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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

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(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 *Arthritis* 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 H_2O and CO_2 (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-hydroxysuccinate 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*, *Acrmetonium* sp. and *F. moniliforme* from *Aphelundra tetragona*, and *Paecilomyces formosus* HQ444388 from *Glycine max* can degrade toxic substances, such as benzoxazolin-2-(3*H*)-one (Schulz et al. 2016), aphelandrine (Christa et al. 1997), jasmonic acid (Bilal et al. 2018), 2-hydroxy-*N*-(2-hydroxypheyl) acetate (Zikmundova et al. 2002), 6-methoxybenzox-azolin-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* 20131E1BL1 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 *Bischofia polycarpa* can completely decompose cinnamic acid (hepatoprotective agent) into CO_2 and H_2O, 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 *Epicoccum 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-methanone (Shang et al. 2019). Triclosan can be degraded into detoxifying metabolites, e.g., hydroquinone, (2*Z*,4*E*)-3-chloro-2,5-dihydroxyhexa-2,4-dienedioic acid, and (2*Z*,4*E*)-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 (Marzall-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 CO_2 and H_2O (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, fluorobenzoate, 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 cellobiohydrolases (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 monooxygenases, 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, endophytic fungi *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, 2,3-dimethoxy-naphthalene, 2,5-furandione dihydro-3-methylene, and other organic substances with fuel value (Maxwell et al. 2018). Notably, the endophytic *Chaetomium globosum* CGMCC 6882 from a well-known folk medicinal plant *Gynostemma pentaphyllum* can successfully transform xanthan (a polymer containing β-1,4-glucosidic bond successfully linked to the main chain and a trisaccharide side-chain containing mannose, gluconic acid, and mannose) into a low-molecular-weight xanthan (LW-XG; the composition of LW-XG was glucose, mannose, and glucuronic acid at a molar ratio of 1.63:1.5:1.0) with antioxidant, anti-arthritis, anti-chondrocyte apoptosis, 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-evolution 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 podophyllotoxin (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 (Bömke and Tudzynski 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* MN544934	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		*Fusarium culmorum* KM362384	Endoglucanase	
5	*Andropogon gayanus*	*Fusarium verticillioides*	Endoglucanase, cellobiase, cellulase	de Almeida et al. (2019)
6	*Phoenix dactylifera* L.	*Penicillium bilaiae* TDPEF30	Protease (especially acidic protease)	Ben et al. (2019)
7	*Simarouba glauca*	*Phomopsis* sp. KX49881	Laccase	Navada et al. (2018)
8	*Laguncularia racemosa*	*Aspergillus awamori*	Endoglucanase, β-glucosidase, xylanase	Maroldi et al. (2018)
9	*Rhizophora mangle*	*Aspergillus niger*	Endoglucanase, β-glucosidase, xylanase	
10	*Cananga odorata*	*Ampelomyces* sp.	Cellulase	Toghueo et al. (2017)
11		*Chaetomium globosum*	Amylase, cellulase	
12		*Colletotrichum fructicola*	Amylase, cellulase, lipase	
13		*Diaporthe* sp.	Amylase, cellulase, lipase	
14		*Fusarium equiseti*	Amylase, cellulase, laccase	
15		*Fusarium oxysporum*	Amylase, cellulase, lipase	
16		*Fusarium solani*	Amylase, cellulase, lipase	
17		*Fusarium striatum*	Amylase, cellulase, lipase	
18		*Guignardia mangiferae*	Amylase, lipase	
19		*Nectria rigidiuscula*	Amylase, cellulase	
20		*Nigrospora oryzae*	Lipase	
21	*Terminalia mantaly*	*Cercospora chrysanthemi*	Amylase, cellulase, lipase	
22		*Cercospora flagellaris*	Cellulase, lipase	
23		*Cercospora olivascens*	Amylase, lipase	
24		*Cercospora* sp.	Amylase, cellulase, lipase	
25		*Colletotrichum gloeosporioides*	Amylase, cellulase, lipase	
26		*Corynespora cassiicola*	Amylase, cellulase, lipase, laccase	
27		*Diaporthales* sp.	Amylase	
28		*Fusarium solani*	Amylase, cellulase	
29		*Hypoxylon investiens*	Amylase, cellulase, lipase	
30		*Nemania bipapillata*	Amylase, Lipase	
31		*Nigrospora oryzae*	Amylase, cellulase, lipase	
32		*Phoma microchlamydospora*	Amylase, cellulase, lipase	
33		*Phomopsis phyllanticolla*	Amylase, cellulase, lipase	
34		*Phomopsis* sp.	Amylase, cellulase, lipase	
35		*Pleosporales* sp.	Cellulase	
36		*Septoria* sp.	Lipase	
37		*Xylaria adscendens*	Amylase, cellulase, lipase, laccase	
38		*Xylaria persicaria*	Amylase, cellulase, lipase	
39		*Xylaria* sp.	Amylase, cellulase, lipase, laccase	
40		*Xylariaceae* sp.	Amylase, cellulase, lipase, laccase	

