the plant journal

SEB SOCIETY FOR EXPERIMENTAL BIOLOGY

The Plant Journal (2021) **108,** 632–645 doi: 10.1111/tpj.15490

FOCUSED REVIEW

Fungal social influencers: secondary metabolites as a platform for shaping the plant-associated community

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Received 28 May 2021; revised 1 September 2021; accepted 3 September 2021; published online 12 September 2021.
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SUMMARY

Fungal secondary metabolites (FSMs) are capable of manipulating plant community dynamics by inhibiting or facilitating the establishment of co-habitating organisms. Although production of FSMs is not crucial for survival of the producer, their absence can indirectly impair growth and/or niche competition of these fungi on the plant. The presence of FSMs with no obvious consequence on the fitness of the producer leaves questions regarding ecological impact. This review investigates how fungi employ FSMs as a platform to mediate fungal–fungal, fungal–bacterial and fungal–animal interactions associated with the plant community. We discuss how the biological function of FSMs may indirectly benefit the producer by altering the dynamics of surrounding organisms. We introduce several instances where FSMs influence antagonistic- or alliance-driven interactions. Part of our aim is to decipher the meaning of the FSM 'language' as it is widely noted to impact the surrounding community. Here, we highlight the contribution of FSMs to plant-associated interaction networks that affect the host either broadly or in ways that may have previously been unclear.

Keywords: secondary metabolites, fungal–fungal interaction, fungal–bacterial interaction, fungal–animal interaction, antagonism, symbiosis, mutualism, plant-associated community, microbiome.

INTRODUCTION

The plant-associated macro- and microbial community is influenced not only by the host plant, but also by the dynamics among the species harbored. Host plants are often parsed into rhizosphere, phyllosphere and endosphere compartments, which house a multitude of organisms including bacteria, fungi, archaea and protists, along with microfauna such as insects, arthropods and nematodes. Due to the vast number of organisms in these communities, three factors to consider when assessing the plant-associated community are: (i) how plant genetics and physiology influence community diversity and composition; (ii) the role of the environment; and (iii) how founder populations influence the dynamics of community succession. Investigation of these three factors has demonstrated that countless variables contribute to specifically shaping plant-associated microbial communities. While research in this field has generally been limited to the influence of the host and the role of the environment (Hacquard, 2016; Hassani et al., 2018), less research has focused on how plant commensal and/or pathogenic microbes shape the plant-associated community for their own benefit. Recent evidence suggests fungal plant pathogens and pests can interfere with community assembly via production of antagonistic molecules (Snelders et al., 2020). For example, fungi have been widely reported to influence their surrounding community by deploying a diverse array of fungal secondary metabolites (FSMs). The vast majority of this research has focused on the production of FSMs by biological control agents (BCAs) and their effects on phytopathogens (Liu and Li, 2005). Currently, little is known regarding FSM usage in naturally occurring ecological systems and how manipulation of the plant-associated community may occur.

For the purposes of this review, FSMs are defined as low-molecular-weight metabolites typically produced by large, multi-modular polyketide synthases, terpenes, non-ribosomal peptide synthetases, or enzymes such as prenyltransferases and dimethylallyl tryptophan synthases

(Brakhage, 2013; Keller, 2019). Unlike primary metabolites, FSMs are not essential for survival. However, their absence can debilitate fungal growth and/or increase niche competition for fungi. FSMs can serve as tools to outcompete other plant-associated organisms as iron-scavenging siderophores, as intra- and inter-kingdom signal molecules, or as metabolic, reproductive and developmental regulators (Demain and Fang, 2000; Stringlis et al., 2018). Several FSMs have been documented to facilitate plant pathogenesis through, for instance, inhibition of host defense responses or by stimulating programed cell death (Stergiopoulos et al., 2013). In contrast, it is uncertain why some FSMs are produced that do not have an obvious impact on the fitness of the producer, i.e. by plant pathogens outside of the host, when effects on the host are absent, or when produced by non-pathogenic, commensal fungi. These examples demonstrate the need for future studies to identify and characterize plant-associated communities. We speculate in such cases where fitness of the producer is unaltered, the biological function of FSMs may benefit the producer by altering the microenvironment and/or surrounding organisms.

Plant-associated microbes compete for nutrients, produce chemical signals for communication, and manufacture antibiotics to attenuate competition in order to establish and survive. Species diversity on and within plant surfaces often fluctuates, resulting in drastic (eliminating microbial groups) to insubstantial (seemingly no effect on resident microbes) effects among plant residents (Andrews and Harris, 2000). Antibiosis drives community structural dynamics when allelopathic FSMs successfully exclude organisms that would otherwise reside in these plant niches (Schulz et al., 2019). Microbes that cohabitate have been shown to trigger FSM gene expression, suggesting a role for FSMs in species dialog (Netzker et al., 2015). In addition to antibiosis, intra- and inter-species communication has also been shown to enhance the fitness of many plant-associated fungi (Calvo et al., 2002). This interplay between organisms within the plant-associated community can lead to a countless array of community permutations that offer manifold opportunities for the evolution of and, in the context of science inquisition, the discovery of highly specialized natural products.

Surveys profiling fungi in natural plant environments have shown fungal communities can be both highly diverse (Jumpponen and Jones, 2009) and deliberately organized (Davison et al., 2011), suggesting intricate fungal interactions occur among the plant community. This review focuses on the utilization of FSMs by plant-associated fungi as a platform for shaping the plant-associated macro- and microbial community. Further, we discuss several examples of antagonism and alliances among fungi, between fungi and bacteria, and between fungi and animals as well as FSMs produced by plant-associated fungi that apparently lack a specific target. A comprehensive summary of the identified FSMs, their producers, recipients and their corresponding literature references is included in Table 1.

FSMS MEDIATE INTRA-FUNGAL ANTAGONISM THROUGH CYTOTOXICITY OR MYCOPARASITISM

Much of our understanding of FSMs in fungal–fungal interactions in the plant environment is based on the study of BCAs. BCAs typically promote plant health through the antagonism of pathogenic fungi or indirect manipulation of the plant-associated community, thereby boosting plant health. Antagonistic interactions among fungi during competition for resources often involve the secretion of antifungal FSMs. The most widely studied antifungal FSMs are derived from the BCA *Trichoderma* (Reino et al., 2008). Members of the genus *Trichoderma* produce an array of FSMs ranging from low-molecular-weight volatile organic compounds (VOCs) that can freely traverse a plant system and indirectly alter the physiology of a fungal competitor (Hung et al., 2015; Werner et al., 2016) to high-molecular-weight molecules, such as peptaibols (Schirmböck et al., 1994; Shi et al., 2012) or gliotoxin (Vargas et al., 2014), that directly act upon proximate fungi.

