

Endophytes: a potential resource for biosynthesis, biotransformation, and biodegradation

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Abstract In natural ecosystems, endophytes, which live in the inner tissues of healthy plants, exhibit complex interactions with their hosts. During a long coevolutionary process with their hosts, endophytes have developed many significant and novel characteristics. In order to maintain a stable symbiosis, endophytes secrete varieties of extracellular enzymes that contribute to colonization and growth. All these specific enzymes, under certain conditions, could be exploited. Nowadays, more and more complex chemical reactions are being replaced by moderate and pollution-free enzymatic reactions. Bacteria have been widely used in bioengineering, but endophytes, as a kind of organism, have not been fully developed. Therefore, great efforts to develop endophyte resources could bring us a variety of benefits, such as novel and effective bioactive compounds that cannot be synthesized by chemical reactions. It is noteworthy that, after long-term coexistence with hosts, endophytes can synthesize biologically active substances similar to the secondary metabolites produced by host plants. This could help us to accumulate many valuable drug compounds such as paclitaxel and camptothecin in a short time period. In addition, endophytes are widespread in plant roots; they can deeply affect soil chemical composition, micro-ecosystems, and physical structure over their life cycle. Besides that, endophytes play an important role in the degradation of plant litter and organic pollutants, which have an active effect on the improvement of soil

fertility. Endophytes are a most promising microbial resource, waiting to be exploited.

Keywords Endophytes · Resource · Biosynthesis · Biotransformation · Biodegradation

Introduction

Endophytes are bacterial or fungal microorganisms that colonize healthy plant tissue intercellularly and/or intracellularly without causing any apparent symptoms of disease (Wilson 1995). They have been isolated from almost every host plant studied so far. The relationship between endophytes and host plants involves both mutualism and antagonism; both of them benefit from the interactions, but they have to establish a harmonious symbiotic system. Plants strictly limit the growth of endophytes, and endophytes use many mechanisms to gradually adapt to their living environments. The potential for biotransformation and a set of specific enzymes could allow them to survive and reproduce (Zikmundova et al. 2002). Endophytes have a powerful ability to transform complex compounds. In addition, experiments have confirmed that, after they have coexisted for a long time, endophytes can produce effective bioactive substances from their host plants *in vitro*, especially when active ingredients are extracted from the host plants subject to a variety of constraints.

It is worth noting that fungi endophytes also have the ability to utilize various organic compounds such as carbon sources, which enables them to play an important role in the degradation of structural components, such as plant leaf litter and wood (Osono and Takeda 2001), and that some fungi with marked decomposing abilities are associated with ligninolytic activity (Urairuj et al. 2003). In addition, it

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has been shown that they have the potential to decompose environmental pollutants and to improve the soil micro-environment (Xiao et al. 2010).

The review is divided into the following sections. First, we summarize the relationships between endophytes and their hosts. In the second section, we briefly introduce the active metabolites produced by endophytes. Then, we focus on the biotransformation and degradation abilities of endophytes.

Relationships between endophytes and their host plants

Endophytes have diverse interactions with their plant hosts. Dark septate endophytes (DSE) within the roots of the hosts are termed endophytic. Some endophytic fungi or bacteria that colonize the roots of herbaceous plants and trees are mutualistic; others inhabit solely above-ground plant tissues, and these may partake in varied and variable interactions with the plant hosts, ranging from symbiotic interaction to parasitism. Both types of associations are apparently asymptomatic and inconspicuous (Redman et al. 2001; Schulz et al. 1998; Strobel and Daisy 2003).

Endophytes and host plants have a relationship that is both mutualistic and antagonistic. Endophyte–host interactions are based on mutual exploitation. However, highly integrated symbioses require the morphological, physiological, and life history traits of the fungus and the host plant to be well matched in order to evolve and persist (Saikkonen et al. 1998). If one side breaks this balance, then the symbiotic relationship disappears.

From their coevolution with endophytes, hosts have received benefits such as increased resistance to herbivores, pathogens, drought, and flooding stress, as well as enhanced competitive abilities (Clay and Schardl 2002). Plant growth-promoting endophytic fungi and bacteria also showed nitrogen-fixing activities and secreted phytohormones such as indole-3-acetic acid (IAA) (Feng et al. 2006; Xin et al. 2009). All these could increase plant nutrition efficiently, thus favoring the plant's growth and yield (Barretti et al. 2008). Pan and Clay (2004) found that ^{14}C movement from labeled leaves was greater in infected plants than in non-infected plants. Studies on enzyme activities, concentrations of amino acids, and ammonium indicated that the interaction with endophytes significantly alters at least nitrogen metabolism.

