

# Tailoring beneficial microbe-plant interactions for “one health”, benefits

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March 24, 2024

## Abstract

Plants are an intrinsic part of the soil community and the “one health concept” considers that human health is intimately connected to the health of animals, plants, and microbial environments. Plant-microbe interactions are a cornerstone of one health, the soil microbiome being comprised of a diverse range of organisms, interacts in the rhizosphere through continuous molecular communications. Soils are a source and reservoir of pathogens, as well as beneficial microorganisms. Hence, the molecular dialogue at the rhizosphere interface is crucial not only for successful plant-microbe interactions but also for crop resilience and stress tolerance. The plant-microbe continuum forms a network of underground “nutrient highways” that benefit both plant and microbial communities. It also serves as a significant sink for atmospheric CO<sub>2</sub>. While microbial diversity is generally positively associated with one health, the host range of beneficial microbes currently limits their successful exploitation with a wide range of microbial communities. We consider the possibility of increasing the host range of beneficial microbes, including arbuscular mycorrhiza fungi (AMF) and rhizobia, and how current genetic incompatibility and/or activation of robust plant defenses, can be overcome while accepting that significant challenges exist in translating laboratory findings into the field. We consider why AMF inoculants and plant growth-promoting microbes are not always beneficial under field conditions and suggest possible approaches for tailoring plant-microbe interactions to assist plant breeding efforts in crop resilience.

## Tailoring beneficial microbe-plant interactions for “one health”, benefits

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**Keywords:** Atmospheric CO<sub>2</sub> levels, host-range specificity, microbial transplantation, receptor-ligand signaling, root microbiome.

## Abstract

Plants are an intrinsic part of the soil community and the “one health concept” considers that human health is intimately connected to the health of animals, plants, and microbial environments. Plant-microbe interactions are a cornerstone of one health, the soil microbiome being comprised of a diverse range of organisms, interacts in the rhizosphere through continuous molecular communications. Soils are a source and reservoir of pathogens, as well as beneficial microorganisms. Hence, the molecular dialogue at the rhizosphere interface is crucial not only for successful plant-microbe interactions but also for crop resilience and stress tolerance. The plant-microbe continuum forms a network of underground “nutrient highways” that benefit both plant and microbial communities. It also serves as a significant sink for atmospheric CO<sub>2</sub>. While microbial diversity is generally positively associated with one health, the host range of beneficial microbes currently limits their successful exploitation with a wide range of microbial communities. We consider the possibility of increasing the host range of beneficial microbes, including arbuscular mycorrhiza fungi (AMF) and rhizobia, and how current genetic incompatibility and/or activation of robust plant defenses, can be overcome while accepting that significant challenges exist in translating laboratory findings into the field. We consider why AMF inoculants and plant growth-promoting microbes are not always beneficial under field conditions and suggest possible approaches for tailoring plant-microbe interactions to assist plant breeding efforts in crop resilience.

## INTRODUCTION

Soil microbial communities are crucial to the “one health” concept because they connect the health of ecosystems, the microbial communities associated with plants, animals, and humans (Fig. 1), functioning as a ‘second genome’ (an ‘extended genotype’ or an ‘eco-holobiont’). The microbial communities of different organisms are interconnected in a manner that influences the fitness and performance of the different prokaryotic and eukaryotic organisms (Banerjee & van der Heijden, 2023). Similar functions can be attributed to microbial communities in the human gut and plant rhizosphere including nutrient uptake, modulating host immunity, prevention of pathogen colonization, and improving overall health. Harnessing the second genome for food production can also lower the environmental impact and residual effect of chemicals on the food chain because they influence nutrient recycling and pollutant degradation, thereby increasing crop resilience to climate variabilities (Trivedi, Batista, Bazany, & Singh, 2022).

Plants have evolved efficient strategies to avoid infection by microbial pathogens such as restricting microbe entry and multiplication. However, plant-microbiome associations go far beyond pathogens, the overall diversity of microbial symbionts, commensals, and amensals being pivotal to the overall health of the biosphere. In particular, the root-driven sequestration of carbon is attributable to the exchange and transport of nutrients between the roots of perennial plants, particularly trees, and rhizosphere bacteria and fungi. Soil microbes are the key drivers of carbon storage in soils, surpassing other soil processes. Since, microbial carbon use efficiency (CUE) is a major determinant of global soil organic carbon storage, understanding the plant-microbe interactions that underpin processes such as CUE can improve nature-based solutions to climate change.

The plant-microbe community includes a diverse range of endophytes, that asymptotically colonize the internal tissues of almost all plants (endosphere), as well as inhabiting the outside (ectosphere) plant organs (Ghatak, Chaturvedi, Waldherr, Subbarao, & Weckwerth, 2023; Sohrabi, Paasch, Liber, & He, 2023). The plant-beneficial bacteria (PBB), arbuscular mycorrhizal fungi (AMF), and plant-growth promoting microorganisms (PGPM) stimulate plant growth and development under optimal and stress conditions through a range of mechanisms (Fig. 2). Rhizosphere establishment and the persistence of beneficial microbes rely on efficient root colonization wherein they feed on the carbohydrates and other exudes. In turn, they assist in the uptake of essential nutrients, particularly nitrogen (N), phosphorus (P) and potassium (K), and produce

phytohormones such as indole-3-acetic acid (IAA), cytokinins (CK) and gibberellins, and also siderophores and thereby enhance plant fitness and resilience to environmental stresses (Bai et al., 2022; Ghatak et al., 2023; Turner, James, & Poole, 2013), such as salt (Chakraborty et al., 2021; Li, La, Zhang, Gao, & Tian, 2021) and drought (Bazany, Wang, Delgado-Baquerizo, Singh, & Trivedi, 2022; de Vries, Griffiths, Knight, Nicolitch, & Williams, 2020).

Seed microbiota including epiphytes that inhabit the seed coat and endophytes that colonize the endosphere, including the embryo, endosperm, aleurone, and perisperm, are central to plant establishment (Nelson, 2018; Nelson, Simoneau, Barret, Mitter, & Compant, 2018). This microbial community not only pioneers next-generation functions in the seedling establishment but also facilitates subsequent microbial colonization from the spermosphere (Fig. 2A). Microbe-assisted solutions to combat the negative impact of climate change may improve plant survival, in a world faced with an increased frequency of heat waves, floods, droughts and contamination of toxic heavy metals. However, a much deeper understanding of inter-organism communication is required to tailor the microbial community for maximizing plant growth and productivity, especially under realistic field scenarios. Building on a firm foundation of previous reviews on this topic such as Saad et al. (2020); Ke et al. (2021) and Banerjee & van der Heijden (2023), we present a synthesis of current research information, while highlighting the constraints to practical feasibility.

