Chapter 13
Bioactive Potentials of Novel Molecules from the Endophytes of Medicinal Plants

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Abstract Microbial endophytes have a long-standing association with numerous plant species. A closer look into their diversity indicates the existence of novel species from biologically diverse regions on the earth, especially the tropics. The novelty is related to their ability to produce diverse chemical structures with reliable bioactive potentials, which has resulted in the addition of new compounds to the unending list of natural products. Hyphenated techniques have fastened the cumbersome screening of crude extracts with reliable bioassays resulting in the elucidation of novel compounds or molecules of interest. Biotechnological approaches are of added advantage in the production of such compounds with remarkable bioactivities. This chapter highlights the fungi and actinomycetes as endophytes from the medicinal and pharmaceutical plants of relevance, host-related metabolites, novel bioactive metabolites of endophytes, and approaches for the augmentation of metabolites and a special mention of the metabolites by *Pestalotiopsis* species. Therefore, endophytes are microbial chemical factories more suited for the production of novel metabolites with therapeutic potentials.

Keywords Endophytic microbes · Diversity · Bioprospecting · Novel structures · Medicinal plants

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13.1 Introduction

Medicinal plants play a pivotal role in the health-care systems, and traditional systems of medicine are in existence due to their healing properties. The traditional use of herbal medicines is in vogue due to their historic and cultural significance. One of the most practiced medicinal systems is the Traditional Chinese Medicines often used to treat 5000 remedies (Li 2000), followed by the Japanese and the Indian traditional medicinal systems. The popularity of these medicinal systems has led to the inclusion of plant-derived medicines in the pharmacopoeias. Of the 10,000–11,500 species documented to be of medicinal use in China (Huang et al. 2015; Pei and Huai 2015), ~563 species are cited in the Chinese Pharmacopoeia (http://www.kew.org/mpns). The Japanese traditional medicine, which is practiced in the Japanese society for more than a thousand years, may be divided into folk medicine and Chinese medicine (Kampo medicine). The popularity of this medicine has augmented the per capita consumption of herbal medicine and is viewed as an alternate to modern medicines due to its safe and efficacious use (Saito 2000).

In the Indian system of medicine, 7000–7500 plants are listed as cure for treating diseases, and Ayurveda, "the science of life," utilizes 2000 medicinal plants in plant-based formulations (Pandey et al. 2013). A survey conducted by Medicinal Plant Names Services (MPNS), The Royal Botanic Gardens, Kew, lists the use of 28,187 species as medicinal (Willis 2017). Regardless of their natural distributions across the continents, they are preferred sources of pharmaceutical drugs for treating diseases. Exploitation of medicinal plants from their original habitat for pharmacological benefits has posed serious threat to biodiversity. Therefore, as an alternative, microbes living inside plants – "the endophytes" – are capable of producing bioactive compounds similar to those of host plants. One of the phenomenal success stories first reported in science is the production of Taxol®, the million dollar drug by the novel endophytic fungus, *Taxomyces andreanae*, isolated from the inner bark of the medicinal tree, *Taxus brevifolia* (Stierle et al. 1993). It is estimated that 10,000 kg of bark from *Taxus* is needed to ensure the yield of 2 g of Taxol for the treatment of various types of cancers (Strobel et al. 1996). Microbial endophytes can be viewed as the most reliable and potential sources of bioactive molecules with immense applications in pharmaceutics and agriculture.

13.2 Endophytes: Terminology and Estimates

The term "endophyte" is derived from the Greek words *endon* = inside and *phyton* = plants and was first introduced by Heinrich Friedrich Link, a German biologist in 1809. It is applied to organisms causing asymptomatic infections within plant tissues (Carroll 1986), as latent pathogens (Clay 1988), inhabiting plant organs without causing harm to hosts (Petrini 1991), and microbes that colonize living, internal tissues of plants without causing any immediate, overt negative effects (Bacon and

White 2000) or residing within the tissues of apparently healthy host plants (Schulz and Boyle 2006). The host range for microbial endophytes include bacteria, archaea, fungi inclusive of yeasts, and unicellular eukaryotes such as algae (Trémouillaux-Guiller et al. 2002) and amoeba (Müller and Döring 2009). Endophytes range from mutualists, symbionts, plant growth enhancers, and biocontrol agents.

Fungi are taxonomically diverse group of organisms holding important roles in the cycling of nutrients and modulation of plant growth in the environment (Taylor and Sinsabaugh 2014). The richness of fungal species globally is estimated at millions, yet <2% of the species are described. Fungal diversity has earlier been estimated conservatively at 1.5 million species (Hawksworth 2001), while Schmit and Mueller (2007) estimated the diversity of fungal species to be 712,000. Reliable approaches such as pyrosequencing and Illumina platforms are often useful to estimate the fungal diversity (Buée et al. 2009; Schmidt et al. 2013). The endophytic fungal estimate includes one million species (Dreyfuss and Chapela 1994).

Actinomycetes are Gram-positive bacteria with high G+C content. They are ubiquitous in field-grown crop plants, which are related to their abundance in rhizosphere soils, and are important component of microbial diversity. They are being recovered from a range of habitats and unusual environments. The diversity estimates of these organisms are a matter of debate as soil samples from various depths and types tend to vary with the actinomycete populations. Vieira and Nahas (2005) provided the total counts for actinomycete populations in three soil types (crop field, tree, and forest) ranging from 79.6 to 88.0 × 10^6 colony-forming units (CFU) g^{-1}. Unlike fungi, such estimates of diversity have not been predicted for the actinomycetes despite their omnipresence in soil.

The diversity, bioactivity, novel molecules, and applications of endophytic fungi (Strobel and Daisy 2003; Kaul et al. 2012) and actinomycetes (Qin et al. 2011; Golinska et al. 2015; Gao et al. 2018) with biotechnological and pharmaceutical relevance are documented. Therefore, this chapter highlights the importance of medicinal plants as sources of drugs, definitions of endophytes and their isolations, endophyte diversity in biodiverse areas, and bioprospection for novel molecules and biological activities.

13.3 Biodiversity Hotspots and the Isolation of Endophytes

The world's plant wealth is harbored in the biodiverse regions known for plant diversity; the epicenters are known as "hotspots," the term coined by Myers (1988), a conservation biologist. In order to qualify for the hotspot status, the area needs to contain endemic vascular plants (1500, 0.5% of the world total of 300,000) whose populations have declined by 70%. At present, 34 hotspot locations are documented by Conservation International (Mittermeier et al. 2004).

A perusal of literature indicates that among the 34 hotspots of plant diversity, a handful of them have been subjected to the isolations of endophytic microbes. The rationale for the selection of plants is based on the ethnobotanical uses, location in

unique environments, and undisturbed habitats (Strobel et al. 2004), and these considerations have led to the listing of the tropical Andes as the lead hotspot location, which boasts of harboring ~6.7% of the global (44%) endemic plant species (Myers et al. 2000).

Inspired by the works of late Monroe Wall and Mansuhk Wani, natural product chemists from the Research Triangle Institute, Gary Strobel, Professor of Plant Sciences from the Montana State University, worked with endophytic microbes from the success achieved by the isolation of Taxol of microbial origin. Deriving impetus from the natural product research, he travelled to tropical wilderness, rain forests, and undisturbed places to collect plant species of ethnobotanical significance, their location in unique environments resulting in the isolation and characterization of a number of endophytes and their products with potential bioactivities (Strobel and Daisy 2003; Strobel et al. 2004).

The Kinshasa reserve in Congo yielded an insulin-mimetic small molecule from the endophytic *Pseudomassaria* sp. (Zhang et al. 1999), and from the Venezuela-Guyana border in the Tepuis range, a unique *Siematoantelerium tepuiense* with Taxol-producing potentials *was* documented (Strobel et al. 1999). A unique *Streptomyces* MSU-2110 producing the peptide antibiotics was isolated from a vine, *Monstera* sp., from the Manu region of the upper Amazon (Ezra et al. 2004). Three hundred medicinally rich plants, sampled from Lake Sandoval area in the Northern Territory, Australia region, yielded 14 strains with antimicrobial potentials (Bascom-Slack et al. 2009). The Northern Territory of Australia is the abode of the aboriginal community, who use stem pieces of snake vine plant (*Kennedia nigriscans*) to treat wounds and infections. The plating of stem fragments resulted in the isolation of a *Streptomyces* sp., producing a newly described class of broad-spectrum peptide antibiotics, munumbicins (Castillo et al. 2002). The nomenclature of this antibiotic was dedicated to Mr. Reggie Munumbi Miller of the Manyallaluk community. The antibiotic kakadumycin was isolated from *Streptomyces* sp., as endophyte of the fern-leaved tree *Grevillea pteridifolia* from this region (Castillo et al. 2003).

The mountainous Southwest China representing the tropical rain forests of Xishuangbanna in the Yunnan Province and Panxi plateau of the Sichuan Province and nature conservation areas of Fujian Province, Southeast China, are treasure houses of pharmaceutically important medicinal plants owing to the unique geographical conditions and abundant rainfall. Plants sampled from these locations have had a long-standing use in TCM, and unique actinomycetes have been reported (Li et al. 2008; Qin et al. 2009a, 2012; Yuan et al. 2008; Zhao et al. 2011). Few medicinal plants of the Malayan peninsula and two hotspots in India, representing the Himalayas and the Western Ghats, regions with endemic species, were sampled for the isolation of endophytic actinomycetes (Zin et al. 2007; Passari et al. 2015; Akshatha et al. 2014).

Papua New Guinea (PNG), Solomon, and Mborokua islands adjacent in the archipelago are the relics of tropical wilderness of biodiversity. Unique endophytic actinomycetes were isolated from the tropical plants of this region (Janso and Carter 2010). PNG is covered with undisturbed rain forests receiving 80–100 cm of rainfall,

and antimycotic compounds were isolated from the endophyte, *Pestalotiopsis jesteri* (Li and Strobel 2001). The Hawaiian Islands in the mid of the Pacific Ocean are separated from the mainland with natural organisms and endophytes identified with bioactive potentials (Li et al. 2016a, b). Endemism, as defined by the high richness of species, is distinct in oceanic islands than the mainland (Mutke et al. 2011). There is tremendous scope for the isolation of newer and more novel endophyte taxa from these centers of plant diversity. The tropical rain forests represent one of the biologically rich and diverse regions on the earth.

The Xishuangbanna tropical rain forest in Southwest China contains plant diversity with 3000 endemic species. Streptomycete endophytes with potential bioactivities were isolated from this region (Li et al. 2008). Many novel species of endophytic actinomycetes reported from the medicinal plants of China have been documented (Nalini and Prakash 2017). It is worthy to note that the tropical rain forest plants are a treasure house of novel endophytic genera and many novel species. A single medicinal tree *Maytenus austroyunnanensis* yielded many novel endophytic actinomycete species, which indeed supports the fact that southwest Chinese tropical rain forest harbors rare and diverse actinomycetes. The actinomycete abundance was related to the geographical conditions in the tropical rain forests at the time of sampling (Qin et al. 2012). Owing to these factors, the chances of finding novel endophytic microbes are high.

13.4 Bioprospecting of Microbial Endophytes for Novel Biologically Active Metabolites

Natural products continue to play a significant role in the discovery of drugs. Microbial natural products represent an important path to the discovery of novel chemicals as therapeutic agents. Due to the onset of new emerging diseases, drug resistance among the pathogenic strains has often resulted in the search for biologically active compounds. Hence, there is a need to pursue microbial sources of novel drugs as therapeutic agents.

13.4.1 Host-Specific Novel Metabolites Produced by Microbial Endophytes

Plant-based therapy in the traditional medicinal practices has often cured many diseases and has led to the search for efficient antimalarial drugs quinine and artemisinin. Health-care practitioners in the TCM and Ayurvedic medicinal systems utilize drugs prepared from the traditional medicinal plants or their analogues to treat ailments (Newman and Cragg 2016), notably malarial fever (artemisinin; *Artemisia annua*), hypertension (reserpine; *Rauwolfia densiflora*), asthma (ephedrine; *Ephedra*

sinica), and cancer (vincristine, vinblastine; *Catharanthus roseus*). The continuous harvesting of medicinal plants from their natural populations is already a threat to biodiversity and, therefore, an alternate strategy to provide inexhaustible supply of drugs needs immediate attention.

Microorganisms have contributed phenomenally through the production of secondary metabolites that are potential sources of drugs. The success achieved in the production of the anticancer drug Taxol® by the endophytic fungus *Taxomyces andreanae* (Stierle et al. 1994) has opened new vistas related to the bioprospecting of microbial endophytes for novel bioactive molecules. In view of this concept, a number of endophytes produce bioactive metabolites akin to the novel host plant metabolites (Table 13.1). The following are the examples for host-specific novel metabolites produced by endophytes.

13.4.1.1 Paclitaxel (Taxol®)

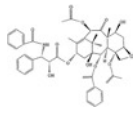
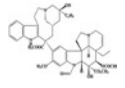
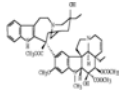
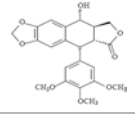
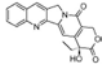
One of the most exciting discoveries in science is the isolation of the anticancer drug Taxol® from the bark of Pacific yew tree *Taxus brevifolia* by natural product chemist group Wani et al. (1971). The uniqueness of the approved anticancer drug lies in its ability to prevent the depolymerization of tubulin during cell division and is effective against ovarian and breast cancer cells. Treating a patient requires 2 g of the drug, which otherwise would mean felling of 12 large yew trees (Hartzell 1991). One of the milestones achieved in the natural product leads is the identification of the Taxol-producing fungus *Taxomyces andreanae* from the bark of the Pacific yew (Stierle et al. 1993). The yield of Taxol produced by this fungus is low, and hence, a promising source of Taxol-producing fungus was later identified as *Pestalotiopsis microspora* from the bark of Himalayan yew tree, *Taxus wallichiana* (Strobel et al. 1996). The Taxol production from *P. microspora* is 60–70 μg L^{-1}. Taxol-producing endophytes are reported from various plant sources (Kaul et al. 2012).

