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ADVANCEMENT IN ENDOPHYTIC MICROBES FROM MEDICINAL PLANTS

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ABSTRACT: This overview firstly highlights biology of endophytic microbes from medicinal plants as well as their chemistry with emphasis on the important merging of microbiology and natural products chemistry and its role in improving our current knowledge of endophytic associations in medicinal plants. Secondary metabolites of medicinal plants-derived endophytes reported in recent years are grouped according to their bioactive properties including antitumor, antimicrobial, growth-promoting, antioxidant, antithrombotic, insecticide and other functions. New insights on distributing characteristics and biodiversity of these endophytes including bacteria, actinomycetes and fungi are also presented. It suggested that endophytic microbe from medicinal plant is a treasure trove of bioactive natural products with a good and potential application prospect in pharmacy and agriculture.

INTRODUCTION: The term 'endophyte' is a kind of microbes which reside in the intracellular or intercellular area of healthy plant tissues during their periods of life or the whole, and don't cause any obvious symptoms or distinct negative effects in their plant hosts¹. Endophytes are the normal organism in plant tissues and shown to be an important part of microecosystem². Investigation of endophytes had not become a hot spot globally until a taxol and taxane producing endophyte, *Taxomyces andreanae*, isolated from *Taxus brevifolia* was reported in 1993³.

Nowadays, more attention is being worldwide paid to endophytic microbes by microbiologists and natural product chemists because of their abundant biological and chemical diversity. Endophytes originated from the formation of higher plants or vascular plants on the earth^{4,5}.

During the long period of co-evolution with host plants, endophytes had adapted themselves to the niches and formed a completely compatible symbiont via gene regulation². In this micro-eco-environment, host plants provide endophytes with photosynthetic products and minerals for their normal growth while endophytes promote the growth and chemical defense of host plants by directly providing with valuable metabolites or transferring the corresponding genes to the host genome^{6,7}. So, endophytic microbes can improve the resistance of their hosts to adverse biotic factors (such as plant pathogens, herbivore, insects, etc.)

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and abiotic factors (such as drought, flood, high salt, improper temperature, etc.). In many cases, the majority of natural products produced by endophytic microorganisms showing antimicrobial activity can protect the host plant against phytopathogens⁸. However, due to factors shaping plant-endophyte interactions, there are some species of endophytes express different lifestyles, by ranging from mutualism through commensalism to parasitism⁹. The factors include genetic background, imbalance in nutrient exchange¹⁰ and environmental variations^{11,12}.

Medicinal plants play important role in human health, especially in the developing countries and poverty-stricken areas. Bioactive natural products of medicinal plants have long been and will continue to be important sources of medicinal raw materials. However, the natural habitats for wild medicinal plants are being threatened by over-use and environmental and geopolitical instabilities¹³.

So, it may become critical to develop alternative sources for medicinal plant products. To date, a large number of evidence listed in **Table 1** has indicated endophytic microbes have the ability to produce the same and/or similar bioactive chemicals as those originated from their host plants, which some are the most valuable compounds such as camptothecin **1**, diosgenin **2**, ginkgolide B **3**, huperzine A **4**, hypericin **5**, podophyllotoxin **6**, taxol **7**, vinblastine **8**, and vincristine **9** (**Figure 1**).

Therefore, it becomes considerable interest in endophyte cultures as a potential alternative to traditional agriculture for the industrial production of valuable natural products.

In this review, we focus on aspects of endophytic microbes from medicinal plants, such as their distributing characteristics, biodiversity and chemodiversity. Moreover, selected secondary metabolites from these endophytes are grouped according to their bioactive properties. So, endophytic microbes can improve the resistance of their hosts to adverse biotic factors (such as plant

pathogens, herbivore, insects, etc.) and abiotic factors (such as drought, flood, high salt, improper temperature, etc.). In many cases, the majority of natural products produced by endophytic microorganisms showing antimicrobial activity can protect the host plant against phytopathogens⁸. However, due to factors shaping plant-endophyte interactions, there are some species of endophytes express different lifestyles, by ranging from mutualism through commensalism to parasitism⁹. The factors include genetic background, imbalance in nutrient exchange¹⁰ and environmental variations^{11,12}.