Only a fraction of the literature focuses on natural occurrences of FSMs compared with characterization of FSMs from known BCAs. Endophytes are a major resource in the search for novel biosynthesis of antifungal FSMs, and have been isolated from leaf, rhizome, root or stem tissues (Ginting et al., 2013; Martínez-Arias et al., 2021; Schulz et al., 2002; Tellenbach et al., 2013). For example, phomopsidin, a mycotoxin that targets eukaryotic cytoskeletons through inhibition of beta-tubulin, was isolated from the endophyte *Hypoxylon rubiginosum* during natural biological control of *Hymenoscyphus fraxineus*, the fungus responsible for ash dieback (Halecker et al., 2020). Additionally, many endophytes produce FSMs that have already been the focus of characterization within *Trichoderma* spp., such as gliotoxin from *Acremonium* spp. (Anisha and Radhakrishnan, 2015), a FSM known to act upon thiol groups and inactivate proteins as well as creating reactive oxygen species (Gardiner et al., 2005). However, mining for endophyte FSMs continues as novel chemical structures (Guo et al., 2020) or configurations (Liu et al., 2012) are identified. Studies have shown that endophyte-derived FSMs, such as stemphyperylenol (Chagas et al., 2013), have strong antifungal properties but show no phytotoxicity, alluding to a primary role in niche competition.

While several studies have reported the induction of antifungal FSM production in fungal co-cultures (Chagas et al., 2013) and that antifungal FSMs are cytotoxic (Son

Table 1 FSMs and their effect on plant-associated organisms as discussed in the text including their corresponding citation

Type of interaction	FSM	Fungal producer(s)	Recipient(s)	Effect	Result	Citation
I	Phomopsidin	*Hypoxylon rubiginosum*	*Hymenoscyphus fraxineus*	Inhibits beta-tubulin, targeting the eukaryotic cytoskeleton	Inhibits fungal growth	Halecker et al., 2020
	Trichokonin	*Trichoderma pseudokoningii*	*Fusarium oxysporum*	Induces apoptosis via exposure to phosphatidylserine, reactive oxygen species and DNA fragmentation	Inhibit spore gemination and hyphal elongation	Shi et al., 2012
	Gliotoxin	*Trichoderma virens*	*Sclerotinia scleroti*	Affects metabolic functions facilitating colonization	Sclerotial degradation	Vargas et al., 2014
	Stemphyperylenol	*Alternaria tenuissima*	*Nigrospora sphaerica*	Fungal-specific cytotoxic effects	Inhibits mycelial growth	Chagas et al., 2013
	Parnafungin	*Fusarium larvarum*	*Candida albicans*	Blocks mRNA adenylation	Inhibits competitor growth	Bills et al., 2009
	Bikaverin	*Fusarium oxysporum*	*Phytophthora infestans*	Antifungal activity	Inhibits mycelial growth	Son et al., 2008
	Flavipin	*Chaetomium globosum*	*Fusarium graminearum, Sclerotinia sclerotiorum* & *Phytophthora capsici*	Antifungal activity	Inhibits mycelial growth	Xiao et al., 2013
	Trichodermin	*Trichoderma* spp.	*Rhizoctonia solani* & *Botrytis cinerea*	Antifungal activity	Inhibits mycelial growth	Malmierca et al., 2012
	Harzianic acid (siderophore)	*Trichoderma* spp.	*Pythium ultimum* & *Talaromyces pinophilus*	Removes available iron from environment	Inhibits competitor growth	Anke et al., 1991; Vinale et al., 2017
	Deoxynivalenol	*Fusarium* sp.	*Trichoderma atroviride*	Represses gene expression of antagonist	Inhibits competitor growth	Lutz et al., 2003
III	Imizoquin	*Aspergillus flavus*	*Ralstonia solanacearum*	Antibacterial activity	Suppresses bacterial growth	Khalid et al., 2018
	Bikaverin	*Fusarium fujikuroi* & *Botrytis cinerea*	*Ralstonia solanacearum*	Antibacterial activity	Protects fungi from bacterial SM ralsolamycin	Spraker et al., 2018
	Beauvericin	*Fusarium fujikuroi* & *Botrytis cinerea*	*Ralstonia solanacearum*	Antibacterial activity	Protects fungi from bacterial SM ralsolamycin	Spraker et al., 2018
IV	Loline alkaloids	*Neotyphodium* sp. & *Epichloë* sp.	*Burkholderia ambifaria*	Carbon source	Stimulation of loline consumers	Roberts and Lindow, 2014; Roberts and Ferraro, 2015
	Rhizonin	*Rhizopus microsporus*	*Burkholderia* sp.	Mycotoxin production	Fungal endosymbiotic bacteria produce mycotoxin for niche establishment	Partida-Martinez et al., 2007
	Rhizoxin	*Rhizopus microsporus*	*Burkholderia* sp.	Cytotoxic activity	Fungal endosymbiotic bacteria produce SM to block mitosis in eukaryotes	Schmitt et al., 2008; Scherlach et al., 2012
	Fumonisin	*Fusarium fujikuroi*	*Enterobacter* sp.	Mycotoxin production	Fungal endosymbiotic bacteria increase production of FSM and increase fungal virulence	Obasa et al., 2020

(continued)

Table 1. (continued)

