FEMS Microbiology Letters, 2022, **369**, 1–14
DOI: 10.1093/femsle/fnac052
Advance access publication date: 23 June 2022
Minireview – Food Microbiology

Endophytic fungi and their bioactive secondary metabolites in medicinal leguminosae plants: nearly untapped medical resources

Zhong-Ya Zhou[1,2], Xi Liu[1,2], Jin-Long Cui[1,*], Jun-Hong Wang[1], Meng-Liang Wang[1], Gang Zhang[3,*]

[1]Institute of Applied Chemistry, Shanxi University, Taiyuan, Shanxi 030006, People's Republic of China
[2]Modern Research Center for Traditional Chinese Medicine, the Key Laboratory of Chemical Biology and Molecular Engineering of Ministry of Education, Shanxi University, Taiyuan, Shanxi 030006, People's Republic of China
[3]College of Pharmacy, Shaanxi University of Chinese Medicine, Century Avenue, Xianyang 712046, China
****Corresponding authors.** Institute of Applied Chemistry, Shanxi University, Taiyuan, Shanxi 030006, People's Republic of China. Tel.: +86-351-7018390; Fax: +86-351-7018390; E-mail: CJL717@163.com. College of Pharmacy, Shaanxi University of Chinese Medicine, Century Avenue, Xianyang 712046, China. E-mail: jaygumling2003@aliyun.com.

One sentence summary: This review presents the diversity, secondary metabolites and biological activities of endophytic fungi of medicinal leguminosae plants.

Abstract

There are many species of Chinese traditional leguminosae family plants that are well known for their medicinal applications, such as *Astragalus membranaceus*, *Catsia tora*, *Glycyrrhiza uralensis*, *Sophora flavescens* and *Albacia acacia*. Their unique bioactive composition and internal phenological environment contribute to the formation of specific and unique endophytic fungal communities, which are important resources for new compounds used in a variety of pharmacological activities. Nonetheless, they have not been systematically studied. In the last decade, nearly 64 genera and thousands of species of endophytic fungi have been discovered from leguminosae plants, as well as 138 secondary metabolites (with 34 new compounds) including flavonoid, alkaloids, phenol, anthraquinone, macrolide, terpenoid, phytohormone and many more. These were shown to have diverse applications and benefits, such as antibacterial, antitumor, antioxidative, immunoregulatory and neuroprotective properties. Here, we provide a summarized overview with the aim of raising awareness of endophytic fungi from medicinal leguminosae plants and providing a comprehensive review of the discoveries of new natural products that may be of medicinal and pharmaceutical importance.

Keywords: Fungal endophyte, medicinal plants, pharmacological activity, new resource, natural product

Introduction

Leguminosae, the third largest family of the plant kingdom, possesses more than 650 genera and 20 000 species of plants, among which at least 11 genera (*Astragalus*, *Senna*, *Glycyrrhiza*, *Albizia*, *Leucaen*, *Medicago*, *Sophora*, *Oxytropis*, *Trifolium*, *Bauhinia* and *Cercis*) and 490 species have been identified as Chinese medicinal plants (Hong et al. 2019). They exhibit various pharmacological activities of traditional chinese medicine, such as "Toniflying qi and strengthenning exterior", "Expel pus and draw toxinclear", "Removing liver and improving vision", "Diuresis and catharsis", "Disperses wind-heat, clears heat, and relieves toxicity" and "Resolve phlegm to relive cough" (Yuan et al. 2016; Mazinani et al. 2017). Recent studies have shown that these plants contain various natural products including alkaloids, flavonoids, terpenoids, polysaccharides, phenols and so on, which have antitumor, antimicrobial, antiviral, antioxidant and other pharmacological activities. In brief, medicinal leguminosae plants (MLPs) play an important role in traditional Chinese medicine.

However, recent studies have shown that plant is not a pure "independent entity", but forms a "symbiotic functor" with its microorganisms (Kungas et al. 2020). These microbes have formed a stable symbiotic relationship with the plant during the long-term co-evolution process, and they colonize the internal plant tissues without causing any apparent disease to their host plant, which are referred to as endophytes (Zhao et al. 2021; Strobel 2018).

The particular category and content of chemical compositions give rise to a unique chemical environment and ecological niche in each specific plant, which is unique selective pressure on symbiotic microbes, and only those microbes that are fully adapted to the new environment are selected to colonize the internal plant tissues (Singh et al. 2021; Kuźniar et al. 2020). Thus, all the successful settlers finally constitute the unique endophytic community in each plant. What is noteworthy is that the species of the endophytes are different from those of the non-endophytic environment. Most of them have undergone genovariation or the alteration of gene function, and have even developed the ability to produce specific compounds for adaptation (Gómez and Luiz 2018). Although the evolutionary mechanism of endophytes is still not fully understood, they have the ability to produce a variety of novel compounds and become a new resource of compounds that are indeed beneficial to the host plants (Berthelot et al. 2017; Kouipou Toghueo and Boyom 2019).

To summarize the metabolites and activities of endophytic fungi from MLPs in the last 10 years, nearly 64 genera of endophytic fungi and 138 secondary metabolites (including 34 new compounds) were found with biological activities such as antitu-

Received: December 6, 2021. **Accepted:** June 7, 2022

mor, antibacterial, antioxidant, immune regulation and neuroprotective activities, which provide scientific reference for the further development of MLPs and understanding of the function of endophytic fungi.

Diversity of endophytic fungi in medicinal leguminosae plants

During long-term co-evolution, leguminosae plants have selectively hosted their special and diverse endophytic fungi based on their mutual benefits during the selection process. These fungal endophytes transmit from generation to generation through the "vertical transmission" mode, forming endophytic fungi that are unique to leguminosae plant species (Palak and Syed 2019; Egamberdieva 2017). For example, endophytic fungi *Undifilum oxytropis* and *Alternaria oxytropis* specifically symbiose with plants of *Astragalus* and *Oxytropis* plant species (Chenchen et al. 2014; Noor et al. 2020; Tan et al. 2019), and the main active substance swainsonine in these plants is produced by these dominant fungi (Chenchen et al. 2014; Baucom et al. 2012). Endophytic fungi have shown tissue specificity due to differences of composition of active substances and ecological niche in different tissues (Fernandes et al. 2015; Russo et al. 2016). For instance, to *Medicago sativa*, the dominant fungi were *Fusarium. oxysporum* 1 and *F. oxysporum* 2 in roots, *Aspergillus cremonium* 1 and *A. cremonium* 2 in stems and *A. strictum* and *A. ochraceus* in leaves, showing obvious tissue specificity (Eman et al. 2020). On the other hand, endophytic fungi show high diversity with different plant tissue, age, physiological state, environment and phenological condition tropisms (Eman et al. 2020). It was found that *Trichoderma* sp. and *Rhizopus* sp. are the dominant species, followed by *Monascus* sp. in *Glycyrrhiza uralensis* located in the Ural region (Yang et al. 2020). But to *G. uralensis* that grows in the northwestern Himalayas, the genera of *Phoma* and *Fusarium* were the dominant community. They constitute the main fungal microflora of the host together with *Phoma* spp., *Fusarium* spp. and *Diaporthe* spp. (Arora et al. 2019).

In summary, there are abundant endophytic fungi in medicinal plants of the leguminous family. They are mainly affiliated to basidiomycota, ascomycota and zygomycota. About 64 genera of endophytic fungi were isolated from 11 MLPs (Table 1). Table 1 shows that 20 genera of endophytic fungi were isolated from the *Albizia* plants, which are the largest group, followed by 16 fungal genera in *Bauhinia* spp., 14 fungal genera in *Senna* spp., 12 fungal genera in *Astragalus* spp., nine fungal genera of *Glycyrrhiza* spp., six fungal genera in *Cercis*, *Oxytropis* or *Medicago* plants, four fungal genera in *Styphnolobium* spp., two fungal genera in *Trifolium* spp. and only one fungal species in *L. leucocephala*. In addition, *Penicillum*, *Trichoderma* and *Fusarium* were prevalent among the 11 genera MLPs. The endophytic fungi of *Albizia* plants were studied most thoroughly, which involves nearly 150 plant species, among which the commonly used medicinal plants are *A. kalkora*, *A. julibrissin*, *A. lebbeck* and *A. crassiramea* (Mookherjee et al. 2020).

Secondary metabolites and activities of endophytic fungi from medicinal leguminosae plants

To date, it was found that endophytic fungi from MLPs exhibited antitumor, antibacterial, antioxidant, immunoregulatory, neuroprotective and other biological activities (Mookherjee et al. 2020; Klypina et al. 2017). A total of 138 compounds including 34 novel compounds were extracted from the fermentation broth of endophytic fungi.

