A Friendly Relationship between Endophytic Fungi and Medicinal Plants: A Systematic Review

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Endophytic fungi or endophytes exist widely inside the healthy tissues of living plants, and are important components of plant micro-ecosystems. Over the long period of evolution, some co-existing endophytes and their host plants have established a special relationship with one and another, which can significantly influence the formation of metabolic products in plants, then affect quality and quantity of crude drugs derived from medicinal plants. This paper will focus on the increasing knowledge of relationships between endophytic fungi and medicinal plants through reviewing of published research data obtained from the last 30 years. The analytical results indicate that the distribution and population structure of endophytes can be considerably affected by factors, such as the genetic background, age, and environmental conditions of their hosts. On the other hand, the endophytic fungi can also confer profound impacts on their host plants by enhancing their growth, increasing their fitness, strengthening their tolerances to abiotic and biotic stresses, and promoting their accumulation of secondary metabolites. All the changes are very important for the production of bioactive components in their hosts. Hence, it is essential to understand such relationships between endophytic fungi and their host medicinal plants. Such knowledge can be well exploited and applied for the production of better and more drugs from medicinal plants.

Keywords: endophytic fungi, medicinal plant, population structure, plant-microbe interaction, secondary metabolite

INTRODUCTION

It is widely considered in a conventional view that the quality and quantity of crude drugs originated from medicinal plants are largely affected by such factors as the genetic background of the concerned plants, ecological habitats where the plants live, and soil nutrients (Dai et al., 2003; Sherameti et al., 2005). However, in the recent years, it is gradually recognized that endophytic fungi or endophytes have played a very important role in affecting the quality and quantity of the crude drugs through a particular fungus-host interaction, indicating that more understanding on the particular relationships between endophytic fungi and medicinal plants is required for promoting crude drug production (Faeth and Fagan, 2002). Although endophytic fungi are one of the most important elements in plant micro-ecosystems that should have significant influences on the growth and development of host plants, our knowledge about the exact relationships between endophytic fungi and their host plants is still very limited. Understanding and exploiting
such relationships will facilitate the ideal production of better
drugs by manipulating the growth conditions of medicinal plants
by, for example, adding a particular group of endophytic fungi
to the plants to improve the drug quality and quantity (Firáková
et al., 2007). Ideally, an alternative method can be developed
to directly produce desired drugs through bioengineering of
the selected medicinal plants and endophytic fungi under a
certain cultural condition, if the fungus-host relationships and
their metabolic mechanisms under cultural conditions are well
understood (Kumaran et al., 2008, 2009). Such an industry style
of manufacture may replace the traditional way to produce drugs,
which essentially depends on natural medicinal plants.

Endophytic fungi belong to mitosporic and meiosporic
ascomycetes that “asymptomatically reside in the internal tissues
of plants beneath the epidermal cell layer, where they colonize
healthy and living tissue via quiescent infections” (Bacon and
White, 2000). There is a great biological diversity of endophytic
fungi, occurring naturally in the temperate regions and tropical
rainforests, where about 300,000 terrestrial host-plant species are
distributed. Each plant species hosts one or more endophytic
fungus species. Endophytic fungi are diverse polyphylectic groups
of microorganisms, and can thrive asymptomatically in different
healthy tissues of living plants above and/or under the ground,
including stems, leaves, and/or roots. It is estimated that over
one million endophytic fungal species occurring in the nature
(Faeth and Fagan, 2002). Schultz classified the fungal endophytic
fungi into three main ecological groups: (a) mycorrizal; (b)
balansicaceous or pasture endophytic fungi; and (c) non pasture
endophytic fungi (Faeth and Fagan, 2002). The bioactive
compounds produced by endophytic fungi, exclusive of those to
their host plants, are very important to increase the adaptability
of both endophytic fungi and their host plants, such as the
tolerances to biotic and abiotic stresses. In addition, these
compounds can induce the production of a plethora of known
and novel biologically active secondary metabolites (Zhang et al.,
2006; Firáková et al., 2007; Rodriguez et al., 2009) that can
be exploited and applied by human as important medicinal
resources.

It is known that the colonization of endophytic fungi is
not an incidental opportunity because of the chemotaxis that
is specific chemicals produced by the host plants. At the
same time, different types of secondary metabolites, such as
saponin and essential oils from medicinal plants, are produced
through long-term co-evolution as a resistance mechanism to the
pathogens, most possibly including endophytic fungi. Therefore,
the secondary metabolites became obstacles for the colonization
of endophytic fungi. To overcome this, endophytic fungi must
secrete the matching detoxification enzymes, such as cellulases,
lactase, xylanase, and protease, to decompose these secondary
metabolites before they penetrate through the defense systems
of the resided host-plants. Once inside the tissues of a host-
plant, the endophytic fungi assumed a quiescent (latent) state,
either for the whole lifetime of the host plant (neutralism) or
for an extended period of time (mutualism or antagonism) until
environmental conditions are favorable for endophytic fungi or
the ontogenetic state of the host changes to the advantage of the
fungi (Sieber, 2007).

During the long period of co-existence and evolutionary
processes, different relationships have been established between
endophytic fungi and their host plants through a particular
fungus-host interaction recognized as: (i) a continuum of
mutualism, (ii) antagonism, and (iii) neutralism. The genetic
background, nutrient level, and ecological habitats of the
medicinal host plants are considered as the pressure-choice
factors on the population structure of the endophytic fungi
that, in turn, confer some kinds of benefits, such as the
induced growth, increased resistance to disease, and/or herbivore
(Rodriguez et al., 2009), as well as accumulated bioactive
components (Firáková et al., 2007), some of which can
be used by human as beneficial medicines. Therefore,
the mutual interrelation between endophytic fungi and their host
plants can impose certain effects on the formulation of
some types of bioactive compounds that can be used by
human.

