cases QS- systems may regulate virulence. The QS has given a new target to attack and attenuate bacterial pathogenicity [51-55].

Mechanisms of QS inhibition

There are a number of ways to inhibit cell-cell communication (or QS) including competitive inhibition, signal binding, degradation of the signaling molecule, and inhibition of genetic regulation systems. The success with competitive inhibition, furanones and many other QSIs has been discovered [56]. These QSIs are based on the C12-AHL structure and cause a reduction in LasR activity. AHL-antibodies have been developed to suppress QS through signal binding [57, 58]. A C12-AHL–protein conjugate was able to sucessfully inhibit *lasB* expression genes, and a similar molecule with extremely high binding affinity for C12-AHL. Blocking S-adenosyl methionine (SAM) or the fatty acid precursors necessary to produce AHLs leads to decreased production of C12-AHL by LasI [58, 59]. Many bacteria including *Bacillus* sp, *Variovorax paradoxus*, *Arthrobacter* sp, and *A. tumefaciens* produce lactonases, enzymes that cleave and deactivate the lactone ring of various AHLs [60, 61]. Lactonase expression in *P. aeruginosa* significant decrease AHL production and virulence factor expression. The practical applications of anti-QS especially in drug resistant bacteria therapy because increased incidence of drug failure due to the large number of pathogenic bacteria developing resistance to available antimicrobials [62].

Linking traditional and modern medicine

The enormous numbers of plants with chemical diversity are basis for medicinal compounds [63]. However, this inherent quality of plants helps to search for new drug molecules. Most plants contain constitutive or inducible defense against phytopathogic bacteria. Plants used medicinally because they contain chemical defenses specific to human pathogens [64,

65]. However, ethnopharmacology is beneficial to traditional societies. The chemical and pharmacological activities of the plants are potentially useful and unique medicinal values. Consequently, most studies focus on ethnopharmacology, depending on the expertise and interests of the researchers [66].

Ethnobotany for looking to the future antimicrobial agents

Although synthetic drugs can be provide pharmacological effects to cure diseases. The high biological diversity is linked to a high chemical diversity that allowing for the evolution of numerous bioactive natural molecules. Many plant and herbal drug molecules already exist in nature and many are waiting for discovery [67-69]. Plants and herbs create specific compounds to serve in reproduction and defense mechanisms [70]. Plants and herbs are having toxic and bioactive compounds to protect them against herbivore and pathogen attacks. Because plants and herbs are rely on chemical defenses. Various plants or herbs and their fruits were shown anti-QS activity in a *C. violaceum* biomonitor strain and on the swarming motility of *E. coli* and *P. aeruginosa* [71]. Fruits including raspberry, blueberry, blackberry, cranberry, and grape, and herbs such as ginger, kale, oregano and turmeric exhibited moderate inhibition of QS processes. However, no compound was obtained in animal as QSIs. The furanones and their synthetic derivatives, the compounds ellagic acid, tannic acid, and epigallocatechin gallate have been shown to inhibit QS in both an *E. coli* and *P. aeruginosa* biomonitor strain [72]. The related polyphenolics should be further explored as anti-QS compounds.

Anti-quorum sensing and antibacterial from ethnobotanicals

Many research based on ethno-botanical for antibacterial activity for demonstrating not only the need for antimicrobial drugs, but also the large number of plant species utilized for bacterial pathogenicities [73]. Although many medicinal plants and herbs base research has led to the discovery of many important medicines, there is not a more overlap between commonly used plant medicines and antimicrobials [74-78]. However, there are some plants that have made their way to the drug developments. The discovery of some natural compounds that inhibit cell-to-cell communication (QS), could provide a novel method of combating pathogenic infections [79]. Anti-QS agents were first characterized from red marine alga, *Delisea pulchura*. This alga was showed anti-fouling properties, and was found to contain halogenated furanones which block AHLs via competitive inhibition and destabilization of LuxR [80]. The structural similarity of furanones allows to competitively inhibit the action of AHL signaling molecules (**1a** and **1b**) (fig **1**) [81]

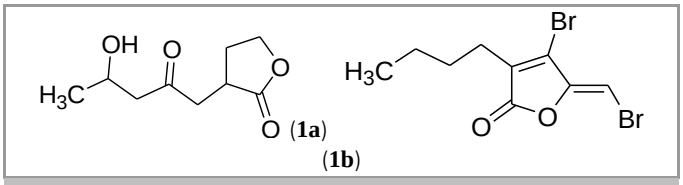

Figure 1. Acyl-homoserine lactones signaling molecules

Various naturally occurring phyto-molecules, particularly extracts from plants and dietary substances, have been evaluated to modulate LuxR-type QS in Gram-negative bacteria. However, mechanism of action of many of these compounds is poorly understood. A significant deviation from the AHL framework is usually observed and there is little structural correlation with any other anti-QS agents whose molecular target is known. For example, the some natural substances are known to modulate various AHL-mediated QS systems or AHL-regulated phenotypes are clove oil (*C.* V*iolaceum* and *P. aeruginosa*), dietary phytochemicals (secondary metabolites of plants, *C.* V*iolaceum* and *P. aeruginosa*) [71,82], honeys (*E. carotovora*, *Yersinia enterocolitica*, *Aeromonas hydrophilia*, and *C.* V*iolaceum*), cranberry juice (*V. har*V*eyi*), extracts of *Tremella fuciformis* (white jelly mushroom, *C.* V*iolaceum*), extracts of some medicinal plants from the Indian subcontinent (*P. aeruginosa*), extracts of pea (*Psium sati*V*um*) seedlings (*C.* V*iolaceum*) [83], extracts of *Medicago truncatula* seedlings (*P. putida* CepR reporter, *E. coli* LuxR reporter, *E. coli* LasR reporter, and *C.* V*iolaceum*) [84] and extracts of South Florida plants (*P. aeruginosa*) [85].

