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Plant-Derived Bioactive Compounds Produced by Endophytic Fungi

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Abstract: Plant endophytic fungi are an important and novel resource of natural bioactive compounds with their potential applications in agriculture, medicine and food industry. In the past two decades, many valuable bioactive compounds with antimicrobial, insecticidal, cytotoxic, and anticancer activities have been successfully discovered from endophytic fungi. During the long period of co-evolution, a friendly relationship was formed between each endophyte and its host plant. Some endophytes have the ability to produce the same or similar bioactive compounds as those originated from their host plants. This review mainly deals with the research progress on endophytic fungi for producing plant-derived bioactive compounds such as paclitaxel, podophyllotoxin, camptothecine, vinblastine, hypericin, and diosgenin. The relations between endophytic fungi and their host plants, biological activities and action mechanisms of these compounds from endophytic fungi, some available strategies for efficiently promoting production of these bioactive compounds, as well as their potential applications in the future will also be discussed. It is beneficial for us to better understand and take advantage of plant endophytic fungi.

Keywords: Endophytic fungi, bioactive compounds, host plants.

INTRODUCTION

Plant endophytic fungi are defined as the fungi which spend the whole or part of their lifecycle colonizing inter- and/or intra-cellularly inside the healthy tissues of the host plants, typically causing no apparent symptoms of disease. They are important components of plant micro-ecosystems [1-3]. Plant endophytic fungi have been found in each plant species examined. It is estimated that there are over one million fungal endophytes existing in nature [4]. Plant endophytic fungi have been recognized as an important and novel resource of natural bioactive products with potential application in agriculture, medicine and food industry [5-7]. Since the "gold" bioactive compound paclitaxel (taxol) was discovered from the endophytic fungus *Taxomyces andreanae* in 1993 [8], many scientists have been increasing their interests in studying fungal endophytes as potential producers of novel and biologically active compounds. In the past two decades, many valuable bioactive compounds with antimicrobial, insecticidal, cytotoxic, and anticancer activities have been successfully discovered from endophytic fungi. These bioactive compounds could be classified as alkaloids, terpenoids, steroids, quinones, lignans, phenols, and lactones [2,9]. During the long period of co-evolution, a friendly relationship was gradually set up between each endophytic fungus and its host plant. The host plant can supply plenteous nutriment and easeful habitation for the survival of its endophytes. On the other hand, the endophytes would produce a number of bioactive constituents for helping the host plants to resist external biotic and abiotic stresses, and benefiting for the host growth in return [3,10]. Some endophytic fungi have developed the ability to produce the same or similar bioactive substances as those originated from their host plants. This is beneficial for us to study the relations between the endophytes and their host plants. In addition, we can develop a substitutable approach for efficiently producing these scarce and valuable bioactive compounds for the purpose of protecting plant resources and natural environment [6,11].

This review mainly deals with the plant-derived bioactive compounds (i.e. paclitaxel, podophyllotoxin, camptothecine, vinblastine, and hypericin) produced by endophytic fungi. The potential relationships between endophytes and their host plants, biological activities and action mechanisms of these compounds, some available strategies for efficiently promoting production of these bioactive compounds, as well as their potential application in the future will also be discussed. This report concentrates on work that appeared in the literature from 1993 to July 2010.

1. PACLITAXEL AND ITS ANALOGUES

Paclitaxel (taxol, **1**), as a well-known and highly functionalized tetracyclic diterpenoid bioactive compound, was originally found from the bark of *Taxus brevifolia* in 1971 [12]. It has been proved to exibit efficient activity against prostate, ovarian, breast, and lung cancers with its unique mode of action that paclitaxel binds to tubulin-β specifically, and prevents their depolymerization during the processes of cell division [13,14]. However, a complete treatment for one patient requires approximately 2 g of paclitaxel administered several times over a few months. To obtain 1 kg of paclitaxel, it requires about 10,000 kg of *Taxus* bark [15], and thousands of trees need to be cut down to obtain this quantity of bark. The scarcity of paclitaxel and negative ecological impact of procuring it encouraged scientists to develop alternative resource and approach for producing this valuable bioactive compound. Fortunately, a paclitaxel-producing