In this paper, we reviewed the studies of endophytic fungi
and medicinal plants for the last 30 years, with a particular
emphasis on the factors that possibly influence the population
structure and distribution of endophytic fungi and benefits to
their host plants from the existence of endophytic fungi. We
hope that this review will provide readers useful information
for understanding the environmental and host-plant factors
affecting endophytic fungi as well as the friendly relationships
between endophytic fungi and medicinal plants, which may
help researchers make better use of the beneficial symbiosis and
expand the way for obtaining high-quality resources of certain
medicinal plants. Ideally, a system mimicking the mutualistic or
antagonistic symbiosis conditions of endophytic fungi and their
host plants may be established to effectively produce the desired
drug compounds through bioengineering, if the relationships
and conditions that promote the production of the compounds
are clearly understood. This review will also discuss the existing
problems in research and potential applications of endophytic
fungi for drug production.

ENVIRONMENTAL AND HOST-PLANT
FACTORS AFFECTING ENDOPHYTIC
FUNGI

Results of the analyses also indicated that the population
structure or distribution pattern of endophytic fungi was
significantly associated with the variation in environments, as
well as the classification and genetic background of host plants
(Table 1, Figure 1A). Data from the reference analysis suggested
that some environmental conditions, such as temperature,
humidity, illumination, geographic location, and vegetation
significantly affected the distribution pattern of endophytic
fungi (Suryanarayanan et al., 2005; Song et al., 2007). For
example, particular conditions determined the distribution
ranges of host plants that in return determine the species
of endophytic fungi and their spore germination, growth,
reproduction, and metabolism during the entire life cycle.
Similarly, results from the analyses suggested that the distribution
of certain endophytic fungal populations was only restricted to
TABLE 1 | Influences of host medicinal plants on the population structure of endophytic fungi.

| Family of host plants (represent species) | Isolation part | Habitat | Factor affecting the population structure | References |
|-----------------------------------------|----------------|---------|------------------------------------------|------------|
| Cactaceae (Cactus sp.)                  | Stem           | Desert of tropical savanna              | Environment: moisture\(^a\) and temperature\(^b\) | Suryanarayanan et al., 2005 |
| Rosaceae (Malus domestica)              | Leaf, flower, fruit | Tropical rainy region                  | Environment: cultivation style\(^c\) | Camatti-Sartori et al., 2005 |
| Leguminosae (Glycyrhiza inflata)        | Root           | Salinized sandy land in warm temperate region | Environment: moisture\(^a\) and temperature\(^b\) | Song et al., 2007 |
| Eucommiaceae (Eucommia ulmoides)       | Leaf, branch, bark | Subtropical mountain and warm temperate semi-humid region | Environment: latitude\(^e\) and temperature\(^b\) | Sun J. et al., 2008 |
| Orchidaceae (Gastrodia elata)           | Tuber, flower  | Hillside forests, wetland in temperate plateau | Environment: latitude\(^e\) | Mo et al., 2008 |
| Euphorbiaceae (Sapium sebiferum)        | Leaf, twig     | Mountain in subtropics                 | Tissue\(^d\) and age of tissue\(^h\) | Dai et al., 2003 |
| Smilacaceae (Heterosmilax japonica)     | Stem           | Subtropical monsoon region             | Season\(^g\) | Gao et al., 2006 |
| Pinaceae (Pinus tabulaeformis)          | Bark, needle, xylem | Forests in warm temperate semi-humid monsoon region | Season\(^g\) | Guo et al., 2008 |
| Teaceae (Camellia japonica)             | Leaf           | Temperate secondary forest             | Tissue\(^d\) and age of tissue\(^h\) | Osono, 2008 |
| Umbelliferae (Apium graveolens, Cichorium intybus, Foeniculum vulgare, Lactuca sativa) | Leaf, root, seed | Mediterranean region                   | Taxonomy of plants\(^f\) | D’Amico et al., 2008 |
| Zingiberaceae (Amomum siamense)         | Leaf, pseudostem, rhizome | Tropical monsoon forest                | Tissue\(^d\) | Bussaban et al., 2001 |
| Compositae (Atractylodes lancea)        | Rhizome        | Mountain in subtropics                 | Tissue\(^d\) and age of tissue\(^h\) | Wang Y. et al., 2009 |
| Asclepiadaceae (Calotropis procera)     | Leaf           | Garden bed                            | Tissue\(^d\) | Nascimento et al., 2015 |

\(^a\)The endophyte colonization was positively correlated with humidity.
\(^b\)The lower species diversity of the endophyte in temperate plants than that in tropical forests trees.
\(^c\)The highest endophytes number under organic cultivation.
\(^d\)The colonization rates of endophytic fungi from high to low in different tissues were bark->needle->xylem.
\(^e\)Different dominant endophytic fungi.
\(^f\)Specific host-endophyte combinations.
\(^g\)The colonization rates of endophytic fungi from high to low were spring->winter->autumn->summer.
\(^h\)The species richness of endophytic fungi increased as tissue aged, especially leaves.