Table 1 (continued)

No.	Plant	Endophytic fungi	Enzyme	References
41	*Terminalia catappa*	*Cercospora olivascens*	Amylase, cellulase, lipase	
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		*Lasiodiplodia 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		*Pestalotiopsis* 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	Orlandelli et al. (2017)
62		*Marasmius cladophyllus* JF767003	α-Amylase	
63		*Phlebia* sp. JF766997	α-Amylase	
64		*Phyllosticta capitalensis* JF766988	α-amylase	
65		*Schizophyllum commune* JF766994	α-amylase	
66	*Curcuma amada*	*Talaromyces pinophilus* KJ372306	L-Asparaginase	Krishnapura et al. (2016)
67	*Bacopa monnieri*	*Pleosporales* sp.	Amylase	Katoch et al. (2014)
68		*Eutypella* sp. E9901c	Amylase	
69		*Fusarium oxysporum* F1TK1	Amylase	
70		*Fomitopsis cf. Meliae* KYO	Cellulase	
71	*Eremophilia longifolia*	*Preussia minima* EL-14	α-Amylase	Zaferanloo et al. (2014)

(Qawasmeh et al. 2015, 2012). Another well studied and confirmed example is swainsonine, a toxin which can seriously poison livestock, and it also is 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*-diglycide, which shows anticancer and antioxidant activity (Harwoko et al. 2019), and *Neosartorya hiratsukae* from *Astragalus*

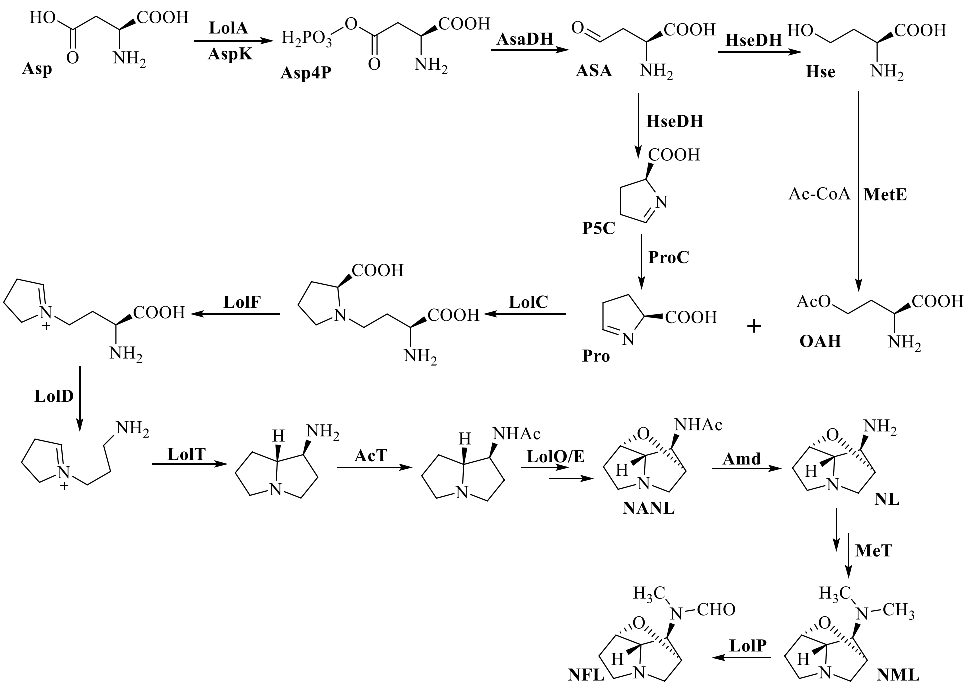


Fig. 1 Important intermediates and end product of the loline alkaloid. (Asp, asparticacid; Asp4P, aspartic acid-4-phosphate; Asa, aspartyl-4-semi-aldehyde; Hse, homoserine; OAH, *O*-acetylhomoserine; P5C, pyrroline-5-carboxylate; Pro, proline; NL, norloline; NML, *N*-methylloline; NFL, *N*-formylloline). Double arrows indicate additional, non-illustrated intermediates

