Review Article

Anti-Quorum Sensing Natural Compounds

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Abstract

Increasing extent of pathogenic resistance to drugs has encouraged the seeking for new anti-virulence drugs. Many pharmacological and pharmacognostical researches are performed to identify new drugs or discover new structures for the development of novel therapeutic agents in the antibiotic treatments. Although many phytochemicals show prominent antimicrobial activity, their power lies in their anti-virulence properties. Quorum sensing (QS) is a bacterial intercellular communication mechanism, which depends on bacterial cell population density and controls the pathogenesis of many organisms by regulating gene expression, including virulence determinants. QS has become an attractive target for the development of novel anti-infective agents that do not rely on the use of antibiotics. Anti-QS compounds are known to have the ability to prohibit bacterial pathogenicity. Medicinal plants offer an attractive repertoire of phytochemicals with novel microbial disease-controlling potential, due to the spectrum of secondary metabolites present in extracts, which include phenolics, quinones, flavonoids, alkaloids, terpenoids, and polyacetylenes. They have recently received considerable attention as a new source of safe and effective QS inhibitory substances. The objective of this review is to give a brief account of the research reports on the plants and natural compounds with anti-QS potential.

Keywords: Anti-virulence, bacterial pathogenicity, natural products, quorum sensing

Introduction

Diseases which caused by bacteria, viruses, fungi, and parasites are an important cause of mortality and morbidity, in all regions of the world particularly in the developing countries.[1] Bacteria and fungi resistance to antibiotics has grown in the last decades, but the rate of discovery of new antibiotics has steadily decreased.[2] The cause behind the lack of antibiotic discoveries are diverse and include among others, the poor return on investment compared to drugs for chronic diseases and regulatory burdens for smaller pharmaceutical companies.[3] Infections caused by resistant pathogens can be overcome using a combination of antibiotics with the variable mode of actions. However, the increased prevalence of pathogen resistant and the formation of bacterial biofilms that are difficult to eradicate have targeted the efforts to find alternatives to the current antibiotic therapy,[4] which is inadequate to control the infection of microbes[5] and creates major public health problems.[6] Thus, various pharmacognostical and pharmacological studies are performed to discover new therapeutic measures to prevent infection among drug-resistant bacterial pathogens.[7] An important approach is to target bacterial cell-to-cell communication, commonly known as quorum sensing (QS).[8] It is a way that bacteria use to sense information from other cells.

Quorum sensing mechanism

The QS mechanism is depend on the synthesis, release, and uptake of autoinducers (AIs) in the surrounding medium, whose concentration related to the density of secreting bacteria. AIs, extracellular signaling molecules, which accumulate in the environment in proportion to cell density is utilized for this intercellular communication.[9-11] Their function is to regulate gene expression in other cells of the community, which in turn, controls a number of bacterial responses. Various bacterial physiological processes, including virulence, motility, luminescence, biofilm formation, sporulation, development of genetic competence, synthesis of peptide antibiotics, production of secreted proteolytic enzymes, and fluorescence are regulated by QS.[12,13] Xavier and Bassler reported that signal molecule production is depending on

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an autoinducing mechanism and their type differs between Gram-negative and Gram-positive bacteria.[14] These signaling molecules and their receptors have been broadly divided into three major classes: (1) *N*-acyl homoserine lactones (AHLs), which vary in the length and oxidation state of the acyl side chain and produced by Gram-negative bacteria to monitor their population density in QS control of gene expression. The signals are synthesized by members of the LuxI family of proteins; (2) oligopeptides or autoinducing peptides, consisting of 5–34 amino acids residues, are generally involved in intercellular communication in Gram-positive bacteria. Many of these peptides are exported by dedicated systems, posttranslationally modified in various ways and finally sensed by other cells through membrane-located receptors that are part of two-component regulatory systems; and (3) AI-2 employed by both Gram-positive and Gram-negative bacteria for interspecies communication. It has been chemically identified as a furanosylborate diester synthesized by members of the LuxS family of proteins.[14-16] Gram-positive bacteria: the precursor peptide AIs are modified and transported out of the cell by ATP-binding cassette exporter complex. When the concentration of the peptide AIs reaches the threshold value, the sensor kinase protein will be activated and phosphorylate the response regulator protein, which will then binds to the target promoter that will lead to QS gene regulation. However, in Gram-negative bacteria, the AIs are produced and diffused freely out of the cell. When the concentration of the AIs reaches the threshold value, a positive feedback loop will be formed that causes more AIs to be synthesized. The AIs produced will bind to their cognate receptor to form an AI-receptor complex which will then binds to the target promoter that lead to QS gene regulation [Figure 1]. The concentration of the AIs increases proportionally with the growth of a bacterial population, and when it reaches a certain point, those molecules diffuse back into the bacteria to regulate the transcription of specified genes responsible of the formation and release of virulence factors, antibiotic production, and biofilm formation.[17] The modulation of the physiological processes controlled by AHLs induces expression of QS genes.[18] All AHLs thus far reported are composed of an acyl chain with an even number of carbon atoms ranging from 4 to 14 in length, ligated to the homoserine lactone moiety [Figure 2].[19] The components of AHL-driven QS systems are typically members of the protein families: LuxI and LuxR. LuxI generates AHLs and LuxR activates or represses the transcription of specific genes such as virulent genes.[14,20]

