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Recent developments in social network disruption approaches to manage bacterial plant diseases

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ABSTRACT

Biotic stresses are one of the major constraints to enhance the agricultural production. Among various biotic stresses, bacterial plant pathogens are often difficult to manage. Further, development of antibiotics resistance in these pathogens led to the emergence of more virulent multidrug resistant strains and hence the management of bacterial pathogens manifolds complex. To counter these pathogens, integration of conventional management practices with modern strategies have emerged as an attractive alternative in mitigating biotic stresses in plants. The community behaviour of bacterial pathogen has revealed the importance of quorum sensing network to communicate among population for effective strategies such as development of antibiotic resistance, phenotypic response including bioluminescence, biofilm formation, biosynthesis of secondary metabolites and even display of virulence. Several plant pathogens including *Pantoea*, *Erwinia*, *Ralstonia* and *Agrobacterium* rely on this social network during their attack on the host plants and cause infections. Therefore, targeting quorum sensing cascade through quorum quenching which is known to impose low evolutionary pressure on the bacterial population, can be an effective alternative. It involves enzyme mediated targeting of network associate molecules known as signals (QS) through the application of QS inhibitors (QSI) and lytic enzymes. Simultaneously, recent development in CRISPR-Cas system has been used to modify the receptors of susceptible host plant during interaction of bacterial pathogen's signalling molecules during infection. Here, in this review, we have discussed the basics of social network and how it can be targeted using their inhibitors and gene editing approaches to mitigate bacterial diseases in plants.

1. Introduction

To continuously feed the growing human population several methods of increasing crop yield have been explored (Edgerton, 2009). One of the major obstacles in enhancing the crop productivity is plant diseases caused by fungi, bacteria, viruses and virus like pathogens. The plant diseases severally affect the quantity as well the quality of the produce and are reported to cause 9.7–15.7% losses (Pinstrup-Andersen, 2001; Savary et al., 2012). Among different plant pathogens, the management of bacterial pathogens is extremely difficult due to the development of antibiotic resistance and emergence of highly virulent strains (McManus and Stockwell, 2001; Arwiyanto, 2014; Sundin et al., 2016). Therefore, understanding the pathogenesis, population behaviour of the pathogens and mechanisms of disease development can help in formulating effective strategies (DunChun et al., 2016).

Cell to cell communication is a part of functioning and development of an organism as well as its interaction with the environment and other organisms. During disease development, both the host plant and pathogen relies on signalling molecules released by their counterparts which ultimately causes susceptibility or resistance in the host plant (Casadevall and Pirofski, 2000; Bahia et al., 2018). Earlier, the cell to cell communication was reported in eukaryotic organisms only but recent studies revealed the social or community behaviour of communications in prokaryotic plant pathogens (Alberts et al., 2002; Nadell et al., 2008; Li and Tian, 2012; Helman and Chernin, 2015). Bacterial population thrives in colonies. The members of colony recognize self and partnering cells. To develop their colonies, bacterial population interacts with each other through quorum sensing. This interaction has been described as social network. The level of complexities of the cell to cell interactions varies significantly from prokaryotic to eukaryotic

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organisms (Cottier and Muhlschlegel, 2012) and it was also shown that how unicellular organisms act as multicellular organisms and co-ordinate among themselves (Hooshangi and Bentley, 2008). Bacterial plant pathogens deploy "Quorum sensing" (QS) to execute their co-operative behaviour. Although, studies on QS started back in late 1960s on the marine bioluminescent bacteria *Vibrio fischeri* but the term was introduced in 1994 (Fuqua et al., 1994). In 1968, it was reported that large populations of *Photobacterium fischeri* and other Gram-negative bacteria is required to remove certain inhibitors of luminescence from the culture media (Kempner and Hanson, 1968; Greenberg 1997). But later on, it was concluded that luminescence was due to the accumulation of autoinducers that occurs at high bacterial cell density (Nealson et al., 1970).

QS in bacterial population involves cell-to-cell communication to coordinate expression of the genes related to the pathogenicity, development of antibiotic resistance, bioluminescence, biofilm formation, secondary metabolites biosynthesis, determination of virulence and other group behavioural activities in a cell density dependent manner *via* specific biomolecules called autoinducers (Fuqua et al., 1994; Rutherford and Bassler, 2012; Hirakawa and Tomita, 2013; Jiang et al., 2019). Similar to hormones, autoinducers (AIs) are small signalling molecules (LaSarre and Federle, 2013; Papenfort and Bassler, 2016; Heckler and Boon, 2019) which function at interspecific and intraspecific levels. Primarily, they are categorised into three major types; acyl-homoserine lactones (AHLs) (in gram negative bacteria), oligopeptide AIs (Gram-positive bacteria) and autoinducer-2 (AI-2), a furanosyl borate diester (serve as universal signal secreted in both gram positive and negative bacteria during interspecies communication) (Gao et al., 2016) (Fig. 1A). The N-acylhomoserine lactone (AHLs) also known as AI-1 are first discovered in *Vibrio fischeri* and is the most widely discovered AIs used by Gram-negative bacteria (Eberhard et al. 1981). However, there are other classes of AIs which include *Pseudomonas* quinolone signal (PQS) (Pesci et al., 1999), diffusible signal factor (DSF) (Barber et al., 1997), indole (Lee and Lee, 2010), PAME (hydroxyl-palmitic acid methyl ester) (Flavier et al., 1997), a small sulfated protein produced by *Xanthomonas oryzae* pv. *oryzae* named as Ax21 and autoinducer-3 (AI-3). In plant pathogenic bacteria, the major characterized signals are AHLs, DSF and Ax21 (McCarthy et al., 2011; Pfeilmeier et al., 2016; Sibanda et al., 2018).

Since QS involves a highly coordinated process, it can be targeted through "Quorum Quenching" (QQ). It involves disruption/ targeted degradation of QS signalling molecules (Dong et al. 2001; Grandclement et al., 2016). QQ operates by recycling or clearing of QS signals either by bacteria itself or by other microorganisms to compete with QS-signal-producing organisms (Grandclement et al., 2016). The plant pathogenic bacteria are dependent on QS to establish pathogenesis in their host plants (Von Bodman et al., 2003). Therefore, targeting of QS could provide resistance to the host plants. Several researchers explained the way by which QQ can reduce the virulence of bacterial pathogens (Guendouze et al., 2017; Rehman and Leiknes, 2018; Utari et al., 2018; Mion et al., 2019; Krzyzek, 2019). The targets for QQ include enzyme mediated breakdown of the signalling molecules of QS biosynthetic pathway, use of competitive inhibitors as QS inhibitors (QSI), blocking receptors of QS signals of bacteria/ plant host through different ways (Kashyap and Sanghera, 2010; Kose-Mutlu et al., 2019). Enzymes such as lactonase which can target lactone ring of QS molecules and antibiotic such as azithromycin with quenching properties have been reported to inhibit QS in bacteria (van Delden et al., 2012; Zeng et al., 2016; Krzyzek, 2019). Various metabolites of plant origin with ability to bind various blocking sites and exhibit multiple mode of action have emerged as an attractive alternate for targeting QS (Deryabin et al., 2019). Three variants of plant derived anti QS products such as specific, nonspecific and indirect have been proposed. The use of plant-based QS inhibitors, co-evolution of plant-parasite and role of one or more QS inhibitors of a single plant species have been discussed (Deryabin et al., 2019).

