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A REVIEW OF THE MUTUALISTIC RELATIONSHIP OF ENDOPHYTIC FUNGI FOR THE PRODUCTION OF BIOACTIVE METABOLITES

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ABSTRACT: Endophytes constitute a remarkably multifarious group of microorganisms ubiquitous in plants and maintain an imperceptible association with their hosts for at least a part of their life cycle. Their enormous biological diversity, coupled with their capability to biosynthesize bioactive secondary metabolites, has provided the impetus for a number of investigations on endophytes. There is a need to search new ecological niches for the potential of natural bioactive agents for different pharmaceutical, agriculture, and industrial application; these should be renewable, eco-friendly, and easily obtainable natural products discovery in the search for new drugs and is the most potent source for the discovery of novel bioactive compounds. Therefore, a large number of bioactive compounds are isolated from plants, bacteria, fungi, and many other organisms. Endophytic fungi, the most promising of these, have been a source of various such bioactive compounds. Many of these compounds are being used for the treatment of a number of diseases. This review emphasis on the biology of fungal endophytes, their discovery, isolation, identification by morphological and molecular methods, production, purification and structure elucidation of the bioactive compounds.

INTRODUCTION: Fungi are important components in every ecosystem, intimately associated with crucial processes like the decomposition, recycling and transportation of nutrients in different environments. It has been estimated that there may be over a million different fungal species on this Earth, of which only a small fraction [approx. 5%] have been identified [1]. There are also many bacteria that exist as plant endophytes; in most instances, they coexist with endophytic fungi.

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The existence of endophytes has been known for over one hundred years. They live as imperfect fungi most of the time and have been described as benign parasites or true symbionts. It has been suggested that they can influence the host plants' distribution, ecology, physiology, and biochemistry [2]. Botanists have conducted much research about the relationship of plant endophytes, especially for grasses such as tall fescue, where it has been exhibited that endophytes produce toxins that discourage insects and other grazing animals [3].

It wasn't until the past decade that endophytes were extensively studied for their potential as novel sources of effective new drugs. Microbes, both fungi, and bacteria, have provided modern medicine or drugs with valuable, effective treatments, including penicillin from the fungus *Penicillium notatum* and bacitracin from *Bacillus* *subtilis*, a common bacterium. Additionally, a potent chemotherapeutic agent, taxol is synthesized by an endophyte of the Pacific Yew tree. Endophytes represent a huge diversity of microbial adaptations that have developed in special and sequestered environments. Their diversity and specialized habituation make them an exciting field of study in the search for new medicines or novel drug-like molecules. The hunt for new drugs is particularly important in view of the fact that so many microorganisms are developing resistance to some of the current drugs. Endophytic fungi are a group of fungi that colonize living and internal tissues of plants without causing any immediate, overt negative effects [4]. Recent studies have revealed these fungi's ubiquity, with an estimated 1 million species of endophytic fungi residing in plants [5] and even lichen [6]. Endophytic fungi represent an important and quantifiable component of fungal biodiversity and are known to affect plant community diversity and structure [7]. According to [1], only about 100,000 fungal species have been described out of a conservative estimate of 1.5 million. Recent studies of endophytic fungi from tropical and temperate forests support the high estimates of species diversity [8-10].

Relationship between Endophytic Fungi and Host Plant: A variety of relationships exist between fungal endophytes and their host plants, ranging from mutualistic or symbiotic to antagonistic or slightly pathogenic [11]. Endophytes may produce an overabundance of substances of potential use in agriculture, industry, and modern medicine such as novel antibiotics, antimycotics, immunosuppressant and anticancer compounds. In addition, the studies of endophytic fungi and their relationships with host plants will shed light on the ecology and evolution of both the endophytes and their hosts: the evolution of endophyte plant symbioses; the ecological factors that influence the direction and strength of the endophyte host plant interaction. Since, natural products are likely adapted to a specific function in nature, searching for novel secondary metabolites should concentrate on organisms that inhabit novel biotopes [12].