Type of interaction	FSM	Fungal producer(s)	Recipient(s)	Effect	Result	Citation
V	Aflavinine	*Eupenicillium crustaceum*	Helicoverpa zea & *Carpophilus hemipterus*	Anti-insectan	Fungus has survival advantage through reduced feeding of fungivore insects	Wang et al., 1995
	Destruxin	*Alternaria brassicae* & *Metarhizium anisopliae*	*Lepidoptera* spp., *Drosophila melanogaster* & *Galleria mellonella*	Anti-insectan	Paralysis of lepidopteran and dipteran insect muscles, cytotoxic effect on malpighian and mesenteral epithelial cells	Kershaw et al., 1999; Ayer and Pena-Rodriguez, 1987; Dumas et al., 1996; Pal et al., 2007; Vey et al., 2002
	Gliotoxin	*Fusarium oxysporum*	*Meloidogyne incognita*	Nematicide	Mortality of juvenile plant parasitic nematode	Hallmann and Sikora, 1996
	Bikaverin	*Fusarium oxysporum*	*Bursaphelenchus xylophilus*	Nematicide	Toxicity fatal to *Bursaphelenchus xylophilus*	Kwon et al., 2007
	Fusaric acid	*Fusarium oxysporum*	*Bursaphelenchus xylophilus*	Nematicide	Toxicity fatal to *Bursaphelenchus xylophilus*	Kwon et al., 2007
	Sterigmatocystin	*Aspergillus* spp.	Fungivore grazers	Mycotoxin with insecticide properties	Provides *Aspergillus* spp. with better protection against fungivore grazers	Bok and Keller, 2004; Rohlfs, 2015
	Phomopsolide	*Phomopsis* spp.	*Scolytus* spp.	Insect feeding deterrent	Beetles preferentially fed on elm bark lacking FSM	Claydon et al., 1985, Grove, 1985, Aljahdali et al., 2020
	Phomopsolidone	*Phomopsis* spp.	*Scolytus* spp.	Insect feeding deterrent	Beetles preferentially fed on elm bark lacking FSM	Claydon et al., 1985, Grove, 1985, Aljahdali et al., 2020
	Peramine	*Neotyphodium coenophialum*	Herbivorous arthropods	Toxic alkaloid	Arthropod diversity reduction	Rudgers and Clay, 2008
VI	Chokol K	*Epichloë typhina*	*Botanophila* sp.	Insect attractant compound	Flies attracted directly to fungal stomata and fertilize fungal fruiting structures	Schiestl et al., 2006
	MME	*Epichloë festucae*	*Botanophila* sp.	Insect attractant compound	Flies attracted directly to fungal stomata and fertilize fungal fruiting structures	Steinebrunner et al., 2008
	Benzaldehyde	*Puccinia monoica*, *P.punctiformis* & *Fusarium xyrophilum*	Pollinator insects	Attractive fragrance mimic and pseudoflower fragrance	Attraction facilitates insect-mediated sexual reproduction	Connick Jr & French, 1991; Roy, 1993; Roy and Raguso, 1997; Cano et al., 2013; Laraba et. al., 2020
	Farnesene	*Fusarium xyrophilum*	Pollinator insects	Attractive fragrance mimic and pseudoflower fragrance	Attraction facilitates insect-mediated sexual reproduction	Laraba et. al., 2020

(continued)

Table 1. (continued)

Type of interaction	FSM	Fungal producer(s)	Recipient(s)	Effect	Result	Citation
	Nerolidol	*Fusarium xyrophilum*	Pollinator insects	Attractive fragrance mimic and pseudoflower fragrance	Attraction facilitates insect-mediated sexual reproduction	Laraba et. al., 2020
	Phenylacetaldehyde	*Puccinia punctiformis*	Pollinator insects	Pseudoflower fragrance	Attracts pollinators and foraging insects	Connick Jr & French, 1991; Cano et al., 2013
	Cinnamic aldehyde	*Monilinia vaccinii-corymbosi*	Pollinator insects	VOC emitted from diseased plants	Insect attractant	McArt et al., 2016
	Linalool	*Monilinia vaccinii-corymbosi*	Pollinator insects	VOC emitted from diseased plants	Insect attractant	McArt et al., 2016
	α-Pinene	*Monilinia vaccinii-corymbosi*	Pollinator insects	VOC emitted from diseased plants	Insect attractant	McArt et al., 2016
	α-Phellandrene	*Puccinia arrhenatheri*	Pollinator insects	Fragrance emitted from diseased leaves	Attracts flower-visiting insects	Naef et al., 2002
	Carvacryl methyl ether	*Puccinia arrhenatheri*	Pollinator insects	Fragrance emitted from diseased leaves and plays defensive role	Attracts flower-visiting insects	Naef et al., 2002

FSM, fungal secondary metabolite; VOC, volatile organic compound.

et al., 2008; Zhang et al., 2013), less is known about specific modes of action that result in fungal cell death. The inhibition of hyphal elongation and conidial germination has been shown for bikaverin produced by the phytopathogen *Fusarium oxysporum* (Son et al., 2008), and flavipin produced by the endophyte *Chaetomium globosum* (Xiao et al., 2013), although the cellular mechanisms underlying their toxicities are not yet reported. Conversely, parnafungins made by the plant pathogen *Fusarium larvarum* demonstrated inhibition of growth in competitor fungi by blocking mRNA adenylation (Bills et al., 2009). Peptaibols produced by *Trichoderma* spp. have shown to induce programed cell death via exposure of phosphatidylserine, the appearance of reactive oxygen species, and fragmentation of nuclear DNA (Shi et al., 2012). These examples offer insight into mechanisms in which FSMs participate in fungal–fungal antagonism.

Among intra-fungal dynamics, mycoparasitism is a common competitive interaction in which FSMs may play a key role. Mycoparasitism is a feature most frequently associated with the order Hypocreales in which a competing fungus serves as a nutrient source. Initially characterized in *Trichoderma* BCAs, mycoparasitism has been exploited to change the plant community via the management of phytopathogens. Historically, many FSMs were initially discovered from studying mycoparasitism, such as the secondary metabolite groups of peptaibiols (including trichokonins; Shi et al., 2012; Szekeres et al., 2005), epipolythiodioxypiperazines (such as gliotoxin; Vargas et al., 2014), terpenoids (including trichodermin and harzianum A; Malmierca et al., 2012) and siderophores (such as harzianic acid; Vinale et al., 2013). Biotrophic fungal mycoparasites tend to specialize in targeting one or few fungal species, as the effectiveness of their artillery (including FSMs) are often species-specific (Speckbacher and Zeilinger, 2018). It is likely that species-specific cues induce the production of FSMs in these mycoparasites. For example, co-culture of mycoparasitic strains with different fungi led to production of unique FSMs, especially in contrast to isolates grown in solitary (Chatterjee et al., 2016). Various studies have shown how fungi may utilize specific FSMs to prepare for mycoparasitism upon direct confrontation with their prey. For instance, some FSMs function in communication or signaling (e.g. siderophores; Vinale et al., 2017), or can detoxify or degrade prey-derived defense compounds (e.g. deoxynivalenol; Lutz et al., 2003). Interestingly, mass spectrometry-based imaging methods are now being used to elucidate how FSMs are spatially and temporally produced during mycoparasitism, and in some cases enable the visualization of FSM interplay between different species (Bohni et al., 2016; Chamoun et al., 2015; Holzlechner et al., 2016; Knowles et al., 2019; Tata et al., 2015), thereby unveiling a new means of interrogating FSMs as an ecological driver (Figure 1).