Anti-QS activity of several plant extracts have been reported recently, and revealed that the QSI organism protect themselves from invasion of other pathogenic microbes. Plant, bacteria, fungi could produce compound which could interfere the QS-regulated gene expression in the invading organism [86,87]. Since the discovery of AHL inhibitors in *D. pulchura*, anti-QS activity and South Florida *Caulerpa* species and various higher plants including various fruits and vegetables [83,88]. *Pisum sativum* (pea) seedlings and root extracts produced an inhibition of pigment production, exochitinase activity, and protease activity in *C. violaceum* [71]. Garlic (*Allium sativum*), carrot (*Daucus carota*), chamomile (*Matricaria* sp.), water lily (*Nymphaea* sp.) and some peppers (*Capsicum* spp.) were found to possess anti-QS activity against a *luxI*-gfp reporter strain. Toluene extract of *Allium sativum* or garlic exhibited anti-QS activity against Gram-negative transcriptional regulators Lux R or Las R [87]. Garlic was also inhibited biofilm formation and prevented nematode death [23]. Not only garlic but also several other plants extract like *Thymus vulgaris* family

Lamiaceae also increase killing effect against *Pseudomonas* species and showned anti-QS activity [71,89].

The antipathogenic, anti-QS activities were observed in extracts of *Laurus nobilis* leaves, flowers, fruits and bark. The *S. oleraceus* exhibited prominent anti-QS activity, almost equals to *L. nobilis* extracts. *Rosmarinus officinalis* leaves and *Tecoma capensis* leaves showed moderate anti-QS activity. Weak anti-QS activities were showed by extracts of *Jasminum sambac* (flowers and leaves), *Populus alba* (leaves) and *Populus nigra* [90]. Recently, hexane extract of clove bud (*Syzygium aromaticum)* has showed significant anti-QS activity against two strain of *P. aeruginosa* [91,92]. Methanolic extract of fruit of *Capparis spinosa* and *Myristica cinnamomea* were showed anti-QS activity [93,94]. *Lagerstroemia speciosa* (*Lythraceae*), prevalent in South-East Asia, modulate the QS activity of some micro-organisms. *Lagerstroemia speciosa* can attenuate QS-related genes (*las* and*rhl*) and their respective signaling molecules like *N*-AHLs, but interestingly not affecting their growth by using a strain *P. aeruginosa* PAO1. Significant inhibition of virulence factors: LasA protease, LasB elastase, and pyoverdin production, was also reported [95]. Extract of *Melicope lunu-ankenda* (Gaertn.), edible plant of Malasyia has showed efficient anti-QS against *P. aeruginosa* PAO1 [96]. Some Chinese traditional system [CTMS] of medicine like *Angelica sinensis* (Umbelliferae), *Cnidium monnieri* (Umbelliferae), *Astragalus membranaceus* (Leguminosae), *Crataegus cuneata* (Rosaceae), *Dioscorea nipponica* (Dioscoreaceae), *Lilium brownii* (Liliaceae), *Aloe barbadensis* (Liliaceae), *Magnolia officinalis* (Magnoliaceae), *Ephedra sinica* (Ephedraceae) and *Panax pseudoginseng* (Araliaceae) showed anti-QS activity against *C. violaceum* and *P. aeruginosa* [97]. *Melaleuca alternifolia* Cheel (Myrtaceae), or tea tree, is an aromatic tree native to Australia and essential oil of *M. alternifolia* showed topical antimicrobial activity. Its anti-microbial activity due to terpinen-4-ol, major monoterpenoid of the oil. Other terpene constituents include γ-terpinene, α-terpineol, cineole, and *p*-cymene and these compounds caused membrane disruption in bacteria. The essential oil fraction of *Origanum vulgare* L. (Lamiaceae) herb native to Europe and Mediterranean is an effective antibacterial and antifungal agents for the gastrointestinal and genitourinary tract infections [98,99]. The antimicrobial effect is attributed to the phenolic monoterpenoids, carvacrol and thymol, along with a number of other terpene alcohols, phenols, and sesquiterpenes. The two main chemotypes of *O. vulgare* showed either high thymol or high carvacrol contents [100], both are showed antimicrobial, however carvacrol is more effective [101]. Oil of oregano has pronounced *in-vitro* antifungal effect against dermatophytes. It also showed antibacterial activity against a causative agent of gastric ulcers , *Helicobacter pylori* [99], and other pathogens like *Haemophyllus influenzae, S. aureus, E. coli, S. pneumoniae*, and *Enterobacter cloacae* [102] and marked effect *in vitro* and *in vivo* model against *C. albicans*. The antimicrobial effect is due to membrane disruption [101]. The oleo-gum resin of various *Commiphora* species (Buseraceae), trees are native to parts of Africa, Asia, India, and the Middle East [98]. It is mainly used in toothpastes due to its antimicrobial properties and also used for topical treatment of wounds and oral mucosa as a mouthwash and antiinflammatory agent. The volatile oil fraction contains monoterpenes such as myrcene, α-camphorine and also furanosesesquiterpenes. The antibacterial activity of *C. mulkul* or *C. wightii* has been tested *in vitro* against Gram positive and Gram negative bacteria and was found equal to kanamycin [98, 103].

QSI Compounds from natural product extracts

Natural plant extracts provided sources for a wide range of biologically active compounds and have yielded a number of compounds that have showed anti-QS activity. Recently, grapefruit juice and its components showed QSI activity [104,105], two types of grapefruit juice, Rio red and Marsh white, both juices shown to inhibit AI-1 and AI-2 receptor systems, based on the *Vibrio harveyi* autoinducer assay. Two furocoumarins, bergamottin (**2a**) and dihydroxybergamottin (**2b**) (Fig. **2**), were evaluated individually. Furocoumarins have showed potent inhibitors of cytochrome P450 and transporter proteins. Both furocoumarins, **2a** and **2b**, were showed strong AI-1 and AI-2 inhibitory activities at concentration as low as 1 μg mL-1. Further investigation showed that both inhibited biofilms in *E. coli* O157:H7, *Salmonella typhimurium* and *P. aeruginosa*, without inhibition of bacterial growth.

