Chapter 11
Bioactive Compounds of Endophytic Fungi Associated with Medicinal Plants

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11.1 Introduction

Endophytic fungi are a diverse group of microorganisms that live asymptomatically in different tissues of living plants (Jia et al. 2016). Despite being important components of plant microhabitat (Jia et al. 2016), endophytic fungi are increasingly present in drug discovery programs mainly due to their capability to produce a diversity of secondary metabolites with pharmacological properties. These fungi may help the host plant in defense against attacking microorganisms, predators, and pests and in return receive their nutrition (Strobel and Daisy 2003; Kaul et al. 2012). From the pharmacological applications perspective, endophytic fungi were reported to produce novel antibacterial, antifungal, antiviral, anti-inflammatory, antitumor, antimalarial, and other bioactive compounds (Nisa et al. 2015; Suman et al. 2016).

According to Strobel and Daisy (2003), Strobel et al. (2004), and Yu et al. (2010), several reasonable plant selection strategies should be followed:

1. Plants growing in areas of great biodiversity also have the prospect of housing larger diversity of endophytes.

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2. Plants growing in special habitats, especially those in deteriorated ecological environment, and possessing special capabilities for survival should also be selected for study. People may learn that the power of plants living in such environment may result from the presence of endophytes.
3. Plants surrounded by pathogen-infected plants but showing no symptoms are more likely to lodge endophytes possessing antimicrobial natural products than other plants.
4. Plants that have been exploited for human use as traditional medicines in some place should be considered for study.
5. Plants which occupied a certain ancient land mass are also more likely to lodge endophytes with active natural products than other plants.

The World Health Organization (WHO) defines medicinal plants as "any plant which in one or more of its organs contains substances that can be used for therapeutic purposes or which are precursors for chemo pharmaceutical semi synthesis." They are frequently selected for screening bioactive compounds (Kaul et al. 2012). The research on endophytic fungi increased considerably after the discovery of taxol, one of the most anticancer agents used in the clinic. This diterpenoid can be produced by the endophytic fungi *Taxomyces andreanae* (Strobel 2003), and, from their host, the medicinal plant *Taxus brevifolia* (Stierle et al. 1995). Therefore, from this discovery, it was evidenced that the endophytic fungi might produce the same metabolites of their host plant. However, it is important to highlight that endophytic fungi are also producers of bioactive secondary metabolites that are different from those produced by their hosts and can be of interest for medicinal applications.

11.2 Antibacterial Compounds

Radic and Strukelj (2012) comment on WHO's constant battle against the ever-increasing multidrug resistance of human pathogenic bacteria, highlighting the urgent need for new alternatives to the currently available broad-spectrum antibiotics. According to Boucher et al. (2009), antibiotic resistance has increased in Gram-positive and Gram-negative pathogens, which represent a serious threat to treatment of infectious diseases. Boucher et al. (2009) also highlight the decrease in the development of new antibacterial drugs and reported a decrease of 75% in new antibacterial drugs over the past 25 years that has been approved by the US Food and Drug Administration (FDA).

The secondary metabolites produced by endophytes associated with medicinal plants may have great potential to treat various infectious diseases. These antimicrobial metabolites are low-molecular-weight organic natural substances active at low concentrations against microorganisms (Guo et al. 2000). The first step toward the discovery of new antibacterial compounds produced by endophytic fungi involves the detection of antibiotic activity in fungal culture extracts. However, in some cases, single compounds present in the crude extract do not show significant

antibacterial activity by themselves but can act synergistically in the extract. The identification and structure elucidation of the active metabolite is essential for the development of new antibiotics (Radic and Strukelj 2012). The secondary metabolites with antibacterial activity, isolated from endophytes of medicinal plants between 2008 and 2018, are listed in the Table 11.1.

Liu et al. (2008) suggest that *Xylaria* sp. YX-28, an endophytic fungus isolated from the medicinal plant *Ginkgo biloba* L., discloses a potent antimicrobial activity and could be a valuable source of new antimicrobial drugs. From *Xylaria* sp. YX-28 fermentation broth 7-amino-4-methylcoumarin **(4)** showed strong antibacterial activities in vitro against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Salmonella typhimurium*, *Salmonella enteritidis*, *Aeromonas hydrophila*, *Yersinia* sp., *Vibrio anguillarum*, *Shigella* sp., and *Vibrio parahaemolyticus* with values of minimal inhibitory concentrations (MIC) ranging from 36 to 142.6 μM. Wu et al. (2018) also studied the endophytic fungi associated with *Ginkgo biloba* L. and obtained *Penicillium cataractum* SYPF 7131, which generated an extract with strong antibacterial activity. From the crude extract of *P. cataractum* SYPF 7131 was isolated the compounds penicimenolidyu A (**67**), penicimenolidyu B (**68**), and rasfonin (**69**) that showed antibacterial activity, mainly, toward *S. aureus*.

A broad diversity of endophytic fungi occurs in the rhizome of *Paris polyphylla* var. *yunnanensis*, a medicinal plant used in traditional Chinese medicine. Some studies have explored the biotechnological potential of these fungi in search of new antimicrobials. Among them, Zhao et al. (2010a) report for the first time the antimicrobial metabolites from the endophytic fungus *Pichia guilliermondii* Ppf9, recovered from rhizome of this plant. From the crude extract of *P. guilliermondii* Ppf9 were obtained three steroids and one nordammarane triterpenoid, ergosta-5,7,22-trienol (**14**), 5α,8α-epidioxyergosta-6,22-dien-3β-ol (**15**), and ergosta-7,22-dien-3β,5α,6β-triol (**16**) and helvolic acid (**17**), which showed activity against *Agrobacterium tumefaciens*, *Escherichia coli*, *Pseudomonas lachrymans*, *Ralstonia solanacearum*, *Xanthomonas vesicatoria*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Staphylococcus haemolyticus*. The helvolic acid (**17**) should be the main antimicrobial component in endophytic fungus *P. guilliermondii* Ppf9 and exhibited the strongest antibacterial activity against *A. tumefaciens*, *E. coli*, *P. lachrymans*, *R. solanacearum*, *X. vesicatoria*, *B. subtilis*, *S. aureus*, and *S. haemolyticus* with MIC values of 2.7, 5.5, 5.5, 2.7, 2.7, 5.5, 87.9, and 10.9 μM, respectively. In addition, from the rhizome of the same plant was obtained the endophytic fungus *Gliomastix murorum* Ppf8, which produced ergosta-5,7,22-trien-3-ol (**33**) and 2,3-dihydro-5-hydroxy-α,α-dimethyl-2-benzofuranmethanol (**34**), compounds that were isolated and shown to be active against *A. tumefaciens*, *E. coli*, *Pseudomonas lachrymans*, *R. solanacearum*, *X. vesicatoria*, *B. subtilis*, and *S. haemolyticus* with the MIC values ranging from 252 to 504 μM. The IC_{50} values of **34** ranged from 140.3 to 366.4 μM (Zhao et al. 2012a). Two sterols and one fatty acid were obtained from the light petroleum extract of the fungus *Fusarium* sp. Ppf4, obtained from the rhizomes of *P. polyphylla* var. *yunnanensis*: 5α, 8α-epidioxyergosta-6, 22-dien-3β-ol (**5**) and ergosta-8(9), 22-diene-3β, 5α, 6β, 7α-tetraol (**6**) and butanedioic acid (**7**). They were assayed against *B. subtilis*, *S. haemolyticus*, *A. tumefaciens*, *E. coli*,

Table 11.1 Antibacterial compounds reported from endophytic fungi recovered from medicinal plants

Fungal endophyte taxa	Medicinal plant/ tissue	Compounds isolated	Biological activity	Minimal inhibition concentration	Reference
Phoma sp.	*Saurauia scaberrinae*/lower crown	**1.** Phomodione ($C_{20}H_{22}O_8$) **2.** Cercosporamide ($C_{16}H_{13}NO_7$) **3.** Usnic acid ($C_{18}H_{16}O_7$)	*Staphylococcus aureus*	2 μg/disk zones of inhibition 0.5 mm	Hoffman et al. (2008)
Xylaria sp.	*Ginkgo biloba*/ twigs	**4.** 7-Amino-4-methylcoumarin ($C_{10}H_9NO_2$)	*Staphylococcus aureus* *Escherichia coli* *Salmonella typhi* *Salmonella typhimurium* *Salmonella enteritidis* *Aeromonas hydrophila* *Yersinia* sp. *Vibrio anguillarum* *Shigella* sp. *Vibrio parahaemolyticus*	91.3 μM 57 μM 114.1 μM 85.6 μM 48.5 μM 22.8 μM 71.3 μM 142.7 μM 36 μM 71.3 μM	Liu et al. (2008)
Fusarium sp.	*Paris polyphylla* var. *yunnanensis*/ rhizomes	**5.** 5α, 8α-epidioxyergosta-6, 22-dien-3β-ol ($C_{28}H_{44}O_3$) **6.** Ergosta-8(9), 22-diene-3β, 5α, 6β, 7α-tetraol ($C_{28}H_{46}O_4$) **7.** Butanedioic acid ($C_4H_6O_4$)	*Bacillus subtilis* *Staphylococcus haemolyticus* *Agrobacterium tumefaciens* *Escherichia coli* *Pseudomonas lachrymans* *Xanthomonas vesicatoria*	349.6–4.5 mM	Huang et al. (2009)
Chloridium sp.	*Azadirachta indica*/ roots	**8.** Javanicin ($C_{15}H_{14}O_6$)	*Escherichia coli* *Bacillus* sp. *Pseudomonas aeruginosa* *Pseudomonas fluorescens*	137.8 μM 137.8 μM 6.9 μM 6.9 μM	Kharwar et al. (2009)

Alternaria sp.	*Sonneratia alba*/ leaves	**9.** Xanalteric acid I ($C_{20}H_{12}O_7$) **10.** Xanalteric acid II ($C_{20}H_{12}O_7$) **11.** Altenusin ($C_{15}H_{14}O_6$)	*Escherichia coli* *Enterococcus faecium* *Enterococcus cloacae* *Staphylococcus aureus* *Streptococcus pneumonia* *Pseudomonas aeruginosa* *Klebsiella pneumonia*	107.6–686 μM	Kjer et al. (2009)
Trichoderma ovalisporum	*Panax notoginseng*/ roots	**12.** Koninginin A ($C_{16}H_{28}O_4$) **13.** Shikimic acid ($C_7H_{10}O_5$)	*Staphylococcus aureus* *Bacillus cereus* *Micrococcus luteus* *Escherichia coli*	5 μg/disk zones of inhibition between 7 and 11 mm	Dang et al. (2010)
Pichia guilliermondii	*Paris polyphylla* var. *yunnanensis*/ rhizomes	**14.** Ergosta-5,7,22-trienol ($C_{28}H_{44}O$) **15.** 5α,8α-epidioxyergosta-6,22-dien-3β-ol ($C_{28}H_{44}O_3$) **16.** Ergosta-7,22-dien-3β,5α,6β-triol ($C_{28}H_{46}O_3$) **17.** Helvolic acid ($C_{33}H_{44}O_8$)	*Agrobacterium tumefaciens* *Escherichia coli* *Pseudomonas lachrymans* *Ralstonia solanacearum* *Xanthomonas vesicatoria* *Bacillus subtilis* *Staphylococcus aureus* *Staphylococcus haemolyticus*	2.7–88 μM	Zhao et al. (2010a)
Phomopsis sp.	*Cistus monspeliensis*	**18.** Phomochromone A ($C_{12}H_{14}O_3$) **19.** Phomochromone B ($C_{12}H_{14}O_4$) **20.** Phomotenone ($C_{11}H_{18}O_2$) **21.** (1*S*,2*S*,4*S*)-trihydroxy-p-menthane ($C_{10}H_{20}O_3$)	*Escherichia coli* *Bacillus megaterium*	0.05 mg/disk zones of inhibition between 6 and 8 mm	Ahmed et al. (2011)
Unidentified ascomycete	*Arbutus unedo*	**22.** Pestalotheol E ($C_{16}H_{24}O_5$) **23.** Pestalotheol F ($C_{16}H_{24}O_5$) **24.** Pestalotheol G ($C_{16}H_{22}O_6$) **25.** Pestalotheol H ($C_{16}H_{24}O_3$) **26.** Anofinic acid ($C_{12}H_{12}O_3$)	*Escherichia coli* *Bacillus megaterium*	50 mg/disk zones of inhibition between 7 and 12 mm	Qin et al. (2011)

(continued)

Table 11.1 (continued)

Fungal endophyte taxa	Medicinal plant/ tissue	Compounds isolated	Biological activity	Minimal inhibition concentration	Reference
Fusarium solani	*Taxus baccata*/bark	**27.** 1-tetradecene ($C_{14}H_{28}$) **28.** 8-octadecanone ($C_{18}H_{36}O$) **29.** 8-pentadecanone ($C_{15}H_{30}O$) **30.** Octylcyclohexane ($C_{14}H_{28}$) **31.** 10-nonadecanone ($C_{19}H_{38}O$)	*Staphylococcus aureus* *Staphylococcus epidermidis* *Bacillus subtilis* *Klebsiella pneumonia* *Escherichia coli* *Shigella flexneri*	1 μg/disk zones of inhibition between 16.3 and 27 mm	Tayung et al. (2011)
Penicillium chrysogenum	*Porteresia coarctata*/leaves	**32.** (3,10-didehydro-3[2(3,3-dimethyl-prop-2-enyl)-3-indolylmethylene]-6-methyl pipera-zine-2,5-dione) ($C_{19}H_{21}O_2N_3$)	*Vibrio cholerae*	10 μg/disk zones of inhibition between 14 and 16 mm	Devi et al. (2012)
Gliomastix murorum	*Paris polyphylla* var. *yunnanensis*/ rhizomes	**33.** Ergosta-5,7,22-trien-3-ol ($C_{28}H_{44}O$) **34.** 2,3-dihydro-5-hydroxy-α,α-dimethyl-2-benzofuranmethanol ($C_{11}H_{14}O_3$)	*Agrobacterium tumefaciens* *Escherichia coli* *Pseudomonas lachrymans* *Ralstonia solanacearum* *Xanthomonas vesicatoria* *Bacillus subtilis* *Staphylococcus haemolyticus*	252–504 μM	Zhao et al. (2012a)
Aspergillus sp.	*Eucommia ulmoides*/roots	**35.** Ergosterol ($C_{28}H_{44}O$) **36.** Cerevisterol ($C_{28}H_{46}O_3$) **37.** 5-Hydroxymethylfuran-3-carboxylic acid ($C_6H_6O_4$) **38.** 5-Methoxymethylfuran-3-carboxylic acid ($C_7H_8O_4$) **39.** Allantoin ($C_4H_6N_4O_3$) **40.** Trypacidin ($C_{18}H_{16}O_7$) **41.** Monomethylsulochrin ($C_{18}H_{18}O_7$)	*Bacillus subtilis* *Staphylococcus aureus* *Staphylococcus faecalis* *Escherichia coli* *Pseudomonas aeruginosa* *Salmonella typhimurium*	7–993 μM	Zhang et al. (2014a)
Botryosphaeria dothidea	*Melia azedarach*/ steam	**42.** Pycnophorin ($C_{20}H_{33}O$)	*Bacillus subtilis* *Staphylococcus aureus*	86.3 μM	Xiao et al. (2014a)

