Plants endophytes: unveiling hidden agenda for bioprospecting toward sustainable agriculture

Anamika Dubey , Muneer Ahmad Malla , Ashwani Kumar , Selvadurai Dayanandan & Mohammad Latif Khan

Published online: 30 Aug 2020.

Submit your article to this journal ⬀

View related articles ⬀

View Crossmark data ⬀

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Check for updates

Plants endophytes: unveiling hidden agenda for bioprospecting toward sustainable agriculture

Anamika Dubey[a] (iD), Muneer Ahmad Malla[b] (iD), Ashwani Kumar[a] (iD), Selvadurai Dayanandan[b,c] and Mohammad Latif Khan[a] (iD)

[a]Department of Botany, Metagenomics and Secretomics Research Laboratory, Dr. Harisingh Gour University (A Central University), Sagar, India; [b]Department of Zoology, Dr. Harisingh Gour University (A Central University), Sagar, India; [c]Biology Department, Centre for Structural and Functional Genomics, Concordia University, Montreal, QC, Canada

ABSTRACT

Endophytic microbes are present in nearly all of the plant species known to date but how they enter and flourish inside a host plant and display multiple benefits like plant growth promotion (PGP), biodegradation, and stress alleviation are still unexplored. Until now, the majority of the research has been conducted assuming that the host–endophyte interaction is analogous to the PGP microbes, although, studies related to the mechanisms of their infection, colonization as well as conferring important traits to the plants are limited. It would be fascinating to explore the role of these endophytic microbes in host gene expression, metabolism, and the modulation of phenotypic traits, under abiotic and biotic stress conditions. In this review, we critically focused on the following areas: (i) endophytic lifestyle and the mechanism of their entry into plant tissues, (ii) how endophytes modulate the immune system of plants and affect the genotypic and phenotypic expression of host plants under abiotic and biotic stress condition, and (iii) the role of omics and other integrated genomic approaches in unraveling complex host–endophyte signaling crosstalk. Furthermore, we discussed their role in phytoremediation of heavy metal stress and whole genomic analysis based on an understanding of different metabolic pathways these endophytes utilize to combat stress.

Introduction

To feed the rapidly growing 7.6 billion human global population which is estimated to reach 9.7 billion by 2050, agricultural practices are under constant pressure to provide augmented yields across the world [1]. Recently, crop production is facing severe threats due to various abiotic and biotic stress conditions. Endophytes represent an eco-friendly alternative for plant growth promotion (PGP) and as a sustainable reservoir of novel bioactive compounds. Endophyte is defined as any microorganism that can grow and flourish inside plant tissues [2]. They are usually recruited by the plants and form an association with their host plant and constitute an essential part of the plant microbiome. According to Sprent [3], the plant–endophytic relationship, is supposed to have evolved more than 60 million years ago and, has played a significant role in maintaining terrestrial ecosystems, therefore, providing benefits to both partners. Studies related to the endophytic microbial community and their roles in plant life have often been ignored for a long time. These endophytic microbes have originated either from the seed or rhizosphere microbial communities. However, studies related to plant–microbiome research have completely changed the scenario and showed that these microbial communities are more flexible and contain genetic information which codes for novel traits beneficial to their host plant [1,4]. Microbial endophytes play an important role in contributing to the health and fitness of their host plant, either by preparing or shielding the host plant against various stress conditions [5–7]. They are found in almost all the ecosystems reducing abiotic and biotic stress in plants by eliciting an immune response, production of antioxidants, and suppressing pathogen growth [2,8]. Endophytes are plant-colonizing microbes that live in a mutualistic symbiotic association with their host plant, and because of their invaluable contribution to the host plant, this coevolution has been looked upon for shaping the factors involved in the coexistence of both the associates and tracking the

reimbursements out of this relationship [9,10]. Many metabolomics studies conducted in the recent past have confirmed that endophyte genes associated with particular metabolites are implicated in PGP by the production of phytohormones like IAA or auxins and gibberellic acid (GA) [8,11,12]. These plant hormones operate as plant protective agents against different insect pests, and microbial pathogens. The great diversity of endophytes, their adjustment to stress conditions, and their metabolite production make them an unlimited source of novel metabolites, whose application can reduce the usage of agrochemicals in medicines and food production [2,8,12–15]. Therefore, more practical and fundamental studies to address the processes leading to the community assemblage and its functioning inside and on the plants are required. Deciphering the interactions between and within various microbial taxa colonizing roots, stem, petiole, and leaves will be a prerequisite for understanding and exploring the regulation of the endophytic microbiome [8]. Some major driving factors are controlling the endophytic community composition and their establishment is chiefly dictated by a series of modulating factors such as a host immune system, host genotype, environmental parameters, microbe–microbe interactions, soil, and food types [16–18]. Among environmental factors like pH, nutritional drivers, temperature, and the availability of oxygen are the major drivers of the microbial community composition [2,8]. However, very less information is available about the diversity, composition, and interaction of these endophytes with plants under stressful environments [7]. However, with the advancement of next-generation sequencing (NGS), genome sequencing, metagenomics, metatranscriptomics, metabolomics, microarray, and comparative genomics approach may provide a comprehensive facet of the endophytic microbial lifestyle [4,5,9,10,16]. Recently, the development of metagenomic and NGS approaches has allowed us to attain a global scrutiny about endophytic diversity and community structure of the endophytic microbiome. The best examples are the studies of the endophytic bacterial population associated with roots of: *Aloe vera* [19], citrus [20], wheat [21], and *Arabidopsis thaliana* [22]. Some researchers have designed and used new dual genome Symbiosis Chip-based tool for studying symbiotic interactions between endophytes and their host plants [23–25]. Plant–endophyte association produces many bioactive compounds such as: taxol [26], artemisin [27], helvolic acid [28], camptothecin [29], huperzine [30], azadirachtin [31], and many more which can be used in various fields of medicine, agriculture, biodegradation, and bioremediation.

In this review, we have critically focused on the endophytic lifestyle and mechanisms of their entry into plants, how they modulate the immune system of the plant, and affect genotypic and phenotypic expression of host plants under abiotic and biotic stress conditions. In this review, we have also discussed the role of genomics and other integrated omics approaches to unravel complex host–endophyte signaling crosstalk.

Endophyte: a way of living inside host plants

Endophytes can enter and colonize tissues of host plants through the horizontal transmission method from the soil to the plants or through vertical seeding methods. It has been assumed that the colonization of endophytes is a passive process. However, the study conducted by Robinson et al. [32] confirmed that the dominant rhizosphere bacteria *Bacillus mycoides* was not capable of colonizing the endosphere of wheat in a gnotobiotic system in the absence of competing bacteria, signifying that colonization is gated. It will be interesting to determine what amount of the microbial community present in the rhizoplane/rhizosphere can truly become endophytic. Successful colonization of the endophytes associates friendly plant–microbe association. When the endophyte enters into the host plant, it is then recognized by the host plant, and crosstalk of signal molecules is initiated. Plants secrete root exudates like flavonoids, which are highly rich in nutrients that act as chemo-attractants for many PGP microbes including endophytes. Lipo-chitooligosaccharides (LCO), known as Nod factors, are well-known signaling molecules that activate the common symbiotic pathway (CSP) in AM or arbuscular mycorrhizal fungi (AMF) and rhizobium-legume symbiosis [33]. Arora and Mishra [34] in their study used flavonoids as a bio-formulation for successful colonization of rhizobia in legume roots. Strigolactone (SL) treatment stimulates the synthesis and release of short-chain chitin oligomers that stimulates plant symbiotic signaling pathways [35]. Recently, the study conducted by Rozpądek et al. [36] reported that the roots *of Arabidopsis thaliana* secrete SL which acts as a signaling molecule for endophytic colonization of *Mucor* sp. A study conducted by Nguema-Ona et al. [37] suggested the important role of arabinogalactan proteins (AGPs), these AGPs are highly glycosylated members of the hydroxyproline-rich glycoprotein (HRGP) superfamily of plant cell wall proteins, in establishing plant–microbe interaction at several levels. These proteins play a specific role in the colonization of the roots, often working as attractants or repellents for microorganisms and in the development of infection.

Several other root exudates like phenolic compounds, organic acids, amino acids, sugars, and some secondary metabolites are now recognized to be secreted by the roots of the plant, which selectively attract endophytes [37,38]. Recent findings on micro-RNAs (miRNAs) and gene expression studies in plants suggest that the pathways and gene responses depend upon the endophytic microbe. Numerous researches proved that during the colonization of plants by mutualistic partners such as rhizobia or AMF there is down-regulation of plant defensive pathways [39]. However, signaling pathways of jasmonic acid (JA)/ethylene (ET)/salicylic acid (SA) work irrespective of the microbe. There are numerous novel bioactive compounds that are produced as a result of plant–endophyte interactions that can be used in various fields of medicine, biodegradation, bioremediation, and agriculture [2,40–42]. Several studies conducted by different researchers suggested the role of the plant innate immune system in allowing endophytic microbes to enter into plant internal tissues [39–42]. Kusajima et al. [40] found that a bacterial endophyte, *Azospirillum sp.* B510 induces systemic disease resistance in rice and additionally, gene expression analysis indicates that ET is essential for endophyte-mediated induced systemic resistance (ISR) in rice. In the case of AMF colonization, the miRNA (-E4D3Z3Y01BW0TQ-) is up-regulated and disrupts GA signaling pathways, known for suppressive action against any mutualistic associations [43]. However, endophytic microbes also used their own defensive mechanisms to shield themselves from plant defense mechanisms. For example, endophytes are known to produce their microbe-associated molecular patterns (MAMPs), which are not recognized by pattern recognition receptors (PRRs) of plants. The first line of defense in plants is the recognition of conserved molecules characteristic of many microbes. These elicitors are also known as MAMPs or pathogen-associated molecular patterns (MAMPs or PAMPs). Plants activate relatively feeble and temporary defensive responses as compared to many other pathogenic interactions [43]. Cord-Landwehr et al. [44] in their study reported that fungal endophytic microbes produce an enzyme chitin deacetylases, which then deacetylate chitosan oligomers that are not perceived by plants' receptors. Plants lead to the generation of reactive oxygen species (ROS) or oxidative burst as a plant defense scheme, endophytes defend themselves by producing a certain types of metabolites, that possesses antioxidants activities such as catalases (CatA), superoxide dismutases (SODs), glutathione-S-transferases (GSTs) peroxidases (POD), and alkyl hydroperoxide reductases (AhpCs) [44].

Endophytes modulating the genotypic and phenotypic expression of host plants against various stresses

Increase in resistance to biotic stresses

Endophytes constitute an important group of widespread, diverse, and mesmerizing plant symbionts, living asymptomatically within the host tissues [45,46] and have the potential to provide defense against a variety of pathogens via the elicitation of different plant responses [8]. When the plant is exposed to different environmental stresses, they initiate the signal mechanism that positively persuades the expression of the stress-responsive genes that enhances the deposition of callose, and pre-invasion defense. Endophytic microbes significantly modulate stress by down regulation of abscisic acid (ABA). Though, ABA affects negatively, by giving signals that elicit systemically acquired resistance (SAR). Among the phytohormones, GA is synthesized inside the plant and endophytes impede the inhibitory effects of DELLA proteins over the plant-growth promoting signals (Figure 1). Many foliar endophytic microbes are well known to regulate the expression of the host gene, affecting host defensive pathways and the physiological response of the host plants [47]. Salicylic acid and JA are two different phytohormones that are known to play an important role against pathogen attacks via the activation of plant defense systems (Figure 1) [48]. Many metabolomics studies conducted in the recent past have confirmed that endophyte genes associated to particular metabolites are implicated in PGP by the production of phytohormones like auxins, GA, and other regulatory chemicals, that increases plant accessibility for nutrients, like nitrogen (N), potassium (K), and phosphorus (P) [11,35,36]. Waqas et al. [49] in their study reported that gibberellin-producing endophytes are known to increase the host's resistance against the intruders through JA and SA pathways. Mitogen-activated protein kinase (MAPK) cascades are highly conserved regulators of various cellular processes, like differentiation, growth, proliferation, stress responses, and death. These protein cascades play a vital role in a variety of abiotic and biotic stress responses. Among microbial, particularly bacterial endophytes are reported to synthesize a variety of novel organic compounds and antifungal metabolites, with a wide spectrum of antimicrobial activity against different nematodes, and plant pathogenic microbes. Endophytes ability to defend host plants from various damages and diseases imposed by pathogenic microbes encourages the research to unravel the primary mechanism [50]. Gao et al. [51] have reviewed
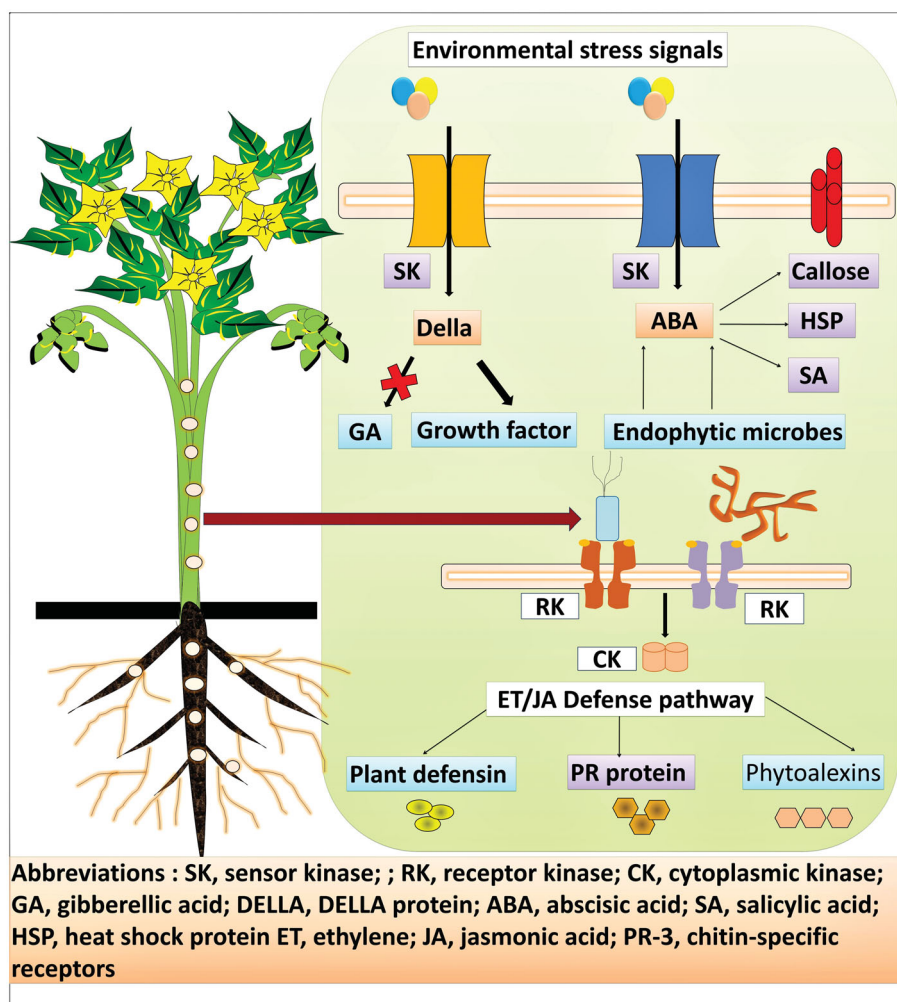
Figure 1. Remediation of abiotic and biotic stress by endophytic microbes. Environmental stress signals positively excite the expression of stress responsive genes, by increasing callose deposition, and pre-invasion defense. Endophytic microbes display the host plant's defensive responses against plant pathogens by the early detection of plant pathogens by cell surface receptor kinase (RK) and followed by cytoplasmic kinases (CK) mediated intercellular response that triggers ET/JA signaling pathway. ABA negatively affects a signal that triggers systemic acquired resistance (SAR) and endophytes modulate stress through down-regulation of ABA. Gibberellins produced by the endophytes or the plants hamper inhibitory effect of DELLA proteins over plant growth promoting signals.

