Chapter 6
An Update on Bioactive Natural Products from Endophytic Fungi of Medicinal Plants

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Abstract Pathogens are developing resistance against the current regime of drugs, which urge the need of novel drugs. This has led scientists to explore natural sources that are safe as well as potent. Microbes have been explored for over decades for natural products and have been the vast reservoir of secondary metabolites of drugs

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potential. Because of their huge diversity and particular habituation, they can act as good resource to obtain bioactive secondary metabolites. Endophytes have been exploited to get drug-like molecules that have antibacterial, antifungal, anticancer, antioxidant, antidiabetic, antileishmaniasis, and antiviral activities. Here we review endophytic fungi as storehouse of naturally occurring bioactive secondary metabolites.

6.1   Introduction

De Bary in 1866 coined the term "endophyte," and according to him, "Endophytes are the microorganisms, which reside inside the plant tissues and are significantly different from those found on the plant surface." Since then a large number of definition were given by various researchers; each definition collectively says "Endophytes are the microbes that reside intra or intercellular in the tissues of host plants and there they do not give rise to any apparent deleterious effects." The endophytes have been found to be an excellent producer of bioactive metabolites of pharmaceutical importance (Bascom-Slack et al. 2009; Pimentel et al. 2011; Brader et al. 2014). Today most of the world population depends on natural products for treating various diseases because of its least side effects. Endophytes are propitious source of bioactive compounds with pharmaceutical importance, and many secondary metabolites of microbial origin are under clinical trials. The natural products were either derived from plants or microorganisms, and among microorganisms, endophytes have the major contribution. Since both plants and microbes have largely been explored for the isolation of compounds, bioprospection of microbes from unique niches would serve to gain the source of new metabolites to combat the upcoming challenges like resistance against the available drugs in the market (Kudo et al. 1998; Zuck 1998; Qin et al. 2010).

Due to extensive diversity of plants, it is expected that microbes residing inside them will act as an excellent source of novel compounds of various bioactivities. An endophytic fungus associates specifically with their host in a facultative or obligate or symbiotic relationship and mediates various signals of mutual relationship (Nair and Padmavathy 2014). These signals depend on the environment which the microbe faces inside the host plant, resulting in the specificity with their host (Dudeja et al. 2012). The endophytes face biotic and abiotic stresses inside the host plant which they overcome through interaction with each other and also with their host plant, resulting to produce diverse secondary metabolites (Liu et al. 2010; Shimizu et al. 2001) (Fig. 6.1). The majority of the bioactive compounds produced by endophytic fungi belong to the different structures and classes, such as quinolones, flavonoids, steroids, phenols, xanthones, terpenoids, etc. (Tan and Zou 2001) exhibiting diverse bioactive potentials including antibacterial, antifungal, antioxidants, antiviral, anticancer, immunosuppressive, etc. (Gunatilaka 2006; Qin et al. 2008). Being a source of structurally diverse and novel metabolites, the endophytic fungi would be
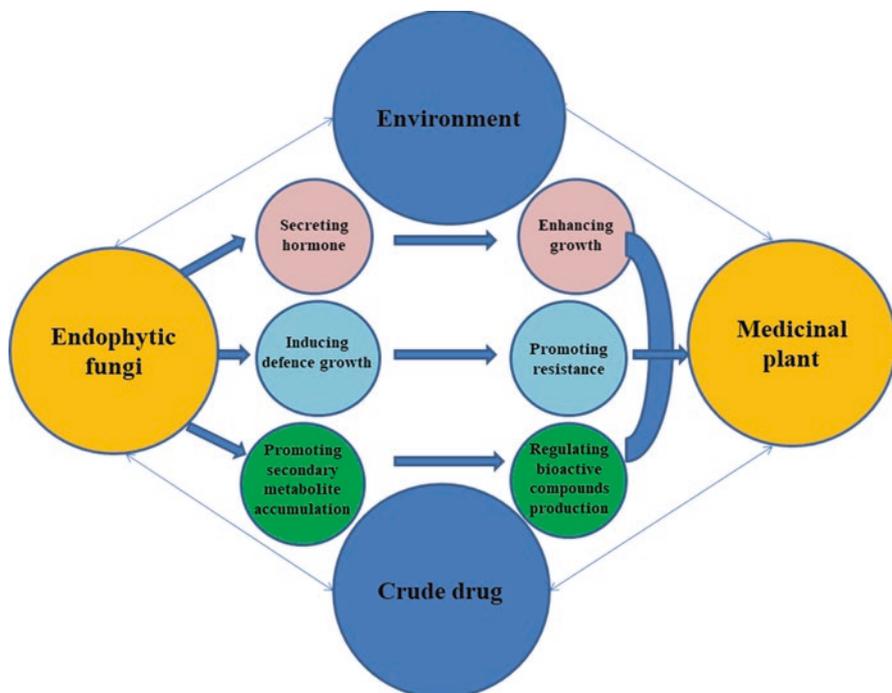
Fig. 6.1 Relationship of endophytic fungi with their host, enhancing growth, promoting resistance, and regulating the production and accumulation of secondary metabolites

promising to obtain the novel compounds if unique niches may explored. A schematic representation to exploit the endophytic fungi for bioactive metabolites has been given in Fig. 6.2.

6.2   Endophytic Fungi as a Storehouse of Bioactive Compounds

Endophytic fungi remain rich sources of many important therapeutic agents. Since decade endophytic fungi have been extensively explored for bioactive natural products. This appears to be emerging area of research which could give a boost to the drug discovery programs. Here we have reviewed and compiled the bioactive compounds reported from the endophytic fungi since the last 5 years. The secondary metabolites of antimicrobial, anticancer, antioxidant, antidiabetic, antileishmaniasis, and antiviral potential obtained from endophytic fungi of medicinal plants are listed and discussed below in the following sections.
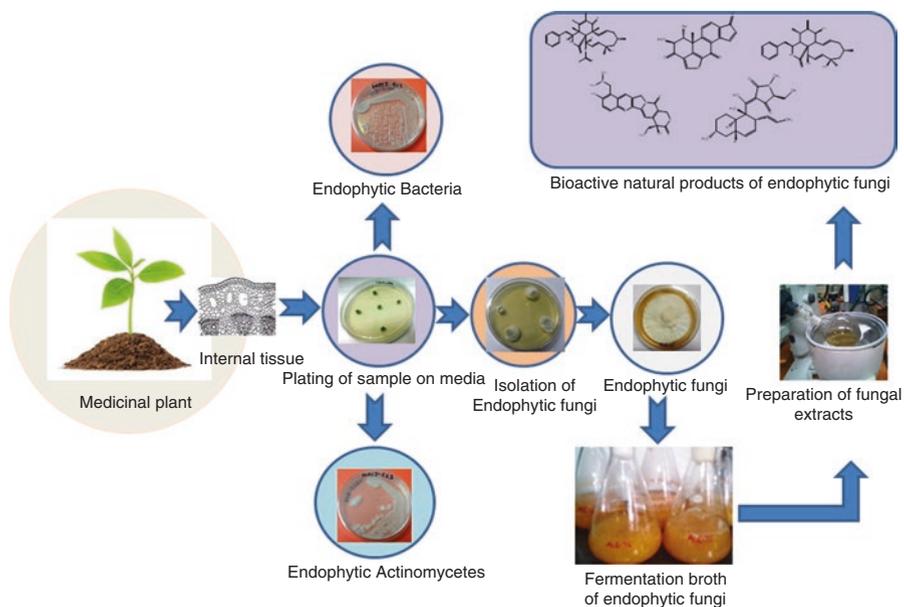
Fig. 6.2 Production of bioactive metabolites in endophytic fungi

6.2.1 Antibacterial Compounds from Endophytic Fungi

Antibacterial compounds can be defined as the molecules which have potential to kill or inhibit the growth of other microorganisms. Since two decades there has been an extensive hike of penicillin-resistant *Enterococcus faecium*, *Staphylococcus pneumonia*, and methicillin-resistant *Staphylococcus aureus* (MRSA). In view of resistance and inadequate number of drugs against the pathogens, there is a need for the hunt of new and diverse drugs that can confront with the upcoming challenges of variety of infections although a huge number of diverse and novel compounds with varied bioactivities have been reported from endophytic fungi but still many more to be discovered. The reviewed literature clearly indicates that the secondary metabolites produced by endophytic fungi belonging to diverse class of compounds such as flavonoids, xanthones, terpenoids, alkaloids, phenols, steroids, and quinines have antibacterial activities (Gao et al. 2018); the recent findings have been enlisted in Table 6.1 and represented in Fig. 6.3.

An endophytic fungus, *Colletotrichum gloeosporioides* of *Lannea coromandelica*, displayed considerable antimicrobial activity. One of the metabolite showed highest zone of inhibition with 25 mm zone formation against *Staphylococcus aureus*. The main compounds responsible for antimicrobial activity were 9-octadecenamide **(1)**, hexadecanamide **(2)**, diethyl phthalate **(3)**, 2-methyl-3-methyl-3-hexene **(4)**, and 3-ethyl-2, 4-dimethyipentane **(5)** (Tayung et al. 2011). In one study, the Di-n-octyl phthalate **(6)** was reported from *Aspergillus terreus* MP15,

Table 6.1 Antibacterial compounds derived from endophytic fungi

Compound	Endophytic fungi	Host plant	References
9-octadecenamide (1), hexadecanamide (2), diethyl phthalate (3), 2-methyl-3-methyl-3-hexene (4), and 3-ethyl-2,4-dimethyi-pentane (5)	*Colletotrichum gloeosporioides*	*Lannea coromandelica*	Tayung et al. (2011)
Di-n-octyl phthalate (6)	*Aspergillus terreus*	*Swietenia macrophylla*	Yin et al. (2015)
Ergosterol (7) and cerevisterol (8)	2L-5	*Ocimum basilicum*	Haque et al. (2005)
Fatty acid and phenolic compound	*Diaporthe phaseolorum*	*Tectona grandis L.f*	Kumala et al. (2015)
Tannins, phenols, and amino acid	*Stemphylium radicinum*	Calyptus	Hussain et al. (2014)
Colletotrichones A (9), colletotrichones B (10), and colletotrichones C (11)	*Colletotrichum* sp. BS4	*Buxus sinica*	Wang et al. (2016)
Equisetin (12)	*Fusarium* sp.	*Opuntia dillenii*	Ratnaweera et al. (2015)
Asperamide A (13) and cerebroside C (14)	*Aspergillus niger*	*Ipomoea batatas*	Shaaban et al. (2013)
Fusarubin methyl ether (15)	*Cladosporium* sp.	*Rauwolfia serpentina*	Khan et al. (2016)
Viriditoxin (16)	*Paecilomyces variotii*	*Laguncularia racemosa*	Silva et al. (2013)
Purpureone (17)	*Purpureocillium lilacinum*	*Rauvolfia macrophylla*	Lenta et al. (2016)
Alternariol 9-methyl ether (18)	*Alternaria* sp.	*Salvia miltiorrhiza*	Lou et al. (2016)
18-ethoxycytochalasin J (19), cytochalasins H (20), and cytochalasins J (21)	*Phomopsis* sp.	*Garcinia kola*	Jouda et al. (2016)
Phomosine A (22) and Phomosine C (23)	*Diaporthe* sp.	*Siparuna gesnerioides*	Sousa et al. (2016)
Terrein (24)	*Aspergillus terreus*	*Achyranthes aspera*	Goutam et al. (2017)
(22E,24R)-stigmasta-5,7,22-trien-3-β-ol (25)	*Aspergillus terreus*	*Carthamus lanatus*	Elkhayat et al. (2016)
Beauvericin (26)	*Epicoccum nigrum*	*Entada abyssinica*	Dzoyem et al. (2017)
Alternariol (27) and 3,7-dihydroxy-9-methoxy-2-methyl-6Hbenzo[c]chromen-6-one (28)	*Alternaria alternata*	*Grewia asiatica*	Deshidi et al. (2017)

