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Review

Understanding metabolic interactions between bacteria and fungi for cross-kingdom consortia applications

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Bacterial–fungal interactions represent fundamental ecological associations that shape microbial community structure across diverse environments. While traditionally framed through the lens of antagonism, bacteria and fungi engage in sophisticated metabolic dialogs extending far beyond simple warfare. Both primary and specialized metabolites function as context-dependent signals, nutrient resources, and modulators of cellular processes that fundamentally influence the physiology, development, and evolutionary trajectory of both fungi and bacteria. Primary metabolites mediate mutualistic relationships through cross-feeding and syntrophy, while specialized metabolites, including volatile organic compounds, lipopeptides, and phenazines, modulate fungal physiology at sub-inhibitory concentrations, reprogramming metabolic networks and triggering adaptive responses without causing cell death. At the molecular level, bacterial metabolites regulate fungal gene expression through transcriptional reprogramming, with consequences that extend to long-term evolutionary adaptation. The complexity of *Bacillus–Trichoderma* interactions exemplifies how these principles translate into ecological outcomes, exhibiting context-dependent transitions from competition to synergism that enhance biocontrol efficacy, plant growth promotion, and organic matter turnover. Recognizing the multifunctional nature of microbial metabolites beyond direct toxicity opens new avenues for rationally engineering cross-kingdom consortia with targeted agricultural and biotechnological applications.

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Bacterial–fungal interactions: more than just inhibition

Bacterial–fungal interactions represent fundamental ecological associations that shape microbial community structure and function across diverse environments, from soil ecosystems to plant-associated microbiomes and the human body. While the majority of research has traditionally focused on antagonistic interactions mediated by antimicrobial compounds, it is now also recognized that bacteria and fungi engage in complex metabolic dialogs that extend far beyond simple warfare. These interactions involve both primary and secondary metabolites that function as signaling molecules, nutrient resources, and modulators of cellular processes, fundamentally influencing the physiology, development, and evolutionary trajectory of both partners. The recognition that microbial metabolites serve multiple functions beyond direct toxicity has transformed our understanding of bacterial–fungal relationships [1]. Rather than viewing these interactions through a purely antagonistic lens, current research reveals a spectrum of interactions ranging from mutualism to competition, often mediated by the same metabolic compounds acting through versatile molecular mechanisms [2]. This complexity is perhaps best illustrated by the observation that metabolites traditionally classified as 'antibacterial' or 'antifungal' can simultaneously serve as signaling molecules that alter gene expression, modulate developmental processes, or facilitate metabolic cooperation under specific ecological contexts [3–6]. Building on seminal reviews on the chemical mediators at the bacterial–fungal interface [7],

we emphasize here the recent advances in how primary and specialized metabolites function as context-dependent signals and ecological drivers, and how this understanding can inform the rational design of cross-kingdom consortia.

Primary metabolites as mediators of mutualistic relationships

Primary metabolites, the essential building blocks of cellular metabolism, play crucial roles in establishing mutualistic bacterial–fungal relationships through mechanisms of cross-feeding and syntrophy. A compelling example of such metabolic interdependence is the interaction between *Bacillus subtilis* and *Aspergillus nidulans*, where thiamine production by the bacterial cells supports fungal growth while fungal mycelia provide spatial organization that benefits bacterial colonization [8]. Such a mutualistic growth mechanism suggests that an exchange of essential nutrients facilitates the establishment of stable co-existence patterns where each partner compensates for the metabolic or developmental limitations of the other. The importance of primary metabolite exchange is further emphasized by recent advances in isotope-labeling approaches. Using ^{13}C-based proteomics, metabolic fluxes have been mapped in co-cultures of yeast *Saccharomyces cerevisiae* and the bacterium *Lactococcus lactis*, revealing intricate patterns of carbon source utilization in which ^{13}C-labeled glucose-derived metabolites, including acetate and amino acids, are exchanged bidirectionally between the partners [9]. Here, primary metabolite sharing is not merely a by-product of co-existence but rather a coordinated process that drives community stability and productivity. The metabolic complementarity observed in these systems suggests that bacteria and fungi may have evolved to exploit each other's metabolic byproducts, creating efficient nutrient cycling networks within microbial communities. In addition to simple nutrient cross-feeding, primary metabolites also serve as molecular cues that coordinate physiological responses across kingdoms [6]. Spatial organization of bacterial–fungal communities facilitates metabolite exchange and shapes the nature of primary-metabolite exchange. In the so-called fungal highway, bacteria such as *Pseudomonas putida* exploit fungal hyphae as dispersal conduits through water-unsaturated soil, while simultaneously accessing carbon-rich fungal exudates [10,11]. This physical association creates micro-environments where local metabolite concentrations reach levels sufficient to influence microbial behavior, establishing feedback loops between metabolic activity and spatial structure.