## MULTIPLE PATHWAYS FOR INTER-ORGANISM COMMUNICATION

### Microbe-derived bioactive metabolites

Microbe-derived compounds that trigger enhanced plant growth and defense are therefore attractive and promising alternatives to agricultural chemicals. In particular, rhizosphere bacteria produce a portfolio of bioactive secondary metabolites (BSMs) and inhibitory allelochemicals that are responsible for Induced Systemic Resistance (IR), biocontrol, and ecological fitness (Fig. 2A). For example, the typical plant-associated species, *Bacillus velezensis* has considerable biocontrol potential, based on its ability to trigger IR leading to rapid and robust defense responses, as well as direct antagonistic actions on pathogens (Ongena et al., 2007). Over 12% of the genome in bacteria such as *B. velezensis* is devoted to the synthesis of compounds that contribute to ecological competence and biocontrol activity. They produce a wide range of non-ribosomally synthesized compounds such as oligopeptides, cyclic lipopeptides (CLPs), and polyketides (PKs), in addition to post-translationally-modified lanthipeptides and bacteriocins. These molecules play a key role in multitrophic interactions because they can be antagonistic with other microbes and/or beneficial to the host via the stimulation of innate immune responses leading to IR. BSMs are not only produced *in vitro* conditions but also *in planta* by bacterial cells evolving as biofilm-structured microcolonies on root tissues (Andrić et al., 2021; Cawoy et al., 2015; Zihalirwa Kulimushi, Argüelles Arias, Franzil, Steels, & Ongena, 2017).

Plant-associated bacteria have evolved a polymer-sensing system to perceive the host. They increase BSM synthesis in response to the perception of root exudates. For example, the production of the cyclic lipopeptide surfactin by *B. velezensis* is stimulated by pectin, which is recognized as a cell surface molecular pattern in root exudates. Surfactin, which is synthesized non-ribosomally by a complex enzyme system, is formed as a mix of naturally coproduced homologs with fatty acid chains of various lengths (Hoff et al., 2021). It optimizes biofilm formation, motility, and early root colonization by the bacterium. It also reinforces the defensive capacity of the host. The IR phenotypes triggered by surfactin and other PBBs are an attractive addition to the crop protection toolbox, as bio-sourced alternatives to chemicals. However, the underlying biochemical and molecular basis for PBB action remains poorly understood.

### Receptor-ligand interaction

The complex and reiterative dialogue between plants and soil microorganisms involves extensive local and systemic communication systems that are based, at least in part, on plant receptors that detect microbe-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs). These molecules are restricted to pathogens and are not generally conserved and shared by a wide range of microbes, trigger IR and play a prominent role in determining the success or failure of any plant/microbe interaction

(Lü, Liu, Yu, Shi, & Liu, 2022). Chitin, which is a fungal cell wall homopolymer of unbranched  $\beta$ -1,4-linked N-acetylglucosamine (GlcNAc), is a key MAMP component that is recognized by plasma-membrane pattern recognition receptors (PRRs) (Lu, Liu, Yu, Shi, & Liu, 2022). The breakdown products of chitin (chitooligosaccharides: COs) are perceived by plant lysin motif (LysM) plasma membrane receptors triggering defence-gene induction, secretion of chitinases, a plasma membrane-derived oxidative burst and restriction of fungal growth (Chen et al., 2021; X. He et al., 2021; Morella et al., 2020; X. Zhou et al., 2022). The secretion of LysM-containing effector proteins that sequester AMF cell-wall derived COs plays a major role in the control of chitin-triggered host immunity (Zeng et al., 2020). Beneficial microbes, including rhizobia and AMF, which inhabit plant tissues can establish a mutualistic relationship with their hosts by either evading or suppressing host immunity (Fig. 2). The molecular dialogue between plant immune system and rhizosphere microbiota not only promotes colonization by beneficial microbes but it also prevents growth-defense trade-offs triggered by the MAMP-rich rhizosphere environment.

Plants secrete a range of chemicals such as flavonoids and strigolactones that are recognized by symbiotic rhizobia, which in turn secrete bacterial lipo-chitooligosaccharides (LCOs or Nod factors) that have a core structure of three to five N-acetyl glucosamines with an acyl chain attached to the non-reducing residue (Escudero-Martinez & Bulgarelli, 2023). Rhizobium Nod factors that are perceived by legumes and *Parasponia* species trigger a common symbiotic signaling (SYM) pathway that involves genes that are also required for AMF symbiosis (Escudero-Martinez et al., 2022; Oyserman et al., 2022). LCO receptor has a well-conserved hydrophobic structural signature that monitors the composition of amphiphilic LCO molecules. Receptor-ligand interactions provide a kinetic proof-reading mechanism for the selective recognition-guided activation of symbiotic signaling in legumes, determining rhizobia-legume compatibility (Gysel et al., 2021). Rhizobial species either have a broad host range (e.g. *Sinorhizobium fredii* NGR234 interactions with over 200 distantly related legumes) a narrow host range like *S. meliloti* that primarily nodulates *M. truncatula* or *M. sativa* (Kelly, Radutoiu, & Stougaard, 2017). Many *S. Meliloti* strains induce incompatible signaling due to two *Nodulation Specificity 1* locus (*NS1a* and *NS1b*) genes that encode malectin-like leucine-rich repeat receptor kinases, which block tissue invasion and root nodule induction. NS1 activation is dependent upon the bacterial gene *rns1* (Root nodule symbiosis) that encodes a type I-secreted protein (Liu et al., 2022).

Unlike the relatively well-characterized interactions between plants, AMF, and rhizobia, the molecular basis for cooperative interactions between PBBs and plants remains poorly characterized. Some PBBs display MAMPs, while others appear to bypass this high-affinity protein receptor-mediated surveillance system that triggers host immune responses. These are then recognized by cell-surface receptors, PRRs. For example, membrane lipid-dependent elicitation by surfactin induces an atypical early immune response including an intra-cellular burst of reactive oxygen species (ROS) and low calcium influx that triggers systemic resistance to *Botrytis cinerea* infection in *Arabidopsis thaliana* (Pršić et al., 2023; Hoff et al., 2021; Pršić & Ongena, 2020). The surfactin-induced activation of enhanced immune responses in *A. thaliana* is mediated by docking into specific sphingolipid-enriched domains leading to host membrane deformation and activation of mechanosensitive ion channels (Pršić et al., 2023).

