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Microbial small molecules – weapons of plant subversion

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Plants live in close association with a myriad of microbes that are generally harmless. However, the minority of microbes that are pathogens can severely impact crop quality and yield, thereby endangering food security. By contrast, beneficial microbes provide plants with important services, such as enhanced nutrient uptake and protection against pests and diseases. Like pathogens, beneficial microbes can modulate host immunity to efficiently colonize the nutrient-rich niches within and around the roots and aerial tissues of a plant, a phenomenon mirroring the establishment of commensal microbes in the human gut. Numerous ingenious mechanisms have been described by which pathogenic and beneficial microbes in the plant microbiome communicate with their host, including the delivery of immune-suppressive effector proteins and the production of phytohormones, toxins and other bioactive molecules. Plants signal to their associated microbes *via* exudation of photosynthetically fixed carbon sources, quorum-sensing mimicry molecules and selective secondary metabolites such as strigolactones and flavonoids. Molecular communication thus forms an integral part of the establishment of both beneficial and pathogenic plant–microbe relations. Here, we review the current knowledge on microbe-derived small molecules that can act as signalling compounds to stimulate plant growth and health by beneficial microbes on the one hand, but also as weapons for plant invasion by pathogens on the other. As an exemplary case, we used comparative genomics to assess the small molecule biosynthetic capabilities of the *Pseudomonas* genus; a genus rich in both plant pathogenic and beneficial microbes. We highlight the biosynthetic potential of individual microbial genomes and the population at large, providing evidence for the hypothesis that the distinction between detrimental and beneficial microbes is increasingly fading. Knowledge on the biosynthesis and molecular activity of microbial small molecules will aid in the development of successful biological agents boosting crop resiliency in a sustainable manner and could also provide scientific routes to pathogen inhibition or eradication.

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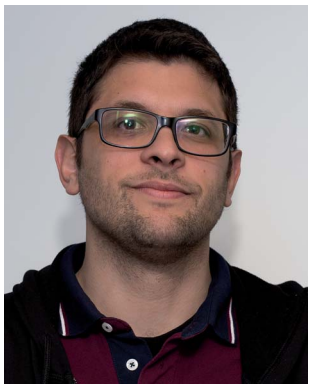
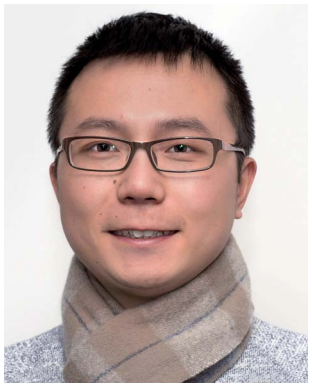
1. Introduction

Plants, unlike animals and insects, are rooted in their environment, and are consequently unable to flee from stressful situations. Therefore, plants employ a variety of mechanisms to tolerate or mitigate stress factors. It is becoming clear that plant-associated microbiota play an important role in plants' ability to avert the negative effects of stress.[1] Through exudation of sugars, amino acids and organic acids, plants invest a significant proportion (up to 20 percent[2,3]) of their photosynthetically-fixed carbon towards the maintenance of their rhizosphere- and phyllosphere-associated microbiota.[4–7] In return, beneficial microbiota, commonly referred to as the plant growth-promoting bacteria (PGPB) and fungi (PGPF) provide plants with important benefits including enhanced mineral uptake, nitrogen fixation and biocontrol,[2,3] which makes them essential for plant growth and health. Establishment of intimate beneficial plant–microbe interactions requires exchange of signalling molecules to tune immunity and promote colonization. A well-studied example is nodule formation that occurs as a symbiosis between nitrogen-fixing bacteria from the order Rhizobiales and Leguminosae plants. Nodule formation requires the coordinated development of bacterial infection and root nodule organogenesis,[8] and is



Ioannis Stringlis received his Ph.D. degree from Utrecht University (2018). During his Ph.D., under the supervision of Prof. Corné Pieterse, he studied responses activated in Arabidopsis roots following recognition of beneficial rhizobacteria and their link with induced systemic resistance and how exudation of coumarins in the rhizosphere can affect microbiome assembly. He received a BSc in Agricultural Biotechnology (2008) and a MSc (2012) in Molecular Plant Pathology from the Agricultural University of Athens. Currently, he is a postdoctoral researcher at Utrecht University. His research focuses on understanding how root immunity is activated and role of secondary metabolites on root–microbe interactions.



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Corné Pieterse was trained in plant breeding and molecular plant pathology at Wageningen University where he obtained his M.Sc. and Ph.D. degrees. Since 2004, he is full professor of Plant–Microbe Interactions and since 2009 scientific director of the Institute of Environmental Biology at Utrecht University. Current research is focused on plant-beneficial functions that are encoded by the root microbiome and the role of plant genes that aid in maximizing profitable functions from the root microbiome. With his research he aims to contribute to grand societal challenges, such as food security and sustainable agriculture.

Melvin Bolton received undergraduate degrees in Biology and Chemistry from Concordia College in 1999. During his graduate research, he received a Fulbright Fellowship to study molecular plant-microbe interactions in the group of Prof. Pierre de Wit at Wageningen University. He received a Ph.D. from North Dakota State University in the Department of Plant Pathology in 2006 followed by postdoctoral research in the USDA-ARS Plant Science Research Unit. Since 2008, he is a Plant Pathologist for the USDA-ARS in Fargo, ND focusing on sugarbeet pathology with emphasis on mechanisms of pathogen virulence and the molecular basis of fungicide resistance.

Ronnie de Jonge studied Biology, Plant Biotechnology, and Phytopathology at Wageningen University and obtained his M.Sc. and Ph.D. degrees in 2007 and 2012, respectively. During his stay as an EMBO postdoctoral fellow at the Bioinformatics and Evolutionary Genomics group at the VIB Center for Plant Systems Biology in Ghent, Belgium he performed comparative genomics analyses of plant pathogenic fungi. In 2015, he returned to The Netherlands as an assistant professor at Utrecht University. His current research focuses on the molecular aspects of root–microbe interactions and makes extensive use of high-throughput, genomics data.

initiated by the biosynthesis of rhizobial nodulation factors upon perception of plant flavonoids. Nodulation factors are recognized by plant receptors and trigger transcriptional and physiological changes that lead to root hair curling and bacteria entrapment, creating a suitable environment for nitrogen fixation and bacterial proliferation.

In addition to such symbiotic relationships, many other naturally free-living microbes can boost plant growth. When associating with their plant host, such microbes can facilitate nutrient uptake, stimulate changes in root architecture[9,10] or promote plant health. For example, plant health may benefit from selected microbes that suppress pathogens through antibiosis or competition for limited nutrients, or trigger a host immune response called induced systemic resistance (ISR).[5,11–13] PGPB and PGPF are increasingly used as biocontrol agents and biostimulants to improve crop health in a sustainable way such as without enhanced input of fertilizers and pesticides. However, unlike well-studied symbioses involving nitrogen-fixing bacteria, relatively little is known about the molecular signals and mechanisms that govern their interaction with the plant.

PGPB promote plant growth and health by interfering with root development. For example, selected *Pseudomonas* spp. strains induce root architecture modifications by activation of developmental programmes that inhibit primary root elongation, while promoting lateral root formation and root hair growth.[14] Such modifications facilitate plant establishment and increase the root's exploratory capacity for water and nutrients. Microbe-induced developmental changes can be observed even without direct contact of the PGPB, demonstrating that gaseous rhizobacterial volatile organic compounds (VOCs) are potent inducers of plant growth[15,16] and are drivers of root architectural changes.[14] VOCs have long been known to play essential roles in the communication with other organisms,[17] including those between plants and their root-associated microbiota.[18–20] Recent work[21–25] further suggest that volatile compounds from both plant pathogenic and plant beneficial microbes have profound effects on plant host transcription and development. Intriguingly, production of VOCs by the fungal root pathogen *Rhizoctonia solani* also enhances growth and accelerates development of *Arabidopsis* similar to VOCs from known beneficial microbes.[24] Future studies should reveal whether these physiological changes in the plant are part of an integrated plant defence strategy. For example, enhanced root growth may be the plants attempt to "outrun" disease. Alternatively, it may be a pathogen's strategy to increase root surface and biomass to boost the chance of successful infection.

Production of VOCs by plant-associated microbes and their subsequent perception by plants is one of the many forms of plant–microbe interactions that could ultimately result in the microbial establishment on and/or within nutrient-rich plant tissue. Successful establishment further depends on the microbes' ability to subvert plant immunity. Immune-suppressive effector proteins that are part of the microbial weaponry are best known for their role at this stage,[26] but also small molecules, also known as natural products or secondary metabolites, contribute to microbial establishment. For example, microbe-derived phytohormones such as auxin, gibberellin and cytokinins (Chart 1) can influence plant physiology in a plant-like manner, toxic compounds can disrupt cellular physiology or inhibit plant growth in general (Charts 2, 3 and 4), and microbial molecules such as siderophores and lipopeptides (Charts 5 and 6) assist in colonization but can also help the plant in nutrient uptake or stimulation of defence priming. Intriguingly, biosynthesis of these plant subverting molecules contributes to the plant-associated lifestyles of both pathogenic and beneficial microbes. In this review, we summarize recent scientific literature, on microbial metabolites that play a role in plant–microbe interactions. We highlight commonalities and particularities among plant pathogenic and beneficial microbes in a context- and host-dependent manner with an emphasis on small, natural molecules of non-proteinaceous origin. We further explore the biosynthetic potential within the genome sequences of the well-studied, plant-, and animal-associated microbial genus *Pseudomonas* emphasizing on traits that are associated with plant–microbe interactions.

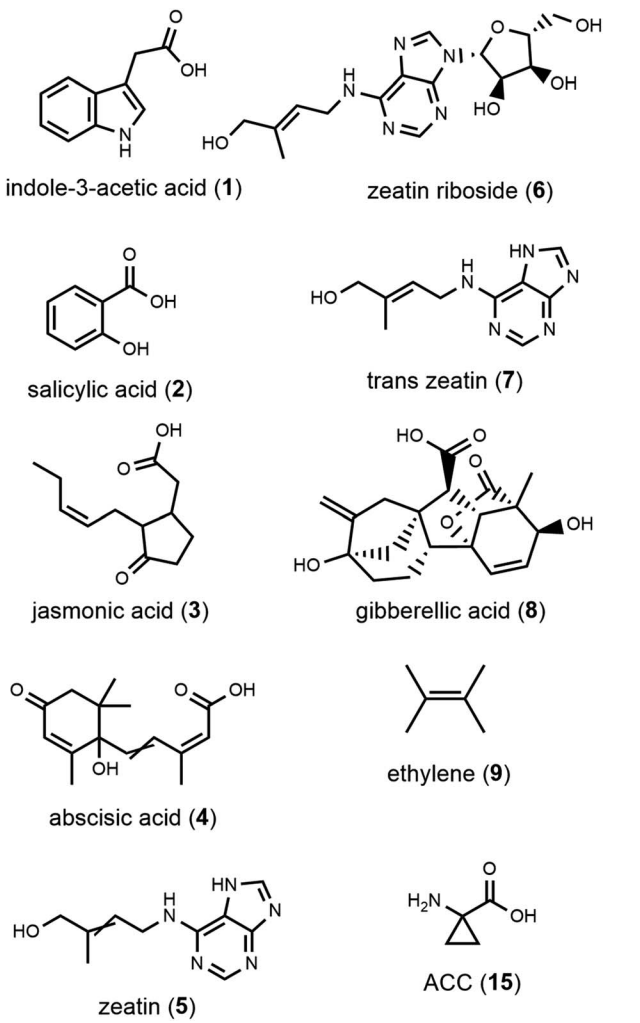


Chart 1 Chemical structures of phytohormones with a role in plant–microbe interactions.