Diaporthe sp.	*Mahonia fortunei*/ leaves	**43.** 19-norlanosta-5(10),6,8,24-tetraene-1α,3β,12β,22S- tetraol ($C_{29}H_{44}O_4$)	*Staphylococcus aureus* *Escherichia coli* *Bacillus subtilis* *Pseudomonas aeruginosa* *Streptococcus pyogenes*	10.9 μM 10.9 μM 4.4 μM 4.4 μM 219 nM	Li et al. (2015a)
Phomopsis liquidambaris	*Cryptolepis buchanani*/steam	**44.** Oblongolide Y ($C_{17}H_{26}O_3$)	*Escherichia coli* *Bacillus subtilis* *Pseudomonas aeruginosa*	89.8 μM 179.6 μM 359.2 μM	Rao & Satish (2015)
Colletotrichum sp.	*Buxus sinica*/leaves	**45.** Colletotrichone A ($C_{18}H_{20}O_7$) **46.** Colletotrichone B ($C_{18}H_{20}O_5$) **47.** Colletotrichone C ($C_{18}H_{22}O_5$)	*Staphylococcus aureus* *Escherichia coli* *Bacillus subtilis*	287–15.8 μM	Wang et al. (2016a)
Penicillium sp.	*Pinellia ternate*/ tubers	**48.** (2*R*)-3′-methoxyl citreovirone ($C_{13}H_{17}O_4Cl_2$) **49.** Helvolic acid ($C_{33}H_{44}O_8$) **50.** Cis-bis-(methylthio)-silvatin ($C_{20}H_{30}N_2O_5S_2$) **51.** Citreovirone ($C_{12}H_{14}Cl_2O_4$) **52.**Trypacidin A ($C_{18}H_{16}O_7$)	*Pseudomonas aeruginosa* *Staphylococcus aureus* *Bacillus subtilis* *Escherichia coli*	8.1–220.7 μM	Yang et al. (2017)
Fusarium solani	*Chlorophora regia*/ roots	**53.** Compounds 1/2 ($C_{21}H_{27}O_6N$) **54.** Compounds 3/4 ($C_{21}H_{27}O_7N$) **55.** Compound 5 ($C_{21}H_{25}O_8N$) **56.** Compound 6 ($C_{22}H_{29}O_7N$) **57.** Compound 7 ($C_{22}H29O_5N$) **58.** Compound 8/9 ($C_{21}H_{27}O_6N$)	*Staphylococcus aureus* *Escherichia coli* *Bacillus subtilis* *Acinetobacter* sp.	11.9–23.8 μM	Kyekyeku et al. (2017)
Epicoccum nigrum	*Ferula sumbul*/leaves	**59.** Di-(2-ethylhexyl) phthalate ($C_{24}H_{38}O_4$)	*Bacillus subtilis* *Staphylococcus aureus* *Escherichia coli*	8 μM 3.7 μM 14.8 μM	Perveen et al. (2017)

(continued)

Table 11.1 (continued)

Fungal endophyte taxa	Medicinal plant/ tissue	Compounds isolated	Biological activity	Minimal inhibition concentration	Reference
Chaetomium sp.	*Scencio stapeliiformis*/arial part	**60.** p-hydroxybenzaldehyde ($C_7H_6O_2$) **61.** Uracil ($C_4H_4N_2O_2$) **62.** 5 effectively ($C_{11}H_{18}N_2O_2$)	*Escherichia coli* *Staphylococcus aureus*	10 µg/disk zones of inhibition between 9 and 11 mm	Tawfik et al. (2017)
Diaporthe terebinthifolii	*Glycyrrhiza glabra*/rhizomes	**63.** (2*E*,4*E*)-6-hydroxynona-2,4-dienoic acid ($C_9H_{14}O_3$) **64.** (*E*)-6-hydroxynon-2-enoic acid ($C_9H_{16}O_3$) **65.** Xylarolide **66.** Phomolide G ($C_{12}H_{20}O_5$)	*Yersinia enterocolitica*	78.4 µM 73.4 µM 72.1 µM 69.2 µM	Yedukondalu et al. (2017)
Penicillium cataractum	*Ginkgo biloba*/ branch	**67.** Penicimenolidyu A ($C_{12}H_{14}O_6$) **68.** Penicimenolidyu B ($C_{13}H_{16}O_7$) **69.** Rasfonin ($C_{25}H_{38}O_6$)	*Staphylococcus aureus* *Bacillus subtilis* *Pseudomonas aeruginosa* *Klebsiella pneumonia* *Escherichia coli*	23–361 µM	Wu et al. (2018)

P. lachrymans, and *X. vesicatoria*, disclosing MIC values in the range 349.6 μM to 4.47 mM and IC_{50} values from 202 μM to 1.5 mM (Huang et al. 2009).

Li et al. (2015a) analyzed secondary metabolites from the endophytic fungus *Diaporthe* sp. LG23 recovered from leaves of *Mahonia fortunei* (Berberidaceae), a medicinal plant used in China as a potent antimicrobial medicine for treating pneumoconiosis, psoriasis, and cough. From *Diaporthe* sp. LG23, a new lanosterol derivative, 19-norlanosta-5(10),6,8,24-tetraene-1α,3β,12β,22S-tetraol **(43)** and six biosynthetically related known ergosterol derivatives were identified. Compound 19-norlanosta-5(10),6,8,24-tetraene-1α,3β,12β,22S-tetraol **(43)**, an unusual fungus-derived 19-nor-lanostane tetracyclic triterpenoid, exhibited pronounced antibacterial efficacy against both Gram-positive and Gram-negative bacteria, especially against clinical isolates of *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *S. aureus*, exhibiting MIC values between 0.2 and 10.9 μM.

Wang et al. (2016a) evaluated the antibacterial potential of *Colletotrichum* sp. BS4 using the OSMAC (One Strain Many Compounds) approach. This fungus was recovered from leaves of the medicinal plant *Buxus sinica*, and after fractionation of its extracts, three new compounds were isolated and identified: colletotrichones A – C (**45–47**). Compound colletotrichone A (**45**) showed pronounced activity against *E. coli* and *B. subtilis*, with MIC values of 0.3 and 2.9 μM, respectively, values comparable to that of standard antibiotics. Additionally, colletotrichone C (**47**) was quite active against the environmental strain of *E. coli*, with MIC value of 15.7 μM. Furthermore, colletotrichone B (**46**) was as active as streptomycin against the clinically relevant RG2 bacterium *S. aureus*, with MIC value of 15.8 μM. Moreover, the authors suggest that *Colletotrichum* sp. BS4 provides some form of azaphilone-mediated chemical defense to the host plant against invading specialist and generalist bacteria.

Perveen et al. (2017) characterized the secondary metabolites of the endophytic fungus *Epicoccum nigrum*, recovered from leaves of medicinal plant *Ferula sumbul*. Compound di-(2-ethylhexyl) phthalate (**69**) was purified, and its antibacterial potential was evaluated against *B. subtilis*, *S. aureus*, and *E. coli*, showing promising activity with MIC values 8, 3.8, and 14.9 μM, respectively.

11.3 Antifungal Compounds

According to Vallabhaneni et al. (2015), fungal diseases are a considerable cause of morbidity and mortality globally. The treatment of mycoses has several limitations, such as undesirable side effects, narrow activity spectrum, and a small number of targets and fungal resistance, all of which corroborates the urgent need to develop new therapeutic strategies (Fuentefria et al. 2018). As for medicine, the agriculture needs novel antifungal compounds against phytopathogenic fungi, which are responsible for great losses in the world agricultural production. The secondary metabolites produced by endophytes associated with medicinal plants may be used

for the fungal treatment. The most important antifungal secondary metabolites from endophytic fungi recovered from medicinal plants, characterized between 2012 and 2018, are listed in Table 11.2 (compounds **1–116**).

Carvalho et al. (2018) reported the antifungal activity of the compounds cytochalasin H (**117**) and J (**118**) isolated from crude extracts of the endophytic fungi *Diaporthe miriciae*, UFMGCB 7719 and UFMGCB 6350, recovered from *Copaifera pubiflora* and *Melocactus ernestii*, respectively, in Brazil. The compounds were tested against the fungal plant pathogens *Colletotrichum fragariae*, *C. gloeosporioides*, *C. acutatum*, *Botrytis cinerea*, *Fusarium oxysporum*, *Phomopsis obscurans*, and *P. viticola* using microdilution broth assays. Cytochalasins H and J showed minor mycelial growth stimulation (hormesis) of *B. cinerea*, *C. acutatum*, *C. fragariae*, *C. gloeosporioides*, and *F. oxysporum*. The cytochalasins at a concentration of at 300 μmol L^{-1} caused, after 144 h, 73% and 36% growth inhibition of *P. obscurans*, respectively, and inhibited the growth of *P. viticola* by 61% and 58%, respectively. Chapla et al. (2014b) also isolated cytochalasin H (**119**) from the endophytic fungi *Phomopsis* sp. obtained from leaves of *Senna spectabilis*. The compound demonstrated antifungal activity against *Cladosporium cladosporioides* and *C. sphaerospermum* inhibiting the fungal growth at 10 and 25 μg/spot, respectively.

Zhang et al. (2014b) reported another cytochalasin from the ethyl acetate extract of the endophyte *Xylaria* sp. XC-16, recovered from leaves of *Toona sinensis*. The bioassay-guided fractionation resulted in the isolation of new cytochalasins Z_{27} (**55**) and Z_{28} (**56**), along with three known compounds *seco*-cytochalasin E (**57**), cytochalasin Z_{18} (**58**), and cytochalasin E (**59**). The anti-phytopathogenic activity of the cytochalsins was evaluated on *Fusarium solani*, *Gibberella saubinetti*, *B. cinerea*, and *Alternaria solani*. Compound **56** showed fungicidal effect against *G. saubinetti* with MIC of 12.5 μM, a value comparable with that of the positive control hymexazol (MIC of 25 μM). In contrast, other compounds displayed MIC values greater than 50 μM against the tested pathogens (Zhang et al. 2014b).

Phomopsis sp. YM 355364, a fungi obtained from *Aconitum carmichaeli* growing in China (Wu et al. 2013a), produces the new steroids (14*β*,22*E*)-9,14-dihydroxyergosta-4,7,22-triene-3,6-dione (**106**) and (5*α*,6*β*,15*β*,22*E*)-6-ethoxy −5,15-dihydroxyergosta-7,22-dien-3-one (**107**), along with those of calvasterols A and B (**108**–**109**) and ganodermaside D (**110**). Compound **106** exhibited antifungal activities against *Candida albicans*, *Hormodendrum compactum*, and *Aspergillus niger*, with MIC values of 145.3, 145.3, and 290.5 μM. Compound **107** showed weak inhibitory activity against *C. albicans* and *Fusarium avenaceum* with MIC of 270.8 μM. Compounds **108** and **110** showed moderate inhibitory activities against *F. avenaceum* at 151.4 and 156.6 μM, respectively. Compound **108** exhibited weak antifungal activities against *Pyricularia oryzae* and *Trichophyton gypseum* with MIC values of 302.9 and 605.8 μM, respectively (Wu et al. 2013a).

Xiao et al. (2013) isolated 80 endophytic fungi from healthy leaves and small branches of *Ginkgo biloba* (China). All the fungi were tested in an antifungal bioassay against *Fusarium graminearum*, *Sclerotinia sclerotiorum*, and *Phytophthora capsici* by the agar diffusion method. Fifteen endophytes were active against at least one of the tested fungi, and *Chaetomium globosum* CDW7 yielded the most

Table 11.2 Antifungal compounds reported from endophytic fungi associated with medicinal plants during 2012–2018

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Fusarium sp.	*Mentha longifolia*/roots	**1.** Fusaripeptide A ($C_{46}H_{75}N_7O_{11}$)	*Candida albicans* *Candida glabrata* *Candida krusei* *Aspergillus fumigates*	0.1 μM 0.2 μM 0.2 μM 0.1 μM	Ibrahim et al. (2018)
Penicillium sp.	*Nerium indicum*/ root	**2**. 3-O-methylviridicatin ($C_{16}H_{13}NO_2$) **3.** Viridicatol ($C_{15}H_{11}NO_3$) **4.** 5-hydroxy-8-methoxy-4-phenylisoquinolin-1(2*H*)-one ($C_{16}H_{13}NO_3$)	*Fusarium graminearum*	**2.** 248.7 μM **3.** 493.6 μM **4.** 467.7 μM	Ma et al. (2017)
			Colletotrichum gloeosporioides	**2.** 497.5 μM **3.** 246.8 μM **4.** 467.7 μM	
			Setosphearia turcica	**2.** 497.5 μM **3.** 246.8 μM **4.** 467.7 μM	
			Alternaria alternata	**2.** 124.2 μM	
			Alternaria brassicae	**3.** 246.8 μM **4.** 116.7 μM **2.** 124.2 μM **3.** 123.2 μM **4.** 116.7 μM	
			Sclerotinia sclerotiorum	**2.** 497.5 μM **3.** 246.8 μM **4.** 467.7 μM	
			Botrytis cinerea	**2.** 497.5 μM **3.** 123.2 μM **4.** 116.7 μM	

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
			Phytophthora capsici	**2.** 994.9 μM **3.** 246.8 μM **4.** 935.4 μM	
			Valsa mali	**2.** 124.2 μM **3.** 123.2 μM **4.** 233.8 μM	
			Peony anthracnose	**2.** 248.7 μM **3.** 246.8 μM **4.** 233.8 μM	
Emericella sp.	*Panax notoginseng*/leaf	**5.** 5-(undeca-3′,5′,7′-trien-1′-yl)furan-2-ol ($C_{15}H_{20}O_2$) **6.** 5-(undeca-3′,5′,7′-trien-1′-yl) furan-2-carbonate ($C_{16}H_{20}O_4$)	*Rhizoctonia solani*	**5.** 107.6 μM **6.** 361.9 μM	Wu et al. (2017)
			Verticillium dahliae	**5.** 27.1 μM **6.** 90.5 μM	
			Helminthosporium maydis	**5.** 13.3 μM **6.** 45.2 μM	
			Fusarium oxysporum	**5.** 107.6 μM **6.** 361.9 μM	
			Fusarium tricinctum	**5.** 107.6 μM **6.** 180.9 μM	
			Botryosphaeria dothidea	**5.** 53.8 μM **6.** 90.5 μM	
			Alternaria fragariae	**5.** 107.6 μM **6.** 180.9 μM	
Chaetomium globosum	*Ginkgo biloba*/leaf	**7.** Chaetoglobosin A ($C_{32}H_{36}N_2O_5$) **8.** Chaetoglobosin D ($C_{32}H_{36}N_2O_5$)	*Sclerotinia sclerotiorum*	**7.** 0.6 μM **8.** 1.2 μM	Zhao et al. (2017)

