



## Microbial natural products activated by plant stress

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The search for new antimicrobial natural products from microorganisms has been limited by the transcriptional silencing of biosynthetic genes when microbes are cultivated outside their ecological environments. Nevertheless, applying knowledge of the ecological roles, for example, microbial defense against plant pathogens, can improve drug discovery efforts. Interactions between plants and their microbiota, during adaptation to pathogen stress, provide ecological cues that induce microenvironments suppressive to pathogens. This article highlights research linking pathogen-induced plant stress signals to the activation of microbial natural product biosynthesis, emphasizing the need for further studies on how plant metabolites can influence biosynthesis in plant-associated microbes.

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### 1. Introduction

Microbial natural products have long served as a significant source of antimicrobial agents, which are essential for maintaining the health of humans, animals, and plants.<sup>1</sup> Advances in genome mining techniques have highlighted significant gaps between a microbe's biosynthetic potential and what is actually observed when it is cultivated in the laboratory. These gaps arise because the ecologically relevant signals that induce biosynthesis are absent in traditional laboratory conditions, resulting in many biosynthetic gene clusters remaining transcriptionally inactive.<sup>2</sup> Therefore, there is an increasing interest in applying

the knowledge of the ecological roles of microbes to enhance drug discovery efforts.<sup>3,4</sup>

Common applications of the ecological environment of microbes to trigger microbial natural product biosynthesis have advanced drug discovery efforts, but still face certain limitations. For instance, employing interspecies or interkingdom co-culturing to facilitate microbial competition and thereby activate silent gene clusters.<sup>5,6</sup> However, not all co-cultures induce biosynthesis of natural products, and establishing production cultivations can be intricate when working with various microbial species. Another approach, which involves varying cultivation conditions such as carbon and nitrogen sources,<sup>7</sup> is untargeted and may not activate silent biosynthetic gene clusters. Additionally, these methods are not suitable for high-throughput screening. In recent years, small-molecule elicitors, such as antimicrobials, have been explored to mimic the chemical cues of an ecological niche in laboratory settings.<sup>6</sup> In this context, it is advantageous to understand the chemical signals that drive microbial biosynthesis of antimicrobial natural products in distinct environments.

One unique environment is that in which plants coexist with their microbiota as holobionts, contributing to the chemical diversity of the microenvironment.<sup>8,9</sup> On one hand, this partnership enhances the plant's ability to adapt to environmental stresses, both abiotic and biotic, and facilitates nutrient acquisition. While plants establish long-term relationships with certain microbes, other associations are temporary, formed only during plant adaptation to stress, which explains the observed heterogeneity in the microbiota.<sup>8,9</sup> For instance, during a pathogen invasion of plants, the microbiota composition changes significantly, and these changes lead to the suppression of the pathogen; however, this effect can sometimes dissipate as the

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pathogen population disappears.<sup>10</sup> On the other hand, the associated microbes, which exist either within the plant endosphere or outside the plant tissues (on the plant surface or in the rhizosphere), access a nutrient-rich environment.<sup>9</sup> Additionally, the fitness of the microbiota is determined by the ability to catabolize substrates and maintain population densities in the environment.<sup>9</sup>

Microorganisms within the rhizosphere are influenced by plant roots as plants secrete both primary and secondary metabolites through their root exudates. While amino acids, organic acids, polysaccharides, sugars, and other nutrients, as well as antibiotics, have been identified as constituents of root exudates, other components may perform functions beyond nutrition or antibiosis.<sup>11</sup> Some schools of thought propose that plants signal through root exudates, using a cry-for-help mechanism to attract beneficial microbes.<sup>9,11</sup> Others argue that there is no deliberate recruitment of microbes; instead, the microbial population is curated as a result of the spatiotemporal chemical gradients arising from the plant's response to stress within its microenvironment.<sup>12</sup> Nevertheless, the consensus is that metabolites associated with plants' perception and response to pathogen attack are known to impact microbial population and metabolism. An example of such metabolites is plant stress hormones.

