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Review Article

Endophytic Fungi: A Potential Source of Bioactive Compounds

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Abstract

Plant based ethno-medicine represents the foundation of modern pharmacology and many pharmaceuticals are derived from compounds extracted from plant. This track still stimulates a worldwide investigational activity aimed at identifying novel bioactive products of plant origin. The discovery of endophytic fungi able to produce many plant-derived drugs has disclosed new horizons for their availability and production on a large scale by the pharmaceutical industry. In the natural products research, a valuable approach is the prospection of uncommon sources and unexplored habitat and endophytic fungi is specially focused because of their ability to produce new and interesting secondary metabolites, which have several biological applications. The endophytes establish exclusive symbiotic relationships with plants and the metabolic interactions may support the synthesis of some similar valuables compounds. Endophytic fungi are diverse group of fungi which are symbiotically associated with plants. These are ubiquitous and occur within all known plant species. This review reveals the importance of endophytic fungi of medicinal plants as a source of bioactive and chemically novel compounds. The endophytic fungi also have plant growth promoting attributes by which these can influence their host plants by enhancing their growth and tolerance to abiotic and biotic stresses. These also serves as a chemical reservoir for antimicrobial, antifungal, anticancer, antioxidant, antiviral and antitubercular compounds for use in the pharmaceutical and agrochemical industries.

Keywords: Endophytes, fungi, antimicrobial activity, anticancer compounds

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Introduction

Endophytic fungi are ubiquitous in nature and reside intercellular or intracellular in the plants, at least for a portion of their lives without causing apparent symptoms of infection. Almost all plants are known to harbor endophytes. The choice of the plant to be used for exploring endophytes for bioactive compounds is important. Secondary metabolites serve in multiple physiologic functions, many of which are common to both plants and microorganisms, and in a way it is intuitive that the same or similar compounds can be produced by ecologically associated entities. Thus, the aim to exploit botanical diversity for the discovery of novel drugs has led to the finding of microbial strains able to synthesize bioactive compounds which previously considered as typical plant products. In the last 25 years, the general evidence that all plants are inhabited by endophytic microorganisms, but in newer finding it was revealed that the latter are also capable of producing plant metabolites, which are considered as a major factor influencing the establishment and evolution of mutualistic interrelations. Therefore, medicinal plants which are known to be used since centuries as an alternative source of medicine are valuable source for bioprospecting endophytes. The fossil record indicates that plants have been associated with endophytic [1] and mycorrhizal [2] fungi for > 400 million year and was likely associated when plants colonized land, thus playing a long and important role in driving the evolution of life on land. For treating infectious diseases, bioactive natural products and their derivatives have historically served as a major source of therapeutic agents [3]. Endophytes have proven to be a rich source of novel natural compounds with structural diversity possessing a wide-spectrum of biological activities. However, fungi isolation in pure cultures has been limited. Less than 5% fungal isolates have been successfully isolated into pure cultures out of over one million fungal endophytes existed in the nature [4]. Endophytic fungi isolated from medicinal plants are more likely exhibit pharmaceutical potentials.

Types of endophytes

Endophytic fungi have been categorized in two groups, clavicipitaceous (C-endophytes) and nonclavicipitaceous (NC-endophytes) endophytes. C-endophytes infect some grasses and their transmission is primarily occurs by vertical passing of fungi on to offspring via seed infections [5]. NC-endophytes can be recovered from asymptomatic tissues of nonvascular plants, ferns and allies, conifers, and angiosperms [6]. Benefits by these fungi appear to depend on the host species, host genotype and environmental conditions [7]. Most of them belong to the Ascomycota and colonize either in,ter or intracellular, localized or systemic. The majority of these isolates belonged to ubiquitous genera are shown in **Table1**.