a fungal endophyte of *Swietenia macrophylla*. The Di-n-octyl phthalate was found to be used as food preservative along with antibacterial potential against foodborne pathogenic bacteria that are *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus spizizenii*, and *Bacillus subtilis* (Yin et al. 2015). Antibacterial compounds can also be used as a food preservative, which acts to control the food spoilage that is the main concern for the problems created in the food chain (Liu and Xu 2008).
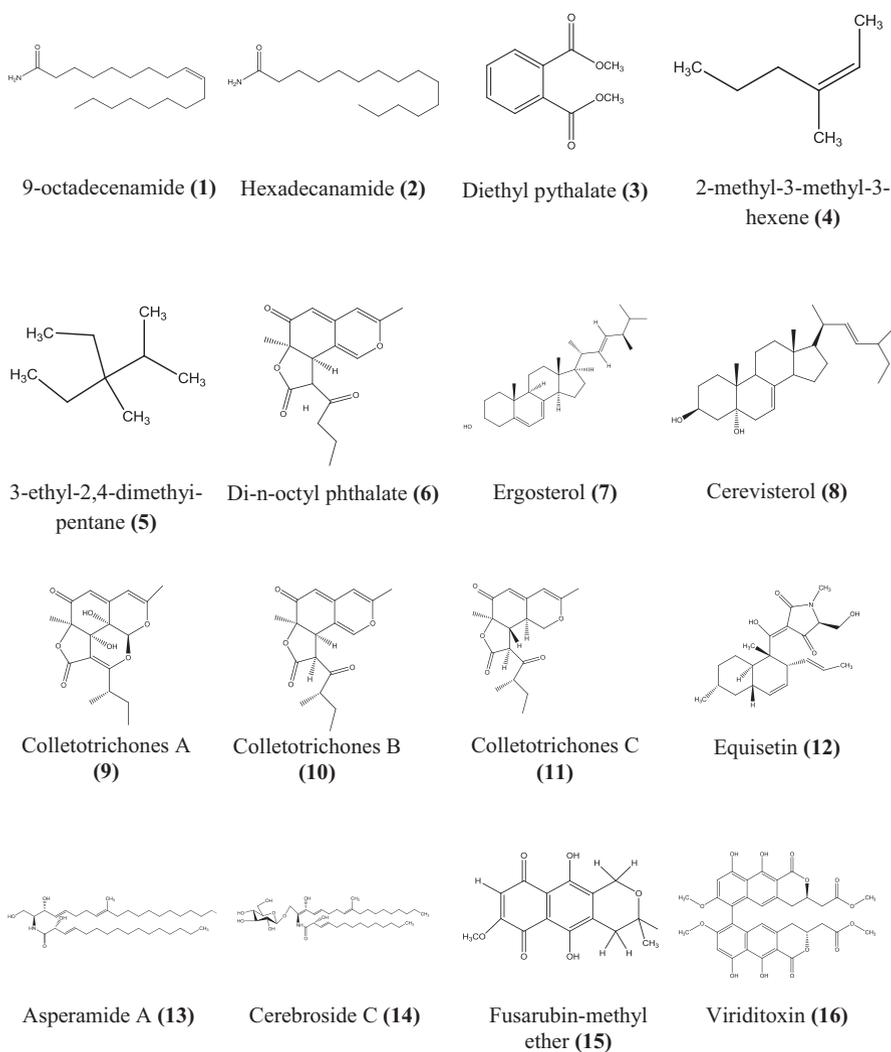
9-octadecenamide **(1)**   Hexadecanamide **(2)**   Diethyl pythalate **(3)**   2-methyl-3-methyl-3-hexene **(4)**

3-ethyl-2,4-dimethyi-pentane **(5)**   Di-n-octyl phthalate **(6)**   Ergosterol **(7)**   Cerevisterol **(8)**

Colletotrichones A **(9)**   Colletotrichones B **(10)**   Colletotrichones C **(11)**   Equisetin **(12)**

Asperamide A **(13)**   Cerebroside C **(14)**   Fusarubin-methyl ether **(15)**   Viriditoxin **(16)**

Fig. 6.3 Antibacterial compounds (**1-28**) from endophytic fungi

Similarly, *Ocimum basilicum* was explored, resulting to obtain 23 endophytic fungi from healthy leaf, stem, and roots. One of the endophytic fungi among them has been reported to produce two steroidal compounds, ergosterol **(7)** and cerevisterol **(8)**. The compounds were found to have antibacterial potential against *Bacillus cereus* and *Staphylococcus aureus* (Haque et al. 2005). Jati tree (*Tectona grandis L.f*) is an herbal plant that acts as host of an endophytic fungus *Diaporthe phaseolorum*. Four fractions were obtained from this fungus by using column chromatography;
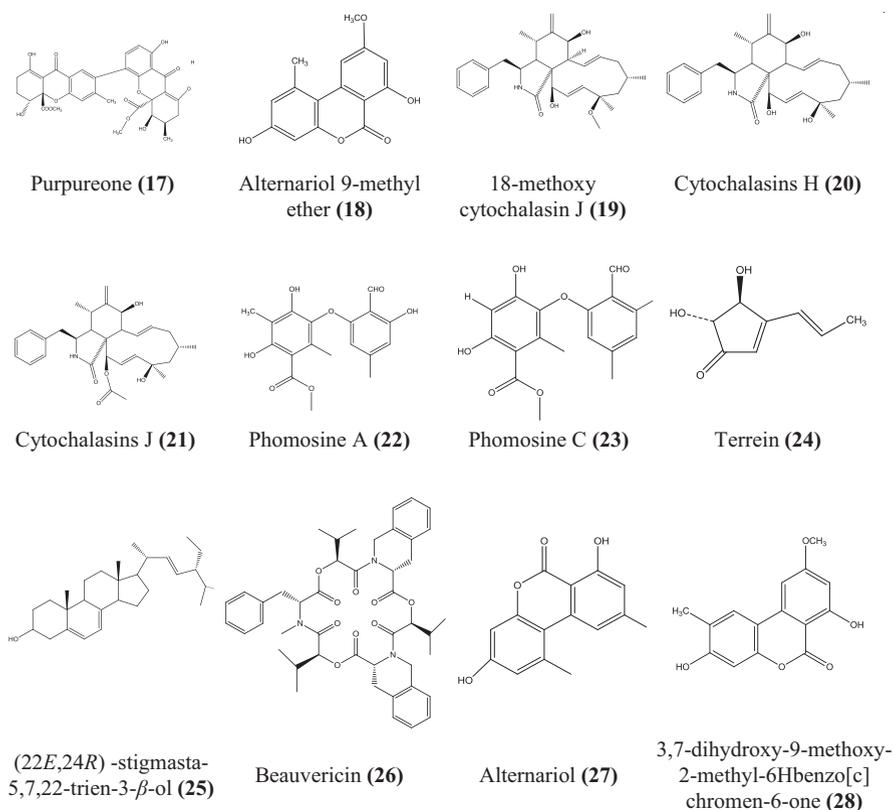
Purpureone **(17)**   Alternariol 9-methyl ether **(18)**   18-methoxy cytochalasin J **(19)**   Cytochalasins H **(20)**

Cytochalasins J **(21)**   Phomosine A **(22)**   Phomosine C **(23)**   Terrein **(24)**

(22*E*,24*R*) -stigmasta-5,7,22-trien-3-*β*-ol **(25)**   Beauvericin **(26)**   Alternariol **(27)**   3,7-dihydroxy-9-methoxy-2-methyl-6Hbenzo[c] chromen-6-one **(28)**

Fig. 6.3 (continued)

consequently the fraction IV was found to have potent antibacterial activity with a zone of inhibition at 11.10 mm when tested against *Staphylococcus aureus*. Further, a fatty acid and a phenolic compound have been reported via GCMS in the bioactive fraction (Kumala et al. 2015).

   Stemphylium radicinum an endophytic fungus was reported from the *Calyptus* roots collected from Misan city of Iraq. The extract of the fungus was found to have tannins, phenols, and amino acid as active secondary metabolites and shows potent activity against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Klebsiella pneumoniae*, and *Streptococcus pyogenes*. The antibacterial activity was performed using the disc diffusion technique, and the zones of inhibition were reported in the range of 22.5–35.5 mm with MIC of 25.0–100 μg/mL (Hussain et al. 2014).

Besides a reported compound chermesinone B, three novel, colletotrichones A−C **(9–11)** were isolated from the fungus *Colletotrichum* sp. BS4. The fungus was isolated from the leaves of traditional medicinal plant *Buxus sinica* of China. The compounds were evaluated for antibacterial potential tested with *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Colletotrichone A **(9)** was having MIC of 0.1 and 1.0 μg/mL against *B. subtilis* and *E.coli*, respectively, whereas the compound **10** and **11** shows activity with MIC value of 5.0 μg/mL against *S. aureus* and *E. coli*, respectively (Wang et al. 2013).

In one study, eight fungi were isolated from *Opuntia dillenii* and reported first time, among them the *Fusarium* sp. and *Aspergillus niger* were found to be the most bioactive. The fractionation of the extract of *Fusarium* sp., followed by bioactivity, led to the isolation of tetramic acid derivative, named equisetin **(12)**. Equisetin exhibited MIC value of 8 μg/mL against *Bacillus subtilis* and 16 μg/mL against MRSA and *Staphylococcus aureus*. The research article also concluded that the endophytic fungi isolated from rough and combative environment can also act as a source for diverse and novel bioactive compounds (Ratnaweera et al. 2015).

Aspergillus niger isolated from the leaves of *Ipomoea batatas* (sweet potato) was found to produce eight diverse bioactive compounds. The isolated compounds were characterized as ergosta-7,22-dien-3β,5α,6α-triol, aurasperone B, aurasperone C, aurasperone F, asperamide A **(13)**, cerebroside C **(14)**, linoleic acid, and R(-)-glycerol monolinoleate. Compounds **13** and **14** exhibited weak to moderate antibacterial activities (11–17 mm), among them cerebroside C showed higher activity than those of the non-glycosylated asperamide A. Cytotoxic examination of the isolated compounds against the brine shrimp confirmed their activities to range between moderate (28–35%) and weak (9–11%) (Naureen et al. 2015).

