Chapter 4
Endophytic Microbes from Medicinal Plants and Their Secondary Metabolites for Agricultural Significances

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Abstract Endophytes constitute an important component of microbial diversity since 20 years, remarkable progress in the field revealed the significance of endophytic microorganisms. Endophytic fungi are an unexplored group of organisms that has huge potential for innovative pharmaceutical substances; they are established as anticancer, antioxidants, antifungal, and anti-inflammatory. Likewise in recent years, incredible progress was made in developing them as therapeutic molecules against diverse ailments. In recent years, more studies are warranted in bioprospecting new endophytic microorganisms and their applications. Bacterial and fungal endophytes ubiquitously reside in internal tissue of living plants. Endophytic fungi distributed out from tropical region to arctic region, possess vast potential in terms of secondary metabolite production. It is pertinent to know that the various bioactive indispensable compounds evaluated by these endophytic fungi are host-specific. They are very significant in augmenting the adaptability of the endophyte and its host plants for instance biotic and abiotic stress tolerance. The ensuing effect is to produce metabolites either primary or secondary that are obliging for fungi themselves, the host plant in addition to the human race thereof. This chapter primarily emphasizes on the ecology, colonization, biodiversity, secondary metabolites from endophytic fungal cultures.

Keywords Endophytic microbial diversity · Medicinal plants · Bioactive compounds · Secondary metabolites

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4.1 Introduction

With the human population rising, a simultaneous boost in diseases along with an increase in the incidence of reemerging diseases is noticed. The key origin of these medical emergencies being drug resistance in pathogenic bacteria, while the solution lies in the discovery of newer drugs to combat resistant bacteria. Numerous ecosystems were previously explored for the bioprospection of antibiotic producing microorganisms counting with terrestrial, marine, freshwater ecosystems. Notably, with the advent of endophytic microorganisms, a new niche is open for drug discovery (Berde 2015).

Endophyte was commonly associated with fungi initially, but now also includes bacteria as well. These microbes may perhaps exert beneficial or detrimental effects on plants and their metabolism. The endophytic microbes dwell in different tissue types within numerous plant species. The endophytic bacteria are ubiquitous in nature. An endophyte completes its life cycle colonizing inter and intracellularly contained by the healthy tissues of the host plant, with no visible symptoms of disease (Wilson 1995). And thus some endophytic microorganisms live in plant tissue without causing considerable harm to the plant.

Plant-associated microbes have been discovered in the fossilized tissues of stems and leaves (Taylor and Taylor 2000). The endophytic microorganisms are believed to have devised genetic systems and acquired as well as donated characteristics (Stierle et al. 1993). The growth, survival, and transmission of endophytic microorganisms to other plants occur vertically or via vectors and are firmly dependant on the host plants. When at least one stage of the life cycle of the endophyte is outside the host plant, it is facultative endophytes. Many substances of medicinal importance found in plants have also been extracted from their endophytes (Yadav 2017; Yadav et al. 2017; Yadav and Yadav 2018). Therefore, the attention is now on studies that are focused on the isolation and application of endophytes from medicinal plants.

Endophytic microorganisms survive inside the host plant tissues and produce novel metabolic compounds, having activity against various pathogens. Researchers have discovered new therapeutic alternatives in the form of bioactive secondary metabolites in endophytes such as antiviral, antibacterial, anticancer, and antidiabetic compounds (Kumar et al. 2015). Recently endophytes are considered as an essential source of secondary metabolites and bioactive antimicrobial natural products. The endophytic bacterial natural products, for example, munumbicins, ecomycins, pseudomycins, and xiamycins are antibacterial, antimycotic, and antiplasmodial in addition to antiviral in nature, respectively (Berde 2015).

Recent studies evidenced counts of natural products including compounds made up of terpenoids, flavonoids, alkaloids, steroids, etc. Metabolites of endophytes have been reported to hinder the growth of a number of microorganisms (Rana et al. 2019c; Yadav 2018). Microbial metabolites are considered as antifungal and antibacterial chemotherapeutic. In 2008, Moricca and Ragazzi reported that genes regulating the communication between an endophyte and a plant are strictly modulated by the environment. Hostile environment induces the production of defense chemicals.