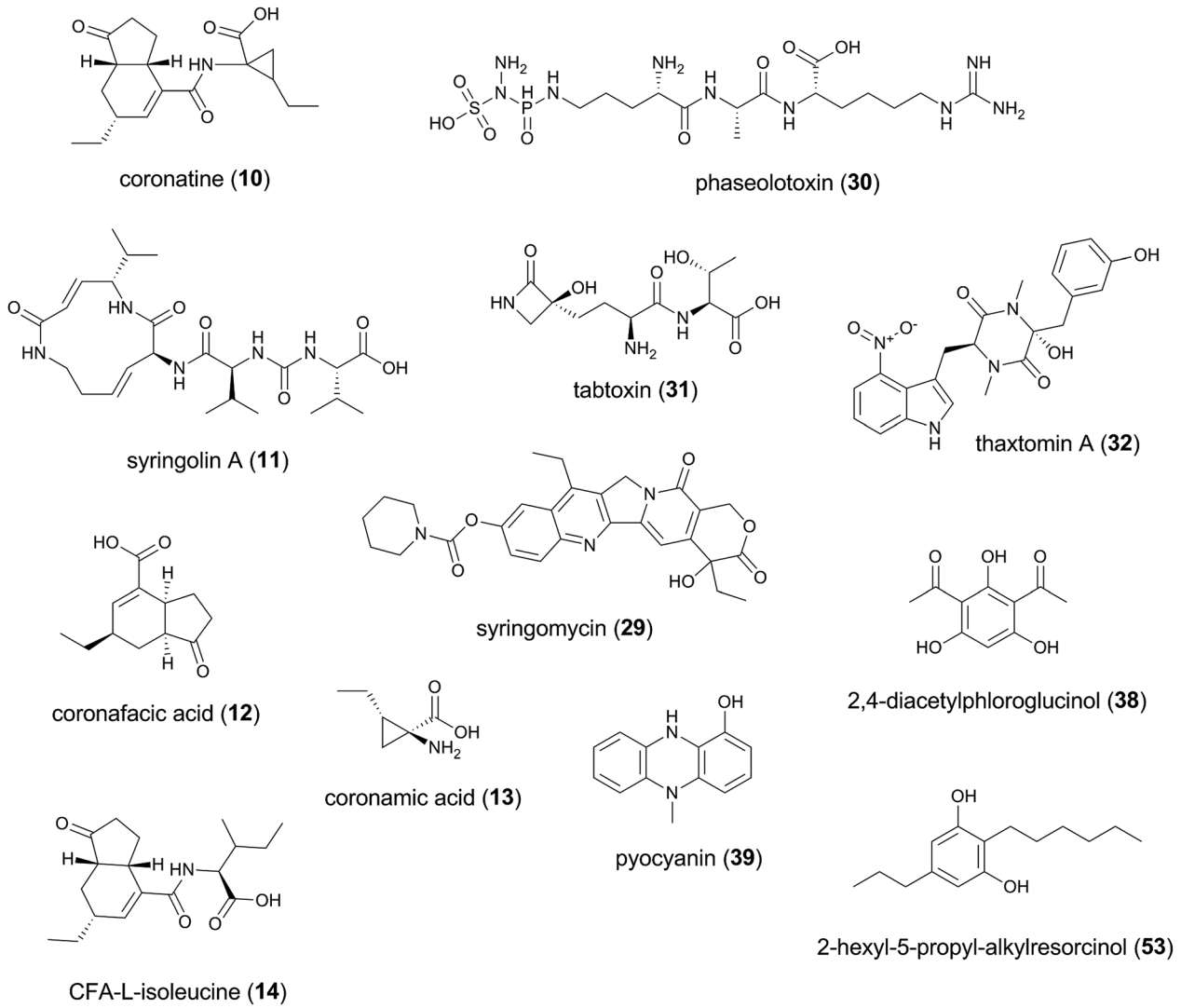


Chart 2 Chemical structures of bacterial toxins or other bacteria-derived toxic compounds with stimulatory activity.

2. Characterized chemical compounds with role in plant–microbe interactions

Many microbial molecules have been identified to date that play a role in the establishment of intricate plant–microbe interactions. Here we broadly classify these molecules in three groups, namely (a) microbe-derived plant hormones (microbial phytohormones), (b) toxins, and (c) stimulatory compounds. In the case of microbial phytohormones we broadly focus on microbial molecules that mimic or influence endogenous plant hormones or their activities as well as microbial enzymes that modify plant hormone abundance and/or distribution. For our review on toxins, we highlight a biochemically highly diverse set of microbial toxins that facilitate plant colonization. Finally, the section on stimulatory compounds refers to a broad group of microbial molecules that typically benefit the producing microbe. However, these molecules not only benefit microbial spread and persistence, they could also act as activators of plant immunity and/or alter plant physiology and consequently they are referenced as stimulatory compounds.

2.1. Microbial phytohormones

Phytohormones play a central role in controlling the way plants grow and develop. Plant hormones, from the Greek word ορμώ meaning *set in motion*, regulate how energy, derived from photosynthesis, is channelled into plant growth, development and reproduction. Unlike animals, plants do not possess specialized organs for the production of phytohormones and typically all cells are capable of their biosynthesis.[27] Through processes of active and passive diffusion, phytohormones travel throughout the plant controlling many important cellular and developmental processes, in an oftentimes concentration- and location-dependent manner. Local integration of the hormonal signalling networks *via* cross-talk directs the appropriate response. Microbes, both pathogenic and beneficial, produce a variety of molecules that may mimic plant hormones such as auxin, cytokinins and gibberellins, or influence their

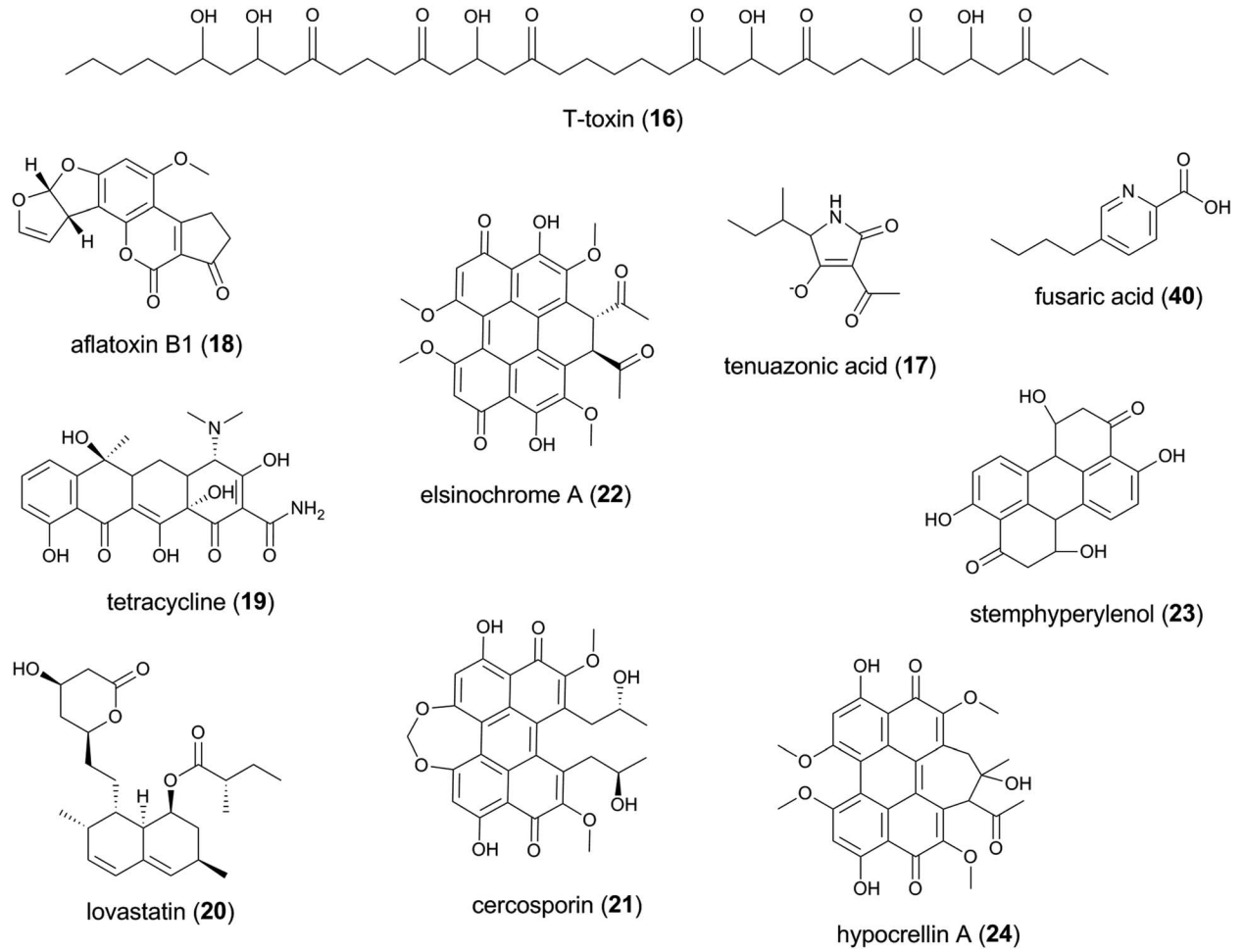


Chart 3 Chemical structures of representative fungal polyketides.

concentration by interfering with host transcription and/or enzymatic pathways.[13,28–32] The production of these phytohormones by microbes is not considered to play a direct role in microbial development but rather contribute to their interaction with the environment, particularly with plants, and are classified as secondary metabolites.

2.1.1. Indole-3-acetic acid. Indole-3-acetic acid (IAA) (**1**) is the main auxin in plants and therefore is critical for plant growth, development, and defence. Microbial production of IAA (**1**) is important for the growth-promoting activities of many beneficial microbes.[31] Indolic compounds such as IAA (**1**) are produced in large quantities in the rhizosphere and may serve as intra- and inter-species signalling molecules.[33] Indoles modulate a variety of processes in bacteria, including biofilm formation, virulence and antibiotic resistance.[33] Interestingly, bacteria that are unable to synthesize indoles themselves can modify or degrade these compounds, consequently contributing to an expanding pool of indole derivatives in nature.[33] Auxins play a central role in the coordination and regulation of many growth- and development-related processes throughout the plant's lifecycle in a concentration- and location-dependent manner both in the above-ground and below-ground tissue.[27] In order to control the fine balance between plant growth and defence, it has long been recognized that auxins are also important regulators of plant defence.[32,34] Auxins may act on the defence-associated compounds salicylic acid (SA) (**2**) and jasmonic acid (JA) (**3**) in an antagonistic and synergistic manner, respectively.[35,36] Activation of auxin signalling has a repressive effect on SA (**2**) accumulation[37] and exogenous application of IAA (**1**) can block the activation of the MAMP (microbe-associated molecular pattern) triggered immunity marker gene *CYP71A12* in *Arabidopsis* roots treated with the MAMP flg22.[38] Interestingly, plant pathogenic root-infecting microbes such as *Fusarium oxysporum* and *Ralstonia solanacearum* and even foliar pathogens such as *P. syringae* modulate auxin activity in roots or leaves to cause disease.[35,39–41]

Plant pathogens have found ways to exploit the auxin machinery of the plant to alter developmental programs for their own benefit.[32,42] For example, the soil bacterium *Agrobacterium tumefaciens* induces cell proliferation and tumour formation in plants through the integration of auxin and cytokinin biosynthesis genes into the genome of the host plant.[43,44] Also, successful infection by plant pathogens oftentimes depends on the invasion of plant tissue through so-called natural openings or cracks such as at the point of emergence of lateral roots or through leaf stomata. Alterations in stomata

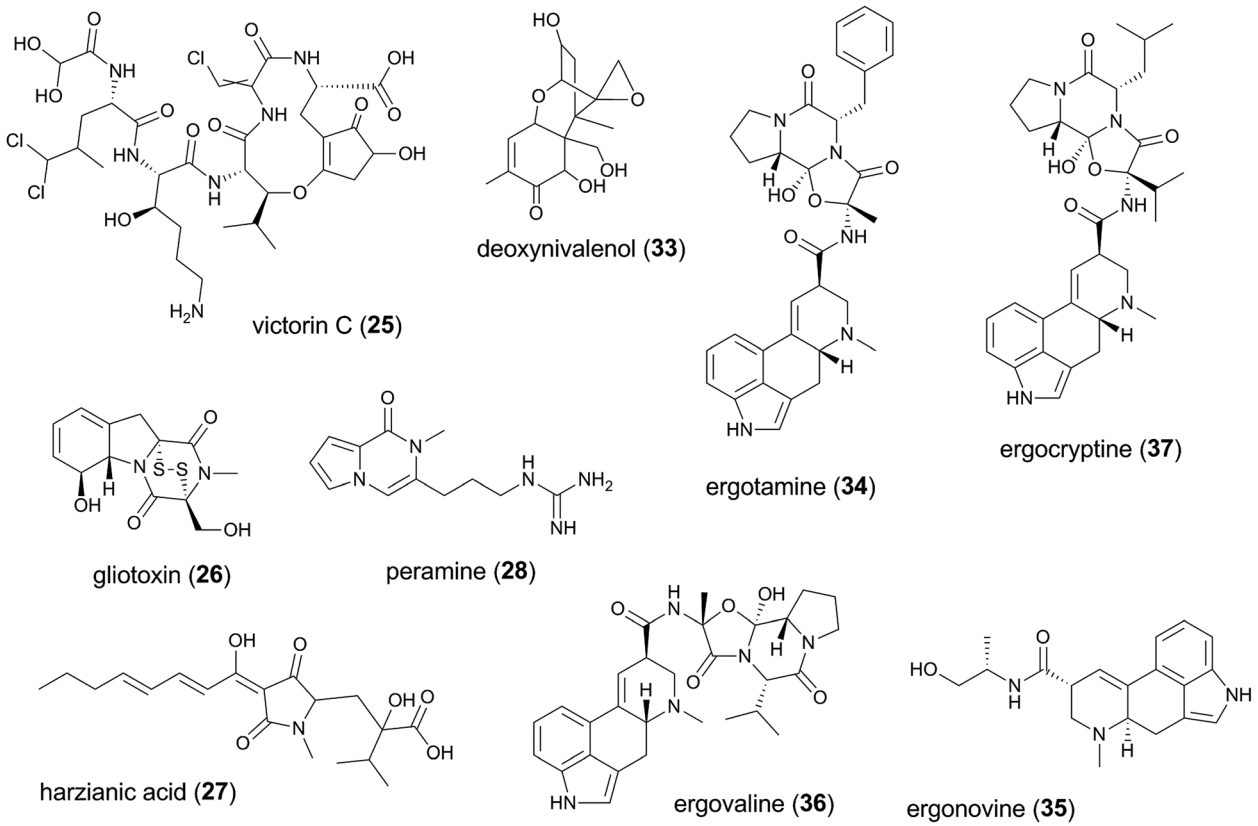


Chart 4 Chemical structures of representative fungal NPRs, terpenes and indole alkaloids.