Influences of Ecological Environments on Population Structure of Endophytic Fungi

We found that ecological or environmental conditions, such as temperature, humidity, and levels of soil nutrition were important factors to determine the types and amount of secondary metabolites of the host plants, which would indirectly affect the population structure of the endophytic fungi. For example, under the conditions of low mean annual sunshine hour and the high mean annual humidity, the host medicinal plants would produce more nutrients that were suitable for the colonization, reproduction, and dissemination of the endophytic fungi (Wu et al., 2013). In contrast, under the cold climatic conditions and inappropriate rates of respiration, oxygen concentration, and pH value, only certain types of host species
could successfully grown. As a consequence, only a limited number of particular endophytic fungi could colonize in the corresponding host plants, resulting a certain degree of regional specificity on population structure of endophytic fungi (Jiang et al., 2010).

We also found that population structure of endophytic fungi normally represented a certain degree of regional specificity. The distribution of endophytic fungi from the same regions presented a high degree of similarity in terms of species taxonomy (D’Amico et al., 2008). Conversely, species and their population structure of endophytic fungi even in the same host plant species from different regions normally presented very low degree of similarity (Jiang et al., 2010).

Influences of Genetic Background of Host Medicinal Plants on Population Structure of Endophytic Fungi

The analysis of relationships between the host genotypes and symbiotic lifestyle expression further revealed that individual isolates of some endophytic fungal species could express either parasitic or mutualistic lifestyles, depending on the colonized host genotype (Redman et al., 2001; Unterseher and Schnittler, 2010). Accordingly, the fungus-host plant relationships should be regarded as flexible interaction, whose directionality was determined by slight differences in fungal gene expression in response to the host reaction, or conversely, by host recognition and response to the fungi. Hence, slight genetic differences in the genomes of both partners controlled the outcome (positive, negative, or neutral) of the symbiosis (Moricca and Ragazzi, 2008). Thus, population structure of endophytic fungi was considerably affected by the genetic background of host plants. Based on the facts indicated by the analyzed references that the fitness of the endophytic fungi largely depended on the fitness of the host medicinal plants, suggesting that the host plants largely determined the colonization and distribution of endophytic fungi in the host plants (Saikkonen et al., 2004).

Furthermore, phase disposition (age) of host plants and tissues may likewise influence species composition of the endophytic community (Sieber, 2007). For example, different endophyte species were found in different tissues such as parenquima, vascular ducts, and dermis of a host plant with different ages.
(Rodrigues, 1994). Such a specific distribution of endophytic species might be related to their ability to utilize specific substrates (Rodrigues, 1994). In addition, differential substrates utilized by different endophytic species demonstrated their resource distribution strategy when lived in the same organ of a host (Carroll and Petrini, 1983), reducing the competition between the endosymbionts. This indicated that the colonization of endophytic fungi was significantly determined by different plant tissues producing differential substrates.

**BENEFICIAL RELATIONSHIPS CONFERRED BY ENDOPHYTIC FUNGI TO HOST PLANTS**

Our analysis based on the selected references further indicated the benefits conferred by some endophytic fungi to their host plants after colonization. Such a beneficial interaction could be presented from three different aspects (Figure 1B). First, some endophytic fungi could produce different plant hormones to enhance the growth of their host plants (Waqas et al., 2012). For example, the growth of wheat (Triticum aestivum L.) could be enhanced by Azospirillum sp. under drought stresses (Dingle and McGee, 2003). Second, some endophytic fungi would produce different bioactive compounds, such as alkaloids, diterpenes, flavonoids, and isoflavonoids, to increase the resistance to biotic and abiotic stresses of their host plants (Firáková et al., 2007; Rodríguez et al., 2009). Third, some endophytic fungi could promote the accumulation of secondary metabolites (including important medicinal components or drugs) originally produced by plants. These metabolites may be produced by both of the host plants or/and endophytic fungi according to the references surveyed (Shwab and Keller, 2008). Owning to the importance of the three aspects, we would present the three types of possible beneficial endophytic fungus-host relationships accordingly.

**Classification of Host Medicinal Plants Interacting with Endophytic Fungi**

The reference survey and analysis showed that a total of 96 medicinal plant species were mutualisms, meaning mutual benefits, in terms of the fungus-host relationships (Tables 1–4). These species were distributed among 46 families (Figure 1C), including Apocynaceae (1 taxon), Araucariaceae (1 taxon), Berberidaceae (2 taxa), Boraginaceae (1 taxon), Cactaceae (1 taxon), Celastraceae (2 taxa), Combretaceae (1 taxon), Compositae (5 taxa), Cucurbitaceae (2 taxa), Cupressaceae (4 taxa), Eucommiaceae (2 taxa), Euphorbiaceae (1 taxon), Ginkgoaceae (3 taxa), Gramineae (4 taxa), Guttiferae (1 taxon), Huperziaceae (3 taxa), Icacinaceae (2 taxa), Iridaceae (1 taxon), Labiatae (2 taxa), Lauraceae (1 taxon), Leguminosae (5 taxa), Liliaceae (3 taxa), Lycopodiaceae (1 taxon), Malvaceae (1 taxon), Meliaceae (1 taxon), Nyssaceae (1 taxon), Orchidaceae (8 taxa), Palmae (1 taxon), Pinaceae (2 taxa), Piperaceae (1 taxon), Podocarpaceae (1 taxon), Pontederiaceae (1 taxon), Pteridaceae (1 taxon), Rosaceae (1 taxon), Rubiaceae (1 taxon), Rutaceae (2 taxa), Sapindaceae (1 taxon), Scrophulariaceae (2 taxa), Smilacaceae (1 taxon), Solanaceae (3 taxa), Taxaceae (11 taxa), Taxodiaceae (1 taxon), Teaceae (1 taxon), Umbelliferae (2 taxa), and Zingiberaceae (2 taxa). The included plant species are commonly used as medicine either by direct consumption or for extracting bioactive components.

