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Bioactive Natural Products from Endophytes: A Review[1]

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Abstract—Endophytes, microorganisms that reside in the internal tissues of living plants without causing any immediate overt negative effects, have been found in every plant species examined to date and recognized as potential sources of novel natural products for exploitation in medicine, agriculture, and industry with more and more bioactive natural products isolated from the microorganisms. In this review, we focus mainly on bioactive natural products from endophytic microorganisms by their different functional roles. The prospect and facing problems of isolating natural products from endophytes are also discussed.

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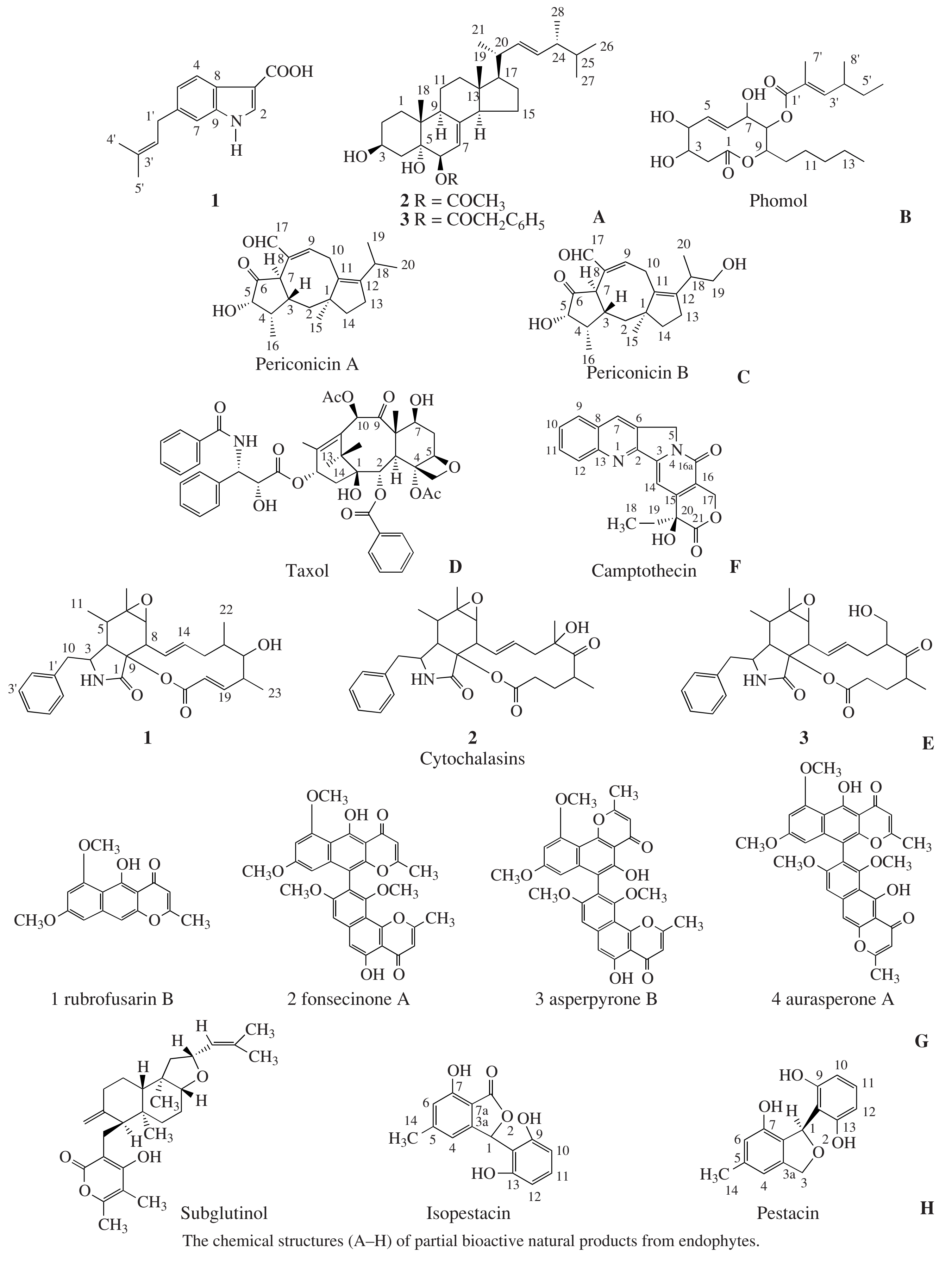
An undenied fact is that, worldwide, people are being threatened by more and more advent diseases such as cancers, AIDS, SARS, bird flu, etc., accompanied with an increasing extent of environmental degradation, loss of biodiversity, and spoilage of land and water caused by excessive toxic organic insecticide, industry sewage, and poisonous gases. Therefore, it is a must for isolating of new and beneficial compounds to provide assistance and relief in all aspects of the human condition. Endophytes, a microorganism that reside in the internal tissues of living plants without causing any immediate overt negative effects, are relatively unstudied and potential sources of novel natural products for exploitation in medicine, agriculture, and industry [1, 2]. Endophytes are ubiquitous with rich biodiversity, which have been found in every plant species examined to date. It is noteworthy that, of the nearly 300000 plant species that exist on the earth, each individual plant is the host to one or more endophytes [2]. In view of special colonization in certain hosts, it is estimated that there may be as many as 1 million different endophyte species, however only a handful of them have been described [3], which means the opportunity to find new and targeting natural products from interesting endophytic microorganisms among myriads of plants in different niches and ecosystems is great. Endophytes are the chemical synthesizers inside plants [4]. Many of them are capable of synthesizing bioactive compounds that can be used by plants for defense against pathogens and some of these compounds have been proven useful for novel drug discovery. Recent studies have reported hundreds of natural products including substance of alkaloids, terpenoids, flavonoids, steroids, etc. from endophytes. Up to now, most of the natural products from endophytes are antibiotics, anticancer agents, biological control agents, and other bioactive compounds by their different functional roles. In this review, we focus mainly on bioactive natural products from endophytic microorganisms by their different functions. The prospect and facing problems of isolating natural products from endophytes are also discussed here.