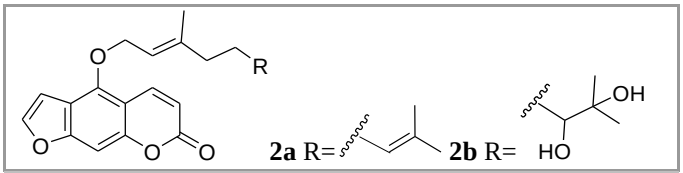

Figure 2. QSIs from grapefruit, bergamottin (**2a**) and dihydroxybergamottin (**2b**).

Several reports on garlic extracts as antibacterial have been reported [106]. The effect of garlic extracts on biofilms of *Candida albicans* at both the adherence and mature phases [107]. Reduction assays of the biofilms using XXT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide) showed reduction at both phases. Using QSI selectors, identified garlic extract as specific for QS-controlled virulence genes in *P. aeruginosa*. *In vitro* analysis of *P. aeruginosa* biofilms showed considerable destruction of the biofilm when exposed to a combination of garlic extract and tobramycin [88]. Several active compounds from the garlic extract (Fig. **3**). Exposure to either compound

alone had little to no effect on the biofilm [87], compounds **3** and **4** all were identified as LuxR antagonists, most significantly cyclic thioacetal **4a** and cyclic disulfide **4b** showed only anti-QS activity, while **3a-d** were also toxic to the bacteria. The *in-vivo* used of garlic extract as a potential therapy for lung infections [108]. Mice infected with *P. aeruginosa* were treated with garlic and tobramycin combination showed significant clearing of the bacterial infections as compared to control group. Through bioassay-guided fractionation, six sulfur-containing compounds from the garlic extract, **3a-d and 4a-b**, were identified that showed anti-QS in a LuxR monitor system [87]. Compounds **3a-d** antagonized LuxR but were toxic to the bacteria. Compounds **4a** and **4b** possessed anti-QS activity exclusively, but only in the LuxR monitor system; none of the sulfur containing compounds **4a** and **4b** have active against *P. aeruginosa* QS. A number of AHL derivatives that incorporated sulfide, sulfinyl, and sulfonyl motifs were found to inhibit either one or both of the LuxR and LasR-QS systems.

Alkaloids from natural sources, recently reported as a natural anti-QS alkaloidal agents, solenopsin A (**5**, Fig. (**9**) [109]. A toxic alkaloid from the fire ant *Solenopsis invicta*, solenopsin A has showed an inhibitor of phosphatidylinositol-3-kinase signaling and angiogenesis [110] as well as a potent cardiorespiratory depressant [111]. In *P. aeruginosa*, solenopsin A is inhibit pyocyanin production, an indication of QS signaling suppression. Synthetic AHLs indicated that the rhl signaling system might be the target of solenopsin. Solenopsin A (**5**), a venom alkaloid from the fire ant *Solenopis invicta*, inhibits QS in *P. aeruginosa* [109]. This compound is structurally reminiscent of OdDHL (natural AHL of the LasR system) in that both contain a long hydrocarbon chain attached to a *N*-containing heterocycle, via a chiral-C; however, both structures contain distinct molecular frameworks. Interestingly, exogenously added BHL, but not OdDHL, restored *P. aeruginosa QS* signaling, suggesting that solenopsin A actually targets the BHL-dependent *rhl QS* system. Solenopsin analogues **5a-e**, (Fig. **4**), no analogue demonstrated to increased anti-QS activity relative to the parent compound. Analogues of **5** with shorter acyl chains, however none showed any increased QSI activity. Further investigations showed that solenopsin A reduced biofilm production in *P. aeruginosa* in a dose dependent manner, indicating a QS signaling suppression mechanism.

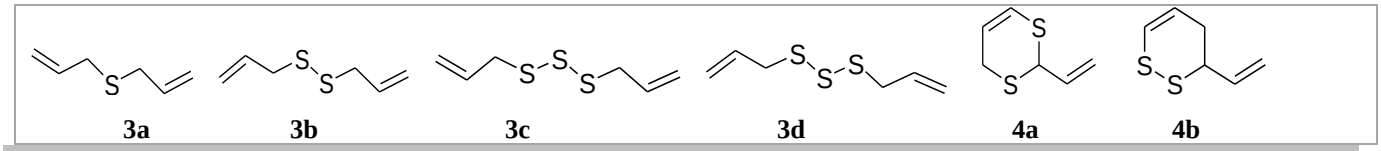

Figure 3. QSIs from garlic extract.