Quorum sensing pathways inhibition

Because QS is implicated in various pathologically relevant events, it is conceivable that inhibitors of bacterial QS could have therapeutically application. There are different ways for QS inhibition in each pathway. They can be summarized as follows: (1) inhibition of AIs synthesis, (2) AIs receptor antagonism, (3) inhibition of targets downstream of receptor binding, (4) sequestration of AIs using, for example, antibodies against AIs, (5) the degradation of AIs using either catalytic antibodies (abzymes) or enzymes (such as lactonases), (6) inhibition of AI secretion/transport, and (7) antibodies that "cover" and therefore block AIs receptors. Not all seven different types of inhibition have been explored in the various pathways identified.[21,22]

Disrupting of this communication system or bacterial QS activity leads to attenuation of microbial virulence.[17,23] Many strategies have been designed to intervene with QS systems, which will have wide application in the control of QS-dependent infections produced by bacterial.[24] This motivated research of inhibition of this process through the utilization of QS inhibitors.[25] The inactivation or degradation of QS signal molecules is known as QS inhibition or quorum quenching (QQ). This can be accomplished by several ways such as through the development of antibodies to QS signal molecules, the enzymatic demolition of QS signal molecules, or through agents which block QS.[26] These strategies interfere with this cell-to-cell communication and monitor the

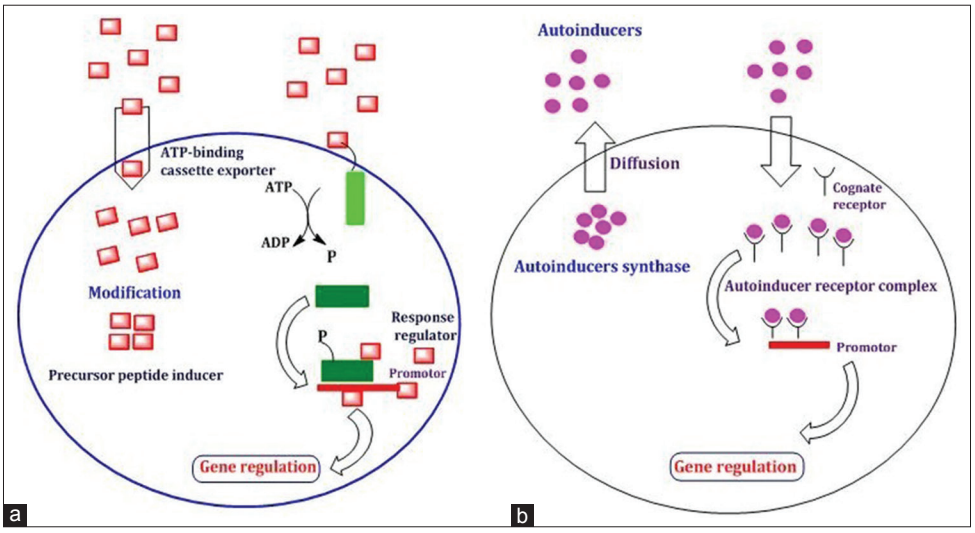

Figure 1: A graphic presentation of QS molecular signaling network of Gram-positive bacteria (a) and Gram-negative bacteria (b)

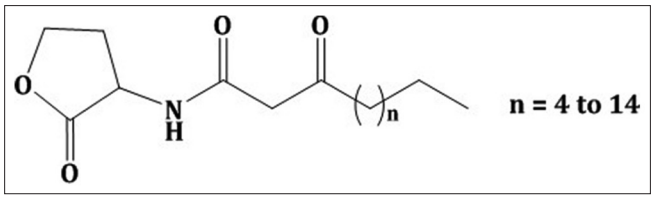

Figure 2: Chemical structures of *N*-acyl homoserine lactones autoinducers

infectious bacteria without stopping their growth, thus averting the development of antibiotics resistance.[25,26] The ideal QS inhibitors have been defined as chemically stable and highly effective low molecular-mass molecules, which exhibit a high degree of specificity for the QS regulator without toxic side effects on the bacteria or an eventual eukaryotic host. Therefore, the development of new, nontoxic, and broad-spectrum QQ drugs from both plants and microorganisms is of great benefit in recent years. Plants produce diverse compounds such as simple phenolics, flavonoids (FLs), alkaloids, and terpenoids.[5,27] There is a great interest in the biological activities and therapeutic roles of these natural products in defeating QS pathogens. Since, there is a growing demand for anti-QS agents to overcome the bacterial resistance to antibiotics, it is necessary to examine and identify alternative and safe approaches for controlling pathogens. The plant kingdom has long been a source of medicines, and as such, there have been many ethnobotanically directed searches for agents that can be used to treat infections. The use of plants, plant products, and their purified components could open up the possibility of using these compounds as novel anti-QS agents. Therefore, this review presents the recent reported researches on the plants and natural products as QQ agents.