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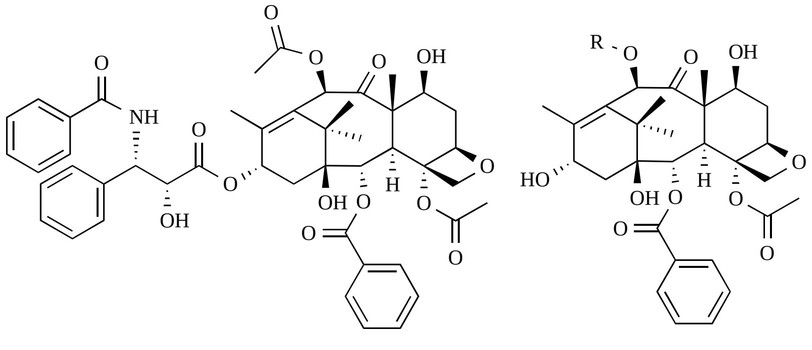
endophytic fungus *Taxomyces andreanae* was successfully discovered from the Pacific yew (*Taxus brevifolia*) by Stierle *et al.* in 1993 [8]. This tremendous finding firstly showed that plant endophytic fungus had the same ability as its host plant to biosynthesize paclitaxel. It provided a novel and promising approach to produce this valuable compound. Since then, many scientists have been increasing their interests in studying fungal endophytes as potential candidates for producing paclitaxel. During the past two decades, searching for paclitaxel-producing endophytic fungi from *Taxus* species as well as from other related plant species has shown much progress. Nevertheless, there are still some problems in application of these endophytic fungi such as low biomass generated by current fungal strains in fermentation, low yield of paclitaxel in culture medium, and unknown pathways of paclitaxel biosynthesis. In order to improve paclitaxel production of these endophytic fungi, some methods have been applied such as mutation screening, protoplast fusion, and metabolic regulation, although the results are not satisfying [16-18].

Up to now, at least 20 genera of endophytic fungi (i.e. *Alternaria, Aspergillus, Botryodiplodia, Botrytis, Cladosporium, Ectostroma, Fusarium, Metarhizium, Monochaetia, Mucor, Nigrospora, Ozonium, Papulaspora, Periconia, Pestalotia, Pestalotiopsis, Phyllosticta, Pithomyces, Taxomyces*, and *Tubercularia*) were screened to have the ability to produce paclitaxel and its analogues such as baccatin III (**2**) or 10-deacetylbaccatin III (**3**) (Fig. (**1**), Table **1**). The hosts of paclitaxel-producing fungi mainly include *Taxus* species (i.e. *T. baccata, T. cuspidata, T. media*, and *T. yunnanensis*) that belong to the family Taxaceae, and non-*Taxus* species such as *Cardiospermum halicacabum* (Spindaceae), *Citrus medica* (Rutaceae), *Cupressus* sp. (Cupressaceae), *Ginkgo biloba* (Ginkgoaceae), *Hibiscus rosa-sinensis* (Malvaceae), *Podocarpus* sp. (Podocarpaceae), *Taxodium* distichum (Taxodiaceae), *Terminalia arjuna* (Combretaceae), *Torreya grandifolia* (Taxaceae), and *Wollemia nobilis* (Araucariaceae). Such a great number and wide range implies that both paclitaxel-producing fungi and their hosts have a broad biological diversity. It is noticeable that some host plants have not yet been screened to produce paclitaxel and (or) its derivatives.

2. PODOPHYLLOTOXIN AND ITS ANALOGUES

Podophyllotoxin (PDT, **4**), a well-known aryltetralin lignan with potent anticancer, antiviral, antioxidant, antibacterial, immunostimulation, and anti-rheumatic properties, mainly occurs in genera of *Diphylleia*, *Dysosma*, *Juniperus* (also called *Sabina*), and *Sinopodophyllum* (also called *Podophyllum*) [52-60]. PDT has been used as a precursor for chemical synthesis of the anticancer drugs like etoposide, teniposide, and etopophose phosphate which act as topoisomerase inhibitors [56,59]. At present, the major supply of podophyllotoxin is from the natural *Sinopodophyllum* plants. Due to this over-exploitation, the *Sinopodophyllum* plants have been declared to be endangered species. In order to satisfy the increasing demand and make it more available, alternative resources and strategies for efficiently producing this valuable compound and its analogues should be developed.

