Chapter 1
An Introduction to Endophytes

Jaya Arora and K.G. Ramawat

Abstract Endophytic micro-organisms are hidden companions of plants living mutually beneficial life inside the host plant. Though these endophytes are supposed to be associated and evolved with land plants, endophytes are recognised in last century. Beneficial effects of endophytes are attaining importance with the possibility of obtaining novel medicinally important compounds as well as their role in increasing crop productivity because they produce a variety of compounds and interact with other micro-organisms, pathogenic and non-pathogenic. With the development of modern tools and techniques of molecular biology, it has become possible to establish correct identity of these micro-organisms and know the interactions with host and other micro-organisms. In this overview, we present current scenario about endophytes and their use for human welfare.

Keywords Bacterial endophytes · Fungal endophytes · Bioactive metabolites
Endophytes in agriculture

1.1 Introduction

Endophytes are organisms living as symptomless colony, maybe during a part of their life cycle, inside the host plants (Stone et al. 2000). The term ‘endophyte’ was coined by de Bary (1866) to distinguish the epiphytic organisms living on surface of plant. Endophytes belong to diverse taxa such as bacterial, fungal, protistic, archaeal and are generally considered as mutualists. Endophytes are defined as

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organisms isolated from surface-sterilised explants or from within the plant tissue and produce no harm to the host plant (Hallman et al. 2011). Endophytes can be recognised as (1) endophytic Clavicipitaceae; (2) fungal endophytes of dicots; (3) endophytic fungi; (4) other systemic fungal endophytes; (5) fungal endophytes of lichens; (6) endophytic fungi of bryophytes and ferns; (7) endophytic fungi of tree bark; (8) fungal endophytes of xylem; (9) fungal endophytes of root; (10) fungal endophytes of galls and cysts; (11) prokaryotic endophytes of plants (includes endophytic bacteria and actinomycetes) (Stone et al. 2000). They receive protection and nutrition from host plants while providing/facilitating nutrient uptake and protection to the plant against biotic and abiotic stresses and pests. There are evidences that the presence of endophyte may not only influence plant growth, developments, fitness and diversity but also population dynamic, plant community diversity and ecosystem functioning (Saikkonen et al. 1998; Hardoim et al. 2015). Endophytes have been evolved with the plants themselves, and during this long period, they have developed all strategies to live, survive, evolve and refine the relationship with the plant (Chap. 8) (Krings et al. 2007; Yu et al. 2010; Selim et al. 2012; Goyal et al. 2017). Use of the term 'infection' thus should be avoided to describe endophytes in general, except those endophytes involved in diseases as causal agents of disease of the host plant.

Endophytic fungi living asymptomatically in plant tissues may present in almost all plants (Saikkonen et al. 1998). One species of an endophyte may be associated with many plant species, and many species of endophytes may be present in the same species. Some endophytes remain as latent in the host plant, while others may interact with other endophytes, pathogenic or non-pathogenic (Zabalgogeazcoa 2008).

Endophytes have evolved mechanisms to live within the plant by defending themselves against all physical and chemical weapons of the plants, e.g. in plant like *Camptotheca acuminata* produces anticancer compound camptothecin which binds to topoisomerase I to stop cell divisions. The endophytic fungus *Fusarium solani* modified its topoisomerase biding site by alterations in amino acids to escape from harmful effects of camptothecin (Kusari et al. 2011). Therefore, endophytes provide two pronged strategy, one for obtaining novel bioactive secondary metabolites with the help of modern tools of chemistry such as selective high-resolution tandem mass spectrometry [equipped with sources such as electrospray ionisation (ESI), or matrix-assisted laser desorption ionisation (MALDI) and analyser such as quadrupole, time of flight (TOF), magnet, Fourier transform ion cyclotron resonance (FT-ICR)], and secondly, they provide clue about mode of action of these bioactive metabolites.

Mycorrhizal fungi form association with plant roots as ectomycorrhiza or endomycorrhiza and play a key role in ecosystem as they modulate nutrient uptake, carbon cycle and also influence soil structure and consequently ecosystem functionality (Van der Heijdan et al. 2015). Mycorrhiza is not discussed in detail in this article (Chap. 11).

In this brief overview, entire gamut of endophyte–plant relationship in terms of plant physiology (nutrition), plant pathology (interaction-protection), improvement