Fusarium chlamydosporium	*Anvillea garciniil* leaf	**9.** Fusarithioamide A (2-(2-aminopropanamido)-*N*-(1-hydroxy-3-mercaptopropyl) benzamide) ($C_{13}H_{19}N_3O_3S$)	*Candida albicans*	8.7 μM	Ibrahim et al. (2016)
Fusarium fujikuroi	*Eleusine coracana*/shoots	**10.** 5-hydroxy 2(3H)-benzofuranone ($C_8H_6O_3$)	*Fusarium graminearum*	**10.** 208.2 μM	Mousa et al. (2016)
Penicillium chrysogenum	*Eleusine coracana*/roots	**11.** Dehydrocostus lactone ($C_{15}H_{18}O_2$)	*Fusarium graminearum*	**11.** 1.1 mM	Mousa et al. (2016)
Penicillium expansum	*Eleusine coracana*/roots	**12.** Harpagoside ($C_{24}H_{30}O_{11}$)	*Fusarium graminearum*	**12.** 63.2 μM	Mousa et al. (2016)
Chaetomium globosum	*Panax notoginseng*/ seeds	**13.** Chaetoglobosin A ($C_{32}H_{36}N_2O_5$) **14.** Chaetoglobosin B ($C_{32}H_{36}N_2O_5$) **15.** Chaetoglobosin E ($C_{32}H_{38}N_2O_5$) **16.** Chaetoglobosin F ($C_{32}H_{38}N_2O_5$) **17.** Penochalasin G ($C_{32}H_{38}N_2O_4$) **18.** Chaetomugilin A ($C_{23}H_{27}ClO_7$) **19.** Chaetomugilin D ($C_{23}H_{27}ClO_6$) **20.** Flavipin ($C_9H_8O_5$)	*Phoma herbarum*	**13.** 121.1 μM **14.** 30.3 μM **15.** 120.6 μM **16.** 30.2 μM **17.** 124.4 μM **18.** 283.9 μM **19.** 294.3 μM **20.** 2.6 mM	Li et al. (2016a)
			Epicoccum nigrum	**13.** 30.3 μM **14.** 15.1 μM **15.** 7.5 μM **16.** <1.9 μM **17.** <1.9 μM **18.** 17.7 μM **19.** 36.8 μM **20.** 1.3 mM	

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Diaporthe maritima	*Picea rubens*/ needles	**21.** Phomopsolide A ($C_{15}H_{18}O_6$) **22.** Phomopsolide B ($C_{15}H_{20}O_6$) **23.** Phomopsolide C ($C_{15}H_{18}O_6$) **24.** Alpha pyrone ($C_{10}H_{10}O_4$)	*Microbotryum violaceum* *Saccharomyces cerevisiae*	**21.** 25 μM **22.** 250 μM **23.** 250 μM **24.** 250 μM	Tanney et al. (2016)
Pestalotiopsis foedan	*Bruguiera sexangula*/branch	**25.** (3*R*,4*R*,6*R*,7*S*)-7-hydroxyl-3,7-dimethyl-oxabicyclo[3.3.1]nonan-2-one ($C_{10}H_{16}O_3$) **26.** (3*R*, 4*R*)-3-(7-methylcyclohexenyl)-propanoic acid	*Botrytis cinerea*	**25.** 16.8 μM **26.** 3.1 μg ml^{-1}	Xu et al. (2016)
			Phytophthora nicotianae	**25.** 34.2 μM **26.** 6.3 μg ml^{-1}	
			Candida albicans	**25.** >542.8 μM **26.** 50 μg ml^{-1}	
Rhizopycnis vagum	*Nicotiana tabacum*/root	**27.** Rhizopycnin D ($C_{14}H_9ClO_5$) **28.** TMC-264 ($C_{16}H_{13}ClO_7$)	*Magnaporthe oryzae*	**27.** 33.8 μM **28.** 34 μM	Lai et al. (2016)
Fusarium sp.	*Ficus carica*/leaf	**29.** Helvolic acid methyl ester ($C_{34}H_{46}O_8$) **30.** Helvolic acid ($C_{33}H_{44}O_8$) **31.** Hydrohelvolic acid	*Botrytis cinerea*	**29.** 42.9 μM **30.** 44 μM **31.** 25 μg ml^{-1}	Liang et al. (2016)
			Colletotrichum gloeosporioides	**29.** 21.5 μM **30.** 22 μM **31.** 12.5 μg ml^{-1}	
			Fusarium oxysporum	**29.** 42.9 μM **30.** 22 μM **31.** 12.5 μg ml^{-1}	
			Fusarium graminearum	**29.** 21.5 μM **30.** 44 μM **31.** 25 μg ml^{-1}	
			Phytophthora capsici	**29.** 21.5 μM **30.** 22 μM **31.** 12.5 μg ml^{-1}	

Trichoderma sp.	*Myoporum bontioides*/root	**32.** Dichlorodiaportinolide ($C_{16}H_{14}Cl_2O_7$) **33.** Dichlorodiaportin ($C_{13}H_{12}Cl_2O_5$)	*Colletotrichum musae*	**32.** 64.2 μM **33.** 470 μM	Li et al. (2016b)
			Rhizoctonia solani	**32.** 16.1 μM **33.** 470 μM	
Trichoderma koningiopsis	*Panax notoginseng*	**34**. Koninginin O ($C_{16}H_{24}O_4$) **35**. Koninginin Q ($C_{17}H_{28}O_5$) **36**. 7-O-methylkoninginin D ($C_{17}H_{28}O_5$)	*Fusarium oxysporum,*	**34.** 456.6 μM **35.** 409.7 μM **36.** NA	Liu et al. (2016a)
			Plectosphaerella cucumerina	**34.** 456.6 μM **35.** 409.7 μM **36.** 409.7 μM	
Trichoderma koningiopsis	*Panax notoginseng*	**37.** Koningiopisin B ($C_{20}H_{34}O_5$) **38.** Koningiopisin C ($C_{16}H_{24}O_4$) **39.** Koningiopisin H ($C_{16}H_{24}O_4$)	*Alternaria panax*	**37.** 180.5 μM **38.** 228.3 μM **39.** 228.3 μM	Liu et al. (2016b)
			Fusarium oxysporum	**37.** NA **38.** 114.1 μM **39.** NA	
			Plectosphaerella cucumerina	**37.** NA **38.** 57.1 μM **39.** NA	
			Fusarium solani	**37.** NA **38.** 114.1 μM **39.** NA	

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Pestalotiopsis sp.	*Dendrobium officinale*/shoots	**40.** (4*S*,6*S*)-6-[(1*S*,2*R*)-1,2-dihydroxypentyl]-4-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one ($C_{11}H_{20}O_6$) **41.** (6*S*,2*E*)-6-hydroxy-3-methoxy-5-oxodec-2-enoic acid ($C_{11}H_{18}O_5$) **42.** LL-P880γ **43.** LL-P880α **44.** Ergosta-5,7,22-trien-3β-ol	*Candida albicans*	**40.** 25.2 μM **41.** 54.3 μM **42.** 12.5 μg ml^{-1} **43.** 6.3 μg ml^{-1} **44.** >400 μg ml^{-1}	Wu et al. (2016)
			Cryptococcus neoformans	**40.** 12.6 μM **41.** 54.3 μM **42.** 50 μg ml^{-1} **43.** 3.1 μg ml^{-1} **44.** 200 μg ml^{-1}	
			Trichophyton rubrum	**40.** 100.7 μM **41.** 27.1 μM **42.** 50 μg mL^{-1} **43.** 50 μg mL^{-1} **44.** >400 μg mL^{-1}	
			Aspergillus fumigatus	**40.** 100.7 μM **41.** 13.6 μM **42.** 50 μg ml^{-1} **43.** 25 μg ml^{-1} **44.** >400 μg ml^{-1}	
Aspergillus terreus	*Carthamus lanatus*/roots	**45.** (22*E*,24*R*)-stigmasta5,7,22-trien-3-β-ol **46.** (*R*)-methyl 4-ethoxy-2-(4-hydroxy-3-(3-methylbut-2-enyl) benzyl)-3-(4-hydroxyphenyl)-5-oxo-2,5-dihydrofuran-2-carboxylate (aspernolide F) ($C_{26}H_{28}O_7$)	*Cryptococcus neoformans*	**45.** 4.4 μg mL^{-1} **46.** 11.5 μM	Ibrahim et al. (2015)

Mycosphaerella sp.	*Eugenia bimarginata*/leaf	**47.** (2*S*,3*R*,4*R*)-(*E*)-2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxoeicos-6,12-dienoic acid ($C_{21}H_{37}NO_6$) **48**. Myriocin ($C_{21}H_{39}NO_6$)	*Cryptococcus neoformans*	**47.** 3.3 μM **48.** 1.2 μM	Pereira et al. (2015)
			Cryptococcus gattii	**47.** 6.3 μM **48.** 1.24 μM	
Xylaria sp.	*Azadirachta indica*/stems	**49.** Guaiane-2,10,11,12-tetraol ($C_{15}H_{28}O_4$) **50.** Guaiane-2,4,10,11,12-pentaol ($C_{15}H_{28}O_5$) **51.** Guaiane-4,5,10,11,12-pentaol ($C_{15}H_{28}O_5$) **52.** Guaiane-1,5,10,11,12- pentaol ($C_{15}H_{28}O_5$) **53.** 11-methoxyguaiane-4,10,12- triol ($C_{16}H_{30}O_4$)	*Candida albicans*	**49.** 1.9 mM **50.** 443.9 μM **51.** 221.9 μM **52.** 111 μM **53.** 111.7 μM	Huang et al. (2015)
			Aspergillus niger	**49.** 939.9 μM **50.** >1.8 mM **51.** 221.9 μM **52.** 887.7 μM **53.** 893.9 μM	
			Pyricularia oryzae	**49.** 469.9 μM **50.** 887.7 μM **51.** 887.7 μM **52.** 111 μM **53.** 893.9 μM	
			Hormodendrum compactum	**49.** 939.9 μM **50.** 887.7 μM **51.** 221.9 μM **52.** 221.9 μM **53.** 893.9 μM	
Trichoderma brevicompactum	*Allium sativum*	**54.** 4β-acetoxy-12,13- epoxy-Δ^9-trichothecene (trichodermin) ($C_{17}H_{24}O_4$)	*Rhizoctonia solani* *Botrytis cinerea* *Colletotrichum lindemuthianum*	855.1 nM 6.9 μM 87.6 μM	Shentu et al. (2014)

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Xylaria sp.	*Toona sinensis*/ leaves	**55.** Cytochalasin Z_{27} ($C_{28}H_{33}NO_6$) **56.** Cytochalasin Z_{28} ($C_{28}H_{33}NO_6$) **57.** *seco*-Cytochalasin E ($C_{29}H_{37}NO_8$) **58.** Cytochalasin Z_{18} ($C_{31}H_{43}NO_9$) **59.** Cytochalasin E ($C_{28}H_{33}NO_7$)	*Gibberella saubinetti*	**55.** 50 μM **56.** 12.5 μM **57.** 100 μM **58.** >100 μM **59.** 100 μM	Zhang et al. (2014b)
			Alternaria solani	**55.** 50 μM **56.** 50 μM **57.** 100 μM **58.** 50 μM **59.** 50 μM	
			Botrytis cinerea	**55.** 100 μM **56.** 100 μM **57.** 100 μM **58.** >100 μM **59.** 100 μM	
			Fusarium solani	**55.** 100 μM **56.** 50 μM **57.** >100 μM **58.** 100 μM **59.** >100 μM	
Botryosphaeria dothidea	*Melia azedarach*/ bark	**60.** Pycnophorin ($C_{27}H_{40}O_4$) **61.** Stemphyperylenol ($C_{20}H_{16}O_6$) **62.** Chaetoglobosin C ($C_{32}H_{36}N_2O_5$) **63.** Djalonensone ($C_{15}H_{12}O_5$) **64.** Alternariol ($C_{14}H_{10}O_5$) **65.** 5′-methoxy-6-methylbiphenyl-3,4,3′-triol ($C_{14}H_{14}O_4$)	*Botrytis cinerea*	**60.** 100 μM **61.** 100 μM **62.** 200 μM **63.** 25 μM **64.** NA **65.** NA **66.** 100 μM **67.** 100 μM **68.** 50 μM	Xiao et al. (2014a)

		66. *β*-sitosterol glucoside **67.** 5-(hydroxymethyl)-1*H*-pyrrole-2-carbaldehyde ($C_6H_7NO_2$) **68.** 5-hydroxymethylfurfural ($C_6H_6O_3$)	*Alternaria solani*	**60.** 6.3 μM **61.** 1.6 μM **62.** 12.5 μM **63.** 25 μM **64.** 12.5 μM **65.** 50 μM **66.** 6.3 μM **67.** 50 μM **68.** 6.3 μM	
Pezicula sp.	*Forsythia viridissima*/twigs	**69.** Mellein ($C_{10}H_{10}O_3$)	*Botrytis cinerea*, *Colletotrichum orbiculare*, *Verticillium dahliae*, *Fusarium oxysporum* f. sp. *cucumerinum*, *Pyricularia oryzae*, *Pestalotia diospyri*, *Pythium ultimum*, *Sclerotinia sclerotiorum*, *Fulvia fulva*	272.9 μM - 846.9 μM - 916.9 μM - 892.9 μM - 666.9 μM - 903.8 μM - 703.6 μM - 1.2 mM - 258.1 μM	Wang et al. (2014)