opening and closure through deregulation of endogenous auxin homeostasis thus could have a significant effect on the plant's resistance to such pathogens.[45,46] Blom *et al.*[16] characterized VOCs from a set of 42 PGPB to show how they can affect plant growth and development and found that particularly indoles, amongst other volatiles, were associated with plant growth promotion. Moreover, the level of indole production correlates with the ability of the producer strain to stimulate plant growth as well as lateral root formation.[47,48] It was further demonstrated by radiolabelling that bacterial indoles are taken up and converted into auxin by the plant,[48] and consequently are able to modulate root developmental programs.[14,48] Transcriptomics analyses performed in our own laboratory[49] revealed that root transcriptome changes in response to the ISR-inducing PGPB *P. simiae* strain WCS417 have a strong auxin signature. Use of the auxin response mutant *tir1afb2afb3* [50] further showed that loss of auxin perception blocks WCS417-mediated *MYB72* activation in the roots, which is essential for the onset of ISR.[49] These results thus corroborate previous findings that auxin signalling plays a dual role in rhizobacteria-mediated modulation of plant immunity and growth.[14,49]

Many rhizobacteria are capable of *de novo* IAA (**1**) synthesis through various biosynthetic pathways such as the indole-3-pyruvic acid (IPA) pathway and the indole-3-acetamide (IAM) pathway, which have been reviewed recently.[31] In short, the IPA pathway is initiated when L-tryptophan gets deaminated by an aminotransferase to form IPA, which is subsequently converted into indole-3-acetylaldehyde (IAAld) by a decarboxylase, and finally oxidized by oxidases to generate IAA (**1**).[31] To date, the responsible enzymes have not all been identified in bacteria. However, *ipdC* encoding indolepyruvate decarboxylase, has been cloned from several bacteria and found to be essential for IAA (**1**) biosynthesis in isolates harbouring it.[31] IAA (**1**) biosynthesis through the IAM pathway has been described primarily for plant pathogenic bacteria. It involves two enzymatic steps, *i.e.* conversion of tryptophan to an IAM intermediate by a tryptophan 2-monooxygenase followed by hydrolysis by a IAM-specific hydrolase to produce IAA (**1**).[31] The two corresponding bacterial genes, *iaaM* and *iaaH* encoding the monooxygenase and the hydrolase respectively, have been identified previously and occur in multiple, but few, bacterial genera including *Pseudomonas*.[51] The presence and transcriptional activity of either *ipdC* or *iaaM* and *iaaH* have been demonstrated to be required for at least some of the growth-promoting activities of beneficial Pseudomonads.[52] In contrast, overexpression of the *iaaM* and *iaaH* genes in *P. savastanoi* subsp. *savastanoi*, causal agent of olive knot disease, resulted in the formation of larger galls and boosted pathogen virulence.[53,54] Some *P. syringae* pathogens are also able to inactivate IAA (**1**) by the activity of IaaL, a IAA-lysine synthetase.[55] IaaL converts IAA (**1**) to a less active derivative by conjugating it to lysine. Interestingly, *IaaL* mutant strains display reduced virulence and are also less competitive than their wildtype progenitors.[54,55] Thus, IAA (**1**) biosynthesis and degradation can be co-opted by both

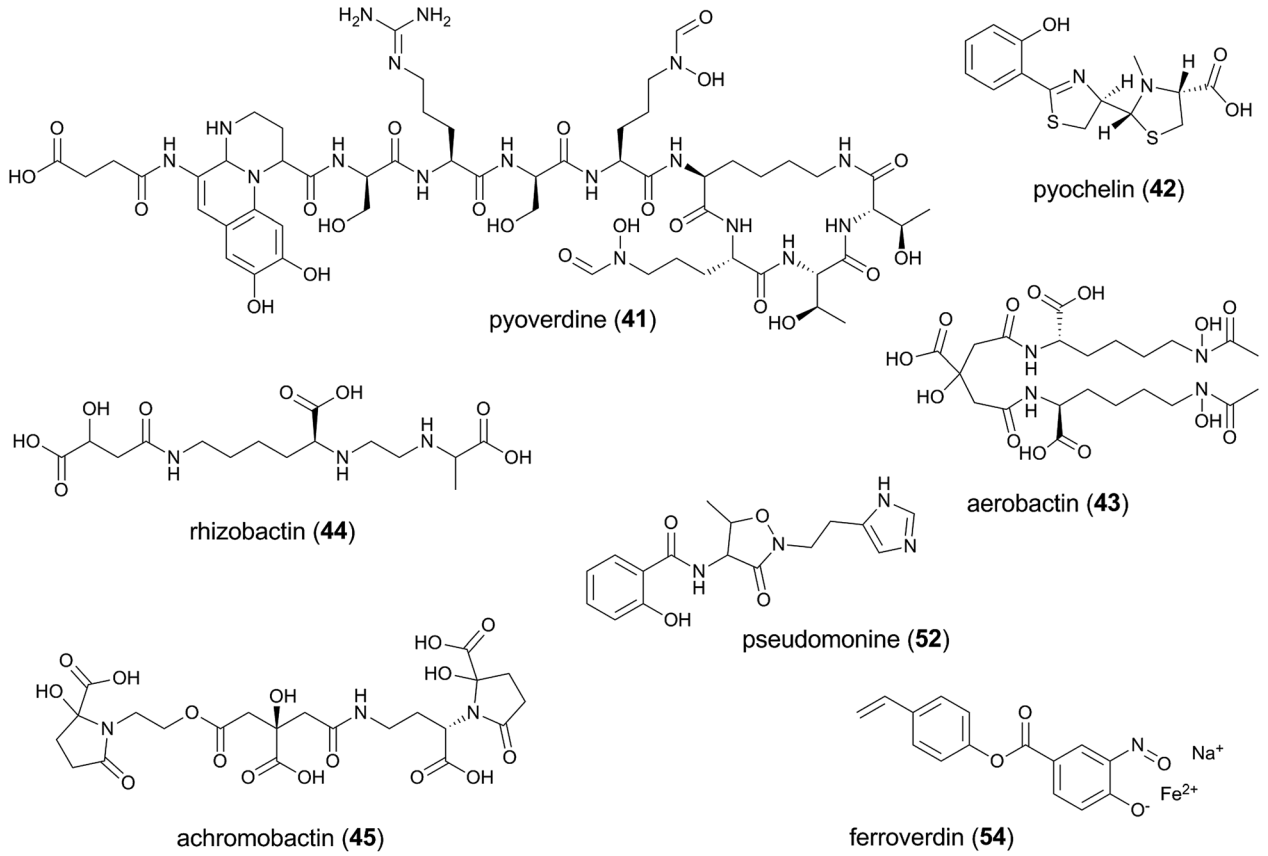


Chart 5 Chemical structures of representative bacterial siderophores.

beneficial and pathogenic microbes, leveraging enhanced colonization as well as symptom development.

Noteworthy, the complete IAM pathway was recently identified in fungi of the *Fusarium* and *Colletotrichum* genera.[56] Close examination of four *Fusarium* species encoding both *iaaH* and *iaaM* revealed that the pathway is functional only in the endophytic, non-pathogenic *F. proliferatum* orchid strain ET1,[56] although biosynthetic activity in the other strains might be more strictly regulated and therefore not observed under the tested conditions. The physiological role of IAA (**1**) production in this strain remains untested, in part due to its endophytic lifestyle on orchids.[56] *IaaM* has also been identified in various other fungi, including the cereal rust pathogen *Puccinia graminis* f. sp. *tritici*.[56] Yin *et al.*[57] demonstrated by means of transient silencing that *iaaM* expression is required for full pathogenicity of this fungus. Thus, it is becoming clear that perturbation of auxin signalling through *de novo* microbial IAA (**1**) biosynthesis is an important strategy of plant-associated microbes to modulate plant physiology and increase microbial success.

2.1.2. Cytokinins. The family of cytokinins (CKs) comprises many important regulators of complex developmental and environmental plant responses such as cell division, leaf senescence, nutrient mobilization and seed germination.[58] In plants, CK biosynthesis is controlled by the isopentenyltransferase (IPT) genes, which encode rate-limiting enzymes that catalyse the first reaction in the biosynthesis of isoprene CK.[66] Cytochrome P450 monooxygenases catalyse the hydroxylation of these isoprene CK precursors that can subsequently be activated by CK phosphoribohydrolases, encoded by members of the *LONELY GUY* (*LOG*) gene family to produce active CKs.[44] Recent evidence on the CK signalling mechanisms further revealed intricate interactions with other signal transduction pathways, including that of auxin[58] and SA (**2**),[59–61] and simultaneously demonstrated that CKs also directly contribute to plant immunity. These direct contributions include accumulation of SA (**2**) in *Arabidopsis*[59] and tobacco,[62] increased phytoalexin biosynthesis[62] and reduction of abscisic acid (ABA) (**4**) levels in tobacco.[63]

CKs have been shown to delay plant senescence by limiting the oxidative burst and maintaining photosynthesis.[64] Considering their role in plant immunity, it is perhaps not surprising that CKs are not solely produced by plants, but also by their associating microbes with contrasting intentions.[44] In fact, the first CK biosynthesis gene, named *tmr* for tumour morphology root, was identified on the T-DNA (transfer) region of the "crown gall" tumour-forming bacterium *A. tumefaciens*.[65] *Tmr* encodes a tRNA-isopentyltransferase (tRNA-IPT), which when expressed by the plant results in the increased accumulation of CKs like zeatin (**5**) and zeatin riboside (**6**), and contributes to tumour formation. *Tmr* and *Tzs*, another, homologous *A. tumefaciens* IPT encoding gene, are found in multiple members of the *Agrobacterium* genus, as well as in other plant pathogenic