Here, we have discussed role of QS in bacterial pathogenesis, developments in the potential of QQ, gene editing and how these can be

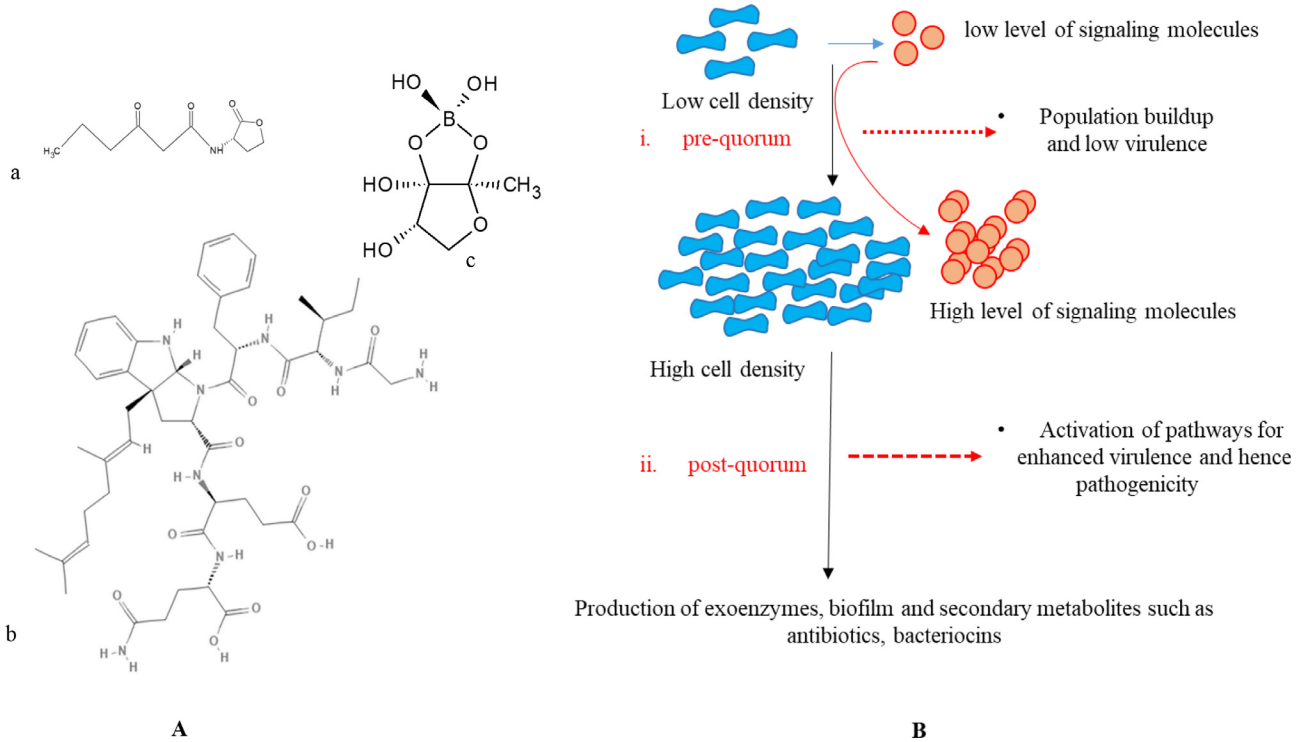

Fig. 1. A- Examples of small signalling molecules known as autoinducers: **a**; N-(3-Oxohexanoyl)-L-homoserine lactone of *Vibrio fischeri* **b**; oligopeptide Comx *Bacillus subtilis*: and **c**; furanosyl borate diester. **B-** Overview of quorum sensing in plant pathogenic bacteria. During pre-quorum phase bacteria increase its number to achieve cell density. During post-quorum phase, a critical level of signaling molecules are produced, these molecules activate the expression of target genes and starts producing exoenzymes and other virulence genes.

used as an alternative or complementary approach for bacterial plant disease management.

2. Quorum sensing in plant pathogenic bacteria

The cell to cell communication involves interaction of signalling molecule with a receptor. In general, the signalling molecule comes from bacteria which interact with receptors embedded in plasma membrane. The interaction of signal and receptor molecules leads to changes in receptor shape and triggers a cascade of downstream events at cellular level. Similar to other bacteria, plant pathogenic bacteria use QS for routine communication among the cells to effectively establish biofilm formation, virulence factor secretion, bioluminescence, developing antibiotic resistance, antibiotic production and sporulation (Ng and Bassler, 2009). The task is performed in two phases- pre-quorum and post-quorum. During initial phase, also known as pre-quorum, bacteria increase its number whereas later in post-quorum phase, bacteria biosynthesize exoenzymes and other products such as biofilm, secondary metabolites like antibiotics and bacteriocins (Fig. 1B). Broadly, QS involves the production of signalling molecules and their accumulation (LaSarre and Federle, 2013). During the pre-quorum phase, low molecular weight signalling molecules (autoinducers) are produced intracellularly and then secreted into the environment. The initial low concentration results in reduced virulence in phytopathogenic bacteria (Soto et al., 2006). But, once a critical concentration of AIs is reached *i.e.* in the post-quorum phase, the virulence of pathogens is increased significantly (Deep et al., 2011). The binding of inducers to the receptor complex further activates the transcription of downstream corresponding genes in the bacteria (Antunes et al., 2010). QS can work at intra or interspecies level and even between the Kingdoms (Atkinson and Williams, 2009) It is found to operate not only during pathogenic interaction of bacteria but also during symbiotic and even antagonistic interactions (Vicente-Soler et al., 2016). Since, QS varies across bacteria depending upon type of signalling molecules and signalling pathways like AHLs, Oligopeptides and furanosyl borate diesters, and their perception (Table 1). These QS mechanisms can be categorised into following subtypes:

2.1. AHL-based QS system

Initially described in bioluminescent *Vibrio fischeri*, this system is widely reported in Gram negative bacteria. Here, the AHL synthase belonging to *LuxI*-type family protein produces signalling molecules which are perceived by an AHL receptor, a cognate receptor (*LuxR*-type family transcription regulator). The expression of *luxCDABE* operon (a luciferase) is regulated by *LuxI* and *LuxR* proteins. The signal molecule 3OC6HSL is generated by *LuxI* and received by *LuxR* to form *LuxR*-HSL complex. Once the cell densities reached optimum level, the concentration of 3OC6HSL also attain their threshold limit. The formation of *LuxR*-HSL complex activates the transcription of *luxCDABE* following the interaction with *LuxR* protein (Fig. 2A). Different types of molecules other than AHL such as Thiolactone ring (AIP), hydroxyl palmitic acid methyl ester (PAME), Foranozil methyl borate (AI-2) and Dodecanoic acid methyl have been reported for cell to cell communication (Miller and Basler, 2001; Bassler, 2002) (Fig. 2A).

AHL-based QS has been reported for the virulence of several plant pathogenic bacteria such as *Erwinia carotovora* responsible for soft rot diseases, *Rhizobium radiobacter* (*Agrobacterium tumefaciens*) causing crown gall, *Xanthomonas campestris* inciting black rot of crucifers, *Ralstonia solanacearum* causing bacterial wilt of various plant species worldwide and *Pseudomonas aeruginosa* causing root infection of plants (Parsek and Greenberg, 2000). In *Erwinia,* the signalling molecules *N*-(3-oxohexanoyl)-L-homoserine lactone (OHHL) regulates the pathogenicity. Once synthesized by *LuxI* type proteins, this molecule binds directly to *LuxR* homologue regulators like *VirR and ExpR* which negatively regulate the production of virulence products in the absence of their ligand (Burr et al. 2006). The mutation in *virR* restores the production of virulence factors like plant cell wall degrading enzymes (PCWDE) and causes rotting of plant tissue (Burr et al., 2006). Similarly, in *Pseudomonas* spp., the QS dependent regulation of virulence genes involves different systems such as *las* and *rhl* (*P. aeruginosa*), *ahl* (*P. syringae*) and *phz* (*P. aurofaciens*, *P. chlororaphis*) (Gambello and Iglewski, 1991; Ochsner et al., 1994; Venturi, 2006). These systems regulate multiple virulence factors involved in the establishment of pathogenicity. The signalling molecules in *P. aeruginosa* include N-(3-oxodidecanoyl) homo-serine lactone (3O-C12-HSL) and N-butyryl homoserine lactone (C_4-HSL). *Pectobacterium carotovora*, the causal agent of soft rots in various plants, macerates the plant tissues by producing pectinases which degrade the plant cell wall and results soft rot of host tissues (Toth and Birch 2005; Liu et al., 2008). Another AHL and autoinducer-2 (AI-2) dependent systems of virulence in *P. carotovora* uses *ExpR* belonging to *LuxR* family of proteins to detect the AHL signal. Similar type of AHL molecules are found to regulate different processes in diverse bacterial pathogens likewise 3-oxo-C6-HSL is involved in production of plant cell wall degrading enzyme by *P. carotovorum,* production of exopolysaccharide by *Pantoea stewartii* and bioluminescence of *V. fischeri* (Eberhard et al., 1981; Pirhonen et al., 1993; Von Bodman and Farrand, 1995; Von Bodman et al., 1998).