TABLE 1: INFLUENCES OF HOST MEDICINAL PLANTS ON THE POPULATION STRUCTURE OF ENDOPHYTIC FUNGI [13-15]

Family of host plants (represent species)	Isolation part	Habitat	Factor affecting the population structure
Cactaceae (Cactus sp.)	Stem	Desert of tropical savanna	Environment: moisture and temperature
Rosaceae (*Malus domestica*)	Leaf, flower, fruit	Tropical rainy region	Environment: cultivation style
Leguminosae (*Glycyrrhiza inflat*)	Root	Salinized sandy land in warm temperate region	Environment: moisture and temperature
Eucommiaceae (*Eucommia ulmoides*)	Leaf, branch, bark	Subtropical mountain and warm temperate semi-humid region	Environment: latitude and temperature Tissue
Orchidaceae (*Gastrodia elata*)	Tuber, flower	Hillside forests, wetland in temperate plateau	Enviroment: latitude Tissue
Euphorbiaceae (*Sapium sebiferum*)	Leaf, twig	Mountain in subtropics	Genetic background Tissue
Smilacaceae (*Heterosmilax japonica*)	Stem	Subtropical monsoon region	Season
Pinaceae (*Pinus tabulaeformis*)	Bark, needle, xylem	Forests in warm temperate semi-humid monsoon region	Season Tissue age
Teaceae (*Camellia japonica*)	Leaf	Temperate secondary forest	Season Tissue age
Zingiberaceae (*Amomum siamense*)	Leaf, pseudostem, rhizome	Tropical monsoon forest	Tissue
Compositae (*Atractylodes lancea*)	Rhizome	Mountain in subtropics	Tissue and age of tissue
Asclepiadaceae (*Calotropis procera*)	Leaf	Garden bed	Tissue

Classification of Endophytic Fungi: Schaechter (2011) [16] stated that endophytic fungi have frequently been divided into two groups based on differences in taxonomy, host range, colonization transmission patterns, tissue specificity and ecological function. Group one is the *Clavicipitaceous endophytes* (C-endophytes) which infect some grasses. Group two is the *Nonclavicipitaceous endophytes* (N Cendophytes). While Rodriguez *et al.*, (2009) [17].

Clavicipitaceous Endophytes (Class I): The Clavicipitaceae is a family of fungi (*Hypocreales; ascomycota*) including free living and symbiotic species associated with insects and fungi or grasses, rushes and sedges [18].

Many of its members produce alkaloids that are toxic to animals and humans. *European investigators first noted clavicipitaceous endophytes of grasse*s in the late 19th century in seeds of *Lolium temulentum*, *L. arvense*, *L. linicolum* and *L. remotum* [18].

***Nonclavicipitaceous Endophytes* (Class II):** Traditionally NC-endophytes treated as a single functional group, while Rodriguez *et al.*, (2009), [19], showed that NC-endophytes represent three distinct functional groups. Class II endophytes include the hyper diverse endophytic fungi associated with leaves of tropical trees as well as the highly diverse associates of above-ground tissues of nonvascular plants, seedless vascular plants, conifers and woody and herbaceous angiosperms in biomes ranging from tropical forests to boreal and Arctic/Antarctic communities [20].

