Endophytes: A Hidden Treasure of Novel Antimicrobial Metabolites

Palak Arora, Tanveer Ahmad, Sadaqat Farooq, and Syed Riyaz-Ul-Hassan

Abstract

An endophyte is a microorganism which colonizes the healthy tissues of the host plant without causing any symptoms of disease. The relationship between the endophyte and the host ranges from latent phytopathogenesis to mutualistic symbiosis. Endophytes obtain nutrition and protection from plants and, in return, help their hosts to adapt to different ecological stress conditions by producing certain functional metabolites. Consequently, endophytes are usually metabolically more active than their non-endophytic counterparts. By virtue of their functions in nature, endophytes produce multitude of natural products, particularly those having potential antimicrobial activities. As all the plants analysed for endophytism have been found to possess such organisms, endophytes represent a comparatively unexplored as well as a huge reservoir of bioactive metabolites. In this chapter, an effort is made to present an overview of the potential of endophytic microorganisms as a source for antimicrobial agents.

Keywords

Endophytes · Antibiotics · Volatile organic compounds (VOCs) · Fungi · Secondary metabolites · Natural products

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1 Introduction

The discovery of new antimicrobial agents is imperative for the treatment of infections caused by drug-resistant pathogens. Microorganisms are a well-known reservoir of bioactive natural products having huge potential in the field of pharmaceutical, industrial and agricultural applications (Demain 1999; Keller et al. 2005). From the foremost antibiotics, such as penicillin and streptomycin, to other life-saving drug molecules, like rapamycin and cyclosporin, microorganisms have contributed numerous molecules to natural product repositories that have the potential to treat human diseases. Natural products derived from microbial sources have been an important source of novel drugs (Clardy and Walsh 2004; Khosla 1997; Sieber and Marahiel 2005). Further, most of the anticancer and antimicrobial drugs currently available in the market are either natural products or their derivatives (reviewed by McAlpine et al. 2005). In comparison to other natural sources, such as plants, microorganisms are both highly diverse and poorly explored. Reports based on estimation of microbial population unfolded that only about 1% of bacteria and 5% of fungi have been identified and characterized, whereas the rest remain unexplored (Heywood 1995; Staley et al. 1997). The contribution of microorganisms to the pharmaceutical industry is further limited by the potentiality of orphan biosynthetic pathways that do not express themselves under optimum conditions (Bok et al. 2006; Hertweck 2009). However, the vast array of techniques pertaining to the growth and manipulation of microorganisms, such as media engineering, co-culture, chemical induction, epigenetic modulation and metabolite re-modelling, coupled with fermentation technology for scale-up, make them suitable for the production of useful natural products, both known and novel (Bok et al. 2006; Knappe et al. 2008; Bergmann et al. 2007; Schroeckh et al. 2009; Riyaz-Ul-Hassan et al. 2012). Hence, microbiologists explore unique niches including extreme environments, such as ocean beds, geothermal vents and cold desserts, in search of novel strains with promising bioactive potential (Staley et al. 1997).

In the recent past, it has been observed that much of the wealth of microbial biodiversity with complex biochemistry and secondary metabolite production resides in plant tissues (Strobel 2006). Interest in such microorganisms, termed as endophytes, increased immensely with the discovery of the billion-dollar anticancer drug, Paclitaxel, which was discovered in an endophytic fungus isolated from *Taxus longifolia* (Stierle et al. 1993). Since this ground-breaking discovery, numerous bioactive molecules have been isolated from endophytic fungi (Strobel 2006; Wang et al. 2011a; Deshmukh et al. 2015). Endophytes share a symbiotic association with the plant host, growing in the interstitial spaces of tissues without causing any adverse effects on the host. The interaction between the partners may vary from a mutualistic association to a balanced antagonism (Strobel and Daisy 2003). Due to their asymptomatic nature, endophytic microorganisms remained a hidden reserve until their potential was realized in the recent years.

As much of the previous research focused on exploring the host-plant metabolites in the endophytic partner (Stierle et al. 1993; Puri et al. 2006; Kusari et al. 2009), the theory of horizontal transfer of the gene clusters, coding for the

secondary metabolites of the host, and other interactions between the plant and its endophytes received much impetus (Strobel and Daisy 2003). Interestingly, later studies suggest that the endophytes possess biosynthetic pathways independent of the plant host (Staniek et al. 2009). However, it could also be logical that the microorganisms produce similar metabolites to those of their endophytic partners, given that they would have more chances of thriving in plant tissues if they were resistant to the present metabolites, thus favouring the findings that many endophytes produce the metabolites of their hosts.

Endophytic microorganisms may influence the ability of the plants to function in the specific environmental conditions. They may also impact the structure of the plant communities by playing crucial roles in colonization, coexistence, competition and dynamics of soil nutrients (Clay and Holah 1999). In other cases, herbaceous plants and grasses are associations with dominant endophytes that produce toxic alkaloids, thus providing protection against herbivores (Braun et al. 2003). Endophytes in woody plants are known to play specific defence roles to prevent them from pathogens (Strobel 2003). Overall, the biology and biochemistry of endophytic microorganisms is a novel emerging field with multitude of ecological outcomes.

Endophytes are metabolically more active than their free-living counterparts, and thus, they have the potential to produce exceedingly high numbers of secondary metabolites, which are often bioactive and of low molecular weight, and are produced as families of related compounds, with production often correlated with a specific stage of morphological differentiation (Keller et al. 2005). Several reasons are attributed to the increased metabolic activity of endophytes. Firstly, the organism needs to evolve in order to survive in the tissues of the plant, thus activating the production of molecules that help in the evasion of host defence mechanisms. Secondly, there exists a balanced antagonism between the endophyte and its host, resulting in the production of several phytotoxins by the microbial symbiont (Strobel and Daisy 2003; Strobel 2006). Recently, it has also been proposed that the chemical constituents of the host plant may bring about permanent epigenetic changes in the endophyte, thus turning on some of its otherwise ‘silent’ biosynthetic pathways (Riyaz-Ul-Hassan et al. 2012).

Endophytes have been known to produce volatile organic compounds (VOCs) with specific or nonspecific antimicrobial activities (Mitchell et al. 2010; Meshram et al. 2013) and may be involved in nature to build microenvironments that kill or inhibit pathogenic microorganisms (Riyaz-Ul-Hassan et al. 2012; Strobel et al. 2011). VOCs are important in the functioning of both atmospheric and soil ecosystems and have potential applications in biotechnological fields, viz. agriculture, industry and medicine. Surprisingly, no two microorganisms, even those that are morphologically and genetically identical, produce the same array of VOCs under similar growth conditions (Kudalkar et al. 2012).

