Review

Silencing the mob: disrupting quorum sensing as a means to fight plant disease

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SUMMARY

Bacteria are able to sense their population's density through a cell–cell communication system, termed 'quorum sensing' (QS). This system regulates gene expression in response to cell density through the constant production and detection of signalling molecules. These molecules commonly act as auto-inducers through the up-regulation of their own synthesis. Many pathogenic bacteria, including those of plants, rely on this communication system for infection of their hosts. The finding that the countering of QS-disrupting mechanisms exists in many prokaryotic and eukaryotic organisms offers a promising novel method to fight disease. During the last decade, several approaches have been proposed to disrupt QS pathways of phytopathogens, and hence to reduce their virulence. Such studies have had varied success *in vivo*, but most lend promising support to the idea that QS manipulation could be a potentially effective method to reduce bacterial-mediated plant disease. This review discusses the various QS-disrupting mechanisms found in both bacteria and plants, as well as the different approaches applied artificially to interfere with QS pathways and thus protect plant health.

Keywords: acylhomoserine lactone, lactonase, plant-pathogenic bacteria, quorum quenching, quorum sensing.

INTRODUCTION

For many years, bacteria were considered to live solely as individual organisms, striving to outcompete their neighbouring siblings. However, this notion is no longer valid and bacterial colonies are now regarded as social communities, which integrate intercellular signals in order to coordinate gene expression for the benefit of the colony. One fascinating phenomenon that clearly projects such cooperative nature is quorum sensing (QS). QS is used by bacteria to regulate their gene expression in a density-dependent manner. This mechanism is mediated by the constant synthesis and perception of small signalling molecules, which proportionally

increase in concentration with increasing cell numbers. In many cases, these signalling molecules participate in forward-feedback loops, whereby a relatively small initial concentration amplifies their own production through transcriptional activation. Once the concentration of these signalling molecules reaches a specific threshold, a signal transduction cascades commences, through the binding to a cognate receptor, resulting in population-wide changes in gene expression (Bassler, 1999). Bacteria use QS systems to regulate many processes, ranging from metabolic and developmental mechanisms to virulence, and it has been estimated that 5%–25% of the genes encoded in a bacterial genome could be regulated by this system (reviewed by Ng and Bassler, 2009; Williams, 2007).

QS can occur among and between species, and a variety of different molecules can be used as signals. Common classes of signalling molecules are *N*-acylhomoserine lactones (AHLs) in Gram-negative bacteria (Fuqua *et al.*, 2001), oligopeptides in Gram-positive bacteria (Kleerebezem *et al.*, 1997) and furanosyl borate diesters, known as autoinducers-2 (AI-2), in both Gram-negative and Gram-positive bacteria (Chen *et al.*, 2002). In recent years, additional types of intercellular signalling compound have been discovered. These include cyclic dipeptides and quinolones in *Pseudomonas aeruginosa* (Holden *et al.*, 1999), small diffusible molecules in *Xanthomonas* spp., *Xylella fastidiosa* and *Burkholderia cenocepacia* (reviewed by Ryan and Dow, 2008), 3-hydroxy-palmitic acid methyl ester in *Ralstonia solanacearum* (Flavier *et al.*, 1997), γ -butyrolactone in *Streptomyces* spp. (Takano, 2006), and others. These signals mediate species-specific as well as species-nonspecific communication systems (An *et al.*, 2006; Ganin *et al.*, 2009; Kimura *et al.*, 2009; Lowery *et al.*, 2008; Ryan and Dow, 2008), and discrete responses to each of these signals allow the different groups of bacteria to coordinate their behaviour according to neighbouring communities. Recently, the field of QS research has expanded beyond prokaryotic interactions, with the realization that many bacterial signals can modulate phenotypes in eukaryotic organisms, which, in turn have evolved mechanisms to sense, respond and interfere with specific QS signals (Hughes and Sperandio, 2008; Joint *et al.*, 2007; Lowery *et al.*, 2008; Mathesius *et al.*, 2003; Schuegger *et al.*, 2006). This review focuses on AHL-mediated QS regulation because of the wealth of reports that link these signals to plant–microbe

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interactions, of both pathogenic and beneficial nature. However, it should be noted that additional signalling molecules are involved and that such interactions and their role are no less important.

QS IN PLANT-PATHOGENIC BACTERIA

Many plant-pathogenic bacteria are dependent on QS to evoke disease. Such dependence arises from the fact that some virulence-related traits are induced only when the bacterial population reaches a specific density threshold (Andersen *et al.*, 2010; Barnard *et al.*, 2007; von Bodman *et al.*, 2003; de Kievit and Iglewski, 2000). Information regarding the role of QS signalling molecules used by Gram-positive phytopathogenic bacteria on infection is lacking, despite the fact that the virulence mechanisms involved in plant infection of many of these bacteria have been studied in detail (Hogenhout and Loria, 2008). Conversely, data regarding QS involvement in the virulent traits of Gram-negative phytopathogenic bacteria have accumulated in the last

decade, providing information of both fundamental and practical importance.

The most studied signalling molecules of Gram-negative bacteria are the AHLs. These molecules comprise a homoserine lactone ring connected to a fatty acyl side-chain. AHLs vary with respect to: (i) the length of the *N*-acyl chains (commonly 4–12 carbons); (ii) the hydroxy or oxo group at the third carbon of the acyl chain; and (iii) the saturated or unsaturated state of the carbon chain. Table 1 presents the major groups of Gram-negative phytopathogens with their associated QS signals and regulated phenotypes.

Soft rot pectobacteria are amongst the better characterized groups of phytopathogens dependent on AHL-QS for infection. These broad-host-range bacteria cause disease in a variety of plant species, including the major crop potato (*Solanum tuberosum*) (Barnard and Salmond, 2007, Barnard *et al.*, 2007; Barras *et al.*, 1994). In several pectobacteria, QS has been reported to regulate the production of plant cell wall-degrading enzymes (PCWDEs) (Barras *et al.*, 1994), including Nip (necrosis-

Table 1 Examples of quorum sensing (QS) signals and QS-dependent traits of plant-pathogenic bacteria.