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Xylaria sp.	*Azadirachta indica*/stem	**70.** (1*S*,4*S*,5*R*,7*R*,10*R*,11*R*)-Guaiane-5,10,11,12-tetraol ($C_{15}H_{28}O_4$) **71.** (1*S*,4*S*,5*S*,7*R*,10*R*,11*S*)-Guaiane-1,10,11,12-tetraol ($C_{15}H_{28}O_4$) **72.** (1*S*,4*S*,5*R*,7*R*,10*R*,11*S*)-Guaiane-5,10,11,12-tetraol ($C_{15}H_{28}O_4$) **73.** (1*S*,4*S*,5*S*,7*R*,10*R*,11*R*)-Guaiane-1,10,11,12-tetraol ($C_{15}H_{28}O_4$) **74.** (1*R*,3*S*,4*R*,5*S*,7*R*,10*R*,11*S*)-Guaiane-3,10,11,12-tetraol ($C_{15}H_{28}O_4$) **75.** (1*R*,3*R*,4*R*,5*S*,7*R*,10*R*,11*R*)-Guaiane-3,10,11,12-tetraol ($C_{15}H_{28}O_4$) **76.** (1*R*,4*S*,5*S*,7*S*,9*R*,10*S*,11*R*)-Guaiane-9,10,11,12-tetraol ($C_{15}H_{28}O_4$) **77.** (1*R*,4*S*,5*S*,7*R*,10*R*,11*S*)-Guaiane-10,11,12-triol ($C_{15}H_{28}O_3$) **78.** (1*R*,4*S*,5*S*,7*R*,10*R*,11*R*)-Guaiane-10,11,12-triol ($C_{15}H_{28}O_3$) **79.** 14α,16-Epoxy-18-norisopimar-7-en-4α-ol ($C_{19}H_{30}O_2$) **80.** 16-O-Sulfo-18-norisopimar-7-en-4α,16-diol ($C_{19}H_{32}O_5S$) **81.** 9-deoxy-hymatoxin A ($C_{20}H_{30}O_6S$)	*Candida albicans*	**70.** 939.9 μM **71.** 117.5 μM **72.** 469.9 μM **73.** 234.9 μM **74.** 234.9 μM **75.** 469.9 μM **76.** 117.5 μM **77.** 499.3 μM **78.** 499.3 μM **79.** 220.4 μM **80.** 171.8 μM **81.** 40.2 μM	Wu et al. (2014)

			Aspergillus niger	**70.** 469.9 µM **71.** 234.9 µM **72.** 939.9 µM **73.** 234.9 µM **74.** 1.9 mM **75.** 1.9 mM **76.** 469.9 µM **77.** 998.5 µM **78.** >2 mM **79.** 220.4 µM **80.** 343.6 µM **81.** 80.3 µM	
			Pyricularia oryzae	**70.** 939.9 µM **71.** 939.9 µM **72.** 469.9 µM **73.** 939.9 µM **74.** 939.9 µM **75.** 469.9 µM **76.** 1.87 mM **77.** 1.99 mM **78.** 998.5 µM **79.** 881.4 µM **80.** 85.9 µM **81.** 40.1 µM	

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
			Fusarium avenaceum	**70.** 1.9 mM **71.** >1.9 mM **72.** 1.9 mM **73.** >1.9 mM **74.** >1.9 mM **75.** 1.9 mM **76.** >1.9 mM **77.** >2 mM **78.** 2 mM **79.** 220.4 µM **80.** 343.6 µM **81.** 160.6 µM	
			Hormodendrum compactum	**70.** 469.9 µM **71.** 235 µM **72.** 939.9 µM **73.** 939.9 µM **74.** 469.9 µM **75.** 469.9 µM **76.** 939.9 µM **77.** 499.3 µM **78.** 998.5 µM **79.** 440.7 µM **80.** 171.8 µM **81.** 160.6 µM	
Bipolaris sp.	*Gynura hispida*/ leaf	**82.** Bipolamides A ($C_{18}H_{29}NO_4$) **83.** Bipolamides B ($C_{12}H_{19}NO$)	*Candida albicans* OUT 6266	**82.** >395.8 µM **83.** 662.3 µM	Siriwach et al. (2014)
			Aspergillus niger ATCC 6275	**82.** >395.8 µM **83.** 331.1 µM	

			Rhizopus oryzae ATCC 10404	**82.** >395.8 μM **83.** 331.1 μM	
			Geotrichum candidum IFO 4598	**82.** >395.8 μM **83.** >662.3 μM	
			Cladosporium cladosporioides FERMS-9	**82.** >395.8 μM **83.** 82.8 μM	
			Alternaria mali NBRC 8984	**82.** >395.8 μM **83.** >662.3 μM	
			Cladosporium cucumerinum NBRC 6370	**82.** >395.8 μM **83.** 165.6 μM	
			Fusarium oxysporum NBRC 31224	**82.** >395.8 μM **83.** 662.3 μM	
Berkleasmium sp.	*Dioscorea zingiberensis*/ rhizomes	**84.** Diepoxin ζ ($C_{20}H_{14}O_7$) **85**. Palmarumycin C11 ($C_{20}H_{14}O_5$) **86**. Palmarumycin C12 **87**. Cladospirone B ($C_{20}H_{14}O_6$) **88**. Palmarumycin C6 **89**. 1,4,7β-trihydroxy8(spirodioxy-1′,8′-naphthyl)-7,8-dihydronaphthalene **90**. Palmarumycin C8 ($C_{20}H_{13}ClO_6$)	*Magnaporthe oryzae*	**84**. 286.6 μM **85**. 96.6 μM **86**. 76.7 μg mL^{-1} **87**. 185 μM **88**. 124.5 μg mL^{-1} **89**. 35.9 μg mL^{-1} **90**. 23.7 μM	Shan et al. (2014)
Exserohilum sp.	*Acer truncatum*/ leaf	**91.** Exserolide C ($C_{16}H_{20}O_6$) **92.** (12*R*)-12-hydroxymonocerin	*Fusarium oxysporum*	**91.** 64.9 μM **92.** 20 μg mL^{-1}	Li et al. (2014)

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Aspergillus sp.	*Melia azedarach*/ stem bark	**93.** Dianhydro-aurasperone C ($C_{31}H_{24}O_{10}$) **94.** Isoaurasperone A ($C_{32}H_{26}O_{10}$) **95.** Fonsecinone A ($C_{32}H_{26}O_{10}$) **96.** Asperpyrone A ($C_{31}H_{24}O_{10}$) **97.** Asperazine ($C_{40}H_{36}N_6O_4$) **98.** Rubrofusarin B ($C_{15}H_{12}O_5$) **99.** (*R*)-3-hydroxybutanonitrile	*Gibberella saubinetti*	**93.** NA **94.** 25 μM **95.** 50 μM **96.** 25 μM **97.** 25 μM **98.** NA **99.** 12.5 μM	Xiao et al. (2014b)
			Magnaporthe grisea	**93–94.** NA **95.** 12.5 μM **96–98.** NA **99.** 25 μM	
			Botrytis cinerea	**93–94.** NA **95.** 25 μM **96.** NA **97.** 50 μM **98–99.** NA	
			Colletotrichum gloeosporioides	**93.** NA **94.** 25 μM **95–98.** NA **99.** 50 μM	
			Alternaria solani	**93.** NA **94.** 12.5 μM **95–97.** 6.3 μM **98.** 12.5 μM **99.** 25 μM	

Trichothecium sp.	*Phyllanthus amarus*/leaf	**100.** Trichothecinol-A ($C_{19}H_{24}O_6$)	*Saccharomyces cerevisiae* *Cryptococcus albidus* var. *diffluens* NCIM 3371 *Cryptococcus albidus* var. *diffluens* NCIM 3372 *Fusarium oxysporum* *Aspergillus flavus* *Trichoderma reesei* *Penicillium expansum* *Trichoderma viride* *Paecilomyces variotii* *Aspergillus niger*	49.3 μM 11.7 μM 7.17 μM 20.6 μM 69.7 μM 43.1 μM 19 μM 105.1 μM 24.9 μM 26.2 μM	Taware et al. (2014)
Pestalotiopsis mangiferae	*Mangifera indica*/leaves	**101.** 4-(2,4,7-trioxa-bicyclo[4.1.0] heptan-3-yl) phenol ($C_{10}H_{10}O_4$)	*Candida albicans*	200.8 nM	Subban et al. (2013)
Chaetomium globosum	*Ginkgo biloba*/leaf	**102.** 1,2-benzenedicarboxaldehyde-3,4,5-trihydroxy-6-methyl (flavipin) ($C_9H_8O_5$)	*Fusarium graminearum* *Sclerotinia sclerotiorum* *Rhizoctonia solani* *Alternaria solani* *Phytophthora capsici*	3.7 μM 18.8 μM 13.4 μM 63 μM 14.1 μM	Xiao et al. (2013)
Chaetomium cupreum	*Macleaya cordata*	**103.** Ergosta-5,7,22-trien-3beta-ol ($C_{28}H_{44}O$)	*Sclerotinia sclerotiorum* *Botrytis cinerea*	315.2 μM 479 μM	Wang et al. (2013)
Pestalotiopsis fici	*Camellia sinensis*/branches	**104..** Ficipyrone A ($C_{14}H_{22}O_5$)	*Gibberella zeae*	15.9 μM	Liu et al. (2013)
Xylaria feejeensis	*Croton lechleri*/ stem	**105.** (4*S*,7*S*,8*S*,9*R*)-4-*O*-succinyl-7,8-dihydroxy-9-heptyl-nonen-9-olide (xyolide) ($C_{20}H_{32}O_8$)	*Pythium ultimum*	425 μM	Baraban et al. (2013)

(continued)

Table 11.2 (continued)

Fungal endophyte taxa	Medicinal Plant/ Tissue	Compounds isolated	Biological activity	EC_{50}/ IC_{50}/MIC	Reference
Phomopsis sp.	*Aconitum carmichaeli*/ stems	**106.** (14*β*,22*E*)-9,14-dihydroxyergosta-4,7,22-triene-3,6-dione ($C_{28}H_{40}O_4$) **107.** (5*α*,6*β*,15*β*,22*E*)-6-ethoxy-5,15-dihydroxyergosta-7,22-dien-3-one ($C_{30}H_{48}O_4$) **108.** Calvasterol A ($C_{28}H_{38}O_3$) **109.** Calvasterol B ($C_{28}H_{40}O_4$) **110.** Ganodermaside D ($C_{28}H_{40}O_2$)	*Candida albicans*	**106.** 145.3 μM **107.** 270.8 μM **108.** >1.2 mM **109.** 290.5 μM **110.** 1.3 mM	Wu et al. (2013a)
			Aspergillus niger	**106.** 290.5 μM **107.** >1.1 mM **108.** 605.8 μM **109.** 581 μM **110.** 626.5 μM	
			Pyricularia oryzae	**106.** >1.2 mM **107.** >1.1 mM **108.** 302.9 μM **109.** >1.2 mM **110.** >1.3 mM	
			Fusarium avenaceum	**106.** 1.2 mM **107.** 270.8 μM **108.** 151.4 μM **109.** 1.2 mM **110.** 156.6 μM	
			Hormodendrum compactum	**106.** 145.3 μM **107.** 541.6 μM **108.** >1.2 mM **109.** 581 μM **110.** 313.3 μM	

			Trichophyton gypseum	**106.** >1.2 mM **107.** 1.08 mM **108.** 605.8 μM **109.** >1.7 μM **110.** 1.3 mM	
Aspergillus sp.	*Gloriosa superba*/seeds	**111.** 6-Methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene11-one-5,6,7,8-tetralene-7-acetamide ($C_{18}H_{19}NO_5$)	*Saccharomyces cerevisiae* *Candida albicans* *Cryptococcus gastricus*	75.9 μM 38 μM 151.8 μM	Budhiraja et al. (2013)
Hyalodendriella sp.	Hybrid 'Neva' (*Populus deltoides* Marsh × *P. nigra* L)/ stems	**112.** 2-chloro-3,7-dihydroxy-9-methoxy-1-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (palmariol B) ($C_{15}H_{11}ClO_5$) **113.** 4,8-dihydroxy-3-methylbenzopyran-1-one (4-hydroxymellein) ($C_{10}H_{10}O_4$) **114.** 3,7-dihydroxy-9-methoxy-1-methyl-6*H*-dibenzo [*b*,*d*]pyran-6-one (alternariol 9-methyl ether) ($C_{15}H_{12}O_5$) **115.** 1,7-dihydroxy-3,9-dimethoxy-4a-methyl-6*H*-dibenzo[*b*,*d*]pyran-2,6 (4a*H*)- dione (botrallin) ($C_{16}H_{14}O_7$)	*Magnaporthe oryzae*	**112.** 387.1 μM **113.** 584 μM **114.** 452.5 μM **115.** 336.8 μM	Meng et al. (2012)
Alternaria sp.	*Trixis vauthieri*/ leaf	**116.** Altenusin ($C_{15}H_{14}O_6$)	Eleven clinical *Paracoccidioides brasiliensis* strains	6.5–107.5 μM	Johann et al. (2012)

NA: inactive. EC_{50} - Half maximal effective concentration. IC_{50} - Half maximal inhibitory concentration. MIC - Minimum inhibitory concentration.

bioactive culture which, after threefold dilution, completely inhibited in vitro the mycelial growth and conidia germination of *F. graminearum.* The in vivo protective efficacy of the diluted broth was 54.9% and its curative efficacy 48.8%. Bioassay-guided fractionation resulted in the isolation of 1,2-benzenedicarboxaldehyde-3,4,5-trihydroxy-6-methyl (flavipin) (**102**) that inhibited the growth of the plant-pathogenic fungi *F. graminearum* (EC_{50} value of 3.7 μM), *S. sclerotiorum* (EC_{50} value of 18.8 μM), *Rhizoctonia solani* (EC_{50} value of 13.4 μM), *P. capsici* (EC_{50} value of 14.1 μM), and *Alternaria solani* (EC_{50} value of 63 μM) (Xiao et al. 2013). In a more recent work, Zhao et al. (2017) reinvestigated *Chaetomium globosum* CDW7 and reported the isolation of six known compounds, namely, chaetoglobosins **A**–**E** and **Vb**. Chaetoglobosins **A** (**7**) and **D** (**8**) exhibited inhibitory activity against *S. sclerotiorum* with IC_{50} values of 0.6 and 1.2 μM, respectively (Zhao et al. 2017).

Zhang et al. (2013) studied the endophytic fungi *Chaetomium globosum*, associated with *G. biloba* growing in China, and isolated the alkaloids chaetoglobosins A, C, D, E, G, and R (**120**–**125**) along with ergosterol (**126**), allantoin (**127**), and uracil (**128**). Chaetoglobosins A, C, D, E, G, and R (**120**–**125**) showed significant growth inhibitory activity against the phytopathogenic fungi *Rhizopus stolonifer* and *Coniothyrium diplodiella* at a concentration of 20 μg/disc. Cao et al. (2016) reported that *Nodulisporium* sp. A2, associated with leaves of *G. biloba*, as producer of the sporothriolide (**129**), a metabolite produced by the fungus, showed potent antifungal activity against *Rhizoctonia solani* and *Sclerotinia sclerotiorum* and inhibits conidium germination of *Magnaporthe oryzae* in vitro and in vivo.

Xu et al. (2016) described a new monoterpene lactone (3*R*,4*R*,6*R*,7*S*)-7-hydroxyl-3,7-dimethyl-oxabicyclo[3.3.1]nonan-2-one (**25**) and the known compound (3*R*, 4*R*)-3-(7-methylcyclohexenyl)-propanoic acid (**26**) from *Pestalotiopsis foedan*, an endophyte fungus obtained from the branch of *Bruguiera sexangula* occurring in China. Both compounds exhibited strong antifungal activities against *B. cinerea* and *Phytophthora nicotianae* with MIC values of 3.1 and 6.3 μg mL^{-1}, respectively, values close to the MIC of the antifungal drug control ketoconazole (3.1 μg mL^{-1}). Compound **26** also displayed modest antifungal activity against *C. albicans,* with a MIC value of 50 μg mL^{-1} (Xu et al. 2016).