Two naphthoquinones, namely, anhydrofusarubin and methyl ether of fusarubin **(15)**, were isolated from an endophytic fungus, *Cladosporium* sp., isolated from the leaves of *Rauwolfia serpentina*. Fusarubin methyl ester at a concentration of 40 μg/disc exhibited prominent antibacterial activities against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus megaterium* with zone of inhibition of 27 mm, 25 mm, 24 mm, and 22 mm, respectively (Khan et al. 2016).

Viriditoxin **(16)** was isolated using column chromatography from *Paecilomyces variotii*, an endophytic fungus isolated from the healthy leaves of *Laguncularia racemosa*. Viriditoxin showed antibacterial activity against *Staphylococcus aureus* and *Enterococcus* sp. with MIC of 0.5 and 2 μg/mL, respectively (Silva et al. 2013). A new ergochromone derivative purpureone **(17)** was reported from an endophytic fungus *Purpureocillium lilacinum*, isolated from the roots of *Rauvolfia macrophylla*. Purpureone exhibited antibacterial activity against *Bacillus cereus*, *Escherichia coli*, and *Providencia stuartii* with MIC values below 62.6 μg/mL (Lenta et al. 2016).

Alternariol 9-methyl ether **(18)** isolated from the extract of *Alternaria* sp., an endophytic fungus from the roots of *Salvia miltiorrhiza Bunge*, inhibited the growth of six bacteria, i.e., *Agrobacterium tumefaciens*, *Bacillus subtilis*, *Pseudomonas lachrymans*, *Ralstonia solanacearum*, *Staphylococcus haemolyticus*, and *Xanthomonas vesicatoria* with MIC values ranging from 25 to 75 μg/mL (Lou et al. 2016).

Three reported cytochalasins that are 18-methoxycytochalasin J **(19)**, cytochalasin H **(20)**, and cytochalasin J **(21)** along with alternariol were reported from *Phomopsis* sp., an endophytic fungus obtained from the nuts of *Garcinia kola*. The cytochalasins exhibited strong activity against *Shigella flexneri*. The antibiotic ampicillin at concentration of 512 μg/mL was not able to show any inhibition against *Vibrio cholerae* NB2, *Vibrio cholerae* PC2, and *Shigella flexneri*, but interestingly *Shigella flexneri* was sensitive to the cytochalasins (Jouda et al. 2016).

Six compounds, 4H-1-benzopyra-4-one-2,3-dihydro-5-hydroxy-2,8-dimetyl, 4H-1-benzopyran-4-one-2,3-dihydro-5-hydroxy-8-(hydroxy-lmethyl)-2-methyl, 4H-1-benzopyra-4-one-2,3-dihydro-5-methoxyl-2,8-dimetyl, phomosine A **(22)**, phomosine C **(23)**, and phomosine D, were isolated from endophytic fungus *Diaporthe* sp. F2934 of *Siparuna gesnerioides*. Compound **22** at concentration 4 μg/mL showed 20% higher inhibition zone diameter (IZD) than vancomycin, standard against *Staphylococcus aureus*. It also exhibited activity against both Gram (+ve) and (−ve) bacteria, with respective IZD of 77–90% and 83–92%. Phomosine C showed an IZD against *S. aureus* (90%), *Micrococcus luteus* (60%), and *Streptococcus oralis* (61%) (Sousa et al. 2016). Terrein **(24)** exhibited IC_{50} of 20 μg/mL against *Enterococcus faecalis* and ˃20 μg/mL against *Staphylococcus aureus* and *Aeromonas hydrophila* (Goutam et al. 2017).

(22E,24R)-stigmasta-5,7,22-trien-3-*β*-ol **(25)** reported from the *Aspergillus terreus* an endophytic fungus isolated from *Carthamus lanatus* roots exhibited a potent activity against MRSA and *Cryptococcus neoformans* with respective IC_{50} values of 2.29 and 10.68 μM (Elkhayat et al. 2016).

In one study, beauvericin **(26)** isolated from *Epicoccum nigrum*, an endophytic fungus of *Entada abyssinica*, had significant antibacterial activity against *Bacillus cereus* and *Salmonella typhimurium* with MIC values of 3.12 and 6.25 μg/mL, respectively (Hewage et al. 2014).

Recently, alternariol **(27)**, alternariol 9-methyl ether, and 3,7-dihydroxy-9-methoxy-2-methyl-6Hbenzo[c]chromen-6-one **(28)** has been reported from an endophytic fungus *Alternaria alternata,* isolated from a well-known folk medicinal plant *Grewia asiatica*. This was the first report for the isolation of *Alternaria alternata* from this plant. Compounds were detected and quantified by a new multimode LC-ESI-MS/MS method using multiple reaction monitoring. Both **27** and **28** exhibited antibacterial activity against *S. aureus* and vancomycin-resistant *Enterococci* (VRE) with MIC values of 32 and 128 μg/mL, respectively, whereas **27** exhibited promising activity against methicillin-resistant *S. aureus* (MRSA)-15187 with MIC value of 8 μg/mL comparable to ciprofloxacin in contrast to 64 μg/mL of **28** (Deshidi et al. 2017).

6.2.2   Antifungal Compounds from Endophytic Fungi

The rate of fungal infection increases during graft transfer, allogeneic transplantation of the bone marrow, and chemotherapy in cancer patients. Still, a very less number of antifungal drugs are there in the market for treating lethal diseases like

aspergillosis, candidiasis, meningitis, fungal eye infection, ringworm, valley fever caused by *Cryptococcus gattii*, histoplasmosis, and sporotrichosis. Due to the evolving pathogenicity and resistance among the fungal pathogens, there is an immediate need of diverse and novel compounds to combat.

Isolation of microbial secondary metabolites has been a natural alternative for various therapeutic applications. Secondary metabolites of endophytic fungi have a great potential in various agricultural, industrial, and medical fields. There are many antifungal compounds that have been isolated from endophytic fungi (Fig. 6.4) which are listed in Table 6.2 and discussed in the following text.
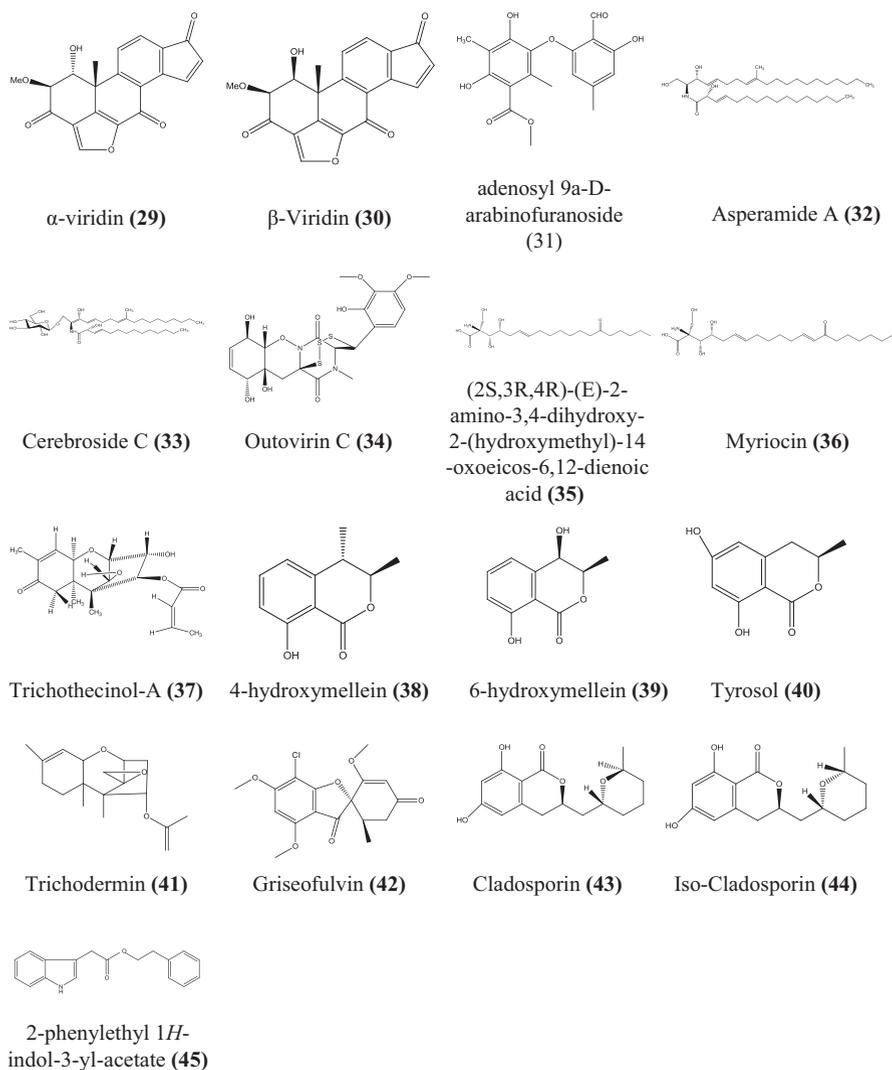
α-viridin **(29)**   β-Viridin **(30)**   adenosyl 9a-D-arabinofuranoside **(31)**   Asperamide A **(32)**

Cerebroside C **(33)**   Outovirin C **(34)**   (2S,3R,4R)-(E)-2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxoeicos-6,12-dienoic acid **(35)**   Myriocin **(36)**

Trichothecinol-A **(37)**   4-hydroxymellein **(38)**   6-hydroxymellein **(39)**   Tyrosol **(40)**

Trichodermin **(41)**   Griseofulvin **(42)**   Cladosporin **(43)**   Iso-Cladosporin **(44)**

2-phenylethyl 1*H*-indol-3-yl-acetate **(45)**

Fig. 6.4 Structures of antifungal compounds (**29–45**) from endophytic fungi

Table 6.2 Antifungal compounds derived from endophytic fungi

Compound	Endophytic fungi	Host plant	References
Terrein (**24**)	*Aspergillus terreus*	*Achyranthes aspera*	Goutam et al. (2017)
α-viridin (**29**), β-viridin (**30**), and adenosyl 9a-D-arabinofuranoside (**31**)	*Trichoderma* sp.	*Centaurea stoebe*	Abdou and Abdelhady (2015)
Asperamide A (**32**) and cerebroside C (**33**)	*Aspergillus niger*	*Ipomoea batatas*	Shaaban et al. (2013)
Outovirin C (**34**)	*Penicillium raciborskii*	*Rhododendron tomentosum*	Kajula et al. (2016)
(2S,3R,4R)-(E)-2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxoeicos-6,12-dienoic acid (**35**) and myriocin (**36**)	*Mycosphaerella* sp.	*Eugenia bimarginata*	Pereira et al. (2015)
Trichothecinol-A (**37**)	*Trichothecium* sp.	*Phyllanthus amarus*	Taware et al. (2014)
4-hydroxymellein (**38**) and 6-hydroxymellein (**39**), tyrosol (**40**), cervesterol (**8**)	*Penicillium* sp.	*Senecio flavus*	Elkhayat and Goda (2017)
Trichodermin (**41**)	*Trichoderma brevicompactum*	*Allium sativum*	Shentu et al. (2014)
Griseofulvin (**42**)	*Nigrospora oryzae*	*Emblica officinalis*	Rathod et al. (2014)
Cladosporin (**43**) and isocladosporin (**44**)	Cladosporium cladosporioides	–	Wang et al. (2013)
2-phenylethyl 1*H*-indol-3-yl-acetate (**45**)	*Colletotrichum gloeosporioides*	*Michelia champaca*	Chapla et al. (2014)

Secondary metabolites α-viridin **(29)**, β-viridin **(30)**, and adenosyl 9a-D-arabinofuranoside **(31)** were reported from an endophytic fungus *Trichoderma* sp. cultured from the stem of the medicinal plant *Centaurea stoebe*. These fungal metabolites **(29–31)** were tested for antifungal potential which shows MIC of 7.81, 15.63, and 8.52 μg/mL against *Aspergillus terreus*, respectively, while against *Fusarium oxysporum*, these compounds have MIC of 57.50, 75.00, and 63.30 μg/mL, respectively (Abdou and Abdelhady 2015).