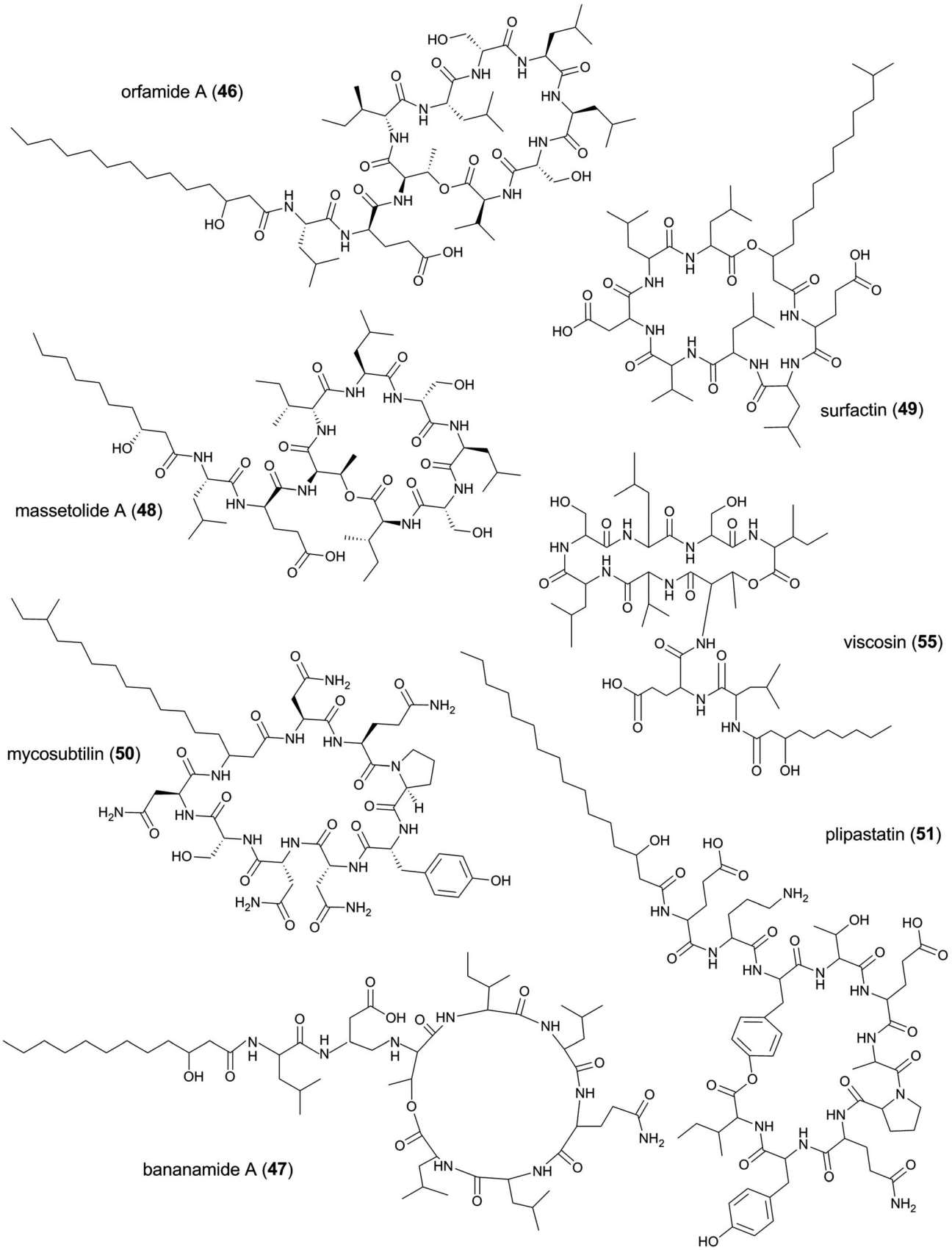


Chart 6 Chemical structures of bacterial lipopeptides with role in plant–microbe interactions.

bacteria, including some Pseudomonads, Xanthomonads and also in the "leafy gall" disease causing-bacterium *Rhodococcus fascians*.[44,66] Plant pathogenic fungi are also known to produce CKs or influence CK signalling. For example, Hinsch *et al.*[67] demonstrated that the plant pathogenic ergot fungus *Claviceps purpurea* is capable of CK synthesis in a plant-like manner. The authors identified two *Arabidopsis LOG5* (ref. 68) homologs encoded in the *C. purpurea* genome, *i.e. cplog* and *cpipt-log*.[67] Both encode a CK phosphoribohydrolase domain, like *Arabidopsis LOG5*, but additionally *cpipt-log* also encodes an IPT and a tRNA-IPT domain. Whereas expression of *cplog* was not significantly affected by growth or infection condition, *cpipt-log* together with an adjacent P450 monooxygenase *cpp450* were strongly induced during the early phases of plant colonization. Targeted mutagenesis confirmed the role of both genes in CK biosynthesis, suggesting that they act in concert and represent a small biosynthetic gene cluster. Accumulation of isopentenyladenine (iP) derivatives in the *cpp450* mutant combined with strongly reduced (97%) concentration of *trans*-zeatin (*t* Z) (**7**) suggest that it encodes a CK-specific cytochrome P450 monooxygenase which catalyses the hydroxylation of iP to form *t* Z (**7**). Interestingly, also *cpipt-log* mutants accumulated less *t* Z (**7**), but no reduction in the amount of iP derivates was observed, although *in vitro* activity was demonstrated. The authors speculate that alternative tRNA-IPTs might act redundantly.[67] The physiological role of CK biosynthesis, particularly *t* Z (**7**), by *C. purpurea in planta* remains elusive, as deletion mutants displayed disease symptoms indistinguishable from wild-type strains.[67] Through genome sequence analyses the authors also showed that many fungal plant pathogens from the orders Hypocreales and Capnodiales contain the necessary gene inventories for CK biosynthesis,[67] although the combination of functional domains as found in CPIPT-LOG is unique for the fungal family Clavicipitaceae and the genus *Fusarium*.

Much like *C. purpurea*, *Magnaporthe oryzae*, causal agent of rice blast disease, is capable of *de novo* CK biosynthesis by means of a tRNA-IPT enzyme (encoded by *cks1*).[69] In this case, CK biosynthesis as well as virulence were lost in the *Δcks1* mutant but loss of virulence could be fully restored by exogenous CK application. Phylogenetic analysis further confirmed that many fungi, pathogenic as well as saprophytic, encode such tRNA-IPT enzymes[67,69] revealing the potentially broad implication of microbial CK biosynthesis on plant–microbe interactions. There is emerging evidence that also plant beneficial microbes produce or interfere with CK homeostasis. In the case of the *Arabidopsis–Bacillus megaterium* interaction, plant cytokinin perception and signalling was responsible for the growth-promoting activities of *B. megaterium*.[70] Similarly, CK biosynthesis contributes to biocontrol activity of *P. fluorescens* strain G20-18 against *P. syringae* infection in *Arabidopsis*.[71] Although the exact biosynthetic mechanism has not been elucidated, a role for *miaA*, encoding a tRNA delta(2)-isopentenylpyrophosphate transferase with similarity to tRNA-IPTs, was proposed.[71] Intriguingly MiaA is conserved throughout the bacterial kingdom and plays an important role in endogenous tRNA modification, and mutations in *miaA* have been implicated previously to have pleiotropic phenotypes, perhaps by directly affecting translation of the general stress response sigma factor RpoS.

2.1.3. Gibberellins. Gibberellins (GAs) are ubiquitous plant hormones that elicit various metabolic functions required for plant growth and development including seed germination, sex expression, and senescence. Similar to CKs, GAs such as gibberellic acid (**8**) were first isolated from a plant pathogen of rice, *F. fujikuroi*, formerly known as *Gibberella fujikuroi*.[72] Gibberellins were isolated and subsequently characterized as active fungal compounds that could mimic pathogen symptom development such as seedling elongation and infertility, upon rice leaf infiltration, and were consequently named after the fungus. GAs may also be produced by endophytic fungi to help plants cope with certain stresses. For example, salinity is an important abiotic stress that prompts plants to deposit organic solutes to maintain adequate root turgor pressure. These stresses cause an induction in defence responses and ultimately poor yield. However, endophytes such as *Porostereum spadicium* have been shown to produce GAs that enhanced the ability of soybean to tolerate salt stress.[73] Similarly, soybean roots inoculated with a specific strain of *Aspergillus fumigatus* exhibited increased shoot length, increased shoot and leaf biomass, and photosynthetic rates under salt stress compared to non-inoculated plants.[74] Exhaustive reviews on the history of gibberellin research, its biological mechanisms, and the ability of plant-associated microbes to produce GAs were published recently by Hedden and Sponsel,[72] and Khan *et al.*[75] There is however only limited knowledge on GA biosynthesis in plant-associated bacteria.[76]

2.1.4. Defence hormones. The defence-related plant hormones JA (**3**) and SA (**2**), as well as ABA (**4**) and ethylene (ET) (**9**) play important roles in many plant–microbe interactions.[77] JA (**3**) and SA (**2**) are critical regulators of plant growth and defence and act antagonistically to combat necrotrophic and biotrophic pathogens respectively.[78] When plants are infected or attacked by necrotrophic pathogens or herbivorous insects, JA (**3**), JA-derivates, and ET (**9**) accumulate resulting in the activation of defence. Conversely, biotrophic pathogens activate SA-dependent defences through NPR1, for NON-EXPRESSOR OF *PR* GENES1, which acts as a transcriptional coactivator of a large set of defence-related genes.[79] Concomitantly, increased SA (**2**) signalling represses the JA (**3**) pathway.[78] This interplay of hormonal networks in the plant is targeted by various microbial mechanisms to suppress defence strategies that are effective against them. Through modulation of hormonal balances, both beneficial and detrimental plant-associated microbes tamper with the plants' ability to trigger the appropriate response. For example, the hemi-biotroph *P. syringae* pv. *tomato* (Pst), causal agent of bacterial speck on tomato, produces coronatine (COR) (**10**), a JA-isoleucine (JA-Ile) mimic and its accumulation results in the activation of defence responses typically associated with the JA pathway. Consequently the SA (**2**) pathway is actively repressed, therewith promoting disease progression.[77,78,80] COR (**10**) contributes to virulence of many *P. syringae* pathovars by inhibiting pathogen- as well as darkness-induced stomatal closure,[45,81] similar to another *P. syringae* phytotoxin, syringolin A[82] (**11**) and both facilitate pathogen entry into the leaf apoplast.

Moreover, *P. syringae* COR (**10**) can also suppress MAMP-activated responses in the roots.[83] COR (**10**) consists of two distinct moieties, a polyketide named coronafacic acid (CFA) (**12**) and a cyclized derivative of isoleucine named coronamic acid (CMA) (**13**),[84] which are synthesized from two distinct pathways. Both pathways have been well-studied and are co-localized on a 32-Kbp region, typically found on a plasmid.[85] Biosynthesis of syringolin A (**11**), a small cyclic peptide, is conferred by a hybrid biosynthetic gene cluster (BGC) consisting of a non-ribosomal peptide synthetase (NRPS) and a NRPS-polyketide synthase (PKS) fusion protein (NRPS-PKS) alongside several auxiliary proteins. Although the production of COR (**10**) and COR-like molecules is primarily studied in *P. syringae*, their production has been reported in various other plant-pathogenic bacteria, including *Xanthomonas campestris* pv. *phormiicola*[86,87] and *Pectobacterium atrosepticum*.[88,89] A biosynthetic pathway resembling that of CFA (**12**) in *P. syringae* has been previously identified in the common scab potato pathogen *Streptomyces scabies*.[90,91] The genus *Streptomyces* includes many different species that are well known for their ability to produce a wide array of secondary metabolites. Only a small number of *Streptomyces* spp. have been described to cause serious crop diseases, with *S. scabies* being the most well-known. Targeted mutagenesis firstly confirmed the critical role of this CFA-like pathway for *S. scabies* pathogenesis,[90] but only recently CFA-L-isoleucine (**14**) has been revealed as the major chemical compound resulting from this pathway.[92,93] Purified CFA-L-isoleucine (**14**) displayed similar toxic properties as COR (**10**), including stunting of radish seedlings and tissue hypertrophy on potato tuber slices,[92] albeit to a lesser extent.

It is frequently reported that SA (**2**) is produced in significant amounts by a variety of beneficial plant – associated microbes. Oftentimes, SA (**2**) production is related to the production of siderophores. These are iron-chelating compounds that assist in bacterial iron acquisition when iron availability is low, and contain a salicylate moiety.[94] It is consequently unclear to what extent microbe-produced SA (**2**) is a mere artefact from *in vitro* culturing, and whether it plays a genuine role in plant–microbe interactions and modulation of host immunity, as was recently reviewed by Bakker *et al.*[94]

Finally, we consider the microbial synthesis and/or microbial modulation of plant synthesis of ET (**9**). ET (**9**) is produced during many plant–pathogen interactions and functions as an important modulator of plant immunity,[78,95] as well as of many other plant stresses such as flooding and drought.[30] It also plays an important role, together with the JA (**3**) pathway, in the interaction with beneficial microbes, necrotrophic pathogens and insects. ET (**9**), unlike JA (**3**) and SA (**2**), acts primarily as a modulator of said hormones through pathway crosstalk.[95] Upon stress conditions, accumulation of ET (**9**) is thought to occur in two phases. First, rapid conversion of the endogenous pool of 1-aminocyclopropane-1-carboxylate (ACC (**15**), the precursor of ET) occurs in the plant to ET (**9**), and secondly, through *de novo* synthesis of ACC (**15**) in the plant. This second phase is typically associated with senescence, chlorosis and leaf abscission, and is thus detrimental for plant development and growth.[30] Here, beneficial PGPB can contribute to plant health under stress conditions by lowering of the plant ACC (**15**) levels through the activity of the enzyme ACC deaminase (ACCd, EC 4.1.99.4). ACCd cleaves ACC (**15**) to form ammonia and α-ketobutyrate thereby lowering the amount of ET (**9**) that can be made in the plant. The corresponding gene, *acdS*, has been isolated from many different species and strains of genera belonging to the phyla Proteobacteria, Firmicutes and Actinobacteria,[30] and ACC deaminase activity has been described for various Pseudomonads.

