Research Article

Fungal Endophytes: Promising Tools for Pharmaceutical Science

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Accepted on: 27-01-2014; **Finalized on:** 31-03-2014.

ABSTRACT

Fungal endophytes are microorganisms that internally infect living plant tissues without causing any visible symptom of infection, and live in mutualistic relationship with plants for at least a part of their life cycle. Every plant in the world is reservoir of one or more number of endophytes. In recent year's special attention have been made towards endophytic fungi because of their ability to synthesize several novel bioactive compounds not previously known to biological system which are important for pharmaceutical, agricultural and industrial sector. This review describes information on endophyte diversity, as well as production of secondary metabolites with special emphasis on anti cancerous, antimicrobial, antiviral, antibiotics along with huge number of other secondary metabolites for commercial exploitation in pharmaceutical and medical field. Furthermore, the chemical potential of endophytic fungi for drug discovery will be discussed with focus on the detection of pharmaceutically valuable plant constituents as products of fungal biosynthesis in recent years. At present a huge world population is suffering from the problem caused by drug resistant microbes (bacteria, parasitic protozoans and fungus) which decreases the efficiency of synthetic drugs. Hence, an intensive search for more and better antibiotics for effective treatment is becoming an emerging research area.

Keywords: Anticancer, Bioactive compounds, Bioremediation, Colonization, Plant growth Promotion, Taxol, Therapeutic agent.

INTRODUCTION

Plants are a potential reservoir of indigenous microbes principally known as endophyte which can reside inside their tissue without giving any visible external symptoms which responsible for nutrient assimilation and their processing, induction of defense system, and synthesis of secondary metabolites.[1,2] They may be fungi[3], bacteria[4] or actinomycetes[5] which colonizes internal living tissues of plants[1] either as obligate or in facultative associated with lower and higher plants without causing any immediate negative or external symptom to host[2] and shows the beneficial effects to their host plant.[6] Endophytes transfer information via interaction with higher plant and also evolved biochemical pathways resulting in the production of various novel bioactive compounds and offer opportunities for discovering products and processes with potential applications in Medicine and biotechnology.[7, 8] Researches are mostly focused on the investigation of fungal endophytic diversity their relationships with host plants, a discovery of natural bioactive compounds, and improving the productivity of some potential candidates by taking advantage of genetic engineering and other measures. Several decades of endophytic fungal research resulted in a sufficient information of bioactive group which are increasing day by day.

History of fungal endophyte studies

Attention towards fungal endophytic studies initiated during early 1900 when Freeman in 1904 has made references from a paper published in 1898, in his paper described fungus from an annual grass[6]. Afterward a series of studies on asymptomatic fungal endophytes were recorded from almost all plant inhabitants in nature from various plant parts.[9,10] geographical locations and different environmental conditions.[10-13]

Relationship with host plant, occurrence and biodiversity of fungal endophytes

Fungal endophytes show a variety of associations with their host plants including from symbiotic or mutualistic or antagonistic or slightly pathogenic.[6] Their associations with host plant influence ecology and evolution of fungal endophytes and their host plant.[14] Fungal endophyte occurrence is not a host specific rather than single endophytes may be inhabitant of different host plant.[15] Their distribution in the plant tissues affected by their ability to utilize nutritional substances synthesize in different part of the same host.[16] Their relationship with host varies from one host to another with ecological and geographical conditions.[1] The interaction between fungal endophyte and host is controlled at the gene level, involving genes of both partners which are modulated by the environment.[17] The encounter of endophyte by host plant modulates the gene expression pattern in host plant.[18] Diversity has multidisciplinary effects on ecosystem such as enhancement of primary productivity, nutrient retention and flow along with the development of resistance to pathogen invasion.[6] Fungal endophytes have been isolated from almost all plant groups range from palm[19], grasses[11], sea grasses[12], large trees[10], lichens[20], medicinal plants.[21] The diversity of fungal endophytes may vary in different plant part and position of host plant in geographically different locations such as temperate or tropical. Most of the fungal endophyte isolated belongs to ascomycetes[22]and several may also basidiomycetes.[19] Endophytic fungi from aquatic[23], temperate[24], tropic[25] and Xerophytic[26] are reported.