Antitumor activity and metabolites

Since Strobel discovered in 1991 that *Taxomyces andreanae*, an endophytic fungus of *Taxus chinensis*, produces taxol, the secondary metabolites and biological activity of endophytic fungi have attracted more attention (Strobel et al. 1993). In recent years, many endophytic fungi and bioactive compounds with antitumor activity have been discovered from MLPs. Among them, there are many studies of the antitumor activity of endophytic fungi from *A. membranaceus*. A strain of *Fusarium* sp. secretes three mycomycin compounds 1-3, and compound 1 has a cytotoxic effect on tumor cell lines MOLT-4, A549, HL-60 and BEL-7402 (Liu et al. 2015); compound 2 has the effect of reversing drug resistance when combined with doxorubicin and other drugs (Liu et al. 2015; Rabindran et al. 2000); compound 3 can bind to the thorny end of actin filaments and disrupt the formation of actin polymers (Liu et al. 2015; Osada 2003). In addition, an endophytic fungus, *Alternaria* sp. from *A. membranaceus*, can produce five novel compounds 4-8 (Fig. 1) with antitumor potential, and among them, compounds 5 and 6 have inhibitory effects on NCI-H460 (human non-small cell lung cancer), SF-268 (human central glioma), MCF-7 (human breast cancer), PC-3M (human metastatic prostate cancer) and MDAMB-231 (human metastatic breast cancer) (Bashyal et al. 2017). Eight 2,5-dicopper pyrazine active compounds 9-16 were extracted from the endophytic *Aspergillus* sp. of *A. membranaceus*, of which compounds 9-11 inhibited prostate cancer, liver cancer, cervical cancer, breast cancer and colon cancer, and can be used as precursor drugs against cancer (Liu et al. 2020). The chromone compound 17 was also extracted to reduce the growth of mammospheres, decrease the proportion of CD44+/CD24- (breast cancer stem cells) cells in breast cancer cells, and reduce the expression of stem cell-associated proteins c-Myc, Sox-2 and Oct4, thus exerting an inhibitory effect on the proliferation and migration of breast cancer cells (de Amorim et al. 2020; Ugai et al. 2020; Liu et al. 2020). he compound 18 belongs to emodin extracted from *Rhizopus* sp. of *A. membranaceus*, which can also inhibit the cytotoxicity of cervical cancer cells (Zhang et al. 2020). Seven aza-anthraquinone compounds 19-25 were extracted from endophytic *Fusarium* sp. of *C. tora*, of which compounds 20 to 23 have significant cytostatic effects on vero tumor cell (Khan et al. 2018), and compound 23 can significantly inhibit the proliferation of the hematological tumor cell line and increase cell apoptosis (Khan et al. 2018; Adorisio et al. 2019). The endophytic fungus *Penicillium sclerotiorum* of *C. tora* produces three volatile compounds 26-28, which can induce apoptosis of cancer cells A549, A431, U251 and HeLa by activating the apoptotic mitochondrial pathway (Kuriakose et al. 2018). The alkaloid compound 29 secreted by the specific endophytic *U. oxytropis* of *A. oxytropis* also exhibits an obvious inhibitory effect on A549 and HeLa cancer cells (Tan et al. 2019; Li and Lu 2019). Five cytochalasin compounds 30-34 from endophytic *Rosellinia sanctaecrucianafenl* of *A. lebbeck* showed significant inhibitory effects on a series of human cancer cell lines, namely MOLT-4, A549, MIAPaCa-2 and MDA-MB-231 (Sharma et al. 2018). Two new compounds 35-36 (Fig. 1) showed cytotoxicity, which were from endophytic *Aspergillus* sp. of *C. chinensis* (Zhao et al. 2021). A known quinone mycotoxin compound 37 can interfere with the metabolic communication of cancer cells and inhibit proliferation of tumor cells (Zhao et al. 2021; Jarolim et al. 2017). All the active metabolites of endophytic fungi from MLPs are summarized in Table 2, and their

Table 1. Genus or species distribution of active endophytic fungi from medicinal leguminosae plants in last decade.

No.	Endophytic fungi (genes or species)	Host plants	References
1	*Acremonium* sp.	*Albizia lebbeck, Medicago sativa, Cercis chinensis, Bauhinia forficata*	Eman et al. 2020; Gioia et al. 2020; Wulandari and Suryantini 2018; Zhao et al. 2021
2	*Alternaria* sp.	*Astragalus lentiginosus, B. forficata, Swainsona canescens, C. chinensis*	Tan et al. 2019; Noor et al. 2020; Bashyal et al. 2017; Zhao et al. 2021
3	*Aspergillus ochraceus*	*M. sativa, B. guianensis*	Eman et al. 2020; Feitosa et al. 2016
4	*A. fumigatus*	*Trifolium repens*	Yang 2013.
5	*Aspergillu* sp.	*Sophora flavescens, Acacia auriculaeformis, B. guianensis*	He et al. 2013; Jiang et al. 2008; Pinheiro et al. 2013
6	*Aspergillus flavus*	*A. lebbeck, Cassia siamea, M. sativa*	Khambhati et al. 2020; Eman et al. 2020
7	*Aspergilus alternata*	*C. chinensis, B. guianensis*	Pinheiro et al. 2013; Zhao et al. 2021
8	*Botrytis* sp.	*A. membranaceus*	Sun et al. 2016; Murali et al. 2007
9	*Bipolaris* sp.	*A. lebbeck*	Ali and Alfayed 2017
10	*Cephalosporium* sp.	*A. membranaceus*	Xu 2016.
11	*Candida albicans*	*M. sativa*	Eman et al. 2020
12	*Chaetospermu* sp.	*A. membranaceus*	Sun et al. 2016
13	*Colletotrichum gloeosporioides*	*Albizia hindsii, B. racemosa*	Murali et al. 2007; González-Teuber et al. 2014
14	*Colletotrichum truncatum*	*A. hindsii*	González-Teuber et al. 2014
15	*Colletotrichum* sp.	*A. hindsii*	Suryanarayanan et al. 2018; González-Teuber et al. 2014
16	*Curvularia* sp.	*A. lebbeck, B. monandra*	Araujo-Melo et al. 2017
17	*Colletotrichum coccodes*	*B. guianensis*	Pinheiro et al. 2017
18	*Dothiorella* sp.	*B. brevipes, C. chinensis*	Bezerra et al. 2019; Hilarino et al. 2011; Zhao et al. 2021
19	*Diaporthe* sp.	*Glycyrrhiza glabra*	Arora et al. 2019
20	*Diaporthe apiculatum*	*Leucaena leucocephala*	Song et al. 2019
21	*Fusarium* sp.	*A. membranaceus, G. glabra, M. sativa, Oxytropis* spp.	Chenchen et al. 2014; Yang et al. 2020; Bezerra et al. 2019; Eman et al. 2020
22	*Fusarium solani*	*Cercis alata, C. echinata, G. glabra, M. sativa*	Khan et al. 2018; Shah et al. 2017; Suryanarayanan et al. 2018
23	*Eupenicillum javanicum*	*A. hindsii*	González-Teuber et al. 2014
24	*Fusarium oxysporum*	*A. hindsii, M. sativa*	González-Teuber et al. 2014; Suryanarayanan et al. 2018
25	*Lasiodiplodia* sp.	*A. amara*	Suryanarayanan et al. 2018
26	*Guisnhardi* sp.	*T. repens, Cassia fistula*	Yang et al. 2013; Ruchikachorn 2005.
27	*Hypoxylon* sp.	*Glycine max, C. fistulal*	Khambhati et al. 2020; Nigg et al. 2014
28	*Embellisia* spp.	*Astragalus* spp., *Oxytropis* spp.	Chenchen et al. 2014
29	*Embellisa oxytropis*	*Astragalus* spp., *Oxytropis* spp.	Chenchen et al. 2014
30	*Fusarium proliferatum*	*Astragalus* spp., *Oxytropis* spp.	Chenchen et al. 2014
31	*Undifilum oxytropis*	*Astragalus* spp., *Oxytropis* spp., *A. membranaceus*	Chenchen et al. 2014
32	*Exserohilum rostratum*	*B. guianensis*	Pinheiro et al. 2013
33	*Mucor* sp.	*A. membranaceus*	Xu 2016.; González-Teuber et al. 2014; Wulandari and Suryantini 2018
34	*Moniliales* sp.	*G. uralensis*	Yang et al. 2020
35	*Moesziomyces bullatus*	*A. hindsii*	González-Teuber et al. 2014
36	*Neocosmospora solani*	*A. lebbeck*	González-Teuber et al. 2014
37	*Paecilomyces variotii*	*A. lebbeck*	González-Teuber et al. 2014
38	*Nemania* sp.	*C. fistula*	Ruchikachorn 2005.
39	*Nigrospra* sp.	*C. fistula*	Ruchikachorn 2005.
40	*Nodulisporium* sp.	*C. fistula*	Nigg et al. 2014
41	*Penicillium* sp.	*A. membranaceus, G. uralensis, C. sappan, C. fistula, S. tonkinensis, B. fortificata, A. decurrens*	Jiang et al. 2008; Gioia et al. 2020; Araujo-Melo et al. 2017; Bezerra et al. 2019; Ruchikachorn 2005.; Li et al. 2012
42	*Paecilomyces* sp.	*Bauhinia pinheiro, A. lebbeck*	Pinheiro et al. 2013; Ali and Alfayed 2017; Wulandari and Suryantini 2018
43	*Paraphaeosphaeria* sp.	*A. lebbeck*	Ali and Alfayed 2017
44	*Pestalotiopsis acaciae*	*A. lebbeck*	Yang et al. 2013; Hilarino et al. 2011
45	*Phoma* sp.	*A. decurrens*	Li et al. 2012
46	*Pichia anomala*	*B. guianensis, A. hindsii*	Li et al. 2012; González-Teuber et al. 2014
47	*Penicillium vulpinum*	*S. tonkinensis*	Qin et al. 2021
48	*Papulospora* sp.	*C. fistula*	Gioia et al. 2020
49	*Penicilium sclerotiorum*	*C. fistula*	Kuriakose et al. 2018
50	*Periconia* sp.	*C. fistula*	Gioia et al. 2020
51	*Phomopsis* sp.	*C. fistula, B. brevipes*	Bezerra et al. 2019; Ruchikachorn 2005.
52	*Psathyrella* sp.	*C. fistula*	Ruchikachorn 2005.
53	*Pestalotiopsis* sp.	*B. brevipes*	Yang et al. 2013; Pinheiro et al. 2013
54	*Rhizopus* sp.	*A. membranaceus, G. uralensis*	Yang et al. 2020; Ugai et al. 2020

Table 1. Continued

No.	Endophytic fungi (genes or species)	Host plants	References
55	*Stilbella* sp.	*A. membranaceus, C. fistula*	Ruchikachorn 2005.
56	*Talaromyces* sp.	*G. uralensis*	Yang et al. 2020
57	*Trichoderma* sp.	*A. membranaceus, G. uralensis, B. juncea, A. lebbeck, Acacia auriculaeformis*	Yang et al. 2020; Bezerra et al. 2019; Wulandari and Suryantini 2018; Jiang et al. 2008
58	*Rhinocladiella* sp.	*G. uralensis*	Yang et al. 2020
59	*Rosellinia sanctae-cruciana*	*A. lebbeck*	Sharma et al. 2018
60	*Verticillium* sp.	*A. lebbeck*	Wulandari and Suryantini 2018
61	*Xylaria* sp.	*S. tonkinensis, A. amara, C. fistula*	Zheng et al. 2018; Xu et al. 2017; Suryanarayanan et al. 2018; Ruchikachorn 2005.
62	*Thdiowiopsis* sp.	*C. fistula*	Ruchikachorn 2005.; Gioia et al. 2020
63	*Scedosporium* sp.	*B. guianensis*	Pinheiro et al. 2013
64	*Scedosporium apiospermum*	*B. guianensis*	Pinheiro et al. 2013

Table 2. Compounds with anticancer activity produced by endophytic fungi from medicinal leguminosae plants.