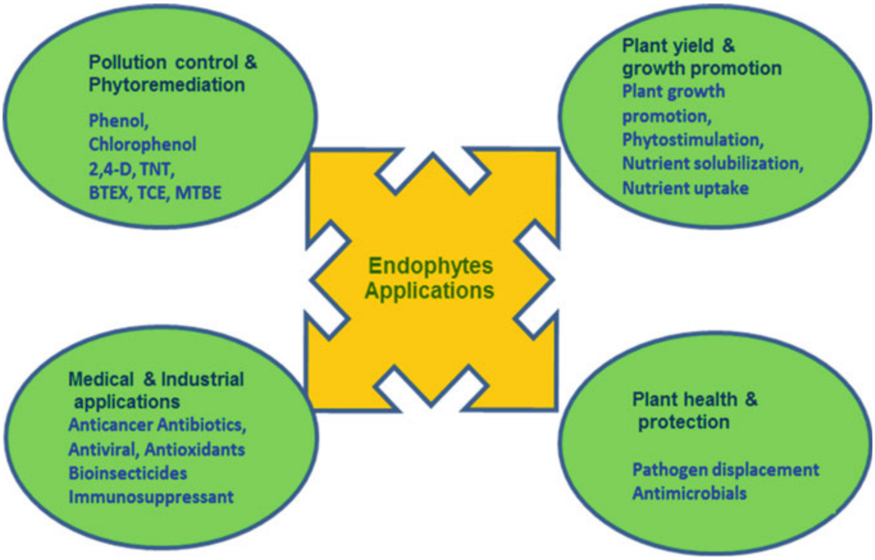

Fig. 1.1 Applications of endophytes in various fields. Examples in each category are symbolic representatives. Pollutant like 2,4-dichlorophenoxyacetic acid (2,4-D) is used as weedicide; petroleum-based products such as benzene–toluene–ethylbenzene–xylene (BTEX), methyl tertiary-butyl ether (MTBE); explosives such as trinitrotoluene used in mining, road and dam making (TNT); trichloroethylene (TCE) is a common solvent

in crop production, pollution control and industrial applications (bioactive molecules) is presented to provide an outlook (Fig. 1.1) of this book. We have tried to summarise these salient applications of endophytes in this brief introduction with the aim that details are presented in various chapters in the book; hence, details of these steps are omitted.

1.2 Origin and Evolution of Endophytes

It is believed that early terrestrial plants evolved in mutualistic association with mycorrhizal fungi which has shaped the plant's life during evolution (Pirozynski and Malloch 1975; Plett and Martin 2015). Fossil record shows that endophytes were associated with land plants for >400 million years ago (Krings et al. 2007). During evolutionary process, plants change habitat from aquatic (oceanic) to terrestrial and were encountered with atmosphere with high carbon dioxide, soil poor in nutrients and fluctuations in temperature and water availability. Under such circumstances, fungi provided endurance to plants to fight with odd conditions and establish themselves on soil (Selosse and Tacon 1998; Bonfante and Selosse 2010). During the same evolutionary period, endophytes have adapted themselves to the plant microenvironment by genetic variation including uptake of some plant's DNA (Germaine et al. 2004). Due to this adaptation and genetic material uptake, endophytes started producing plant metabolites or their precursors (Stierle et al. 1993, Zhang et al. 2006). Now, endophytes are known to occur in all short of habitats and in different plants such as mosses, ferns, lichens, shrubs, grasses and deciduous and coniferous trees (Sun and Guo 2012). Therefore, they are important part of the ecosystem.

Bacterial endophytes may originate from rhizosphere and phyllosphere microflora and penetrated through roots to reach the xylem tissues (Sturz and Nowak 2000). Preferable site of attachment may be apical root zone with thin-walled cells and basal root zone. Micro-organisms enter the basal root zone through cuts, wounds and other natural opening or made their entry by dissolving cell wall by enzymes such as cellulase and pectinase (Fig. 1.2). Bacteria form small colonies, and cellulase helps in breaking β 1-4 linkage bond of cellulose. Besides cellulase, endophytes produce pectinase, lipoidase, proteinase, phenoloxidase and lignin catabolic enzymes to establish themselves (Wang and Dai 2011). Generally, nitrogen-fixing bacteria (Rhizobia) produce morphological changes in the roots by forming root nodules; otherwise, endophytes remain silent without any morphological change in the system (Malfanova et al. 2013). Only a few bacteria cross the endodermal barrier and enter the xylem tissues. From xylem, bacteria spread to all tissues and organs including reproductive organs and thus penetrates in the developing seeds. Endophytic bacterial density decreases with increasing distance from roots, the rich source of nutrients. In case of fungal endophytes, growth of mycelium is generally along the longitudinal axis of the organ. Endophytes are transferred from generation to generation through seeds (vertical transmission) or may be transferred to allied species through plant part decay/soil (horizontal transmission) (Zabalgogeazcoa 2008; Herrera et al. 2016). This is evident by the fact that generally, meristems are considered free from pathogens, but unique symbiotic *Methylobacterium* endophyte has been reported in Scott pine seedlings which influences functioning of many genes related to growth and development (Pirttila et al. 2008). Therefore, endophytes were associated with plants during their evolution as land plants from very beginning having a mutual relationship. Selected common endophytes and their host are presented in Table 1.1. It is evident from the data presented in the table that diverse plants such as monocots, dicots, trees, gymnosperms and bryophytes contain endophytes.

