This era of biotechnological tools: an insight into endophytic mycobiota

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Owing to the outbreak of fatal diseases that require searching for new compounds with high activity and/or novel action mechanisms, screening for promising sources of biologically active compounds that fulfill the current needs of humanity is a matter of life and death. Fungi generally and endophytic ones specifically represent future factories and potent biotechnological tools for production of bioactive natural substances, which could extend healthy life span of humanity (as done by penicillin from centuries), and are considered promising alternatives for some high costly produced chemicals and drugs. The present review highlights some bioactive secondary metabolites, produced by fungal endophytes, involved in medical, pharmaceutical, agricultural, and industrial applications.

Keywords:
biological activities, biotechnology, endophytic fungi, pigments, secondary metabolites, taxol

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Introduction

Endophytic mycobiota are fungi that commonly spend their life cycle (or part of it) inhabiting intercellular and/or intracellular spaces in the tissues of healthy plants without harmful aspects [1,2]. Literally, the word endophyte indeed describes location of these microorganisms: 'endo' means inside and 'phyte' means plants. These endophytes have key roles in enhancing the adaptation of host plants to environmental stresses such as salinity [3] and temperature [4]. Moreover, endophytes play important roles in promoting plant growth [5], and protecting the host plant from some pathogens [6–8].

Endophytes have been isolated from almost all plants, trees, palms, sea grasses, and lichens [9–11]. Many reports described the isolation process of endophytes from different plants as well as the predominance of some genera in a given plant species. However, the presence of such endophytes depends on many factors including environmental factors such as the geographical and topographic patterns, growing season, total soluble salts and pH of the soil, as well as nature and age of the host plant [12,13].

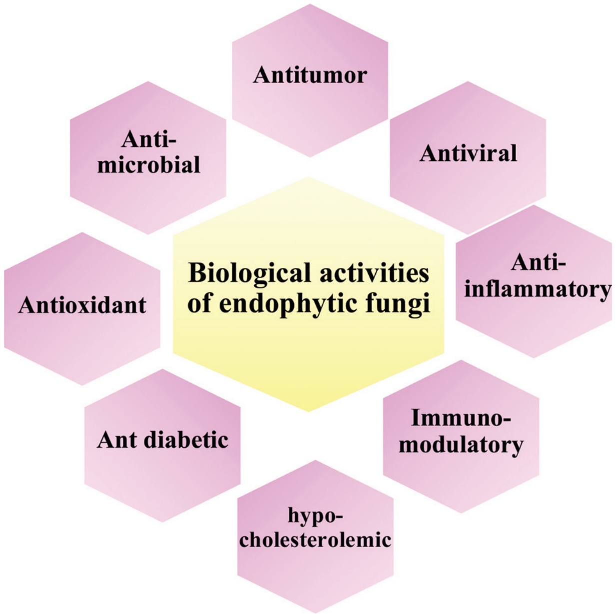
Various biological activities such as antitumor, antibacterial, antiviral, antimalarial, antidiabetic, hypocholesterolemic, and immunomodulatory are reported (Fig. 1) for some metabolites secreted by endophytic fungi, such as phenols, alkaloids, isoprenoids, steroids, isocoumarines, perylene derivatives, quinones, furandiones, xanthones, terpenoids, depsipeptides, cytochalasin, polyketides, proteins, peptides, lipids, shikimates, and glycosides [14,15]. Furthermore, endophytes produce various low-molecular-weight volatile organic compounds such as alcohols, ketones, esters, acids, and hydrocarbons [16]. On the contrary, many enzymes produced by endophytes are used nowadays in the industries of food, cosmetics, biofuels, paper, cellulose, textile, fine chemicals, detergents, biomaterials, and leather [17,18].

This review highlights some of the biotechnological applications of some fungal endophytes' secondary metabolites. Understanding the industrial, agriculture and/or medical importance of such products encourages screening for novel endophytic isolates, which represent an inexhaustible source for secondary metabolites, with potential biological activities and numerous benefits in different fields of biotechnology.

