Quorum sensing intervened bacterial signaling: Pursuit of its cognizance and repression

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Abstract

Bacteria communicate within a system by means of a density dependent mechanism known as quorum sensing which regulate the metabolic and behavioral activities of a bacterial community. This sort of interaction occurs through a dialect of chemical signals called as autoinducers synthesized by bacteria. Bacterial quorum sensing occurs through various complex pathways depending upon specious diversity. Therefore the cognizance of quorum sensing mechanism will enable the regulation and thereby constrain bacterial communication. Inhibition strategies of quorum sensing are collectively called as quorum quenching; through which bacteria are incapacitated of its interaction with each other. Many virulence mechanism such as sporulation, biofilm formation, toxin production can be blocked by quorum quenching. Usually quorum quenching mechanisms can be broadly classified into enzymatic methods and non-enzymatic methods. Substantial understanding of bacterial communication and its inhibition enhances the development of novel antibacterial therapeutic drugs. In this review we have discussed the types and mechanisms of quorum sensing and various methods to inhibit and regulate density dependent bacterial communication.

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1. Introduction

Communication stands crucial in progress of a fraternity and it’s observed that bacteria too communicate with each, which is collectively called as Quorum sensing. This is a density dependent mechanism where communication is mediated by signaling molecules termed as autoinducers; it assists bacterial community to coordinate and work as a single unit in a population [1–3]. Numerous bacterial functions such as secondary metabolism production, sporulation, biofilm formation and symbiosis are regulated by quorum sensing mechanism [4,5]. All bacterial quorum sensing systems fulfills three basic precepts i. Concentration dependent response to autoinducers; where autoinducers are secreted outside the cell and later inflexed depending on autoinducer concentration [6,7], ii. Bacteria consists specialized receptors in its cell membrane or in cytoplasm that sense and respond to concentration of autoinducer, iii. Detection of autoinducers by receptors recommence quorum sensing loop thereby bacterial virulence [8,9]. Quorum sensing was first observed in a gram negative marine bacteria Vibrio fischeri [10] as studies showed that phenotype bioluminescence was regulated by quorum sensing machinery [11,12]. Since then many bacteria have been successfully scrutinized for their quorum sensing ability. Understanding of quorum sensing open up possibilities of regulating bacterial virulence as far as the immense role of quorum sensing upon it is concerned [13]. Recently studies have been carried out to down regulate bacterial quorum sensing and this strategy is collectively called quorum quenching [14,15]. Inhibiting communication of a bacterial population disables them to initiate most of its virulence activity which help host for an effective immunological clearance. In this review we discuss about the types and mechanisms of quorum sensing and different approaches of quorum quenching through which bacterial communication can be inhibited.

2. Autoinducers: alphabets of bacterial dialect

Specialized signaling molecule; autoinducers play a key role in quorum sensing and consequently considered as alphabets of bacterial language. Autoinducers are studied under three different classes based on their structure and specific function; they are AHLs (Acyl Homoserine Lactones), AIP (Autoinducing Peptides) and Autoinducer-2 (AI-2) [16]. AHLs are small diffusible molecules with a core lactone ring and acyl side chain which is responsible for facilitating signaling in gram negative bacteria [17]. Quorum sensing in gram positive bacteria are found to be mediated by AIPs which are short peptide chains synthesized in cell. AIP lack free transportation across the cell membrane hence requires specialized membrane transport proteins [18,19]. AI-2 are furonone derived signaling molecules found functioning in both gram negative and gram positive bacteria [20] also exhibit features of both AHLs and AIPs [21]. Signaling molecules are produced inside the bacterial cells which will be processed internally or externally hinge upon the organism. Despite of their functional and structural differences, autoinducers possess certain common characteristics such as high degree of receptor specificity and transport across cell membrane which may be active or passive.