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TABLE1: VALUABLE COMPOUNDS-PRODUCING ENDOPHYTES AND THEIR HOST PLANTS

Compound	Endophyte	Strain No.	Host plant	
camptothecin	<i>Alternaria alternata</i> (Fr.) Keissl	MTCC 5477	<i>Miquelia dentate</i> Bedd. ¹⁴	
	<i>Bacillus cereus</i>	ChST	<i>M. dentate</i> Bedd. ¹⁵	
	<i>B. sp.</i>	CPC3	<i>M. dentate</i> Bedd. ¹⁵	
	<i>B. subtilis</i>	PXJ-5	<i>M. dentate</i> Bedd. ¹⁵	
	<i>Entrophospora infrequens</i>	RJMEF 001	<i>Nothapodytes foetida</i> ^{16, 17}	
	<i>Fomitopsis sp.</i> P. Karst	MTCC 10177	<i>M. dentate</i> Bedd. ¹⁴	
	<i>Fusarium solani</i>	INFU/Ca/KF/3	<i>Camptochaeca acuminata</i> ¹⁸	
		MTCC 9667, 9668	<i>Apodytes dimidiata</i> E. Mey. Ex Arn ¹⁹	
		<i>Lysinibacillus sp.</i>	JN160728	<i>M. dentate</i> Bedd. ¹⁵
		<i>Neurospora sp.</i>	ZP5SE	<i>N. foetida</i> ²⁰
diosgenin	<i>Phomopsis sp.</i>	Sacc	<i>M. dentate</i> Bedd. ¹⁴	
	<i>B. subtilis</i>	RZ07	<i>Paris polyphylla chinensis</i> ²¹	
	<i>Cephalosporium sp.</i>	84	<i>P. polyphylla</i> var. <i>yunnanensis</i> ²²	
	<i>Exiguobacterium acetylicum</i>	RZ03	<i>P. polyphylla chinensis</i> ²¹	
ginkgolide B	<i>Paecilomyces sp.</i>	80	<i>P. polyphylla</i> var. <i>yunnanensis</i> ²²	
	<i>F. oxysporum</i>	SY0056	<i>Gingo biloba</i> ²³	
huperzine A	<i>Colletotrichum gloeosporoides</i>	ES026	<i>Huperiaceae serrate</i> ²⁴	
	<i>Sharaia sp.</i>	Slf14	<i>H. serrate</i> ^{25, 26}	
hypericin	<i>Thielavia subthermophila</i>	INFU/Hp/KF/34B	<i>Hypericum perforatum</i> ^{27, 28}	
podophyllotoxin	<i>F. oxysporum</i>	JRE1	<i>Juniperus recurva</i> ²⁹	
	<i>F. solani</i>	P1	<i>Podophyllum hexandrum</i> ³⁰	
	<i>Phialocephala fortinii</i> Wang & Wilcox	PPE5	<i>P. peltatum</i> ³¹	
	<i>P. fortinii</i> Wang & Wilcox	PPE7	<i>P. peltatum</i> ³¹	
	<i>Trametes hirsuta</i>		<i>P. hexandrum</i> ³²	
	<i>A. sp.</i>	Ja-69	<i>Taxus cuspidate</i> ³³	
taxol	<i>Aspergillus niger</i> var. <i>taxi</i>	HD86-9	<i>T. cuspidate</i> ³⁴	
	<i>F. culmorum</i>	SVJM072	<i>Tinospora cordifolia</i> ³⁵	
	<i>Pestalotiopsis microspora</i>	CP-4	<i>Taxodium distichum</i> ³⁶	
		NE-32	<i>Taxus wallichiana</i> ³⁷	
			<i>T. wallichiana</i> ³⁸	
	<i>P. neglecta</i>	BSL045	<i>T. cuspidate</i> Sieb. & Zucc. ³⁹	
		BSL038	<i>T. cuspidata</i> Sieb. & Zucc. ³⁹	
	<i>Taxomyces andreanae</i>		<i>T. brevifolia</i> ³	
vinblastine	<i>Tubercularia sp.</i>	TF5	<i>T. mairei</i> ⁴⁰	
	<i>F. oxysporum</i>		<i>Catharanthus roseus</i> ⁴¹	
vincristine	<i>F. oxysporum</i>		<i>C. roseus</i> ⁴¹	