and broadly proposed three special types of protective communications between endophytes and pathogens in plants, namely: (i) direct inhibition, wherein the defense is mainly confined and presented antibiosis (production of secondary metabolites as antifungal, antibacterial, and nematicidal compounds), (ii) indirect inhibition is innate plant defense (ISR and SAR) pathways are elicited, and (iii) occupation of ecological niches. Endophytic microbes colonize host plants more rapidly than consistent pathogens which often lead to exhaustion of nutrient resources [50]. A very recent study conducted by Jiao et al. [52] showed positive biocontrol against tobacco powdery mildew disease in tobacco by application of the beneficial endophyte *Bacillus amyloliquefaciens* YN201732 by involving systemic resistance mechanisms. Halecker et al. [53]

reported a fungal endophyte, *Hypoxylon rubiginosum* with promising biocontrol potential against ash dieback disease (*Hymenoscyphus fraxineus*), by producing phomopsidin, an antifungal metabolite. The study conducted by Liu et al. [54] isolated an antifungal protein from the wheat endophytic bacterial strain *Bacillus subtilis* EDR4 which inhibits the growth of: *Fusarium oxysporum* f.sp. *vasinfectum*, *F. graminearum*, *G. graminis* var. *tritici*, *B. cinerea*, and *R. cerealis*, and *Macrophoma kuwatsukai*.

Endophytic bacteria *Bacillus mojavensis* and *B. cereus* colonizing rice (*Oryza sativa*) exhibited antimicrobial activity against the fungal pathogens of rice: *Fusarium proliferum*, *Fusarium verticillioides*, *F. fujikuroi*, *Magnaporthe salvinii*, and *M. grisea* [55]. Current study has reported the positive role of the endophytic bacterium *Pseudomonas*

putida BP25 which was associated with the roots of black pepper. This bacterium suppresses the growth of various phytopathogens like: *Pythium myriotylum*, *Phytophthora capsici*, *Athelia rolfsii*, *Rhizoctonia solani*, *Gibberella moniliformis*, *Colletotrichum gloeosporioides*, and parasitic nematodes, such as *Radopholus similis*, by producing a variety of VOCs [56]. The study conducted by Gond et al. [57] used two endophytic bacteria strains *Bacillus subtilis* and *B. amyloliquefaciens* for colonizing seeds of *Zea mays* were observed to inhibit the growth of the fungus *Fusarium moniliforme* by producing antifungal lipopeptides. For the very first time, Etminani and Harighi [58] in their study reported that the endophytic bacteria *Bacillus*, *Pantoea*, *Pseudomonas*, *Stenotrophomonas*, and *Serratia*, isolated from wild pistachio showed positive biocontrol of the phytopathogenic bacterial strains *Pseudomonas tolaasii* and *Pseudomonas syringae*. Similarly, Hashem et al. [13] in their study reported the biocontrol potential of *Bacillus subtilis* (Bera 71) by inhibiting the growth of *Macrophomina phaseolina* causing (tassi) goid disease in the mung bean by producing iturin an antifungal lipopeptide. Recently, Singh et al. [59] in their studies showed that endophytic bacteria associated with *Ziziphora capitata* and *Hypericum perforatum* belonging to *Achromobacter*, *Arthrobacter*, *Bacillus*, *Enterobacter*, *Erwinia*, *Pantoea*, *Pseudomonas*, *Serratia*, and *Stenotrophomonas*. However, their study concluded that *H. perforatum*, when compared with *Z. capitata*, had antibacterial activity and supported the colonization of more bacterial communities with antagonistic activity. Rosmarinic acid provides dynamic antimicrobial activity against a wide range of microbial communities colonizing the rhizospheric area of the soil was induced in the exudates produced by the hairy root cultures of sweet basil following a challenge by *Pythium ultimum* [60] (Table 1). Most of the endophytic formulation products for growth enhancement and biocontrol activity are based on *Bacillus* and *Trichoderma* strains due to seed formulation issues, although *Pseudomonas*-based products have also been commercialized in recent years [70].

Increase in resistance to abiotic stresses

Pragmatic consistency of microbial endophytic community patterns is believed to support the notion of fundamental principles and the forces responsible for driving the community composition and formation. While preliminary endophytic microbiome structures and their composition are similar to their respective seed banks, including air and soil, they become more plant-specific as the plant grows and develops [71]. Many abiotic stresses like drought stress, salinity, extreme temperatures, alkalinity, oxidative stress, and heavy metal toxicity are threats to agricultural ecosystems. Endophytes adopt various molecular mechanisms to mitigate the effects of stress [56]. The environmental stress signals perceived by various membrane receptors like G-protein coupled receptors (GPCRs), receptor-like kinases (RLKs), ion channels, and histidine kinases. This brings changes to the cytoplasmic Ca^{2+} levels and produces secondary messengers like ROS, ABA, inositol phosphates (IPs), etc. These secondary signaling molecules initiate the phosphorylation of protein cascade by various kinases like protein phosphatases, protein kinases CIPKs, and CDPKs. They further activate different transcription factors like bZIP, DREB/CBF, MYC/MYB, AREB/ABF, WRKY, etc. through the events of phosphorylation and de-phosphorylation. These transcription factors lead to the activation of various stress-responsive genes which include expression of genes that encode for heat shock proteins (HSPs), lipid transfer protein (LTP), late embryogenesis abundant (LEA) protein, antioxidants, ion transporters, and osmolytes, etc. Finally, resistance against stress conditions is generated and the damages are being repaired [1,72]. Therefore, stress tolerance in plants is primarily induced by the generation of free radicals like ROS, and production of anti-stress metabolites via expression of stress-responsive genes [7,12]. Bacterial endophytes, plant growth potential is explained through several proposed mechanisms. Several endophytes help to increase accessibility to nutrients, e.g. nitrogen and phosphorus or metals, or produce metabolites that could regulate plant growth development and defense responses, such as the well-known plant hormones like auxins, GA, ABA, cytokinin, ET, SA, SLs, brassinosteroids, and jasmonates [12,73] (Figure 1). Many endophytic microbes produce defensive molecules, like proline, carotenoids, and melatonins which play a defensive role against abiotic stress. The action is not localized, in fact endophytic microbes may also produce volatile organic carbon (VOC), which is involved in the initial recognition/interaction by the host plant and can also be precursors of main signaling molecules. A very interesting example is the accumulation of melatonins, which happen in grapevines, when inoculated with *Bacillus amyloliquefaciens* neutralizing the adverse effects of drought, cold, and salinity stress [74]. This bacterial strain also reduces the up-regulation of serotonin *N*-acetyl-transferase and tryptophan decarboxylase transcription. Another example includes the production of carotenoids in the host plant as precursors of phytohormones, ABA, or detoxifying enzymes, such as ACC deaminase, that control ET production and subsequently the impairment elicited upon stress. Certainly, melatonin is a strong antioxidant that

Table 1. Role of endophytic microbes in biotic stress alleviation (ND: no data).

S.No.	Bacterial strain	Isolation source	Test plant	Reported roles	Experimental setup	Secondary metabolites	Methods used for purification and identification of compounds	References
Role of bacterial endophytes on biotic stress tolerance								
1.	Bacillus subtilis (BERA 71)	Roots of Talh tree	Mung bean (Vigna radiata)	Depicted plant growth promoting as well as biocontrol activity against Macrophomina phaseolina (causes gold disease).	Dual plate culture assay and pot experiment	Reported production of an antifungal compound Iturin (antifungal lipopeptide) production	Thin layer chromatography (TLC)	[61]
2.	Bacillus subtilis EDR4	Wheat roots	ND	Suppresses growth of Fusarium oxysporum, F. gramineraum, Macrophoma kuwatsukai, etc.	Dual plate culture assay	Antifungal protein E2	Anion exchange and PAGE hydrophobic interaction chromatography	[62]
3.	Bacillus amyloliquefaciens and B. subtilis	Maize (Zea mays) seeds	ND	Inhibit growth of Fusarium moniliforme. Upregulation of pathogenesis related genes	Dual plate culture assay	Production of lipopeptides	MALDI-TOF	[57,63]
4.	Bacillus oryzicola YC7007	Rice (Oryza sativa) seeds	Oryza sativa	Biocontrol bakane disease of rice caused by Fusarium fujikuroi	Pot trails and nursery (greenhouse)	ISR and antibiotic production	ND	[64]
5.	Bacillus mojavens and B. cereus	Rice (Oryza sativa)	Oryza sativa	Suppresses growth of rice fungal pathogen Fusarium fujikuroi, F. verticilliodes, F. proliferum, Magnaporthe salvinii, M. grise	Dual plate culture assay	ND	ND	[65]
6.	Bacillus subtilis C9	ND	Zoysia grass	Inhibit colonization of Rhizoctonia solani in Zoysia grass and enhances plant growth. Triggers ISR of plant	Dual plate culture assay and pot experiment	Isomer of acetyl butanediol	^{1}H, ^{13}C NMR, and mass spectroscopy analysis	[66]
7.	Pseudomonas stutzeri E25 and Stenotrophomonas maltophilia CR71	Physalis ixocarpa	Tomato (Lycopersicon esculentum)	Inhibit growth of fungal pathogen Botrytis cinerea	Pot experiment	Production of VOCs	Phase micro-extraction gas chromatography mass spectroscopy GC–MS	[67]
8.	Bacillus, Pseudomonas, Stenotrophomonas, Pantoea, and Serratia	Leaves and stem of Pistacia atlantica	ND	Biocontrol of Pseudomonas tolaasii and P. syringe	Dual plate culture assay	Produces siderophores, protease and HCN	ND	[58]
Role of fungal endophytes on biotic stress tolerance								
9.	Trichoderma and Fusarium	Rice (Oryza sativa)	Rice (Oryza sativa)	Biocontrol of Meloidogyne graminicola nematode causing root rot disease in rice	Pot experiment	ND	ND	[68]
10.	Trichoderma gamsii YIMPH30019	Roots of Panix notoginseng	Panix notoginseng	Shows positive biocontrol activity against Fusarium flocciferum, Phoma, Scytalidium, lignicola, Epicocum nigrum	Dual plate culture assay and pot experiment	Production of VOCs like ketones, dimethyl disulfide, methanethiol, dibenzofuran, etc.	GC–MS	[69]

increases CuZn SOD, ascorbate peroxidase, Fe-SOD, and thylakoid-bound catalase activities [11,74]. To achieve its beneficial effect, melatonins can be used in exogenous applications. However, melatonin-producing endophytic microbes may have long-term effects on the endogenous melatonin levels in plants once they enter inside plant tissues. Waqas et al. [49], in their study, reviewed that a cross-talk exists between ABA-mediated stomatal movements. The biosynthesis of ABA and ABA-mediated signaling pathways are generally activated by the presence of useful microbes populating the plant endosphere. These microbe mediated pathways contribute toward plant health under salt stress conditions. The upregulation of different genes including aquaporins and dehydrins plays a role in mitigating the abiotic stresses in rice plants when inoculated by the endophytic fungus *Trichoderma harzianum* [61,75]. *Bacillus subtilis* (BERA 71), an endophytic bacterium improves the salt tolerance [76] and AM colonization improves drought tolerance [77] in chickpea by regulating plant defense mechanisms.