Antitumor medication (taxol)

Taxol (Paclitaxel) is a tetracyclic diterpene lactam that has been approved as a human cancer medication by the Food and Drug Administration owing to its high potency, low toxicity, and broad-spectrum anti-tumor activity [19]. Taxol was first isolated from western yew (*Taxus brevifolia*) [20], and its action mechanism includes inhibiting of microtubule

Figure 1



Biological activities exerted by metabolites produced by endophytic fungi.

depolymerization during cell cycle and cell growth, and then initiating cell apoptosis [21].

Nowadays, endophytic fungi are used as a biotechnological tool to produce taxol in short time and high productivity in comparison with the traditional production of taxol from yew tree species, as extraction of 1 kg of taxol requires cutting of ~300 trees, which is a huge ecological loss [22,23]. It is worth noting that full course in cancer treatment requires consuming ~2.5–3.0 g of taxol [24].

Taxol was produced for the first time from endophytes in 1993 by Stierle *et al.* [25] using the endophytic fungus *Taxomyces andreanae*, which colonizes yew trees. Successive studies have been reported investigating endophytic fungi capable of producing taxol, such as *Pestalotiopsis microspora* isolated from the Himalayan yew (*Taxus wallichiana*) [26], *Bartalinia robillardoides* Tassi isolated from Indian bael (*Aegle marmelos* Correa ex Roxb) [27], *Chaetomella raphigera* isolated from Arjun tree (*Terminalia arjuna*) [28], *Gliocladium* sp. isolated from English yew (*Taxus baccata*) [29], *Fusarium oxysporum* from a mangrove tree (*Rhizophora annamalayana*) [30], *Guignardia mangiferae* isolated from Anglojap yew (*Taxus media*) [31], *Fusarium redolens* isolated from east Himalayan yew (*Taxus baccata L.* subsp. *wallichiana* Zucc.) [32], *Phoma medicaginis* isolated also from Himalayan yew (*T. wallichiana* var. mairei) [33] and *Grammothele lineata* isolated from Jute mallow (*Corchorus olitorius*) [34].

Pigment production

Most of the natural dyes are eco-friendly (nontoxic and nonpolluting), have low cost of production, are less hazardous to health [35], and usually causes no allergic reactions in comparison with synthetic dyes. Moreover, some of these natural dyes have extra advantages over synthetic dyes such as having antioxidant and antimicrobial activities [36,37].

Generally, the produced pigments were tested for their color stability, by applying the dye on a set of four pieces of cloth (cotton, silk, wool, and polyester), and then their color properties were characterized [38]. Some mushroom extracts give colorful dyes such as *Bankera violascens*, which produces green dye; *Agaricus arvensis*, which generates blue shades; *Chroogomphus vinicolor*, which gives red dye; and *Collybia iocephala*, which gives a purple-blue dye [39]. However, cultivating these mushrooms under laboratory conditions is very difficult, and hence such mushrooms are not suitable for industrial production of dyes.

On the contrary, many ascomycetous and basidiomycetous fungi produce pigments such as anthraquinones, anthraquinone carboxylic acids and pre-anthraquinones as secondary metabolites, and these pigments can be extracted and then used in industries such as textile dying, cosmetics, as a food coloring ingredient, and in pharmaceuticals [40]. Some dematiaceous fungi such as *Curvularia lunata* and *Alternaria alternata* produce stable pigments used in textile dyeing [41], *Monascus roseus* produces pink to orange shades [42], *Helminthosporium avenae* produces bronze coloration [42], *Penicillium purpurogenum* produces red dye [43] and *Paecilomyces sinclairii* produces red dye [44].

Endophytes participate also in pigment production. A red dye was produced by an endophytic fungus identified as *Penicillium* sp., isolated from the leaves of the medicinal plant *Polygonum multiflorum* [45]. The reddish orange pigment lawsone (hennotannic acid) was produced by the endophytic fungus *Gibberella moniliformis* isolated from the leaf tissues of henna tree [46].

Biodegradation of polymers

Fungi have the most sophisticated and complex enzymatic machinery that are involved in countless applications in all biotechnological fields, owing to their magical capability of performing chemically difficult reactions. An example of the use of fungal enzymes is plastic biodegradation. Hence, fungi have been screened for their ability to degrade polymers. Many species were capable of doing such a mission, thanks to laccase enzymes, which have nonspecific oxidative action mechanism [47]. *Myceliophthora* sp. is one of the most potent reported fungi so far in terms of its ability to biodegrade polymer through metabolizing insoluble polymer and partially solubilizing it [48].