Bacterium	QS molecule	Phenotype	Reference
AHL signals			
<i>Pseudomonas syringae</i> pv. <i>tabaci</i> *	3-oxo-C6-HSL, C6-HSL	Negative regulation of biosurfactant, extracellular polysaccharides, iron acquisition, virulence	Shaw <i>et al.</i> (1997); Taguchi <i>et al.</i> (2006)
<i>Pseudomonas syringae</i> pv. <i>syringae</i> *	3-oxo-C6-HSL	Exopolysaccharide (EPS), oxidative stress tolerance, extracellular degrading enzymes, negative regulator of swarming	Dumenyo <i>et al.</i> (1998); Quinones <i>et al.</i> (2004, 2005)
<i>Pantoea stewartii</i> ssp. <i>stewartii</i>	3-oxo-C6-HSL	EPS stewartian, biofilm development, host colonization	Beck von Bodman and Farrand (1995); Koutsoudis <i>et al.</i> (2006)
<i>Agrobacterium tumefaciens</i> *	3-oxo-C8-HSL	Ti plasmid conjugal transfer genes	Farrand <i>et al.</i> (2002); Zhang <i>et al.</i> (1993)
<i>Pectobacterium atrosepticum</i> *	3-oxo-C6-HSL, C6-HSL†, 3-oxo-C8-HSL and 3-oxo-C10-HSL†	Extracellular cell wall-degrading enzymes, antibiotic carbapenem, virulence factor	Corbett <i>et al.</i> (2005); Crépin <i>et al.</i> (2012)
<i>Pectobacterium carotovorum</i> *	3-oxo-C6-HSL, C6-HSL, 3-oxo-C8-HSL	Extracellular cell wall-degrading enzymes, antibiotic carbapenem, harpin HrpN	Barnard <i>et al.</i> (2007); Barnard and Salmond (2007); Crépin <i>et al.</i> (2012); Mukherjee <i>et al.</i> (1997, 2000)
<i>Dickeya dadantii</i> *	3-oxo-C6-HSL, 3-oxo-C8-HSL	Role of AHL not known	Crépin <i>et al.</i> (2012)
<i>Dickeya zeae</i>	3-oxo-C6-HSL, C6-HSL	Cell motility, aggregation	Hussain <i>et al.</i> (2008)
<i>Burkholderia glumae</i>	C6-HSL, C8-HSL	Toxoflavin biosynthesis and transport	Kim <i>et al.</i> (2004)
Non-AHL signals			
<i>Ralstonia solanacearum</i> *	3-Hydroxypalmitic acid methyl ester	EPS, endoglucanase, pectin methyl esterase	Flavier <i>et al.</i> (1997)
<i>Xanthomonas oryzae</i> pv. <i>oryzae</i> *	DSF, BDSF, CDSF	EPS, extracellular xylanase	He <i>et al.</i> (2010)
<i>Xanthomonas campestris</i> pv. <i>campestris</i> *	DF, DSF	Xanthomonadin, EPS, extracellular enzymes, biofilm dispersal, oxidative stress tolerance	Barber <i>et al.</i> (1997); Dow <i>et al.</i> (2003); He <i>et al.</i> (2011, 2006); Wang <i>et al.</i> (2004)
<i>Xylella fastidiosa</i> *	DSF (<i>Xylella</i>)	Biofilm formation in insects	Colnaghi Simionato <i>et al.</i> (2007); Newman <i>et al.</i> (2004)
<i>Dickeya dadantii</i>	VFM signal	Extracellular cell wall-degrading enzymes	Nasser <i>et al.</i> (2013)

C6-HSL, *N*-hexanoyl-L-homoserine lactone; C8-HSL, *N*-octanoyl-L-homoserine lactone; 3-oxo-C6-HSL, *N*-(3-oxohexanoyl)-L-homoserine lactone; 3-oxo-C8-HSL, *N*-(3-oxooctanoyl)-L-homoserine lactone; 3-oxo-C10-HSL, *N*-(3-oxodecanoyl)-L-homoserine lactone; AHL, *N*-acylhomoserine lactone; DF, dodecenoic acid, 3-hydroxybenzoic acid; BDSF and CDSF, *cis*-11-methyldodeca-2,5-dienoic acid; DSF (*Xylella*), 12-methyl-tetradecanoic acid; VFM, virulence factor modulating signal—the signal has not yet been identified.

*Included in the list of the Top 10 bacterial phytopathogenic species, according to Mansfield *et al.* (2012).

†Trace amounts.

inducing virulence protein), Svx (secreted virulence factor) (Corbett *et al.*, 2005; Mattinen *et al.*, 2004), the antibiotic carbapenem (Barnard *et al.*, 2007; Whitehead *et al.*, 2002) and the type III secreted harpin HrpN (Mukherjee *et al.*, 1997). These are controlled by the AHLs *N*-(3-oxohexanoyl)-L-homoserine lactone (3-oxo-C6-HSL) and/or *N*-(3-oxooctanoyl)-L-homoserine lactone (3-oxo-C8-HSL) (Barnard and Salmond, 2007). Recent microarray analysis studies carried out by Liu *et al.* (2008) have suggested that QS is a master regulator of phytopathogenesis in *Pectobacterium atrosepticum*, thus having an even greater contribution to pathogenesis than previously thought, and highlighting the importance of targeting these pathways as a means to fight *pectobacteria*-mediated infections.

As a result of the important role played by QS in the induction of virulence-related traits in pathogenic bacteria, many studies have

aimed to identify antagonistic molecules and enzymes that disturb QS pathways. Wide-range screening procedures of both synthetic and natural compounds are being employed as a strategy to fight disease in both plants and animals. The mechanism of interference with QS is termed 'quorum quenching' (QQ) and can be achieved in several ways: (i) inhibition of the transcription/activity of enzymes involved in the biosynthesis of QS signalling molecules; (ii) destruction of the QS signalling molecules in the medium and thus the prevention of their accumulation; and (iii) inhibition of the activation of QS receptors (Chernin *et al.*, 2011; Czajkowski and Jafra, 2009; Dong *et al.*, 2001, 2007). Of these three mechanisms, the most studied and applied method, with regard to plant pathology, is the use of AHL-degrading enzymes against soft rot *pectobacteria*.

Figure 1 presents an overview of the different QS manipulation mechanisms affecting plant-microbe interactions.

