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# Quorum Sensing in *Pseudomonas aeruginosa*

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**Quorum sensing (QS) is a significant signaling regulation in bacteria. In *Pseudomona aeruginosa*, the three known QS systems, Las, Rhl and PQS have been elucidated thoroughly. However, there are many mechanisms still need to be fully understood. In this review, we present state-of-the-art research of the regulation of QS systems in *P. aeruginosa*, and discuss the potential inhibitor of QS reported by a wide range of studies.**

**Key words:** *Pseudomonas aeruginosa*; Quorum sensing; Quorum sensing inhibitor.

*Pseudomonas aeruginosa* is a versatile and ubiquitous opportunistic pathogen that causes serious nosocomial infections. Besides, *Pseudomonas aeruginosa* is also the leading cause of Gram-negative infections in immuno compromised individuals, including those suffering from cystic fibrosis[1]. Virulence factors and hydrolytic enzymes secreted by *P. aeruginosa* are coordinately regulated in cell density dependent manner, which termed as quorum sensing[2]. QS system is a type of global regulatory systems found in most microbe species, and govern diverse biological functions, such as virulence and biofilm formation[3]. Research on quorum sensing may help to develop antimicrobial agents to treat infections caused by pathogens. Among the microbes with quorum sensing system, *P. aeruginosa* is a model organism for study QS[4].The QS response is based on the accumulation of molecule signals in the extracellular medium to interact with specific transcriptional regulators, and then arise responsive downstream proteins expression[5]. The accumulated molecule signals are called autoinducers (AIs)[2]. There are three QS systems in *P. aeruginosa* distinguished by different autoinducers, Las/Rhl systems based on N-acyl-homoserine lactones and PQS system based on quinolones[6]. The overall synthetic mechanisms of three QS systems in *P. aeruginosa* will be discussed in the following paragraphs respectively.

**N-acylatedhomoserine lactones mediated Las and Rhl systems**

The autoinducer N-3-oxo-dodecanoyl-homoserine lactone (3OC12-HSL) produced by synthase LasI, can bind to its signal receptor LasR and then activate the transcription of target genes[7-9]. In cellular environment, LasRand acyl-HSL readily dissociate. After dissociation, LasR can remain in a properly folded conformation capable of reassociating with signal, but in the absence of acyl-HSL ligand, LasR can fold into an active conformation in vivo[10].Purified LasR-3C-HSL compound exists as a dimer in solution and binds tightly[11]. By using the approach of covalent attachment of a reactive mimic of the 3C-HSL to LasR, there is evidence showing that LasR is not

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distributed evenly throughout the cytoplasmic membrane but instead concentrated at the poles of the *P. aeruginosa* cell[12].

Another is the Rhl system, which is mediated by the N-butanoylhomoserine lactone (C4-HSL). The signal synthase RhlI generates C4-HSL, and then the signal can be received by the receptor RhlR, forming a compound to regulate the certain gene expressions[13-15]. C4-HSL is required for the transcription of RhlR, but unnecessary for its dimerization[16]. Gene *acp1*, one of three genes encoding acyl carrier proteins, was found behaving as substrate for RhlI in vivo[17]. Though Las system controls regulation of many virulence factors, there is evidence showing that in a *lasR* mutant, transcriptional regulator RhlR is able to overcome the absence of Las system by activating LasR controlled functions, including production of 3-oxo-C (12)-HSL[18]. Moreover, 3C-HSL and C4-HSL molecules are metalloenzymes containing two zinc ions in catalysis[19], and both can enter mammalian cells for binding of LasR and RhlR respectively[20]. Besides, research shows that acyl-HSL signals can trigger expression of a large number of acyl-HSL dependent genes regardless of growth phase[21].