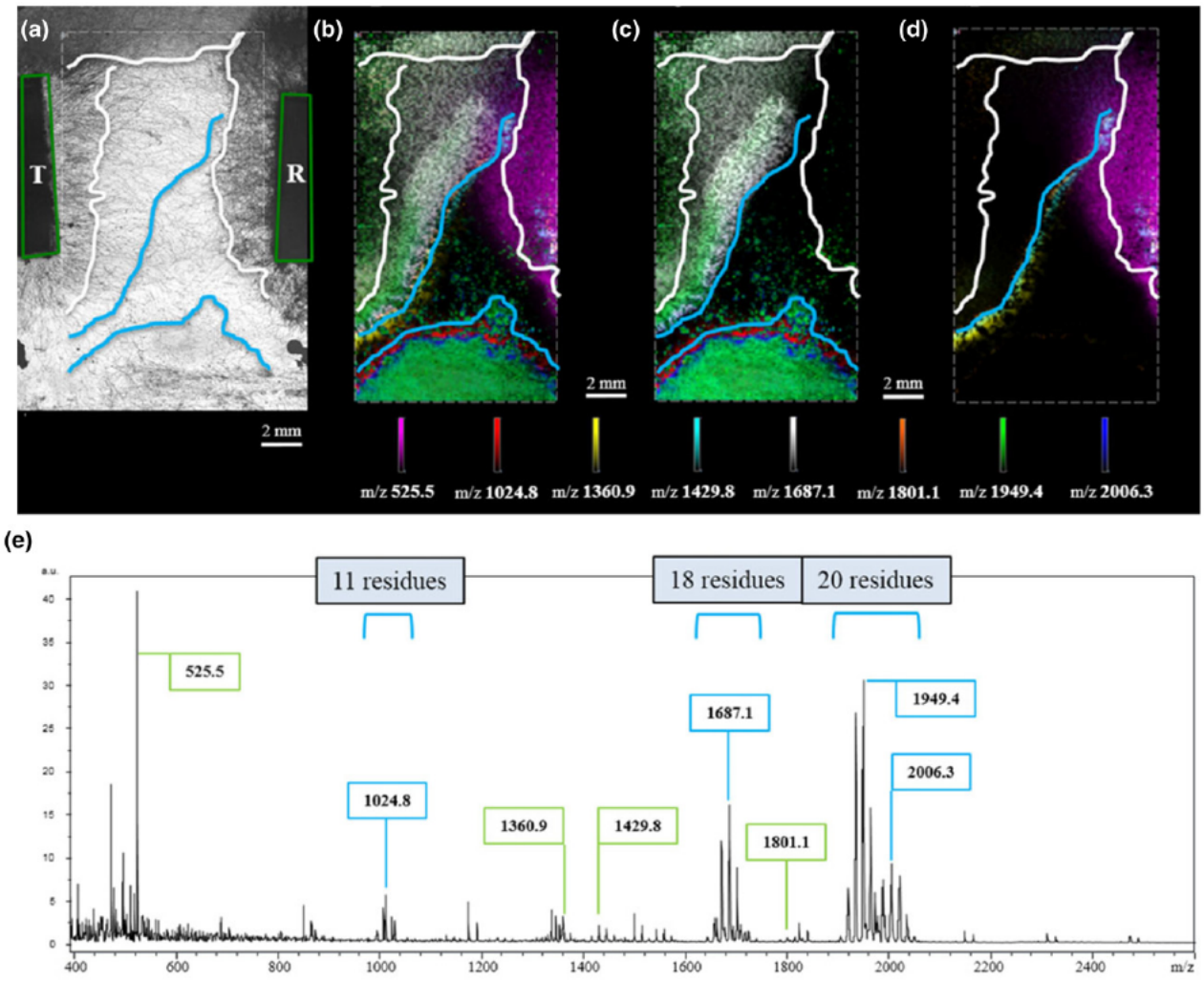

Figure 1. MALDI MSI of physically interacting *Trichoderma atroviride* (T) and *Ralstonia solani* (R) hyphae.
(a) Light microscopic image showing points of inoculation (green tetragons), the outer rim of hyphal growth for both species (white lines) and borders for features detected by MSI (blue lines).
(b) Molecular distributions of selected secondary metabolites localized by MALDI MSI.
(c) *Trichoderma atroviride* specific metabolites.
(d) *Ralstonia solani* specific metabolites.
(e) Profile mass spectrum exhibiting signals assigned to *R. solani* (marked in green) and *T. atroviride* (marked in blue). Figure and legend reprinted from Holzlechner M *et al.* (2016) *Proteomics*, 16, 1742–1746, with permission from Wiley.

FSMS MAY MEDIATE INTRA-FUNGAL ALLIANCES VIA SYNTROPHY OR CHEMICAL COMMUNICATION

Fungal alliances could strongly influence plant community composition when either nutritional syntrophy (or cross-feeding) or molecular communication occur. Although no specific FSMs have been implicated in fungal–fungal cooperation among the plant community, it is not unlikely that these interactions occur. It has been shown arbuscular mycorrhizal fungi in forest systems form non-random communities (Davison et al., 2011), and co-habitating fungi have been commonly observed together on plants to balance the community structure (Mack and Rudgers, 2008; Schulz et al., 2015). These observations support the possibility that different fungal species can respond cooperatively to common chemical signals or perhaps take advantage of other intra-fungal-derived secondary metabolites that are in excess in the environment. Moreover, it has been well established that FSMs can mediate shared chemical signaling and defense between fungi and many other microbes and macro-eukaryotes (Cano et al., 2013; Schmidt et al., 2017), as we discuss in later sections. Future research into FSM-dependent fungal–fungal alliances among the plant-associated organisms could potentially

guide the engineering and formulation of highly effective synthetic fungal BCA communities.