Fig. 1 Overview of the different quorum sensing (QS) manipulation mechanisms occurring in various plant-microbe interactions. The following examples are indicated. (1) Ajoene for natural QS-inhibiting substances produced by plants. (2) Karakin1 for natural QS-inducing substances produced by plants. (3) Dimethyl disulfide for bacterial volatiles inhibiting QS. (4, 5) *N*-Acylhomoserine lactone (AHL) produced by epiphytic bacteria or transgenic plants, respectively. Pointed arrows show QS-inducing mechanisms; T-shaped signs show QS-inhibiting mechanisms. Grey ovals indicate AHL-degrading enzymes; brown ellipses indicate affected bacteria (e.g. phytopathogens); purple ellipses indicate plant-associated bacteria (e.g. plant growth-promoting rhizobacteria, PGPR). Figure was drawn by Rachel Dror.

DISRUPTION OF QS BY AHL-DEGRADING ENZYMES

It is now commonly accepted that bacteria employ QQ enzymes that can inhibit the QS pathways of their neighbours. These enzymes are not necessarily produced in order to inhibit the QS pathways of neighbouring bacteria, but could rather serve to degrade the QS signalling molecules and render them as available food and energy sources (Leadbetter and Greenberg, 2000).

The first QQ enzyme was identified and purified from the Gram-positive *Bacillus* sp. strain 240B1 (Dong *et al.*, 2000). The gene encoding the enzyme was named *aiiA* (for AI inactivation), and its protein product was shown to inactivate AHL signals by hydrolysis of the lactone ring (Dong *et al.*, 2001). Expression of *aiiA* in *Pectobacterium carotovorum* (formerly named *Erwinia carotovora*) decreased significantly AHL release and soft rot disease symptoms in different detached tissues of potato, eggplant, Chinese cabbage, carrot and celery.

Additional QQ activities were identified in a soil isolate of *Variovorax paradoxus* (Leadbetter and Greenberg, 2000) and, later, in *Ralstonia* strain XJ12B. The enzyme (AiiD) isolated from *Ralstonia* sp. exhibited an acylase activity, and was capable of hydrolysis of the AHL amide, releasing homoserine lactone and the corresponding fatty acid (Lin *et al.*, 2003). Expression of *aiiD* in *P. aeruginosa* decreased significantly the concentration of AHL released by the transformed bacterium, as well as its ability to swarm and produce extracellular proteolytic enzymes. Figure 2 demonstrates the enzymatic breakdown of AHLs by lactonase and acylase.

Throughout the years, additional AHL-degrading enzymes have been identified in several bacterial species, among them *Bacillus* spp. (Dong *et al.*, 2002; Han *et al.*, 2010; Rowley *et al.*, 2009), *Pseudomonas* spp. (Fekete *et al.*, 2010; Huang *et al.*, 2003; Uroz *et al.*, 2003), *Rhodococcus* spp. (Park *et al.*, 2006; Uroz *et al.*, 2005), *Comamonas* spp. (Uroz *et al.*, 2003), *Agrobacterium*

tumefaciens (Haudecoeur *et al.*, 2009; Khan and Farrand, 2009; Zhang *et al.*, 2002), *Actinobacter* sp. (Kang *et al.*, 2004), *Arthrobacter* sp., *Klebsiella pneumonia* (Park *et al.*, 2003), *Ochrobactrum* sp. (Mei *et al.*, 2010), *Microbacterium* spp. (Wang *et al.*, 2012), *Brucella melitensis* (Terwagne *et al.*, 2013) and *Ralstonia* sp. (Chen *et al.*, 2009; Han *et al.*, 2010).

As apparent from the above list, AHL-degrading enzymes have been identified in both Gram-positive and Gram-negative bacteria, including in AHL-producing strains, which probably use them to regulate QS as reported in *A. tumefaciens* (Khan and Farrand, 2009).

TRANSGENIC PLANTS WITH AHL-DEGRADING ENZYMES

Several studies have shown that, in the laboratory, transgenic plants expressing bacterial AHL-degrading enzymes are more resistant to infection by phytopathogens. Dong *et al.* (2001) initially showed that *aiiA* could be expressed in tobacco and potato plants. Compared with control plants, transgenic plants expressing the *aiiA* lactonase from *Bacillus* sp. exhibited a significant reduction in the maceration area of leaves (tobacco) or tubers (potato) when infected with *Pe. carotovorum*. The authors suggested that the activity of the expressed enzyme slowed down the production of virulence factors, thereby providing the host plant with time to build up the defence mechanism that could eventually overcome the pathogenic invaders.

Ban *et al.* (2009) used a similar approach when transforming *Amorophophallus konjac* with a lactonase (*aiiA*) from *Bacillus thuringiensis*. Transgenic plants expressing *aiiA* showed enhanced resistance (in terms of lesion size on leaves) to *Pe. carotovorum* infection when compared with control plants.

It is worth noting that some plants naturally synthesize QQ enzymes with comparable activities to bacterial AHL-degrading enzymes (Amara *et al.*, 2011; Barea *et al.*, 2013). Extracts from legumes, including alfalfa, clover, lotus and yam beans, have

Fig. 2 Degradation of *N*-acylhomoserine lactone (AHL) by lactonase and acylase enzymes.

been reported to possess AHL-degrading capabilities. AHL degradation was detected only on *N*-hexanoyl-HSL (C6-HSL) and not on AHL containing longer acyl chains (Delalande *et al.*, 2005; Götz *et al.*, 2007). The temperature dependence of this activity suggested that the observed degradation was enzymatic. The biochemical nature of the enzymes has not been verified to date, but the comparison of the AHL-to-HS ratio in yam beans suggested that the degrading activity can be related to lactonases.

Although the use of transgenic plants expressing bacterial AHL-degrading enzymes shows promising results, large-scale application of genetically modified plants in the field is problematic because of potential ecological risks and negative public opinion with regard to transgenic crops. A more acceptable approach (discussed below), in which bacteria harbouring AHL-degrading enzymes are used as biocontrol agents, is currently being examined by various researchers.