Plants activate complex hormonal networks that induce their physical and chemical defenses against pathogen invasion. These defense-related pathways include the jasmonate, salicylate, and ethylene pathways.<sup>13</sup> Moreover, pathways like abscisic acid, auxin, cytokinin, brassinosteroid, gibberellic acid, and strigolactone pathways – though mainly involved in plant development – can also directly interfere with plant defensive responses (Fig. 1).<sup>13</sup> The role of plant defense-related hormonal pathways in the assembly of beneficial microbes in the rhizosphere has previously been reviewed.<sup>11,14</sup> Yet, the involvement of these pathways in activating microbial biosynthesis of natural products has been understudied, despite increasing evidence of their significance for understanding the chemical interplay

between plants and their microbiota, as well as their potential for drug discovery. This article highlights the limited reports linking plant-stress hormones to the activation of natural product biosynthesis and other defense mechanisms in plant-beneficial microbes, thereby revealing this knowledge gap. However, this highlight does not review antimicrobial metabolites produced by plants against pathogens; instead, such reviews are available.<sup>15–17</sup> Furthermore, comprehensive reviews of the discovery of natural products from specific soil microbes have been published.<sup>18–20</sup>

## 2. Plant hormone-mediated activation of antimicrobial natural product biosynthesis in plant-beneficial microorganisms

In 2011, Jousset and colleagues demonstrated that plants involved in multipartite interactions with their microbiota could induce beneficial bacteria to produce antifungal compounds.<sup>21</sup> In a split root setup, when *Pythium ultimum*, a pathogenic oomycete, infected one side of a barley root system, and *Pseudomonas fluorescens* CHA0 colonized the healthy roots, the biosynthesis of the antifungal 2,4-diacetylphloroglucinol (Fig. 2) was activated by plant signals. Notably, this process occurred without direct contact between the beneficial bacteria and the fungal pathogen.<sup>21</sup> This study suggests that, in addition to compounds in root exudates that attract and maintain the microbiota, specific stress signals from plants also play a role in plant-microbial communication. Initially, plant stress hormones were not linked to the induction of microbial natural product biosynthesis, as their functions were thought to be confined within the plant's internal system. However, microtiter quantities have been detected in root exudates.<sup>11</sup> Emerging studies further demonstrate that soil bacteria from various genera can detect and respond to these plant hormones by producing antibiotics and exhibiting pathogen-inhibiting traits, as discussed below.



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### 2.1. The jasmonate pathway effect on microbial metabolism

Jasmonate signaling is associated with activating plant systemic defense, particularly against necrotrophic pathogens – pathogens that kill host cells during invasion – and herbivorous insects.<sup>22</sup> The variation in bacterial and archaeal composition within the rhizosphere as a result of activating the jasmonate-dependent hormonal pathway in plants was initially demonstrated by Carvahais and colleagues.<sup>23,24</sup> The authors noted that the activation of this pathway potentially favored the proliferation of microbes associated with plant-protecting activities over those that promoted plant nutrient uptake.<sup>23</sup> This restructuring of the microbial composition may be due to changes induced by the jasmonate pathway within the complex plant hormone signaling network, given that this pathway interacts positively or negatively with other plant hormones.<sup>13</sup> In other studies, jasmonate compounds facilitated the chemoattraction of some plant-beneficial bacteria<sup>25,26</sup> and plant pathogens.<sup>27</sup>



