MINI-REVIEW

Biotransformation ability of endophytic fungi: from species evolution to industrial applications

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Abstract

Increased understanding of the interactions between endophytic fungi and plants has led to the discovery of a new generation of chemical compounds and processes between endophytic fungi and plants. Due to the long-term co-evolution between fungal endophytes and host plants, endophytes have evolved special biotransformation abilities, which can have critical consequences on plant metabolic processes and their composition. Biotransformation or bioconversion can impact the synthesis and decomposition of hormones, sugars, amino acids, vitamins, lipids, proteins, and various secondary metabolites, including flavonoids, polysaccharides, and terpenes. Endophytic fungi produce enzymes and various bioactive secondary metabolites with industrial value and can degrade or sequester inorganic and organic small molecules and macromolecules (e.g., toxins, pollutants, heavy metals). These fungi also have the ability to cause highly selective catalytic conversion of high-value compounds in an environmentally friendly manner, which can be important for the production/innovation of bioactive molecules, food and nutrition, agriculture, and environment. This work mainly summarized recent research progress in this field, providing a reference for further research and application of fungal endophytes.

Key points

• The industrial value of degradation of endophytes was summarized.
• The commercial value for the pharmaceutical industry is reviewed.

Graphical abstract

Keywords Endophytic fungi · Biotransformation · Natural product · Bioconversion · Co-evolution

Introduction

Bacterial and fungal endophytes deeply involved in the physiology and metabolism of host plants can be found in almost all studied plants (Chen et al. 2020). Plant survival and development is often inseparable from the participation of such endophytes (Adamo et al. 2020). Therefore, plants should no longer be simply regarded as independent individuals; rather, they must be considered “symbiotic functional bodies” containing internal microorganisms (Kuzniar et al. 2020). In particular, endophytic fungi sustain part or their entire life cycle within healthy plants without causing any obvious diseases (Strobel 2018).

Of the 300,000 species of plants existing on earth, about one-sixth produce compounds potentially useful in disease treatment, able to synthesize various bioactive compounds, within the special internal environments in plants whose habitats are different from the ordinary environment (e.g., soil) for microorganisms (Nisa et al. 2015). These special habitats provide unique niches for a large number of endophytic fungi (Li et al. 2020a).

Among recent studies on secondary metabolites of fungi, 51% of newly discovered compounds with pharmacological activity have been found from endophytic fungi, with many showing versatile biological functions, including promoting plant nutrient absorption and helping plants cope with stress.
(Liu et al. 2020; Pilsyk et al. 2020; Xiao et al. 2020). They are also deeply involved in plant physiology and metabolism, including gene exchange, signal induction, and element sharing with plants. In addition, fungal secondary metabolites can be involved in regulating plant gene expression, modulating the activity and direction of branched metabolic pathways, and modifying plant metabolites and their production. With respect to the latter, fungal endophytes often impact the amount and concentration of (final) metabolites accumulating in plants tissues. In terms of the level of metabolic modifications, endophytic fungi can directly synthesize or decompose some metabolites; i.e., they can affect the metabolite composition of medicinal plants through biotransformation. For example, the endophytic fungi Flavobacterium sp. GE 32 and Arthritus sp. GE 17–18 in Panax ginseng can transform ginsenoside Rb1 that has low bioavailability into ginsenoside Rg3 and C-K (these products from ginseng root have been implicated in having a host of human health benefits), which has high bioavailability (Fu 2019; Fu et al. 2016).

Endophytic fungi complement the biotransformation capacity of the host plant, thus helping solve issues in complex compound production and the decomposition of difficult substances, such as industrial waste and pollutants. Biotransformation, including decomposition and synthesis affected by endophytic fungi both in vivo (in plant) and in vitro, is an area of significant active research. Recent advances have been successfully applied in drug synthesis (Louis et al. 2019), pollutant degradation, and food fermentation, e.g., wine brewing (Rho et al. 2020), thus providing opportunities for green and efficient solutions to industrial challenges. However, correlated summaries on these applications are largely lacking. The present study focuses on the biosynthesis and biodegradation abilities of endophytic fungi relevant to various applications, i.e., biotransformations and catalyses, to provide a scientific reference for sustainable production.

Research progress on the biodegradation activity of endophytic fungi

The research on and application of biodegradation activities of endophytic fungi includes the decomposition of small organic molecules and polymers.

Progress in degradation of small organic molecules by endophytic fungi

A balanced but potentially antagonistic relationship often exists between endophytic fungi and host plants (Schulz et al. 2015). Plants activate their defense system when many fungal endophytes initiate colonization, but the fungus often disrupt these defense responses by targeting plant defensive signaling factors to suppress host responses allowing for establishment within the plant more easily. For example, endophytic Mucor sp. KU234656 and Epichloë festucae KM400586, which have various hosts, decompose plant signaling molecules such as strigolactones (plant hormones that stimulate branching) and salicylic acid (plant hormones that regulate the plant immune system), to facilitate the penetration of the fungus into plant tissues (Rozpadek et al. 2018; Ambrose et al. 2015). Such fungal decomposing abilities are attributed to degradative enzyme systems, which include carbohydrate esterases, glycoside hydrolases, and polysaccharide lyases (Gramaje et al. 2020). Some endophytic fungi have evolved metabolic abilities to decompose plant-specific organic substances; for instance, Phomopsis liquidambari from the bark of Bischofia polycarpa can degrade sinapic acid (one of the most representative methoxy phenolic pollutants) to H2O and CO2 (Xie et al. 2016). Further to this, Burkholderia cenocepacia 869T2 from the roots of Vetiveria zizanioides has the unique ability to dechlorinate the compound dioxin (persistent carcinogenic byproducts of anthropogenic activities) into dibenzo-p-dioxin and subsequently decompose it into catechol and 2-hydroxy-succinate with low carcinogenicity (Nguyen et al. 2021). Endophytic fungi also develop various abilities to directly decompose defense substances. For example, Fusarium verticillioides from Zea mays, Acrmenion tum sp. and F. moniliforme from Aphelundra tetragona, and Paecilomyces formosus HQ44388 from Glycine max can degrade toxic substances, such as benzoxazolin-2-(3H)-one (Schulz et al. 2016), aphelandrine (Christa et al. 1997), jasmonic acid (Bilal et al. 2018), 2-hydroxy-N-(2-hydroxyxphyl) acetate (Zikmundova et al. 2002), 6-methoxy-benzoxazolin-2-one, and 2-benzoxazolinone (Glenn et al. 2016), in plants to adapt to the environment and establish a balanced symbiotic relationship with plants.

