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REVIEW ARTICLE

Endophytic microbes and their diverse beneficial aspects in various sectors: A critical insight

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Abstract

Endophytes are ubiquitous and grow in plant tissues without causing any harmful effects to the host. They include different groups of microorganisms such as bacteria, fungi and actinomycetes. Along with the host plants, the existing endophytes also co-evolve after a long relationship between them. Host plant-endophyte interaction is similar to that of plant growth promoting microbes as they induce the growth of the host plant and increase resilience against biotic and abiotic stresses. The interaction of plant endophytes at the molecular level and the effect of endophytes on host gene expression is a new field of study and are still rarely explored. Endophytes act as a promising resource of many invaluable bioactive secondary metabolites. Some of these bioactive compounds include alkaloids, polyphenols, sterols, xanthones, terpenoids, flavones, coumarins, polyketides, quinones, saponins, tannins, benzopyrones, dibenzofurans. These secondary metabolites are beneficial for agriculture, industrial and pharmacological purposes. As endophytes have beneficial effects in sustainable agriculture, plant disease management, pharmaceuticals, industry and environmental management in an eco-friendly way, thus improving the strategy of application of endophytes as biological agents in every aspect of our life is a very challenging field of research. Our aim in this present review is to focus on plant-endophyte interactions and their various dimensions in order to address some future possibilities for expediting the bioactive secondary metabolite production.

Keywords

Endophytes; bioactive secondary metabolites; plant growth promoting microbes; sustainable agriculture; pharmaceuticals

Introduction

The term 'Endophyte' was first introduced by de Bary in the year 1886 (1). The word endophyte literally means any organism that exists within the plant tissue. These organisms may be beneficial symbionts, neutralists, commensals, or may be pathogenic. A further refined restricted definition of endophyte considers only beneficial plant microorganisms (bacteria, fungi etc.) that asymptomatically live within the plants in mutualistic alliance.

Endophytes colonize in the root, petioles, stem, leaves, fruits, inflorescence, seeds, buds and also in dead plant cells (2-4). Endophytes differ from mycorrhizal symbiosis by lacking specialized structures (vesicles and arbuscules).

They are an under-investigated group of microorganisms that represent a plentiful and renewable source of bioactive chemical compounds which have a huge importance in a wide variety of medical, industrial and agricultural field (5). They are responsible for partial or complete biosynthesis of secondary metabolites of host plants and play an important role in controlling the physiological activity of host plants (1). Endophytes are important for eco-friendly management of environment and agricultural sustainability (6). They play a positive role in maintaining plant health by increasing resistance to abiotic and biotic stresses (1) and even they have the ability to degrade plastics (7). They promote crop productivity, activate plant defense system, protect plants from pathogens and improve soil fertility (8, 9). Endophytic microbes have a prominent capacity as biocontrolling agents to improve plant growth and development (8). In addition, they have been reported to contribute to the medicinal properties of ethnobotanically important plants (9). Bioactive chemical compounds extracted from endophytes include quinones, steroids, alkaloids, phenolic acids, saponins, terpenoids and tannins that possess antimicrobial, antiparasitic, insecticidal, anticancer and other properties (1, 10).

The co-evolution of the plants and their symbionts is of great significance to reveal the factors involved in the coexistence of both the partners. Different modern molecular techniques including genome sequencing, microarray, next generation sequencing, metagenomics and metatranscriptomics provide various information regarding endophytes. This review aimed to focus on multidimensional interactions between endophytes and their host plants and to highlight the versatility of endophyte performance. A brief overview of endophytes along with their general classification, mode of colonization, methods of isolation and identification and beneficial aspects are discussed in this review.

Materials and Methods

Methods of isolation and identification of endophyte

Endophytes are isolated from various plant parts such as root, stem, leaves, bark, petiole, bud etc. No doubt, it is quite cumbersome to detect and identify endophytic microbes. However, several researchers have used different molecular techniques for the isolation of endophytes which are stated in Fig. 1.

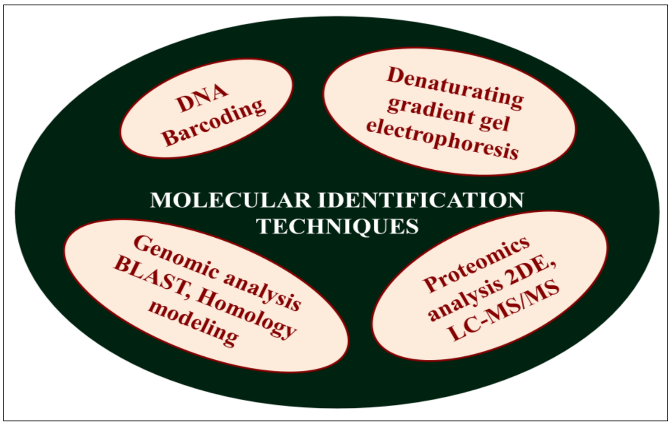

Fig. 1. Molecular techniques for identification of endophytes (BLAST, 2DE, LC-MS/MS represent Basic Local Alignment Search Tool, Two-dimensional gel electrophoresis, and Liquid Chromatography-Tandem Mass Spectrometry respectively).

Usually, endophytes are isolated by surface sterilization followed by culturing from tissue extract or by direct culturing of plant tissues on media, suitable for fungi, or bacteria or actinomycetes (2). Different microbial media are used to isolate endophytes, whereas Mycological Agar Medium (MCA) provides the maximum number of isolates (11). Usually, identification of endophytes is based on morphology of colony or hyphae, characteristics of spores. However, the identities are subsequently verified by using molecular methods such as Polymerase Chain Reaction (PCR), Internal Transcribed Spacer (ITS) sequence analysis etc. Presently very large database of sequences such as Gene bank and the AFTOL (Assembling the Fungal Tree of Life) are available for fungal species identification (12).

General classification of Endophyte

Both fungi and bacteria are the most common microbes existing as endophyte as represented in Fig. 2.

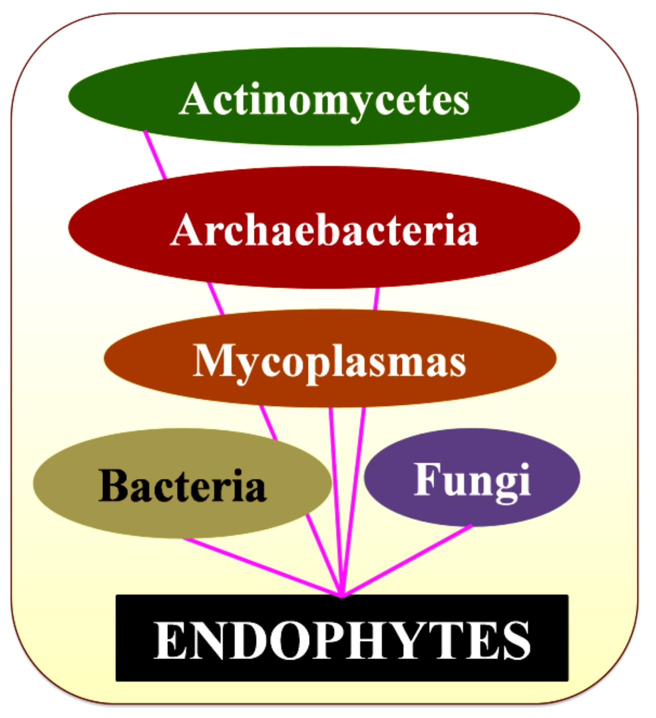

Fig. 2. Types of Endophytes.

Other types of microorganisms, viz., archaebacteria, actinomycetes (transitional forms between bacteria and fungi) and mycoplasmas exist in the plants as endophytes which are also presented in Fig. 2. The diversity of endophytic bacteria ranges from gram-negative to gram-positive bacteria such as *Enterobacter, Bacillus, Pseudomonas, Microbacterium* and *Burkholderia* (13-16). In recent years, a special attention has been given on the endophytic fungi because of its ability to produce good numbers of bioactive secondary metabolites. Endophytic fungi mainly consist of members of Ascomycota, Basidiomycota, Zygomycota and Oomycota. There are two major groups of endophytic fungi known as non clavicipitaceous endophytes (NC-endophytes) and clavicipitaceous endophytes (C-endophytes) (17).

Clavicipitaceous endophytic fungi

These are mainly predominant in grasses and grouped as Class 1 endophytes (17). Class 1 includes again Type I, Type II and Type III categories. With their host plants, these types exert pathogenic to symbiotic type of interactions, whereas any harming effect has not been found for Type III. Class 1 endophytic fungi include some benefits like as improving plant biomass, decreasing herbivory, enhancing the production of chemicals that are toxic to animals, and increasing the plant production (17).

Non clavicipitaceous endophytic fungi

These are mostly common in vascular and non-vascular plant species and grouped into three classes namely Class 2, Class 3 and Class 4 (17). Class 2 endophytes are found both in above and below ground tissue. Class 3 endophytes are found only in the above ground tissue. Class 4 endophytes are restricted to host roots. Dark septate endophytes (DSE) are the largest group in Class 4 (17). The fungal genera those are commonly isolated as endophytes include *Fusarium* sp., *Colletotrichum* sp., *Phoma* sp., *Pestalotiopsis* sp., *Xylaria* sp., *Cladosporium* sp., *Penicillium* sp., *Phyllosticta* sp. and *Acremonium* sp. (18).