Phytochemicals as Quorum Sensing-inhibitors

In this section, an overview of the QS inhibitory activity of the compounds derived plants that have been used since ancient times as traditional medicine. Plant-derived compounds are mostly secondary metabolites, most of which are phenols or their oxygen-substituted derivatives. These secondary metabolites possess various benefits, including antimicrobial properties against pathogenic microbes.[25] Major groups of compounds that are responsible for antimicrobial activity from plants include phenolics, phenolic acids, quinones, saponins, FLs, tannins, coumarins, terpenoids, and alkaloids.[28,29] Variations in the structure and chemical composition of these compounds result in differences in their QS inhibitory action [Figure 3].

Halogenated furanones produced by the benthic marine macroalga *Delisea pulchra* were the first identified anti-QS compounds. They were found to inhibit the QS-regulated behaviors by competitively bind to the LuxR type proteins. Thus, promote their rate of proteolytic degradation without killing the bacteria for their role in inhibiting biofilm formation.[25,29] Furthermore, the plant constituents such as naringenin, oroidin, salicylic acid, ursolic acid, cinnamaldehyde, methyl eugenol, as well as extracts of garlic and edible fruits, had anti-biofilm properties toward various pathogens.[30]

Dwivedi and Singh 2016 investigated the effects of the natural compounds, embelin and piperine on the biofilm-formation property of *Streptococcus mutans* using the microtiter plate method. It was found that minimum biofilm inhibitory concentration of embelin was 0.0620 ± 0.03 mg/mL, whereas that of piperine was 0.0407 ± 0.03 mg/mL, which was lower than that of embelin. These compounds might exhibited their effects by inhibiting the activity of receptors and molecules involved in the QS pathway, which is required for biofilm formation.[31]

The anti-QS potential of an anacardic acids mixture (AAM) isolated from *Amphipterygium adstringens* as well as its hexane extract (HE) on the rhamnolipid and pyocyanin production constraint as well as decrease of elastase activity, all being QS-controlled virulence factors expressed in the pathogenic bacteria *Pseudomonas aeruginosa*. They induced a 91.6% and 94% inhibition of the violacein production at concentrations 55 and 166 μg/mL, respectively without affecting the viability of the bacterium. Moreover, AAM inhibited pyocyanin (86% at 200 μg/mL) and rhamnolipid (91% at 500 μg/mL) production and decrease the elastase (75% at 500 μg/mL) activity in *P. aeruginosa* without affecting its development.[32]

Kang *et al*. reported that piericidin A and glucopiericidin A isolated from *Streptomyces xanthocidicus* KPP01532 are potential QS inhibitors that suppress the expression of the virulence genes (pelC, pehA, celV, and nip) of *Erwinia carotovora* subsp. *Atroseptica* (a plant pathogen that causes blackleg and soft rot diseases on potato stems and tubers).[33] Malabaricone C isolated from the bark of *Myristica cinnamomea* inhibited violacein production by *Chromobacterium violaceum* CV026. Furthermore, it inhibited the QS-regulated pyocyanin production and biofilm formation in *P. aeruginosa* PAO1.[34]

FLs are a large class of phenylpropanoid-derived plant metabolites that are classified according to the degree of oxidation of their C-ring and whose structural diversity results from substitutions of their carbon skeleton through hydroxylation, glycosylation, methylation, acylation, and prenylation.[35,36] Some FLs have been shown to inhibit gyrase activity, nucleic acid synthesis, type IV topoisomerase, cytoplasmic membrane functions, and energy metabolism.[37] FLs are also known for their implication in cell-to-cell communication mechanisms involved in the establishment of the symbiosis between rhizobia bacteria and their respective legume hosts.[35]

The flavone, baicalein has been shown to inhibit biofilm formation, which is QS dependent in *P. aeruginosa* PAO1 (at micromolar concentrations) as well as to promote the proteolysis of the *Agrobacterium tumefaciens* QS-signal receptor TraR in *Escherichia coli* cells at millimolar concentrations.[38,39] Vikram *et al*. screened many of the citrus plants FLs for their ability to interfere with QS-dependent bioluminescence mechanisms and biofilm formation.[40]