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 albendazole 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 (*R*)-1-phenylethanol and (*S*)-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 *Aphelandra* can catalyze the transformation of nigranoic acid (drugs for preventing cerebral ischemia–reperfusion injury) into new compounds with high biological activity (Qin et al. 2019). The endophytic *Colletotrichum gloeosporioides* and

Table 2 Unique pharmacological active substances of endophytic fungi in medicinal plants

No.	Host plant	Endophytic fungi	Chemical name	Pharmacological activity	References
1	Ryegrass	*Epichloe festucae Lp*TG-1	Lolitrem B	Central nervous toxicity	Reddy et al. (2020)
2	*Aster tataricus*	*Cyanodermella asteris*	Astin A	Antitumor activity	Schafhauser et al. (2019)
3	*Smallanthus sonchifolius*	*Nigrospora sphaerica*	(22*E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one		Gallo et al. (2009)
4		*Phoma betae*	8-hydroxy-6-methoxy-3-methylisocoumarin		
5	*Rhizophora racemosa*	*Pseudopestalotiopsis 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 formicum* YU.101029	Stelliosphaerols A	Anti-*Staphylococcus aureus*	Forcina et al. (2015)
11			Stelliosphaerols B		
12	*Vernonia amygdalina*	*Curvularia papendorfii* KR673909	Kheiric acid	The anti-virus activities of human coronavirus 229E, feline coronavirus FCV F9, and *Staphylococus* 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-2,6,10-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		Diaporthe *Phaseolorum* KU512679	3,4-Bis(2-ethylhexyl)phthalic acid	Antitumor activity	
17			3-Hydroxypropanoic acid	Antitumor, genotoxicity	
19	*Ephedra aphylla*	*Pleospora tarda*	Alternariol	Significant antiviral effect on HSV-2 and VSV	Selim et al. (2018)
20			Alternariol-(9)-methyl ether		
21	*Caesalpinia echinata*	Nectria pseudotrichia KF611677	Etyl trichoderonic acid A	Significant antileishmanial activity	Cota et al. (2018)
22			6′-Acetoxy-piliformic acid		
23					

Table 2 (continued)

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* TPDTF1.4	3,7-Dihydroxy-9-methoxy-1-methyl-6*H*-benzo[c]chromen-6-one	Significant cytotoxic effect on murine lymphama cell line L5178Y cells	Lai et al. (2013)
32			(2*R*,3*S*,7a*R*,10a*S*,10b*S*)-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]chromeno[2,3-b]pyrrole-6-carboxylic acid	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(3*H*)-one	Activity of anti-*Staphylococcus aureus* and *methicillin–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-enoate		
38			2-Phenylacetic acid		
39	*Cephalotaxus fortunei*	*Xylaria* sp. KU645984.1	Xylariasins A	Cytotoxic activity	Ma et al. (2021)

Table 2 (continued)

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			Phomopsone C		
43	*Cyclosorus parasiticus*	*Diaporthe* sp. SC-J0138	Diaporthichalasin D	Cytotoxic activity	Yang et al. (2020a)
44			Diaporthichalasin H		
45	*Nicotiana tabacum*	*Rhizopycnis vagum* KM095527	Rhizoperemophilane J		Wang et al. (2020)
46			Rhizoperemophilane N		
47	*Salvia miltiorrhiza*	*Streptomyces* sp. PKU-EA00015	Strepimidazoles A	Antifungal activity	Sun et al. (2020)
48			Strepimidazoles B		
49			Strepimidazoles C		
50			Strepimidazoles D		
51			Strepimidazoles E		
52			Strepimidazoles F		
53			Strepimidazoles G		
54	*Elaeis guineensis* Jacq	*Streptomyces palmae* CMU-AB204	(*Z*)-5-(o-tolyl)pent-4-enoic acid	Antifungal activity	Sujarit et al. (2020)
55			(*Z*)-7-(o-tolyl)hept-6-enoic acid		
56			(*Z*)-11-(o-tolyl)undec-10-enoic acid	Antibacterial activity	
57			(*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			Mazaphilones H		
60	*Stryphnodendron adstringens*	*Diaporthe* cf. *Heveae* LGMF1631	Cladosporin B	Antibacterial activity	Savi et al. (2020)
61	Marine sponges	*Penicillium solitum* MN365722	Solitumine A	Cytotoxic, antibiotic, anti-Leishmania, anti-Trypanosoma cruzi, and inhibition of proteasome activity	Rodriguez et al. (2020)
62			Solitumine B		
63			Solitumidines A		
64			Solitumidines B		
65			Solitumidines C		
66			Solitumidines D		