Mode of colonization of endophyte

Endophytes show vertical transmission (from maternal plant to seeds) or horizontal transmission (from plant to plant) as presented in Fig. 3.

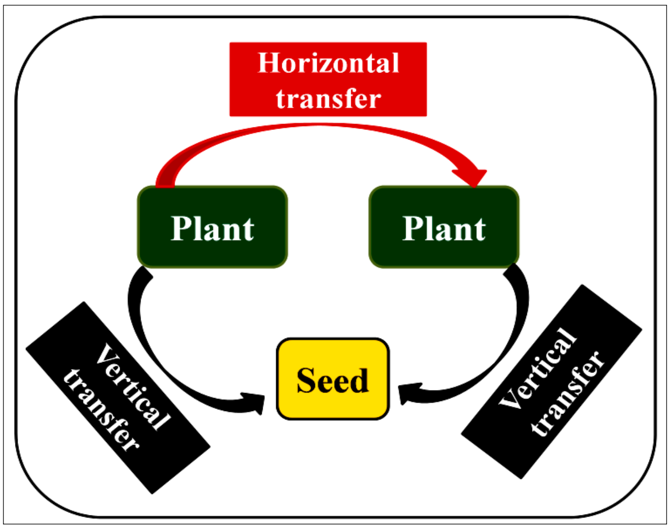

Fig. 3. Mode of colonization of endophytes.

In horizontal transmission, recruitment of microbes from the soils is an important mechanism for plants to gain endophytes (19). This may be accomplished by passive entry through natural openings and wounds, whereas other microbes use lytic enzymes to gain active entry into plant cells and tissues. Endophytes secrete cell wall degrading endo-glucanase and endo-polygalacturonase to gain entry into internal plant cells and tissues (20).

Endophytes- Multifaceted activities

Endophytes show versatility in their actions. These have a great impact on the sustainability of agriculture. In addition, they are also capable of producing bioactive secondary metabolites that are widely used as antibacterial, anticancer, antidiabetic, immunosuppressive and antimalarial agents. This section is divided into 3 main parts viz., endophytes in plant growth regulation, pharmaceutical importance of endophytes and applications of endophytes.

Endophytes in plant growth regulation

Many beneficial endophytes have been discovered that increase the plant fitness and crop productivity through various ways which are schematically demonstrated in Fig. 4**.**

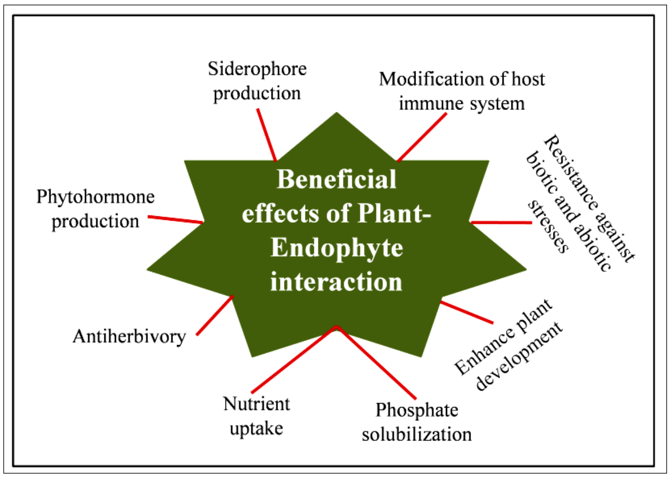

Fig. 4. Endophytes- In plant growth regulation.

Endophytes in nutrient acquisition

Endophytic microbes connect the plant, rhizospheric microbes and soil to promote nutrient solubilization and further send nutrients to the plant roots making the soil-plant -microbe continuum, this process is called 'rhizophagy cycle' as shown in Fig. 5.

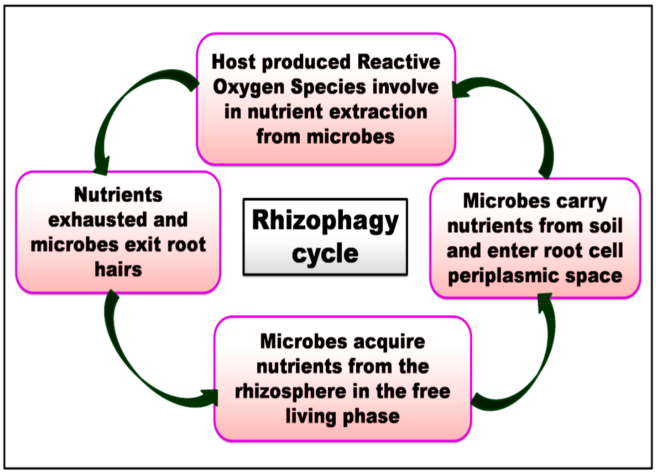

Fig. 5. Diagrammatic representation of the Rhizophagy Cycle.

In the rhizophagy cycle microbes alternate between a root intracellular phase and a free-living soil phase. Microbes acquire soil nutrients in the free-living soil phase and nutrients are extracted through the exposure to host-produced reactive oxygen species in the intracellular endophytic phase. Recent experiments have suggested that multiple nutrients such as nitrogen (N), phosphorus (P), zinc (Zn) etc. may be obtained in the rhizophagy cycle (21-23). Endophytes enhance the concentration of N and P in roots and shoots of endophyte-inoculated plants (24-27).

Endophytes in phosphate solubilisation

Phosphorus (P) is one of the major nutrients needed for the growth and development of plants. But the maximum amount of soil P is not in phyto-available form. It has been reported that many endophytes (*Cochliobolus setosphaeria, Azospirillum* sp., *Azotobacter* sp.) solubilize the insoluble soil phosphate to make it available for plant use (28) as discussed in Fig. 6.

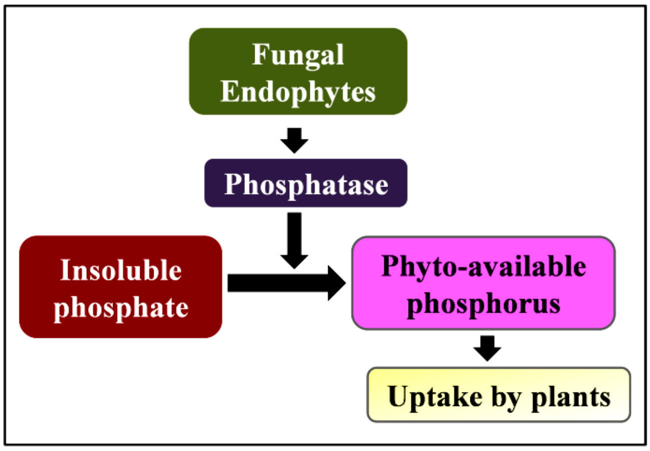

Fig. 6. Schematic representation- Endophytes in phosphate solubilization.

Solubilization of phosphate with secretion of phytase enzymes has been documented by an endophytic actinomycetes *Streptomyces* sp, which significantly stimulates plant growth (29).

Endophytes in siderophore production

Siderophores are low molecular weight iron chelating compounds which can be produced by endophytes and make iron available only for the plants but not for the pathogens. Ferrous ion (Fe^{2+}) is oxidized to ferric ion (Fe^{3+}) - siderophore complex in the bacterial membrane and later enters into the cell by endophytes. Some endophytes such as *Pseudomonas* sp. (30), *Streptomyces* sp., *Nocardia* sp. (31) have also been reported to produce siderophores.

Endophytes in the utilization of 1-Aminocyclopropane-1-Carboxylic Acid (ACC)

During extreme environmental conditions including pathogenicity, drought, salinity and heavy metal, the level of Ethylene (C_2H_4) increases in the plant. This may result in alteration of the cellular processes and defoliation causing low yield of the crop (32). Many bacterial endophytes (*Bacillus, Enterobacter, Burkholderia, Pseudomonas, Ralstonia*) are able to produce ACC deaminase which trap the ACC (C_2H_4 precursor) and change it into ammonia (NH_3) and alpha-ketobutyrate (33), thus reducing plants' C_2H_4 concentration.

Endophytes in the development of roots and their architecture

The function of whole genome (genome of host and its symbionts) is actually responsible for the overall development and performance of the host plant. Plant growth regulators, produced by endophytes affect the root architecture and its development (34). Endophyte regulates the nutrient acquisition by plant roots, phytohormones levels and the levels of reactive oxygen species/antioxidants (ROS/AOX) status of plant root cells which induce the root system architecture (RSA) genes that control the development of roots and its architecture as represented in Fig. 7.

It has been observed that the distribution and frequency of root branches differ in response to different endophytic treatments (35). Significant increases in root length and average root diameter have been observed after the inoculation of endophytic fungus, *Fusarium oxysporum* on *Arabidopsis thaliana* (36).