When an equilibrium is attained between an endophytic fungus and its host plant(s), a mutual relationship is established. Endophytic fungi can help plants avoid external damage through contributions of their unique biodegradation capability. For example, the endophytic fungus Neurospora intermedia MF362953 isolated from Saccharum officinarum can decompose phenylurea herbicide diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea] (Morais et al. 2017). Some endophytic fungi can degrade some host plants’ compounds, but the biochemical mechanism(s) of how these compounds are degraded has yet to be clearly elucidated. For instance, Paraconiothyrium variabilis LCP5644 from Cephalotaxus harringtonia and F. oxysporum 2T12J01A from Andrographis paniculata can decompose O-glycosides and change the metabolite profile of the host (Tian et al. 2014; Wang et al. 2014). Some endophytic fungi from Salvia miltiorrhiza can degrade limonene, geraniol, and pinene (plant essential oil components) into intermediates of terpenoid biosynthesis to produce new valuable biological products, and Mucor circinelloides DF20 from Salvia miltiorrhiza can promote tanshinone (pharmacological active component of host plant) biosynthesis and accumulation.
in *Salvia miltiorrhiza* root (Chen et al. 2018, 2021). However, the degradation of endophytic fungi can sometimes destroy the medicinal substances of plants. For example, *Alternaria eureka* 20131E11L from *Ruscus aculeatus* can transform the spirochete alcohol skeleton of neoruscogenin, which used to treat chronic venous insufficiency, varicose veins, and hemorrhoids, into a cholesterol skeleton (Ozcinar et al. 2018), and endophytic fungal *P. liquidambari* from *Bischophia polycarpa* can completely decompose cinnamic acid (hepatoprotective agent) into CO₂ and H₂O, rendering it impossible for plants to synthesize flavonoids, thus reducing the active quality of medicinal plants (Xie and Dai 2015).

Endophytic fungi not only exhibit their degradation ability within the host plant but also display high degradation activity outside the plant. Nine endophytic fungi isolated from *Plantago lanceolata*, including *Aspergillus niger*, *Eurotium repens*, *Leptosphaerulina chartatum*, A. nidulans, *E. amstelodami*, *Cladosporium pseudocladosporioides*, *Penicillium chrysogenum*, *Bipolaris* sp., and *Epichloë nigrum*, have been shown to be able to decompose non-steroidal anti-inflammatory drugs, such as diclofenac, diflunisal, ibuprofen, mefenamic, and piroxicam in vitro (Gonda et al. 2016). Endophytic fungi with unique biodegradation capabilities benefit from various enzymes co-evolved with host plants for a long time, particularly α-L-rhamnohydrolase, β-N-acetylhexosaminidase, and urease, which have industrial application values (Gramaje et al. 2020; Atmaca 2019). Many additives that are difficult to treat in the industry, such as reactive dark blue, reactive green, reactive turquoise blue, reactive brilliant red, reactive brilliant orange, triclosan, and malachite green (listed as a carcinogen by the Food and Drug Administration), are considered as common pollutants in the aquaculture industry (Zhou et al. 2018b). Three endophytic fungi, *Myrothecium verrucaria* DJTU-sh7, *Glomerella* sp., and *Talaromyces stollii*, isolated from *Taxus chinensis* can degrade reactive dark blue, reactive green, reactive black, reactive turquoise blue, reactive brilliant orange, and reactive brilliant red (refractory chemical dyes) (Hao et al. 2016). *Klebsiella aerogenes* M2017452 from *Cyperus rotundus* can degrade malachite green to nontoxic substances, e.g., N,N-dimethylaniline and 2-(4-dimethylamino-phenyl)-phenyl-methanal (Shang et al. 2019). Triclosan can be degraded into detoxifying metabolites, e.g., hydroquinone, (2Z,4E)-3-chloro-2,5-dihydroxyhexa-2,4-dienedioic acid, and (2Z,4E)-3-chloro-2,5-dihydroxyhexa-2,4-dienedial by *Penicillium oxalicum* FJ196840 isolated from *Artemisia annua* (Tian et al. 2018). In addition, endophytic fungi can be used to degrade organic substances, such as polycyclic aromatic hydrocarbon (Tardif et al. 2016), triphenylmethane (Gao et al. 2020a), cyanide (Al-Badri et al. 2020), azo compounds (Marzell-Pereira et al. 2019), and phenols (Rusanova et al. 2019), in industrial wastewater. For example, *Trichoderma harzianum* PTA-10317 from *Taraxacum officinale* L. can completely decompose phenanthrene (polycyclic aromatic hydrocarbon pollutant) into CO₂ and H₂O (Repas et al. 2017). Furthermore, endophytic fungus *P. liquidambari* from *Oryza sativa* can degrade more than 10 small molecule organic chemical pollutants, such as bisphenol, chloroalkane, chloroalkene, caprolactam, polyaromatic hydrocarbon, naphthalene, chlorochlorochlorohexane, chlorobenzene, aminobenzoate, styrene, fluorenbzoate, atrazine, dioxin, toluene, benzoate, and ethylbenzene (Zhou et al. 2017).

**Progress in the degradation of organic polymers by endophytic fungi**

Endophytic fungi have acquired the ability to decompose the aging cell wall and breakthrough various plant barriers in the process of establishing symbiosis with host plants by evolution. These interactions are aimed towards the fungus obtaining nutrients from the plant, but can also have the consequence of eliminating host “waste” byproducts, i.e., compounds that the plant cannot use, but may, in some instances, accumulate within plant tissues leading to toxicity (Suryanarayanan et al. 2012). In addition, fungal endoglucanases and celllobiohydrolases (endo- and exo-cellulases) can degrade cellulose and hemicellulose of plant for their invading or mutualistic symbiosis (Adamo et al. 2020). The unique biodegradation process of organic polymers in endophytic fungi often requires the assistance of redox system enzymes, such as lytic polysaccharide monoxygenases, ligninolytic peroxidases, laccase, and other enzymes produced by endophytic fungi, cellulose, and lignin as a major component of cell wall aging, which can be transformed into nutrients of endophytic fungi (Mathe et al. 2019). For example, *Rickenella mellea* JGI 334,780 from *Alloclavaria purpurea* can transform lignin, cellulose, hemicellulose, and lignin-like polymers in plant aging cell walls into their nutrients or help plant to dispose garbage (Korotkin et al. 2018). Endophytic fungi can produce endo-1,4-β-xylanase, xylan α-glucuronidase, acetylxylan esterase, and xylan acetylsterase to degrade xylan, while chitin can be degraded into nutrients by chitinase, polysaccharide lyase, and N-acetylglucosaminidase, all enzymes that can be produced by various endophytic fungi (Aranda-Martinez et al. 2016). For example, *Hymenoscyphus ericae* and *Pochonia chlamydosporia* can decompose chitin from other invading microorganisms, fungal residual body, or soil into N-acetylglucosamine, thus providing an organic nitrogen source for plants (Kerley et al. 1995).