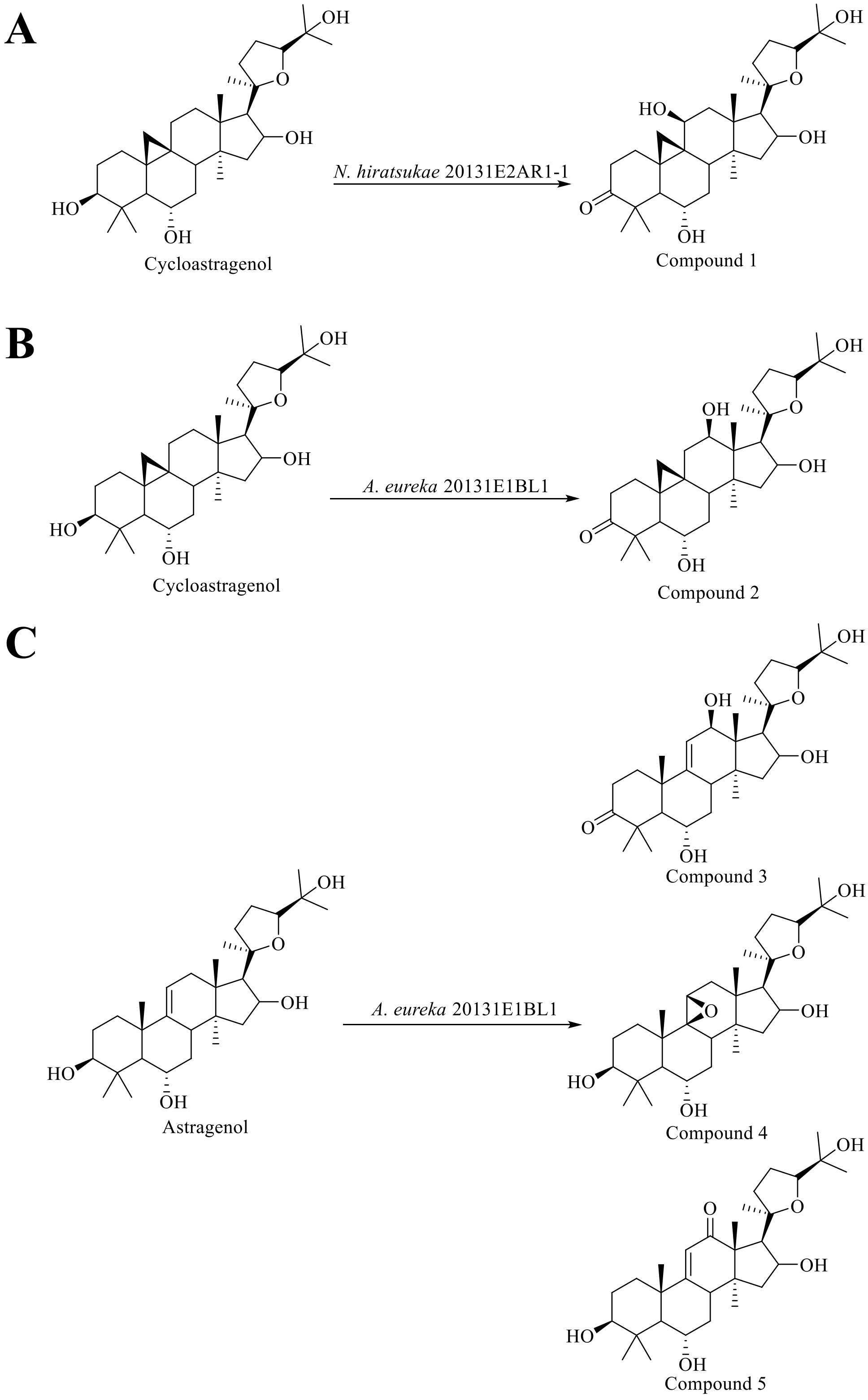
Table 2 (continued)