Obviously, these medicinal plant species from different families have their distribution in particular ecological habitats. Among these species, 16 species, such as Glycyrrhiza uralensis, Pflodendron amurense, and Rehmannia glutinosa etc. were mainly distributed in temperate regions, and 20 species, such as Amomum siamense, Cinchona ledgeriana, and Cinnamomum camphora var. Borneol etc. were only found in tropical regions. Forty species, such as Atractylodes lancea, Diosmosa veitchii, and Salvia militiorrhiza etc. were mainly distributed in subtropical regions. Four species, such as Apium graveolens and Foeniculum vulgare etc. were mainly distributed in Mediterranean region. Interestingly, some species were only found in extreme conditions, such as Cactus sp. in savanna deserts, Saussurea involucrata, Sinopodophyllum hexandrum, and Pedicularis sp. in high elevation.

The data obtained from the taxonomy of the total medicinal plants involved in the reference survey and analysis for last 30 years (Figure 1C) showed that the species associated with Taxaceae and Orchidaceae are higher than that of other family and accounted for 11 and 8, respectively.

Among the plants of family Taxaceae, all are related with endophytes which can produce taxol with antitumor activity. In 1993, an endophytic fungus, Taxomyces andreanae, was isolated from the bark of Taxus brevifolia and was shown to produce Taxol under in vitro axenic culture conditions (Stierle et al., 1993). Numerous reports are available on the pronounced variability in Taxol production from various endophytic fungal isolates across different batch cultures (Gangadevi and Muthumary, 2009). Paclitaxel (taxol) is a kind of diterpenoids American scientists isolated from the Pacific yew extract as a natural secondary metabolites in 1960s. It has significant anti-tumor activity, particularly ovarian cancer, uterine cancer, breast cancer with high incidence. So these important discoveries are worth further studying. Followed by the family Taxaceae, papers reporting Orchidaceae accounted of eight for the second highest reports and it has the potential to be developed further. Most of them are related with the endophytes which can promote on the growth of the host plants (Zhang J. et al., 1999; Guo and Wang, 2001). In nature, almost all orchid endophytic fungi invariably belong to the genus Rhizoctonia and are believed to be essential symbionts for both the germination of seeds and the development of the young heterotrophic plantlets. In most orchids the plant eventually becomes photosynthetic, while some species are known to remain heterotrophic throughout their life for providing nutrition to survive. The endophyte found in the adult plant is generally assumed to be the true symbiont of seeds and protocorms, and from the behavior of endophytes isolated from roots in culture with the host seeds various views have been put forward about specificity of the relationship between hosts and endophytes. Thus, it is of great importance to study the relationship between orchids and their endophytic fungi, as well as the plants of these two families.
Promotion of Fitness and Growth of Host Plants

Results indicated that some endophytic fungi could increase the fitness and growth of host plants by increasing hormones, such as indole-3-acetic acid, indole-3-acetonitrile, and cytokinins. Endophytic fungi could also promote the growth of their host plants by obtaining nutritional elements such as nitrogen and phosphorus useful for plants (Zhang et al., 2006; Hartley and Gange, 2009). For example, Mycena dendrobi could promote the seed germination and growth of the host plant Gastrodia elata by secreting indoleacetic acid (Guo and Wang, 2001). In addition, Metarhizium robertii translocated nitrogen directly from insects to its host plants through hyphae (Behie et al., 2012). Interestingly, results showed that most hormones were produced by endophytic fungi isolated from the roots of host plants. A few references also reported that some endophytic fungi could promote the growth and fitness of the host plants by activating the expression of a certain enzymes and genes (Chen et al., 2005). For example, Piriformospora indica increased the growth of tobacco roots by stimulating the expression of nitrate reductase and the starch-degrading enzyme (glucan-water dikinase) (Sherameti et al., 2005) (Table 2).

Increase of Resistance to Stresses for Host Plants

The references showed that certain endophytic fungi could enhance the resistance of host plants to biotic and abiotic stresses by producing bioactive compounds (chemicals) (Nejad and Johnson, 2000; Cavagli et al., 2004) (Table 3). In symbiotically conferred stress tolerance, the endophytic fungi were considered to act as a type of biological trigger that activated the defense systems of a host (Rodriguez and Redman, 2008). For example, endophytic fungi that were inoculated to crop plants improved the resistance and yield of the crops (Kozyrovska et al., 1996), and such an endophytic-mediated plant resistance to pathogens was more likely the result of direct competition between host plants and pathogens.

Interestingly, in many cases, the tolerance to biotic stresses was correlated with the bioactive compounds produced by endophytic fungi (Saikkonen et al., 1998; Tan and Zou, 2001; Zhang et al., 2006) that had antimicrobial activity against pathogens (Gunatilaka, 2006). Moreover, chemicals produced by endophytic fungi were toxic or distasteful to insects (Hartley and Gange, 2009), protecting the host plants from the attacks of insects. For example, alkaloids produced by endophytic fungi in the genus Neotyphodium could confer deterrence to their host plants, increasing their survival from the attacks by insects. With the increased stress tolerance, host plants infected by endophytic fungi could outcompete native plants without fungal infection, and consequently became invasive (Tofern et al., 1999; Clement et al., 2005).