2.2. Peptide based QS system

Unlike Gram negative bacteria where bacterial cells communicate *via* AHL, in Gram positive bacteria, communication occur through peptides (Sturme et al., 2002; Deep et al., 2011; Kalia, 2013; LaSarre and Federle, 2013). Peptide based QS is found to play role in the regulation of genetic competence in *Bacillus subtilis* (Tortosa and Dubnau, 1999) and synthesis of other metabolic products such as bacteriocins and antibiotics which are effective against closely related strains and other organisms, respectively. The small peptides are produced during catabolism of large peptides/oligopeptides, modified by the post-translational events and then released outside the cell. They are recognized specifically *via* two component regulatory systems of a histidine protein kinase receptor located at membrane and an intracellular receptor (Fig. 2B). The diffusion of small peptides across the membrane is facilitated by ATP-binding cassette (ABC)-type transporters (Turovskiy et al., 2007; Umesha and Shivakumar, 2013). Majority of the autoinducing peptides are involved in cell to cell communication with few exceptions like nisin and subtilin which additionally possess antimicrobial activities (Sturme et al., 2002). The peptide molecules are involved in different roles such as Phr peptides in *Bacillus subtilis* inhibit Rap phosphatases (Pottathil and Lazazzera, 2003; Perego, 2013) whereas peptides in *Enterococcus faecalis* stimulate or inhibit conjugative plasmid transfer by interacting with PrgX or PrgX-like proteins (Dunny, 2013), PlcR-associated PapR peptides are involved in triggering virulence whereas NprR-associated NprX peptides are found to control the necrotrophic properties of *Bacillus cereus* (Slamti et al., 2014). The peptide signals are detected by a membrane bound sensor kinase. The interaction of peptide ligand induces a phosphorylation cascade which ultimately results in activation or repression of QS target genes (Fig. 2B). This oligopeptide dependent messaging system is similar to cytokine signalling in eukaryotic cells.

2.3. AI-2 based QS systems

AI-2 represents non-specific autoinducers which are common in both Gram-negative and Gram-positive bacteria. The linear chemical product of LuxS 4,5-dihydroxy-2,3-pentanedione (DPD) is an unstable molecule and cannot be characterized based on classical chemical and biochemical methods. Therefore, structure of AI-2 is not known in most of the cases (Antunes and Ferreira, 2009). The first time AI-2 known as furanosyl borate diester in *V. harveyi* was identified along with two classes of AIs *viz*., (3-hydroxybutyryl)-homoserine lactone (HAI-1, AHL)

Table 1
List of plant pathogens bacteria, their autoinducers, their synthases, and receptors deployed for pathogenesis.

Pathogens	Autoinducer	Signal synthase-regulator	Controlled mechanism	References
Vibrio fischeri	3OC6HSL [N-(3-oxo-hexanoyl)-L-homoserine lactone]	LuxI-LuxR	To regulate bioluminescence	Perez et al., 2011; Verma and Miyashiro, 2013
V. fischeri	C8HSL	AinS-AinR	Luminescence, motility and acetate utilization	Perez et al., 2011
V. fischeri	Furanosyl borate diester (AI2)	LuxS-LuxPQ (two-component sensor kinase)	Luminescence (small contribution to luminescence regulation as compared to acyl homoserine lactone)	Perez et al., 2011
Pseudomonas syringae	3-oxo-C6-AHL	AhlI-AhlR/ PsyI-PsyR	Fitness, motility and virulence (by producing Exopolysaccharides)	Von Bodman et al., 2003; Quinones et al., 2005; Venturi, 2006; Cheng et al., 2017; Liu et al., 2020
Pectobacterium carotovorum sub sp. *carotovorum*	3-oxo-C8-AHL and 3-oxo-C6-AHL; autoinducer-2 (AI-2)-dependent signaling systems	CarI-CarR/ ExpI-ExpR/ VirR/AhlI	Expression of plant cell wall degrading enzymes	Pollumaa et al., 2012; Garge and Nerurkar, 2016; Ha et al., 2018; Li et al., 2019
Pantoea stewartii	3OC6HSL	EsaI-EsaR	EPS production	Von Bodman et al., 2003; Schu et al., 2009; Ramachandran and Stevens, 2013; Ramachandran et al., 2014; Kernell Burke et al., 2015
Xanthomonas campestris pv. *campestris; X. oryzae* pv. *oryzae*; X. axonopodis pv. citri	DSF signal (*cis*-11-methyl-2-dodecenoic acid)	RpfF-RpfCG (two component system)	Synthesis of extracellular enzymes and the Xanthan (EPS)	He et al., 2009; Deng et al., 2011; Huang et al., 2013; Wang et al., 2016; Li et al., 2019
Xylella fastidiosa	DSF signal (*Xf*DSF)	RpfF-RpfCG (two component system)	Biofilm formation and cellular density	Ionescu et al., 2013; Ionescu et al., 2016; Mendes et al., 2016
Ralstonia solanacearum	Hexanoyl and Octanoyl homoserine lactones;	SolI- SolR	solI/ solR genes inactivation doesn't affects the virulence	Von Bodman et al., 2003; Gallego et al., 2016; Bocsanczy et al., 2017; Sibanda et al., 2018
Ralstonia solanacearum	3-hydroxypalmitic acid methyl ester (3-OHPAME)	PhcB-PhcA (PhcS&R)	Controls the activity of phenotype conversion; production, EPS synthesis, motility and siderophore production	Flavier et al., 1997; Gallego et al., 2016; Hikichi et al., 2017; Perrier et al., 2018; Hayashi et al., 2019; Wang et al., 2020
Agrobacterium tumefaceins	OC8HSL	TraI-TraR	Expression of virulence genes; T-DNA (transfer DNA) transfer and its integration into the host genome	Haudecoeur and Faure, 2010; Lang and Faure, 2014; Dessaux and Faure, 2018
Streptomyces species	2-isocapryloyl-3R-hydroxymethyl γ-butyrolactone (A-factor/GBLs)	AfsA/ScbA-ArpA/ScbR	Secondary metabolism and/or morphological development, streptomycin biosynthesis, yellow pigment production and sporulation (Antibiotics production)	Takano et al., 2001; Horinouchi and Beppu, 2007; Polkade et al., 2016; Lin et al., 2018