Some plant species can grow in heavy metal and pesticides polluted soils. Plants exhibit several physiological/genetic strategies to deal with varied soil contaminants, including those derived from anthropogenic activities. A significant plant mechanism involved in phytoremediation is the recruitment of beneficial bacterial endophytes. More importantly, some bacterial endophytes have evolved with the ability to resist or tolerate high concentrations of contaminants that also display PGP traits [9]. Endophytes alleviate metal phytotoxicity via extracellular precipitation, biotransformation, intracellular accumulation, and the
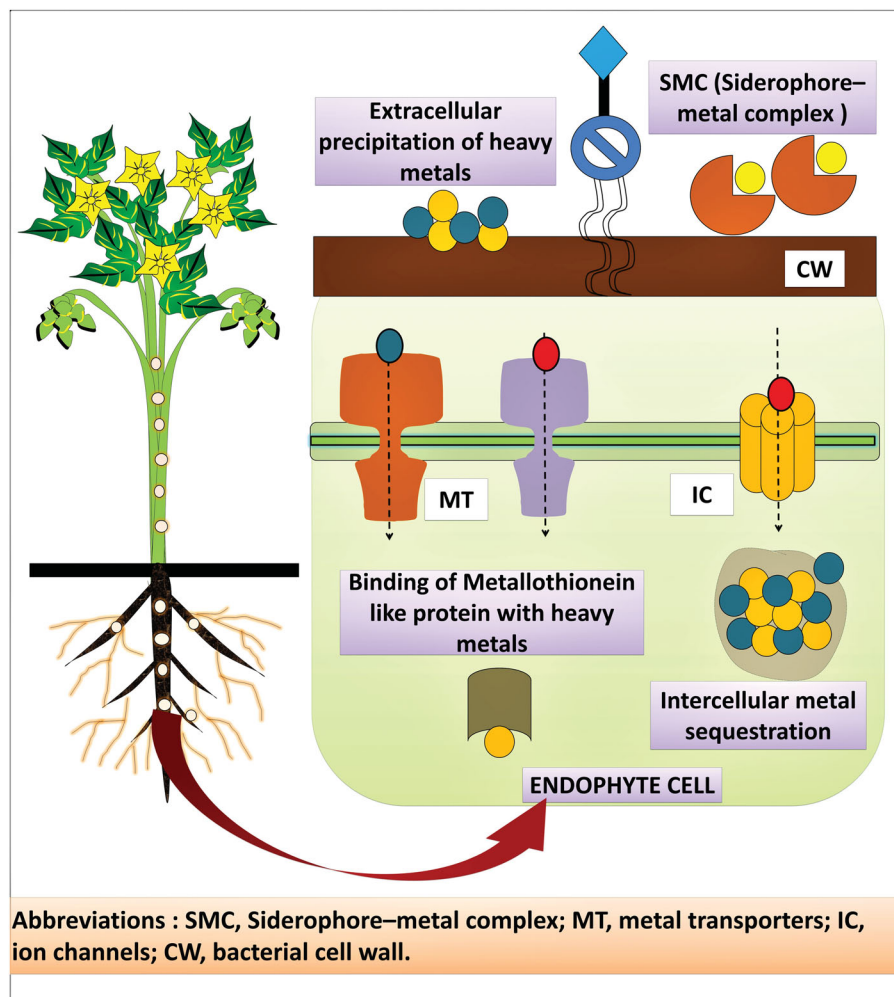
Figure 2. Endophyte mediated phytoremediation. Endophytes utilize the following mechanisms for microbial assisted bioremediation: (i) sequestration of toxic heavy metals by intracellular metal binding proteins and cell wall components or by peptides such as phytochelatins and metallothioneins (MT) along with compounds such as a fungus produces hydroxamate siderophores and bacterial siderophores which are generally catecholate, (ii) alteration of biochemical pathways to block metal uptake, (iii) conversion of metals to innocuous forms by enzymes, and (iv) reduction of the intracellular concentration of metals using precise efflux systems.

sequestration of toxic metal ions into nontoxic or less toxic forms [78] (Figure 2). The reported metal-resistant endophytic microbes belong to various taxa; in fungi including *Alternaria*, *Mucor*, *Aspergillus*, *Phoma*, *Microsphaeropsis*, *Steganosporium*, and *Peyronellaea*. In bacteria, these includes *Bacillus*, *Pseudomonas*, *Arthrobacter*, *Paenibacillus*, *Curtobacterium*, *Enterobacter*, *Clostridium*, *Leifsonia*, *Staphylococcus*, *Xanthomonadaceae*, *Stenotrophomonas*, *Sanguibacte*, and *Microbacterium* [79,80]. In a recent study, many endophytic bacteria were isolated from the Zn/Cd hyper-accumulator plant *Sedum plumbizincicola*, and among them only five isolates exhibited PGP, were selected for further study [81]. These PGP activities include the production of IAA, phosphate, and phosphorus solubilization, production of siderophores, and ACC deaminase activity. Additionally, these strains showed high tolerance against heavy metals like Pb, Zn and Cd. The result of the inoculation of this heavy metal-tolerant ACC-deaminase producing bacterial strains on the growth of *S. plumbizincicola* and its uptake of Pb, Zn, and Cd in heavy-metal contaminated soils were also tested in pot-trials. *Bacillus pumilus* strain E2S2 drastically increased the Cd uptake by plants, and further increase the plant shoot and root length, as well as dry and fresh biomass as compared to non-inoculated plants. Thus, an endophytic bacterial strain isolated from *S. plumbizincicola* enhances its phytoextraction ability and, at the same time, promotes plant growth. The study conducted by Kong et al. [82], showed the effect of the *Sinorhizobium meliloti* strain CCNWSX0020, the rhizobial endosymbiont on the host plant *Medicago lupulina* under copper stress. This particular strain enhances the nitrogen content as well as the growth of the plant. Additionally, rhizobial symbiosis also promotes the accumulation of copper in roots and shoots of the plant. Therefore, many genes, that are involved in antioxidant responses, were also up-regulated in plants when treated with the endophytic bacterium in the presence of high levels of copper. Endophytic microbes have the potential to synthesize different "protective" compounds such as antioxidants, carbohydrates, and proline to cope up with abiotic stress conditions [83]. Hence, *S. meliloti* not only promotes metal uptake and plant growth, but also induces the plant antioxidative defense responses during copper stress. Studies have reported the accumulation of proline in pepper (*Capsicum annuum* L., Solanales: Solanaceae) plants when inoculated with two endophytic bacterial strains *Bacillus* spp. and *Arthrobacter* sp. under drought stress condition [84]. The study conducted by the Damodaran et al. [85] showed that when gladiolus plants were inoculated with the endophytic bacterial strains: *Bacillus subtilis* strain CSR-G-1, *B. pumilus* CSR-B-2, *B. marisflavi* CSR-G-4, *B. saffensis* CSR-G-5, *B. thuringiensis* CSRB-3,

and *B. cereus* CSR-B-1 plants can tolerate high sodium stress by increasing phenylalanine lyase, SOD, peroxidase, and catalase enzyme activity (Table 2). Also, there are some research deficiencies in this area that need to focus upon are: (i) less information is available about phytoremediation by endophytic fungi, all the previous studies were mainly focused upon endophytic bacteria assisted phytoremediation. (ii) Though these endophytes and their associated host plants can degrade a broad range of contaminants, most of the compounds are often degraded slowly or some are not degraded at all. In order to utilize endophytes in this technology, more engineered endophytes with biodegradative potential should be identified and used [8].

Modulation of the plant's immune system by endophytes

At present, one of the biggest challenges is to find and track the mechanism of how the endophytic microbes flourish inside the host plant. Plants usually establish interactions with microbes that have detrimental or beneficial effects on health and fitness. It has been stated that symbiosis with endophytic microbes confers additional defensive mechanisms in the host plants [1,42,95]. More precisely, these symbiotic organisms modulate the plant hormonal pathways implicated in defense, to colonize host plants, and also to establish symbiosis [95,96]. Endophytes are an active source of bioactive compounds such as alkaloids and these compounds are well known to confer protection to the host plant. The association between plants and microbes can have significant consequences on the host's immune system [97]. Many species of mycorrhizal fungi and rhizobacteria induce certain types of systemic defenses, known as MIR (mycorrhiza-induced resistance) and ISR, respectively [1,42,95]. The term "Induced Systemic Resistance" is a generic term for the induced state of resistance in plants triggered by biological or chemical inducers, which protects non-exposed parts against future attacks by pathogenic microbes [42]. Piercing through to the host, endophytes have to cross the first line of highly sophisticated defenses of the plant immune system. This process involves the identification of conserved molecules, termed pathogen- or microbe-associated molecular patterns (PAMPs or MAMPs) [98]. Peptidoglycans, elongation factors TU (EF-Tu;elf18/26), lipopolysaccharides, flagellin (Flg;flg22), bacterial SOD, betaglycan bacterial cold shock proteins (RNP1motif), β-glucans from oomycetes, and chitin are the most worked upon MAMPs [98]. These MAMPs are recognized by specific receptor molecules present on the

Table 2. Role of endophytic microbes in biotic stress alleviation (ND: no data).