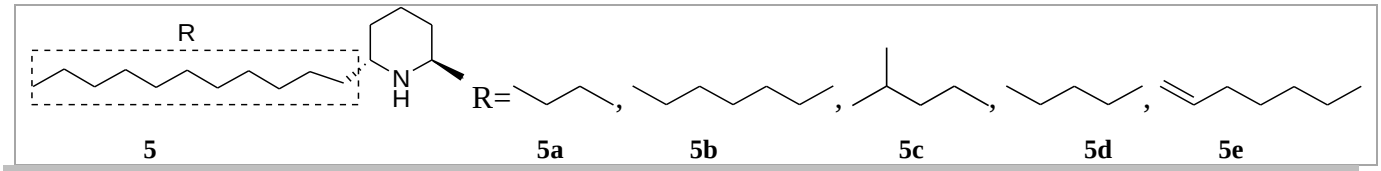

Figure 4. Alkaloid QSI, solenopsin A, isolated from *Solenopsis invicta.*

Essential oils from various plants can affect biofilm formation and structure, among these cinnamaldehyde (**6a**) and its derivatives (Fig. **5**). The cinnamaldehyde showed *E. coli* biofilms inhibitor. The connection of cinnamaldehyde to QS was first demonstrated by Gilbert and co-workers [112,113], who showed the compounds ability to inhibit both AI-1 and AI-2 receptor systems. The bioluminescence of the 3-oxo-C4-HSL mediated *V.harveyi* BB886, as well as the AI-2 responsive reporter strain *V.harveyi* BB170 were significantly inhibited at 60 and 100 μmol mL^{-1} respectively. The effects of cinnamaldehyde and substituted cinnamaldehyde derivatives on AI-2 reporter systems by examine the bioluminescence of several *V. harveyi* mutants. The two most potent compounds were cinnamaldehyde and 2-nitrocinnamaldehdye (**6b**). The inhibitors affected the target protein LuxR and further studies with these compounds showed biofilms inhibitory effect on two vibrio mutants, *V. anguillarum* 4411 and *V. vulnificus* LMG [114]. The **6a** affected the total mass of the biofilm, but not the number of viable cells. These compounds were affecting the production/accumulation of the exopolysacccharide matrix. Plant essential oil components and isolated those that modulated biofilm formation in *E. coli* [112,113].

One of these components was identified as cinnamaldehyde (**6a**), which was reported as an inhibitor of 3-oxo-C6-HSL (OHHL) QS in *E. coli* and 3-hydroxy-C4-HSL QS in *V. harveyi* at sub inhibitory concentrations (Figure 5) [112]. In the case of *V. harveyi*, inhibition was not selective for AHL QS, with the AI-2 system also being affected. Interestingly,

cinnamaldehyde (**6a**) had less effect on *lasR* promoter activity, induced by OdDHL, in an *E. coli* strain containing a LasR biosensor (OdDHL inducible). The 3-C aliphatic side chain of cinnamaldehyde (**6a**) may interfere with the binding of the smaller 3-OH-C4- and 3-oxo-C6-HSL AHLs to their cognate receptors but was not sufficiently long enough to reduce the binding of OdDHL to LasR. Recently, *p*-coumaric acid (**6c**), has putative antagonistic activity against *Chromobacterium*, *Agrobacterium*, and *Pseudomonas* QS. *p*-Coumaric acid (**6c**) and cinnamaldehyde (**6a**) share a common structural motif, namely, an R-unsaturated carbonyl functionality connected to a phenyl ring system. Recently, extracts of the bark of *Combretum albiflorum* for their capacity to inhibit the production of extracellular virulence factors in *P. aeruginosa*.

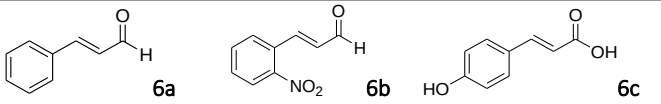

Figure 5. Cinnamaldehyde (**6a**), 2-nitrocinnamaldehdye (**6b**) and *p*-Coumaric acid (**6c**).

Extract from other plant species have been shown to inhibit bacterial QS. While the specific anti-QS compounds from these extracts were not reported, so further investigation is necessary to identify their active compounds. The QSI activity by vanilla extract in the mutant *Chromobacterium violaceum* CV026 which lack the autoinducer synthase [115]. The inhibition of QS-controlled virulence factors in *P. aeruginosa* by extracts from several South Florida plants [116]. Three of these extracts, those from *Conocarpus erectus*, *Bucida buceras* and *Callistemon viminalis,* showed inhibition of *LasA* protease, *LasB* elastase, pyoverdin production and biofilm production.

Polyphenolic QSI Compounds

Polyphenols are well known antioxidant, and have been shown to effect on biofilms. The connection between polyphenols and QS is established [117] by both biofilm and QS inhibition for such compounds (-)-epigallocatechin (**7**, EGCG), ellagic acid (**8**) and tannic acid (**9**) (Fig. (**6**). by using two AHL-dependent QS strains *P. putida* (pKR-C12) and *E. coli* MT102, and identified as antagonistic effect. EGCG was the most active followed by ellagic acid, then tannic acid. Biofilm inhibition was showed against in *B. cepacia*. Tannic acid showed little reduction in film thickness, both EGCG and ellagic produced a marked reduction, with ellagic acid being the most effective. Several other polyphenols have shown promise as anti-QS activity (Fig. **7**). The antagonistic effect of pyrogallol (**10**) analogues was on QS systems in *V. harveyi* [118], a different approach to screening compounds for potential anti-QS activity was reported [119]. Using the crystal structure of TraR from *A. tumefaciens*, various compounds from TCM with antibacterial activities were compared to known QSIs, furanone C30. Some compounds showed docking scores higher than that of furanone C30. Of those, few compounds were shown to inhibit biofilm formation in *P. aeruginosa*, the most potent being the flavanoid baicalein (**11**). In addition, **11** showed to have a marked synergistic effect, reducing biofilm formation when used in combination with the antibiotic, ampicillin. Baicalein was also shown to promote proteolysis of the receptor TraR protein in *E. coli*. Rosmarinic acid (**12**), from the root of sweet basil, is a caffeic acid ester showed inhibitory growth of some *Pseudomonas* species and interfere with QS activity [120]. Several active fractions containing flavonoid-like compounds; one active compounds flavan-3-ol catechin (**13**), which was also found to have a negative impact on the transcription of several other QS-related genes in this bacterium. Catechin (**13**) is thought to possibly interfere with the perception of the native AHL by the LuxR homologue RhlR, though little is known about the precise mechanism of action [87].