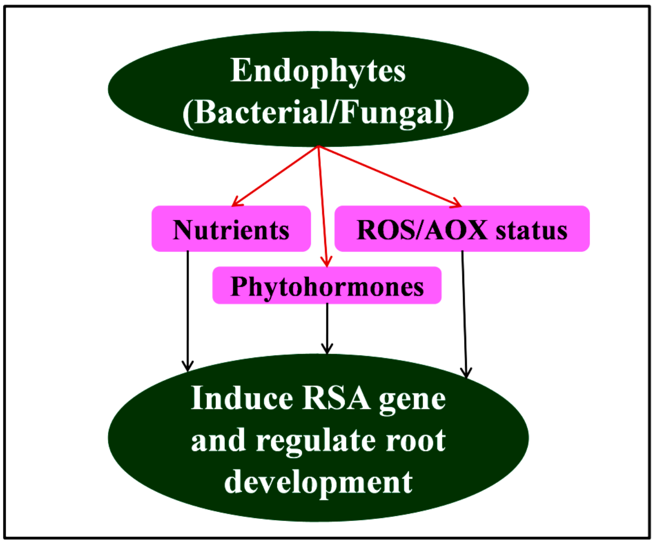

Fig. 7. Endophyte mediated mechanism of root development (ROS, AOX and RSA represent Reactive Oxygen Species, Antioxidant and Root system architecture respectively).

Endophytes in plant growth promotion

Endophytic microbes promote the plant growth by acquiring essential nutrients and modulating the level of phytohormones. Microbial endophytes produce growth regulator such as Nitric oxide (NO), Auxins and C_2H_4. Endophytic colonization increases the biosynthesis of Auxin and genes related to cell wall acidification and Auxin transport proteins (AUX1) (37). NO and C_2H_4 promote root hair elongation. Endophytic microbes improve root growth and root-branching patterns, leading to more plant growth. Inoculation of endophyte *Burkholderia* sp. in *Solanum tuberosum* and *Vitis vinifera* promotes the plant growth by inhibiting the hormone C_2H_4 through the production of high level of ACC deaminase (38, 39). After inoculation of *Cladosporium sphaerospermum* into the roots of *Glycine max* L., a significant enhancement of bioactive Gibberellic Acid (GA3, GA4 and GA7) production has been reported (40).

Endophytes in biotic stress tolerance

Endophytes suppress the activity of phytopathogens via antagonistic activity. Systemic acquired resistance (SAR) and Induced systemic resistance (ISR) play important role during plant stress responses against phytopathogens (41). Through induction of pathogenesis-related genes, *Fusarium solani* elicited ISR against *Septoria lycopersici* (42). *Phytoptophthora* infection has also been reported to reduce in *Colletotrichum tropicale* inoculated *Theobroma cacao* (25). A mutational study has shown that the fungal metabolites protect plants from herbivory. Endophytic bacteria are also known to produce various volatile organic compounds (VOCs) (43) with broad spectrum antimicrobial activity against phytopathogenic bacteria, fungi and nematodes. Endophytic microbe *Pseudomonas putida* inhibits various phytopathogens such as *Gibberella moniliformis, Phytoptophthora capsici, Rhizoctonia solani* and *Pythium myriotylum* (44). The use of *Rhizobium* as a biocontrol agent against phytopathogens *Macrophomina* *phaseolina* has been reported (45). Endophytic *Pseudomonas fluorescens* has been shown to be a biocontrol agent against phytopathogen *Verticillium dahliae* (46). Endophytic fungi enhance the production of low molecular weight antimicrobial compounds called Phytoalexins (47). Thus gene pools of endophytes and the host plant work in tandem to protect the plant from pathogens.

Endophytes in abiotic stress tolerance

Endophytes increase abiotic stress tolerance in plants by inducing stress responsive genes, generation of scavenger molecule, and synthesis of metabolites. Some endophytic and rhizospheric bacteria namely *Pseudomonas, Achromobacter* and *Bacillus* have been reported to produce Abscisic Acid (ABA) in axenic cultures (48). ABA mediates stomatal closure to combat osmotic and other abiotic stresses. In rice, abiotic stress tolerance has been shown to enhance after inoculation of endophytic *Trichoderma harzianum*, which up regulates the expression of aquaporin, dehydrin and malonialdehyde genes (49). Endophytes are also involved in transcriptional regulation, cellular homeostasis and the detoxification of ROS (50). Salt stress tolerance in *Arabidopsis* can be induced by inoculating the endophyte *Enterobacter* sp. which increases the production of 2-keto-4-methyl thiobutyric acid (KMBA), which modulates the plant C_2H_4 signalling pathway (51). Endophytic bacteria reduce metal phytotoxicity through intracellular accumulation, sequestration or bio transformation of toxic metal ions to less toxic or non toxic forms. Heavy metals, important agents for inducing oxidative damage, are also prevented by endophytes. Inoculation of endophytic bacteria *Methylobacterium* and *Burkholderia* sp. on *Lycopersicon esculentum* L. has been reported to decrease the toxicity and accumulation of Nickel (Ni) and Cadmium (Cd) (52). Inoculation of plants with the endophytic bacterium *Pseudomonas* inhibits herbicide accumulation in plant tissues (53).

Endophytes in the protection of host plant from Reactive Oxygen Species (ROS)

Any kind of environmental stress eventually leads to ROS generation and causes oxidative damage to plant tissues (54). Endophytes enhance the expression of ROS degrading genes in the host plant like superoxide dismutase (SOD) and glutathione reductase (GR) (55) as discussed in Fig. 8.

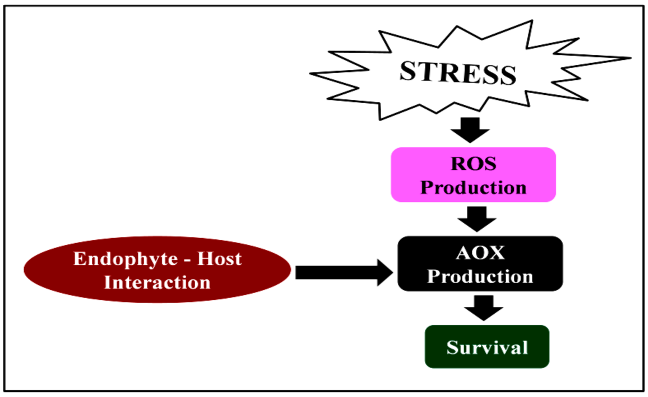

Fig. 8. Endophyte mediated AOX production to scavenge ROS (ROS and AOX indicate Reactive Oxygen Species and Antioxidants respectively).

Up regulation of ROS degrading genes reduce the oxidative damage in plants. Inoculation of endophytic fungus *Piriformospora indica* in *Brassica rapa* upregulates the expression of antioxidant enzymes such as peroxidases, catalases and SOD (56).

Endophytes in the modification of hosts' immune system

When endophytic bacteria penetrate into the host plant, the molecular patterns (microbe-associated molecular patterns-MAMPs or pathogen-associated molecular patterns-PAMPs) associated with these are recognized by the pattern recognition receptors (PRRs) present on cell membrane of host plant cell (57) as discussed in Fig. 9.

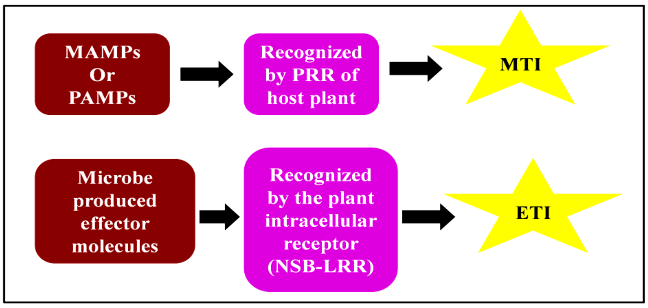

Fig. 9. Plant immune system response against bacterial and fungal pathogen (where, MAMPs- Microbe associated molecular patterns, PAMPs- Pathogen associated molecular patterns, PRR- Patterns reorganisation receptors, NSB-LRR- Nucleotide binding site- Leucine rich repeat, MTI and ETI are MAMP-triggered immunity and Effector triggered immunity respectively).

Peptidoglycan, Elongation Factor TU, Lipopolysaccharides, Flagellin, bacterial cold shock protein, β-glycan, chitin are most common MAMPs (57). In case of fungal endophytes, chitin specific receptors (PR-3) recognize the chitin oligomers present on the fungal cell wall, triggering the plants' immune system (58). Some fungal endophytes produce chitin deacetylases, which deacetylate chitosan oligomers that are not perceived by plants' receptors, thus they prevent themselves from being recognized (59). Protein secretion systems in bacteria also modulate the immune system of the plants. Among the different types of protein secretion systems, type III and type IV are the most important for pathogenic bacteria to deliver effector proteins into the plants (60).

Endophytes against herbivory

Some endophytes produce some compounds in their host plants that reduce herbivory by insects and other herbivores. Fungal endophyte *Epichloe* promotes the production of alkaloid and promotes the jasmonic acid pathway in the host plant that deters feeding by herbivores (61) as shown in Fig. 10.

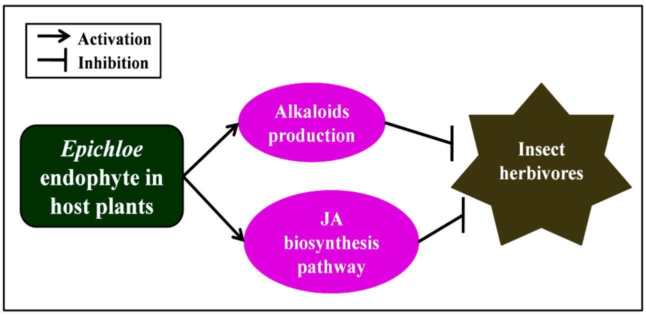

Fig. 10. Schematic representation- Endophyte mediated Antiherbivory (JA represents Jasmonic Acid).