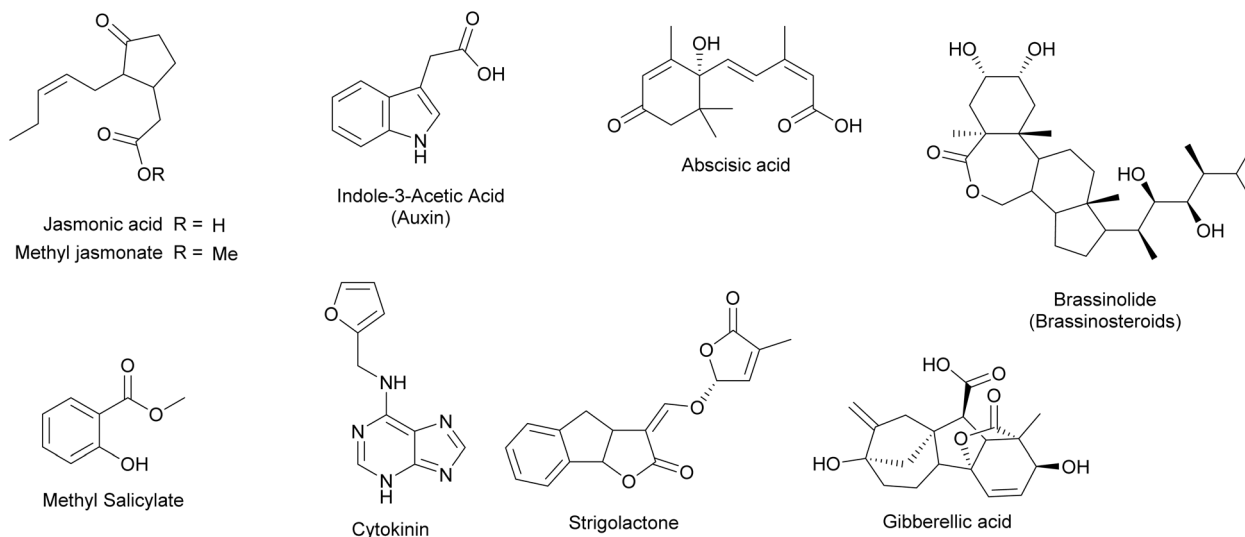


Fig. 1 Structures of plant hormones that either regulate or interfere with plant defensive responses.

Furthermore, chemoattraction induces motility in gliding bacteria, including some with predatory traits, and genes involved in gliding motility are suggested to be co-activated with natural product biosynthetic genes in these organisms.<sup>28</sup> We previously reported that the plant-associated Myxobacterium, *Archangium* sp. strain Cb G35, showed increased swarm expansion when exposed to methyl jasmonate, indicating attraction.<sup>25</sup> While this increase was similar to inducing swarming with decanoic acid, which is suggested to regulate the *frz* signaling involved with myxobacterial chemotaxis,<sup>29</sup> the exact mechanism by which methyl jasmonate activates swarming remains unknown. Myxobacteria are generalist predators of bacteria and fungi.<sup>25</sup> Our metabolomics and transcriptomics

studies revealed plant signal-driven metabolic changes, such as the production of uncharacterized secondary metabolites and lytic enzymes, which suggested active predatory behavior of the bacterium when methyl jasmonate was detected in the culture media.<sup>25</sup> These results could help discover new metabolites from myxobacteria, as unique mass features were observed under the induced conditions.

An example of a plant jasmonate-induced biosynthesis of a known antimicrobial natural product was documented in actinobacteria. Micromolar concentrations of either jasmonic acid or methyl jasmonate are commonly used exogenously to investigate jasmonate-dependent effects in plants and the associated microbiota.<sup>23,25,30</sup> Studies with actinobacteria have