S.No.	Bacterial strain	Isolated from	Test plant	Stress condition	Reported roles	Experimental setup	Antioxidants/secondary metabolites	References
Role of bacterial endophytes in abiotic stress tolerance								
1.	Sinorhizobium meliloti strain CCNWSX0020	Root nodules of Medicago lupulina	Medicago lupulina	Heavy metal stress: copper stress	Enhances Medicago lupulina growth in copper contaminated soil	Petri plate and pot trails	ND	[86]
2.	Sinorhizobium meliloti CCNWSX0020	Root nodules of Medicago lupulina	Medicago lupulina	Heavy metal stress: nickel and cobalt stress	Enhances Medicago lupulina growth in nickel and cobalt contaminated soil	Pot trails	ND	[87]
3.	Enterobacter sp. strain PDN3	Stem of Populus deltoides nigra	Populus deltoides nigra	Chemical pollution: TCE contamination in ground water	Phytoremediation of TCE from groundwater	Field trials	ND	[88]
4.	Bacillus subtilis (BERA 71)	Talh tree (Acacia gerrardii)	Chickpea (Cicer arietinum)	Salinity stress	Enhanced plant biomass, production of photosynthetic pigment under salinity stress condition	Pot experiment	Increase in levels of ROS and lipid peroxidation in plants under salinity stress conditions	[77]
5.	Burkholderia cepacia J62, Microbacterium JYC17	Leaves of Mosla oxydans	Rape (Brassica napus)	Heavy metal stress	Increases growth, copper uptake antioxidant activity, and bacterial community structure in Brassica napus	Green house and field trails	Increases the content of non-enzymatic antioxidant like ASA, and GSH thereby reduction of oxidative stress caused by heavy metals and the content of POD, and TBARS	[89]
6.	Bacillus subtilis strain CSR-G-1, B. pumilus CSR-B-2, B. marisflavi CSR-G-4, B. saffensis CSR-G-5, B. thuringiensis CSRB-3, and B. cereus CSR-B-1	Gladiolus plants	Gladiolus plants	Sodium stress	Higher number of spike/florets and marketable spikes	Pot experiment	Increasing phenylalanine lyase, SOD, POD, CAT, antioxidant enzyme activity	[85]
7.	Bacillus spp. and Arthrobacter sp.	Seeds of pepper	Pepper (Capsicum annuum)	Drought stress	Increases growth of Capsicum annuum plant under drought stress condition by proline accumulation and having strong ACC deaminase activity	Pot experiment	Accumulation of proline	[90]
Role of fungal endophytes in abiotic stress tolerance								
8.	Exophila pisciphila	Roots of Zea mays	Zea mays	Cadmium stress	Decreases in cadmium phytotoxicity	Tissue culture	Enhanced antioxidant enzyme activity	[91]
9.	AMF	Talh tree (Acacia gerrardii)	Chickpea (Cicer arietinum)	Drought stress	Increases plant growth under drought condition by enhancing RWC and MSI	Pot experiment	Up regulation of antioxidant enzyme system, prevention of ROS accumulation and oxidative stress under drought stress conditions	[77]
10.	Curvularia protuberata	Dichanthelium lanuginosum	Dichanthelium lanuginosum	High temperature	Increases high temperature tolerance in Dichanthelium lanuginosum growing in Yellowstone park	Field condition	ND	[92]
11.	AMF	Jatropha curcas L.	Jatropha curcas L.	Salt stress	Increases plant growth under salt stress condition in Jatropha curcas L. by accumulation of proline, chlorophyll, and sugar	Pot experiment	Accumulation of proline, chlorophyll, and sugar. Increased glomalin production	[93,94]
12.	AMF	Jatropha curcas L.	Jatropha curcas L.	Salt stress	Alleviate deleterious effect of Na_2SO_4 salt stress condition in Jatropha curcas L. by improved morphological, physiological, and biochemical parameters like plant biomass, RWC, chlorophyll, sugar, proline, electrolyte leakage, and lipid peroxidation in Jatropha curcas L.	Pot experiment	Enhanced antioxidants enzymes activity SOD, POD, CAT, etc.	[15]
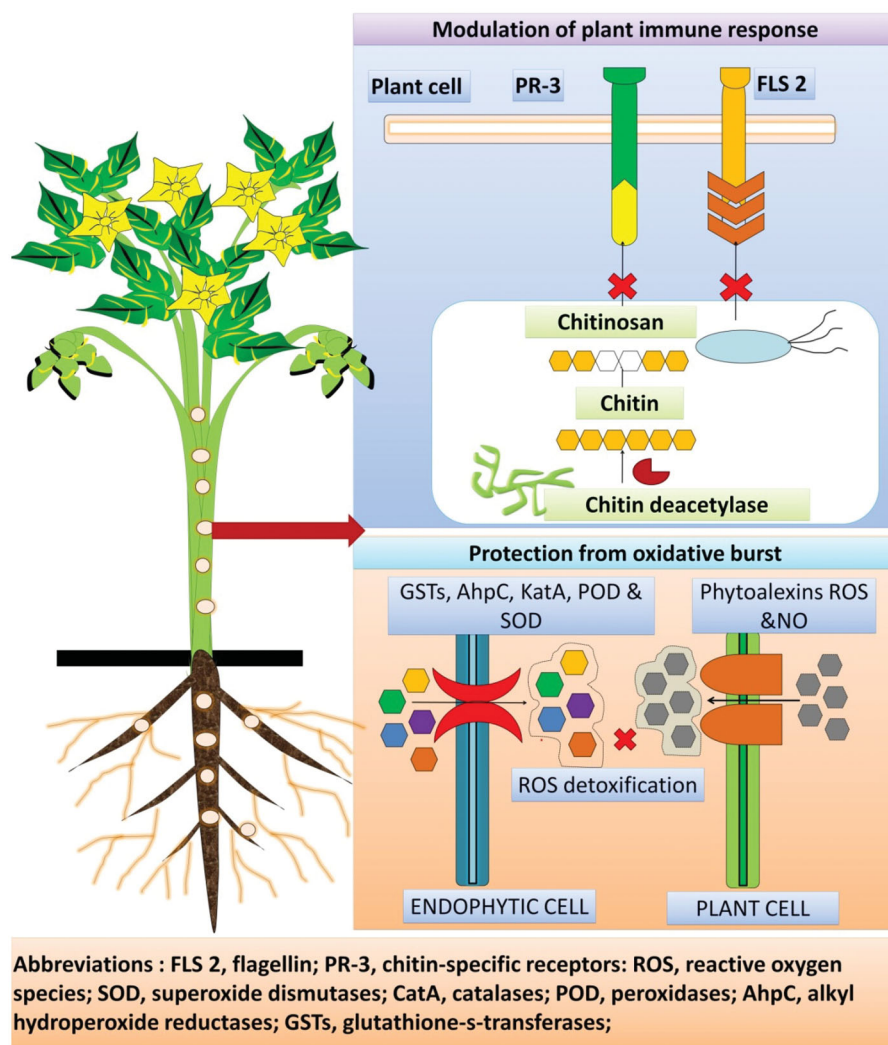
Figure 3. The action mechanism of endophytes in the modulation of plant immune response and protection from an oxidative burst. Endophytic fungi modulates plants immune system by producing chitin deacetylases, for deacetylation of chitosan oligomers. This prevents them from being recognized by (PR-3) chitin specific receptors of the plant that recognize chitin oligomers. Perception of flagellin (FLS 2) from endophytes also differs from plant pathogens. Various osmolytes and ROS or reactive oxygen species, produced by plants during the stress conditions, are generally neutralized by the enzyme produced by the endophytes such as CatA, POD, GSTs, SOD, and AhpC.

surface of plant cells and are termed as PRRs. Similar to microbial endophytes, the fungal endophytes, also have specific receptors, the chitin-receptors (PR-3) recognize chitin oligomers formed on fungal cell wall (Figure 3) [99].

Endophytes are also known for their mechanisms to protect themselves from plant defense mechanisms. For example, Cord-Landwehr et al. [44], in their study, stated that fungal endophytes either mask the chitin by deacetylating it into chitosan via chitin deacetylases enzyme or covering it into other molecules, hence, preventing themselves from being recognized. Studies also suggest that endophytic bacteria produce their MAMPs, which are either not recognized by PRRs present on the cell surface of the host plants or plants prompt a weak defensive response compared to pathogenic interactions [43]. Similarly, Trdá et al. [100] in their study concluded

that grapevine exhibited a different type of perception in response to flagellin (FLS 2) when encountered with two different types of endophytes such as *Burkholderia phytofirmans* and bacterial pathogens *Pseudomonas aeruginosa* and *Xanthomonas campestris*. In the case of the production of ROS, as a plant defense system, endophytes defend themselves by generating different antioxidant enzymes [101] (Figure 3).

Omics approaches for better understanding of plant–endophyte interactions

A comprehensive and detailed understanding of plant–endophyte interactions is important to realize the value of these microbial communities, which are sources of industrially important enzymes, novel

metabolites, and stress relievers of the host plant. However, several valuable facets of endophytes are still unknown [16,102]. Modern high-throughput genomic studies have revolutionized the microbiome research by uncovering the gray areas of endophytism, permit the exploration of endophytes, enable the sequencing of a larger number of microbes and inspire *in depth* analyses of microbial communities by taxonomic classification, phylogeny, and evolutionary studies [103]. Whole genome analysis of endophytic microbes translates all the relevant information that is a requisite for an organism to nurture under favorable and harsh conditions depending on the plant's habitats. Along with the house-keeping machinery, these microbial genomes also translate genes that are essential for their plant beneficial properties and endophytic lifestyle. Detailed and comprehensive knowledge of the mechanisms of host infestation and the role of endophytes could be used to improve agricultural management in terms of biocontrol, PGP, and phytoremediation [9,10,16]. Complete genome analysis of endophytes revealed the genetic traits that directly or indirectly influence the colonizing preferences as well as different bioactivities. This also helps in the identification of specific genes involved in the mechanism of PGP, antibiotic production, antibiotic resistance, endophytic secretory system, insertion elements, transport system, surface attachment, and other related metabolic mechanisms [104]. The whole-genome also provides deep insights into a better understanding of the evolution and ecology of endophytes. Fungal endophytes belonging to order sebacinales have gained considerable attention due to their stress tolerance and PGP potential [105]. *Pirifomospora indica* (order sebacinales) represent as a model for studying symbiotic interactions. Whole-genome sequencing analysis of *P. indica* has revealed its potential as a plant probiotics agent. The presence of genes encoding hydrolases, *N*-acyl homoserine lactone synthases, hyper adherence factors, and fusaric acid resistance proteins, etc., emphasize the biotechnological potential of the endophytic bacterium *Pantoea ananatis* [106]. Therefore, the whole genomes of many fungal and bacterial endophytes have been sequenced (Table 3), and this list is becoming further populated. These available genomes of endophytic microbes serve as the model systems to study microbe–microbe and plant–microbe interactions. Further, individual genome sequences improve the data analysis in meta omics (microarray, core microbiome, NGS, comparative genomics, metagenomics, proteomics, metabolomics, metatranscriptomics, and fluxomics) studies of plant-associated microbes. The comparative genomic

sequencing analysis provides insight into endophytic behavior [104,130].

Next-generation sequencing analysis was used to reveal the unculturable and culturable bacterial endophytes in *Aloe vera*, for estimating its microbial range and to elucidate the colonization pattern of these microbes inside their host [19]. Metagenomic approaches along with *Insilco* analysis will provide novel phylogenetic and functional insight about the endophytes [131,132]. The study conducted by Tian et al. [131] investigated the comparative community structure and the functional attributes of tomato root-associated microbiomes in healthy and root-knot nematode, infected roots. The study conducted by Delmotte et al. [133] and Rastogi et al. [134] used community proteogenomics for identifying the exclusive traits of phyllosphere bacteria colonizing *Arabidopsis* leaf. One should know the limitations of NGS technologies before using it for experimental studies. Main limitations of genome sequencing studies are the presence of a high ratio of sequences with no homolog in public databases. Metagenomic studies of the sample collected from the same place would overcome the limitation to a great extent [135].

Microarray-based techniques have set the current genome-based studies with the tools for endophyte gene profiling and studies are related to specific gene expression, investigation of symbiotic host plant communications, and many others for transcriptomic analysis. The study conducted by Felitti et al. [136] described the potential of *Neotyphodium* and *Epichloe* endophyte cDNA microarrays (Endochip™ and Nchip™ microarrays) for transcriptome analysis. Microarray analysis of the transcriptome of endophytic-*Pseudomonas* infected *Arabidopsis* revealed the downregulation of ET responsive genes whereas genes related to nodule formation and plant hormone production were upregulated [137]. For studying, symbiotic interactions the dual genome Symbiosis Chip-based tool has been used. This tool allows a simultaneous understanding of endophyte host interactions and the expression of genes in both the partners of the association [23]. The study conducted by Barnett et al. [23] used a Symbiosis Chip-based tool, Affymetrix Gene Chip to study the synchronize differentiation of *Sinorhizobium meliloti* and its host plant *Medicago truncatula* during nodule formation. The expression profiling of *S. meliloti* grown with the host plant signaling molecule luteolin is defined in rich and minimal media of strains modified in the expression of key regulatory proteins (RpoN, NodD1, and NodD3). A similar study was conducted by Güldener et al. [24] for profiling the gene expression of

Table 3. List of endophytes whose whole genomes have been sequenced (recent data 2017–2019) (ND: no data).

Endophytic microbe	Name	Isolated from	Reported role	References
Fungal endophyte	Arthrinium phaeospermum	Bambusa pervariabilis and Dendrocalamopisis grandis	Pathogenic fungus infecting plants, animals, and humans	[107]
	Amphirosellinia nigrospora JS-1675	Pteris cretica	Plant pathogenic fungus	[108]
	Penicillium brasilianum strain LaBioMMi 136	Melia azedarach	Production of bioactive secondary metabolites like alkaloids, insecticidal meroterpenes, Brasiliamides, penicillic acid, and spirohexalines, which are novel inhibitors of bacterial undecaprenyl pyrophosphate synthase	[109]
	Fusarium tricinctum	Taxus baccata	Source of various secondary metabolites like antifungal lipopeptides	[110]
	Gaeumannomyces sp. strain JS-464	Phragmites communis	Source of secondary metabolites which showed significant no reduction activity	[111]
	Fusarium solani JS-169	Morus alba (Mulberry)	Antifungal activity	[112]
Bacterial endophyte	Burkholderia stabilis	Ginseng	Produces antimicrobial compounds against root rot disease in ginseng.	[113]
	Pantoea sp., strain CCBC3-3-1	Cotinus coggygria branch	Biocontrol activity against plant pathogens	[114]
	Bacillus velezensis PG12	Apple fruit	Good candidates for use as biopesticides, biofertilizers, biostimulators, and potential biocontrol agent improves crop yield and quality. Produces secondary metabolites with antimicrobial activity.	[115]
	Kosakonia radicincitans UYSO10	Sugarcane (Saccharum officinarum)	Promotes plant growth promotion by nitrogen fixation and phytohormone production	[116]
	Pseudomonas spp.	Grapevine tissue	Showed antagonistic activity against Grapevine trunk disease pathogens	[117]
	Microbacterium	Switch grass	ND	[118]
	Bacillus velezensis	Maize	Antimicrobial activity against human and fungal pathogens. Produces biofilm, cyclic lipopetides, ISR response in plants.	[119]
	Microbacterium hydrothermale	Mirabilis jalapa	Antimicrobial activity against Pseudomonas, Candida albicans, Escherichia coli, Staphylococcus aureus, and Microbacterium hydrothermale.	[120]
	Bacillus pumilus SCAL1	Solanum lycopersicum L.	Promotes plant growth promotion and high temperature stress tolerance	[121]
	Chryseobacterium indologenes PgBE177	Panax quinquefolius	Antimicrobial activity against Pseudomonas syringae. Presence of bacteriocin gene cluster and enhances plant growth.	[122]
	Salinicola tamaricis	Tamaxrix chinensis	Tolerate heavy metal stress like nickel, copper, manganese, and lead	[123]
	Streptomyces cavourensis	Cinnamomum cassia	Produces cytotoxic and antimicrobial bioactive metabolites	[62]
	Klebsiella variicola and Klebsiella pneumoniae	Sugarcane	Having essential genes for plant growth promotion. Detoxification and nitrogen fixation	[124]
	Herbaspirillum sp. strain WT00C	Tea (Camellia sinensis)	Ability to reduce selenite/selenate into red elemental selenium and many agronomics benefits	[125]
	Bacillus aryabhattai strain SQU-R12	Phoenix dactylifera L. Tea	Produces phytohormones and ACC deaminase enzyme	[126]
	Streptomyces sp. GKU 895	Sugarcane	Plant growth promoting activity and produces secondary metabolites	[127]
	Variovorax paradoxus KB5	Arabidopsis thaliana	Antagonistic activity against a phytopathogen, Pseudomonas syringae	[128]
	Pseudomonas stutzeri strain KMS55	Rice roots	High biological nitrogen fixation ability	[129]

Fusarium graminearum in vitro and in planta. Rädecker et al. [25] studied metabolic interactions in Cnidarian-Symbiodinium symbioses by using Aiptasia Model. Recently evolving endophytic core microbiome is responsible for defining functions within ecosystems, therefore, very few studies have been conducted on the endophytic core microbiomes of specific plants [21,138]. The study conducted by Munir et al. [20] has reported on the endophytic core microbiome of 24 different varieties of citrus growing in nine different regions of China using culture-dependent analysis and 16S rRNA gene sequencing. Kuźniar et al. [21], in their study, used a culture-independent approach for exploring the endophytic core microbiome of two varieties of

wheat (*Triticum aestivum* L. and *Triticum spelta* L.) which was reported for the first time. Meta proteomics and metabolomics help to identify proteins and metabolites respectively, resulting from co-metabolism of the host and, can be used as reliable biomarkers that represent the end products of metabolic interactions among the host plant and the microbe. Conversely, an indirect lysis method was used for isolating the total protein from endophytes under diverse stress conditions and protein fingerprints were obtained after 2,D-gel electrophoresis, which can be used to reveal the role of endophytes under diverse stress conditions [135]. Lery et al. [139] have investigated the molecular aspects of the *Gluconacetobacter diazotrophicus*–sugarcane interaction by using quantitative mass spectrometry based proteomic analysis. Therefore, in this study, more than 400 proteins were analyzed out of which 78 proteins were expressed differentially between the control cultures and bacterial–plant interaction model.