These interactions are not only beneficial for hosts, but provide nourishment for endophytes. We propose that endophytes decompose some plant metabolites with ectoenzymes in order to obtain enough nutrition and energy to survive in the plant tissues. In addition, endophytes extensively colonize the host's roots and have potential for growth in the rhizosphere, which in turn could improve the host's mineral supply (Schulz et al. 2002).

It is worth noting that host plants will not tolerate uncontrolled growth of endophytes. They are likely to have particularly strong effects on the growth of these fungi. Plants have many mechanisms to limit the growth of endophytes, including producing a variety of toxic metabolites. It is well known that terpenoids serve in plant–fungus interactions as both constitutive and special induced chemical defenses (Jurc et al. 1999). Studies have proven that terpenes not only affect the diversity of leaf fungal communities but can also determine the extent of fungal colonization (Mucciarelli et al. 2007). But, over their long period of coevolution, endophytes have gradually formed a variety of tolerance mechanisms toward hosts' metabolites. They may degrade macromolecule compounds into small molecules or convert toxic substances to others in order to increase their adaptability. Our perspective is that, besides metabolites, some enzymes (e.g., hydrolase and protease) that exist in plant tissue fluids probably inhibit the growth of hyphae.

Interestingly, not only can plants exhibit defense reactions toward fungi but fungi can also be aggressive toward their hosts. There are several facets of fungal virulence (Costa et al. 2000; Peters et al. 1998). One is the secretion of exoenzymes to colonize a plant host, and another is the production of mycotoxins (Schulz et al. 2002).

In conclusion, endophytes and hosts both possess ecological advantages. The endophytes studied produce the exoenzymes necessary to infect and colonize hosts. Hosts can have the same defense reactions—preformed and induced defense-related enzymes and metabolites. Key elements for the evolution of the endophyte–plant symbioses are more complex, and involve multi-species and environment interactions that drive the life histories of coevolving fungi and host plants (Saikkonen et al. 2004).

Screening novel bioactive secondary metabolites from endophytes

Endophytes experience long-term symbiotic relationships with their host plants, and many of them may produce bioactive substances as part of these relationships; thus, we cannot ignore their applications for the production of bioactive substances. Worldwide scientific efforts to isolate endophytes and study their natural products are now under way.

It has been surmised that endophytes and hosts have similar pathways for synthesizing secondary metabolites due to gene transfer. That is to say, they live in the same habitat, and through long-term coexistence and direct contact, they have exchanged genetic material.

Endophytes are groups of microorganisms with the characteristics of diversity, complexity and specificity. We

believe that the structure types of active compounds produced by endophytes have been far beyond those produced by their host plants, and the former have become an important source of novel biologically active secondary metabolites.

In fact, the proportion of novel structures produced by endophytes (51%) is considerably higher than that produced by soil isolates (38%) (Schulz et al. 2002). Endophytic microbes are being studied as potential sources of new bioactive substances because they have so many potential applications. In addition, metabolic interactions between endophytes and their hosts may induce synthesis of active secondary metabolites.

Generally speaking, there are several applications of endophytes for the production of novel metabolites. First, because of overcollection of wild plants, natural sources of traditional medicines are in short supply. It has been reported that many endophytes could produce substances of potential use to modern medicine, including gentiopicrin, taxol, cryptocin, pentaketide alkaloids, and so on (Yin et al. 2009; Gangadevi and Muthumary 2008; Li et al. 2000; Brady and Clardy 2000; Barros and Rodrigues 2005).

Improving existing drugs by modifying them with endophytes is another way to exploit novel metabolites. For example, camptothecin is a potent antineoplastic agent, but it is compromised in therapeutic applications due to its very low solubility in aqueous media and high toxicity. An endophytic fungus from *Camptotheca acuminata* produces camptothecin (1), 9-methoxycamptothecin (2), and 10-hydroxycamptothecin (3) (Kusari et al. 2009). Compounds (2) and (3) are two important analogues of compound (1) with lower toxicity and potential anticancer efficacy.