Plants growing in extreme habitats ought to be screened for isolation of endophytes and their metabolites. Plants present in various environmental conditions including tropic, temperate, xerophytic, and aquatic, harbor the endophytic microorganisms. The endophyte associated plants produce various metabolites that induce resistance. It is notable that symbiotic plant triggers defense system more promptly than non symbiotic plants following a pathogen encounter (Jalgaonwala et al. 2011).

In the plant–microbe relationship, the endophytes supply nutrients to the plant, protect the plant from the invasion of pathogenic microorganisms, and in return, get space to colonize. The various activities of endophytes such as nitrogen fixation, solubilizing iron, and production of metabolites for plant protection enable the endophyte to help in the associate plant growth (Marx 2004; Porras-Soriano et al. 2009; Ryan et al. 2008; Rana et al. 2019a, b). The endophytes produce excess substances of impending use to modern medicine, agriculture, and industry. Endophytes were documented to produce a variety of biological activities such as antibiotic, anti-inflammatory, antiviral, anticancer, and antioxidant (Kado 1992; Kobayashi and Palumboo 2000; Yadav et al. 2019a, b, c).

4.2 Ecology of Endophytic Bacteria

The endophytic bacteria were perhaps isolated from monocotyledonous as well as dicotyledonous plants, including woody tree species, for example, oak (Brooks et al. 1994) and pear (Whitesides and Spotts 1991), as well as herbaceous crop plants, such as sugar beets (Jacobs et al. 1985) and maize (Gutierrez-Zamora and Martinez-Romero 2001). Diversity linked with bacterial endophytes occurs in plant species and also in colonizing bacterial taxa.

Plants can be colonized concurrently by a variety of endophytic bacteria. Plant endophytic bacteria have been classified into 82 genera within Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Actinobacteria Firmicutes, and *Bacteroidetes* and most of them fit into Alphaproteobacteria, Betaproteobacteria, and Gammaproteobacteria (Lodewyckx et al. 2002; Rosenblueth and Martínez-Romero 2006). While new endophytes are being continuously reported from different plant species. Within a particular plant, in the different tissues, different bacterial and fungal species can colonize. Thus, the plant itself forms a complex microecosystem, providing niche/habitats for the endophytes as per their preferences (Kour et al. 2019b, c). These habitats are not only exemplified by plant external surfaces, where epiphytic bacteria predominate, but also by internal tissues especially in xylem and phloem, where many microorganisms penetrate and survive.

The distribution of endophytic bacteria in different parts of the plant was first observed by Gardner et al. (1982). The endophytic bacteria present in the xylem fluid of Florida citrus tree roots was identified by the authors. Among the 13 genera found, the most dominant species were *Pseudomonas* amounting to 40% while *Enterobacter* comprised of 18%. This stable biodiversity is considered to be the most important condition in the establishment of any ecosystem.

4.3 Colonization of Plant by Endophytes

In some cases, endophytic bacteria may be transferred through the seed. These endophytic bacteria can stimulate plant growth and their progress in the host tissue. Endophytic microorganisms having the ability to fix atmospheric nitrogen and solubilize phosphate, as well as the ability to eliminate soil contaminants, play a crucial role in increasing the soil fertility.

Even though bacteria are prokaryotes and fungi are eukaryotes, they share many qualities of their relationship with plant hosts. In both the cases, colonization of root tissues is internal as well as external. Mostly it is systemical. The mode of colonization, however, differs in the two. Bacteria primarily colonize intercellularly and are mostly found in the vascular tissues of host plants. This helps the endophyte in its distribution. Asymptomatic colonization of the roots by fungi may be intercellular or intracellular in nature.

4.4 Natural Products from Endophytic Bacteria as Secondary Metabolites

Knowing the importance of endophytic microbial community, the endophytic microbial composition of the medicinal plants should be studied, identity of the microorganisms should be carried out, and the endophytic microbial preservation should be given preference in research. Secondly, there is a need to bioprospect the endophytes for other industrial applications also apart from antibiotics. The relationship between the geographical distribution of plants and their endophytic composition, as well as the plant–microbe relation needs to be established.