The combination of multi-omics approaches increases assurance in recognizing diagnostic and curative biomarkers as well as providing a testable hypothesis. Therefore, to investigate the evolving hypothesis generated as a result of these approaches and to demarcate mechanisms by which microorganisms influence the host, a highly convenient experimental system with a reduced complication to study communications between microbes and its host should be designed. Several studies have been conducted by different researchers using different omics techniques, for exploring the role of endophytes in producing novel bioactive compounds [28,140]. The modern omics-based techniques and approaches need to be explored to study endophyte biology along with their putative role in host ecology.

Endophytes are the treasure house of bioactive compounds

Metabolomic analysis has revealed that endophytes are the treasure house of bioactive compounds. Endophytes are well known for their bioactive metabolite production potential along with their contribution to plant health and fitness, protection against various stresses, enhancing the growth and productivity of plants, and their ability for xenobiotic degradation. The extraction of these metabolites from endophytic microbes is affected by many factors, such as their geographical location, the climatic conditions, and the different sample collecting seasons [141]. These endophytes have various implications in biotechnology, pharmaceutical, and drug discovery. The secondary

metabolites secreted by endophytic microbes are generally classified into different functional groups, like: flavonoids, alkaloids, chinones, steroids, benzopyranones, phenolic acids, saponins, quinones, tannins, xanthones, tetralones, and terpenoids [142]. These secondary metabolites include an array of compounds such as: insecticide azadirachtin [31], antibiotics [143,144], anti-cancer bis indole alkaloids [145,146], antimicrobial and anti-mycobacteria compounds [147], and biopesticidal compounds [140]. The study conducted by different scientists has focused upon the isolation and characterization of bioactive compounds from fungal endophytes [28,143,148–150] (Table 4). Endophytic bacteria, especially those associated with ethnomedicinal plants serve as the reservoirs of natural products and therapeutic compounds for their application as novel bioactive agents and the reduction of oxidative stress [151]. Endophytes also synthesize several extracellular hydrolases like: esterases, proteinase, cellulases, and lipases, to develop the resistance against different plant invasions [152]. Endophytes produce antibiotic compounds like: ampicillin, oxacillin, gallic acid, cefalexin, and catechin, and have bactericidal activities [153]. The symbiotic co-evolution between endophytes and plants has recognized a unique association that considerably influences the production of secondary metabolites, i.e. bioactive compounds in plants [46]. Interaction of endophytes with its host plant considerably influences the physiological action of the host plant; these changes comprise the activation of silent gene clusters that lead to the production of novel secondary metabolites. A bacterial endophyte *Pseudonocardia* induces the production of artemisin in an *Artemisia* plant by inducing the expression of cytochrome P_{450} oxidoreductase genes and cytochrome P_{450} monooxygenase [27]. Taxol is one of the most-studied bioactive compounds produced by the fungal endophyte *Taxomyces andreanae* with anti-cancer activity this endophyte colonizes its host, yew plant. The genomes of this endophyte do not confirm any substantial sequence homology with genes involved in the biosynthesis of taxol found in *Taxus* spp. This further indicates that this endophytic fungus might have autonomously developed the biosynthesis pathway of taxol [26]. The hypothesis put forward by Howitz and Sinclair [154] states that clusters of a homologous gene present in microbes and the plant may become cross-activated by stress-induced molecules from endophytes or host plants under certain conditions. Several reports on the distinct effect of endophytic microbes on host plant secondary metabolite production are available, but the mechanisms involved are unidentified. There are a number of bioactive

Table 4. Bioactive compounds produced by fungal endophytes (ND: no data).

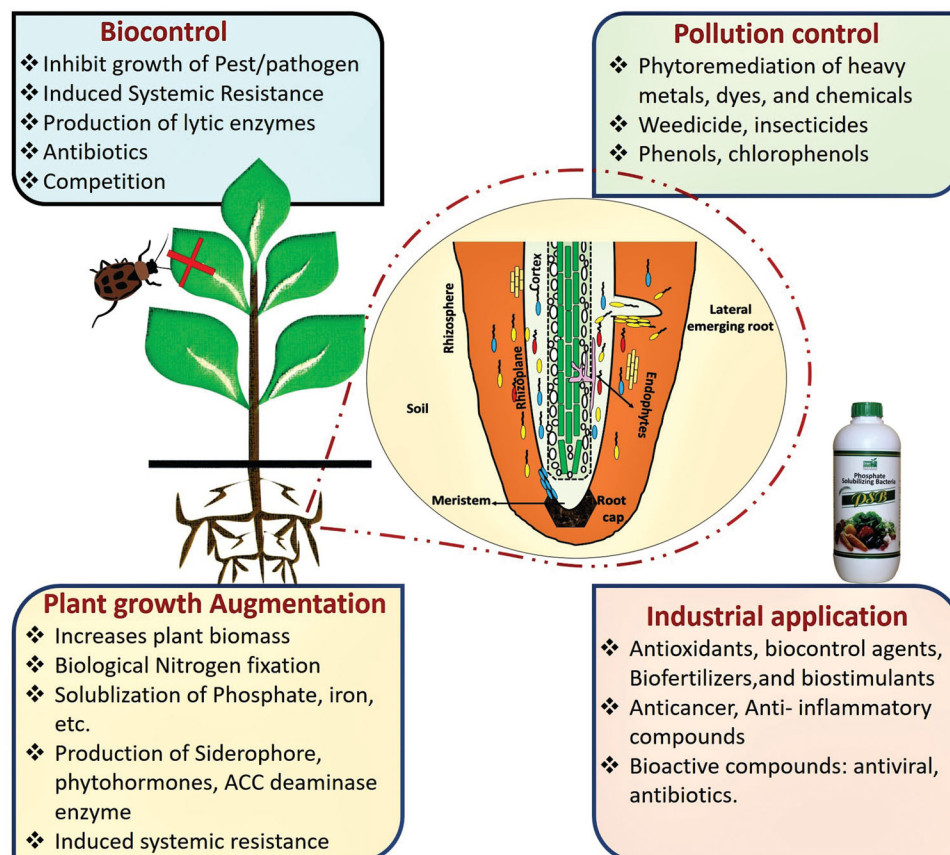| S.No.	Bioactive compound	Fungal endophyte	Host plant	Reported roles	Methods employed	References
1.	Taxol	*Taxomyces andreanae*	*Taxus brevifolia*	Anticancer	C14 labeled study ESI-MS	[28,50,149]
		Metarhizium anisopliae	*T. chinensis*	Anticancer	HPLC-MS	[28,149]
		Mucor rouxianus	*T. chinensis*	Anticancer	HPLC-MS	[28,149]
		Pestalotiopsis quepinii	*Wollemia nobilis*	Anticancer	Taxol immunoassay, TLC	[28,149]
		Aspergillus fumigatus	*Podocarpus* sp.	Anticancer	HPLC	[28,149]
2.	Resveratrol	*Alternaria* sp.	*Vitis vinifera*	Anticancer	HPLC	[28,149]
3.	Vinblastine	*Alternaria* sp.	*Catharanthus roseus*	Anticancer	HPLC	[28,149]
4.	Paclitaxel	*Metarhizium anisopliae*	*Taxus brevifolia*	Anticancer	HPLC, ion exchange and silica gel chromatography	[19]
5.	Camptothecin	*Entrophospora infrequens*	*Nothapodytes foetida*	Antifungal and cytotoxic properties	LC–MS	[20,32]
		Alternaria sp.	*Camptotheca acuminata*	Antifungal and cytotoxic properties	HPLC	[28,32]
		Fusarium solani	*Camptotheca acuminata*	Antifungal and cytotoxic properties	^{1}H NMR and LC–HRMS	[28,32]
6.	Huperzine	*Huperzia serrate*	ND	Inhibitor of cholinesterase	HPLC,TLC, RP-HPLC, and mass spectroscopy	[21]
7.	Jesteron, sordaricin, clavatol, and javanicin	*Pestalotiopsis jester*, *Fusarium sp, Chloridium sp.*	*Torreya mairei*	Antifungal and antibacterial properties	ND	[22]
8.	Lauric acid, myristic acid, pentadecanoic acid, duroquinone, amylmetacresol, and tetradecanoic acid	*Aspergillus flavus* and *Nigrospora sphaerica*	*Tectona grandis*	Insecticidal activity against *Eligma narcissus, Atteva fabriciella,* and *Hyblaea puera*	GC–MS	[50]
9.	Chaetoglobosin A	*Chaetomium globosum*	ND	Nematicidal activity against *Meloidogyne spp.* (causing root-knot disease)	HPLC	[50]
10.	Chaetoglobosin A	*Nigrospora sp*	Segon plant	Nematicidal activity against *Meloidogyne spp.* (causing root–knot disease)	ND	[50]
11.	Phomopsichalasin	*Phomopsis* sp.	*Salix gracilistyla* var. mlanostachys	Antibacterial and antifungal activity	ND	[28,149]
12.	Agarwood oil	*Bortyosphaeria sp.*, *Colletotricum sp., Xylaria sp.,* and *Lasiodiplodia sp.*	*Aquilaria sinensis*	Anti-inflammatory, analgesic, and antiarthritic	ND	[28,149]
13.	Phomol	*Phomopsis* sp.	*Erythrina cristagalli*	Antifungal, antibacterial, and cytotoxic activity	Spectroscopic methods	[28,149]
14.	Capsaicin	*Alternaria* sp.	*Capsicum annuum*	Anti-inflammatory	LC–MS/MS	[28,149]
15.	Pestacin	*Pestalotiopsis microspora*	*Terminalia morobensis coode*	Antioxidant and antifungal activity against *Phytium ultimum*	Silica gel chromatography, X-ray diffraction, and NMR for prediction of structure	[149]
16.	Cryptocin	*Cryptosporiopsis cf. quercina*	*Tripterygium wildfordii*	Anti-mycotic activity against *Pyricularia oryzae* (causes blast disease in Rice)	ND	[28,149]
17.	Azadirachtin	*Eupenicillium parvum*	*Azadirachta indica*	Anti-feedant	LC–HRMS	[31]
18.	Piperine	*Periconia sp*	*Piper longum*	Anti-inflammatory	LC–MS/MS	[50]
19.	Rugulosin	*Phialocephala scopiformis*	*Picea glauca*	Antifeeding activity against the spruce budworm *Choristoneura fumiferana*	ND	[50]
20.	Ethyl acetate extract of endophyte	*Nigrospora oryzae*	*Oscimum sanctum*	Antimicrobial activity against *Bacillus subtilis, B. cereus, Salmonella typhimurium, Klebsiella pneumoniae, Staphylococcus aureus* and *Escherichia coli*	ND	[50]
21.	Botryosphaerin H	*Botryosphaeria* sp.	*Huperzia serrata*	Anti-nematicidal activity	Silica gel chromatography, X-ray diffraction, and NMR	[28,33,149]
22.	Palmitic acid, 2H pyran-2-one,5,6-diydro-6-pentyl and methyl ester	*Macrophomina phaseolina*	ND	Antifungal activity against *Sclerotinia sclerotiorum*	GC–MS	[28,149]

compounds, like: diosgenin, vinblastine, paclitaxel, hypericin, camptothecin, and podophyllotoxin extracted from fungal endophytes used commercially both in pharmaceutical and agricultural fields [28].