Endophytic fungal enzymes have been gradually used in industrial production, and the production of amylase, cellulase, laccase, lipase, protein, xylanase, pectinase, phytase, and phenoxidase has been matured and industrialized (Correa et al. 2014). A summary of the latest research results on
endophytic fungal enzymes in the last 5 years is shown in Table 1.

With respect to industrial applications, a combination of the decomposition ability of endophytic fungi with physical and chemical pretreatment may reduce the loss of purely physical and chemical pretreatment. For example, in the sugar production industry, endophytic Ulocladium sp. from Eucalyptus Globus and F. verticillioides from Andropogon gayanus can be used to pretreat raw materials to improve the yield of sugar (de Almeida et al. 2019). The endophytic fungus Hypoxylon sp. CI-4 in T. distichum can transform cellulose into 1-acetyl-2-(1-hydroxyethyl)-cyclohexene, 3,2,3-dimethoxy-naphthalene, 2,5-furandione dihydro-cellulose into 1-acetyl-2-(1-hydroxyethyl)-cyclohexene, anti-chondrocyte apoptosis, and anti-Staphylococcus aureus of LW-XG was glucose, mannose, and glucuronic acid at a low-molecular-weight xanthan (LW-XG; the composition chain containing mannose, gluconic acid, and mannose) into a low-molecular-weight xanthan (LW-XG; the composition of LW-XG was glucose, mannose, and gluconic acid at a molar ratio of 1.63:1.5:1.0) with antioxidant, anti-arthritis, anti-cholesterol, acetopyrosis, and anti-Staphylococcus aureus (Hu et al. 2019). These fungi also have a commercial value in environmental and industrial waste treatment. For example, the serine hydrolase secreted by Guignardia mangiferae E2702C and Zopfiella karachiensis E2719A can be used to treat synthetic material polyester polyurethane under anaerobic conditions (Russell et al. 2011).

Research progress on the biosynthesis of natural products by endophytic fungi

Endophytic fungi directly synthesize various natural products in plants

The reciprocal relationship between endophytic fungi and the host has been verified; however, many aspects of the complex co-evolutionary mechanisms that mediate these interactions remain unclear (Lu et al. 2019). Such co-evolutionary adaptations have been selected for the ability of endophytic fungi to produce signal substances that are either similar or different from the host, and endophytic fungi can provide new avenues for screening for efficient synthetic drugs, compounds useful in agriculture (plant growth promotion, protection from abiotic stress, protection from pathogens, etc.), food safety (harvest, post-harvest, storage), and other industrial applications (biofuels, bioplastics, etc.).

Endophytic fungi can produce various phytohormones, such as phytohormone indole-3-acetic acid, gibberellic acid, cytokinin, and phytoalexins, which were successively found from the endophytic fungi Serendipita indica, F. fujikuroi MI58289, and Piriformospora indica DSM11827 (Inaji et al. 2020; Niehaus et al. 2016; Li et al. 2016b). This finding indicated that endophytic fungi can participate in host signal regulation and affect host physiological and metabolic activities (Yuan et al. 2016; Bilal et al. 2018; Guarino et al. 2020).

Endophytic fungi can also synthesize some “simulated secondary metabolites” similar to or the same as host plants through “gene exchange” with host plants. The gene clusters mediating the synthesis of some of these “shared” metabolites have been proposed to be endophytic fungal origin, having been transferred to host plants through their long co-evolutionary history (Glenn et al. 2016). Currently, paclitaxel (an antineoplastic) (Shao et al. 2021), camptothecin (for antitumor) (Kaur et al. 2020), cinchonine (for treatment of malaria disease) (Maehara et al. 2011), and podophylotoxin (inhibit herpes virus) (Vasundhara et al. 2016) can be synthesized by endophytic fungi and more than 90 high medicinal value metabolites (Archana et al. 2021). However, in other cases, the biosynthetic pathway mediating the synthesis of similar bioactive metabolites found in both endophytic fungi and their plant hosts has been found to be completely different. For example, the pathway for gibberellic acid (GA) biosynthesis of Gibberella fujikuroi IMI 58,289 is different from their host plants, and the fungal GAs is synthesized from acetyl-CoA via mevalonic acid pathway, but most plants, at least in the green parts, are predominantly produced by the methyl erythritol phosphate pathway (Böhmke and Tuzdynski 2009). The taxol (anticancer drug) biosynthetic pathway found in the endophytic fungus A. nidulans has low homology to the one reported for plant Taxus spp., suggesting that the taxol biosynthesis ability of this endophytic fungi may have evolved independently of the plant one (Elena et al. 2020).

Some compounds synthesized by endophytic fungi are not made by host plant but are released into the tissues of host plant and can cause changes in the chemical composition of the host plant. For example, fungal ergot alkaloid and loline alkaloids can accumulate in plant tissues and which are important toxic substances to livestock (Fig. 1). These compounds were originally thought to be produced by the plant, Lolium perenne, until they were discovered to be exclusively produced by L. perenne endophytic E. festucae and Epichloë fungal species (Katrin et al. 2020; Panaccione et al. 2017). On the basis of these findings, scientists have reinoculated L. perenne with genetically modified Epichloë spp. as E^AR1 and E^AR37, in which production of the toxic alkaloids has been abolished, and leading to the elimination of the toxic substances in host plants, and improved quality of pasture production. These fungi are currently commercialized in Australia, North America, and other places.
Table 1  Industrial application of enzyme from endophytic fungi in medicinal plants