1.3 Endophyte Diversity

The presence of asymptomatic endophytic fungi in plants was known since nineteenth century (Guerin 1898). It is estimated that more than 1 million endophytic fungal species exist compared to the existence of number of vascular plant species in ratio of 1:4–5 fungi per plant (Sun and Guo 2012). Bacterial endophytes from more than 200 bacterial genera from 16 phyla of both culturable and unculturable

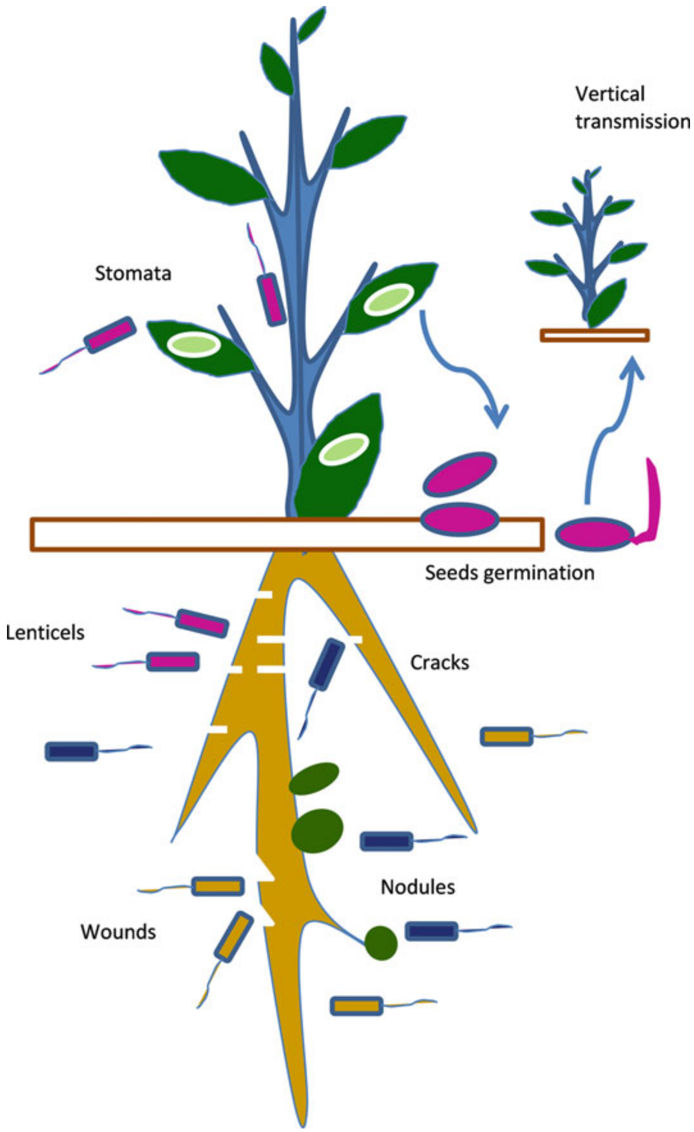

Fig. 1.2 Infection of host plant and transmission of endophytes from generation to generation (*vertical*) through infection of reproductive parts and seeds and allied plants (*horizontal*) through movement in soil. Endophytes enter through cuts, wounds and natural openings like stomata

bacteria belonging to *Acidobacteria, Actinobacteria, Aquificae, Bacteroidetes, Cholorobi, Chloroflexi, Cyanobacteria, Deinococcus-Thermus, Firmicutes, Fusobacteria, Gemmatimonadetes, Nitrospira, Planctomycetes, Proteobacteria, Spirochaetes* and *Verrucomicrobiae* have been reported (Hallmann et al. 2011; Sun

Table 1.1 Common endophytes of plants

Endophyte	Plant species	References
Fungal endophytes		
Acremonium sp.	*Taxus chinensis* *Huperzia serrata*	Liu et al. (2009) Glienke-Blanco et al. (2002)
Aspergillus sp.	*Datura stramonium* *Moringa olifera* *Prosopis chilensis*	Mahdi et al. (2014)
Cladosporium sp. *C. herbarum*	*Opuntia ficus indica* *Cinnamomum camphora* *Lycopersicum esculentum* Mill. *Triticum aestivum*	Bezerra et al. (2012) He et al. (2012) Larran et al. (2001) Larran et al. (2002)
Colletotrichum sp. *C. gloeosporiodes*	*Triticum aestivum* *Citrus plants* *Cinnamomum camphora* *Pasania edulis* *Ginkgo biloba* L. *Tectona grandis and Samanea saman* *Huperzia serrata* *Cinnamomum camphora* *Lycopersicum esculentum* Mill.	Larran et al. (2002) Glienke-Blanco et al. (2002) He et al. (2012) Hata and Sone (2008) Thongsandee et al. (2012) Chareprasert et al. (2006) Wang et al. (2011) He el al. (2012) Larran et al. (2001)
Curvularia sp.	*Datura stramonium* *Moringa olifera*	Mahdi et al. (2014)
Penicillium sp.	*Lycopersicum esculentum* Mill. *Huperzia serrata*	Larran et al. (2001) Wang et al. (2011)
Phyllosticta sp.	*Citrus sp.* *Pasania edulis* *Coffea arabica* *Quercus variabilis* *Centella asiatica* *Panax quinquefolium* *Ginkgo biloba* L.	Glienke-Blanco et al. (2002) Hata and Sone (2008) Santamaria and Bayman (2005) Wang et al. (2007) Rakotoniriana et al. (2008) Xing et al. (2010) Thongsandee et al. (2012)
Phomopsis sp.	*Pasania edulis* *Ginkgo biloba* L. *Tectona grandis and Samanea saman* *Taxus chinensis*	Hata and Sone (2008) Thongsandee et al. (2012) Chareprasert et al. (2006) Liu et al. (2009)
Stemphylium globuliferum	*Avicennia marina*	Moussa et al. (2016)
Bacterial endophytes		
Bacillus megatarium	*Medicago satavia,*	Stajkovic et al. (2009)
B. thuringiensis, B. subtilis subsp *subtilis*	*Musa sp.*	Souza et al. (2014)
Burkholderia cepacia	*Lupinus luteus*	Barac et al. (2004)
Enterobacter asburiae	*Ipomoea batatas*	Asis and Adachi (2003)