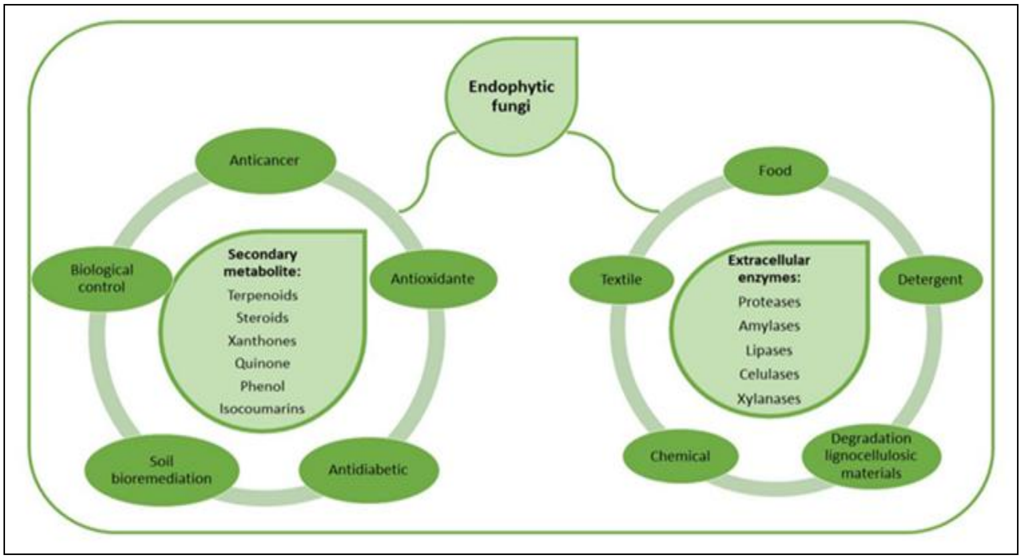

FIG. 1: BIOTECHNOLOGY APPLICATION OF SECONDARY METABOLITES AND EXTRACELLULAR ENZYMES PRODUCED FROM ENDOPHYTIC FUNGI

TABLE 2: LIST OF SOME BIOACTIVE COMPOUNDS PRODUCED BY ENDOPHYTIC FUNGI POSSESSING BIOLOGICAL ACTIVITIES [21-26]

Endophytic Fungi	Host Plant	Bioactive Compounds	Biological Properties	Activity Level
Phomopsis sp. CFS42	*Cephalotaxus fortunei*	Polyketides	Antifungal activity	MIC = 2.5 µg/mL
Chaetomium globosum	*Ginkgo biloba*	Azaphilone alkaloids	Anticancer activity	IC_{50} = 53.4 µM
Alternariaal ternata AE1	*Azadirachta indica*	Phenolics and flavonoids	Antioxidant properties	IC_{50} = 38 µg/mL
Mycosphaerella nawae ZJLQ129	*Smilax china*	Amide derivative	Immunosuppressant activity	30 and 300 nM
Phomopsis sp. CGMCC No. 5416	*Achyranthes bidentata*	Chromanones	Antiviral activity	IC_{50} =32.5 µg/ ml
Gliocladium sp. MR41	*Culture collection*	Polyols	Antitubercular properties	MIC = 3.13 µg/mL
Penicillium roqueforti and *Trichoderma reesei*	*Solanum surattense*	Ferulic acid, cinnamic acid, quercetin, and rutin	Antibacterial activity	MBC = 2.5 µg/mL
Trichoderma asperellum T1	Culture collection	6-pentyl-2H-pyran-2-one (6-PP)	Antifungal and plant	61.31% Inhibition

Cladosporium cladosporioides	*Zygophyllum mandavillei*	3-phenylpropionic acid, 5j-hydroxyasperentin	Antifungal activity	MIC = 15.62 μg/mL
Diaporthe phaseolorum 92C	*Combretum lanceolatum*	18-Des-hydroxy Cytochalasin	Antiparasitic activity	IC_{50} = 50 μg/mL
Phyllosticta capitalensi	*Tibouchina granulosa*	Brefeldin and heptelidic acid	Antiparasitic activity	IC_{50} = 50.13 μg/mL,
Fusarium solani	*Glycyrrhiza glabra*	Fusarubin, 3-O-methylfusarubin, and javanicin	Antitubercular activity	MIC = 8 μg/mL

Identification of Fungal Endophytes: Morphological identification of endophytic fungi by mycologists is a critical step [27].

TABLE 3: FUNGAL ENDOPHYTES ISOLATED FROM VARIOUS PLANTS [28-32]