**4-quinolone signals mediated PQS system**

While 4-quinolones have long been discovered as antimicrobial agent, its signaling properties was not found until recent years[22]. The signal 2-heptyl-3-hydroxy-4-quinolone, referred to as *Pseudomonas* quinolone signal, is the third intercellular signal found in *P.aeruginosa*[23]. The precursor anthranilate generated from either the kynurenine pathway or the PhnABanthranilate synthase, is converted into HHQ by PqsABCD proteins[24].PqsH catalyzes the terminal step in PQS production, by using the substrates HHQ, NADH and oxygen to generate PQS[25]. Transcriptional regulator PqsR modulates a variety of genes expression by binding with either PQS or HHQ, since the two signals are both the ligands of PqsR[26]. Under the existence of PQS, PqsR can bind the promoter pqsABCDE to induce the expression[27]. The first four genes pqsABCD are required for HHQ production, while pqsE is reported for activation of PQS-controlled virulence factors in the absence of PqsR and PQS[27, 28].Besides, there is evidence showing that a trafficking system exists in P. aeruginosa, which could package the molecule PQS into the membrane vesicles for coordinating group behavior[29].

**QS systems in regulating the production of pathogenicity factors**

P. aeruginosa secrets a number of extracellular virulence factors to cause infections in mammalian cells. Quorum sensing is one of the most important regulatory systems for the expression of traits with pathogenicity. Microarray analysis have demonstrated that the Las and Rhl QS systems controlled the transcription of over 300 genes, representing about 6% of the P. aeruginosa genome[30], including many virulence factors synthesis gene or the regulating gene. However, some results demonstrate that P. aeruginosa isolates with deficient QS system are still capable of causing infections and tend to be less susceptible to antimicrobials[31].

**Virulence factors controlled by Las and Rhl systems**

The homoserine lactones mediated Las and Rhl systems control the production of multiple virulence factors involved in acute infection and host cell damage. Elastase, exotoxin A and alkaline protease are controled by the Las system[8,32]. Protease IV expression was also shown to be regulated by the Las system in *P. aeruginosa*[33]. RhlR, which is sensed by the C4-HSL molecule, could induce the expression of several genes, including the synthase gene of rhamnolipids[14], pyocyanin[34]and elastase.Research shows that, in PA14, RhlR was found to play a critical role in counteracting the cellular immune response toward host during the early stage of infection[35].

The Las and Rhl systems could activate the expresson of H2-T6SS genes, which belong to type VI secretion systems (T6SS), and thus contribute in pathogenesis of *P. aeruginosa* in chronic infections[36]. In *lasI* and *rhlI*mutants, the expression of operon pel, which is essential for the prodution of a glucose-rich matrix exopolysaccharide, is significantly reduced[37]. Besides, there is research demonstrating that in a *lasIRrhlIR* quadruple knockout mutant in PAO1, protease and elastase level and production of pyoverdin are reduced remarkably. However, the twiching motility is unaffected; using the lung infection model in mouse, results shows that the immunogenicity, infectiveness and persistence of this mutant is similar to wild type PAO1[38].

**Rhamnolipid**

Rhamnolipids are a kind of important virulence factors secreted by *P. aeruginosa*. They are important in motility, cell-to-cell interactions, cellular differentiation and formation biofilms[39].Evidence shows that rhamnolipids are able to cripple and eliminate the host defense, causing necrotic death of polymorphonuclear leukocytes (PMNs), and thus contributing in increased tolerance of PA biofilms to PMNs[40, 41]. The production of rhamnolipids starts from RhlA, which is responsible for catalyzing the synthesis of the fatty acid dimer moiety and free 3-(3-hydroxyalkanoyloxy) alkanoic acid (HAA). Protein RhlB and RhlC then catalyze the transfer of dTDP-L-rhamnose to HAA or previously generated monorhamnolipid[42]. RhlR could activate the transcription of *rhlAB* by responding to C4-HSL molecule, and inhibit the transcription of *rhlAB* in the absence of C4-HSL[43].