Laccases are used also in the detoxification of pollutants and in bioremediation of phenolic and nonphenolic compounds [49]. Moreover, these enzymes can successfully biodegrade wood, azo dyes [50], and jet fuel into simple compounds that can be used as nutrients. Moreover, these enzymes are involved in pulp delignification, in paper processing, in textile industry to improve the whiteness during conventional bleaching of cotton [51], and in the synthesis of some fine chemicals [52–55].

Laccases were produced by many endophytes such as *Monotospora* sp., isolated from Bahama grass (*Cynodon dactylon*) [56], *Colletotrichum gloeosporioides* gr. Isolated from Piper beetle [57], *Daldinia* sp. isolated from the leaves of Himalayan cypress (*Cupressus torulosa*) [49], and *Myrothecium verrucaria* isolated from pigeon pea [58].

Other enzymes used in applications

According to global markets, enzymes occupy an extremely important position in terms of sales as biotechnological tools. Enzymes are involved in leather tanning, starch and food processing, textile industry, protein hydrolysis, pharmaceutical and chemical manufacturing, detergent production, and as biofuel [59–66]. Moreover, many enzymes are involved in biodegradation of residual wastes [67,68], and in detoxification of heavy metals and many other toxic compounds [69,70].

Many fungi are capable of producing more than one enzyme efficiently; here, we will focus on some enzyme production, such as proteases, which are one of the largest and most diverse families of enzymes occupying a superior position in the list of total worldwide enzyme sales [71]. Proteases have a wide range of applications especially as analytical tools in basic research and molecular biology [72], peptides synthesis [73], leather processing [74], detergent production [75], meat tenderization [76], cheese manufacture, pharmaceutical industry [77], and many other industrial applications [78,79]. Endophytes such as *Acremonium typhinum* isolated from *Poa ampla* secrete proteinase [80], whereas *F. oxysporum* isolated from *Musa* sp. (Banana); *A. alternate*, isolated from *Eremophila longifolia* (Berrigan), and *A. alternata* isolated from gymnosperm tree *C. torulosa* (Himalayan cypress) produce protease [81–83].

On the contrary, fungal pectinases represent ~25% of the sales of global food and industrial enzymes [84]. Pectinases are involved in many industrial applications such as improving extraction of juices [85] and decreasing the viscosity of fruit juices [86]. They have other applications related to plant–fungal interactions [87]. Generally, pectinases are secreted by endophytes to facilitate their entrance through the cell wall of the host plant [88]. Aspergilli were the most potent genera used for commercial production of pectinases in the field of food processing [89]. Many endophytic fungi have the ability to synthesis pectinases such as *Talaromyces* sp. isolated from the medicinal plant *Calophyllum inophyllum* (Alexandrian laurel balltree) [90], and *Aspergillus japonicus* isolated from *Opuntia ficus-indica* Mill. (Forage cactus) [91].

Another example of the important enzyme group is amylases, which are also ranked among the most important enzymes used in many biotechnological, food and pharmaceutical applications, especially those concerned with starch hydrolysis and cyclodextrin production [92]. Amylases were secreted by endophytes such as *Discosia* sp. isolated from *C. inophyllum* (Alexandrian laurel balltree) [93], *Cylindrocephalum* sp. isolated from *Alpinia calcarata* (Haw.) Roscoe (Cardamom ginger) [90], and *Preussia minima* isolated from *E. longifolia* (berrigan) [94].

There is an endless list of enzymes used enormously in various fields, and fungi are the ideal producers of such enzymes. Therefore, research and screening for new fungal isolates that produce enzymes, investigating new biotechnological application, and studying those enzymes biochemical characteristics might lead to identification of novel enzymes with novel and improved applications.