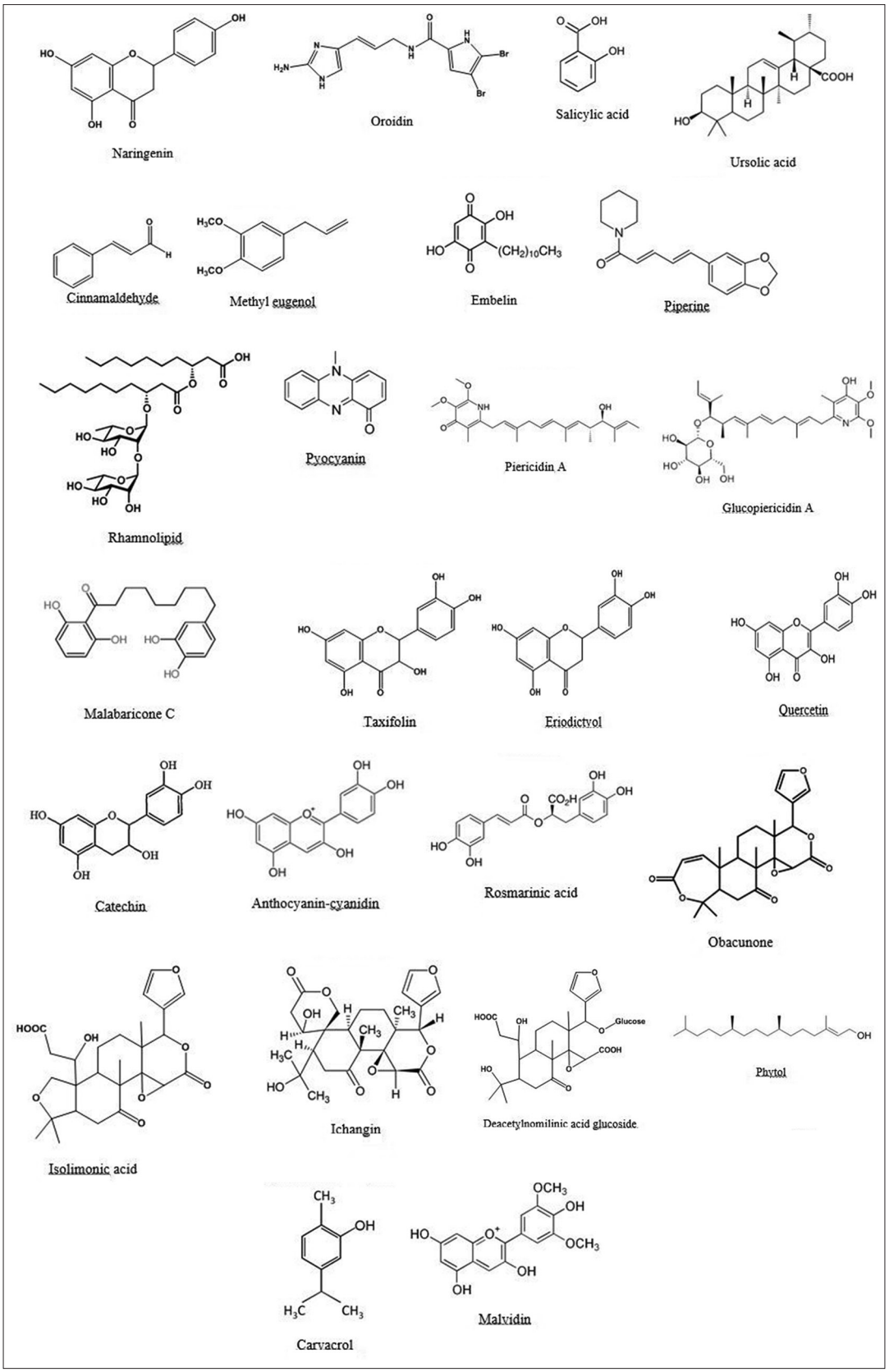

Figure 3: Some phytochemicals as quorum sensing inhibitors

The results showed that naringenin reduces the induction of bioluminescence by the QS signals HAI-1 and AI-2 in *Vibrio harveyi* reporter strains as well as the production of biofilm by *V. harveyi* BB120 and *E. coli* 0157:H7. Moreover, the

expression of three type III secretion system genes suggested to be controlled by cell-to-cell signaling, is down-regulated by naringenin.[40]

Flavanones, naringenin, eriodictyol, and taxifolin identified in the extract of *Combretum albiflorum* significantly reduced the production of pyocyanin and elastase in *P. aeruginosa* without affecting bacterial growth. Further, naringenin and taxifolin reduced the expression of several QS-controlled genes (i.e., lasI, lasR, rhlI, rhlR, lasA, lasB, phzA1, and rhlA) in *P. aeruginosa* PAO1.[41]

Vandeputte *et al*. stated that the action of naringenin most probably results from a combination of the reduction of the production of both AHL molecules (which is corroborated by the down-regulation of the expression of the lasI and rhlI genes) and of the capacity of the LuxR-type transcription factors to perceive their cognate molecules, with a consequent reduction of the expression of QS-related genes.[41] It is noteworthy that lasI and rhlI mutants deficient in AHL synthesis is indeed impaired in their capacity to express a wide range of QS genes, among which are lasB (encoding lasB elastase), rhlA (encoding the first protein involved in the production of rhamnolipids), and the phz operon involved in the production of pyocyanin.[42,43]