| No. | Plant               | Endophytic fungi       | Enzyme                                           | References                        |
|-----|---------------------|------------------------|--------------------------------------------------|-----------------------------------|
| 1   | Allium cepa         | Beauveria bassiana     | Xylanase, endoglucanase                          | Amobonye et al. (2021)            |
| 2   | Coffee plants       | Induratia sp. CML4013  | Lipase, amylase, protease, phytase, pectinase, cellulase | Monteiro et al. (2020)            |
| 3   | Vitis labrusca L.   | Diaporthe sp. KM362392 | Endoglucanase                                   | Felber et al. (2019)              |
| 4   | Andropogon gayanus  | Fusarium culmorum      | Endoglucanase                                   | de Almeida et al. (2019)          |
| 5   | Phoenix dactylifera L. | Penicillium biliae TDPEF30 | Protease (especially acidic protease)           | Ben et al. (2019)                 |
| 6   | Simarouba glauca    | Phomopsis sp. KX49881  | Laccase                                          | Navada et al. (2018)              |
| 7   | Laguncularia racemosa | Aspergillus awamori     | Endoglucanase, β-glucosidase, xylanase          | Maroldi et al. (2018)             |
| 8   | Rhizophora mangle   | Aspergillus niger      | Cellulase                                        |                                   |
| 9   | Cananga odorata     | Cercospora chrysanthemi | Amylase, cellulase, lipase                      | Toghueo et al. (2017)             |
| 10  | Chaetomium globosum | Cercospora flagellaris | Cellulase                                        |                                   |
| 11  | Colletotrichum fructicola | Cercospora olivascens     | Amylase, lipase                                 |                                   |
| 12  | Diaporthe sp.       | Fusarium equiseti      | Amylase, cellulase, laccase                      |                                   |
| 13  | Fusarium oxysporum  | Fusarium solani        | Amylase, cellulase, lipase                      |                                   |
| 14  | Fusarium striatum   | Fusarium solani        | Amylase, cellulase, lipase                      |                                   |
| 15  | Guignardia mangiferae | Phoma microchlamydospora | Amylase, cellulase, lipase                      |                                   |
| 16  | Nectria rigidiuscula | Phomopsis phyllanticolla | Amylase, cellulase, lipase                      |                                   |
| 17  | Nigrospora oryzae   | Pleosporales sp.       | Cellulase                                        |                                   |
| 18  | Terminalia mantaly  | Septoria sp.           | Lipase                                           |                                   |
| 19  | Cercospora chrysanthemi | Diaportheales sp.     | Amylase, cellulase, lipase                      |                                   |
| 20  | Cercospora flagellaris | Corynespora cassiicola | Amylase, cellulase, lipase                      |                                   |
| 21  | Cercospora sp.      | Fusarium solani        | Amylase, cellulase, lipase                      |                                   |
| 22  | Hypoxylon investiens | Nemania bipapillata    | Amylase, Lipase                                 |                                   |
| 23  | Nigrospora oryzae   | Phoma microchlamydospora | Amylase, cellulase, lipase                      |                                   |
| 24  | Phomopsis phyllanticolla | Phomopsis sp. | Amylase, cellulase, lipase                      |                                   |
| 25  | Pleosporales sp.    | Pleosporales sp.       | Cellulase                                        |                                   |
| 26  | Septoria sp.        | Xylaria adscendens     | Amylase, cellulase, lipase, laccase             |                                   |
| 27  | Xylaria persicaria  | Xylaria sp.            | Amylase, cellulase, lipase                      |                                   |
| 28  | Xylariaceae sp.     | Xylariaceae sp.        | Amylase, cellulase, lipase, laccase             |                                   |
Another well-studied and confirmed example is swainsonine, a toxin which can seriously poison livestock, and it is also one of the main bioactive chemicals in several Fabaceae plants, produced by endophytic Undifilum spp. and Alternaria spp., which were dominant fungal endophytes from Astragalus, Oxytropis, and Swainsona of Fabaceae plants (Moodley et al. 2019; Ren et al. 2017). A significant number of novel compounds with diverse activities continues to be found in various endophytic fungi, including flavonoids, alkaloids, and terpenoids (with main finds summarized in Table 2).

### Highly selective catalytic activities of endophytic fungi

The use of endophytic fungi as a biocatalyst for the production of high-yield and high-purity compounds in an environmentally friendly manner has attracted significant research interest (Scalvenzi 2014). The catalysis and transformation of endophytic fungi have been mainly used for the following purposes: (i) overcoming the difficulties in chemical synthesis; (ii) improving the activity or reducing the toxicity of lead drugs; and (iii) assisting in the study of the structure–activity relationship of drugs (Özçinar et al. 2018).

Endophytic fungi can selectively catalyze the synthesis of O-glycoside and O-ether bonds. Endophytic Penicillium sp. JQ228238 from Polygonum cuspidatum can transform resveratrol into pterostilbene, which shows more metabolic stability and stronger anti-inflammatory and antioxidant activities (Xu et al. 2020), Epicoccum nigrum from Salix sp. can transform flavonoids into kaempferol-O-diglycoside, which shows anticancer and antioxidant activity (Harwoko et al. 2019), and Neosartorya hiratsukae from Astragalus.

| No. | Plant Endophytic fungi | Enzyme | References |
|-----|------------------------|--------|------------|
| 41  | Terminalia catappa Cercospora olivascens | Amylase, cellulase, lipase | Orlandelli et al. (2017) |
| 42  | Cladosporium tenuissimum | Amylase | |
| 43  | Diaporthe sp. | Amylase, cellulase | |
| 44  | Fusarium decemcellulare | Amylase, cellulase | |
| 45  | Fusicoccum sp. | Amylase, cellulase, lipase | |
| 46  | Guignardia mangiferae | Lipase | |
| 47  | Hypoxylon investiens | Amylase, cellulase, lipase, laccase | |
| 48  | Lasidiopodia theobromae | Amylase, cellulase | |
| 49  | Mycosphaerella thailandica | Amylase | |
| 50  | Ophioceras leptosporum | Amylase, lipase | |
| 51  | Paraconiothyrium variabile | Amylase, cellulase, lipase | |
| 52  | Penicillium chermesinum | Amylase, cellulase | |
| 53  | Penicillium parvum | Amylase, cellulase, lipase | |
| 54  | Pestalotopsis sp. | Cellulase, lipase, laccase | |
| 55  | Phomopsis theicola | Amylase, cellulase | |
| 56  | Pseudocercospora sp. | Amylase, lipase | |
| 57  | Pseudofusicoccum kimberleyense | Amylase | |
| 58  | Xylaria apiculata | Amylase | |
| 59  | Xylaria castorea | Amylase, cellulase, lipase | |
| 60  | Xylaria sp. | Amylase, cellulase, lipase | |
| 61  | Piper hispidum Sw Bipolaris sp. JF767001 | α-amylase | Krishnapura et al. (2016) |
| 62  | Marasmius cladothyllum JF767003 | α-Amylase | Katoh et al. (2014) |
| 63  | Phlebia sp. JF766997 | α-Amylase | |
| 64  | Phyllosticta capitalensis JF766988 | α-amylase | |
| 65  | Schizothyrium commune JF766994 | α-amylase | |
| 66  | Curcuma amada Talaromycyes pinophilus KJ372306 | l-Asparaginase | |
| 67  | Bacopa monnieri Pleosporales sp. | Amylase | |
| 68  | Eutypella sp. E9901c | Amylase | |
| 69  | Fusarium oxysporum FITK1 | Amylase | |
| 70  | Fomitopsis cf. Meliae KYO | Cellulase | |
| 71  | Eremophila longifolia Preussia minima EL-14 | α-Amylase | Zaferanloo et al. (2014) |
*angustifolius* is able to transform neoruscogenin into neoruscogenin-1-\(O\)-\(β\)-glucopyranoside, which is a potential leading compound with anti-inflammatory and anti-tumor activities (Özçinar et al. 2018). In addition, endophytic fungi can catalyze the synthesis of N-glycoside and amide bonds with high selectivity. For example, *F. verticillioides* from *Zea mays* catalyzed the formation of the N-glycosidic bond of carbamate to produce N-(2-hydroxyphenyl)-malonic acid with anticancer and antioxidant activity, and *P. brasiliensis* from *Zea mays* promoted the formation of an amide bond between halogenated benzoic acid and amino acid (Fill et al. 2018; Schulz et al. 2016). The most commercial potential of endophyte is highly regioselective oxidation to hydroxyl, carbonyl, and epoxy groups. Four endophytic fungi, *P. oxalicum* FJ196840, *F. oxysporum*, *G. cingulata*, and *Umbelopsis isabellina* FJ872076.1, from *Senna spectabilis* and *Centella asiatica* can catalyze the formation of the benzene ring in artemisinic acid (synthetic precursor of antimalarial drug artemisinin), carbonylation, diterpene ketation, enantioselective hydroxylation of (\(-\))-(\(S\))-propranolol (medicine for treating arrhythmia, angina pectoris, and hypertension), and artemisinic acid (Hao et al. 2018; Monteiro et al. 2017; Borges et al. 2009; Gao et al. 2015). *Pestalotiopsis microspora* JF487784 in *Huperzia serrata* can hydroxylate ursolic acid at special sites (Fu et al. 2011). In addition, similar bioconversion effects have been reported by endophytic fungi; for instance, *Phomopsis sp.* KY113119 and *Neofusicoccum sp.* MF276906 from *Pinus sp.* can efficiently catalyze (\(+\)-(\(R\))-limonene to limonene-1,2-diol (Bier et al. 2017; Cecati et al. 2018), and endophytic *Nodulisporium sp.* JN254790 from *Panax notoginseng* can convert the carbon–carbon double bonds of ginsenosides Re to dihydroxy, forming a novel compound with antiplatelet aggregation activity, vinaginsenoside R13 (Luo et al. 2013). *F. oxysporum* from *C. roseus* can glycosylate vinblastine and finally produce vincristine with antitumor activity (Kumar et al. 2013). The redox reaction of endophytic fungi also has stereoselectivity. For example, *P. crustosum* and *A. fumigatus* DSM 21,023 from *Viguiera robusta* and *Juniperus communis* can catalyze highly enantioselective oxidation albdendazole and deoxypodophyllotoxin to (\(-\))-albendazole sulfoxide (drug for treating cerebral cysticercosis) and podophyllotoxin, respectively (Carrao et al. 2011; Kusari et al. 2009). Four endophytic fungi, namely, *N. parvum* from *Illicium verum* and *Bacillus megaterium*, *Pseudomonas* sp., and *P. chrysogenum* from *Raphanus sativus* were used for the stereoselective catalytic reduction of carbonyl group and the catalyzation of the reduction of acetophenone to (\(+\))-1-phenylethanol and (\(-\))-1-phenylethanol (Li et al. 2016a; Rodriguez et al. 2015). They can even catalyze specific regional chemical reactions. For instance, *P. brasilianum* from *Melia azedarach* can catalyze the Baeyer Villiger reaction regiochemistry of 1-indanone to produce two compounds: dihydrocoumarin and (\(-\)-(\(R\))-3-hydroxy-1-indanone (Fill et al. 2012).