FSMS MEDIATE FUNGAL–BACTERIAL ANTAGONISM TO COMMUNICATE WARFARE AND IMPOSE ANTIBIOSIS

Fungi and bacteria are both major constituents of the plant community and contributors to overall health of a given host through biological control, by increasing host plant immunity, or by increasing host plant productivity (Deveau et al., 2018). Their physical overlap provides a likely opportunity for interaction mediated by secondary metabolites that affect the fitness of neighboring microbes (Scherlach et al., 2013). Such interactions are very common in soil, and a well-studied example, generally referred to as soil fungistasis, describes the inability of fungal spores to germinate in soil under conditions that normally favor such germination and is typically observed in microbially active soils (Bakker et al., 2020). Thus, cross-kingdom interactions appear to play an important role in driving ecosystem dynamics. Plant-associated fungi and bacteria have been widely reported to produce highly diverse secondary metabolites in co-culture (Akone et al., 2016; Ola et al., 2013) and, through these compounds, microbes induce cross-kingdom metabolome changes (Schmidt et al., 2017). Investigation of FSM-mediated cross-kingdom interaction has provided evidence that physical interaction among microbes is not necessary to alter the community, as diffusible signals can produce long-distance effects on other microbes (Schroeckh et al., 2009).

Many FSMs are produced in response to bacterial signaling as an antagonistic means of directly reducing bacterial fitness. Concurrent *in vitro* transcriptomic profiling of the plant pathogenic fungus *Rhizoctonia solani* and plant-associated bacteria in the genus *Serratia* revealed differential upregulation of secondary metabolite gene clusters in both organisms suggesting inter-species communication or antibiosis via the release of toxins (Gkarmiri et al., 2015). Differential expression of FSMs in response to antagonistic bacteria has been widely documented in many fungal–bacterial interaction systems (Han et al., 2017; Khalid et al., 2018; Krause et al., 2020). Surprisingly, these examples illustrate a general tendency towards a global decrease in FSM production, presumably to redirect biosynthetic energy away from FSMs that are not needed for bacterial antagonism in exchange for heightened production of a select subset of FSMs that likely provide a competitive advantage. For example, the fungus *Aspergillus flavus* increases production of the FSM imizoquin in the presence of the antagonist bacterial phytopathogen *Ralstonia solanacearum* while also stimulating its own germination in co-culture (Khalid et al., 2018).

Although these examples show changes in FSM production during fungal–bacterial antagonistic interactions, these changes potentially represent a complex language in which FSMs comprise one form of dialog at the community level. For example, fungi and bacteria exhibit an ongoing FSM exchange to communicate warfare (Spraker et al., 2014). It was shown that bacterial biosynthesis of ralsolamycin induced chlamydospore production in diverse fungal taxa, possibly to create housing for bacteria within these structures (Spraker et al., 2016). In response to ralsolamycin, *Fusarium fujikuroi* and *Botrytis cinerea* produced the antibacterial FSMs bikaverin and beauvericin to negate bacterial invasion (Spraker et al., 2018). Additional research is still necessary to show the extent at which FSM production for bacterial antagonism commonly occurs among fungi within the plant-associated community.

FSMS MEDIATE FUNGAL–BACTERIAL ALLIANCES BY RECRUITING COOPERATIVE CONSTITUENTS

Fungi have been clearly observed to alter the host plant bacterial microbiome upon their establishment (Seybold et al., 2020). The strength of this selection is demonstrated among fescue grasses colonized by fungal endophytes that produce the alkaloid FSM loline. Leaf and root microbiota of these grasses are highly enriched in bacteria consuming loline as a carbon source (Roberts and Ferraro, 2015; Roberts and Lindow, 2014). Although this FSM functions in bacterial recruitment, how and whether selection for loline consumers directly benefits loline-producing fungi remains unresolved. It is conceivable that this selection may exclude other microbial species, potentially ensuring host colonization by a co-evolved or at least compatible, non-antagonistic, non-pathogenic bacterial cohort for these fungi. The most highly-enriched bacterium as a result of fungal loline production was the loline consumer *Burkholderia ambifaria*, a species implicated in inhibition of fungal plant pathogens and plant growth promotion (Groenhagen et al., 2013). Fungal loline production also has been shown to directly antagonize insect pests (Wilkinson et al., 2000), illustrating how fungi may utilize these compounds for multiple purposes.

Plant-associated fungi can also serve as a 'sub-host' with their own specific bacteriome that accompanies healthy or diseased states, potentially affecting fungal fitness, including FSM production. Research has shown the bacteriome of fungi may be as important as the host plant for prompting fungi to produce FSMs (Schulz-Bohm et al., 2017). This phenomenon was demonstrated in the plant-associated fungus *Rhizopus microsporus*, which produces the FSM mycotoxin rhizonin only in the presence of a *Burkholderia* spp. endosymbiont (Partida-Martinez et al., 2007). This multilayered interaction illustrates how bacterial-induced FSM production underpins a competitive advantage against other fungi seeking to colonize the same niche. Additionally, *R. microsporus* produces the secondary metabolite rhizoxin, a putative phytotoxin shown to block

mitosis in eukaryotes (Schmitt et al., 2008). However, it was later demonstrated that the bacterial partner synthesizes rhizoxin, which the fungal partner modifies to enhance phytotoxicity (Scherlach et al., 2012). Another example of fungal–bacterial partnerships was observed between the plant pathogen *F. fujikuroi* and two endosymbiotic *Enterobacter* species that induce production of fumonisin (Obasa et al., 2020), a mycotoxin responsible for kidney and liver damage in animals, and serves as a virulence factor during plant colonization (Abbas et al., 2000). Specifically, *F. fujikuroi* hyphae housing these bacteria produced significantly more toxin and exhibited higher virulence than those lacking the endosymbiont (Obasa et al., 2020). Countless symbiotic relationships exist among fungi and bacteria, and their coevolution on plant hosts have likely led to increased diversity in unique FSMs based on their specific couplings, metabolisms, lifestyles or plant-associated compartments.

FSMS MEDIATE FUNGAL–ANIMAL ANTAGONISM BY DETERRING FUNGIVORY OR HERBIVORY

Studies focusing on the function of FSMs in fungal–animal interactions largely explore antagonism around competition for nutritional resources. Such interactions have been observed to alter foraging habits and subsequently reduce fitness among animals. The evolutionary arms race between animals and fungi and how FSM production mediates fungal survival are still relatively unexplored. Literature surrounding antagonistic relationships between animals and fungi involve direct and indirect grazing via fungivory and herbivory, respectively.