AHL-DEGRADING BACTERIA AS BIOCONTROL AGENTS

The use of plant-beneficial bacteria to improve plant health has been studied for many years as an alternative to conventional chemical-based agriculture. In this regard, a relatively new emerging field of study is the use of bacterial biocontrol agents to manipulate QS pathways. This field of study also presents an alternative approach to the genetic modification of plants with bacterial lactonases. Molina *et al.* (2003) were the first to report the use of bacteria expressing native or ectopic AHL-degrading enzymes as biocontrol agents. The authors examined two phytopathogenic bacteria, *Pe. carotovorum* and *A. tumefaciens*, and two biocontrol agents: (i) *Bacillus* sp. A24, natively expressing AHL-degrading enzyme; and (ii) genetically engineered *P. fluorescens* with the plasmid pME6863, carrying the *aiiA* gene from *Bacillus* sp. A24. Co-inoculation of *Pe. carotovorum*-infected potato plants with wild-type *Bacillus* sp. A24, or the genetically engineered *P. fluorescens* P3/pME6863 strain, resulted in a significant decrease in tissue rot symptoms compared with the controls. Suppression of potato soft rot was observed even when the AHL-degrading *P. fluorescens* P3/pME6863 was applied to tubers 2 days after the pathogen, indicating that biocontrol was not only preventative, but also curative. In addition, co-inoculation of tomato plants with the pathogen *A. tumefaciens* and the biocontrol agents *P. fluorescens* P3/pME6863 and *Bacillus* sp. A24 significantly reduced the amount and weight of galls.

Since the work of Molina *et al.*, many additional studies have demonstrated effective biocontrol activity obtained by applying bacteria harbouring AHL-degrading enzymes to plants. Several of these studies have focused on bacteria belonging to the genus *Rhodococcus*. These bacteria possess three QQ enzymatic activ-

ities, lactonase, amidohydrolase and reductase (Park *et al.*, 2006; Uroz *et al.*, 2005), and are native to potato rhizospheres (Cirou *et al.*, 2007, 2011; Jafra *et al.*, 2006). The native bacterial community could have an advantage over 'immigrants', as biocontrol agents must be able to cope with the competitive conditions of the rhizosphere, and 'rhizosphere competence' is more likely to belong to indigenous bacteria. Indeed, the biostimulation of native AHL-degrading *Rhodococcus* spp. by γ -caprolactones increased significantly the occurrence of *Rhodococcus* spp. in hydroponic systems for the culture of potatoes. Moreover, isolated *Rhodococcus* strains from the enriched system exhibited efficient biocontrol activity against soft rot of potato tubers (Cirou *et al.*, 2007, 2011, 2012).

Recently, the construction of bifunctional recombinant strains by the transformation of natural plant growth-promoting rhizobacteria (PGPR) with an AHL-degrading gene has also been proposed as a method to enhance the efficiency of QQ biocontrol agents to fight plant diseases. *Lysobacter enzymogenes* is considered to be an effective PGPR and has been reported to control diseases caused by fungal pathogens, including *Rhizoctonia solani*, *Fusarium solani* and *F. graminearum*, and by the oomycete *Phytophthora capsici* (Hayward *et al.*, 2010; Jochum *et al.*, 2006; Qian *et al.*, 2009). However, *L. enzymogenes* does not serve as an efficient biocontrol agent against *Pectobacterium* spp. In attempts to improve the biocontrol spectrum of *L. enzymogenes*, Qian *et al.* (2010) transformed these bacteria with a lactonase gene *aiiA*, transcribed by a strong and constitutive *Escherichia coli* promoter. Indeed, genetically engineered *Lysobacter* strains decreased significantly bacterial soft rot symptoms of Chinese cabbages *in vitro* and cactus *in vivo*. Li *et al.* (2011) also constructed a bifunctional recombinant strain by expressing an *aiiA* gene of *B. thuringiensis* in *P. putida* cells. The authors succeeded to localize the AiiA protein to the surface of *P. putida* cells by fusing it to an ice nucleation InaQ-N anchoring motif. The genetically modified *P. putida* cells reduced significantly the maceration area of potato slices infected with *Pe. carotovorum* compared with the parental *P. putida* wild-type strain.

Construction of recombinant strains with an AHL-degrading gene has also been proven to be useful for the identification of QS-regulated functions in plant-associated bacteria, including traits important for their beneficial biocontrol and plant growth-promoting properties (reviewed by Chernin, 2011).

The wide distribution and diversity of AHL-degrading bacteria provides opportunities for their use as effective biocontrol agents against AHL-utilizing phytopathogens. However, to the best of our knowledge, the biocontrol efficiency of such biocontrol agents has not yet been demonstrated in the field, and further experiments need to be performed in order to fully estimate the potential applicability and success of such a method. In addition, although

successful in decreasing specific disease indices, the use of AHL-degrading biocontrol agents could lead to non-target interactions that might interfere with the biocontrol activity of other strains. Molina *et al.* (2003) illustrated this problem by co-inoculating *P. chlororaphis* PCL1391 with *P. fluorescens* P3/pME6863. *Pseudomonas chlororaphis* produces antibiotics that suppress tomato vascular wilt caused by *F. oxysporum*. Co-inoculation of this biocontrol agent with the AHL degrader *P. fluorescens* P3/pME6863 interfered with its antimycotic activity and abolished the protection against vascular wilt. Thus, the possibility of non-target interactions that can interfere with the biocontrol activity or beneficial traits of other strains should be considered when applying an AHL-degrading biocontrol agent to the rhizosphere.

DISRUPTION OF QS BY BACTERIAL VOLATILES

Volatile organic compounds (VOCs) are low-molecular-mass molecules defined as airborne organic metabolites vaporized into the atmosphere (Insam and Seewald, 2010; Wheatley, 2002; Yuan *et al.*, 2009). Over recent years, VOCs produced by plant-associated bacteria have received increasing attention because of their involvement in inter-kingdom, long-distance communication with plants (Mendes *et al.*, 2013). Many of these bacterial VOCs have provided new sources of compounds with antibiotic (Dandurishvili *et al.*, 2011; Kai *et al.*, 2009; Wenke *et al.*, 2010), induced systemic resistance (Farag *et al.*, 2013) and plant growth-promoting (Bailly and Weisskopf, 2012; Blom *et al.*, 2011) activities. A group of volatile sulfur compounds, such as dimethyl sulfide, dimethyl disulfide (DMDS) and dimethyl trisulfide, is commonly produced by bacteria (Schulz and Dickschat, 2007). DMDS was measured as the main volatile in the headspace of *Serratia plymuthica* strain IC1270, and was shown to efficiently suppress the growth of *Agrobacterium* strains (Dandurishvili *et al.*, 2011). Similarly, DMDS has been shown to be produced by *S. plymuthica* HRO-C48 (Müller *et al.*, 2009), *Burkholderia ambifaria* (Groenhagen *et al.*, 2013) and by certain plants, including species of *Allium* and *Brassica* (Kyung and Lee, 2001). In addition to their inhibitory and toxic effects against a wide range of prokaryotic and eukaryotic organisms, bacterial VOCs, specifically DMDS, have been shown recently to have strong QQ activity (Chernin *et al.*, 2011). VOCs produced by the rhizospheric strains B-4117 of *P. fluorescens* and IC1270 of *S. plymuthica* act as inhibitors of the QS network mediated by AHLs. Treatment of AHL-producing biocontrol strains *P. fluorescens* 2-79 and *P. chlororaphis* 449, as well as the opportunistic pathogen *P. aeruginosa* PAO1, with DMDS drastically decreased the amount of AHLs produced by these bacteria. Similar results were obtained when exposing these bacteria to a pool of VOCs emitted by strain *S. plymuthica* IC1270, among which DMDS was the major headspace volatile (Dandurishvili *et al.*, 2011). This decrease was observed in AHLs

