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

Debapriya Choudhury, Santanu Tarafdar, Nasrin Parvin, Rajarshi Rit, Sanchali Roy, Sudip Kr. Sadhu & Sikha Dutta*

Applied and Molecular Mycology and Plant Pathology Laboratory, CAS Department of Botany, The University of Burdwan, Purba Bardhaman 713 104, West Bengal, India

*Email: sikha.bu.academia@gmail.com

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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.

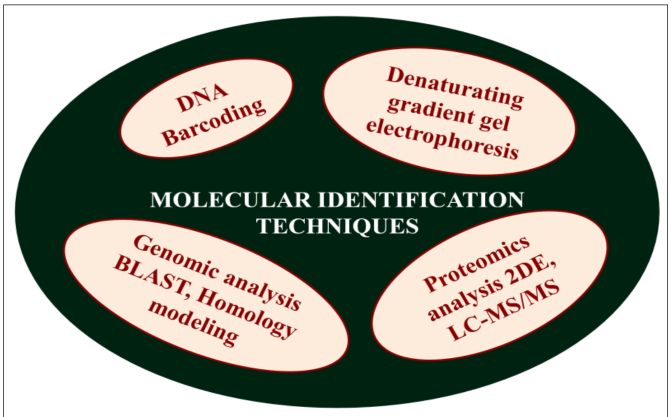

Fig. 1. Molecular techniques for identification of endophytes (BLAST, 2DE, LC-MS/MS represent Basic Local Alignment Search Tool, Two-dimensional gel electrophoresis, and Liquid Chromatography-Tandem Mass Spectrometry respectively).

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.

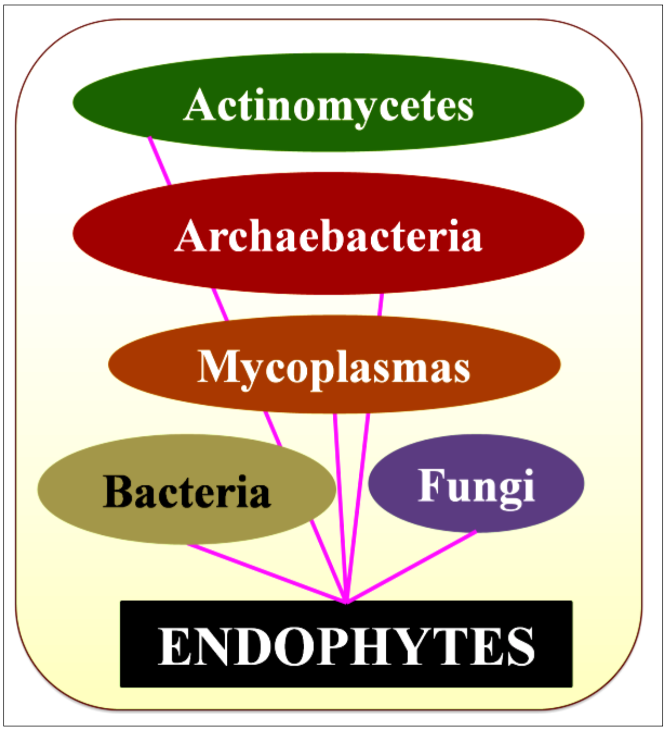

Fig. 2. Types of Endophytes.

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.

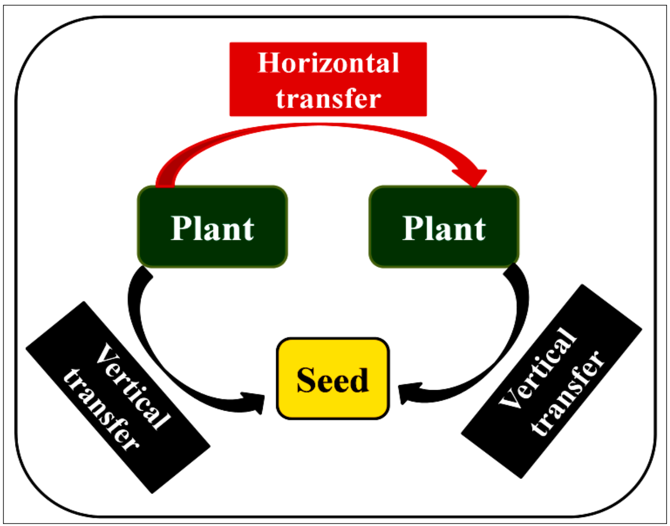

Fig. 3. Mode of colonization of endophytes.