No.	Compound name	Endophytic fungi	Host plant	References
1	fumitremorgin B	*Fusarium* sp.	*Astragalus membranaceus*	Liu et al. 2015
2	fumitremorgin C	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015; Rabindran et al. 2000
3	cyclotryprostatin B	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015; Osada 2003
4	**(–)-(10E,15S)-4,6-dichloro-10(11)-dehydrocurvularin**	*Alternaria* sp.	*A. membranaceus*	Bashyal et al. 2017
5	**(–)-(10E,15S)-6-chloro-10(11)-dehydrocurvularin**	*Alternaria* sp.	*A. membranaceus*	Bashyal et al. 2017
6	**(–)-(10E,15S)-10(11)-dehydrocurvularin**	*Alternaria* sp.	*A. membranaceus*	Bashyal et al. 2017
7	**alterperylenepoxide A**	*Alternaria* sp.	*A. membranaceus*	Bashyal et al. 2017
8	**thioperylenol**	*Alternaria* sp.	*A. membranaceus*	Bashyal et al. 2017
9	cyclo-(Pro-Gly)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
10	cyclo-(Pro-Leu)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
11	cyclo-(Pro-Ile)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
12	cyclo-(Pro-Val)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
13	cyclo-(Phe-Gly)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
14	cyclo-(Phe-Ala)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
15	cyclo-(Pro-Tyr)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
16	cyclo-(Pro-Phe)	*Aspergillus* sp.	*A. membranaceus*	Liu et al. 2020
17	(-)-6-methoxymellein	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Ugai et al. 2020; Liu 2020.
18	emodin 8-O-Methyl Ether	*Rhizopus* sp.	*A. membranaceus*	Zhang et al. 2020
19	ergosterol	*Fusarium* sp.	*Cercis alata*	Khan et al. 2018
20	4-hydroxybenzaldehyde	*Fusarium* sp.	*C. alata*	Khan et al. 2018
21	bostrycoidin	*Fusarium* sp.	*C. alata*	Khan et al. 2018
22	fusarubin	*Fusarium* sp.	*C. alata*	Khan et al. 2018
23	3-deoxyfusarubin	*Fusarium solani*	*C. tora*	Khan et al. 2018; Adorisio et al. 2019
24	3,5,9-trihydroxyergosta-7,22-diene-6-one	*F. solani*	*C. alata*	Khan et al. 2018
25	anhydrofusarubin	*F. solani*	*C. alata*	Khan et al. 2018
26	hexadecanoic acid	*Penicillium sclerotiorum*	*C. alata*	Kuriakose et al. 2018
27	oleic acid	*P. sclerotiorum*	*C. alata*	Kuriakose et al. 2018
28	benzoic acid	*P. sclerotiorum*	*C. alata*	Kuriakose et al. 2018
29	swainsonine	*Undifilum oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Li and Lu 2019
30	jammosporin A	*Rosellinia sanctae-cruciana*	*Albizia lebbeck*	Sharma et al. 2018
31	19,20-epoxy cytochalasin D	*R. sanctae-cruciana*	*A. lebbeck*	Sharma et al. 2018
32	cytochalasin D	*R. sanctae-cruciana*	*A. lebbeck*	Sharma et al. 2018
33	19,20-epoxy cytochalasin C	*R. sanctae-cruciana*	*A. lebbeck*	Sharma et al. 2018
34	cytochalasin C	*R. sanctae-cruciana*	*A. lebbeck*	Sharma et al. 2018
35	**(+)-5’-dehydroxytalaroflavone**	*A. alternata*	*Cercis chinensis*	Zhao et al. 2021
36	**(-)-5’-dehydroxytalaroflavone**	*A. alternata*	*C. chinensis*	Zhao et al. 2021
37	altertoxin I	*A. alternata*	*C. chinensis*	Zhao et al. 2021; Jarolim et al. 2017

Note: The compounds with text in bold are new compounds.

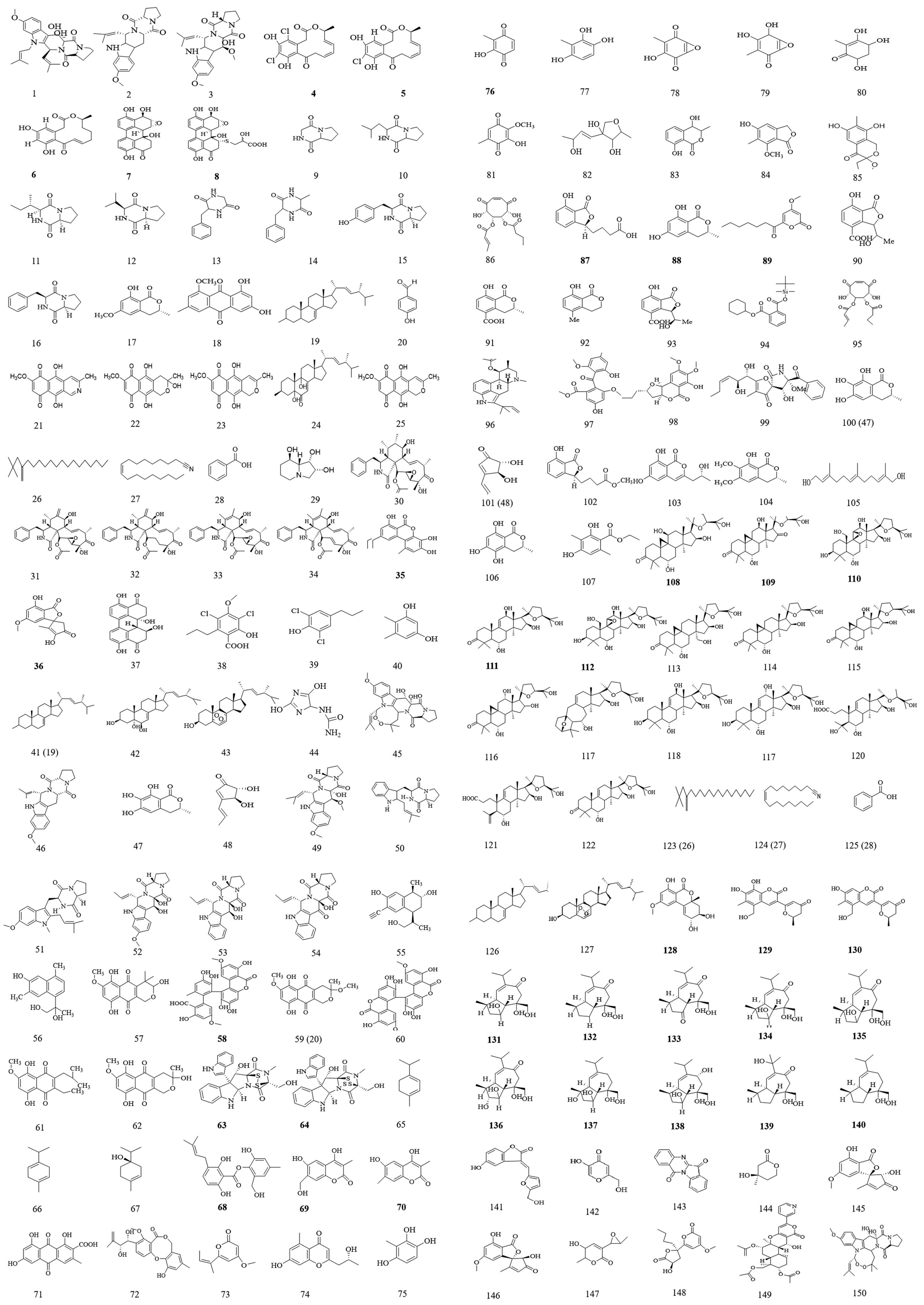

Figure 1. Compounds (1-150) with antitumor, antimicrobial, antioxidant and other activities from endophytic fungi of medicinal leguminosae plants. Compound numbers are compiled according to the order of appearance in the text. The compounds with text in bold are new compounds. The numbers in parentheses are the order in which they first appear.

structures including new compounds **4**, **5**, **6**, **7**, **8**, **35** and **36** are depicted in Fig. 1.

Antibacterial activity and metabolites

Studies have shown that plenty of endophytic fungi and their metabolites are indicated to have activities of antibacterial and other pathogenic microorganisms in MLPs. Currently, at least 10 genera of endophytic fungi with antibacterial activity have been found in MLPs such as *A. membranaceus*, *S. cassiae*, *G. uralensis*, *S. flavescens*, etc. Those bacterium-inhibiting fungi include *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Listeria monocytogenes*, *S. enterica* and *Escherichia coli* and other pathogenic bacteria. It was reported that 62 active compounds 38-99, have antibacteria functions. These active compounds and their original endophytic fungi are summarized in Table 3, and their structures including new compounds **62**, **63**, **67**, **68**, **69**, **75**, **86**, **87** and **88** are exhibited in Fig. 1.