Undifilum, an endophytic fungus, has been confirmed to produce toxic indolizidine alkaloid Swainsonine which is a potent anti-herbivore compound (62). More research is needed to make endophytic fungi and bacteria more convenient in crop pest management.

Pharmaceutical importance of endophytes

Endophytes are considered as the store house of bioactive compounds (1). These bioactive secondary metabolites are extensively used in wide range of biological and pharmacological activities including antibacterial, antidiabetic, antimalarial, anticancerous and immunosuppressive applications as stated in Fig. 11.

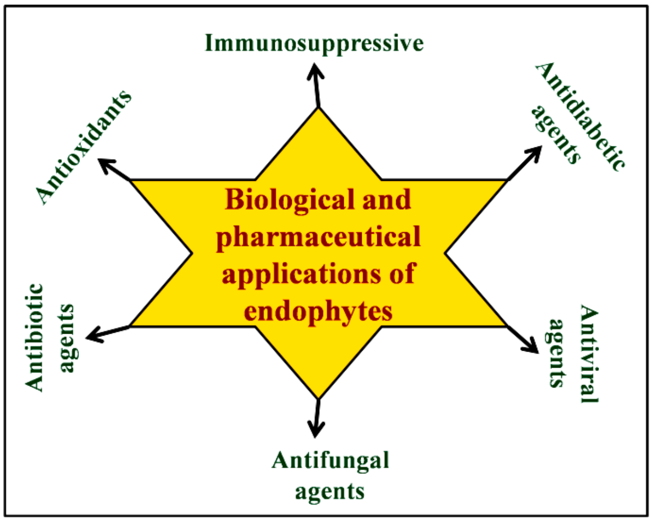

Fig. 11. Pharmaceutical significance of the compounds extracted from endophytes.

These secondary metabolites include alkaloids, flavonoids, steroids, terpenoids, peptides, polyketones, quinols, phenols, saponins, tannins, benzopyranones (63, 64).

Production of antioxidants (AOX) from endophytes

AOX are biological substances that prevent oxidation of chemical compounds. AOX protect cells from damage caused by ROS and free radicals. ROS cause various diseases in humans, some of these including respiratory diseases, cancer, neurodegenerative, digestive diseases (65), hypertension, atherosclerosis and diabetes (66). Endophytes synthesize polysaccharides having antioxidant activity. AOX are used as natural biological therapy for the treatment of various human diseases. A variety of new AOX can be obtained from plants and microorganisms to combat different diseases caused from ROS. Some of the natural and new AOX include Pestacin and Isopestacin obtained from endophyte *Pestalotiopsis microspora* (67, 68), and Lapachol, Coumarin, Tetrahydroxy-1-methylxanthon, p-tyrosol, Borneol, Rutin obtained from fungal endophytes possess anticacinogenic, antimutagenic or anti-inflammatory properties. These compounds with antioxidant properties are effective in counteracting the effects of ROS.

Antidiabetic agents from endophytes

The non peptidal fungal metabolite Demethyl Asterri Quinone B-1(L-783,281) possessing insulin like activity has been produced by endophytic fungus *Pseudomassaria* sp., collected from African rain forest (69). Antidiabetic peptides have been isolated from the endophytic fungi *Aspergillus awamori* by using high-performance-liquid chromatography (HPLC) (70). Antidiabetic compounds have been extracted from many endophytes like *Nigrospora* sp., *Fusarium* sp., *Alternaria* sp., *Phoma* sp. (5). Bioactive compounds having antidiabetic activity have been isolated from the endophytic fungi associated with two prominent medicinal plants *Rauwolfia densiflora* and *Leucas ciliata* (47).

Antiviral agents from endophytes

The bio-prospecting of endophytic fungi for the synthesis of antiviral agent is a very promising and fascinating area of study. The antiviral compounds namely Cytonic acid A and B, Cyclosporine v and Podophyllo toxin have been reported from some fungal endophytes (71). Antiviral compounds from endophytic fungi possess strong activity against some virus like HIV, Dengue virus, Influenza virus. For example, endophytic fungus *Alternaria tenuissima* produces Alter toxin, an effective compound against HIV-1 virus (72). A *Bruguiera gymnorrhiza* endophyte *Streptomyces* sp. strain GT 2002/1503 has been reported to exhibit antiviral actions against HIV infection by the production of Xiamycin A (73). The antiviral compound Pyrazine, produced from *Jishengella endophytica*, acts against Ibinfluenza A virus (Sub type H1N1) (74).

Anticancer agents from endophytes

Many endophyte derived secondary metabolites act as anticancer agents as stated in Fig. 12.

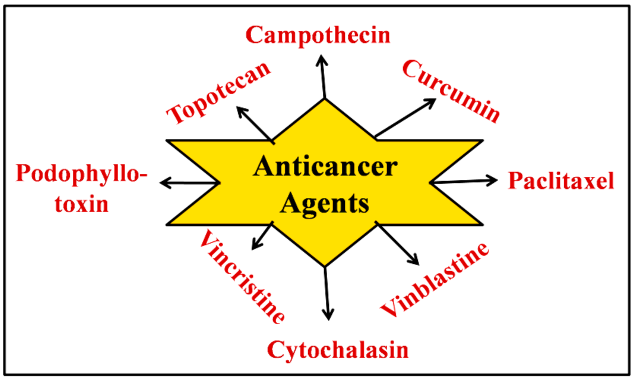

Fig. 12. Different anticancer agents derived from endophytes.

Paclitaxel, a potent anticancer drug has been derived from *Taxomyces andreanae,* an endophytic fungus of *Taxus brevifolia* (75). Many other endophytic fungi like *Seimatoantlerium nepalense*, *Seimatoantlerium tepuiense, Tubercularia* sp. have also been reported to produce Paclitaxel (76). Furthermore, Paclitaxel production has also been reported from *Pestalotiopsis* sp. and *Periconia* sp. (77). Another popular anticancer drug obtained from *Catharanthus roseus* are Vincristine and Vinblastine (78). *Fusarium oxysporum*, isolated from *Catharanthus roseus* also capable to produce these drugs (79). Another anticancer agent Podophyllotoxin is produced by *Podophyllum* sp. (80). Alternatively, Podophyllotoxin has been obtained from the endophytes such as *Trametes hirsuta* (81), *Phialo-*

cephala fortinii isolated from *Podophyllum peltatum* (82), *Fusarium oxysporum* isolated from *Juniperus recurva* (83), *Aspergillus fumigatus* isolated from *Juniperus communis* (84). Anticancerous compound Camptothecin, is an important precursor for the synthesis of Topotecan and Irinotecan that are clinically useful anticancer drugs (85), has been isolated from *Fusarium solani*. Endophytic fungi such as *Phoma, Xylaria, Hypoxylon* produce Cytochalasins (86) which show antitumour activity but Cytochalasins have been reported as cytotoxic agents (87, 88).

Immunosuppressive agents from endophyte

Fungal endophytes are capable of synthesizing certain compounds having immunosuppressive action which are used in the treatment of autoimmune disorders such as insulin dependent diabetes, rheumatoid arthritis and to prevent allograft rejection in transplant patients. *Fusarium subglutinan*, an endophytic fungus isolated from *Tripterygium wilfordii* produces Subglutinol A and B which act as immunosuppressant (71). The synthesis of mycophenolic acid from endophytic fungi in the genera *Aspergillus*, *Penicillium*, and *Septoria* has been reported (89). Mycophenolic acid is a potent immunosuppressant and has been shown to be used in the treatment of autoimmune diseases (90). Subglutinol A and Colutelin A, produced from endophytic fungi, are alternative immunosuppressive drugs for the treatment of autoimmune diseases (71). Thus, fungal endophytes act as a source of affordable immunosuppressive therapeutic drugs that can be used in the treatment of autoimmune diseases and post transplantation care.

Applications of endophytes

Crop management

The most promising application of endophytes is to enhance the production in agricultural field as discussed in Fig. 13.

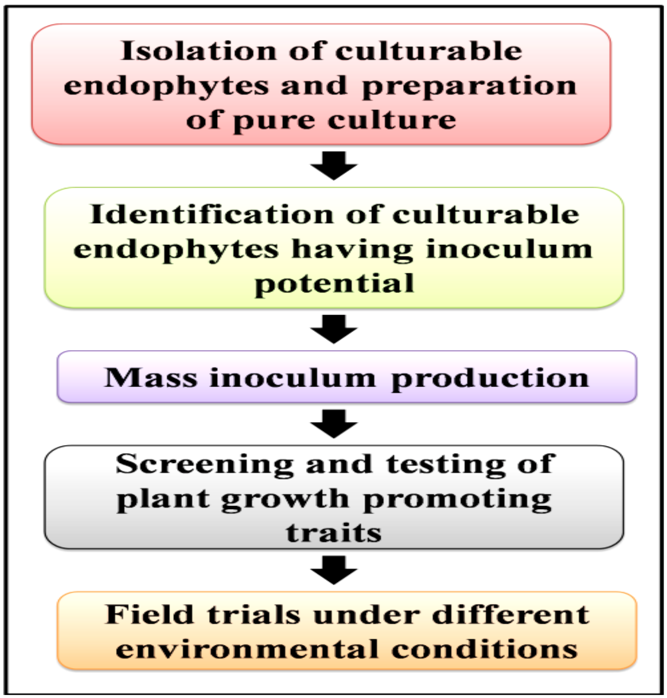

Fig. 13. Successive steps for the screening of plant growth promoting endophytes.