Endophytic actinomycetes are being bioprospected for their ability to produce anticancer metabolites. Actinomycetes isolated from the lignified woody tissues and herbaceous tissues of yew from different locations in Italy were identified as taxane producers (Caruso et al. 2000). The genera *Streptomyces*, *Micromonospora*, and *Kitasatospora* were identified as taxane producers (50–100 ng L^{-}). This is the first report of endophytic actinomycetes as taxane producers from the woody and herbaceous yew tissues.

13.4.1.2 Camptothecin

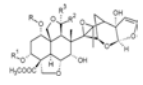
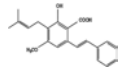
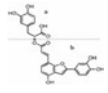
Camptothecin (CPT) is an antitumor chemotherapeutic agent isolated from the bark of the Chinese medicinal tree *Camptotheca acuminata* Decne. (Icacinaceae) (Wall et al. 1966) and was first approved by FDA for the treatment of colon cancer, and reports indicated its efficacy for treating various types of cancers. The drug has severe side effects and hence was thoroughly discouraged for clinical use in 1972,

Table 13.1 Host-related novel bioactive metabolites produced by the fungal endophytes of medicinal plants

Fungal endophyte	Plant species	Host-related metabolites	Chemical structure	Chemical group	Bioactivity	References
Taxomyces andreanae	*Taxus brevifolia* Nutt.	Taxol		Diterpenoid	Anticancer	Stierle et al. (1993)
Pestalotiopsis microspora	*Taxus wallichiana* Zucc.	Taxane			Antileukemia; antitumor	Strobel et al. (1996)
Mycelia sterilia 97 CY-3	*Catharanthus roseus* L.	Vincristine		Monoterpenoid indole alkaloids	NA	Yang et al. (2004)
Fusarium oxysporum		Vincristine and vinblastine			Antiproliferative/ apoptosis	Kumar et al. (2013)
Talaromyces radicus-Cr-P20		Vincristine and vinblastine			Cytotoxic (MDA-MB-231)	Palem et al. (2015)
Nigrospora sphaerica		Vinblastine				Ayob et al. (2017)
Chaetomium globosum		Vinblastine				Zafari et al. (2018)
Phialocephala fortinii	*Podophyllum peltatum* L.	Podophyllotoxin		Aryl tetralin lignan	Antineoplastic	Eyberger et al. (2006)
Trametes hirsuta						Puri et al. (2006)
Entrophosphora infrequens	*Nothapodytes foetida* (Wight) Sluemer	Camptothecin		Alkaloid	Antineoplastic; anticancer	Puri et al. (2005), Rehman et al. (2008), and Kusari et al. (2009)
Neurospora sp.						
Fusarium solani						
Trichoderma atroviride LY357	*Camptotheca acuminata* Decne					Pu et al. (2013)

(continued)

Table 13.1 (continued)

Fungal endophyte	Plant species	Host-related metabolites	Chemical structure	Chemical group	Bioactivity	References
C. globosum	*Hypericum perforatum* L.	Hypericin		Naphthodianthrone derivative	Antiviral; cytotoxic	Kusari et al. (2008)
Eupenicillium parvum	*Azadirachta indica* A. Juss. (Meliaceae)	Azadirachtin A-B		Oxygenated tetranortriterpenoid	Antifeedant; insect-growth regulating	Kusari et al. (2012)
F. solani (ERP-07)	*Cajanus cajan* L. (Millsp.) (Fabaceae)	Cajaninstilbene acid		Stilbene carboxylic acid	Antioxidative	Zhao et al. (2012)
F. oxysporum (ERP-10)						
Fusarium proliferatum (ERP-13)						
T. atroviride D16	*Salvia miltiorrhiza* Bunge (Lamiaceae)	Tanshinones		Diterpenoid quinones	NA	Ming et al. (2012)
Phoma glomerata D14		Salvianolic acids		Phenolic acids		Li et al. (2016d)

NA not available

and in the 1980s the drug gained attention as it acts as a poison to the DNA topoisomerase I (TOP I) and as a cellular target (Jaxel et al. 1989). CPT is isolated from non-related plant families, and several structural analogues have been chemically synthesized.

Camptothecin, an alkaloid and a potent antineoplastic agent, was isolated from an endophytic fungus *Entrophospora infrequens* residing in *Nothapodytes foetida* (Puri et al. 2005). In vitro cytotoxicity assay of the compound against human cancer cell lines (A-549/lung cancer, HEP-2/liver cancer, OVCAR-5 for ovarian cancer) was comparable with the standard (Puri et al. 2005). Camptothecin and its analogues 9-methoxycamptothecin and 10-hydroxycamptothecin were extracted from *Fusarium solani* inhabiting *Camptotheca acuminata* (Kusari et al. 2009) collected from Yunnan Province of China. The latter two are precursors for the synthesis of anticancer drugs topotecan and irinotecan. Standardized conditions for the production of CPT from endophytic *Trichoderma atroviride* LY357 at 197.82 μg ml^{-1} was developed by Pu et al. (2013). A 50- to 75-fold increase of CPT yield was obtained when the optimized fermentation conditions, elicitor, and adsorbent resin were combined and applied to the culture of the seventh and eighth generations.

13.4.1.3 Hypericin

Hypericin is obtained from *Hypericum perforatum* (Clusiaceae), the perennial medicinal herb commonly known as St. John's wort, and has long been associated with wound healing, diuretic, antibiotic, and antiviral properties (Bombardelli and Morazzoni 1995). It acts as an antidepressant due to monoamine oxidase inhibiting property in comparison to the standard drug imipramine. Kusari et al. (2008) identified a fungal endophyte, *Chaetomium globosum*, from the surface-sterilized stem fragments of *H. perforatum* collected from wild high altitudinal populations of Jammu and Kashmir, India. The fungus produced hypericin and its precursor emodin intracellularly, at 35 ± 2 μg/100 g and 113 ± 1 μg/100 g dry weight of fungal mycelia under shake flask conditions after 6–7 days of incubation.

13.4.1.4 Podophyllotoxin

Podophyllotoxin (PTOX) was first isolated from the North American plant *Podophyllum peltatum* L., commonly known as the American mandrake in 1880. This natural product has been also isolated from the Indian podophyllum, *Podophyllum emodi* (Ramos et al. 2001). PTOX is the most abundant lignan in podophyllin, a resin produced by species of the genus *Podophyllum*, *and the derivatives etoposide and teneposide are used in the treatment of cancers and venereal warts.* PTOX prevents cell growth via polymerization of tubulin, leading to the arrest in cell cycle and suppression of the formation of the mitotic spindles and microtubules (Ardalani et al. 2017). The endophytic fungi *Trametes hirsute* and *Phialocephala fortinii* isolated from *Podophyllum peltatum* produce

podophyllotoxin (0.5–189 μg L^{-1}) and other related aryl tetralin lignans with anticancer potential (Puri et al. 2006; Eyberger et al. 2006).

13.4.1.5 Azadirachtin

Azadirachta indica A. Juss., commonly known as the Indian neem or Indian lilac, is one of the most used medicinal plants growing abundantly in India. Traditionally, neem-based formulations have been used to cure fever, pain, leprosy, and malaria in Ayurvedic and Unani medical treatments, but the most striking property of neem tree reported to date is its insect-repellent property (Veitch et al. 2008) due to azadirachtin that acts as antifeedant. Azadirachtins A and B were characterized from the secondary metabolites of the fungal endophyte *Eupenicillium parvum* isolated from the healthy plant parts of neem tree from northern India (Kusari et al. 2012). Quantification of azadirachtins indicated that A was measured at 0.4 μg 100 g^{-1} dry weight of fungal mycelia and 43 μg L^{-1} from the spent broth, whereas B contained 0.05 μg 100 g^{-1} dry weight of fungal mycelia and 11 μg L^{-1} from the spent broth, respectively.

13.4.1.6 Vincristine

The endemic medicinal plant of Madagascar *Catharanthus roseus* known as Madagascar periwinkle is used in the treatment of solid tumors and leukemia. The vinca alkaloids are monoterpenoid indole alkaloids with high therapeutic value. Vincristine and vinblastine were discovered in the 1950s by Eli Lilly Pharmaceutical Company in Indianapolis, USA, and Noble Research Group in Toronto (Duge de Bernonville et al. 2015). Due to the importance of vinca alkaloids in cancer therapy, numerous research groups have identified fungal sources of alkaloid production. *Fusarium oxysporum* (Kumar et al. 2013) produced vinca alkaloids vincristine (670 μg L^{-1}) and vinblastine (70 μg L^{-1}). In *Talaromyces radicus*, different culture media induced the production of vincristine (67 μg L^{-1}) and vinblastine (76 μg L^{-1}) (Palem et al. 2015). The compounds showed antiproliferative activity tested against HeLa cell line with IC_{50} value of 20 μg ml^{-1}. The apoptosis-inducing activity of fungus-derived vincristine was proven through cell cycle analysis, loss of mitochondrial membrane potential, and DNA fragmentation patterns. Ayob et al. (2017) reported the intracellular quantitation of vinblastine produced (0.868 μg ml^{-1}) from the mycelia of endophytic *Nigrospora sphaerica*. Cytotoxicity studies with the human breast cancer cell line MDA-MB 231 with various concentrations (6.35–400 μg ml^{-1}) showed positive results with IC_{50} value of >32 and 350 μg ml^{-1} for vinblastine that was purified from the crude fungal and leaf extracts, respectively. Recently, vinblastine (78 μg L^{-1}) characterized from the culture filtrate of *C. globosum* was evaluated for the cytotoxic bioactivity against conidial germination of the rice blast fungus, *Pyricularia oryzae*. The compound exhibited cytotoxicity at IC_{50} value of 5 μg ml^{-1} (Zafari et al. 2018).

13.4.1.7 Cajaninstilbene Acid

Cajaninstilbene acid (CSA), a major stilbene, is found as a phytoconstituent in the legume crop, *Cajanus cajan* (L.) Millsp. and has traditional medicinal use. The pharmacological effects of CSA are well known, and the antioxidant activity is on par with the natural antioxidant resveratrol (Wu et al. 2011). Three CSA-producing fungi were isolated from *C. cajan* plants growing in China and identified as *Fusarium solani* (ERP-07), *Fusarium oxysporum* (ERP-10), and *Fusarium proliferatum* (ERP-13), respectively (Zhao et al. 2012). ERP-13 produced CSA in the culture medium at 504.8 ± 20.1 μg/L. In DPPH radical scavenging assay, the inhibition percentage was on par to that of standard CSA. This study for the first time reported the characterization of natural antioxidant CSA from the endophytic fungi *F. solani* and *F. proliferatum* from pigeon pea.

13.4.1.8 Tanshinones and Salvianolic Acids

The Chinese herb *Salvia miltiorrhiza* also known as "danshen" is a traditional medicinal plant. Two main compounds from this plant are salvianolic acids and tanshinones, the novel phenolic acids and diterpenoid quinones, respectively. The quinone compounds are known to have anticarcinogenic, antihypertensive, antiatherogenic properties, while the phenolic acids promote cardio- and cerebrovascular health (Ming et al. 2012; Chun-Yan et al. 2015).

S. miltiorrhiza plants collected from the Shanxi Province of China harbored the fungal endophytes *Trichoderma atroviride* D16 and *Phoma glomerata* D14, and the secondary metabolites of the endophytes contained the host-specific compounds, tanshinones (Ming et al. 2012) and salvianolic acids (Li et al. 2016d). The compounds were detected in the mycelia as well as the culture broth. The root tissue-colonized endophyte *C. globosum* D38 was able to increase the production of tanshinones in cocultivation with hairy root cultures of *S. miltiorrhiza* (Zhai et al. 2018).

A number of traditionally useful medicinal plants have yielded endophytes producing novel molecules with bioactive potentials (Venieraki et al. 2017). Many endophytes are potential producers of host-plant metabolites, with promising yield under the influence of elicitors or by altering the fermentation conditions. Modern methods to augment the yield can be exploited for pharmaceutical benefits.

13.4.2 Bioactive Potentials of Novel Microbial Metabolites

Metabolites from soil microorganisms especially fungi and actinomycetes are reliable platforms for drug discovery. Novel antibiotics from microbial strains, especially soil actinomycetes, have contributed to the development of life-saving drugs. Microbial endophytes from plant sources are by far proven to be reliable sources of

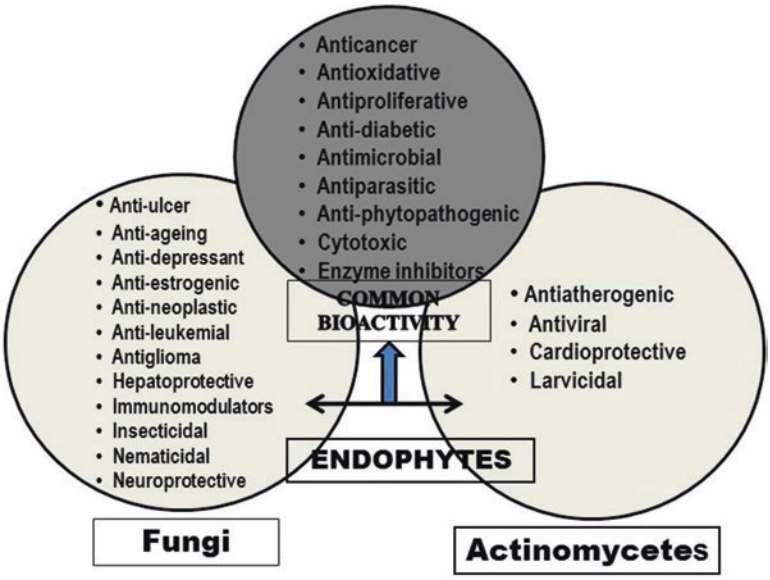


Fig. 13.1 Illustration of biological activities of endophytic fungi and actinomycetes from the medicinal plants

new metabolites with potent biological activities. Over the past 25 years, metabolites from endophytes have been bioprospected for various bioactivities, and some of them are common to both fungal and actinomycete groups (Fig. 13.1). Based on a detailed literature review, the distinct biological activities of novel molecules, the chemical class of compounds, and their sources for both fungal (Table 13.2) and the actinomycete endophytes (Table 13.3) are presented in the following sections.