with both short and long chains, including unsubstituted and substituted derivatives. The authors suggested that these VOCs suppressed the transcription of genes encoding the corresponding AHL synthases. However, no quantitative correlation was observed between the extent of the decrease in transcription of AHL-encoding genes and the inhibition of AHL production. Thus, it is likely that additional factors might be involved in the suppression of AHL biosynthesis. Notably, QS pathways returned to normal function after stopping VOC treatment, indicating that the observed QQ effect was reversible (Chernin *et al.*, 2011). Obviously, VOCs and AHLs can compete in the same bacterium, affecting its ability to induce the QS response. Thus, in bacteria producing both DMDS and AHLs, QS induction will depend on the mutual interactions between these signals (Chernin *et al.*, 2013; Müller *et al.*, 2009). Despite the high abundance of bacterial VOCs and AHLs in the plant's environment, studies demonstrating actual QQ activities of bacterial VOCs against plant pathogens are lacking, and the question of whether such interactions occur under natural conditions, e.g. in the rhizosphere, remains to be addressed.

EFFECT OF AHL ON PLANTS

Plant-associated habitats (rhizosphere, phyllosphere, endosphere) are potentially favourable for QS signalling, because they are spatially structured and are colonized, at least locally, at a high cell density by diverse bacterial populations. Experimental evidence supports this assertion (reviewed by Faure *et al.*, 2009). Ten to twenty per cent of the cultivable bacteria in rhizospheric environments are AHL-producing strains, which communicate at both the intra- and inter-species level (D'Angelo-Picard *et al.*, 2004; Steidle *et al.*, 2001, 2002). Moreover, AHL signalling is implicated in the manifestation of plant-associated phenotypes in pathogenic, symbiotic and biocontrol bacterial strains. The functions controlled by QS are highly diverse, including the horizontal transfer of plasmids in *A. tumefaciens* and the regulation of rhizospheric competence factors, such as antibiotic synthesis, in many biocontrol strains (e.g. *Bacillus*, *Pseudomonas*, *Serratia*), as well as functions that are directly implicated in plant-bacteria associations, such as virulence factors (reviewed by Hartman *et al.*, 2014). It is not surprising, therefore, that plants are able to perceive bacterial QS molecules and respond to them with changes in gene expression and modifications in development. Schuëgger *et al.* (2006) first reported that AHL signals produced by *S. liquefaciens* MG1 and *P. putida* IsoF in the rhizosphere increase systemic resistance of tomato plants against the fungal leaf pathogen *Alternaria alternata*, and systemically induce salicylic acid- and ethylene-dependent defence genes. In addition, AHL signalling molecules of *S. plymuthica* HRO-C48 were shown to be responsible for protection of cucumbers against *Pythium apahnidematum*, as well as for the

induction of systemic resistance against *Botrytis cinerea* in bean and tomato plants (Pang *et al.*, 2009). Accordingly, the mutant of *S. plymuthica* HRO-C48, impaired in the production of AHLs, could not provide this protection. Mathesius *et al.* (2003) used proteome analysis to show that the model legume *Medicago truncatula* is able to detect nanomolar to micromolar concentrations of bacterial AHLs from both symbiotic (*Sinorhizobium meliloti*) and pathogenic (*Pseudomonas aeruginosa*) bacteria. Depending on AHL structure, concentration and time of exposure, the authors recorded a change in translation of over 150 proteins, as well as in the nature of compounds secreted by the plants.

Several studies have reported that various AHL molecules can be transported within plants. Götz *et al.* (2007) demonstrated the translocation of both C6-HSL and *N*-octanoyl-L-homoserine lactone (C8-HSL) from roots into barley shoots, whereas *N*-decanoyl-L-homoserine lactone (C10-HSL) was not transported. Similarly, C6-HSL, but not C10-HSL, was translocated from roots to shoots in Arabidopsis plants, thereby promoting root growth (von Rad *et al.*, 2008). In turn, C10-HSL was shown to modulate root development, whereas *N*-dodecanoyl-L-homoserine lactone (C12-HSL) strongly induced root hair formation (Ortiz-Castro *et al.*, 2008). Schikora *et al.* (2011) published results suggesting that *N*-(3-oxotetradecanoyl)-L-homoserine lactone (oxo-C14-HSL) and, to a lesser extent, *N*-(3-hydroxytetradecanoyl)-L-homoserine lactone (OH-C14-HSL) induced resistance against the powdery mildew fungi *Golovinomyces orontii* in Arabidopsis and *Blumeria graminis* f. sp. *hordei* in barley plants. In addition, oxo-C14-HSL-treated Arabidopsis plants were more resistant against the bacterial pathogen *P. syringae* pv. *tomato*. From the above, it appears that long-chain AHLs (C12–C14) are more efficient in inducing systemic resistance, whereas short chains, which can be translocated in the plant, can better induce growth. In addition to the effect of variable chain length on plant responses, modifications at the γ positions in the fatty acid chain of AHLs have also been found to play a role. Substitution by a hydroxy (OH) or oxy (O) group at this position affects plants differently, with the oxy group substitution being more effective in resistance induction. Schikora *et al.* (2011) demonstrated that oxo-C14-HSL induced the activation of mitogen-activated protein kinases (MAP-kinases) AtMPK3 and AtMPK6, followed by a higher expression of certain defence-related transcription factors. It is known that the induction of different MAP-kinase cascades is one of the first steps in pathogen perception, and that AtMPK6 and AtMPK3 play an important role in the signalling cascades of several pattern recognition receptors that are crucial in the induction of defence mechanisms in plants (reviewed by Pitzschke *et al.*, 2009). Subsequent work by this group described a negative correlation between the length of AHL lipid chains and growth promotion of *A. thaliana*, and a positive correlation

between the induction of defence mechanisms and the length of the lipid moieties (Schenk *et al.*, 2012). Altogether, these results suggest that AHLs, commonly produced in the rhizosphere, are crucial factors in plant pathology, influencing both the bacterial and plant community.