The endophytes colonize a particular niche, i.e., the plant tissue, which helps them in their role as biocontrol agents similar to that of phytopathogens. There are numerous reports about the role of the endophytic microorganisms in controlling plant pathogens, insects, and nematodes, and also in accelerating seedling emergence, enhancing growth of plants, and helping in plant establishment under adverse conditions (Kour et al. 2019a; Suman et al. 2016). Disease development is prevented due to the de novo production of varied new compounds and antifungal metabolites.

According to Lodewyckx et al. (2002), endophytes include bacterial genera that was found in soil, such as *Pseudomonas, Burkholderia,* and *Bacillus*. A wide range of diverse range of secondary metabolic products including antibiotics, anticancer compounds, volatile organic compounds, antifungal, antiviral, insecticidal, and immunosuppressant agents are obtained from these genera. Extensive number of biologically active compounds have been isolated from endophytic microorganisms; however, there still remains a largely untapped source of novel natural products.

Guo et al. 2000 reported cytonic acids that act on viruses namely cytomegaloviruses. There are very few reports of antiviral from endophyte bacteria. Sun et al. (2006) have worked on the endophyte *B. amyloliquefaciens* (ES-2) isolated from a herb *Scutellaria baicalensis* Georgi. The endophyte produces fengycins and surfactins which have antibacterial and antifungal properties. Zhou et al. (2015) has reported an endophytic fungi *Aspergillus versicolor* producing antiviral butyrolactones. Settu et al. (2010) have worked on the endophytes of *Andrographis paniculola*. Endophytes of these plants possess activity against Gram-positive and Gram-negative bacteria. Khaled et al. (2018) have worked on endophytic fungi of Egyptian medicinal plants and have found these isolates to possess antiviral and antioxidant activities.

4.4.1 Endophytes as a Source of Antibiotics

Medicinal plants have been used in the treatment of numerous infections and diseases, with their medicinal applications described in the Ayurveda. The compounds responsible for these medical applications are present in the plants and are alo obtained from the endopytic bacteria and fungi, endophytic in these plants. These natural compounds offer a great diversity of chemical structures that can be researched and applied for betterment of mankind (Berde 2015). Research on secondary metabolites with antimicrobial activity is essential with the development of antibiotic resistance in pathogens and the problem of emerging and reemerging diseases. The potential endophytic microorganisms can be utilized to address these problems.

Numerous synthetic drugs have been developed based on the lead compounds isolated from natural products. The classical example cited is that of the prototypical taxane isolated by Wani et al. in 1971, from the bark of a yew tree *Taxus brevifolia*. In 1996, Strobel et al. reported an endophytic fungus (*Pestalotiopsis microspora*) found in Yew tree with ability to produce Taxol. Like fungal endophytic cultures, endophytic bacteria also have potential of synthesizing novel natural products. Work is being focussed in order to explore endophytic bacteria for new and unique natural products of commercial importance. Endophytes thus are a source for antibacterial, antifungal, antidiabetic, antioxidant, and immunosuppressive products. Ecomycins, Pseudomycins, Munumbicins are some examples of the unique antibiotics obtained from endophytes.

4.4.1.1 Diterpenes

A large number of compounds with cytotoxic activity have been found to be produced by endophytic fungi over the years. Paclitaxel or Taxol is an antitumor compound reported from endophytes of number of plants. *Pestalotiopsis microspora* endophytic fungal species isolated from *Taxodium distichum* (Li et al. 1996) and *Taxus wallichiana* (Strobel et al. 1996) have been reported to produce paclitaxel. The endophytic fungal isolate *Penicillium raistrickii*endophytic in *Taxus brevifolia* was found to produce paclitaxel as well as baccatin III (Stierle and Stierle 2000). Earlier, from the same plant species, an endophytic fungi *Taxomyces andreanae* was reported, producing paclitaxel and baccatin (Strobel et al. 1993). There are two more reports of Paclitaxel production by *Pestalotiopsis* species. *Pestalotiopsis pausiceta* associated with *Cardiospermum helicacabum* (Gangadevi et al. 2008) and *Pestalotiopsis terminaliae* endophytic in the plant *Terminalia arjuna* (Gangadevi and Muthamary 2009a). Scientists have reported another endophytic fungus isolated from *Terminalia arjuna*, identified as *Chaetomella raphigera*, also to produce paclitaxel (Gangadevi and Muthamary 2009b). Production of paclitaxel was reported from an endophyte, *Bartalinia robillardoides*, of the medicinal plant *Aegle marmelos* or Indian bael (Gangadevi and Muthamary 2008).