**Phenazines**

Phenazines are secondary metabolites synthesized by *Pseudomonas* species and other bacteria. The precusor phenazine-1-carboxylic acid (PCA) is synthesized by two operons *phzA1B1C1D1E1F1G1* (*phzA1*) and *phzA2B2C2D2E2F2G2* (*phzA2*)[44]. Then PCA is transferred into three products: 1-hydroxy-phenazine (1-HP), pyocyanin (PYO) and phenazine-1-carboxamide (PCN) with the enzymes encoding by genes*phzH*, *phzS* and *phzM*[45, 46]. Pyocyaninis a blue, redox-active phenazine, possessing the most amounts secreted by *P. aeruginosa*. Pyocyanin is proved to be virulent to mammalian cells and related to CF[47]. Another property of phenazine is its signal molecule role in regulating in *P. aeruginosa*. Study demonstrates that in PAO1 and PA14, phenazines could regulate several genes, including resistance-nodulation-cell division (RND) efflux pump MexGHI-OpmD and redox control, and inhibit the expression of genes involved in ferric iron acquisition[48]. The *phz* operons are in the control of Rhl and PQS systems[49], as well as theGacA/S two-component system[50].

**Virulence factors controlled by PQS systems**

The PQS system has been show to control several virulence factors, including pyocyanin, elastase and lectin[51].Furthermore, transcription regulator PqsR could negatively regulate the expression of *exoS* and *exoT*, which belong to the type III secretion system in *P. aeruginosa*[5]. There is study showing thatPqsE is required for the production of secondary metabolites such as pyocyanin; besides, *pqsE* and *pqsA* are both required for the mature biofilm development[53]. Moreover, a volatile and low weight molecule, 2-amino acetophenone (2-AA) could mediate the onset and establishment of chronic infections by inhibit the expression of *pqsR*[54].

**Autoinducer mediated pathogenesis in *P. aeruginosa***

There are increasingly more research demonstrating that autoinducers: 3C-HSL, C4-HSL and quinolones play a role in arising immune responses and causing pathogenesis to mammalian cells. Evidences show that 3C-HSL specifically promotes induction of apoptosis, which may be associated with cytotoxicity induced by 3C-HSL in macrophages and neutrophils[55]. It is also found to induce proinflammatory cytokine production in airway epithelial cells by dysregulated calcium storage or signaling in CF cells[56]. Moreover, 3C-HSL is able to modulate human intestinal epithelial Caco-2 cell migration with a partner IQGAP, which further triggers essential changes in cytoskeleton network and bacterial-human cell communication[57]. Furthermore, in the presence of 3C-HSL, monocytes are negatively affected in host[58]; wound contraction was increased, myofibroblasts was changed and cyclooxygenase-2 expression was induced, which related to the inflammatory examination[59].

HSLs are secreted from biofilm in *P. aeruginosa* to enhance the growth of neighboring cells by contacting with surfaces[60]. Besides, the signal molecule OdDHL of quorum sensing can delay the onset of type I diabetes in the NOD mouse model by inhibiting the proliferation of naive T cells and differentiation of T cell subsets[61]. Moreover, HHQ and PQS produced by *P. aeruginosa* could also suppress host innate immune responses by reducing the nuclear factor-kappaB and delaying inhibition of kappaB[62]. The multidrug efflux pump MexEF-OprN could modulate quorum sensing through secretion of a signal molecule belonging to HAQ family, for which MexEF-OprN could be activated in infection without antibiotics[63]. However, C4-HSL production decreased and quorum-sensing ability was

abolished when in anaerobic condition, resulting in the suppression of secretion of many virulence factors[64].

**Regulation of QS systems in *P. aeruginosa***

The QS systems in *P. aeruginosa* could interact with each other in regulation. Among the three, Las system seems to be at the top of signaling, since LasR could activate the expression of *rhlI* and *rhlR*, as well as *pqsR* apart from modulating the downstream-regulated genes[65]. However, recent results show that RhlR could complement the phenotypes controlled by the Las system in a *lasR*mutant[18]. Additionally, RhlR is able to negatively regulate the expression of *pqsR*[66], while *pqsR*increases the expression of *rhlI*[27].