Distributing Characteristics: Many studies have indicated that endophytic microbes are widely distributed in organs of medicinal plants, including roots, stems, leaves, flowers, fruits and seeds. According to morphological characteristics and intergenic transcribed spacer (ITS) sequences, such as 16S rDNA and 18S rDNA, endophytic microbes are classified into endophytic bacteria, endophytic actinomycetes and endophytic fungi. They are also divided into obligative endophytes and facultative endophytes based on their parasitic characters. The distribution of endophytes in medicinal plants was affected by two factors, environment and host. The former includes climate and geographic

conditions. For instance, endophytic *Cladosporium herbarum* (Pers.) Link, *Aureobasidium pullulans* (de Bary) Arn and *Alternaria alternata* (Fr.) Keissl are frequently discovered in mesotherm medicinal plants. However, few of them were isolated from tropical plants⁴². In forest, the distribution of endophytic microbes is strong correlated with canopy density (the ratio of canopy coverage area to surface area) and crown height. Plant crowns with high density and uniform closeness possess more endophytes than those with the open, bare and mixed⁴³. As far as the same host concerned, environment also determines the composition of endophytic microbes⁴⁴.

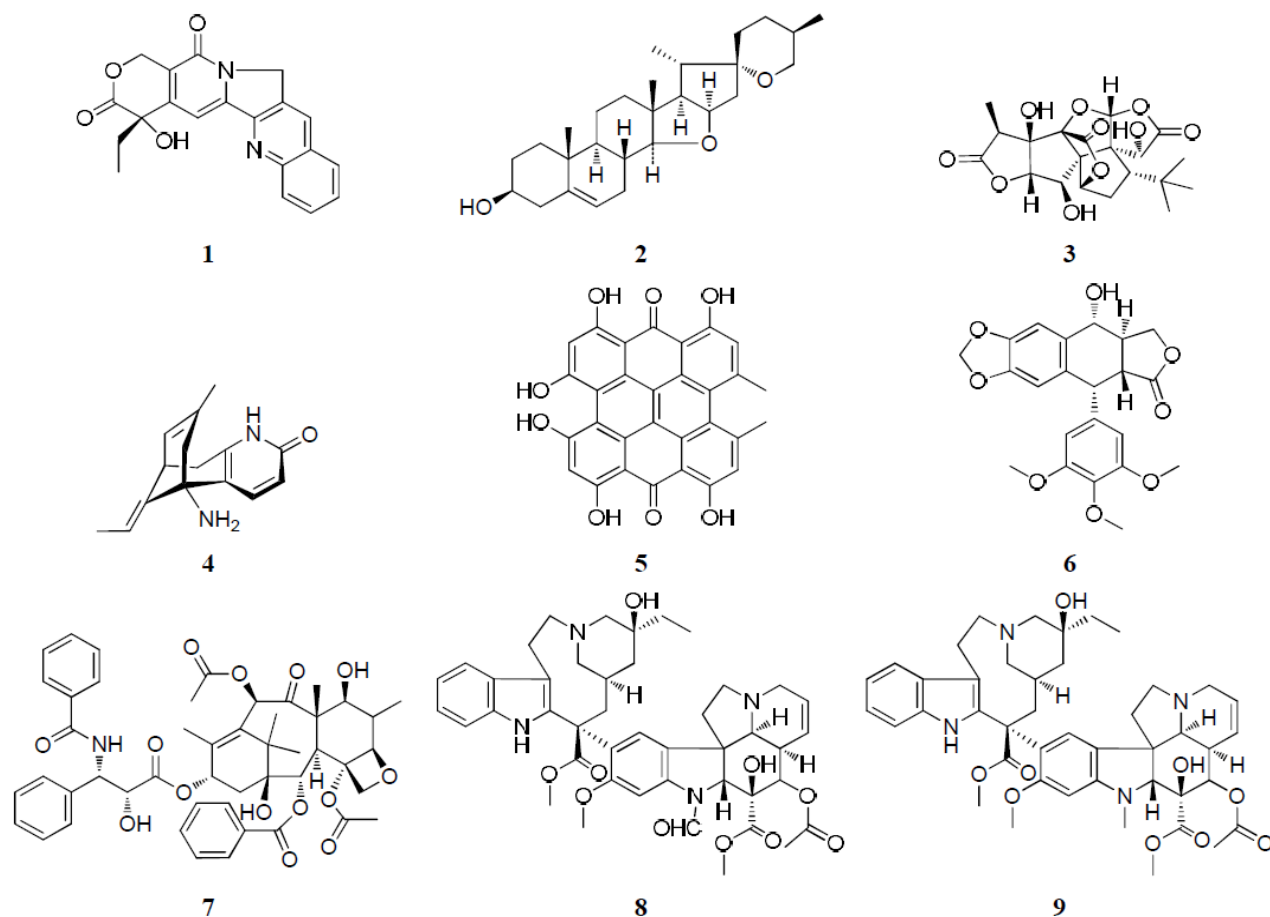


FIGURE 1: CHEMICAL STRUCTURES OF THE ENDOPHYTE-PRODUCING VALUABLE COMPOUNDS ORIGINALLY FROM THEIR HOST PLANTS

According to the study carried by Suryanarayanan and Vijaykrishna⁴⁵, the assemblage of the root growing in the soil was found to increase significantly when compared to the root growing in the air. At the same time, it showed that the soil could serve as reservoir for some endophytes.