### Redox-mediated signalling

An intrinsic feature of both PAMP and MAMP triggered responses, as well as physical and chemical perturbations to the plant plasma membrane, is the propagation of waves of ROS and cytoplasmic calcium ( $[Ca^{2+}]_{cyt}$ ) accumulation from the cell perceiving the signal to all cells throughout the plant (Fig. 2B). Together with fluctuations in electric wave potentials, the ROS wave triggers long-distance systemic defense signaling cascades that induce IR throughout the plant. The ROS wave is an essential systemic signaling system in plants, that contributes to plant-to-plant communication (Szechyńska-Hebda et al., 2022) and plant-to-microorganism interactions (Y. Zhou et al., 2019). Moreover, this signaling system has now been reported in a wide range of organisms (in microorganisms, plants, and mammalian cells) and cell communities (Fichman, Rowland, Oliver, & Mittler, 2023). This universal cell-to-cell communication mechanism probably evolved as part of the stress- or quorum-sensing mechanisms, is a fundamental link between differ-

ent organisms within a given environment or ecosystem. The “one health” concept is based on accumulating evidence that humans, animals, plants, microbiomes, and the environment are inseparably interlinked and impact each other constantly.

ROS signaling plays an important role in plant and animal interactions with microorganisms. The ROS wave is triggered by the oxidative burst, which occurs as a result of the activation of plasma membrane-bound NADPH oxidases (Respiratory Burst Oxidase Homologues: Rboh) and cell wall peroxidases. These enzymes generate superoxide in the apoplastic space i.e. the external space around the cell walls, which stores water and nutrients. The oxidative burst is one of the earliest plant responses to infection by microbes such as endophytes (Sahu et al., 2022). The apoplast has a low antioxidant capacity but it is rich in antifreeze proteins and pathogen-related proteins (PR-proteins) such as proteinase inhibitors, defensins, thionins, and lipid transfer proteins that together represent 23–33% of the total apoplastic fluid proteins (Farvardin et al., 2020).

In the case of pathogens, the prolonged activation of Rboh and other ROS-producing enzymes results in the hypersensitive response (HR) that prevents the spread of the pathogen from the attacked cell to neighboring cells. Endophyte-triggered ROS generation does not lead to HR but in contrast, triggers systemic signaling leading to defense gene expression (Sahu et al., 2022) and wide-ranging enhanced protection against biotic and abiotic stresses (Godara & Ramakrishna, 2023). The oxidative burst facilitates the oxidation of secondary compounds in the apoplast/cell wall environment, such as the conversion of sesquiterpenoids to oxygenous sesquiterpenoids through chemical oxidation and differing degrees of oxidation. Endophytes also activate the expression of genes encoding key enzymes involved in secondary metabolism, such as those involved in sesquiterpenoid biosynthesis, creating an array of sesquiterpenoid hydrocarbon scaffolds (J.-Y. Zhou, Yuan, Li, Ning, & Dai, 2016). For example, the microbe-induced oxidative burst and oxygenous sesquiterpenoid accumulation occur synchronously upon colonization of the medicinal plant *Atractylodes lancea* by *Pseudomonas fluorescens* ALEB7B. Sesquiterpenoids such as hinesol,  $\beta$ -eudesmol, atractylone, and caryophyllene oxide have medicinal properties protecting against rheumatic diseases, digestive disorders, night blindness, and influenza (J.-Y. Zhou et al., 2016).

#### Phytohormone-based signalling

Phytohormones such as SLs and karrikins (KARs) condition pre-symbiosis rhizosphere communication with AMFs. *Arabidopsis thaliana* (a non-mycorrhizal plant) SLs and KARs receptors D14 (Dwarf14) and KAI2 (Karrikin-insensitive 2; rice homolog of D14L) activate downstream signaling through the MAX2 (More axillary growth 2) E3 ligase. MAX2 targets different members of the SMAX1-LIKE (Suppressor of MAX2-1-like) family of transcriptional repressors for degradation (Q. Wang, Smith, & Huang, 2022). The *d14l* and *d3* mutants show impaired AMF colonization (Gutjahr et al., 2015). Perception of AMF by the rice  $\alpha/\beta$ -fold hydrolase D14L (Dwarf14-Like; an evolutionary paralogue of D14) leads to D3 (Dwarf3; a homolog of MAX2)-mediated signaling, stimulating fungal metabolism, allowing rapid hyphal growth in roots and expanding colonization. KAI2 functions are conserved in monocots (Meng et al., 2022). SMAX1 operates downstream of the D14L/D3 receptor to negatively regulate AMF symbiosis. Rice *smx1* mutants show enhanced expression of SL biosynthesis genes, indicating that SL-KAR crosstalk is required for efficient AMF symbiosis (Choi et al., 2020).

Gibberellic acid (GA) and the associated GRAS family DELLA TFs mediate transcriptional reprogramming during arbuscule development. GA binding to its receptor induces the degradation of DELLA proteins that repress GA signaling (Fig. 1A). The *della* mutants of *M. truncatula* (Floss, Levesque-Tremblay, Park, & Harrison, 2016) and rice (Yu et al., 2014) exhibit impaired AMF symbiosis. Similarly, the exogenous application of GA inhibited arbuscule branching in pea roots (El Ghachtouli, Martin-Tanguy, Paynot, & Gianinazzi, 1996). Expression of the MIG1 (Mycorrhiza-induced GRAS1) GRAS-type TF, which is a key regulator of cortical cell expansion, is a prerequisite for arbuscule development. The expression of dominant-active DELLA proteins rescues the loss-of-arbuscule phenotype of the *mig1* mutants. Hence, MIG1 and DELLA act together to promote cortical radial cell expansion (Fig. 1A) (Heck et al., 2016). The MIG1-DELLA-mediated positive regulation cascade is fine-tuned by MIG3 (a MIG1 paralogue)-SCL3 (Scarecrow-like 3, GRAS TF),

which acts as a negative regulator of arbuscule development in *M. truncatula* (Seemann et al., 2022). Salicylic acid (SA) also regulates root/microbiome interactions in response to nutrient deficiency (Kim et al., 2022). Rhizobia- and AMF-induced microbial signals are transduced via nuclear-localized calcium oscillations, generated by CNGC15 (Cyclic-nucleotide gated channel 15). The calcium-bound form of calmodulin 2 (holo-CaM2) is required to sustain prolonged CNGC15-dependent calcium oscillations. An engineered holo-CaM2 enhanced root nodule symbiosis but not arbuscular mycorrhization, indicating that the holo-CaM2-CNGC15s module is specific to Rhizobial symbiosis (Del Cerro et al., 2022). Calcium-phytohormone crosstalk functions alongside bi-directional nutrient exchange to establish rhizobia/AMF symbioses.