Table 1 Different **e**ndophytic fungi and their host plants

Endophytic fungi	**Host plant**	**References**
Tubercularia sp. strain TF5	*Taxus mairei*	[8]
Rhinocladiella sp	*Tripterygium wilfordii*	[9]
Muscodor vitigenus	*Paullinia paullinioides*	[10]
Pestalotiopsis microspora	*Terminalia morobensis*	[11]
2L-5	*Ocimum basilicum*	[12]
Pestalotiopsis sp.	*Jatropha curcas*	[13]
Marssonina sp	*Calotropis gigantean*	[13]
Xylaria sp. YX-28	*Ginkgo biloba L.*	[14]
Chaetomium sp.	*Salvia officinalis*	[15]
Fusarium solani	*Camptotheca acuminata*	[16]
Fusarium solani	*Taxus chinensis*	[17]
Armillaria mellea	*Gastrodia elata*	[18]

Effect of Climate on Endophytic Population

Endophytic population varies from plant to plant and from species to species. Within the same species it not only varies from region to region but also differs with change in climatic conditions of the same region. Chareprasert *et al.*, [19] studied the temporal changes in relative frequency of total endophytic fungi. They found that matured leaves of teak (*Tectona grandis L.*) and rain tree (*Samanea saman Merr*.) had greater number of genera and species, with higher colonization frequency, than those in the young leaves and their occurrence in leaves increased during rainy season. Not only climate but seasons and plant part also affects their occurrence [20].

Plant-Endophyte Interactions

Any plant-fungal interaction is preceded by a physical encounter between a plant and a fungus, followed by several physical and chemical barriers that must be overcome to successfully establish an association (**Figure 1**).

To address how an endophyte avoids activating the host defenses, ensures self-resistance before being in capacitated by the toxic metabolites of the host, and manages to grow within its host without causing visible manifestations of infection or disease was initially proposed the ‘‘balanced antagonism’’ hypothesis [22, 23] (Figure 1(1)). This hypothesis proposed that asymptomatic colonization is a balance of antagonisms between the host and the endophyte. Endophytes and pathogens both possess many virulence factors that are countered by plant defense mechanisms. If fungal virulence and plant defense are balanced, the association remains apparently asymptomatic and avirulent. This phase is only a transitory period where environmental factors play a major role to destabilize the delicate balance of antagonisms. If the plant defense mechanisms completely counteract the fungal virulence factors, the fungus will perish. Conversely, if the plant succumbs to the virulence of the fungus, a plant-pathogen relationship would lead to plant disease (Figure 1(2)). They might be influenced by certain intrinsic or environmental factors to express factors that lead to pathogenicity because many endophytes could possibly be latent pathogens [24] (Figure 1 (3)). The plant-endophyte interaction might not be just equilibrium between virulence and defense, but a much more complex and precisely controlled interaction. Endophytes might protect host plants by creating a heterogeneous chemical composition within and among plant organs that are otherwise genetically uniform [25] according to the ‘‘mosaic effect’’ theory. Endophytes might assist their corresponding host plants as ‘‘acquired immune systems’’ [26] holds by the other theory. Howitz and Sinclair [27] proposed ‘‘xenohormesis’’ hypothesis states that signaling and stress induced molecules from plants can be sensed by heterotrophs (animals and microbes), which have developed such ability under evolutionary selective pressures. The heterotrophs might have retained the capacity to sense chemical cues in plants to start producing similar secondary metabolites again, though they have gradually lost the capacity to biosynthesize these compounds. Hence, it is possible that certain gene clusters have remained homologous over evolutionary time across plants, microbes, and animals, and these might be activated by suitable plant-endophyte and/or endophyte-endophyte associations. It is possible that various so-called ‘‘plant metabolites’’ could in fact be the biosynthetic products of their endophytes.