(continued)

Table 1.1 (continued)

Endophyte	Plant species	References
Erwinia sp.	*Glycine max*	Kuklinsky-Sobral et al. (2004)
Citrobacter	*Musa sp.*	Martinez et al. (2003)
Microbacterium sps.	*Pogonatherum paniceum*	Koskimaki et al. (2010)
Pantoea	*Soyabean (bot name)*	Kuklinsky-Sobral et al. (2004)
Pseudomonas saponiphilia	*Dendrobium candidum*	Wu et al. (2016)
Pseudomonas sp.	*Piper nigrum*	Arvind et al. (2009)
Rhizobium radiobacter	*Daucus carota*	Surette et al. (2003)
Staphylococcus saprophyticus	*Carrot*	Surette et al. (2003)
Micrococcus	*Oryza sativa*	Mbai et al. (2013)
Sporosarcina aquimarina	*Avicennia marina*	Rylo Sona Janarthine et al. (2011)
Other endophytes		
Nostoc	*Leiosporoceros dussii* (Anthocerophyta) *Anthoceros fusiformis and Blasia pusilla*	Villarreal and Renzaglia (2006) Costa et al. (2001)
Oscillatoria	*Alternanthera sessilis*	Keshri and Chatterjee (2010)

and Guo 2012; Sessitsch et al. 2012; Malfonova et al. 2013). Nevertheless, the most prime endophytes belong to three major phyla (Actinobacteria, Proteobacteria and Firmicutes) and include members of *Azoarcus*, *Acetobacter* (renamed as *Gluconobacter*), *Bacillus*, *Enterobacter*, *Burkholderia*, *Herbaspirillum*, *Pseudomonas*, *Serratia*, *Stenotrophomonas* and *Streptomyces* (Malfonova et al. 2013). However, the actual identified numbers of endophytes are very less.

Endophytes gain importance in recent past for their commercial and industrial exploitation. It was after landmark discovery of toxicosis caused by *Neotyphodium coenophialum* (Family Clavicipitaceae) in cattle eating the grass, *Festuca arundinacea* (Bacon et al. 1977). It was recorded that the grass was systemically infected by the fungus without apparent symptoms and that is why escaped from noticing the diseased leaves. The fungus produces several toxic alkaloids which were the actual cause of toxicosis in cattle. This is one example of a fungal endophyte causing toxicity, but a plethora of endophytes may inhabit grasses, and some may remain latent (Zabalgogeazcoa 2008). Due to adaptation and evolution, endophytes of cultivated plants and their wild relatives may differ significantly (Ofek-Lalzar et al. 2016).

Conventionally, micro-organisms are identified on the basis of morphological characters, but in case of bacteria, it is difficult to characterise them on the basis of morphological characters because of their small size. Hence, some physiological characters of growth and nutrition are added for identification. Modern tools of molecular biology and genetics are helpful in clearly establishing their identity, and genetic bar coding is one of them (Diaz et al. 2012; Sun and Guo 2012). Bar coding of plants and animals is already done to characterise the species, and it is now used for the micro-organisms. Genomic characterisation of living organisms is lead by the Consortium for the Barcode of Life (CBoL; http://barcodeoflife.org/). This information is used for taxonomic classification of the organisms; thus, morphological characters have become of secondary importance. Instead of mitochondrial DNA used for animals and algae, for plants and fungi, ribosomal DNA is used for taxonomy, phylogeny and identification purposes (Rodriguez et al. 2009) because mitochondrial DNA in these organisms has not changed much during evolution. Internal transcribed spacer (ITS) is the most commonly used DNA barcode in molecular identification of endophytes (Sun and Guo 2012) in ecological and diversity studies. Modern techniques of molecular biology are helpful in identification of endophytes, and availability of such facilities in more laboratories associated with microscopic techniques will help in proper characterisation of large number endophytes and will establish their diversity (Chap. 7).

1.4 Isolation of Endophytes

Criteria for isolation of endophytes are closely related to isolation of bioactive molecules, e.g. importance of the plant and its bioactive molecule, rarity of compound, endemic nature of the plant and its environment (Tiwari 2015). Generally, endophytes are isolated from surface-disinfectant tissues grown on a synthetic medium and may or may not containing extracts of host tissues (Galney and Newcombe 2006; Hata and Sone 2008). But synthetic medium may not support the growth of obligate parasites resulting in not getting information about such endophytes. Endophytes have been isolated from almost all the plant parts including leaves, scales, roots, stem and resin canals and even from meristems (Pirttila et al. 2008). Identification of endophytic fungi is done as used for fungi using morphological characters of colony, vegetative hyphae and asexual/sexual spores (conidial development, size, shape, conidia, attachment of conidia and shape of conidial head) (Nagamani et al. 2006). With the advent of tools and techniques of molecular biology, it has become feasible to characterise these micro-organisms on the basis of their molecular markers and establish identity. It was only after the use of tools of molecular biology that many more endophytes could be identified (Duong et al. 2006). These tools are gaining importance in establishing phylogenetic relationship between different taxa also (Duong et al. 2006; Sun and Guo 2012).