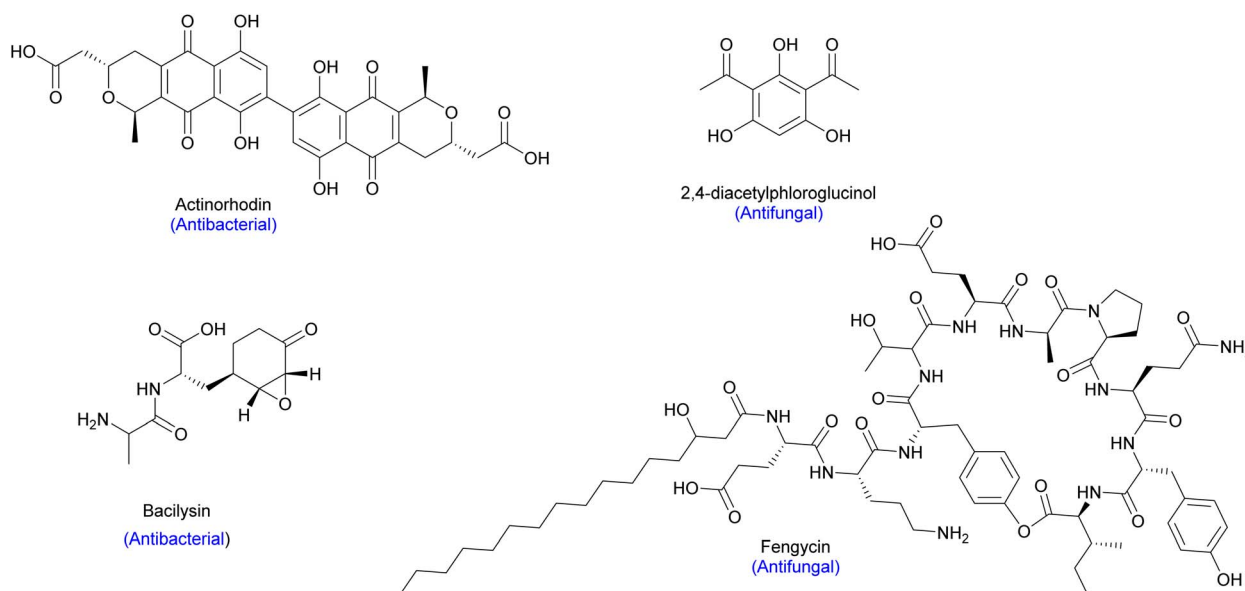


Fig. 2 Structures of microbial metabolites that are induced by plant-stress hormones. The known activities of these metabolites are highlighted in blue.



shown that, although high concentrations of jasmonic acid can be toxic, both jasmonic acid and methyl jasmonate induce the biosynthesis of natural products in strains.<sup>31</sup> In an effort to discover new bioactive compounds from *Streptomyces*, van der Meij and colleagues reported increased antimicrobial activity in both *S. coelicolor* and *S. roseifaciens*, among the tested strains, when cultivated in the presence of jasmonates.<sup>31</sup> What was particularly intriguing about these findings was that the unique responses from both strains depended on whether methyl jasmonate or jasmonic acid was perceived. For instance, in *S. coelicolor*, methyl jasmonate more strongly induced the production of the polyketide antibiotic actinorhodin (Fig. 2), whereas jasmonic acid increased the production of the antimicrobial prodiginines. Conversely, in *S. roseifaciens*, increased antimicrobial activity was observed only in the presence of jasmonic acid.<sup>31</sup> Nonetheless, a mechanistic understanding of how jasmonate activates *Streptomyces* biosynthetic gene clusters is lacking.

## 2.2. The salicylate pathway effect on microbial metabolism

Like jasmonate signaling, the activation of the salicylate-dependent hormonal pathway in plants reflects the plant's activation of systemic resistance against pathogens, but in this case, biotrophic or hemibiotrophic plant pathogens that parasitize living host cells.<sup>22</sup> Altering salicylate signaling in plants also affects microbial diversity, indicating that this hormone plays a role in shaping the plant's microbial community during disease resistance.<sup>32,33</sup> Lebeis and colleagues reported that wild-type plants, compared to isogenic mutants lacking salicylate-dependent signaling, showed increased abundance of specific microbial taxa in the rhizosphere, suggesting that the plant hormone may also act as a growth signal, enabling the taxa to outcompete the evading pathogen.<sup>32</sup> However, only a few studies have directly linked plant salicylate signaling with the activation of microbial natural product biosynthesis.