Role of endophytes in sustainable agriculture production

The unique skill of endophytic microbes to enter, establish and colonize plant internal tissues causes them to be present with multi-faceted useful traits that enhance plant productivity [41]. The question that then arises is: how do endophytic microbes succeed in conferring these positive functional traits on plants? Endophytes are omnipresent and diverse microbes that are found in different ecological niches in plant tissues. Research has shown that endophytes have functional traits with associated undesirable effects of climate change on the survival and growth of susceptible plant species, already published literature supports the facts that endophytic microbes can assist plants to alleviate the adverse effect of abiotic stresses including: flooding [12], high salinity [15,76,93,94], higher temperatures [92,155], heavy metal stress [87,91,123,156], and frequent droughts [14,90] by producing bioactive metabolites, gene expression related resistance, and changes in enzyme metabolism (Tables 1 and 2). Therefore, another significant role of microbial endophytes is that they have the potential to suppress the growth of phytopathogens by the production of antifungal compounds against them. Numerous studies have reported the promising growth-promoting potential of bacterial endophytes on different crops, including: wheat, rice, canola, tomato, potato, and other crops [13,54,63,106,129]. The use of endophytes to control pest damage has also been reported in the: faba bean, cotton, tomato, banana, common bean, and coffee plant [41,56]. Endophytes increase plant growth by helping plants in nutrient acquisition like: nitrogen, phosphorus iron, and by producing phytohormones [11,35,83]. Fungal and bacterial endophytes have shown immense potential as an eco-friendly, sustainable alternative in the agriculture system for food production. Several studies conducted by different researchers by using endophytic microbes have shown their roles to be potential: bio-fertilizer [34,73], bioeffector [82,150], biostimulant [12–15], biopesticide [6], and also as a biocontrol agent [13,52,53] and these endophytic microbes serve their extraordinary role in the field of agricultural crop production (Figure 4). A number of metabolites of endophytes isolated from medicinal plants, forests, agriculture, and mangroves mainly related to the Firmicutes phyla, possess distinctive plant-growth-promoting and biocontrol properties [157]. In general, *Bacillus* and actinobacteria endophytes produce aromatic compounds like phytohormones, polysaccharides, and lipopeptides thus representing a

Biocontrol
❖ Inhibit growth of Pest/pathogen
❖ Induced Systemic Resistance
❖ Production of lytic enzymes
❖ Antibiotics
❖ Competition

Pollution control
❖ Phytoremediation of heavy metals, dyes, and chemicals
❖ Weedicide, insecticides
❖ Phenols, chlorophenols

Plant growth Augmentation
❖ Increases plant biomass
❖ Biological Nitrogen fixation
❖ Solublization of Phosphate, iron, etc.
❖ Production of Siderophore, phytohormones, ACC deaminase enzyme
❖ Induced systemic resistance

Industrial application
❖ Antioxidants, biocontrol agents, Biofertilizers,and biostimulants
❖ Anticancer, Anti- inflammatory compounds
❖ Bioactive compounds: antiviral, antibiotics.

Figure 4. Multiple applications of endophytes in sustainable agriculture production.

great prospective for crop management and PGP strategies [83]. Additionally, actinobacteria have been shown to produce metabolites with antitumor and antimicrobial activities, that are useful in medicinal, veterinary, and agricultural fields [6]. The best possible strategies related to the application of endophytic microbes in agricultural systems have not yet been explored. However, the most frequently used approach is to add endophytes as seed dressings or directly into the soil. However, the use of these endophytes based bioinoculations is unsuccessful on field sites due to problems associated with the establishment of the endophytes. Keeping in view the biological potential and their role in plant growth and development, the endophytes in the future need to be explored in order to achieve the targets of environmental sustainability, agricultural productivity and to act as a source of novel biomolecules for different aspects related to human health and industrial sectors.

Conclusions and future perspectives

Plant acts as true "filters" of microbial communities living in soil by selecting the successful and proficient endophytes. Endophytes represent as an eco-friendly alternative for PGP and as a sustainable reservoir of novel bioactive compounds. Rapidly increasing research related to endophytic microbes is bringing them into the spotlight. Copious endophytic microbes and their genes are now being recognized, providing knowledge about their symbiotic relationship and mechanism of action. Still, there are big gaps regarding the lifestyle and the working of these microbes. Research shows that only about 1–2% of known species of plants have been studied for endophytic associations and most of these are from land plants, whereas aquatic plants (lakes, ocean, etc.) are completely unexplored. Several essential bioactive compounds produced by plant–endophyte associations can be used in various fields of: medicine, agriculture, biodegradation, and bioremediation. The promising use of endophytes-based nanoparticles has shown promising results for drug development in the future. To harness the maximum benefits, there is a need to develop endophyte-based bio formulations. These bio formulations will be more effective when applied directly to aerial or seeds parts. When microbes enter the plant tissue, it will not face further competition, unlike rhizosphere microbes. Moreover, the benefits are directly transferred to the host plant in a closed-circuit system where metabolite leakage is negligible. These bioformulations can also be very valuable for the remediation of polluted soils.

Endophytes may thus surmount many of the shortcomings related to conventional bio formulations. However, for the commercial success of this bioformulation as a next-generation bio formulation, a comprehensive understanding of the following is required: (i) strategies to establish symbiotic association between host plant and endophyte, (ii) mode of transmission, and (iii) molecular and genetic bases of plant–endophyte interactions. It is high time to deduce the physiology and biochemistry of endophytes up to the metabolomics and genomic levels. To date, there are no such databases exclusively available for endophytic microbes and their metabolites, which can be a possible solution for many problems. There is the need to explore complete genomics and the integrated metabolism of the plant–endophyte association to acquire benefits from this astonishing association!

Disclosure statement

The authors declare that they have no conflict of interest.

Funding

ORCID

Anamika Dubey 🔘 http://orcid.org/0000-0003-1200-8379
Muneer Ahmad Malla 🔘 http://orcid.org/0000-0001-7878-6240
Ashwani Kumar 🔘 http://orcid.org/0000-0002-8453-3183
Mohammad Latif Khan 🔘 http://orcid.org/0000-0001-6849-0307

References

[1] Dubey A, Kumar A, Abd_Allah EF, et al. Growing more with less: breeding and developing drought resilient soybean to improve food security. Ecol Indic. 2019;105:425–437.

[2] Kumar A, Dubey A. Rhizosphere microbiome: engineering bacterial competitiveness for enhancing crop production. J Adv Res. 2020;24:337–352.

[3] Sprent JI. 60Ma of legume nodulation. What's new? What's changing? J Exp Bot. 2008;59(5):1081–1084.

[4] Ali S, Duan J, Charles TC, et al. A bioinformatics approach to the determination of genes involved in endophytic behavior in Burkholderia spp. J Theor Biol. 2014;343:193–198.

[5] Dubey A, Malla MA, Khan F, et al. Soil microbiome: a key player for conservation of soil health under changing climate. Biodivers Conserv. 2019;28(8–9): 2405–2429.

[6] Lugtenberg BJJ, Caradus JR, Johnson LJ. Fungal endophytes for sustainable crop production. FEMS Microbiol Ecol. 2016;92(12):fiw194.

[7] Lata R, Chowdhury S, Gond SK, et al. Induction of abiotic stress tolerance in plants by endophytic microbes. Lett Appl Microbiol. 2018;66(4):268–276.

[8] Khare E, Mishra J, Arora NK. Multifaceted interactions between endophytes and plant: developments and prospects. Front Microbiol. 2018;9:2732.

[9] Malla MA, Dubey A, Yadav S, et al. Understanding and designing the strategies for the microbe-mediated remediation of environmental contaminants using omics approaches. Front Microbiol. 2018;9: 1132.

[10] Malla MA, Dubey A, Kumar A, et al. Exploring the human microbiome: the potential future role of next-generation sequencing in disease diagnosis and treatment. Front Immunol. 2018;9:2868.

[11] Arnao MB, Hernández-Ruiz J. Melatonin and its relationship to plant hormones. Ann Bot. 2018;121(2): 195–207.

[12] Wani SH, Kumar V, Shriram V, et al. Phytohormones and their metabolic engineering for abiotic stress tolerance in crop plants. Crop J. 2016;4(3):162–176.

[13] Hashem A, Abd_Allah EF, Alqarawi AA, et al. Plant defense approach of Bacillus subtilis (BERA 71) against Macrophomina phaseolina (Tassi) Goid in mung bean. J Plant Interact 2017;12:390–401.

[14] Kumar A, Vyas P, Kumar D, et al. Screening and characterization of Achromobacter xylosoxidans isolated from rhizosphere of Jatropha curcas L. (energy crop) for plant-growth-promoting traits. J Adv Res Biotechnol. 2018;3(1):1–8.

[15] Kumar A, Sharma S, Mishra S, et al. Arbuscular mycorrhizal inoculation improves growth and antioxidative response of Jatropha curcas (L.) under Na$_2$SO$_4$ salt stress. Plant Biosyst. 2015;149(2):260–269.

[16] Patil A, Dubey A, Malla MA, et al. Complete genome sequence of Lactobacillus plantarum strain JDARSH, isolated from sheep milk. Microbiol Resour Announc. 2020;9:e01199-19.

[17] Hameed A, Dilfuza E, Abd_Allah EF, et al. Salinity stress and arbuscular mycorrhizal symbiosis in plants. In: Miransari M. editor. Use of microbes for the alleviation of soil stresses, Vol. 1. New York (NY): Spinger;2014. p. 139–159.

[18] Edwards J, Johnson C, Santos-Medellín C, et al. Structure, variation, and assembly of the root-associated microbiomes of structure, variation, and assembly rice. Proc Natl Acad Sci USA. 2015;112: E911–E920.

[19] Akinsanya MA, Goh JK, Lim SP, et al. Metagenomics study of endophytic bacteria in Aloe vera using next-generation technology. Genom Data. 2015;6: 159–163.

[20] Munir S, Li Y, He P, et al. Core endophyte communities of different citrus varieties from citrus growing regions in China. Sci Rep. 2020;10(1):3648.

[21] Kuźniar A, Włodarczyk K, Grządziel J, et al. Culture-independent analysis of an endophytic core microbiome in two species of wheat: Triticum aestivum L. (cv. 'Hondia') and the first report of microbiota in Triticum spelta L. (cv. 'Rokosz'). Syst Appl Microbiol. 2020;43(1):126025.

[22] Bulgarelli D, Rott M, Schlaeppi K, et al. Revealing structure and assembly cues for Arabidopsis root-inhabiting bacterial microbiota. Nature. 2012; 488(7409):91–95.

[23] Barnett MJ, Toman CJ, Fisher RF, et al. A dual-genome symbiosis chip for coordinate study of signal exchange and development in a prokaryote–host interaction. Proc Natl Acad Sci USA. 2004;101(47): 16636–16641.

[24] Güldener U, Seong KY, Boddu J, et al. Development of a Fusarium graminearum Affymetrix GeneChip for profiling fungal gene expression in vitro and in planta. Fungal Genet Biol. 2006;43(5):316–325.

[25] Rädecker N, Raina JB, Pernice M, et al. Using Aiptasia as a model to study metabolic interactions in Cnidarian-Symbiodinium symbioses. Front Physiol. 2018;9:214.

[26] Heinig U, Scholz S, Jennewein S. Getting to the bottom of Taxol biosynthesis by fungi. Fungal Divers. 2013;60(1):161–170.

[27] Li J, Zhao GZ, Varma A, et al. An endophytic Pseudonocardia species induces the production of artemisinin in Artemisia annua. PLoS One. 2012;7(12): e51410.

[28] Kumar S, Aharwal RP, Shukla H, et al. Endophytic fungi: as a source of antimicrobials bioactive compounds. World J Pharm Pharm Sci. 2014;3(2): 1179–1197.

[29] Zhang Y, Han T, Ming Q, et al. Alkaloids produced by endophytic fungi: a review. Nat Prod Commun. 2012; 7(7):963–968.

[30] Nair DN, Padmavathy S. Impact of endophytic microorganisms on plants, environment and humans. Sci World J. 2014;2014:250693.

[31] Kusari S, Verma VC, Lamshoeft M, et al. An endophytic fungus from Azadirachta indica A. Juss. that produces azadirachtin. World J Microbiol Biotechnol. 2012;28(3):1287–1294.

[32] Robinson RJ, Fraaije BA, Clark IM, et al. Wheat seed embryo excision enables the creation of axenic seedlings and Koch's postulates testing of putative bacterial endophytes. Sci Rep. 2016;6:25581.

[33] Gough C, Cullimore J. Lipo-chitooligosaccharide signaling in endosymbiotic plant–microbe interactions. Mol Plant Microbe Interact. 2011;24(8):867–878.

[34] Arora NK, Mishra J. Prospecting the roles of metabolites and additives in future bioformulations for sustainable agriculture. Appl Soil Ecol. 2016;107: 405–407.

[35] López-Ráez JA, Shirasu K, Foo E. Strigolactones in plant interactions with beneficial and detrimental organisms: the Yin and Yang. Trends Plant Sci. 2017; 22(6):527–537.

[36] Rozpądek P, Domka AM, Nosek M, et al. The role of strigolactone in the cross-talk between Arabidopsis

thaliana and the endophytic fungus *Mucor* sp. Front Microbiol. 2018;9:441.

[37] Nguema-Ona E, Vicré-Gibouin M, Cannesan MA, et al. Arabinogalactan proteins in root–microbe interactions. Trends Plant Sci. 2013;18(8):440–449.

[38] Chagas MB, de O, Prazeres dos Santos I, Nascimento da Silva LC, et al. Antimicrobial activity of cultivable endophytic fungi associated with *Hancornia speciosa* gomes bark. Open Microbiol J. 2017;11(1):179–188.

[39] Fouad MO, Essahibi A, Benhiba L, et al. Effectiveness of arbuscular mycorrhizal fungi in the protection of olive plants against oxidative stress induced by drought. Span J Agric Res. 2014;12(3):763–771.