The light-induced GmSTF3/4 (soybean TGACG-motif binding factor 3/4) and FLOWERING LOCUS T (GmFTs) proteins function as mobile shoot-to-root signals. CCaMK (calcium- and calmodulin-dependent protein kinase) mediated phosphorylation of GmSTF3 triggers the formation of a GmSTF3-GmFT2a complex, which activates the expression of nodule inception (NIN) and nuclear factor Y (NF-YA1 and NF-YB1) that together regulate nodule organogenesis. The CCaMK-STF-FT module ensures a sustained shoot carbon supply (T. Wang et al., 2021). Rhizobial colonization, which is impaired in *della* mutants, is tightly controlled by host-derived GA signals. DELLA proteins promote the formation of the CCaMK-IPD3 complex. They also interact with NSP2 (Nodulation Signaling Pathway2), enhancing the expression of Nod-factor-inducible genes that are required for NSP1 binding to the NIN promoter. In this way, DELLA integration of the IPD3 and NSP1/2 pathways provides the transcriptional framework for successful root nodulation (Jin et al., 2016).

While our knowledge of inter-organism ROS signal communication remains rudimentary, it is evident that the cell-to-cell transmission of ROS waves and its crosstalk with hormones is a central feature of communication between the cells of a single organism and between different organisms (Fichman, Zandalinas, Peck, Luan, & Mittler, 2022). For example, ROS-dependent auxin production in tomato shoots triggers systemic signaling that enhances root strigolactone biosynthesis, promoting AMF symbiosis, and thus increasing orthophosphate (Pi) uptake and utilization (Zhou et al., 2019). Such studies provide new insights into potential targets for the manipulation of symbiosis for high nutrient utilization, particularly under future climate change scenarios, where plant nutrient accumulation will be increasingly challenged (Dong, Gruda, Lam, Li, & Duan, 2018; Loladze, 2014).

### Bi-directional nutrient exchange

The requirement for essential soil nutrients such as nitrogen (N) and phosphate (P), is another major driver for symbiotic associations between plants and beneficial microorganisms including AMFs and nitrogen-fixing rhizobia. AMF establishes root symbiosis with more than 80% of terrestrial plants (Chan, 2022; Dey & Ghosh, 2022). The partnership is mutually beneficial but not exclusive i.e. plants can form associations with multiple microorganisms simultaneously. Such associations assist plants in the acquisition of water and essential minerals, particularly P and N (Wipf, Krajinski, van Tuinen, Recorbet, & Courty, 2019). In return, AMF and other microorganisms receive assimilated carbon. AMF-mediated N/P uptake pathways function alongside the plant nutrient transport systems, providing a greatly expanded network of nutrient uptake from distal regions beyond the normal reach of roots or root hairs.

Plants control the AMF symbioses to the availability of orthophosphate (Pi), the preferred form of P taken up by roots (H. Lu et al., 2022). The plant Pi sensing SYG1/Pho81/XPR1 (SPX)—PHOSPHATE STARVATION RESPONSE (PHR) pathway regulates AMF symbiosis in crops such as rice (Shi et al., 2021), *Medicago* (J. Li et al., 2021) and tomato (Liao et al., 2022). The SPXs Pi sensing proteins regulate the activity of the PHR family of R2R3 MYB transcription factors (TF). Many genes required for AMF symbiosis have PHR1-binding sites (P1BS) and are activated by PHR binding (Fig. 1B). SPX negatively regulates PHR in rice and tomato, and hence, suppresses AMF symbiosis under moderate-Pi or Pi-replete conditions. In contrast, the *Medicago* MtSPX1 and MtSPX3 proteins are positive regulators of AMF colonization through the regulation of strigolactone (SLs) biosynthesis. Thus, there appears to be a diversification of SPX functions between cereals and legumes (J. Li et al., 2021).

The activation of a subset of Pi-starvation induced or phosphate-starvation response (PSR) genes, is a functional marker of successful AMF symbiosis (Fig 1B). However, the genetic predisposition of the host plant is a major determinant of the efficiency of AMF symbiosis, as observed in maize accessions (Sawers et al., 2017). PHR2 (Phosphate Starvation Response 2) is a major transcription factor regulating PSR in rice. It promotes AMF colonization by activating pre-contact signaling genes and mediates mycorrhizal Pi uptake (Das et al., 2022). The *OsADK1* (Arbuscule Development Kinase 1) receptor-like kinase, which is required for mycorrhizal colonization and arbuscule development, is an OsPHR2 target (Shi et al., 2022). The *Rhizophagus irregularis* SPX-domain containing PTs regulates arbuscule development and fine-tunes symbiotic Pi transfer -to the plant (Xie et al., 2022). Similarly, the *Gigaspora margarita* high-affinity PT, GigmPT transceptor activates a protein kinase A-mediated signaling cascade leading to Pi transport (Xie et al., 2016). Other AMF-activated genes such as *LjPT4* and *MtPT4* also serve Pi sensing functions in *L. japonicus* and *M. truncatula*, respectively (Volpe, Giovannetti, Sun, Fiorilli, & Bonfante, 2016). The extraradical AMF also transports Pi-solubilizing bacteria (PSB) that enhance organic P mineralization and increase Pi delivery to plants, via AMF-independent pathways (F. Jiang, Zhang, Zhou, George, & Feng, 2021).