In 2015, a connection was established between plant-stress hormones and the biosynthesis of natural products in *Bacillus*. Methyl salicylate induced the DegS–DegU two-component regulatory system, which controls the biosynthesis of bacilysin and fengycin in *B. subtilis* (Fig. 2).<sup>34</sup> The Gram-positive soil bacterium, *B. subtilis*, well known for promoting plant health, has been extensively studied in the agricultural context for biocontrol purposes due to its capacity to produce antibiotics and lytic enzymes.<sup>35</sup> In spot assays, wild-type strains showed a clear inhibition zone against *Escherichia coli* when methyl salicylate was added to the culture medium. In contrast, deletion mutants lacking the bacilysin biosynthetic genes ( $\Delta bacA-F$ ) lost this inhibitory effect. In a similar experimental setup, the DegU deletion mutants, but not  $\Delta bacA-F$ , lost antifungal activity against the plant pathogen *Fusarium oxysporum*.<sup>34</sup> This antifungal activity was attributed to the activation of fengycin biosynthesis by the regulatory system, suggesting that *B. subtilis* responds to plant methyl salicylate through the DegS–DegU two-component system. Additionally, this response was unique to methyl salicylate among structurally related compounds tested.<sup>34</sup> It is important to note that

methyl jasmonate did not elicit these responses in the strain, indicating that *B. subtilis* may be recruited and activated to produce antimicrobial natural products during plant stress-induced activation of the salicylate pathway.

## 2.3. The current landscape of antimicrobial natural product discovery from plant microbiota during plant stress

Although there are reports of plant stress hormone-mediated activation of antimicrobial production, current research has not yet shown the activation of new microbial biosynthetic gene clusters that led to the discovery of new antimicrobial natural products from plant-beneficial microorganisms. While much of the existing research focuses on well-studied bacterial groups like *Streptomyces* and *Bacillus*, it could be improved by exploring less-studied groups, especially those involved in protecting plants from pathogens. Furthermore, these highlighted examples focus on bacterial perception and response to plant stress hormones; however, plant-beneficial microbiota also include archaea, fungi, and protists. Studying how plant stress hormones alter the metabolism of plant microbiota may provide new opportunities to discover antimicrobials from these microbes, based on their ecological roles in suppressing pathogens.

## 3. Pathogen interference with plant activation of the microbiota

Based on studies over the last few decades, it is evident that hormonal pathways involved in plant defense also influence the assembly of plant-associated microbes. Theoretically, pathogen disruption of these signaling pathways will interfere with microbial assembly, colonization, and defense against pathogen attack. Generally, plants resist pathogen entry through complex hormonal networks; yet, not all plant stress-related hormones act synergistically.<sup>13</sup> The activation of some hormonal pathways suppresses others, with the most common example being the interaction between salicylate- and jasmonate-dependent pathways. As a result, pathogens exploit this antagonistic hormonal crosstalk by biosynthesizing mimics of plant hormones to promote infection.<sup>36</sup> For example, the plant pathogenic biotroph *Pseudomonas syringae* produces

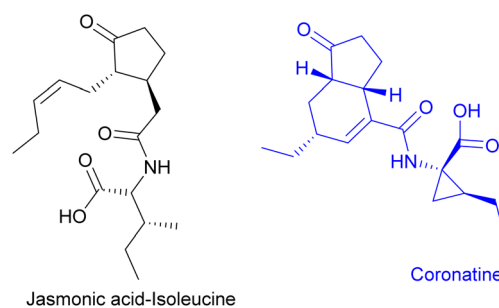


Fig. 3 Structure of a plant hormone and the pathogen-derived mimic. Coronatine, highlighted in blue, mimics the active plant hormone, jasmonic acid–isoleucine conjugate.