Species, tissues and ages of medicinal plants also affect endophytic distribution^{46, 47}. Due to the result of the adaptation to different physiological conditions in host plants, endophytic microbes exhibit species, organ and tissue specificity. Wei isolated 16 *Pestalotiopsis* spp. from *Podocarpus macrophylla*, 7 species from *Camellia sasanqua*, 5 from each of *C. nitidissima* Chi, *C. sinensis* and *Podocarpus nagi*, 4 in *C. japonica*, 3 in each of *C. oleifera*, *Taxus yunnanensis* and *T. chinensis* var. *mairei*, and 2 in *C. reticulata*⁴⁸. The colonization frequencies of endophytic *Pestalotiopsis* in leaves of *C. japonica*, *C. nitidissima*, *C. sasanqua*, *C. sinensis*, *P. macrophyllus*, *P. nagi* and *Taxus*

chinensis var. *mairei* were less than 2%, and those in *C. oleifera* and *T. yunnanensis* were as much as 18.9% and 29.6%, respectively. The colonization frequencies of endophytic fungi in twigs were relatively higher than those in leaves. According to the results of research on *Ficus benghalensis*⁴⁵, the number of endophytic species in the lamina and the petiole was nearly same, while the number of isolates was lower in aerial root than that in leaf tissues.

The similar results found in Douglas fir⁴⁹, Oregon white oak⁵⁰ and *Azadirachta indica* A. Juss^{51, 52} suggest that the aged tissues harbor more endophytes than the young. The species richness and diversity of endophytic fungi are significantly affected by plant tissue. Li et al⁵³ isolated 54 species of endophytic fungi from roots, stems and leaves of *Erigeron breviscapus*, which *Fusarium* sp. and *Alternaria* sp. were the dominant.

Endophytic *F. solani*, *F. venfricosum* and *Acremonium* spp. could be found in roots of *Dendrobium loddigesii* Rolfe while only *Colletotrichum* spp. inhabited in its leaves⁵⁴. The species richness was 1.2 2.5-folds higher in the branches and barks of *Taxus chinensis* var. *mairiei* than that in the leaves⁵⁵. The richness index of endophytic microbes was also increased with the growth age of their host plant^{56,57}.

Biological Diversity:

Medicinal plants are a rich source of endophytic microbes. According to statistical data made by Sun and his co-workers, the species number of endophytic fungus from medicinal plants reaches up to 171 till 2006, including Ascomycetes, Basidiomycetes, Zygomycetes, Oomycetes, mitotic spore fungi and no spore fungi⁵⁸.

Endophytic Bacteria: Endophytic bacteria from medicinal plants were rarely reported. During these years, however, there has been an increasing tendency of reports that endophytic bacteria were discovered in medicinal plants, such as *Astragalus membranaceus* var *mongholicus*⁵⁹, *Codonopsis pilosula*⁵⁹, *Fructus forsythiae*⁵⁹, *Platycodon grandiflorum*⁵⁶, *Taxus chinensis*⁶⁰.

Endophytic Actinomycetes: Actinomycetes had been found to produce more than 50,000 bioactive secondary metabolites, such as antibiotics, antitumor agents, immunosuppressive chemicals and enzymes. So, more attention had been paid on isolating actinomycetes from different resources. Endophytic actinomycetes from medicinal plants, however, were rarely reported by comparison with those from soil and marine. Forty-one endophytic actinomycetes from 13 medicinal plants (*Alisma orientalis*, *Aucklandia lappa*, *Chrysanthemum morifolium*, *Curcuma longa*, *Curcuma wenyajin*, *Cyathula officinalia*, *Ligusticum chuanxiong*, *Ophiopogon japonicus*, *Platycodon grandiflorum*, *Polygonatum cyrtoneura*, *Pueraria lobata*, *Rhodiola crenulata*, *Salvia miltiorrhiza*) were classified into two genera *Streptomyces* and *Micromonospora* using genotypic approaches⁶¹.