Antioxidant activity and metabolites

Antioxidant effect is another activity presenting in endophytic fungi that is associated with MLPs. These fungi were mainly derived from *Astragalus*, *Albizia* and *Cercis* plant species. Among them, eight compounds 100-107 with antioxidant potential (Ugai et al. 2020; de Barber et al. 2004; Osada 2003.; Zaehle et al. 2014) were successfully obtained from endophytic *Aspergillus* sp. from *Astragalus* spp., which also participate in metabolism as catalysts and regulators, and are a class of metabolites with natural antioxidant activity. In addition, the combined co-culture of endophytic fungi *A. eureka*, *Neosartorya hiratsukae* and *Camarosporium laburnicola* of *A. membranaceus* can biotransform the active component cyclic astragalosol to 10 compounds 108-122, which include five new compounds 111, 115, 118, 120 and 122 (Fig. 1) with telomerase activity in neonatal human primary epidermal keratinocytes. Compounds 115 and 121 indicate the strongest antioxidant activity, followed by compounds 114 and 117 (Ekiz et al. 2019). Three hemiterpene compounds 123-125 (26-28) exhibited antioxidant activity from endophytic *P. sclerotiorum* of *C. sclerotiorum*. The scavenging ability of superoxide, hydrogen peroxide and hydroxyl radical was enhanced and the scavenging ability of nitric oxide synthase was decreased with increasing of the concentration of the compounds (Kuriakose et al. 2018). In addition, alcoholic substance compounds 126-127 were extracted from endophytic fungi of *A. membranaceus* (Kuriakose et al. 2018), *S. cassiae* (Alvarez et al. 2021; Liu et al. 2015; Wong-Deyrup et al. 2021) and *C. chinensis* (Feitosa et al. 2016). Among them, the vast majority of steroids exhibited antioxidant, antiproliferative and anti-inflammatory activities (Kuriakose et al. 2018; Duan et al. 2021; Feitosa et al. 2016). A fungicomycin compound 128, a dicholinesterase inhibitor, was extracted from endophytic *Alternaria* sp. from *C. chinensis*, which showed high antioxidant activity (Zhao et al. 2021; Bhagat et al. 2016). These active compounds and their original endophytic fungi are listed in Table 4, and their structures including new compounds **111**, **115**, **118**, **120**, **122** are shown in Fig. 1.

Other active metabolites

Stimulating the dormant biosynthetic genes of endophytic fungus *Aspergillus* sp. from *A. membranaceus* using suberoylanilide hydroxamic acid inducers successfully yielded two new 3-(4-oxopyran)-chromen-2-one compounds 129-130. They are also conjugated with 3-pyranocoumarins, a rare class of fungal metabolites with monoamine oxidase inhibitory and antioxidant effects, which may be a lead drug against Alzheimer's disease (de Amorim et al. 2020). *Undifilum oxytropis* is a representative strain from locoweed. Ten new peroxy-sesquiterpenoid compounds 131-140 were extracted from it, and all exhibit neurotoxic, immunosuppressive, cytotoxic or antiviral effects (Tan et al. 2019; Chenchen et al. 2014). The endophytic fungus *Rhizopus* sp. from *A. membranaceus* produces compound 141 with anti-influenza viral property (Zhang et al. 2020). It also produces compound 142 with melanin-specific inhibitory effect, which prevents tyrosinase from activation after entering into skin cells and thus inhibits melanin formation (Zhang et al. 2020). And it also generates quinazolinone alkaloid compound 143, which is mainly used for the treatment of cuts, ulcers, snakebites, acne and various inflammatory diseases (Zhang et al. 2020). The compound 144, extracted from the endophytic fungus *Aspergillus* sp. of *B. variegata*, is involved in brain nerve damage and the mevalonate metabolic pathway with an important intermediate transport and regulatory role in the metabolic cycle (Cecatto et al. 2017; Feitosa et al. 2016; González-Teuber et al. 2014). Various isomers were extracted from *Alternaria* sp. of *C. chinensis*, of which compounds 145-146 selectively inhibit the activity of eukaryotic DNA polymerase (pols) families X and Y (Zhao et al. 2021; Naganuma et al. 2008). Compound 147 was extracted from endophytic fungus *Aspergillus* sp. of *M. sativa*, which exhibits anti-inflammatory activity against formylmethionyl leucine-stimulated inflammation, mainly inhibiting the release of elastase (Eman et al. 2020; Hu et al. 2020). Compound 148 extracted from the endophytic *Pestalotiopsis* sp. of *A. Durazz* is a dopaminergic antagonist, 5-hydroxytryptamine antagonist and α-adrenergic antagonist with antipsychotic and psychotropic pharmacological activity (Yang et al. 2013). Moreover, compounds 149-150 were extracted from the endophytic fungus *Aspergillus* sp. from *T. repens*, of which compound 149 is an inhibitor of cholesterol acetyltransferase with medical applications (Yang et al. 2016). The compound 150 causes severe shock in infected animals by inhibiting Ca^{2+}-activated K^{+} channels, and also inhibits the M-phase of the mammalian cell cycle (Yang et al. 2016; Rabindran et al. 2000; Kawashima et al. 2002). The above active compounds are summarized in Table 5, and their structures including eight new compounds **129-136** are shown in Fig. 1.

Concluding remarks and future challenges

In conclusion, the endophytic fungi of MLPs are a vast treasure trove for overcoming the difficulties of high pollution and long production cycle in the production of chemically synthesized drugs. They have great application value and development potential (Wink 2013.; Skiada et al. 2019; Alam et al. 2020). Regrettably, although there are many reports on finding and isolation from various novel bioactive compounds from endophytic fungi, there are few examples of stable applications in industrial production, which require the continuous expansion of the number of endophytes and screening of more active strains and compounds. However, there are still many unsolved issues and challenges: (1) a large number of endophytic fungi have been found by using high-throughput sequencing technology, but many have not been isolated by existing culture or other separation technologies. On the one hand, it may be generally believed that endophytes cannot survive outside their original internal environment or that there is no perfect medium for all microorganisms to grow. On the other hand, there may be a synergistic effect between them and their hosts or other microorganisms, which means some growth factors from other living organisms may have supported their growth, and may need to be studied in detail one after another, which will

Table 3. Compounds with antimicrobial activity produced by endophytic fungi of medicinal leguminosae plants.

No.	Compounds	Antimicrobial activity	Endophytic fungi	Host plant	References
38	diferanisole A	*S. aureus*	*Chaetomium* sp.	*Astragalus chinensisis*	Liu and Zhang et al. 2019; Liu and Zhao et al. 2017
39	2,6-dichloro-4-propylphenol	*S. aureus, L. monocytogenes, S. entericaa* and *E. coli*	*Chaetomium* sp.	*A. chinensis*	Liu and Zhang et al. 2019; Liu and Zhao et al. 2017
40	4,5-dimethylresorcinol	Destructive soil-borne fungal pathogens - *S. rolfsii*	*Chaetomium* sp.	*A. chinensis*	Liu and Zhang et al. 2019; Liu and Zhao et al. 2017
41 (19)	ergosterol	Fungus-target of action of azoles and ketones	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015; Álvarez et al. 2021; Wong et al. 2021; Duan et al. 2021
42	cerevisterol	Antibacterial activity	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015; Alam et al. 2020
43	ergosterol peroxide	Fungal pathogens	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015; Álvarez et al. 2021; Wong-Deyrup et al. 2021; Tiam et al. 2021
44	allantoin	*Mycobacterium tuberculosis* and *Plasmodium falciparum*	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015; Tiam et al. 2021
45	verruculogen	*F. solani, F. moniliforme, F. equiseti, R. solani* and *C. astragalis*	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015
46 (2)	fumitremorgin C	Antibacterial activity	*Fusarium* sp.	*A. membranaceus*	Liu et al. 2015
47	(-)-6,7-dihydroxymellein	Antibacterial, cytotoxic, phytotoxic and nematicidal activities	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Bashyal et al. 2017
48	(+)-terrein	Natural antibacterial and antiproliferative activity	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Bashyal et al. 2017
49	cyclotryprostatin B	*F. solani, F. moniliforme, F. equiseti, R. solani*	*Penicillium* sp.	*A. membranaceus*	Liu et al. 2018
50	tryprostatin B	*F. moniliforme*	*Penicillium* sp.	*A. membranaceus*	Liu et al. 2018
51	tryprostatin A	*R. Solani* and *C. astragalis*	*Penicillium* sp.	*A. membranaceus*	Liu et al. 2018
52	cyclotryprostatin A	*F. moniliforme* and *F. equiseti*	*Penicillium* sp.	*A. membranaceus*	Liu et al. 2018
53	cyclotryprostatin C	*R. Solani* and *C. astragalis*	*Penicillium* sp.	*A. membranaceus*	Liu et al. 2018
54	cyclotryprostatin D	*R. Solani* and *C. astragalis*	*Penicillium* sp.	*A. membranaceus*	Liu et al. 2018
55	3,11,12-trihydroxycadalene	*C. sphaerospermum* and *C. cladosporioides*	*Phomopis cassiae*	*Cassia spectabilis*	Silva et al. 2006
56	3,12-dihydroxycadalene	*C. sphaerospermum* and *C. cladosporioides*	*P. cassiae*	*C. spectabilis*	Silva et al. 2006
57	3,6,9-trihydroxy-7-methoxy-4,4-dimethyl-3,4-dihydro-1*H*-benzo[g]isochromene-5,10-dione	Gram-positive and Gram-negative bacteria, especially against *M. tuberculosis* H37Rv	*Fusarium solani*	*Glycyrrhiza glabra*	Seki et al. 2011; Shah et al. 2017
58	**bialternacin G**	*Ralstonia solanacearum, Xanthomonas oryzae* pv. oryzicola and *Xanthomonas oryzae* pv. *oryzae*-phytopathogenic bacteria	*Aspergilus alternata*	*C. chinensis*	Zhao et al. 2021
59 (20)	fusarubin	*M. tuberculosis, S. aureus, Klebsiella pneumonia*-mechanism of action similar to broad-spectrum antibiotics such as quinolones	*F. solani*	*Glycyrrhiza glabra*	Seki et al. 2011; Shah et al. 2017
60	verrulactone A	*Ralstonia solanacearum, Xanthomonas oryzae* pv. *oryzicola* and *Xanthomonas oryzae* pv. *oryzae*-phytopathogenic bacteria	*A. alternata*	*C. chinensis*	Zhao et al. 2021
61	3-O-methylfusarubin	Antibacterial activity	*A. alternata*	*C. chinensis*	Seki et al. 2011