Quercetin (80 μg/mL) showed a significant reduction in QS-dependent phenotypes such as violacein production, biofilm formation, exopolysaccharide (EPS) production, motility, and alginate production in a concentration-dependent manner. It can act as a competitive inhibitor for signaling compound toward lasR receptor pathway.[44] Moreover, it significantly inhibited biofilm formation and production of virulence factors, including pyocyanin, protease, and elastase at a lower concentration. Furthermore, the expression levels of lasI, lasR, rhlI, and rhlR were significantly reduced by 34%, 68%, 57%, and 50%, respectively, in response to 16 μg/mL quercetin.[45]

Moreover, catechin isolated from *C. albiflorum* (Tul.) Jongkind (*Combretaceae*) had a significant negative effect on pyocyanin and elastase productions and biofilm formation, as well as on the expression of the QS-regulated genes lasB and rhlA and of the key QS regulatory genes lasI, lasR, rhlI, and rhlR. It might interfere with the perception of the QS signal *N*-butanoyl-l-homoserine lactone by RhlR, leading to a reduction of the production of QS factors.[46]

Gopu and Shetty reported that the naturally occurring anthocyanin-cyanidin significantly inhibited QS-dependent phenotypes such as biofilm formation (72.43%), violacein production (73.96%), and EPS production (68.65%) in the opportunistic pathogen *Klebsiella pneumoniae* in a concentration-dependent manner.[47] Rosmarinic acid extracted from sweet basil bound to the QS-regulator RhlR of *P. aeruginosa* PAO1 and competed with the bacterial ligand *N*-butanoyl-homoserine lactone (C4-HSL). Furthermore, it stimulated a greater increase in RhlR-mediated transcription *in vitro* than that of C4-HSL. In *P. aeruginosa*, rosmarinic acid-induced QS-dependent gene expression and increased biofilm formation and the production of the virulence factors pyocyanin and elastase.[48] The disulphides and trisulphides metabolites which are extracted from garlic can inhibit LuxR-based QS inhibition in *P. aeruginosa*.[49] Naturally occurring furocoumarins from grapefruit showed strong inhibition of AI-1 and AI-2 activities based on the *V. harveyi* AI bioassay. In addition, they hinder the formation of biofilm in *E. coli*, *Salmonella typhimurium*, and *P. aeruginosa*.[50] Moreover, obacunone a grapefruit limonoid has been proven to have a strong antagonistic activity against both AHL and AI-2 systems, biofilm formation, and enterohemorrhagic *E. coli* virulence.[51]

The citrus limonoids, isolimonic acid, and ichangin are potent inhibitors of EHEC biofilm and adhesion to Caco-2 cells. They repressed locus of enterocyte effacement-encoded genes and flhDC. Furthermore, isolimonic acid interferes with AI-3/epinephrine activated cell-to-cell signaling pathway.[52] Moreover, isolimonic acid, deacetylnomilinic acid glucoside, and ichangin demonstrated significant inhibition of AI-mediated cell-to-cell signaling and biofilm formation. In addition, isolimonic acid and ichangin induced expression of the response regulator gene luxO.[53]

The diterpene phytol reduced the biofilm formation, twitching, and flagella motility of *P. aeruginosa* PAO1. It exhibited good *P. aeruginosa* pyocyanin inhibitory activity.[54] Carvacrol, one of the major antimicrobial components of oregano oil, inhibited the formation of biofilms of *C. violaceum* ATCC 12472, *Salmonella enterica* subsp. *Typhimurium* DT104, and *Staphylococcus aureus* 0074. Furthermore, it reduced expression of civil (a gene coding for the N-acyl-L-homoserine lactone synthase), production of violacein, and chitinase activity (both regulated by QS).[55]

The total anthocyanin of *Syzygium cumini* (STA) specifically inhibited the violacein production in *C. violaceum*, biofilm formation, and EPS production in *K. pneumoniae* up to 82%, 79.94%, and 64.29%, respectively. The QS inhibitory activity of *S. cumini* was attributed to malvidin, which reduce the violacein production, biofilm formation, and EPS production of *K. pneumoniae* in a concentration-dependent manner.[44]

Mohamed *et al*. reported that mangostanaxanthone I and α-mangostin isolated from isolated from the pericarp of *Garcinia mangostana*, possessed QS inhibitory activity against *C. violaceum* ATCC 12472 with MIC values 2 and 3 μg/mL, respectively compared to (+) - catechin (MIC 2 μg/mL).[1]