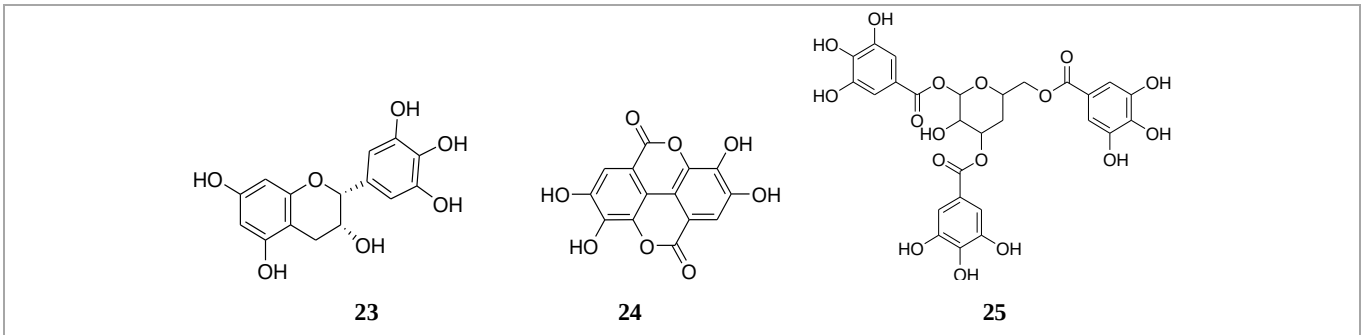

Figure 6. Polyphenolic QSIs, (-)-epigallocatechin (7), ellagic acid (8) and tannic acid (9).

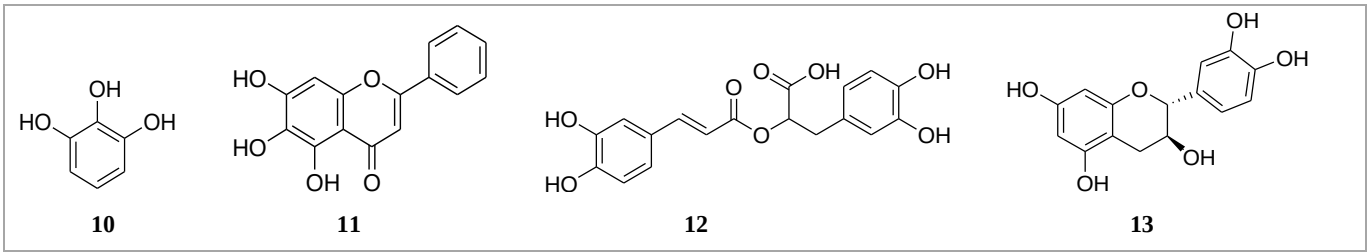

Figure 7. Polyphenolic QSIs, pyrogallol (10) and baicalein (11) and Rosmarinic acid (12) Catechin (13).

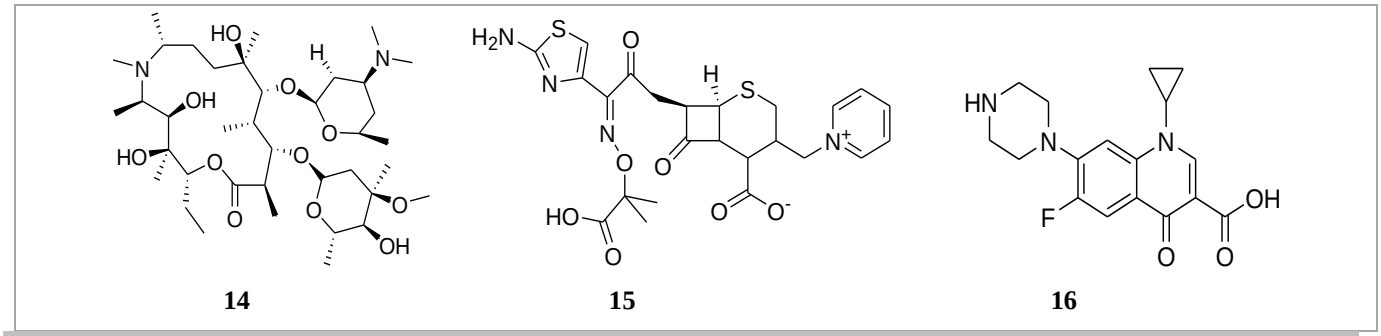

Figure 8. Polyphenolic QSIs, pyrogallol (10) and baicalein (11) and Rosmarinic acid (12) Catechin (13).

Polypeptide QSI Compounds

The signaling molecules in QS systems of gram-positive bacteria are often polypeptides. One of the most extensively investigated anti-QS peptides has been RNAIII inhibiting peptide (RIP; YSPWTNF-NH2). RIP interferes with the QSQ1 system in gram-positive bacteria. QSQ1 consists of autoinducer-RNAIII-activating protein (RAP) and its target molecule TRAP. RIP competes with RAP for TRAP binding. Consequently TRAP phosphorylation is inhibited and agr expression is reduced. This QS system has potential target for new antibacterial agents, particularly against resistant strains [121]. Evidence has shown RIP to be effective against *S. aureus* by the disruption of QS mechanisms [122,123]. Numerous researchs have showed specific *in-vivo* evidence for biofilm inhibition in *S. aureus* and *S. epidermidis* [124-128]. The use of polymethylmethacrylate beads loaded with RIP has also showed an effective system for treatment of drug resistant film from orthopedic pathogens [129]. RIP has also showed synergistic with a variety of antibiotics drug in eliminating biofilms from both *S. aureus* and *S. epidermidis* [130-133]. Considerably, SQS2 sensing inhibitors, which rely on agr-encoded auotinducing peptides (AIPs), while several groups have reported the inhibitory AIPs [134-138].