The whole genome sequencing of microorganisms ushered a new area in the field of natural product research and drug discovery. The available knowledge about genetics and enzymology of natural products synthesized from microorganisms have expedited the identification and analysis of gene clusters involved in

biosynthesis of natural products in sequenced microbial genomes (Fischbach and Walsh 2006). Genome analysis of one of the first sequenced microbes, *Streptomyces coelicolor*, revealed that there are many more gene clusters encoding biosynthetic pathways than there are known natural products of the organism (Bentley et al. 2002). Similar observations have now been reported for several diverse, sequenced microorganisms, such as *Aspergillus* (Bok et al. 2006), *Streptomyces avermitilis* (Ikeda et al. 2003), *Saccharopolyspora erythraea* (Oliynyk et al. 2007), *Pseudomonas fluorescens* (Paulsen et al. 2005) and *Salinispora tropica* (Udwary et al. 2007). These studies revealed that many novel natural compounds are still unidentified and thus unexplored from natural sources and indicated that the withdrawal of big pharmaceutical companies from natural product drug discovery was premature. Over the past several years, genome mining for new natural products and biosynthetic pathways has become a rapidly advancing field (Corre and Challis 2007; Challis 2008). These findings strongly support the one-strain-many-compounds (OSMAC) approach, according to which varying growth conditions can positively influence the metabolite profile of microorganisms. Therefore, a multitude of potentially useful natural products still awaits discovery (Peric-Concha and Long 2003).

In this chapter, we review the potential of antimicrobial compounds obtained from endophytic microorganisms with potential and touch-up on the board techniques employed in the field of endophytic biology.

2 Why Endophytes?

In the battle against the increase of drug-resistant pathogens, there is an urgent need for novel alternatives to currently used antibiotics. Exploration of the unique niches of biodiversity leads to the discovery of new natural products, and the perusal of literature suggests that the microorganisms residing within the plant are an enormous untapped source of potential bioactive molecules (Menpara and Chanda 2013).

For a better understanding of why endophytes have been playing a key role in antimicrobial research, it is necessary to review their role in nature. Endophytes colonize internal plant tissues without causing any symptoms of disease. They are diverse at the species level, phylogenetically abundant, ecologically primed, evolutionarily strong and are an unexplored group of taxonomic, genetic and functional diversity. Endophytes are ubiquitous and have been found in every studied plant. Microbes enter tissues of the plant through the roots or wounds or rather by creating wounds through the production of enzymes like cellulases. It is still unknown why plant's defence mechanisms are ineffective against colonization by endophytes or why plants and endophytes coexist. Regardless, there exists a symbiotic (mutually beneficial) relationship between a plant and its endophytes; the endophytes are benefitted by their access to plant nutrients, and the plant is benefitted by protections provided by the endophytes against pathogens, the promotion of plant growth and increased tolerances to biotic and abiotic stressors. Recently, it was shown that plant microsymbionts produce a variety of secondary metabolites that not only play a major role in providing defences to the host but which also aid in specific

interactions and communication with the plant (Brader et al. 2014). Due to the constant process of microbial strain development by passage through various stages of plant growth and development, as well as their acquired ecological functions, endophytes have evolved into proficient producers of bioactive secondary metabolites (Strobel et al. 2004; Porras-Alfaro and Bayman 2011; Nalli et al. 2015).

Endophytes, in particular, assist their hosts in evading pathogens by producing antimicrobial secondary metabolites. The potential antimicrobial activity of these strains may be due to their evolution over billions of years in diverse ecological niches and natural habitats (Strobel et al. 2004; Aly et al. 2011; Mousa and Raizada 2013).

Many studies have revealed a novel role of endophytes in the improvement of plant physiology, where some are known to interact directly or indirectly with mineral and nutrient uptake by the host plant (Singh et al. 2011a). In one study, it was revealed that endophytic fungi present in drought-tolerant species not only exert their action through the storage and secretion of sugars and alcohols but also through triggering minor changes in leaf physiology, which ultimately leads to reduced transpiration losses (Auge et al. 2008). It has also been seen that under heavy metal stress, endophytes protect the host plant by reducing metal accumulation and transport (Yamaji et al. 2016).

Some endophytic microorganisms are known to confer their own ecological functions, such as thermal tolerance, to the plants. They can also affect community structure and microbial interactions, which are the lead determinants of biodiversity in plants, and can interact with the systems of the host plant by influencing the availability of nutrients and by their ability to provide resistance to biotic and abiotic stress. Importantly, endophytes can be modified in such a way that their positive effects are exploited. For example, *Leifsonia xyli*, a xylem-inhabiting bacterial endophyte, has been genetically modified with a gene from *Bacillus thuringiensis*, thereby producing delta-endotoxin, which is active against insects in nature, especially Lepidoptera and Coleoptera (Mills et al. 2001). Endophytes can also be used as biological control agents (BCAs) and are advantageous over conventional BCAs due to their ability to be directly applied to the seeds, thereby avoiding the treatment of a large number of established plants (Ezra et al. 2009).

Various groups have been working on endophytes, and a significant amount of literature is available on the field. However, as stated before, the primary focus has been in isolating promising plant metabolites from the endophytes of the host, with considerable success (Puri et al. 2006; Kusari et al. 2009). Other works have focused on using endophytes as growth-promoting agents in various plants/crops (Tiwari et al. 2010; Singh et al. 2013; Wani et al. 2017). The endophytes studied have been mostly acquired from individual plants sporadically, but significant efforts have been made to bioprospect the endophytes from different locations (Raviraja 2005; Puri et al. 2006; Shweta et al. 2013; Qadri et al. 2013, 2014; Arora et al. 2016; Yu et al. 2010; Yedukondalu et al. 2017). Considering the enormity of the biodiversity, concerted efforts are needed to tap the endophytic microorganisms for bioprospection. It seems also logical to isolate and characterize sustainable microbial compounds from these endophytes and to use new biology for known endophyte-produced molecules in order to discover bioactivities that have so far not been elucidated.

3 Endophytes as a Source of Bioactive Antimicrobials

Bioactive molecules from endophytes have potential uses in medicine, agriculture, cosmetics and the food industry (Strobel and Daisy 2003; Shukla et al. 2014). Classes of bioactive metabolites obtained from endophytes include, but are not limited to, alkaloids, cytochalasins, polyketides, terpenoids, flavonoids, steroids, cyclohexanones, depsipeptides, lactones, lignans, peptides and quinines with antimicrobial, anticancer, antioxidant, insecticide and immunosuppressant potential (Fig. 1) (Guo et al. 2008; Kharwar et al. 2011; Mousa and Raizada 2013). Thus, numerous bioactive molecules of microbial origin have been characterized from endophytes, and many more await isolation (Mousa and Raizada 2013).

The extraction of secondary metabolites from the endophytic isolates is a crucial step (Fig. 2). It is affected by a number of factors, including solvent used and the methods employed for extraction. The evolution of the microorganism, which may have incorporated genetic information from its host plant, is known to directly influence the production of secondary bioactive metabolites that help them to adapt and carry out specific functions, such as protection the host from insects, pathogens and grazing animals (Gouda et al. 2016).