N availability regulates plant-AMF symbiosis through proteins such as OsNPF4.5. Knockout lines lacking OsNPF4.5 functions had fewer arbuscules and lower (45%) symbiotic nitrate uptake (S. Wang et al., 2020). The lipids and carbohydrates in root exudates support fungal growth (Kameoka & Gutjahr, 2022; Salmeron-Santiago et al., 2021). Lipid provision involves two lipid biosynthetic enzymes (FatM and RAM2) and two ABC transporters (STR1 and 2; Stunted Arbuscule 1 and 2). FatM (An acyl-ACP thioesterase) increases plastid export of 16:0 fatty acids (Fig. 1A). Thereafter, RAM2 (Required for Arbuscular Mycorrhization 2) produces 16:0 b-monoacylglycerol, which is exported from the root cells across the peri-arbuscular membrane (Bravo, Brands, Wewer, Dormann, & Harrison, 2017). The *M. truncatula* AP2/ERF family transcription factor MtWRI5a binds to *STR* and other AMF-specific gene promoters (such as *MtPT4*) to promote lipid and Pi transport from host-to-AMF and AMF-to-host, respectively (Y. Jiang et al., 2018). The CBX1 (CTTC Motif-Binding Transcription Factor 1; a WRI1 homolog), which is enriched in AMF-regulated genes, activates *L. japonicus* *LjPT4* and lipid-metabolism genes (Xue et al., 2018). The rice *Osadk1* -defective mutants have low expression of *RAM1* and *WRI5* and produce fewer arbuscules (Shi et al., 2022). These findings suggest that MtWRI5a, LjCBX1, and OsADK1 are master regulators of bidirectional nutrient transport.

## PLANT HOLOBIONT ENHANCES ENVIRONMENTAL STRESS TOLERANCE

Plant-associated microbial communities are known to impart tolerance against salt (Chakraborty et al., 2021; H. Li et al., 2021) and drought (Bazany et al., 2022; de Vries et al., 2020) stress conditions. Salt-induced decreases in root nodulation (Singh & Valdes-Lopez, 2023) involve the expression of a glycogen synthase kinase 3 (GSK3)-like kinase, GmSK2-8, which phosphorylates GmNSP1a, preventing the binding of symbiotic genes such as *GmNINa* and reducing nodulation (C. He et al., 2021). The salt-inducible GmNAC181 TF activates *GmNINa* expression and maintains soybean nodulation under salt stress (X. Wang et al., 2022). Drought triggers a compartment-specific restructuring of rice root microbiota in rice, particularly in the endosphere. Drought increases the prevalence of monoderm bacteria, which lack an outer cell membrane and contain thick cell walls (Santos-Medellin et al., 2021; Xu et al., 2018). Apart from providing drought adaptation, the microbial communities also contribute to drought-induced stress memory in rice, through compositional shifts that help plants to survive better upon re-watering (Fig. 2B) (Santos-Medellin et al., 2021). In the bioenergy model grass *Panicum hallii*, AMFs inoculation under water-limiting conditions has been shown to impart resistance to sensitive bacterial communities in the hydrosphere, indicating fungal-bacterial synergy (Hestrin et al., 2022). However, these findings need more careful investigation, while designing microbe-based solutions for realistic field scenarios. For instance, drought-induced increased prevalence of beneficial microbes in rhizospheres has been demonstrated to induce risk factors for harmful fungi (Lei, Ding, Xu, & Zhang, 2023).

Stress as well as nutrient-limiting conditions have been shown to alter innate immunity, which helps in recruiting beneficial microbes. Pi-starvation induced transcriptional regulator PHR1 activates the expression

of *RALF* (Rapid alkalization factor) genes. RALF peptides hijack the FERONIA kinase to suppress plant immunity and allow colonization by specialized root microbiota such as *Pseudomonas fluorescens* (Fig. 2C) (Tang et al., 2022). FERONIA inhibitors, including reversine and staurosporine, enhance innate immunity against soil-borne diseases in tobacco, tomato, and rice without imposing growth penalties (H. B. Liu et al., 2023). *Feronia* mutants show low ROS accumulation and harbor elevated levels of rhizosphere pseudomonads, suggesting that FERONIA participates in the discrimination of beneficial and harmful microbes (Song et al., 2021). Additionally, the water-deficit conditions release flavonoids that reshape the root microbiome by attracting *Aeromonas* species that enhance dehydration resistance in plants (D. He et al., 2022). Apart from plant exudates, the core bacterial commensals and host tryptophan-derived specialized metabolites also function to control the overgrowth of fungal species (Wolinska et al., 2021), thereby maintaining host-microbe as well as microbe-microbe homeostasis. Taken together, the role of stress in shaping the plant microbial signature is clear; however, the cause-effect relationship is yet to be established.

## **BENEFICIAL PLANT-MICROBE INTERACTIONS: AN ECOLOGICAL PERSPECTIVE**

The soil microbial community is intricately interwoven with plant health. Beneficial plant-microbe interactions are an indispensable component for restoring ecosystem loss due to excessive use of chemical fertilizers and pesticides. For example, nitrogen (N) fertilizers are responsible for nearly 5% emissions of global greenhouse gas (GHG) mainly nitrous oxide, which is 300 times more potent than CO<sub>2</sub>, in terms of heat-trapping (Y. Gao & Cabrera Serrenho, 2023; Wen et al., 2021). Similarly, phosphorus (P) is another rate-limiting nutrient and almost 80% of applied P-fertilizer is lost due to the inefficient acquisition by the plants, imposing an economic burden on the farmers. The long-term excessive application of N- and P-fertilizers causes soil acidification and eutrophication of fresh-water bodies and is therefore not sustainable. Many beneficial bacteria/fungi in the rhizosphere, collectively termed plant-growth promoting microbes (PGPMs), support plant growth by increasing nutrient-use efficiency, biotic/abiotic stress tolerance, and disease resistance. Rhizobacteria and free-living diazotrophs mediate biological N-fixation in nodulating and non-nodulating crops, respectively (Wen et al., 2021). PGPMs also secrete different organic acids to solubilize insoluble-P and hence, significantly reduce the usage of P-fertilizer, without jeopardizing crop yield. Apart from fertilizers, the over-application of chemical pesticides is another serious concern that can increase resistance among pathogenic microbes. Besides, entering of hazardous pesticides into the food chain can create a toxic ecosystem. PGPMs serve as biological alternatives to these pesticides and hence, maintain a disease-suppressive environment in soil, through multifaceted ways including antibiosis, parasitism, competition for resources, and predation in addition to providing induced systemic resistance in plants (Fig. 4A). Along with mitigating biotic-stress, PGPMs also provide the dual benefit of providing tolerance towards abiotic stresses, whose occurrence increased as a repercussion of global climate change (Mitter, Tosi, Obregón, Dunfield, & Germida, 2021). Intensive agricultural practices also decrease the soil's organic carbon, deteriorating soil fertility along with accelerating global warming as more carbon reaches the environment. PGPMs use the photosynthesized CO<sub>2</sub> for maintaining their growth and hence increase soil organic carbon, contributing to climate restoration (Fig. 4A). Recently, a global scale study has also established a positive correlation between plant-mycorrhiza association and soil carbon content (Soudzilovskaia et al., 2019). Climate change is also reshaping forest ecosystems by driving species beyond their evolved resilience, with some of them even facing the fate of extinction. Nurturing trees by microbial symbionts acclimatized to specific climatic conditions safeguard their existence by providing climate tolerance (Allsup, George, & Lankau, 2023; Baldrian, López-Mondéjar, & Kohout, 2023). Taken together, supporting the beneficial microbe-plant interactions will not only reduce the negative impacts of climate change on plant fitness but, will also reduce the use of chemical-based fertilizers/pesticides.