3. AHL mediated bacterial communication

AHL mediated quorum sensing is intensely studied in gram negative bacteria that constitutes maximum pathogenic strains in it. Numerous virulence factors in gram negative bacteria such as bacterial adhesion, biofilm formation, exoyme secretion, pigment production are regulated by N-Acyl homoserine lactone(AHL) dependent quorum sensing [22,23]. Typical quorum sensing system in gram negative bacteria contains two integrant; an autoinducer synthase which is responsible to synthesize AHLs [24,25] and an autoinducer receptor cum transcriptional activator [26]. AHL mediated signaling is highly intra-specious specific due to peculiar receptor binding sites that recognize only precise AHLs [27–29] thus signals produced by one specious will not disturb the communication mechanism of other [30,31]. Modification in AHL structure is accomplished by varying number of Carbon and modification upon R-group [32] which gives advantage to bacteria in an endosymbiont environment. Some important signaling systems mediated by AHLs are discussed here.

3.1. LuxIR: typical gram negative bacterial quorum sensing system

LuxIR quorum sensing circuit stands archetypal of gram negative bacterial communication (Fig. 1) as over hundred gram negative bacterial strains communicate by the engagement of LuxIR homologues genes [33]. SmaIR in Serratia marcescens [34,35], CviIR in Chromobacterium violaceum [36,37], hanIR in Halomonas anti- cariensis [38] and TraIR of Agrobacterium tumefaciens [39] all work based on the principle of LuxIR but with slight variations in AHLs. This is the first studied bacterial linguistics model and was discovered in marine bioluminescence bacteria Vibrio harveyi which is capable to lead a free and symbiotic lifestyle [40]. This system is based in the reactions mediated by LuxI and LuxR. LuxI is an autoinducer synthase that catalyze the interaction between S-adenosylmethionine and acyl carrier protein which leads into the formation of N-(3-Oxohexanoyl)-l-homoserine lactone which subsequently functions as autoinducer [25,41,42]. AHL will be dispersed out of cell until a specific threshold level is attained. In high external concentrations, AHL will be taken back into the cell which sequentially interact with LuxR. If not bound with AHL, in free state LuxR will be degraded inside bacterial cell, whereas after forming LuxR-AHL complex it will be capped from degrading [43]. LuxR-AHL complex binds upon Lux promoter region that initiate bioluminescence and other quorum sensing regulated functions [44,45].

3.2. LasIR-RhlIR: overlapping quorum sensing system

LasIR-RhlIR is serially arranged overlapping quorum sensing circuits observed in Pseudomonas aeruginosa where LasIR and RhlIR are arranged one after other in a series (Fig. 2) [46,47]. *Pseudomonas aeruginosa* is a widely observed human opportunistic pathogen which is mainly concerned with nosocomial infections upon patients suffering from Cancer, AIDS and cystic fibrosis [48,49]. It produces virulent factors such as elastase, protease, exotoxin A that collectively cause serious tissue damage in mammals.
Such mechanisms are found to be controlled by Quorum sensing circuits [51].

Signaling is initiated by the production of AHL (3OC12-homoserine lactone) by LasI which act as a homologous of LuxI [52]. AHL will be diffused out of the cell and in high concentration it will be in taken and binds with LasR. Numerous activities such as production of elastase, protease and exotoxins are triggered by LasR-AHL complex [53]. Other than triggering this virulence factor production LasR-AHL also initiate the second system RhlR [54]. As a result RhlI produce a secondary AHL (C4-homoserine lactone) that binds with RhlR resulting in the production of subsequent products such as sidophores and pyocyanin [55,56]. All Quorum
sensing controlled mechanism in *Pseudomonas aeruginosa* is regulated by any one circuit but immense overlap between this systems are noted [57,58] which enables to carry on virulence by any one system [59].

3.3. ExpIR: virulence down regulating quorum sensing system

ExpIR mediated quorum sensing is observed in opportunistic plant pathogen *Erwinia carotovora* (Fig. 3) that frequently causes soft rot in plants [60]. Study of Exp IR system have lot of economic importance on it as soft rot disease affect lot of economic crop plants such as potato, carrot, pineapple, cucumber, onion. It is also observed that Exp IR also regulate synthesis of antibiotics such as carbapenem β-lactum which give dominance to the bacteria to survive in a high bacterial diverse rhizosphere [61].