Bioactive metabolites extracted from endophytic fungi often show cytotoxic activity. Sometimes, these fungi are selected from medicinal plants. For example, five new secondary metabolite extracts from the fungus *Stemhylium globuliferum*, which was isolated from the medicinal plant *Mentha pulegium*, exhibited considerable cytotoxicity when tested in vitro against L5178Y mouse lymphoma cells (Debbab et al. 2009). Extracts of the fungal endophyte *Ampelomyces* sp. isolated from the medicinal plant *Urospermum picroides* also exhibited considerable cytotoxic activity when tested against L5178Y cells in vitro (Aly et al. 2008). In another test, 38 compounds were extracted from the endophytic fungus *Paecilomyces* sp. isolated from *Panax ginseng*, and some of them showed antihuman-pathogenic-fungus activity and antitumor activity (Xu et al. 2009). All these metabolites could be widely used in the treatment of human diseases in the future.

Besides the secondary metabolites produced by fungi, some endophytic bacteria associated with host plants can also produce bioactive compounds, e.g., phytohormones that promote the growth of the host, especially in harsh

environments (Lata et al. 2006). For example, three strains isolated from sunflowers grown under drought conditions produced jasmonic acid (JA), 12-oxo-phytodienoic acid (OPDA), and abscisic acid (ABA). All these bacterial strains have technological implications for agriculture and improved growth of sunflower crops (Forchetti et al. 2007).

Many reviews have reported that endophytes produce bioactive secondary metabolites. In general, the substances synthesized have belonged to diverse structural groups and derivatives: terpene, flavonoid, alkaloid, quinone, benzofuran, dihydroisocoumarin, cyclohexanone, and stearic acid. Most novel compounds showed antimicrobial, antioxidant, antineoplastic, antileishmanial, and antiproliferative activities, cytotoxicity, and other important biological functions (Ge et al. 2009; Pongcharoen et al. 2006; You et al. 2009; Liu et al. 2009; Chomcheon et al. 2009; Wei et al. 2007; Tansuwan et al. 2007; Borges et al. 2009a, b).

In short, utilization of a group such as the fungal endophytes is one aspect of intelligent screening. Many groups of these microbes in special and different habitats are waiting to be developed.

Metabolic transformation of bioactive substances by endophytes

When we talk about endophytes, we may first discuss their mechanisms of adaptation. On the one hand, endophytes have a strong tolerance toward hosts' unique metabolites, including some toxic substances. On the other hand, only with excellent biotransformation abilities can they face the various external environments directly.

Biotransformation can be defined as the chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound, or it may result in the production of an active metabolite of an inactive parent compound. As outlined above, endophytes live inside the plant tissue, and their specific habitat gives them distinctive characteristics. However, little research has been done in this field.

Generally speaking, biotransformation reactions mediated by endophytes have the following applications.

Detoxification effects toward toxic metabolites produced by host plants

In order to adapt to the ecological environment, plants have developed many mechanisms to overcome microbial diseases, including the production of a variety of toxic secondary metabolites. Some are present in healthy plants and some are synthesized when pathogens attack. The detoxification of these highly bioactive defense compounds is an important ability of many endophytes. In other words,

the transformation abilities of endophytes, to a certain extent, decide the colonization range of their hosts.

Benzoxazinones are a unique class of compounds for defense against pests, like bacteria, fungi, and insects. When the plant defense response is triggered, hydroxamic acids are chemically transformed into toxic benzoxazinone 2-benzoxazinone (BOA) or the less toxic lactams 2-hydroxy-1,4-benzoxazin-3-(2*H*)-one (HBOA) and some other toxic compounds. In a previous study, a fungal pathogen was found to transform BOA (Saunders and Kohn 2009). Zikmundova et al. (2002) isolated four endophytic fungi; in in vitro experiments, one of them, *Fusarium sambucinum*, detoxified BOA and HBOA to *N*-(2-hydroxyphenyl)malonamic acid. Others transformed HBOA to 2-Hydroxy-*N*-(2-hydroxyphenyl)acetamide, *N*-(2-hydroxyphenyl)acetamide, and some other structural analogues (Fig. 1).

The endophytic fungi extensively metabolized HBOA and transformed it to less toxic metabolites; the enzymes involved might include oxidase and reductases, e.g., cytochrome P-450 monooxygenases (Zikmundova et al. 2002).

Stereoselective biotransformation mediated by endophytes

The stereo- and regioselective synthesis of target compounds is one of the most important subjects in synthetic organic chemistry. The biotransformation of exogenous substances has been widely used and studied for the synthesis of chiral compounds (Hamada et al. 2003).