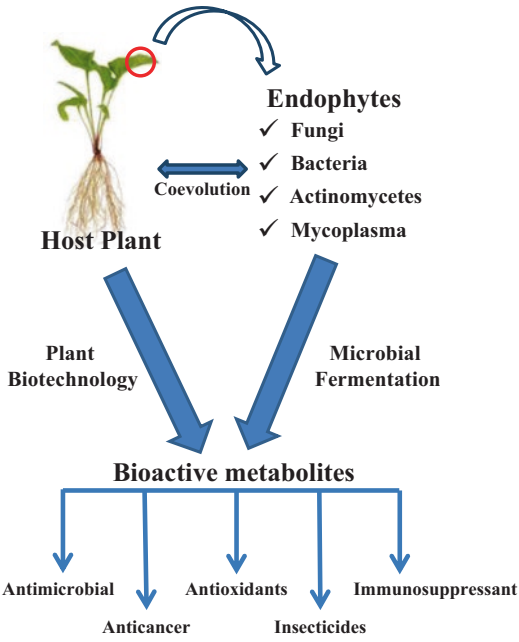


Fig. 1 Plant-endophyte symbiotic relationship along with their potential applications. Endophytes are associated with plants in various forms including fungi, bacteria, actinomycetes and mycoplasma. They are known to produce bioactives that serve as antimicrobial, anticancer, antioxidant, insecticide and immunosuppressant compounds

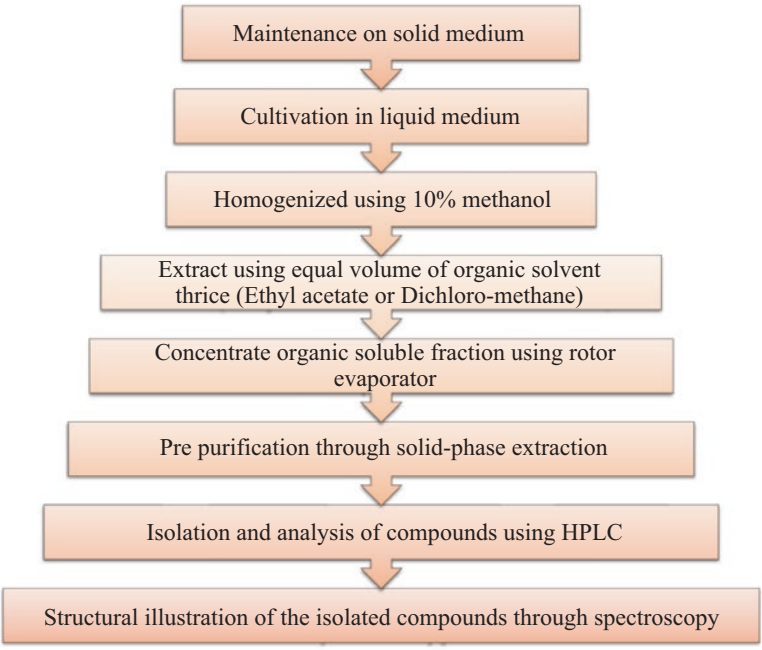


Fig. 2 Extraction of secondary metabolites from endophytes

A list of endophytic microorganisms, with their host plants and identified antimicrobial activities that have been discovered in recent years, is provided in Table 1, and the chemical structures of potential secondary metabolites isolated from endophytes are illustrated in Fig. 3. Some of the most promising agents are discussed below:

- **Leucinostatin A**, produced by the endophyte, *Acremonium* sp., which originated from *Taxus baccata*, has exhibited antimicrobial activity against *Pythium ultimum* with a 50% inhibitory concentration of less than 1 μmol (Strobel et al. 1997).
- **Ecomycins** belong to a novel family of lipopeptides containing uncommon amino acids, such as β-hydroxy aspartic acid and homoserine, which exhibit antimycotic potential. Ecomycin A, B and C are isolated from *Pseudomonas viridiflava*, a plant-associated bacterium having significant bioactivities against a broad spectrum of human and plant pathogens. Ecomycin B, in particular, exhibited the most potential, with an MIC of 40 mg/ml against *Cryptococcus neoformans* and 31 mg/ml against *Candida albicans* (Miller et al. 1998).
- **Cryptocandin**, a unique lipopeptide with significant antimycotic activity, was isolated from the endophytic fungus *Cryptosporiopsis quercina*. It was reported with the MIC value of 0.03–0.07 μg/ml against the fungal pathogens *Candida albicans*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*. It was also found to be active against a number of fungal phytopathogens, including *Sclerotinia sclerotiorum* and *Botrytis cinerea* (Strobel et al. 1999).

Table 1 A list of endophytic microorganisms, with their host plants and identified antimicrobial activities that have been discovered in recent years

Endophyte	Host Plant	Activity against pathogens	References
Colletotrichum sp.	*Artemisia annua*	*Rhizoctonia cereal*, *Phytophthora capsici* and *Helminthosporium sativum*	Lu et al. (2000)
Colletotrichum gloeosporioides	*Artemisia mongolica*	*Bacillus subtilis, Staphylococcus aureus* and *Sarcina lutea*	Zou et al. (2000)
Phomopsis longicolla	*Dicerandra frutescens*	*B. subtilis* and *S. aureus*	Wagenaar and Clardy (2001)
Paenibacillus polymyxa, *Bacillus* sp. and *Pseudomonas poae*	*Panax ginseng*	*Achlya klebsiana* and *Pythium spinosum*	Adhikari et al. (2001)
Streptomyces sp.	*Monstera* sp.	*Cryptococcus neoformans*	Ezra et al. (2004)
Nodulisporium sp.	*Juniperus cedre*	*B. megaterium*, *Chlorella Fusca*, *Microbotryum violaceum* and *Septoria tritici*	Dai et al. (2006)
Phomopsis cassia	*Cassia spectabilis*	*Cladosporium cladosporioides* and *C. sphaerospermum*	Silva et al. (2006)
B. amyloliquefaciens	*Scutellaria baicalensis Georgi*	*Streptococcus thermophilus*, *Saccharomyces cerevisiae*, *Botryodiplodia theobromae* and *Penicillium expansum*	Sun et al. (2006)
Botryosphaeria mamane	*Garcinia mangostana*	*S. aureus* and MRSA	Pongcharoen et al. (2007)
Phomopsis sp.	*Excoecaria agallocha*	*Candida albicans* and *Fusarium oxysporum*	Huang et al. (2008)
Ampelomyces sp.	*Urospermum picroides*	*S. aureus, S. epidermidis* and *Enterococcus faecalis*	Aly et al. (2008)
Phomopsis sp.	*Garcinia dulcis*	*Mycobacterium tuberculosis*	Rukachaisirikul et al. (2008)
Phoma sp.	*Saurauia scaberrinae*	*S. aureus*	Hoffman et al. (2008)
Penicillium sp.	*Acrostichum aureum*	*S. aureus* and *Candida albicans*	Cui et al. (2008)
Penicillium sp.	*Cerbera manghas*	*S. aureus*	Han et al. (2008)
Edenia gomezpompae	*Callicarpa acuminate*	*P. capsici, P. parasitica, F. oxysporum* and *Alternaria solani*	Macias Rubalcava et al. (2008)
Coniothyrium sp.	*Sideritis chamaedryfolia*	*Escherichia coli* and *B. megaterium*	Krohn et al. (2008a)
Dinemasporium strigosum	*Calystegia sepium*	*B. megaterium*	Krohn et al. (2008b)
Chaetomium globosum	*Viguiera robusta*	*S. aureus* and *E. coli*	Momesso et al. (2008)