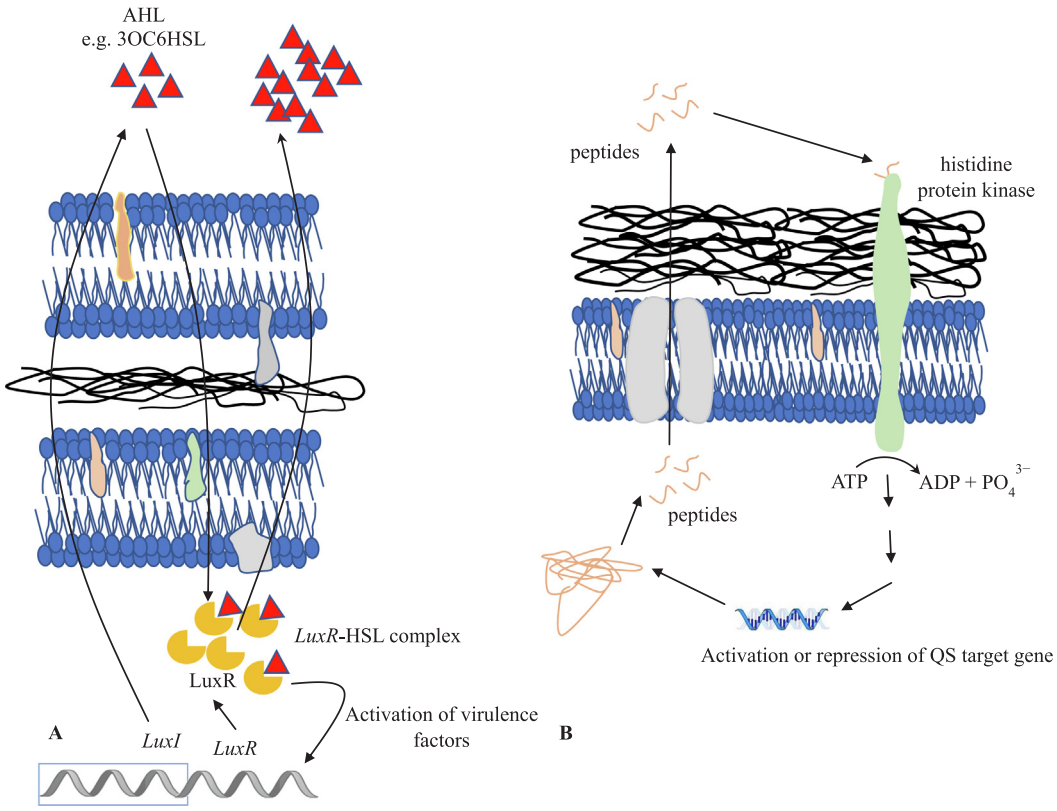

Fig. 2. Pictorial representation of quorum sensing system in plant pathogenic bacteria: **A**- in Gram negative *Rhizobium radiobacter* (*Agrobacterium tumefaciens)* causing crown gall, *Xanthomonas campestris* inciting black rot of crucifers, *Ralstonia solanacearum* causing bacterial wilt of various plant species worldwide and *Pseudomonas aeruginosa* causing root infection of plants. Here, the signaling molecules such as 3OC6HSL generated by *LuxI* interact with *LuxR* to form *LuxR*-HSL complex. This complex activates the transcription of virulence factors like plant cell wall degrading enzymes (PCWDE) or other genes; and **B**- Peptide based social network reported in Gram positive bacteria. Here, the small peptides produced from the metabolism of large peptides/oligopeptides, and then modified using post-translational processing, are released outside the cell. The diffusion of small peptides across the membrane is facilitated by ATP-binding cassette. The processed and fully mature peptide is then recognized specifically *via* two component regulatory systems containing a histidine protein kinase receptor located at membrane and an intracellular receptor.

and a long chain amino ketone [(Z) 3-aminoundec-2-en-4-one (CAI1)] (Bassler et al., 1994) (Fig. 3). AI-2 inducer was reported for its role in bioluminescence (Bassler et al., 1994), biofilm formation (Anetzberger et al., 2009), siderophore production (Lilley and Bassler, 2000) and type III secretion system (Henke and Bassler, 2004). The signalling molecules in *V. harveyi* are biosynthesized by the enzymatic activity of 5́-methylthioadenosine/S-adenosylhomocysteine nucleosidase (MTAN) and the metalloenzyme LuxS, using precursor S-adenosylhomocysteine (SAH) (LaSarre and Federle, 2013). The *luxS* gene encodes a precursor 3A-methyl-5,6-dihydro-furo (2,3-D) (1,3,2) dioxaborole-2,2,6,6 A-tetraol, which is required for the biosynthesis of AI-2. Two proteins LuxP, a soluble protein located in periplasm and LuxQ, a hybrid two-component sensor kinase response regulator protein detect AI-2 (Fig. 3). The signals are detected primarily by LuxP, which subsequently activate LuxQ (Surette et al., 1999). AI-2 molecules have been observed to control or influence various functions like biofilm formation and antibiotic resistance in *Moraxella catarrhalis* (Armbruster et al., 2010) and virulence in *Pseudomonas aeruginosa* (Duan et al., 2003).

2.4. Other molecules involved in QS systems

Other molecules such as 2-Hepta-3-hydroxy-4(1H)-quinolone (*Pseudomonas* quinolone signal) and its precursor 2-heptyl-4(1H)-hydroxyquinoline have been reported to act as signalling factors (LaSarre and Federle, 2013). These molecules interact with the transcriptional regulator PqsR, and then regulate the target gene expression. The other signalling molecule known as DSF identified in *Xanthomonas campestris pv. campestris*, is also utilized by *Burkholderia cenocepacia* and *Xylella fastidiosa* (Dow et al., 2003; Ryan et al. 2015). The synthesis of DSF is regulated by a cluster of genes known as *Rpf* which ultimately leads to the biosynthesis of extracellular enzymes and xanthan type of exopolysaccharide (EPS). Here, the signal recognition and transduction are composed of a sensor unit RpfC and other regulatory unit RpfG. The mutations within the cluster are reported to down-regulate extracellular enzyme and EPS production which ultimately reduces the virulence (Barber et al., 1997). The DSF mediated signalling influence the virulence of *Xanthomonas* spp. and *Xylella fastidiosa*. Besides this, signalling compounds such as fatty acyl methyl ester in *Ralstonia solanacearum* (Flavier et al., 1997) and butyrolactones with antifungal activities in *Pseudomonas aeurofaciens* have also been reported (Gamard et al., 1997).

3. Quorum sensing and its role in pathogenicity of the pathogen

QS is one of the vital component of interaction between pathogenic bacteria and its host plant. A number of studies have reported the role of QS in bacterial pathogenicity (Von Bodman et al., 2003; Venturi and Fuqua, 2013; Vrancken et al., 2013; Benali et al., 2014; Pfeilmeier et al., 2016). Some of the plant pathogenic bacterium-QS based virulence systems are described here in details:

3.1. Xanthomonas campestris pv. campestris and Xylella fastidiosa

Xanthomonas campestris pv. *campestris* (*Xcc*) and *Xylella fastidiosa* belong to Gram-negative bacteria. These plant pathogens are responsible for black rot of crucifers and Pierce's disease, respectively (He

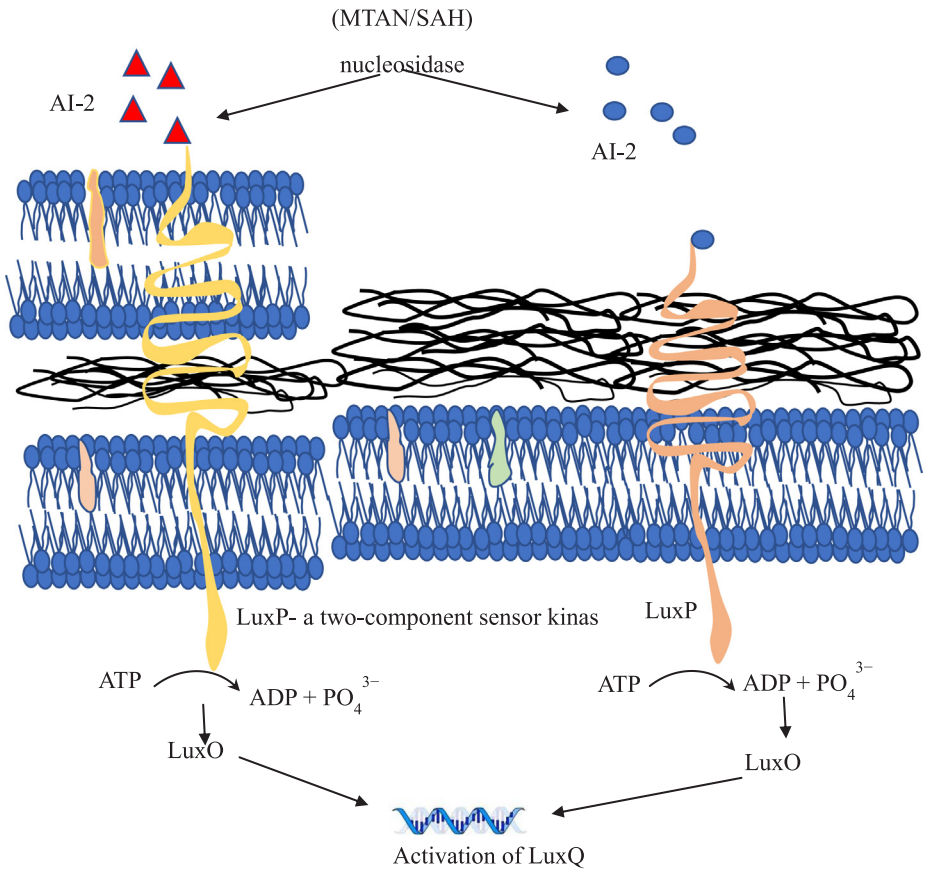

Fig. 3. Quorum sensing in Gram-negative and Gram-positive bacteria: the signaling molecules are biosynthesized by the enzymatic activity of 5́-methylthioadenosine/S-adenosylhomocysteine nucleosidase (MTAN) and the metalloenzyme LuxS using precursor S-adenosylhomocysteine (SAH). Two proteins including LuxP, a soluble protein located in periplasm, and LuxQ, a hybrid two-component sensor kinase response regulator protein detect AI-2. The signals are detected primarily by LuxP, which subsequently activate LuxQ.