Endophytic fungi have been employed to change the three-dimensional conformation of compounds because of their effective biotransformation enzymes. Therefore, some researchers have tried to use endophytes to obtain more active substances.

Thioridazine (THD), a phenothiazine neuroleptic drug, is commercially available as a racemic mixture of the enantiomers. THD-2-SO and THD-2-SO₂ are metabolites

considered pharmacologically active, while THD-5-SO contributes to the cardio-toxicity of the drug. The (R) and (S) configurations of THD and their metabolites are related to the chiral carbon at position 2 or 5 in the piperidyl ring. Four endophytic fungi showed stereoselective biotransformation potential. *Phomopsis* sp. presented (S)-THD-2-SO; *Glomerella cingulata* presented (S)-THD-5-SO; *Diaporthe phaseolorum* presented (S)-THD-2-SO, (R)-THD-2-SO; and *Aspergillus fumigatus* presented (S)-THD-2-SO, (R)-THD-2-SO, respectively (Borges et al. 2008) (Fig. 2). The results of this study showed that different metabolites could be obtained by using different types of fungi and those metabolite productions were stereoselective.

Flavans are well known as free-radical scavengers. Agusta et al. (2005) isolated 35 filamentous endophytic fungi from young stems of *Camellia sinensis* collected in different areas. One of them, *Diaporthe* sp., transformed different kinds of flavans to many chemical derivatives. It stereoselectively oxidized the C-4 carbon of flavans possessing a 2*R*-substitution from the same direction to the configuration of 3-hydroxyl function. Subsequent experiments proved that the biooxidation occurs in an endoenzyme manner using molecular oxygen (Fig. 3).

The optically active tetrahydrofuran lignans display a wide range of pharmacological activities, including anti-parasite activity and antibacterial activity. One endophytic fungus, *Phomopsis* sp. obtained from *Viguiera arenaria*, led to the formation of a new compound. This procedure could convert unreactive methoxy groups to hydroxyl functions of a tetrahydrofuran lignan under mild conditions which may increase the solubility of (-)-grandisin and showed activity similar to the natural precursor (Verza et al. 2009).

Utilization of endophytes for region- and stereoselective production of novel products may be a smart strategy. It may allow us to eliminate drawbacks of precursor substances and/or obtain novel compounds that cannot be synthesized by chemical methods.

Fig. 1 Schema of biotransformation of BOA and HBOA by endophytic fungi isolated from *Aphelandra tetragona*

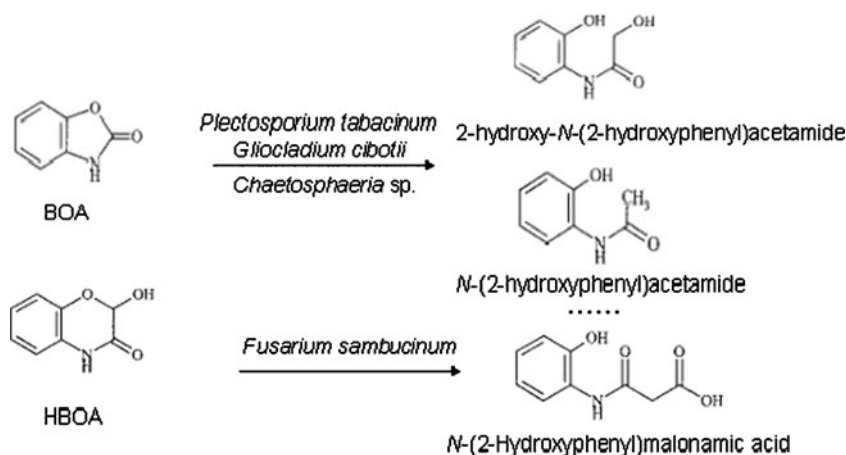
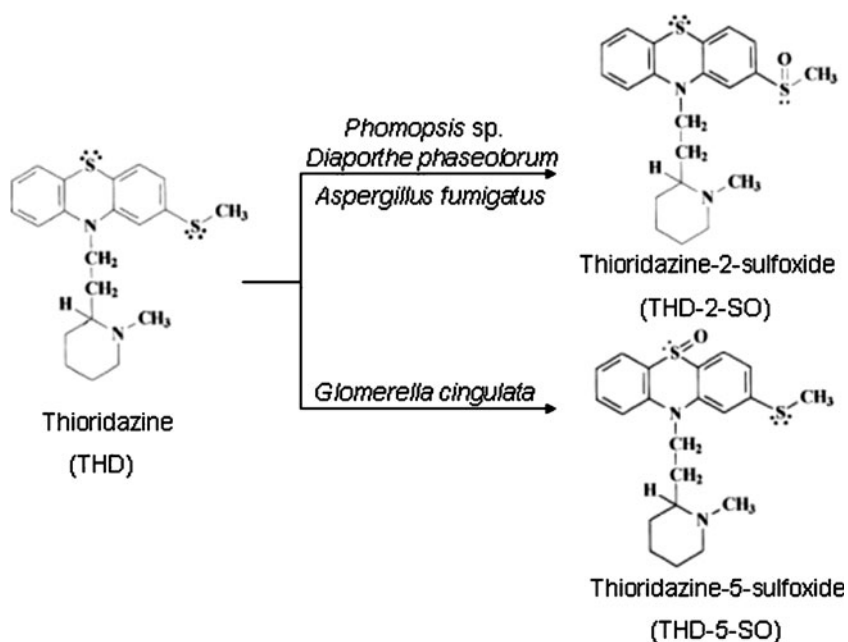