The structures of podophyllotoxin and its analogues are shown in Fig. (**2**), and the endophytic fungi and their host plants are listed in Table **2**. Yang *et al.* first reported six endophytic fungi obtained from *Sinopodophyllum hexandrum*, *Diphylleia sinensis*, and *Dysosma veitchii* that had the ability to produce podophyllotoxin [52]. Later, Lu *et al.* also reported that an endophytic *Alternaria* sp. obtained from *Sabina vulgaris* could produce PDT [53]. Eyberger *et al.* successfully obtained two endophytic *Phialocephala fortinii* strains PPE5 and PPE7 from the rhizomes of *Sinopodophyllum peltatum* that could produce PDT with yields of 0.5-189 μg/L in liquid suspension culture [59]. Other PDT-producing endophytic fungi including *Alternaria* sp. from *Sinopodophyllum hexandrum* [54], and *Fusarium oxysporum* from *Sabina recurva* [56] have also been reported. Puri *et al.* reported an endophytic fungus *Trametes hirsuta* isolated from *Sinopodophyllum hexandrum* that could produce PDT, podophyllotoxin-β-D-glucoside (PDTG, **5**) and 4'-demethylpodophyllotoxin (DMP, **6**) in Sabouraud broth culture [60]. Deoxypodophylltoxin (DPDT, **7**) as the anticancer pro-drug was found in the endophytic *Aspergillus fumigatus* isolated from *Juniperus communis* [55]. These results provided a promising way of exploring endophytic fungi as the alternative source to produce podophyllotoxin and its analogues at lower costs.



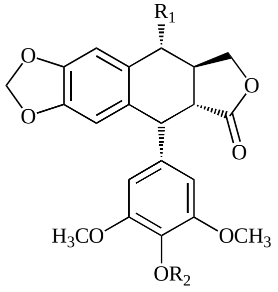
Paclitaxel (**1**)

2 R=$COCH_3$
3 R=H

Fig. (1). Structures of paclitaxel and its analogues (**1-3**).

Table 1. Paclitaxel-Producing Endophytic Fungi and Their Host Plants

Endophytic fungus	Fungal strain	Host plant	Paclitaxel yield (μg/L)	References
Alternaria sp.	Ja-69	*Taxus cuspidata*	0.16	[19]
Alternaria sp.	-	*Ginkgo biloba*	0.12-0.26	[20]
Alternaria alternate	TPF6	*Taxus chinensis* var. *mairei*	84.5	[21]
Aspergillus fumigatus	EPTP-1	*Podocarpus* sp.	557.8	[22]
Aspergillus niger var. *taxi*	HD86-9	*Taxus cuspidata*	273.6	[23]
Botryodiplodia theobromae	BT115	*Taxus baccata*	280.5	[24]
Botrytis sp.	XT2	*Taxus chinensis* var. *mairei*	161.24	[25]
Botrytis sp.	HD181-23	*Taxus cuspidata*	206.34	[26]
Cladosporium cladosporioides	MD2	*Taxus media*	800	[27]
Ectostroma sp.	XT5	*Taxus chinensis* var. *mairei*	276.75	[25]
Fusarium arthrosporioides	F-40	*Taxus cuspidata*	131	[28]
Fusarium lateritium	Tbp-9	*Taxus baccata*	0.13	[19]
Fusarium mairei	Y1117	*Taxus chinensis* var. *mairei*	2.7	[29]
Fusarium mairei	UH23	*Taxus chinensis* var. *mairei*	286.4	[30]
Fusarium solani	-	*Taxus celebica*	1.6	[31]
Fusarium solani	Tax-3	*Taxus chinensis*	163.35	[32]
Metarhizium anisopliae	H-27	*Taxus chinensis*	846.1	[33]
Monochaetia sp.	Tbp-2	*Taxus baccata*	0.10	[19]
Mucor rouxianus	DA10	*Taxus chinensis*	-	[34]
Nigrospora sp.	SGLAf14	*Taxus globosa*	0.142-0.221	[35]
Ozonium sp.	BT2	*Taxus chinensis* var. *mairei*	4-18	[36]
Papulaspora sp.	XT17	*Taxus chinensis* var. *mairei*	10.25	[25]
Periconia sp.	No. 2026	*Torreya grandifolia*	0.03-0.83	[37]
Pestalotia bicilia	Tbx-2	*Taxus baccata*	1.08	[19]
Pestalotiopsis breviseta	-	*Ervatamia divaricata*	64	[38]
Pestalotiopsis guepinii	W-1f-2	*Wollemia nobilis*	0.49	[39]
Pestalotiopsis microspora	Ja-73	*Taxus cuspidata*	0.27	[19]
Pestalotiopsis microspora	Ne-32	*Taxus wallachiana*	0.5	[19]
Pestalotiopsis microspora	No. 1040	*Taxus wallachiana*	0.06-0.07	[40]
Pestalotiopsis microspora	Cp-4	*Taxodium distichum*	0.05-1.49	[41]
Pestalotiopsis microspora	Ne 32	*Taxus wallachiana*	0.34-1.83	[42]
Pestalotiopsis neglecta	BSL045	*Taxus cuspidata*	375	[43]
Pestalotiopsis pauciseta	CHP-11	*Cardiospermum halicacabum*	113.3	[44]
Pestalotiopsis sp.	W-x-3	*Wollemia nobilis*	0.13	[39]
Pestalotiopsis sp.	W-1f-1	*Wollemia nobilis*	0.17	[39]
Pestalotiopsis terminaliae	TAP-15	*Terminalia arjuna*	211.1	[45]
Pestalotiopsis versicolor	BSL038	*Taxus cuspidata*	478	[43]
Phyllosticta citricarpa	No.598	*Citrus medica*	265	[46]
Phyllosticta dioscoreae	No.605	*Hibiscus rosa-sinensis*	298	[47]
Phyllosticta spinarum	No.625	*Cupressus* sp.	235	[48]
Pithomyces sp.	P-96	*Taxus sumatrana*	0.095	[19]
Taxomyces andreanae	-	*Taxus brevifolia*	0.024-0.05	[8]
Taxomyces sp.	-	*Taxus yunnanensis*	2.3	[49]
Tubercularia sp.	TF$_5$	*Taxus chinensis* var. *mairei*	185.4	[50]
Unidentified	YF$_1$	*Taxus yunnanensis*	-	[51]