4.4.1.2 Polyketides

Curvularia geniculate, an endophytic fungus, isolated from *Catunaregam tomentosa*, is reported to produce 5 hybrid peptide–polyketides, curvularides A–E. Curvularide B showed antifungal activity against *C. albicans*in in addition to synergistic activity with a fluconazole drug. A number of polyketides have been reported from endophytic fungal strains, shown in Table 4.1.

4.4.1.3 Lignans

Podophyllotoxin is a lignin with antimitotic and tubulin polymerase inhibition activity. Its derivatives namely, etoposide, teniposide, and etoposide phosphate, are preferably used in the treatment of cancer. A number of endophytes have been reported for podophyllotoxin production. Endophytic fungi *Tramates hirsute* isolated from dried rhizomes of *Podophyllum hexandrum* produces podophyllotoxin and its derivatives (Puri et al. 2006). Another report of fungal endophyte producing podophyllotoxin from *Podophyllum peltatum* has been cited. The endophyte was identified as *Phialocephala fortinii* (Eyberger et al. 2006). *Fusarium oxysporum*, an endophyte isolated from *Juniperus recurve*, a medicinal plant found in the Himalayas, was found to produce Podophyllotoxin (Kour et al. 2008). Podophyllotoxin has also been isolated from an *Alternaria* species, an endophyte of the plant *Juniperus vulgaris*(Lu et al. 2006) and *Aspergillus fumigatus*, endophyte of *Juniperus communis* L. Horstmann (Kusari et al. 2009).

4.4.1.4 Terpenoids

Stierle and Stierle (2000) have reported the isolation of endophytic *Penicillium* species from *Taxus brevifolia* (Yew). Of these endophytes, *Penicillium brevicompactum* is reported to produce a terpenoid, mycophenolic acid. This compound is antifungal, an immune suppressant drug and used in the treatment of Dengue.

Table 4.1 Polyketides produced by endophytic fungi

Compound	Uses	Host plant	Endophytic fungi	References
Griseofulvin	Antifungal	*Abies holophylla (Manchurian fir)*	*Xylaria* sp.	Park et al. (2005)
		Pinus strobus (White pine)	*Xylaria* sp.	Richardson et al. (2014)
		Vaccinium augustifolium (Blue berry shrub)		
		Taxus brevifolia	*Penicillium* sp.	Stierle et al. (1995), Stierle and Stierle (2000)
Brefeldin A	Antifungal, antiviral, and anticancer, protein transport inhibitor	*Texus mairei* *Torruia grandis*	*Paecilomycs* sp.	Wang et al. (2002)
		Torruia grandis	*Aspergillus clavatus*	
Sequoiatones	Antitumor (Breast Cancer)	*Sequoia sempervirens*	*Aspergillus paraciticus*	Stierle et al. (2001)
Sequoiamonascins	Antitumor (Breast, lung and CNS)	*Sequoia sempervirens*	*Aspergillus paraciticus*	Stierle et al. (2003)
Torreyanic acid	Anticancer	*Torrueya taxifolia*	*Pestalotiopsis microspore*	Lee et al. (1996)
Nodulisporins A, B, C	Antifungal	*Juniperus cedrus*	*Nodulis porium* sp	Dai et al. (2006)
Nodulisporins D, E, F	Antibacterial, antifungal, antialgal	*Arica arborea*	*Nodulis porium* sp	Dai et al. (2009)
Phomopsolides	Insecticidal (antibeetle), antibacterial	*Taxus brevifolia*	*Phomopsis oblonga*	Grove (1985)
		Taxus brevifolia	*Penicillium* sp	Steirle et al. (1997)
Rugulosin	Antilarval (Sprous budworm	*Balsam fir*	*Hormonema dematioids*	Calhoun et al. (1992)
Methyl(2Z,4E)-6(acetyloxy)-5-formyl-7-oxoocta-2,4-dienoate (Macrolide pyrinopherol)	Antifungal	*Pinus strobus*	*Lophodermium* sp.	Sumarah et al. (2011)

4.4.1.5 Terpenes

Many compounds belonging to this group have been isolated from endophytic fungal cultures and have been tabulated below in Table 4.2.