13.4.2.1 Antimicrobial Compounds

Antimicrobial agents are the low-molecular-weight organic natural substances produced by microorganisms that are active at low concentrations against test microorganisms (Guo et al. 2000).

Novel Antimicrobial Metabolites from Fungal Endophytes

Phomopsichalasin, a cytochalasin-type compound, was the first antimicrobial agent produced by endophytic *Phomopsis* sp. It markedly differs from other cytochalasans in possessing a 13-membered tricyclic system that replaces the macrolide ring (Horn et al. 1995). The antimicrobial activity of the compound was tested positive against the test bacteria and yeast at 4 μg/disk in the disk diffusion assay. The potent antimycotics characterized from the cultures of the endophytic fungus *C. quercina*

Table 13.2 Novel metabolites produced by the fungal endophytes of medicinal plants and their bioactivities

Fungal endophyte	Plant species	Place of collection	Metabolites	Chemical group	Bioactivity	References
Anti-inflammatory						
Phomopsis sp.	*Erythrina crista-galli*	Argentina	Phomol	Polyketide lactone	Anti-inflammatory	Weber et al. (2004)
			Mevinic acid			
Periconia sp.	*Annona muricata*		Periconianone A	Sesquiterpenoids	Neural anti-inflammatory	Zhang et al. (2014a)
T. atroviride	*Lycoris radiata*	Hubei Province, China	Atrichodermone A	3-amino-5-hydroxy-5-vinyl-2-cyclo- penten-1-one dimer	Anti-inflammatory	Zhou et al. (2017)
			Atrichodermone B	Cyclopentenone		
			Atrichodermone C	Sesquiterpene		
Aspergillus terreus	–		Asperimides A–D	Butanolides	Anti-inflammatory	Liao et al. (2018)
Aspergillus sp.			Terrusnolides A–D	Butanolides	Anti-inflammatory	Qi et al. (2018)
Fusarium tricinctum SYPF 7082	*Panax notoginseng*	Yunnan Province, China	Rigidiusculamide E; [−(a-oxyisohexanoyl-N-methyl-leucyl)2-]	Alkaloids	Anti-inflammatory	Sun et al. (2018)
Fusarium sp.	*Mentha longifolia*		Fusaristerols B–D	Ergosterols	Anti-inflammatory	Khayat et al. (2019)
Immunosuppressants						
Fusarium subglutinans	*T. wilfordii*		Subglutinols A–B	α-Pyrone	Immunosuppressants	Lee et al. (1995a, b)
Colletotrichum dematium		Tropical rain forest, Costa Rica	Colutellin A	Peptide	Immunosuppressants	Ren et al. (2008)
Antimicrobial						
Phomopsis sp.	*Salix gracilistyla* var. *melanostachys*	Wakehurst, UK	Phomopsichalasin	Cytochalasin (3-ring system)	Antifungal; antibacterial	Horn et al. (1995)
Cryptosporiopsis cf. *quercina*	*T. wilfordii*	–	Cryptocandin A	Peptide antibiotic	Antimycotic	Strobel et al. (1999)
			Cryptocin	Tetramic acid	Antifungal	Li et al. (2000)

(continued)

Table 13.2 (continued)

Fungal endophyte	Plant species	Place of collection	Metabolites	Chemical group	Bioactivity	References
Unidentified fungus	*Daphnopsis americana*	Guanacaste National Park, Costa Rica	Guanacastepene A	Diterpenoids	Antibacterial	Brady et al. (2000c)
Cytospora sp.	*Conocarpus erectus*	Guanacaste National Park, Costa Rica	Cytoskyrins A–B	Bisanthraquinones	Antibacterial; biochemical induction assay (BIA)	Singh et al. (2007), Brady et al. (2000b)
			Cytosporones A–E	Octaketide antibiotics		
Colletotrichum sp.	*Artemisia annua*	Nanjing, China	Isoprenylindole-3-carboxylic acid; 3b,5a-dihydroxy-6b-acetoxy-ergosta-7,22-diene; 3b,5a-dihydroxy-6b-phenylacetyloxyergosta-7,22-diene	Ergosterol derivatives	Antifungal (fungistatic)	Lu et al. (2000)
Colletotrichum gloeosporioides	*Artemisia mongolica*	Nanjing, China	Colletrotic acid		Antibacterial; antifungal	Zou et al. (2000)
Periconia sp. OBW-15	*Taxus cuspidata*	Kangwon region, Korea	Periconicins A–B	Fusicocane diterpenes	Antibacterial	Kim et al. (2004)
Phomopsis sp.	*E. crista -galli*	Argentina	Phomol	Polyketide lactone	Antifungal; antibacterial	Weber et al. (2004)
Non-sporulating sp.	*Knightia excelsa*	Valley forests of New Zealand	Spiro-mamakone	Spirobisnaphthalene	Antibacterial	Van der Sar et al. (2006)
Cephalosporium acremonium	*Trachelospermum jasminoides*		Cephalosol	Unprecedented carbon skeleton	Antimicrobial	Zhang et al. (2008a, b)

Blennoria sp.	*Carpobrotus edulis*	Canary Islands	Blennolides A–G	Benzopyran polyketides (chromanone subunits/γ-lactone moiety)	Antifungal	Zhang et al. (2008a)
Chalara sp.	*Artemisia vulgaris*		Isofusidienols A–D	Benzopyran with chromone oxepine moiety	Antibacterial	Lösgen et al. (2008)
Microsphaeropsis sp.	*Lycium intricatum*		Microsphaeropsones A–C	Benzopyran with oxepino[2,3-b] chromen-6-one		Krohn et al. (2009)
Fusidium sp.	*Mentha arvensis*	Lower Saxony, Germany	Fusidilactones A–C	Polycyclic lactones with bicyclic and oxoadamantane skeleton	Antifungal; weak antibacterial	Krohn et al. (2002)
Cryptosporiopsis sp.	*Viburnum tinus*	Gomera	Viburspiran	8-membered maleic anhydride	Antifungal	Saleem et al. (2011)
			Cryptosporioptide	Polyketide (functionalized benzopyrone)	Antibacterial	Saleem et al. (2013)
Phomopsis CMU-LMA	*Alpinia malaccensis*		Benquinone	Lactone (14 membered)	Antibacterial	Adelin et al. (2011)
Microsphaeropsis arundinis PSU-G-18	*Garcinia hombroniana*	Songkhla Province, Thailand	Microsphaerodiolin	Modiolin	Moderate antifungal activity	Sommart et al. (2012)
			Microsphaerophthalides A–G	Phthalides		
Chaetomium sp.	*Zanthoxylum leprieurii*	Cameroon	Chaetosidone A	Depsidone (orsellic acid derivative)	Antibacterial	Talontsi et al. (2013)
Penicillium raciborskii	*Rhododendron tomentosum*	Oulu, Finland	Outovirins A–C	Epipolythiodiketopiperazines	Antifungal	Kajula et al. (2014)
Penicillium namyslowskii	*Rhododendron tomentosum*	Oulu, Finland	Dechlorodehydrogriseofulvin	Polyketide	Antifungal	Wubshet et al. (2013)
Aspergillus sp.	*M. azedarach*		Aspertryptanthrins A–C	Diketopiperazine alkaloids		Lhamo et al. (2015)

(continued)

Table 13.2 (continued)

Fungal endophyte	Plant species	Place of collection	Metabolites	Chemical group	Bioactivity	References
Trichoderma sp.	*Myoporum bontioides*	China	Dichlorodiaportinolide	Isocoumarin	Antifungal	Li et al. (2016c)
Simplicillium sp. PSU-H41	*Hevea brasiliensis*	Songkhla province, Thailand	Simplicidones A–I	Depsidones	Weak antibacterial and antifungal	Saetang et al. (2017)
			Simplicilopyrone	α-Pyrone		
Dendrothyrium variisporum	*Globularia alypum*	Algeria	(5S)-cis-gregatin B	Furanone derivatives	Antifungal	Teponno et al. (2017)
			Graminin D	Anthranilic acid derivatives		
			2-phenylethyl 3-hydroxyanthranilate;			
			phenylmethyl anthranilate; 3-hydroxy-3-methylbutyl anthranilate			
Anticancer, antitumor, antiproliferative, and cytotoxic compounds						
T. andreanae	*T. brevifolia*	Montana, USA	Taxol; taxane	Diterpenoids	Anticancer	Stierle et al. (1993)
Rhinocladiella sp.	*Tripterygium wilfordii*		Cytochalasins H-J	Cytochalasins	Antitumor	Wagenaar et al. (2000)
			Epoxycytochalasin H			
Phomopsis longicolla	*Mentha* sp.		Dicerandols	Dimer	Cytotoxic	Wagenaar and Clardy (2001)
Chaetomium sp.	*Adenophora axilliflora*		Chaetominine	Tripeptide alkaloid	Cytotoxic	Jiao et al. (2006)
Non-sporulating sp.	*Knightia excelsa*	Valley forests of New Zealand	Spiro-mamakone	Spirobisnaphthalene	Anticancer (leukemia)	Van der Sar et al. (2006)

Chaetomium globosum IFB-E019	*Imperata cylindrica*	Jiangsu Province, China	Chaetoglobosin U	Cytochalasan alkaloid	Cytotoxic	Ding et al. (2006)
Hypoxylon truncatum	*A. annua*	Nanjing, China	Daldinones C–D	Benzo[j]fluoranthene	Cytotoxic	Gu et al. (2007)
C. globosum	*Imperata cylindrica*		Chaetoglobins A–B	Heterocyclic azaphilone alkaloids	Cytotoxic	Ge et al. (2008)
Edenia sp.	*Petrea volubilis*	Coiba National Park, Panama	Palmarumycin CP_{17}–CP_{18}	1,8-dihydroxynaphthalene derived spiroketal unit linked to a second oxidized naphthalene unit	Weak cytotoxic	Martinez-Luis et al. (2008)
Alternaria sp.	*Polygonum senegalense*	Egypt	Alternariol 5-*O*-sulfate	Sulfated derivatives of alternariol and its monomethyl ethers	Cytotoxic	Aly et al. (2008)
			Alternariol 5-*O*-methyl			
			Ether-4′-*O*-sulfate			
			3′-Hydroxyalternariol			
			5-*O*-methyl ether, desmethylaltenusin, alterlactone			
			Alternaric acid			
Alternaria sp.	*Carex aridula*		(−) Alternarlactam	Polyketide with cyclopentenone and isoquinolinone pharmacophores	Antitumor	Zhang et al. (2010)

(continued)

Table 13.2 (continued)

Fungal endophyte	Plant species	Place of collection	Metabolites	Chemical group	Bioactivity	References
Phomopsis CMU-LMA	*Alpinia malaccensis*		Benquinone	Lactone (14 membered)	Cytotoxic	Adelin et al. (2011)
Fusarium sp. LN-10	*M. azedarach*	China	Fusariumine	Isocoumarin	Cytotoxic	Yang et al. (2012)
Fusarium sp. BCC14842	*Bambusa* sp.	Nam Nao National Park, Thailand	4-Hydroxydihydronorjavanicin; dihydronaphthalenone; diastereomer	Dihydronaphthalenones	Weak to moderate cytotoxic	Kornsakulkarn et al. (2011)
			3, 5-hydroxydihydrofusarubins A, B, and D; methyl ether derivatives			
Stemphylium globuliferum	*Mentha pulegium*	Morocco	Tetrahydroanthraquinone	Anthracene derivatives	Antitumor/cytotoxic	Debbab et al. (2009)
			Tetrahydroanthraquinone dimers			
Penicillium sp.	*C. roseus*		Citreoviripyrone A	α-Pyrone polyketide	Cytotoxic	Asai et al. (2013)
Chaetomium sp.	*Zanthoxylum leprieurii*	Cameroon	Chaetosidone A	Depsidone	Weak cytotoxicity	Talontsi et al. (2013)
Trichoderma atroviride	*Taxus baccata*	France	Harzianes 1–4	Tetracyclic diterpene	Weak cytotoxic	Adelin et al. (2014)
Penicillium manginii	*P. notoginseng*	China	Duclauxamide A1	Heptacyclic oligophenalenone dimer	Cytotoxic	Cao et al. (2015)
Trichoderma gamsii			Trichoderones A–B	Cytochalasans	Weak cytotoxic	Ding et al. (2012, 2013)
			Trichodermone			
Aspergillus versicolor	*Paris polyphylla* var. *yunnanensis*	China	Aspergillines A–E	Oxygenated cyclopiazonic acid-derived alkaloids	Anti-tobacco mosaic virus (TMV); cytotoxic	Zhou et al. (2014)
Alternaria phragmospora	*Vinca rosea*	–		α-Pyrone	Antileukemic	Metwaly et al. (2014b)
Fusarium sp. PDB51F5.	NA	NA	Fusaraisochromenone; fusaraisochromanone	Isochromenone; isochromanone	Weak cytotoxicity	Boonyaketgoson et al. (2015)