1.5 Endophytes and Plant Protection

Endophytes are known to provide various types of protections to their host plant, viz. endurance to grow in hot springs, deter herbivores by producing toxic alkaloids in grasses and provide protection from pests in dicots (Zhang et al. 2006). Endophytes share everything with an invading pathogen in the host plant. Increasing evidences suggest that endophytes interact with the pathogen in different ways in different hosts, and resultantly, altered physiology may suppress the growth of the pathogen, alter nutrient balance in favour of endophyte or stimulate the plant's defence mechanism (Zabalgogeazcoa 2008; Bushby et al. 2016). Many endophytic species produce antibiotics and antifungal compounds (Istifadah and McGee 2006) and provide protection against pathogen with reduced severity (Zabalgogeazcoa 2008). Colonisation of plants by fungal endophyte provides a better protection against plant nematodes. This is a complex phenomenon, and mechanism of this antagonism is poorly understood (Schouten 2016). Thus, endophytes influence functioning of pathosystem and consequently plant's survival, diversity and conservation (Bushby et al. 2016).

About 1000 insect pathogenic fungi ranging from class Chytridiomycetes to Basidiomycetes are known to occur as endophyte, which are closely related to grass endophytic fungi such as *Claviceps* and *Epichloë* (Moonjely et al. 2016). The process of cross-protection is well established in case of viruses. Similar to cross-protection, endophytes provide protection to various pests and herbivores and there is need to understand mechanism underlying this process to exploit it for crop protection (Chap. 4).

1.6 Endophytes and Metabolites

Several important medicines are obtained from plants such as vincristine, vinblastine, camptothecin, quinine and taxol (Ramawat et al. 2009), while more than 8500 bioactive metabolites of fungal origin are known (Demain and Sanchez 2009; Goyal et al. 2017). Association of an endophytic fungi *Taxomyces adreanae* present in *Taxus baccata* to taxol biosynthesis fuelled the search for endophytic fungi associated with promising bioactive molecules and their derivatives (Nicoletti and Fiorentino 2015). This has two repercussions: one the complex evolutionary insight about the microbes and the host plants and second, the possibility of obtaining new bioactive compounds. As we are discussing in different parts of this chapter, isolation and identification of endophytes is still a challenging task, and subsequently, establishment of correlation with the bioactive molecule production is another important task. The challenges to produce them commercially are many (Kusari and Spiteller 2011). Endophytes may produce diverse chemicals as illustrated by classic example of gibberellin production by *Fusarium oxysporum* causing foolish seedling disease of rice. The other classes of compounds include alkaloids, essential oils, terpenes, azadirachtins, coumarins, flavonoids, lignans and several others (Nicoletti and Fiorentino 2015). A large number of secondary metabolites of potential therapeutic value in cancer, as antioxidants and antimicrobials such as azadirachtin A, B, camptothecin, citrinal B, cytochalasin N, diosgenin, gliotoxin, germacrane-type sesquiterpenes, ginkgolide-B, huperzine A, penicillide derivatives and α-pyrone analogues, piperine, podophyllotoxin, taxol (Paclitaxel), have been isolated from endophytes, and some of the selected examples for bioactive molecules produced by endophytic fungi (Fig. 1.3) and their host plants are presented in Table 1.2. Besides their production, biotransformation of secondary metabolites has been successfully attempted by using endophytes (Pimentel et al. 2011; Wang and Dia 2011). Biotransformation can be defined as the chemical alteration of an exogenous substance by or in a biological system (Wang and Dia 2011). It has been observed