Endophytes promote the growth of host plants as well as increase the tolerance to abiotic and biotic stresses. Currently, chemical fertilizers and chemical pesticides are being used excessively, which has a negative impact on agriculture and the environment. For organic farming, the demand for biofertilizers and biopesticides is increasing day by day. Since endophytes are used as a powerful biofertilizer (91), endophytologists are trying to integrate endophytes into modern agricultural practices in the most efficient and beneficial ways (92).

Role of endophytes in medical field

Endophytes associated with medicinal plants are considered as important sources of secondary metabolites which possess antidiabetic, antitumor, antiviral, antimicrobial, antioxidant, anti-inflammatory and insecticidal properties (93). In some cases, endophytes produce secondary metabolites similar to the host plant, making them equally efficient for drug development. Thus they can be used to treat multidrug resistance infections in humans (9). Endophytic fungi from the root of *Balanophora polyandra* can produce natural AOX and antibacterial compounds that have wide implications not only in pharmaceutical industry but also in agriculture (94). Crude extract of *Bacillus* sp. strain AS_3, *Peribacillus* sp. strain AS_2 and *Lysinibacillus* sp. strain AS_1 has been proven to exhibit growth inhibition of cancer cell lines at a concentration of 1,000 µg/ml (93). *Pestalotiopsis microspora* is important for the production of natural AOX Pestacin and Isopestacin (67, 68). *Alternaria tenuissima* and *Streptomyces* sp. strain GT 2002/1503 have been considered as the sources of antiviral agents (72, 73). Large number of plants and associated endophytes are still unexplored which gain the interest of researchers to explore these microbes for drug discovery (95).

Production of biofuel

Endophytes have been extensively studied as they are able to produce a wide range of natural chemical products. A recent remarkable discovery is that some endophytes are involved in the production of hydrocarbons that have the potential to be used as fuels. Endophytic fungus *Hypoxylon* sp. is known to produce volatile compounds having potential value as fuels (96). *Gliocladium roseum* has been reported to produce more than forty VOCs with fuel potential which are termed as "mycodisel" (97).

Role of endophytes in phytoremediation

Plants can break down or sequester certain organic and inorganic pollutants. Endophytes stimulate this biodegradation process which is diagrammatically represented in Fig. 14.

It has been reported that *Burkholderia* sp., an endophytic bacterium, can break down trichloroethylene (TCE) (98). Another endophytic fungus *Pestalotiopsis microspora* is capable of digesting polyurethane plastics (7). Further research is required to explore new endophytes having the potentiality to degrade the pollutants.

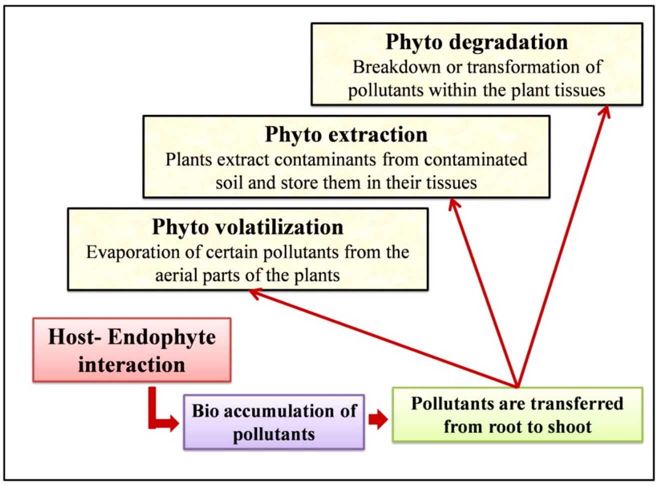

Fig. 14. Plant-Endophyte synergistic interaction in Phytoremediation.

Conclusion and future prospects

Endophytes extend their multifarious activities to promote agricultural and environmental sustainability. They accelerate plant growth and productivity without any adverse effects on the environment. At present, excessive use of chemical fertilizers, herbicides, pesticides and fungicides reduces the food quality and also harms the soil health. The use of endophytes in agriculture can reduce the application of chemical compounds and maintain the food and soil quality. Through nutrient acquisition, endophytes enhance nutrient uptake by the plants, besides this, they make the plants resistant to biotic and abiotic stresses which ultimately increase plant growth and productivity. Endophytes can exhibit plant growth promoting activities such as nitrogen fixation, hormone modulation, phosphate solubilization and siderophore production. Endophytes play an important role in the reducing of environmental contamination through phytoremediation. Moreover, endophytes play important role in plant disease management.

Endophytes have a great impact in biomedical field. They produce a variety of bioactive compounds such as terpenoids, peptides, alkaloids, flavonoids, steroids, saponins, tannins, quinols, phenols, benzopyranones and polyketones. These bioactive compounds are the sources of antimalarial, anticancerous, antibacterial, antiviral, antioxidant, antifungal, antiinflamatory and antidiabetic agents.

In this review, we have represented multiple functions of endophytes including nutrient acquisition, phosphate solubilization, siderophore production, ACC utilization, plant growth promotion, plant root development, biotic and abiotic stress management, host immune system modulation, antidiabetic and anticancerous compounds production and production of antioxidant, antiviral and immunosuppressive agents.

Today, researchers are trying to create the novel bioactive compounds from endophytes which can be used to treat human diseases and to make endophytes more convenient in agricultural systems. The production of these bioactive compounds is controlled by the expression of gene cluster (99). Understanding the expression and regulation of the genes involved is very challenging. In this regard, further research with multidisciplinary scientific approaches including molecular genetics, metabolomics, genome mining, bioinformatics etc. is required to understand the host-endophyte interactions that may provide opportunities in agriculture, industry and medicine

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Authors contributions

SD provided the main concept of the review. Literature study was done by DC. About the whole work, all the Authors (DC, ST, NP, RR, SR, SKS, and SD) were discussed among them and finally the manuscript was prepared by DC. All the Authors helped in formatting.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

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References

1. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: a treasure house of bioactive compounds of medicinal importance. Frontiers in microbiology. 2016 Sep 29; 7:1538. https://dx.doi.org/10.3389%2Ffmicb.2016.01538
2. Hata K, Sone K. Isolation of endophytes from leaves of *Neolitsea sericea* in broadleaf and conifer stands. Mycoscience. 2008 Aug 1; 49(4):229-32. https://doi.org/10.1007/S10267-008-0411-Y
3. Specian V, Sarragiotto MH, Pamphile JA, Clemente E. Chemical characterization of bioactive compounds from the endophytic fungus *Diaporthe helianthi* isolated from *Luehea divaricata*. Brazilian Journal of Microbiology. 2012 Sep; 43(3):1174-82. https://doi.org/10.1590/s1517-838220120003000045
4. Stępniewska Z, Kuźniar A. Endophytic microorganisms—promising applications in bioremediation of greenhouse gases. Applied Microbiology and Biotechnology. 2013 Nov; 97(22): 9589 -96. https://doi.org/10.1007/s00253-013-5235-9
5. Gupta S, Chaturvedi P, Kulkarni MG, Van Staden J. A critical review on exploiting the pharmaceutical potential of plant endophytic fungi. Biotechnology advances. 2020 Mar 1; 39:107462. https://doi.org/10.1016/j.biotechadv.2019.107462
6. Verma H, Kumar D, Kumar V, Kumari M, Singh SK, Sharma VK *et al*. The potential application of endophytes in management of stress from drought and salinity in crop plants. Microorganisms. 2021 Aug 13; 9(8):1729. https://doi.org/10.3390/microorganisms9081729
7. Russell JR, Huang J, Anand P, Kucera K, Sandoval AG, Dantzler KW *et al*. Biodegradation of polyester polyurethane by endophytic fungi. Applied and environmental microbiology. 2011 Sep 1; 77(17):6076-84. https://doi.org/10.1128/AEM.00521-11.

8. Mukherjee A, Bhowmick S, Yadav S, Rashid MM, Chouhan GK, Vaishya JK, Verma JP. Re-vitalizing of endophytic microbes for soil health management and plant protection. 3Biotech. 2021 Sep; 11(9):1-7. https://doi.org/10.1007/s13205-021-02931-4

9. Pasrija P, Girdhar M, Kumar M, Arora S, Katyal A. Endophytes: an unexplored treasure to combat Multidrug resistance. Phytomedicine Plus. 2022 Feb 28; 2(2):100249. https://doi.org/10.1016/j.phyplu.2022.100249

10. Abd Rahman AN, Tett SE, Staatz CE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in patients with autoimmune disease. Clinical pharmacokinetics. 2013 May; 52 (5):303-31. https://doi.org/10.1007/s40262-013-0039-8

11. Verma SK, Sahu PK, Kumar K, Pal G, Gond SK, Kharwar RN, White JF. Endophyte roles in nutrient acquisition, root system architecture development and oxidative stress tolerance. Journal of Applied Microbiology. 2021 Nov; 131(5):2161-77. https://doi.org/10.1111/jam.15111.