4.4.2 Heterospirocyclic Compounds

Two heterospirocyclic compounds useful in the treatment of cancer have been found to be produced by endophytic fungal cultures. Pseurotin A is antibacterial in addition to being anticancer. It is produced by *Penicillium raistrickii*, an endophyte of the plant *Taxus brevifolia* (Stierle and Stierle 2000) and *Penicillium janczewskii* KM Zalessky, associated with the *Prumnopitys andina* (Schmeda-Hieschmann et al. 2008). Tauramin is an anticancer compound produced by the endophytic fungi *Phyllosticta spinarum* isolated from *Platycladus orientilis* (Wijeratne et al. 2008).

4.4.2.1 Antimicrobial Peptides

Antimicrobial Peptides (AMPs) are the new generation of native peptide molecules. These are found in all living beings. They are being referred to as natural antibiotics. The AMPs are reported to have a very wide activity against a large spectrum of pathogenic microorganisms as well as protozoan and metazoan parasites (Liu et al. 2000; Vizioli and Salzet 2002). All of these components are main elements involved directly in the innate immune response of their hosts. This activity comprises of the expression of fluid phase proteins that recognize pathogen-associated molecular patterns. The response of the antibiotic peptides is quick, highly efficient, and with broad host activity range (Hoffmann and Reichhart 2002).

4.4.2.2 Antimicrobial Peptides from Endophytes

Endophytic bacteria compete with the pathogenic organisms and prevent them from colonizing the plant tissues. Secondary metabolites produced by the endophytes prevents the growth of pathogens microorganisms, thus playing a role in the plant defense mechanisms. AMPS are molecules of choice for drug development due to specificity for their targets with higher degree of interactions. Antibacterial cyclo-(Pro-Thr) and cyclo-(Pro-Tyr) are produced by endophytic fungus *Penicillium* sp, endophytic fungi found in mangrove plant *Acrostichum aureurm*. Both peptides demonstrated activity against *Staphylococcus aureus* and *Candida albicans*.

Epichlicin, a novel cyclic peptide was reported from the endophytic fungus *Epichloe typhina*, found in plant *Phleum pretense* L. The peptide was antagonistic at low concentrations, against the *Cladosporium phlei* spores, the fungal pathogen of the timothy plant (Seto et al. 2007).

Table 4.2 Terpenes isolated from fungal endophytic isolates

Compound	Uses	Host plant	Endophytic fungi	References
5-(Hydroxymethyl)-2-(20-trimethyltetrahydro-2H-Pyran-2-yl)-Phenol	Antifungal	*Pinus strobus*	*Lophodermium* sp.	Sumarah et al. (2011)
Phomadecalin	Activity against Pseudomonas aeruginosa	*Pinus* sp.	*Microdiplodia* sp. *KS 75-1*	Hatakeyama et al. (2010)
Xylarenones	Antitumour antimicrobial	*Torreya jackii CHUN*	*Xylaria* sp. *NCYZ*	Hu et al. (2008)
Tuberculariols	Anticancer	*Taxux mairei*	*Tubercularia* sp. *TF5*	Xu et al. (2009)
Enfumafungin	Antifungal	*Juniperus communis*	*Hormonema* sp.	Pelaez et al. (2000)
Periconicins (DitStrobelerpene)	Antibacterial, antifugal against Tricophyton rubrum	*Taxus cuspidate*	*Periconia* sp.	Kim et al. (2004)
Heptelidic acid (Konigic acid)	Anticancer, antimalarial, antilarval (Spruce budworm)	*Abies balsamea*	*Phyllosticta* sp.	Calhoun et al. (1992), Kim and Choong (2009), Tanak et al. (1998)
Isopimaratriene-dione and trion analogs (diterpenoids)	Antilarval (Spruc budworm) and insect toxin	*Balsom fir*	Unidentified endophyte	Findlay et al. (1995a)
Remulosin and Mellein analogs	Antilarval (Spruce budworm)	*Picea muriana BSP*	*Canoplea elegantula (Cooke) M.B.Ellis*	Findlay et al. (1995b)