## **BROADENING HOST-RANGE SPECIFICITY FOR PRODUCING “GREENER” CLIMATE**

The increasing levels of CO<sub>2</sub> in the atmosphere drive photosynthesis and biomass accumulation in C3 crops (Ainsworth & Long, 2021). This CO<sub>2</sub> fertilization effect increases plant growth but negatively impacts crop nutritional quality (Myers et al., 2014) with marked reductions in N, P, and other essential mineral nutrients

(McGrath & Lobell, 2013). The increasing requirement for essential soil nutrients is an important driver for improving symbiotic associations between plants and beneficial microorganisms (Chan, 2022; Dey & Ghosh, 2022). Multiple approaches are underway to broaden host-range specificity (Fig. 3) and to minimize high CO<sub>2</sub>-induced decreases in crop quality. Of these, altering and/or suppressing host-induced immunity is perhaps the most important. For example, the downstream target of MtRAM1, *MtKIN3*, suppresses host defenses and supports AMF symbiosis (Irving et al., 2022), while also regulating plant N responses. Rhizobia produces several effectors that manipulate host defense signaling pathways. For example, the soybean Nodulation outer protein T (NopT, an effector protease from *Sinorhizobium* sp.) activates the GmPBS1-mediated resistance pathway and impairs nodule formation (Khan et al., 2022). Similarly, the GmNNL1 (Nodule Number Locus 1; an R protein) protein directly interacts with the NopP effector from *Bradyrhizobium* USDA110 to trigger immunity and inhibit nodulation (B. Zhang et al., 2021). Thus, genetic engineering of effector proteins to block defense but support symbiosis could broaden the range of beneficial plant-microbe interaction (Fig. 3A). Dual-sensing receptors can widen the host-range of beneficial microbes (Fig. 3B). For example, the expression of chimeric “Nod-Myc” receptor in which the ectodomains of OsMYR1 and OsCERK1 were replaced by homologous *M. truncatula* sequences in rice led to increased Nod factor-induced calcium oscillations (J. He et al., 2019). Similarly, the binding affinity of the *L. Japonicas* receptor kinaseEPR3a (Exopolysaccharide receptor 3a) that binds AMF-specific glucans, as well as with rhizobia-specific exopolysaccharide (EPS) could function as a dual receptor. In addition, trans-kingdom signaling can also be exploited to enhance interactions with beneficial microbes [85,86]. For example, barley lines expressing the plant-derived signal rhizopine, which controls the N<sub>2</sub>-fixation related gene expression in bacteria (Fig. 3C), can associate with *Azorhizobium caulinodans*, which has a rhizopine uptake system and usually forms a nitrogen-fixing symbiosis with *Sesbania*.

For any PGPM, it is crucial to colonize as well as sustain in the dynamic environment also called rhizo-competence which in part depends on host genetics. Identification of intraspecific variation controlling microbial selection and shaping root-associated microbiomes remains challenging (Zboralski, Saadia, Novinscak, & Filion, 2022). Nevertheless, genome-wide association studies (GWAS) appear to be a potentially powerful tool in identifying host genetic loci which are microbes responsive (Fig. 3D). To explore this, previous efforts have demonstrated, the dependence of rhizosphere microbial communities on distinct genotypes of the same host species including maize and sorghum. Moreover, in *A. thaliana* host SNPs controlling defense and cell wall integrity affected microbial community variation (Deng et al., 2021). Such precision-based microbiome management in the future could assist in engineering high-yielding/climate-resilient crops.

## ENGINEERING PLANT-MICROBE INTERACTION FOR NEXT GENERATION AGRICULTURE

The one health concept is based on a growing understanding that humans, animals, plants, microbiomes, and the environment are inseparably linked and impact each other constantly. The presence and stress levels experienced by different organisms within an ecosystem could therefore be transmitted from one to another through cell-to-cell ROS wave signaling. Stress experiences may be transmitted between plants and the soil microbiomes, by variations in the exchange of ROS signals. The application of genetic engineering approaches that serve to support symbiosis by blocking or minimizing the recognition-induced oxidative burst and activating host defenses must take such interactions into account, not only because they could increase the susceptibility of plants to pathogen attack but because they could also disrupt or interfere with a wide range of inter-organism communications within a given ecosystem.

Next-generation agriculture will be comprised of at least three components: enhanced crop production, minimal agri-inputs in the form of pesticides/fertilizers, and enhanced microbial carbon sequestration (Fig. 4A). Although, tailored plant-microbe interactions promise to meet all these three expectations, the AKP (Anna Karenina Principle) must be addressed. AKP considers that dysbiotic microbiomes are intrinsically different, while healthy microbiota are similar (Arnault, Mony, & Vandenkoornhuys, 2023). Nevertheless, some strategies have already proved to be successful. For example, rhizosphere microbiome transplantation (RMT), in which microbial communities from either extreme environments or from a tolerant cultivar are

inoculated to enhance growth or suppress stress responses (Fig. 4B) (Poppeliers, Sanchez-Gil, & de Jonge, 2023). RMT-mediated enhanced plant growth is poorly understood but could be stress-specific in nature. For example, changes in the drought and cold tolerance of tree species were associated with increased and decreased AMF diversity, respectively (Allsup et al., 2023).