Antimicrobial and antiviral activities

Many reports have described endophytic fungi exerting antimicrobial activities [95,96], such as *Phomopsis* sp., which produces phomopsichalasin [97]; the antifungal compound, cryptocandin, produced by *Cryptosporiopsis* cf. *quercina* [98]; and the antiparasitic metabolite, cercosporin, produced by *Mycosphaerella* sp. [99]. On the contrary, cytonic acid A and B were isolated from *Cytonaema* sp. These compounds are inhibitor of human cytomegalovirus protease [100].

Endophytes as biocontrol agents and plant growth promoters

Endophytes can protect and promote the growth of their host plant in different ways such as by synthesizing phytohormones, increasing their host plant tolerance to external stress, inducing its defense system, and/or acting as a biocontrol agent that vanquishes pathogen threats in their host plant [2,101–103]. Many endophytes were reported to inhibit specific plant pathogens *in vivo* and *in vitro*. For example, *C. gloeosporioides* isolated from Cacao is used to biologically control *Phytophthora* sp. and *Moniliophthora roreri*, causing frosty pod rot and witches broom diseases in cacao, respectively [104]. Plants pathogens *Aspergillus flavus* and *Fusarium verticillioides* were sensitive to Pyrrocidines A and B produced by the endophytic fungus, *Acremonium zeae*, isolated from maize [105]. *Phomopsis cassiae* secretes cadinane sesquiterpenes that protects its host *Cassia spectabilis* from the pathogenicity of *Cladosporium sphaerospermum*, and *C. cladosporioides* [106]. *Trichoderma harzianum* isolated from onion stalks showed antagonistic activity *in vitro* against the onion purple blotch pathogen *Alternaria porri* [107].

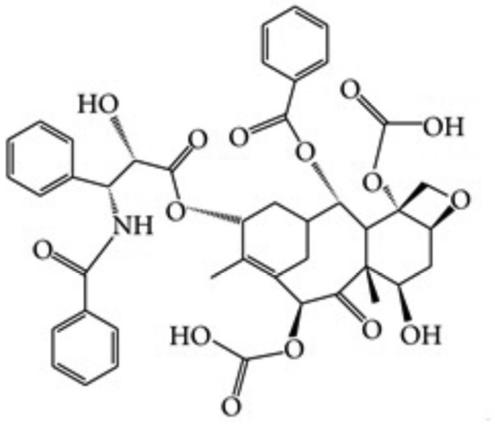
On the contrary, endophytes have a well-established role as an economical and eco-friendly plant growth promoter, which leads to an increase in crop production [108]. For example, the endophytic fungus *Piriformospora indica* isolated from roots of many plants was commonly used as a plant growth promoter [109].

There are unlimited uses of the numerous promising secondary metabolites originated and secreted by endophytes, and many examples are listed in Table 1. The chemical structures of some of these important metabolites are illustrated in Fig. 2. Screening and isolation of new endophytes can be the low-cost alternative for many currently used compounds. More studies are encouraged to understand and investigate metabolites secreted by these microorganisms and study activities and action mechanisms of novel ones, in addition to elucidating the relation between these endophytes and their host plant. Finally, further work is required to commercialize the production of biologically active compounds by endophytic fungi.

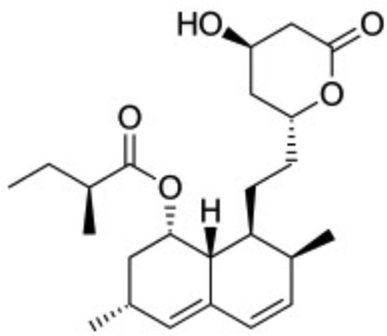
Table 1 List of some endophytes, their host plants, and their isolated biologically active metabolites