and Zhang, 2008; Chatterjee et al., 2008). *X. campestris* pv. *campestris* infects plants belonging to family cruciferae. The symptoms on diseased plant appear in the form of V-shaped chlorotic or necrotic lesions, which later on results in wilting, stunting and stem rotting (Meenu et al., 2013; Vicente and Holub, 2013). On the other side, *X. fastidiosa* is a xylem colonizing plant pathogen responsible for Pierce's disease in grapes, variegated chlorosis in citrus and leaf scorches of coffee (Hopkins and Purcell, 2002). These pathogens share cell–cell signalling system which uses signalling molecule "Diffusible Signalling Factor" (DSF). However, the transcripts expressed in both of the pathogens differs (Cai et al., 2017). The *rpf* gene cluster regulates the DSF which further modulates the expression of pathogenicity factors such as xanthan, cell-wall-hydrolysing enzymes (CWDEs) including endoglucanases, proteases and endomannases and other glucans (Kakkar et al., 2015). The biosynthesis of DSF requires putative enoyl-CoA hydratase- a key enzyme from *rpfF* gene cluster whereas the two-component signal transduction system *rpfC-rpfG* is involved in downstream sensing and transduction of DSF signals (Guo et al., 2012; Ryan et al., 2015). Moreover, the turnover of DSF is determined by *rpfB* gene cluster. In *Xanthomonas axonopodis* pv. *citri*, the DSF mediated alterations of biofilm formation involved in early attachment to host surface and *in planta* growth of the pathogen on citrus plants (Li et al., 2019). In both *X. campestris* pv. *campestris* and *X. oryzae* pv. *oryzae*, the DSF-deficient mutants have reduced virulence whereas mutant strains of *X. fastidiosa* are reported hypervirulent on grapes (Chatterjee et al., 2008).

3.2. Erwinia carotovora

Erwinia carotovora, a Gram-negative bacterium has several pathogenic subspecies with different host specificity. For example, *E. carotovora* subsp. *atroseptica* responsible for blackleg (stem rot) of potato, whereas *E. carotovora* subsp. *carotovora* has wide host range and typically causes soft rot of potatoes, carrots and beets. *E. carotovora* degrades the host cell wall by using CWDEs such as pectinases, pectate lyases, cellulases and proteases (Corbett et al., 2005). These exo-enzymes are translocated to periplasmic surface by means of type-II secretion system. The production of CWDEs in *E. carotovora* is regulated by the presence of signalling molecule N-(3-oxohexanoyl)-L-homoserine lactone (OHHL) (Andersson et al., 2000). The OHHL biosynthesis is governed by *LuxI* homologue *expI/carI* (*CarA-H*) gene (Andersson et al., 2000). In some cases, *E. carotovora* subsp. *carotovora* strains are known to produce β-lactam antibiotic, 1-carbapen-2-em-3 carboxylic acid (carbapenem or Car), through CarR, an OHHL-dependent positive regulator of genes (Bosgelmez-Tınaz, 2003). The production of exoenzymes by *Erwinia* spp. is regulated by both global positive ((ExpI, ExpA, ExpS, ExpM, Hor, AepA, RexZ, RsmB) and negative regulators (RsmA, HexA, KdgR, RpoS) (Andersson et al., 2000). In *E. stewartii*, QS is regulated by *esaR* and *esaI*, the former is involved in the production of OHHL and later acts as a repressor.

3.3. Ralstonia solanacearum

Ralstonia solanacearum, another Gram-negative bacterium is a soil borne pathogen. Worldwide, it is known to cause bacterial wilt in many crops. The pathogen produces EPS which enters xylem vessels and directly blocks water movement and results in wilted and drooped appearance (Alvarez et al., 2010). The expression of virulent determinant genes in *R. solanacearum* is mediated by the QS system which uses N-acyl homoserine lactones (AHLs) (mainly hexanoyl and octanoyl homoserine lactone) as signalling molecules. Other signalling molecules such as 3-OH-palmitic acid methyl ester (3-OH-PAME), and 2-hydroxy-4-(methylamino-phenyl-methyl) cyclopentanone implicated have also been reported for their role in biofilm formation (Mole et al., 2007; Gallego et al., 2016). The 3-OH-PAME signal molecules in *R. solanacearum* regulates the phenotype conversion (Phc A) which further controls various pathogenicity traits like exozyme production, EPS

biosynthesis, motility and siderophore production. The putative operon PhcBSR (Q) is depicted to control the 3-OH-PAME signalling. The *PhcB* (methyltransferase) component of putative operon PhcBSR encodes 3-OH-PAME synthase involved in the biosynthesis of 3-OH-PAME or 3-OH-MAME, a membrane-bound histidine kinase *PhcS* and a downstream response regulator *PhcR* (Clough et al., 1997; Mole et al., 2007). Once the 3-OH-PAME level reaches the critical threshold, *PhcA* gets activated and resulting in a downstream response. The other *SolR/SolI* system analogous to the Phc system in *R. solanacearum* regulate several genes but its downstream target and transduction mechanisms are different. Here, *SolI* encodes for an enzyme which is responsible for the synthesis of N-octanoyl- and N-hexanoyl-homoserine lactones. Once the critical level is attained, it binds to the *SolR* transcriptional activator and ultimately, turns the downstream transcription of different transcripts and thus provides a two-stage hierarchical cell density sensing system in *R. solanacearum* (Schell, 2000).

3.4. Agrobacterium (Rhizobium) radiobacter

The species of *Agrobacterium* are known for their ability to transfer DNA (T-DNA) into host plant and cause crown gall diseases in different plants. It is widely used in genetic engineering to raise transgenic plants. Isolates infecting human beings are affiliated to *Agrobacterium* (*Rhizobium*) *radiobacter* species whereas phytopathogenic strains have been designated under the synonym *Agrobacterium tumefaciens*. Three pathogenic species of *Agrobacterium* (*Rhizobium*) are well known such as *Agrobacterium tumefaciens* known for crown gall disease; *A. rhizogenes* for hairy root disease in dicots; and *A. vitis* for crown gall of grapevine. The pathogenic species of *Rhizobium* infects the dicot plants through wounds in response to phenolic compounds such as Acetosyringone released by the plants. The released compounds stimulate the expression of virulence genes in *Agrobacterium* for T-DNA (transfer DNA) transfer and integration into the host plant genome. The QS in *Rhizobium* share its similarity to LuxI/LuxR system. Here, TraI protein (LuxI like) is involved in the production of AHL molecule N-3-oxooctanoyl-L-homoserine lactone (OC8HSL). The receptor protein TraR (similar to LuxR) interacts with signalling molecules and then activates the downstream regulatory pathways (Lang and Faure, 2014). During the transformation and integration of T-DNA into the plant genome, the level of signalling molecule is very low and accumulation of gamma-aminobutyrate (GABA) and its by-product in wounded cells impede the QS response. After integration, T-DNA initiates the biosynthesis of plant growth regulators such as auxins, cytokinins and conjugal opines. These growth regulators are used as carbon source by pathogen and then triggers the biosynthesis of receptor protein TraR (White and Winans, 2007; Wang et al., 2014). The DNA-binding activity of OC8HSL-TraR complex at low level of signalling molecules are negatively affected by the TraM protein which interferes with regulation of Tra-operon. Besides low level of signalling molecules due to low cell density, the amount of GABA and its derivatives are found to provoke the expression of lactonase AiiB and AttM, which catalyse the cleavage of free signalling molecules. Once the amount of signalling molecules achieves a critical level, then the antagonist activity of TraM and lactonase-catalysing degradation of OC8HSL is inhibited and the transcription of different Ti-plasmid genes is activated (Haudecoeur and faure, 2010).