(continued)

Table 1 (continued)

Endophyte	Host Plant	Activity against pathogens	References
Xylaria sp.	*Ginkgo biloba*	*S. aureus, E. coli, S. typhi, S. typhimurium, S. enteritidis, A. hydrophila, Yersinia* sp., *V. anguillarum, Shigella* sp. and *V. parahaemolyticus*	Liu et al. (2008)
Microdochium bolleyi	*Fagonia cretica*	*E. coli* and *B. megaterium*	Zhang et al. (2008)
Pestalotiopsis sp.	Lichen *Clavaroids* sp.	*S. aureus*	Ding et al. (2009)
B. subtilis	Wheat	*Gaeumannomyces graminis* var. *tritici* (Ggt)	Liu et al. (2009)
Nodulisporium sp.	*Erica arborea*	*B. megaterium*	Dai et al. (2009)
B. licheniformis, B. pumilus, Bacillus sp.	*Platycodon grandiflorum*	*P. capsici, F. oxysporum, Rhizoctonia solani* and *Pythium ultimum*	Islam et al. (2010)
Enterobacter sp., *B. subtilis*	*Raphanus sativus L*	*E. coli, Pseudomonas aeruginosa, Salmonella enterica, S. enteritidis, S. typhimurium, Shigella flexneri, Shigella sonnei, B. cereus, Listeria innocua, L. ivanovii, L. monocytogenes* and *S. aureus*	Seo et al. (2010)
Pichia guilliermondii	*Paris polyphylla*	*A. tumefaciens, E. coli, P. lachrymans, R. solanacearum, X. vesicatoria, B. subtilis, S. aureus* and *S. haemolyticus*	Zhao et al. (2010)
Paenibacillus sp.	*Manihot esculenta*	*R. solani*	Canova et al. (2010)
Burkholderia sp.	*Huperzia serrata*	*P. capsici, F. graminearum* and *Sclerotinia libertiana*	Wang et al. (2010)
Phoma sp.	*Salsola oppositifolia*	*B. subtilis* and *E. coli*	Loesgen et al. (2011)
Microdiplodia sp.	*Lycium intricatum*	*Legionella pneumophila*	Siddiqui et al. (2011)
Streptomyces sp.	*Kandelia candel*	Methicillin-Resistant *S. aureus* and Vancomycin-Resistant *Enterococcus faecalis*	Ding et al. (2011)
Penicillium chrysogenum	*Marine red alga Laurencia* sp.	MRSA, *P. fluorescens, P. aeruginosa* and *S. epidermidis*	Gao et al. (2011)
Fusarium oxysporum	*Cinnamomum kanehirae*	MRSA and *B. subtilis*	Wang et al. (2011b)
Phomopsis longicolla	*Bostrychia radicans*	*S. aureus* and *S. saprophyticus*	Erbert et al. (2012)
Diaporthe phaseolorum	*Laguncularia racemosa*	*S. aureus* and *S. typhi*	Sebastianes et al. (2012)

(continued)

Table 1 (continued)

Endophyte	Host Plant	Activity against pathogens	References
B. amyloliquefaciens	*Memecylon edule, Tinospora cordifolia*	*B. subtilis, E. coli, S. aureus, Pseudomonas aeruginosa* and *Candida albicans*	Bhoonobtong et al. (2012)
Dothideomycete sp.	*Tiliacora triandra*	*S. aureus* and MRSA	Senadeera et al. (2012)
Aspergillus sp.	*Bruguiera gymnorrhiza*	*S. aureus* and *B. subtilis*	Li et al. (2012)
Nigrospora sp.	*Pongamia pinnata*	MRSA, *E. coli, P. aeruginosa, P. fluorescens* and *S. epidermidis*	Shang et al. (2012)
Pestalotiopsis mangiferae	*Mangifera indica*	*B. subtilis*, *P. aeruginosa* and *K. pneumoniae*	Subban et al. (2013)
Coniothyrium sp.	*Salsola oppositifolia*	*E. coli* and *B. megaterium*	Sun et al. (2013b)
Microsphaeropsis arundinis	*Pinus* sp.	*S. aureus*	Luo et al. (2013)
Bacillus sp., *Pseudomonas* sp.	*Plectranthus tenuiflorus*	*S. aureus, E. coli, Klebsiella pneumoniae, Streptococcus agalactiae, Proteus mirabilis* and *Candida albicans*	El-Deeb et al. (2013)
B. amyloliquefaciens, B. methylotrophicus	*Panax notoginseng*	*F. oxysporum, Ralstonia* sp. and *Meloidogyne hapla*	Ma et al. (2013)
Lewia infectoria	*Besleria insolita*	*S. aureus*	Casella et al. (2013)
B. subtilis, Pseudomonas fluorescens	*Centella asiatica*	*Colletotrichum higginsianum*	Rakotoniriana et al. (2013)
B. subtilis, C. flaccumfaciens, Ps. Fluorescens, P. ananatis	*Panicum virgatum L.*	*Trichoderma virens* and *Rhizoctonia solani*	Gagne-Bourgue et al. (2013)
Cryptosporiopsis sp.	*Viburnum tinus*	*B. megaterium*	Saleem et al. (2013)
B. subtilis, B. licheniformis	*Codonopsis lanceolata*	*Phytophthora capsici*, *F. oxysporum* and *Rhizoctonia solani*	Kang et al. (2013)
Streptomyces sp.	*Polygonum cuspidatum*	*Aspergillus niger*, *Aspergillus fumigatus*, *Klebsiella pneumoniae, S. aureus* and *B. subtilis*	Sun et al. (2013a)
Aspergillus sp.	*Bauhinia guianensis*	*B. subtilis, E. coli, P. aeruginosa* and *S. aureus*	Pinheiro et al. (2013)
Phialophora mustea	*Crocus sativus*	*C. albicans*	Nalli et al. (2015)
Phoma sp.	*Glycyrrhiza glabra*	*S. aureus* and *S. pyogenes*	Arora et al. (2016)
Diaporthe terebinthifolii	*Glycyrrhiza glabra*	*Candida albicans*	Yedukondalu et al. (2017)

- The antifungal agent, **cryptocin**, was isolated from an endophytic strain of *Cryptosporiopsis quercina* from the inner bark of the stems of *Tripterygium wilfordii*. Cryptocin is a unique tetramic acid exhibiting antimycotic activity against *Pyricularia oryzae* with the MIC value of 0.39 μg/ml. It also possesses activity against a wide variety of plant-pathogenic, but not human-pathogenic, fungi (Li et al. 2000).
- The continual natural occurrence of cyclohexane epoxides and the exploration of their biological activities have gained interest within pharmacologists, biologists and chemists (Marco-Contelles et al. 2004). **Jesterone** and **hydroxy-jesterone** are potential cyclohexenone epoxides recovered from the fungal endophyte, *Pestalotiopsis*