Endophytic fungi	Host plants		Metabolites	Importance	References
	Scientific names	Common names			
Phomopsis sp.	*Erythrina crista-galli*	Coral tree	Mevinic acid	Anti-inflammatory	[110]
Pestalotiopsis microspora	*Terminalia morobensis*	Arjun tree	Pestacin and isopestacin	Antioxidant	[111]
Aspergillus clavatonanicus	*Torreya mairei*	Maire's yew	Clavatol	Antimicrobial	[112]
Cytonaema sp.	*Quercus* sp.	Oak	Cytonic acid A and B	Inhibitor of human cytomegalovirus protease	[100]
Aspergillus niger PN2	*Taxus baccata*	English yew	Lovastatin	Lowering blood cholesterol	[113]
Xylaria sp. XC-16	*Toona sinensis*	Chinese mahogany	Cytochalasins	Anticancer	[114]
Fusarium subglutinans	*Tripterygium wilfordii*	Thunder duke vine	Subglutinol A and B	Immunosuppressive activity	[115]
Penicillium sp.	*Quercus variabilis*	Chinese cork oak	Penicidones A, B, and C	Cytotoxic	[116]
Gliocladium roseum (NRRL 50072)	*Eucryphia cordifolia*	The ulmo	2,6-dimethyl, 3,3,5-trimethyl; cyclohexene, 4-methyl; decane, 3,3,6-trimethyl; and undecane, 4,4dimethyl (volatile hydrocarbons)	Biofuels	[117]
Alternaria alternata RSF-6L	*Solanum nigrum*	Black nightshade	Indole acetic acid	Promote plant growth	[102]
Penicillium chrysogenum	*Teucrium polium* L.	Felty germander	Indole acetic acid	Promote plant growth	[118]
Trichoderma gamsii YIM PH30019	*Panax notoginseng*	Chinese ginseng	VOCs such as dimethyl disulfide, dibenzofuran, methanethiol, ketones	Biocontrol agent	[119]
Cochliobolus sp.(UFMGCB-555)	*Piptadenia adiantoides (Fabaceae)*	Piptadenia adiantoides	Cochlioquinone A and isocochlioquinone A	Leishmanicidal activity	[120]

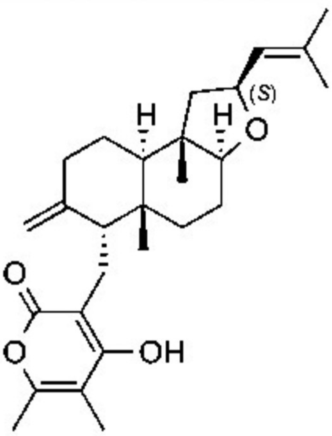
Figure 2



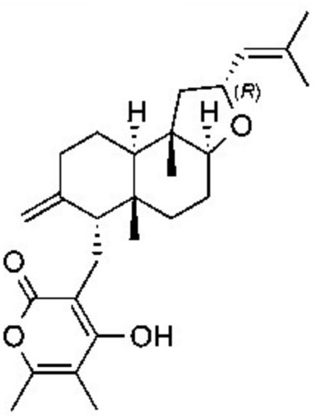
Taxol



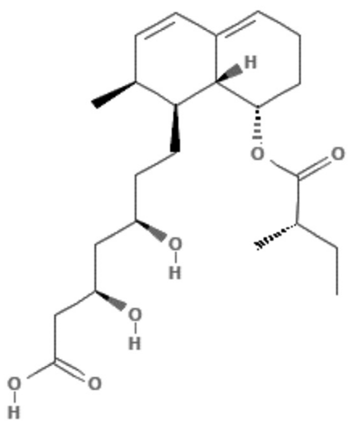
Lovastatin



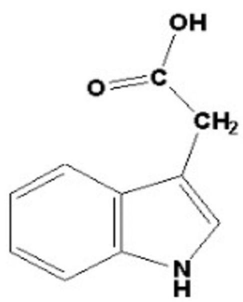
Subglutinol A



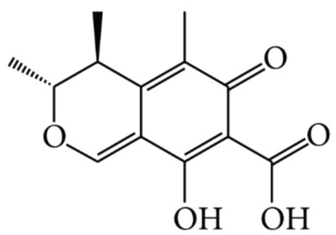
Subglutinol B



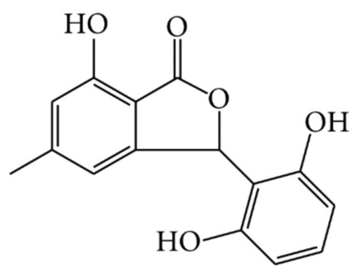
Mevinic acid



Indole acetic acid



Citrinin



Pestacin

Chemical structure of some important metabolites produced by endophytic mycobiota.

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Conflicts of interest

There are no conflicts of interest.

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