In addition to the interaction within the three QS systems, there are several modulators playing a role in regulating the QS systems in *P. aeruginosa*. The LuxR-type homologues QscRwas firstly found to regulate the expression of *lasB* and *phzA2*, which are controlled by Las/Rhl systems[67]. More up-to-date studies demonstrate that QscR regulates genes by binding to promoters that have elements similar in sequence to those found in LasR- or RhlR-dependent promoters, and requiring 3C-HSL[68]. The signal 3C-HSL generated by LasI serves as a signal molecule for QscR, in the absence of an acyl-HSL, QscR polypeptides fold properly and free QscR does not accumulate. Thus, QscR appears to be an integral component of the QS circuitry[69, 70].Though QscR responds to 3C-HSL for regulating, evidence demonstrates that QscR could also be activated by *non-P. aeruginosa* signal, such as N-deanoyl HSL (C10) and N-3-hydroxydecanoyl HSL, while the response are stronger than 3C-HSL induced[71]. The transcription regulator Vfr is a homologue of the Escherichia coli cAMP receptor protein-CRP, maintaining many residues important for CRP to bind cAMP, DNA and interact with RNA polymerase at target promoters[72].In the promoter region of *lasR*, there is a functional CRP-binding consensus sequence (CCS) for binding of Vfr, resulting in the regulation of LasR by Vfr[73].For regulating the transcription of *rhlR*, Vfr directly binds several Vfr-binding sites (VBSs) in *rhlR* promoter region, one of the VBS has a negative effect on transcription, while two of them overlap with las-box[74]. On the upstream of *lasI*, the *rsaL* gene produced protein RsaL was found to negatively modulate LasI expression by binding to its promoter region, and thus inhibits the production of 3C-HSL and dependent genes expression[75, 76]. Besides, Rsal could regulate 130 genes independent of 3C-HSL pathways[75].Recently, a negative QS regulator, quorum threshold expression element, namelyQteE, could inhibit QS by reducing LasR protein stability and decrease RhlR accumulation by blocking Rhl-mediated signaling[77]. Moreover, the protein QslA also demonstrates the similar effect as QteE and RsaL. By protein-protein interaction with LasR, QslA negatively regulate QS systems[78]. In contrast, gene PA1196 positively controls the expression of the Rhl and PQS systems, affecting bacterial motility and multiple virulence factors expression via the QS systems[79]

In *P. aeruginosa*, the central regulator RpoS is involved in the regulation of extracellular alginate, pyocyanin, exotoxin A and responsible for sensitivity of cell to environments[80].Though initial reports indicate that RpoS negatively regulates AHL QS through repression of *rhlI* expression[81], and many genes regulated by QS are also modulated by RpoS in response to stationary phase[82], the interaction of RpoS and QS systems remains unclear. Besides, probable conclusion of these two systems is that they act independently, since AHL QS is cell-density-related response and RpoS is a stationary-phase response[83].Alternative sigma factor RpoN plays an important role in regulating several metabolic functions and virulence in *P. aeruginosa*[84].Research shows that in RpoN mutant, the expression of *lasR* and *lasI* genes is elevated at low cell densities, as well as *rhlR* and *rhlI*[85]. And under certain media conditions, RpoN is a positive regulator of *rhlI* transcription[86]. Gene vqsR is a member of the LuxR family and possesses a las-box in its upstream region thus LasR could directly regulate *vqsR*. Inactivation of *vqsR* decreases the production of N-acylhomoserine lactones and the secretion of exoproducts. In the mean while, pathogenesis is also diminished for *P. aeruginosa*[87, 88].Besides, VqsR exists as a homodimer in solution and binds the promoter region of qscR with the motif of TCGCCN (8) GGCGA to regulate QS systems indirectly. However, VqsR negatively regulate QscR[89].VqsM, transcriptional regulator with an AraC-type helix-turn-helix DNA binding domain at the C-terminal of the peptide, seems to through

modulation of VqsR to regulate QS systems in *P. aeruginosa*[90].