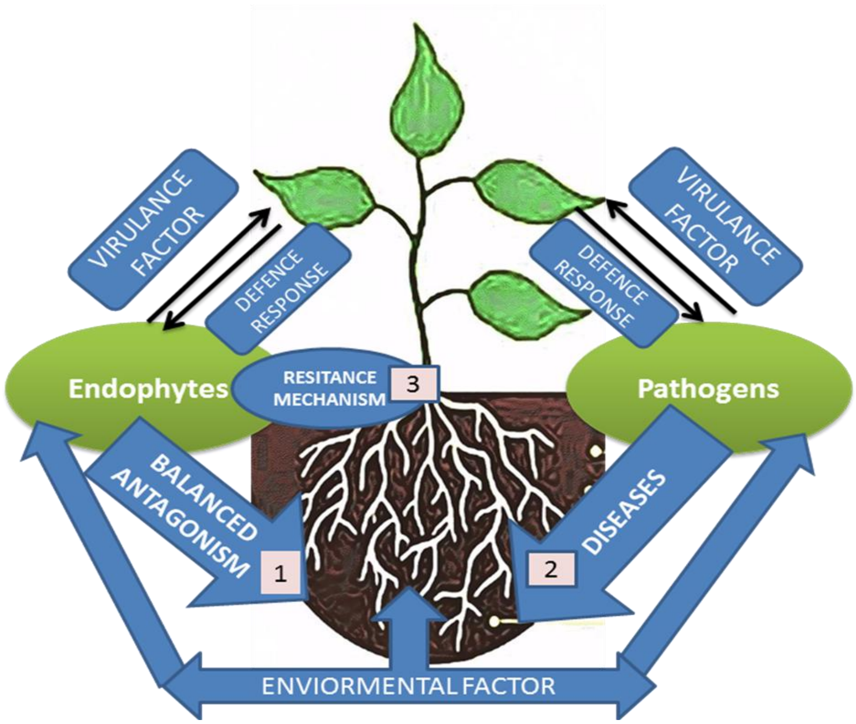

Figure 1 Chemical ecological schematic interpretation of plant fungus cost benefit interactions with emphasis on endophytic fungi (1) Balanced antagonism hypothesis is shown (2) Plant disease caused by pathogenic fungi is presented (3) Endophyte survival strategy is illustrated [21].

Endophytes as a source of bioactive metabolites

Plants endophytes associated with medicinal plants are chemical synthesizers which produce secondary metabolites can be exploited for curing many diseases. Many researchers isolated and identified various bioactive metabolites from endophytic fungi [28, 29]. Fermentation of endophytic fungi with potential for bioactive compound production has several advantages, like reproducible and dependable productivity. It can be grown in fermenters to provide inexhaustible supply of bioactive compound and thus can be exploited commercially. For optimizing various biosynthetic pathways by direct changes in the culture conditions can be explored as a method which leads to the production of derivatives and analogues of novel compounds [30]. Some of the important categories of bioactive metabolites produced by fungal endophytes of medicinal plants are discussed in **Table 2**.

Antimicrobial Activity

Antibiotic activity beard by metabolites can be defined as low-molecular-weight organic natural substances made by microorganisms that are active at low concentrations against other microorganisms. Antimicrobial activity possessed by some endophytic fungi that may be involved in a symbiotic association with a host plant [42]. By human kind the antimicrobial compounds can be used not only as drugs but also as food preservatives for the control of food spoilage and food-borne diseases, which is a serious concern in the world food chain [43]. From endophyte, *Armillaria mellea* a large number of antimicrobial compounds were isolated belonging to several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids which showed antimicrobial activity against Gram positive bacteria, yeast and fungi [44]. Endophytic fungus *Penicillium janthinellum* residing in the fruits of *Melia azedarach*a produced compound polyketide citrinin showed 100% antibacterial activity against *Leishmania sp*. [45]. Antibacterial compound YX-28 was isolated from *Ginkgo biloba L*. having activity against several food-borne and food spoilage microorganisms including *Staphylococcus aureus, Escherichia coli, Salmonella sp., Yersinia sp., Vibrio sp., Candida albicans, Penicillium expansum,* and *Aspergillus niger,* especially to *Aeromonas hydrophila,* and was suggested to be used as natural preservative in food.

Table 2 List of biological activities and bioactive compounds isolated from endophytic fungi

Endophytic fungi	Host plant	Chemical compound	Biological activities	Reference
Muscodor albus	*Cinnamomum Zeylanicum*	1-butano,3-methylacetate	Antimicrobial	[31]
Chaetomium chiversii C5-36-62	*Ephedra Fasciculata*	Radicicol	Cytotoxic	[32]
Phomopsis sp.	*Erythrina crista-galli*	Isoflavonoids	Antimicrobial	[33]
Xylaria sp. YX-28	*Ginkgo biloba*	7-amino-4-Methylcoumarin	Antimicrobial	[34]
Phomopsis sp.	*Plumeria acutifolia*	Terpenoid	Antimicrobial	[35]
MuscodorCrispans	*Ananas Ananassoides*	propanoic acid, methyl ester, 2-methylbutyl ester, Ethanol	Antibiotic	[36]
Emericella sp.	*Aegiceras corniculatum*	Emerimidine A, Emeriphenolicins B, Aspernidine A and B, Austin, Austinol, Dehydroaustin, Acetoxydehydroaustin	Antiviral	[37]
*Muscodor albus*E-6	*Guazuma ulmifolia*	Caryophyllene, phenylethyl alcohol, 2-phenylethyl ester, bulnesene	Antibiotic	[38]
Ampelomyces sp.	*Urospermum picroides*	3-Omethyl alaternin & altersolanol A	Antimicrobial	[39]
Chloridium sp.	*Azadirachta indica* A. Juss	Javanicin	Antibacterial	[40]
Streptomyces NRRL 30562	*Kennedia nigricans*	Munumbicin A,B,C and D	Antimicrobial	[39]
Cryptosporiopsis quercina	*Tvipterigeum wilfordii*	Cryptocandin	Antimicrobial	[41]