An actinomycete strain YIM60475^T was isolated from the roots of *Maytenus austroyunnanensis*, a traditional Chinese medicinal plant. On the foundation of phenotypic and phylogenetic

characteristics, the strain was belonged to the genus *Streptomyces*. Through DNA-DNA hybridization and comparison of physiological and chemical characteristics indicated that the strain was a new and named as *Streptomyces mayteni* sp. nov.⁶².

Endophytic Fungi: Endophytic fungi are ubiquitously distributed in medicinal plants. To date, numerous studies of their biodiversity from medicinal plants had been reported, such as *Huperzia serrata*⁶³, *Orchid* sp.⁵⁴. Ma et al successfully isolated 22 species of taxol-producing endophytes from 12 yews, among of them, *Taxomyces andreanae* and *Nodulisporium sylviforme* were determined as new species⁶⁴.

It suggested that endophytes from medicinal plants are valuable and have great potential application in biopharmacy. 48 fungal strains were isolated from roots, leaves and stems of *Dendrobium loddigesii* Rolf⁵⁴. By using morphological and molecular biological methods, these endophytic fungi were classified into 18 genera. Among these isolates, *Fusarium* and *Acremonium* were dominant species. A total of 116 fungi were isolated and characterized from the bark, branches, leaves and roots of healthy *Taxus globosa* based on morphological characteristics through phylogenetic analysis of their 28S rDNA sequences⁶⁵.

The results suggested that 57 fungal strains belonged to Ascomycota (77.2%) and Basidiomycota (22.8%) and had twelve species, including *Coniochaetales*, *Eurotiales*, *Hypocreales*, *Phyllachorales*, *Pleosporales*, *Pezizales*, *Sordariomycetidae*, *Sordariales*, *Trichosphaeriales*, *Xylariales*, *Agaricales* and *Polyporales*. The taxa *Alternaria* sp., *Aspergillus* sp., *Cochliobolus* sp., *Coprinellus domesticus*, *Hypoxylon* sp., *Polyporus arcularius*, *Xylaria juruensis* and *Xylariaceae* were the most frequently isolated strains. The genera *Annulohypoxylon*, *Cercophora*, *Conoplea*, *Daldinia*, *Lecythophora*, *Letendreaea*, *Massarina*, *Phialophorophoma*, *Sporormia*, *Xylomelasma*, *Coprinellus*, *Polyporus* and *Trametes* were the first time isolated from yews. By analyzing sporulation, ITS sequence and phylogenetic analysis, 2861 endophytic fungi derived from 69 leaves of *Cinnamomum camphora* were grouped into 39 taxa, including 36 *Ascomycetes* and 3 *Basidiomycetes*⁶⁶.

A total number of 401 culturable fungal endophytes were isolated from 10 *Dendrobium* medicinal plants (Orchidaceae) and were found that *Dendrobium*, *Acremonium*, *Alternaria*, *Ampelomyces*, *Bionectria*, *Cladosporium*, *Colletotrichum*, *Fusarium*, *Verticillium* and *Xylaria* were the dominant genus⁶⁷. Based on morphological characteristics and 18S rRNA gene sequence, a novel endophytic fungus was identified as *Colletotrichum gloeosporioides* from *Vitex negundo* L.⁶⁸. Kharwar et al isolated 149 endophytic fungi from *Adenocalymma alliaceum* Miers, a traditional Brazilian medicinal plant used to treat colds, fevers and headaches⁶⁹.

Among these isolates grouped into 17 fungal species, *Alternaria alternate*, *Aspergillus niger*, *Stenella agalis*, *Fusarium oxysporum*, *Curvularia lunata* and *Fusarium roseum* were the dominant species. A survey of the endophytic fungi from *Pinus tabulaeformis* in northeast China indicated that approximately 11% of isolates did not produce spores. Based on similar cultural characters, other endophytic fungi were grouped into 74 morphotypes and were further identified as Basidiomycota and Ascomycota based on phylogenetic analysis of the 5.8S gene and internal transcribed spacer (ITS1 and ITS2) regions as well as sequence similarity comparison⁷⁰.

Chemical Diversity: According to endosymbiotic theory, endophytes from medicinal plants could metabolize the same or similar active phytochemicals as their hosts during the course of mutualistic symbiosis⁶⁹. Biological diversity of endophytes from medicinal plants determines their chemical diversity. As one of rich sources of bioactive natural products, endophytic microbes from medicinal plants have potential application in development of new drugs and biocontrol agents^{54, 71, 72}.