4. Quorum quenching

Understanding the community behaviour through quorum sensing in bacteria gained the attention of researchers worldwide through which different pathogenic bacteria can be targeted. The disruption of quorum sensing or build-up of high cell density behaviours of bacteria through “Quorum quenching” has emerged as an attractive target (Schauder et al., 2001). During the early growth and developmental phase, bacterial pathogens rely on quorum quenching process to suppress the quorum sensing pathways of surrounding members (Leadbetter and Greenberg, 2000). The first quorum suppressing molecule was identified in 2001 from *Bacillus* sp. 240B1 (Dong et al., 2001). From the last couple of years, large number of AHL-degrading enzymes have been identified among bacterial species including *Bacillus* spp. (Rowley et al., 2009; Han et al., 2010), *Pseudomonas* spp. (Huang et al., 2003; Fekete et al., 2010), *Ralstonia* spp. (Chen et al., 2009; Han et al., 2010) and *Rhizobium radiobacter* (Zhang et al., 2002; Haudecoeur et al., 2009). Quorum sensing inhibitors either interfere with signalling molecules or degrade the quorum sensing pathways (Rasmussen and Givskov, 2006).

Initially, quorum quenching inhibitors were characterized in seaweed (Rasmussen et al., 2000), and thereafter, these inhibitors were identified in plant species (Vattem et al., 2007; Adonizio et al., 2008) and fungi (Zhu and Sun, 2008). These inhibitors include enzymes degrading signalling molecules and secondary metabolites such as furanones and their analogs (Zang et al., 2009; Liu et al., 2010; Steenackers et al., 2010), glycosylated flavonoids (Brango-Vanegas et al., 2014), bismuth porphyrin complexes (Galkin et al., 2015) and glycomonoterpenols (Mukherji and Prabhune, 2015), heavy metals (Vega et al., 2014) as well as different nanomaterials (Wagh et al., 2013; Miller et al., 2015; Singh et al., 2015). The quorum quenching differs in Gram positive and negative bacteria (Singh et al., 2016; Zhang and Li, 2016; Grandclement et al., 2016) and the disruption of quorum sensing pathways can be manifested either due to the signal inhibition and degradation of pathways.

4.1. Complete inactivation or degradation of QS signals

The metabolism or degradation of signaling molecules of AHL results in inhibition of QS signal process. The targeted degradation or inactivation of signaling molecules is one of the most suggested, convenient and effective approach for targeting pathogenic bacteria (Alksne and Projan 2000; LaSarre and Federle, 2013). The degradation or inactivation of signaling molecules can be achieved using enzymatic or non-enzymatic approaches. This strategy was first reported against soft rot disease caused by *E. carotovora* by transforming decay causing bacteria with *aiiA*, an autoinducer inactivation gene. The *aiiA* encoded enzyme inactivated the AHL QS signals and resulted resistance in different crops such as potato, tobacco, brinjal, chinese cabbage, carrot and celery plant (Dong et al., 2000). Since then, the *aiiA* gene has been used against various plant pathogens *P. aeruginosa* and *Burkholderia thailandensis* (Reimmann et al., 2002; Ulrich, 2004). These enzymes have been reported from both QS and non-QS microorganisms (Li et al., 2008). The enzyme enoyl-ACP reductase inhibitor triclosan was found to reduce AHL level under *in vitro* conditions (Hoang and Schweizer, 1999). The production of enzyme encoded by *AiiA* causes specific degradation of AHL molecules (Dong et al., 2000, 2001; Wang et al., 2004; Lee et al., 2002). Although, the enzymes responsible for the inactivation of DSF, PQS and AI-2 have been identified but most of them target only AHL signals. In 2002, another AHL inactivating gene *AttM* with lactonases activity sharing over 28% similarity with *aiiA*, has been identified from *Rhizobium tumefaciens* causing crown gall in stone and pome fruits (Zhang et al., 2002). In addition to enzyme mediated degradation, non-enzymatic method of inactivation has also been reported. The increase in pH of plant during soft rotting by *E. amylovora* lyses the AHL molecules (Yates et al., 2002). Similar strategies are being used by several eukaryotic systems to counter the QS process in *B. cereus*, *B. mycoides* and *B. thuringiensis*.

4.2. Inhibition of QS signals perception and suppression of biosynthetic pathway and global repressor genes

The quorum sensing processes in pathogenic bacteria can be targeted either by competitive blockage through structural analogs of signaling molecules or destruction of receptor proteins. Some of the plant derived molecules known as quorum sensing inhibitor (QSI)

Table 2
Examples of few natural and synthetic quorum sensing inhibitors.

S.No.	Targets	Inhibitors	Source	Affected Phenotype	References
01.	N-acylhomoserine lactones	Microscopic Yeast, *Trichosporon loubieri*	Tropical Wetland Waters	——	Wong et al., 2013
02.	N-acylhomoserine lactones	Halogenated furanones	*Delisea pulchra*, seaweed	Swarming motility in *Serratia liquefaciens*	Givskov et al., 1996
03.	N-acylhomoserine lactones	Mosloflavone	*Mosla soochouensis*	Virulence phenotypes and biofilm formation in *Pseudomonas aeruginosa* PAO1	Hnamte et al., 2019
04.	3-oxo-C12-HSL (N-acylhomoserine lactones)	Sulforaphane and Erucin	Broccoli and cruciferous vegetables	LasR system in *Pseudomonas aeruginosa*.	Ganin et al., 2012
05.	Histidine protein kinase	Anacardic acids mixture (AAM)	*Amphipterygium adstringens*, Medicinal Plant	Violacein production in *Chromobacterium violaceum*; Rhamnolipid, pyocyanin production and elastase activity in *Pseudomonas aeruginosa*	Castillo-Juarez et al., (2013)
06.	Unknown	Piericidin A and glucopiericidin A	*Streptomyces xanthocidicus* KPP01532	Expression of genes *PelC, CelV, and PehA a* encoding hydrolytic enzymes in *Erwinia carotovora* subsp. *atroseptica*	Kang et al., 2016
07.	HAI-1, AI-2 signalling, Type 3 secretory system	Naringenin	Citrus species	Biofilm formation in *Escherichia coli* O157:H7 and *Vibrio harveyi*	Vikram et al., 2010
08.	*las*, *rhl*, and *pqs* Quorum sensing system	Diallyl disulfide (DADS)	Garlic	Virulence factor production (elastase, pyocyanin, biofilm, and swarming motility) of *P. aeruginosa* PAO1	Li et al., 2019
09.	3-oxo-C12-HSL and C4-HSL AHL signal	Eugenol (4-allyl-2-methoxyphenol)	Clove, Cinnamon, and Bay	Biofilm formation and swarming motility in *P. aeruginosa*, violacein production in *Chromobacterium violaceum*	Lou et al., 2019
10.	*lasB* gene	Itaconimides	Synthetic	Virulence factor viz., elastase, rhamnolipid, and pyocyanin production in *P. aeruginosa*	Fong et al., 2019
11.	*rhlR*, QS regulator gene; 3-oxo-C12-homoserine lactone (3OC12-HSL) and butyryl-homoserine lactone (C4-HSL)	Azithromycin		Virulence in *P. aeruginosa*	Zeng et al., 2016
12.	Not known	Acyclic and cyclic glyoxamide derivatives		Inhibition of biofilm formation in *P. aeruginosa* and *E. coli*	Nizalapur et al., 2017
13.	Bioisosteres of N-acylhomoserine Lactones	Imidazolines		Violacein production by *Chromobacterium violaceum*; Prodigiosin production in *Serratia marcescens*	Reyes-Arellano et al., 2012
14.	3-oxohexanoyl-HSL (OHHL)	1,5-dihydropyrrol-2-ones		Expression of green fluorescent protein (GFP) in *E. coli*	Goh et al., 2015
15.	3-oxo-C12-HSL and C4-HSL	SM23, β-Lactamase Inhibitor boronic acid derivative		Biofilm formation and virulence factors such as pyoverdine, pyocyanin and elastase production by *P. aeruginosa*	Peppoloni et al., 2020
16.	N-acylhomoserine lactones	γ-Caprolactone		Biostimulation of Quorum quenching activity of *Rhodococcus erythropolis*	Chane et al., 2019
17.	AI-2 QS autoinducer	Thiazolidinediones and dioxazaborocanes		Effect on bioluminescence in *V. harveyi*	Brackman et al., 2013
18.	Acyl homoserine lactone	Methyl gallate (MG)		Motility, biofilm, proteolytic, elastase, rhamnolipid and pyocyanin, activity in *P. aeruginosa*	Hossain et al., 2017