QSI Antiobiotics

Antibiotics are the first choice for many microbial infections, in many cases the lack of bactericidal activity caused them useless. In chronic *P. aeruginosa* infections of cystic fibrosis, macrolides such as azithromycin (**14**, AZM) are not often included in the treatment regimen. However, more evidence that low (sub-MIC) doses of a number of antibiotics (Fig. (**8**) which may elicit a variety of other effects. The AZM is to interfere with QS regulation in *P. aeruginosa* PAO1 [139]. The azithromycin interferes with transcription of AI synthase. Investigations reported that some different antibiotics for QSI activity [140]. The screens on QSIS1 revealed three compounds with strong QSI activity, such as ceftazidime (**15**, CFT) and ciprofloxacin (**16**, CPR), as well as the AZM. The direct connection between QSI effects and biofilm formation showed that AZM reduced the adherence of *P. aeruginosa* to polystyrene at low concentrations (1-2 mg/L). The connection between biofilm inhibition and inhibition of AI synthesis [141] concluded that the biofilm inhibition was at least partially due to interference of both C4-HSL and 3-oxo-C12-HSL formation. This would reduce the production of extracellular virulence factors which is necessary for biofilm formation. The *in-vivo* effect of AZM [142] of chronic *P. aeruginosa* lung infections gave significant improvement of clearance of alginate biofilms and reduced the severity of lung pathology. Presumably, due a suppression of QS-regulated virulence facts, in particular LasB expression, thus impairing the bacteria's ability to produce fully formed the biofilms.

QSI Compounds from fungi

Anti-QS agents were first described in the red marine alga *Delisea pulchra* [3], in a south Florida alga and a few higher plants [84,108]. In search for QSIs in some medicinal plants, it has been shown that terrestrial plants not only produce autoinducer [143] increases to confound the bacterial QS system [116,144]. The anti-QS medicinal plants, efficient screenings confirmed some plants, *Conocarpus erectus*, *Chamaesyce hypericifolia*, *Callistemon viminalis*, *Bucida buceras*, *Tetrazygia bicolor*, and *Quercus virginiana*, have anti-QS properties using *Chromobacterium violaceum* and

Agrobacterium tumefaciens NTL4 strains as biomonitors. These plants showed potentially therapeutic effects against bacterial infections (Bauer and Mathesius 2004). The fungal metabolites that interfere with bacterial QS signaling [23] reported the screening of various penicillium species. The initial screen used the QSIS1 selector, which identifies lux inhibitors, with a secondary screen using QSIS2 selector for *P. aeruginosa* QS systems. Various extracts were showed QSI effects. Two of these secondary metabolites were penicillic acid (**17**) and patulin (**18**) (Fig **9**). Both were showed QS-controlled gene expression in *P. aeruginosa*, most likely affecting the RhlR and LasR proteins. *In vitro* studies showed that *P. aeruginosa* PAO1 biofilms treated with patulin were more susceptible to the antibiotic tobramycin. The *in vivo* study showed the use of patulin as a used for pulmonary infections with *P. aeruginosa*. The QSI showed a significantly lower mortality rate and faster lung clearance. These two compounds were effect on biofilms of *Klebsiella sp, B. subtilis* and *Bacillus cereus* [145]. The study was to measure any interaction with LuxR AI-2 sensing and LuxS based AI-2 production, two receptors that could not be evaluated in the *P. aeruginosa* PAO1. Interestingly, penicillic acid alone had no effect on biofilms, however in combination with ethylendiaminetetracetic acid (EDTA) it enhanced biofilm formation in both *Klebsiella sp.* and *B. cereus*. Patulin alone promoted biofilm formation in *B. cereus* with a significant enhancement in both bacillus species when combined with EDTA.

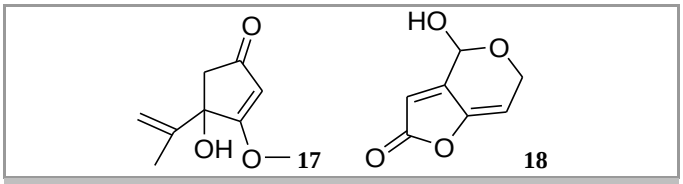

Figure 9. QSI fungal metabolites, penicillic acid (**17**) and patulin (**18**)

Brominated furanones

Furanones are compounds which have substantial interest due to their considerable QSI activity of brominated furanones or fimbrolides. Natural furanones were isolated from red algae *Delisea pulchra*, which produces more than 30 of furanones as secondary metabolites. The algae use as protection against colonization from both prokaryotes and eukaryotes. These compounds were interfered with QS-controlled swarming phenomenon in *Serratia liquefaciens* and *Proteus mirabilis* [43]. These furanones interfering with AHL-mediated QS is extensive [3,80,146] with a number of compounds showing promise as QSIs (Fig. (**10**).

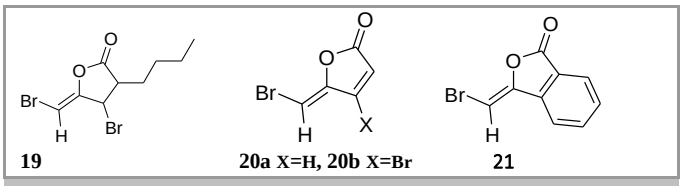

Figure 10. Natural and non natural brominated furanones

One furanone isolated from *D. pulchra* showed direct effect on biofilm formation is (*5Z*)-4-bromo-5-(bromomethylene)-3-butyl-2-(*5H*)-furanone (**19**) [147]. Compound **19** inhibited biofilm formation of *E. coli* XL1-blue on mild steel surfaces with little toxicity to the bacteria. Further studies [148] showed, with a variety of *E. coli* mutants, point to the inhibition of the AI-2 system as the target for the furanone. Further evidence for AI-2 interaction was reported in *Bacillus subtilis*, where **19** reduced biofilms significantly at 40 μg mL^{-1} [149] and using full-genome DNA microarrays showed **19** to induce 92 different genes in *B. subtilis* [150]. Similar growth inhibition was also shown in *Desulfotomaculum orientis* [30,150]. These compounds showed to disrupt AHL QS [62], these compounds increased the susceptibility of the bacteria to the antibiotics. In addition, biofilms grown in the presence of **20b** were readily dissolved overnight by sodium dodecyl sulfate. Furanone **21** had biofilm inhibition against the gram-positive bacteria, *S. epidermidis*, reducing biofilm formation by 68%, while having no effect on the growth of the bacteria [151].