[1] The text was submitted by the authors in English.

ANTIBIOTICS FROM ENDOPHYTES

Antibiotics, defined as low-molecular-weight organic natural products made by microorganisms that are active at low concentration against other microorganisms [5], are the most bioactive natural products isolated from endophytes. Strobel and Daisy have summarized the discovery of antibiotics from the first discovery of penicillin to most of the novel antibiotics isolated from endophytes up to 2003 [2]. Many of them are proved to be of importance. Take three new antimicrobial metabolites isolated from the culture of *Colletotrichum* sp. [6], for example, *Artemisia annua* is a traditional Chinese herb that is well recognized for its synthesis of artemisinin (an antimalarial drug). The three new metabolites isolated from the culture of *Colletotrichum* sp. in *A. annua* were detected to not only have activity against human-pathogenic fungi and bacteria but also be fungistatic to plant-pathogenic fungi, and their structures were elucidated by a combination of spectroscopic methods (IR, MS, ^{1}H, and ^{13}C NMR) as seen in Fig. 1a. In this review, further recent progress on endophytic antibiotics' researches is added. Ezra et al.



The chemical structures (A–H) of partial bioactive natural products from endophytes.

[7] reported that coronamycin, a complex of novel peptide antibiotics with activity against pythiaceous fungi and the human fungal pathogen *Cryptococcus neoformans*, produced by a verticillate *Streptomyces* sp. isolated as an endophyte from an epiphytic vine *Monstera* sp. It was also active against the malarial parasite, *Plasmodium falciparum*, with an IC50 (inhibitory concentration 50%) of 9.0 ng ml^{-1}.

Weber et al. [8] found another novel antibiotic-phomol, isolated from fermentations of an endophytic fungus *Phomopsis species* from the medicinal plant *Erythrina crista*. This compound was characterized to be a polyketide lactone and its structure was elucidated by spectroscopic methods (Fig. 1b). Also in 2004, two new fusicoccane diterpencs, named pcriconicins A and B, with antibacterial activities were isolated by bioassay-guided fractionation from an endophytic fungus P*ericonia* sp., collected from small branches of *Taxus cuspidata*. The structures of the new compounds were determined by combined spectroscopic methods (Fig. 1c) [9].

Most recently, another two antibiotics, pyrrocidines A and B, have been reported by chemical studies of an organic extract from maize kernel fermentations of *Acremonium zeae* (NRRL 13540), which displayed significant antifungal activity against *Aspergillus flavus* and *Fusariwn verticillioides*. Wicklow et al. revealed that the metabolites accounting for this activity were two antibiotics pyrrocidines A and B [10].