Manipulation of the soil microbiome, associated crop management practices, and applied crop design are important components of solutions to address climate change. Much attention has also focussed on engineering nitrogen-fixing nodulation traits in non-leguminous crop plants (Huisman & Geurts, 2020). However, environmental perturbations exert effects on the diversity of plant microbial communities, with varying effects depending on the plant species and developmental stage. For example, drought increases the release of flavonoids in root exudates. These reshape the root microbiome by attracting *Aeromonas* species that enhance dehydration resistance in plants (He et al., 2022). In addition, core bacterial commensals and host tryptophan-derived specialized metabolites participate in the control of fungal species (Wolinska et al., 2021). The changes in the relative abundance of Actinobacteria and Proteobacteria were reported in rice cultivated under drought conditions, an effect that persisted after stress alleviation (Santos-Medellin et al., 2021). In sorghum, drought increased the abundance of *Actinobacteria* and decreased pathogenic genera (*Fusarium*, *Gibberella*, and *Sarocladium*) compared with well-watered controls (Gao et al., 2020; Xu et al., 2018). Drought-stressed sorghum plants in soils with *Arthrobacter* bacteria suffered more than those in which bacteria of the genus *Variovorax* were abundant (Qi et al., 2022). In contrast, *Arthrobacter* alleviated drought-stress effects in wheat (Hone et al., 2021). The presence of endospheric *Streptomyces* was correlated with drought tolerance in several plant species (Fitzpatrick et al., 2018).

Microbiome-inspired methods are promising innovations to enhance the stress resilience of crops. Roots grown in natural- and agro-ecosystems preferentially recruit PBB and AMF in drought situations (Song & Haney, 2021; Williams & de Vries, 2020; Zhao et al., 2023). Therefore, commercial AMF inoculants, added as a supplement to agricultural lands, have considerable potential in the alleviation of drought and nutrient deficiency in plants (Salomon et al., 2022). The application of microbial consortia may be more efficient than single-strain inocula in enhancing stress tolerance (Bradáčová et al., 2019). However, while AMF richness increases in barley roots under drought, AMF performance (colonization and the abundance of arbuscules and vesicles) decreases, indicating antagonistic interactions (Sendek et al., 2019). However, while drought increases the prevalence of beneficial microbes in rhizosheaths, it also increases the risk of penetration by harmful fungi (Lei et al., 2023). Moreover, a limitation factor in the application of such information concerns the diverse nature of AMF functionality depending on environmental effects.

Native synthetic microbial communities (SynComs) from plants grown under optimal conditions can be used to boost plant growth in poor soils (Fig. 4C) (M. Jiang et al., 2023). For example, SynComs application promotes the growth of *A. thaliana*, in an innate immunity-dependent manner (Wolinska et al., 2021). Cross-kingdom (fungi and bacteria) SynComs were more effective in suppressing fusarium-wilt disease in tomato than fungi or bacteria alone (X. Zhou et al., 2022). RMT and SynComs have yet to be tested for field applications, due to low efficiency in isolating functionally beneficial microbiomes. Multiple approaches based on screening natural variation, mathematical modeling, RAMAN-spectra, and successive passaging are being used to map the microbial community networks (Chen et al., 2021; X. He et al., 2021; Morella et al., 2020). The root-secreted chemicals or exudates comprised of photosynthetically fixed carbon as well as diverse signaling molecules including  $\gamma$ -aminobutyric acid, malate, and citrate, also contribute to shaping rhizosphere microbiome (Fig. 4D) (W. Zhang & Mason, 2022). In addition, microbe-derived secretory proteins YukeE cause iron leakage in plant roots, which contributes to root colonization by beneficial rhizobacterium *Bacillus velezensis* (Y. Liu et al., 2023). Microbiome engineering to improve the composition of root exudates/secretomes will help determine the host-derived factors that synchronize interactions between beneficial and resident microbiomes (Escudero-Martinez & Bulgarelli, 2023). QTLs that determine the root-microbiota composition of crops contain genes such as the iron regulator FIT and water channel aquaporin SITIP2.3 in tomato (Oyserman et al., 2022) and Nucleotide-Binding-Leucine-Rich-Repeat (NLR) in barley (Escudero-Martinez et al., 2022). Apart from the genotypes, the heritable component also needs to be accounted, especially in the context of microbiome-assisted molecular crop breeding.

## CONCLUSION AND PERSPECTIVES

In conclusion, recent advances confirm that the soil microbiome is key to soil and plant health, as discussed above. It is perhaps not surprising that plant-microbe interactions have not been exploited for agricultural purposes ago, given the relatively poor indicators of success under field conditions. However, our understanding of the potential positive effects of PGPM has greatly increased in recent years, as has our knowledge of underpinning mechanisms, particularly the molecules involved in inter-organism communication. Thus, while there are substantial gaps in current knowledge, plant-microbe interactions are an attractive target for improving crop resilience and for achieving sustainable yields under unfavourable environmental conditions. Ultimately, the optimisation of plant-microbe interactions will be pivotal to strategies aimed at the long-term carbon sequestration in soils that is crucial to nature-based solutions to climate change. Microorganisms are at the core of the global carbon cycle, not least because they are responsible for more than 50% of annual CO<sub>2</sub>/methane transformations and contribute to almost 50% of the annual global CO<sub>2</sub>-sequestration. Engineering a more sustainable carbon cycle requires a detailed molecular mechanism-based understanding of the enzymes involved in CO<sub>2</sub>/methane interconversions. This essential knowledge is a prerequisite for viable microbe-based solutions to climate change.

Tailoring the soil microbiome to boost plant yield is currently restricted to agricultural practices and adding probiotic microbial consortia, largely because gene editing approaches are limited by societal acceptance. Ambitious objectives have been set in Europe and in other continents to ensure food sovereignty, while enhancing agricultural sustainability. Such targets have to incorporate climate change reliance traits, together with a much higher efficiency in the use of essential resources particularly water, and soil nutrients. An ultimate aim is to reduce reliance on fertilizers and plant protection products. It will not be possible to achieve these goals without a revolution in plant breeding that includes a continuous flow of innovation and technology transfer, incorporating new knowledge as it becomes available. This requires a substantial acceleration in the development of new plant varieties that have improved microbial associations, and so can use available resources much more efficiently, and are better adapted to climate change. The rapid introduction of such varieties will only be possible if breeders have access to all of the available tools and technologies, and crucially that Government registration and legislation accepts new genomic technologies that are at the heart of current accelerated breeding opportunities.