Alternaria alternata, *Cladosporium cladosporioides*, *Chaetomium globosum*, *C. hebarum*, *Gliocladium roseum*, *Curvularia lunata*, *Nigrospora shaerica*, *and Phyllosticta* spp. were characterize as frequent occurring endophytic fungus in leaf of medicinal climber and grasses.[11] A semiarid region of Pakistan, where climatic conditions are extremely high and rainfall is less helps in understanding the frequency of colonization of endophytic mycoflora and species richness of medicinal plant *Withania somnifera.* Among the endophytic fungal isolates four isolate belongs to class Ascomycetes and twenty isolate belongs to class Deuteromycetes. Highest species richness was noted from the stem and *Alternaria alternata* was found to be the most dominant endophyte. In the isolated class of fungi, Deuteromycetes were found to be the most prevalent.[27] *Hevea brasiliensis* were studied to determine the total fugal endophytic inhabitant in the leaves and sapwood along with identification of differences between respective communities. Sapwood has greater endophytic fungal diversity in comparison to the leaves while their colonization frequency is more in the leaves as compare to the sapwood.[9] Investigation of endophytic fungal diversity has been done on the basis of its relative frequency, isolation and colonization rates in medicinal plants (*Adhathoda vasica, Ocimum sanctum, Withania somnifera, Cannabis sativa* and *Viola odorata*) of Himachal Pradesh, India which cover 15 fungal genera and 18 species (*A. clavatus, A. flavus, A. variecolor, Penicillium chrsogenum, Aspergillus niger, Alternaria alternata, Curvularia lunata, Haplosporium sp., Phoma sp., Nigrospora sp., Colletotrichum sp., Cladosporium sp., Stemphylium sp., Fusarium sp., Geotrichum sp., Phomopsis sp., Trichoderma sp.* and *Rhizopus sp.*).[21] An attempt was made to analyze diversity, distribution and phylogeny among endophytic fungus from the different plant sources on the basis of ITS1-5.8S-ITS2 sequence of Western Himalayas which showed diverse taxonomic affinities among isolated fungal endophytes. In total of 72 endophytic fungal strains isolated only two belongs to Basodiomycete whereas the rest are belong to Ascomycetes. *Alternaria* spp. and *Fusarium* spp. consists more than half (54.2%) of the strains isolated. Most of the genera of *Alternaria* strains reported from *Artemisia annua* and *Rauwolfia serpentine* whereas most of the *Fusarium* spp. was reported to inhabitant of *Artemesia annua, Withania somnifera, Platanus orientalis*. The fungal endophytes obtained from the conifers which include the *Pinus roxburgii, Cedrus deodara* and *Abies pindrow* harbored the most diverse endophytic fungi, belonging to 13 different genera offered significant taxonomic variants.[13]

Bioactive Compounds from Fungal Endophytes

Fungal endophytes are an attractive group of microorganism harboring a number of bioactive natural products includes flavonoids, alkaloids, terpenoids, peptides, steroids and phenols etc. which could be utilized for exploitation in medical, agricultural and pharmaceuticals. However, most of the fungal endophyte yet to remain discovered. According to an estimate about 4,000 secondary metabolites having an active role in different aspects had been reported from fungi so called “creative fungi” which include species of *Penicillium, Fusarium, Aspergillus* and *Acremonium* until 2003 but less report from endophytes.[28,6] Strobel isolated a number of bioactive compounds from fungal endophytes including anticancer compound Taxol, antibiotic with great bioactivities and unique structures recognized as great potential value in medical and pharmaceuticals.[29-32,7] Plants with medicinal value have been predictable as a repository of fungal endophytic arsenals with novel metabolites of pharmaceutical, medicinal, agriculture and industrial importance.[29-36,7,8]