Castillo et al. [11] studied a solvent extract of the crude fluid from cultures of Streptomyces NRRL 30562, an endophyte isolated from snakevine and found that the solvent extract possessed wide-spectrum antibiotic activity. Mass spectrometric analyses of the extracted peptide antibiotics showed that they had identical masses (1445) but different retention times on HPLC. All compounds showed activity against gram-positive and gram-negative bacteria, and the plant pathogenic fungus *Pythium ultimum* was found to be sensitive to these novel antibiotics. Besides the above mentioned endophytic microorganisms and their antibiotic natural products, there are a plethora of endophytes, with no certain compound isolated, having been reported to show antibiotic activities against tested microorganisms. In order to develop the endophytic fungi from medicinal plants of family Euphorbiaceae, Dai et al. [12] screened the endophytic fungi from four kinds of medicinal plants of family Euphorbiaceae and detected the antibacterial activity of these strains. Their results indicated that 11 strains of a total of 43 (25.58%) belonged to *Alternaria* spp., *Fusarium* spp., *Chaetomium* spp., *Coniothyium* spp., and *Phomopsis* spp. showed the steadiness antibacterial activity against tested bacterium such as *Staphylococcus aureus* and *Bacillus subtilis* etc. In 2005, Zeng et al. [13] tested antibiotic activity of 24 isolates of endophytic fungi isolated from the rhizomes of *Polygonum cuspidatum* through antimicrobial experiments in vitro. The result showed that three isolates of them identified as *Aspergillus, Penicillium*, and *Mycetia sterillia* were able to produce antibiotic active substances, but with no further study of what these substances were. In 2006, by studying the bioactivity of the endophytic fungi isolated from *Sinopodophyllum hexandnim* and *Diphylleia sinensis,* Wang et al. [14] found that most of the cultured broths of the endophyte strains have different bioactivities. The strains of highest bioactivity mainly belong to *Fusarium, Cylindrocarpon, Trichoderma* and *Torula*. The endophytic fungi isolated from *Sinopodophyllum hexandnim* have higher antifungal activity while the fungi isolated from *Diphylleia sinensis* have higher bioactivity of antibacterium and antibrine shrimp. These reported endophytes provide potential good resources to isolate valuable bioactive substances.

ANTICANCER AGENTS FROM ENDOPHYTES

Undoubtedly, one of the most surprising findings of endophyte studies is the isolation of taxol-producing endophyte *Taxomyces andreanae* [15]. The diterpenoid taxol (Fig. 1d) has been approved by FDA as one of the most potent anticancer drugs, but the supply of this drug has been limited for the destructive collection of yew tree, the main source of taxol. The finding of *Taxomyces andreanae* provides another alternative approach for taxol production by microorganism fermentation. Since then, several research groups successively have reported their findings on taxol-producing endophytes [16–19]. Recently, an endophytic fungus strain BT2 from *Taxus chinensis* var. *mairei* has been isolated by our research group. This endophyte was detected to produce taxol and its precursor taxane baccatin III by HPLC and LC-MS, and the extract of the endophytic cultures was shown to have strong toxicity to liver cancer cells 7402 and lung cancer cells A549 [20].

As a selectively cytotoxic quinone dimmer, torreyanic acid is another important anticancer agent. Lee et al. [21] reported the isolation of an endophyte strain *P. microspore* from *T. taxifolia* (Florida torreya) and the extraction of torreyanic acid from cultures of this endophyte. After being tested in several cancer cell lines, the isolated torreyanic acid was demonstrated to be 5 to 10 times more potent in those lines that are sensitive to protein kinase C agonists and causes cell death by apoptosis.

The alkaloids are other kinds of anticancer agents, usually found in endophytic fungi. Wagenaar et al. reported identification of three novel cytochalasins, bearing antitumor activity, from an endophyte *Rhinocladiella* sp. [22]. Extensive NMR and HRCIMS experiments identified these new compounds as 22-oxa-12-cytochalasins (Fig. 1e).

Puri et al. [23] established the methodology for isolation, identification, and characterization of a novel fungal endophyte (*Trametes hirsute*) that produces aryl tetralin lignans detected by HPLC, LC-MS, LC/MS-MS, and NMR. The lignans produced by the microorganism are biologically active, and exhibit potent antioxidant, anticancer, and radioprotective properties.

Camptothecin, the naturally occurring enantiomer (Fig. 1f), was first isolated by Wall et al. [24] from the wood of *Camptotheca acuminate* Decne (Nyssaceae), which is a plant native to mainland China. Camptothecin and its derivatives show strong antineoplastic activity. The drug is already used in China for the treatment of skin diseases. A fungal endophytic isolate, camptothecin, has been isolated from the inner bark of the plant *Nothapodytes foetida* from the western coast of India. The fungus, which belongs to the family Phycomycetes, produced the anticancer drug lead compound camptothecin when grown in a synthetic liquid medium (Sabouraud broth) under shake flask and bench scale fermentation conditions. The compound was identified by means of chromatographic and spectroscopic methods. The biological activity of this compound was tested using an in vitro cytotoxicity assay against human cancer cell lines (A-549 for lung cancer, HEP-2 for liver cancer, OVCAR-5 for ovarian cancer) in comparison with the standard authentic example, resulting in comparable activities [25].