mimic the signaling molecules involved in quorum sensing process and form a stable QSI receptor protein complex. The QSI molecules impede the signal-receptor complex formation and negatively affect the transcription of downstream processes associated with normal quorum sensing process (Teplitski et al., 2000). These inhibitor molecules have been reported from natural resources, genetically (Gonzalez and Keshavan, 2006) (Table 2). Under natural conditions, organisms coexist and compete with each other. The production of quenchers to disrupt social behaviour of other organisms is routinely deployed to get competitive edge over others. All prokaryotic as well as eukaryotic organisms are known to produce these quenchers which are known as natural QSI (Kalia, 2013). However, these inhibitors are produced in low amount, thereof, such limitations can be easily overcome by using their synthetic analogues. These synthetic inhibitors are produced by alternations in side chain of AHL or ring moiety (Kalia, 2013). (Table 2)

Different metabolites of natural as well as synthetic analogs of AHLs have been reported for their role as QSIs. For example, thiolactones, lactams, solenopsin, L-Canavanine and isothiocyanate iberin can target the QS-system in P. aeruginosa (Gonzalez and Keshavan, 2006; Park et al., 2008; Malladi et al., 2011; McInnis and Blackwell, 2011; Jakobsen et al., 2012). Other inhibitors include furanones and their structural derivatives such as bismuth porphyrin complexes, heavy metals and nanomaterials (Liu et al., 2010; Vega et al., 2014; Galkin et al., 2015; Miller et al., 2015; Singh et al., 2015). The furanones share structural similarity to AHLs and hence act as inhibitors. In some cases, they are reported for their role in degrading LuxR-type protein or decreasing the DNA-binding activity of the transcriptional regulator protein Lux (Gonzalez and Keshavan, 2006; Zhang and Li, 2016; Zhang and Li, 2016). S-adenosylmethionine (SAM) analogues such as S-adenosylhomocysteine, S-adenosylcysteine and sinefungin have been identified as specific inhibitors of quorum sensing without any side effects to the eukaryotic enzymes which uses SAM (Hentzer and Givskov 2003).

The other effective methods of suppressing quorum sensing process involve modulating the behavior of regulators and targeting downstream pathways (de Kievit and Iglewski 2000). The global repressor genes such as *rsaL* of *P. aeruginosa* (de Kievit et al., 1999) and *rsmA* of *E. carotovora* subsp. *carotovora* T1 have been characterized (Cui et al., 1995). The intermediate analogue products of AIs can also be explored for targeted interruption of quorum sensing process. The inhibitory effect of furanones was largely due to their role as competitor and the structural similarity with AHLs. However, studies also reported the role of furanones in the degradation of LuxR-type proteins (Manefield et al., 2002) or suppression of DNA-binding affinity of transcription regulatory protein LuxR (Defoirdt et al., 2010). The furanones were also reported to disrupt the AI-2 biosynthetic pathway through covalent modification and inactivation of LuxS system (Zang et al., 2009). The quorum sensing inhibitors such as allyl benzo[β]thiophene-3-carboxylate 1,1-dioxide was found to target LuxPQ (Zhu et al., 2012) whereas thiazolidinediones and dioxazaborocane were reported to target LuxR in *V. harveyi* (Brackman et al., 2013) (Table 2).

5. Quorum quenching mediated approach for bacterial plant disease management

Bacterial pathogens are known for their ability to penetrate the host plant and build up population inside tissues for enhanced plant infection. The intracellular location of these pathogens is inaccessible for chemicals hence the management of such pathogens is a challenging task (Sundin et al., 2016). Moreover, the development of multiple drug resistance in plant pathogenic strains of bacteria is alarming and further escalatesthe management of biotic stresses across the globe. These pathogens are one of stubborn plant pathogens and limiting factors in enhancing the crop yields e.g., the bacterial canker of kiwifruits caused by *Pseudomonas syringae* pv. *actinidiae* in New Zealand (Everett et al., 2011) and the zebra chip of potato disease caused by *Candidatus*, *Liberobacter solanacearum* in Mexico (Secor et al., 2009).

The present scenario demands integrated approach to effectively combat these stresses using conventional and advanced methods which can effectively handle the development of more antibiotic resistance in plant pathogenic bacteria (Sundin et al., 2016). For this, the genes targeting quorum sensing can be used for raising transgenic plants or biocontrol agents with ability to block quorum sensing regulating pathways which can reduce the pathogenicity or pathogen virulence. Targeting quorum dependent pathogens with quorum quenchers can be a useful strategy. Although, the use of QQ tools are still at infancy stage but both *in vitro* and *in vivo* studies have revealed the effectiveness of this approach for bacterial disease management. The significant reduction in the population and virulence of *Pectobacterium carotovora* subsp *carotovora* BR1 (PccBR1) was observed when AHL signal degrading *Lysinibacillus* sp. Gs50 were cultured together. The ability to degrade AHL signal was attributed to the production of a 29 kDa protein (*AdeH*) which hydrolyzed the lactone ring of AHL. It also led to significant decrease in tissue maceration in infected potato (Garge and Nerurkar 2016). Genetic engineering of an AHL degrading lactonase encoding gene *HqiA* in *P. carotovorum* pathogen led to inhibition of quorum sensing and other downstream events such as tissue maceration (Torres et al., 2017).

The quorum quenching methods have broad mode of actions and found effective against vast range of signalling molecules (Defoirdt et al., 2010). For example, the AHL lactonase can act on a wide range of AHLs (Dong et al., 2007). Raising transgenic plants with bacterial AHL synthase or quorum quenchers encoding enzymes led to enhance tolerance against quorum sensing dependent pathogen e.g.in transgenic tobacco plants expressing *expI* gene encoding AHL of *P. carotovorum* (Mae et al., 2001). The transformation of *AiiA of Bacillus* in *Pichia pastoris* GS115 increased suppression of *Erwinia carotovora* responsible for soft rot in elephant yam (Wu et al., 2016). The genetic engineering of ineffective biocontrol strains of *Pseudomonas fluorescens* P3 with *aiiA* gene led to the development of biocontrol ability in P3 strain against *Erwinia carotovora* and *Agrobacterium tumefaciens* pathogens of potato and tomato, respectively (Molina et al., 2003). Several other studies have revealed the potential of quorum quenchers-based methods in plant diseases management (Molina et al., 2005; Cho et al., 2007; Ban et al., 2009; Vanjildorj et al., 2009). In addition, extracts from algae and higher plants have been recommended as competitive inhibitors for signalling (Givskov et al., 1996; Defoirdt et al., 2010). Other approaches involving use of non-competitive inhibitors (Hentzer et al., 2003) and application of monoclonal antibodies for mimicking the naturally occurring AHL acyl chains of various lengths and oxidation states (Kaufmann et al., 2006).

Since the quorum quenching based plant disease management system attenuates the virulence of the pathogens rather than killing them. It would decrease the selective pressures otherwise associated with antimicrobial agents and lead to the development of resistance in due course (Alagarasan et al., 2017).