In *P. aeruginosa*, there are a number of two-component systems in regulating. The GacA/GacS two-component regulatory system, which is responsible for regulating several secondary metabolites and virulence factors, positively regulates *lasR* and *rhlR* gene expression[91]. Besides, the responded post-transcription regulator RsmA negatively regulates the synthesis of both 3C-HSL and C4-HSL, in consistent with the result above[92]. The two-component regulatory system PprA-PprB controls the membrane permeability and antibiotic sensitivity of *P. aeruginosa*. Mutation of *pprB* induces the regulation of QS-controlled genes, and decreases the expression of *lasI*, *rhlI* and *rhlR*. Besides, PprB also could influence the sensitivity of *P. aeruginosa* to exogenous OdDHL[93]. Moreover, two-component system BqsS-BqsR could promote conversion of anthranilate to PQS and affect the production of C4-HSL, and thus modulate biofilm decay in *P. aeruginosa*[94]. Furthermore, CzcRS two-component system is found to respond to metals as zinc, cadmium and cobalt in *P. aeruginosa*. Especially, CzcR co-regulates carbeapenem antibiotic resistance by repression the expression of the OprDporin. Study demonstrates that CzcR affects the expression of many genes involved in virulence even in the absence of inducible metals. Moreover, autoinducers 3C-HSL and C4-HSL are impaired in the absence of CzcR. It is important to point out that CzcR could localize on the promoter of several regulated genes such as *oprD*, *phzA1* and *lasI*[95].

In addition, several proteins are able to regulate the production of autoinducers, for instance, 3C-HSL and C4-HSL were altered in *mvaT* mutant[96]; PtxR increases the production of 3C-HSL and reduces the expression of *rhlI*[97]; The product of PA2385 could degrase 3C-HSL[98]; In mutant of tonB1, the 3C-HSL production decreased99. Lon protease, a member of the ATP-dependent protease family, could repress the expression of LasR/LasI by degrading LasI and HSL synthase[100]; In the *oprF* mutant, production of acyl-homoserine lactone reduced and delayed, PQS production was