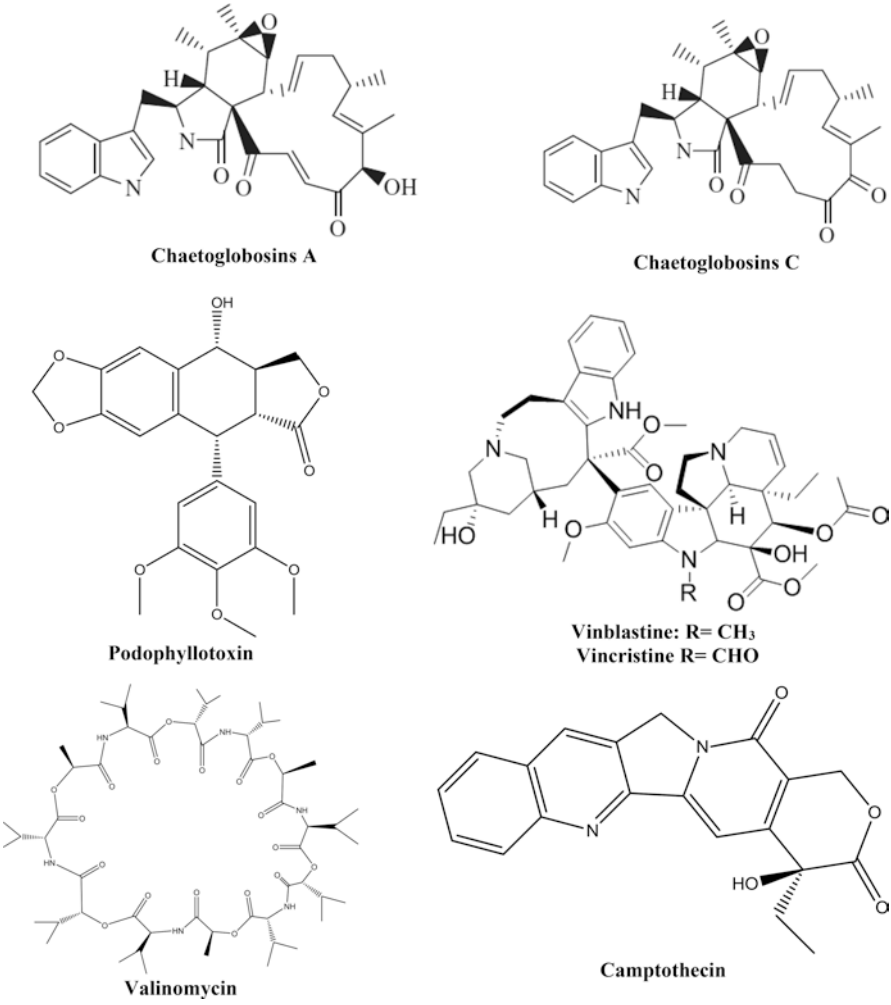
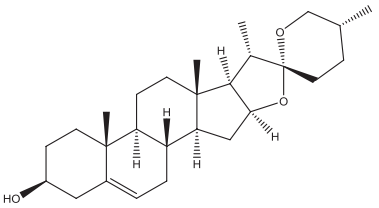
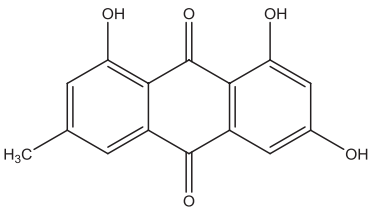


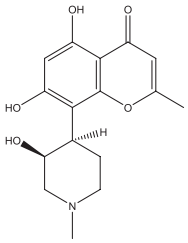
Fig. 3 Chemical structures of potential secondary metabolites isolated from endophytes



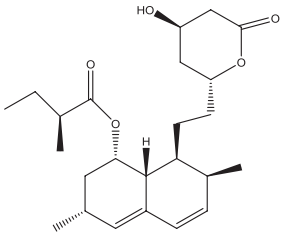
Diosgenin



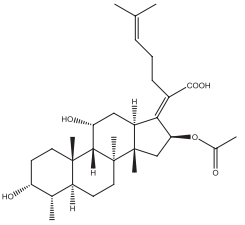
Emodin



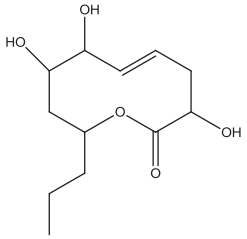
Rohitukine



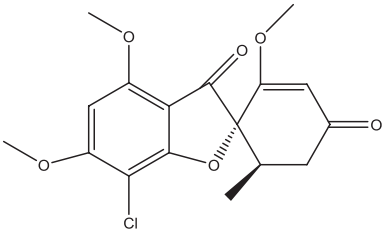
Lovastatin



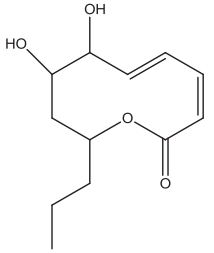
Fusidic acid



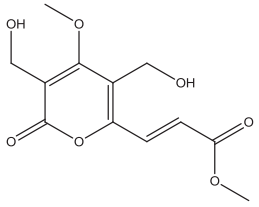
Phomolide-G



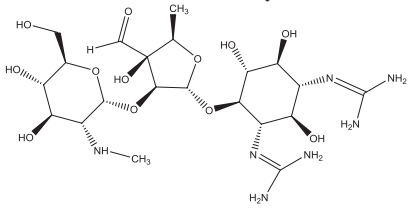
Griseofulvin



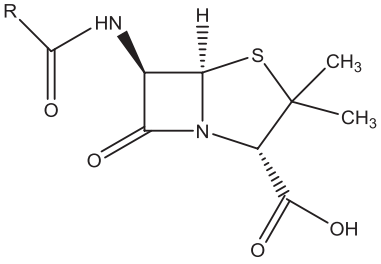
Xylarolide



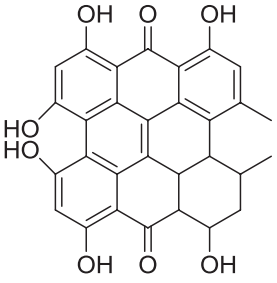
Rosellisin



Streptomycin



Pencillin R: variable group



Hypericin

Fig. 3 (continued)