Table 3. Continued

No.	Compounds	Antimicrobial activity	Endophytic fungi	Host plant	References
62	javanicin	*E. coli*, *Klebsiella pneumonia*, *S. aureus* and *M. tuberculosis*	*A. alternata*	*C. chinensis*	Seki et al. 2011
63	**(3S,5aR,10bR,11S,11aS)-11-hydroxy-3-(hydroxymethyl)-10b-(1-*H*-indol-3-yl)-2-methyl-2,3,5a,6,10b,11-hexahydro-3,11a-epidithiopyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4-dione**	*S. aureus* and *S. pyogenes*-preventing biofilm formation of pathogens and synergistic effect with streptomycin inhibits transcription or translation *in vitro*, and also inhibits the production of vitellin	*P. cucurbitacearum*	*G. glabra*	Arora et al. 2016
64	**(4S,6aR,11bR,12S,12aS)-12-hydroxy-4-(hydroxymethyl)-11b-(1*H*-indol-3-yl)-14-methyl-6a,7,11b,12-tetrahydro-4,12a-(epimino-methano)[1,2,3,5]trithiazepino[5',4':1,5]pyrrolo[2,3-b]indole-5,13(4*H*)-dione**	*S. aureus* and *S. pyogenes*-preventing biofilm formation of pathogens and synergistic effect with streptomycin inhibits transcription or translation *in vitro* and also inhibits the production of vitellin	*P. cucurbitacearum*	*G. glabra*	Arora et al. 2016
65	α-terpinene	Antibacterial activity	*D. apiculatum*	*Leucaena leucocephala*	Song et al. 2019; Baldissera et al. 2016; Quiroga et al. 2019
66	γ-terpinene	Antibacterial activity	*D. apiculatum*	*L. leucocephala*	Song et al. 2019
67	(-)-4-terpineol	Antibacterial activity	*D. apiculatum*	*L. leucocephala*	Song et al. 2019; Shapira et al. 2016
68	**2'-hydroxy-6'-hydroxymethyl-4'-methylphenyl-2,6-dihydroxy-3-(2-isopentenyl)benzoate**	Antibacterial activity	*Pestalotiopsis acaciae*	*Albizia lebbeck*	Yang et al. 2013
69	**4,6-dihydroxy-7-hydroxymethyl-3-methylcoumarin**	Antibacterial activity	*P. acaciae*	*A. lebbeck*	Yang et al. 2013
70	**4,6-dihydroxy-3,7-dimethylcoumarin**	Antibacterial activity	*P. acaciae*	*A. lebbeck*	Yang et al. 2013
71	endocrocin	Antibacterial and antifungal activities	*P. acaciae*	*A. lebbeck*	Yang et al. 2013; Khambhati et al. 2020; Qin et al. 2021
72	pestalotiollide B	Antibacterial and antifungal activities	*P. acaciae*	*A. lebbeck*	Yang et al. 2013
73	pestalotiopyrone G	Antibacterial and antifungal activities	*P. acaciae*	*A. lebbeck*	Yang et al. 2013
74	7-hydroxy-2-(2-hydroxypropyl)-5-methylchromone	Antibacterial and antifungal activities	*P. acaciae*	*A. lebbeck*	Yang et al. 2013
75	versicolin	*A. versicolor-pathogens* of *B. variabilis*	*Aspergillus* sp.	*Medicago sativa*	Eman et al. 2020
76	**3-hydroxytoluquinone**	Antibacterial activity	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020
77	phenoxyacetic acid	Antibacterial activity	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020; Han et al. 2010; Trotel-Aziz et al. 2019
78	terreic acid	*Nterobacter cloacae* and *Escherichia*	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020; Han et al. 2010; Trotel-Aziz et al. 2019

Table 3. Continued

No.	Compounds	Antimicrobial activity	Endophytic fungi	Host plant	References
79	terremutin	*Nterobacter cloacae* and *Escherichia*-covalent inhibition of cell wall biosynthesis enzyme MurA	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020; Hu et al. 2002; Kang et al. 2013
80	terredionol	Antibacterial activity potential	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020
81	fumigatin	Lipophilic yeast *Malassezia furfur*-epidermal skin disease pathogens	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020; Hu et al. 2020
82	isoaspinonene	Antibacterial activity	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020
83	4-hydroxymellein	Antibiotic activity-with structure of iso-chromone	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020
84	nidulol	Antibacterial activity	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020
85	terreinol	Antibacterial activity	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020
86	anshanmycin	Fungi, bacteria, actinomycetes and other pathogens in varying degrees, especially on fungi	*Aspergillu terreus*	*Sophora flavescens*	Qin et al. 2021
87	**(-)-3-carboxypropyl-7-hydroxyphthalide**	*B. subtilis*, *Shigella dysenteriae* and *Enterobacter areogenes*	*Penicillium vulpinum*	*S. flavescens*	Zheng et al. 2018
88	**(-)-3-carboxypropyl-7-hydroxyphthalide methyl ester**	*E. areogenes*	*P. vulpinum*	*S. flavescen*	Zheng et al. 2018; Xu et al. 2017
89	**6-heptanoyl-4-methoxy-2*H*-pyran-2-one**	*B. Subtilis*, *Escherichia coli*, *B. megaterium*, *S. aureus*, *Shigella dysenteriae* and *S. paratyphi*	*Xylaria* sp.	*S. flavescens*	Zheng et al. 2018
90	xylarphthalide A	*B. subtilis* and *B. cereus*	*Xylaria* sp.	*S. flavescens*	Zheng et al. 2018
91	(-)-5-carboxylmellein	*B. Subtilis*, *B. anthracis*, *B. megaterium*, *S. aureus* and *E. coli*	*Xylaria* sp.	*S. flavescens*	Zheng et al. 2018
92	(-)-5-methylmellein	*B. Subtilis*, *S. Aureus*, *B. megaterium*, *E. coli* and *S. dysenteriae*	*Xylaria* sp.	*S. flavescens*	Zheng et al. 2018
93	xylapeptides B	*B. subtilis*, *B. cereus*, *B. megaterium*, *Micrococcus luteus*, *S. aureus*, *Shigella castellani* and *Canidia albicans*	*Xylaria* sp.	*S. tonkinensis*	Zheng et al. 2018; Xu et al. 2017
94	1,2-benzenedicarboxylic acid butyl cyclohexyl ester	Anti-corrosion bactericidal effect-industrial production	*Penicillium* sp.	*S. flavescens*	Yu et al. 2014; Che et al. 2012; Zhai et al. 2012
95 (86)	6,7-(2′*E*)dibutenyl-5,8-dihydroxy-(*Z*)-cyclooct-2-ene-1,4-dione	*Botryosphaeria berengriana*, *Physalospora piricola*, *Cladosporium cucumerinum* and *F. oxysporum*-improving the beneficial flora in soil and protecting the soil microbial environment	*Penicillium* sp.	*S. flavescens*	Yu et al. 2014; He et al. 2013; Jiang et al. 2008
96	fumigaclavine C	*E. coli*, *Pseudomonas aeruginosa*, *S. aureus* and *B. subtilis*	*Aspergillus* sp.	*Trifolium repens* and *Bauhinia guianensis*	Yang et al. 2016; Liu et al. 2015; Pinheiro et al. 2013; Zaehle et al. 2014
97	monomethylsulochrin	*E. coli*, *P. aeruginosa*, *S. aureus*, *B. subtilis* and *Helicobacter pylori*	*Aspergillus* sp.	*T. repens* and *B. guianensis*	Yang 2013.; Wang et al. 2010
98	monocerin	*E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus* and *S. typhimurium*	*Aspergillus* sp.	*B. guianensis*	Feitosa et al. 2016

Note: The compounds with text in bold are new compounds.

Table 4. Antioxidant compounds from endophytic fungi of medicinal leguminosae plants.

No.	Compounds	Endophytic fungi	Host plant	References
100 (47)	(-)-6,7-dihydroxymellein	*Aspergillus* sp.	*Astragalus membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
101 (48)	(+)-terrein	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
102	(-)-6-hydroxymellein	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
103	(-)-orthosporin	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
104	(-)-6,7-dimethoxymellein	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
105	(2E,6E,10E)-12-hydroxyfarnesol	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
106	(-)-5,6-dihydroxymellein	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014
107	ethyl-3-methylorsellinate	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020; Osada 2003.; Zaehle et al. 2014; de Barber et al. 2004
108	**20(R),24(S)-epoxy-6α,11β,16β,25-tetrahydroxycycloartan-3-one**	*Alternaria eureka*, *Neosartorya hiratsukae* and *Camarosporium laburnicola*	*A. membranaceus*	Ekiz et al. 2019
109	**20(R),24(S)-epoxy-6α,12β,25-trihydroxycycloartan-3,16-dione.**	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
110	**20(R),24(S)-epoxy-6α,12β,16β,25-tetrahydroxylanost-9(11)-en-3-one**	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
111	**9β,11;20(R),24(S)-diepoxy-3β,6α,16β,19β,25-pentahydroxycycloartane**	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
112	**20(R),24-(S)-epoxy-3β,6α,16β,25-tetrahydroxylanost-9(11)-en-12-one**	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
113	20(R),24(S)-epoxy-6α,16β,25,30-tetrahydroxycycloartan-3-one	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
114	20(R),24(S)-epoxy-6α,16β,25-trihydroxycycloartan-3-one	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
115	20(R),24(S)-epoxy-3β,6α,12β,16β,25-pentahydroxycycloartane	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
116	20(R),24(S)-epoxy-3β,6α,12α,16β),25-pentahydroxycycloartane	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
117	20(R),24(S)-6α,16β,25-trihdroxy-3β,10β;20,24-diepoxy-9,10-seco-cycloartan-9(11)-ene	*A. eureka*, *N.* hiratsukae and C. laburnicola	*A. membranaceus*	Ekiz et al. 2019
118	20(R),24(S)-epoxy-3β,6α,12β,16β,25-pentahydroxylanost-9(11)-ene	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
119	20(R),24(S)-epoxy-3β,6α,12α,16β,25-pentahydroxylanost-9(11)-ene	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
120	3-((2S,3R,3aR,6S,7S,8S,9bS)-2,8-dihydroxy-7-(2-hydroxypropan-2-yl)-3-((2R,5S)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)-3a,6,9b-trimethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1H-cyclopenta[a]naphthalen-6-yl)propanoic acid	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
121	3-((2S,3R,3aR,6S,7S,8S,9bS)-2,8-dihydroxy-3-((2R,5S)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl)-3a,6,9b-trimethyl-7-(prop-1-en-2-yl)-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1H-cyclopenta[a]naphthalen-6-yl)propanoic acid	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019