Exp circuit is initiated by the production of OHHL by Exp I. Unlike other QS systems the virulence factors of bacteria *Erwina carotovora* is such as pectate lyase, pectin lyases, cellulases and proteases are positively influenced by the OHHL alone [62] OHHL also triggers the action of Exp R by forming conjugated complex but Exp R have no significant role in bacterial virulence in fact it is found decreasing exozyme production by bacteria [63]. This stand in contrast to many other bacterial virulence mechanism whereas virulence is triggered by regulatory protein not directly by AHL. The difference possessed by Exp IR system found to help bacteria against host defense mechanism [64]. Exp R bind with low density of AHL would produce only less exozyme hence low level of effect; this indeed provokes host defense mechanism which challenges the existence of bacteria. Where as in *Erwinia carotovora* ExpR neutralizes the low AHL density which inhibits the production of exozyme. Therefore exozymes will be produced only in high level of OHHL.

### 4. Peptide mediated bacterial communication

The signaling in gram positive bacteria are controlled by Oligopeptide which is commonly referred as autoinducer peptides [AIPs] [65]. AIPs are produced inside the bacterial cell as pro-AIP which will be processed and modified inside or outside the cell hinge upon the organism [66]. Unlike AHL signaling molecule AIP's are impermeable to cell membrane hence requires specialized transport proteins for the inward and outward carriage of AIP's [67]. This transport of AIP's are generally accomplished by cell membrane bound sensor kinases [68]. Competence mechanism such as sporulation in *Bacillus subtilis* virulence initiation by *Staphylococcus aureus*, *Listeria monocytogenes*, *Clostridium perfringens*, *Enterococcus faecalis* are regulated by Quorum sensing systems [69–73]. Even though gram positive Quorum sensing circuits have a general resemblance some small variation in mechanism is observed depending on specious and living environment which is discussed here

#### 4.1. Two component system in gram positive bacteria

Most of the gram positive bacterial linguistics are depending upon membrane bound two component system that identify signaling molecule autoinducer peptides (Fig. 4) [74,75]. A classic example for two component quorum sensing system is found in *Staphylococcus aureus* [76]. This is a nosocomial pathogen which is normally concerned with skin infection if neglected leads to bacteremia and sepsis [77].

Virulence and communication of this bacteria is regulated by Arg locus which is a combination of two transcripts RNA II and RNA III [78]. Pro-AIP will be produced by ArgD one among the four component of Quorum sensing system. Pro-AIP will be processed and modified by Arg B after which it will be transported out by

![Fig. 3. ExpIR mediated signaling in *Erwinia carotovora* which is homologues to LuxIR signaling circuit.](image-url)
During the course of modification pro-AIP that of 47 amino acid residue will be derived to 9 residue peptide. In high bacterial density, AIP will accumulate extra cellular environment and attain a certain threshold level. In this stage Arg C; a trans membrane protein will get activated which in turn bind with AIP [80]. Agr C is a histidine kinase which phosphorylate by the combination of AIP. Hence available phosphate group interacts with Agr A which is the response regulator [81]. Agr C and Agr A together constitute two component system. Activation of Agr C - Agr A activates the transportation of RNA II which continues the quorum sensing circuit and RNA III that is responsible for virulence [82].

4.2. Extracellular protease processed AIP quorum sensing circuit

In some gram positive bacteria processing of pro AIP is done in the external environment of bacterial cell by extracellular protease enzymes after which AIP will be transported back to cell for regulating transcription (Fig. 5) [83]. Many virulent factors like sporulation and enzyme production in Bacillus cereus, plasmid transfer in Enterococcus faecalis are regulated by such mechanism [84,85].

Quorum sensing circuit in Bacillus cereus is a significant example for extracellular protease processed AIPs. A 48 amino acid long pap R intercellular pro-AIP is been produced by pap R gene. An amino terminal signaling peptide present in pro-AIP will initiate a secretory pathway due to which PRO-AIP is been taken out of bacterial cells and will be processed by an extracellular protease into an active AIP [86,87]. Once the concentration of processed AIP reach a threshold level it will be transported inside bacterial cell by oligopeptide permease trans membrane protein [88]. It is observed that only processed pap R could interact with oligopeptide permease system whereas during the process pro -AIP will be degraded into peptides of 5, 7, 8 and 11. This is because of the specific activity of Intercellular transcription regulator plc R upon pentapeptide and heptapeptide [89]. Interaction of AIP on transcription factor plc R brings conformational changes and initiate plc R oligomerization which subsequently induces production of virulence factors [90].