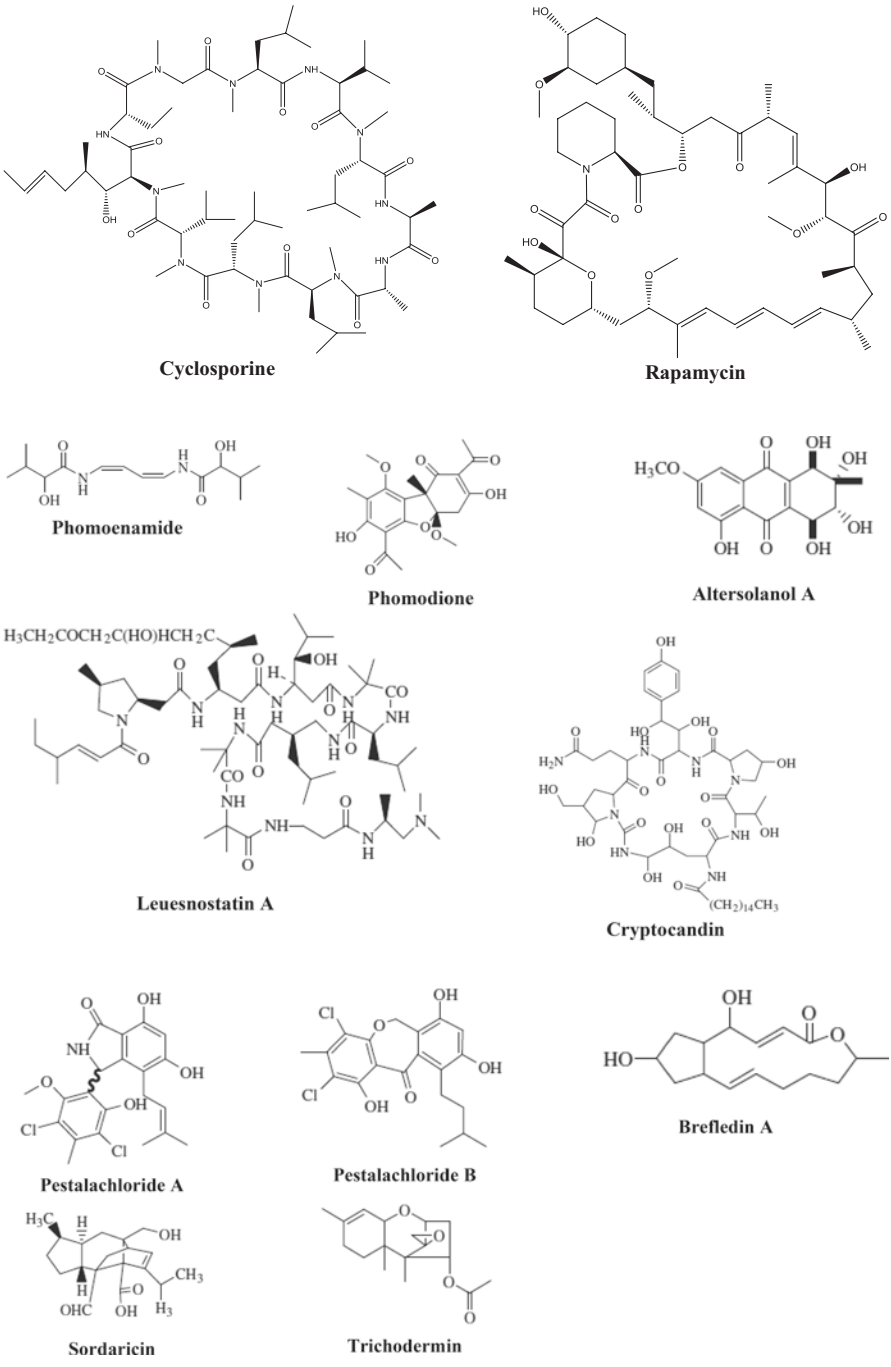


Fig. 3 (continued)

jester, with bioactive potential against *Pythium ultimum*. In particular, it showed selective antimycotic activity against the oomycetous fungi, which are some of the most phytopathogenic of all disease-causing fungi (Li and Strobel 2001).

- **Pestacin**, from *Pestalotiopsis microspore*, an endophytic fungus indigenous to Papua New Guinea, exhibits moderate antifungal and antioxidant activity (Harper et al. 2003).
- **Brefeldin A** is a fungal metabolite, exhibiting antitumor, antimitotic, antifungal and antiviral activities (Harri et al. 1963). Brefeldin A has been isolated from an endophytic culture of *Cladosporium* sp. associated with *Quercus variabilis*.
- **Echinocandins** are a group of lipopeptides with potential antifungal activities against *Candida albicans*, *Candida parapsilosis* and *Candida guilliermondii* (Grover 2010). Several echinocandins (A, B, C, D and H) have been isolated from endophytic *Cryptosporiopsis* sp. and *Pezicula* sp. (Noble et al. 1991). The antimicrobial compounds, ergosterol and 5a,8a-epidioxyergosterol, were isolated from the endophytic fungus *Nodulisporium* sp., which is associated with *Juniperus cedre* (Dai et al. 2006).
- **Munumbicins** were described as a novel group of antibiotics with a broad range of activity against many human pathogens and fungal phytopathogens. Four munumbicins (A, B, C and D) were isolated from *Streptomyces* sp., an endophyte of the medicinal plant, *Kennedia nigriscans*, also known as snake vine. In particular, munumbicin B exhibits the MIC value of 2.5 μg/ml against *S. aureus* (including MRSA), and munumbicin D showed activity against the malarial parasite *Plasmodium falciparum,* displaying the IC_{50} value of 4.5 ng/ml (Castillo et al. 2002). In another study, the structurally similar munumbicins E-4 and E-5 were isolated from *Streptomyces* sp. Both E-4 and E-5 showed potent activity against *Pythium ultimum* and were also active against *Plasmodium falciparum*, with IC_{50} values of 0.50 and 0.87 μg/m, respectively (Castillo et al. 2006).
- Five new octaketides, named the **cytosporones** (A, B, C, D and E), from the culture broth of two endophytic fungi, *Cytospora* sp. and *Diaporthe* sp., were isolated from the tissues of *Conocarpus erecta* and *Forsteronia spicata* plants, respectively. Cytosporones D and E displayed strong antibacterial activity, with an MIC for cytosporone D against representative strains of *E. faecalis*, *S. aureus* and *E. coli* and the fungus *C. albicans* of 8, 8, 64 and 4 μg/ml, respectively (Brady et al. 2000). In another report, cytosporone B and C were isolated from *Phomopsis* sp., an endophytic fungus of mangrove, and these compounds inhibited *C. albicans* and *F. oxysporum*, with MIC values ranging from 32 to 64 mg/ml (Huang et al. 2008).
- **Altersolanol A**, isolated from *Ampelomyces* sp., is an endophyte of the medicinal plant, *Urospermum picroides*, and has exhibited antimicrobial activity against the bacterial pathogens *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Enterococcus faecalis* at MICs of 12.5 and 12.5–25 mg/ml, respectively (Haraguchi et al. 1992; Aly et al. 2008).
- **Phomoenamide**, an antibacterial alkaloid, was isolated from the endophytic fungus *Phomopsis* sp., along with five more metabolites: phomonitroester, deacetyl phomoxanthone B, dicerandrol A, (1S,2S,4S)-p-menthane-1,2,4-triol and uridine. Phomoenamide exhibited moderate activity with the MIC value of 6.25 mg/ml against *Mycobacterium tuberculosis* (Rukachaisirikul et al. 2008).