MANIPULATION OF QS-DEPENDENT PATHWAYS BY PLANTS

As a result of the importance of QS signalling in plant-associated habitats, it is not surprising that plants are able to produce compounds that serve as both agonists and antagonists of QS pathways. Dozens of plant molecules, whose production profiles change with the developmental stage of the plant, have been isolated and catalogued for their potential to interfere with bacterial signalling (Teplitski *et al.*, 2000, 2004). Several plant species secrete AHL mimics, which can either stimulate or inhibit bacterial AHL QS systems (reviewed by Bauer and Mathesius, 2004; Teplitski *et al.*, 2011). QS biomimics have been discovered in plants and bacteria (McDougald *et al.*, 2007). The detection of AHL mimics has been reported in secretions of pea, rice, soyabean, tomato, crown vetch, *M. truncatula* and from the unicellular algae *Chlamydomonas reinhardtii* (Degrassi *et al.*, 2007; Gao *et al.*, 2003; Teplitski *et al.*, 2000, 2004). The precise source, structure and biological significance of these AHL mimics from plants are currently unknown, and their function is still speculative. The first natural compound shown to inhibit QS was discovered in the red marine alga *Delisea pulchra*. Givskov *et al.* (1996) found that the alga produces halogenated furanones, structurally related to homoserine lactones, which bind to the AHL receptors and increase their turnover. Similar effects have also been reported in the green alga *Ulva lactuca* (Rasmussen and Givskov, 2006). Notably, QQ activity was found in about 25% of ~280 extracts from marine organisms (reviewed by Harder *et al.*, 2014), demonstrating the potential for the further identification of specific QS antagonists from marine organisms (Skindersoe *et al.*, 2008).

Since the first discovery of QS inhibitors of plant origin, many more such compounds have been discovered in plants (reviewed by Koh *et al.*, 2013; LaSarre and Federle, 2013; Rasmussen and Givskov, 2006). These compounds have been examined extensively for potential application in medicine, agriculture and various industries, ranging from the pharmaceutical, cosmetic and food biotechnology to the textile industry. The QS-inhibitory effects of plant extracts have been studied mainly in human pathogens, and there is hardly any information on the effect of such compounds on plant pathogens. However, as several QS pathways of human and plant pathogens possess homologous receptors and AIs, we believe that important information can be obtained using the data reported for human pathogen systems for the study of plant–pathogen interactions.

Table 2 Examples of quorum quenching (QQ) compounds produced by plants.

Plant	Source	QQ compound	Reference
<i>Allium sativum</i> (garlic)	Bulb extracts	Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide)	Bjarnsholt <i>et al.</i> (2005); Jakobsen <i>et al.</i> (2012b); Rasmussen <i>et al.</i> (2005a)
		DMDS (dimethyl disulfide, CH ₃ -S-S-CH ₃)	Chernin <i>et al.</i> (2011); Kyung and Lee (2001)
		<i>p</i> -Coumaric acid	Bodini <i>et al.</i> (2009); Schaeffer <i>et al.</i> (2008)
<i>Armoracia rusticana</i> (horseradish)	Root extracts	Isothiocyanate iberin [1-isothiocyanato-3-(methylsulfinyl)propane]	Jakobsen <i>et al.</i> (2012a)
<i>Brassica oleracea</i> (broccoli)	Extracts, synthetic preparations	Isothiocyanates sulforaphane (4-methyl sulfinyl butyl isothiocyanate) and its precursor erucin (4-methyl thiobutyl isothiocyanate), analogues of iberin	Ganin <i>et al.</i> (2013)
<i>Carex pumila</i> (sand sedge)	Extracts	Resveratrol dimer ϵ -viniferin (5-[(2 <i>R</i> ,3 <i>R</i>)-6-hydroxy-2-(4-hydroxyphenyl)-4-[(<i>E</i>)-2-(4-hydroxyphenyl)ethenyl]-2,3-dihydro-1-benzofuran-3-yl]benzene-1,3-diol)	Cho <i>et al.</i> (2013)
<i>Citrus</i> spp.	Extracts	<i>O</i> -Glycosylated flavonoids naringenin [5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one], neohesperidin, hesperidin	Truchado <i>et al.</i> (2012); Vikram <i>et al.</i> (2010)
<i>Citrus × paradisi</i> (grapefruit)	Juice	Furanocoumarin (6',7'-dihydroxybergamottin); oxygenated triterpenoid obacunone (obacunic acid)	Girenavar <i>et al.</i> (2008); Vikram <i>et al.</i> (2010)
<i>Curcuma longa</i> (turmeric)	Extracts	Curcumin [(1 <i>E</i> ,6 <i>E</i>)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]	Rudrappa and Bais (2008)
<i>Elettaria cardamomun</i> (green cardamom)	Essential oil	Cineol, syn/eucalyptol (1,3,3-trimethyl-2-oxabicyclo [2,2,2]octane)	Jaramillo-Colorado <i>et al.</i> (2012)
Fruits (e.g. apple, pear, peach, banana, pineapple, grape)	Extracts	Patulin (4-hydroxy-4 <i>H</i> -furo[3,2- <i>c</i>]pyran-2(6 <i>H</i>)-one)	Rasmussen <i>et al.</i> (2005a)
Forest plants	Smoke	Karrikins (a family of butenolides related to 3-methyl-2 <i>H</i> -furo[2,3- <i>c</i>]pyran-2-one)	Mandabi <i>et al.</i> (2014)
<i>Lippia alba</i> (bushy <i>Lippia</i>)	Essential oil	Limonene-carvone and citral (geranial-neral)	Jaramillo-Colorado <i>et al.</i> (2012)
<i>Medicago sativa</i> (alfalfa)	Seed exudates	An arginine analogue L-canavanine ((2 <i>S</i>)-2-amino-4-[(diaminomethylidene)amino]oxy)butanoic acid)	Keshavan <i>et al.</i> (2005)
<i>Minthostachys mollis</i> (muña)	Essential oil	Monoterpene pulegone [(<i>R</i>)-5-methyl-2-(1-methylethylidene)cyclohexanone]	Jaramillo-Colorado <i>et al.</i> (2012)
<i>Myristica cinnamomea</i> (nutmeg)	Nut extracts	Malabaricone C	Chong <i>et al.</i> (2011)
<i>Ocimum basilicum</i> (sweet basil)	Root exudates	Rosmarinic acid (α - <i>o</i> -caffeoyl-3,4-dihydroxyphenyl lactic acid)	Walker <i>et al.</i> (2004)
<i>Ocotea</i> sp.	Essential oil	Terpene α -pinene [(1 <i>S</i> ,5 <i>S</i>)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene ((-)- α -pinene)]	Jaramillo-Colorado <i>et al.</i> (2012)
<i>Origanum vulgare</i> (oregano)	Essential oil	Carvacrol	Burt <i>et al.</i> (2014)
<i>Psidium guajava</i> (guava)	Extracts	Quercetin, quercetin-3- <i>O</i> -arabinoside	Vasavi <i>et al.</i> (2014)
<i>Swinglea glutinosa</i> (Tabog)	Essential oil	Monoterpene β -pinene (6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane)	Jaramillo-Colorado <i>et al.</i> (2012)
<i>Zingiber officinale</i> (ginger)	Essential oil	Monocyclic sesquiterpene α -zingiberene [2-methyl-5-(6-methylhept-5-en-2-yl)cyclohexa-1,3-diene]	Jaramillo-Colorado <i>et al.</i> (2012)
Apple, pear, peach, apricot, banana, pineapple and grape	Fruit extracts	Polyketide lactone patulin (4-hydroxy-4 <i>H</i> -furo[3,2- <i>c</i>]pyran-2(6 <i>H</i>)-one)	Rasmussen <i>et al.</i> (2005a)