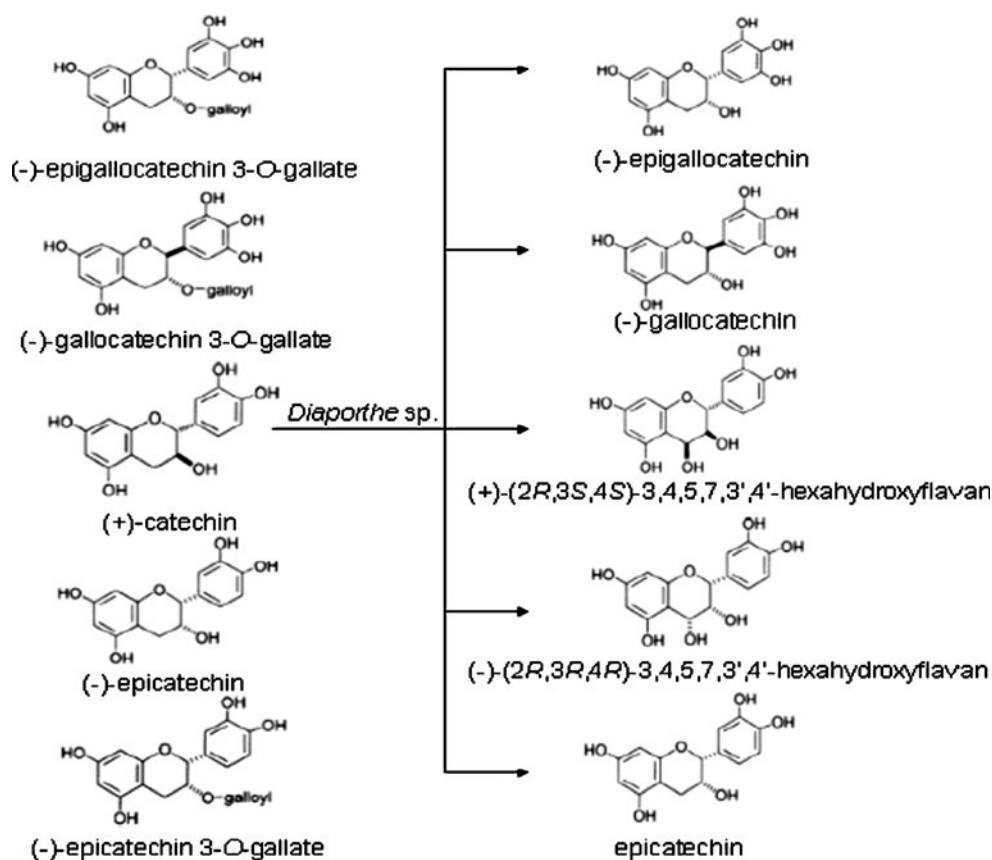
Fig. 2 Molecular structure of THD, THD-2-SO, and THD-5-SO



Simulation of drug metabolism in vivo of mammals by endophytes

Endophytes may be a useful resource for research into drug metabolism. Sometimes, enzymatic reactions mediated by endophytes are similar to metabolic responses in mammals.

Fig. 3 Stereoselective oxidation of flavans by endophytic fungus isolated from *Camellia sinensis* (L.)