In addition, endophytic fungi could produce a vast variety of antioxidant compounds (Table 3) that could protect their hosts by enhancing tolerance to abiotic stresses (Herrera-Carrillo et al., 2009; Torres et al., 2009). In supporting of this, several studies had demonstrated increased production

### TABLE 2 | Host medicinal plants with enhanced growth conferred by endophytic fungi.

| Host plant          | Endophytic fungi                          | Mechanism                                                                 | References                                    |
|---------------------|-------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------|
| Atracty lancea      | Sclerotium sp.                            | Increase cell protection from desiccationin and leaf metabolic capability of host | Chen et al., 2008                           |
| Cucumis sativus     | Phoma glomerata, Penicillum sp.            | Secret phytohormones viz. Gibberellins and Indoleacetic acid               | Waqas et al., 2012                           |
| Anoectochilus formosanus | Epulorhiza sp.                      | Enhance four enzyme activities enzyme activities of chitinase, β-1, 3-glucase, phenylalanine ammonia-lyase, and polyphenoloxidase | Tang et al., 2008                            |
| Anoectochilus roxburghii | Epulorhiza sp., Mycena anoectochila     | Enhance enzyme activities                                                   | Yu and Guo, 2000; Chen et al., 2005          |
| Cymbidium sinense   | Mycena orchidcola                         | Secret the plant hormones                                                   | Zhang J. et al., 1999                        |
| Dendrobium candidum | Mycena dendrobii                          | Secret the plant hormones                                                   | Zhang J. et al., 1999                        |
| Dendrobium nobile, D. chrysanthum | Epulorhiza sp., Mycena sp., Tulasnellales, Stebacinales, Cantharellales | Enhance the absorption of nutrient in plants promoting the seed germination of host | Chen and Guo, 2005                           |
| Gastrodia elata     | Mycena dendrobii, M. osmundicola, Mycena orchidcola, M. anoectochila | Secret the plant hormones promoting the seed germination of host | Guo and Wang, 2001                           |
| Pecteilis susannae  | Epulorhiza sp., Fusarium sp.              | Enhance the absorption of N, P, and K elements in plants promoting the seed germination of host | Chutima et al., 2011                         |
| Monochoria vaginalis| Penicillum sp., Aspergillus sp.            | Secret gibberelins                                                          | Ahmad et al., 2010                           |
| Pedicularis sp.     | Dark septate endophytic fungi (DSEF)      | Increase their nutrient utilization efficiency                               | Li and Guan, 2007                            |
| Rehmannia glutinosa | Ceratobasidium sp.                        | Secret indoleacetic acid                                                    | Chen B. et al., 2011                          |
| Nicotiana attenuata | Sebacina vernifera                        | Enhance the absorption of nutrient and promote the growth and fitness of by inhibiting ethylene signaling | Barazani et al., 2007                        |
| Sesbania sesban     | Funneliformis mosseae, Rhizophagus intraradicesand Claridoeglomorus etunicatum | Secret the plant hormones                                                   | Abd_AlAh, et al., 2015                        |
of antioxidant compounds (e.g., flavonoids and other phenolic antioxidants) in endophyte-infected plants (Richardson et al., 1992; Harper et al., 2003; Huang et al., 2007a,b). Furthermore, it was shown that endophytic fungi possessing metal sequestration or chelation systems were able to increase tolerances of their host plants to the presence of heavy metals, thereby, assisting their hosts to survive in contaminated soil (Weyens et al., 2010).