Antifungal activity

Some endophytes shows antifungal activities like *Serratia marcescens* was recovered from *Rhyncholacis penicillata* which produces Oocydin A, a novel antioomycetous compound having the properties of a chlorinated macrocyclic lactone [46]. To control the ever-threatening presence of oomyceteous fungi such as *Pythium* and *Phytophthora* in agriculture, Oocydin A is being considered a good option [46]. From the endophytic fungus *Pestalotiopsis*, two compounds Pestalachlorides A and B display a significant antifungal activity against three plant pathogenic fungi, *Fusarium culmorum, Gibberella zeae,* and *Verticillium albo-atrum* [47]. Chaetomugilin A and D with antifungal activities isolated from endophytic fungus *Chaetomium globosum* collected from *Ginkgo biloba* [48]. Cytosporone B and C were purified from a mangrove endophytic fungus, *Phomopsis sp*. and inhibit the activity of two fungi *Candida albicans* and *Fusarium oxysporum*.

Anticancer compounds

Research on novel anti-cancer drugs is today's need due to its high worldwide mortality rate causing by cancer. A powerful antimitotic agent Taxol with excellent activity against a range of cancers, was originally isolated from *Taxus brevifolia* plant [49]. By enhancing the assembly of microtubules and inhibiting their depolymerisation it can kill tumor cells [50]. This compound is the world's first billion-dollar anticancer drug and used to treat breast, lung, ovarian cancer and other human tissue proliferating disease. Endophyte *Taxomyces andreanae* producing Taxol has provided an alternative approach to obtain a cheaper and more available product via microorganism fermentation [51]. Some endophytic fungi belonging to different genera such as *Taxomyces andreanae, Pestalotiopsis microspora, Alternaria alternata, Periconia* sp., *Pithomyces* sp., *Chaetomella raphigera, Monochaetia* sp., *Seimatoantlerium nepalense, Botryodiplodia theobromae*, and *Bartalinia robillardoides* are reported to produce Taxol. *Nothapodytes foetida*, a medicinal plant native to the Western Ghats, India, have *Entrophospora infrequens* SW116 endophyte, which was found to produce camptothecin [52]. Cytotoxicity against the human leukemia K562 and colon cancer SW1116 cell lines was recorded by an alkaloid Chaetominine obtained from *Chaetomium* sp. IFB-E015, an endophytic fungus from *Adenophora axiliflora* [53]. From the endophytic fungus *Phaeosphaeri avenari* bioactive compounds Phaeosphoramides A and B were isolated. Phaeosphoramide A was found to be an inhibitor of the signal transducer and activator of transcription (STAT)-3, which plays a vital role in regulating cell growth and survival, constituting a target for anticancer therapy [54]. *Trametes hirsuta* a novel fungal endophyte, produced podophyllotoxin and other related aryl tetralin lignans with potent anticancer properties [52].

Antioxidant compounds

Antioxidants are the compounds which protection to the cells caused by free radicals. Free radical mediated reactions are associated with degenerative diseases like cancer, Alzheimer's disease etc [55]. Owing to the fact that only few antioxidants are approved for clinical applications there is a need to search for new and effective antioxidants. Discovery of pestacin and isopestacin as antioxidant compounds from *Pestalotiopsis microspora* residing in *Terminalia morobensis* plant led to the exploration of antioxidant potential of this less explored group of fungi [56]. Graphislactone A was isolated from *Cephalosporium* sp. IFB-E001, an endophytic in *Trachelspermum jasminoides*. *In-vitro*, the compound was confirmed to have stronger antioxidant activity as compared to butylated hydroxytoluene and ascorbic acid which were used as positive control [57].