In one study, asperamide A **(32)** and cerebroside C **(33)** displayed moderate to high activities against *Candida albicans* (13–15 mm) and *Mucor miehi* (16–18 mm) and the microalgae *Chlorella vulgaris* (13–14 mm), *Chlorella sorokiniana* (12–14 mm), and *Scenedesmus subspicatus* (13–15 mm) (Naureen et al. 2015).

Three novel epithiodiketopiperazine compounds outovirin A, outovirin B, and outovirin C **(34)** have been reported from the extracts of endophytic fungi *Penicillium raciborskii*, isolated from *Rhododendron tomentosum*. The essential oil and crude extracts of this plant have a number of properties like anti-insecticidal, antioxidant, and antimicrobial; leaves and flower extracts have traditionally been used in the primitive time for the treatment of various infections. Outovirin A is the first reported epimonothiodiketopiperazine, and outovirin C represents first most reported trisul-

fide gliovirin-like compound. Outovirin C inhibited growth of *Fusarium oxysporum*, *Botrytis cinerea*, *and Verticillium dahliae* at a mild concentration of 0.38 mM (207 μg/mL), but a more significant inhibition of growth was observed at a higher concentration of 0.76 mM (413 μg/mL) (Kajula et al. 2016).

Similarly, two eicosanoic acid compounds, (2S,3R,4R)-(E)-2-amino-3,4-dihydroxy-2-(hydroxymethyl)-14-oxoeicos-6,12-dienoic acid **(35)** and myriocin **(36)**, were isolated using bioassay-guided fractionation of crude extract by semi-prep HPLC and liquid-liquid partitioning of an endophytic fungus *Mycosphaerella* sp. UFMGCB 2032 cultured from *Eugenia bimarginata* DC. Both the compounds exhibited strong antifungal activity against *Cryptococcus neoformans* and *Cryptococcus gattii* and showed MIC values in the range of 1.3–2.50 μg/mL and 0.5 μg/mL, respectively (Pereira et al. 2015).

In one study trichothecinol-A **(37)** a sesquiterpene was reported for the very first time. The compound was isolated from an endophytic fungus *Trichothecium* sp. cultured from *Phyllanthus amarus*. Also, it exhibited moderate inhibition of *Cryptococcus albidus* var. *diffluens* (NCIM 3371 and 3372) with MIC values of 36 and 20 μg/mL, respectively, and against *Penicillium expansum* (NCIM 939) with MIC of 36 μg/mL (Taware et al. 2014). Recently, four compounds were reported from an endophytic fungus *Penicillium* sp. and characterized as 4-methylmellein, 4-hydroxymellein **(38)**, 6-hydroxymellein **(39)**, and tyrosol **(40)**. These compounds had shown activity against *Candida albicans*, *Fusarium oxysporum*, and *Aspergillus flavus* at the concentration of 50 μg per disc, with zones of inhibition in the range of 6–8 mm (Elkhayat and Goda 2017).

Trichodermin **(41)** was characterized from *Trichoderma brevicompactum*, an endophytic fungus strain 0248, reported from garlic. Bioactivity-guided fractionation was used to isolate this compound and identified by spectral analysis and mass spectrometry. Trichodermin showed potent antifungal activity against *Rhizoctonia solani* and *Botrytis cinerea* with an EC$_{50}$ of 0.25 μg/mL and 2.02 μg/mL, respectively (Shentu et al. 2014).

Similarly, the compound griseofulvin **(42)** was reported from *Nigrospora oryzae*, an endophytic fungus isolated from *Emblica officinalis*. Griseofulvin exhibited antifungal activity against *Fusarium oxysporum*, *Trichophyton mentagrophytes*, and *Microsporum canis* (Rathod et al. 2014).

The extract of *Fusarium proliferatum* an endophytic fungus cultured from *Syzygium cordatum* showed 100% cytotoxicity at 100 μg/mL against the brine shrimp *Artemia salina*. Upon fractionation seven biologically active colored compounds were isolated, namely, ergosta-5,7,22-trien-3β-ol, nectriafurone-8-methyl ether, 9-*O*-methyl fusarubin, bostrycoidin, bostrycoidin-9-methyl ether, and 8-hydroxy-5,6-dimethoxy-2-methyl-3-(2-oxo-propyl)-1,4-naphthoquinone. Fraction BS749_AR was having structural similarity to nectriafurone-8-methyl ether and labeled as compound 7. Due to the small amount of fraction, confirmation of the proposed structure and measuring its 2D NMR spectra was not possible. This fraction inhibited *Staphylococcus aureus* with zone diameter of 11 mm at 40 μg/paper disc. It also exhibited antifungal activity against *Rhizoctonia solani*

and *Aphanomyces cochlioides* with zone diameter of 11 and 10 mm, respectively (Dame et al. 2016).

Cladosporin **(43)**, isocladosporin **(44)**, 5′-hydroxyasperentin, and cladosporin-8-methyl ether were reported from crude extract of an endophytic fungus *Cladosporium cladosporioides* using bioassay-guided fractionation, and acetylation of 5′-hydroxyasperentin was used to synthesize a novel compound 5′,6-diacetylcladosporin. Compound **43** at 30 μM showed 92.7, 90.1, 95.4, and 79.9% growth inhibition of plant pathogens *Colletotrichum acutatum*, *Colletotrichum fragariae*, *Colletotrichum gloeosporioides*, and *Plasmopara viticola*, respectively, while **44** at the same concentration exhibited 50.4, 60.2, and 83.0% growth inhibition. This was the first report of 5-hydroxyasperentin and cladosporin-8-methyl ether from *Cladosporium cladosporioides* (Wang et al. 2013). 2-phenylethyl 1*H*-indol-3-yl-acetate **(45)** reported from an endophytic fungus *Colletotrichum gloeosporioides* cultured from *Michelia champaca* showed propitious antifungal activity against *Cladosporium cladosporioides* and *Cladosporium sphaerospermum* as same as that of the positive standard nystatin (Chapla et al. 2014).

Terrein **(24)** was recently isolated and characterized from an endophytic fungus *Aspergillus terreus* JAS-2 cultured from *Achyranthes aspera* traditional medicinal plant. Analysis of NMR data (¹H proton and ¹³C) and Fourier-transform infrared spectroscopy confirmed and characterized the product as 4,5-Dihydroxy-3-(1-propenyl)-2-cyclopenten-1-one (Goutam et al. 2017). Ten microgram/microliter concentration of terrein had shown inhibition of *Bipolaris sorokiniana* (57.14%), *Aspergillus flavus* (52.5%), and *Alternaria alternata* (91.25%) as compared to positive standard; 1 μg/μL was found sufficient for 100% growth inhibition of *Phytophthora drechsleri*. Terrein had also shown antioxidant potential by DPPH scavenging with IC$_{50}$ value of 112 μg/mL.

6.2.3 Anticancer Compounds from Endophytic Fungi

Through literature it is evident that the search for anticancer natural molecules always remains on priority in bioprospection of fungal endophytes, and there are many new compounds (Fig. 6.5) which were reported in recent 5 years, as listed in Table 6.3.

Taxol is a well-known diterpenoid for its anticancer activity (Wani and Taylor 1971); it was initially reported from the bark of western yew plant, *Taxus brevifolia*. The main function of taxol is to inhibit tubulin depolymerization during cell division. Taxol production from fungal endophytes using large-scale fermentation process is cost-effective and safe (Page et al. 2000). It has been reported from many endophytic fungi of genera *Alternaria*, *Fusarium*, *Monochaetia*, *Pestalotia*, *Pestalotiopsis*, *Pithomyces*, and *Taxomyces* (Strobel et al. 1996), and more than 20 fungal genera were identified for the biosynthesis of anticancer drug paclitaxel and its derivatives (Zhao et al. 2010).

Taxol **(46)** was also isolated from the endophytic fungus that is *Phomopsis longicolla* of *Aliyar* plant, and approximately 381 μg/mL amount of it was detected

Taxol **(46)**   Anhydrofusarubin **(47)**   Cytochalasin D **(48)**   Phomocytochalasin **(49)**

Cytochalasin N **(50)**   RKS-1778 **(51)**   Dankasterone B **(52)**   Cyclo(L-Ile-L-Leu) **(53)**

Vincristine **(54)**

methyl 9-dihydro-8-
trihydroxy-9-oxo-
Hxanthene-
1-carboxylate **(55)**

(E)-methyl 2-
hydroxy-6, 6-
dimethyl hept-3-
enoate **(56)**

11-dehydroxy
epoxyphomalin A **(57)**

10-deacetybaccatin **(58)**   Camptothecin **(59)**   Homoharringtonine **(60)**   Pyrrocidine A **(61)**
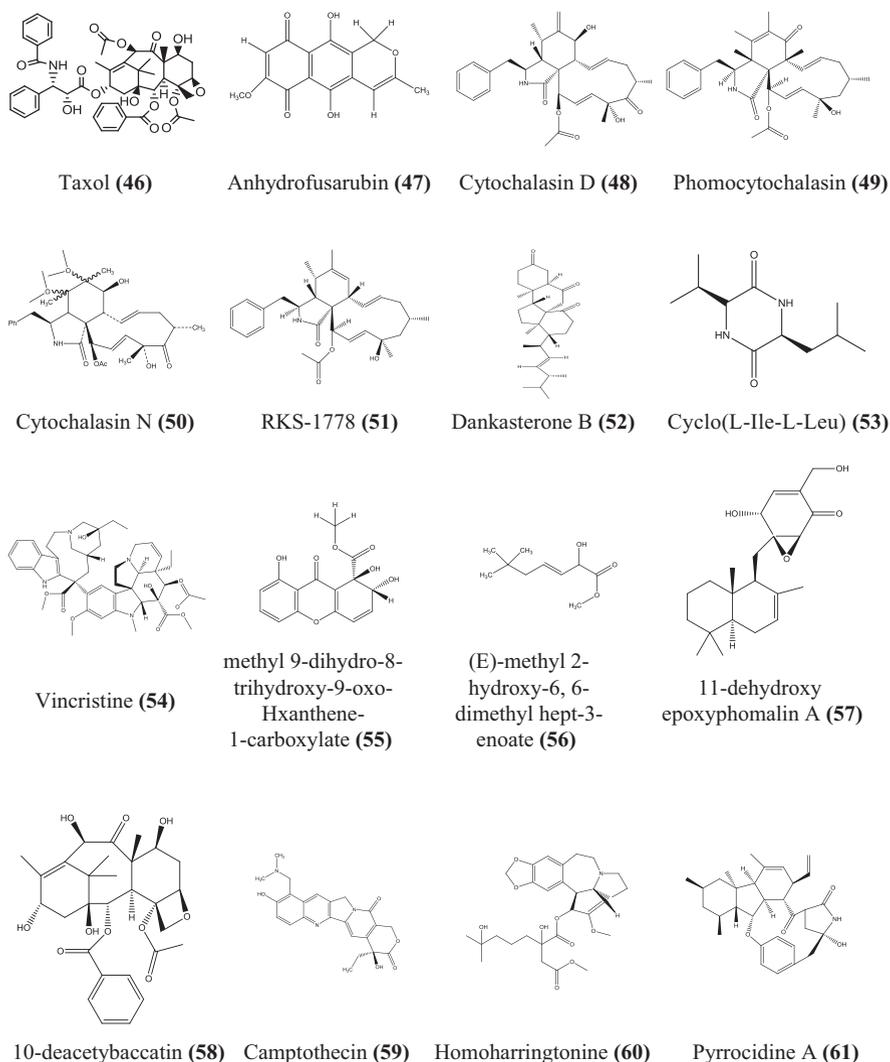
Fig. 6.5 Structures of anticancer compounds (**46–77**) from endophytic fungi