[40] Kusajima M, Shima S, Fujita M, et al. Involvement of ethylene signaling in *Azospirillum sp.* B510-induced disease resistance in rice. Biosci Biotechnol Biochem. 2018;82(9):1522–1526.

[41] Kumar A, Sharma S, Mishra S. Evaluating effect of arbuscular mycorrhizal fungal consortia and *Azotobacter chroococcum* in improving biomass yield of *Jatropha curcas*. Plant Biosyst. 2016;150(5): 1056–1064.

[42] Pieterse CMJ, Zamioudis C, Berendsen RL, et al. Induced systemic resistance by beneficial microbes. Annu Rev Phytopathol. 2014;52(1):347–375.

[43] Vandenkoornhuyse P, Quaiser A, Duhamel M, et al. The importance of the microbiome of the plant holobiont. New Phytol. 2015;206(4):1196–1206.

[44] Cord-Landwehr S, Melcher RLJ, Kolkenbrock S, et al. A chitin deacetylase from the endophytic fungus *Pestalotiopsis* sp. efficiently inactivates the elicitor activity of chitin oligomers in rice cells. Sci Rep. 2016;6:38018.

[45] Cui JL, Wang YN, Jiao J, et al. Fungal endophyte-induced salidroside and tyrosol biosynthesis combined with signal cross-talk and the mechanism of enzyme gene expression in *Rhodiola crenulata*. Sci Rep. 2017;7(1):12540.

[46] Jia M, Chen L, Xin HL, et al. A friendly relationship between endophytic fungi and medicinal plants: a systematic review. Front Microbiol. 2016;7:906.

[47] Salam N, Khieu TN, Liu MJ, et al. Endophytic Actinobacteria associated with *Dracaena cochinchinensis* Lour.: isolation, diversity, and their cytotoxic activities. Biomed Res Int. 2017;2017:1308563.

[48] Xu Y, Liu F, Zhu S, et al. The maize NBS-LRR gene ZmNBS25 enhances disease resistance in rice and *Arabidopsis*. Front Plant Sci. 2018;9:1033.

[49] Waqas M, Khan AL, Hamayun M, et al. Endophytic fungi promote plant growth and mitigate the adverse effects of stem rot: an example of *Penicillium citrinum* and *Aspergillus terreus*. J Plant Interact. 2015; 10(1):280–287. p. 275–290.

[50] Chowdhary K, Sharma S. Potential of fungal endophytes in plant growth and disease management. In: Singh D, Singh H, Prabha R, editors. Plant–microbe interactions in agro-ecological perspectives. Singapore: Springer; 2017. p. 275–290.

[51] Gao FU, Dai CC, Liu XZ. Mechanisms of fungal endophytes in plant protection against pathogens. Afr J Microbiol Res. 2010;4(13):1346–1351.

[52] Jiao R, Munir S, He P, et al. Biocontrol potential of the endophytic *Bacillus amyloliquefaciens* YN201732 against tobacco powdery mildew and its growth promotion. Biol Control. 2020;143:104160.

[53] Halecker S, Wennrich JP, Rodrigo S, et al. Fungal endophytes for biocontrol of ash dieback: the antagonistic potential of *Hypoxylon rubiginosum*. Fungal Ecol. 2020;45:100918.

[54] Liu B, Huang L, Buchenauer H, et al. Isolation and partial characterization of an antifungal protein from the endophytic *Bacillus subtilis* strain EDR4. Pestic Biochem Physiol. 2010;98(2):305–311.

[55] Etesami H, Alikhani HA. Evaluation of Gram-positive rhizosphere and endophytic bacteria for biological control of fungal rice (*Oryzia sativa* L.) pathogens. Eur J Plant Pathol. 2017;147(1):7–14.

[56] Sheoran N, Valiya Nadakkakath A, Munjal V, et al. Genetic analysis of plant endophytic *Pseudomonas putida* BP25 and chemo-profiling of its antimicrobial volatile organic compounds. Microbiol Res. 2015;173: 66–78.

[57] Gond SK, Bergen MS, Torres MS, et al. Endophytic *Bacillus* spp. produce antifungal lipopeptides and induce host defence gene expression in maize. Microbiol Res. 2015;172:79–87.

[58] Etminani F, Harighi B. Isolation and identification of endophytic bacteria with plant growth promoting activity and biocontrol potential from wild pistachio trees. Plant Pathol J. 2018;34(3):208–217.

[59] Singh M, Kumar A, Singh R, et al. Endophytic bacteria: a new source of bioactive compounds. 3 Biotech. 2017;7(5):315.

[60] Qin J, Li MJ, Wang P, et al. ChIP-Array: combinatory analysis of ChIP-seq/chip and microarray gene expression data to discover direct/indirect targets of a transcription factor. Nucleic Acids Res. 2011;39: 430–436.

[61] Abd-Allah EF, Alqarawi AA, Hashem A, et al. Endophytic bacterium *Bacillus subtilis* (BERA 71) improves salt tolerance in chickpea plants by regulating the plant defense mechanisms. J Plant Interact. 2018;13(1):37–44.

[62] Vu HNT, Nguyen DT, Nguyen HQ, et al. Antimicrobial and cytotoxic properties of bioactive metabolites produced by *Streptomyces cavourensis* YBQ59 isolated from *Cinnamomum cassia* Prels in Yen Bai Province of Vietnam. Curr Microbiol. 2018;75(10): 1247–1255.

[63] Cavaglieri L, Orlando J, Rodríguez MI, et al. Biocontrol of *Bacillus subtilis* against *Fusarium verticillioides* in vitro and at the maize root level. Res Microbiol. 2005;156(5–6):748–754.

[64] Chung EJ, Hossain MT, Khan A, et al. *Bacillus oryzicola sp.* Nov., an endophytic bacterium isolated from the roots of rice with antimicrobial, plant growth promoting, and systemic resistance inducing activities in rice. Plant Pathol J. 2015;31(2):152–164.

[65] Etesami H, Alikhani HA. *Bacillus* species as the most promising bacterial biocontrol agents in rhizosphere and endorhiza of plants grown in rotation with each other. Eur J Plant Pathol. 2018;150(2):497–506.

[66] Islam R, Jeong YT, Lee YS, et al. Isolation and identification of antifungal compounds from *Bacillus subtilis* C9 Inhibiting the growth of plant pathogenic fungi. Mycobiology. 2012;40(1):59–66.

[67] Rojas-Solís D, Zetter-Salmón E, Contreras-Pérez M, et al. *Pseudomonas stutzeri* E25 and *Stenotrophomonas maltophilia* CR71 endophytes produce antifungal volatile organic compounds and exhibit additive plant growth-promoting effects. Biocatal Agric Biotechnol. 2018;13:46–52.

[68] Le HTT, Padgham JL, Sikora RA. Biological control of the rice root-knot nematode *Meloidogyne graminicola* on rice, using endophytic and rhizosphere fungi. Int J Pest Manag. 2009;55(1):31–36.

[69] Chen JL, Sun SZ, Miao CP, et al. Endophytic *Trichoderma gamsii* YIM PH30019: a promising biocontrol agent with hyperosmolar, mycoparasitism, and antagonistic activities of induced volatile organic compounds on root-rot pathogenic fungi of *Panax notoginseng*. J Ginseng Res. 2016;40(4):315–324.

[70] Berg G, Smalla K. Plant species and soil type cooperatively shape the structure and function of microbial communities in the rhizosphere. FEMS Microbiol Ecol. 2009;68(1):1–13.

[71] Kumar A, Dames JF, Gupta A, et al. Current developments in arbuscular mycorrhizal fungi research and its role in salinity stress alleviation: A biotechnological perspective. Crit Rev Biotechnol. 2015;35(4): 461–474.

[72] Suzuki N, Rivero RM, Shulaev V, et al. Abiotic and biotic stress combinations. New Phytol. 2014;203(1): 32–43.

[73] Santoyo G, Moreno-Hagelsieb G, del Carmen Orozco-Mosqueda M, et al. Plant growth-promoting bacterial endophytes. Microbiol Res. 2016;183:92–99.

[74] Jiao J, Ma Y, Chen S, et al. Melatonin-producing endophytic bacteria from grapevine roots promote the abiotic stress-induced production of endogenous melatonin in their hosts. Front Plant Sci. 2016;7:1387.

[75] Pandey V, Ansari MW, Tula S, et al. Dose-dependent response of *Trichoderma harzianum* in improving drought tolerance in rice genotypes. Planta. 2016; 243(5):1251–1264.

[76] Bagri DS, Upadhyaya DC, Kumar A, et al. Overexpression of PDX-II gene in potato (*Solanum tuberosum* L.) leads to the enhanced accumulation of vitamin B6 in tuber tissues and tolerance to abiotic stresses. Plant Sci. 2018;272:265–275.

[77] Hashem A, Kumar A, Al-Dbass AM, et al. Arbuscular mycorrhizal fungi and biochar improves drought tolerance in chickpea. Saudi J Biol Sci. 2018;26(3): 614–624.

[78] Ojuederie OB, Babalola OO. Microbial and plant-assisted bioremediation of heavy metal polluted environments: a review. Int J Environ Res Public Health. 2017;14(12):1504.

[79] Osman GEH, Abulreesh HH, Elbanna K, et al. Recent progress in metal–microbe interactions: prospects in bioremediation. J Pure Appl Microbiol. 2019;13(1): 13–26.

[80] Tirry N, Tahri Joutey N, Sayel H, et al. Screening of plant growth promoting traits in heavy metals resistant bacteria: prospects in phytoremediation. J Genet Eng Biotechnol. 2018;16(2):613–619.

[81] Dubey A, Kumar A, Khan ML. Role of biostimulants for enhancing abiotic stress tolerance in Fabaceae plants. In: Hasanuzzaman M, Araújo S, Gill S, editors. The plant family Fabaceae. Singapore: Springer; 2020. p. 223–236.

[82] Kong Z, Mohamad OA, Deng Z, et al. Rhizobial symbiosis effect on the growth, metal uptake, and antioxidant responses of *Medicago lupulina* under copper stress. Environ Sci Pollut Res Int. 2015;22(16): 12479–12489.

[83] Ahmad P, Kumar A, Gupta A. et al. Polyamines: role in plant under abiotic stress. In: Ashraf M, Ozturk, M, Ahmad M, et al. editors. Crop production for agriculture improvement. Dordrecht: Springer; 2012. p. 491–512.

[84] Sziderics AH, Rasche F, Trognitz F, et al. Bacterial endophytes contribute to abiotic stress adaptation in pepper plants (*Capsicum annuum* L.). Can J Microbiol. 2007;53(11):1195–1202.

[85] Damodaran T, Rai RB, Jha SK, et al. Rhizosphere and endophytic bacteria for induction of salt tolerance in gladiolus grown in sodic soils. J Plant Interact. 2014; 9(1):577–584.

[86] Li Z, Ma Z, Hao X, et al. Genes conferring copper resistance in *Sinorhizobium meliloti* CCNWSX0020 also promote the growth of *Medicago lupulina* in copper-contaminated soil. Appl Environ Microbiol. 2014;80(6):1961–1971.

[87] Li Z, Song X, Wang J, et al. Nickel and cobalt resistance properties of *Sinorhizobium meliloti* isolated from *Medicago lupulina* growing in gold mine tailing. PeerJ. 2018;6:e5202.

[88] Doty SL, Freeman JL, Cohu CM, et al. Enhanced degradation of TCE on a superfund site using endophyte-assisted poplar tree phytoremediation. Environ Sci Technol. 2017;51(17):10050–10058.

[89] Ren XM, Guo SJ, Tian W, et al. Effects of plant growth-promoting bacteria (PGPB) inoculation on the growth, antioxidant activity, cu uptake, and bacterial community structure of rape (*Brassica napus* L.) grown in Cu-contaminated agricultural soil. Front Microbiol. 2019;10:1455.

[90] Saikia J, Sarma RK, Dhandia R, et al. Alleviation of drought stress in pulse crops with ACC deaminase producing rhizobacteria isolated from acidic soil of Northeast India. Sci Rep. 2018;8(1):3560.

[91] Wang JL, Li T, Liu GY, et al. Unraveling the role of dark septate endophyte (DSE) colonizing maize (*Zea mays*) under cadmium stress: physiological, cytological and genic aspects. Sci Rep. 2016;6:22028.

[92] Márquez LM, Redman RS, Rodriguez RJ, et al. A virus in a fungus in a plant: three-way symbiosis required for thermal tolerance. Science. 2007;315(5811): 513–515.

[93] Porcel R, Aroca R, Ruiz-Lozano JM. Salinity stress alleviation using arbuscular mycorrhizal fungi. A review. Agron Sustain Dev. 2012;32(1):181–200.

[94] Kumar A, Sharma S, Mishra S. Influence of arbuscular mycorrhizal (AM) fungi and salinity on seedling growth, solute accumulation, and mycorrhizal

dependency of *Jatropha curcas* L. J Plant Growth Regul. 2010;29(3):297–306.

[95] Pozo MJ, López-Ráez JA, Azcón-Aguilar C, et al. Phytohormones as integrators of environmental signals in the regulation of mycorrhizal symbioses. New Phytol. 2015;205(4):1431–1436.

[96] Gutjahr C. Phytohormone signaling in arbuscular mycorrhiza development. Curr Opin Plant Biol. 2014; 20:26–34.