2.2. Toxins

The role of secondary metabolites in agricultural research has also been intensely studied owing to toxin contamination of food and livestock feed and their effect on virulence in several plant–pathogen interactions. For example, the worst crop epidemic in U.S. agricultural history occurred in 1970 due to the wide cultivation of maize hybrids with Texas male sterile cytoplasm that was exceptionally sensitive to a secondary metabolite called T-toxin (**16**) produced by a previously unknown race of the fungal pathogen *Cochliobolus heterostrophus*.[96] In this section, we focus primarily on secondary metabolite toxins in various plant–fungus interactions since fungi are most commonly associated with disease in crop plants. Nevertheless, we also highlight multiple bacterial toxins that contribute to the pathogenic lifestyle of the plant pathogenic bacteria *S. scabies* and *P. syringae*, in addition to the previously mentioned *P. syringae* toxins COR (**10**) and syringolin A (**11**) that interfere with defence hormone signalling in the plant.

Despite their enormous chemical complexity and diversity, secondary metabolites all arise from a limited number of precursors from primary metabolism. Consequently, fungal secondary metabolites are generally classified into four canonical chemical categories based on the enzyme class involved in the biosynthesis of the first intermediate. These include the polyketides (*e.g.* aflatoxin, T-toxin, and perylenequinone toxins), non-ribosomal peptides (NPRs; *e.g.* HC-toxin and sirodesmin siderophores such as ferricrocin), terpenes (*e.g.* T-2 toxin and gibberellins), and indole alkaloids (*e.g.* ergotamine, paxilline and lolitrems). Biosynthesis in each secondary metabolite category is governed by the core enzymes PKSs, NRPSs, terpene synthases/cyclases, and dimethylallyl tryptophan synthases (DMATSs), respectively. Hybrids of these classes have been identified in several fungal species,[97] much alike the previously described biosynthetic pathways for the bacterial toxins COR (**10**) and syringolin A (**11**). Recently, the biosynthetic pathway responsible for the mycotoxin tenuazonic acid (TeA) (**17**), a proposed hybrid of an isoleucine and two acetates[98] and among the most toxic weapons of *Alternaria* spp., was unveiled in the rice pathogen *M. oryzae*.[99] In *M. oryzae*, TeA (**17**) is synthesized from TeA synthetase 1 (TAS1), a unique hybrid NRPS-PKS enzyme.[99]

2.2.1. Polyketides. Polyketides are the most abundant fungal secondary metabolites, representing structurally and functionally diverse groups of small molecules from environmental toxins such as aflatoxin B1 (**18**) to pharmaceutical agents such as tetracycline (**19**) or the cholesterol-lowering drug

lovastatin (**20**).[100] Fungal polyketides are assembled in a linear fashion by large proteins called type I PKSs, which contain a multi-domain module required for one round of chain elongation and modification reactions that can be repeated.[101] Consequently, diversity of fungal polyketide structures results in part from the number of iterations and other modification reactions that occur *via* the PKS enzyme. Additionally, post-PKS tailoring enzymes often found in a gene cluster near the PKS may further modify the polyketide.

Among the most intriguing of fungal polyketides are the perylenequinones. Perylenequinones share a characteristic pentacyclic conjugated chromophore that gives rise to the ability to produce reactive oxygen species (ROS) in the presence of oxygen and ambient light. One of the most well-studied perylenequinones is cercosporin (**21**) produced by most members of *Cercospora*, a fungal genus comprised of many well-known and destructive plant pathogens found world-wide.[102,103] Cercosporin (**21**) can readily penetrate plant leaves, with ROS causing indiscriminate cellular damage within minutes of exposure.[104] Indeed, cercosporin (**21**) is nearly universally toxic to diverse groups of organisms including bacteria, mammals, plants and many fungal species with the key exception of cercosporin-producing fungi, which intriguingly are resistant and therefore exhibit cercosporin (**21**) auto-resistance.[105] Cercosporin-deficient mutants are typically less virulent, indicating a role for cercosporin (**21**) in pathogenicity.[106] Although cercosporin (**21**) was thought to be limited to *Cercospora* spp., the cercosporin (**21**) biosynthesis gene cluster was recently shown to be conserved in a diverse group of plant pathogens and production of cercosporin (**21**) extended to the important plant pathogen genus *Colletotrichum*.[107] Other well-studied perylenequinones are elsinochromes, such as elsinochrome A (**22**) produced by *Elsinoe fawcetti*, an important pathogen of citrus. Like cercosporin (**21**), elsinochromes induce electrolyte leakage and produce ROS in a light-dependent manner.[108,109]

Although the utility of perylenequinones to inflict damage to host cells in plant–pathogen interactions is somewhat obvious, the role that polyketides may play in beneficial situations is not as clear. For example, *Alternaria* spp. are well-known endophytes of plants,[110] yet produce highly toxic secondary metabolites *in planta* including perylenequinones and TeA (**17**). In response to the endophytic fungus *Nigrospora sphaerica*, the endophyte *A. tenuissima* induces production of the antifungal perylenequinone stemphyperylenol (**23**), a compound that is non-toxic to the host plant of both species, suggesting stemphyperylenol (**23**) is produced to control growth of other fungi without damaging the host plant.[111] Intriguingly, *Alternaria* spp. are one of the few fungal species outside the *Cercospora* genus known to be resistant to cercosporin (**21**).[105] Also, some endophytic fungi such as *Shiraia* sp.,[112,113] and *Penicillium chrysogenum*[114] produce the perylenequinone hypocrellin A (**24**), another potent activator of ROS, which is known to contribute to virulence.[115] It is further hypothesized that perylenequinone-induced ROS may also serve as important signalling molecules between the host and the endophyte.[116]

2.2.2. NRPs. NRPs are derived from amino acids by multi-domain, multi-modular enzymes called NRPSs. Incorporated amino acids can be proteinogenic or non-proteinogenic in nature, which are connected in a linear or cyclic fashion. Diversity among NRPs diversity occurs from the length of the peptide chain, whether it is cyclized, and variations in domain function.[100] Like polyketides, further modifications may occur by tailoring enzymes encoded in the NRPS gene cluster.

One of the most infamous NRPs is victorin C (**25**), a cyclic pentapeptide synthesized by *Cochliobolus victoriae*, the causal agent of oat Victoria Blight. In the 1940s, Victoria Blight emerged due to widespread cultivation of oat varieties containing the *Pc2* resistance gene that conditioned resistance to crown rust, but also inadvertently conditioned sensitivity to victorin (**25**) and susceptibility to victorin-producing *C. victoriae* strains.[117] In *Arabidopsis*, victorin (**25**) sensitivity and disease susceptibility is conferred by *LOV*, an NB-LRR gene.[118] Such genes are classic plant resistance genes, suggesting that *C. victoriae* highjacks defence pathways to cause disease.[117]

Trichoderma spp. are often used as biocontrol agents for plant disease initiated by pathogens such as *Phytophthora infestans* and *R. solani*.[119] The cyclic NRP gliotoxin (**26**) is a critical component of the ability of *Trichoderma* strains to ward off such plant pathogens.[120] For example, gliotoxin (**26**) can be an effective seed treatment to ward off *R. solani*.[121] Biosynthesis of gliotoxin (**26**) in the human pathogen *A. fumigatus* has been suggested to involve a 12-gene cluster containing a NRPS inferred from a comparative genomics approach.[122] Interestingly, gliotoxin (**26**) is critical for virulence in *A. fumigatus*. Upon uptake by the host cell, the gliotoxin (**26**) disulphide bridge is reduced, which allows it to inactivate host proteins through the production of host protein-gliotoxin disulphides that also leads to the production of ROS that damage host cells.[123] Another, *Trichoderma* secondary metabolite with potent biocontrol and plant growth promoting capabilities is harzianic acid (HA) (**27**). HA (**27**), a tetramic acid derivative, produced by *T. harzianum* inhibits the growth of various plant pathogens such as *Pythium irregulare* and *Sclerotinia sclerotiorum*. Recently, Vinale *et al.*[124] showed that HA (**27**) has significant ferric iron chelating activity. Therefore, it is tempting to speculate that such activity contributes to its biocontrol activity and plant growth promotion. The pathway for HA (**27**) biosynthesis in *T. harzianum* is yet to be elucidated, but multiple reports suggest a common hybrid PKS-NRPS origin for the tetramic acids;[125–127] the precursor for HA (**27**). Inspection of the published *T. harzianum* genomes at the JGI MycoCosm database revealed five such hybrid enzymes, and future research endeavours are likely to reveal the HA (**27**) BGC.

Peramine (**28**) is a NRP that is an insect feeding deterrent produced by *Epichloë* spp., which are mutualistic endophytes of grasses.[128] *Epichloë festucae* strains containing a mutated *perA* gene, encoding the NRPS peramine synthetase, were unable to produce peramine (**28**) and rye grass harbouring this mutant was more susceptible to weevil feeding damage than ryegrass containing the wildtype strain, confirming that peramine (**28**) is critical for the feeding deterrent property.[129] The intricate relationship between a plant, a fungus, and an insect predator underscores the evolutionary complexity of these interactions.

The class of bacterial lipodepsipeptide toxins, such as syringomycin (**29**), syringopeptin and corpeptin, are known to cause direct cellular damage to plants by their pore forming capacity and consequently contribute to the virulence.[130,131] Cichopeptin A and B from *P. cichorii* and corpeptin from *P. corrugata* and *P. mediterranea*, contribute to pathogenicity through their phytotoxic properties on plants.[131–133] Comparative analysis further showed that cichopeptin and corpeptin are produced from conserved NRPS-type BGCs.[131,132] Other modified peptide toxins produced by phytopathogenic bacteria include phaseolotoxin (**30**), mangotoxin and tabtoxin (**31**), produced by *P. syringae* pathovars, and thaxtomin A (**32**) produced by *S. scabies*.[91,134] When applied directly to plant tissue, all toxins trigger rapid cellular damage, including chlorosis and necrosis, albeit *via* distinct mechanisms. Phaseolotoxin (**30**), mangotoxin and tabtoxin (**31**) target enzymes involved in amino acid biosynthesis and interfere with nitrogen metabolism in the host. Tabtoxin (**31**), once taken up by plant cells, is hydrolysed to release its toxic moiety which subsequently stimulates chlorophyll degradation.[134] Thaxtomin A (**32**) targets cellulose biosynthesis in the plant, tampering with cell wall biosynthesis gene expression and it concomitantly depletes cellulose synthase complexes from the plant plasma membrane.[91] In accordance with their impact on plant cell physiology, these toxins contribute to pathogen virulence.[91,134] Interestingly, thaxtomin A (**32**)-deficient, endophytic *Streptomyces* sp. enhance resistance to *S. scabies* on potato.[135]

2.2.3. Terpenes. Terpene synthesis is governed by terpene cyclases, enzymes essential for the biosynthesis of different terpenes from substrates such as geranyl, farnesyl and geranylgeranyl diphosphates.[100] Classes of terpenes include the sesqui-, di-, and triterpenoids. Besides the scaffold-generating terpene synthases and cyclases, tailoring enzymes are often clustered together to generate the final bioactive toxin.[136]

Fusarium head blight of wheat and barley is a globally-important disease that can destroy a high-yielding crop within a few weeks of harvest.[137] Not only does *F. graminearum* cause yield and quality losses due to the infection of kernels, but infected grain may contain significant levels of trichothecenes making it unfit for food or livestock feed.[138] Of particular interest is deoxynivalenol (DON) (**33**), commonly known as vomitoxin, which is a trichothecene linked to nausea and vomiting in humans and food refusal and diarrhoea in animals.[139] Consequently, the DON (**33**) biosynthesis pathway has been the focus of significant study. The pathway is activated by the transcription factor TRI6, which regulates expression of structural genes involved in DON (**33**) biosynthesis and responds to nutrient availability.[140] Interestingly, *Fusarium* species often grow endophytically on phylogenetically-diverse native grasses, yet little DON (**33**) or other trichothecenes accumulate in these wild grasses compared to cultivated wheat.[141] It remains to be seen whether wild grass species can metabolize the toxins or if they are not induced by *Fusarium* spp. during colonization in these niches.