Peyronellaea coffeae-arabicae	*Pritchardia lowreyana*	Hawaii	Peyronellins A–C	Polyketide sesquiterpenes	Anticancer	Li et al. (2016b)
Phomopsis sp.			Phomopchalasins A–B	Cytochalasans	Anticancer (antimigrative)	Yan et al. (2016)
T. atroviride	*Lycoris radiata*	Hubei Province, China	Atrichodermone A	3-amino-5-hydroxy-5-vinyl-2-cyclopenten-1-one dimer	Cytotoxic	Zhou et al. (2017)
			Atrichodermone B	Cyclopentenone		
			Atrichodermone C	Sesquiterpene		
Phoma sp. YN02-P-3	–	–	Phomones	α-Pyrone	Cytotoxic	Sang et al. (2017)
Nigrospora BCC47789	–	–	Hydroanthraquinone	Anthraquinones	Cytotoxic	Kornsakulkarn et al. (2018)
			Nigrosporones A–B			
Aspergillus sp.	*Paeonia ostii*		Aspergillates A–E	Globoscinic acid derivatives	Cytotoxic	Wang et al. (2018)
Dendrothyrium variisporum	*Globularia alypum*	Algeria	2-Phenylethyl 3-hydroxyanthranilate	Anthranilic acid derivative	Moderate cytotoxicity	Teponno et al. (2017)
Aspergillus sp.	*Pinellia ternata*		Seco-cytochalasins A–F	Cytochalasans	Cytotoxic	Xin et al. (2019)
			Asperlactones G–H			
Phoma bellidis	*Tricyrtis maculata*		Bellidisins A–D	Polyketides	Cytotoxic	Wang et al. (2019)
T. wortmannii	*T. wilfordii*		Wortmannines F–G	Pyranones	PI3Kα inhibition (cancer therapeutics)	Zhao et al. (2019)
Antidiabetic compounds						
Pseudomassaria sp.	–	Kinshasa Republic, Congo	Demethylasterriquinone	Nonpeptide	Insulin-mimetic	Zhang et al. (1999)

(continued)

Table 13.2 (continued)

Fungal endophyte	Plant species	Place of collection	Metabolites	Chemical group	Bioactivity	References
Nigrospora sphaerica	*Oxya chinensis*	Guangzhou, China	Nigrosporamide A	Pyrrolidinone derivative	α-Amylase inhibition	Zhu et al. (2018)
			4-Prenyloxyclavatol	Acetophenone derivative		
Antiviral						
Cytonaema sp.	*Quercus* sp.	UK	Cytonic acids A–B	*p*-tridepsides	hCMV protease inhibitors	Guo et al. (2000)
Aspergillus versicolor	*Paris polyphylla* var. *yunnanensis*	China	Aspergillines A–E	Oxygenated cyclopiazonic acid-derived alkaloids	Anti-tobacco mosaic virus (TMV)	Zhou et al. (2014)
Periconia sp. F-31	*Annona muricata*	China	Periconiasin G	Cytochalasan with 7/6/5 tricyclic ring system	Anti-HIV	Zhang et al. (2016)
Nigrospora sp. YE3033	*Aconitum carmichaelii*		6-*O*-demethyl-4-dehydroxyaltersolanol A;8,11-didehydrochermesinone B;(7*S*)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione	Hydroanthroquinone	Anti-H1N1	Zhang et al. (2016)
				Azaphilones		
Phoma sp.	*Aconitum vilmoriniana*	–	Phomanolide	Sesquiterpene (14-nordrimane type)	Anti-H1N1	Liu et al. (2019)
Anti-parasitic						
Phomopsis sp.	*Tectona grandis*	Thailand	Phomoxanthones A–B	Xanthone dimers	Antimalarial	Isaka et al. (2001)
Exserohilum rostratum	*Stemona* sp.	Thailand	11-hydroxymonocerin	Monocerin derivative	Antimalarial	Sappapan et al. (2008)
Edenia sp.	*Petrea volubilis*	Coiba National park, Panama	Palmarumycin CP_{17}–CP_{18}	1,8-Dihydroxynaphthalene-derived spiroketal unit linked to a second oxidized naphthalene unit	Anti-parasitic (leishmanial)	Martinez-Luis et al. (2008)

Codinaeopsis gonytrichoides	*Vochysia guatemalensis*	Costa Rica	Codinaeopsin	Tryptophan polyketide	Anti-parasitic (plasmodial)	Kontnik and Clardy (2008)
Chalara alabamensis	*Asterogyne martiana*	Costa Rica	Asterogynins A–B	Steroids (isoprenoids)	Anti-parasitic	Cao et al. (2010)
Delitzchia winteri	–	Costa Rica	Delitzchianones A–B;	Naphthaquinones	Moderate anti-plasmodial activity	Cao and Clardy (2011)
Phomatospora bellawinteri			8-Acetoxy pestalopyrone	δ-lactone		
Insecticidal						
Unidentified sp.	*Gaultheria procumbens*		5-Hydroxy-2-(1′hydroxy-5′-methyl4′-hexenyl)benzofuran; 5-Hydroxy-2-(1′oxo-5′-methyl4′-hexenyl) benzofuran	Benzofurans	Anti-insect	Findlay et al. (1997)
Nodulisporium sp.	*Bontia daphnoides*		Nodulisporic acids	Indole diterpenes	Anti-insect	Demain (2000)
Novel chemical structures with unusual bioactivities						
Fusarium pallidoroseum		Merck	Apicidins A–C	Cyclic tetrapeptides	Anti-protozoal	DarkinRattray et al. (1996)
Fusidium sp.	*Mentha arvensis*	Lower Saxony, Germany	Fusidilactones A–C	Polycyclic lactones with bicyclic and oxoadamantane skeleton	Antialgal	Krohn et al. (2002)
			Fusidilactones D–E	γ-Lactones		Qin et al. (2009a)
Penicillium chrysogenum	*Cistanche deserticola*	Northwest China	Chrysogenamide A	Alkaloid	Neuroprotective	Lin et al. (2008)

(continued)

Table 13.2 (continued)

Fungal endophyte	Plant species	Place of collection	Metabolites	Chemical group	Bioactivity	References
A. terreus	*A. annua*	Zijin Mountain, China	16-α-hydroxy-5*N*-acetyllaardeemin	Alkaloid	Anti-acetylcholinesterase	Ge et al. (2010)
Penicillium dangeardii	*Lysidice rhodostegia*	China	Penicillactones A–C	Spirocyclic anhydride moiety	Inhibiting β-glucoronidase from leucocytes	Liu et al. (2013)
Phoma sp.	*Garcinia* sp.	Thailand	Phomoxanthones A–B	Lactones	Antitubercular	Isaka et al. (2001)
Phomopsis sp.	*Garcinia dulcis*	Thailand	Phomoenamide	Amides	Antitubercular	Rukachaisirikul et al. (2008)
			Phomonitroester	Ester		
Diaporthe sp.	*Pandanus amaryllifolius*		Diaporthenone	Benzopyranones	Antitubercular	Bungihan et al. (2011)
T. wortmannii	*T. wilfordii*	–	Secovironolide	Furanosteroid	Antidepressant (monoamine oxidase inhibitory)	Ding et al. (2015)
			Epoxyvirone			
F. subglutinans	*Tripterygium wilfordii*		Subglutinols A–B	α-Pyrone	Antiestrogenic	Lim et al. (2015)
Novel chemical structures with no bioactivities						
Penicillium janthinellum	*M. azedarach*	Brazil	Janthinone	Lactone	No antimalarial activity detected	Marinho et al. (2005)
Eupenicillium sp.	*Glochidion ferdinandi*	Toohey Forest, QLD, Australia	Phomoxins B–C	Polyketide with cyclic carbonate moiety	No antimicrobial activity	Davis et al. (2005)

Fusarium sp. LN-12	*M. azedarach*	China	Fusarimine	Isoquinoline alkaloid	Inactive to phytotoxicity and cytotoxicity	Yang et al. (2012)
Xylaria sp. PSU-H182	*H. brasiliensis*	Trang Province, Thailand	Xylaromanones A – B; (R)-4-Hydroxy-2-ethyl-2-cyclohexen-1-one; 2,3-Dihydroxy-N-methoxy-6-propylbenzamide	Dimeric chromanones; cyclohexenone; benzamide	No activity in antimalarial, antibacterial, and cytotoxic assays	Maha et al. (2016)
T. wortmannii LGT-4	*T. wilfordii*		Wortmannines A–C	Wortmannin derivative with an unusual five-membered B ring	No cytotoxicity	Fu et al. (2016)
Chaetoconis sp. FT087	*Osmoxylon novoguineensis*	Waimea Valley, Hawaii, USA	Chaetopenoids A–F	Sesquiterpene derivatives (eremophilane type)	No antibacterial and anti-proliferative activities	Li et al. (2016a)
N. sphaerica	*V. rosea*	Egypt	Nigrosphaerin A	Isochromene derivatives	No activity in antileishmanial, antimicrobial, and cytotoxic assays	Metwaly et al. (2014a)
Simplicillium sp. PSU-H41	*H. brasiliensis*	Songkhla Province, Thailand	Simplicidones A, C	Depsidones	No cytotoxicity	Saetang et al. (2017)

'–' not available

Table 13.3 Novel bioactive metabolites produced by the actinomycete endophytes of medicinal plants

Actinomycetes	Plant species	Sampling site	Metabolites	Chemical group	Bioactivity	Reference
Streptomyces NRRL 30562	*Kennedia nigriscans*	Northern Territory, Australia	Munumbicins A–D	Peptide antibiotics	Antibacterial; antimalarial	Castillo et al. (2002)
Streptomyces NRRL 3052			Munumbicins E-4 and E-5			Castillo et al. (2006)
Streptomyces NRRL 30566	*Grevillea pteridifolia*	Northern Territory, Australia	Kakadumycin A	Peptide antibiotics	Antibacterial; antimalarial	Castillo et al. (2003)
Streptomyces (MSU-2110)	*Monstera* sp.	Manu region, Upper Amazon, Peru	Coronamycin	Peptide antibiotics	Antifungal; antimalarial	Ezra et al. (2004)
Nonomuraea sp.	*Artemisia vulgaris*	Sao Paulo, Brazil	Brartemicin	Trehalose-derived antibiotic	Anti-metastatic/ anti-invasive	Igarashi et al. (2009)
Micromonospora sp.	*Abrus pulchellus* subsp. *pulchellus*	Thailand	Maklamicin	Polyketide	Antibacterial	Igarashi et al. (2011)
Microbispora sp. GMKU 363	*Clinacanthus siamensis*	Thailand	Linfuranone A	Polyketide	Antidiabetic; antiatherogenic	Indananda et al. (2013)
Streptomyces sp. YIM 65408	*T. wilfordii*	China	1″-*O*-methyl-8-hydroxymethyl-daidzein	Isoflavone	Antioxidative	Yang et al. (2013)
Streptomyces sp. YIM 66017	*Alpinia oxyphylla*	China	2–6-Dimethoxy, terephthalic acid	Benzenedicarboxylic acid	Antimicrobial; antioxidative	Zhou et al. (2014)
			Flavensomycinoic acid	Alkaloid	Cytotoxic	Zhou et al. (2013)

Streptomyces sp. BT01	*Boesenbergia rotunda*	Thailand	7-Methoxy-3, 3′,4′,6-tetrahydroxy flavones; 2′,7-dihydroxy-4′,5′-dimethoxyisoflavone	Phenolics (flavonoids)	Antibacterial	Taechowisan et al. (2014)
Streptomyces sp. YIM 66142	–	–	Medilamine C	ʊ-Hydroxy alkylamine derivative	Reduced cytotoxicity	Zhang et al. (2014b)
Streptomyces sp.	*Camellia sinensis*	China TCM	Rubrolone B	Tropolone alkaloid	Cardioprotection	Yan et al. (2016)
Streptomyces kebangsaanensis	*Portulaca oleracea*	Nensai reserve forest, Pahang, Malaysia	6-(2-Hydroxy-4-methoxyphenoxy carbonyl)	Phenazine compound	–	Remali et al. (2017)
			Phenazine-1-carboxylic acid			

'–' not available

are cryptocandin, a peptide with unique amino acid 3-hydroxy-4-hydroxy methyl proline, and cryptocin, a tetramic acid (Strobel et al. 1999; Li et al. 2000). Both compounds were effective in inhibiting selective phytopathogens *Sclerotinia sclerotiorum*, *Botrytis cinerea*, and *P. oryzae* (MIC 0.39 μg ml^{-1}).

Terpenoids are the major group of compounds produced by fungal endophytes and possess antimicrobial activity. Guanacastepene, a diterpenoid from the unidentified Costa Rican endophytic fungus, showed potent antibacterial activity against *Enterococcus faecalis* (MRSA and VREF strain) (Brady et al. 2000c, 2001). Three new ergosterol derivatives, isoprenylindole-3-carboxylic acid; 3b,5a-dihydroxy-6b-acetoxy-ergosta-7,22-diene; and 3b,5a-dihydroxy-6b-phenylacetyloxyergosta-7,22-diene, from *Colletotrichum* sp. showed antibacterial and fungistatic effects (200 μg ml^{-1}, Lu et al. 2000). Colletotric acid inhibited the growth of *Bacillus subtilis*, *Staphylococcus aureus*, and *Sarcina lutea* with MICs of 25, 50, and 50 μg ml^{-1}, respectively, and the crop pathogenic fungus *Helminthosporium sativum* (MIC: 50 μg ml^{-1}) (Zou et al. 2000). Periconicins A and B are fusicoccane diterpenes, i.e., diterpenes with a glycosylated isoprene unit resembling the carbon skeleton as fusicoccin, but differ in possessing a trans stereochemistry with C-1 methyl and C-3 hydrogen. They are novel compounds isolated from *Periconia* sp., from the inner bark of *Taxus cuspidata*, from Korea (Kim et al. 2004). Periconicin A exhibited significant antibacterial activity against *B. subtilis*, *S. aureus*, *Klebsiella pneumoniae*, and *Salmonella typhimurium* with minimum inhibitory concentrations in the range of 3.12–12.5 g ml^{-1} with the antibiotic gentamicin. Periconicin B exhibited modest antibacterial activity against the same strains of bacteria with MICs in the range of 25–50 μg ml^{-1}. Therefore, these compounds could be suggested as lead compounds for the development of antibacterial agents for many bacterial strains.

The polyketide groups of compounds are prevalent among the fungal secondary metabolites and are identified bearing alternating carbonyl and methylene groups and have antimicrobial and immunosuppressive properties. Phomol, a polyketide lactone, was identified from the endophyte of the Argentinian medicinal tree *E. crista-galli* and exhibited antifungal activity (Weber et al. 2004). Benzopyran and polyketides consisting of rare chromanones, blennolides A–G, with highly substituted γ–lactone moiety and two unusual chromanone units were isolated from endophytic *Blennaria* sp. from Canary Islands (Zhang et al. 2008a), which displayed moderate antifungal activity against *Microbotryum violaceum* (50 μg/disk). New benzopyrans with chromone oxepine moiety (isofusidienols A-D) and oxepino [2,3-b] chromen-6-one (microsphaeropsones A-C) were characterized from endophytic *Chalara* sp. (Lösgen et al. 2008) and *Microsphaeropsis* sp. (Krohn et al. 2009). Isofusidienols A and B exhibited strong antibacterial activity against *B. subtilis* (15 μg/disk).