4 R_1=OH, R_2=CH_3
5 R_1=OGlu, R_2=CH_3
6 R_1=OH, R_2=H
7 R_1=R_2=H

Fig. (2). Structures of podophyllotoxin and its analogues (**4**-**7**).

3. CAMPTOTHECINE AND ITS ANALOGUES

Camptothecin (CPT, **8**), a pentacyclic quinoline alkaloid, was firstly isolated from the wood of *Camptotheca acuminata* (Nyssaceae) by Wall *et al*. in 1966 [61]. CPT and its analogue10-hydroxycamptothecin (**10**) are regarded as two of the most effective antineoplastic agents [62]. The primary action mechanism of CPT is inhibiting the intra-nuclear enzyme topoisomerase-1, which is required in DNA replication and transcription during cell proliferation [62]. Hycamtin (topotecan) and Camtostar (irinotecan), two of the famous CPT semi-synthetic drugs, have already been in clinical use against ovarian, small lung, and refractory ovarian cancers popularly all over the world [63]. Presently, the major supply of CPT is still from the wild trees, i.e. *Camptotheca acuminata* (Nyssaceae) and *Nothapodytes nimmoniana* (Icacinaceae). Increasing demand of this compound has resulted in extensive cropping of the trees in China and India. To avoid this disastrous exploitation, it is necessary to further find high yielding candidates and alternative resources to produce this bioactive compound and its analogues [66,67].

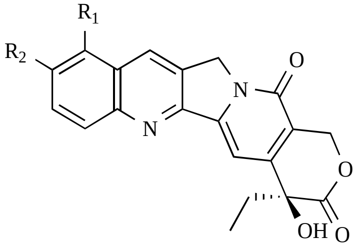
Puri *et al*. first reported in 2005 an endophytic fungus *Entrophospora infrequens* obtained from plant *Nothapodytes foetida* that had the ability to produce camptothecin [65]. Later, Amna *et al*. performed kinetic studies of the growth and CPT accumulation of the endophyte *E. infrequens* in suspension culture either with the shake flasks or in a bioreactor, and demonstrated that this endophyte could be a potential alternative microorganism to produce CPT [66]. Rehman *et al*. also successfully discovered a CPT-producing endophytic fungus *Neurospora* sp. from the seeds of *Nothapodytes foetida* in 2008 [69]. More recently, Kusari *et al*. reported that an endophytic fungus *Fusarium solani* obtained from *Camptotheca acuminata* could produce CPT, 9-methoxycamptothecin (**9**) and 10-hydroxycamptothecin (**10**) in Sabouraud dextrose broth [68]. Min and Wang showed that an unidentified endophytic fungal strain XK001 from *Camptotheca acuminata* could produce 10-hydroxycamptothecin with yield of 677 μg/L [71]. Shweta *et al*. successfully found that two endophytic *Fusarium solani* strains

Table 2. Podophyllotoxin and Its Analogues Produced by the Endophytic Fungi and Their Host Plants