Bioassay-guided fractionation of the endophytic fungus *Phoma* sp., isolated from roots of *Eleusine coracana*, resulted in the identification of four antifungal compounds, 3-hydroxy-4-(3-hydroxyphenyl)-2-quinolonemonohydrate (viridicatol alkaloid) (**130**), 3-acetyl-5-sec-butyltetramicacid (tenuazonic acid) (**131**), alternariol **(132)**, and alternariol-5-O-methyl ether or djalonensone(3,7-dihydroxy-9-methoxy-1-methyl-6H-dibenzo[b,d]pyran-6-one) (**133**). The antifungal activity of the compounds **130**–**133** was evaluated using the agar disc diffusion method (20 μl of 5 mg mL^{-1}) and produced growth inhibition zones of 1.8, 2, 1.5, and 1.5 mm, respectively (Mousa et al. 2015). The extract of the endophytic *Seimatosporium* sp., isolated from *Salsola oppositifolia* (Spain), was further purified to give pure new compound, 5,6,7,8-tetrahydro-1,5-dihydroxy-3-methoxy-8-oxonaphthalene-2-carbaldehyde (seimatorone) (**134**), and the known compounds, 1-(2,6-dihydroxyphenyl)-3-hydroxybutan-1-one (**135**), 1-(2,6-dihydroxyphenyl)butan-1-one (**136**), 1-(2-hydroxy-6-methoxyphenyl) butan-1-one (**137**), 5-hydroxy-2-methyl-4*H*-chromen-4-one (**138**), 2,3-dihydro-5-hy-

droxy-2-methyl-4*H*-chromen-4-one (**139**), 8-methoxynaphthalen-1-ol (**140**), nodulisporin A (**141**), nodulisporin B (**142**), and daldinol (**143**). Seimatorone demonstrated antifungal activity against *Microbotryum violaceum* in the agar diffusion assay with partial inhibition, once there was some growth within the zone of inhibition (Hussain et al. 2015).

Chapla et al. (2014a) characterized the new compound, 2-phenylethyl 1*H*-indol-3-yl-acetate (**144**), and seven known compounds, uracil (**145**), cyclo-(*S**-Pro-*S**-Tyr) (**146**), cyclo-(*S**-Pro-*S**-Val) (**147**), 2(2-aminophenyl)-acetic acid (**148**), 2(4-hydroxyphenyl)acetic acid (**149**), 4-hydroxybenzamide (**150**), and 2-(2-hydroxyphenyl)-acetic acid (**151**), from the endophytic fungus *Colletotrichum gloeosporioides* associated with leaves of *Michelia champaca* (*Magnoliaceae*) growing in São Paulo, Brazil. All compounds were evaluated for their antifungal activities against two phytopathogenic fungi, *C. cladosporioides* and *C. sphaerospermum*, using the Thin-layer chromatography (TLC) diffusion method at 100 μg/spot and nystatin at 1 μg/spot as positive control. Compounds **144**, **150,** and **151** exhibited activity against both fungal species, while compound **149** was highly active against *C. cladosporioides* but showed only moderate activity on *C. sphaerospermum*. When compounds **144**, **149**, **150,** and **151** were evaluated at doses ranging from 1 to 100 μg/spot, **144** exhibited potent antifungal activity at 5 μg, which was similar to that observed for the positive control (nystatin), demonstrating the potential of **144** as an antifungal agent. Compounds **149**, **150,** and **151** exhibited moderate antifungal activity at 25 μg (Chapla et al. 2014a).

The ethyl acetate extract of endophytic fungus *Coniothyrium* sp., isolated from *Salsola oppositifolia* (Canary Islands), afforded the known hydroxyanthraquinones, pachybasin (**152**), 1,7-dihydroxy-3-methyl-9,10-anthraquinone (**153**), phomarin (**154**), and 1-hydroxy-3-hydroxymethyl-9,10-anthraquinone (**155**), together with four new derivatives having a tetralone moiety, namely, coniothyrinones A–D (**156**–**159**). When tested in the agar diffusion assay (0.05 mg) on *Microbotryum violaceum*, *B. cinerea*, and *Septoria tritici*, compounds **154**, **155**, and **156** showed strong antifungal activity against *M. violaceum* (10, 8, and 7.5 mm of the zone of inhibition, respectively) and *B. cinerea* (9, 9, and 12.5 mm of the zone of inhibition, respectively) (Sun et al. 2013).

Huang et al. (2015) obtained five new guaiane sesquiterpenes **49–53** from the culture broth of the endophytic fungus *Xylaria* sp. YM 311647, which were isolated from *Azadirachta indica*. The compounds were evaluated against the pathogenic fungi *C. albicans*, *A. niger*, *P. oryzae*, *F. avenaceum*, and *Hormodendrum compactum* by means of the broth microdilution method. All compounds exhibited moderate or weak antifungal activities against *P. oryzae* and *H. compactum* with MIC values varying from 111 to 939.9 μM, with compound **52** being the most active against *P. oryzae*. Compounds **51** and **52** exhibited moderate antifungal activities against *H. compactum* with MIC value 221.9 μM. In addition, compounds **52** and **53** showed the most potent antifungal activities against *C. albicans* with MIC values of 110.96 and 111.7 μM, respectively. Compound **51** showed moderate inhibitory activities against *C. albicans*, *A. niger*, and *H. compactum* with MIC value of

221.9 μM. None of the compounds showed activity against *F. avenaceum* (Huang et al. 2015).

Two new tetranorlabdane diterpenoids, named botryosphaerin G (**160**) and H (**161**), along with seven known tetranorlabdane diterpenes, 13,14,15,16-tetranorlabd-7-en-19,6β:12,17-diolide (**162**), botryosphaerin A (**163**), 3a,10b-dimethyl-1,2,3,3a,5a,7,10b,10c-octahydro-5,8-dioxa-acephenanthrylene-4,9-dione (**164**), acrostalidic acid (**165**), botryosphaerin B (**166**), LL-Z1271β (**167**), and acrostalic acid (**168**), were isolated from the endophytic fungus *Botryosphaeria* sp. P483 associated with the Chinese medicinal plant *Huperzia serrata*. Compounds **161** and **162** showed antifungal activity against phytopathogenic fungi *Gaeumannomyces graminis*, *Fusarium moniliforme*, *F. solani*, *F. oxysporum*, and *Pyricularia oryzae* using the disk diffusion method at 100 μg/disk (Chen et al. 2015).

Pereira et al. (2015) demonstrated that the crude extract of the endophytic fungus *Mycosphaerella* sp. UFMGCB 2032, recovered from *Eugenia bimarginata* (Brazil), exhibited outstanding antifungal activity against *Cryptococcus neoformans* and *C. gattii*, with MIC values of 31.2 μg mL^{-1} and 7.8 μg mL^{-1}, respectively. The fractionation of this extract afforded two eicosanoic acids, (2*S*,3*R*,4*R*)-(*E*)-2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxoeicos-6,12-dienoic acid (**47**) with MIC values of 3.3 and 6.3 μM against *C. neoformans* and *C. gattii*, respectively, and myriocin (**48**), with MIC values of 1.24 μM to both targets. Nalli et al. (2015) reported the identification of four new bioactive metabolites, phialomustin A–D (**169–172**), isolated from the endophytic fungus *Phialophora mustea* associated with the corms of *Crocus sativus.* Compounds **171** and **172** showed antifungal activities against *C. albicans* with IC_{50} values of 14.3 and 73.6 μM, respectively. Compound **171** was active against *A. fumigatus*, *A. parasiticus*, and *A. flavus* with IC_{50} values of 60.6, 35.2, and 84.4 μM, respectively (Nalli et al. 2015).

The chemical evaluation of the crude extract of the endophytic *Guignardia* sp., from *Euphorbia sieboldiana* leaves, led to the isolation of nine new meroterpenes, guignardones J-L (**173–175**), 13-hydroxylated guignardone A (**176**), 12-hydroxylated guignardone A (**177**), 17-hydroxylated guignardone A (**178**), guignardones M-O (**179–181**), and a new dioxolanone derivative, 10-hydroxylated guignardianone C (**182**), together with seven known compounds, guignardones A-C (**183–185**), guignardones G and H (**186–187**), guignardic acid (**188**), and palmarumycin C11 (**189**). The compounds were evaluated for their inhibitory effects alone and with fluconazole on the growth and biofilms of *C. albicans*. At 6.3 μg mL^{-1} concentration, combined with 0.031 μg mL^{-1} of fluconazole, compounds **180** and **188** showed inhibition on the growth of *C. albicans* with fractional inhibitory concentration index values of 0.2 and 0.2, respectively (Li et al. 2015b).

Altenusin (**190**), isoochracinic acid (**191**), altenuic acid (**192**), and 2,5-dimethyl-7-hydroxychromone (**193**) were isolated from *Alternaria alternata* associated with *Terminalia chebula* (Thailand). All compounds were investigated for their activity on *Candida albicans* using disc diffusion assay. Altenusin (**190**) exhibited weak activity against *C. albicans* with an unclear inhibition zone diameter of 8.3 mm (at the concentration of 256 μg/disc). In the presence of a subinhibitory concentration

of ketoconazole at 0.1 μg mL^{-1}, altenusin produced a clear inhibition zone diameter of 19.2 mm (Phaopongthai et al. 2013).

Li et al. (2014) obtained six new isocoumarin derivatives, exserolides A–F (**194**–**199**), together with four known metabolites, monocerin (**200**), 11-hydroxymonocerin (**201**), (12R)–(**202**), and (12S)-12-hydroxymonocerin (**203**). They were isolated from the ethyl acetate (EtOAc) extract of endophytic fungus *Exserohilum* sp., recovered from the leaves of *Acer truncatum* (China). All the compounds were tested for their antifungal activity against the plant pathogenic fungus *F. oxysporum*. Compounds **196** and **202** displayed MIC value of 20 μg mL^{-1}, while the positive control amphotericin B showed a MIC value of 0.6 μg mL^{-1} (Li et al. 2014). Two compounds named *cis*-4-acetoxyoxymellein (**204**) and 8-deoxy-6-hydroxy-*cis*-4-acetoxyoxymellein (**205**) were identified by Hussain et al. (2014) from an unidentified endophytic fungus isolated from *Meliotus dentatus*. Both compounds showed significant antifungal effect toward *M. violaceum*, *B. cinerea*, and *Septoria tritici* when tested in the agar diffusion assay.

Carvalho et al. (2016) reported the identification of the compounds (−)-5-methylmellein (**206**) and (−)-(3*R*)-8-hydroxy-6-methoxy-3,5-dimethyl-3,4-dihydroisocoumarin (**207**) from the endophytic *Biscogniauxia mediterranea* EPU38CA associated with *Echinacea purpurea* (USA). The compounds were evaluated against plant pathogenic fungi at a dose of 300 μM, with the compound **206** showing weak activity against *P. obscurans*, *P. viticola*, and *F. oxysporum* with 43.5, 36, and 5% of inhibition, respectively. Using the same methodology, compound **207** showed antifungal activity against *B. cinerea* (58%), *P. viticola* (50%), and *P. obscurans* (70%). *B. mediterranea* was also isolated from the plant *Opuntia humifusa* (USA) by Silva-Hughes et al. (2015) and yielded (−)-5-methylmellein (**208**), a compound that displayed moderate antifungal activity against the phytopathogenic fungi *P. obscurans* (63.5% growth inhibition) and *F. oxysporum* (20.1%).

Kajula et al. (2016) identified three new epithiodiketopiperazine natural products, outovirin A–C (**209**–**211**), produced by the endophytic fungus *Penicillium raciborskii* isolated from *Rhododendron tomentosum*. The authors evaluated the antifungal activity of the compounds against *F. oxysporum*, *B. cinerea*, and *Verticillium dahliae* by microspectrophotometry using a dose-response growth inhibition assay. Outovirin C inhibited growth of all fungal isolates at a low concentration of 0.4 mM, but a more significant growth inhibition was observed at the higher concentration of 0.8 mM. This compound was most active against *B. cinerea* (57% inhibition) and slightly less effective against *V. dahliae* (45% inhibition) (Kajula et al. 2016).

Four new compounds, murranofuran A (**212**), murranolide A (**213**), murranopyrone (**214**), and murranoic acid A (**215**), along with six known metabolites, *N*-(2-hydroxy-6-methoxyphenyl)acetamide (**216**), curvularin (**217**), (*S*)-dehydrocurvularin (**218**), pyrenolide A (**219**), modiolide A (**220**), and 8-hydroxy-6-methoxy-3-methylisocoumarin (**221**), were identified from the *Curvularia* sp., an endophytic fungus isolated from *Murraya koenigii* (Bangladesh). The compounds were subjected to motility, inhibitory, and zoosporicidal activity tests

against *Phytophthora capsici* at different concentration and time-course activities. The most noticeable zoospore motility-inhibitory activity was exhibited by pyrenolide A (**219**), where the highest activity (100%) was achieved at a very low concentration (0.5 μg mL^{-1}) within a short time (30 min). Compounds **213**, **214**, **217**, **218**, **220**, and **221** exhibited zoospore motility impairment activity, but with IC_{50} values in the range 50–100 μg mL^{-1} (Mondol et al. 2017).

Silva et al. (2017a) described the isolation, structure, and antifungal activity of three new isoaigialones, A–C (**222**–**224**), along with aigialone (**225**) from the endophytic fungus *Phaeoacremonium* sp. isolated from leaves of *Senna spectabilis* (Brazil). Using direct bioautography all the compounds were evaluated against *C. cladosporioides* and *C. sphaerospermum*. The compounds **223** and **225** exhibited antifungal activity, with a detection limit of 5 μg/spot, for both species of *Cladosporium*, while compound **224** displayed weak activity (detection limit >5 μg/spot), with a detection limit of 25 μg/spot.

The compounds epicolactone (**226**) and epicoccolides A and B (**227**–**228**), together with seven known metabolites, were obtained from the endophytic fungus *Epicoccum* sp. CAFTBO isolated from *Theobroma cacao*. The compounds **226**–**228** exhibited antifungal activity in the agar diffusion test against *Pythium ultimum* and *Rhizoctonia solani* with MIC values of 20–80 μg/disk (Talontsi et al. 2013).

11.4 Antiviral Compounds

Viral diseases are among the greatest concerns among the infectious diseases. WHO has released a list of priority diseases and pathogens for the year 2018 and among these diseases are Crimean-Congo hemorrhagic fever, Ebola, Zika, and Chikungunya virus (OPAS - OMS 2018). Thus, recent research attempts to identify antiviral compounds to produce vaccines, aiming at an immunization of the population.