One of the most important scientific applications of endophytic fungal catalytic activity is their use to assist in the study of the drug structure–activity relationships. For example, *Penicillium sp.* SWUKD4.1850 from the root of *Aphe-landra* can catalyze the transformation of nigroniacid (drugs for preventing cerebral ischemia–reperfusion injury) into new compounds with high biological activity (Qin et al. 2019). The endophytic *Colletotrichum gloeosporioides* and

![Diagram](image-url)
| No. | Host plant          | Endophytic fungi             | Chemical name                                                                 | Pharmacological activity                  | References            |
|-----|---------------------|-----------------------------|-------------------------------------------------------------------------------|--------------------------------------------|------------------------|
| 1   | Ryegrass            | *Epichloe festucae* LpTG-1  | Lolitrem B                                                                    | Central nervous toxicity                   | Reddy et al. (2020)    |
| 2   | *Aster tataricus*   | *Cyanoderma asteris*        | Astin A                                                                       | Antitumor activity                        | Schafhauser et al. (2019) |
| 3   | *Smallanthus sonchifolius* | *Nigrospora sphaerica* (22E, 24R)-ergosta-4,6,8(14),22-tetraen-3-one |                                                                    | Antitumor activity                        | Gallo et al. (2009)    |
| 4   | *Phoma betae*       |                             | 8-hydroxy-6-methoxy-3-methylisocoumarin                                       |                                            |                        |
| 5   | *Rhizophora racemosa* | *Pseudopestalotiosis theae MN814071* | cytosporins W                                                                 | Cytotoxicity                               | Yu et al. (2020)       |
| 6   | *Achyranthes bidentata* | *Phomopsis* sp. CGMCC 5416 | Phomochromanone A                                                              | Anti-HIV-1 activity                        | Yang et al. (2020b)    |
| 7   |                     |                             | Phomochromanone B                                                              |                                            |                        |
| 8   |                     |                             | Phomochromanone C                                                              | Anti-PANC-1 cancer cells                   |                        |
| 9   | *Gynostemma Pentaphylla* | Chaetomium sp. JN180937.1 | Exopolysaccharide (composed of glucose, mannose, arabinose, and galactose in the ratio of 78.29:8.99:8.64:4.08) | Antioxidation and inhibition of cell proliferation | Zhang et al. (2017)    |
| 10  | *Duroia hirsuta*    | *Stelliosphaera formicium* YU.101029 | Stelliosphaerols A                                                            | Anti-Staphylococcus aureus                 | Forcina et al. (2015)  |
| 11  |                     |                             | Stelliosphaerols B                                                             |                                            |                        |
| 12  | *Vernonia amygdalina* | *Curvularia papendorff* KR673909 | Kheiric acid                                                                  | The anti-virus activities of human coronavirus 229E, feline coronavirus FCV F9, and *Staphylococcus* sp. could inhibit the proliferation of human breast cancer MCF7 cells | Khiralla et al. (2020) |
| 13  | *Markhamia platycalyx* | *Aspergillus flocculus*     | 5,9-Dihydroxy-2,4,6,8,10-pentamethyldodeca-6,10-trienal                        | Anti-parasite activity of parasite *Trypanosoma Bruce* | Tawfike et al. (2019)  |
| 14  | Extensive host plants | *Diaporthe vochysiae* LGMF1583 | Vochysiamides A                                                                | Activity against gram-negative bacteria, *Klebsiella pneumoniae* | Noriler et al. (2019)  |
| 15  | *Paullinia cupana*  | *Trichoderma asperellum* KU512700 | 1-Hydroxy-8-methoxyanthracene-9,10-dione                                        | Broad-spectrum antibacterial activity      | Silva et al. (2018)    |
| 16  | *Ephedra aphylla*   | *Diaporthe Phaseolorum* KU512679 | 3,4-Bis(2-ethylhexyl)phthalic acid                                           | Antitumor activity                        |                        |
| 17  |                     |                             | 3-Hydroxypropanoic acid                                                        | Antitumor, genotoxicity                    |                        |
| 18  | *Caesalpinia echinata* | *Pleospora tarda*          | Altemariol                                                                     | Significant antiviral effect on HSV-2 and VSV | Selim et al. (2018)    |
| 19  |                     |                             | Altemariol-(9)-methyl ether                                                   |                                            |                        |
| 20  |                     |                             | Ethyl trichoderonic acid                                                       | Significant antileishmanial activity       | Cota et al. (2018)     |
| 21  |                     |                             | 6'-Acetoxy-piliformal acid                                                     |                                            |                        |
| No. | Host plant       | Endophytic fungi | Chemical name | Pharmacological activity                                                                 | References          |
|-----|------------------|------------------|---------------|------------------------------------------------------------------------------------------|---------------------|
| 24  | *Entada abyssinica* | Epicoccum nigrum 10,672/SFR/CAM | Beauvericin   | Significant resistance to three gram-negative bacteria *Bacillus cereus*, *Salmonella typhimurium*, *Staphylococcus aureus* | Dzoyem et al. (2017) |
| 25  |                   |                  | Indole-3-carboxylic acid | Significant inhibition of *Enterococcus faecalis*                                           |                     |
| 26  |                  |                  | Parahydroxybenzaldehyde | Weak cytotoxicity and antioxidant activity                                                  |                     |
| 27  |                  |                  | Quinizarin     | Weak cytotoxicity and antioxidant activity                                                  |                     |
| 28  | *Hypericum perforatum* | *Thielavia subthermophila* | Hypericin      | It can be used in photodynamic therapy (PDT) of variable pathogenic diseases, light-activated hypericin acts as a strong pro-oxidant agent with antimicrobial and antigenic properties | Jendželovská et al. (2016) |
| 29  | *Cinnamomum mollissimum* | *Phoma sp.* | 4-Hydroxymellein | Significant inhibitory effect on P388 murine leukemic cells and *Bacillus subtilis*         | Santiago et al. (2014) |
| 30  | *Fucus serratus*   |                  | Phomafuranol   | Significant antibacterial, antifungal, and algal activity                                  | Hussain et al. (2014) |
| 31  | *Ocimum tenuiflorum* | *Penicillium Citrinum TPTDF1.4* | 3,7-Dihydroxy-9-methoxy-1-methyl-6H-benzo[c]chromen-6-one | Significant cytotoxic effect on murine lymphoma cell line L5178Y cells                   | Lai et al. (2013)   |
| 32  |                  |                  | (2R,3S,7aR,10aS,10bS)-5-Hydroxy-2,3,4-trimethyl-8-((E)-2-methyl-3-oxodec-8-enoyl)-2,3,7a,8,9,10,10a,10b-octahydropyrano[2′,3′,4′:4,5] chromen-2,3-b| Significant anti-*Staphylococcus aureus* ATCC 29,213 activity |                     |
| 33  | *Laurencia*       | *Penicillium Chrysogenum QEN-24S* | Penicisteroids A | Antifungal and cytotoxic activity                                                          | Gao et al. (2011)   |
| 34  | *Juniperus communis* L. Horstmann | *Aspergillus fumigatus Fresenius DSM 21,023* | Deoxypodophyllotoxin | Antibacterial and anticancer effects                                                        | Kusari et al. (2009) |
| 35  | *Kennedia nigriscans* | *Streptomyces sp. NRRL 3052* | Munumbicins E-4, Munumbicins E-5 | Broad-spectrum antibiotics                                                               | Castillo et al. (2006) |
| 36  | *Helianthus annuus* | *Nigrospora sphaerica TISTR3654* | 5-Pentyldihydrofuran-2(3H)-one | Activity of anti-*Staphylococcus aureus* and *meticillin*-resistant *S. aureus*, the activity of anti-fungi *Talaromyces marneffei* and the significant cytotoxic effect on A549 human cancer cell | Supaphon and Preedanon (2019) |
| 37  |                  |                  | (Z)-Methyl 4-(isobutyryloxy)but-3-enolate | 2-Phenylacetic acid                                                                 |                     |
| 38  |                  |                  | 2-Phenylacetic acid | Cytotoxic activity                                                                        | Ma et al. (2021)    |
| 39  | *Cephalotaxus fortunei* | *Xylaria sp. KU645984.1* | Xylariasins A | Cytotoxic activity                                                                        |                     |
| No. | Host plant                  | Endophytic fungi        | Chemical name                        | Pharmacological activity                          | References          |
|-----|-----------------------------|-------------------------|--------------------------------------|--------------------------------------------------|---------------------|
| 40  | Marine red alga             | *Acremonium vitellinum* MH726097 | 6,8-di-O-Methylbipolarin             | Insecticidal activity                            | Yuan et al. (2020)  |
| 41  | *Achyranthes bidentata*     | *Phomopsis* sp. CGMCC 5416 | Chermesinone B                       | Anti-HIV-1 virus, cytotoxic activity             | Yang et al. (2020b) |
| 42  | *Cyclosorus parasiticus*    | *Phomopsone* C           |                                     |                                                  |                     |
| 43  | *Nicotiana tabacum*         | *Diaporthe* sp. SC-J0138 | Diaporthichalasin D                 | Cytotoxic activity                               | Yang et al. (2020a) |
| 44  | *Cyclosorus parasiticus*    | *Diaporthe* sp. SC-J0138 | Diaporthichalasin H                 |                                                  |                     |
| 45  | *Nicotiana tabacum*         | *Phomopsis* sp. CGMCC 5416 | Chermesinone B                       | Anti-HIV-1 virus, cytotoxic activity             | Yang et al. (2020a) |
| 46  | *Nicotiana tabacum*         | *Diaporthe* sp. SC-J0138 | Diaporthichalasin H                 | Cytotoxic activity                               |                     |
| 47  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles A                    | Antifungal activity                              | Sun et al. (2020)   |
| 48  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles B                    |                                                  |                     |
| 49  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles C                    |                                                  |                     |
| 50  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles D                    |                                                  |                     |
| 51  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles E                    |                                                  |                     |
| 52  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles F                    |                                                  |                     |
| 53  | *Salvia miltiorrhiza*       | *Phomopsis* sp. PKU-EA00015 | Strepimidazoles G                    |                                                  |                     |
| 54  | *Elaeis guineensis* Jacq    | *Streptomyces palmae* CMU-AB204 | (Z)-5-(o-tolyl)pent-4-enoic acid     | Antifungal activity                              | Sun et al. (2020)   |
| 55  | *Elaeis guineensis* Jacq    | *Streptomyces palmae* CMU-AB204 | (Z)-7-(o-tolyl)hept-6-enoic acid     |                                                  |                     |
| 56  | *Elaeis guineensis* Jacq    | *Streptomyces palmae* CMU-AB204 | (Z)-11-(o-tolyl)undec-10-enoic acid  | Antibacterial activity                           | Shao et al. (2020)  |