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**.**

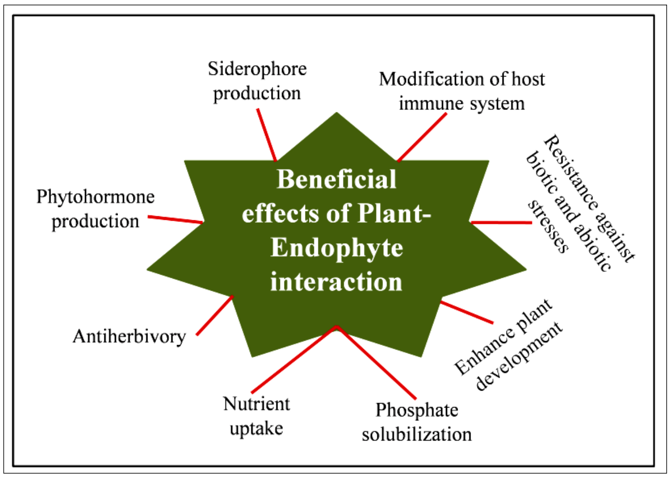

Fig. 4. Endophytes- In plant growth regulation.

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.

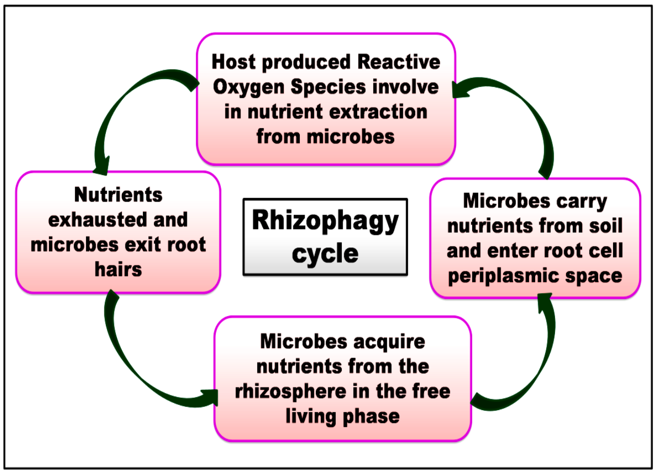

Fig. 5. Diagrammatic representation of the Rhizophagy Cycle.

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.

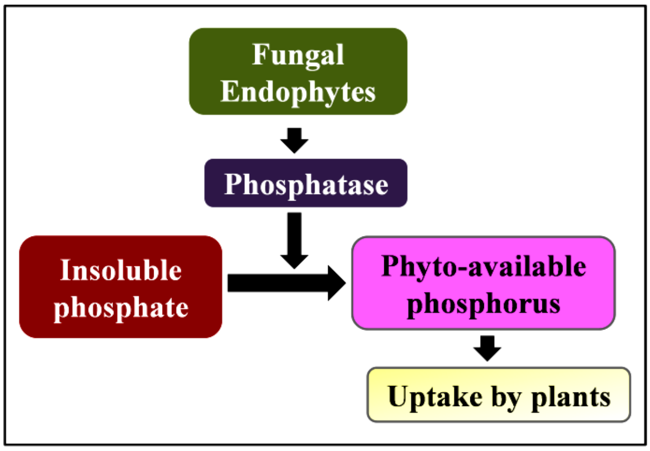

Fig. 6. Schematic representation- Endophytes in phosphate solubilization.

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).

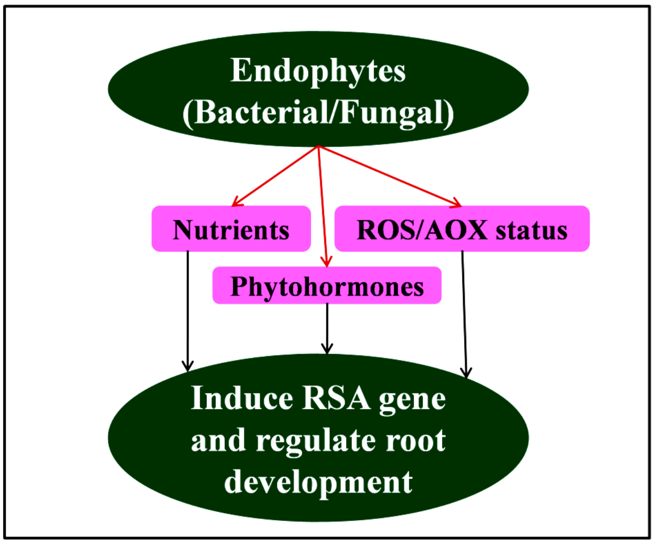

Fig. 7. Endophyte mediated mechanism of root development (ROS, AOX and RSA represent Reactive Oxygen Species, Antioxidant and Root system architecture respectively).