As already mentioned, endophytic fungi are a promising source of biologically active secondary metabolites with numerous applications, including the production of antiviral compounds (Pamphile et al. 2017). However, there had been few reports on antiviral metabolites from endophytic fungi, even though those found show promising results (Kaul et al. 2012). Zhang et al. (2011a, b) isolated from the inner shell of *Aegiceras corniculatum* the endophytic fungus *Emericella* sp. that can produce two isoindolone derivatives. These two substances showed moderate antiviral activity with IC_{50} of 42.1 and 62.1 μg mL^{-1}, against influenza A (H_1N_1). *Aegiceras corniculatum* is a plant that grows in mangroves of tropical and subtropical regions. Species of *Aegiceras* are known to be used in the treatment of ulcers, liver damage, asthma, diabetes, and rheumatism and as an anti-inflammatory agent (Roome et al. 2008).

Guo et al. (2000) isolated the endophytic *Cytonaema* sp. from tissues of *Quercus* sp., which was able to produce the cytonic acids A and B and described as having antiviral activity since they are inhibitors of human cytomegalovirus protease, with IC_{50} of 43 μM and 11 μM, respectively. Plants of this genus are used by indigenous

peoples in Canada for the treatment of diabetes and its complications (McCune and Johns 2002).

Hinnuloquinone is another antiviral compound that inhibits human immunodeficiency virus type 1 protease (HIV-1) (Singh et al. 2004; Kumar et al. 2014). This compound had already been isolated from an endophytic fungus associated with the leaves of *Quercus coccifera* (Baker and Satish 2015). *Quercus coccifera* is used for wound healing in the villages of Yunt Mountain in Turkey (Ugurlu and Secmen 2008).

Pullarin A is a compound produced by the endophytic *Pullaria sp.*, which was reported to be associated with the leaves of *Caulophyllum* sp. grown in Thailand. This compound showed antiviral activity with IC_{50} of 3.3 μg mL^{-1} against herpes virus type 1 - HSV-1 (Isaka et al. 2007; Borges et al. 2009).

11.5 Antitumor Compounds

According to the WHO, the number of deaths caused by the diverse types of cancer in the world can reach 8.8 million people annually. Estimates indicate that 14 million people develop cancer every year and by 2030 that number should reach 21 million people (OPAS/OMS 2017). As a result, the search for new treatments has grown significantly throughout the world. The search of anticancer secondary metabolites produced by endophytic fungi associated with medicinal plants has been studied since the discovery of taxol, first isolated from the bark of *Taxus brevifolia* in 1971. Taxol has proven efficacy against prostate, ovarian, breast, and lung cancers (Zhao et al. 2010b; Manju et al. 2012). Interestingly, taxol was also found in *Taxomyces andreanae,* an endophytic fungus isolated from the bark of *T. brevifolia*. Other studies demonstrated that taxol can be produced by endophytic fungi isolated from other plants (Pandi et al. 2011). Qiao et al. (2017), for example, isolated the taxol from the endophytic fungus *Aspergillus aculeatinus*, isolated from the inner and outer bark of the plant *Taxus chinensis* var. *mairei*. The endophytic fungus *Cladosporium* sp., isolated from the leaves and stem of the *Taxus baccata* plant in the northern forest of Iran, was also able to produce taxol (Kasaei et al. 2017). Taxol prevents tubulin molecules from depolymerizing during cell division processes. This happens because this compound inhibits cell replication and migration, stopping the cycle of division of mitosis in late phase G2 (Strobel and Daisy 2003; Yang and Horwitz 2017).

Camptotheca acuminata is a plant native to central China and widely used in the popular medicine. This species is rich in camptothecin (Lin et al. 2007), an anticancer compound that acts on the enzyme topoisomerase I which is responsible for the relaxation or not of the DNA molecule during the processes of replication and transcription (Kusari et al. 2009). It was later found that the endophytic fungus *Fusarium solani*, originating from the inner bark of this *C. acuminata* was also able to produce camptothecin (Kusari et al. 2012). Moreover, there are also reports of its production by other endophytic fungi associated with other plant species, for example, the

endophytic fungus *Entrophospora infrequens* isolated from the inner bark of *Nothapodytes foetida syn. N. nimmoniana* (Gowda et al. 2002; Puri et al. 2005). This plant, growing on the west coast of India, is used as anticancer, antimalarial, bactericidal, antioxidant, anti-inflammatory, and fungicidal, to treat anemia and HIV infections (Khan et al. 2013). Su et al. (2014) isolated camptothecin from the endophytic fungi *Alternaria alternata*, *C. gloeosporioides*, *Fusarium nematophilum*, and *Phomopsis vaccinia*, all isolated from the leaves, twigs, and roots of *C. cuminata*. From this plant yet another endophytic fungus, *Fusarium solani*, also produces camptothecin (Ran et al. 2017).

Podophyllum hexandrum is a plant that lives in high altitudes and is native to alpine and subalpine areas of the Himalayas. It has been used since antiquity in traditional Indian and Chinese medicine to treat metabolic imbalance. More recently, its activity against monocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas, bacterial and viral infections, venereal warts, rheumatoid arthralgia associated with limb numbness, and different types of cancer, such as brain, lung, and bladder, has been described (Chawla et al. 2005). *Podophyllum hexandrum* produces a substance called podophyllotoxin that is a precursor to the synthesis of three anticancer compounds: etoposide, teniposide, and etoposide phosphate (You 2005). These compounds inhibit DNA topoisomerase II and are used to treat cancer of the lung, testicles, and some leukemias, among others (Xu et al. 2009; Chandra 2012). Puri et al. (2006) isolated the endophytic fungus *Trametes hirsuta* from the rhizomes of *P. hexandrum*, which was able to produce podophyllotoxin under laboratory conditions. It has also been isolated from the endophytic *Fusarium oxysporum* associated with the plant *Juniperus recurva* (Kour et al. 2008). *Phialocephala fortini*, an endophytic fungus associated with *Podophyllum peltatum*, also produces this substance. In India, this plant is used in the treatment of snakebite, cancer, vermifuge, and ulcers (Eyberger et al. 2006; Silva et al. 2017b). Podophyllotoxin was also isolated from the endophytic *Fusarium solani* isolated from the root of the plant *P. hexandrum* (Nadeem 2012).

Ergoflavine is an anticancer compound isolated from the Indian medicinal plant *Mimusops elengi* (Kaul et al. 2012). All parts of this plant are known to have medicinal properties. The fruits are used for chronic dysentery and constipation; the flowers relieve headaches and are used against ulcer; and the bark is used to increase fertility in women and also has activity against ulcer (Verekar et al. 2017). Deshmukh et al. (2009) isolated from the leaves of *M. elengi* an endophytic fungus that was shown to produce ergoflavine, significantly active against the proliferation of pancreatic, renal, and lung cancer cells.

Cytochalasins are a large group of secondary metabolites produced by various species of fungi, comprising about 60 different compounds. The first cytochalasins to be studied were A and B. They inhibit actin, sugar uptake, and blocks ion channels (Goietsenoven et al. 2011). Pongcharoen et al. (2006) isolated cytokinins produced by the endophytic fungus *Eutypella scoparia* associated with the plant *Garcinia dulcis*. In Thailand, *G. dulcis* leaves are used for the treatment of inflammation in the lymphatic, mumps, and goiter ducts (Abu et al. 2015). Wagenaar et al. (2000) also report the production of cytochalasins by another endophytic fungi,

Rhinocladiella sp., isolated from *Tripterygium wilfordii*. This plant is endemic in southern China and used to treat immune and inflammatory diseases (OuYang et al. 2007). Caetoglobesins are cytochlasin arrays, and many of them are toxic to human cancer cell lines. More than 40 have been identified and many of them are produced by fungi (Zhang et al. 2010). Caetoglobosin U, a secondary metabolite of the endophytic fungus *Chaetomium globosum*, isolated from the medicinal plant *Imperata cylindrica*, used in the treatment of dysentery and urinary tract infections, was shown to display anticancer activity (Ding et al. 2006; Krishnaiah et al. 2009). Caetoglobesins C, E, and F, among others, were also isolated from this fungal species, but this time isolated from the *G. biloba* plant (Li et al. 2014). The seeds of this plant are used for the treatment of asthma and cough and the leaves are used for heart problems and skin infections (Mahadevan and Park 2008).

Vincristine is another anticancer compound and acts by disrupting mitosis by binding to tubulin dimers, inhibiting the assembly of microtubules (Aly et al. 2010). Kumar et al. (2013) isolated vinscritin from the culture of endophytic fungus *Fusarium oxysporum*, which was associated with the medicinal plant *Catharanthus roseus*. The roots of this plant are used to control blood pressure, and this characteristic is related to the alkaloids present in it. Table 11.3 shows other anticancer compounds isolated from endophytic fungi of medicinal plants in the last 8 years.

11.6 Acetylcholinesterase Inhibitors

Alzheimer's disease (AD) is an age-related neurodegenerative disease with cognitive and neuropsychiatric manifestations that result in progressive disability (Zhao and Tang 2002). According to Alzheimer's Disease International (ADI), 47 million people lived with dementia in the world in 2016 and this number can increase to more than 131 million by 2050 as populations age. That can be related to the AD that lead to a progressive decline in cognitive function that is substantially increased among people aged 65 years or more (Prince et al. 2016).

Cholinesterase inhibitors are important substances recommended for the treatment of cognitive deficits and associated behavioral abnormalities in patients with mild-to-moderate AD (Weinstock 1999; Ballard 2002). The cholinesterase inhibitors can inactivate the enzyme acetylcholinesterase (AChE), preventing the inactivation of acetylcholine (Ach) after its release from the neuron, increasing its ability to stimulate nicotinic and muscarinic receptors (Weinstock 1999; Zhao and Tang 2002). There are no available treatments that stop or reverse the progression of the disease, fact that reinforces the importance of developing medicines that would at least slow the progression of the symptoms (Duthey 2013).

Oliveira et al. (2011) reported the AChE inhibition of (3R,4R)-3,4-dihydro-4,6-dihydroxy-3-methyl-1-oxo-1H-isochromene-5-carboxylic acid produced by the fungus *Xylaria* sp., isolated from the plant *Piper aduncun* with minimum amount required for inhibition of 3 μg compared with the galantamine used as positive control with minimum amount required for inhibition of 1 μg. Singh et al. (2012)

Table 11.3 Antitumor compounds reported from endophytic fungi from medicinal plants

Fungal endophytic taxa	Medicinal plant/tissue	Compound isolated	Biological activity	IC_{50}	Reference
Aspergillus glaucus	*Ipomoea batatas*/leaves	**1.** 2, 14-dihydrox-7-drimen-12, 11-olide	HepG2 MCF-7	229 μM 156.6 μM	Asker et al. (2013)
Penicillium sp.	*Tripterygium wilfordii*/ leaves	**2.** 3-*O*- methylfunicone	KB	90.9 μM	Chen et al. (2014)
Annulohypoxylon squamulosum	*Cinnamomum* sp./stem bark	**3.** (3*S*)-7-hydroxymellein	MCF-7 NCI-H460 SF-268	2.8 μM 3.2 μM 2.9 μM	Cheng et al. (2012)
Aspergillus sp.	*Gloriosa superba*/seeds	**4.** 6- methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide	MCF-7 THP-1	151.8 μM 91.1 μM	Budhiraja et al. (2013)
Botryotinia fuckeliana	*Ajuga decumbens*/roots	**5.** (12)-cytochalasin	7721 A549 HepG2 MCF-7	0.9 μM 0.7 μM 0.6 μM 0.6 μM	Lin et al. (2015)
Penicillium janthinellum	*Panax ginseng*/roots	**6.** Penicillic acid	MKN45 LOVO A549 MDA-MB-435 HepG2 HL-60	16.7 μM 13 μM 43.8 μM 36.9 μM 21.6 μM 4.7 μM	Zheng et al. (2013)
Alternaria alternata	*Capsicum annuum*/fruits	**7.** Alternariol-10-methyl ether	HL-60 A549 PC-3 HeLa A431 Mia PaCa-2 T47D	85 μM >100 μM > 100 μM > 100 μM 95 μM > 100 μM > 100 μM	Devari et al. (2014)

Chaetomium globosum	*Curcuma wenyujin*/leaves	**8.** Chaetoglobosin X	MFC H22	15.1 μM 7.5 μM	Wang et al. (2012)
Penicillium sp.	*Tripterygium wilfordii*/ leaves	**9.** Deoxyfunicone	KB	22.6 μM	Chen et al. (2014)
Xylaria sp.	*Licuala spinosa*	10. Eremophilanolides 1, 2 e 3	KB MCF-7 NHI-H187	3.8–2 μM	Isaka et al. (2010)
Perenniporia tephropora	*Taxus chinensis var. maire*/ bark	**11.** Ergosterol	HeLa SMMC-771 PANC-1	2.9 μM 29.3 μM 29.7 μM	Wu et al. (2013b)
Eupenicillium sp.	*Xanthium sibiricum*/roots	**12.** Eupenicinicol D	THP-1	8 μM	Li et al. (2017)
Penicillium sp.	*Tripterygium wilfordii*/ leaves	**13.** Funicone	KB	13.2 μM	Chen et al. (2014)
Penicillium melinii	*Panax ginseng*/root	**14.** Ginsenocin	MKN45 LOVO A549 MDA-MB-435 HepG2 HL-60	7.3 μM 8.4 μM 19.3 μM 5.3 μM 9 μM 1.9 μM	Zheng et al. (2013)
Massrison sp.	*Rehmannia glutinosa*/roots	**15.** Massarigenin D	L-O2 HepG-2 MCF-7 A549	84.8 μM 92.7 μM 49.9 μM 50.8 μM	Sun et al. (2011)
Penicillium brefeldianum	*Pinellia ternata*/rizhome	**16.** N-demethyl melearoride A	HepG2 U2-OS MDA-MB-231	> 50 μM > 50 μM 36.6 μM	Gao et al. (2017)
Phomopsis sp.	*Musa acuminata* /leaves	**17.** Oblongolides Z	KB BC NCI-H187 Vero	37 μM 26 μM 32 μM 60 μM	Bunyapaiboonsri et al. (2010)

(continued)

Table 11.3 (continued)

Fungal endophytic taxa	Medicinal plant/tissue	Compound isolated	Biological activity	IC_{50}	Reference
Cochliobolus kusanoi	*Nerium oleander*	**18.** Oosporein	A549	21 μM	Alurappa et al. (2014)
Massrison sp.	*Rehmannia glutinosa*/roots	**19.** Paecilospirone	L-O2 HepG2 MCF-7 A549	24.4 μM 20.4 μM 14.9 μM 13.4 μM	Sun et al. (2011)
Penicillium sp.	*Tripterygium wilfordii*/leaves	**20.** Penifupyrone	KB	4.7 μM	Chen et al. (2014)
Perenniporia tephropora	*Taxus chinensis var. maire*/bark	**21.** Perenniporin A	HeLa SMMC-771 PANC-1	108.2 μM 161.7 μM 157.2 μM	Wu et al. (2013b)
Phomopsis amygdale	*Corylus avellana*/roots, branches and leaves	**22.** Pestalotin	MDA-MB-231 PC-3 HT-29	194.6 μM 95.9 μM 77.9 μM	Akay et al. (2014)
Cryptosporiopsis sp.	*Clidemia hirta*	**23.** (*R*)-5-hydroxy-2-methylchroman-4-one	HL-60	25.9 μM	Zilla et al. (2013)
Phomopsis amygdale	*Corylus avellana*	**24.** (S)-4-butoxy-6-((S)-1- hydroxypentyl)-5,6-dihydro-2H-pyran-2-one	MDA-MB-231 PC-3 HT-29	94.6 μM 516.2 μM 320.6 μM	Akay et al. (2014)
Cephalotheca faveolata	*Eugenia jambolona*/leaves	**25.** Sclerotiorin	HCT-116	0.6 μM	Giridharan et al. (2012)
Massrison sp.	*Rehmannia glutinosa*/roots	**26.** Spiromassaritone	L-O2 HepG2 MCF-7 A-549	32.1 μM 25 μM 30.3 μM 43.7 μM	Sun et al. (2011)
Penicillium brefeldianum	*Pinellia ternata*/rizhome	**27.** Spirotryprostatin F	HepG2 U2-OS MDA-MB-231	35.5 μM > 50 μM 14.1 μM	Gao et al. (2017)

screened endophytic fungi associated with *Ricinus communis* for its inhibitory activity on AChE. They found six active strains, and the best results were from the extract of the fungus *Alternaria* sp. with 78% of inhibition and an IC50 of 40 μg mL^{-1}. Na et al. (2016) isolated the fungus *Geomyces* sp. from the plant *Nerium indicum* that showed high inhibitory activity with an IC50 value of 5.2 μg mL^{-1} that might be related to substances derived from vincamine produced by this fungus. Chapla et al. (2014a) identified six fungal isolates with inhibitory AChE activity recovered from the medicinal plant *Michelia champaca*, with the species *C. gloeosporioides*, *Phomopsis stipata*, and *Xylaria* sp. showing the highest activity.