Plant By-products as Quorum Sensing-inhibitors

Lee *et al*. (2011) reported that acacia and multifloral Korean honeys at low concentrations (0.5% v/v) were capable of reducing biofilm formation in an enterohemorrhagic *E. coli* strain due to their contents of fructose and glucose, that appeared to be the main contributors to biofilm formation

inhibition.[56] Truchado *et al*. studied the effect of chestnut honey and its aqueous and methanolic extracts on biofilm formation by *Yersinia enterocolitica*, *E. carotovora*, and *Aeromonas* hydrophila.[57] Chestnut honey and its aqueous extract showed a significant QS inhibitory activity through the inhibition of AHL production and degradation of AHLs by the bacterial strains. While its methanolic extract did not possess any effect. In another study, Truchado *et al*. stated that the phenolic compounds, including rutin, ellagic, and chlorogenic acids were capable of reducing the concentration of ALHs on E. carotovora and Y. enterocolitica.[58] Savka *et al*. showed that the FL pinocembrin, which regulates immune genes in the western honey bee Apis mellifera, can disrupt AHL-dependent QS in bacteria. This referred to the potential role of the phenolic honey constituents as QS inhibitory.[59] Moreover, the study conducted by Truchado *et al*. on 29 unifloral honeys showed that most of them were capable of interfering with QS, especially chestnut and linden honeys had the highest anti-QS activity.[60] Whereas, orange and rosemary honeys were less effective. Further studies carried out on New Zealand manuka (Leptospermum scoparium) honey revealed that this honey can inhibit biofilm formation of clinically important pathogenic bacteria such as Proteus mirabilis,[61] S. aureus,[62] and Clostridium difficile.[63] Three nectar honeys (eucalyptus, thyme, and forest) and two honeydew honeys (fir and Metcalfa) from Italy were assessed for their anti-QS activities. All inhibited violacein production in C. violaceum in a dose dependent manner, thus demonstrating their ability to affect QS-regulated biofilm formation.[64] Chenia has studied QS inhibitory activity of four extracts of Kigelia africana fruit using the C. violaceum and A. tumefaciens biosensor systems. All extracts showed varying levels of anti-QS activity with zones of violacein inhibition ranging from 9 to 10 mm in the following order: hexane > dichloromethane > ethyl acetate > methanol. Inhibition was concentration dependent, with the ≥90% inhibition being obtained with ≥1.3 mg/mL of the HE. They also affected the LuxI and LuxR activities, indicating that the phytochemicals targeted both QS signal and receptor.[65]

The anti-QS activity of the FL fraction of *Psidium guajava* L. leaves was determined using a biosensor bioassay with the mutant *C. violaceum* CV026. In addition, its effect on QS-regulated violacein production in *C. violaceum* ATCC12472 and pyocyanin production, proteolytic, elastolytic activities, swarming motility, and biofilm formation in *P. aeruginosa* PAO1 was performed. The FL-fraction showed concentration-dependent decreases in violacein production in *C. violaceum* 12472 and inhibited pyocyanin production, proteolytic and elastolytic activities, swarming motility, and biofilm formation in *P. aeruginosa* PAO1. Interestingly, the FL-fraction did not inhibit AHL synthesis. Quercetin and quercetin-3-O-arabinoside the major FLs in FL fraction, inhibited violacein production in *C. violaceum* 12472, at 50 and 100 μg/mL, respectively.[66] It was also reported that the *P. guajava* extract guava leaf extract (GLE) significantly down-regulated 816 genes which comprises 19% of the *C. violaceum* MTCC 2656 genome by at least 3-fold. These genes were distributed throughout the genome and were associated with virulence, motility and other cellular processes, many of which have been described as quorum regulated in *C. violaceum* and other Gram-negative bacteria. Interestingly, GLE did not affect the growth of the bacteria. However, GLE-treated *C. violaceum* cells were restrained from causing lysis of human hepatoma cell line, HepG2, indicating a positive relationship between the QS-regulated genes and pathogenicity.[67]

The anti-QS activity of the ethyl acetate fraction (EAF) of *S. cumini* L. and *Pimenta dioica* L. was screened using *C. violaceum* CV026 biosensor bioassay. It is noteworthy that, all the tested plant extracts completely inhibited AHL-mediated violacein production in 0.75–1.0 mg/mL concentration in *C. violaceum*. However, synthesis of AHL in *C. violaceum* was not inhibited by the plant extracts.[68] Husain *et al*. reported that the oil of peppermint (*Mentha piperita*) at sub-minimum inhibitory concentrations (sub-MICs) strongly interfered with AHLs-regulated virulence factors and biofilm formation in *P. aeruginosa* and *A. hydrophila* due to menthol, which interferes with QS systems of various Gram-negative pathogens comprising diverse AHL molecules. It reduced the AHL-dependent production of violacein, virulence factors, and biofilm. Moreover, it significantly enhanced survival of the nematode *Caenorhabditis elegans*.[69]