Specialized metabolites as signaling molecules and regulators of development

While specialized metabolites (SMs) are often studied for their antimicrobial properties, their most relevant ecological role lies in how they reprogram metabolic networks across kingdoms including altering gene expression, remodeling cellular membranes, and shifting energy metabolism, at concentrations that do not necessarily cause cell death [4,5]. Such metabolic reprogramming operates in both directions: bacterial SMs reshape fungal physiology, while fungal metabolites simultaneously alter bacterial behavior and fitness [12]. Among SMs, volatile organic compounds (VOCs) mediate long-distance bacterial–fungal communication [13]. The chemical composition of VOCs encodes information about microbial identity, metabolic state [14], and environmental context [15], which enables spatially separated organisms to sense and respond to distant neighbors before physical contact occurs. For example, the bacterium *Rahnella aquatilis* produces VOCs, including 3-methyl-1-butanol and 2-phenylethyl methyl ether, that reprogram the metabolism and development of the fungal plant pathogen *Colletotrichum gloeosporioides* in plant tissues, through mechanisms involving metabolic alteration rather than direct toxicity [16]. Bacterial VOCs can thus influence fungal behavior at sub-inhibitory concentrations, acting as environmental cues that trigger adaptive responses in fungal communities [16]. Bacterial lipopeptides reprogram fungal physiology through direct membrane targeting. The bacterium *Pantoea agglomerans* inhibits the plant-pathogenic fungus *Fusarium graminearum* by binding to ergosterol-enriched lipid rafts, functional microdomains that coordinate membrane-associated signaling, thereby disrupting membrane organization and downstream cellular signaling cascades, including signal transduction, protein trafficking, and developmental transitions [17]. By targeting lipid rafts, a single SM class can simultaneously manipulate multiple interconnected aspects of fungal cell biology. Phenazines represent a structurally distinct class of bacterial SMs that reprogram fungal physiology through redox-based mechanisms. Phenazines produced by the bacterium *Pseudomonas aeruginosa* alter metabolism and biofilm formation in the fungus *Candida albicans* by disrupting electron transfer and redox cycling [18,19], shifting fungal energy metabolism independently of direct fungicidal activity. Fungal metabolites reciprocally reprogram bacterial behavior, underlining the bidirectional nature of SM-mediated interactions. Exometabolites produced by the biocontrol fungus *Trichoderma atroviride* impose genome-wide fitness effects on co-occurring bacteria, selectively favoring genes involved in detoxification, membrane transport, and metabolic remodeling [12]. This bidirectional metabolic reprogramming drives resource partitioning between bacterial and fungal populations, with each partner continuously reshaping the metabolic landscape available to the other. The capacity of SMs to reprogram metabolic networks ultimately depends on their ability to alter gene expression, which is a molecular dimension explored in the following section.

Molecular mechanisms of bacteria–fungi interaction: gene regulation, cellular response, and evolutionary adaptation