Leucinostatin A, an antitumor and antifungal peptide was isolated from extracts of *Acremonium* sp. associated with *Taxus baccata* (Strobel et al. 1997). The endophytic fungi, *Penicillium raistrickii* endophytic in *Taxus brevifolia*, produced the peptide Cycloaspeptide A, and also other nitrogen containing compounds such as Benzomalvin C (analgesic anti-inflammatory), Fiscalin B (mycotoxins), Oxaline (anticancer), and Roquefortine C (anticancer) (Stierle and Stierle 2000). Noble et al. (1991) reported the isolation of compound Echinocandin from endophytic fungal cultures *Cryptosporiosis* sp and *Pezicula* sp. endophytic in the plants *Pinus sylvestris* and *Fagus sylvatica*.

4.4.2.3 Ecomycins

The endophytic bacterium, *Pseudomonas viridiflava* was reported to produce compounds called as Ecomycins. The ecomycins, lipopeptides in nature, contain unusual amino acids such as homoserine and β-hydroxy aspartic acid. Three lipopeptides produced by *P. viridiflava* strain EB273 were identified and characterized (Harrison et al. 1991).

4.4.2.4 Pseudomycins

Pseudomycins are antifungal produced by *Pseudomonas syringae*, a plant-associated bacterium (Harrison et al. 1991). These antifungal peptides are lipopeptides containing amino acids like L-chlorothreonine, D- and L-diaminobutyric acid, and L-hydroxyl aspartic acid. Pseudomycin A shows activity against *Candida albicans,* an oppurtunistic pathogen. Pseudomycins A–C contain hydroxyaspartic acid, arginine, lysine, serine, and diaminobutyric acid. They are active against fungal plant pathogens including *C. albicans* and *C. neoformans*.

4.4.2.5 Munumbicins

The munumbicins are made up of 4 bioactive substances having a broad activity spectrum against fungal and bacterial plant pathogens as well as *Plasmodium* species. Castillo et al. (2002) have reported the production of munumbicins by *Streptomyce*s NRRL 30562, an endophytic bacterium of *Kennedia nigriscans*, a medicinal plant native to Australia. The activity of these compounds was against Gram-positive bacteria including the methicillin-resistant strain of *S.aureus* (MRSA, ATCC 33591) and a vancomycin-resistant strain of *E. faecalis* (VREF, ATCC 51299). Munumbin B is effective against multiple-drug-resistant (MDR) *Mycobacteriumtuberculosis,* an acid-fast bacterium, while munumbicins C and D are effective against the malarial parasite *Plasmodium falciparum*.

4.4.2.6 Polyhydroxy Butyrate

Polyhydroxy butyrate (PHB) and poly-3-hydroxyalkanoate (PHA) are the most widely produced microbial bioplastics. These are gaining attention due to their commercial value. Many naturally occurring species of bacteria have the ability to produce bioplastics, as proven by their genomic analysis studies (Kalia et al. 2003). *Herbaspirillum seropedicae*, a diazotrophic endophyte, is found in a variety of higher plants. Catalán et al. (2007) have shown that *H. seropedicae* produces significant levels of PHB, when grown on a range of carbon sources. Degradation of polymer in the host system takes place over the time. Hence there is a possibility of the use of these polymers in drug delivery in cases where slow release of compound is needed.

4.5 Conclusion and Future Perspectives

This chapter highlights the need for novel pharmaceutical solutions to fight emerging and reemerging infections. Endophytic microorganisms are a promising source, as these fungi and bacteria are constantly at war with pathogenic microbes to create an ecological niche for themselves. They produce secondary metabolites as a source of communication and defense. These need to be bioprospected in order to tackle the medical problems being faced presently and will appear in the future too.

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