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.

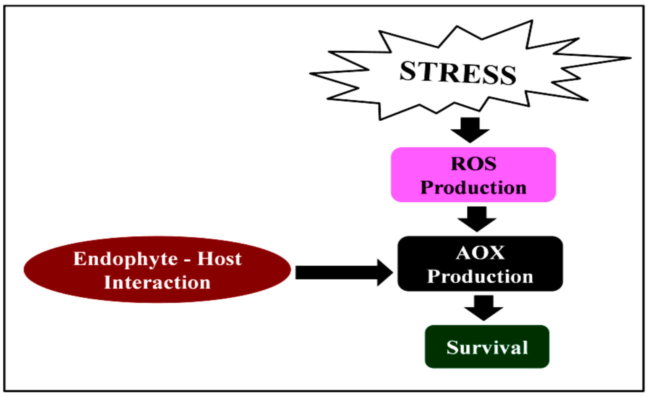

Fig. 8. Endophyte mediated AOX production to scavenge ROS (ROS and AOX indicate Reactive Oxygen Species and Antioxidants respectively).

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.

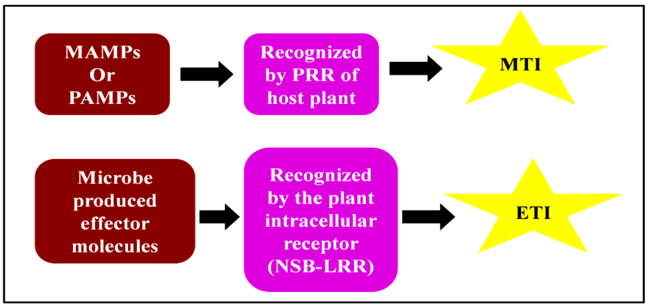

Fig. 9. Plant immune system response against bacterial and fungal pathogen (where, MAMPs- Microbe associated molecular patterns, PAMPs- Pathogen associated molecular patterns, PRR- Patterns reorganisation receptors, NSB-LRR- Nucleotide binding site- Leucine rich repeat, MTI and ETI are MAMP-triggered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

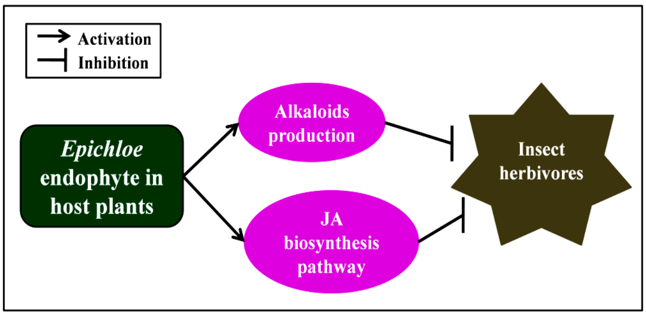

Fig. 10. Schematic representation- Endophyte mediated Antiherbivory (JA represents Jasmonic Acid).

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.

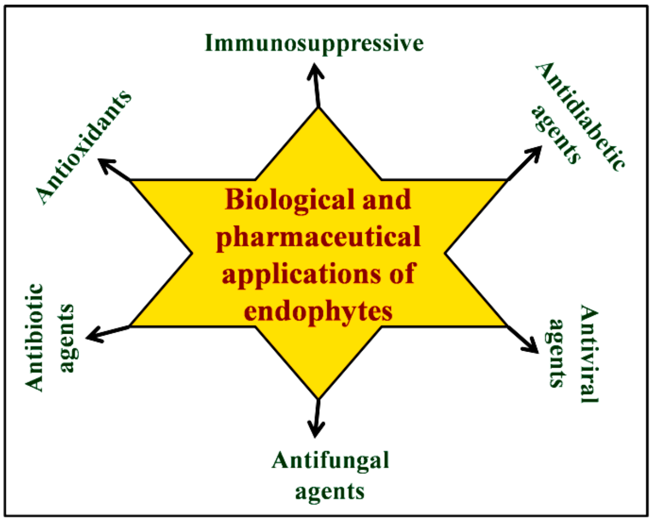

Fig. 11. Pharmaceutical significance of the compounds extracted from endophytes.