4.3. Competitive quorum-sensing system

In this type of Quorum sensing; network of different phenotype would antagonize each other based upon the desired lifestyle of bacteria [46]. This is moreover a combination of other two above mentioned systems. Bacillus subtilis stands as a perfect example of such signaling circuits (Fig. 6). In this bacteria signaling system of competence and sporulation influence each other based on necessity. Competence in bacteria is controlled by Com X peptide which is a ten amino acid [91] sized and processed and secreted by Com Q [92]. In high density: Com X is identified by an histidine kinase Com P that initiate formation of Com X - Com P complex which eventually trigger autophosphorylation that enable Com A to consume a phosphate group [93]. Com A is a DNA binding response regulator that initiate numerous competence mechanism [94].

In other hand this bacteria also produce another oligopeptide by gene phr C and called as CSF (competence and sporulation factor). From cytoplasm CSF is effluxed out by transmembrane proteins [95]. In optimum threshold level CSF is taken back into the bacterial cell by by oligopeptide permease [96]. Internalized CSF have two positive fates depending upon its internal concentrations. In low concentrations CSF bind with cytoplasmic protein Rap C and promote bacterial competence [97]. Rap C protein in free state disturbs Com A hence bacterial competence. Therefore CPS-Rap C complex leads to smooth regulation of bacterial competence. In the high internal concentration level CSF form a complex with

![Fig. 4. Agr circuit depended two component quorum sensing system is found in Staphylococcus aureus.](image-url)
Rap B protein hence induce sporulation [98]. In free state Rap B block sporulation by phosphorylation of SPOOF gene which is responsible for sporulation [99]. Complex formation between CSF-Rap B also ensures the availability of Rap C to inhibit competence.

5. Bacterial silencing: taking antibacterial strategy to a new dimension

The mechanism through which bacteria are made “silent” by blocking quorum sensing system is called as quorum quenching.
In this era of antibiotic depletion world is searching for new remedies against bacterial infections. Quorum sensing targeted antibacterial therapy has evolved new revolution in this field. Suppression of Quorum quenching have immense value in clearing bacterial infections such as chronic lung infections in CF patients, severe wound infection [100,101]. Quorum sensing targeting drugs basically does not killing the bacteria but it is only attenuating bacterial virulence [102] and offers additional time to host defense mechanism that effect in better immunological clearance of pathogen. Quorum sensing circuit targeted treatment against *Staphylococcus aureus* [103], *Pseudomonas aeruginosa* [104], *Vibrio cholera* [105] were successful and comprehensive. Not only in pharmacological field but agriculture, aqua culture, industries are also found benefited by quorum quenching. There are many strategies which can be relied for blocking bacterial communication which is generally classified as enzymatic and non-enzymatic quorum quenching methods. There are many techniques to find appropriate quorum quencher such as cross streak assay, disc diffusion method, overlay assay, metagenomic analysis, microarray based screening. The choice of technique vary with the requirement. In this part we discuss some important quorum quenching methods and its applications.

6. Enzymatic quorum quenching

Enzymatic quorum quenching is concerned with altering conformation and structure of signaling molecule which eventually block bacterial communication. These quorum quenching enzymes are mostly derived from microorganisms which is found to give benefit to the producer in a competitive environment [106,107]. This hypothesis of bacterial benefit by producing quorum quenching enzymes are based on the discovery co-existence between quorum sensing and quorum quenching bacteria [108,109]. Four different types of chemical reactions are observed behind enzymatic quorum sensing they are decarboxylation, deamination acylase and lactonase activity [110]. So far enzymes those found degrading signal molecules are studied under three categories which is constituted by lactonase enzymes, acylase enzymes and oxydoreductase enzymes.

6.1. Lactonase mediated quorum quenching

AHL lactonases hydrolyze lactonase ring of the signaling molecules due to which opened ring structure will be formed (Fig. 7). It is also observed that lactonase enzyme doesn’t disturb anything other than lactone ring. [111,112]. It was believed that enzyme hydrolyze amide linkage between lactone and acyl side chain but recent studies on structure and function proved that ester link is affected. Based on phylogeny lactonase belongs to metallo-beta-lactonase superfamily and phosphotriesterase family among which maximum candidates belong to metallo-beta-lactamase superfamily [113,114]. AHL lactonase are extensively produced by bacteria those have no phylogenetic relation suggests that enzyme production is not dependent upon taxonomic classification. First analyzed bacterial AHL-lactonase is AiiA24B1, a product of aiiA gene possessed by *Bacillus* sp. 24B1 [115]. Since then many bacteria were found producing AHL lactonases which is homologous of AiiA [116]. A thermostable lactonase enzyme namely GKL was obtained from *Geobacillus kaustophilus* which belonged to phosphotriesterase family and showed relatively low paraoxonase activity suggesting its non-involvement of phosphate ester as substrate [117]. *Geobacillus stearothermophilus* was observed to produce low