Microbiologist Schutz affirmed that the probability of discovering a new compound derived from endophytes could reach up to 51%, while the probability was only 38% from soil-derived microbes⁷³. To date, over 2,000 natural products have been isolated from endophytes associated with medicinal plants, including alkaloids, steroids, terpenes, coumarins, quinones, lactone, polysaccharide, peptides.

Biological assays indicated that the culture broth of endophytes and/or their secondary metabolites had a broad spectrum of functions. Based on bioactivity in the important fields of indication, their chemical diversity of was summarized below.

Antitumor substances: The discovery of the taxol-producing endophytic fungus *Taxomyces andreanae* from the pacific yew *Taxus brevifolia* had set the stage for exploring the natural secondary metabolites from the endophytes^{3, 64}. Till now, many other taxol-producing endophytic fungi were also been identified from medicinal plants besides *Taxus* sp., such as *Pestalotiopsis breviseta* from *Adenocalymma alliaceum* Miers⁷⁴, *P. microspora* from Theaceae⁴⁸, *P. pauciseta* VM1 from *Tabebuia pentaphylla*⁷⁵ and *Periconia* sp. from *Torreya grandifolia*⁷⁶. An endophytic *Myrothecium Cda.* in the fruit of *Camptotheca acuminata* was found to make camptothecin analogues⁷⁷.

Three new cytotoxic 22-oxa-[12]-cytochalasins **10-12 (Figure 2)** were isolated from a culture of endophytic *Rhinochrysiella* sp. '309' colonizing in *Tripterygium wilfordii* (family Celastraceae), a viney medicinal plant used to treat arthritis and other autoimmune diseases⁷⁸. In addition to secondary metabolites from endophytic fungi, some extracts of fermentation broth of endophytes were shown to be toxic to cancer cells. For example, the CHCl₃ extract of *Pantoea agglomerans* from *Prunella vulgaris* had potent activity against liver cancer cell line Hep G2 with an IC₅₀ of 0.12 µg/mL⁷⁹.

Antimicrobial chemicals: Numerous medicinal plants had been reported to possess antimicrobial endophytes, such as *Astragalus membranaceus*⁵⁸, *Cinnamomum tonkinense*⁸⁰, *Cinnamomum zeylanicum*⁸¹, *Colletotrichum* sp.⁸², *Ginkgo biloba* L.⁸³, *Lippia sidoides* Cham.⁵⁷, *Opuntia ficusindica* Mill⁸⁴, *Tripterygium wilfordii*⁸⁵, *Torreya grandis*⁸⁶, *Thevetia peruviana*⁸⁷, et al. An endophytic *Streptomyces* NRRL30562 from *Kennedia nigricans* was found to produce four new oligopeptides, munumbicins A, B, C and D⁸⁸. These compounds had a wide spectrum of activities against many human as well as plant pathogenic fungi and bacteria, and a *Plasmodium* sp.

Metabolites made by a new endophyte *Colletotrichum gloeosporioides* from *Vitex negundo* Linn. exhibited strong activity against multidrug-resistant *Staphylococcus aureus* with a minimal inhibitory concentration of 31.25 µg/mL⁶⁸. Of all 28 fungal endophytes from *Aquilaria sinensis*, 18 strains exhibited strong inhibitory effects on *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Aspergillus fumigatus*⁸⁹. An endophytic *Phoma* sp. ZJWCF006 associated with a traditional Chinese medicine *Arisaema erubescens*, was shown to produce four antibiotics, (3*S*)-3,6,7-trihydroxy- α -tetralone **13**, cercosporamide **14**, β -sitosterol **15** and trichodermin **16** (**Figure 2**)⁹⁰. Two endophytic fungal strains, HAB10R12 and HAB11R3, isolated from Malaysian medicinal plants had potent inhibitory effects on bacterial and fungal pathogens, which were comparable to a number of current commercial antibacterial and antifungal agents⁹¹.

Plant hormones: Endophytic microbes play an important role in promoting growth of their hosts through secreting phytohormones. An endophytic fungus *Colletotrichum* sp. from *Artemisia annua*, a traditional Chinese medicine makes artemisinine, was found to produce heteroauxin **17** (**Figure 2**)⁸². Two endophytic strains, *Methlovorus mays* and *Methylobacterium mesophilicum*, had a tendency to synthesize and excrete cytokinins, including heteroauxin **17**, gibberellin **18**, abscisin **19**, zeatin **20** and its riboside **21** (**Figure 2**)⁹².