Wang et al. (2016b) investigated the medicinal plant *Huperzia serrata* from the Jinggang Mountain region (China) for the presence of endophytic fungi with acetylcholinesterase inhibitory activity. From the 247 strains isolated, 221 generated extracts with in vitro AChE inhibitory activity, with 4 of them, namely, *Coletotrichum* spp., *Ascomycota* spp., *Sarcosomataceae* spp., and *Dothideomycetes* spp. causing more than 80% inhibition. Dong et al. (2014) analyzed *H. serrata* from the Tianmu Mountains of Hangzhou (China) for endophytic fungi producing huperzine A (HupA), a substance produced by the plant itself and known for its high AChE inhibitory activity. They found that the fungus *Trichoderma* sp. seems to produce this substance, yielding an extract capable of inhibiting AChE by 81.9%. The fungi recorded for producing HupA and other potential substances are listed in the Table 11.4.

Table 11.4 Compounds with activity of AchE inhibition reported from endophytic fungi from medicinal plants.

Fungal endophyte taxa	Host plant/Tissue	Compouds isolated	IC_{50}	Reference
Chaetomium sp.	*Huperzia serrata*	**1.** 3β-hydroxy-5,9-epoxy-(22*E*,24*R*) -ergosta-7,22-dien-6-one ($C_{28}H_{42}O_3$)	–	Yu et al. (2016)
Shiraia sp.	*Huperzia serrata*/leaves	**2.** Huperzine A ($C_{15}H_{18}N_2O$)	–	Zhu et al. (2010)
Chaetomium globosum	*Panax notoginseng*/seed	**3.** Epicoccolide B ($C_{18}H_{14}O_8$) **4.** 3-Methoxyepicoccone	5.5 μM –	Li et al. (2016a)
Alternaria alternata	*Vinca rosea*/branches	**5.** Altenuene ($C_5H_{16}O_6$)	–	Bhagat et al. (2016)
Aspergillus versicolor	*Huperzia serrata*/leaves	**6.** Avertoxin B ($C_{28}H_{37}O_9$)	14.9 μM	Wang et al. (2016b)
Cladosporium cladosporioides	*Huperzia serrata*/leaves	**7.** Huperzine A ($C_{15}H_{18}N_2O$)	–	Zhang et al. (2011)
Aspergillus terreus	*Artemisia annua*/stems	**8.** 16α-hydroxy-5-N-acetylardeemin ($C_{28}H_{28}N_4O_4Na$)	58.3 μM	Ge et al. (2010)
Bipolaris sorokiniana	*Rhayza stricta*/leaves	**9.** Bipolarisenol ($C_{16}H_{13}O_6$)	223.1 mM	Khan et al. (2015)

11.7 Antioxidant Activity

Antioxidant substances protect cells from injury caused by free radicals produced by the natural metabolism during aerobic respiration (Yehye et al. 2015). These radicals have an important physiological role but may cause toxic effects leading to degenerative diseases like cancer and Alzheimer's disease (Kaul et al. 2012; Yehye et al. 2015). The antioxidant activity of endophytic fungi extracts might be related to the production of flavonoid and phenolic compounds, making them act as reducing agents and hydrogen donors due to their redox properties (Qiu et al. 2010; Khan et al. 2017). Besides the uses in the pharmaceutical industry, the potent activity found in the endophytic extracts can be used as a natural antioxidant in the food industry (Nath et al. 2012; Rana et al. 2018a, b; Yadav et al. 2017). The importance of exploring new sources of effective antioxidants is related to the low number of antioxidants approved for clinical applications (Kaul et al. 2012).

The compound 1.1-diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical widely accepted as a tool to analyze the antioxidant ability of extracts. When a substance with antioxidant activity interacts with DPPH, it transfers electrons or hydrogen atoms neutralizing its free radical character and causing changes in its color (Naik et al. 2003). Using this method, Singh et al. (2016) found phenolic compounds with IC_{50} value of 22.5 μg mL^{-1} in the extract of the endophytic fungus *Cladosporium velox*, isolated from the medicinal plant *Tinospora cordifolia*.

Tejesvi et al. (2008) searched for antioxidant activity in endophytic *Pestalotiopsis* species associated with medicinal plants growing in southern India. They found three fungi with significant scavenging activity (over 80%): *Pestalotiopsis theae* (TA-37), isolated from the bark of the medicinal plant *Terminalia arjuna*, presenting an IC_{50} value of 14 μg mL^{-1}; *Pestalotiopsis* sp. 3 (TA-60), isolated from the root of *Terminalia arjuna* with an IC_{50} value of 25 μg mL^{-1}; and *Pestalotiopsis virgatula*, isolated from the bark of *Terminalia chebula* with an IC_{50} of 27 μg mL^{-1}.

Nath et al. (2012) found four endophytic fungi with antioxidant activity occurring in the medicinal plant *Emblica officinalis*. The fungus *Phomopsis* sp. isolated from the stem showed the most significant IC_{50} value of 17.4 μg mL^{-1}, a value comparable with that of ascorbic acid (15 μg mL^{-1}) used as positive control. In addition, the fungi identified as *Diaporthe* sp. and *Xylaria* sp., isolated from the root and stem of *Epacris* sp., were also considered active, with IC_{50} values in the range of 18.9 μg mL^{-1}–29.4 μg mL^{-1}. The same group studied the fungi *Cholletotrichum gloeosporoides*, *Penicillium* sp., and *Aspergillus awamori*, all isolated from the plant *Rauwolfia serpentina,* for their ability to produce antioxidant compounds showing that *A. awamori* was most effective with extract disclosing the highest scavenging activity in the DPPH test (Nath et al. 2013).

Khiralla et al. (2015) investigated five Sudanese medicinal plants for endophytic fungi with potential antioxidant activity. Among 21 endophytes isolated, the fungus *Aspergillus* sp. from the seed of *Trigonella foenum-graecium* showed the most significant results, with an IC_{50} value of 18.0 μg mL^{-1} in the DPPH assay. Jayanthi

et al. (2011) reported that a *Phomopsis* sp. isolated from the medicinal plant *Mesua ferrea* disclosed an IC_{50} value of 31.3 μg mL^{-1}, while the positive control, ascorbic acid, showed an IC_{50} value of 11.1 μg mL^{-1}.

Shukla et al. (2012) showed that *Paecilomyces variotti*, one of the endophytic fungi isolated from the root of *Ocimum sanctum,* yielded an extract with IC50 value of 71.8 μg mL^{-1} in the DPPH test and 110.9 μg mL^{-1} for the scavenging of the hydroxyl radical. Yadav et al. (2014) disclosed the antioxidant activity and total phenolic content (TPC) of endophytic fungi isolated from *Eugenia jambolana.* They found two potential fungi with scavenging activity higher than 80%, *Chaetomium* sp. that present the highest concentration of phenolic compounds among all isolates and *Aspergillus* sp. Other two techniques were used to measure the antioxidant activity of these fungi: hydrogen peroxide scavenging assay and reducing power assay, confirming the antioxidant potential of compounds produced by these fungi.

Bhagobaty and Joshi (2012) isolated endophytic fungi from plants growing in the "sacred forests" of India. They measured their antioxidant potential using DPPH and FRAP assays. The latter measures the UV absorbance of ferrous ions. The tests showed that the fungus *Mortierella hyalina,* isolated from the plant *Osbeckia stellata,* has a good potential, with a FRAP value of 1.316 μM and a percentage of free radical scavenging activity of 79.7%. In these assays, the control substance ascorbic acid has a FRAP value of 2.000 μM and free radical scavenging activity of 64%.

Huang et al. (2007) isolated bioactive fungi from the medicinal plant *Nerium oleander* and used the ABTS method to test the total antioxidant capacity of the fungi extracts. Most of the fungal strains (75%) showed moderate antioxidant capacities with values ranging from 20 to 50 μmol trolox/100 mL culture. The fungus *Chaetomium* sp. presented the highest antioxidant capacity, that is, 151 μmol trolox/100 mL culture.

Srinivasan et al. (2010) evaluated the antioxidant property of the endophytic fungus *Phyllosticta* sp. isolated from the leaves of *Guazuma tomentosa* using the DPPH and ABTS methods. The results showed the potential antioxidant of the fungus extract, that contains phenolic and flavonoid substances, with EC50 values of 580 μg mL^{-1} for the DPPH radical test and 2030 μg mL^{-1} for the ABTS radical test.

Qiu et al. (2010) identified two flavonoid-producing endophytic fungi with antioxidant activity in the twigs of *G. biloba*. *Aspergillus nidulans* and *Aspergillus oryzae* showed antioxidant activity on the hydroxyl radical scavenging activity test of 34% and 58%, respectively. Substances from endophytic fungi isolated from medicinal plants that present antioxidant activity are listed in the Table 11.5.

11.8 Neglected Tropical Diseases

Neglected tropical diseases (NTDs) are a diverse group of infectious diseases caused by bacteria, parasites, protozoans, or viruses, which prevail especially in tropical and subtropical regions (Lenzi et al. 2018). According to reports published by World

Table 11.5 Compounds with antioxidant activity reported from endophytic fungi from medicinal plants

Fungal endophyte	Host plant/tissue	Compounds isolated	IC_{50} (DPPH)	Reference
Pseudocercospora sp.	*Elaeocarpus sylvestris*/stems	**1.** Terreic acid ($C_7H_6O_4$)	58.6 mM	Pirihantini and Tachibana (2017)
Fusarium solani *Fusarium oxysporum* *Fusarium proliferatum*	*Cajanus cajan*/roots	**2.** Cajaninstilbene acid ($C_{21}H_{22}O_4$)	-	Zhao et al. (2012b)
Cephalosporium sp.	*Trachelospermum jasminoides* /leaves	**3.** Graphislactone A ($C_{16}H_{14}O_6$)	9.6 mM	Selim et al. (2014)
Chaetomium globosum	*Panax notoginseng* /seeds	**4.** Flavipin ($C_9H_8O_5$) **5.** Epicoccone ($C_9H_8O_5$) **6.** 3-Methoxyepicoccone ($C_{10}H_9O_6$) **7.** Epicoccolide A ($C_{18}H_{14}O_9$) **8.** Epicoccolide B ($C_{18}H_{14}O_8$)	18.9 mM 58.6 mM 49.7 mM 13.9 mM 32.4 mM	Li et al. (2016a)

Health Organization (WHO), the diseases of major concern are Chagas disease and visceral leishmaniasis (WHO 2017).

The frequency of drug-resistant parasites has greatly increased, and most treatments involve highly toxic drugs. In addition, the chemotherapeutic agents used in patients with these diseases have lacked effectiveness. Thus, there is an urgent need to search for novel drugs from previously unexplored sources, including natural products, to combat the global health problems posed by parasitic infections (Martínez-Luis et al. 2011).

Historically, natural products are a good strategy when searching for new bioactive compounds, they provide a basis for both design and synthesis of derivative compounds aiming at optimizing biological activity and minimizing side effects (Scotti et al. 2010; Schulze et al. 2015). The ongoing development of new antiparasitic agents is important to overcome the limitations related to the high toxicity of the drugs currently available for the treatment of diseases caused by tropical parasites (Croft et al. 2006). Despite advances in the discovery and development of plant-derived drugs, NTDs continue to cause morbidity and mortality in hundreds of millions of people, especially in poor areas (Goupil and McKerrow 2014).

While endophytic fungi are an abundant and reliable source of metabolites with medicinal and agrochemical applications, they have been only scarcely explored as sources of antiparasitic agents (Martínez-Luis et al. 2011). Because these fungal endophytes are promising sources of bioactive metabolites, they could be used to produce important antiparasitic compounds to treat NTDs such as trypanosomiasis, leishmaniasis, and malaria.

11.8.1 Trypanosomiasis

Chagas disease (or American trypanosomiasis) is a parasitic illness that results from infection by the hemoflagellate protozoan *Trypanosoma cruzi* (*T. cruzi*). The transmission of Chagas disease occurs primarily through the bite of an infected triatomine bug on an individual. Triatomines are insects that usually belong to the genera *Triatoma*, *Rhodnius*, or *Panstrongylus*, which are commonly known as "barbeiros" in Brazil and "kissing bugs" in the United States, due to their preference for biting the faces of sleeping people. These insect genera include more than 140 species, of which 61 are endemic to Brazil (Costa and Peterson 2012). According to WHO, and in common with other neglected tropical diseases, "Chagas disease is a proxy for poverty and disadvantage: it affects populations with low visibility and little political voice, causes stigma and discrimination, is relatively neglected by researchers, and has a considerable impact on morbidity and mortality" (Coura and Dias 2009).