BIOLOGICAL CONTROL AGENTS FROM ENDOPHYTES

With an aim at decreasing the extent of environmental degradation, loss of biodiversity, and spoilage of land and water caused by excessive toxic organic insecticide, industry sewage, and poisonous gases, biological control as a new efficient method, is becoming widely used in killing insects or pathogens, and environmental remediation. There have been many reports about endophytes being capable of producing antibiotics as we have mentioned above, which can be used instead of toxic organic compounds in preventing baneful microorganisms spreading. In addition, endophytes have also showed other bioactivities in biological control. Some recent research has been done showing that plant endophytes might be partially responsible for the degradation of environmental toxins. Van Aken [26] reported that a newly discovered organism *Methylobacterium populum* sp. nov., strain BJ001, existed as a plant endophyte and was involved in the degradation of energetic compounds such as 2,4,6-trinitrotoluene, hexahydro-1,3,5-trinitro-1,3,5-triazine, and hexahydro-1,3,5- trimtro-1,3,5-triazine. Newman and Reynolds [27] reported that plants inoculated with VM1330, an engineered endophyte, had been shown to increase plant tolerance to toluene and to decrease the transpiration of toluene to the atmosphere.

Although currently bioinsecticides only occupy a small amount of the insecticide market, this kind of biocompounds is becoming more and more widely used. Strobel and Daisy summarized several reported endophytic insecticides such as nodulisporic acid, benzofuran, and naphthalene [2]. Sumarah et al. [28] reported that white spruce needles colonized with the rugulosin-producing endophyte 5WS22E1 (DAOM 229536) contained rugulosin in detectable concentrations that impaired spruce budworm growth.

The basidiomycete fungus *Crinipellis pemiciosa* (Stahel) Singer, a causal agent of Witches' Broom Disease of cacao (*Theobroma cacao* L.) proved to be particularly difficult to control, is the main factor limiting cacao production in the Americas. Pod losses of up to 90% are experienced in affected areas as evidenced by the 50% drop in production in the Bahia province, Brazil following the arrival of the *C. perniciosa* in the area in 1989. In order to evaluate the potential of endophytes as a biological control agent of this phytopathogen, the endophytic fungal community of resistant and susceptible cacao plants as well as affected branches was studied by Rubini et al. [29]. The fungal community studied by Rubini et al. was identified by morphological traits and rDNA sequencing as belonging to the genera *Acremonium, Blastomyces, Botryosphaeria, Cladosporium, Colletotrichum, Cordyceps, Diaporthe, Fusarium, Geotrichitm, Gibberella, Gliocladium, Lasiodipiodia, Monilochoetes, Nectria, Pestalotiopsis, Phomopsis, Pleurotus, Pseudofusarium, Rhizopycnis, Syncephalastrum, Trichoderma, Verticillium,* and *Xylaria*. These fungi were evaluated both in vitro and in vivo by their ability to inhibit *C. perniciosa*. Among these, some were identified as potential antagonists with one fungus *Gliocladium catenulatum* alone reducing the incidence of Witches' Broom Disease in cacao seedlings to 70% [29].

In most cases the relationship between endophytes and the host plants is symbiotic and probably mutualistic. The endophytes gain shelter, nutrition, and dissemination via host propagules, and on the other hand, the colonization and propagation of endophytes may in some ways offer significant benefits to their host plants by producing a plethora of bioactive substances that provide protection and survival value to the plants, such as enhancement of stress-, insect-, and disease-resistance, productivity improvement, and herbicide activities [30].

These facts indicate that endophytes play an important role in the ecological community. But how does it work? This is a hot issue and is worthy of further study for biologists worldwide. Many endophytes are reported to be capable of fixing nitrogen [31–35] and plants infected by endophytes are also proved to enhance uptake of phosphorus, another important element for plant growth [36, 37]. In addition, endophytes can produce a substance of plant hormones such as auxin and IAA, which is a must for plant growth and development regulation [38]. Verma et al. [39] discovered a plant-root-colonizing basidiomycete fungus *Piriformospora indica* in the Indian Thar Desert, which was shown to provide strong growth-promoting activity during its symbiosis with a broad spectrum of plants. In 2005, Frank Waller et al. [40] reported on the potential of *Piriformospora indica* to induce resistance to fungal diseases and tolerance to salt stress in the monocotyledonous plant barley. The beneficial effect on the defense status was detected in distal leaves, demonstrating a systemic induction of resistance by a root-endophytic fungus. The systemically altered "defense readiness" was associated with an elevated antioxidative capacity due to an activation of the glutathione-ascorbate cycle and results in an overall increase in grain yield. Consequently, they concluded that because *P. indica* could be easily propagated in the absence of a host plant, the fungus could be exploited to increase disease resistance and yield in crop plants.