Novel fusidilactones A and B and a rare fusidilactone C with an oxoadamantane skeleton, a spiro acetal structure, and two ether-bridged hemiacetals were isolated from the fungal endophyte *Fusidium* sp. (Krohn et al. 2002) and exhibited antifungal and weak antibacterial activity. Benquinone, a polyketide with 14-membered lactone formed due to the cyclization of benquinol, is a novel antibacterial compound found to inhibit *B. subtilis* (Adelin et al. 2011). New bioactive polyketide,

cryptosporioptide, a functionalized benzopyrone was obtained from *Cryptosporiopsis* sp., with antifungal activity against *Bacillus megaterium* (Saleem et al. 2013).

Structurally unique metabolites such as depsidone with 2,4-dihydroxy-benzoic acid linked with ether and ester bonds such as chaetosidone A with orsellic acid derivatives were isolated from the Cameroonian endophyte, *Chaetomium* sp. (Talontsi et al. 2013), which displayed antibacterial activity against *B. cereus* and *S. aureus* at 40 μg/disk.

Epipolythiodiketopiperazine (ETP) alkaloids constitute a large and diverse family of biologically active secondary metabolites produced by a number of filamentous fungi including the genus *Penicillium* (Boyer et al. 2013). These small-molecule natural products are characterized by the incorporation of an intramolecular polysulfide bridge at the α,α′-positions of a *cyclo*-dipeptide (or diketopiperazine – DKP). Three novel α-β bridged ETP alkaloids, outovirins A–C, were characterized from the cultures of *P. raciborskii*, the endophytic fungus of *R. tomentosum* (Kajula et al. 2014). Outovirin C exhibited active antifungal assay against *B. cinerea* at low concentration (0.38 mM).

Indole alkaloids, with one or more indole/indoline moieties, are one of the largest classes of nitrogen-containing secondary metabolites. Indole diketopiperazine alkaloids are a special subclass of indole alkaloids. They are biogenetically derived from tryptophan, and commonly isolated from fungi of the genus *Penicillium* and *Aspergillus* (Wen et al. 2018). Aspertryptathrins A–C, new indole diketopiperazine alkaloids from *Aspergillus* sp. from *M. azedarach*, possess a 6/5/6/6 trypanthrin framework formed from tryptophan unit and an anthranilate residue. An unusual 16-membered ring skeleton is characteristic of C (Lhamo et al. 2015).

Viburspiran, a new antifungal class of maleic anhydride, belongs to octadride, having an eight-membered ring with two maleic anhydride units. It was isolated from endophytic *Cryptosporiopsis* sp. and exhibited antifungal activity against *B. cinerea* and *M. violaceum* (Saleem et al. 2011). Two new bisanthraquinones, cytoskyrins A and B, and five new related octaketides, cytosporones A–E, were isolated from the endophyte *Cytospora* sp. from Guanacaste National Park, Costa Rica (Singh et al. 2007). Cytoskyrin A exhibited potent in vitro antibacterial (MICs 0.03–0.25 μg/mL) and DNA-damaging activities (10 ng/spot), whereas cytoskyrin B was inactive in these assays. Among the cytosporones, only D and E exhibited Gram-positive activity, but they were inactive in the biochemical induction assay. Novel furanone and anthranilic acid derivatives were isolated from *Dendrothyrium variisporum*; the compound 2-phenylethyl 3-hydroxyanthranilate showed antimicrobial activity against a panel of test organisms (Teponno et al. 2017).

Two novel compounds from *Nigrospora sphaerica*, nigrosporamide A and 4-prenyloxyclavatol, were tested for their antifungal potentials (Zhu et al. 2018). Nigrosporamide exhibited higher antifungal activity against *C. gloeosporioides* with a MIC of 25.14 μM than triadimefon (MIC 272.39 μM), the positive control, which showed weak activity to *F. oxysporum* (MIC 401.62 μM) and *C. musae* (MIC 803.23 μM), respectively. The antifungal activities of 4-prenyloxyclavatol were weak, with MIC values of 402.71–805.41 μM.

Novel Antimicrobial Metabolites from Actinomycetes as Pharmaceutical and Agricultural Agents

Antibiotics are important drugs for health care and are preferred due to their potent therapeutic applications and have desired pharmacokinetic properties for the clinical use (Farner and Zazopoulos 2005). The actinomycetes are prolific producers of antibiotics. Plant-associated endophytic actinomycetes have produced a wide range of antibiotics with novel chemical structures (Matsumoto and Takahashi 2017). The genera *Streptomyces* and *Micromonospora* are the potential producers of antibiotics. Munumbicins are novel peptide antibiotics produced by the endophytic *Streptomyces* spp., from the ethnomedicinal plants of the Upper Amazon and Northern Territory of Australia, and were effective against Gram-positive bacteria *Bacillus anthracis* and *Mycobacterium tuberculosis* (Castillo et al. 2002, 2006). Kakadumycins produced by *Streptomyces* sp. 30,566 depicted impressive activity against *B. anthracis* (MIC0.2 to 0.3 μg ml^{-1}) (Castillo et al. 2003), and the antimycotic coronamycin produced by *Streptomyces* NRRL 30562 at 2 μg ml^{-1} (MIC) is effective against pythiaceous fungi and the human pathogen *Cryptococcus neoformans* (MIC 4 μg ml^{-1}) (Ezra et al. 2004). The endophyte was tested against agriculturally important plant pathogens along with *S. griseoviridis* formulation (Mycostop). The former produced inhibition zones twice that of the latter, to be considered for the product development as a potential agricultural agent.

Maklamycin, an antibacterial polyketide from *Micromonospora* isolated from the Thai medicinal plant Maklam phueak (*Abrus pulchellus*), has shown activity against Gram-positive bacteria at 0.2–13 μg ml^{-1} (Igarashi et al. 2011). Recently, novel flavonoids, benzamide, and lactone-producing *Streptomyces* spp. from Thai, Chinese, and Vietnamese medicinal species were identified to have antibacterial and/or antifungal activities (Taechowisan et al. 2014; Yang et al. 2015a, b; Vu et al. 2018). There is a need to discover newer antimicrobial agents from the endophytic actinomycetes for antibiotics.

13.4.2.2 Novel Anticancer and Cytotoxic Compounds

Natural compounds derived from plants and microorganisms are being screened for the anticancer properties and cytotoxicity studies. Recent mechanisms in the ontogeny of tumor cells and their conversion into metastasis have led to the classification and therapeutic applications of anticancer compounds. Antibiotics are used in cancer therapy.

Novel Anticancer/Antitumor Metabolites from Endophytic Fungi

An insight into novel anticancer and cytotoxic agents from plant-derived drugs had tremendous impact on the drug industry with the identification of paclitaxel as the world's first anticancer drug. Many type genera of noted plant families have yielded

cytotoxic agents and are discussed in Sect. 13.4.1 of the chapter. However, the path to the discovery of anticancer agents by endophytic microbes was the identification of the Taxol-/Paclitaxel-producing fungus *T. andreanae*, from the inner bark of *T. brevifolia* (Stierle et al. 1993). It is not an exaggeration to document the exceptional enthusiasm of natural product researchers generated by this outcome over the past 25 years in the quest to isolate, identify, and characterize the bioactive compounds and their analogues from endophytic microbes.

Novel cytochalasin compounds cytochalasins H–J from *Rhinocladiella* sp. (Wagenaar et al. 2000) and a cytochalasan alkaloid chaetoglobosin U from a fungal endophyte *C. globosum* IFB-E019 (Ding et al. 2006) exhibited cytotoxic activity against nasopharyngeal epidermoid tumor cell line. New sulfated derivatives of alternariol and its monomethyl ethers along with four new compounds were isolated from *Alternaria* sp., an endophyte of *P. senegalense* (Aly et al. 2008). Alternariol 5-*O*-sulfate and desmethylaltenusin exhibited cytotoxicity against L5178Y lymphoma cells with EC_{50} values of 4.5 and 6.2 μg ml^{-1}, respectively.

Six new seco-cytochalasins A–F and two new asperlactones G–H were isolated from the solid cultures of an endophytic fungus *Aspergillus* sp. from the tubers of *P. ternata* (Xin et al. 2019). Compounds E and F were rare seco-cytochalasins possessing an α, β-unsaturated furanone structure in their side chains. These isolates exhibited cytotoxicity against human lung cancer A-549 cell line with IC_{50} values ranging from 7.8 to 70.2 μM. D and exerted a three-fold enhancement of doxorubicin susceptibility on doxorubicin-resistant human breast cancer (MCF-7/DOX) cell line (16 μM).

Four new polyketides bellidisins A–D were isolated from the rice fermentation extract of endophytic *Phoma bellidis* (Wang et al. 2019). The cytotoxicity was evaluated against human cancer cell lines HL-60, A549, SMMC-7721, MCF-7, and SW480. Compound D showed significant cytotoxicity on all five cell lines with IC_{50} value ranged between 3.40 to 15.25 μM, stronger than cisplatin (4.86–27.70 μM). Benquoine, a polyketide with 14-membered lactone from *Phomopsis* sp., exhibited weak cytotoxicity against the colonic epithelial cancer cell line HCT-116 with IC_{50} value of 210 nM (Adelin et al. 2011).

Three new anthracene derivatives, tetrahydroanthraquinone and two tetrahydroanthraquinone hetero dimers, were isolated from *Stemphylium globuliferum* (Debbab et al. 2012). Nigrosporone A, a new hydroanthraquinone, and a new naturally occurring nigrosporone B together were isolated from an endophytic fungus, *Nigrospora* sp. BCC 47789. Nigrosporone A showed cytotoxic activity (Kornsakulkarn et al. 2018). The compounds were analyzed for their cytotoxic activities. Tetrahydroanthraquinone showed cytotoxicity against murine cancer cell line L5178Y. Five novel globoscinic acid derivatives, aspergillates A–E, were isolated from the endophytic fung-us, *Aspergillus* sp. derived from *Paeonia ostii* (Wang et al. 2018). Cytotoxic activities against five selected tested tumor cell lines were evaluated.

Few novel metabolites from endophytic fungi do exhibit weak cytotoxicity as in chaetosidone A (Talontsi et al. 2013), fusaraisochromenone and fusaraisochromanone (Boonyaketgoson et al. 2015), palmarumycins (Martinez-Luis et al. 2008),

trichoderones A–B (Ding et al. 2012, 2013), and harzianes (Adelin et al. 2014). Cytoskyrin A, a bisanthraquinone from *Cytospora* sp., exhibited poor cytotoxicity against tumor cell lines (IC_{50} > 5 μg/mL) compared to known antitumor agents (Singh et al. 2007).

The phosphatidylinositol 3-kinase (PI3K) pathway is frequently activated in human cancers. Therefore, PI3K has become an important anticancer drug target, and currently, pharmaceutical developments of PI3K inhibitors are in pipeline (Zhao et al. 2010). Two new pyranone compounds, wortmannines F and G, were characterized from *T. wortmannii*, the endophytic fungus of the medicinal plant, *T. wilfordii* (Zhao et al. 2019). The compounds were tested for the phosphatidylinositol 3-kinase inhibition. Both compounds showed inhibitory activity with IC_{50} value of 25 and 5 μM, respectively.

Novel metabolites from endophytes inactive in cytotoxicity assays are documented for janthinone, phomoxins, fusarimines, xylaromanones, wortmannines A–C, chaetopenoids, nigrosphaerin, and simplicillins A and C (Table 13.2).

Novel Anticancer/Cytotoxic Metabolites from Endophytic Actinomycetes

Endophytes do produce beneficial compounds with medicinal applications, as demonstrated by Taxol, the anticancer drug produced by *Taxomyces andreanae* (Strobel and Daisy 2003). With impetus received from the endophytic fungal success on Taxol, Caruso et al. (2000) isolated the first taxane-producing *Streptomyces*, *Micromonospora*, and *Kitasatospora* spp., from the bark tissue of *Taxus baccata* and *T. brevifolia.* Anticancer compounds are being isolated and tested for their efficacy in various cell lines. The peptide antibiotic coronamycin from *Streptomyces* sp. (MSU-2110) showed cytotoxic potentials on par with Taxol by inhibiting the HMEC and BT20 cell lines (IC_{50} 5–10 μg ml^{-1}) (Ezra et al. 2004).

Brartemicin, a trehalose-derived antibiotic and a novel inhibitor of metastasis produced by *Nonomuraea* sp., was isolated from the Brazilian medicinal plant, *Artemisia vulgaris* (Igarashi et al. 2009). This compound indicated anti-invasive property of murine colon carcinoma cells (IC_{50} 0.39 μM) with no toxicity. Flavensomycinoic acid, a cytotoxic alkaloid from *Streptomyce*s sp. YIM66017 (Zhou et al. 2013), exhibited potent cytotoxicity to MCF-7, the breast cancer cell line (IC_{50} 17.0 μM). Medilamine C, a novel ʊ-hydroxy alkylamine derivative from *Streptomyces* sp. YIM 66142, showed reduced cytotoxicity (Zhang et al. 2014b). Tumor metastasis involves a cascade of events leading to high mortality rates, and therefore, the discovery of tumor metastasis inhibitory or anti-invasive compounds from the actinomycetes holds great promise.

13.4.2.3 Antioxidants

Antioxidants are defined as "any substance when present in low concentrations compared to those of an oxidisable substrate significantly delays or prevents the oxidation of that substance" (Halliwell and Gutteridge 1989). Antioxidants are derived from food sources and have been proven to have numerous health benefits. Microbial endophytes have provided few antioxidant molecules with unique structures, but their clinical applications are limited.