The impact of bacterial metabolites on fungal gene regulation represents a frontier in understanding interkingdom interactions. The bacterium *Streptomyces rapamycinicus* specifically activates silent biosynthetic gene clusters in the fungus *A. nidulans*, resulting in the production of the polyketide orsellinic acid and its derivatives [20,21]. Induction of orsellinic acid-related gene expression requires direct contact between the bacterium and the fungus and is triggered by Saga/Ada-mediated histone acetylation in *A. nidulans* [20]. Similarly, *Pseudomonas piscium* secreted phenazine reduces *F. graminearum* virulence by altering histone acetylation patterns, effectively reprogramming fungal gene expression through epigenetic modifications [22]. These examples highlight how bacteria can reprogram fungal gene expression through epigenetic mechanisms, with potential effects that extend beyond the immediate interaction. By altering chromatin accessibility, bacterial metabolites influence which fungal genes are expressed; though whether such changes become fixed as heritable alterations in fungal phenotypes remains to be demonstrated. The evolutionary consequences of bacterial–fungal metabolic interactions are increasingly apparent, although adaptive evolutionary studies remain few, and the long-term effects of the observed processes remain unclear. Co-culturing the cheese rind bacterium *Staphylococcus xylosus* with the fungi *Debaryomyces hansenii* or *Penicillium solitum* promotes parallel evolution of global transcriptional regulators across independently evolving lineages of the bacterium [23,24], demonstrating that fungal partners exert strong selective pressure on bacterial regulatory networks. Similarly, the presence of the soil fungal pathogen *Setophoma terrestris* selects for quorum-sensing mutants of *B. subtilis*. These mutants display decreased antifungal lipopeptide production but increased production of VOCs, including 2-heptanone and 2-octanone with antifungal activity [25]. These examples highlight that metabolic interactions are not static but rather dynamic and continuously reshape bacterial and fungal genomes and phenotypes. During co-culture with the fungus *Aspergillus niger*, *B. subtilis* strains are selected that display enhanced surface colonization and competitive fitness [26], further illustrating how fungal presence reshapes bacterial behavior through metabolite-driven selection.

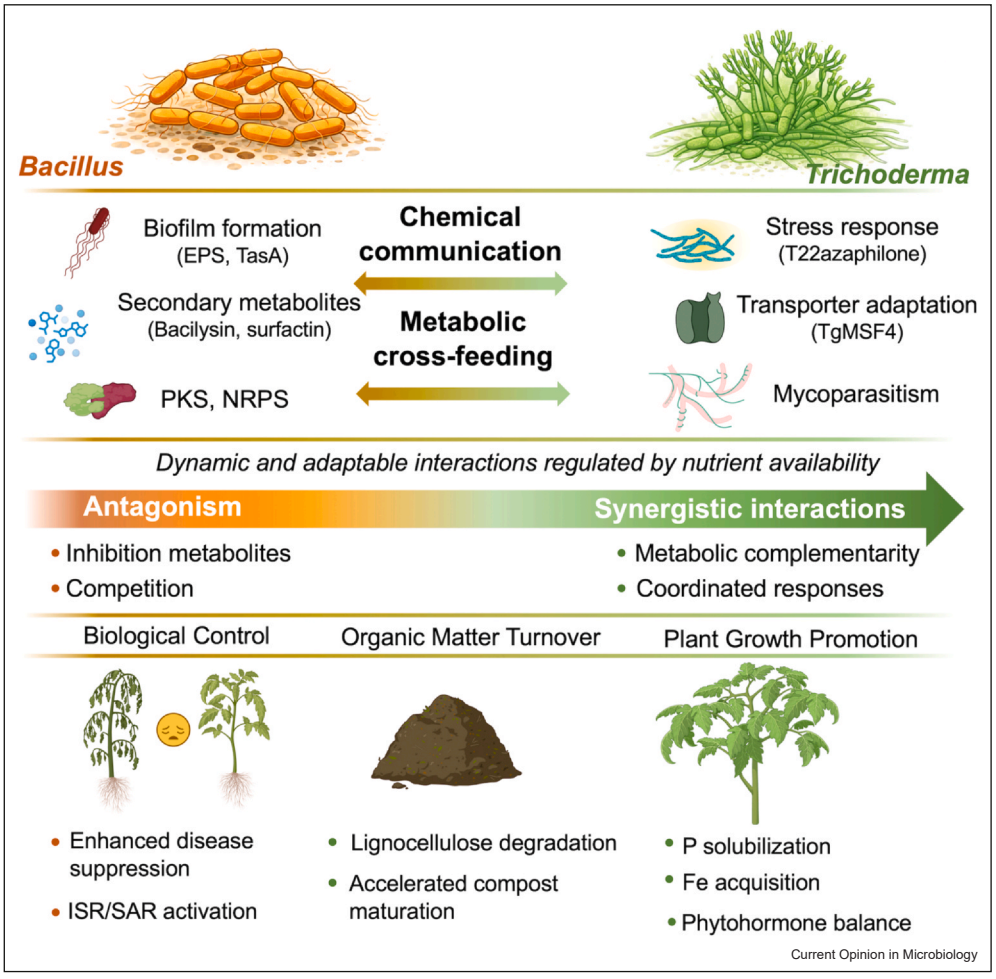
Ecological implications: from antagonism to mutualism