Endophytic fungus	Fungal strain	Host plant	Content or yield of the compounds	References
Alternaria sp.	-	*Sinopodophyllum hexandrum* (=*Podophyllum hexandrum*)	-	[52]
Alternaria sp.	SC13	*Juniperus vulgaris* (=*Sabina vulgaris*)	-	[53]
Alternaria neesex	Ty	*Sinopodophyllum hexandrum*	PDT 2.4 μg/L	[54]
Aspergillus fumigatus	INFU/Jc/KF/6	*Juniperus communis*	DPDT 0.04 μg/g dry mycelia and 3.0 μg/L broth	[55]
Fusarium oxysporum	JRE1	*Juniperus recurva* (=*Sabina recurva*)	PDT 28 μg/g	[56]
Monilia sp.	-	*Dysosma veitchii*	-	[52]
Penicillium sp.	-	*Sinopodophyllum hexandrum*	-	[52]
Penicillium sp.	-	*Diphylleia sinensis*	-	[52]
Penicillium sp.	-	*Dysosma veitchii*	-	[52]
Penicillium implicatum	SJ21	*Diphylleia sinensis*	-	[57]
Penicillium implication	2BNO1	*Dysosma veitchii*	-	[58]
Phialocephala fortinii	PPE5, PPE7	*Sinopodophyllum peltatum*	PDT 0.5-189 μg/L	[59]
Trametes hirsuta	-	*Sinopodophyllum hexandrum*	PDT 30 μg/g	[60]

Abbreviations: deoxypodophyllotoxin (DPDT); podophyllotoxin (PDT).

MTCC9667 and MTCC9668 from *Apodytes dimidiata* (Icacinaceae) had the ability to produce CPT (**8**) with yields of 0.37 µg/g for MTCC9667 and 0.53 µg/g for MTCC9668, respectively. Furthermore, the endophyte MTCC9668 could produce 9-methoxycamptothecin (**9**) and 10-hydroxycamptothecin (**10**) with yields of 0.45 µg/g and 0.082 µg/g, respectively [67]. The structures of camptothecins and its analogues are shown in Fig. (**3**), and the camptothecin-producing endophytic fungi and their host plants are listed in Table **3**.



8 $R_1=R_2=H$
9 $R_1=OCH_3$, $R_2=H$
10 $R_1=H$, $R_2=OH$

Fig. (3). Structures of camptothecine and its analogues (**8-10**).

4. VINBLASTINE AND ITS ANALOGUES

Vinblastine (**11**) and vincristine (**12**) (Fig. (**4**)), the terpenoid indole alkaloids derived from the coupling of vindoline and catharanthine monomers, are two well-known anticancer agents [72,73]. The primary action mechanism of vincristine is *via* interference with microtubule formation and mitotic spindle dynamics, disruption of intracellular transport, and decreasing tumour blood flow, with the latter probably as a consequence of anti-angiogenesis [72,74]. Guo *et al.* first reported in 1998 an endophytic fungus *Alternaria* sp. isolated from the phloem of *Catharanthus roseus* that had the ability to produce vinblastine (**11**) [75]. Later, Zhang *et al.* discovered an endophytic *Fusarium oxysporum* from the pholem of *C. roseus* that could produce vincristine (**12**) [76]. Yang *et al.* also found an unidentified vincristine-producing endophytic fungus from the leaves of *C. roseus* in 2004 [77] (Table **4**).

5. OTHER BIOACTIVE COMPOUNDS

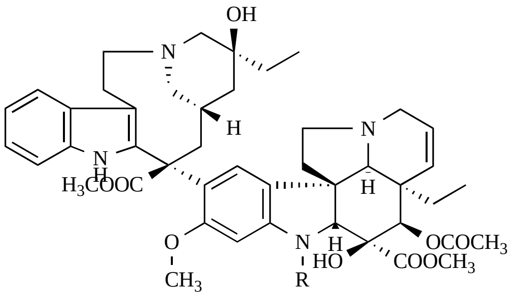
There are some other plant-derived bioactive compounds that could also be biosynthesized by their endophytic fungi. These pronounced bioactive compounds mainly include hypericin (**13**), emodin (**14**), diosgenin (**15**), toosendanin (**16**), huperzine A (**17**), α-irone (**18**), β-irone (**19**), and flavonoids (shown in Fig. (**5**) and Table **5**). Li *et al* first reported that an endophytic fungus *Acremonium* (2F09P03B) obtained from *Huperzia serrata* could produce huperzine A (**17**), a lycopodium alkaloid. They further optimized its fermentation conditions for the production of huperzine A [78]. Zhou *et al.* reported that an endophytic fungus *Penicillium chrysogenum* obtained from *Lycopodium serratum* could also produce huperzine A as much as 4.761 mg/L in liquid culture [89]. Ju *et al.* discovered two endophytic fungi *Blastomyces* sp. (HA15) and *Botrytis* sp. (HA23) from *Phlegmariurus cryptomerianus* that had the ability to produce huperzine A [82].