Table 4. Continued

No.	Compounds	Endophytic fungi	Host plant	References
122	20(R),24(S)-epoxy-6α,16β,25-trihydroxy lanost-9(11)-en-3-one	*A. eureka*, *N. hiratsukae* and *C. laburnicola*	*A. membranaceus*	Ekiz et al. 2019
123 (26)	hexadecanoic acid	*Penicilium sclerotiorum*	*Cercis alata*	Kuriakose et al. 2018
124 (27)	oleic acid	*P. sclerotiorum*	*C. alata*	Kuriakose et al. 2018
125 (28)	benzoic acid	*P. sclerotiorum*	*C. alata*	Kuriakose et al. 2018
126 (19)	ergosterol	*Aspergillus* sp.	*B. guianensis*	Kuriakose et al. 2018; Alvarez et al. 2021; Liu et al. 2015; Wong-Deyrup et al. 2021; Feitosa et al. 2016
127 (43)	ergosterol peroxide	*Aspergillus* sp.	*B. guianensis*	Kuriakose et al. 2018; Duan et al. 2021; Feitosa et al. 2016
128	altenuene	*A. alternata*	*C. chinensis*	Zhao et al. 2021; Bhagat et al. 2016

Note: The compounds with text in bold are new compounds.

Table 5. Summary of other active compounds from endophytic fungi of medicinal leguminosae plants.

No.	Compounds	Endophytic fungi	Host plant	References
129	**aspyranochromenones A**	*Aspergillus* sp.	*Astragalus membranaceus*	de Amorim et al. 2020
130	**aspyranochromenones B**	*Aspergillus* sp.	*A. membranaceus*	de Amorim et al. 2020
131	**(1R,3aS,4S,8aS)-3,4-dihydroxy-4-(hydroxymethyl)-7-isopropyl-1-methyl-2,3,3a,4,5,8a-hexahydroazulen-6(1H)-one**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
132	**(1S,3aR,4S,8aS)-1,4-dihydroxy-4-(hydroxymethyl)-7-isopropyl-1-methyl-2,3,3a,4,5,8a-hexahydroazulen-6(1H)-one**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
133	**(3R,3aS,8S,8aR)-8-hydroxy-8-(hydroxymethyl)-5-isopropyl-3-methyl-2,3,3a,7,8,8a-hexahydroazulene-1,6-dione**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
134	**(3S,3aR,8S,8aR)-8-hydroxy-8-(hydroxymethyl)-5-isopropyl-3-methyl-2,3,3a,7,8,8a-hexahydroazulene-1,6-dione**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
135	**(1R,3aR,8aS)-3-hydroxy-4-(hydroxymethyl)-7-isopropyl-1-methyl-2,3,3a,4,5,8a-hexahydroazulen-6(1H)-one**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp	Tan et al. 2019; Chenchen et al. 2014
136	**(1S,2R,3aS,4S,8aR)-2,3,4-trihydroxy-4-(hydroxymethyl)-7-isopropyl-1-methyl-2,3,3a,4,5,8a-hexahydroazulen-6(1H)-one**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
137	**(1S,3aS,4S,8aS)-4-(hydroxymethyl)-7-isopropyl-1-methyl-1,2,3,3a,4,5,6,8a-octahydroazulene-1,3,4-triol**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
138	**(1S,3R,3aS,6S,8S,8aS)-8-(hydroxymethyl)-5-isopropyl-3-methyl-1,2,3,3a,6,7,8,8a-octahydroazulene-1,6,8-triol**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
139	**(1R,3aR,4S,8aS)-4-hydroxy-4-(hydroxymethyl)-7-(2-hydroxypropan-2-yl)-1-methyl-2,3,3a,4,5,8a-hexahydroazulen-6(1H)-one**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
140	**(1R,3aR,4S,8aS)-4-(hydroxymethyl)-7-isopropyl-1-methyl-1,2,3,3a,4,5,6,8a-octahydroazulen-4-ol**	*U. oxytropis*	*Astragalus* spp. and *Oxytropis* spp.	Tan et al. 2019; Chenchen et al. 2014
141	cannabifolactone A	*Rhizopus* sp.	*A. membranaceus*	Zhang et al. 2020
142	kojic acid	*Rhizopus* sp.	*A. membranaceus*	Zhang et al. 2020
143	tryptanthrin	*Rhizopus* sp.	*A. membranaceus*	Zhang et al. 2020
144	mevalonolactone	*Aspergillus* sp.	*B. guianensis*	Feitosa et al. 2016
145	**(+)-talaroflavone**	*A. alternata*	*C. chinensis*	Zhao et al. 2021; Naganuma et al. 2008
146	**(-)-talaroflavone**	*A. alternata*	*C. chinensis*	Zhao et al. 2021; Naganuma et al. 2008
147	aspyrone	*Aspergillus* sp.	*M. sativa*	Eman et al. 2020; Hu et al. 2020
148	spiperone A	*P. acaciae*	*A. lebbeck*	Yang et al. 2013; Khambhati et al. 2020
149	pyripyropene A	*Aspergillus* sp.	*Trifolium repens*	Yang et al. 2016
150(45)	verruculogen	*Aspergillus* sp.	*T. repens*	Yang et al. 2016; Rabindran et al. 2000; Kawashima et al. 2002

Note: The compounds with text in bold are new compounds.

be a long-term and challenging task; (2) the action mechanism of endophytic fungi and their active substances are not fully clear. Due to the complexity of species-species interaction, the focus of future research may include molecular pathways involved in interactions among an enormous number of endophytic fungi, huge quantity of other microorganisms and their host plants as complex, yet very well-evolved and adapted ecosystems; and signal transductions between endophytic fungi and their hosts related to the mechanisms exchange; (3) the most common problem in application is that the bio-activity of endophytic fungi and their ability to produce active compounds decrease gradually with an increase in the number of sub-cultures of endophytes, and the related mechanism is still unclear. For example, the endophytic fungus *F. soloni* of *Camptotheca acuminate* had a diminished (or even no) capacity to produce cephaeline. Subsequent studies confirmed that the endophyte lacks the iso-carotene synthase (strigosidine synthase) that is supplied by the host plant, leading to an inability to synthesize cephaeline in culture (Kusari et al. 2011); and (4) in the future, the research on active strains should be centered on characterizing the endo-environment of MLPs' hosts themselves as well, which may be useful to further explore the medicinal application potential of endophytic fungi. Furthermore, the research direction is also reflected in the gene modifications of active strains to improve their performances for sustainable application in the future.

Supplementary data

Supplementary data are available at *FEMSLE* online.

Funding

This work was financially supported by Research Project Supported by Shanxi Scholarship Council of China (2020-013), the Basic Research Program of Shanxi Province (20210302123428), Fund Program for the Scientific Activities of Selected Returned Overseas Professionals in Shanxi Province (20220004) and the National Natural Science Foundation of China (No. 31670328).

Conflict of interest. These authors declare that there is no conflict of financial or research interest.

References

Adorisio S, Fierabracci A, Muscari I *et al. Fusarubin* and *Anhydrofusarubin* isolated from a *Cladosporium* species inhibit cell growth in human cancer cell lines.*Toxins* 2019;**11**:503.

Alam MB, Chowdhury NS, Sohrab MH *et al.* Cerevisterol alleviates inflammation via suppression of MAPK/NF-κB/AP-1 and activation of the Nrf2/HO-1 signaling cascade. *Biomolecules* 2020;**10**:199.

Ali BZ, Alfayed AA. Endophytic fungi from leaves and twigs of *Albizia lebbeck* and their antifungal activity. *Ibn AL Haitham J Pure Appl Sci* 2017;**27**:24–33.

Álvarez M, Rodríguez A, Bermúdez E *et al.* Development of a methodology for estimating the ergosterol in meat product-borne toxigenic moulds to evaluate antifungal agents. *Foods* 2021;**10**:438.

Araujo-Melo R, Souza I, Oliveira C *et al.* Isolation and identification of endophyte microorganisms from *Bauhinia monandra* leaves, mainly actinobacteria. *Biotechnol J Int* 2017;**17**:1–12.

Arora P, Wani ZA, Ahmad T *et al.* Community structure, spatial distribution, diversity and functional characterization of culturable endophytic fungi associated with *Glycyrrhiza glabra* L.. *Fungal Biology* 2019;**123**:373–383.

Arora P, Wani ZA, Nalli Y *et al.* Antimicrobial potential of thiodiketopiperazine derivatives produced by *Phoma* sp., an endophyte of *Glycyrrhiza* glabra Linn. *Microb Ecol* 2016;**72**:802–812.

Baldissera MD, Grando TH, Souza CF *et al. In vitro* and *in vivo* action of terpinen-4-ol, γ-terpinene, and α-terpinene against *Trypanosoma evansi*. *Exp Parasitol* 2016;**162**:43–48.

Bashyal BP, Wijeratne EM, Tillotson J *et al. J Nat Prod* 2017;**80**: 427–433.

Baucom DL, Romero M, Belfon R *et al.* Two new species of *Undifilum*, fungal endophytes of *Astragalus* (locoweeds) in the United States *Botany* 2012;**90**:1–14.

Berthelot C, Perrin Y, Leyval C *et al.* Melanization and ageing are not drawbacks for successful agro-transformation of dark septate endophytes. *Fungal Biol* 2017;**121**:652–663.

Bezerra JDP, da Silva LF, de Souza-Motta CM. The explosion of brazilian endophytic fungal diversity: taxonomy and biotechnological potentials. In Satyanarayana T, Deshmukh SK, Deshpande MV (Eds.), *Advancing Frontiers in Mycology & Mycotechnology*. Singapore. Springer Nature Singapore Pte Ltd 2019;405–433.