OTHER BIOACTIVE COMPOUNDS FROM ENDOPHYTES

Among natural products isolated from endophytes, there are other bioactive compounds which have special or more than one kind of function different from those reported above. In 2004, Song et al. [41] reported that they obtained four known compounds naphtho-γ-pyrones rubrofusarin B, fonsecinone A, asperpyrone B, and aurasperone A (Fig. 1g) from fractionation of the extract of *Aspergillus niger* IFB-E003, an endophyte in *Cyndon dactylon*. Rubrofusarin B was shown to be cytotoxic to the colon cancer cell line SW1116 (IC5O: 4.5 μg/ml), and aurasperone A, inhibitory on xanthine oxidase (XO) (IC50: 10.9 uM). Moreover, the four naphtho-γ-pyrones exhibited growth inhibitions against the five test microbes with minimal inhibitory concentrations (MICs) ranging in between 1.9 and 31.2 μg/ml. The present recognition of rubrofusarin B and aurasperone A as strong coinhibitors on XO, colon cancer cell, and some microbial pathogens is of significance for the imperative discovery of new relevant therapeutic agents. Other special functional bioactive natural products such as pectin lyase, immunosuppressive agent subglutionol (Fig. 1h), antioxidants pestacin and isopestacin (Fig. 1), antidiabetic and antiviral agents, etc. are listed in the table. These natural products with special functions expand endophytes use arenas.

THE PROSPECT AND FACING PROBLEMS OF ENDOPHYTES AND THEIR NATURAL PRODUCTS

With the accelerating knowledge accumulation concerning symbionts, endophytes have been demonstrated to be a rich and reliable source of biological active and/or chemically novel compounds that may foster great medicinal or agricultural potentials [47]. But we finally have to say that although studies on endophytes have been widely carried out for a long time and the progress is inspiring, problems still exist in the following areas:

—The natural products isolated from endophytes are usually too low to be detected and characterized, especially more difficulty in unknown substances.

—Many endophytes have been proved to show diversiform bioactivities such as antimicroorganisms, plant growth, tolerance enhancement, etc., but what the certain compound acts is seldom isolated and characterized.

—Up to now, most studies on endophytes have been conducted by cultivation. However, the actual diversity of endophyte colonizing plants is inevitably decreased for not all of endophytes can be cultured by this approach, which means the chance of obtaining natural products from these uncultured endophytes is limited.

Meanwhile, in view that some plants generating bioactive natural products have associated endophytes that produce the same natural products [15–17, 20, 48, 49] and the fact of the short generation time and high growth rate of microbes, the endophyte has become a good choice for functional substances production in a wide variety of medical, agricultural, and industrial arenas. In addition, among the vast plant kingdom, only a handful of plant species colonized by endophytes have been studied. The successive researches on most other plant resources will surely give more surprises of bioactive and chemically novel compounds, and more and more isolated endophytes will enrich the microorganisms' biodiversity. Furthermore, the study of mechanisms through which endophytes exist and respond to their surroundings and a closer relationship between

Endophytes and their produced natural products with special functions

Metabolite	Endophyte	Host	Function	Reference
Naphthopyrone metabolites	*Aspergillus niger*	*Cyndon dactylon*	Co-inhibitors of xanthine oxidase, SW1116 cell and some microbial growths	[41]
Subglutionol	*Fusarium subglutinans*	*Triptergium wilfordii*	Immunosuppressive	[42]
Nonpeptid L-783, 281	*Pseudomassaria* sp.	Africanan rainforest	Antidiabetic agent	[43]
Cytonic acids	*Cytonaema* sp.	unreported	Antiviral agent	[44]
Pectin lyase	*Paenibacillus amylolyticus*	*Coffea arabica*	Pectin lyase activity	[45]
Pestacin, isopestacin	*Pestalotiopsis microspora*	*Terminalia morobensis*	Antioxidant	[46]

endophytes and their hosts must be further strengthened and investigated for better understanding of the roles of endophytes.

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