using HPLC. Podophyllotoxin is the precursor for the three clinically approved
anticancer drugs, Etoposide™, Etopophos™, and Teniposide™. Occurrence of this
compound is very less in nature that cannot meet the requirements for the production
of these well-known antineoplastic compounds in the medical industry. The search
for the natural production of this compound was started, and this was reported from
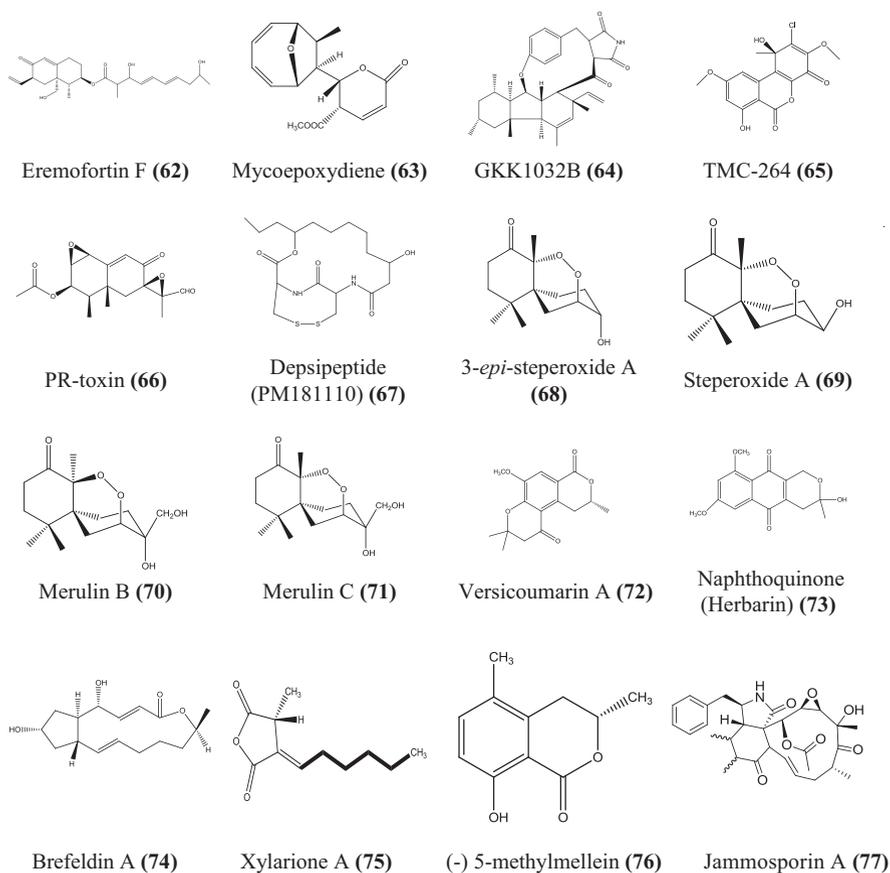the endophytic fungus *Alternaria tenuissima* cultured from roots of *Sinopodophyllum*

Eremofortin F **(62)**   Mycoepoxydiene **(63)**   GKK1032B **(64)**   TMC-264 **(65)**

PR-toxin **(66)**   Depsipeptide (PM181110) **(67)**   3-*epi*-steperoxide A **(68)**   Steperoxide A **(69)**

Merulin B **(70)**   Merulin C **(71)**   Versicoumarin A **(72)**   Naphthoquinone (Herbarin) **(73)**

Brefeldin A **(74)**   Xylarione A **(75)**   (-) 5-methylmellein **(76)**   Jammosporin A **(77)**

Fig. 6.5 (continued)

emodi (Wall.). HPLC was used for the isolation and quantification purposes and confirmed by using available authentic standards (Liang et al. 2015). This report concluded that using fermentation, podophyllotoxin can be isolated on large scale to fulfill clinical demands and also confirmed that endophytes isolated from the plant can produce the same compound because of its coevolution with their host due to the uptake of host genomes (Stierle et al. 1993).

Similarly, anhydrofusarubin **(47)** and methyl ether of fusarubin **(15)** isolated from the endophytic fungus *Cladosporium* sp. cultured from *Rauwolfia serpentina* leaves showed potent cytotoxicity against human leukemia cells (K-562) with IC_{50} values of 3.97 μg/mL and 3.58 μg/mL, respectively (Khan et al. 2016).

Table 6.3 Anticancer compounds derived from endophytic fungi

Compounds	Endophytic fungus	Host plant	References
18-methoxycytochalasin J (**19**), cytochalasin H (**20**), cytochalasin J (**21**), and alternariol (**27**)	*Phomopsis* sp.	*Garcinia kola*	Jouda et al. (2016)
Terrein (**24**)	*Aspergillus terreus*	*Achyranthes aspera*	Goutam et al. (2017)
α-viridin (**29**) and β-viridin (**30**)	*Trichoderma* species	*Centaurea stoebe*	Abdou and Abdelhady (2015)
Trichothecinol-A (**37**)	*Trichothecium* sp.	*Phyllanthus amarus*	Taware et al. (2014)
4-hydroxymellein (**38**) and 6-hydroxymellein (**39**)	*Penicillium* sp.	*Senecio flavus*	Elkhayat and Goda 2017
Anhydrofusarubin (**47**) and fusarubin methyl ether (**15**)	*Cladosporium* sp.	*Rauwolfia serpentina*	Khan et al. (2016)
Cytochalasin D (**48**)	*Xylaria* sp.	Seaweed	de Felício et al. (2015)
Phomocytochalasin (**49**), cytochalasin H (**19**), cytochalasin N (**50**), RKS-1778 (**51**), dankasterone B (**52**), and Cyclo(L-Ile-L-Leu) (**53**)	*Phomopsis theicola*	*Litsea hypophaea*	Hsiao et al. (2016)
Vinblastine and vincristine (**54**)	*Eutypella* sp.	*Catharanthus roseus*	Hani and Eman (2015)
11-dehydroxy epoxyphomalin A (**57**)	*Peyronellaea coffeae-arabicae*	*Pritchardia lowreyana*	Li et al. (2015b)
10-deacetylbaccatin III (**58**)	*Trichoderma* sp.	*Taxus wallichiana*	Li et al. (2015b)
Camptothecin (**59**)	*Fusarium oxysporum*	*Nothapodytes foetida*	Musavi et al. (2015)
Homoharringtonine (**60**)	*Alternaria tenuissima*	*Cephalotaxus hainanensis* Li	Hu et al. (2016)
Pyrrocidine A (**61**)	*Neonectria ramulariae*	*Cylindrocarpon* sp. and *Acremonium zeae*	Uesugi et al. (2016)
Eremofortin F (**62**) and mycoepoxydiene (**63**)	*Sabicea cinerea*	*Rubiaceae* sp.	Mandavid et al. (2015)
GKK1032B (**64**)	Penicillium citrinum	G. mangostana	Qader et al. (2015)
TMC-264 (**65**) and PR-toxin (**66**)	*Penicillium Chermesinum*	*Heritiera Littoralis*	Darsih et al. (2015)
Depsipeptide (PM181110) (**67**)	*Phomopsis glabrae*	*Pongamia pinnata*	Verekar et al. (2014)
3-*epi*-steperoxide A (**68**), steperoxide A (**69**), merulin B (**70**), and merulin C (**71**)	*Pseudolagarobasidium acaciicola*	*Bruguiera gymnorrhiza*	Wibowo et al. (2014)

(continued)

Table 6.3 (continued)

Compounds	Endophytic fungus	Host plant	References
Versicoumarin A **(72)**	*Aspergillus versicolor*	*Paris marmorata*	Ye et al. (2014)
Naphthoquinone (herbarin) **(73)**	*Dendryphion nanum*	*Ficus religiosa*	Mishra et al. (2013)
Brefeldin A **(74)**	*Penicillium* sp.	*Panax notoginseng*	Xie et al. (2017)
Xylarione A **(75)** and (-)5-methylmellein **(76)**	*Xylaria psidii*	*Aegle marmelos*	Arora et al. (2016)
Jammosporin A **(77)**	*Rosellinia sanctae-cruciana*	*Albizia lebbeck*	Sharma et al. (2018)
E2.2	*Colletotrichum gloeosporioides*	*Phaleria macrocarpa*	Gasong and Tjandrawinata (2016)
α-Pyrone derivative	*Pestalotiopsis microspore*	*Taxus chinensis*	Li et al. (2015a)

In one study an endophytic fungus, *Colletotrichum gloeosporioides* of *Phaleria macrocarpa*, was reported to yield E2.2 compound. This compound is responsible for its anticancer activity toward MDA-MB-231 and MCF-7 human breast adenocarcinoma cell lines. Phloroglucinol was found to better enhance the production of this compound. Production was found high when incubated in PDB medium, pH 5.0, and kept for 15 days in incubation (Gasong and Tjandrawinata 2016).

A well-known anticancer and antibiotic, cytochalasin D **(48)**, was isolated from *Xylaria* sp. This was the first report for the isolation of cytochalasin from marine seaweed endophyte (de Felício et al. 2015). Recently, three reported cytochalasins, 18-methoxycytochalasin J **(19)**, cytochalasin H **(20)**, and cytochalasin J **(21)**, along with one more compound named alternariol **(27)** characterized from an endophytic fungus *Phomopsis* sp. showed promising cytotoxic activity against human cancer cells with IC_{50} in the range of 3.66–35.69 µg/mL and without any toxicity against normal cell lines (Jouda et al. 2016). A new cytochalasin along with five reported cytochalasins has been characterized from the solid-state fermentation of *Phomopsis theicola* BCRC 09F0213, an endophytic fungus isolated from the leaves of *Litsea hypophaea* Hayata. In one study, a new cytochalasin named as Phomocytochalasin **(49)** and five others were reported as cytochalasin H **(20)**, cytochalasin N **(50)**, RKS-1778 **(51)**, dankasterone B **(52)**, and cyclo(L-Ile-L-Leu) **(53)**. Among the isolated compounds, cytochalasin N showed nitric oxide inhibitory activity with IC_{50} values of 77.8 µM, whereas the other cytochalasins have shown IC_{50} values >100 µM. All the isolates were also tested for interleukin-6 (IL-6) inhibitory activity and showed IC_{50} values of >100 µM. The cytochalasin H showed progesterone receptor antagonism with IC_{50} values of 1.42 µM compared with positive standard RU486 with IC_{50} of 0.063 nM (Hsiao et al. 2016).