### TABLE 3 | Host medicinal plants with enhanced defense responses conferred by endophytic fungi.

| Host plant | Endophytic fungi | Type of stresses | Mechanism | References |
|------------|-----------------|------------------|-----------|------------|
| Chrysanthemum morifolium | Chaetomium globosum, Botrytis sp. | Salt stress | Increase POD activity and soluble protein content | Liu et al., 2011 |
| Glycyrrhiza uralensis | Arbuscular mycorrhiza, Penicillium griseofulvum | Drought and salt stress | Reduce injury of water stress by increase protective enzymes’ activity and osmotic contents | Wang L. et al., 2009 |
| Salvia miltiorrhiza | Arbuscular mycorrhiza, Penicillium griseofulvum | Drought stress | Increase the absorption of nutrient and alter metabolic activities in host | Meng and He, 2011 |
| Cordia alliodora | Leucocarpinus gongylophorus | Insect | Produce some chemicals antagonistic to ants’ fungal symbiont | Bottrill et al., 2011 |
| Phoenix dactylifera | Beauveria bassiana, Lecanicillium dimorpium, L. cf. psalliotae | Insect: date palm pests | Modulate the expression of cell division-related proteins in host | Gómez-Vidal S., mez-Vidal et al., 2009 |
| Cirsium arvense | Chaetomium cochlodes, Cladosporium cladosporioides, Trichoderma viride | Insect: foliar feeding insects | Produce some chemicals toxic to pathogens | Gage et al., 2012 |
| Cucumis sativus | Chaetomium Ch1001 | Insect: root-knot nematode Meloidogyne incognita | Produced abscisic acid affecting motility of the second stage juveniles of insects | Yan et al., 2011 |
| Picea rubens | 150 foliar fungal endophytes | Insects: Choristoneura fumiferana | Produce some chemicals toxic to insects | Sumarah et al., 2010 |
| Atractylodes lancea | Gillmaniella sp. AL12. | Pathogenic fungi | Produce jasmonic acid inducing defense responses | Ren and Dai, 2012 |
| Curcuma wenyujin | Chaetomium globosum L18 | Pathogenic fungi | Produce some chemicals toxic to pathogens | Wang et al., 2012 |
| Maytenus hookeri | Trichothecium roseum | Pathogenic fungi | Produce trichothecin toxic to pathogens | Zhang et al., 2010 |
| Phragmites australis | Cladosporium cladosporioides, Stachybotrys elegans, and Cylindrocarpon sp. | Pathogenic fungi | Produce cell wall-degrading enzymes to kill pathogenic fungi | Cao et al., 2009 |
| Cassia spectabilis | Phomopsis cassiae | Pathogenic fungi: Cadosporium cladosporioides, and C. cladosporioides | Produce cadinane sesquiterpenoids toxic to pathogens | Silva et al., 2006 |
| Angelica sinensis | Bacillus subtilis, Myxoma sp. | Pathogenic fungi: Fusarium oxysporum and F. Solani | Produce some chemicals toxic to pathogens | Yang et al., 2012 |
| Hordeum vulgare var. disticum | Acremonium biocili, A. furcatum, Aspergillus fumigatus, Cylindrocarpon sp., C. destructans, Dactyliaria sp., Fusarium equiseti, Phoma herbarum, P. leveillei | Pathogenic fungi: Gaeumannomyces graminis var. Tritic | Improve the competence for space inhibiting the colonization of pathogens | Maciá-Vicente et al., 2008 |
| Triticum aestivum cv. “Morocco” | Chaetomium sp, Phoma sp. | Pathogenic fungi: Puccinia recondita | Activate defense reactions of the plant | Dingle and McGee, 2003 |
| Tripterisium wilfordii | Cryptosporiopsis cf. quercina | Pathogenic fungi: Pyricularia oryzae | Produce cryptocin and cryptocandin toxic to pathogens | Strobel et al., 1999 |
| Oryza sativa | Sordariomycetes sp. | Pb²⁺ stress | Inhibition of electron transport from the quinone acceptor QA to QB | Li and Zhang, 2015 |
| Capsicum annuum | Penicilium resedanum LK6 | Heat stress | Improve nutrient, proline and flavonoid contents, modulate amino acid metabolism | Khan et al., 2013 |

**Promoting the Accumulation of Bioactive Compounds of Medicinal Plants**

Results from our reference analyses clearly indicated that some endophytic fungi with ability promoted the accumulation of secondary metabolites of host plants, which influenced the quantity and quality of drugs (Chen et al., 2016). Some endophytic fungi could produce diverse classes of phytochemicals—secondary metabolites originally from plants,
including the well-known compounds such as paclitaxel (also known as taxol) (Stierle et al., 1993), podophyllotoxin (Eyberger et al., 2006; Puri et al., 2006), deoxypodophyllotoxin (Kusari et al., 2009a), camptothecin, and structural analogs (Puri et al., 2005; Kusari et al., 2009c, 2011; Shweta et al., 2010), hypericin and emodin (Kusari et al., 2008, 2009b), and azadirachtin (Kusari et al., 2012) (Table 4). In fact, the best known example of anticancer compound taxol was found in the taxol-producing endophytic fungi T. andreanae that was isolated from T. brevifolia (Stierle et al., 1995). Many endophytic fungi colonized in other host plant species, such as S. nepalense, S. tenuis, S. tenuis (Bashyal, 1999), T. andreanae sp. strain T5 (Wang J. et al., 2006), and Metarhizium anisopliae (Liu et al., 2009), were also found to produce taxol.

Other endophytic fungi could promote the formation and accumulation of secondary metabolites that were only produced by host plants. For example, Coetotrichum gloesporioides could induce the production of Artemisinin in hairy-root cultures of Artemisia annua (Wang J. W. et al., 2006). These compounds commonly function as bioactivities for antitumor, antipyretic, antimalarial, analgesic, or anti-inflammatory in medicinal treatments.

CONCLUSION AND PERSPECTIVES

This review highlights the environmental and host-plant factors that can possibly influence the population structure and distribution of endophytic fungi, as well as the benefits these endophites provide to their host plants. The fungus-host relationships reveal that the distribution and population structure of endophytic fungi rely largely on the taxonomy, genetic background, age, and tissues of the host plants, in addition to the types of environments. These findings can assist in the investigation of bioactive compounds produced by a certain host medicinal plant under specific environment conditions. In addition, we have observed that there are three types of beneficial interactions between endophytic fungi and their host plants namely: (1) enhancement of the growth of host medicinal plants, (2) increase in the resistance of the host plants to biotic and abiotic stresses, and (3) accumulation of secondary metabolites, including bioactive compounds used as drugs, produced originally by the medicinal plants. These findings have important practical implications for obtaining and producing drugs with improved quality and higher quantity.

Interestingly, genuine medicinal materials with the highest quality and best effects to a certain disease seems to have a special relationship with endophytic fungi. Special types of endophytic fungi of medicinal plants may be associated with the production of specific bioactive compounds needed by human. For example, a medicinal plant Huperzia serrata found in tropical region can produce Huperzine-A compounds that are considered being stimulated by endophytic fungi Acremonium sp. and Shiraia sp. (Wang Y. et al., 2009; Wang et al., 2011; Zhou et al., 2009). This is the reason why in traditional Chinese medicine, doctors prefer to use a particular medicinal plants from a particular geographical locations or habitats where the content and chemical types of particular compounds can be expected. Therefore, understanding the distribution and population structure patterns of endophytic fungi will provide a theoretical guide for effectively exploring bioactive compounds of drugs produced by a special host medicinal plant in particular tissues under special environment conditions.