12. Xu J. Fungal DNA barcoding. Genome. 2016; 59(11):913-32. https://doi.org/10.1139/gen-2016-0046

13. Long HH, Schmidt DD, Baldwin IT. Native bacterial endophytes promote host growth in a species-specific manner; phytohormone manipulations do not result in common growth responses. PLoS One. 2008 Jul 16; 3(7):e2702. https://dx.doi.org/10.1371%2Fjournal.pone.0002702

14. Naveed M, Mitter B, Reichenauer TG, Wieczorek K, Sessitsch A. Increased drought stress resilience of maize through endophytic colonization by *Burkholderia phytofirmans* PsJN and *Enterobacter* sp. FD17. Environmental and Experimental Botany. 2014 Jan 1; 97:30-39. http://dx.doi.org/10.1016/j.envexpbot.2013.09.014

15. Riggs PJ, Chelius MK, Iniguez AL, Kaeppler SM, Triplett EW. Enhanced maize productivity by inoculation with diazotrophic bacteria. Functional Plant Biology. 2001 Sep 3; 28(9):829-36. http://dx.doi.org/10.1071/PP01045

16. Sheng XF, Xia JJ, Jiang CY, He LY, Qian M. Characterization of heavy metal-resistant endophytic bacteria from rape (*Brassica napus*) roots and their potential in promoting the growth and lead accumulation of rape. Environmental pollution. 2008 Dec 1; 156(3):1164-70. https://doi.org/10.1016/j.envpol.2008.04.007

17. Rodriguez RJ, Henson J, van Volkenburgh E, Hoy M, Wright L, Beckwith F *et al*. Fungal endophytes: diversity and functional roles. New Phytol. 2009; 182:314-30. https://doi.org/10.1111/j.1469-8137.2009.02773.x

18. Rashmi M, Kushveer JS, Sarma VV. A worldwide list of endophytic fungi with notes on ecology and diversity. Mycosphere. 2019 Nov 30; 10(1):798-1079. http://dx.doi.org/10.5943/mycosphere/10/1/19

19. Hallmann J, Quadt-Hallmann A, Miller WG, Sikora RA, Lindow SE. Endophytic colonization of plants by the biocontrol agent *Rhizobium etli* G12 in relation to *Meloidogyne incognita* infection. Phytopathology. 2001 Apr; 91(4):415-22. https://doi.org/10.1094/phyto.2001.91.4.415

20. Compant S, Reiter B, Sessitsch A, Nowak J, Clément C, Ait Barka E. Endophytic colonization of *Vitis vinifera* L. by plant growth-promoting bacterium *Burkholderia* sp. strain PsJN. Applied and Environmental Microbiology. 2005 Apr; 71(4):1685-93. https://doi.org/10.1128/aem.71.4.1685-1693.2005

21. Das PP, Singh KR, Nagpure G, Mansoori A, Singh RP, Ghazi IA *et al*. Plant-soil-microbes: A tripartite interaction for nutrient acquisition and better plant growth for sustainable agricultural practices. Environmental Research. 2022 Nov 1; 214:113821. https://doi.org/10.1016/j.envres.2022.113821

22. White JF, Kingsley KL, Verma SK, Kowalski KP. Rhizophagy cycle: an oxidative process in plants for nutrient extraction from symbiotic microbes. Microorganisms. 2018 Sep; 6(3):95. https://doi.org/10.3390/microorganisms6030095.

23. White JF, Torres MS, Verma SK, Elmore MT, Kowalski KP, Kingsley KL. Evidence for widespread microbivory of endophytic bacteria in roots of vascular plants through oxidative degradation in root cell periplasmic spaces. In: Singh AK, Kumar A, Singh PK, editors. PGPR amelioration in sustainable agriculture. Woodhead; 2019 Jan 1. p. 167-93. https://doi.org/10.1016/B978-0-12-815879-1.00009-4

24. Bajaj R, Huang Y, Gebrechristos S, Mikolajczyk B, Brown H, Prasad R *et al*. Transcriptional responses of soybean roots to colonization with the root endophytic fungus *Piriformospora indica* reveals altered phenylpropanoid and secondary metabolism. Scientific Reports. 2018 Jul 6; 8(1):1-8. https://doi.org/10.1038/s41598-018-26809-3

25. Christian N, Herre EA, Clay K. Foliar endophytic fungi alter patterns of nitrogen uptake and distribution in *Theobroma cacao*. New Phytologist. 2019 May; 222(3):1573-83. https://doi.org/10.1111/nph.15693

26. Waqas M, Kim YH, Khan AL, Shahzad R, Asaf S, Hamayun M *et al*. Additive effects due to biochar and endophyte application enable soybean to enhance nutrient uptake and modulate nutritional parameters. Journal of Zhejiang University-Science B. 2017 Feb; 18(2):109-24.https://doi.org/10.1631/jzus.B1500262

27. Yakti W, Kovács GM, Vági P, Franken P. Impact of dark septate endophytes on tomato growth and nutrient uptake. Plant Ecology and Diversity. 2018 Nov 2; 11(5-6):637-48. https://doi.org/10.1080/17550874.2019.1610912

28. Alori ET, Glick BR, Babalola OO. Microbial phosphorus solubilization and its potential for use in sustainable agriculture. Frontiers in microbiology. 2017 Jun 2; 8:971. https://doi.org/10.3389/fmicb.2017.00971

29. Jog R, Pandya M, Nareshkumar G, Rajkumar S. Mechanism of phosphate solubilization and antifungal activity of *Streptomyces* spp. isolated from wheat roots and rhizosphere and their application in improving plant growth. Microbiology. 2014 Apr 1; 160 (4):778-88. https://doi.org/10.1099/mic.0.074146-0

30. Sharma A, Johri BN. Growth promoting influence of siderophore -producing *Pseudomonas* strains GRP3A and PRS9 in maize (*Zea mays* L.) under iron limiting conditions. Microbiological Research. 2003 Jan 1; 158(3):243-48. https://doi.org/10.1078/0944-5013-00197

31. Singh R, Dubey AK. Diversity and applications of endophytic actinobacteria of plants in special and other ecological niches. Frontiers in Microbiology. 2018 Aug 8; 9:1767.https://doi.org/10.3389/fmicb.2018.01767

32. Bhattacharyya PN, Jha DK. Plant growth-promoting rhizobacteria (PGPR): Emergence in agriculture. World J. Microbiol. Biotechnol. 2012; 28:1327–1350. https://doi.org/10.1007/s12045-016-0421-6

33. Gupta S, Pandey S. ACC deaminase producing bacteria with multifarious plant growth promoting traits alleviates salinity stress in French bean (*Phaseolus vulgaris*) plants. Frontiers in Microbiology. 2019 Jul 9; 10:1506. https://doi.org/10.3389/fmicb.2019.01506

34. Lamont BB. Structure, ecology and physiology of root clusters–a review. Plant and Soil. 2003 Jan; 248(1):1-9. https://doi.org/10.1023/A:1022314613217

35. Crush JR, Popay AJ, Waller J. Effect of different *Neotyphodium* endophytes on root distribution of a perennial ryegrass (*Lolium perenne* L.) cultivar. New Zealand Journal of Agricultural Research. 2004 Sep 1; 47(3):345-49. https://doi.org/10.1080/00288233.2004.9513603

36. Martinuz A, Zewdu G, Ludwig N, Grundler F, Sikora RA, Schouten A. The application of *Arabidopsis thaliana* in studying tripartite interactions among plants, beneficial fungal endophytes and biotrophic plant-parasitic nematodes. Planta. 2015 Apr; 241 (4):1015-25. https://doi.org/10.1007/s00425-014-2237-5