coronatine (Fig. 3), which, owing to its structural similarity to the plant's jasmonic acid–isoleucine conjugate, competes for the same binding pocket with high affinity.<sup>37</sup> This competition activates the jasmonate pathway at the expense of the salicylate pathway; however, activating the salicylate hormonal pathway is essential for inducing the plant's systemic resistance against biotrophic pathogens like *P. syringae*.<sup>37</sup> With regard to the plant microbiota, activation of this jasmonate pathway will facilitate the colonization of microbes that respond to the hormone, which may not provide the same defensive functions as those responsive to the salicylate pathway. Similar coronafacoyl metabolites have been produced by plant pathogens across various bacterial genera and fungi.<sup>36,38</sup> Moreover, there are documented examples of pathogen-generated mimics that disrupt not only the jasmonate pathway but also the cytokinin, gibberellin, strigolactone, and abscisic acid pathways in plants, which alter the chemical environment of plant microbiota.<sup>36</sup> Other strategies employed by pathogens to hijack plant stress responses include enzymatic degradation of hormones,<sup>39</sup> production of effector proteins,<sup>40,41</sup> exopolysaccharides<sup>42</sup> and toxins,<sup>43</sup> which are beyond the scope of this highlight article. It remains unclear whether pathogens' perception of plant-stress hormones triggers the biosynthesis of disruptive mimics, and if plant-beneficial microbes detect and respond to pathogen-generated mimics in the same way as plant hormones in the microenvironment. Furthermore, there is a lack of research on how pathogen-generated mimics might stimulate or suppress the biosynthesis of antimicrobial natural products within plant microbiota. Therefore, studies using multipartite interactions, such as plant-beneficial microbe–pathogen models, to discover new antimicrobials should consider potential pathogen interference.

#### 4. What we can learn from disease-suppressive soils

The disease-suppressive soil phenomenon, in which plants are naturally protected from soil-borne pathogens through the

activities of beneficial microorganisms, has intrigued researchers seeking to identify the key traits necessary to develop an optimal biocontrol consortium.<sup>44,45</sup> The microbial taxa in these suppressive soils are typically characterized using genomic and transcriptomic techniques.<sup>45–47</sup> Historically, *Pseudomonas*, *Bacillus*, and *Trichoderma* species have been among the most extensively studied organisms for pathogen control.<sup>48,49</sup> However, recent studies have revealed more taxa associated with disease suppression.<sup>46,47</sup> Pathogen suppression can occur through various mechanisms, including triggering plant systemic resistance, attenuating virulence factors, generating extracellular lytic enzymes, and producing antibiotics.<sup>48,50</sup> Moreover, this pathogen antagonism has likely been evolutionarily optimized to prevent deleterious effects on the plant's overall microbial community and structure.<sup>51</sup>

Disease-suppressive soils provide valuable insights into the interactions between plants and microbial communities, with research advancing due to the development of new techniques for studying these interactions. Carrión and colleagues demonstrated, using a bacterial consortium, the induced transcription of gene clusters encoding potentially novel non-ribosomal peptides (NRPs) and hybrid NRP/polyketides in a soil suppressive to the fungus *Rhizoctonia solani*.<sup>50</sup> In the same study, the authors reported the enrichment of specific bacterial taxa belonging to the *Pseudomonadota* and *Bacteroidota* phyla, along with genes involved in carbohydrate metabolism and signal transduction, which contributed to the suppression.<sup>50</sup> Similarly, in four different soils that inhibit another fungal pathogen, *Fusarium culmorum*, wheat was protected from the fungus through the enrichment of biosynthetic gene clusters encoding known siderophores, lipopeptides, and the antifungal compound 2,4-diacetylphloroglucinol.<sup>47</sup> Furthermore, Tracanna and colleagues observed a convergence among the adenylation domain profiles of the bacterial population in the aforementioned suppressive soils, with a particular enrichment of A-domains associated with cyclic peptides.<sup>47</sup> These reports highlight microbial taxa that exhibit metabolic responses to plant stress, which can be prioritized to discover new bioactive natural products.