Catharanthus roseus is a well-known herbal plant for the synthesis of two valuable anticancer compounds, vincristine and vinblastine. Recently, the production of vincristine **(54)** was reported from an endophytic fungus *Eutypella* sp. CrP14 isolated from the stem of *Catharanthus roseus*. The presence of vincristine was confirmed using chromatographic and spectroscopic analysis. Vincristine showed potent cytotoxic activity in the MTT assay against human squamous carcinoma cells – A431. It was also able to induce apoptosis and causes loss of mitochondrial membrane potential, DNA fragmentation, and generation of reactive oxygen species (Kuriakose et al. 2016).

In one study methyl 9-dihydro-8-trihydroxy-9-oxo-Hxanthene-1-carboxylate **(55)** and (E)-methyl 2-hydroxy-6, 6-dimethyl hept-3-enoate **(56)** were reported from the *Chaetomium globosum*, which suppress the growth of Michigan Cancer Foundation-7 (MCF-7) breast cancer cell line and human liver carcinoma cancer cell line (HepG-2) (Hani and Eman 2015).

The fungus *Peyronellaea coffeae-arabicae* isolated from *Pritchardia lowreyana* was explored, from which peyronellins A–C and 11-dehydroxy epoxyphomalin A **(57)** were obtained. The compound **57** was found to inhibit STAT3 at 5 μm along with potent anticancer activity (IC_{50} 0.5 μM) against ovarian cancer cell lines (OVCAR3) (Li et al. 2016).

Taxol is produced in a semisynthetic method using two precursors baccatin III and 10-deacetylbaccatin III; vast literature is available where these two precursors are produced along with taxol. Endophytic fungi add special references in the production of 10-deacetylbaccatin III **(58)** by *Trichoderma* sp. isolated from *Taxus wallichiana* (Li et al. 2015b).

Camptothecin (CPT) is a topoisomerase I-DNA inhibitor and was first reported from *Camptotheca acuminata* Decne (Nyssaceae), a deciduous tree of South China, which has attained inordinate attention due to its potential antitumor activities in experimental studies. In the last decade, camptothecin (CPT) **(59)** along with its analogues such as 9-methoxycamptothecin (MCPT) and 10-hydroxycamptothecin (HCPT) was found to be produced by many endophytic fungi isolated from plant *Camptotheca acuminata* and many plants belonging to the family *Icacinaceae* (Musavi et al. 2015). There are a number of problems regarding production of these compounds by fermentation, as in many endophytic fungal strains like *Fusarium solani* (Kusari et al. 2011) and *Aspergillus* sp. (Pu et al. 2013); after subsequent subculturing the loss of the biosynthetic ability was observed. Recently, Venugopalan and Srivastava (2015) highlighted the increased production of CPT by endophytic fungi *F. solani* isolated from *Camptotheca acuminata*.

α-Viridin **(29)**, β-viridin **(30)**, and adenosyl 9a-D-arabinofuranoside **(31)** were reported from an endophytic *Trichoderma* sp. cultured from the stems of the medicinal plant *Centaurea stoebe*. **29–31** shows promising cytotoxic and antitumor effects on different cancer cell lines such as HUVEC, K-562, and HeLa. β-Viridin shows GI_{50} value of 0.5 and 0.25 μg/mL against HUVEC and K-562 cell lines, respectively, whereas α-viridin shows GI_{50} of 0.02 and 0.01 μg/mL, respectively. α-Viridin and β-viridin show potent cytotoxicity with CC_{50} (HeLa) of 29.09 and 11.43 μg/mL, respectively. A novel *α*-pyrone derivative, together with four reported metabolites,

was isolated from *Pestalotiopsis microspora*, an endophytic fungus cultured from the stem of *Taxus chinensis* on the solid-state media. Both antimicrobial and anticancer activities were evaluated, but this compound did not have any significant activity (Li et al. 2015b).

Homoharringtonine (HHT) **(60)** is a natural alkaloid obtained from the bark of *Cephalotaxus hainanensis* and is widely used for treating human chronic myeloid leukemia. Due to slow growing and scarcity of the plant, there is a need for some other alternative that can fulfill the rising requirement of the drug in the market. An endophytic fungus *Alternaria tenuissima* isolated from this plant was found to produce the compound homoharringtonine; this supports the theory that endophytes during its coevolution with plants had gained the ability to synthesize the same product as host plant. The extract of endophytic fungi exhibited strong antiproliferative activity against K562, NB4, and HL-60 cancer cell lines with the IC_{50} values 67.25 ± 4.26, 65.02 ± 4.75, and 99.23 ± 4.26 μg/mL, respectively. Activity may be due to additional compounds in the crude extract that shows synergetic effect. Screening of HHT production was carried out using HPLC analysis and comparing the mass with that of standard (Hu et al. 2016).

Pyrrocidines A **(61)** is a natural metabolite of alkaloid class and reported from endophytic fungi (*Cylindrocarpon* sp. and *Acremonium zeae*), and it is well known for its antimicrobial activity. This compound is also capable of inducing shrinkage of nuclear DNA and its breakage into small fragments and activation of caspase activity in HL60 cancer cell lines. Its action of inducing apoptosis is different from other clinically approved drugs in the market, and it is due to the presence of unique α,β-unsaturated carbonyl moiety in the molecule (Uesugi et al. 2016).

In one study four metabolites, altiloxin A, enamidin, eremofortin F **(62)**, and mycoepoxydiene **(63)**, were reported from the *Sabicea cinerea*, an endophytic fungus closely related to *Diaporthe pseudomangiferae* obtained from the leaves of a plant of Rubiaceae family. Mycoepoxydiene and altiloxin A are well-known metabolites, whereas enamidin and eremofortin F were reported first time in the literature. Mycoepoxydiene showed promising cytotoxic activity with IC_{50} values of 7.5, 17.7, and 15.8 μM against KB, MDA-MB-435, and MRC5 cancer cell lines, respectively. Altiloxin A and enamidin showed no effect ($IC_{50} > 30$ μM) on all tested cell lines, and eremofortin F was cytotoxic on KB and MRC5 cells ($IC_{50} = 13.9$ and 12.2 μM, respectively) (Mandavid et al. 2015).

An endophytic fungus *Penicillium citrinum* isolated from the pericarp surface of *Garcinia mangostana* was reported to produce GKK1032B **(64)**, citrinin, and ergosterol. Citrinin is a nephrotoxin mycotoxin that is repeatedly synthesized by fungus *P. citrinum* (Malmstrøm et al. 2000). GKK1032B an antitumor antibiotic was first reported from unidentified species of *Penicillium* in 2001 along with two more metabolites GKK1032A1 and GKK1032A2 (Koizumi et al. 2001). Pastre et al. in 2007 reported reisolation of the compound from an endophytic fungi *Penicillium* sp. of *Melia azedarach* and *Murraya paniculata*. This was the third time to report isolation of GKK1032B from *Penicillium citrinum*. Since this class of metabolites has not been isolated from any other species of *Penicillium*, it was concluded that the

two unidentified *Penicillium* strains in the previous papers can be *P. citrinum* (Qader et al. 2015).

Similarly, new fungal metabolites, penicilliumolide A, penicilliumolide B, penicilliumolide C, and penicilliumolide D, a derivative of PR-toxin, along with three reported compounds, TMC-264 **(65)**, PR-toxin **(66)**, and a sesquiterpene, were isolated from *Penicillium chermesinum*, an endophytic fungus of a mangrove tree, *Heritiera littoralis*. The TMC-264 and PR-toxin showed effective as well as selective cytotoxicity against some cancer cell lines. TMC-264 also showed similar cytotoxic activity as of standard doxorubicin against T47D and MDA-MB231 cancer cell lines, and its cytotoxicity against HepG2 cell line was higher than etoposide. Derivatives of TMC-264 did not possess the activity; therefore, it is concluded that the cytotoxicity of TMC-264 was probably because of the presence of β-chloro-substituted α,β-unsaturated ketone in its structure (Darsih et al. 2015).

A new depsipeptide (PM181110) **(67)** was isolated from *Phomopsis glabrae*, an endophytic fungus cultured from the leaves of *Pongamia pinnata*. The compound was tested for its cytotoxicity against a panel of 40 human tumor cell lines out of which it showed activity in a concentration-dependent manner against all cell lines of bladder, colon, gastric, head and neck, liver, lung (non-small-cell lung carcinoma), mammary, ovarian, pancreatic, prostate, renal, and uterus cancer, as well as melanoma, pleural mesothelioma, and sarcoma. Pancreatic cancer cell line PAXF 546L (IC_{50}, 0.016 μM) and the lung cancer cell line LXFA 526 L (IC_{50}, 0.021 μM) were the most sensitive cell lines. The compound also exhibited ex vivo efficiency toward all human tumor xenografts (mean IC_{50} 0.245 μM) (Verekar et al. 2014).

In one study, two new norsesquiterpenes citicoline A and spiroacaciicolide A, a new nor-chamigrane 3-*epi*-steperoxide A **(68)**, along with three known compounds steperoxide A **(69)**, merulin B **(70)**, and merulin C **(71)**, were reported from an endophytic fungus *Pseudolagarobasidium acaciicola*, cultured from a mangrove tree *Bruguiera gymnorrhiza*. The compounds **68–71** showed cytotoxic activity toward many cancer cell lines. Among them compounds **70** and **71** displayed promising cytotoxic activity against MOLT-3, HuCCA-1, A549, HepG2, HL-60, MDA-MB-231, T47D, and HeLa cancer cell lines with IC_{50} in the ranges of 0.68–3.71 and 0.67–5.25 μg/mL, respectively. Compound **70** exhibited weak cytotoxic activity with an IC_{50} range of 11.94–49.08 μg/mL, whereas compound **71** exhibited the most potent cytotoxic activity against HL-60 cancer cells, with an IC_{50} value of 0.08 μg/mL, and in addition displayed IC_{50} value in the range of 0.19–3.75 μg/mL against other tested cell lines (Wibowo et al. 2014).

Versicoumarin A **(72)** was reported from an endophytic fungus *Aspergillus versicolor* cultured from the rhizomes of Paris marmorata plant. This compound exhibited strong cytotoxicities against A549 and MCF7cancer cells with IC_{50} values of 3.8 and 4.0 mM, respectively (Ye et al. 2014).

Two naphthoquinones were isolated from *Dendryphionnanum*, an endophytic fungus of *Ficus religiosa*. This was the first report for the isolation of naphthoquinone compounds from this fungus. Naphthoquinone antibiotic herbarin **(73)** exhibited potent inhibition of TNF-α and IL-6 cytokine production in human mononuclear

cell line (THP-1) induced with LPS with IC_{50} of 0.60 ± 0.100 μM and 0.06 ± 0.009 μM, respectively (Mishra et al. 2013).