Fungi have evolved FSMs as effective deterrents of herbivorous animals. One such example occurs between corn earworm *Helicoverpa zea* and dried fruit beetle *Carpophilus hemipterus* and fungus *Eupenicillium crustaceum*. Larvae from these two insect species showed either a 79% reduction in weight gain (*H. zea*) or a 42% reduction in feeding rate (*C. hemipterus*) when exposed to naturally occurring levels of an aflavinine analog from *E. crustaceum* (Wang et al., 1995). Rudgers and Clay (2008) speculated arthropods may be directly affected by fungal FSMs, such as peramine, due to a correlation between reduced arthropod abundance and high diversity in plant-associated fungal communities (Rudgers and Clay, 2008). FSMs modulate virulence and fecundity among animal populations through weakening of insect and nematode immune systems as a scheme to deter herbivory. Initially characterized in the phytopathogenic fungus *Alternaria brassicae* (Ayer and Pena-Rodriguez, 1987), the FSM destruxin has been shown to participate in suppression of the hormonal immune response of insects, including *Lepidoptera* spp. (Dumas et al., 1996), *Drosophila melanogaster* (Pal et al., 2007) and *Galleria mellonella* (Vey et al., 2002). Nematode fitness has been observed to be penalized in part by specific FSMs in plant communities. For juveniles of the plant-parasitic nematode *Meloidogyne incognita*, 24 h of exposure to a *F. oxysporum* gliotoxin-containing broth resulted in a 100% mortality rate (Hallmann and Sikora, 1996). In another demonstration of nematicide activity, Kwon et al. (2007) identified bikaverin and fusaric acid FSMs from *F. oxysporum* capable of terminating the pine wilt nematode *Bursaphelenchus xylophilus* (Kwon et al., 2007).

In addition to negating herbivory, FSM mechanisms evolved to dissuade fungivores can impact selective grazing by arthropod species, and consequently may remodel fungal–animal plant communities. For instance, springtail insects can perceive fungal VOCs and redirect their foraging away from emitted fungal toxins (Staaden et al., 2011). Although the mechanisms and specific compound combinations have yet to be thoroughly explored, there is evidence FSMs may serve as a protective mechanism. By producing compounds with bitter or poisonous properties, FSMs such as phomopsolide and phomopsolidone from the endophyte *Phomopsis* spp. have shown to be a driver for feeding preference (Aljahdali et al., 2020; Claydon et al., 1985; Grove, 1985).

Many fungi synthesize secondary metabolites under the control of the master regulator velvet protein complex (VelB-VeA-LaeA) to deter fungivores and herbivores in plant-associated communities. Although best characterized in *Aspergillus*, many plant-associated fungi such as *Fusarium* spp., *Trichoderma* spp. and *Ustilago maydis* contain the widely conserved velvet protein complex (Bayram and Braus, 2012; Kim et al., 2002; Li et al., 2006; Wiemann et al., 2010). The velvet protein complex is involved in secondary metabolite regulation in addition to fungal development (Kato et al., 2003; López-Berges et al., 2013). One of the important genes involved in resistance to fungivory may be *LaeA*, which is involved in epigenetic control of many filamentous FSMs (Ortiz et al., 2013). FSM synthesis mediated by LaeA can be a fungal strategy for preventing fungivores from grazing (Rohlfs, 2015). To illustrate, gene expression of the corresponding *LaeA* gene was significantly upregulated in *Aspergillus nidulans* colonies challenged with feeding by the fruit fly, *D. melanogaster*. The rate of insect survival was higher when feeding on *Aspergillus* Δ*laeA* mutants compared with the wild-type fungus in both *D. melanogaster* (Trienens and Rohlfs, 2012) and springtail fungivores (Stötefeld et al., 2012). A specific FSM unable to be produced because of the deletion of *LaeA* is sterigmatocystin (Bok and Keller, 2004). Interestingly, deeper evaluation has shown biosynthesis of sterigmatocystin itself is more impactful for fungivore resistance than the potential insecticidal properties of the toxin alone, likely because the acetyl-coA precursor and intermediates are able to siphon into other FSM pathways (Rohlfs, 2015).

For fungi contending with plant-associated animals, the velvet protein complex may be providing an energy-saving

strategy for fungal competitors by mediating FSM production. In this case, FSMs work to deter plant-associated macrobial community constituents that may prey upon the fungus itself or its plant habitat. Although outside of the scope of this review, it is worth noting the extensive research that has been put into the effects of many mycotoxin FSMs on animals, with a focus on mammals. While numerous mammals are facultatively mycophagous, mammals do not typically feed exclusively on fungi, and interactions involving mammals and fungal FSMs have mostly been in the realm of toxicity research. Co-evolution between fungi and animals is not well understood; however, the aforementioned studies offer an ecological context for FSM-mediated antagonism towards animals that utilize plant tissues as their main resource.

FSMS MEDIATE FUNGAL–ANIMAL ALLIANCES FOR DISSEMINATION THROUGH POLLINATOR RECRUITMENT

Fungal secondary metabolites are also involved in mutualistic relationships with animals in ways that shape the plant-associated community. Plant-associated insects, particularly pollinators, are recruited to facilitate fungal reproduction, thus shaping the plant-associated community. For example, FSMs may act as signals to insect pollinators indicating oviposit locations or nutritional resources, occurring by means of floral mimicry and chemoattractant production. When insects carry gametes of different mating types, the proximal exposure of otherwise isolated strains may facilitate sexual reproduction (Roy, 1993), providing an evolutionary advantage of increased genetic diversity through recombination (McDonald and Linde, 2002).

Pollinators flock to sites of potential nutritional resources in anticipation of consuming sugars produced by floral plants, and fungal outcrossing is promoted when pollinators bring sexually compatible strains together (Roy and Raguso, 1997). Certain fungal species have evolved floral mimicry strategies to attract pollinators by developing pseudoflower structures (Figure 2). For example, *Fusarium xyrophilum* produces pseudoflowers during infection of perennial *Xyris* grass that emit FSM volatiles such as benzaldehyde, farnesenes and nerolidol (Laraba et al., 2020). Additionally, *Puccinia monoica* produces phenylacetaldehyde and benzaldehyde FSMs during production of pseudoflowers (Cano et al., 2013). Pollinator visitation to *Ranunculaceae* species or *P. monoica* pseudoflowers increases when the two species are associated with one another (Roy, 1993). The *P. monoica* pseudoflower has a higher sugar content than that of the host flower, and the host may benefit from increased duration of pollinator visitation due to abundant nutritional and sugar resources (Cano et al., 2013). Another example of floral mimicry by fungi is *Monilinia vaccinii-corymbosi* (*Mvc*), which produces a pseudoflower that emits cinnamic aldehyde, α-pinene and linalool FSMs. Reports propose *Mvc* has evolved to produce FSMs to mimic floral scents and attract insects, mainly those in the orders Diptera and Hymenoptera, thereby aiding in asexual spore transmission (McArt et al., 2016). This study showed that volatile profiles of *Mvc*-produced pseudoflowers were similar to those emitted by genuine flowers. Additionally, pollinating insects were attracted to pseudoflower-derived FSM volatiles and thus may successfully carry *Mvc* spores, supporting the proposed hypothesis that pseudoflowers have evolved to