Bhagat J, Kaur A, Kaur R *et al.* Cholinesterase inhibitor (*Altenuene*) from an endophytic fungus *Alternaria alternata*: optimization, purification and characterization. *J Appl Microbiol* 2016;**121**:1015–1025.

Cecatto C, Amaral AU, da Silva JC *et al.* Mevalonolactone disrupts mitochondrial functions and induces permeability transition pore opening in rat brain mitochondria: Implications for the pathogenesis of mevalonic aciduria. *Neurochem Int* 2017;**108**: 133–145.

Che JM, Chen Z, Shi H *et al.* Functional components in *Brevibacillus brevis* FJAT-0809-GLX determined by GC/MSD. *Fujian Journal of Agricultural Sciences* 2012;**27**:1106–1111.

Chenchen W, Wenlong W, Xiaoxue L *et al.* Pathogenesis and preventive treatment for animal disease due to locoweed poisoning. *Environ Toxicol Pharmacol* 2014;**37**:336–347.

de Amorim MR, Wijeratne EMK, Zhou S *et al.* An epigenetic modifier induces production of 3-(4-oxopyrano)-chromen-2-ones in *Aspergillus* sp. AST0006, an endophytic fungus of *Astragalus lentiginosus*. *Tetrahedron* 2020;**76**:131525.

DeBarber AE, Bleyle LA, Roullet JB *et al.* Omega-hydroxylation of farnesol by mammalian cytochromes p450. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 2004;**1682**: 18–27.

Duan C, Ge X, Wang J *et al.* EErgosterol peroxide exhibits antiviral and immunomodulatory abilities against porcine deltacoronavirus (PDCoV) via suppression of NF-κB and p38/MAPK signaling pathways *in vitro*. *Int Immunopharmacol* 2021;**93**: 107317.

Egamberdieva D, Wirth S, Behrendt U *et al.* Antimicrobial activity of medicinal plants correlates with the proportion of antagonistic endophytes. *Frontiers in Microbiology* 2017;**8**:199.

Ekiz G, Yılmaz S, Yusufoglu H *et al.* Microbial transformation of cycloastragenol and astragenol by endophytic fungi isolated from *Astragalus* species. *J Nat Prod.* 2019;**82**:2979–2985.

Eman ZA, Hala MF, Usama R.A *et al.* Antimicrobial and extracellular oxidative enzyme activities of endophytic fungi isolated from alfalfa (Medicago sativa) assisted by metabolic profiling. *S. Afr. J. Bot* 2020;**134**:156–162.

Feitosa AO, Dias AC, Ramos GD *et al.* Lethality of cytochalasin B and other compounds isolated from fungus *Aspergillus* sp. (Trichocomaceae) endophyte of *Bauhinia guianensis* (Fabaceae). *Revista Argentina de Microbiologãa* 2016;**48**:259–263.

Fernandes EG, Pereira OL, da Silva CC *et al.* Diversity of endophytic fungi in *Glycine* max..*Microbiol Res* 2015;**181**:84–92.

Gioia L, d'Errico G, Sinno M *et al.* A survey of endophytic fungi associated with high-risk plants imported for ornamental purposes. *Agriculture* 2020;**10**:643.

Gómez OC, Luiz JHH. Endophytic fungi isolated from medicinal plants: future prospects of bioactive natural products from *Tabebuia/Handroanthus* endophytes. *Appl Microbiol Biotechnol* 2018;**102**:9105–9119.

González-Teuber M, Jiménez-Alemán GH, Boland W. Foliar endophytic fungi as potential protectors from pathogens in myrmecophytic *Acacia* plants. *Communicative & Integrative Biology* 2014;**7**:e970500.

Han H, Yang Y, Olesen SH *et al.* The fungal product terreic acid is a covalent inhibitor of the bacterial cell wall biosynthetic enzyme UDP-N-acetylglucosamine 1-carboxyvinyltransferase (MurA). *Biochemistry* 2010;**49**:4276–4282.

He L, Liu N, Wang Y *et al.* Isolation an antimicrobial action of endophytic fungi from *Sophora flavescens* and effects on microorganism circumstances in soil. *Procedia Environ Sci* 2013;**18**:264–270.

Hilarino MPA, de Silveira FAO, Oki Y *et al.* Distribution of the endophytic fungi community in leaves of *Bauhinia brevipes* (Fabaceae). *Acta Botanica Brasilica* 2011;**25**:815–821.

Hong L, Lisha Y, Yiqin P *et al.* A survey of wild legume resources and bean proteins in China. *Biotic Resources* 2019;**41**:185–194.

Hu F, Schmidt K, Stoyanova S *et al.* Radical scavengers from the entomogenous deuteromycete *Beauveria amorpha*. *Planta Med* 2002;**68**:64–65.

Hu HC, Li CY, Tsai YH *et al.* Secondary metabolites and bioactivities of *Aspergillus ochraceopetaliformis* isolated from *Anthurium brownii*. *ACS Omega* 2020;**5**:20991–20999.

Jarolim K, Del Favero G, Pahlke G *et al.* Activation of the Nrf2-ARE pathway by the *Alternaria alternata* mycotoxins altertoxin I and II. *Arch Toxicol* 2017;**91**:203–216.

Jiang M, Cao L, Zhang R.Effects of Acacia (*Acacia auriculaeformis* A. Cunn) -associated fungi on mustard (*Brassica juncea* (L.) Coss. var. foliosa Bailey) growth in Cd- and Ni-contaminated soils. *Lett Appl Microbiol* 2008;**47**:561–565.

Kang D, Son GH, Park HM *et al.* Culture condition-dependent metabolite profiling of *Aspergillus fumigatus* with antifungal activity. *Fungal Biol* 2013;**117**:211–219.

Kawashima LM, Soares LMV, Massaguer PR. The development of an analytical method for two mycotoxins, patulin and verruculogen, and survey of their presence in commercial tomato pulp. *Brazilian J Microbiol* 2002;**33**:269–273.

Khambhati VH, Abbas HK, Sulyok M *et al.*. First report of the production of mycotoxins and other secondary metabolites by *Macrophomina phaseolina* (Tassi) Goid. isolates from soybeans (*Glycine max *L.) symptomatic with charcoal rot disease.*J Fungi (Basel)* 2020;**6**:332.

Khan N, Afroz F, Begum MN *et al.* Endophytic *Fusarium solani*: a rich source of cytotoxic and antimicrobial napthaquinone and aza-anthraquinone derivatives.*Toxicol Rep* 2018;**5**:970–976.

Klypina N, Pinch M,Schutte BJ *et al.* Water-deficit stress tolerance differs between two locoweed genera (*Astragalus and Oxytropis*) with fungal endophytes.*Weed Sci* 2017;**65**: 626–638.

Kouipou Toghueo RM, Boyom FF. Endophytes from ethno-pharmacological plants: Sources of novel antioxidants-A systematic review. *Biocat Agric Biotechnol* 2019;**22**:101430.

Küngas K, Bahram M, Põldmaa K.Host tree organ is the primary driver of endophytic fungal community structure in a hemiboreal forest. *FEMS Microbiol Ecol* 2020;**96**:fiz199.

Kuriakose GC, Lakshmanan M D, Bp A *et al.* Extract of *Penicillium sclerotiorum* an endophytic fungus isolated from *Cassia fistula* L. induces cell cycle arrest leading to apoptosis through mitochondrial membrane depolarization in human cervical cancer cells. *Biomed Pharmacother* 2018;**105**:1062–1071.

Kusari S, Zühlke S, Spiteller M. Effect of artificial reconstitution of the interaction between the plant *Camptotheca acuminata* and the fungal endophyte *Fusarium solani* on camptothecin biosynthesis. *J Nat Prod* 2011;**74**:764–775.

Kuźniar A, Włodarczyk K, Grządziel J *et al.* Culture-independent analysis of an endophytic core microbiome in two species of wheat: *Triticum aestivum* L. (cv. 'Hondia') and the first report of microbiota in *Triticum spelta* L. (cv. 'Rokosz').*Syst Appl Microbiol* 2020;**43**:126025.

Li HY, Li DW, He CM *et al.* Diversity and heavy metal tolerance of endophytic fungi from six dominant plant species in a Pb-Zn mine wasteland in China. *Fungal Ecol* 2012;**5**:309–315.

Liu P, Zhang D, Shi R *et al.* Antimicrobial potential of endophytic fungi from *Astragalus chinensis*. *3 Biotech* 2019;**9**:405.

Liu P, Zhao H, Luo Y. Anti-aging implications of *Astragalus Membranaceus* (Huangqi): a well-known Chinese tonic *Aging Dis* 2017;**8**:868–886.

Li X, Lu P. Transcriptome profiles of *Alternaria oxytropis* provides insights into swainsonine biosynthesis. *Sci Rep* 2019;**9**:6021.

Liu R, Li H, Yang J *et al.* Indole diketopiperazines from endophytic fungus of *Astragalus membranaceus* and biological evaluation. *Chem Nat Compd* 2018;**54**:1196–1198.

Liu R, Li H, Yang J. 2,5-Diketopiperazines from *Aspergillus* sp., the endophytic fungus of *Astragalus membranaceus* and their anticancer assay. *Chem Nat Compd* 2020;**56**:583–585.

Liu X, Li H, Zhou F *et al.* Secondary metabolites of *Fusarium* sp., an endophytic fungus in *Astragalus membranaceus*. *Chem Nat Compd* 2015;**51**:1199–1201.

Liu R, Choi HS, Kim SL *et al.* 6-Methoxymellein isolated from carrot (*Daucus carota* L.) targets breast cancer stem cells by regulating NF-κB signaling. *Molecules* 2020;**25**:4374.

Mazinani Z, Zamani M, Sardari S. Isolation and identification of phyllospheric bacteria possessing antimicrobial activity from *Astragalus obtusifolius*, *Prosopis juliflora*, *Xanthium strumarium* and *Hippocrepis unisiliqousa*. *Avicenna J Med Biotechnol* 2017;**9**:31–37.

Mookherjee A, Mitra M, Kutty NN *et al.* Characterization of endo-metabolome exhibiting antimicrobial and antioxidant activities from endophytic fungus *Cercospora* sp. PM018. *S Afr J Bot* 2020;**134**:264–272.