Those metabolic pathways and active metabolites could be useful in studies of metabolism in mammals.

Betulinic acid and betulonic acid are natural triterpenes found in many plants that exhibit important biological properties, e.g., antineuroblastoma and antiviral activity. The endophytic fungi *Arthrobotrys*, *Chaetophoma*, *Dema-*

tium, and *Colletotrichum* showed mild and selective oxidation reactions that could convert betulinic acid to many oxygenated derivatives (Bastos et al. 2007) (Fig. 4). Some of these oxidizing reactions also occurred in mammals.

Some endophytes both simulate mammalian metabolic reactions and have a transformation process that is strictly stereoselective. Propranolol (Prop) is a non-cardioselective β -adrenergic blocking agent that is widely used in the treatment of cardiovascular diseases. Prop enantiomers are quite different, with the β -blocking activity predominantly related to (-)-(S)-Prop, which is about 100 times more potent than (+)-(R)-Prop. Its major metabolite in mammals is 4-hydroxypropranolol (4-OH-Prop) and it has the same efficacy as Prop. One fungus, *Glomerella cingulata* isolated from *V. arenaria*, can transform 47.8% of (-)-(S)-Prop to (-)-(S)-4-OH-Prop and particularly with no formation of (+)-(R)-4-OH-Prop in 72 h of incubation. This method could be further used to obtain some specific metabolites in higher quantities for pharmacodynamic applications (Borges et al. 2009a, b) (Fig. 5).

Endophytes have a special life history of long-term coexistence with host plants. Whether they have significant metabolic transformation capacities even after being isolated and how to create a new living environment to keep them efficient are main directions for future research.

Biodegradation effects of endophytes

For a long time, the role of endophytes in the degradation of plant debris has been neglected. Endophytes can produce manifold extracellular enzymes, including pectinase, cellulose, lipoidase, proteinase, phenoloxidase, and lignin catabolic enzymes (Oses et al. 2006; Tan and Zou 2001; Bischoff et al. 2009). All these enzymes are necessary to penetrate and colonize the host plants. When the plants die, the endophytes, together with the litter, fall on the ground. At this time, under certain circumstances, endophytes utilize various ingredients of plant residues as sources of carbon, such as glycose, oligosaccharide, cellulose, hemicellulose, lignin, keratin, pectin, lipids, and protein

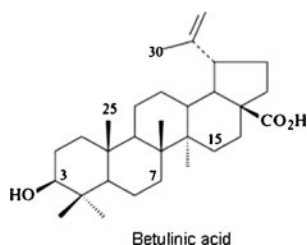


Fig. 4 Structure of betulinic acid and potential selective oxidation positions: C-3, C-7, C-15, C-25, and C-30

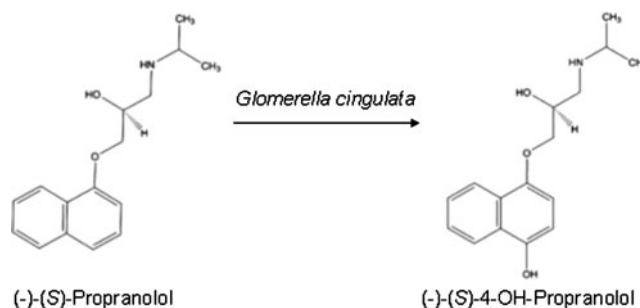


Fig. 5 Molecular structures of (-)-(S)-Prop and (-)-(S)-4-OH-Prop

(Kudanga and Mwenje 2005; Urairuj et al. 2003; Tomita 2003; Lumyong et al. 2002). Depending on the effectiveness of the extracellular enzymes, plant residues can be rapidly decomposed.