37. Lee YC, Johnson JM, Chien CT, Sun C, Cai D, Lou B *et al*. Growth promotion of Chinese cabbage and *Arabidopsis* by *Piriformospora indica* is not stimulated by mycelium-synthesized auxin. Molecular plant-microbe interactions. 2011 Apr; 24(4):421-31. https://doi.org/10.1094/MPMI-05-10-0110
38. Barka EA, Belarbi A, Hachet C, Nowak J, Audran JC. Enhancement of *in vitro* growth and resistance to gray mould of *Vitis vinifera* co-cultured with plant growth-promoting rhizobacteria. FEMS microbiology letters. 2000 May 1; 186(1):91-95. https://doi.org/10.1111/j.1574-6968.2000.tb09087.x
39. Frommel MI, Nowak J, Lazarovits G. Growth enhancement and developmental modifications of *in vitro* grown potato (*Solanum tuberosum* spp. *tuberosum*) as affected by a nonfluorescent *Pseudomonas* sp. Plant Physiology. 1991 Jul; 96(3):928-36. https://doi.org/10.1104/pp.96.3.928
40. Hamayun M, Afzal Khan S, Ahmad N, Tang DS, Kang SM, Na CI *et al*. *Cladosporium sphaerospermum* as a new plant growth-promoting endophyte from the roots of *Glycine max* (L.) Merr. World Journal of Microbiology and Biotechnology. 2009 Apr; 25 (4):627-32.https//doi.org/10.1007/s11274-009-9982-9
41. Choudhary DK, Prakash A, Johri BN. Induced systemic resistance (ISR) in plants: mechanism of action. Indian Journal of Microbiology. 2007 Dec; 47(4):289-97. https://doi.org/10.1007/s12088-007-0054-2
42. Kavroulakis N, Ntougias S, Zervakis GI, Ehaliotis C, Haralampidis K, Papadopoulou KK. Role of ethylene in the protection of tomato plants against soil-borne fungal pathogens conferred by an endophytic *Fusarium solani* strain. Journal of Experimental Botany. 2007 Nov 1; 58(14):3853-64. https://doi.org/10.1093/jxb/erm230
43. D'Alessandro MA, Erb M, Ton J, Brandenburg A, Karlen D, Zopfi J, Turlings TC. Volatiles produced by soil-borne endophytic bacteria increase plant pathogen resistance and affect tritrophic interactions. Plant, Cell and Environment. 2014 Apr; 37 (4):813-26. https://dx.doi.org/10.1111%2Fpce.12220
44. Sheoran N, Nadakkakath AV, Munjal V, Kundu A, Subaharan K, Venugopal V *et al*. Genetic analysis of plant endophytic *Pseudomonas putida* BP25 and chemo-profiling of its antimicrobial volatile organic compounds. Microbiological Research. 2015 Apr 1; 173:66-78. https://doi.org/10.1016/j.micres.2015.02.001
45. Arora NK, Kang SC, Maheshwari DK. Isolation of siderophore-producing strains of *Rhizobium meliloti* and their biocontrol potential against *Macrophomina phaseolina* that causes charcoal rot of groundnut. Current Science. 2001 Sep 25:673-77. https://www.jstor.org/stable/24106362
46. Mercado-Blanco J, Rodrıguez-Jurado D, Hervás A, Jiménez-Dıaz RM. Suppression of Verticillium wilt in olive planting stocks by root-associated fluorescent *Pseudomonas* spp. Biological Control. 2004 Jun 1; 30(2):474-86. https://doi.org/10.1016/j.biocontrol.2004.02.002
47. Fadiji AE, Babalola OO. Elucidating mechanisms of endophytes used in plant protection and other bioactivities with multifunctional prospects. Frontiers in Bioengineering and Biotechnology. 2020 May 15; 8:467. https://doi.org/10.3389/fbioe.2020.00467
48. Fracetto GG, Peres LE, Lambais MR. Gene expression analyses in tomato near isogenic lines provide evidence for ethylene and abscisic acid biosynthesis fine-tuning during arbuscular mycorrhiza development. Archives of Microbiology. 2017 Jul; 199 (5):787-98. https://doi.org/10.1007/s00203-017-1354-5
49. Pandey V, Ansari MW, Tula S, Yadav S, Sahoo RK, Shukla N *et al*. Dose-dependent response of *Trichoderma harzianum* in improving drought tolerance in rice genotypes. Planta. 2016 May; 243 (5):1251-64. https://doi.org/10.1007/s00425-016-2482-x
50. Sheibani-Tezerji R, Rattei T, Sessitsch A, Trognitz F, Mitter B. Transcriptome profiling of the endophyte *Burkholderia phytofirmans* PsJN indicates sensing of the plant environment and drought stress. MBio. 2015 Oct 30; 6(5):e00621-15. https://dx.doi.org/10.1128%2FmBio.00621-15
51. De Zelicourt A, Al-Yousif M, Hirt H. Rhizosphere microbes as essential partners for plant stress tolerance. Molecular Plant. 2013 Mar 1; 6(2):242-45. http://doi.org/10.1093/mp/sst028
52. Madhaiyan M, Poonguzhali S, Sa T. Metal tolerating methylotrophic bacteria reduces nickel and cadmium toxicity and promotes plant growth of tomato (*Lycopersicon esculentum* L.). Chemosphere. 2007 Sep 1; 69(2):220-28. https://doi.org/10.1016/j.chemosphere.2007.04.017
53. Germaine KJ, Liu X, Cabellos GG, Hogan JP, Ryan D, Dowling DN. Bacterial endophyte-enhanced phytoremediation of the organochlorine herbicide 2, 4-dichlorophenoxyacetic acid. FEMS Microbiology Ecology. 2006 Aug 1; 57(2):302-10. https://doi.org/10.1111/j.1574-6941.2006.00121.x
54. Sharma P, Jha AB, Dubey RS, Pessarakli M. Reactive oxygen species, oxidative damage, and antioxidative defense mechanism in plants under stressful conditions. Journal of botany. 2012 Apr 24; 2012:1-26. https://doi.org/10.1155/2012/217037
55. Kandel SL, Joubert PM, Doty SL. Bacterial endophyte colonization and distribution within plants. Microorganisms. 2017 Dec; 5 (4):77. https://dx.doi.org/10.3390%2Fmicroorganisms5040077
56. Sun C, Johnson JM, Cai D, Sherameti I, Oelmüller R, Lou B. *Piriformospora indica* confers drought tolerance in Chinese cabbage leaves by stimulating antioxidant enzymes, the expression of drought-related genes and the plastid-localized CAS protein. Journal of Plant Physiology. 2010 Aug 15; 167(12):1009-17. https://doi.org/10.1016/j.jplph.2010.02.013
57. Newman MA, Sundelin T, Nielsen JT, Erbs G. MAMP (microbe-associated molecular pattern) triggered immunity in plants. Frontiers in Plant Science. 2013 May 16; 4:139. https://doi.org/10.3389/fpls.2013.00139
58. Sanchez-Vallet A, Mesters JR, Thomma BP. The battle for chitin recognition in plant-microbe interactions. FEMS Microbiology Reviews. 2015 Mar 1; 39(2):171-83. https://doi.org/10.1093/femsre/fuu003
59. Cord-Landwehr S, Melcher RL, Kolkenbrock S, Moerschbacher BM. A chitin deacetylase from the endophytic fungus *Pestalotiopsis* sp. efficiently inactivates the elicitor activity of chitin oligomers in rice cells. Scientific Reports. 2016 Nov 30; 6(1):1-1. https://dx.doi.org/10.1038%2Fsrep38018
60. Green ER, Mecsas J. Bacterial secretion systems: an overview. Microbiology Spectrum. 2016 Feb 26; 4(1):1-19. https://dx.doi.org/10.1128%2Fmicrobiolspec.VMBF-0012-2015
61. Bastias DA, Martínez-Ghersa MA, Ballaré CL, Gundel PE. *Epichloë* fungal endophytes and plant defenses: not just alkaloids. Trends in Plant Science. 2017 Nov 1; 22(11):939-48. http://dx.doi.org/10.1016/j.tplants.2017.08.005
62. Wu C, Han T, Lu H, Zhao B. The toxicology mechanism of endophytic fungus and swainsonine in locoweed. Environmental Toxicology and Pharmacology. 2016 Oct 1; 47:38-46. https://doi.org/10.1016/j.etap.2016.08.018
63. Singh M, Kumar A, Singh R, Pandey KD. Endophytic bacteria: a new source of bioactive compounds. 3Biotech. 2017 Oct; 7(5):1-4. https://dx.doi.org/10.1007%2Fs13205-017-0942-z
64. Maulidia V, Soesanto L, Syamsuddin S, Khairan K, Hamaguchi T, Hasegawa K, Sriwati R. Secondary metabolites produced by endophytic bacteria against the Root-Knot Nematode (*Meloidogyne* sp.). Biodiversitas Journal of Biological Diversity. 2020 Oct 20; 21(11): 5270-5. http://dx.doi.org/10.13057/biodiv/d211130

65. Liu Z, Ren Z, Zhang J, Chuang CC, Kandaswamy E, Zhou T, Zuo L. Role of ROS and nutritional antioxidants in human diseases. Frontiers in Physiology. 2018 May 17; 9:477. https://doi.org/10.3389/fphys.2018.00477

66. Ochoa CD, Wu RF, Terada LS. ROS signaling and ER stress in cardiovascular disease. Molecular Aspects of Medicine. 2018 Oct 1; 63:18-29. https://doi.org/10.1016/j.mam.2018.03.002

67. Harper JK, Arif AM, Ford EJ, Strobel GA, Porco Jr JA, Tomer DP *et al*. Pestacin: a 1, 3-dihydro isobenzofuran from *Pestalotiopsis microspora* possessing antioxidant and antimycotic activities. Tetrahedron. 2003 Mar 31; 59(14):2471-76. http://dx.doi.org/10.1016/S0040-4020(03)00255-2

68. Strobel G, Ford E, Worapong J, Harper JK, Arif AM, Grant DM *et al*. Isopestacin, an isobenzofuranone from *Pestalotiopsis microspora*, possessing antifungal and antioxidant activities. Phytochemistry. 2002 May 1; 60(2):179-83. http://dx.doi.org/10.1016/S0031-9422(02)00062-6

69. Zhang B, Salituro G, Szalkowski D, Li Z, Zhang Y, Royo I *et al*. Discovery of a small molecule insulin mimetic with antidiabetic activity in mice. Science. 1999 May 7; 284(5416):974-77. https://doi.org/10.1126/science.284.5416.974

70. Singh B, Kaur A. Antidiabetic potential of a peptide isolated from an endophytic *Aspergillus awamori*. Journal of Applied Microbiology. 2016 Feb; 120(2):301-11. https://doi.org/10.1111/jam.12998