- **Pestalachloride A and B** have been isolated from and endophytic strain of *Pestalotiopsis adusta* and showed significant antifungal activity against three phytopathogens, including *Fusarium culmorum*, *Gibberella zeae and Verticillium aibo-atrum* (Li et al. 2008).
- The **sordarin** family of compounds, characterized by a unique tetracyclic diterpene core, inhibits protein synthesis in fungi (Liang 2008). Sordaricin, produced by an endophytic fungal isolate *Xylaria* sp., recovered from the leaves of *Garcinia dulcis*, displayed moderate activity against a variety of fungal pathogens (Pongcharoen et al. 2008).
- **Chaetoglobosins**, well-known mycotoxins, have gained interest due to a large number of biological activities, viz. cytotoxic, antifungal, phytotoxic and nematicidal (Li et al. 2014). Till now, more than 40 chaetoglobosins have been reported from the cultures of some fungi, most belonging to the genus *Chaetomium*. Chaetoglobosins A, G, V, Vb and C were characterized from the culture of an endophytic strain *C. globosum* isolated from the leaves of *Ginkgo biloba* (Qin et al. 2009).
- The **non-nitrogenous methyl phenalenones** produced by a fungal endophyte, *Coniothyrium cereal*, possessed potential antimicrobial activity. Coniosclerodione, coniosclerodione, (–)-cereo lactone and (–)-scleroderolide showed strong antimicrobial activity against *S. aureus* SG 511. Z-coniosclerodinol, (S, S)-sclerodinol and coniolactone inhibited the growth of *Mycobacterium phlei* in agar diffusion assay. Also, trypethelone strongly inhibited the growth of *M. phlei*, *S. aureus* and *E. coli* (Elsebai et al. 2011a, b).
- **Azaphilones** or **azaphilonoids** are a structurally variable family of fungal polyketide metabolites exhibiting a wide range of significant biological functions, including antimicrobial, antiviral, cytotoxic, anticancer and anti-inflammatory activities (Gao et al. 2013). Pestafolide A, a novel antifungal azaphilone, has been isolated from the solid cultures of an endophytic isolate, *Pestalotiopsis foedan* (Ding et al. 2008). Four new azaphilone-derived molecules, Phialomustin A–D, were isolated and characterized from an endophytic fungus, *Phialophora mustea*, obtained from *Crocus sativus*. Compounds C and D displayed significant antifungal activities, with IC_{50} values of 14.3 and 73.6 μM against *Candida albicans* (Nalli et al. 2015).
- **Diketopiperazines** are the smallest cyclic peptides known for having important biological activities, such as antifungal, antibacterial, antitumor, antiviral, antihyperglycaemic and glycosidase inhibition. They also have the potential to disrupt bacterial biofilm formation (Carvalho and Abraham 2012). Five new sulphide diketopiperazine derivatives, penicibrocazines A–E, were isolated from the culture extract of *Penicillium brocae*, an endophytic strain recovered from the tissues of the marine mangrove plant *Avicennia marina.* Compound B showed antimicrobial activity against a few of the test pathogens, with the MIC values ranging from 0.25 to 64 μg/ml (Meng et al. 2015). Also, the chemical investigation of an endophytic strain, *Phoma* sp., associated with *Glycyrrhiza glabra*, led to the isolation of two thiodiketopiperazine derivatives. Both of these compounds inhibited the growth of several bacterial pathogens especially that of *Staphylococcus aureus* and *Streptococcus pyogenes*, with IC_{50} values of less than 10 μM. In addition, the compounds strongly inhibited biofilm formation by both of the pathogens (Arora et al. 2016).

- Two new fatty acid-derived metabolites, **diapolic acids A and B,** were isolated from the crude extract of *Diaporthe terebinthifolii*, with moderate antimicrobial potential against *Yersinia enterocolitica* (Yedukondalu et al. 2017).
- **Javanicin**, a highly functionalized naphthoquinone, was recovered from an endophytic fungus, *Chloridium* sp., isolated from the fresh tissues of neem. It exhibits strong antibacterial potential against *P. aeruginosa* and *P. fluorescens*, with thee MIC value of 2 μg/ml (Kharwar et al. 2009).

In the past years, natural and biological control agents against insects, pests and diseases affecting plants have attracted more attention as a way to reduce the use of insecticides and pesticides in agriculture biotechnology. In this regard, endophytes have gained much focus as a promising source of such agents. Earlier studies have reported that biological control of many plant diseases could be achieved by using antagonistic endophytes. Different bacterial species, namely, *Alcaligenes* spp., *Kluyvera* spp. (de Assis et al. 1998), *Pseudomonas fluorescens*, *P. alcaligenes*, *P. putida*, *Flavobacterium* spp., *Bacillus megaterium* (Reiter et al. 2002), *B. pumilus* (Benhamou et al. 1998), *Microbacterium* spp., *Clavibacter michiganensis*, *Curtobacterium* spp. and *B. subtilis* (Zinniel et al. 2002), and fungal species, namely, *Coniothyrium carteri*, *Fusarium larvarum*, *Truncatella spadicea* (Qadri et al. 2014), *Trichoderma harzianum*, *Porostereum* sp., *Alternaria* sp., *Alternaria alternata* and *Botrytis fabiopsis* (Wani et al. 2016) have been reported as endophytes that were inhibitory to plant pathogens. The fungi *Fusarium* and *Neotyphodium* have been found active against nematodes and *Triticum* spp., respectively (Pocasangre et al. 2000; Tunali et al. 2000).

Thus, a myriad of antimicrobial bioactivities have been recovered from endophytic species, and it is believed that these bioactivities can aid in solving the current threat of drug-resistant pathogens.

4 Antimicrobial Volatile Organic Compounds (VOCs)

VOCs are considered important chemicals produced by microorganisms in the environment that impact the kinetics of the ecosystem and vice versa (Wheatley 2002). Under optimum conditions, VOCs produced by microorganisms are consistent and reproducible. The discovery of the mycodiesel-producing organism *Ascocoryne* sp. (Strobel et al. 2008; Griffin et al. 2010), and further exploration of antimicrobial VOCs of *Muscodor* species (Strobel 2006a), led to the conclusion that fungal isolates produce diverse batteries of VOCs having potential applications in industrial as well as agriculture. In this chapter, the NIST database chemical terminology has been used for naming the VOC compounds.

In agriculture, the interest in fungal VOCs is for their potential as biological control (biocontrol) agents to combat fungal pests through the employment of a more environmentally sound pest management strategy, namely, by reducing fungicide use on crop plants (Morath et al. 2012). That is, since VOCs are naturally occurring, they have the potential to be used as possible alternatives to hazardous fungicides, pesticides and insecticides (Kanchiswamy et al. 2015).

Several potential VOC-producing endophytes with great industrial and agricultural potential have been reported in the last two decades. These compounds belong to different chemical classes, such as terpenoids and benzene derivatives, naphthalene derivatives, cycloalkanes, alcohols, organic acids, ketones and aldehydes, and often have antimicrobial potential, suggesting that these volatile substances may play an important role in nature to create microenvironments free of challenging microorganisms (Riyaz-Ul-Hassan et al. 2012; Strobel et al. 2011). Some of the most promising endophyte produced VOCs and are detailed in the following paragraphs.

More than 28 volatile organic compounds were isolated from the fungal endophyte *Muscodor albus*, associated with *Cinnamomum zeylanicum*, which are found to be potent antimicrobials, as they completely inhibited the majority of the test pathogens, including *Escherichia coli*, *Staphylococcus aureus*, *Micrococcus luteus, Bacillus subtilis* and some fungal pathogens, killing them within a period of 3 days. These VOCs are mixtures of gases belonging to five classes, made up of alcohols, organic acids, esters, ketones and lipids, among which the most effective were the esters, with 1-butanol-3-methyl-acetate having the highest activity (Strobel et al. 2001).