The ecological outcomes of bacterial–fungal metabolic interactions span a continuum from mutualism to antagonism, often determined by environmental context and the specific metabolites involved. The complex association between *Rhizopus microsporus* and its bacterial endosymbiont *Mycetohabitans* (formerly *Burkholderia*) illustrates this complexity, where a molecular dialog defines mutualistic or antagonistic outcome depending on the genetic makeup of the fungus [27]. Central to this dialogue is the antimitotic polyketide rhizoxin that is produced by the bacterial endosymbiont and structurally modified within the fungal host. This interaction between an endofungal bacterium and the fungal host exemplifies a true metabolic cooperation in which a bacterially-derived compound is co-produced by both partners [28,29]. Notably, the genetic makeup of the bacterial partner similarly shapes the outcome of such relationships [30]. Such context-dependent interaction suggests that metabolites might function as negotiation tools that allow bacteria and fungi to assess environmental conditions and adjust their relationship accordingly. Endosymbiotic association provides extreme examples of metabolic integration, where bacterial metabolism becomes intimately linked with fungal fitness. *Candidatus* Mycoavidus necroximicus protects *Mortierella verticillata* from nematode attack, with bacterial metabolites extending their protective effects beyond direct bacterial–fungal interactions to influence tritrophic relationships [31]. These defensive symbioses reveal that metabolic interactions can have cascading effects throughout ecological networks, with bacterial SMs serving as mediators of complex multispecies relationships. An intriguing example of bacteria–fungi interactions is the transition from antagonistic to cooperative interactions. *Bacillus velezensis* and *Trichoderma guizhouense* act synergistically to control *Fusarium* wilt disease, where the bacterial–fungal metabolic interactions enhance overall biocontrol efficacy [2], described below in more detail. Transformation from potential competitors into functional allies suggests that metabolic signaling facilitates the formation of cooperative partnerships where ecological circumstances favor collaboration over competition.

Interactions between *Bacillus* and *Trichoderma*

The genus *Trichoderma*, one of the most important biocontrol fungi for applications in soil ecosystems [32], exhibits a unique and complex interaction with *Bacillus* species. Early studies predominantly emphasized the antagonistic effects of *Bacillus* against fungi, focusing on antibiotic production and fungal growth inhibition [33]. However, co-cultivation and interaction-focused studies revealed that the relationship between *Bacillus* and *Trichoderma* is not limited to simple antagonism but instead constitutes a multilevel interaction network spanning molecular signaling through diffusible metabolites, physiological responses such as altered stress tolerance and secondary metabolism, and ecological functions including biocontrol efficacy and plant growth promotion. This dual interaction scenario is striking: although *B. velezensis* and *T. guizhouense* antagonize one another on