Host plant	Identified Endophytic fungus
Oryza sativa	*Alternaria alternata, Cladosporium tenuissimum, Epicoccum purpurescens, Fusarium equiseti, F. oxysporum, Hymenula cerealis, Phoma sorghina, Pleospora herbarum, Pythium sp., Trematosphaeria sp., Fusarium sp. Penicillium sp. Aspergillus sp. Paecilomyces sp. Pyricularia Sacc, Helminthos porium* sp. Yeast, Sterile mycelium
Manilkara bidentata	Xylaria sp., Colletotrichumcras sipes, Pestalotiopsis versicolor
Lycopersicon esculentum	*Alternaria alternata, Colletotrichum gloeosporioides, Cladosporium sp., Penicillium sp., Arthrinium sp., Chaetomium globosum, Colletotrichum coccodes, Nigrospora sphaerica, Phomopsis sp., Ulocladium alternariae, Stemphyliumbotryosum*
Taxus cuspidate	*Alternaria sp.*
Nothapodyt esfoetida	*Neurospora sp.*
Camellia sinensis (Tea)	*Fusarium sp., Penicillium sp., Diporthe sp., Schizophillum sp.*
Coffee	*Aspergillus, Bipolaris, Cladosporium, Clonostachys, Colletotrichum, Epicoccum, Fusarium,Guignardia, Mycospharella, Phomopsis, Rosellinia, Talaromyces, Trichoderma, Xylaria*
Quercus variabilis	*Aspergillus sp., Penicillium sp., Alternaria sp., Cladosporium sp., Fusarium sp., Rhizoctonia sp.*
Azadira chtaindica	*Phomopsisoblonga, Cladosporiumcladorsporioides, Pestalotiopsissp, Trochoderma sp., Aspergillus sp., Periconia, Stenella, Drechslera*
Huperzia serrata	*Acremonium sp.*
Ananas ananassoides	*Muscodorcrispans*
Jatrophacurcas	*Leptosphaeria sp.*
Paris polyphylla var. Yunnanensis	*Fusarium, Gliocladiopsisirregularis, Gliomastixmurorum var. murorum, Aspergillusfumigatus, Cylindrocarpon, Podospora sp., Plectosphaerellacucumerina, Pichiaguilliermondii, Neonectria radicicola*
Foeniculum vulgare	*Acremonium, Alternaria, Fusarium, Plectosporium*
Antiaris toxicaria	*Trichothecium, acremonium, Rhizoctonia*
Iris germanica	*Rhizopusoryzae*
Saussurea involucrate	*Cylindrocarpan sp. Phoma sp., Fusarium sp.*
Dendrobium devonianum	*Fusarium sp., Phoma sp., Epicoccumnigrum*
Podocarpus species	*Aspergillus fumigates*
Hemionitisariflora	*Several endophytic fungi*
Oryza granulate	*Dothideomycetes, Arthrinium sp., Magnaporthe sp., Muscador sp.*
Actinidia macrosperma	*Acremoniumfurcatum, Cylindrocarponpauciseptatum, Trichodermacitrinoviride, Paecilomycesmarquandii, Chaetomiumglobosum*
Solanum cernuum Vell.	*Arthrobotrysfoliicola, Colletotrichumgloeosporioides, Coprinellus radians, Glomerellaacutata, Diatrypellafrostii, Phomaglomerata, Mucor sp., Phlebiasubserialis, Phomamoricola, Phanerochaetesordida, Colletotrichum sp.*

Methods for Isolation of Fungal Endophytes: Isolation by cutting of selected plant parts. Isolation by Blender shaft. Isolation by Mortar and Pestle

TABLE 4: MEDIA USED FOR ISOLATION OF FUNGAL ENDOPHYTES [33]

Media Name	Composition (g/L)
Wickerham medium	Malt extract 3, Peptone 5, Yeast extract 3, Glucose 10 pH- 7.2
SAB	Peptone 10, Dextrose 20, agar 15
YM agar	Malt extract 10, Yeast extract 2, Agar 20.
CYA	Czapek 10, Yeast extract 5, Sucrose 30, K2HPO4, Agar 15
YES	Sucrose 150, Yeast extract 20, MgSO4.7H2O 0.5, CuSO4.5H2O 0.005, ZnSO4. 7H2O 0.01.
MEA	Malt extract 30, Peptone 5, agar 15, Chloramphenicol 0.1
PDA	Potato 200, Dextrose 20, agar 15

Production and Optimization of Endophyte-Derived Bioactive Compounds [34]:

Production of Bioactive Compounds from Fungal Endophytes: The symbiotic relationship among endophytic fungi and plants gives the powerful ability to produce new bioactive compounds. However, there are two main substrate-based methods for producing bioactive compounds: solid-state fermentation and submerged-state fermentation [34].