![Fig. 7. Structural modification by the hydrolase action of lactonase which disables bacterial signaling.](image-url)
catalytic enzyme but with high thermo stability [118]. Ther-
mostable lactonase enzyme were also produced by Geobacillus cal-
doxylosilyticus YS-8 and Geobacillus kaustophilus HTA426 [119,120].
It was also evident that some bacterial strains produce lac-
tonase enzyme that show major deviation from aiiA gene product.
For instance, AiiM lactonase enzyme was obtained from Agrobac-
terium tumefaciens [121] AiiD of Arthrobacter, Ochrobactrum pro-
duced Aid H AiiM of Microbacterium testaceum, Qsd A of Rhodococcus [122–125] all were examples of lactonases that showed deviation from aiiA. It was believed that AiiA hydrolyze amide linkage between lactone and acyl side chain but recent studies on structure and function of AiiM proved that ester link is the one got attacked by enzyme. Crystal structure of AiiA suggested that there are two \( Zn^{2+} \) ions present in active center and these metal ions are very much essential for the catalytic activity and folding of enzyme [126]. Analysis on lactonase from Bacillus thuringiensis indicated that Zn1 binds to His 104, His 106 and His 109 however Z2 binds up on Asp 108, His 109 and His 235 [127] substitution of di-zinc by di-cobalt, di-manganese and di-
cadmium suppressed the lactonase activity which proves the role of Zn ion in enzyme activity [128].

6.2. Acylase mediated quorum quenching

Acylase are the group of quorum sensing enzyme that hydro-
lyze amide bond between homoserine lactone and acyl side chain (Fig. 8) [129]. Major number of identified AHL acylases belong to Ntn Hydrolase superfamily and are classified into two clusters referred as AAC and Qui P cluster [130]. These two cluster differ in their substrate specificity whereas AAC specifically degrade AHL’s longer than C8-HSL however Qui P cluster have a varying range of catalytic activity [131] initial reports of acylase enzyme was by gram negative bacterium Variovorax paradoxus that effi-
ciently degraded AHL in growth media [129]. Till date many bacte-
rial strains have been studied for its production of acylase enzyme. Gram positive Streptomyces Sp. was found producing acylase enzyme. This stand first such example for gram positive bacteria [132] AiiD from Raistronia sp. XJ128 effectively degraded short and long AHLs. Actinoplanes utahensis and Brevundimonas diminuta produced acylase those with high similarities to Raistronia acylase [133] acylase in substrate selection. Bacterial strain Pseudomonas syringae strain B728a were immensely studied for the ability to produce two acylase namely Hac A and Hac B [134]. Many other bacteria such as Sheewanella sp. [135] Tenacibaculum maritimum [136], Comamonas testosterone [137] were also able to produce acyl-
ase. From the structural analysis it was observed that acylase enzyme is composed of two or more sub units. Amino acid sequence usually consists of four domains those are signal peptide, Alpha-subunit, Linear spacer and Beta-subunit [138]. Pro acylase enzyme is not functional and it will be converted to activate enzyme by proteolysis.

6.3. Oxidoreductase mediated quorum quenching

Oxidreducatase mediated Quorum quenching is targeting signal receptor specificity towards AHL signals. This enzymes modify the chemical structure of AHLs that disable them to interact with receptor and hence blocking signaling pathway (Fig. 9) such reports were first observed in Rhodococcus erythropolis [139]. AHL oxidoreductase obtained from Bacillus megaterium found oxidising \( -1,2,3 \) carbons of acyl chain [140]. There are not much reports obtained about oxidoreductases but NADH-dependent BpiBoa enzyme [141] obtained from Burkholderia GG4 give great hope to carry on more intense study in the possibility of structural remodeling of AHL signal molecules.