Novel Antioxidant Compounds from Endophytic Fungi

The antioxidant compounds pestacin and isopestacin were isolated from the cultures of *Pestalotiopsis microspora* residing in *Terminalia morobensis* near the Sepik River drainage of Papua New Guinea (Harper et al. 2003). 4,6-Dihydroxy-5-methoxy-7-methylphthalide, a new isobenzofuranone derivative obtained from *Cephalosporium* sp. AL031 in *Sinarundinaria nitida* sampled from Yunnan Province of China, exhibited EC_{50} value of 10 μM in 1,1-diphenyl-2-picryhydrazyl (DPPH) radical scavenging assay (Huang et al. 2012). Cajaninstilbene acid (CSA), 3-hydroxy-4-prenyl-5-methoxystilbene-2-carboxylic acid, has been reported from *Fusarium* spp., an endophyte of pigeon pea *Cajanus cajan* (Zhao et al. 2012) with medicinal benefits. The antioxidative potential was tested in DPPH radical scavenging assay, with CSA exhibiting 80% scavenging potentials on par with the standard at a concentration of 500 μg ml^{-1}.

Novel Antioxidant Compounds from Endophytic Actinomycetes

A new daidzein derivative, 1″-*O*-methyl-8-hydroxymethyl-daidzein, was isolated from *Streptomyces* sp. YIM 65408, an endophyte of *Tripterygium wilfordii* cultivated in soybean powder containing medium (Yang et al. 2013). In the radical scavenging assay by 2,2-diphenyl-1-picrylhydrazyl method, the compound showed an IC_{50} value at 0.60 mmol/L.

2,6-Dimethoxy terephthalic acid, a new natural product isolated from the culture filtrate of *Streptomyces* sp. YIM66017, from *Alpinia oxyphylla* exhibited significant antioxidant activity in anti-radical assay with IC_{50} values of 4.61 and 57.12 μg ml^{-1}, respectively (Zhou et al. 2014). The actinomycetes are undoubtedly the largest producers of bioactive substances and are a challenge to microbiologists and natural product chemists to examine the potentiality of the products for therapeutic applications.

13.4.2.4 Novel Antidiabetic Compounds from Endophytes

Diabetes is a serious medical condition resulting in the early breakdown of starch into sugar resulting in hypo- or hyperglycemia. Therapeutic targets to counter diabetes by employing antidiabetic agents, through the inhibitory action of carbohydrate hydrolyzing enzymes such as α-glucosidase and α-amylase enzymes, glucose transporters, insulin receptor substrates, etc.

A fungal nonpeptidal metabolite was isolated from the endophytic fungus *Pseudomassaria* sp., collected from the rain forest plant, near Kinshasa, Republic of Congo (Zhang et al. 1999). The nonpeptidyl, small molecule, insulin-mimetic compound (demethylasterriquinone B-1, DMAQ-B1) was isolated from a mixture of metabolites. Oral administration of DMAQ-B1 resulted in significant lowering of glucose in two mouse models of diabetes (Salituro et al. 2001). DMAQ-B1 represents the first orally active insulin-mimetic agent and as a novel therapeutic target in diabetic patients.

Nigrosporamide A and 4-prenyloxyclavatol, two novel compounds isolated from *N. sphaerica* (Zhu et al. 2018), were tested for their in vitro α-glucosidase inhibitory activity with the positive control acarbose currently used clinically in combination with antidiabetic agents to control the blood glucose level of patients. Nigrosporamide A exhibited high α-glucosidase inhibitory activity (IC_{50} value 120.3 μM), which was three times more potent than acarbose (IC_{50}, 446.7 μM). 4-prenyloxyclavatol was inactive with $IC_{50} > 520.34$ μM.

The well-proven inhibitors induce side effects, and therefore the need is to screen newer inhibitors and to identify potential α-amylase and glucosidase inhibitors from natural sources to minimize the side effects. Linfuranone A, a novel polyketide isolated from the actinomycete endophyte *Microbispora* sp. from Thai medicinal plant *Clinacanthus siamensis*, displayed antidiabetic potential in mouse cell lines (Indananda et al. 2013). Recent findings indicate the potential of endophytic actinomycetes as glucosidase and amylase inhibitors (Pujianto et al. 2012; Akshatha et al. 2014).

13.4.2.5 Anti-inflammatory Molecules

Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. An effective anti-inflammatory drug should be able to inhibit the development of inflammation without interfering in normal homeostasis. Current approaches to overcome the inflammation include the use of immune selective anti-inflammatory derivatives, selective glucocorticoid receptor agonist, resolvins and protectins, and TNF inhibitors (Dhingra et al. 2015). A number of herbal drugs have been identified in the past that can target inflammatory cytokines. Therefore, a safe and efficient drug molecule to confer protection against inflammation is urgently needed.

Novel anti-inflammatory class of compounds such as lactones, sesquiterpenes (oids), butanolides, and ergosterols are characterized from the endophytic fungi. Phomol and mevinic acid are the first anti-inflammatory novel compounds isolated from *Phoma* sp. Periconianones A from the endophytic *Periconia* sp. are novel sesquiterpenes and exhibited anti-inflammatory activity in mouse microglia BV2 cells (Zhang et al. 2014a), the immune cells of the nervous system. Asperimides A–D isolated from the tropical *A. terreus* are novel aromatic butanolides consisting of maleimide core (Liao et al. 2018). The compounds were tested for their inhibitory effects in lipopolysaccharide-mediated RAW 264.7 cells, and inhibitory effects were noted in A and C with IC_{50} value of 1.26 and 0.78 and μM, respectively.

The endophytic fungus *T. atroviride* from the bulb of *Lycoris radiata* produced a novel 3-amino-5-hydroxy-5-vinyl-2-cyclopenten-1-one dimer, atrichodermone A; a new cyclopentenone derivative, atrichodermone B; and a new sesquiterpene, atrichodermone C, together with three known cyclopentenone derivatives (Zhou et al. 2017). Compounds were evaluated for their cytotoxicity against HL60 and U937 cell lines, as well as anti-inflammatory effect against the production of the pro-inflammatory cytokines TNF-α and IL-1β.

Novel butanolides, terrusnolides A–D from *A. terreus* with anti-inflammatory potential, were isolated from an endophyte of the Chinese medicinal plant *T. wilfordii* (Qi et al. 2018). The anti-inflammatory effects of compounds were evaluated in vitro in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. The compounds exhibited excellent inhibitory effects on the production of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and nitric oxide (NO) in LPS-induced macrophages, comparable with the positive control (indomethacin). Results indicate terrusnolides A–D as new natural compounds for the treatment of inflammation.

Two new alkaloids, rigidiusculamide E and [−α-oxyisohexanoyl-N-methyl-leucyl)$_2^-$, were characterized from the endophytic *Fusarium tricinctum* from the roots of the Chinese medicinal plant *P. notoginseng* (Sun et al. 2018). The anti-inflammatory effects of compounds were evaluated in vitro in RAW 264.7 macrophage cell line for the inhibition of NO production. [−α-Oxyisohexanoyl-N-methyl-leucyl)$_2^-$ exhibited excellent inhibitory effects on the production of NO with the IC_{50} value of 18.1 μM.

Three new ergosterol derivatives, namely, fusaristerols B [(22*E*,24*R*)-3-palmitoyl-19(10→6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol] (1), C [(22*E*,24*R*)-ergosta-7,22-diene-3*β*,6*β*,9*α*-triol] (3), and D [(22*E*,24*R*)-ergosta-7,22-diene-3β,5α,6β,9*α*-tetraol 6-acetate] (4), were characterized from the endophytic *Fusarium* sp. isolated from *Mentha longifolia* L. roots (Khayat et al. 2019). The metabolites were assessed for 5-lipoxygenase (5-LOX) inhibitory potential. Compound **1** possessed 5-LOX inhibitory potential with an IC_{50}s of 3.61 μM, compared to that of indomethacin (IC_{50} 1.17 μM)

13.4.2.6 Insecticidal Compounds

Insects often damage the standing crop produced by their feeding behavior and are a menace. Synthetic insecticides are used to control the damages caused by the pests and are considered harmful. Alternate methods to control insects involve the use of biopesticides and integrated approaches. One of the earliest insecticidal agents to control moths is naphthalene, the insect repellent. An endophytic fungus *Muscodor vitigenus* from a liana produces the organic compound naphthalene (Daisy et al. 2002). Two novel benzofurans, namely, 5-hydroxy-2-(1′hydroxy-5′-methyl-4′-hexenyl) benzofuran and 5-hydroxy-2-(1′oxo-5′-methyl-4′-hexenyl) benzofuran, were isolated from an unidentified endophyte from *G. procumbens* with toxic effects on the larvae of spruce bud worm (Findlay et al. 1997). Newer sources of novel insecticidal agents need to be investigated with endophytic microbes.

13.4.2.7 Anti-parasitic Compounds

Mosquito-borne parasitic diseases such as malaria and lymphatic filariasis are prevalent worldwide. The parasitic infections caused by the protozoans are a major concern, as the causal agent *Plasmodium falciparum* is responsible for the cerebral fever, which can be of great concern. Antimalarial drugs are efficacious; however over a long period of use, the parasite often tends to develop resistance, and there is a need to search for newer and safer anti-parasitic drugs. A number of plant and microbial-based insecticides are preferred due to their selective toxicity and safe handling. Bioprospecting of endophytic strains reveal their larvicidal potentials.

Novel Compounds from Fungal Endophytes

Anti-parasitic compounds such as novel xanthone dimers, phomoxanthones A and B (Isaka et al. 2001), 11-hydroxymonocerin (Sappapan et al. 2008), and two *Xylaria* benzoquinone metabolites, xylariaquinones and 2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione, have shown inhibition to *P. falciparum*. Novel antileishmanial metabolites, viz., CP17 and CP18, were identified from the secondary metabolites of *Edenia* sp., the endophytic fungus from Panamanian medicinal plant, *Petrea volubilis* (Martinez-Luis et al. 2008). The metabolites exhibited selective toxicity against *Leishmania donovani* with EC_{50} values of 1.34 and 0.62 μM, whereas in the positive control, amphotericin B, the EC_{50} value was 0.09 μM. The fungal endophytes from the Costa Rican medicinal plants yielded anti-plasmodial novel metabolites such as codinaeopsin, a polyketide (Kontnik and Clardy 2008), and the isoprenoid asterogynins (Cao et al. 2010).

Phomanolide from endophytic *Phoma* sp. having 14-nordrimane structure was identified with antiviral activity against influenza A virus (A/Puerto Rico/8/34, H1N1) with IC_{50} values of 2.96 ± 0.64 μg ml^{-1} (Liu et al. 2019). A novel hydroanthraquinone derivative, 6-*O*-demethyl-4-dehydroxyaltersolanol A, and two new azaphilones, 8,11-didehydrochermesinone B and (7*S*)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione, were

isolated from *Nigrospora* sp. YE3033, an endophytic fungus of *Aconitum carmichaelii* (Zhang et al. 2016). The hydroanthroquinone exhibited the inhibitory effects on influenza viral strain of A/Puerto Rico/8/34 (H1N1) with the IC_{50} values of 2.59 μg/ml^{-1}, while the low cytotoxicity of 8,11-didehydrochermesinone B (CC_{50} value of 184.75 μg ml^{-1}) holds promising potential in the development of anti-influenza A virus drugs.

Novel Compounds from Endophytic Actinomycetes

A pioneering study by Castillo et al. (2002, 2006) revealed the anti-plasmodial potential of the newly described peptide antibiotics, munumbicins C and D with low toxicity and coronamycins produced by the endophytic *Streptomyces* NRRL 30562 and *Streptomyces* sp. (MSU-2110) from *K. nigriscans* the snake vine plant and the follow-me vine, *Monstera* sp. The antibiotics showed remarkable activity with IC_{50} of 0.5 and 0.87 μg ml^{-1} and 9.0 ng ml^{-1} against the parasite, *P. falciparum*.

13.4.2.8 Immunosuppressive Compounds

Immunosuppressive drugs are used to prevent allograft rejection in transplant patients and to treat autoimmune diseases such as rheumatoid arthritis and insulin-dependent diabetes. Approved immunosuppressive agents such as cyclosporin A and FK506 possess some undesirable side effects, and there is a need for better immunosuppressive agents.

The first endophytic fungal novel immunosuppressant, subglutinols A and B, was characterized from the liquid culture of *Fusarium subglutinans* residing in the medicinal plant *T. wilfordii* (Lee et al. 1995a). IC_{50} value of subglutinols in the mixed lymphocyte reaction and thymocyte proliferation assays indicated 0.1 μM and was equipotent to that of the standard drug cyclosporin in one of the assays. Therefore, the nontoxic nature of compound is a criterion to be considered as a potential drug. Endophytes produce immunomodulatory compounds.

Pestalotiopsis leucothes, isolated from the Chinese medicinal plant *T. wilfordii*, produces immunomodulatory compounds (Kumar et al. 2005). One compound BS significantly inhibited the production of cytokines such as interleukin (IL)-1β, IL-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α, by peripheral blood mononuclear cells (PBMNC) and soluble IL-2 receptor expression at concentrations greater than 1 μg ml^{-1}. The inhibition of PHA stimulated PBMNC proliferation, and IL-2 and sIL-2R production by BS indicates that it is a T cell-specific immunosuppressant. The endophytic fungus *Colletotrichum dematium* isolated from the tropical rain forest Costa Rican medicinal plant *Pteromischum* sp. produces a novel immunosuppressive compound colutellin A (Ren et al. 2008). It inhibited CD4 T cell activation of IL-2 production with an IC_{50} of 167.3 potential immunosuppressive activity of this compound. In cytotoxicity experiments, the compound exhibited no toxicity and has potential to be developed as a novel immunosuppressive drug.

13.4.2.9 Other Biological Activities of Novel Compounds from Endophytes

The secondary metabolites or novel compounds derived from the endophytes have therapeutic applications as algicidal, antidepressant, neuroprotective, and antitubercular molecules.