2.2.4. Indole alkaloids. Indole alkaloids are typically derived from tryptophan and dimethylallyl pyrophosphate, with the first committed step catalysed by DMAT.[100] Probably the best-known alkaloids are the ergot alkaloids, such as ergotamine (**34**), ergonovine (**35**), ergovaline (**36**) and ergocryptine (**37**), produced by species in the fungal clade Clavicipitaceae.[142] *Claviceps* spp. produce resting structures called ergots on grass species, which ultimately contaminate food and feed sources with ergot alkaloids. Consumption of contaminated grains has caused mass poisonings in history.[142] However, evidence for the ecological roles of ergot alkaloids suggests they provide protection to ergot-producing fungi from insects and herbivore feeding.[143–145] Alkaloid concentrations in perennial rye grass were shown to increase with plant age and were effected by seasonal timing, suggesting that climate change may have an effect on endophyte/host dynamics.[146]

2.3. Stimulatory compounds

PGPB and PGPF promote plant growth and health in various ways, with microbial production of phytohormones being one of them. Some PGPB boost plant immunity by inducing systemic defence priming known as ISR.[12] A multitude of determinants have been identified as elicitors of ISR, including cell envelope components such as lipopolysaccharides (LPS), and secreted compounds like siderophores, (cyclic) lipopeptides (LPs), volatiles, antibiotics such as 2,4-diacetylphloroglucinol (DAPG) (**38**) and the phenazine pyocyanin (**39**), quorum sensing molecules such as the *N*-acyl homoserine lactones, as well as flagella (reviewed by De Vleesschauwer and Höfte[147]). Application of multiple purified bacterial determinants could reproduce ISR in the absence of the bacteria. Nevertheless, individual knockout mutants that no longer produce the respective determinants were not impaired in their ability to elicit ISR, suggesting that bacterial determinants may act redundantly in the elicitation of ISR.[148–150] Different plant beneficial *Pseudomonas* strains trigger ISR on a partially overlapping set of plants.[148,150] Comparative genome analyses of three Pseudomonads, *i.e. P. simiae* strain WCS417, *P. capeferrum* strain WCS358 and *P. defensor* strain WCS374, with differential capacities to trigger ISR on various plants, revealed multiple compounds that could act as determinants of ISR. These include their respective siderophores and a cyclic LP (CLP) in WCS358.[150]. Siderophores and LPs play important roles in the natural life of the bacteria that produce them.

2.3.1. Siderophores. Siderophores are low molecular weight compounds that sequester ferric ions (Fe^{3+}) in the environment and are typically produced by microbes under conditions of low iron availability. In most natural soils, iron availability is low as poorly soluble ferric hydroxides dominate the pool of iron. Through their iron-sequestering activities, the producing microbes can compete with their neighbours including soil-borne pathogens, an important trait for biological control strains.[151] In the case of *P. protegens* strain Pf-5 it was demonstrated that its siderophores contribute to resistance towards the mycotoxin fusaric acid (**40**) produced by several soil-borne pathogens of the genus *Fusarium*, through their iron sequestration activities.[152] Competition for iron is important for the lifestyles of both plant and microbial pathogens, and consequently perturbation of iron homeostasis is a key

interaction platform between plants and pathogens.[153–156] Plants on the one hand can use iron-withholding tactics to reduce pathogen virulence or to locally increase iron levels to activate a toxic oxidative burst. Pathogens counteract such measures by producing siderophores that can acquire iron from the host and thereby act as virulence factors.[153,156] *P. aeruginosa*, the causal agent of severe lung disease infections, relies on the production of the siderophores pyoverdine (**41**) and pyochelin (**42**) to infect mice.[157] However, the animal model species *Caenorhabditis elegans*, recognizes *P. aeruginosa* pyochelin (**42**) through chemosensory detection by GPCRs (G protein-coupled receptors) resulting in pathogen avoidance and host survival.[158] Noteworthy, many plant pathogens,[123] and insect pathogens[159,160] rely on the production of siderophores to cause full disease in their hosts. In agreement with their ability to modulate behaviour in *C. elegans*, siderophores not only act as virulence factors, they can also be perceived by the host triggering a variety of responses in an iron-dependent and -independent manner.[156]

Two major pathways exist for siderophore biosynthesis. One depends on NRPSs and the other involves siderophore synthetases that are part of the IucA/IucC family of proteins.[161] A classic example of the former are the fluorescent pigments in the large and diverse pyoverdine class, involved with the characteristic appearance of the fluorescent Pseudomonads.[162] Pyoverdines are produced by many *Pseudomonas* spp., and biosynthesis within one strain involves as many as seven genomically dispersed BGCs.[163] Siderophores produced through the second pathway, also known as the NRPS-independent pathway or NIS pathway, are less frequently observed and studied to a lesser extent (reviewed by Challis, 2005 (ref. 164)). Nevertheless, since the initial discovery of the involvement of the IucA and IucC siderophore synthetases in the biosynthesis of aerobactin (**43**) in *Escherichia coli*, various other siderophores, including rhizobactin (**44**), achromobactin (**45**), desferrioxamines and vibrioferrin, were linked to biosynthetic pathways incorporating *IucC*/*IucA* homologs. Some pyoverdines can alleviate symptoms associated with iron deprivation in *Arabidopsis*, possibly by boosting the expression of genes involved in iron uptake such as *IRT1* and *FRO2*.[155,156] Also, siderophores from diverse Pseudomonads can trigger ISR in a plant-specific manner.[147,150]

2.3.2. Lipopeptides. LPs are composed of a lipid tail linked to short linear or cyclic oligopeptide (CLPs). They act as microbial surfactants (biosurfactants), which function to lower surface or interfacial tension.[165] Biosurfactants are produced by many organisms, including bacteria and fungi, and through their activity they can affect cell differentiation, signalling, biofilm formation and motility. In plant-related environments they have been associated with so-called wettability, or the ability to reduce surface tension to water. Wetting of plant leaves is thought to promote microbial cell motility on them, and might also provide a stage for exchange of signals and nutrients, and consequently it contributes to pathogen virulence.[166] Besides their role as biosurfactants, LPs are also well known for their broad-spectrum antimicrobial activity, particularly as an important defence mechanism against protozoa.[165] The proposed primary mode of action is pore formation in membranes, leading to imbalance in transmembrane ion fluxes and cell death. LPs, and in particular CLPs, differ greatly in their structural appearance resulting from variability in the length and composition of the lipid moiety and the type, number and configuration of the amino acids in the peptide chain.[163,165] Like many siderophores, CLPs are synthesized *via* large multidomain NRPSs that are part of even larger BGCs incorporating various additional proteins related to transcriptional and post-transcriptional regulation as well as transport. Through their biosurfactant activities, LPs enhance beneficial as well as detrimental microbes with regards to their potential to colonize their respective hosts.

The plant growth-promoting bacterium *P. protegens* strain CHA0 produces the CLP orfamide A (**46**), through the *ofa* BGC, which aids in its swarming motility. Orfamides play an important role in biocontrol activities through their antimicrobial activities.[167] Intriguingly, orfamides also possess dose-dependent insecticidal activities, and consequently orfamide-producing strains can be used as biocontrol measures against insect pests on crops.[167–169] Orfamide A (**46**) belongs to the larger orfamide family, also encompassing the poaeamides[170] and the recently discovered bananamides (*e.g.* bananamide A (**47**)).[171] Poaeamide A produced by the endophyte *P. poae* contributes to plant rhizosphere colonization as well as suppression of soil-borne plant pathogens.[170] Remarkably, poaeamide-deficient mutants accumulate at higher density than the respective wildtype on the roots of *R. solani* tolerant sugarbeet plants. Also, D'aes *et al.* (2014) showed that the interplay between two different classes of CLPs produced by *Pseudomonas* sp. CMR12a determine its ability to form biofilms and achieve settlement on plant root surfaces.[172] Localized cell density can greatly affect the exerting lifestyle through quorum sensing (QS), and thus differences in the spatial distribution and root surface adherence may contribute to the overall higher colony numbers for the CLP mutants.[170]

A variety of CLPs, like siderophores, affect host immunity. In this regard, they resemble MAMPs that are recognized by host cell surface receptors, representing the first surveillance system of the host for non-self-perception.[173] A multitude of both recent and past research has shown that purified CLPs from *Pseudomonas*, *Bacillus* and *Streptomyces* spp. can stimulate host immune responses and trigger ISR.[165,174] Tran *et al.*[175] and Ongena *et al.*[176] were among the first to report CLP-mediated stimulation of ISR in tomato by massetolide A (**48**) from *P. fluorescens*, and in tomato and bean by fengycins and surfactins from *B. subtilis* respectively. More recently, Farace *et al.*[177] showed that three CLPs produced by *B. subtilis*, surfactin (**49**), mycosubtilin (**50**) and plipastatin (**51**), are each independently perceived by grapevine cells,[177] and activate partially overlapping signalling pathways and defence responses. Importantly, application of each of these LPs can protect grapevine leaves against the necrotrophic pathogen *Botrytis cinerea*.[177] Similarly, *Pseudomonas* sp. CMR12a produces two classes of CLPs, namely orfamides and sessilins, that stimulate defence responses in rice and consequently activate ISR against diverse plant pathogens such as *M. oryzae* and *C. miyabeanus* in a differential, concentration-dependent manner.[178,179] The LPs

produced by members of the *Pseudomonas* and *Bacillus* genera are structurally and functionally highly diverse,[165] further corroborated by the extensive genomic variability at the relevant BGCs.[171,180]

3. *In silico* and *in vivo* mining for functional biosynthetic pathways of novel small natural compounds

3.1. Comparative genome analyses-driven pathway identification

Comparative genome analyses, or comparative genomics, is a field of biological research in which genomic features encoded by different organisms or strains are compared. It involves DNA and/or protein sequence alignment, and can incorporate phylogenetic interference with hundreds to thousands of gene families, commonly referred to as phylogenomics.[181] Comparison of individual gene trees with the accepted taxonomy further allows for the identification of lateral or horizontal gene or gene cluster transfer events, as these typically behave differently from what is expected based on that same taxonomy. Comparative analyses of ten *P. fluorescens* genomes revealed multiple pathways for the biosynthesis of the siderophores achromobactin (**45**) and pseudomonine (**52**) and the antibiotic 2-hexyl-5-propyl-alkylresorcinol (**53**).[163] Moreover, core and pangenome analysis of these ten genomes demonstrated that only 45–52% of the predicted coding genes is shared between all genomes, highlighting an enormous genetic heterogeneity.[163] Likewise, previously Flury *et al.*[168] examined the phylogenetic distribution of the *fit* toxin gene across the *P. fluorescence* group. The Fit toxin is the best studied bacterial virulence factor against insects and it contributes to biocontrol activity of various Pseudomonads, such as *P. protegens* strain CHA0. By comparing the phylogenetic distribution of *fit* with insecticidal activity assays it was demonstrated that the presence of this gene is a determining factor in the biocontrol potential of Pseudomonads.[168]

3.1.1. Case study: the *Pseudomonas* genus. To further highlight the enormous genetic diversity and capacity across a single plant-associated bacterial genus and simultaneously demonstrate the power of comparative genomics we here survey a custom set of 168 *Pseudomonas* genomes for their potential to synthesize natural products that can affect microbial interaction with plants. The 168 genomes are selected from public databases to represent the breadth of genetic diversity across the genus, and incorporate most plant-associated Pseudomonads based on their annotation in NCBI GenBank (Fig. 1). Many plant-associated Pseudomonads, both of pathogenic and beneficial nature, encode the capacity to synthesize the auxin indole-3-acetic acid or IAA (**1**) *via* the IAM and IPA pathways in their genome sequences. Here, we detected 118 and 29 homologues for *iaaM* and *iaaH* respectively, involved with IAA (**1**) biosynthesis *via* the IAM pathway, but only three *ipdC* genes, involved with IAA (**1**) biosynthesis *via* the IPA pathway (Fig. 1). All 168 genomes except one, contain a *miaA* ortholog. *MiaA* encodes a tRNA modification enzyme that was previously reported to be an important determinant for microbial biosynthesis of the cytokinins (**5**, **6**, **7**). In the beneficial *P. fluorescens* strain G20-18, miaA contributes to biocontrol activity against *P. syringae* on *Arabidopsis*. Curiously, the universal distribution we observe here supports a role for *miaA* in primary metabolism instead, which was also reported previously in *P. chlororaphis* strain 30–84.[182] Nevertheless, *miaA* mutants in G20-18 accumulate to similar density *in planta* and therefore differences in bacterial growth cannot fully explain the lack of biocontrol in the *miaA* mutant.[71] We also identified 16 candidate *acdS* genes, across 16 genomes, which included pathogenic and beneficial species (Fig. 1). *AcdS*, regulated by acdR, encodes the ACC deaminase which can break down the precursor for the phytohormone ethylene (**9**), ACC (**15**), and can thus affect ethylene levels in the plant. In conclusion, both pathogenic and beneficial Pseudomonads can use similar mechanisms to modulate plant hormone levels.