Another strain of *Muscodor*, namely *Muscodor crispans*, was also found to produce antimicrobial VOCs, namely, propanoic acid, 2-methyl-1-butanol, 3-methyl-1-butanol, 3-methyl-acetate, 2-methyl-2-methyl butyl ester and ethanol. The VOCs of the fungus were effective against a wide range of plant pathogens, including the fungi *Pythium ultimum*, *Phytophthora cinnamomi*, *Sclerotinia sclerotiorum* and *Mycosphaerella fijiensis* (the black sigatoka pathogen of bananas), and the serious bacterial pathogen of citrus plants, *Xanthomonas axonopodis pv. citri*. In addition, the VOCs of *M. crispans* killed several human pathogens, including *Yersinia pestis*, *Mycobacterium tuberculosis* and *Staphylococcus aureus*.

Artificial mixtures of fungal VOCs have also been constituted and evaluated for antimicrobial potential (Mitchell et al. 2010). A synthetic mixture of the VOCs from *M. crispans* demonstrated antimicrobial effects against a broad range of human and plant pathogens, including fungi, bacteria and oomycetes. *Pythium insidiosum* is an oomycete capable of causing a life-threatening disease in humans, called pythiosis. The synthetic mixture, at amounts as low as 2.5 µl, significantly reduced the growth of all *P. insidiosum* isolates by at least 80% (Krajaejun et al. 2012). VOCs produced by *M. yucatanensis* were also found effective against several fungi. Epigenetic modulation of this organism was found to induce the production of several new VOCs and other molecules (Qadri et al. 2017).

An endophytic fungus of *Persea indica*, identified as *Hypoxylon* sp., produced 1,8-cineole, 1-methyl-1,4-cyclohexadiene, the tentatively identified (+)-.alpha.-methylene-.alpha.-fenchocamphorone, and several other unidentified compounds. Six-day-old cultures of this endophyte displayed maximum antimicrobial activity against several pathogens. This was the first report of the production of 1,8-cineole by a fungal culture (Tomsheck et al. 2010). It was later found that epigenetic modulation of this endophytic fungus resulted in phenotypic changes, as well as modulation VOC profiles (Riyaz-Ul-Hassan et al. 2012). Similarly, the endophyte, *Hypoxylon* sp., produced a unique an array of bioactive VOCs, including 1,8-cineole. The

organism uniquely produced a series of ketones, including acetone; 2-pentanone; 3-hexanone, 4-methyl; 3-hexanone, 2,4- dimethyl; and 2-hexanone, 4-methyl, and 5-hepten, 2-one, and these account for about 25% of the total, *Hypoxylon*-produced VOCs. The VOCs of this isolate were selective active against a number of plant pathogens and induced the death of *Phytophthora palmivora*, *Rhizoctonia solani* and *Sclerotinia sclerotiorum*, and a 100% inhibition of *Phytophthora cinnamomi*, with only slight to no inhibition of the other pathogens that were tested. From this work, it has becoming increasingly apparent that each isolate of this endophytic *Nodulisporium* spp., including *Daldina* sp. and *Hypoxylon* spp. teleomorphs, seems to produce their own unique set of VOCs (Riyaz-Ul-Hassan et al. 2013).

An endophytic *Phomopsis* sp. was found to produce a unique mixture of VOCs, including sabinene, which is a monoterpene with a peppery odour, only previously known from higher plants. Additional VOCs produced by this organism were 1-butanol, 3-methyl; benzene ethanol; and 1-propanol, 2-methyl and 2-propanone. The gases of *Phomopsis* sp. also possessed antifungal properties, with the IC_{50} values for an artificial gas mixture varying between 8 and 25.65 μl/ml (Singh et al. 2011b). The endophytic fungus *Phoma* sp., associated with the creosote bush, also produced a mixture of VOCs, including a series of sesquiterpenoids, some alcohols and several reduced naphthalene derivatives. The gases emitted by *Phoma* sp. possessed antifungal properties, and the compounds were markedly similar to that of a methanolic extract of the host plant (Strobel et al. 2011).

Thus, endophytic fungi are capable of producing unique arrays of VOCs with antimicrobial activities, having applications in several fields. These applications include alternate fuels, perfumery, biodegradation and decontamination of human and animal wastes, biofumigation, and post-harvest food processing, to name a few.

5 Exploration of New Endophytic Metabolites by Culture-Independent Methods

Molecular approaches have conservatively estimated that microbial diversity is highly unexplored, with only about 1% of bacteria and 5% of fungi characterized so far. Surprisingly, less than 1% of microorganisms can be cultivated by with current laboratory techniques (Amann et al. 1995). Thus, culture techniques inadvertently prejudice our perspective on microbial diversity, including that of both prokaryotic and eukaryotic phyla (Connon and Giovannoni 2002). In particular, endophytic fungi are well known for their potential to produce diverse and active secondary metabolites. The identification and characterization of microbial communities in the environments have been reformed by the use of molecular methods involving PCR amplification of rRNA and conserved protein genes, such as histones and beta tubulins (Vianna et al. 2009; Tejesvi and Prakash 2009). Traditional methods, such as restriction fragment length polymorphisms (RFLP), terminal restriction fragment length polymorphisms (T-RFLP), single-strand conformation polymorphism (SSCP) and quantitative PCR (qPCR) (Laguerre et al. 1994; Lee et al. 1996; Dunbar et al. 2000; Takai and Horikoshi 2000), have been in practice for more than two

decades, but they can only be applied for the identification of microorganisms and not for functional screening. Now, with the development of next-generation sequencing techniques, researchers have gained new methods, such as metagenomics and metaproteomics (Felczykowska et al. 2012; Jang et al. 2012), that have enabled the functional screening and identification of candidate gene-encoded proteins from endophytes for their use in agricultural, food and pharmaceutical industries. Recently, many bioactive compounds have been discovered by means of metagenomics, particularly antibacterials, such as indigo, turbomycins, violacein and nocardamine, all of which were isolated from soil samples (Banik and Brady 2010).

6 Conclusion

Endophytes constitute an enormously diverse microbial resource for bioprospecting, due to the fact that they are usually metabolically proficient. Their capability to produce vast spectrums of natural products is attributed to their diverse functions in nature. In fact, similar organisms isolated from different plants in the same region, or those isolated from the same plants in different regions, may produce different metabolites. These endophytes may play an important role in conferring pathogen resistance to their host by virtue of their metabolites, and therefore, they are of particular interest for the isolation of novel antimicrobial agents. The search for endophytes should be preferentially conducted in the areas of high biodiversity, as their diversity is directly linked to that of the plants. Preference for bioprospecting may be given to taxonomically novel microorganisms, as novel taxonomy may lead to the discovery of new natural products. Once isolated, endophyte potential may be explored through use of media manipulations, inducers, epigenetic modulators, fermentation technology, co-culture and other biotechnological approaches. Thus, given their potential to aid in the fight against antimicrobial resistance, a concerted effort is needed to explore the vast array of endophytes for the discovery of novel antimicrobial agents.

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