Antibiotics from fungal endophytes

Endophytic fungus was reported to synthesize a wide variety of such natural product (anti-biotic) which has antagonistic activity against several pathogens and commercially utilized for pharmaceutical, medical and agricultural purposes.[37-41] An endophytic fungus *Colletotrichum gloeosporioides* were recognized as having activity against human pathogenic bacteria and fungus along with their fungistatic nature to plant pathogen fungus isolated from *Artemisia Annua* a Chinese traditional herb known to produce artemisinin (an antimalarial drug). The nature of bioactive compound was elucidated by different combination of spectroscopic method.[42] Coronamycin a novel antibiotic produced by *Streptomyces* sp. isolated from *Monstera* sp inhibit the human pathogenic fungus *Cryptococcus Neoformans* and having acted against the malaria parasite *Plasmodium Falciparum*.[39] Phomal from the *Phomopsis Species* isolated from the medicinal plant *Erythrina crista,* identified to have a structure of the polyketide lactone by the spectroscopic method.[43]

Anticancer agents from fungal endophytes

There are several reports in which endophytic fungus produces the bioactive compound act as anticancer agents.[29–36, 7, 8]

Paclitaxel (Taxol) is the major bioactive compound and is obtained from a number of plant sp. Including in the bark of the Pacific yew tree world’s first billion dollar anticancerous drug which is a tetracyclic diterpenoid bioactive compound was obtained from the bark of *Taxus* species.[29-31,44-49] It has been found to active against various kinds of cancers and functions by stabilizing the microtubules and disrupting their dynamic equilibrium.[50] But the *Taxus* trees are rare and produce a small amount of Taxol being expensive and low availability it is unable to fulfill the demand so an alternative strategy should be essentially developed to fulfill the demand.[8] Taxol (paclitaxel) is an attractive invention from an endophytic fungus generated more attention in the treatment of various cancers because of its unique mode of action as compared to other anticancer agent. The other Taxol producing endophyte were investigated in a number of genera of endophytic fungus, which includes *Phyllosticta spinarum*[34], *Bartalinia robillardoides*[8], *Pestalotiopsis terminaliae*[33], *Botryodiplodia theobromae*.[51] Podophyllotoxin is an aryltetralin Lignan have been used as a precursor for synthesis of anticancer drug and with antimicrobial and antioxidative properties, mainly occurs in genera of an endangered species *Sinopodophyllum* (or *Podophyllum*). Podophyllotoxin are known to as the important precursor of anticancer drugs like etoposide, teniposide, and etopophos phosphate.[52,53] *Aspergillus fumigatus* isolated from *Juniperus communis* L.[54], *Fusarium oxysporum* from *Juniperus recurva*[53] and *Phialocephala fortinii* isolated from *Podophyllum peltatum*[55] are important fungal endophytic sources of Podophyllotoxin. Camptothecin, a pentacyclic quinoline alkaloid, and its analogue10-hydroxycamptothecin have been identified as effective antineoplastic agents and important precursors of anticancer drug topotecan, and irinotecan[56] inhibiting the intranuclear enzyme topoisomerase-I, required for DNA replication and transcription.[57] It has been principally isolated from the *Camptotheca acuminate, Apodytes dimidiate* and *Nothapodytes nimmoniana*.[58-60] Several investigations related to Campothecin produced by endophytic fungus have been described. Ergoflavin a dimeric xanthene belonging to ergochrome class is effective in cancer is isolated from an endophytic fungus from the Indian medicinal host *Mimusops elengi*.[61] Vinblastine and vincristine, the terpenoid indole alkaloids act as anticancer agents, interfere with microtubule and mitotic spindle.[62] Torreyanic acid, a selectively cytotoxic quinone dimer, isolated from a *P. microspora* strain from the endangered tree *Torreya taxifolia*, causes cell death by apoptosis.[63] Rubrofusarin B has to show cytotoxic activity in the colon cancer cell line SW1116 and rubrofusarin B and aurasperone A are strong coinhibitors of xanthine oxidase (XO), colon cancer cell and some microbial pathogens extracted from the fungal endophyte *Aspergillus niger* IFB-E003 of grass *Cyndon dactylon*.[64] L-asparaginase (LA) can well recognize to treat acute lymphoblastic leukemia and tumor cells and hence used as an antineoplastic agent.[65] Thirunavukkarasu *et al.*[12] investigated the production of L-asparaginase enzyme by the endophytic fungi isolated from green, brown and red algae. Out of 82 isolates, 64 were able to synthesize L-asparaginase. Genera such as *Aspergillus*, *Cladosporium*, *Fusarium* and *Penicillium* were actively produced the enzyme. *Fusarium* sp. isolated from the *Sargassum wightii* showed the maximum activity.