71. Adeleke BS, Babalola OO. Pharmacological potential of fungal endophytes associated with medicinal plants: A review. Journal of Fungi. 2021 Feb; 7(2):147. https://doi.org/10.3390/jof7020147

72. Bashyal BP, Wellensiek BP, Ramakrishnan R, Faeth SH, Ahmad N, Gunatilaka AL. Altertoxins with potent anti-HIV activity from *Alternaria tenuissima* QUE1Se, a fungal endophyte of *Quercus emoryi*. Bioorganic and Medicinal Chemistry. 2014 Nov 1; 22 (21):6112-16.http://dx.doi.org/10.1016/j.bmc.2014.08.039

73. Ding L, Münch J, Goerls H, Maier A, Fiebig HH, Lin WH, Hertweck C. Xiamycin, a pentacyclic indolosesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. Bioorganic & Medicinal Chemistry Letters. 2010 Nov 15; 20(22):6685-7. https://doi.org/10.1016/j.bmcl.2010.09.010

74. Wang P, Kong F, Wei J, Wang Y, Wang W, Hong K, Zhu W. Alkaloids from the mangrove-derived actinomycete *Jishengella endophytica* 161111. Marine Drugs. 2014 Jan; 12(1):477-90. https://dx.doi.org/10.3390%2Fmd12010477

75. Stierle A, Strobel G, Stierle D, Grothaus P, Bignami G. The search for a taxol-producing microorganism among the endophytic fungi of the Pacific yew, *Taxus brevifolia*. Journal of Natural Products. 1995 Sep; 58(9):1315-24. https://doi.org/10.1021/np50123a002

76. Bashyal B, Li JY, Strobel G, Hess WM, Sidhu R. *Seimatoantlerium nepalense*, an endophytic taxol producing coelomycete from Himalayan yew (*Taxus wallachiana*). Mycotaxon. 1999. 72:33-42.

77. Strobel GA, Hess WM, Li JY, Ford E, Sears J, Sidhu RS, Summerell B. *Pestalotiopsis guepinii*, a taxol-producing endophyte of the *Wollemi* pine, *Wollemia nobilis*. Australian Journal of Botany. 1997; 45(6):1073-82. https://doi.org/10.1071/BT96094

78. Almagro L, Fernández-Pérez F, Pedreño MA. Indole alkaloids from *Catharanthus roseus*: bioproduction and their effect on human health. Molecules. 2015 Feb; 20(2):2973-3000. https://dx.doi.org/10.3390%2Fmolecules20022973

79. Kumar A, Patil D, Rajamohanan PR, Ahmad A. Isolation, purification and characterization of vinblastine and vincristine from endophytic fungus *Fusarium oxysporum* isolated from *Catharanthus roseus*. PloS one. 2013 Sep 16; 8(9):e71805. https://doi.org/10.1371/journal.pone.0071805

80. Biswas D, Biswas P, Nandy S, Mukherjee A, Pandey DK, Dey A. Endophytes producing podophyllotoxin from *Podophyllum* sp. and other plants: A review on isolation, extraction and bottlenecks. South African Journal of Botany. 2020 Nov 1; 134:303-13. https://doi.org/10.1016/j.sajb.2020.02.038

81. Puri SC, Nazir A, Chawla R, Arora R, Riyaz-ul-Hasan S, Amna T *et al*. The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. Journal of Biotechnology. 2006 Apr 20; 122(4):494-510. https://doi.org/10.1016/j.jbiotec.2005.10.015

82. Eyberger AL, Dondapati R, Porter JR. Endophyte fungal isolates from *Podophyllum peltatum* produce podophyllotoxin. Journal of Natural Products. 2006 Aug 25; 69(8):1121-24. https://doi.org/10.1021/np060174f

83. Kour A, Shawl AS, Rehman S, Sultan P, Qazi PH, Suden P *et al*. Isolation and identification of an endophytic strain of *Fusarium oxysporum* producing podophyllotoxin from *Juniperus recurva*. World Journal of Microbiology and Biotechnology. 2008 Jul; 24 (7):1115-21. https://doi.org/10.1007/s11274-007-9582-5

84. Kusari S, Lamshöft M, Spiteller M. *Aspergillus fumigatus* Fresenius, an endophytic fungus from *Juniperus communis* L. Horstmann as a novel source of the anticancer pro-drug deoxypodophyllotoxin. Journal of Applied Microbiology. 2009 Sep; 107 (3):1019-30. https://doi.org/10.1111/j.1365-2672.2009.04285.x

85. Shweta S, Zuehlke S, Ramesha BT, Priti V, Kumar PM, Ravikanth G *et al*. Endophytic fungal strains of *Fusarium solani*, from *Apodytes dimidiata* E. Mey. ex Arn. (Icacinaceae) produce camptothecin, 10-hydroxycamptothecin and 9-methoxycamptothecin. Phytochemistry. 2010 Jan 1; 71(1):117-22. https://doi.org/10.1016/j.phytochem.2009.09.030

86. Manganyi MC, Ateba CN. Untapped potentials of endophytic fungi: A review of novel bioactive compounds with biological applications. Microorganisms. 2020 Dec; 8(12):1934. https://doi.org/10.3390/microorganisms8121934

87. Huang FY, Mei WL, Li YN, Tan GH, Dai HF, Guo JL *et al*. The antitumour activities induced by pegylated liposomal cytochalasin D in murine models. European Journal of Cancer. 2012 Sep 1;48 (14):2260-69. https://doi.org/10.1016/j.ejca.2011.12.018

88. Trendowski M, Mitchell JM, Corsette CM, Acquafondata C, Fondy TP. Chemotherapy with cytochalasin congeners *in vitro* and *in vivo* against murine models. Investigational New Drugs. 2015 Apr; 33(2):290-99. https://dx.doi.org/10.1007%2Fs10637-014-0203-5

89. Song X, Tu R, Mei X, Wu S, Lan B, Zhang L, Luo X, Liu J, Luo M. A mycophenolic acid derivative from the fungus *Penicillium* sp. SCSIO sof101. Natural Product Research. 2020 May 2; 34(9):1206-12. https://doi.org/10.1080/14786419.2018.1553881

90. Kumar M, Saxena R, Tomar RS. Endophytic microorganisms: promising candidate as biofertilizer. In: Panpatte D, Jhala Y, Vyas R, Shelat H, editors. Microorganisms for green revolution. 6. Singapore: Springer; 2017. p. 77-85. https://doi.org/10.1007/978-981-10-6241-4_4)

91. Le Cocq K, Gurr SJ, Hirsch PR, Mauchline TH. Exploitation of endophytes for sustainable agricultural intensification. Molecular Plant Pathology. 2017 Apr; 18(3):469-73. https://dx.doi.org/10.1111%2Fmpp.12483

92. Firáková S, Šturdíková M, Múčková M. Bioactive secondary metabolites produced by microorganisms associated with plants. Biologia. 2007 Jun; 62(3):251-57. http://dx.doi.org/10.2478/s11756-007-0044-1

93. Maela MP, van der Walt H, Serepa-Dlamini MH. The antibacterial and anticancer activities and Bioactive constituents' identification of *Alectra sessiliflora* bacterial endophytes. Frontiers in Microbiology. 2022 Jul 5; 13:870821. https://doi.org/10.3389/fmicb.2022.870821

94. Wu C, Wang W, Wang X, Shahid H, Yang Y, Wang Y *et al*. Diversity and communities of culturable endophytic fungi from the root

holoparasite *Balanophora polyandra* Griff. and their antibacterial and antioxidant activities. Annals of Microbiology. 2022 May 24; 72(19):1-11. https://doi.org/10.1186/s13213-022-01676-6

95. Gupta J, Sharma S. Endophytic fungi: A new hope for drug discovery. In: Singh J, Gehlot P Editors. New and Future Developments in Microbial Biotechnology and Bioengineering. Elsevier; 2020 Jan 1. p. 39-49. https://doi.org/10.1016/B978-0-12-821006-2.00004-2

96. Maxwell T, Blair RG, Wang Y, Kettring AH, Moore SD, Rex M, Harper JK. A solvent-free approach for converting cellulose waste into volatile organic compounds with endophytic fungi. Journal of Fungi. 2018 Sep; 4(3):102. https://doi.org/10.3390/jof4030102

97. Strobel GA, Knighton WB, Kluck K, Ren Y, Livinghouse T, Griffin M *et al*. The production of myco-diesel hydrocarbons and their derivatives by the endophytic fungus *Gliocladium roseum* (NRRL 50072). Microbiology. 2010; 156(2):3830-83. https://doi.org/10.1099/mic.0.2008/022186-0

98. Kang JW, Doty SL. Cometabolic degradation of trichloroethylene by *Burkholderia cepacia* G4 with poplar leaf homogenate. Canadian Journal of Microbiology. 2014; 60(7):487-90. https://doi.org/10.1139/cjm-2014-0095

99. Rashmi M, Venkateswara SV. Secondary metabolite production by endophytic fungi: the gene clusters, nature, and expression. In: Jha S, Editors. Endophytes and secondary metabolites. Cham: Springer; 2019. p. 475-90. https://doi.org/10.1007/978-3-319-90484-9_20

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