Algicidal Compounds

Algicides are chemicals which check or kill the growth caused by the algal genera. Filamentous chlorophyceae, blue green algae, and dinoflagellates cause excessive growth by sporadic blooms, which adversely affect the aquatic systems. Therefore, algicides are used to check the growth of harmful algal populations. Novel compounds, fusidilactones A–E, were isolated from *Fusidium* sp. and were evaluated for the algicidal activity by the in vitro growth inhibition assay. Algicidal activity against *Chlorella fusca* was detected by measuring the zone of inhibition (Krohn et al. 2002; Qin et al. 2009a).

Antitubercular Compounds

Tuberculosis is a chronic respiration disease caused by *Mycobacterium tuberculosis.* It results in persistent cough and blood-tinged sputum. Antitubercular compounds are effective against the pathogen, but some strains develop resistance to the drugs, and this necessitates the search for novel antitubercular compounds. The products from endophytes are sources of novel antitubercular compounds.

Novel antitubercular compounds have been isolated from *Phoma* spp. as endophytes of *Garcinia* spp. from Thailand. The compounds phomoxanthones, phomoenamide, and phomonitroester exhibited significant activity against *M. tuberculosis* (Isaka et al. 2001; Rukachaisirikul et al. 2008). A virulent strain of *M. tuberculosis* was inhibited by diaporthenones A and B and benzopyranones from *Diaporthe* sp. (Bungihan et al. 2011).

Antidepressant Compounds

Major depressive disorder (MDD) is a chronic, recurring, and debilitating mental illness that is the most common mood disorder in several countries. Several monoamine-based pharmacological drug classes have been developed and approved for the treatment of MDD; however, remission rates are less than 60%, and there is a delayed onset before remission of depressive symptoms is achieved (Hillhouse and Porter 2015). Drugs derived from natural products are used to treat depression but are with serious side effects. So, lookout for new sources of drugs from microbial endophytes is in progress. Secovironolide, the first example of a furanosteroid

scaffold bearing a five-membered B ring from *Talaromyces wortmannii*, was tested for monoamine oxidase (MAO) inhibitory activity and showed weak antidepressant activity (Ding et al. 2015).

Anti-acetylcholinesterase Compounds

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease, with symptomology that typically includes confusion, memory loss, impaired cognitive and emotional function, and dementia (Alzheimer's Disease International 2015) Hence, drugs that mimic acetylcholine activity (cholinomimetics) or drugs that limit acetylcholine breakdown (AChE inhibitors) have provided a therapeutic strategy to augment cholinergic signalling in AD patients. 16-α-hydroxy-5*N*-acetyllaardeemin is a novel alkaloid from endophytic *A. terreus* in *A. annua* (Ge et al. 2010). The inhibitory activity of the compound was investigated in the in vitro *assay.* The compound showed inhibitory activity with EC_{50} value of 58.3 μM against the positive control, tacrine (37.9 μM).

Neuroprotective Compounds

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive cognitive and memory impairment and neuronal cell death (Cummings 2004). Drugs approved to treat AD are acetylcholinesterase inhibitors or the receptor agonists; both have profound side effects. Therefore, alternate drugs are essential to treat AD. Microbial endophytes have tremendous applications in agriculture and therapeutics.

A novel alkaloid of the macfortine group, chrysogenamide, was isolated from root endophytic *P. chrysogenum* in the Chinese medicinal plant, *Cistanche deserticola* (Lin et al. 2008). The compound exerted neuroprotective effects in human neuroblastoma SH-SY5Y cell lines. The effect of chrysogenamide A on neurocytes was evaluated using oxidative stress-induced cell death by MTT assay. The oxidative stress by hydrogen peroxide resulted in a decrease in the cell viability by 43% as compared with control group. Chrysogenamide A inhibited cell death induced by hydrogen peroxide by improving cell viability by 59.6% at concentration of 1×10^4 μM.

Antiestrogenic Compounds

Subglutinol A, the immunosuppressive compound isolated from *F. subglutinans*, was tested for the antiestrogenic potentials (Lim et al. 2015). The compound blocked the 17β-induced estradiol activated receptor plasmids and estrogen-response target genes.

Cardioprotective Compounds

Rubralone, a novel compound from *Streptomyces* sp., was tested against rat cardiomyocytes (Yan et al. 2016). The compound had no toxicity effects at a concentration of 100 μM but showed an increase in the viability of the H_2O_2-induced injury to cardiomyocytes, suggesting protective ability.

13.5 Novel Bioactive Molecules from *Pestalotiopsis* Species

The genus *Pestalotiopsis* is distributed worldwide and is a common inhabitant of a range of substrata. Its occurrence was first documented by Raj (1993) as a rain forest species. *Pestalotiopsis* species may reside as endophytes in the bark of tree trunk, twigs, and leaves and are genetically diverse (Tejesvi et al. 2007). Since the first isolation of *Pestalotiopsis microspora* as an endophyte, producing the anticancer drug paclitaxel, the genus has contributed significantly towards understanding the concept of horizontal gene transfer from the "host to endophyte" and to drug discovery. *Pestalotiopsis* spp. are often associated as endophytes of the rain forest plant species and produce metabolites that virtually govern all bioactivities ranging from antioxidant and antimicrobial to anticancer activities (Table 13.4). They are readily identified on agar plate by the white to cream mycelia often with conidiomata, the acervulus erumpent with black ooze (Fig. 13.2a) and fusiform conidia consisting of four cells with hyaline terminal and basal cells (Fig. 13.2b). *Pestalotiopsis* spp. are distinctly recognized by the appendages in the terminal cell that are unbranched.

13.5.1 Antioxidant Compounds

Two novel antioxidant compounds, pestacin and isopestacin, were isolated from *Terminalia morobensis* endophyte, *P. microspora* in the Riverine Sepik drainage in Papua New Guinea (Harper et al. 2003). Pestacin, a 1, 3-dihydro isobenzofuran, naturally occurs as a racemic mixture and functions by cleaving a reactive C–H bond and through O–H abstraction; the antioxidant activity is one order higher than that of trolox, a vitamin E derivative. The presence of a unique doubly benzylic carbon is necessary for a strong antioxidant activity and racemization. Isopestacin, an isobenzofuranone, has structural similarities to flavonoids and attributes to its antioxidant effect by scavenging both superoxide and hydroxyl free radicals (Strobel et al. 2002). It differs from other isobenzofuranones in possessing a substituted benzene ring attached at the C-3 position of the furanone ring.

Table 13.4 Novel bioactive metabolites produced by *Pestalotiopsis* endophytes of medicinal plants

Endophyte	Plant species	Sampling site	Metabolites	Chemical group	Bioactivity	Reference
Pestalotiopsis microspora	*Torreya taxifolia*	Ravine slopes of Apalachicola River, Florida	Pestaloside, torreyanic acid	B-glucoside	Antifungal; cytotoxic	Lee et al. (1995a, b)
			Pestalopyrone; hydroxypestalopyrone	Quinone dimer	Phytotoxic	Lee et al. (1996)
				Pyrones (lactones)		
P. microspora	*T. wallichiana*	Foot hills of Himalayas, Nepal	Paclitaxel	Diterpenoid	Anticancer	Strobel et al. (1996)
P. microspora	*Taxodium distichum*	Swamp forest, central coast, South Carolina	Taxol	Diterpenoid	Anticancer	Li et al. (1996)
Pestalotiopsis spp.	*Taxus brevifolia*	Bozeman, Montana, USA	Pestalotiopsins A–B (caryophyllene type); C-methylated acetogenins; 2-hydroxydimeninol; humulane	Sesquiterpenoid	Immunosuppressant	Pulici et al. (1996a, b, c)
Pestalotiopsis guepini	*Wollemia nobilis*	Wollemi National Park, Sydney, Australia	Paclitaxel	Diterpenoid	Anticancer	Strobel et al. (1997)
P. microspora	*T. taxifolia*		Ambuic acid	Cyclohexenenone	Antifungal	Li et al. (2001)
Monochaetia sp.						
Pestalotiopsis jesteri	*Fragraea bodenii*		Jesterone	Cyclohexenenone epoxides	Antimycotic/ antioomycete	Li and Strobel (2001)
			Hydroxyjesterone			
P. microspora	*T. morobensis*	Sepik River, Papua New Guinea	Isopestacin	Isobenzofuranone	Antimicrobial	Strobel et al. (2002)
			Pestacin	1,3-Dihydro-isobenzofuran	Antioxidant	Harper et al. (2003)

(continued)

Table 13.4 (continued)

Endophyte	Plant species	Sampling site	Metabolites	Chemical group	Bioactivity	Reference
Pestalotiopsis sp.	*Pinus taeda*	–	Pestalotiopsolide A; taedolidol; 6-epitaedolidol	Sesquiterpenes	–	Magnani et al. (2003)
Pestalotiopsis foedan	Unidentified tree	Hainan Province, PRC	Pestaphthalides A–B	Isobenzofuranones	Antifungal	Ding et al. (2008)
			Pestafolide	Spiro azaphilone derivative		
Pestalotiopsis theae	Unidentified tree	Jianfeng Mountain, Hainan Province, China	Pestalotheols A–D	Isoprenylated chromenone	Anti-HIV	Liu et al. (2008a, b)
Pestalotiopsis fici			Pestaloficiols A–L	Isoprenylated chromenone	Anti-HIV	Liu et al. (2008a)
			Chloropupukeananin	Functionalized tricycle-decane skeleton	Anti-HIV	Liu et al. (2008b)
			Pestalofones A–E	Cyclohexanones	Anti-HIV	Liu et al. (2009a, b)
Pestalotiopsis terminaliae	*Terminalia arjuna*	Herbal Science Center, Chennai	Taxol	Diterpenoid	Anticancer (apoptosis	Gangadevi and Muthumary (2009)
Pestalotiopsis sp.	*Melaleuca quinquenervia* (Myrtaceae)	Toohey Forest, Queensland, Australia	Pestalactams A–C	Alkylated caprolactams	Anti-parasitic; cytotoxic	Davis et al. (2010)

Pestalotiopsis virgatula	*Terminalia chebula*	Gopalswami Hills, Mysore, India	9-Hydroxybenzo [c]oxepin-3[1] H-one;	Benzo[c]oxepin	–	Kesting et al. (2009, 2011)
			Pestalospiranes A and B	Skeleton		Li et al. (2011)
			Virgatolides A–C	Benzo[c]oxepin motif		
				Benzanulated 6,6- spiroketal class with 2 γ-lactone units		
Pestalotiopsis mangiferae	*Hyptis dilalata*	Central Panama	Mangiferaelactone	Polyhydroxylated macrolide	Antibacterial	Ortega et al. (2014)
Pestalotiopsis crassiuscula	*Fragaria chiloensis*	NITE Biological Resource	4,6-Dihydroxy	Coumarin		Yang et al. (2014)
		Center, PRC	7-Hydroxymethyl-3-Methoxymethylcoumarin			
P. microspora	*Taxus chinensis*	Hubei province, China	Pestalopyrone A	α-Pyrone	No antimicrobial activity	Li et al. (2015)
Pestalotiopsis versicolor		NITE Biological Resource	4,6-Dihydroxy-7-formyl-3-methylcoumarin;	Coumarin	No antifungal activity	Yang et al. (2015a, b)
		Center, PRC	6-[(7S,8R)-8-Propyloxiran-1-yl]-4-methoxy-pyran-2-one	α-Pyrone		
Pestalotiopsis sp. M-23	*Leucosceptrum canum* (Lamiaceae)	Kunming Botanic Gardens, PRC	2a,8adihydroxy-6,7-en-isodrimeninol;	Drimane derivatives	Antibacterial	Kuang et al. (2016)
				Isochromone derivative		
			2ahydroxy-7a,8a-epoxy-isodrimeninol;			
			11-Dehydro-3a-hydroxyisodrimeninol;			
			4,10-Dihydroxy-gamahorin			

(continued)

Table 13.4 (continued)

Endophyte	Plant species	Sampling site	Metabolites	Chemical group	Bioactivity	Reference
Pestalotiopsis adusta	Unidentified tree sp.	Hainan Province, Peoples Republic of China (PRC)	Pestalachlorides A–C	Chlorinated benzophenone alkaloid	Antifungal	Li et al. (2008)
	Clerodendrum canescens	Zhejiang Province, PRC	(10*S*)-12,16-epoxy-17(15→16)-abeo-3,5,8,12,15-abietapentaen-2,7,11,14-tetraone;	Diterpenoid	Cytotoxic	Xu et al. (2016)
	Sinopodophyllum hexandrum	Qinling Mountain, China	Pestalotiopsins D–G	Sesquiterpenes	Cytotoxic	Xiao et al. (2017)
			Pestalotiophols A–B			
			Pestalotiopsin H			
P. microspora	*Taxodium mucronatum*	Ootacamund, South India	7-Epi-10-deacetyltaxol	Diterpenoid	Anticancer (apoptosis)	Subban et al. (2017)
Pestalotiopsis sp. FT172	*Myrsine sandwicensis* A. DC (Myrsinaceae)	Mokuleia Forest Reserve, Hawaii	Pestallic acids A–E	Ambuic acid derivatives	Anti-proliferative	Li et al. (2017)
			Pestalotiotones A–B	Polyketides		Li et al. (2018)
Pestalotiopsis palmarum	*Sinomenium acutum* (Thunb.) Rehd et Wils.	–	Sinopestalotiollides A–D	Diphenyl ether derivatives	Cytotoxic	Xiao et al. (2018)

'–' not available

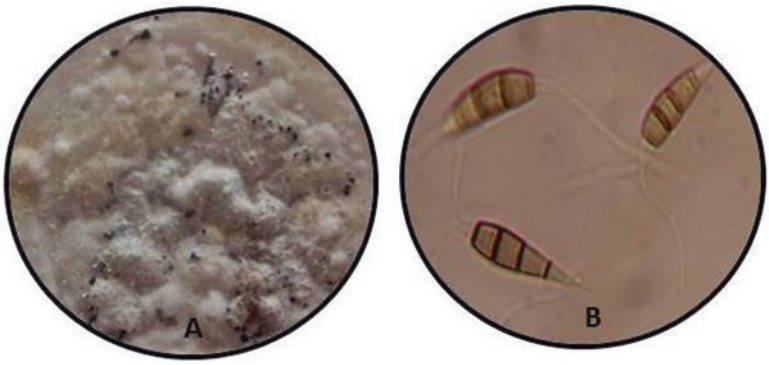


Fig. 13.2 *Pestalotiopsis* sp. isolated as an endophyte of the medicinal plant from Western Ghats, *Phyllanthus amarus* (Schum. & Thonn.) surface-sterilized stem fragments. (**a**) *Pestalotiopsis* colony on potato dextrose agar plate with pinhead-like acervulus and black conidial ooze. (**b**) Fusiform conidia with terminal unbranched appendages in light microscopy (10× magnification)

13.5.2 Anticancer and Cytotoxic Compounds

One of the first anticancer compound produced by *P. microspora*, isolated from the Himalayan yew bark, is paclitaxel, a diterpenoid (Strobel et al. 1996), confirmed by monoclonal antibody and spectroscopy techniques. The yield of the drug was 60–70 μg l^{-1}. This wonder molecule consists of β-phenylalanine unit which is used in the treatment of ovarian and breast cancers as it inhibits the depolymerization of tubulin molecules as a prelude to cell division (Schiff and Horowitz 1980). *P. microspora* is known to produce 7-epi-10-deacetyltaxol, a derivative of Taxol (Subban et al. 2017). *P. guepini* is an endophytic Taxol-producing fungus isolated from the ancient relic, Wollemi pine from the Wollemi Pine National Park of southwest Australia (Strobel et al. 1997).