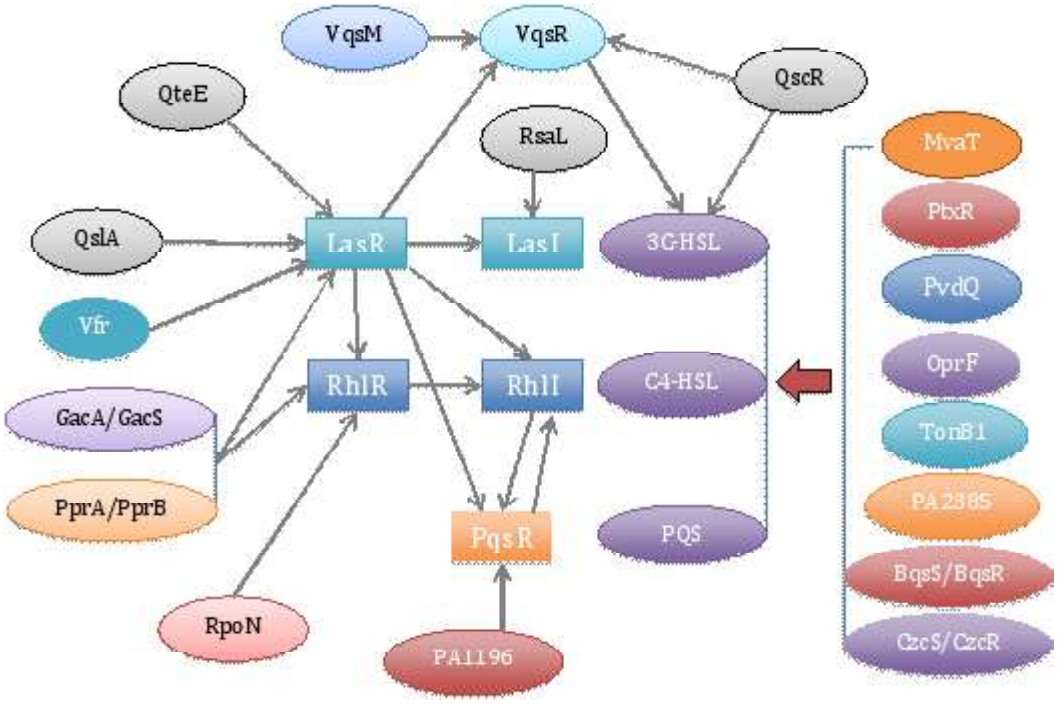


**Fig. 1.** Description of the quorum sensing modulation and related regulators in *Pseudomonas aeruginosa*. Normal arrows indicate stimulating effects and dotted arrows represent inhibitory effects. Details for all the proteins can be found in the text. The model is incomplete but shows important regulators

also decreased and HHQ accumulated[101]. Besides, PvdQ, which is involved in iron homeostasis by playing a role in the biosynthesis of pyoverdine, the major siderphore of *P. aeruginosa*, could degrade AHLs by behaving as a acylase enzyme and hydrolyzing 3C-HSL molecules[102].

**Quorum sensing as a target for therapy**

Since the arise of antibiotic resistance for recent years, the conventional treatment of inhibition growth or killing cells may be alternative by targeting at QS signaling. QS does not control processes essential for cellular survival or growth, but play an important role in causing infections caused by *P. aeruginosa*. Besides, many deficient QS signaling pathogens lost the ability to infect or cause less severe infections, also providing the possibility for developing drugs interfere with QS signaling. There are multiple approaches to develop potential drugs by interfering with QS signaling, including the known antibiotics behaving QS inhibitor property, analogs or enzymes targeting at the autoinducers and QS inhibitor found in natural plant extracts.

Though the function of antibiotics for inhibiting bacterial growth was used for over a century, another property of antibiotics for signaling was only found in recent years. Many researches show that antibiotics at sub-inhibitory concentrations could interfere with signaling, and thus regulate the production of virulence factors. Minimum-inhibitory concentrations of tobramycin and ceftazidime were associated with reduced C4-HSL. Besides, sub-MIC concentrations of tobramycin could also reduce 3C-HSL[103]. DNA microarrays and RT-PCR method also support the finding that azithromycin, ceftazidime and ciprofloxacin under sub-inhibitory concentrations decrease the expression of QS-controlled virulence factors by influencing the flux of 3C-HSL[104].Further study elucidates that the low concentrations of azithromycin decreases the expression of most N-acyl homoserine lactone (AHL) synthesis enzymes upstream of *lasI* and *rhlI*, and thus reduces the production of AHLs[105]. Besides the effect of azithromycin on AHLs, at sub-MIC concentrations, it also significantly inhibits the swimming, swarming and twitching motilities, and biofilm formation in vivo. However, whether theses phenotypes changes interfere with QS are still unknown[106].