Figure 1

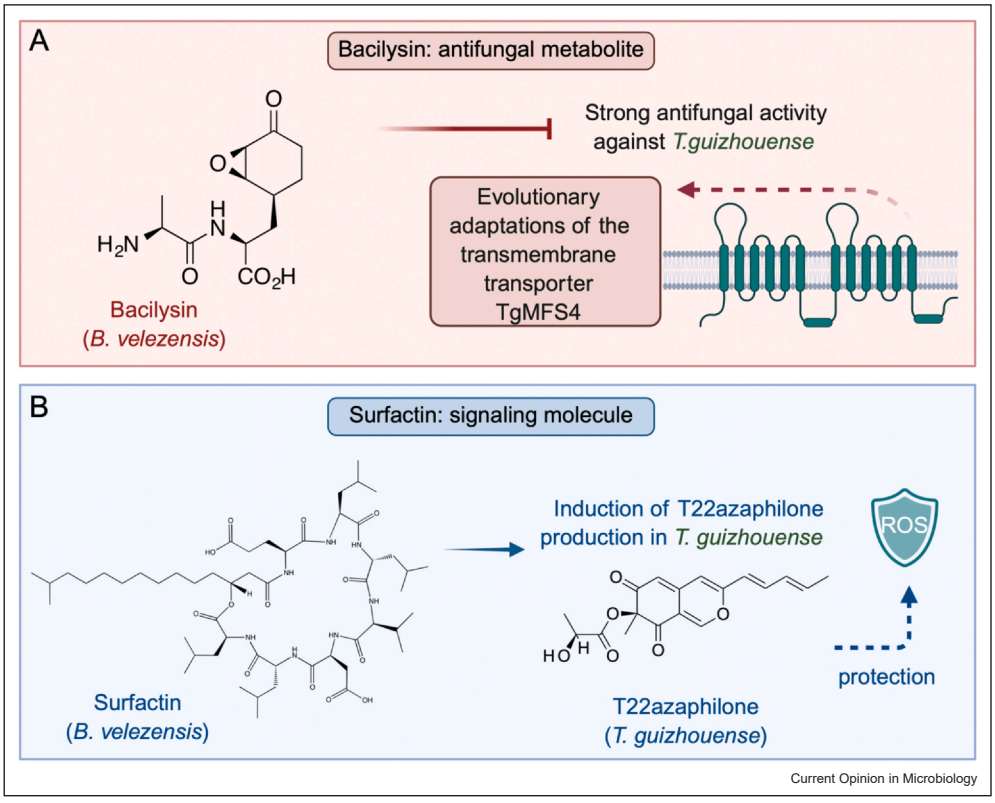


Conceptual model of interactions between *Bacillus* and *Trichoderma*. Bacterial–fungal interactions are mediated by chemical communication and metabolic cross-feeding, involving biofilm formation, secondary metabolites, and fungal adaptive responses. These dynamic interactions shift along a continuum from antagonism to synergism depending on nutrient conditions, ultimately contributing to biocontrol, organic matter turnover, and plant growth promotion. Certain elements of the figure were created on Biorender.com.

agar, the relative abundances of the two genera are positively correlated across global soil metagenomes and act synergistically to suppress *Fusarium* wilt and promote plant growth [2]. Understanding this context-dependent interaction requires elucidating the metabolite-mediated mechanisms that allow competing biocontrol agents to coexist. *Bacillus–Trichoderma* association is influenced by both physical and chemical interactions (Figure 1). *B. velezensis* colonizes *T. guizhouense* hyphae through biofilm formation that is dependent on extracellular polysaccharides and the protein fibers [34], a strategy that appears conserved across *Bacillus*-filamentous fungi interactions [35–37]. At the molecular level, contact with fungi activates the stress sigma factor σ^B in *B. velezensis*, which upregulates biosynthetic gene clusters for antimicrobial specialized metabolites [2]. The resulting metabolites play strikingly different roles (Figure 2). For example, bacilysin exhibits strong antifungal activity, which *Trichoderma* counters via the transmembrane transporter TgMFS4 [38]. Surfactin, by contrast, acts as a signal rather than a weapon: it stimulates T22azaphilone production in *T. guizhouense*, a protective metabolite that shields the fungus from oxidative stress [2].

Additionally, co-cultivation induces pronounced interaction-dependent shifts in SM production, including activation of cryptic biosynthetic gene cluster expression and corresponding SM production [39]. Metabolic cross-feeding between *Trichoderma* and *Bacillus* further modulates bacterial lipopeptide biosynthesis, suggesting the chemical outputs are dynamically reshaped by interkingdom interactions [40]. Collectively, *Bacillus–Trichoderma* interactions rely on sophisticated chemical communication networks that extend beyond simple

Figure 2



Dual role of *B. velezensis* specialized metabolites on *T. guizhouense*. Bacilysin has strong antifungal influence **(a)**, while surfactin induces T22azaphilone production in *T. guizhouense* **(b)**. The figure was created on Biorender.com.

unidirectional antagonism and can be tuned to promote context-dependent mutual benefits.

Bacillus–Trichoderma interactions also display pronounced environment-dependent dynamics. Co-cultivation of *Trichoderma asperellum* with *Bacillus amyloliquefaciens* induces extensive transcriptional reprogramming in *Trichoderma*, including altered expression of genes encoding proteins involved in spore development, SM production, mycoparasitism, and stress responses, indicating active physiological adjustment in the fungus in the presence of the bacterium [41]. Moreover, metabolic interactions between the two organisms enhance amino acid production and pathogen inhibition, demonstrating that interaction outcomes shift over time and depend on metabolic context [42]. Environmental factors strongly modulate these interactions. Under nutrient-limited conditions, metabolic cross-feeding and reciprocal metabolic adjustments become more pronounced, reshaping interaction outcomes and stress-associated interaction modes [8]. Altogether, *Bacillus–Trichoderma* interactions are highly dynamic and context-dependent, with nutrient availability acting as a key regulator that drives shifts along a continuum from antagonism to synergistic interactions.