Recently, Brefeldin A **(74)** produced from *Penicillium* sp., an endophytic fungus isolated from the healthy root of *Panax notoginseng*, showed strong anticancer activity against 293 (human renal epithelial cell line), HepG2, Huh (human hepato-cellular carcinoma cell line), and KB (human oral epidermoid carcinoma cell line) with ID_{50} value of 0.45 ± 0.008, 0.0024 ± 0.002, 0.035 ± 0.005, and 0.06 ± 0.009 μM, respectively (Xie et al. 2017).

One new compound xylarione A **(75)** along with (-) 5-methylmellein **(76)** has been reported from an endophytic fungus *Xylaria psidii* cultured from the leaves of a well-known traditional medicinal plant, *Aegle marmelos*, also called "Bael" in Hindi. Both the compounds were active against pancreatic cancer cell line (MIA-Pa-Ca-2) and exhibited cytotoxicity with IC_{50} values of 16.0 and 19.0 μM, respectively. Compounds were capable of cell arrest at the sub-G1 phase, exhibited different signs of apoptotic mechanism, and also cause loss of MMP in a dose-dependent manner when analyzed using flow cytometry. This result concludes that these metabolites can be modified for making its derivatives and for making more potent drugs (Arora et al. 2016).

One new cytochalasin, named jammosporin A (**77**), and four known compounds 19,20-epoxycytochalasin D, cytochalasin D, 19,20-epoxycytochalasin C, and cyto-chalasin C, were isolated from the endophytic fungus *Rosellinia sanctae-cruciana*, cultured from the leaves of medicinal plant *Albizia lebbeck*. Compound **77** showed considerable cytotoxic potential against the human leukemia cancer cell line (MOLT-4) with IC_{50} values of 20.0 μM. This was the first report for the isolation of this class of secondary metabolites in *Rosellinia sanctae-cruciana* fungus from this plant (Sharma et al. 2018).

As discussed in the earlier section about the compounds 4-hydroxymellein **(38)** and 6-hydroxymellein **(39)** having antifungal activity, both the compounds also exhibited cytotoxic activity toward MCF-7 cancer cell lines with ED_{50} value of 6.1 and 8.3 μg/mL, respectively (Elkhayat and Goda 2017). Similarly, the compound **35** at concentration of 500 nM exhibits 50% cell death in HeLa and B16F10 cells and 25% in MDA-MB-231 cells (Taware et al. 2014).

6.2.4 Antioxidant Compounds from Endophytic Fungi

Antioxidants of natural origin are the compounds that are commonly found in medicinal plants, fruits, and vegetables. However, it is reported that a large number of secondary metabolites from fungal endophytes are having potent antioxidant activity, and some of the recent compounds (Fig. 6.6) are listed in Table 6.4.

Recently, two antioxidant compounds, terreic acid **(78)** and 6-methylsalicylic acid **(79)**, were reported from *Pestalotiopsis* sp. EST 02, an endophytic fungus of plant *Elaeocarpus sylvestris*. Both the compounds have shown potent DPPH radical
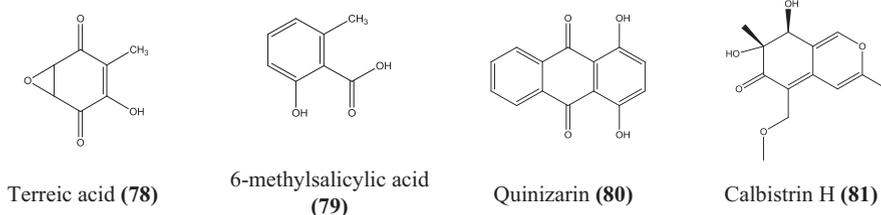
Terreic acid **(78)**   6-methylsalicylic acid   Quinizarin **(80)**   Calbistrin H **(81)**
                                        (79)

Fig. 6.6 Structures of antioxidant compounds (**78–81**) from endophytic fungi

Table 6.4 Antioxidant compounds derived from endophytic fungi

Compounds	Endophytic fungi	Host plant	References
Terreic acid **(78)** and 6-methylsalicylic acid **(79)**	*Pestalotiopsis* sp.	*Elaeocarpus sylvestris*	Prihantini and Tachibana (2017)
Anthraquinone quinizarin **(80)**	*Epicoccum nigrum*	*Entada abyssinica*	Dzoyem et al. (2017)
Calbistrin H **(81)**	*Dothideomycete* sp.	–	Hewage et al. (2014)

scavenging activity with IC_{50} value of 0.22 ± 0.02 mmol/L and 3.87 ± 0.27 mmol/L, respectively. The compounds also showed good activities from the reducing power and β-carotene bleaching assays (Prihantini and Tachibana 2017).

The four compounds beauvericin, parahydroxybenzaldehyde, indole-3-carboxylic acid, and quinizarin were isolated from *Epicoccum nigrum*, an endophytic fungus of *Entada abyssinica*. Anthraquinone quinizarin **(80)** exhibited excellent scavenging activity having IC_{50} values of 10.86 and 11.36 μg/mL in the ABTS and DPPH assays, respectively (Dzoyem et al. 2017).

Calbistrin H **(81)** was reported from an endophytic fungus *Dothideomycete* sp. CRI7 on PDB medium using one strain many compounds (OSMAC) approach. It shows radical scavenging potential with an IC_{50} value of 21.7 μM (Hewage et al. 2014).
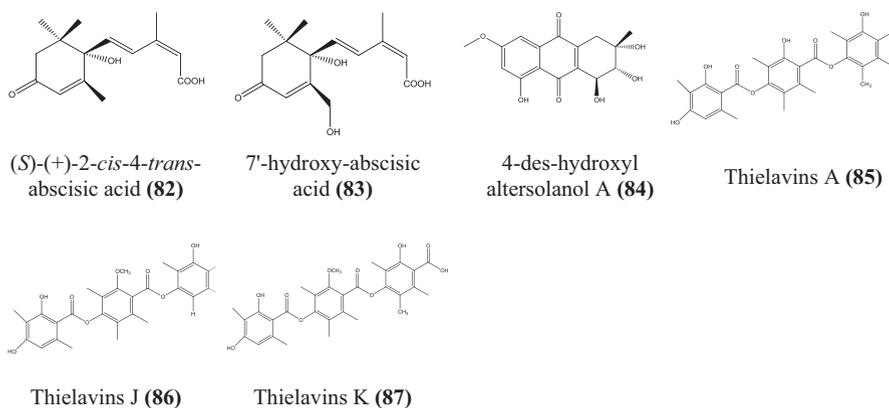
6.2.5 Antidiabetic Compounds from Endophytic Fungi

Diabetes mellitus is a metabolic disease caused by a defect in secretion of insulin and its action. Since diabetes prevalence has been rising, urge to find natural products of antidiabetic potential. The recent findings have been listed in Table 6.5 and represented in Fig. 6.7.

An endophytic fungus *Dendryphion nanum* (Nees) S. Hughes was isolated from the leaves of *Ficus religiosa* from which a naphthoquinone compound herbarin **(73)**

Table 6.5 Antidiabetic compounds derived from endophytic fungi

Compound	Endophytic fungi	Host plant	References
Naphthoquinone (herbarin) **(73)**	*Dendryphion nanum*	*Ficus religiosa*	Mishra et al. (2013)
(*S*)-(+)-2-*cis*-4-*trans*-abscisic acid **(82)**, 7′-hydroxy-abscisic acid **(83)**, and 4-des-hydroxyl altersolanol A **(84)**	*Nigrospora oryzae*	*Combretum dolichopetalum*	Uzor et al. (2017)
Thielavins A **(85)**, J **(86)**, and K **(87)**	MEXU 27095	*Hintonia latiflora*	Rivera-Chávez et al. (2013)

(*S*)-(+)-2-*cis*-4-*trans*-abscisic acid **(82)**   7′-hydroxy-abscisic acid **(83)**   4-des-hydroxyl altersolanol A **(84)**   Thielavins A **(85)**

Thielavins J **(86)**   Thielavins K **(87)**

Fig. 6.7 Structures of antidiabetic compounds (**82–87**) from endophytic fungi

was isolated. The herbarin was found to induce the glucose uptake in rat skeleton muscle with IC_{50} of 0.80 ± 0.090 μM in the presence of insulin (Mishra et al. 2013).

A peptide was obtained via semi-prep HPLC from an endophytic fungus *Aspergillus awamori* of *Acacia nilotica*. The peptide was further resolved using SDS-PAGE to determine its molecular weight, which was found to be of 22 kDa size. The peptide resulted in a mixed type of inhibition against both α-amylase and α- glucosidase and showed IC_{50} values of 3.75 and 5.625 μg/mL, respectively (Singh and Kaur 2016).

Three metabolites (*S*)-(+)-2-*cis*-4-*trans*-abscisic acid **(82)**, 7′-hydroxy-abscisic acid **(83)**, and 4-des-hydroxyl altersolanol A **(84)** were isolated from *Nigrospora oryzae*, an endophytic fungus of *Combretum dolichopetalum*. The crude extract of the fungus reduced the fasting blood sugar by 30.79% in 3 h; simultaneously the compounds also showed reduction of 46.37% (3 h), 44.96% (9 h), and 43.70% (9 h), respectively. Comparable activity of extract and compounds was found with that of standard glibenclamide (reduction of 48.72% in 9 h) (Uzor et al. 2017).

MEXU 27095, an endophytic fungus, was isolated from the Mexican medicinal plant *Hintonia latiflora*, and the bioassay-guided fractionation of the bioactive organic extract resulted in the separation of three tridepsides, namely, thielavins A, J, and K (**85–87**). Compounds **85–87** were capable of inhibiting α-glucosidase (α-GHY) *Saccharomyces cerevisiae* in a concentration-dependent manner and exhibited IC_{50} values of 23.8, 15.8, and 22.1 μM, respectively. Inhibitory action of the compounds was higher than that of the standard acarbose ($IC_{50} = 545$ μM), used as a positive control for the analysis (Rivera-Chávez et al. 2013).

6.2.6   Antileishmaniasis Compounds from Endophytic Fungi

Leishmaniasis is a serious health problem worldwide, mainly in tropical and sub-tropical areas where the protozoan has developed resistance to current available drugs in the market. In the absence of effective vaccines, still now chemotherapy plays an important role in fighting this disease. Therefore, the search for novel, effective, and safe drugs is essential for the treatment, control, and prevention of leishmaniasis. Natural products derived from various endophytic fungi associated with medicinal plants have shown promise as a potential source for antiprotozoal drugs (Table 6.6) (Fig. 6.8).

Terrenolide S (**88**), a novel derivative of butenolide, along with six already reported compounds, (22*E*,24*R*)-stigmasta-5,7,22-trien-3-*β*-ol (**89**), stigmast-4-ene-3-one (**90**), stigmasta-4,6,8(14),22-tetraen-3-one, terretonin A, terretonin, and buty-rolactone VI, had recently been isolated from *Aspergillus terreus*, an endophytic fungus cultured from the roots of *Carthamus lanatus.* Compounds **88–90** showed antileishmaniasis against *Leishmania donovani* and exhibited IC_{50} values of 11.24, 15.32, and 27.27 μM, respectively (Elkhayat et al. 2016).