| 57  | *Elaeis guineensis* Jacq    | *Streptomyces palmae* CMU-AB204 | (Z)-12-(o-tolyl)dodec-11-enoic acid  |                                                  |                     |
| 58  | *Aconitum vilmorinianum*    | *Penicillium variabile* HM469398 | Mazaphilones G                       | Inhibitory effects nitric oxide production       | Shao et al. (2020)  |
| 59  | *Aconitum vilmorinianum*    | *Penicillium variabile* HM469398 | Mazaphilones H                       |                                                  |                     |
| 60  | *Stryphnodendron adstringens* | *Diaporthe* cf. *Heveae* LGMF1631 | Cladosporin B                       | Antibacterial activity                           | Savi et al. (2020)  |
| 61  | Marine sponges              | *Penicillium solitum* MN365722 | Solitumin A                         | Cytotoxic, antibiotic, anti-Leishmania, anti-Trypanosoma cruzi, and inhibition of proteasome activity | Rodriguez et al. (2020) |
| 62  | Marine sponges              | *Penicillium solitum* MN365722 | Solitumin B                         |                                                  |                     |
| 63  | Marine sponges              | *Penicillium solitum* MN365722 | Solitumidines A                      |                                                  |                     |
| 64  | Marine sponges              | *Penicillium solitum* MN365722 | Solitumidines B                     |                                                  |                     |
| 65  | Marine sponges              | *Penicillium solitum* MN365722 | Solitumidines C                      |                                                  |                     |
| 66  | Marine sponges              | *Penicillium solitum* MN365722 | Solitumidines D                     |                                                  |                     |
| No. | Host plant           | Endophytic fungi          | Chemical name                                                                 | Pharmacological activity                                                                 | References                  |
|-----|----------------------|---------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------|
| 67  | *Globularia alypum*  | Battamyces globularicolaMB 832,845 | (3R,6Z)-3-Thiomethyl-6-[4-O-([2E]-4-hydroxy-3-methylbut-2-enyl]benzylidene]piperazine-2,5-dione | Cytotoxic activity                                                                   | Noumeur et al. (2020)       |
| 68  |                      |                           | (3R,6Z)-3-Thiomethyl-6-[4-O-([2Z]-4-hydroxy-3-methylbut-2-enyl]benzylidene]piperazine-2,5-dione |                                                                                          |                             |
| 69  |                      |                           | (3R,6Z)-3-Hydroxy-6-[4-O-(3-methylbut-2-enyl]benzylidene]piperazine-2,5-dione |                                                                                          |                             |
| 70  |                      |                           | (3R,6Z)-3-Thiomethyl-6-[4-O-(3-methylbut-2-enyl]benzylidene]piperazine-2,5-dione |                                                                                          |                             |
| 71  |                      |                           | (3S,6R)-3,6-Bisthiomethyl-6-[4-O-[(2Z)-4-hydroxy-3-methylbut-2-enyl]phenylmethyl]piperazine-2,5-dione |                                                                                          |                             |
| 72  | *Ceriops tagal*      | *Colletotrichum gloeosporioides* MF508974 | (5R,7S)-5,7-Dihydroxy-2-propyl-5,6,7,8-tetrahydro-4H-chromen-4-one | Cytotoxic activity and inhibition effect of COX-2 enzyme                              | Luo et al. (2020)           |
| 73  | *Kandelia candel*    | *Colletotrichum tropicale* SCSIO 41,022 | Colletoidinole A                                                                 |                                                                                          |                             |
| 74  |                      |                           | Methyl 2-(1H-indol-3-yl)-2-(3-(2-methoxy-2-oxoethyl)-1H-indol-2-yl)acetate |                                                                                          |                             |
| 75  | *Lycoris radiata*    | *Aspergillus versicolor* MG821480 | Proversilins C                                                                | Inhibition effect of HL-60 cell growth                                                  | Li et al. (2020b)           |
| 76  |                      |                           | Proversilins E                                                                |                                                                                          |                             |
| 77  | *Callistemon subulatus* | *Aspergillus* sp. MH665645 | Isoshinamethone                                                               | Anticancer activity                                                                     | Kamel et al. (2020)         |
| 78  | *Melia azedarach* Linn | *Diaporthe eucalyptorum* KACC48653 | Eucalyptacid A                                                                | Antifungal activity                                                                     | Gaet al. (2020b)            |
| 79  | *Fucus vesiculosus*  | *Pyrenochaetopsis* sp. FVE-001 | Pyrenosetins A                                                                | Anticancer activity                                                                     | Fan et al. (2020)           |
| 80  |                      |                           | Pyrenosetins B                                                                |                                                                                          |                             |
| 81  | *Ceriops tagal*      | *Talaromyces assiutensis* JN899320.1 | Talarocyclopenta A                                                             | Inhibitory effects nitric oxide production                                               | Cai et al. (2020)           |
| 82  |                      |                           | Asperitaconic B                                                               |                                                                                          |                             |
| 83  |                      |                           | Talarocyclopenta B                                                             | Antibacterial activity and inhibitory effects nitric oxide production                  |                             |
| 84  | *Rhizophora stylosa* | *Aspergillus terreus* SCAU011 | Asperbutenolide A                                                              | Inhibition effect of COX-2 enzyme                                                      | Bao et al. (2020)           |
| No. | Host plant               | Endophytic fungi               | Chemical name                                                                 | Pharmacological activity                  | References   |
|-----|-------------------------|--------------------------------|--------------------------------------------------------------------------------|--------------------------------------------|--------------|
| 85  | Acanthus ilicifolius L. | Epicoccum nigrum SCNU-F0002  | 1-(4-hydroxy-2-methoxybenzofuran-5-yl)butan-1-one                              | Antibacterial activity                     | Yan et al. (2019) |
| 86  | Vochysia diversgens    | Diporthe vochysiae LGMF1583   | Vochysiamide B                                                                   |                                            | Noriler et al. (2019) |
| 87  | Rhizophora apiculata B1| Aspergillus sp. MK629267      | Asperfuranoids A                                                                 |                                            | Cai et al. (2019) |
| 88  |                        |                                | Asperfuranoids B                                                                 |                                            |              |
| 89  |                        |                                | Asperfuranoids C                                                                 |                                            |              |
| 90  |                        |                                | Asperpanoid A                                                                    |                                            |              |
| 91  |                        |                                | Asperpanoid B                                                                    |                                            |              |
| 92  | Lemna gibba             | Streptomyces sp. MF347418     | 8-Hydroxy-3,4-dihydro-1H-quinolin-2-one                                         | Antibacterial and cytotoxic activity       | Mahmoud et al. (2018) |
| 93  |                        |                                | 3,4-Dihydro-1H-quinolin-2-one                                                   |                                            |              |
| 94  |                        |                                | 8-Methoxy-3,4-dihydro-1H-quinolin-2-one                                         |                                            |              |
| 95  | Pulicaria crispa        | Aspergillus versicolor         | Aspernolides L                                                                   | Antibacterial, antifungal, cytotoxic and   | Ibrahim et al. (2018) |
| 96  |                        |                                | Aspernolides M                                                                   | antimalarial activities                    |              |
| 97  | Casearia sylvestris    | Colletotrichum crassipes CSY-03| 1-Phenylethyl-O-α-L-rhamnopyranoside                                            | Inhibition effect of acetylcholine-        | Chapla et al. (2018) |
| 98  | Dugetia stelechantha   | Talaromyces stipitatus DgCr2 2.1b| Paecillin D                                                                     | Antibacterial activity                     | da Silva et al. (2017) |
| 99  | Nicotiana tabacum      | Rhizophycus vagum Nitaf 22    | Rhizopyncinolide A                                                               |                                            | Lai et al. (2016) |
| 100 |                        |                                | Rhizopyncin C                                                                    |                                            |              |
| 101 |                        |                                | Rhizopyncin D                                                                    |                                            |              |
| 102 | Rhizophora stylosa     | Aspergillus terreus FC118      | Exopolysaccharide (composed of D-galacturonic acid, rhamnose, D-mannose, glucose, and D-galactose in ratio of 0.45:3.02:3.25:1.00:0.95) | Anti-obesity activity                     | Yu et al. (2019) |
| 103 | Angelica sinensis      | Alternaria tenuissima MH035972.1| Fumigaclavine C                                                                  | Antioxidant activity                       | Wang et al. (2019) |
| 104 | Salvia miltiorrhiza    | Bipolaris sorokiniana KLBMPSM007| Cochloquinone B                                                                   | Antibacterial activity                     | Zhu et al. (2020) |
| 105 | Bergenia purpurascens  | Saccharicola bicolor KT367526 | Bicolorins B                                                                     | Antifungal activity                        | Zhao et al. (2020) |
| 106 |                        |                                | Bicolorins D                                                                     |                                            |              |
| 107 | Oxya chinensis Thunberg| Nigrospora sphaerica ZMT05    | Nigrosporamide A                                                                 |                                            | Zhu et al. (2017) |
| 108 |                        |                                | 4-Prenyloxyclavatol                                                              |                                            |              |
| 109 | Dendrobium officinale  | Nigrospora oryzae              | Nigrosirpexin A                                                                   | Inhibition effect of acetylcholine-        | Zhou et al. (2018a) |