Nano-enabled approaches have the potential to overcome the limitations of traditional microbiome engineering, such as the absence of specificity in attaining targeted manipulation, collateral fatality to microbial diversity, and lack of reliable robust results (Fig. 4E) (Hussain et al., 2023; You, Kerner, Shanmugam, & Khodakovskaya, 2023). However, the application of novel nanomaterials still requires comprehensive profiling to evaluate long-term efficacy on plant productivity and ecosystem health (Ahmed, Noman, Gardea-Torresdey, White, & Li, 2023). To date, the beneficial actions of such approaches have been studied largely under controlled conditions and hence effective translation into the field is uncertain. The practical relevance of increasing mechanistic knowledge hence requires extensive study under field conditions, where environmental constraints influence to composition and effectiveness of plant/microbiome interactions. Such information is essential to understand how we might best apply inoculants to fields, which remains a significant challenge (Kaminsky et al. 2018). Nevertheless, the strategies discussed above have as yet untapped potential, and are particularly important in developing countries (Ashwathi, 2019).

Soil microbial communities are not constant and vary according to developmental stage, tissue type, and sampling time (Quiza et al., 2023). Our increasing knowledge of the leaf and root microbiomes has demonstrated the diversity of bacteria that are adapted for survival on, as well as within plants. The phyllosphere is a conducive niche for horizontal gene transfer (HGT) between epiphytic bacterial strains, the plant surface thus provides a niche for the evolution of new variants. Gaining a deeper understanding of this dynamic environment for gene exchange and the emergence of new strains, together with the exploitation of the remarkable genomic diversity within epiphytic populations, will help overcome current limitations in host-range specificity and allow potential jumping to other host plants. This together, with a better understanding of the plethora of signalling molecules including ROS (and associated redox post-translational modifications)

that contribute to the dialogue between plants and microbes, will provide an improved road map for exploitation of the bi/tri/multi-partite interactions with beneficial microbes that will underpin sustainable next-generation agriculture.

## ACKNOWLEDGMENT

CHF thanks the Science and Engineering Research Board of India for a VAJRA fellowship (VJR/2019/000068).

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**Fig. 1: Microbiomes serve as the foundation for one health:** The health of plants, humans, and the environment are interconnected and rely on close association with microbial communities. The beneficial microbial microbes in the plant rhizosphere determine plant productivity by assisting in seed germination, foraging for nutrients under nutrient-limiting conditions, or nutrient recycling along with providing abiotic and biotic stress tolerance through production metabolites and modulating host immunity respectively. In humans, the beneficial microbes introduced via direct consumption of plant products or indirect exposure through the environment contribute to overall health maintenance by boosting the immune system against pathogens, reducing the usage of antimicrobial compounds, and providing some essential nutrients. The beneficial microbes can offer a sustainable solution for the conservation of nature by replacing chemical fertilizers and pesticides responsible for global warming and environmental pollution.

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**Fig. 2: Mechanisms for plant-microbe interactions.** Plant/microbe interactions occur in spermosphere, rhizosphere, and phyllosphere. Microbes in the spermosphere aid seedling establishment by controlling germination and the secretion of compounds that inhibit competing pathogenic microbes. The plant/microbe chemical communication network involves primary and secondary metabolites that attract beneficial microbes and restrict pathogenic microbes. Beneficial microbes secrete allelochemicals with biocontrol activity. Phytohormones including indole acetic acid (IAA), cytokinin (CK), gibberellic acid (GA), strigolactone (SL), and

salicylic acid (SA) are secreted by both plants and microbes. Soil microbes not only enhance plant immunity by triggering systemic resistance responses via MAMP-triggered immunity or effector-triggered immunity, but they also directly inhibit invading pathogens. Beneficial microbes can successfully evade plant immune surveillance by deploying effector proteins to suppress plant immune response (A). The microbe-derived PAMPs and MAMPs are perceived by plasma-membrane-localized pattern-recognition receptors (PRRs) that trigger signaling events including Ca influx, activation of plasma membrane-bound NADPH oxidases (RBOH) that produce reactive oxygen species (ROS burst). Oscillations in calcium concentrations (calcium spiking) and ROS waves act together with a network of signalling proteins as well as Ca-dependent protein kinases (CDPKs, CCaMKs and CIPKs) to control transcriptional reprogramming, activation of defense-related genes, secondary metabolite production, and defence hormone synthesis. This system triggers immune response throughout the plant resulting in systemic acquired resistance (B). Current concepts concerning this signalling cascade are described in detail in the accompanying text.

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**Fig. 3: Genetic approaches to broaden the host range of beneficial microbes.** Microbe-derived effector proteins can be engineered to block host defenses and initiate symbiosis (A). Genetic engineering approach to recreate nodule organogenesis in non-legume plants. The Myc-receptor, which recognizes AMF-produced Myc-factors, has been engineered to perceive Nod factors by replacing the outer domain of the receptor. This induces the formation of nodule-like structures by activating a common symbiotic signaling pathway (CSSP) (B). Another approach is to facilitate the association between nitrogen-fixing microbes and cereals including rhizopine synthesis in plants such as wheat and rice. Rhizopine is sensed by nitrogen-fixing bacteria via biosensor plasmids that encode rhizopine-binding proteins and rhizopine-dependent transcription factors (TF). These proteins drive the downstream expression of genes encoding proteins required for nitrogen fixation (C). Finally, the recruitment of root-associated microbiota is dependent on host genetics. Genome wide association study mapping will identify novel genetic loci that control microbial selection to facilitate breeding efforts to improve crop resilience (D).

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**Fig. 4: Holobiont approaches for next-generation agriculture.** Beneficial microbes can reduce the agricultural use of fertilizers and chemical pesticides, and contribute to rhizosphere carbon sink capacity (A). Rhizosphere microbiomes from plants inhabiting extreme environments or stress-tolerant cultivars and can be transplanted can be used in phytoremediation and soil improvement approaches (B). Synthetic microbial communities (SynCom) can augment crop quality. High quality crop production systems can be used to source SynComs. High-throughput sequencing and systems biology approaches can be used to identify appropriate SynCom systems. Network analysis provides information on core microbial taxa and hubs and facilitates the selection of best candidate microbes for further screening. The efficacy and ecological impacts of SynComs must be validated in field studies (C). Composites of the signaling chemicals found in root exudates including flavonoids,  $\gamma$ -aminobutyric acid, malate, and citrate can be applied to soils to attract beneficial microbes (D). Nanomaterial-based approaches are also an attractive approach for improving plant health by releasing trapped soil nutrients and modulating root exudates (E).