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.

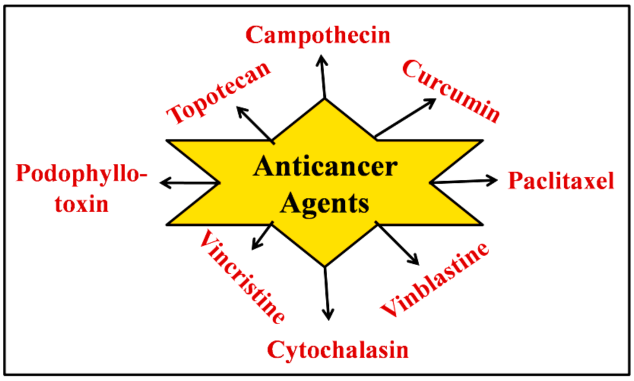

Fig. 12. Different anticancer agents derived from endophytes.

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 anti-cancer drugs (85), has been isolated from *Fusarium solani*. Endophytic fungi such as *Phoma, Xylaria, Hypoxylon* produce Cytochalasins (86) which show anti-tumour 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.

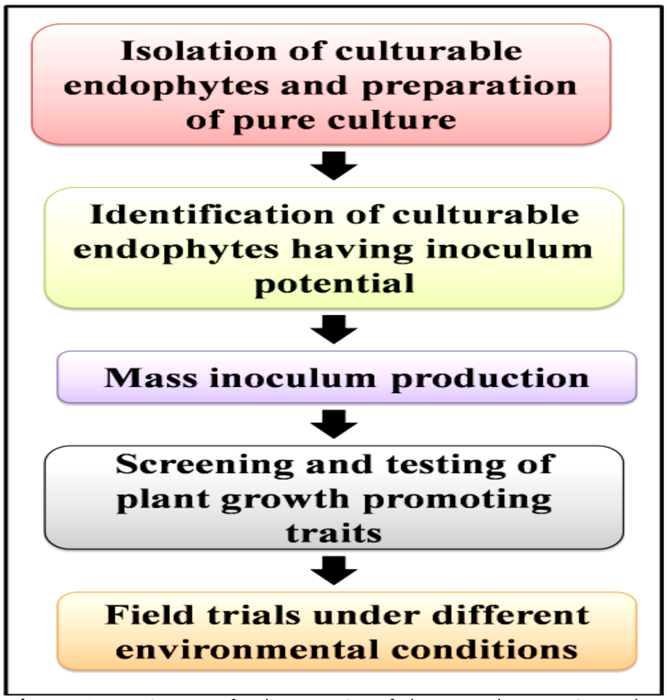

Fig. 13. Successive steps for the screening of plant growth promoting endophytes.

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 "myco-disel" (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.

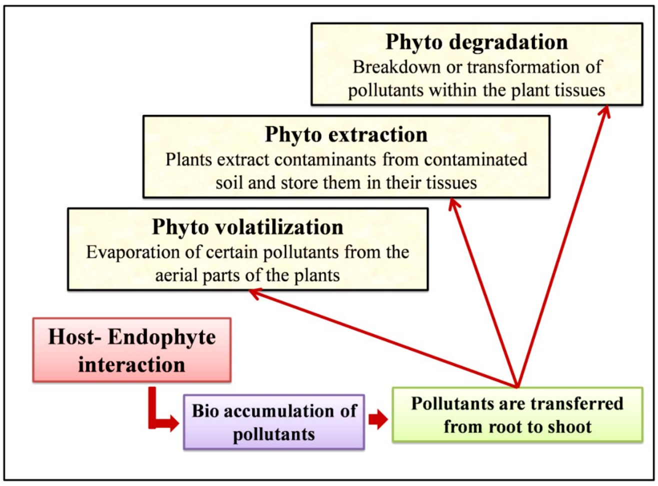

Fig. 14. Plant-Endophyte synergistic interaction in Phytoremediation.

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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