Antioxidant agents: Four endophytic fungi from a medicinal plant, *Dioscorea opposita*, were shown to have strong antioxidant activities⁹³. Wu et al firstly reported two antioxidant-producing actinomycetes, *Amycolatopsis* sp. A00066 and A00089, which were respectively isolated from *Camptotheca acuminata*, *Taxus chinensis*⁹⁴. In addition to make an anticancer agent lapachol **22** (**Figure 2**), two endophytic strains *Aspergillus niger* and *A. alternate* colonized in *Tabebuia argentea* exhibited strong antioxidant capacity for their metabolizing high level of phenolics⁹⁵. Four endophytic strains *Fusarium* sp., *Sphaeriothyrium* sp., *Penicillium* sp. and *Arthrimum* sp. from *Rhododendron tomentosum* Harmaja were found to

produce more antioxidant compounds in enriched media⁹⁶.

Antithrombotics: Six secondary metabolites lumichrome **23**, genistein **24**, daidzein **25**, cyclo-Pro-Val **26**, cyclo-Pro-Phe **27** and methyl 2,4,5-trimethoxybenzoate **28** (**Figure 2**) produced by an endophytic strain *Rahnella aquatilis* from Taiwanese herbal plant *Emilia sonchifolia* were shown to have notable inhibitory effects on platelet aggregation⁷⁹. Another endophytic *Fusarium* sp. CPCC 480097 was found to produce an antithrombotic substance, 28 kDa single-chain fibrinolytic enzymes, which could inhibit the transformation of fibrinogen to fibrin⁹⁷.

Insecticides: An insect repellents, naphthalene **29** (**Figure 2**), which was produced by a novel endophytic fungus *Muscodar vitigenus* from *Paullinia paullinioides* growing in the understory of the rainforests of the Peruvian Amazon⁹⁸. An endophytic strain *Geotrichum* sp. AL4 associated with *Azadirachta indica* was reported to make two new chlorinated epimeric 1,3-oxazinane derivatives **30-31** (**Figure 2**), which exhibited inhibitory activity against two nematodes, *Bursaphelenchus xylophilus* and *Panagrellus redivevus*⁹⁹.

Other bioactive substances: Other bioactive metabolites of endophytes from medicinal plants were also reported. Two new immunosuppressive compounds, subglutinols A **32** and B **33** (**Figure 2**), were isolated and identified from an endophytic *Fusarium subglutinans* associated with *Tripterygium wilfordii*¹⁰⁰. A new neuroprotective alkaloid chrysogenamide A **34** (**Figure 2**) was obtained from an endophytic *Penicillium chrysogenum* associated with *Cistanche deserticola*¹⁰¹.

Research Prospect: There are about 100,000 species of medicinal plants on the earth. Endophytic microbe is ubiquitous in medicinal plants. Up to now, however, no more than 500 species had been worldwide investigated. Furthermore, 15,000 medicinal plants are at risk from habitat destruction, overharvesting and big business. So, it is urgent to take efficient methods to protect these endangered plants and study their endophytic association.