Antiviral compounds

The discovery of the potential of endophytes for the production of antiviral compounds is still in its infancy. There are only limited numbers of compounds reported as antiviral agents from endophytes. The main limitation to antiviral compound discovery is most probably related to the absence of antiviral screening system in most of the compound discovery programs. Two novel compounds cytonic acid A ($C_{32}H_{36}O_{10}$) and B ($C_{32}H_{36}O_{10}$) have been isolated from *Cytonaema* sp. Isomers of p-tridepside are reported to be the novel human cytomegalovirus protease inhibitors and their structure was elucidated by mass spectrometry and NMR methods [58]. Singh *et al*., [59] reported an antiviral compound Hinnuliquinone, a potent inhibitor of the HIV-1 protease, from the endophytic fungi inhabiting in the leaves of Oak trees (*Quercus coccifera*). Four new compounds have been isolated from *Pullularia* sp. BCC 8613. The compounds isolated were Pullularins A–D (cyclo hexadepsi-peptides). Pullularin A exhibited activities against the herpes simplex virus type-1 and also against the malaria parasite *Plasmodium falciparum* K1 [60]. From the fungal endophyte *Pestalotiopsis theae* of an unidentified tree on Jianfeng Mountain, China isolated an important antiviral compound Pestalotheol- C which showed anti-HIV properties [47].

Antitubercular compounds

The World Health Organization (WHO) estimated that currently 50 million people are infected and 1500 people die each hour from tuberculosis worldwide. After emergence and spread of *Mycobacterium tuberculosis* resistant strains to multiple drugs, the search for new anti-mycobacterial agents has started. The globe recognized medicinal plants as repository for fungal endophytes with metabolites containing novel molecular structure and biologically active compounds against various human pathogenic diseases for potential use in modern medicine. Endophytic fungi from *Garcinia* sp. are good source for exploring the possibility of new antimycobacterial drugs. From the endophytic fungus *Phomopsis* sp. of *Garcinia* sp. Phomoxanthone A and B were isolated which exhibits significant activity against *M. tuberculosis* [61]. Some metabolites such as Phomoenamide and Phomonitroester inhibiting *M. tuberculosis* were also reported to be produced by *Phomopsis* sp. isolated from *Garcini adulcis* [62].Tenuazonic acid was isolated by bioassay guided fractionation of dichloromethane extract of *Alternaria alternate* which was found to be active against *M. tuberculosis* [63]. *Diaporthe sp*. isolated from *Pandanus amaryllifolius* leaves produced two new benzopyran, diaportheone A and B which inhibit the growth of virulent strains of *M. tuberculosis* [64].

Conclusions

Endophytes have proven to be a rich source of novel natural compounds with a wide-spectrum of biological activities and a high level of structural diversity. Bioactive natural compounds produced by endophytes have shown promising potential and usefulness in safety and human health concerns. Taking advantage of modern biotechnology such as genetic engineering, metabolic technology and microbial fermentation process, we can better understand and manipulate this important microorganism resource, and make it more beneficial for the mankind. Discovering new chemical compounds from natural products is very important for formulating new drugs. Endophytic fungi have received more attention as they can sometimes produce bioactive compounds analogous to their hosts. Isolation of endophytic fungi from medicinal and other plants to produce biologically active agents for biological utilization on a large commercial scale is possible because they can easily culture in laboratory instead of harvesting plants and affecting the environmental biodiversity. Medicinal plant acts as a richest source of endophytic fungi. Research on endophytic fungi are a new and exciting avenue for biotechnology, opening the possibility of discovering new ways of economically using fungal species for both biological control and plant growth promotion. Due to their great importance were showed in plants, scientists have exploited endophytic fungi very much attention for detection of bioactive compounds in the form of antimicrobial activity, anticancer activity etc. The endophytic fungi secreted alkaloids, terpenoids, flavonoids, and steroids, which were also known as secondary metabolites responsible for showing antimicrobial activity or anticancer activity. It becomes sensible to review on past achievements in the field of endophytic research, opening up broader opportunities for the scientific community. Endophytic fungi are excellent sources of bioactive natural products that can be used to satisfy demand of pharmaceutical industries.

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