Ellagitannin, a natural compound from various medicinal plants have shown anti-QS activity particularly against various Gram-negative bacteria [85,152]. Sub inhibitory concentrations of phenyl lactic acid, produced by *Lactobacillus* probiotic strains, have been shown to attenuate *P. aeruginosa* virulence and pathogenicity by interfering different regulated processes of QS. Tannic acid, a plant polyphenol, also showed anti-QS various Gram-negative bacteria. Ethanolic extracts of the plants *Sonchus oleraceus* and *Laurus nobilis* showed anti-QS in the Gram-negative bacterium *C.* V*iolaceum* [90]. Vanillin extracts have anti-QS activity in *C.* V*iolaceum*, [115] and vanillin (**22**) may be the active agent. Secondary metabolites of the North Sea bryozoan *Flustra foliacea* having a variety of brominated alkaloids, two of which (**23, 24**) were found to specifically block AHL-regulated gene expression. Both compounds caused a reduction in the signal intensities in biosensor strains of *P. putidia* and *E. coli*. In addition, compound **23** was reduced the production of extracellular proteases in *P. aeruginosa*, a phenotype associated with the virulence of pathogens, which is under the stringent control of AHL-dependent QS systems. The extracts of the red alga *Ahnfeltiopsis flabelliformis* inhibited QS mediated by OHL and the TraR transcriptional activator protein [153]. Compounds betonicine (**25**), floridoside (**26**), and

isethionic acid (**27**), each of these compounds were showed QSI activities (Fig. **11**). None of the three compounds exhibited inhibition when tested individually. In contrast, a complex of floridoside and isethionic acid revealed a dose-dependent inhibition on OHL activity, these two compounds are responsible for the inhibition activity of red algae extract. Unexpectedly, betocine and *cis*-betocine showed a dose-dependent stimulatory effect in TraR-mediated QS responses.

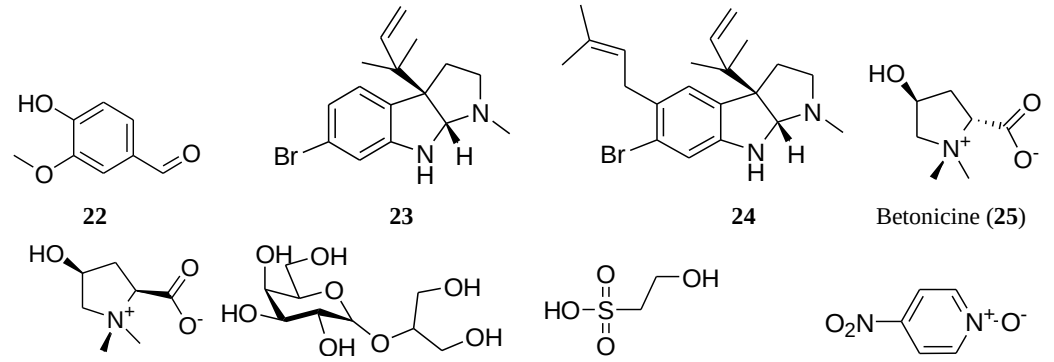

Figure 11. Quorum sensing inhibitors (vanillin 22), (alkaloids 23 and 24) and (solenopsin A and analogues 25-27).

A extracts from food sources and herbal medicines for QSIs and reported that 4-nitropyridine-*N*-oxide (**28**) and toluene extracts of garlic specifically inhibit QS-regulated gene expression in *P. aeruginosa*. Subsequent in vitro studies on *P. aeruginosa* biofilms demonstrated that garlic extract significantly reduced the tolerance of the bacteria to the antibiotic tobramycin. The garlic extracts can antagonize the activity of the QS receptors AhyR and TraR. Recently, garlic extract promotes rapid clearing of mice pulmonary *P. aeruginosa* infections [108].

Applications

Pathogen and pest (undesirable organism in environment) management comprise current applications of QS-technology. Inhibition of QS signaling is the most obvious, most omnipresent application of QS knowledge. The targeting of QS for the treatment of bacterial infections were reported in various studies [154,155]. Some examples using various aspects of QS are discussed. *Staphylococcal* subspecies, such as methicillin-resistant *S. aureus*, remain one of the most opportunistic pathogens. The QS inhibit the development of *S. aureus* and *S. epidermidis* biofilms. Both strains were susceptible to an RNA III inhibiting peptide (RIP), a specific QSI that interferes with the gene locus agr, which is responsible for *staphylococcal* toxicity [125]. When RIP was added to the culture, the cells were less able to form a biofilm. Expanding this approach to include antibiotics, the effect of combining RIP with seven different combinations of antibiotics and found that in every case the combination of RIP and an antibiotic greatly improved the performance of the antibiotic [125]. Looking to Gram-negative bacterial infections, *P. aeruginosa* from intubated patients revealed quorum-signalling targets that could be potentially inhibited to prevent the formation of biofilms [156]. Most of the QS genes expressed were classified as transcription factors. High concentrations of AI-2 were detected in sputum from cystic fibrosis patients. The research found that *P. aeruginosa* transcriptional virulence factors could be stimulated by oral pharyngeal microflora and that high concentrations of AI-2 were present in in vitro cultures of both *P. aeruginosa* and the host microflora, indicating that the host's own bacteria might be stimulating the growth of *P. aeruginosa* [157]. Plants have long been known to interact with symbiont bacteria through QS signaling, and plant pathogens use QS signaling to colonise their hosts.