Ecological functions and synergism between *Bacillus* and *Trichoderma*

In biological control applications, *Bacillus* and *Trichoderma* frequently display synergistic effects that exceed those of individual strains. For example, the combined application of *Trichoderma virens* Gl006 and *B. velezensis* Bs006 enhances *Fusarium oxysporum* suppression [43]. Such synergy is commonly associated with complementary antimicrobial activities, activation of induced systemic resistance and systemic acquired resistance in plants, and enhanced production of biocontrol-related factors, including hydrolytic enzymes and siderophores [44,45].

Beyond disease suppression, *Bacillus–Trichoderma* consortia also promote plant growth through metabolically complementary functions. Co-inoculation of *T. asperellum* and *B. subtilis* increases plant biomass beyond additive effects [46], likely through coordinated improvement of nutrient availability and phytohormone balance, including phosphorus solubilization, iron acquisition, and regulation of root and shoot development [47–49]. Such synergistic interaction extends beyond plant-associated systems. In aerobic composting, co-inoculation of *T. viridis* and *B.*

subtilis accelerated compost maturation and enhanced lignocellulose degradation compared with single inoculations [50], highlighting the broader ecological relevance of *Bacillus–Trichoderma* synergism in organic matter turnover.

Applications: from metabolic insight to consortium design

Understanding the transition from competition to cooperation requires moving beyond simple characterizations of metabolites as 'antimicrobial' or 'beneficial' to recognizing their roles as context-dependent signals that mediate complex ecological negotiations. As highlighted in this review, metabolic cross-feeding, signaling via SMs, and interaction-driven transcriptional reprogramming collectively enable bacteria and fungi to transition from competition to cooperation in a context-dependent manner.

From an application perspective, metabolite-mediated processes provide a conceptual basis for constructing defined microbial consortia [51]. Because interaction outcomes are context-dependent, which is shifting with nutrient availability, partner identity, and the presence of shared pathogens, consortium design is best approached not as a linear translation of single mechanisms into products, but as an iterative, ecology-informed process that works within these constraints. In agricultural systems, bacterial–fungal consortia, such as those containing *Bacillus* and *Trichoderma*, exhibit synergistic effects in plant disease suppression, nutrient mobilization, and growth promotion, outperforming single-strain inoculants [52]. Similarly, in environmental biotechnology, bacteria–fungi interactions can enhance organic matter decomposition and pollutant degradation through division of metabolic labor and spatial organization within biofilms [53]. Notably, interaction-induced activation of cryptic biosynthetic pathways and metabolite diversification further expands the functional repertoire of microbial communities, offering opportunities for natural product discovery and improved biocontrol strategies [4].

The practical deployment of bacteria–fungi interaction-based systems remains constrained by major bottlenecks such as predictability and ecological stability [54]. Achieving predictability requires dissecting the gene-to-metabolite-to-phenotype relationships underlying bacteria–fungi interactions. Key enabling approaches include targeted genetic manipulation (gene deletion, overexpression, and biosynthetic gene cluster activation), paired transcriptomic and metabolomic profiling of interaction zones, and computational metabolic modeling, which together can map the regulatory networks and metabolite exchanges that govern inter-kingdom coordination [55]. In parallel, ecological stability depends on rational community design [56]. Strategic selection of consortium members, together with a balanced integration of top-down (natural community assembly) and bottom-up (mechanism-driven construction) approaches, will be critical to maximize cooperative interactions while minimizing functional collapse [56–60]. For example, cross-kingdom defined microbial communities assembled via complementary top-down (host-selected taxa) and bottom-up (antagonist-based) strategies were demonstrated to suppress *Fusarium* root rot across multiple plant compartments in soybean, with each strategy eliciting distinct host transcriptional and metabolic responses [61]. Collectively, integrating mechanistic understanding of metabolite exchange with iterative, ecology-guided design will move the field from descriptive ecology toward the rational construction of stable, programmable multi-kingdom systems for sustainable agriculture, environmental remediation, and industrial biotechnology.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Akos T Kovacs reports financial support was provided by the European Union. Yixu Wang reports financial support was provided by the European Union. Zhihui Xu reports financial support was provided by the Jiangsu Provincial Key Research and Development Program. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- • of special interest
- •• of outstanding interest

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