![Fig. 8. Structural modification by the hydrolase action of acylase because of which quorum sensing circuit is compromised.](image-url)
7. Non enzymatic quorum quenching

This is a widely used quorum quenching method now a day. Basic principle of this mechanism is to block communication signals rather than degrading it. Blocking of signaling molecules are generally done by competitive inhibition or by structural modification [142]. However quorum sensing antagonistic molecules either bind with signal receptors which enable the interaction of receptor-signal molecule or bind with signaling molecule which disable them to interact with receptors. In the present study, some of the non-enzymatic quorum quenching components have been discussed.

One among the popular strategy is using prokaryotic byproducts to regulate the quorum se mechanism in a quorum sensing bacterial strain. Numerous reports of bacterial byproducts to be a quorum quencher have been postulated. Isobutyramide and 3-methyl-N-(2-phenylethyl)-butyramide produced by *Halobacillus salinus* was able to target Lux system of *Vibrio harveyi* [143] in the same way *Bacillus cereus* strain D28 effectively inhibited AHL mediated quorum sensing in *Chromobacterium violaceum* [144]. Toxin production in *Staphylococcus* Sp. found successfully reduced by cyclic dipeptides produced by *Lactobacillus reuteri* [145]. Yayurea A and B purified from gram positive bacteria *Staphylococcus delphini* showed its action against QS mediated mechanisms such as pigment production, bioluminance and biofilm formation [146]. CvIIR gene found inhibited by Cis-9-octadecenoic acid produced by unusual bacteria *Stenotrophomonas maltophilia* BJ01 which was isolated from rhizosphere [147]. In the same way many reports of Cynobacterial products inhibited bacterial quorum sensing. One well studied blue green algae for quorum quenching is *Blennothrix cantharidosmum* due to its abundance production of tumonic acids (E, F, G and G). These compounds were effective in regulating bioluminescence in *Vibrio harveyi* [148]. *Lyngbya majuscula* has evolved a strong individual and it was found that chemical components like lyngbic acid, lyngbyoic acid, Malynolide, Pitinoic acid and peptides as microcolins which was produced by them have shown quorum sensing antagonistic action [149–151]. *Leptolyngbya crosbyana* found producing Honauins that showed inhibition of quorum sensing mediated bacterial communication [152].

In this post antibiotic era fungal metabolites have evolved as important quorum quenching tools. An early report of fungal metabolites that block bacterial communication was by patulin and penicillic acid which were produced by *Penicillium coprobium* and *Penicillium radicicola* respectively. This extracts found very effective in blocking quorum sensing of *Pseudomonas aeruginosa*. In vivo studies conducted in mouse models indicated that there were rapid clearance of pathogens which was treated with patulin compared with the placebo group [153]. Later the quorum quenching antagonistic action of a sesquiterpine farnesol extracted from *Candida albicans* was reported. Addition of farnesol as well as co-culture with fungal strain decreased the pyocyanin production, a quorum sensing controlled system in *Pseudomonas aeruginosa*. This report suggests the advantage of quorum quenching organism in an ecosystem [154]. A secondary fungal metabolic ambuic acid purified from fungal strain KAP-21 was reported very efficient against quorum sensing in gram positive bacterial strains where it inhibited the quorum-sensing-mediated gelatinase production without influencing the growth of *Enterococcus faecalis* also targeted the biosynthesis of a cyclic peptide quormone called gelatinase biosynthesis-activating pheromone. Furthermore, ambuic acid also inhibited the biosynthesis of the cyclic peptide quorrones of *Staphylococcus aureus* and *Listeria innocua*. These results...
suggest the potential use of ambic acid as a lead compound of anti-pathogenic drugs that target the quorum sensing- mediated virulence expression of gram-positive bacteria [155].

Aspergillus sp produced Kojic acid that inhibited quorum sensing dependent biofilm formation by regulating Lux system. Kojic acid inhibited formation of microbial communities on glass slides, decreasing the densities of bacteria this study suggests that natural products with quorum sensing inhibitory properties can be used for controlling biofouling communities [156]. Polyhydroxyanthraquinones purified from distinct red guttates of the endophytic fungus Penicillium restrictum efficiently inhibited quorum sensing in clinical isolate of Methicillin-resistant Staphylococcus aureus (MRSA) [157]. Recent studies on marine endosymbiotic fungi revealed the quorum quenching activity of four different genera Sarocladium, Fusarium, Epicoccum, and Khusdia. These strains proved an abundant source of novel secondary metabolites against bacterial quorum sensing [158].