Note: The table continues with additional entries not shown here.
Fig. 2 Endophytic fungus *N. hiratsukae* 20131E2AR1-1 and *A. eureka* 20131E1BL1 catalyze the transformation of cycloastragenol and astragenol to new compound with new bioactivity.
P. crustosum from Viguiera robusta, and Fusarium spp. from V. arenaria can all transform diketopiperazine to produce several antitumor diketopiperazine derivatives, such as (3R, 5aR, 65, 10aR)-6-hydroxy-3-(hydroxymethyl)-2-methyl-3,10a-bis(methyl-thio)-2,3,5a,6,10,10a-hexahydro-pyrazino[1,2-α]indole-1,4-dione and 6-hydr- oxy-3-(hydroxymethyl)-2-methyl-3-(methythio)-2,3,10,10a-tetrahydro-pyrazino[1,2-α]indole-1,4- dione (Guimaraes et al. 2010). The unique habitat of endophytic fungi makes them “micro-evolve” to some unique ability to synthesize certain novel skeleton compounds. For example, F. oxysporum ATCC MYA 4623 can catalyze hydrazine to form novel skeleton compounds with anti-inflammatory activity, 3-methyl-1,2,4-triazolo[3,4-α]phthalazine (Almeida et al. 2018). Two endophytic fungi, A. eureka 20131E1BL1 and N. hiratsukae 20131E2AR1-1 from Astragalus sp., can modify cycloastragenol and astragenol to produce new compounds 1–5 (Fig. 2) that have telomerase inhibitory effects and are expected to be used in anti-aging and anti-Alzheimer’s disease (Ekiz et al. 2019).