Zhou and his co-workers screened a few diosgenin-producing endophytic fungi from *Paris polyphylla* var. *yunnanensis* [83,84]. Zhang *et al.* reported that an endophytic fungus *Rhizopus oryzae* (94Y-01) from the rhizomes of *Iris germanica* could produce α- and β-irones, and its culture conditions were then optimized [90]. Wang *et al.* discovered three endophytic fungal isolates from *Melia azedarach* that had the ability to produce toosendanin (**16**) [93]. Kusari *et al.* reported that an endophytic fungus isolated from the stems of *Hypericum perforatum* (St. John's Wort) which had the ability to produce hypericin (**13**) and emodin (**14**) with large amounts in the culture medium [85]. Furthermore, some endophytic fungi isolated from flavonoid-producing plants have been examined for the synthesis of flavonoids, however the structures have not been elucidated yet [79-81,86-88,92,93]. All the results mentioned above clearly showed that endophytic fungi could be an alternative resource for

Table 3. Camptothecin-Producing Endophytic Fungi and Their Host Plants

Endophytic fungus	Fungal strain	Host plant	Camptothecin content or yield	References
Botryosphaeria parva	UAS015	*Nothapodytes nimmoniana*	-	[64]
Entrophospora infrequens	RJMEF 001	*Nothapodytes foetida*	-	[65]
Entrophospora infrequens	5124	*Nothapodytes foetida*	49.6 µg/g	[66]
Fusarium sacchari	UAS013	*Nothapodytes nimmoniana*	-	[64]
Fusarium solani	MTCC 9667	*Apodytes dimidiata*	0.37 µg/g	[67]
Fusarium solani	MTCC 9668	*Apodytes dimidiata*	0.53 µg/g	[67]
Fusarium solani	INFU/Ca/KF/3	*Camptotheca acuminata*	-	[68]
Neurospora sp.	ZP5SE	*Nothapodytes foetida*	-	[69]
Nodulisporium sp.	-	*Nothapodytes foetida*	5.5 µg/g	[70]
Unidentified	XK001	*Camptotheca acuminata*	-	[71]

efficiently producing valuable bioactive compounds in the future.



11 R=CH_3
12 R=CHO

Fig. (4). Structures of vinblastine (**11**) and vincristine (**12**).