A quorum signaling in plant–pathogen symbiont interactions discusses some of the potential applications that could arise from these relationships [50]. *Erwinia carotovora* and *Agrobacterium tumefaciens* of AHL expression and repression in the plant rhizosphere [158]. Plant–microbe relationships with potential for pathogen control. *Burkholderia cepacia* in onions [159], *Ceratocystis ulmi* (a fungus that causes Dutch elm disease) [160], *Sinorhizobium melilot* (symbiont) and *P. aeruginosa* (pathogen) in legumes [161], and wine grape consortia [162]. Part of the biocontrol activity of *Bacillus thuringiensis* is through AHL lactonase, an AHL-degrading enzyme [163]. Biocontrol efficacy against *E. carotovara* was reduced in *B. thuringiensis* mutated for AHL lactonase. Also, strains of *E. coli* and *Bacillus fusiformis* lacking AHL lactonase showed a similar lack of anti-microbial capability when cultivated on potatoes [162]. Interestingly, B. thuringiensis did not inhibit the growth of *E. carotovara*, but rather, inhibited its virulence and ability to cause soft rot disease in potatoes. The virulence inhibition capability of B. thuringiensis might make it a candidate for fighting bacterial infections. The demonstrated the effect of

recombinant AHL lactonase in transforming strains incapable of biocontrol into biocontrol agents [164]. *P. fluorescens* was transformed with the aiiA gene encoding AHL lactonase under a constitutive promoter. AHL-degrading capability in-vitro and the ability to inhibit growth of aquatic biofilms [165] is another potential application of QSIs [166]. In a screen for fungicidal bacteria reported finding numerous strains capable of degrading invasive *Gymnodinium catenatum* [167]. Included in the fungicidal strains were *Pseudomonas* ssp. expressing AI-2; however, the occurrence of AI-2 did not correlate with fungicidal activity. In activated sewage sludge, QS has been shown to change the characteristics of waste water [168] and AHL compounds to activated sewage sludge and found an increase in the phenol degradative capacity. In a nonaquatic study of food spoilage, neither AI-2 nor AHL signalling correlated with biofilm formation of Gram negative bacteria [169]. The role of quorum signaling, especially with respect to its applicability to biological control, the problem with a wide variety of infections and their contribution to the antibiotic resistance of certain bacteria, have made controlling them an important facet in managing and removed bacterial infections. The structurally diverse groups of molecules have shown QSIs. By identifying active QSIs, various are natural QS compounds taken from different sources; the mechanism of QSI can be better understood. These QSIs hold great potential for the design of more effective antibacterial agents. The QS systems are regarded as new targets for antimicrobial strategies. In this perspective, it is important to consider the potential implication of horizontal transfers in the reacquisition of virulence.

Discussion

Applications for QS sensing are presently limited by perceptive of QS mechanisms. The use of QS, further perceptive of quorum functionality is required before the influence of this can be realized. The capability to block QS and makes the use of isolated compounds for driving protein expression. The full-scale treatment of the bacterial quorum circuit in a biotechnological purpose remains an unfulfilled goal. QS driven gene expression was used in concert with complicated regulation in eukaryotic cells to finely control product synthesis [170,171]. The method was effective in a rat model. The significance of the work is that it demonstrates a potential 'infection driven' gene therapy, where the existence of a bacterial extracellular signal may drive the expression of genes designed to fight the infection. Many bacteria utilize sophisticated regulatory systems to ensure that some functions are only expressed when a particular population density has reached [172-174]. The QS described form of density-dependent gene regulation which relies on the making and perception of small signal molecules by bacterial cells. As in many pathogenic bacteria the production of virulence factors is QS regulated, it has been suggested that this form of gene regulation allows the bacteria to remain invisible to the defense systems of the host until the population is sufficiently large to successfully establish the infection. The polyphenolic compounds can interfere with bacterial QS. These polyphenols are widely distributed in the plants and may be important for promoting plant fitness.

Future perspectives

The use of small molecules to modulate bacterial QS systems has attracted significant interest over the course of the last 15 years. Various structurally diverse nonnative activators and inhibitors have been discovered; provide researchers with an expansive set of chemical tools to study this form of intercellular communication. Ultimately, strategies based upon the chemical modulation of bacterial QS may prove to be of value in a wide range of fields, including medicinal, agricultural, and environmental. However, chemotherapeutics purposes remain a long way off. Attaining a combination of efficacy *and* selectivity (small molecule modulation of a specific QS-regulated phenotype in a given bacterial species) presents a significant challenge [175,176]. There is a significant need for the standardization of the assays to study small-molecule modulation of QS-pathways. This facilitates the elucidation of more accurate SAR data for QS-modulators, which should enhance the perceptive of the molecular features crucial for desired biological activities. There is a definite need for more detailed fundamental studies into the molecular basis of QS modulation, that is, the mechanisms of action of small-molecule activators and inhibitors in terms of the fundamental bonding interactions involved. Such information would provide a scaffold for a deeper perceptive of the performance of existing small molecule modulators on a molecular level and also facilitate the rational de novo design of new next-generation agents with improved molecular properties (efficacy and selectivity). The field of small-molecule modulation of QS can be considered, in many regards, to still be in its infancy [177-182]. There is, thus, considerable scope for further exciting developments to be made in this area; the reliance of QS upon a language of small molecules undoubtedly means that chemists will play an integral role in such progress.

Conclusions

The plant kingdom has long been a source of diverse medicinal compounds, many ethnobotanically directed searches for agents that can be used to treat pathogenic infections, mainly focused on bactericidal effects. Our focus to anti-QS and anti-virulence properties may reveal quorum-quenching compounds from medicinal plants for provide a novel method for the treatment of infections against resistant strain of microorganism particularly against *P. aeruginosa*. The effects of the

medicinal plant extracts on *P. aeruginosa* are quite complicated and maybe extend beyond the domain of the QS control hypothesis. The failure of existing antibiotics to control infection makes it crucial to find alternatives to currently available drugs. The pathogenicity in many bacteria is regulated by QS that is the key regulator of virulence and biofilm formation in *P. aeruginosa* and other relevant bacteria. Various plants showed their effects on *P. aeruginosa* virulence factors and the QS system with significant inhibition of LasA protease, LasB elastase, pyoverdin production, and biofilm formation. In fact, an anti-QS approach has already shown promise in the battle against *P. aeruginosa* infections. However, the reduction of QS gene expression and signaling molecule levels and the end effect on virulence factor production provide some insight into why these plants were used in the past and how they can be used in the future to combat *P. aeruginosa* and other bacterial infections.

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