See reviews by Koh *et al.* (2013), LaSarre and Federle (2013) and Rasmussen and Givskov (2006) for more examples and references.

Table 2 provides examples of the known plant compounds with defined QQ activity. Of these compounds, the best studied examples are derived from garlic. Strong QS-inhibiting activity of garlic extracts was revealed using *P. aeruginosa* reporter strains (Bjarnsholt *et al.*, 2005). For many years, the exact compound responsible for the QQ activity of garlic was not known. However, recently an allyl sulfide, called ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide), was identified as the major bioactive QQ compound (Jakobsen *et al.*, 2012b). In *P. aeruginosa*, ajoene

specifically affects a narrow set of QS-regulated genes, including those involved in the production of the toxic glycolipid rhamnolipid, which plays an important role in the virulence of *P. aeruginosa* in mammals. The fact that ajoene inhibits only a fraction of the QS pathway suggests that the interaction of the inhibitor with its target may occur at the post-transcriptional level. Apparently, ajoene is not the sole QQ compound of garlic, and other compounds have also been shown to have QQ activity. In addition to DMDS detected in garlic extracts (Kyung and Lee,

2001) and mentioned above as a strong QS inhibitor (Chernin *et al.*, 2011), a pronounced QQ activity was also described for *p*-coumaric and hydroxycinnamic acids, produced as a part of the lignin pathway, as well as in response to wounds and nutritional stress, by a wide variety of edible plants, including garlic. These compounds have also been discovered in some bacteria, such as *Rhodopseudomonas palustris* and *Bradyrhizobium* sp. (Bodini *et al.*, 2009; Schaeffer *et al.*, 2008).

Additional substances, which have been reported to inhibit QS and the virulence of *P. aeruginosa*, include iberin [1-isothiocyanato-3-(methylsulfinyl) propane] from horseradish (*Armoracia rusticana*), and sulforaphane and erucin, which are highly abundant in broccoli and other cruciferous vegetables (Jakobsen *et al.*, 2012a). These compounds act as antagonists of the transcriptional activator LasR, thereby strongly affecting QS-controlled phenotypes, such as biofilm formation and pyocyanin production in wild-type *P. aeruginosa* strain PAO1. *Pseudomonas aeruginosa* is not a major plant pathogen; nevertheless, Ganin *et al.* (2013) suggested that sulforaphane and erucin could potentially be effective against plant pathogens, such as the broccoli pathogen *P. fluorescens* 5064, which, like *P. aeruginosa*, produces biosurfactants as an important virulence factor. Another example is the polyketide lactone patulin (4-hydroxy-4*H*-furo[3,2-*c*]pyran-2(6*H*)-one) produced by *Penicillium coprobium* (Rasmussen *et al.*, 2005b), and naturally occurring in fruits, such as apple, pear, peach, apricot, banana, pineapple and grape (Rasmussen *et al.*, 2005a). Microarray analysis has revealed that patulin targeted ~45% of QS-controlled genes in *P. aeruginosa*, suggesting that this compound specifically affects LasR and RhlR QS regulators (Rasmussen *et al.*, 2005b).

A family of butenolides related to 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one, called karrikins, was discovered in forest plant smoke, but was also found to be active in plants not normally associated with fire, including *Arabidopsis* (Flematti *et al.*, 2004). Karrikins stimulate seed germination and influence seedling growth. Chemical similarities between karrikins and strigolactones, a group of plant hormones that alter shoot and root architecture, allow plants to employ a common signal transduction pathway to respond to distinct environmental signals (reviewed by Nelson *et al.*, 2012). Structural similarities were also revealed between karrikins and certain QS molecules (AI-1 and AI-2 AIs), as well as the QS inhibitor, the lactone patulin. Recently, Mandabi *et al.* (2014) have shown that two members of the karrikin family (KAR1 and KAR2) inhibit the *rhl* QS system of *P. aeruginosa* employing C4-HSL, without interacting with the *las* QS system employing 3-oxo-C12-HSL. Accordingly, the addition of KAR1/KAR2 to *P. aeruginosa* strain PAO1 (wild-type) reduced the production of pyocyanin, controlled in part by the RhlR QS response regulator. The QQ effect of these karrikins was apparently specific to C4-HSL, as they did not affect the QS systems of the plant pathogen *P. syringae*, which

employs 3-oxo-C6-HSL as its AI. Notably, the same karrikins acted as QS mimic (agonists) compounds of 3-oxo-C8-HSL, the main QS signal produced by the Tra QS system of *A. tumefaciens*. The effect of the karrikin KAR1 on *P. aeruginosa* virulence was examined using *Arabidopsis thaliana* plants and lettuce midribs. KAR1 was unable to prevent infection of *Arabidopsis* plants, but did significantly reduce the loss of plant leaves from 24 to 48 h post-infection. A less significant, but apparent reduction was also observed in the induction of soft rot in lettuce midribs (Mandabi *et al.*, 2014).

