Review Paper:

Bioactive secondary metabolites and their exploitation in the pharmaceutical industry produced by endophytic fungi

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Abstract

Historically, bioactive compounds produced by animals, plants and microorganisms have been a rich source of lead molecules in drug discovery. Plant and endophytic fungi are considered a source of a plethora of bioactive compounds with potential applications in the agriculture, pharmaceutical and food industry. Endophytic fungi are ubiquitous microorganisms living asymptomatically within the tissue of higher plants without causing any adverse effects or visible symptoms.

In this scenario, fungal endophytic bioactive compounds have an important function to endorse plant growth through diverse mechanisms. They are equally important economically to humans by plating as antibiotics, drugs, medicines, compounds of high relevance in research, or compounds useful in the food industry. Many antibiotics such as ivermectin and validamycin and anti-cancerous compounds such as taxol, cytospolides Q, P, colletotriolide, mycoleptodiscin B etc. have been successfully isolated from endophytic fungi. This review will highlight the different fungal endophytic classes and their exolites for medicinal use and applications in pharmaceuticals.

Keywords: Endophytic fungi, secondary metabolites, antibiotics, drugs, pharmaceuticals.

Introduction

Endophytes are a group of microorganisms that contain mostly bacteria and fungi which infect plant tissue without affecting any adverse/negative changes with plants for at least a part of their life cycle. Endophytic fungi belong to the group of highly diverse fungi that are generally found with all classes of vascular plants, bryophytes, ferns grasses and cultivated crops of either monocots or dicots[1].The plants and endophytes are symbiotically related to each other, thus benefitting the plant by protecting them from pathogens and stress and enhancing the nutrient uptake.

In turn, endophytes obtain their nutrition from the plants[2]. One of the most significant roles of endophytic fungi is to instigate the biological degradation of dead plants, which is essential for the nutrient cycle[3]. Endophytic fungi enter through the root of the plant with the help of natural gaps or insects and can be found in any part of the plant but mostly on the upper part of the plant generally leaves. The endophytic fungi may transfer vertically or horizontally from one generation to another in which vertical transfer occurs by the seeds or during plant reproduction and horizontal transfer occurs by air, water and insects[4].

Endophytic fungi may present entirely in all parts of the plant including stem, root and leaves, but mycorrhizal fungi colonize in the plant root only and grow into the rhizosphere to produce a number of bioactive metabolites. It can serve as an exceptional source of plant derived drugs (as camptothecin, diosgenin, hypericin, paclitaxel, podophyllotoxin andvinblastine) used against numerous ailments isolated from various endophytes. It has been also used in various industries such as cosmetics, food and agriculture and industries[5,6] that function as defensive weapons to protect the host plant from pests and diseases.[7,8]

In this review, we mainly focus on the occurrences and types of endophytic fungi releasing bioactive compounds and their uses in various therapeutic diseases.

Occurrence of endophytic fungi

In recent past, over one million endophytes have been extracted by researchers from plant parts (root, shoot and leaves), belonging to the tropical ecosystems. There are approx. 300,000 plant containing at least one or more endophyte (s)[9] found in Australia, Asia, America, Africa and some Pacific and Atlantic islands. The diversity of endophytic fungi is expected to be high in the dry tropical forest of southern India[10]. According to Rodriguez et al[30], cytospolides Q and P, colletotriolide, mycoleptodiscin B and fungal endophytes have been characterized into two major groups based on plant host, taxonomy and ecological function[11].

Clavicipitaceous (C-Endophytes): Clavicipitaceous endophytes belong to the family *Clavicipitaceae*, with genera *Balansia*, *Cordyceps*, *Myriogenospora* and *Neotyphodium*. C-endophytes or class-1 endophytes infect some cool and warm season grasses and may present within the plant shoot without causing any adverse/negative effects. These endophytes are transferred vertically by passing fungi from one offspring to another via seed infection.

Class-1 endophytes are present in the seeds of *Lolium temulentum, L. arvense, L. linicolum* and *L. remotum*[10].

Non Clavicipitaceous (NC-Endophytes): The taxonomy of non-clavicipitaceous endophytes has not been well-defined, but major species of this endophyte with genera are: *Aspergillus, Arthrobotrys, Alternaria, Colletotrichum, Cladosporium, Coprinellus, Fusarium, Penicillium* and *Paecilomyces.*

On the basis of differences in life history, ecological interaction and mode of reproduction, these endophytes are classified into three major classes namely class 2, class 3 and class 4. NC-Endophytes colonize into shoot and root tissues of terrestrial plants, nonvascular plants, angiosperms, ferns and gymnosperms[11].