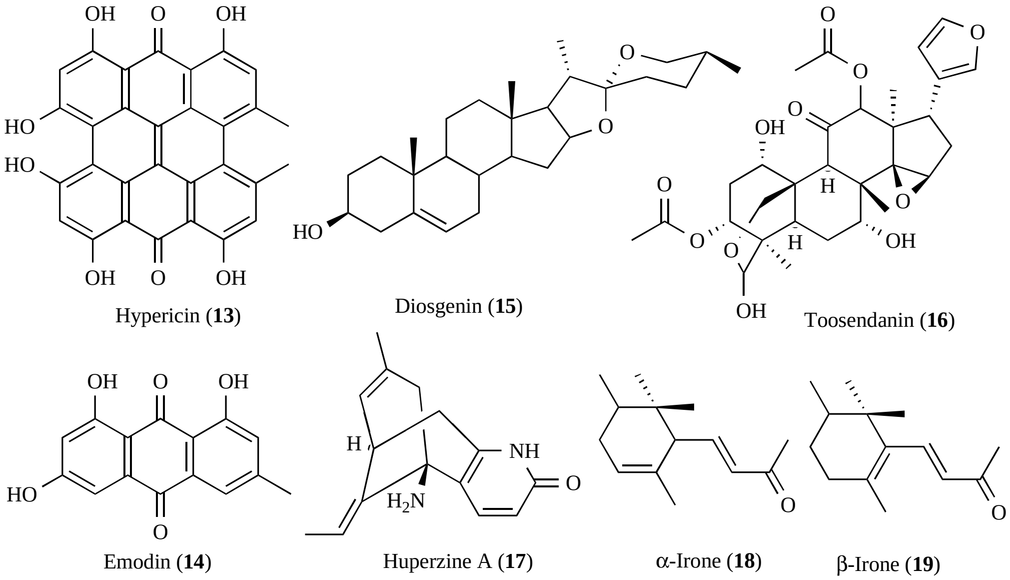
6. CONCLUSIONS AND FUTURE PERSPECTIVES

Plant endophytic fungi, as a novel and abundant resource of microorganisms, have the special ability to produce the same or similar bioactive compounds originating from their host plants as well as other bioactive constituents. This remarkable ability has aroused the interest of many researchers both in basic research and applied fields. In the past two decades, scientists mainly focused on the investigation of endophytic fungal diversity, clarifying the relationships between endophytic fungi and their host plants, and seeking for natural bioactive compounds originated from endophytic fungi. In addition, improving the productivity of some potential candidates by taking advantage of genetic engineering, microbial fermentation projects and other efficient measures was well developed [5]. Up to now, hundreds of plants have been investigated for their endophytic fungi, and many of them have been examined to produce a diversity of compounds. Many novel and valuable bioactive compounds with antimicrobial, insecticidal, cytotoxic, and anticancer activities have been successfully obtained from endophytic fungi [95-99]. The evidence of plant-associated microbes discovered in the fossilized tissues of stems and leaves indicated that the endophytic associations may have evolved from the time that higher plants first appeared on the earth, hundreds of millions of years ago [100]. Carroll suggested that some phytopathogens in the environment were related to endophytes and had an endophytic origin [101]. A few microorganisms appear actively to penetrate plant tissues through invading openings or wounds, as well as proactively using hydrolytic enzymes such as cellulase and pectinase [2]. During the long period of co-evolution, endophytic fungi have adapted themselves to their special microenvironments gradually by genetic variation, including uptake of some plant DNA segments into their own genomes, as well as insertion their own DNA segments into the host genomes. This could have led to certain endophytes have the ability to biosynthesize some "phytochemicals" originated from their host plants [2,8]. One typical example was the production of gibberellins from both fungi and plants [102]. The outline of the bioactive compounds from both endophytic fungi and their host plants along with their potential applications is shown in Fig. (**6**).

It is believed that plant endophytic fungi as a novel mine of natural bioactive compounds have great potential applications in agriculture, medicine and food industry [5,7]. Taking advantage of modern biotechnology such as genetic engineering, metabolic technology, and microbial fermentation processes, we can better understand and manipulate this important microorganism resource, and make it more beneficial for mankind [103-105]. The first step is to search for potential endophytic fungal resource from nature. Secondly, through mutation selection, protoplast fusion, gene manipulation, and other DNA recombination techniques, the candidates with high productivity suitable for industrial fermentation could be selected [106]. Furthermore, colonizing and expression of relevant functional genes in the biosynthetic pathways are also beneficial for improving the productivity of the candidates. It is well known that microbial fermentation is a sophisticated project, and it has been widely used in many occasions for a long time. Penicillin, avermectin, validamycin, and other well-known antibiotics have been successfully produced through large scale fermentation processes. Compared with plant cell culture, the culture medium for fungal cells is simple, inexpensive with the abundant supply, and the production cost is relatively low. Moreover, the period of fermentation is short, and the microbial fermentation processes can provide the best growth and breeding conditions, and various culture parameters can be easily optimized according to the specific applications. In addition, many feasible strategies could be adopted for efficiently enhancing bioactive compound production during the fermentation processes. These strategies mainly include feeding

Table 4. Vinblastine and Vincristine Produced by the Endophytic Fungi and Their Host Plants

Endophytic fungus	Fungal strain	Host plant	Content or yield of the compounds	References
Alternaria sp.	97CG1	*Catharanthus roseus*	Vinblastine -	[75]
Fusarium oxysporum	97CG3	*Catharanthus roseus*	Vincristine -	[76]
Unidentified	97CY_3	*Catharanthus roseus*	Vincristine 0.205μg/L	[77]



Hypericin (**13**) Diosgenin (**15**) Toosendanin (**16**)

Emodin (**14**) Huperzine A (**17**) α-Irone (**18**) β-Irone (**19**)

Fig. (5). Structures of other bioactive compounds (**13-19**).