Solid state Fermentation (SSF): Solid State fermentation is widely used for the production of the bioactive compound from the fungal endophytes [34]. These biomolecules are mostly metabolites generated by endophytic fungi grown on solid support selected for this purpose. In this fermentation process, different solid substrates such as Wheat bran, Rice bran, coconut oil cake, vegetable waste, gram husk, orange peel, sugarcane bagasse etc, were used with pure cultures of endophytic fungi [34].

SSF enables the optimal growth of endophytic fungi, permitting the mycelium to spread on the surface of solid compounds through which air can flow [34]. SSF uses culture substratum with low water levels. The solid medium contains both the substrates and solid support. After fermentation, fermented media are mixed with effective solvent and further used for purification and analysis [34].

Submerged Fermentation: In submerged fermentation, enzymes and other reactive compounds are submerged in a liquid such as alcohol, oil, or nutrient broth. Endophytic fungi are sited in a small closed flask containing the rich nutrient broth with a high volume of oxygen. The in situ production of enzymes results in the production of bioactive molecules. Batch Fed fermentation method is commonly used, which utilizes the sterilized nutrients under optimized conditions along with fungal endophytes, increasing density. The addition of nutrients maintains the growth rate of fungal endophytes, also reduces risk of an overflow of metabolism [34].

Optimization of Production of Bioactive Compounds from Fungal Endophytes [35]: Optimization of both fermentation processes depends on considerations of carbon homes and nitrogen homes, inoculums, phosphorus, organic acids, surfactants, incubation period, temperature, moisture level, and pH level under optimized conditions to achieve the greatest production of bioactive compounds from fungal endophytes.

- Effect of different medium
- Effect of carbon sources
- Effect of nitrogen sources
- Effect of inoculum amount
- Effect of inoculum time
- Effect of pH and temperature [35]

TABLE 5: MEDIA USED FOR THE PRODUCTION OF BIOACTIVE COMPOUNDS BY FUNGAL ENDOPHYTES [36]

Sr. no.	Medium	Conditions
1	Liquid Wickerhammedium	26°C, 21days
2	S7medium	26°C, 21days
3	Minimalmedium	28°C,10-14days
4	Lactose & Starch Caseinbroth	37°C, 120rpm, 18 days

5	M2medium	28°C, 124rpm, 7days
6	C2broth, Sabourauds broth, PDB, MEB	28°C, 10days
7	Nutrient Broth	30°C,120rpm, 5days
8	Liquid fermentation	37°C,120rpm, 18 days
9	Nutrient Broth	30°C, 124rpm, 24 hrs
10	Cornmeal medium	26°C, 21days

Novel fungal Endophytes Verses Novel Bioactive Compounds [37-42]: Discovering novel bioactive compounds from undiscovered endophytes is the current trend. Not all endophytes are culturable, and these may produce useful bioactive metabolites. Metabolomics of endophyte-infected and endophyte-free plant hosts could reveal intersections in secondary metabolite paths that may be pushed into synthesizing novel chemical species or lead compounds, another possibility of manipulating these chemo-diverse organisms [37].

In fungal endophytes, genes coding for enzymes of secondary metabolic pathways usually occurs as gene clusters being positioned in the same locus and co-expressed. These gene clusters are known to evolve swiftly through multiple rearrangements, duplication, and losses and are capable of interspecific feast through horizontal gene transfer. It is important to screen fungal species for their secondary metabolite assortment under different growing conditions; culture parameters such as composition of growth medium, aeration, pH and the presence of certain enzyme inhibitors change vividly the secondary metabolite profile and even induce the synthesis of several new metabolites [38] is because the synthetic capability of endophytes, like in other organisms, has been fine tuned by natural selection over millions of years. Smith *et al.* (2008) united sequence analysis with bioassay procedures to explore the endophyte diversity of the tropics. Their results suggest that tropical plants harbour a substantial portion of undiscovered endophytes that may be vested with novel biochemical diversity. Hence, including fungal endophytes in natural product discovery programs is necessary. Testing endophytes isolated from different tissues of plant hosts and plants growing in unusual and less studied habitats will be more productive [39-42].

CONCLUSION: Isolation of fungal endophytes from medicinal and other plants may result in methods to produce biologically active agents for biological exploitation on a large commercial scale, as they are easily cultured in a laboratory and fermenter instead of harvesting plants and affecting the eco-friendly biodiversity.

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