Table 6.6 Antileishmaniasis compounds derived from endophytic fungi

Compound	Endophytic fungi	Host plant	References
Purpureone (**17**)	*Purpureocillium lilacinum*	*Rauvolfia macrophylla*	Lenta et al. (2016)
Alternariol 9-methyl ether (**18**)	*Alternaria* sp.	*Salvia miltiorrhiza*	Lou et al. (2016)
Terrenolide S (**88**), (22*E*,24*R*)-stigmasta-5,7,22-trien-3-*β*-ol (**89**) and stigmast-4-ene-3-one (**90**)	*Aspergillus terreus*	*Carthamus lanatus*	Elkhayat et al. (2016)
(6-S)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione (**91**) and (6-R)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione (**92**)	*Trichosporum* sp.	*Trigonella foenum-graecum*	Metwaly et al. (2015)

Terrenolide S **(88)**

(22E,24R)-stigmasta-
5,7,22-trien-3-β-ol **(89)**

stigmast-4-ene-3-
one **(90)**

(6-R)-3-(1,3-dihydroxy
propyl)-6-(2-methylpropyl)
piperazine-2,5-dione **(91)**

(6-S)-3-(1,3-dihydroxy
propyl)-6-(2-methylpropyl)
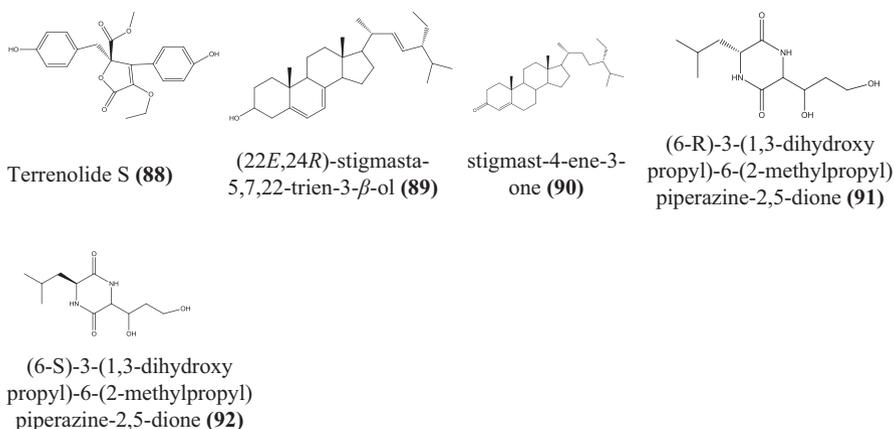piperazine-2,5-dione **(92)**

Fig. 6.8 Structures of antileishmaniasis compounds (**88–92**) from endophytic fungi

Two new diketopiperazine alkaloid isomers (6-S)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione **(91)** and (6-R)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione **(92)** were isolated from an endophytic fungus *Trichosporum* sp. cultured from the seeds of *Trigonella foenum-graecum*. Three chiral centers in both these compounds were not identified due to very low in amount. The compounds **91–92** exhibited moderate antileishmanial activities with IC_{50} values of 96.3 and 82.5 µg/mL, respectively (Metwaly et al. 2015).

Enniatins (ENs) are a group of antibiotics having six-membered cyclic depsipeptides formed by the combination of three molecules of D-α-hydroxyisovaleric acid and three N-methyl-L-amino acids commonly reported in the literature being produced by *Fusarium* sp. Six enniatins, namely, ENs A, A1, B, B1, B2, and Q, were reported via LCMS from the methanolic extract of *Fusarium tricinctum*, an endophytic fungus cultured from the fruits of *Hordeum sativum* cultivated on rice medium. The methanolic extract of this fungus exhibited mild antibacterial and antileishmanial activity against *L. donovani* ATTC 39930D with an IC_{50} value of 16.96 µg/mL. Moreover the extract at 100 µg/mL was also capable of inhibiting the activity of thioredoxin reductase enzyme present in *Plasmodium falciparum* by a factor of 95% (Zaher et al. 2015).

The antibacterial compound **17** also displayed excellent antileishmanial activity against *L. donovani* with an IC_{50} value of 0.63 µg/mL (0.87 µm) and with good selectivity (SI = 49.5) against the L6 cell line (Lenta et al. 2016). Similarly, the compound **18** inhibited spore germination in *Magnaporthe oryzae* with an IC_{50} value of 87.18 µg/mL. The compound also exhibited antinematodal activity against *Caenorhabditis elegans* and *Bursaphelenchus xylophilus* with an IC_{50} value of 74.62 µg/mL and 98.17 µg/mL, respectively (Lou et al. 2016).

6.2.7   Antiviral Compounds from Endophytic Fungi

These days the attack of various viruses causing dreadful effects on human lives is very common. In view of evolving new strains of dreadful viruses, there is a requirement of the search for cheaper, safer, and more robust drug alternative from natural sources like endophytic fungi. Few antiviral compounds have been reported from various endophytic fungi (Fig. 6.9), as listed in Table 6.7.

Three novel isocoumarins, versicoumarins A–C, with four reported isocoumarins, were characterized from an endophytic fungus *Aspergillus versicolor* cultured from *Paris marmorata* plant rhizomes. Versicoumarin A **(72)** exhibited significant anti-TMV activity with 28.6%, inhibition that was comparable to that of positive standard ningnanmycin (31.5%) (Ye et al. 2014). Brefeldin A **(74)** reported from *Penicillium* sp., which is discussed as anticancer compound, also exhibited potent antiviral activity against HCV (hepatitis C virus) and HBV (hepatitis B virus) with an ID_{50} value of 0.022 and >0.008 μM, respectively (Xie et al. 2017).

The fungus *Pestalotiopsis thea*, isolated from *Fagara zanthoxyloides*, yielded three known compounds chloroisosulochrin **(93)**, ficipyrone A, and pestheic acid. Compound **93** exhibited potent inhibition with an IC_{50} value of 4.22 ± 1.03 μM comparable with that of the standard ribavirin, having IC_{50} value of 4.91 ± 1.85 μM. The rest of the compounds exhibited mild inhibition with IC_{50} values in the range of 45.00 ± 0.98–259.23 ± 2.36 μM (Uzor et al. 2016).

The fungus *Periconia* sp. F-31, isolated from *Annona muricata*, was explored and yielded pericoannosin A **(94)**, periconiasin D, periconiasin E, and periconiasin F **(95)**. Compounds **94** and **95** showed considerable anti-HIV activity with IC_{50} of 69.6 and 29.2 μM, respectively (Zhang et al. 2015).
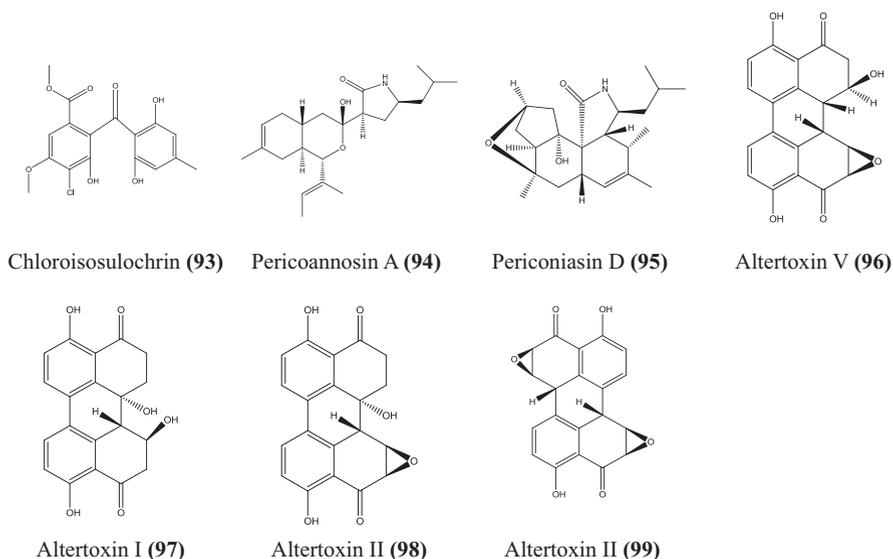

Chloroisosulochrin **(93)**   Pericoannosin A **(94)**   Periconiasin D **(95)**   Altertoxin V **(96)**

Altertoxin I **(97)**   Altertoxin II **(98)**   Altertoxin II **(99)**

Fig. 6.9 Structures of antiviral compounds (**93–99**) from endophytic fungi

Table 6.7 Antiviral compounds derived from endophytic fungi

Compounds	Endophytic fungi	Host plant	References
Versicoumarin A (**72**)	*Aspergillus versicolor*	*Paris marmorata*	Ye et al. (2014)
Brefeldin A (**74**)	*Penicillium* sp.	*Panax notoginseng*	Xie et al. (2017)
Chloroisosulochrin (**93**)	*Pestalotiopsis thea*	*Fagara zanthoxyloides*	Uzor et al. (2016)
Pericoannosin A (**94**)	*Periconia* sp.	*Annona muricata*	Zhang et al. (2015)
Pericoannosin D (**95**)			
Altertoxin V (**96**)	*Alternaria tenuissima*	*Quercus emoryi*	Bashyal et al. (2014)
Altertoxin I (**97**)			
Altertoxin II (**98**)			
Altertoxin III (**99**)			

During the bioprospection of endophytic fungi of Sonoran Desert plants, *Alternaria tenuissima* was isolated from *Quercus emoryi*. In screening of natural product extract library and bioactivity-guided fractionation, altertoxin V (**96**), altertoxin I (**97**), altertoxin II (**98**), altertoxin III (**99**), and altertoxin IV were isolated and characterized. Compounds **96, 97, 98**, **and 99** have completely inhibited the replication of the HIV-1 virus at a very lower concentration with 0.50, 2.20, 0.30, and 1.50 μM, respectively (Bashyal et al. 2014).

6.3   Conclusion

Endophytes stay in the internal tissues of the host plants in symbiotic relationship. They are considered to be a rich source for the production of diverse bioactive metabolites and responsible to cause physiological modification in the host which results in the production of compounds required for tolerating biotic and abiotic stresses by plant. The extensive ability of endophytic fungi to synthesize products of pharmaceutical importance led the researchers and scientists to do the sampling from unique niches so that structurally diverse compounds can be isolated. In cases the endophyte gains the ability to produce either the same or different compounds from the host, the production of the same metabolite as of host plant is due to the long coevolution with their host. In the past two decades, researchers have focused on studying fungal diversity, better understanding of their relationship with the host, isolation of novel metabolites from fungus, and different ways to increase the yield of isolated bioactive compounds using genetic engineering and media engineering, improving culture conditions, and using one strain many compounds (OSMAC) approach. Endophytic fungi are considered as a boon for the society due to their ability to produce diverse metabolites of broad applications in various fields like agriculture, horticulture, medical, and industries. Instantly in favor of mankind, there is a need for the hunt of novel and diverse compounds to combat the upcoming challenges of drug resistance among pathogens.

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