Approximately 7–eight million individuals have Chagas disease, and 50,000 new cases are diagnosed every year in Latin America, North America, and Europe. It is estimated that more than 90 million individuals are currently at risk of infection with the Chagas disease's etiologic agent (Coura and Dias 2009; WHO 2014; Vazquez et al. 2015). The conventional treatment is based on benzimidazole (Bayer Health Care—Lampit®) and nifurtimox (Roche— Rochagan® or Radanil®), which were developed over 100 years ago. Both drugs have strong side effects, such as appetite loss, vomiting, polyneuropathy, and dermopathy. The long-term treatment required combined with the strong side effects contributes to frequent desistence (Guedes et al. 2011). Additionally, benzimidazole and nifurtimox are mostly effective for the blood forms in the acute phase and not so effective against the intracellular forms in the chronic phase (Muelas-Serrano et al. 2002).

Human African trypanosomiasis (or sleeping sickness) is a fatal vector-borne parasitic disease caused by *Trypanosoma brucei brucei* transmitted by the tsetse fly (*Glossina* spp.). This neglected tropical disease occurs only in rural areas of sub-Saharan Africa (Simarro et al. 2011). To date, only a few drugs have been approved for the treatment of human African trypanosomiasis. These include suramin, pentamidine, melarsoprol, eflornithine, and the combination of nifurtomox/eflornithine. Most of the drugs are old, having been discovered in the 1940s and 1950s, and have adverse effects such as nausea, vomiting, fatigue, seizures, fever, diarrhea, hypoglycemia, abdominal cramping, peripheral neuropathy, hypertension, heart damage, and neutropenia on the patients (Jacobs et al. 2011). For the reasons describe above, mining and developing new trypanosomiasis drugs from natural products is crucial and essential because endophytic fungi offer a high number of natural products with diverse chemical structures and novel pharmacological mechanism of action.

11.8.2 Leishmaniasis

Leishmaniasis is a group of human diseases caused by protozoan species of the genus *Leishmania*, which are prevalent in tropical and subtropical areas of the world. Brazil is among the ten countries affected by 90% of the cases worldwide of both cutaneous and visceral leishmaniasis (WHO 2010). More than one million people are being victimized by leishmaniasis worldwide, and reported fatalities are of around 30,000 annually (Kamhawi 2017). There are around 20 species of *Leishmania* (*Trypanosomatidae*), which can cause three variations of the leishmaniasis disease: cutaneous, mucocutaneous, or visceral leishmaniasis (Dawit et al. 2013).

Leishmania (*Viannia*) *braziliensis* is the main etiological agent of American tegumentary leishmaniasis and has the highest incidence in Brazil. This group of infectious diseases has different clinical forms that are associated with the molecular diversity of the parasite and host immune response (Pereira et al. 2017). The visceral manifestation of the disease is usually caused by *Leishmania donovani* and *Leishmania infantum*, and it can affect internal body organs. It is also popularly known as kala-azar and can be fatal (Clem 2010).

There is no vaccine to control these diseases (Dawit et al. 2013). The current therapy consists of sodium stibugluconate (Pentosam®), meglumine antimonate (Glucantime®), miltefosine, amphotericin B, and paromomycin. The first drugs used for treatment were the antimonials. However, in the 1970s, the parasites started to show resistance to pentavalent sodium antimony gluconate, even at high doses, and as a result, these drugs were mostly abandoned. Miltefosine has replaced antimonials as a treatment in cases of resistance. However, it has also been associated with increasing resistance. Treatment with amphotericin B is effective, but it has highly nephrotoxic effects. The treatment can also be inhibited by cost, access, and difficulties in obtaining oral formulations of the drug (Hefnawy et al. 2017). Thus, there is a need for the discovery of new leads or scaffolds that can be used to develop less toxic drugs and alternative oral treatments (Prates et al. 2017).

11.8.3 Trypanocidal and Leishmanicidal Compounds from Endophytic Fungi

The major bioactive metabolites obtained from endophytic fungi associated with medicinal plants presenting trypanocidal and leishmanicidal activities are listed in Table 11.6. The fungi obtained from the medicinal plant *Caesalpinia echinata*, popularly known as Brazilwood, were tested against *L. amazonensis* and *T. cruzi*. The isolates from *Fusarium* sp., *Nectria mauritiicola*, and *Xylaria* sp. were able to inhibit *L. amazonensis* growth, and the isolate from *Fusarium sp*. was able to inhibit *T. cruzi* growth. The ethyl acetate (EtOAc) of *Fusarium* sp. showed the most promising result by inhibiting 92% of *T. cruzi* growth at a dose of 20 μg mL^{-1}. The extract of *Fusarium* sp. was subjected to fractionation, which revealed beauvericin as the

Table 11.6 Trypanocidal and leishmanicidal compounds reported from endophytic fungi associated with medicinal plants

Fungal endophyte	Medicinal plant/tissue	Compounds isolated	Biological activity	IC_{50}	Reference
Fusarium sp.	*Caesalpinia echinata*/stem	**1.** Beauvericin ($C_{45}H_{55}N_3O_9$)	*Trypanosoma cruzi*	1.9 μg ml^{-1}	Campos et al. (2015)
Nectria pseudotrichia	*Caesalpinia echinata*/stem	**2.** EtOAc extract	*Leishmania* (*Leishmania*) *amazonensis*	4.6 μg ml^{-1}	Campos et al. (2015)
Nectria pseudotrichia	*Caesalpinia echinata*/stem	**3.** 10-acetyl trichoderonic acid A **4.** 6′-acetoxy-piliformic acid **7.** Hydroheptelidic acid	*Leishmania* (*Viannia*) *brasiliensis*	21.4 μM 28.3 μM 24.8 μM	Cota et al. (2018)
Microthyriaceae sp.	*Paspalum conjugatum*	**10.** Sterigmatocystin ($C_{18}H_{12}O_6$)	*Trypanosoma cruzi*	0.1 μmol L^{-1}	Almeida et al. (2014)
Lasiodiplodia theobromae	*Vitex pinnata*/leaves	**12.** Cladosporim B **13.** Desmethyl-lasiodiplodin	*Trypanosoma brucei brucei*	17.8 μM 22.5 μM	Kamal et al. (2016)
Diaporthe phaseolorum-92C	*Combretum lanceolatum*/roots	**15.** 18-des-hydroxy cytochalasin H	*Leishmania* (*Leishmania*) *amazonensis*	9.2 μg ml-1	Brissow et al. (2018)
Aspergillus terreus	*Carthamus lanatus*/roots	**16.** Terrenolide S **17.** (22*E*,24*R*)-stigmasta-5,7,22-trien-3-β-ol **18.** Stigmast-4-ene-3-one	*Leishmania donovani*	27. 3 μM 15.3 μM 11.2 μM	Elkhayata et al. (2015)
Aspergillus terreus-F7	*Hyptis suaveolens*	**23.** Terrein ($C_8H_{10}O_3$) **24.** Butyrolactone I ($C_{24}H_{24}O_7$) **25.** Butyrolactone V ($C_{24}H_{24}O_8$)	*Leishmania* (*Leishmania*) *amazonensis*	23.7 μM 26.0 μM 78.6 μM	Silva et al. (2017c)
Aspergillus calidoustus	*Acanthospermum australe*/leaves	**26.** Ophiobolin K **27.** 6-epi-ophiobolin K ($C_{25}H_{36}O_3$)	*Trypanosoma cruzi*	13.0 μM 9.6 μM	Carvalho et al. (2015)
Cochliobolus sativus	*Vernonia polyanthes*/leaves	**28.** Mixture of cochlioquinone A and isocochlioquinone A **29.** Anhydrocochlioquinone	*Leishmania* (*Leishmania*) *amazonensis*	10.2 μg ml^{-1} 50.5 μg ml^{-1}	Nascimento et al. (2015)

EtOAc ethyl acetate

active compound. While the crude extract of *Fusarium* sp. showed an IC_{50} of 30 μg mL^{-1} (**2**) in the assay with *T. cruzi* forms expressing the β-galactosidase gene, beauvericin showed an IC_{50} value times smaller (1.9 μg mL^{-1}, 2.4 μM) (**1**). The EtOAc extract from the culture of *Nectria pseudotrichia* was active against amastigote-like forms of *Leishmania* (*Leishmania*) *amazonensis* showing an IC_{50} value of 4.6 μg mL^{-1} (**2**) (Campos et al. 2015). Fractionation of *Nectria pseudotrichia* extracts yielded seven compounds, 10-acetyl trichoderonic acid A (**3**), 6′-acetoxypiliformic acid (**4**), 5′,6′-dehydropiliformic acid (**5**), piliformic acid (**6**), hydroheptelidic acid (**7**), xylaric acid D (**8**), and cytochalasin D (**9**). Compounds **3**, **4**, and **7** were the most active against *Leishmania* (*Viannia*) *braziliensis*, with IC_{50} values of 21.4, 28.3, and 24.8 μM, respectively, and showed low toxicity to Vero and THP-1 cells (Cota et al. 2018).

When screening for natural products with antiparasitic activity, the endophytic fungus, *Microthyriaceae* sp., was isolated from aboveground tissue of the tropical medicinal grass *Paspalum conjugatum* (*Poaceae*) in Panama. Cultivation followed by bioassay-guided chromatographic fractionation of the extract led to the isolation of the new polyketide integrasone B (**9**) and two known mycotoxins, sterigmatocystin (**10**) and secosterigmatocystin (**11**). Sterigmatocystin was found to be the main antiparasitic compound in the extract of fermentation broth of this fungus, possessing potent and selective antiparasitic activity against *T. cruzi*, with an IC_{50} value of 0.13 μmol L^{-1}. Compounds **10** and **11** showed high cytotoxicity against Vero cells (IC_{50} of 0.1 and 1 μmol L^{-1} respectively) (Almeida et al. 2014).

The endophyte *Lasiodiplodia theobromae* obtained from the leaves of *Vitex pinnata*, a medicinal plant of Malaysia, displayed activity against *Trypanosoma brucei brucei*. Three known compounds were isolated, namely, cladospirone B (**12**), desmethyl-lasiodiplodin (**13**), and *R*-(−)-mellein (**14**). Cladospirone B and desmethyllasiodiplodin compounds exhibited good activity against *T. b. brucei* with minimum inhibitory concentrations of 17.8 μM and 22.5 μM, respectively (Kamal et al. 2016).

Brissow et al. (2018) demonstrated that crude EtOAc extracts of *Diaporthe phaseolorum*, an endophytic fungus isolated from the roots of *Combretum lanceolatum* Pohl ex Eichler, a Brazilian medicinal plant, showed trypanocidal activity at 20 μg mL^{-1}, reducing 82% of the number of amastigotes and trypomastigotes of *T. cruzi*. The compound 18-des-hydroxy Cytochalasin H (**15**) was isolated and evaluated for leishmanicidal and tripanocidal activities. The compound reduced the viability of *L. amazonenses* promastigotes with an IC_{50} value of 9.2 μg mL^{-1}.

From the endophytic fungus *Aspergillus terreus* isolated from roots of *Carthamus lanatus* L. (*Asteraceae*), one new butenolide derivative, Terrenolide S (**16**), together with six known compounds, (22E,24R)-stigmasta-5,7,22-trien-3-β-ol (**17**), stigmast-4-ene-3-one (**18**), stigmasta-4,6,8(14),22-tetraen-3-one (**19**), terretonin A (**20**), terretonin (**21**), and butyrolactone VI (22), has been isolated. Compounds **16**, **17,** and **18** exhibited antileishmanial activity toward *L. donovani* with IC_{50} values of 27.3, 15.3, and 11.2 μM, respectively, and IC_{90} values of 167, 40.6, and 14.7 μM, respectively (Elkhayata et al. 2015). The same kind of endophyte, the fungus *Aspergillus terreus* obtained from *Hyptis suaveolens* (L.) Poit, growing in the Brazilian wetland known as the Pantanal, showed trypanocidal and leishmanicidal

activities. Three compounds were isolated from the acetate extract of the fungal culture: terrein (**23**), butyrolactone I (**24**), and butyrolactone V (**25**). Compounds **23**, **24**, and **25** exerted moderate leishmanicidal activity against *L. amazonensis*, IC_{50} = 23.7, 26.0, and 78.6 μM, respectively. Furthermore, compounds **24** and **25** were examined for the trypanocidal effect on L929 cells from mouse connective tissue infected with *T. cruzi* amastigotes and promastigotes. Both compounds were inactive or toxic. Compounds **24** and **25** killed 100% of the cells at 94.2 and 181.6 μM, respectively. It was the first report on the leishmanicidal activity of compounds **23**, **24**, and **25** against *L. amazonensis* (Silva et al. 2017c).

Carvalho et al. (2015) obtained the endophytic fungus *Aspergillus calidoustus* isolated from leaves of *Acanthospermum australe* (*Asteraceae*), a medicinal plant native to the Brazilian savannah. From this endophyte, they recovered two compounds, ophiobolin K (**26**) and 6-epi-ophiobolin K (**27**), which showed trypanocidal activities with IC_{50} values of 13.0 and 9.6 μM against *T. cruzi*. However, these compounds were also cytotoxic to the fibroblast host cells of *T. cruzi*.

Nascimento et al. (2015) reported that endophytes associated with the medicinal plant *Vernonia polyanthes* are a potential source of leishmanicidal compounds. They recovered 16 endophythes from leaves of this plant growing in Brazil, and the fungal culture crude ethanol extracts were tested for their antileishmanial activity. The most active extract was obtained from *Cochliobolus sativus* (IC_{50} = 3.0 μg mL^{-1}). From this extract, a mixture of cochlioquinone A and isocochlioquinone A (**28**), and anhydrocochlioquinone A (**29**), was obtained. The mixture **28** exhibited a good antileishmanial activity, with an IC_{50} value of 10.2 μg mL^{-1}. Anhydrocochlioquinone A also presented an antileishmanial activity, but its IC_{50} value was five times higher (50.5 μg mL^{-1}).

11.9 Conclusion

Considering the high number of vegetal species living in the world, it is important to understand the methods and criteria to select the host plant for the study of endophyte communities in order to provide the best opportunities to isolate novel and potential endophytic fungi. Among the criteria used and described at the literature stands out the choice of medicinal plants (plants that have an ethnobotanical history), because that plants might be considered important reservoir of a promising source of novel endophytes and their compounds can be useful for human health and veterinary. The infectious/parasitic diseases and cancer, for example, discussed in this chapter still demand a special attention and need of investment in research considering the high mortality rate generated by some of them, together with the inexistence of an effective treatment without side effects and resistance. In this context, endophytic fungi are an alternative that might offer a high number of natural products with diverse chemical structures and novel pharmacological action's mechanism. Endophytic taxa mainly of the genus *Aspergillus*, *Chaetomium*, *Diaporthe*/*Phomopsis* complex, *Fusarium*, and *Penicillium* are potential producers

of bioactive compounds for the treatment of those diseases. Additionally, endophytes may contribute to their host plant and for the industry by producing a plethora of substances; however, the search for better treatments remains an important challenge and a constant niche to be explored.

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