In the last decade, many other inhibitors of QS have been discovered using high-throughput screening of both pure compounds and mixtures (reviewed by Amara *et al.*, 2011; Koh *et al.*, 2013; LaSarre and Federle, 2013; Sintim *et al.*, 2010). However, despite the wide range of phytochemicals identified as QQ compounds, knowledge about their specific involvement in plant-microbe interactions is still limited. A study reported by Palmer *et al.* (2011) indicated that the application of synthetic AHL modulators to plants might serve to reduce plant disease. In their work, the authors examined the efficiency of non-native QQ compounds to reduce disease outcome in potato tubers and beans infected with *Pe. carotovorum*. This work suggested that such QQ compounds can retain their activity profiles when introduced into the examined pathosystems. However, they noted that the inhibition of virulence in *Pe. carotovorum* infections was highly dependent on the dosage and timing of addition of the synthetic inhibitor. Therefore, with regard to plant pathology, the important question that still needs to be addressed is whether these QQ compounds play a role in protecting plants against plant pathogens under native conditions.

TRANSGENIC PLANTS ENCODING BACTERIAL AHL SYNTHASE

In plant pathogens, the QS system ensures the timely activation of specific phenotypes responsible for successful infection of the host plant. A premature activation of these bacterial phenotypes could thus trigger a defence response by the host, which might be able, at such an early time point, to overcome the pathogenic population. Therefore, a potential converse approach to QQ may be premature QS induction. Similar to the above-described QQ techniques, premature QS induction can be carried out through the genetic modification of plants to produce AHL or by the use of beneficial AHL-producing bacteria as biocontrol agents.

Reduction in disease progression as a result of increased AHL synthesis has been reported to occur through the interactions of *P. syringae* pv. *syringae* (*Pss*) with other plant epiphytic bacteria. *Pss* uses 3-oxo-C6-HSL to regulate the expression of genes conferring extracellular polysaccharide production, motility and factors contributing to virulence to plants (Quinones *et al.*, 2004,

2005). Dulla and Lindow (2009) found that a relatively high proportion of bacterial epiphytes produce the cognate AHL of *Pss*, sometimes at levels of up to 18 times higher than those produced by *Pss* itself. The authors demonstrated that the production of oxo-C6-HSL by these epiphytes caused the induction of QS in *Pss*, resulting in suppressed swarming motility and subsequent disease of the leaf.

Fray *et al.* (1999) were the first to express a bacterial AHL synthase gene in plants. The authors targeted the product of an AHL synthase gene (*yenI*) from *Yersinia enterocolitica* to the chloroplasts of tobacco plants. Transformed plants synthesized the cognate 3-oxo-C6-HSL and C6-HSL signalling molecules in sufficient amounts to induce a response in recombinant bacterial AHL biosensors, as well as to restore phenazine biosynthesis to an AHL-deficient *P. aureofaciens* strain.

Mäe *et al.* (2001) continued this line of work by constructing transgenic tobacco lines expressing the AHL synthesizing gene, *exlI*, from the plant pathogen *Pe. carotovorum*. The authors examined whether AHL production *in planta* would increase plant resistance against *Pe. carotovorum* infection. Indeed, the AHL-producing transgenic lines exhibited enhanced resistance to *Pe. carotovorum* infection compared with the parental lines, even after prolonged incubation (48 h) with the pathogen. However, different results were obtained when the AHL synthase gene (*yenI*) was transformed into the host plant potato. Toth *et al.* (2004) examined the effects of AHL production on disease development in potato following inoculation with soft rot pectobacteria. As opposed to non-host plants, the production of AHL in transgenic potato plants increased both the onset and severity of disease in potato stem and tuber inoculations.

The contrasting results of expression of bacterial AHL synthase into host and non-host plants emphasize the need for further research on the interaction between the virulent pathways of the pathogens and defence mechanisms of the host. However, this by no means diminishes the importance of studies examining ways to decrease virulent traits of phytopathogens by disturbing their QS-regulated pathways.

CONCLUDING REMARKS

It is now clear that the distribution and perception of QS signals during plant–microbe interactions profoundly affect plant health. The ability to control and manipulate the distribution of these signals could therefore provide efficient means to reduce disease and protect plant health. Promising results of *in vitro* and glass-house experiments have been presented, especially in the pathosystem *Pe. carotovorum*–potato with the employment of AHL-degrading bacteria as biocontrol agents. The efficiency of this method has yet to be demonstrated in the field because, similar to other biocontrol agents, for effective results to be produced, bacterial agents need to exhibit rhizosphere competence as well as

QQ ability. QQ enzymes degrade a wide range of AHLs; the fact that QS regulates both ‘helpful’ traits in beneficial bacteria (e.g. the production of antifungal compounds) and virulent traits in pathogens demands care in application, mainly because the proportions of advantages compared with disadvantages could change according to environmental conditions and community structure. Another possible application for QS manipulation is the use of QS antagonists. Compared with AHL-degrading enzymes, QS antagonists have a narrower spectrum of activity and thus could target specific pathogens. However, the disadvantage of this mechanism is that the longevity of these chemicals in the rhizosphere could be low and highly dependent on environmental conditions. Whatever mechanisms are used—QQ enzymes or QQ antagonists—it is clear that efficient application requires a full understanding of the specific QQ mechanisms and how they will be affected by various environmental conditions. Nevertheless, the manipulation of QS pathways is a promising method for the modification of the plant–microbe interaction in favour of plants. This is especially valuable in the light of the tight bounds between virulence and QS in pathogenic bacteria, as well as with regard to the input of man-made plant protection chemicals into the environment, which may cause the pollution of foods and concomitant health risks.

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