Another feature commonly associated with plant beneficial microbes is their capacity to control fungal diseases *via* competition for iron using high affinity siderophores. Moreover, there is extensive literature on the stimulation of ISR by beneficial microbes that suggest an important role for siderophores.[12] Siderophore biosynthesis typically proceeds *via* a NRPS-dependent or NRPS-independent (NIS) fashion. Scanning of the 168 *Pseudomonas* genome sequences for BGCs associated with siderophore biosynthesis *via* the NIS pathway by antiSMASH[183] revealed 46 such BGCs (Fig. 1). Examination of the predicted NRPS BGCs by cross-comparisons with known BGCs for siderophore production[150,163,184,185] as well as the siderophores pseudomonine (**52**),[186] ferroverdin (**54**),[187] paenibactin,[188] xanthoferrin[189] and turnerbactin[190] yielded an additional set of 253 NRPS-dependent BGCs for the biosynthesis of siderophores. Overall, we identified 292 BGCs associated with siderophore biosynthesis, and each genome encodes between 0 and 4 BGCs related to siderophore production (Fig. 1). From the distribution, it becomes apparent that the biosynthetic potential for (diverse) siderophore production coincides with a plant-associated lifestyle, be it pathogenic or beneficial, as well as animal/human pathology (particularly *P. aeruginosa* strains).

In addition to siderophores, NRPSs are also key to biosynthesis of lipopeptides and other natural products. To obtain a more broad understanding of the capacity to synthetize lipopeptides and other NRPs and/or derivates, we calculated NRPS-BGC cluster-to-cluster pairwise distances *via* mash sketch[191] analysis on amino acid level (k-mer = 9) using the coding sequences from antiSMASH predicted BGCs as input. Pairwise distances were transformed into an all-versus-all distance matrix and used to generate a neighbour joining tree with Phylip (Fig. 2). The NRPS-BGC phylogeny reflects known literature and highlights the astonishing diversity of BGCs across this selected set of 168 *Pseudomonas* genomes. BGCs for siderophores and CLPs are mostly distinct, with multiple exceptions. For example, it appears that at least one (of two) BGCs involved with viscosin (**55**) biosynthesis clusters alongside a large clade of BGCs associated with biosynthesis of the siderophore pyoverdine (**41**). The BGCs for COR (**10**) and

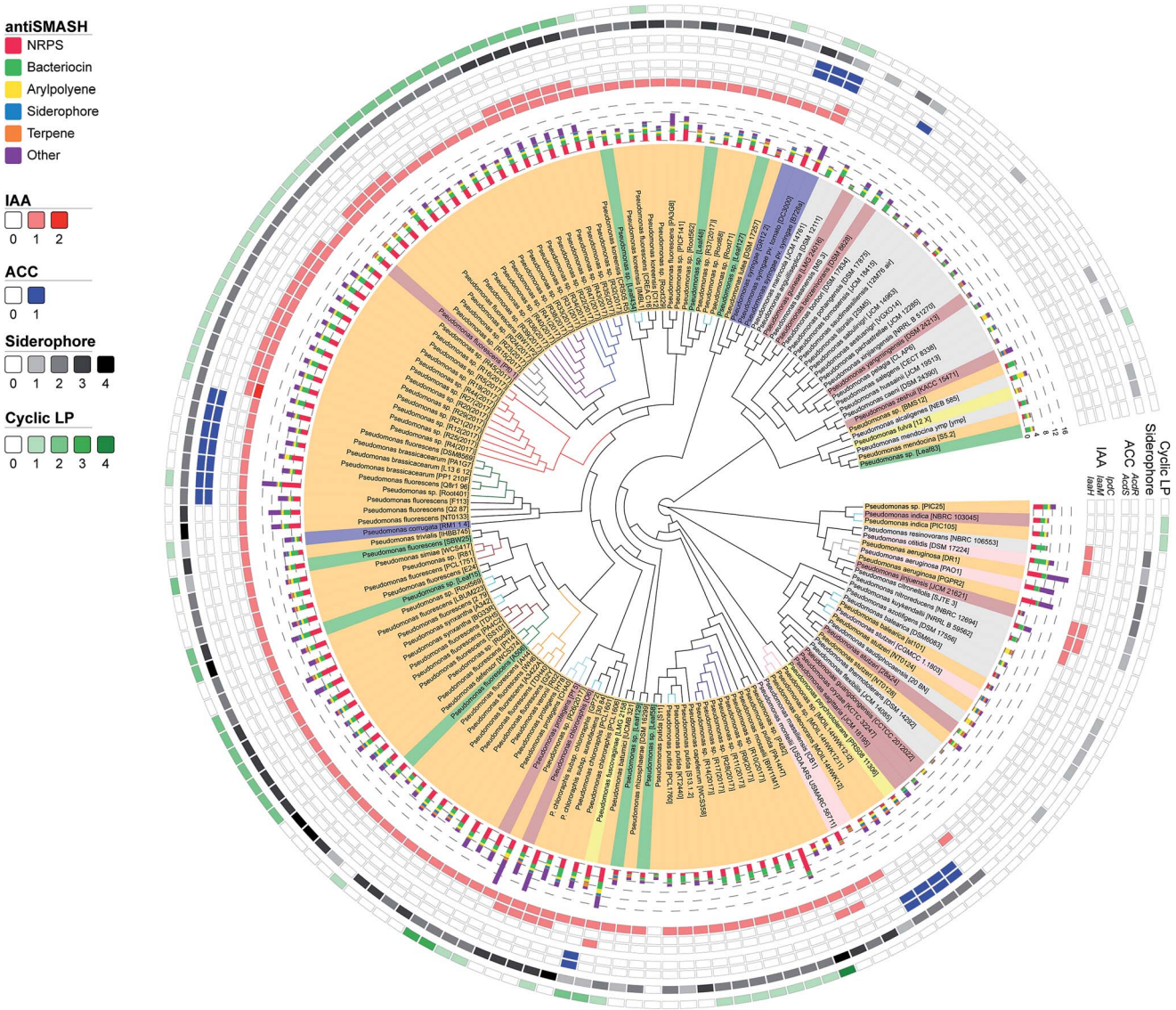


Fig. 1 Whole-genome phylogeny of the *Pseudomonas* genus. The phylogenetic tree, represented by the circular cladogram, is built by Phylip from 28 224 (168 times 168) Mash-derived genome-to-genome pair-wise distances.[191] Genomes with distances below 0.05, equivalent to an average nucleotide identity of 95% or larger, are considered as the same species and are depicted with same-coloured branches. *Pseudomonas* genomes were selected from the NCBI database based on three criteria: (1) when depicted as 'representative genomes', (2) when obtained from the phyllosphere or rhizosphere and (3) based on reports in the literature. Coloured shades highlight the source of collection and/or pathogenic status, and refer to (agricultural) soil (brown), rhizosphere (orange), phyllosphere (green), other plant-associated niches (seeds, rice paddies; yellow), plant pathogen (blue), human and/or animal pathogen (pink) or from a variety of other niches such as oil brines, sludge and contaminated soils (grey). The last category consequently reflects a generally non-plant associated lifestyle. The stacked bar chart reflects the number of predicted BGCs by antiSMASH.[183] The outer rings display the frequency of genes or gene clusters involved with IAA (**1**) biosynthesis, ACC (**15**) deaminase activity, and siderophores and cyclic LPs (Charts 5 and 6).

syringafactin cluster alongside the large clade of CLPs, but are markedly different and support the current hypothesis that they are synthesized only by pathogenic *P. syringae* strains.[183,185] Based on BLAST analysis, only *P. corrugata* RM-1-1-4 of the 168 *Pseudomonas* genomes encodes the *crpDE*[132] pathway for corpeptin biosynthesis. Nonetheless, the phylogenetic analysis presented here suggest that evolutionary conserved BGCs critical for biosynthesis of the related peptin-like CLPs fuscopeptin and syringopeptin (*syp*[192]) can be found in various other Pseudomonads, including the plant pathogenic bacteria *P. syringae* pv. *syringae* strain B278a and *P. fuscovaginae* strain LMG 2158, and several others (Fig. 2).

3.1.2. Microbiome-level comparisons. In contrast to the individual genome comparisons, sequencing-based profiling of entire microbial communities, or microbiomes, combined with comparative sequence analyses has gained increasing attention recently. This methodology, in which the abundance and activity of all microbial members of a community is determined *via* high-throughput DNA (or RNA) sequencing is coined metagenomics/metatranscriptomics.[193] Consequently, research into

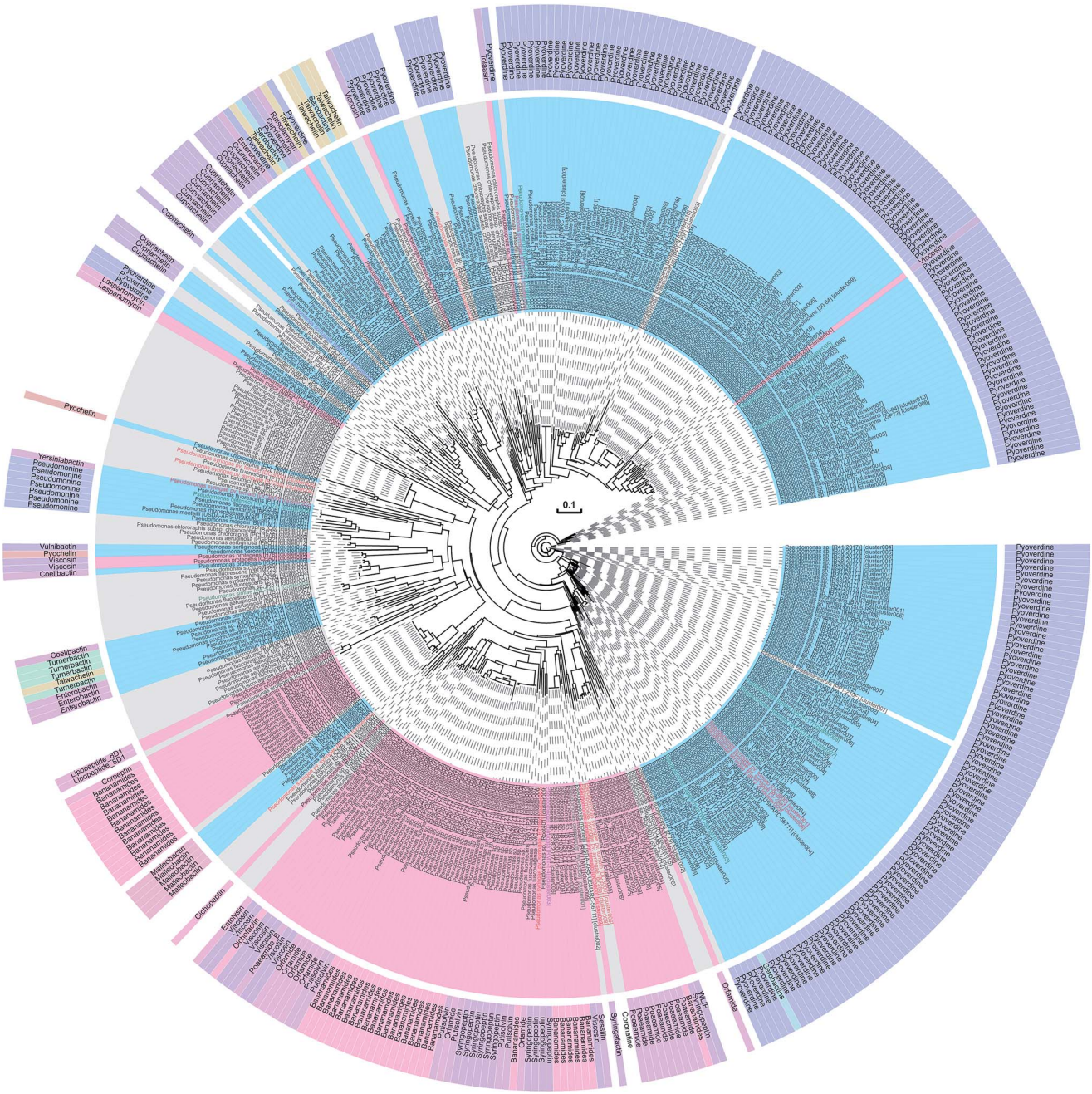


Fig. 2 Phylogeny of 449 NRPS biosynthetic gene clusters from 168 *Pseudomonas* genomes. The phylogenetic tree, represented by the circular phylogram in which branch length depicts distance, is built from 201 601 (449 times 449) Mash-derived BGC pair-wise distances. Coloured shades distinguish BGCs predicted for siderophore biosynthesis (blue), cyclic lipopeptides (pink) or a group of other products, oftentimes antibiotics (grey). The leaf names of few BGCs are coloured based on their origin, *i.e.* those from Berendsen *et al.*[150] (WCS strains) are in green, and plant pathogenic strains are in purple. As predicted from the clusterBLAST analyses, syringopeptin-like BGCs appear in various other Pseudomonads.