Class-2 Endophytes: The class-2 endophytes belong to the phylum Ascomycota to basidiomycota. Class-2 endophytes are mutualistic, avoiding abiotic stress via symbiosis and obtaining nutrition for growth and reproduction from host tissues. Class-2 endophytes asymptomatically colonize into root, stem and leaves and transfer vertically from one generation to another via seed coat and rhizomes. These fungal endophytes have been used in agriculture biology to reduce the problem of water, drought and salination stresses[11].

Class-3 Endophytes: They belong to the phylum ascomycota and basidiomycota. Class-3 endophytes generally colonize the tissue of stem and transfer horizontally from one offspring. This type of endophytic fungi is generally found in photosynthetic tissue, wood and lichens[11].

Class-4 Endophytes: Merlin observed a pigmented brown to blackish coloured fungus, which is associated with terrestrial plant roots[12]. He named this fungus as mycelium radicus astrovirens (MRA)[11]. Nowadays, these fungi are referred to as 'dark septate endophytes' (DSE) and are found worldwide throughout the tropical ecosystem, Antarctic, Arctic, African coastal plains and lowlands in the root of plants. More than 135 species of DSE are reported in root tissue by Peyronel. DSE represents a huge and exciting class of endophytes that have not yet been well defined taxonomically or ecologically. Many authors have reported that *P. fortinii* is usually present in the root and transfers their genetic material horizontally from one to other genera as the best example of dark septate endophyte (DSE)[11].

Fungal entophytes and bioactives

Over the last 20 years, a variety of bioactive compounds with a number of biological activities and chemical structures have been discovered. It has been shown that endophytic fungi produce several pharmacologically important compounds such as anticancer anti-oxidant, antifungal.[13]

Anti-cancerous metabolites: Cancer is defined as uncontrolled development of abnormal cells resulting in a cluster of diseases cytospolides Q and P, colletotriolide, mycoleptodiscin B that influence different normal tissues and organs of the body. Eventually, cancer extends to different parts of the body, generates new tumors and ultimately leads to death. The data as of 2007 indicated a death rate of 7.6 million people due to cancer globally and is estimated to increase to 17.5 million by 2050, basically due to an increased population, aging, lifestyle and surrounding pressure which accounts for smoking and coverage of carcinogens[14].

Natural drugs produced from plants suffer from various limitations formed at particular growth periods and over definite ecological circumstances. Extraction and accumulation of natural products also have various limitations like slow plant growth and an appropriate growth phase. As a result of these restrictions linked with the yield and susceptibility of plants as basis of novel secondary metabolites, microbes provide as a vital and unlimited cause of new compositions having medicinal prospective[15].

Currently, endophytic fungi have been targeted by biotechnological industries due to its pharmacological properties. At the present time, thousands of anti-cancerous compounds have been isolated from different endophytic fungi worldwide by biotechnological interventions[15].

Antioxidant metabolites: By various cellular processes, free radicals and reactive oxygen species (ROS) are formed which play a useful role in signal transduction; however, excessive production of ROS causes a variety of adverse effects in cells and tissues. Because of these adverse effects, a wide range of chronic and acute diseases such as cancer, Alzheimer, asthma, atherosclerosis, hypertension, ischemia/reperfusion injury, cardiovascular disease, ageing, diabetes, inflammatory joint disease are developed[16] (Table 1).

Antifungal activity: Endophytic fungi also produce some secondary metabolites with antifungal activity. *Gilmaniella* sp. AL12 is an endophytic fungus that produces jasmonic acid, which induces defense responses against fungus. Some other endophytic fungi such as *Chaetomium globosum* L18, *Trichothecium roseum, Phomopsis cassiae*, *Myxormia* sp. and *Cryptosporiopsis* cf. *quercina* produce chemicals against pathogens. Endophytic fungi such as *Choiromyces aboriginum*, *Stachybotrys elegans* and *Cylindrocarpon* sp. produce cell wall degrading enzymes to kill pathogenic fungi.