Quorum quenching ability is identified in several natural or synthetic compounds. Many of them are found to target at the autoinducers to block quorum sensing. Synthetic furanones could decrease the pathogenesis of *P. aeruginosa*, accelerate lung bacterial clearance by interfering with N-acyl homoserine lactone, and thus suppressing QS signaling[107].Enzymes has autoinducer degrading ability is another approach for development of QS inhibitors. For instance, a novel hydrolase derived from the soil metagenome, designed as BpiB05, targets on N-acyl-homoserine lactones, could reduce the QS-controlled phenotypes, such as motility, pyocyanin synthesis and biofilm formation in *P. aeruginosa*[108].Synthetic analogs of autoinducer are also approaches to block QS. For instance, N-octanoylcyclopentylamide (C8-CPA) was found to inhibit QS moderately, and synthesized analog of C8-CPA, N-decanolycyclopentylamide (C10-CPA) could inhibit the expression of lasB and *rhlI*, as well as the production of virulence factors. Besides, C10-CPA could also inhibit the induction of both *lasI* and *rhlA* via their autoinducers respectively[109].Another example is the 3C-HSL synthetic analogs, which substituting the head part of 3C-HSL with different aromatic rings, show good inhibition effects on LasR activity in the in vivo bioassay[110]. In addition, a set of AI-2 analogs with small incremental changes in alkyl substitution on C-2, which demonstrates the agonistic and antagonistic potential as QS attenuators in *P. aeruginosa*[111]. There are also analogs targeting at PQS system, whose signaling depends on the PQS, which is synthesed by anthranilic acid (AA). Analogs of AA are able to specifically inhibited HAQ biosynthesis and disrupted PqsR-dependent gene expression. Besides, the compounds restrict the systemic dissemination of *P. aeruginosa* and morality in mice, without pertubing bacterial viability and inhibitiedosmoprotection[112].

Recently, the quorum sensing inhibitors found from natural plant extracts have become a novel and effect approach. Preliminary research found that garlic extract had specificity for QS-controlled virulence genes in *P. aeruginosa* and reduced the biofilm tolerance to tobramycin treatment[113]. Further study shows that the decreased pathogenesis exposure to garlic extracts due to the inhibition of QS[114]; More recent results indicate the primary functional part of garlic to be ajoene, a sulfur-containg compound with potential as an

anti-pathogenic drug[115]. Apart from garlic extracts, ginseng was also identified to suppress the production of LasA and LasB, as well as negatively regulated the synthesis of AHL molecules without affecting the growth of *P. aeruginosa*[116].Moreover six sesquiterpene lactones (SLs) of the goyazensolide and isogoyazensolide-type isolated from the Argentine herb Centratherumpunctatum were evaluated for the ability to inhibit virulence factors of *P. aeruginosa* ATCC 27853, such as biofilm formation, elastase activity and production of AHLs[117].14-alpha-lipoyl andrographolide (AL-1), a derivate of Andrographolide extracted from a herb, inhibit biofilm formation and increase the sensitivity of *P. aeruginosa* to a varity of antibiotics. Further studies shows that AL-1 could repress the transcriptional level of QS-regulated genes and reduce the expression levels of *lasR*, *lasI*, *rhlR* and *rhlI* in a dose-dependent manner[118]. A variety of compounds are able to inhibit QS controlled phenotypes, for instance, Gamma-aminobutyric acid (GABA) synthesized by Psudomonas fluorescent reduced the cytotoxicity and virulence of PAO1 while not affecting its growth[119]; Caffeine was also identified for inhibiting AHLs production and swarming of *P. aeruginosa*[120]; And eugenol, the major constituent of clove extract, inhibited the production of virulence factors, including violacein, elastase, pyocyanin and biofilm formation in *P. aeruginosa* when at a sub-inhibitory concentrations. However, the detail mechanisms of these compounds still needs to be investigated[121].

## CONCLUSION

Plenty of work has focused on the quorum sensing signaling. In this review, we discussed the quorum sensing systems in *P. aeruginosa*, which is an opportunistic pathogen causing serious infections in immunocompromised patients. Despite the fact that the pathogenesis and regulation of QS systems are studied numerously, details mechanisms still need to be fully elucidated. Furthermore, targeting of QS for developing drugs becomes a novel approach as compare to traditional antibiotics searching, and it is urgent to screen out new compounds targeting at QS since the antibiotic resistance is constantly arising.

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