microbial community ecology has expanded dramatically in the last decade. The microbial communities associated with plant roots (the root microbiome) and leaves (the phyllosphere microbiome), much like those that colonize the human gut, play an important role in plant functioning as they influence plant physiology and development.[1] A more comprehensive understanding of these microbiomes will greatly benefit future endeavours to manipulate crop plants to protect them from biotic and abiotic stressors and boost yield.[1,194–196] Chapelle *et al.*[197] used metagenome and metatranscriptome sequencing to determine the composition and activity of the rhizosphere microbiome of sugar beet plants grown in soils that are naturally suppressive against the soil-borne fungal pathogen *R. solani*. Comparative metagenome/transcriptome analyses of the

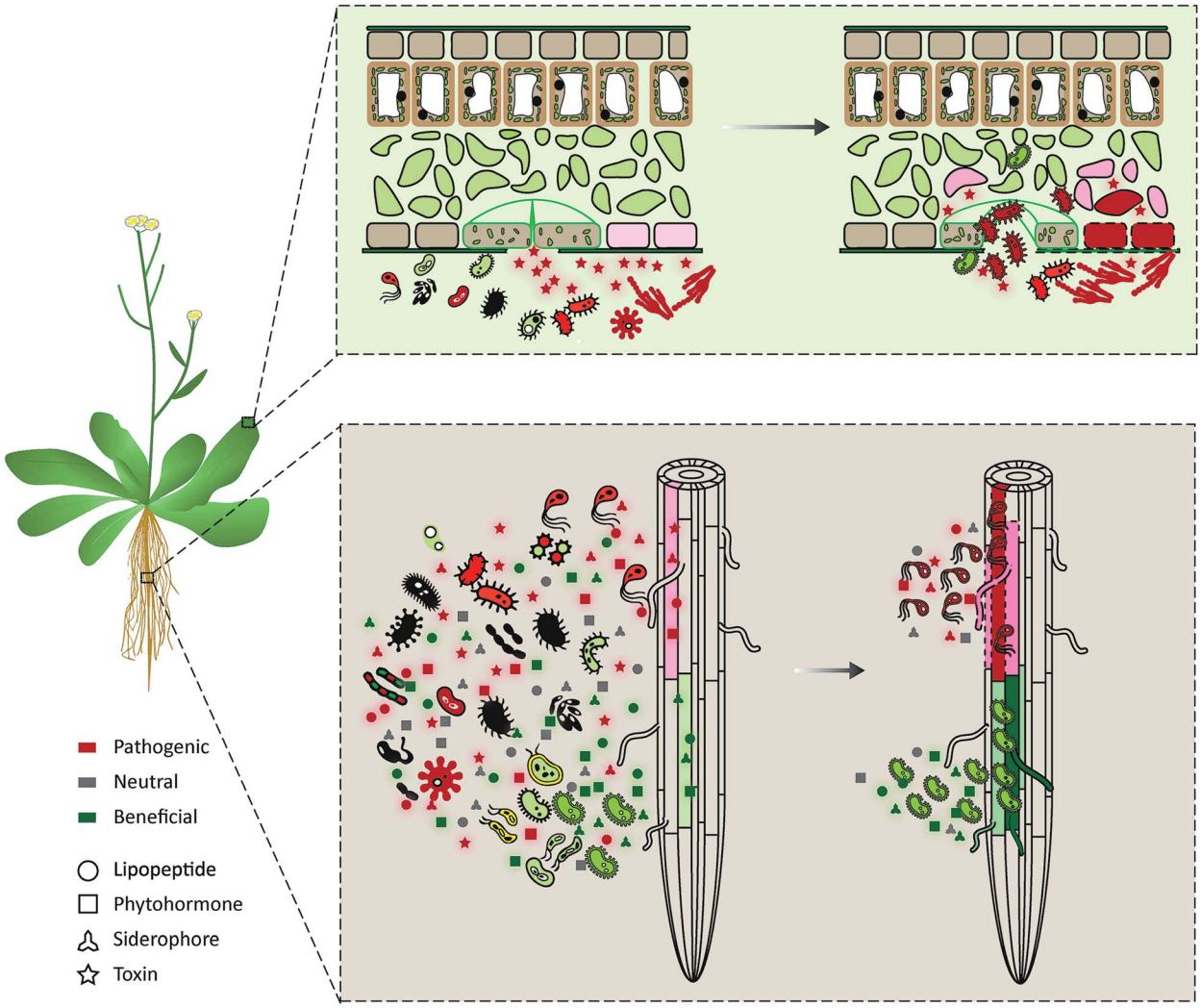
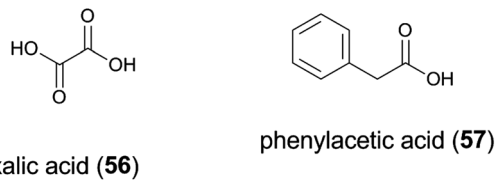


Fig. 3 Microbial small molecules subvert plant immunity, and alter plant physiology and development. Plants both above-ground and below-ground interact with a myriad of microbes that can be pathogenic (red), neutral (black) or beneficial (green). To become established in the plant, these microbes resort to various, overlapping strategies to subvert plant immunity and maximize colonization. Production of toxins facilitates pathogen entry or can induce cellular damage (red zones) whereas lipopeptides with biosurfactant properties enable microbial movement towards and along the plant. Microbe-derived phytohormones on the other hand affect general plant development and physiology, by altering root architecture or inducing cellular proliferation, boosting plant growth by beneficial microbes (green zones) or facilitating disease development by pathogens (red zones).

rhizosphere microbiome community identified members of the Oxalobacteraceae, Burkholderiaceae, Sphingobacteriaceae and Sphingomonadaceae bacterial families to be enriched in the rhizosphere upon fungal invasion. Moreover, bacterial stress-related genes for the stringent response (*ppGpp* metabolism) and oxidative stress were upregulated within these families. The direct biological triggers of these changes are yet to be identified, but it is hypothesized that oxidative stress or acidic stress incurred by oxalic acid (**56**) or phenylacetic acid (**57**) production by *R. solani* plays an important role (Chart 7).[197] Within our laboratory we are currently investigating the impact of genotype- and environment-driven plant root exudation on microbial activity in the rhizosphere, related to iron-deprivation and ISR.[1,196,198] By combining metagenome sequence assembly, computational BGC identification and transcriptional activity profiling *via* metatranscriptome sequencing, we aim to identify exudate-responsive microbial BGCs that interact with host plant physiology and development under the tested conditions.



oxalic acid (**56**) phenylacetic acid (**57**)

Chart 7 *R. solani* organic acids that play a role in plant–microbiome interactions.

3.2. Identification of microbial compounds of plant–microbe interactions through functional genomics screens

In addition to sequence- or computationally-derived identification of genes, pathways and putative compounds with roles in plant–microbe interactions, various research teams are undertaking high-throughput functional genomics screening. High-throughput screens can involve targeted disruption of all bacterial genes within a certain species or strain followed by individual or combinatorial assessment,[199] but also expression of DNA fragments of selected species or strains, and/or metagenomic fragments in a heterologous host.[200,201] Genome-wide identification of bacterial colonization genes in *P. simiae* strain WCS417 by Cole *et al.*[202] *via* barcoded transposon mutagenesis sequencing (TnSeq) led to the identification of 115 genes that are required for maximal competitive colonization of the *Arabidopsis* rhizosphere. A number of these genes could be readily linked to established rhizosphere competence traits such as motility and carbon metabolism,[203] whereas for others no previous implication in rhizosphere competence was observed. All but one of these genes are non-unique and can be found in other *Pseudomonas* genomes based on our orthogroup assignment here. The frequency of orthologs range from 3 till 448, and we anticipate that sensible integration of this resource and others helps to predict universal mechanisms of plant–microbe interactions.

4. Concluding remarks

In this review of recent literature on the biological role of microbe-derived natural products on microbial associations with plants we observe interesting parallels between microbes that are detrimental and those that are beneficial for the plant. Both groups of microbes use analogous strategies to colonize their host, and thus this division, to some extent, is context-dependent. Even more so, certain pathogenic microbes might cause severe disease on one plant, but are endophytic on others. It is uncertain whether the molecular mechanisms employed by these microbes are different on the different hosts. In the case of *Fusarium* head blight, caused by *F. graminearum*, it was shown that symptomatic infections on cultivated wheat and barley differ from asymptomatic infections on alternative native grasses.[141] On the former, significant accumulation of trichothecene mycotoxins is observed, whereas those are absent from the latter. This is congruent with previous work suggesting that mycotoxin production by *F. graminearum* is required for full disease symptom development on cultivated wheat.[204] An open question is whether *F. graminearum* does not produce these mycotoxins whilst infecting native grasses, or whether these grasses have evolved mechanisms to metabolize or detoxify them. It is not unlikely that other agriculturally eminent plant pathogens can also resort in wild relatives of their cognate crops or in other uncultivated plants. A classic example of such is black stem rust on wheat caused by *P. graminis* f. sp. *tritici*. To complete its sexual lifecycle, *Puccinia* depends on an alternative host, the barberry (*Berberis vulgaris*). It should be noted that *Puccinia* does cause disease on this alternative host. The interaction between the model plant *Arabidopsis* and the endophytic fungus *C. tofieldiae* represents another attractive example of the dynamic nature of plant–microbe interactions. *C. tofieldiae* was originally isolated from asymptomatic *Arabidopsis* plants, and re-inoculations on germ-free *Arabidopsis* confirmed its ability to colonize the root interior without causing discernible disease symptoms.[205,206] Thus, under these conditions *C. tofieldiae* behaves as a true endophyte, distinct from other *Colletotrichum* species that are notorious agents of anthracnose disease on a multitude of host plants. Moreover, when plants were grown under phosphate-starvation conditions, *C. tofieldiae* promotes plant growth by active translocation of phosphate into the plant.[205] Intriguingly, plant growth promotion by *C. tofieldiae* depends on functional tryptophan-derived indole glucosinolate metabolism; and the absence thereof flips the interaction from beneficial to detrimental.[205,207] Noteworthy, we have recently shown that *C. tofieldiae*, unlike related *Colletotrichum* species, lacks the entire cercosporin (**21**) toxin biosynthetic gene cluster and we postulate that loss of this pathway might be associated with its endophytic lifestyle.[107]

As we have highlighted, natural products play an important role in the communication between microbes and plants. Through the production and/or modulation of phytohormones (Chart 1), microbes subvert plant physiology and immunity to maximize microbial proliferation. Whereas in some cases this results in a mutualistic association in which microbial expansion goes hand in hand with growth promotion, in other cases plants succumb to pathogenic microbes resulting in disease development, and in the case of agriculture diminished yields. Toxins on the other hand are not only of concern because they contribute to disease development in the case of many plant pathogens, but they also may cause severe problems if consumed by animals (Charts 2, 3 and 4). Aflatoxin and aflatoxin-like compounds produced by *Aspergillus* species cause frequent problems for human consumption as they are important risk factors for the development of (liver) cancer in humans. Due to its status as mycotoxin, contaminated foods, and feeds, cannot be sold and thus in addition to its health effects it also has severe economic consequences. Thus, knowledge on natural product biosynthesis is not only important in the context of food security, it also has significant impact on food safety.

Understanding the why, how, when and where of microbial natural product biosynthesis in relation to plant growth and health will be vital to provide maximal benefits of beneficial microbes and limit the impact of pathogenic ones. We envisage that in the future, microbial bioinoculants could be supplemented with natural products (Charts 5 and 6) that stimulate microbial establishment on the plant and promote plant health and growth. Also, better understanding of toxin biosynthesis might aid in the development of detoxifying microbial inoculants, much alike the principles of contaminated soil phytoremediation.

The computational case study presented here across the well-studied genus *Pseudomonas*, which incorporated plant beneficial, detrimental and human pathogenic strains and

species, has revealed the tremendous diversity across this genus and should help to direct research towards understanding the role of Pseudomonads in the environment. This data appears to support a picture in which pathogenic, commensal and beneficial microbes are more similar than previously anticipated and consequently the strict lifestyle boundaries as defined in older literature are fading (Fig. 3). Considering the dynamic nature of these genomes, such information also greatly affects the way by which we assess the pathogenic or beneficial potential of a certain sample or strain. The rapidly advancing fields of host–microbiome interactions, bioinformatics, metabolomics and metagenomics will be highly instrumental in uncovering novel mechanisms and microbial molecules by which pathogens and beneficial microbes interact with their host, and in the development of novel strategies for sustainable crop protection.

5. Conflicts of interest

There are no conflicts of interest to declare.

6. Acknowledgements

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