Immunomodulatory compounds: The discovery of immunomodulatory agents from endophytic fungi lacing up the noxious side effects, with enhanced bioavailability and a long duration is of great actuality[26]. The first immunomodulatory compound is cyclosporine-A produced by the endophytic fungi *Tolypocladium inflatum.* The other immunomodulatory compound is Subglutinol-A, B produced by an endophytic fungi *Fusarium subglutinans*[27]. Mycophenolic acid and Collutelin A are also immunomodulatory compounds produced by the endophytic fungi *Penicillium* and *Colletotrichum dematium* respectively.[28]

Antiviral compounds: Alternatively use of antibiotic products isolated from endophytic fungi inhibits some viruses. More recently, Wellensiek et al[45] isolated hundreds of metabolites from endophytic fungi of desert plants and evaluated the inhibitory effects on HIV-1 replication. After multiple rounds of fractionation and antiviral evaluation, four compounds were identified as a potent inhibiter of HIV-1 replication.

Even though the compounds from endophytes having antiviral activity are in infancy, some compounds have been found promising. The main challenging in compound discovery is the absence of the systems related to antiviral screening in compound discovery programs[34].

Anti-malarial compounds: Malaria is a common disease caused by a parasite from the *Plasmodium* species. This parasite infects humans by the female anopheles mosquito and causes severe infection and even death. Chloroquine is the most common drug used against malarial infection because chloroquine is cheap and easily available, but it has been found that *P. falciparum* can be resistant to chloroquinein[36,37].

Table 1
Endophytes and host derived metabolites used as antioxidant

Endophytes	Host	Antioxidant
Pestalotiopsis microspora[17]	*Terminalia morobensis*	Pestacin
		isopestacin
Cochliobolus nisikado[18]	*Cinnamomum camphora* chvar. Borneol	Borneol
Fusarium oxysporum, Neonectria macrodidym, F. proliferatum, F. solani[19]	*Cajanus cajan*	Cajaninstilbene acid
Cephalosporium sp.[20,21]	*Trachelospermum jasminoides*	Graphislactone A
	Sinarundinaria nitida	4,6-dihydroxy-5-methoxy-7-methylphthalide

Table 2
Endophytes and host derived metabolites used as anti-fungal activities

Endophytes	Host	Anti-fungus	Mechanism
Gilmaniella sp. AL12[22]	*Atractylodes lancea*	Unidentified	Produce jasmonic acid inducing defense responses
Chaetomium globosum L18[23]	*Curcuma wenyujin*	Unidentified	Some metabolites anti- pathogens
Trichothecium roseum[24]	*Maytenus hookeri*	Unidentified	Trichothecin used as a anti-pathogens
Cylindrocarpon sp., *Choiromyces aboriginum, Stachybotrys elegans*[25]	*Phragmites australis*	Unidentified	Realizing antifungal to kill pathogenic fungi.
Phomopsis cassiae[18]	*Cassia spectabilis*	*Cadosporium sphaerospermum* and *C. cladosporioides*	Produce cadinane sesquiterpenoids toxic to pathogens
Myxormia sp.[18]	*Angelica sinensis*	*Fusarium oxysporum* and *F. solani*	Produce some chemicals toxic to pathogens
Cryptosporiopsis cf. *quercina*[18]	*Triptergyium wilfordii*	*Pyricularia oryzae*	Produce cryptocin and cryptocandin toxic to pathogens

Table 3
Endophytes and host derived metabolites used as immunomodulatory agents

Endophytes	Host	Immunomodulatory agents
Fusarium subglutinans[29]	*Tripterygium wilfordii*	Subglutinol-A, Subglutinol-B
Tolypocladium inflatum[30]	Produced by submerged fermentation	cyclosporine-A
Penicillium brevicompactum[31]	Production in aerial hyphea	Mycophenolic acid
Colletotrichum dematium[32]	*Pteromischum* sp.	Collutelin A

Metwaly et al[25] extracted *Trichosporum* sp. from *Trigonella foenum-graecum* known as endophytes. Two new diketopiperazine alkaloid isomers, namely (6-*S*)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl) piperazine-2, 2,5-dione and (6- *R*)-3-(1,3-dihydroxypropyl)-6-(2-methylpropyl)piperazine-2,5-dione, showed anti-leishmanial activities against *Leishmania donovani* with IC_{50} values of 96.3 and 82.5 µg/ml, respectively.[38]

Endophytic fungi and novel peptides: There have been a number of peptides isolated by researchers from endophytic fungi for drug development because of the higher degree of interactions. In a recent study, it has been reported that instead of metabolite production, endophytic fungi are also producing peptides with higher pharmacological activities. It has been reported that there is no difference in the structure of peptides isolated from endophytic fungi and non-endophytic microorganisms. Therefore, endophytic fungi use the same biosynthetic pathway as non-endophytic microorganisms[42].