There have been some reports of quorum quenching by some invertebrate animals such as Molluscs, Arthropods and Annelida. First among them is honey a product by honey bee that efficiently reduced bacterial communication. Honey was found antagonizing LasR and RhlR quorum sensing systems [159,160]. Another report says the efficacy of solenopsin A produced by fire ant that effectively regulated rhl circuits [161]. LuxR signaling was greatly influenced by byproducts of Annelids and Molluscs as cerembranchoids from Pseudoplexaura flagellosa and exadates from Caenohabditis elegans showed anti quorum sensing action [162,163]. Add on to these Poriferans also had some great deal in neutralizing bacterial quorum sensing. Luffaria variabilis inhibited the action of Lux regulatory proteins by its metabolite secomanoalide [164] and hymenialdisin an alkaloid produced by Hymeniacidon aldis also had inhibitory effect on LuxL and LasR proteins [156].

Since the ancient medical era plants and plant products have contributed a lot against disease and infections. In the same way many plant products were found antagonizing bacterial communication. L-Canavanine obtained from Medicago sativa influenced ExpR and CviR [165] and thereby suppressed the biofilm formation of pathogens. 2,5-di-O-galloyl-d-Hamamelose obtained from Hamamamellis virginiana which is commonly called as witch hazel and obacunone from grapes possessed ability to inhibit quorum sensing [166]. CviR and RhlR controlled quorum sensing was inhibited by plant derivatives Benzopyran and Catchain [167]. Malabaricorne C purified from Myristica cinnamomea as well as Curcumin from Curcuma longa regulated quorum sensing dependent biofilm development [168,169]. Along with this, many other several macromolecules such as chitosan is also found to have high degree of quorum quenching ability [170,171]. This recent observation could open up new dimensions of quorum quenching studies.

8. Significance and future aspects of quorum quenching mediated bacterial silencing

Strategy of quorum quenching is widely employed in various fields as a powerful weapon against bacterial caused misfortunes. In agricultural field a great loss is being occurred due to the pathogenic action of bacteria. Quorum quenching has been effectively applied to remediate such issues, among them a major breakthrough have been reported against soft rot disease [172,173]. The disease can be controlled either by introducing a gene into plants whose products block AHL synthesis or by the employment of AHL degrading bacteria [174,175]. Transgenic plants that express AiiA lacconase were pretty much effective against infection by Pectobacterium carotovorum [111]. Despite achieving this successful hypothesis, the less acceptability of transgenic food around the globe limits this method. Biofouling has grown as a major concern over years which accumulates the microorganisms on the surfaces those are in contact with water [176]. Quorum quenching agents can be successfully employed to reduce bacterial reduce biofouling [177].

In pharmacology, quorum quenching compounds have initialized a new aeon of antibacterial treatment. The main principle behind this strategy is the down regulation of quorum sensing which mediates virulence factor production by quorum quenching [178]. Many Quorum quenching compounds have been experimented for its pharmacological activity either by blocking AHL signal or by degrading AHL signals. It is observed that enzymatic quorum quencher could be of great significance in antibacterial therapy as they inactivate signaling molecule without messing with bacterial metabolism [179]. It is also observed that database of quorum quenching molecules for different bacteria are available which could aid the future research in this field. Databases such as Quorumpeps [180] which deliberately explains about quorum quenching peptides and Sigmol [181] that contains data of prokaryotic are perfect examples of quorum quenching databases. Even though numerous studies are emerging about quorum quenching molecules as antibacterial drugs, much of the component haven’t reached clinical level due to their low biocompatibility. Thus the discovery of novel quorum quenching component without toxic effects could pave the way towards new pastures of antibacterial therapy.

9. Conclusions

Quorum sensing is a bacterial density depended mechanism which regulate virulence. It is controlled by signalling molecules termed as autoinducers. It is evident that by manipulating the signalling circuit of bacterial communication it is possible to attenuate pathogen.

Conflict of interest

We declare ‘no conflict of interest’.

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