[97] Gensollen T, Iyer SS, Kasper DL, et al. How colonization by microbiota in early life shapes the immune system. Science. 2016;352(6285):539–544.

[98] Newman M-A, Sundelin T, Nielsen JT, et al. MAMP (microbe-associated molecular pattern) triggered immunity in plants. Front Plant Sci. 2013;4:139.

[99] Sánchez-Vallet A, Mesters JR, Thomma BPHJ. The battle for chitin recognition in plant–microbe interactions. FEMS Microbiol Rev. 2015;39(2):171–183.

[100] Trdá L, Boutrot F, Claverie J, et al. Perception of pathogenic or beneficial bacteria and their evasion of host immunity: pattern recognition receptors in the frontline. Front Plant Sci. 2015;6:219.

[101] Staerck C, Gastebois A, Vandeputte P, et al. Microbial antioxidant defense enzymes. Microb Pathog. 2017; 110:56–65.

[102] Krishna SBN, Dubey A, Malla MA, et al. Integrating microbiome network: establishing linkages between plants, microbes and human health. Open Microbiol J. 2019;13(1):330–342.

[103] Berendsen RL, van Verk MC, Stringlis IA, et al. Unearthing the genomes of plant-beneficial Pseudomonas model strains WCS358, WCS374 and WCS417. BMC Genomics. 2015;16(1):539.

[104] Subudhi E, Sahoo RK, Dey S, et al. Unraveling plant–endophyte interactions: an omics insight; 2019. p. 249–267. Available from:

[105] Busby PE, Peay KG, Newcombe G. Common foliar fungi of *Populus trichocarpa* modify Melampsora rust disease severity. New Phytol. 2016;209(4):1681–1692.

[106] Megías E, Megías M, Ollero FJ, et al. Draft genome sequence of P*antoea ananatis* strain AMG521, a rice plant growth-promoting bacterial endophyte isolated from the Guadalquivir marshes in southern Spain. Genome Announc. 2016;4(1):e01681–15.

[107] Li S, Tang Y, Fang X, et al. Whole-genome sequence of *Arthrinium phaeospermum*, a globally distributed pathogenic fungus. Genomics. 2020;112(1):919–929.

[108] Jeon J, Park S-Y, Kim JA, et al. Draft genome sequence of *Amphirosellinia nigrospora* JS-1675, an endophytic fungus from *Pteris cretica*. Microbiol Resour Announc. 2019;8:e00069-19.

[109] Fill TP, Baretta JF, de Almeida LGP, et al. Draft genome sequence of the fungus *Penicillium brasilianum* (strain LaBioMMi 136), a plant endophyte from *Melia azedarach*. Microbiol Resour Announc. 2018;7(21): e01235.

[110] Meena N, Vasundhara M, Reddy MS, et al. Draft genome sequence of a fungus (*Fusarium tricinctum*) cultured from a monoisolate native to the Himalayas. Genome Announc. 2018;6(20):e00365-18.

[111] Kim JA, Jeon J, Kim KT, et al. Draft genome sequence of an endophytic fungus, *Gaeumannomyces sp.* strain

JS-464, isolated from a reed plant, *Phragmites communis*. Genome Announc. 2017;5(31):e00734.

[112] Kim JA, Jeon J, Park SY, et al. Genome sequence of an endophytic fungus, *Fusarium solani* JS-169, which has antifungal activity. Genome Announc. 2017;5(42): e01071-17.

[113] Kim H, Mohanta TK, Park YH, et al. Complete genome sequence of the mountain-cultivated ginseng endophyte *Burkholderia stabilis* and its antimicrobial compounds against ginseng root rot disease. Biol Control. 2020;140:104126.

[114] Zhou J, Xia F, Che S, et al. Complete genome sequence of *Pantoea* sp. strain CCBC3-3-1, an antagonistic endophytic bacterium isolated from a *Cotinus coggygria* branch. Microbiol Resour Announc. 2019;8: e01004-19.

[115] Zeng Q, Xie J, Li Y, et al. Draft genome sequence of an endophytic biocontrol bacterium, *Bacillus velezensis* PG12, isolated from apple fruit. Microbiol Resour Announc. 2019;8:e00468-19.

[116] Beracochea M, Taulé C, Battistoni F. Draft genome sequence of *Kosakonia radicincitans* UYSO10, an endophytic plant growth-promoting bacterium of sugarcane (*Saccharum officinarum*). Microbiol Resour Announc. 2019;8:e01000.

[117] Niem J, Billones-Baaijens R, Savocchia S, et al. Draft genome sequences of endophytic *Pseudomonas spp.* isolated from grapevine tissue and antagonistic to Grapevine trunk disease pathogens. Microbiol Resour Announc. 2019;8(26):e00345-19.

[118] Sahib MR, Yang P, Bokros N, et al. Improved draft genome sequence of *Microbacterium sp.* strain LKL04, a bacterial endophyte associated with switchgrass plants. Microbiol Resour Announc. 2019;8:e00927.

[119] Aremu BR, Prigent-Combaret C, Babalola OO. Draft genome sequence of *Bacillus velezensis* strain ZeaDK315 Endo16. Microbiol Resour Announc. 2019; 8:e00136.

[120] Passari AK, Rajput V, Zothanpuia , et al. Draft genome sequence of plant growth-promoting endophytic *Microbacterium hydrothermale* BPSAC84, isolated from the medicinal plant *Mirabilis jalapa*. Microbiol Resour Announc. 2019;8:e00406-19.

[121] Mukhtar T, Afridi MS, McArthur R, et al. Draft genome sequence of *Bacillus pumilus* SCAL1, an endophytic heat-tolerant plant growth-promoting bacterium. Genome Announc. 2018;6:18.

[122] Hong CE, Kim JU, Lee JW, et al. Complete genome sequence of the endophytic bacterium Chryseobacterium indologenes PgBE177, isolated from Panax quinquefolius. Microbiol Resour Announc. 2018; 7:e01234–18.

[123] Shang N, Zhu Q, Dai M, et al. Complete genome sequence of the heavy-metal-tolerant endophytic type strain of *Salinicola tamaricis*. Genome Announc. 2018;6(16):e00358-18.

[124] Reyna-Flores F, Barrios-Camacho H, Dantán-González E, et al. Draft genome sequences of endophytic isolates of *Klebsiella variicola* and *Klebsiella pneumoniae* obtained from the same sugarcane plant. Genome Announc. 2018;6(12):e00147-18.

[125] Cheng W, Zhan G, Liu W, et al. Draft genome sequence of endophytic *Herbaspirillum sp.* strain WT00C, a tea plant growth-promoting bacterium. Genome Announc. 2017;5(11):e01719-16.

[126] Yaish MW. Draft genome sequence of the endophytic *Bacillus aryabhattai* strain squ-r12, identified from *Phoenix dactylifera* L. roots. Genome Announc. 2017;5(32):e00718-17.

[127] Kruasuwan W, Salih TS, Brozio S, et al. Draft genome sequence of plant growth-promoting endophytic *Streptomyces sp.* GKU 895 isolated from the roots of sugarcane. Genome Announc. 2017;5(19):e00358-17.

[128] Hong CE, Jo SH, Jo IH, et al. Draft genome sequence of the endophytic bacterium *Variovorax paradoxus* KB5, which has antagonistic activity against a phytopathogen, *Pseudomonas syringae* pv. tomato DC3000. Genome Announc. 2017;5(36):e00950-17.

[129] Annapurna K, Govindasamy V, Sharma M, et al. Draft genome sequence of *Pseudomonas stutzeri* strain KMS 55, an endophytic diazotroph isolated from rice roots. Genome Announc. 2017;5(40):e00972-17.

[130] Tringe SG, Von Mering C, Kobayashi A, et al. Comparative metagenomics of microbial communities. Science. 2005;308(5721):554–557.

[131] Tian BY, Cao Y, Zhang KQ. Metagenomic insights into communities, functions of endophytes, and their associates with infection by root-knot nematode, *Meloidogyne incognita*, in tomato roots. Sci Rep. 2015;5:17087.

[132] Wemheuer F, Wemheuer B, Daniel R, et al. Deciphering bacterial and fungal endophyte communities in leaves of two maple trees with green islands. Sci Rep. 2019;9(1):14183.

[133] Delmotte N, Knief C, Chaffron S, et al. Community proteogenomics reveals insights into the physiology of phyllosphere bacteria. Proc Natl Acad Sci U S A. 2009;106(38):16428–16433.

[134] Rastogi G, Coaker GL, Leveau JHJ. New insights into the structure and function of phyllosphere microbiota through high-throughput molecular approaches. FEMS Microbiol Lett. 2013;348(1):1–10.

[135] Kaul S, Sharma TK, Dhar M. "Omics" tools for better understanding the plant–endophyte interactions. Front Plant Sci. 2016;7:955.

[136] Felitti S, Shields K, Ramsperger M, et al. Transcriptome analysis of *Neotyphodium* and *Epichloë* grass endophytes. Fungal Genet Biol. 2006;43(7):465–475.

[137] Wang Y, Ohara Y, Nakayashiki H, et al. Microarray analysis of the gene expression profile induced by the endophytic plant growth-promoting rhizobacteria, *Pseudomonas fluorescens* FPT9601-T5 in *Arabidopsis*. Mol Plant Microbe Interact. 2005;18(5):385–396.

[138] Chen X, Krug L, Yang H, et al. *Nicotiana tabacum* seed endophytic communities share a common core structure and genotype-specific signatures in diverging cultivars. Comput Struct Biotechnol J. 2020;18:287–295.

[139] Lery LMS, Hemerly AS, Nogueira EM, et al. Quantitative proteomic analysis of the interaction between the endophytic plant-growth-promoting bacterium *Gluconacetobacter diazotrophicus* and sugarcane. Mol Plant Microbe Interact. 2011;24(5):562–576.

[140] Andrés MF, Diaz CE, Giménez C, et al. Endophytic fungi as novel sources of biopesticides: the Macaronesian Laurel forest, a case study. Phytochem Rev. 2017;16(5):1009–1022.

[141] Shukla ST, Habbu PV, Kulkarni VH, et al. Endophytic microbes: a novel source for biologically/pharmacologically active secondary metabolites. Asian J Pharmacol Toxicol. 2014;7(5):1–16.

[142] Gouda S, Das G, Sen SK, et al. Endophytes: a treasure house of bioactive compounds of medicinal importance. Front Microbiol. 2016;7:1538–1538.

[143] Martinez-Klimova E, Rodríguez-Peña K, Sánchez S. Endophytes as sources of antibiotics. Biochem Pharmacol. 2017;134:1–17.

[144] Guzmán-Trampe S, Rodríguez-Peña K, Espinosa-Gómez A, et al. Endophytes as a potential source of new antibiotics. Antibiot Curr Innov Fut Trends. 2015;175–206.

[145] Kumar A, Patil D, Rajamohanan PR, et al. Isolation, purification and characterization of vinblastine and vincristine from endophytic fungus *Fusarium oxysporum* isolated from *Catharanthus roseus*. PLoS One. 2013;8(9):e71805.

[146] Palem PPC, Kuriakose GC, Jayabaskaran C. An endophytic fungus, *Talaromyces radicus*, isolated from *Catharanthus roseus*, produces vincristine and vinblastine, which induce apoptotic cell death. PLoS One. 2015;10(12):e0144476.

[147] Flewelling AJ, Currie J, Gray CA, et al. Endophytes from marine macroalgae: promising sources of novel natural products. Curr Sci. 2015;109:88–111.

[148] Chhipa H, Chowdhary K, Kaushik N. Artificial production of agarwood oil in *Aquilaria sp.* by fungi: a review. Phytochem Rev. 2017;16(5):835–860.

[149] Naik S, Shaanker RU, Ravikanth G, et al. How and why do endophytes produce plant secondary metabolites? Symbiosis. 2019;78(3):193–201.

[150] Li HY, Wei DQ, Shen M, et al. Endophytes and their role in phytoremediation. Fungal Divers. 2012;54(1):11–18.

[151] Nongkhlaw FMW, Joshi SR. Investigation on the bioactivity of culturable endophytic and epiphytic bacteria associated with ethnomedicinal plants. J Infect Dev Ctries. 2015;9(9):954–961.

[152] Tan RX, Zou WX. Endophytes: a rich source of functional metabolites. Nat Prod Rep. 2001;18(4):448–459.

[153] Akiyama H. Antibacterial action of several tannins against *Staphylococcus aureus*. J Antimicrob Chemother. 2001;48(4):487–491.

[154] Howitz KT, Sinclair DA. Xenohormesis: sensing the chemical cues of other species. Cell. 2008;133(3):387–391.

[155] Card S, Johnson L, Teasdale S, et al. Deciphering endophyte behaviour: the link between endophyte biology and efficacious biological control agents. FEMS Microbiol Ecol. 2016;92(8):fiw114.

[156] Mesa V, Navazas A, González-Gil R, et al. Use of endophytic and rhizosphere bacteria to improve phytoremediation of arsenic-contaminated industrial

soils by autochthonous *Betula celtiberica*. Appl Environ Microbiol. 2017;83(8):e03411.

[157]   Waghunde RR, Shelake RM, Shinde MS, et al. Endophyte microbes: a weapon for plant health management. In: Panpatte D, Jhala Y, Vyas R, et al., editors. Microorganisms for green revolution. Microorganisms for sustainability. Vol. 6. Singapore: Springer; 2017. p. 303–325.