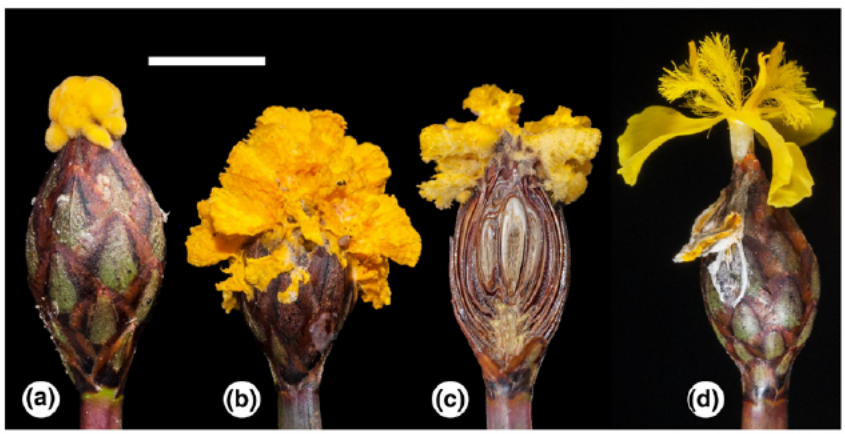

Figure 2. Comparison of *Xyris* flower and *Fusarium xyrophilum* pseudoflowers collected in the Cuyuni-Mazaruni region of Guyana in 2010.
(a) Young yellow-orange pseudoflower produced by *F. xyrophilum* emerging at tip of cone-like spike of *Xyris surinamensis*.
(b) Mature pseudoflower of *F. xyrophilum* enveloping the entire *X. surinamensis* spike.
(c) Longitudinal section of *X. surinamensis* spike showing partial fruit development in the center and pseudoflower of *F. xyrophilum*.
(d) Healthy yellow flower of *X. surinamensis* shown for comparison, with lateral petals and prominent erect hairlike staminodes. Scale bar: 5 mm (a–d). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Figure and legend reprinted from Laraba I *et al.* (2020) *Fungal Genetics and Biology*, 144, 103 466, with permission from Elsevier.

mimic flower chemo-attractants towards insect vectors to aid in fungal dispersion and sexual reproduction (McArt et al., 2016).

Many examples exist of volatile FSMs signaling pollinators through chemoattractants that ultimately facilitate fungal reproduction. Female *Phorbia phrenione* flies are drawn by pollinator attractant FSMs, such as chokol K and methyl(Z)-3-methyldodec-2-enoate (MME), emitted by *Epichloë* species (Schiestl et al., 2006; Steinebrunner et al., 2008). MME generates a potentially attractive odor for *Botanophila* flies that may maximize fungal cross-fertilization by the transport of spores to multiple plant hosts (Bultman et al., 1998). Additionally, female *P. phrenione* participate in outcrossing *Epichloë typhina* spermatia by ovipositing their eggs on the fungus. Consequently, *P. phrenione* larvae hatch and feed on fungal tissue (Bultman et al., 1998). Although these described findings putatively describe FSM activity, work describing pollinator attraction by chokol K and other FSMs suggests they are likely drivers in pollinator attraction. Chokol K alone can act as an attractant to pollinators and has a secondary function to inhibit establishment of other fungi, ultimately benefiting *Epichloë* spp. fitness, and perhaps enhancing host plant defense (Schiestl et al., 2006). Benzaldehyde and phenylacetaldehyde are compounds emitted by both the Canadian thistle plant as well as the fungal species *Puccinia punctiformis*. Compounds produced by Canadian thistle are mimicked in FSM production by *P. punctiformis* for the purpose of attracting pollinators that can then promote fungal outcrossing (Connick Jr and French, 1991). Another rust species that colonizes Barberry, *Puccinia arrhenatheri*, emits chemoattractant FSMs, useful for mimicry strategies such as coloring and nutritional resource production, to attract insects (Naef et al., 2002). Some of the identified FSM compounds produced by the spermatia of this rust species include the isoprenoid monoterpenes α-phellandrene and carvacryl methyl ether, which are shown to attract pollinators (Naef et al., 2002).

There are numerous examples involving insect pollinators and fungal FSMs alliances in plant-associated communities, yet the involvement of other animal–fungal alliances has been far less explored. This is likely due to difficulty exploring interplay in natural habitats as a result of the ephemeral interaction due to animals' mobility. Alternatively, there may be a lack of interest in the ecology between plant-associated fungus and animal if there is not a related pressing concern. However, it is likely more examples exist in natural settings that allow for animal–fungal partnerships mediated by fungal FSMs.

CONCLUSIONS

In light of the current state of FSM research, it is patently clear that we understand neither the full repertoire nor the functional potential of plant-associated FSMs. Many known FSMs exert no clear effect on the plant host, leading us to postulate that these molecules are involved in competitive interactions. For example, pyrrocidines, produced by many plant-associated fungi, have both antibacterial (He et al., 2002) and antifungal (Gao et al., 2020) properties, while other FSMs are only produced in the presence of other specific organisms (Brakhage and Schroeckh, 2011; Wakefield et al., 2017). In addition, *in vitro* challenge assays between plant-associated fungi and other microorganisms have revealed the production of cryptic FSMs (Serrano et al., 2017). Given the multiplicity of potential interactions that can occur within the plant-associated community, we are inclined to speculate the full range of secondary metabolites is effectively indeterminate.