Importantly, the application of target endophytic fungi can promote seed germination of many host plant species. The significance of this application can increase opportunities for the germination of those seeds that cannot germinate under the normal conditions. For example, seeds of some rare and endangered medicinal species, such as Dendrobium nobile and D. chrysanthum in the orchid family, are extremely difficult to germinate under normal conditions. However, with the application of endophytic fungi in the genus Mycena, these seeds can germinate successfully, which has facilitated the artificial culture of these medicinal plants (Chen and Guo, 2005). This is particularly useful for the rare and endangered medicinal plants that are used in breeding programs where seed germination is crucial.

The most valuable application is to utilize the advantages of endophytic fungi that can promote the accumulation of secondary metabolites originally produced by plants. Through such an application, we can enhance the synthesis and accumulation of bioactive compounds of the host medicinal plants for higher quality of crude drugs, by adding particular endophytic fungi to the plants. This application may open a complete new dimension for the production of natural medicines in an extremely effective manner, given that the relationship between endophytic fungi and their host medicinal plants is completely understood.

Unfortunately, much of the work reported on the beneficial strains is confined to experimental studies, and more efforts should be put into field trials and applications to obtain higher-quality drugs. Also, the mechanisms of the interactions between endophytic fungi and their host plants have not been clearly defined. In addition, the research emphasis of endophyte need to be addressed over the next several decades, such as:

- Build a bioengineering system to mimick the mutualistic/antagonism symbiosis of endophytic fungi and their host plants, and facilitate the production of the bioactive compounds.
- Set up a guide for rapid screening of plant endophytic fungi beneficial to host plants other than isolate all strains uncritically.
- Establish target endophytic fungi library for plant breeding in order to protect the endangered medicinal plants by using seed germination.
- Solve the degradation problem of target endophytic fungi that can produce desired metabolites.
- Make better use of beneficial strains in planting and cultivating medicinal plants so the pharmaceutical products can be improved.
| Endophytic fungi | Plant-secondary metabolite | Host plant | Bioactivity of secondary metabolite | References |
|-----------------|---------------------------|------------|------------------------------------|------------|
| Alternaria sp.  | Berberine                 | Phellodendron amurense | Antimicrobial                      | Duan, 2009 |
| Fusarium solani | Camptothecin              | Apodytes dimidiata    | Antitumor                          | Shweta et al., 2010 |
| Entrophospora infrequens, Neurospora sp. | Camptothecin | Notaphyloides foetida | Antimicrobial                      | Amna et al., 2006; Rehman et al., 2008 |
| Fusarium solani | Camptothecin              | Camptotheca acuminata | Antimicrobial                      | Kusari et al., 2009c |
| Phomopsis sp., Diaporthe sp., Schizophyllum sp., Penicillium sp., Fomitopsis sp., Arthrinium sp. | Cinchona alkaloids: quinine, quinidine, cinchonidine, and cinchonine | Cinchona ledgeriana | Antipyretic and anti-malarial, analgesic and anti-inflammatory | Maehara et al., 2012 |
| Blastomyces sp., Botrytis sp. | Huperzine A | Phlegmariurus cryptomerianus | Anticholinesterase | Ju et al., 2009 |
| Penicillium chrysogenum | Huperzine A | Lycopodium serratum | Antimicrobial                      | Zhou et al., 2009 |
| Acremonium sp. | Huperzine A, Spermine | Fritillaria ussuriensis | Antimicrobial                      | Kusari et al., 2009c |
| Pestalotiopsis guepinii, Pestalotiopsis terminaliae | Paclitaxel | Woleoria nobilis | Antimicrobial                      | Gangadevi and Muthumary, 2009 |
| Phyllosticta spinarum | Paclitaxel | Cupressus sp. | Antimicrobial                      | Senthil Kumaran et al., 2008 |
| Alternaria sp. | Paclitaxel | Ginkgo biloba | Antimicrobial                      | Kim and Ford, 1999 |
| Phyllosticta dioscoreae | Paclitaxel | Hibiscus rosa-sinensis | Antimicrobial                      | Kumaran et al., 2009 |
| Aspergillus fumigatus | Paclitaxel | Podocarpus sp. | Antimicrobial                      | Sun D. et al., 2008 |
| Phyllosticta citricarpa | Paclitaxel | Citrus medica | Antimicrobial                      | Kumar et al., 2008 |
| Pestalotiopsis pauciseta | Paclitaxel | Cardiospermum helicacabum | Antimicrobial                      | Gangadevi et al., 2008 |
| Botryodiplodia theobroma, Fusarium lateritum, Monochaetia sp., Pestalotia bicilia | Paclitaxel | Taxus baccata | Antimicrobial                      | Vennkutelmalam et al., 2008 |
| Taxomyces andreanum | Paclitaxel | Taxus brevifolia | Antimicrobial                      | Stierle et al., 1995 |
| Fusarium solani | Paclitaxel | Taxus celebica | Antimicrobial                      | Chakravarthi et al., 2008 |
| Fusarium solani, Metarhizium anisopliae, Mucor rouxianus | Paclitaxel | Taxus chinensis | Antimicrobial                      | Deng et al., 2009; Liu et al., 2009 |
| Ozenium sp., Alternaria alternata, Botrytis sp., Ectostroma sp., Fusarium mairei, Papulaspora sp., Tubercularia sp. | Paclitaxel | Taxus chinensis var. mairei | Antimicrobial                      | Zhou et al., 2007; Guo et al., 2009; Wu et al., 2013 |
| Alternaria sp., Aspergillus niger var. taxii, Botrytis sp., Fusarium arthrosporioidae, Pestalotiopsis microspora | Paclitaxel | Taxus cuspidata | Antimicrobial                      | Kim and Ford, 1999 |
| Cladosporium cladosporio | Paclitaxel | Taxus media | Antimicrobial                      | Zhang et al., 2009 |
| Pilomyces sp. | Paclitaxel | Taxus sumatrana | Antimicrobial                      | Strobel et al., 1996 |
| Pestalotiopsis microspora, Sporormia minima, Trichothecium sp. | Paclitaxel | Taxus walachiana | Antimicrobial                      | Shrestha et al., 2001 |
| Taxomyces sp. | Paclitaxel | Taxus yunnanensis | Antimicrobial                      | Qiu et al., 1994 |
| Periconia sp. | Paclitaxel | Torreya grandiflora | Antimicrobial                      | Li et al., 1998 |
| Pestalotiopsis microspora | Paclitaxel | Taxodium distichum | Antimicrobial                      | Li et al., 1996 |
| Aspergillus nidulans, A. oryzae | Quercetin | Ginkgo biloba | Anti-inflammatory                   | Qiu et al., 2010 |
| Unidentified | Rutin | Pteris multifida | Antibacterial and antioxidant       | Fan et al., 2007 |
| Rhizopus oryzae | α-Irone, β-Irone | Iris germanica | Anti-inflammatory                   | Zhang L. et al., 1999 |
| Penicillium implicatum | Podophyllotoxin | Diaphyelia sinesis | Antimicrobial                      | Zeng et al., 2004 |
| Monilia sp., Penicillium implicatum | Podophyllotoxin | Dysosma veitchii | Antimicrobial                      | Yang et al., 2003 |