Previous research has indicated that endophytes play an important role in the degradation of plant debris. Oses et al. (2006) found that four endophytic fungi isolated from Chilean tree species *Drimys winteri* and *Prumnopitys andina*, which belonged to the basidiomycete class, were able to develop a non-selective white-rot wood decay pattern. In agar solid media, they displayed positive reactions to phenoloxidase and cellulose. After being treated with the fungi, wood chips presented weight and component losses. Muller et al. (2001) collected spruce needles in different time periods and carried out decomposition experiments using needle endophytes. The results showed that fungi surviving on the needle surfaces acted as pioneer decomposers. For another experiment, endophytic fungi were isolated from different-aged surface-sterilized pods of *Colophospermum mopane*. All three, *Alternaria*, *Phoma*, and *Phomopsis*, showed lignocellulolytic enzyme activity. According to Scanning Electron Microscope (SEM) analyses, *Phoma* was capable of utilizing moderately lignified mesophyll cells, whereas *Phomopsis* and *Alternaria* could degrade heavily lignified fibers. Endophytes that display lignocellulolytic abilities may significantly accelerate the decay of pods, allowing effective germination of seeds in an arid environment when conditions are favorable (Jordaan et al. 2006). In our experiment, a strain of the endophyte *Phomsis* sp. B3 was screened from the inner bark of *Bischofia polycarpa*. It accelerated the decomposition of peanut straw (Shi et al. 2004).

Studies have proven that a large number of lignocellulose degradation strains exist in endophytes, e.g., *Xylaria* sp., *Geniculosporium*, *Coccomyces* sp., and *Monotospora* sp. (Koide et al. 2005; Osono and Takeda 2001, 2002; Wang et al. 2006). They play a greater role in the degradation of plant residues. However, the role of fungal endophytes in wood degradation remains unclear; there is great diversity in the ways different wood-decaying fungi transform their hosts and substrates (Oses et al. 2006).

Research into the use of fungi to clean up environmental pollutants has gained momentum in past years; however, most studies have focused on the white-rot fungi (Marco-Urrea et al. 2008; Nikiforova et al. 2009). In our experiments, we found that endophytic fungi might be a novel and important resource for the degradation of polycyclic aromatic hydrocarbons (PAHs), a class of toxic environmental pollutants. A strain, *Ceratobasidium stevensii* isolated from the *Eupharbiaceae* plant, removed 89.51% of phenanthrene when added to fungal cultures after 10 days of incubation (Dai et al. 2010). It can be confirmed that the endophyte fungi *Ceratobasidium stevensii* was very efficient in metabolizing phenanthrene. The potential for screening and optimizing more endophytic fungi for degradation of PAHs and other pollutants may be exploited in bioremediation applications.

Methylobacterium populum sp. nov., strain BJ001 (Aken et al. 2004), which exists as a plant endophyte, is involved in the degradation of energetic compounds such as 2,4,6-trinitrotoluene (TNT), hexahydro-1,3,5-trinitro-1,3,5-triazine (HMX), and hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) (Aken et al. 2004). Other research carried out by Phillips et al. (2008) showed that strain *Pseudomonas* sp. exhibited alkane hydrocarbon degradation potential, while *Brevundimonas* and *Pseudomonas rhodesiae* were associated with increased PAH degradation potential and activity. On the other hand, when a toluene-degradation plasmid of *Burkholderia cepacia* G4 was introduced into *B. cepacia* L. S.2.4, a natural endophyte of yellow lupine, the engineered endophytic bacteria strongly degraded toluene, resulting in a marked decrease in its phytotoxicity (Barac et al. 2004).

Endophytes also have significant applications for changing the surrounding environment. A plant–bacterium association of the cardon cactus *Pachycereus pringlei* promotes the establishment of seedlings and growth on igneous rocks without soil. These bacteria weather several rock types and minerals, release large amounts of useful minerals for plants from the rocks, fix in vitro N₂, produce volatile and non-volatile organic acids, and reduce rock particle size to form mineral soil (Puente et al. 2009). This is probably because endophytes moved to the rhizosphere and participated in rock weathering and transformation of minerals (Newman and Reynolds 2005). The results indicate that plant–endophyte symbiosis is a powerful tool for improving the soil environment.

Conclusion

The wide variety of endophytes that exist within the world's plants have not been fully investigated. The unique habitats of endophytes make them more purposeful and selective in biological conversion and degradation. Endophytes will be useful for microbial conversion, and they

have great potential for the synthesis of biologically active metabolites that will be developed and widely used.

In the future, it may be possible for us to explore and utilize endophyte resources in many ways. For one thing, we can seek novel endophytes from plants that grow in extreme environments. For another, we should try to search for suitable and efficient methods to find more effective bioactive compounds from numerous endophytes. Finally, increasing the yield and content of active ingredients in known strains according to genetic engineering and metabolic regulation will be promising for large-scale production.

Fungi have proven to be sources of economically important enzymes for environmental restoration and other fields; however, endophytes have only recently been prospected for studies. Therefore, endophytes are an interesting niche waiting to be exploited.

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