Anti-QS-dependent therapeutic function of clove oil was evaluated against *P. aeruginosa* PAO1 and *A. hydrophila* WAF-38. Subinhibitory concentrations of the clove oil demonstrated significant reduction of las-regulated and rhl-regulated virulence factors: LasB, total protease, chitinase, and pyocyanin production, swimming motility, and EPS production. Furthermore, it reduced the biofilm forming capability of PAO1 and *A. hydrophila* WAF-38. Further, the PAO1-preinfected *C. elegans* displayed an enhanced survival when treated with 1.6% v/v of clove oil.[70]

Khan *et al*. reported that clove oil showed promising anti-QS activity on both *C. violaceum* CV12472 and CVO26 with zones of pigment inhibition 19 and 17 mm, respectively, followed by cinnamon, lavender, and peppermint oils. The sub-MICs of clove oil revealed 78.4% reduction in violacein production and up to 78% reduction in swarming motility in *P. aeruginosa* PAO1.[71]

Trigonella foenum-graecum L. (Fenugreek, Leguminosae) seed methanol extract exhibited significant inhibition of AHL-regulated virulence factors: protease, lasB elastase, pyocyanin production, chitinase, EPS, and swarming motility in *P. aeruginosa* PAO1 and PAF79. Further, it reduced the QS dependent virulence factor in the aquatic pathogen *A. hydrophila* WAF38. It decreased the biofilm forming abilities of PAO1, PAF79, and WAF38 and AHL levels and subsequent down-regulation of *lasB* gene. The major compound detected in the extract is caffeine, which reduced the production of QS regulated virulence factors and biofilm at 200 μg/mL concentration.[72]

Shukla and Bhathena (2016) reported that the extracts rich in hydrolysable tannins of *Phyllanthus emblica*, *Terminalia bellirica*, *Terminalia chebula*, *Punica granatum*, *S. cumini*, and *Mangifera indica* (flower) exhibited a broad spectrum anti-QS activity that is affecting activity of AHLs as well as AIs over a wide range of subinhibitory concentrations. All the extracts showed distinct protein binding ability and may be disrupting QS either by inactivating enzymes responsible for the synthesis of the AIs or by binding to protein receptors of QS signals.[73]

The dichloromethane extract from root barks of *Cordia gilletii* was found to quench the production of pyocyanin, a QS-dependent virulence factor in *P. aeruginosa* PAO1. Moreover, it specifically inhibits the expression of several QS-regulated genes (i.e., lasB, rhlA, lasI, lasR, rhlI, and rhlR) and reduces biofilm formation by PAO1.[74]

Six south Florida medicinal plants – *Conocarpus erectus* (*Combretaceae*), *Chamaecyce hypericifolia* (Euphorbiaceae), *Callistemon viminalis* (Myrtaceae), *Bucida buceras* (*Combretaceae*), *Tetrazygia bicolor* (*Melastomataceae*), and *Quercus virginiana* (*Fagaceae*) were assessed for their anti-QS activities against *P. aeruginosa* PAO1. The *C. erectus*, *B. buceras*, and *C. viminalis* extracts caused a significant inhibition of lasA protease, lasB elastase, pyoverdin production, and biofilm formation. In addition, each plant presented a distinct effect profile on the las and rhl QS genes and their respective signaling molecules. Furthermore, the extracts of all plants caused inhibition of QS genes and QS-controlled factors, with marginal effects on bacterial growth, suggesting that the QQ mechanisms are unrelated to static or cidal effects.[75]

QS-blocking properties of garlic have been demonstrated by Rasmussen *et al*., 2005 and Persson *et al*., reported that the crude extract of garlic specifically inhibits 92 QS-regulated gene expressions in *P. aeruginosa and* the amounts of mRNA of neither lasI, lasR, rhlI, nor rhlR (the key components of the las and Rhl QS communication systems in *P. aeruginosa*) were notably affected by the garlic treatment.[76,77]

The essential oils (EOs) of tea tree (*Melaleuca alternifolia* [Maiden & Betche] Cheel) and rosemary (*Rosmarinus officinalis* L.) and extracts of propolis, bee pollen, and pomegranate (*P. granatum* L.) as well as resveratrol were evaluated for their QS inhibitory activities. All these samples showed a significant drop in violacein production even at the low-tested concentration; 0.125 µL/mL to rosemary, 0.25 to tea tree, 1 µL/mL to propolis, 5 µL/mL to pollen, 20 µg/mL to resveratrol, and 40 µg/mL to pomegranate extract. Their minimum QS inhibitory concentrations are 0.21, 0.21, 1.14, 8.67, 24.87, and 20.80 µL/mL, respectively. These results revealed that tea tree EO and rosemary EO showed the highest anti-QS activity, while resveratrol and pomegranate extract showed the lowest inhibitory activity.[78] Lamberte *et al*. reported that the extracts of propolis have also been proven to inhibit the production of violacein in *C. violaceum*, as well as the lasA and lasB protease activities in *P. aeruginosa*.[79]