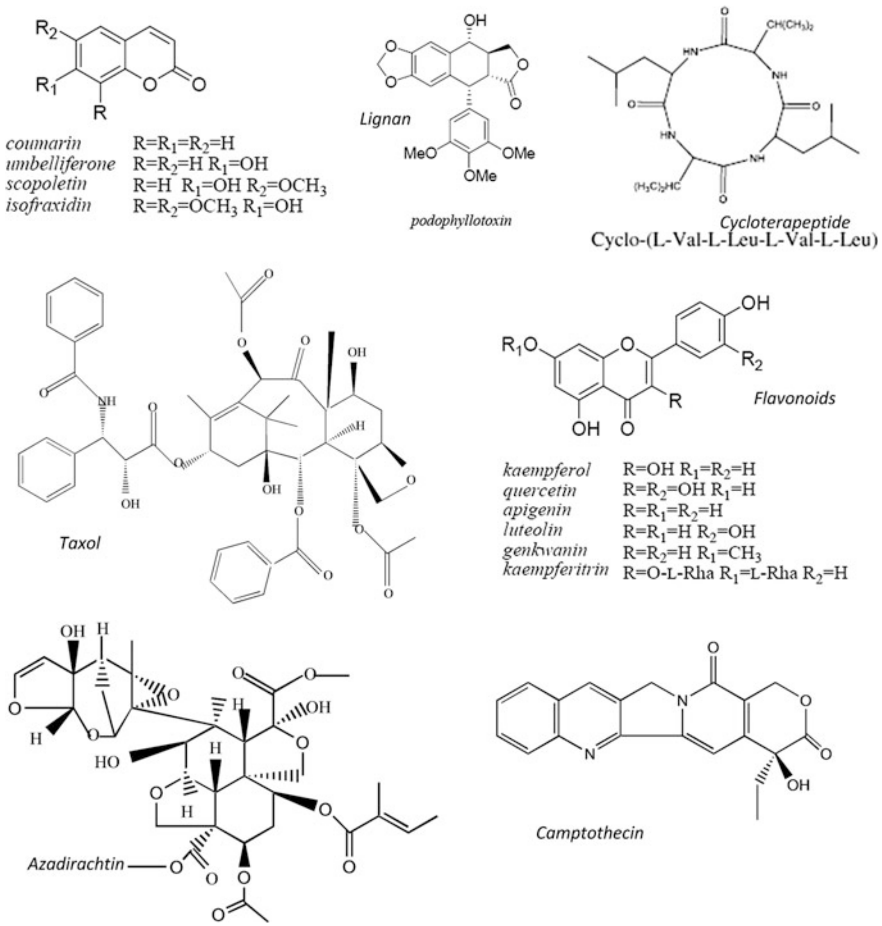

Fig. 1.3 Selected bioactive molecules associated with endophytes and their hosts

Table 1.2 Selected examples of bioactive metabolites produced by endophytes

Compound (Metabolite)	Bioactivity	Endophyte	Plant species	References
(-)-(1R,4R)-1,4-(2,3)-indolmethane-1-methyl-2,4-dihydro-1H-pyrazino-[2,1-b]-quinazoline-3,6-dione	Antifungal and cytotoxic	*Penicillium vinaceum*	*Crocus sativus*	Zheng et al. (2012)
2,3-dihydro,2,2-dimethyl-4 (1H)-quinazolinone	Cytotoxic activity	Actinobacteria-*Streptomyces*	*Lychnophora ericoides*	Conti et al. (2016)
β-sitosterol	Antifungal	*Phoma sp.*	*Arisaema erubescens*	Wang et al. (2012)
Azadirachtin A and B	Insecticidal	*Eupenicillium parvum*	*Azadirachta indica*	Kusari et al. (2012)
Bacctatin III	Anticancer	*Diaporthe phaseolorum, Trichoderma sp.*	Taxus wallichiana var. mairei	Zaiyou et al. (2013), Li et al. (2015)
Campyridones A-D (pyridone alkaloids)	Cytotoxic against Hela cells	*Campylocarpon sp.*	*Sonneratia caseolaris*	Zhu et al. (2016)
Camptothecin	Anticancer	*Fusarium solani*	*Camptotheca accuminata, Apodytes dimidiata*	Shweta et al. (2010), Kusari et al. (2009)
Caryolanes	Anticancer	*Streptomyces sp.*	*Bruguiera gymnorrhiza*	Ding et al. (2015)
Citrinal B	Cytotoxic	*Colletotrichum capsici*	*Capsicum sp.*	Wang et al. (2016)
Cryptocin	antimycotic	*Cryptosporiopsiscf. quercina*	*Tripterygium wilfordii.*	Li et al. (2000)
Cytochalasin N, Cytochalasin H and Epoxycytochalasin H	Antifungal	*Phomopsis sp.*	*Gossypium hirsutum*	Fu et al. (2011)
Diosgenin	Steroidal drugs, oestrogenic effects, antispasmodic	*Cephalosporium sp.*	*Paris pollyphylla*	Cao et al. (2007)

(continued)

Table 1.2 (continued)

Compound (Metabolite)	Bioactivity	Endophyte	Plant species	References
Epipolythiodioxopiperazine and Gliotoxin	Antifungal	*Chaetomium globosum*	*Ginkgo biloba*	Li et al. (2011)
Extracellular enzymes and Auxins (IAA)	Plant growth promoting activity	*Penicillum citrinum, Preussia sp., Aureobasidium*	*Boswellia sacra*	Khan et al. (2016)
Germacrane-type sesquiterpenes	Treatment of cardiovascular disease and cancer	*Streptomyces griseus subsp.*	*Kandelia candel.*	Guan et al. (2005)
Ginkgolide-B	Antiallergic and anti-inflammatory	*Fusarium oxysporum*	*Ginkgo biloba*	Cui et al. (2012)
Huperzine A	Treatment of Alzheimer's disease. Memory enhancement	*Penicillium chrysogenum* *Penicillium* sp.	*Lycopodium serratum* *Huperza seretta*	Zhou et al. (2009)
Hypericin	Antidepressant. Mood enhancing, antiviral	*Chaetomium globosum*	*Hypericum perforatum*	Kusari et al. (2008)
Lipopeptides	Antifungal	*Bacillus amyloliquefaciens*	Ornamental plants	Zouari et al. (2016)
Peimisine and imperialine-3-β-D glucoside	Antitumor and antitussive	*Fusarium redolens*	*Fritillaria unibracteata*	Pan et al. (2015)
Penicillide derivatives and α-pyrone analogues	Proteasome inhibitory activity	*Pestalotiopsis sydowiana*	*Phragmites communis*	Xia et al. (2016)
Phomenone, Phaseolinone	Antifungal	*Xylaria sp.*	*Piper aduncum*	Silva et al. (2010)
Piperine	Antimicrobial, antidepressant, anticancer	*Colletotrichum gloeosporioides*	*Piper nigrum*	Chithra et al. (2014)
Podophyllotoxin	Anticancer, antimicrobial, antirheumatic	*Phialocephala fortinii*	*Podophyllum peltatum*	Eyberger et al. (2006)
Taxol (Paclitaxel)	Anticancer	*Taxomyces andreanae* and other several sp.	*Taxus brevifolia*	Kusari et al. (2014)