Murali TS, Suryanarayanan TS, Venkatesan G. ungal endophyte communities in two tropical forests of southern India: diversity and host affiliation. *Mycol Prog* 2007;**6**:191–199.

Naganuma M, Nishida M, Kuramochi K *et al.* 1-deoxyrubralactone, a novel specific inhibitor of families X and Y of eukaryotic DNA polymerases from a fungal strain derived from sea algae. *Bioorg Med Chem* 2008;**16**:2939–2944.

Nigg J, Strobel G, Knighton WB *et al.* Functionalized para-substituted benzenes as 1,8-cineole production modulators in an endophytic *Nodulisporium* species. *Microbiology* 2014;**160**:1772–1782.

Noor AI, Neyaz M, Cook D *et al.* Molecular characterization of a fungal ketide synthase gene among swainsonine-producing *Alternaria* species in the USA. *Curr Microbiol* 2020;**77**:2554–2563.

Osada H. Development and application of bioprobes for mammalian cell cycle analyses. *Curr Med Chem* 2003;**10**:727–732.

Palak A, Syed R. Endohyphal bacteria; the prokaryotic modulators of host fungal biology. *Fungal Biol Rev* 2019;**33**:72–81.

Pinheiro EA, Carvalho JM, dos Santos DC *et al.* Antibacterial activity of alkaloids produced by endophytic fungus *Aspergillus* sp. EJC08 isolated from medical plant *Bauhinia guianensis*. *Nat Prod Res* 2013;**27**:1633–1638.

Pinheiro EA, Pina JR, Feitosa AO *et al.* Bioprospecting of antimicrobial activity of extracts of endophytic fungi from *Bauhinia guianensis*. *Revista Argentina de Microbiologãa* 2017;**49**:3–6.

Qin Y, Liu X, Lin J *et al.* Two new phthalide derivatives from the endophytic fungus *Penicillium vulpinum* isolated from *Sophora tonkinensi*. *Nat Prod Res* 2021;**35**:421–427.

Quiroga PR, Nepote V, Baumgartner MT. Contribution of organic acids to α-terpinene antioxidant activity. *Food Chem* 2019;**277**:267–272.

Rabindran SK, Ross DD, Doyle LA *et al.* Fumitremorgin C reverses multidrug resistance in cells transfected with the breast cancer resistance protein. *Cancer Res* 2000;**60**:47–50.

Ruchikachorn N. *Endophytic fungi of Cassia Fistula L. Ph.D. Thesis*, Liverpool John Moores University Liverpool, UK 2005.

Russo ML, Pelizza SA, Cabello MN *et al.* Endophytic fungi from selected varieties of soybean (*Glycine max* L. Merr.) and corn (*Zea mays* L.) grown in an agricultural area of Argentina. *Revista Argentina de MicrobiologÃa* 2016;**48**:154–160.

Seki H, Sawai S, Ohyama K *et al.* Triterpene functional genomics in licorice for identification of CYP72A154 involved in the biosynthesis of glycyrrhizin. *Plant Cell* 2011;**23**:4112–4123.

Shah A, Rather MA, Hassan QP *et al.* Discovery of anti-microbial and anti-tubercular molecules from *Fusarium solani:* an endophyte of *Glycyrrhiza glabra*. *J Appl Microbiol* 2017;**122**:1168–1176.

Shapira S, Pleban S, Kazanov D *et al.* TTerpinen-4-ol: a novel and promising therapeutic agent for human gastrointestinal cancers. *PLoS One* 2016;**11**:e0156540.

Sharma N, Kushwaha M, Arora D *et al.* New cytochalasin from *Rosellinia sanctae*-cruciana, an endophytic fungus of *Albizia lebbeck*. *J Appl Microbiol* 2018;**125**:111–120.

Silva GH, Teles HL, Zanardi LM *et al.* Cadinane sesquiterpenoids of *Phomopsis cassiae*, an endophytic fungus associated with *Cassia spectabilis* (Leguminosae). *Phytochemistry* 2006;**67**:1964–1969.

Singh A, Singh DK, Kharwar RN *et al.* Fungal endophytes as efficient sources of plant-derived bioactive compounds and their prospective applications in natural product drug discovery: insights, avenues, and challenges. *Microorganisms* 2021;**9**:197.

Skiada V, Faccio A, Kavroulakis N *et al.* Colonization of legumes by an endophytic *Fusarium solani* strain FsK reveals common features to symbionts or pathogenss. *Fungal Genet Biol* 2019;**127**:60–74.

Song XY, Wang H, Ren F *et al.* An endophytic *Diaporthe apiculatum* produces monoterpenes with inhibitory activity against phytopathogenic fungi. *Antibiotics* 2019;**8**:231.

Strobel G, Stierle A, Stierle D *et al.* *Taxomyces andreanae*, a proposed new taxon for a bulbilliferous hyphomycete associated with Pacific yew (*Taxus brevifolia*). *Environ Toxicol Pharmacol* 1993;**37**:71–80.

Strobel G. The emergence of endophytic microbes and their biological promise. *Journal of Fungi* 2018;**4**:57.

Suryanarayanan TS, Devarajan PT, Girivasan KP *et al.* The host range of multi-host endophytic fungi. *Curr Sci* 2018;**115**:1963–1969.

Tan X, Zhang X, Yu M *et al.* Sesquiterpenoids and mycotoxin swainsonine from the locoweed endophytic fungus *Alternaria oxytropis*. *Phytochemistry* 2019;**164**:154–161.

Tiam ER, Bikobo DSN, Ndassa IM *et al.* Experimental and computational studies of an antiplasmodial derivative of allantoin; antimycobacterial essential oil from *Cordia batesii* WERNHAM (Boraginaceae). *BMC Chemistry* 2021;**15**:15.

Trotel-Aziz P, Abou-Mansour E, Courteaux B *et al.* *Bacillus subtilis* PTA-271 counteracts botryosphaeria dieback in grapevine, triggering immune responses and detoxification of fungal phytotoxins. *Front Plant Sci* 2019;**10**:25.

Ugai T, Minami A, Tanaka S *et al.* Biosynthetic machinery of 6-hydroxymellein derivatives leading to cyclohelminthols and palmaenones. *Chem Bio Chem* 2020;**21**:360–367.

Wang FW, Ye YH, Ding H *et al.* Benzophenones from *Guignardia* sp. IFB-E028, an endophyte on *Hopea hainanensis*. *Chem Biodiversity* 2010;**7**:216–220.

Wink M. Evolution of secondary metabolites in legumes (Fabaceae). *S Afr J Bot* 2013;**89**:164–175.

Wong-Deyrup SW, Song X, Ng TW *et al.* Plant-derived isoquinoline alkaloids that target ergosterol biosynthesis discovered by using a novel antifungal screening tool. *Biomed Pharmacother* 2021;**137**:111348.

Wulandari RS, Suryantini R. Growth of *Albizia* in vitro: endophytic fungi as plant growth promote of *Albizia*. *Int Sch Sci Res Inn* 2018;**12**:8.

Zhai XL, Yang JG, Shen LL *et al.* Selection and identification of a biocontrol bacteria strain with inhibitory activity against TMV and PVY. *Scientia Agricultura Sinica* 2012;**45**:2180–2188.

Xu WF, Hou XM, Yao FH *et al.* Xylapeptide A, an antibacterial cyclopentapeptide with an uncommon L-pipecolinic acid moiety from the associated fungus *Xylaria* sp. (GDG-102). *Sci Rep* 2017;**7**:6937.

Xu HC. Studies on secondary metabolites and their activities of endophytic fungi from *Astragalus membranaceus* (Fisch.) Bge. Paihua. *Heilongjiang University Heilongjiang China* 2016. https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201901&file name=1016185683.nh

Yang MJ, Zhang T, Yan ZH *et al.* Isolation and activity evaluation of endophytic fungi from *Glycyrrhiza uralensis*. *Chin Tradit Herb Drug* 2020;**51**:4546.

Yang XL, Awakawa T, Wakimoto T *et al.* Induced production of novel prenyldepside and coumarins in endophytic fungi *Pestalotiopsis acaciae*. *Tetrahedron Lett* 2013;**54**:5814–5817.

Yang YX, Dong XP, Yan YM, Tao M, Qian Luo. Studies on secondary metabolites produced by endophytic *Aspergillus fumigatus* from *Trifolium repens*. *Nat Prod Res Dev* 2016;**25**:64–67.

Yang YX. Derivatives in endophytic *Aspergillus fumigatus* from *Trifolium repens* and their bioactivity. *Nat Prod Res Dev* 2013;**28**:864–867.

Yuan H, Ma Q, Ye L *et al.* The traditional medicine and modern medicine from natural products. *Molecules* 2016;**21**:559.

Yu N, He L, Liu DD. Isolation and identification of active ingredients in metabolites of endophytic fungus BS002 from *S. flavescens*. *Nat Prod Res Dev* 2014;**26**:1030–1033.

Sun Y, Wang TL, Wang XY *et al.* Screening of active endophytic fungi from *Astragalus membranaceus* (Hengshan) by secondary model. *Shaanxi J Agric Sci* 2016;**62**:44–46.

Zaehle C, Gressler M, Shelest E *et al.* Terrein biosynthesis in *Aspergillus terreus* and its impact on phytotoxicity. *Chem Biol* 2014;**21**:719–731.

Zhao S, Wang B, Tian K *et al.* Novel metabolites from the *Cercis chinensis* derived endophytic fungus *Alternaria alternata* ZHJG5 and their antibacterial activities. *Pest Manage Sci* 2021;**77**:2264–2271.

Zhang HC, An ZP, Zhou F. Secondary metabolites from *Rhizopus* sp., an endophytic fungus in *Astragalus membranaceus* and preliminary evaluation of inhibition of plant pathogen activity. *Chem Nat Compd* 2020;**56**:366–369.

Zheng N, Yao F, Liang X *et al.* A new phthalide from the endophytic fungus *Xylaria* sp. GDG-102. *Nat Prod Res* 2018;**32**:755–760.