Currently, non-ribosomal peptide synthetases (NRPSs) evaluate the peptide producing capability of isolated endophytic fungi or bacteria. Some endophytic fungi are not capable of producing peptides because their NPRS gene clusters are silent having imperative therapeutic applications such as anticancer agents, antibiotics, antifungals, immunosuppressants, herbicides, insecticides, enzyme inhibitors and siderophores.[42,43]

An endophytic fungi *Talaromyces wortmannii* produces two peptides namely Talaromins A and B from the aloe vera plant[44]. Epichloënin A and B were identified from *Lolium perenne* infected with endophytic fungi *E. festucae*. Fusaristatin A and B are two cyclic lipopeptides isolated from the endophytic fungi of *Fusarium* sp.[42] . Fusaristatin A and B have anti-cancerous properties against lung cancer cells LU65. 1962A, cyclo-(D-Leu-Gly-L-Tyr-L-Val-Gly-S–O Leu) and 1962B, cyclo-(D-Leu-Gly-L-Phe-L-Val-Gly-S–O-Leu) had shown anti-cancerous activity isolated from *Aspergillus terreus*, from *Kandelia candel*[45].

Table 4
Endophytes and host derived metabolites used as antiviral agents

Endophytes	Host	Antiviral agents
Cytonaema sp.[34]	*Quercus* sp.	cytonic acid A cytonic acid B
Enterococcus faecium[35]	*Quercus coccifera*	Hinnuliquinone

Table 5
Endophytes and host derived metabolites used as antiviral agents

Endophytes	Host	Antimalarial agents	Parasites
Embellisia sp.[39]	*Stemona* sp.	11-hydroxymonocerin	*P. falciparum*
		12-hydroxymonocerin	
Xylaria sp.[40]	*Sandoricum koetjape*	2-chloro-5-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione	
		Xylariaquinone A	
Trichoderma sp.[41]	*Tinaspora crispa* L.	7- hydroxy-3,4,5-trimethyl-6-on-2,3,4,6-tetrahydroisoquinoline-8-carboxylic	
		2,5-dihydroxy-1-(hydroxymethyl)pyridin-4-on	

Table 6
Endophytes and host derived peptides used in numerous diseases

Endophytes	Host	Peptide
Talaromyces wortmannii	*Aloe barbadensis* Mill.	Talaromins A and B
Epichloe festucae	*Lolium perenne*	Epichloënin A and B
Fusarium sp.	*Oryza sativa*	Fusaristatins A and B
Aspergillus terreus	*Kandelia candel*	Depsipeptides 1962A, 1962B
Penicillium sp.	*Acrostichum aureurm*	Cyclo-(Pro-Thr), Cyclo-(Pro-Tyr)
Epichloe typhina	*Phleum pretense* L.	Epichlicin
Curvularia geniculata	*Catunaregam tomentosa*	Curvularides A–E
Colletotrichum dematium	*Pteromischum* sp.	Colutellin A
Trichothecium roseum	*Imperata cylindrical* L.	Trichomides A and B
Bipolaris sorokiniana	*Rhazya stricta*	BZR-cotoxin I and IV

Cyclo-(Pro-Thr) and Cyclo-(Pro-Tyr*) from Penicillium* sp. isolated from *Acrostichum aureurm* showed antibacterial activity against *Staphylococcus aureus* and *Candida albicans.* Epichlicin known as novel peptides isolated from *Epichloe typhina endophytes* showed a strong antifungal activity against *Cladosporium phlei*[46].

Conclusion

The need for new bioactive compounds to overcome the growing problems of disease causing pathogens is of increasing importance. Many endophytic fungi are able to produce antiviral, antifungal, antimalarial, antibacterial, anti-cancerous and antileishmanial compounds in preliminary tests. Endophytic fungi also reduce the use of chemical fertilizers by producing growth hormones in the host plant. Endophytic microorganisms are also used in modern biotechnology, such as microbial fermentation processes, metabolic technology, genetic engineering and food processing. Many antibiotics such as ivermectin and validamycin have been successfully developed through the fermentation technology.

Compared to cell cultures, the fermentation period is short, low production costs, simple process and it provides the best growth and easily enhances the bioactive compound production by adding biotic and abiotic factors and/or by adding inhibitors or using special enzymes. In summary, endophytic fungi attract much attention in the research community for potential exploitation as an available source for therapeutic compounds that can be used in various fields such as medical, pharmaceutical, food and cosmetics.

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