Table 5. Other Bioactive Compounds-Producing Endophytic Fungi and Their Host Plants

Endophytic fungus	Fungal strain	Host plant	Bioactive compounds	References
Acremonium sp.	2F09P03B	*Huperzia serrata*	Huperzine A	[78]
Alternaria tenuissima	Y2-3	*Vaccinium* sp.	Flavonoids	[79]
Aspergillus fumigatus	D37	*Davidia involucrata*	Flavonoids	[80]
Aspergillus nidulans	ST22	*Ginkgo biloba*	Flavonoids	[81]
Aspergillus oryzae	SX10	*Ginkgo biloba*	Flavonoids	[81]
Blastomyces sp.	HA15	*Phlegmariurus cryptomerianus*	Huperzine A	[82]
Botrytis sp.	HA23	*Phlegmariurus cryptomerianus*	Huperzine A	[82]
Cephalosporium sp.	84	*Paris polyphylla* var. *yunnanensis*	Diosgenin	[83,84]
Chaetomium globosum	INFU/Hp/KF/34B	*Hypericum perforatum*	Hypericin, Emodin	[85]
Colletotrichum acutatum	QC102	*Ginkgo biloba*	Flavonoids	[86]
Colletotrichum sp.	EG4	*Ginkgo biloba*	Flavonoids	[87]
Nodulisporium hyalosporum	GL-2	*Ginkgo biloba*	Flavonoids	[88]
Paecilomyces sp.	80	*Paris polyphylla* var. *yunnanensis*	Diosgenin	[83,84]
Penicillium chrysogenum	SHB	*Lycopodium serratum*	Huperzine A	[89]
Rhizopus oryzae	94Y-01	*Iris germanica*	α-Irone, β-Irone	[90]
Shiraia sp.	Slf14	*Huperzia serrata*	Huperzine A	[91]
Unidentified	DZY5	*Eucommia ulmoids*	Flavonoids	[92]
Unidentified	L5-5	*Vaccinium* sp.	Flavonoids	[79]
Unidentified	O-L-5, O-SC II-4, O-RC-3	*Melia azedarach*	Toosendanin	[93]
Xylaria sp.	YX-28	*Ginkgo biloba*	Flavonoids	[94]

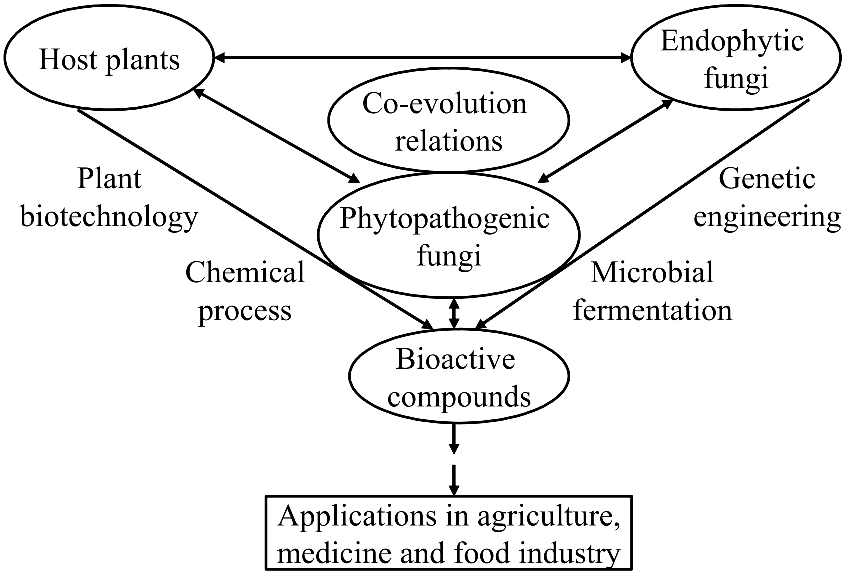


Fig. (6). Outline of the bioactive compounds from both endophytic fungi and their host plants along with their potential applications.

precursors, adding biotic and abiotic elicitors, appending inhibitors, using special enzymes and other substances through metabolic investigation [107,108].

After more than two decades of research, much progress about plant endophytic fungi has been achieved though there are still many issues (i.e. how to distinguish the isolated fungus to be the endophyte, parasite or epiphyte; isolation and taxonomical identification of each isolated endophyte; clarifying the relationships between endophytes and their hosts; elucidating bioactive compounds as well as their biosynthetic pathways in endophytic fungi; promoting production of these bioactive compounds in fungal fermentation processes; and understanding action mechanisms of these bioactive compounds, etc.) needed to be further clarified and resolved. With the development of molecular biotechnology and chemical process, much more attentions and devotions paid to this novel and important resource, we can better understand and take advantage of them.

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