6. CRISPR-Cas system for engineering disrupted quorum sensing pathways against bacterial pathogen

Bacterial pathogens build their population to achieve high cell density which is a pre-requisite for showing virulence. It is well established that how quorum sensing in plant pathogenic bacteria regulates several events including the formation of biofilms and social behaviour to effectively infect the host plant. The development of biofilm is also associated with the development of multi drug-resistance. The resistance in plant against pathogens is regulated by three plant growth regulators; jasmonic acid (JA), salicylic acid (SA) and ethylene (ET). Thus, the biosynthesis of these plant growth regulators and pathogen interacting and feeding could be targeted using CRISPR/Cas9 (Das et al., 2019; Haque et al., 2018; Peele and Venkateswarulu, 2018). A number of gene editing tools including use of Zinc-Finger Nuclease, Transcription Activator-Like Effector Nucleases and recently

Table 3
Examples of genes edited using CRISPR and other approaches to confer disease resistance against plant pathogenic bacteria.

S.No.	Plant	Target gene of host plant	Pathogen	Significance	References
1.	Tomato	SlJAZ2	*Pseudomonas syringae* pv. *tomato* (Pto) DC3000	Development of resistance to biotrophic pathogens for tomato bacterial speck disease without compromising resistance against necrotrophs.	(Ortigosa et al., 2019)
2.	Cassava	RXam1, MeWRKY20-MeATG8a/8f/8h (MeATG8a, MeATG8f, MeATG8h)	*Xanthomonas axonopodis* pv. *manihotis* (Xam)	The overexpression of RXam1 led to decrease in bacterial growth of XamCIO136	(Díaz Tatis et al., 2018)
3.	Cassava	MeDELLAs, MebZIPs (MebZIP3, MebZIP5) and MeRAVs	bacterial blight resistance	MeDELLAs were identified as positive regulators of disease resistance against cassava bacterial blight MeRAV1 and MeRAV2 as common and upstream transcription factors of melatonin synthesis n plant disease resistance against cassava bacterial blight	(Li et al., 2018; Li X. et al., 2017; Wei et al., 2018)
4.	Cotton	GhERF-IIb3	Bacterial blight caused by Xanthomonas citri pv. malvacearum (Xcm) resistance	The transcription factor GhERF-IIb3, a positive regulator of the JA pathway led enhanced defence response against bacterial infection	(Cacas et al., 2017)
5.	Grapefruit Duncan	CsLOB1	Canker	CRISPR/Cas9/sgRNA was deployed to modify the canker susceptibility gene CsLOB1	(Jia et al., 2017)
6.	Tomato	Exon-3, SlDMR6–1	Pseudomonas syringae, Xanthomonas gardneri, X. perforans, Phytophthora capsici Susceptibility factor in Pseudomonas syringae pv. tomato or *Phytophthora capsici* infection	CRISPR-Cas9 mediated gene editing of a DMR6 ortholog in tomato conferred broad-spectrum of disease resistance *P. syringae* pv. *tomato* and *Phytophthora capsici*	(Thomazella and Brail, 2016)
7	Citrus (Duncan grape fruit)	PthA4 effector binding elements (EBEs)	Imparts susceptibility to canker induced by the pathogenicity factor ptha4	Modification of promoter binding elements in PthA4 effector binding elements of CsLOB1 which is a susceptibility gene for citrus canker alleviated the XccΔpthA4:dCsLOB1.3 mediated infection.	(Jia et al., 2016)
8	Banana	Hrap, Pfl	*Xanthomonas campestris* pv. *musacearum* resistance	Transgenic lines expressing the Hrap and Pflp genes were found resistant to Banana Xanthomonas wilt	(Tripathi et al., 2010, 2014; Namukwaya et al., 2012)
9	Apple and grape	DIPM-1, 2, 4	Fire blight (Erwinia amylovora)	MLO-7, a susceptible gene in grape cultivar was targeted to increase resistance against powdery mildew in grape cultivar whereas DIPM-1, DIPM-2, and DIPM-4 in the apple was edited to enhance resistance against fire blight disease.	(Malnoy et al., 2016)
10	Rice	SWEET13- Sucrose transporter	Bacterial blight (*Xanthomonas oryzae* pv. *oryzae*)	The mutation of OsSWEET13 using CRISPR/Cas9 led to decrease susceptibility.	(Zhou et al., 2015)

developed Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-Associated Protein-9 nuclease (Cas9) have been explored. Among these, CRISPR-Cas system initially discovered in bacteria as a part of adaptive immunity to counter phage infections and foreign plasmids is nowadays widely used for various applications. The CRISPR system uses an endonuclease Cas9 and a short guide RNA known as sgRNA help the former to specifically cleave genome. The specificity of sgRNA is responsible helps in avoiding its off-target activity (Sameeullah et al., 2018; Haque et al., 2018; Peele and Venkateswarulu, 2018; Das et al., 2019).

Studies on quorum sensing have provided detail insight about the mechanisms adopted by pathogens during infection. Therefore, different components of quorum sensing in pathogenic bacteria have been targeted successfully. For example, the biofilm forming ability of pathogenic bacteria involves the expression of several genes. In human pathogenic strains of *Acinetobacter*, *AbaI* gene involved in biofilm formation has been targeted to develop gene knockouts (Peele and Venkateswarulu, 2018). Different variants of CRISPR system such as dCas9 fused with activator proteins, dCas9-based CRISPRi (interference) has been effectively applied in plants and other organisms either to activate or suppress the transcription (Gilbert et al., 2013; Piatek et al., 2015; Haque et al., 2018; Das et al., 2019). Additionally, dCas9-based epigenetic studies on effectors have successfully reactivated the silenced genes or transposons via histone modification and demethylation in different organisms (Hilton et al., 2015; Gallego-Bartolomé et al., 2018). Simultaneously, multiple gene editing using CRISPR technology could be useful in exploring the plant pathogenicity genes involved in invasion of the pathogen (Sameeullah et al., 2018; Haque et al., 2018).

Several studies have reported use of CRISPR/Cas9 in treating viral and fungal pathogenicity; however reports to counter bacterial diseases in plants are limited. The resistance has been achieved by targeting the candidate genes of susceptible host plants (Table 3). The mutation in OsSWEET13, susceptible gene of rice plants via CRISPR/Cas9 led to resistance against *Xanthomonas oryzae* pv. *Oryzae* responsible for bacterial blight (Zhou et al., 2015). Similarly, targeting SlDMR6–1 and a truncated version of SlDMR6 (DMR6 ortholog) which is upregulated during *Pseudomonas syringae* pv. infection in tomato plants (de Toledo Thomazella et al., 2016) or *Phytophthora capsici* (Langner et al., 2018) conferred broad-spectrum resistance against *P. syringae*, *P. capsica*, *X. gardneri* and *X. perforans* (Thomazella and Brail, 2016; Langner et al., 2018). A pathogenicity receptor DspE of *E. amylovora* responsible for fire blight in apple and members of Rosaceae families interact with DIPM genes encoding four leucine-rich-repeats, receptor- like serine/theonine kinases (Borejsza-Wysocka et al., 2006; Malnoy et al., 2016). Using CRISPR/Cas9, the DIPM and other four genes has been successfully edited to develop resistance (Malnoy et al., 2016; Borrelli et al., 2018). Although limited reported are available, still CRISPR based gene editing has been applied for various agricultural crops against different bacterial plant pathogens (Table 3).

7. Future prospects and conclusions

The development of multidrug resistant bacterial strains demands alternative strategies for the effective management of bacterial infections in plants. A better understanding of the role of quorum sensing in social behaviour of plant pathogenic bacteria has emerged as attractive method for developing efficient plant disease management strategies. Already genetic engineering of transgenic plants and microorganisms with ability to suppress the community behaviour of plant pathogenic bacteria through targeted quorum quenching have yielded promising results under *in vitro* and *in vivo* conditions. In parallel, the usage of natural and synthetic signalling molecules inhibitors can be effective, easy and could prove a milestone in delivering product for field application. The genetic engineering of biocontrol agents and plant beneficial microbes are still underexplored and can open new avenues for developing sustainable methods for plant diseases without any side effects to our ecosystem. In present scenario, coupling of quorum sensing network with CRISPR could be game changing in developing resistance to bacterial pathogens in plants. Further, coupling latest method of genetic engineering such as CRISPR-Cas system for developing targeted pathogen specific resistance needs attention of researchers worldwide. Although promising and infancy stage field applications and sustainability is still a big hurdle. Moreover, the downside of quenchers-based inhibition and their possible role in development of resistance needs stringent evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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