Conclusion and future perspectives

Although much of the research on endophytic fungi is still in its infancy, their biodegradation and biosynthesis capacity is receiving increasing research attention. Results from this research can have the potential to promote revolutionary developments of industries ranging from food safety and security to the discovery of novel biopharmaceutical compounds to understanding basic aspects of organisal interactions and evolution. However, some difficulties are still encountered in studies on endophytic fungi. These include:

1. Lack of culture conditions: given the operational complexity of the plant internal environment and the often unique habitats of medicinal plants, although a large number of endophytic fungi have been detected using high-throughput sequencing, a significant number of endophytic fungi still cannot be effectively cultured in vitro.

2. In vitro passage affects fungal physiology: For those fungi that can be cultured, in vitro passage often leads to decreasing activities of desired biological processes. Owing to the complexity of the interaction between endophytic fungi and their host plants and current limitations on the factors that mediate these interactions, in many instances, the biotransformation activity, efficiency, and desired product formation capabilities of many isolated endophytic fungi gradually decrease with increasing generations of subculturing on synthetic media, thus limiting potential commercialization efforts. As one example, the ability to synthesize camptothecin gradually declines in F. solani INFU/Ca/KF/3 because of the lack of its host

C. acuminata continually providing stritosidine synthases in vitro (Kusari et al. 2011). Increasing our understanding and ability to manipulate these species interaction mechanisms is necessary.

3. Poor understanding of the networks that mediate establishment and regulation of the fungal-plant interaction. Our current understanding of the factors that mediate host responses, fungal persistence, and (biochemical) pathway interactions remains limited. For example, the content of wihanolid A in Withania somnifera can be increased by 147% when infected with Sarocladium kilense F800957 compared with those not infected (Ramesh et al. 2019). This regulatory mechanism also needs to be further elucidated.

Future directions:

1. Although a lot of biotransforming activities have been found in plants, only a few of them are applied to mass production in real life. Thus, the future efforts should focus on strengthening the continuous industrial application research in vivo and in vitro.

2. Application of high-throughput “omics” to the fungal endophyte-plant interactions. Use of high-throughput sequencing technology including transcriptomics, coupled to proteomics and metabolomics, should be applied to gain mechanistic insights into the degree of integration of fungal and plant genetic and biochemical networks. The application of information networks, artificial intelligence, and other disciplines, using network models to simulate the signal and material exchange and sharing of species interaction, should also be developed to study the biotransformation mechanisms of endophytic fungi.

3. Continued screening and isolation of fungal endophytes and novel screening and isolation of fungal endophytes and novel approaches at maintaining desired traits during in vitro culturing should be encouraged.

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Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.
Conflict of interest The authors declare no competing interests.

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