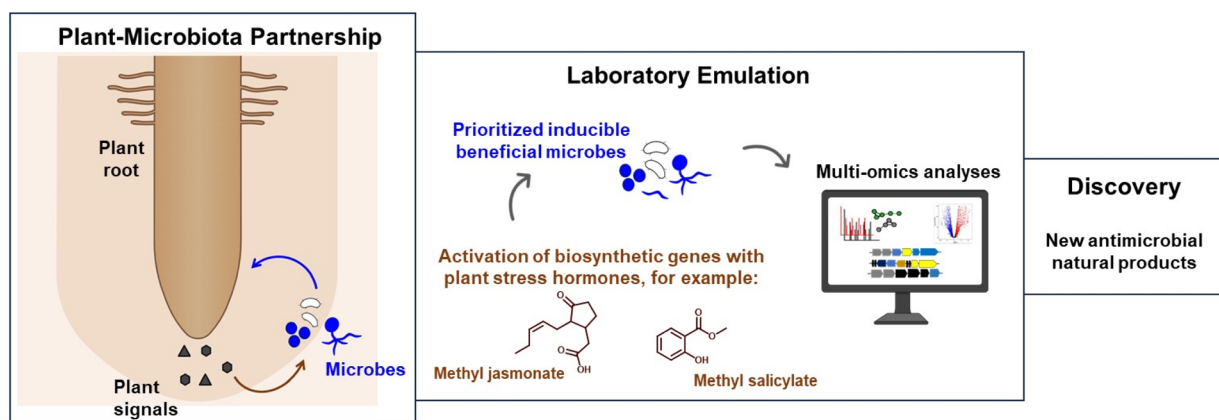


Fig. 4 A general overview of discovering new antimicrobials by understanding the partnerships between plants and their microbiota that support plant health, and using this knowledge in laboratory cultivations, combined with multi-omics analyses.



## 5. Conclusion and outlook

Recent studies have linked plant-stress hormones to the activation of natural product biosynthesis and other defense mechanisms in plant-beneficial microorganisms. Understanding the direct communication between plants and their microbiota is essential when exploring new ways to harness the full biosynthetic potential of plant-associated microbes. In this highlight article, we provided examples of how the ecological role of plant microbiota, specifically in plant defense, can be leveraged to induce microbial biosynthesis of antimicrobials. Therefore, studies that incorporate plant stress hormones into laboratory cultivation of various plant microbiota strains to activate biosynthetic pathways, along with high-throughput genome mining and multi-omics analyses to identify and characterize these pathways, will facilitate the discovery of new natural products (Fig. 4). Furthermore, these hormones, as part of the ecological cues of the plant microbiota, can be leveraged to design sophisticated cultivation strategies that could activate silent biosynthetic gene clusters on a scale suitable for natural product discovery and development.

Some of the studies mentioned here observed phenotypic changes in microbial metabolism in response to plant stress hormones such as jasmonate and salicylate, but did not explore how microbial perception of these hormones triggered gene expression. Studying how microbes detect and respond to plant stress hormones is essential to fully understand the partnerships that connect interactions to the regulation of antimicrobial natural product production. For instance, employing genetic manipulation techniques such as gene deletion or replacement *via* recombination, transposon mutagenesis, or CRISPR-Cas9 engineering will facilitate an understanding of the mechanisms underlying the chemical-mediated interplay within such systems.<sup>52–54</sup>

The interaction between plants and their microbiota, influenced by plant stress, is a promising field for future research aimed at enhancing natural product discovery.

## 6. Conflicts of interest

There are no conflicts of interest to declare.

## 7. Data availability

There are no primary research results, software, or code included, and no new data was generated or analyzed for this highlight.

## 8. Acknowledgements

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