No.	Host plant	Endophytic fungi	Chemical name	Pharmacological activity	References
67	*Globularia alypum*	Batnamyces globulariicolaMB 832,845	(3*R*,6*Z*)-3-Thiomethyl-6-[4-*O*-[(2*E*)-4-hydroxy-3-methylbut-2-enyl] benzylidene]piperazine-2,5-dione	Cytotoxic activity	Noumeur et al. (2020)
68			(3*R*,6*Z*)-3-Thiomethyl-6-[4-*O*-[(2*Z*)-4-hydroxy-3-methylbut-2-enyl] benzylidene]piperazine-2,5-dione		
69			(3*R*,6*Z*)-3-Hydroxy-6-[4-*O*-(3-methylbut-2-enyl)benzylidene]piperazine-2,5-dione		
70			(3*R*,6*Z*)-3-Thiomethyl-6-[4-*O*-(3-methylbut-2-enyl)benzylidene]piperazine-2,5-dione		
71			(3*S*,6*R*)-3,6-Bisthiomethyl-6-[4-*O*-[(2*Z*)-4-hydroxy-3-methylbut-2-enyl] phenylmethyl]piperazine-2,5-dione		
72	*Ceriops tagal*	*Colletotrichum gloeosporioides* MF508974	(5*R*,7*S*)-5,7-Dihydroxy-2-propyl-5,6,7,8-tetrahydro-4*H*-chromen-4-one		Luo et al. (2020)
73	*Kandelia candel*	*Colletotrichum tropicale* SCSIO 41,022	Colletoindole A	Cytotoxic activity and inhibition effect of COX-2 enzyme	Lin et al. (2020)
74			Methyl 2-(1*H*-indol-3-yl)-2-(3-(2-methoxy-2- oxoethyl)-1 *h*-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	Isoshamixanthone	Anticancer activity	Kamel et al. (2020)
78	*Melia azedarach* Linn	*Diaporthe eucalyptorum* KACC48653	Eucalyptacid A	Antifungal activity	Gaoet 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)

Table 2 (continued)

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 divergens*	*Diporthe vochysiae* LGMF1583	Vochysiamide B		Noriler et al. (2019)
87	*Rhizophora apiculata* Bl	*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-1*H*-quinolin-2-one	Antibacterial and cytotoxic activity	Mahmoud et al. (2018)
93			3,4-Dihydro-1*H*-quinolin-2-one		
94			8-Methoxy-3,4-dihydro-1*H*-quinolin-2-one		
95	*Pulicaria crispa*	*Aspergillus versicolor*	Aspernolides L	Antibacterial, antifungal, cytotoxic and antimalarial activities	Ibrahim et al. (2018)
96			Aspernolides M		
97	*Casearia sylvestris*	*Colletotrichum crassipes* CSY-03	1-Phenylethyl-*O*-α-*L*-rhamnopyranoside	Inhibition effect of acetylcholine- sterase	Chapla et al. (2018)
98	*Duguetia stelechantha*	*Talaromyces stipitatus* DgCr2 2.1b	Paecillin D	Antibacterial activity	da Silva et al. (2017)
99	*Nicotiana tabacum*	*Rhizopycnis vagum Nitaf 22*	Rhizopycnolide A		Lai et al. (2016)
100			Rhizopycnin C		
101			Rhizopycnin D		
102	*Rhizophora stylosa*	*Aspergillus terreus* FC118	Fumigaclavine C	Anti-obesity activity	Yu et al. (2019)
103	*Angelica sinensis*	*Alternaria tenuissima* MH035972.1	Exopolysaccharide (composed of *D*-galacturonic acid, rhamnose, *D*-mannose, glucose, and *D*-galactose in ratio of 0.45:3.02:3.25:1.0:0.95)	Antioxidant activity	Wang et al. (2019)
104	*Salvia miltiorrhiza*	*Bipolaris sorokiniana* KLBMPSM007	Cochlioquinone 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- sterase	Zhou et al. (2018a)

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 (3*R*, 5a*R*, 6*S*, 10a*R*)-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-(methylthio)-2,3,10,10a-tetrahydropy-razino[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 organismal 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 wihanolide A in *Withania somnifera* can be increased by 147% when infected with *Sarocladium kiliense* 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 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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