(continued)

Table 1.2 (continued)

Compound (Metabolite)	Bioactivity	Endophyte	Plant species	References
Thiodiketopiperazine derivatives	Antimicrobial activity (*Staphylococcus aureus*, *S. pyrogenes*)	*Phoma sp.*	*Glycyrrhiza glabra*	Arora et al. (2016)
Resveratrol	Anticancer Lifespan increasing activity	*Aspergillus niger*	*Wine grape* *Carbernet Sauvignon*	Liu et al. (2016)
Vinblastine	Anticancer	*Alternaria*	*Catharanthus roseus*	Guo et al. (1998)
Vincristine	Anticancer	*Fusarium oxysporum*	*Catharanthus roseus*	Zhang et al. (2000)
Vindoline	Antimitotic activity	*Curvularia sp.*, *Choanephora infundibuliphera*	*Catharanthus roseus*	Pandey et al. (2016)

that alterations in the basic molecule may result in a more potent physiologically active compound; e.g., semisynthetic compounds developed from taxol and podophyllotoxin are more potent than the basic molecule (Ramawat et al. 2009). It is evident that several compounds important in medicine, agriculture and industry are produced by endophytes (Chap. 12).

Details of secondary metabolites and other useful metabolites can be found in recent reviews on endophytes (Pimentel et al. 2011; Tiwari 2015; Nisa et al. 2015; Venugopalan and Srivastava 2015; Rehman 2016). Because endophytes influence the growth and metabolism of host plant by influencing nutrients uptake and endurance, they also influence the production of bioactive secondary metabolites of these host plants (Jia et al. 2016). Production of secondary metabolites by endophyte will follow the same course as a plant or fungal metabolites. Once endophyte is isolated and production of metabolites is established, then strategies can be used for its large-scale production using biosynthetic pathway manipulation and other

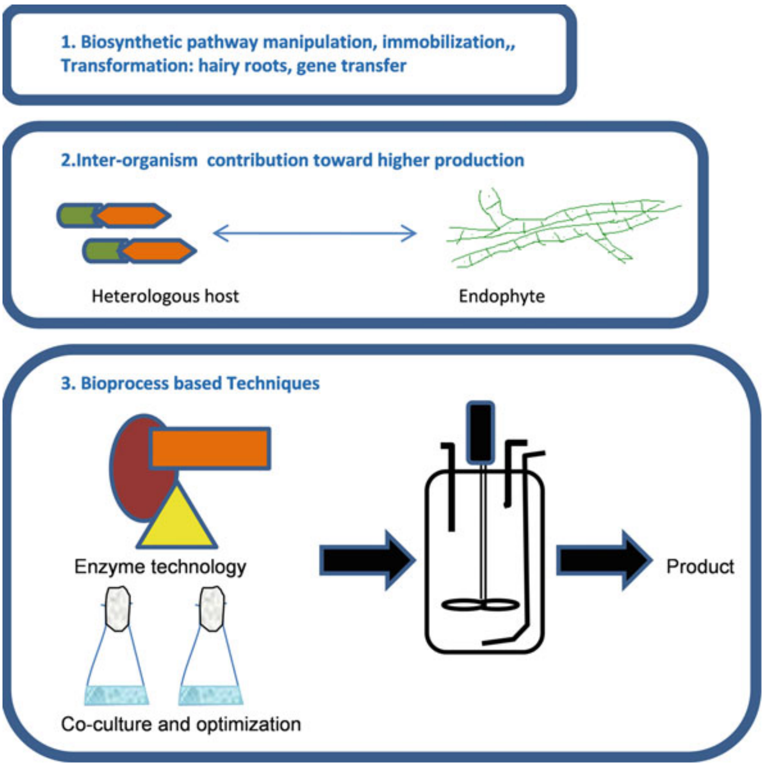

Fig. 1.4 Possible strategies for obtaining secondary metabolites using endophytes. Biosynthetic pathway manipulation and genetic transformation using Agrobacterium species are well-established techniques for plant cells. Several products are produced using heterologous expression system. Scale-up production technology and downstream processing of selected metabolites require optimisation of production system

techniques of biotechnology (Fig. 1.4). Use of heterologous expression system and scale-up production are useful steps towards industrial production of secondary metabolites (Suthar and Ramawat 2010; Goyal et al. 2011, 2015).

Polysaccharides and enzyme production are commonly associated with bacterial endophytes. Due to this, process of gummosis is considered as a result of endophyte association in most of the gum-yielding trees (Arora and Ramawat 2014). Besides enzymes (which are proteins), several other proteins have been isolated and characterised from bacterial endophytes. In recent past, cyclic and non-cyclic peptides have been isolated and characterised from several endophytes showing potential applications such as anticancer, immunosuppressant, antifungal and other activities (Abdalla and Matasyoh 2014). It is evident from the above account that a wide variety of useful metabolites are produced by endophytes. There is a need to integrate available different technologies such as tools of molecular biology for their identification, use of tools of chemistry for identification of bioactive metabolites and biotechnology for scale-up production of metabolites to explore and exploit the potentiality of endophytes for human welfare.