Vattem *et al*. found that raspberry (*Rubus idaeus*), blueberry (*Vaccinium angustifolium*), and grape (*Vitis* sp.) extracts inhibited AHL activity-mediated violacein production by 60%, 42%, and 20%, respectively. Basil (*Ocimum basilicum*) had the highest activity and decreased the pigment formation by 78%. Thyme (*Thymus* sp.) and Kale (*Brassica oleracea*) decreased the pigment formation by 60% and were followed by rosemary (*R. officinalis*), ginger (*Zingiber officinale*), and turmeric (*Curcuma longa*) which decreased violacein formation by 40%. Oregano (*Origanum vulgare*) did not affect the pigment production in *C. violaceum* O26 (CVO26).[80]

Vegetables as carrot, chamomile, and water lily as well as an array of peppers have been proven to have anti-QS activity against the LuxI-gfp reporter strain.[29] Moreover, pea seedlings and root exudates are also found to inhibit pigment production, exochitinase activity, and protease activity in *C. violaceum*.[29] *Medicago truncatula*, rice, tomato, and soybean can also produce substances that mimic the activities of the AHL.[29,81]

Plant root-associated fungi such as *Phialocephala fortinii* and *Meliniomyces variabili* and an Ascomycete isolate have been found to have the ability to degrade the AHL and have been proposed as an option for diminishing the bacterial virulence.[82]

The leaves extracts of *Myoporum laetum* G. Forst., *Adhatoda vasica* Nees, and *Bauhinia purpurea* L. possessed strong QS inhibitory/AHL-mediated violacein inhibition activities, while extracts of *Piper longum* L., *T. officinale* F. H. Wigg., and *Lantana camara* L. showed moderate QS inhibitory activities.[83] The extracts of *C. erectus* L.(*Combretaceae*), *C. hypericifolia* (L.) Millsp. (Euphorbiaceae), *C. viminalis* (Sol. ex Gaertn.) G. Don (Myrtaceae), *Bucida burceras* L. (*Combretaceae*), *T. bicolor* (Mill.) Cogn. (*Melastomataceae*), and *Quercus virginiana* Mill. (*Fagaceae*) showed QS inhibition on *C. violaceum* and *A. tumefaciens*.[84]

The EOs of *Piper bredemeyeri*, *Piper bogotense*, and *Piper brachypodom* showed inhibiting QS on *C. violaceum* CV026.[85] The ethanolic extract of *Scutellaria baicalensis* Georgi was found to inhibit violacein production, a QS-regulated behavior in *C. violaceum* CV026. In addition, it was also able to inhibit QS-regulated virulence in *Pectobacterium carotovorum* subsp. *Carotovorum*.[86]

Ethanolic and methanolic extracts of *Manilkara hexandra* Roxb (Sapotaceae), and methanolic extract of *Pyrus pyrifolia* Burm (Rosaceae) seeds enhanced QS-regulated violacein production in *C. violaceum*.[87] *Vanilla planifolia* Andrews extract significantly reduced violacein production on *C. violaceum* CV026 in a concentration-dependent manner.[25]

The EOs of *Lippia alba* showed anti-QS activity through the inhibition of the QS-controlled violacein pigment production by *C. violaceum* CV026.[88]

The ethyl acetate extract and butanol fraction of *Nymphaea tetragona* (Water Lily) significantly inhibited pigment production of *C. violaceum*.[89] Oregano EO (concentration 0.0156, 0.0312,

0.0625, and 0.125 mg/mL) showed a significant anti-QS activity expressed as inhibition of violacein production by *C. violaceum*.[90]

The extracts of the Malaysian plants; *Parkia speciosa*, *Cosmos cardatus*, *Centella asiatica, Manihot esculenta* leaf sprigs, *Psophocarpus tetragonolobus*, *Polygonum minus,* and *Oenanthe javanica* were tested for their anti-QS potentials on *C. violaceum* ATCC 12472. It is noteworthy that the highest anti-QS activity was recorded by *P. minus* and *C. asiatica* extracts.[91] The extract of *Bellis perennis* showed promising anti-QS activity on *C. violaceum* CV026. It inhibited QS-regulated violacein production in *C. violaceum* ATCC 12472 and swarming motility in *P. aeruginosa* PA01.[92] *Salvadora persica* methanol extract showed inhibition of violacein production in *C. violaceum*.[93]

Conclusion

In the last few decades, many researches have been learned about the mechanisms used by bacteria to communicate and control virulence traits. New molecules and their effects on microbial virulence continue to be discovered. It is clear that the relation between QS and bacterial virulence represents a promising area from which new, effective anti-virulence drugs can emerge. The examples mentioned here demonstrate that inhibition of virulence through inhibition of QS is possible and somewhat practical. Utilization of these products could also be a more cost-effective way. However, further research is needed to determine their mechanism of action and the optimum levels of anti-QS agents that can be safely applied.

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Conflicts of interest

There are no conflicts of interest.

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