(Continued)
TABLE 4 | Continued

| Endophytic fungi                        | Plant-secondary metabolite | Host plant                                      | Bioactivity of secondary metabolite | References |
|----------------------------------------|----------------------------|-------------------------------------------------|------------------------------------|------------|
| *Penicillium sp.*, *Phialocephala fortunii*, *Trametes hirsuta*, *Alternaria neesex* | Podophyllotoxin            | Sinopodophyllum hexandrum                        | Antitumor                          | Li, 2007   |
| *Fusarium oxysporum*                   | Podophyllotoxin            | Juniperus recurva                               | Antitumor                          | Kour et al., 2008 |
| *Alternaria sp.*                       | Podophyllotoxin            | Sabina vulgaris                                 | Antitumor                          | Lu et al., 2006 |
| *Chaetomium globosum*                  | Hypericin                  | Hypericum perforatum                            | Anti-depressant                     | Kusari et al., 2008 |
| *Trichoderma atrovire D16*             | Tanshinone IIA and tanshinone I | Salvia miltiorrhiza                              | Antibacterial and anti-inflammatory | Ming et al., 2011 |
| Sordariomycete sp.                     | Chlorogenic acid           | Eucommia ulmoides                               | Antimicrobial and antitumor         | Chen et al., 2010 |
| *Cephalosporium sp.*, *Paeckelomyces sp.* | Diosgenin                  | Paris polyphlla var. yunnanensis                | Antitumor, anti-inflammatory, and cardiovascular-protection | Cao et al., 2007 |
| *Fusarium oxysporum*, *Neoeucnica macrodidiym*, *F. solani*, *F. proliferatum* | Cajaninstitene acid        | Cajanus cajan                                   | Antioxidant, hypotriglyceremic, and hypoglycemic | Zhao et al., 2012 |
| *Cochlubolus niskadoi*                 | Borneol                    | Cinnamomum camphora chvar. Borneol              | Anti-inflammatoire, antioxidant     | Chen M. et al., 2011 |
| *Fusarium oxysporum*                   | Ginkgolide B               | Ginkgo biloba                                   | Anti-shock, anti-inflammatory       | Cui et al., 2012 |
| Unidentified                           | Toosendarin                | Melia azedarach                                 | Contact toxicity, stomach toxicity, and anti-feeding | Zhao et al., 2011 |
| *Fusarium redolens*                    | Peimisine and imperaline-3p-D-glucoside | Fritillaria unibracteata var. wabuensis     | Get rid of sputum, cough, and antim tumor | Pan et al., 2015 |
| *Colletotrichum gloesporioides*        | Piperine                   | Piper nigrum                                    | Antimicrobial, antidepressant, anti-inflammatory, and anticancer | Chithra et al., 2014 |

Such knowledge can be well exploited and applied for obtaining better drugs from medicinal plants. We believe that this review provides new insights into drug discovery and clinical utility which can be further improved by investigating endophytes further as these have the potential of playing a key front line role in the treatment of various diseases.

AUTHOR CONTRIBUTIONS

Reviewed and finalized manuscript: TH, LQ; Completed the article writing: MJ, LC; Integrated information of tables, analyzed data, and made pictures: HX, CZ; Took charge of the manuscript language: KR.

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