1.7 Useful Biological Activities of Endophytes

Endophytes producing toxic substances protect host from insects and herbivores. *Neotyphodium* and *Epichloë* are an example of host beneficial endophytes which not only provide antiherbivore defence but also better nutrient uptake and drought tolerance to host plant (Schard et al. 2004). Other species of similar functions of defence and growth promotion are *Piriformospora indica* (Waller et al. 2005), *Acremonium strictum* (Hol et al. 2007) and some *Stagonospora* species (Ernst et al. 2003). In case of banana, endophytic bacteria (*Bacillus amyloliquefaciens*, *B. subtilis* subsp *subtilis* and *B. thuringiensis*) provide protection against fungal (*Fusarium oxysporum* f. sp *cubense* and *Colletotrichum guaranicola)* pathogens (Souza et al. 2014). Endophytic fungi isolated from different plants (Fig. 1.5) have shown antifungal activity.

1.8 Endophytes in Agriculture

Agriculture is major economic activity and livelihood of millions of people particularly in developing countries. Increasing population needs to be fed by increasing the production and productivity of agricultural produce, and novel strategies are required. Endophytes are gaining importance because of their role in plant growth stimulation, protection against biotic and abiotic stresses and pests via modulation of growth hormone signalling, higher seed yield and plant growth hormones (Miliute et al. 2015). Consequently, this has profound effects on agricultural traits of crop plants (Fig. 1.5) which hold promises for eco-friendly and

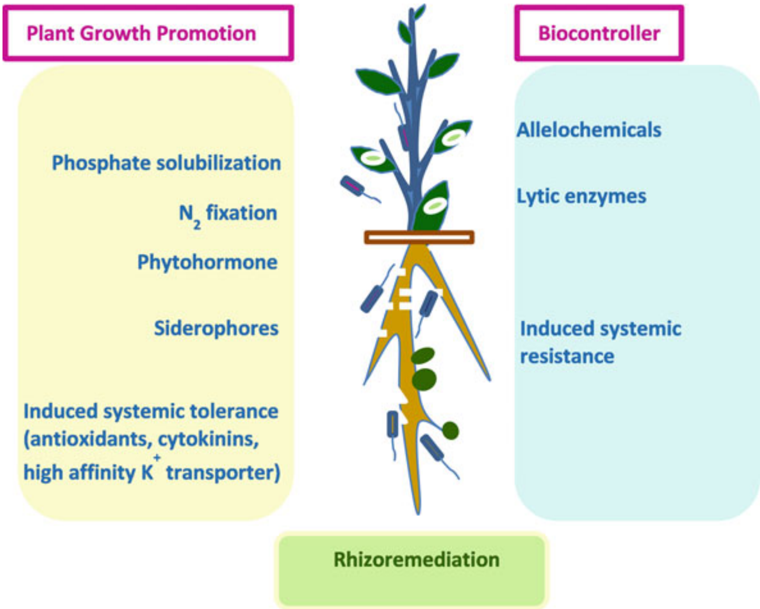

Fig. 1.5 Application of associative bacteria for sustainable agriculture, producing substances for plant growth and also suppressing the growth of pathogens and competitive plants

economically sustainable agriculture (Hallman et al. 2011; Rai et al. 2014). The wild relatives of wheat (*Triticum dicoccoides* and *Aegilops sharonensis*) harbour many useful endophytes of diverse taxonomic groups which are absent in cultivated modern-day wheat (*T. aestivum*) (Ofek-Lalzar et al. 2016). Use of modern agricultural practices such as fertiliser and chemicals to control pathogens and pests alters the balance between endophytes and its host (cultivated plant) as well as structure and function of soil. Such chemical environment is absent for wild relatives and endophytes thrive well in the system (Minz et al. 2011). Similarly, modern breeding methods cause changes in genotype of cultivated plant making them free from several insects, pests and endophytes. These changes have profound effect of agricultural traits and association of endophytes (Ofek-Lalzar et al. 2016). Therefore, bacterial endophytes hold a great promise for sustainable agriculture production along with health and nutritive values (Chap. 9).

1.9 Conclusions

Research on endophytes has gained momentum in last three decades as evident by >31,400 publications (primary research papers and reviews) on Google Scholar and data about their beneficial properties. Sustainable agriculture requires self-contained functioning and low-cost eco-friendly inputs. To meet the ever-increasing food demand, biological nature-dependent developments are welcomed. Endophytes play an important role in plant physiology and functioning of agroecosystem. Application of tools and techniques of molecular biology has provided insight into their diversity and genomic structure. This book is a timely compilation of state of technology developed towards better understanding these micro-organisms. Better isolation techniques, faster genomic data mining and sequence matching will be helpful in the identification of endophytes and knowing their diversity as well as usefulness. Production of various useful drugs in large quantity is still a challenge as biosynthesis involves several genes. If some useful genes are identified on endophyte genome, it will be helpful in elucidating the pathway and consequently biosynthesis of secondary metabolites of choice in desired quantities.

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