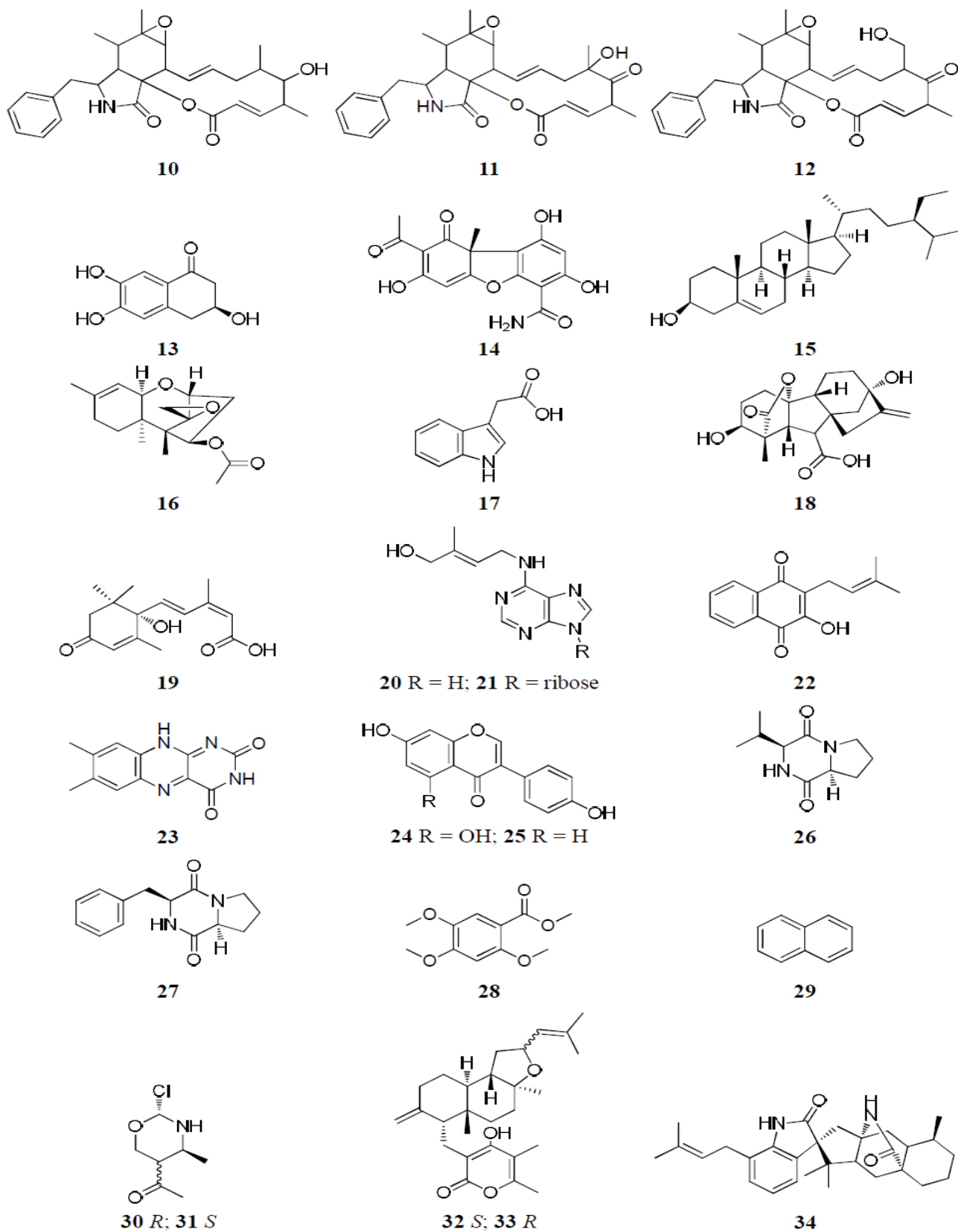


FIGURE 2: CHEMICAL STRUCTURES OF BIOACTIVE COMPOUNDS FROM ENDOPHYTES ASSOCIATED WITH MEDICINAL PLANTS

Microbiologists Ganley¹⁰² and Petrini¹⁰³ believed that endophytic species is over one million. As a special kind of microorganism, endophytes could produce abundant bioactive metabolites with potential application in medicine and agriculture. So, endophytes from medicinal plants have a broad prospect in the future.

During the past three decade, great successes had been achieved in the study of endophytic microbes. However, the possibility of industrial production of bioactive metabolites from endophytes is still low. For example, the yields of taxol from three endophytic *Metarhizium anisopliae*, *Bartalinia robillardoides*, *Colletotrichum gloeosporioides* were respectively as much as 846.1 µg/L¹⁰⁴, 164.3 µg/L¹⁰⁵, 187.6 µg/L¹⁰⁶. This output was too low to carry out commercial production. In addition, methods used to isolate endophytes from medicinal plants especially the new and unculturable microbes should be improved. Identification of endophytic microorganisms should combine phylogentic analysis with the traditional approaches, including microscopic analysis of morphological characteristics.

Both chromatographic and spectroscopic techniques are applied to investigate endophytic chemical diversity, such as high performance liquid chromatography (HPLC), 1D- and 2D- nuclear magnetic resonance (NMR) and so on. In addition, secondary metabolites of endophytic microbes from medicinal plants should be biologically assayed using various testing models and their biosynthetic pathways should be clarified at molecular and gene level.

CONCLUSION: Medicinal plants are a precious source of endophytic microbes which possess abundant biological and chemical diversity. These endophytes not only make the same bioactive compounds originally from their host plants but also have the ability to produce more novel chemicals with potent bioactivities. They have become a rich source of natural products, which some of them could be used as new drug candidates and agrochemicals.

Therefore, it is very important to pay more attention on the studies of biology and chemistry of endophytes from medicinal plants.

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