A cytotoxic quinone dimer, torreyanic acid, isolated from *P. microspora* endophytic on the endangered tree Florida torreya is a more potent cytotoxic agent to several cancer cell lines, inducing cell death by apoptosis with values ranging from 5.1 to 65.0 μM. It is known to induce the G1 arrest of G0 synchronized cells (Lee et al. 1995a, b). Two lactone derivatives, pestalopyrones and hydroxypestalopyrones, with phytotoxic properties were derived from *P. microspora* (Lee et al. 1996). Pestaloficiols (A–L) are isoprenylated chromenone type of metabolites from *P. fici* (Liu et al. 2008b), and L showed cytotoxicity against MCF-7 and HeLa cell lines (IC_{50} 8.7 and 17.4 μM, respectively). Novel ambuic acid derivatives, pestallic acids A–E, were characterized from the Hawaiian *Pestalotiopsis* sp. FT187 with pestallic acid E exhibiting antiproliferative effect (IC_{50} 3.3 μM) in A2780 and cisplantin-resistant A2780 cell lines (Li et al. 2017). New diphenyl ether derivatives named sinopestalotiollides A–D with strong cytotoxic potentials against HeLa, HCT116, and A549 cell lines were characterized from *P. palmarum* (Xiao et al. 2018).

Three novel caprolactams, pestalactams A–C, were identified from the endophyte of Australian forest plant. Compounds A–B exhibited modest cytotoxicity in the mammalian cell lines, MCF-7 and NFF, with 12–64% inhibition at 100 μM concentration (Davis et al. 2010).

13.5.3 Antimicrobial Compounds

Pestaloside, a novel β-glucoside, is an antifungal compound inhibiting the growth of plant pathogenic fungi such as *Cladosporium* sp., *Rhizoctonia solani*, and *Geotrichum candidum* (Lee et al. 1995b). Ambuic acid, a novel organic acid with a functionalized cyclohexanone moiety found in the antibiotic tetracycline, was isolated from *Pestalotiopsis* sp. (Li et al. 2001). It was tested against a number of phytopathogens and found to be effective against *P. ultimum* at 25 μg ml^{-1}. Three caryophyllene-rich sesquiterpenes, pestalotiopsins A–C and humulane and drimane derivatives, were characterized (Pulici et al. 1996a, b, c). Two novel cyclohexanone epoxides, viz., jesterone and hydroxyjesterone, are a rare class of oxygenated cyclohexanoids and are antioomycete compounds from a novel endophytic fungus from Papua New Guinea, *P. jesteri* (Li and Strobel 2001). Noticeable activity of jesterone was against the oomycete pathogens *Phytophthora cinnamomi* and *Aphanomyces* sp. with MICs of 6.5 μg ml^{-1}.

The antioomycete activity of pestacin was determined against the root-invading pathogen *P. ultimum* with the MIC of 10 μg ml^{-1} (Harper et al. 2003). A new reduced spiro azaphilone derivative pestafolide A and pestaphthalides A and B, two new isobenzofuranones, were isolated from solid cultures of *P. foedan*. Pestafolide A displayed antifungal activity against *A. fumigatus* with a zone of inhibition of 10 mm at100 μg/disk. Pestaphthalide A showed activity against *Candida albicans*, and pestaphthalide B (43) showed activity against *G. candidum* with 11 mm zone of inhibition (fluconazole, 18–28 mm zones of inhibition for *C. albicans*, *A. fumigatus*, and *G. candidum* at 100 lg/disk) (Ding et al. 2008).

Pestalachlorides (A–C) are chlorinated benzophenones characterized from the extracts of *P. adusta*. Pestalachloride A displayed potent antifungal activity against *Fusarium culmorum* with IC_{50} value of 0.89 μM, while pestalachloride B exhibited remarkable activity against *Gibberella zeae* with an IC_{50} value of 1.1 μM. Pestalachloride C did not show antifungal activity against the test plant pathogens (Li et al. 2008). Pestalofones (C–D) are cyclohexanone derivatives from *P. fici* and exhibited inhibitory effects against *Aspergillus fumigatus* with IC_{50} values of 1.1 and 0.90 μM (Liu et al. 2009a).

Mangiferaelactone, a new polyhydroxylated macrolide, was isolated from the solid cultures of *P. mangiferae* from the Panamanian medicinal species, *H. dilatata* (Ortega et al. 2014). The compound showed antibacterial activity against *B. cereus* (MIC 0.55 μg ml^{-1}) and *Listeria monocytogenes* (MIC 1.68 μg ml^{-1}).

13.5.4 Antiviral Compounds

The isoprenylated chromenone type of metabolites, pestaloficiols (A–L), from *P. fici* displayed antiviral activity. Compounds A, B, D, G, H, J, and K inhibited the HIV-1 replication in C8166 cells (Liu et al. 2008b). Pestalotheols (A–D) from *P. theae* are derived from two isoprene units and a polyketide and displayed inhibitory activity against HIV-1 replication in C8166 cells (Liu et al. 2008b). Pestalofones (A–E) are cyclohexanone derivatives from *P. fici.* Compounds A, B, and D exhibited inhibitory effects against HIV-1 replication in C8166 cells with EC_{50} values of 90.4, 64, and 93.7 μM (Liu et al. 2009a).

13.5.5 Anti-parasitic Compounds

Pestalactams A–C are novel caprolactams identified from the endophyte of Australian plant *Melaleuca quinquenervia* (Myrtaceae). Compounds A–B exhibited modest cytotoxicity against malarial parasite cell lines, Dd2 (chloroquinone resistant) and 3D7 (chloroquinone sensitive), with 16–41% inhibition at 25 μM concentration (Davis et al. 2010).

Pestalotiopsis spp. produce the most reliable source of bioactive metabolites and are often associated with the tropical plant species. Worldwide >200 spp. are documented as pathogens and endophytes. Their nomenclature as the criterion for the evaluation of species phylogenetically is based on the relationship with the host plant (Jeewon et al. 2004), and novel species are documented. Among them, *P. microspora* is a distinct endophytic organism with metabolic diversity. Li et al. (2001) in their publication report that among the *P. microspora* strains collected from various rain forests, the strain from highland area of Papua New Guinea was of interest, as it coincided with the discovery of the perfect stage of *P. microspora* and *Pestalosphaeria hansensii*, thus providing evidence for the completion of life cycle of the endophyte. Yet, another seminal contribution from this strain is the isolation of, a novel antifungal compound, ambuic acid. The term “ambua” in Huli language of the highlands refers to the yellow color of clay, which is used as a source of facial decoration during tribal celebrations. The irony here is that the methylene chloride extract of the strain was also “yellow in color!”

13.6 Isolation, Identification, and Augmentation of Bioactive Compounds Using Worldwide Unique Technology Platform

13.6.1 Hyphenated Techniques

A technique where in a separation technique is coupled with an online spectroscopic detection technology is known as hyphenated technique, e.g., gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), liquid chromatography-Fourier-transform infrared (LC-FTIR) spectrometry, and liquid chromatography-nuclear magnetic resonance-mass spectrometry (LC-NMR-MS). Recent advances in hyphenated analytical techniques have remarkably widened their applications to the analysis of complex biomaterials, especially natural products (Sarker and Nahar 2012). The extracts of endophytic organisms are complex mixtures and require high-resolution bioassays and the state-of-the-art hyphenated techniques to overcome the characterization of metabolites by the usual characterization of individual metabolites (Kesting et al. 2009, 2011). The liquid cultures of bioactive culturable endophytes are upscaled to 500–2000 ml. Fungi will be grown to stationary growth phase and the extracts tested for antimicrobial activity. Extracts with activity are subjected to analysis based on simultaneous chemical and antimicrobial profiling with the aim of assessing the antimicrobial activity at the individual molecular level. This will be performed using a new worldwide unique technology platform (Schmidt et al. 2012), based on a hyphenated HPLC-SPE-NMR system further coupled with high-resolution bioassay, i.e., HPLC-MS-SPE-NMR/HR bioassay. The principles of this approach and proof-of-concept studies with a series of assays have recently been published (Grosso et al. 2013; Agnolet et al. 2012).

The simultaneous chemical and pharmacological profiling is based on the use of NMR hyphenation, i.e., an integrated and computer-managed process where components of a mixture are separated by HPLC on analytical scale (mg amounts of extracts containing μg or ng amounts of individual compounds), the individual peaks separated from HPLC mobile phase by solid-phase extraction (SPE), and the compounds submitted to structure determination by NMR (supported by MS). The use of the HPLC-SPE-NMR technology platform in natural products research has been developed and optimized by Staerk et al. (2009) and has demonstrated that the technology is applicable for the identification of a broad range of complex natural products present in crude mixtures (Staerk et al. 2009; Kesting et al. 2011). The hyphenated techniques have unravelled the bioassay-guided characterization of metabolites from *P. namyslowskii*, *P. raciborskii*, and *P. virgatula* endophytic extracts of medicinal plants (Kesting et al. 2011; Wubshet et al. 2013; Kajula et al. 2014). The significance of the technology is that the structure elucidation can target antimicrobial analytes only and performed very quickly and rigorously with very small amounts of extracts.

13.6.2 Augmentation of Bioactive Metabolite Production by Biotransformation

Endophytic microbes are bestowed with the ability to produce bioactive metabolites which is strongly influenced by a number of factors such as the host plant location, ethnomedicinal uses, and the ecosystem types. Several research groups have succeeded in elucidating the potential benefits of these microbes and their bioactive products through biotechnological processes. Bioactive metabolites from endophytes have promising potentials; the safety and concerns for human health and demands necessitate the search for synthetic drugs. Alternative methods to obtain bioactive compounds through the biotransformation method by microbial transformation have been successful for the aromatic compounds (Borges et al. 2009). Biotransformation of tetrahydrofuran lignan by endophytic *Phomopsis* sp. has led to the formation of a new compound 3,4-dimethyl-2-(4′hydroxy-3′5-dimethoxy phenyl)-5-methoxy-tetrahydrofuran with trypanocidal activity on par with the natural precursor compound against the Chagas disease parasite, *Trypanosoma cruzi* (Verza et al. 2009). The use of endophytes in the biotransformation of terpenes through the enzymatic reactions for the production of novel flavor compounds is reported (Pimentel et al. 2011).

The production of camptothecin by *F. oxysporum kolhapuriensis* isolated from the endangered medicinal plant *N. foetida* was further augmented by using whey from the dairy waste as the medium. The optimized medium yielded 283 ± 0.27 mg l^{-1} of CPT (Bhalkar et al. 2015) through the response surface methodology, which proved cost-effective. Therefore, biotechnological approaches offer tremendous potential in the production of bioactive metabolites.

13.7 Biosynthetic Potential of Endophytes

The diversity of microbes in unique environments has led to the isolation and discovery of compounds with novel chemical structures. Targeting a compound for a particular biological activity involves the screening of a number of strains against wide targets with the resulting positives designated as “leads.” Deciphering the mechanisms in the biosynthesis of secondary metabolites has proven useful in knowing the metabolite-producing potential of a strain. The genomes of fungi and actinomycetes encode for the synthesis of molecules through the polyketide synthase (PKS) and non-ribosomal peptide synthetase (NPKS) genes. Using known primers, the ability of strains to produce the secondary metabolites through the detection of these genes is reported (Qin et al. 2009b; Janso and Carter 2010; Zhao et al. 2011). More so, the biosynthetic potential of culturable rhizhospheric microbes with that of Chinese medicinal plants in the Panxi Plateau yielded reliable results in terms of antimicrobial potentials and culture-independent methods (Zhao et al. 2012). This technique curtails the need to screen a number of fermentation products

of the strains for bioactivities. The biosynthetic potentials of a rare strain can be exploited for the metabolite-producing capacity, but a rare actinomycete may not produce any natural products as in the case of *Planotetraspora*, a rare taxonomic group (Janso and Carter 2010).

13.8 Conclusion

The endophytic microorganisms have generated unusual interests in the bioprospection of their chemical products. Their diversity is associated with medicinal plant species, around the globe, and ensures them to be the most extensively investigated group of microbes. With the breakthrough of the anti-cancer compound to the most recently described neuroprotective and antidiabetic compounds, endophytes have diversified their metabolite-producing potentials suiting newer bioactivities. It is intriguing to understand as to why the endophytic microbes behave differently in their chemical ability to produce novel chemical structures as bioactive compounds. Interestingly, the biosynthetic pathway plays the key role in the formation of new structures, in diverse chemical class of compounds. Ultimately, the endophyte research still continues to benefit both the researcher and the society as long as the organisms tend to produce "novel" compounds of pharmacological interest.

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