Many FSMs are considered to be non-host-specific community modifiers, i.e. likely have broad functions that affect a wider range of species than the plant host and/or the associated community wherein it was produced (Mitchell, 1984). The term non-host-specific community modifier has mostly been explored in the context of plant pathogenic fungi. These FSMs have historically been deemed as virulence factors for plant invasion but are now explored for alternative functions. Cercosporin (Daub and Ehrenshaft, 2000) and beticolin (Milat et al., 2010) produced by the plant pathogenic fungus *Cercospora beticola* are two examples of FSMs initially characterized as virulence factors in sugar beet infection, but were subsequently discovered to be toxic towards other organisms (Daub and Ehrenshaft, 2000). Although the non-host-specific toxicity of these FSMs is informally described, no reports have explicitly investigated the range of impacted organisms, plant-associated or otherwise. Extracts of both beticolin and cercosporin act as selective antibiotics against only a limited subset of bacteria isolated from sugar beet (Figure 3), suggesting these FSMs may also be produced for

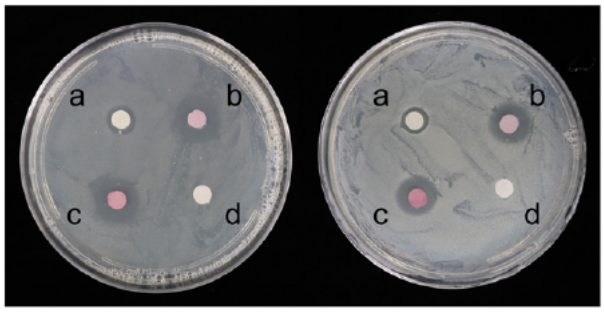

Figure 3. Fungal secondary metabolites (FSMs) cercosporin and beticolin isolated from *Cercospora beticola* inhibit the growth of bacteria isolated from sugar beet tissues.
A total of 10^6 CFU mL^{-1} of bacteria (left: *Paenibacillus* sp.; right: *Staphylococcus* sp.) was spread on a plate and allowed to dry. Ten microliters of each (a) beticolin extract, (b) cercosporin extract, (c) manufacturer-produced 20 m_M cercosporin standard or (d) methanol was placed on filter disk, allowed to dry and placed on Mueller-Hinton agar. Plates were incubated upside down at 30°C overnight.

the purpose of outcompeting specific microbes during infection.

It is important to note that there is a paucity of direct evidence that FSMs affect community composition because this field is in its infancy. At present, very few studies exist that explore FSMs in their naturally occurring plant environment. This may be a result of lack of funding or a general lack of interest if the fungal producer will not solve an imminent agricultural problem. For example, current FSM-related *in planta* studies often involve the search for BCAs to aid in management of plant pathogens on economically important agricultural crops. An elegant study by Halecker et al. (2020) emphasizes the necessity of *in planta* experiments as several potential BCA fungal endophytes inhibited the ash dieback pathogen during co-culture *in vitro*, yet were not appropriate for application because they also caused disease symptoms on axenically grown European ash. This does not negate the importance of co-culturing for FSM discovery as many studies identified cryptically produced FSMs only in the presence of other microbes. However, co-culturing fungi with a single organism for the purpose of uncovering metabolite function is not likely to show the entire picture of the FSM's role on the plant surface. FSMs may exhibit complex interactions with multiple community participants, and current techniques do not allow such detailed detection. Additionally, there are no current tools that allow for direct evidence of a FSM's ability to change community structure. Indirect methods of testing FSMs tend to show co-occupancy associations where there is selection for certain organisms on the plant when FSM producers are present (compared with when they are absent) but do not address how or why this occurs. Lastly, and perhaps obviously, we cannot say anything about what we do not know, i.e. those organisms in plant environments that are unculturable. It is unknown how these organisms may be influenced by FSMs or how they influence the community if they are the FSM producer themselves. Although the full range of FSM functions are not fully understood at present, *in planta* imaging, transcriptomics and microbiome studies using FSM biosynthesis knockout mutants may uncover the impacts of these compounds on plant-associated community structure and dynamics. Looking to the future, phytobiome studies are quickly advancing with new methods aimed to capture the entirety of the microbial community in a manner that better allows the study of such complex systems (Singer et al., 2021).

Technological advances in *in situ* research will hopefully enable a more rigorous and systematic decoding of the fungal 'language' of FSMs, thereby clarifying the full audience and the biological effects of the message. Unfortunately, the limited, current understanding of FSM interactions represents a superficial accounting of the versatility and utility with which these compounds can serve as a platform to influence the macro- and microbial plant-associated community. The exchange of FSMs can clearly mediate both beneficial and antagonistic interactions, within and across species, and for purposes that may

Box 1. Summary

- Fungal secondary metabolites (FSMs) are defined as fungal-produced low-molecular-weight metabolites typically synthesized by large, multi-modular polyketide synthases, terpenes, non-ribosomal peptide synthetases, or enzymes such as prenyltransferases and dimethylallyl tryptophan synthases.
- FSMs are not essential for survival, although their absence can debilitate growth and/or niche competition of the producing fungus.
- FSMs are capable of manipulating plant community dynamics by inhibiting or facilitating the establishment of co-habitating organisms such as other fungi, bacteria or animals.
- In addition to toxicity, FSMs may have multiple functions in altering the plant and its associated community.
- Research on how FSMs affect the plant-associated community is in its infancy and, consequently, many limitations exist in showing direct roles of FSMs including constraints with current methods of assessment and a lack of *in planta* studies.

Box 2. Open questions

- Why do some fungi have the capability to synthesize fungal secondary metabolites (FSMs) with no obvious beneficial impact to the producer?
- Can FSMs exhibit multifunctional purposes regarding cooperation and/or antagonism of non-self organisms?
- How do FSM profiles change in a natural environment compared with an artificially induced interaction?
- To what extent does the plant host or environment affect FSM production as it pertains to shaping the plant community?
- Has the ability to produce FSMs co-evolved with not only the plant host but also the plant-associated community?
- How can researchers formulate *in planta* studies to identify specific FSMs involved in community modification?

remain unclear in the absence of prolonged and extensive research. However, the few aspects of FSM communication and metabolism that have received attention clearly point to a vast reservoir of natural products that, outside of the plant-associated community context and microbial signaling, may aid in almost countless foreseeable and as-of-yet unrealized applications.

ACKNOWLEDGEMENTS

The Bolton Laboratory is funded by USDA CRIS Project 3060-21000-044-00-D and grants from the Sugarbeet Research and Education Board of ND and MN and the Beet Sugar Development Foundation. A sincere thank you to Dr Isaac V. Greenhut for his constructive criticism of this manuscript and Mari B. Natwick for help with images. The authors declare no conflict of interest.

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