Table 1: Endophytes as producer of Antibiotics

Endophytic Fungus	Source	Antibiotic	Ref.
Fusarium sp.	*Selaginella pallescens*	CR377 a pentaketide antifungal agent	86
Colletotrichum gloeosporioides	*Artemisia mongolica*	Colletotric acid (active against *Helminthsporium sativum*)	87
Colletotrichum gloeosporioides	*Artemisia Annua*	metabolites with antimicrobial activity	42
Cytonaema sp.	-	Cytonic acids A and B (anti-viral) human cytomegalovirus protease inhibitors	88
Gliocladium sp.	*Eucryphia cordifolia*	Annulene (volatile antimicrobial)	89
Streptomyces munumbi	*Kennedia nigriscans*	Munumbicins A, B, C, & D (Antibiotics)	37
Cryptosporiopsis cf. quercina	*Tripterigeum wilfordii*	Cryptocandin (Antibiotics)	90
P. viridiflava	Grass species	Ecomycins (Antibiotics)	91
Xylaria sp. F0010	*Abies holophylla*	Griseofulvin (antifungal antibiotic agent)	40
Streptomyces sp. NRRL 30566	*Grevillea pteridifolia*	Kakadumycins (antibiotics)	38
Cladosporium sp	*Quercus variabilis*	brefeldin A (antifungal antibiotic)	41
Streptomyces sp.	*Monstera* sp.	Coronamycin (antibiotic)	39
P. microspora	*Torreya taxifolia*	Torreyanic acid (Anticancer agent and Antibiotic)	63
Phomopsis Species	*Erythrina crista*	Phomol	43
P. ericonia	*Taxus Cuspidate*	Pcriconicins A and B	92

Lu *et al.*[3] evaluated the cytotoxic activities against brine shrimp and antitumor activity against different types of tumor cells by endophytic fungus isolated from Chinese medicinal plant *Actinidia macrosperma.* Cytotoxic activity has been reported from all most all of the isolates with AM07 (4.86 μg/mL), AM11 (7.71 μg/mL), and AM17 (14.88 μg/mL) exhibited significant toxicity against brine shrimp. The MTT assay was used to assess the antitumor activity. 76.5% of endophytic fungi showed antitumor activity in HepG2, MCF7, and SGC- 7901 cell lines, 82.4% in A549 and HeLa cell lines. The isolate AM07, AM11 and AM17 have a potential antitumor activity which could be utilized to treat various cancer diseases and require further study for their exploration.[3] Recently Shan *et al.*[66] extracted six spirobisnaphthalenes compound including diepoxin κ, palmarumycin C13, palmarumycin C16, palmarumycin C15, diepoxin δ and diepoxin γ from the crude extract of fungal endophyte *Berkleasmium* sp.

Dzf12, isolated from the medicinal plant *Dioscorea zingiberensis* with the help of High-speed counter-current chromatography (HSCCC) and structurally illustrated with the help of spectrometrically. Spirobisnaphthalenes having several medicinal properties including antimicrobial[67], cytotoxic[68], anti-tumor[69] and inhibitors of DNA gyrase[70], topoisomerase II[69] and thus are potential candidates in cancer chemotherapy.

Table 2: Endophytic fungal products as anticancer agents

Endophytic Fungus	Source	Anti-cancer agent	Ref.
Corylus avellana; Seimatoantlerium nepalense; Alternaria sp.; *Tubercularia* sp.; *Sporormia minima* & *Trichothecium* sp.; *Alternaria alternate; Ozonium* sp.; *Botrytis* sp. & *Papulaspora* sp.; *Fusarium mairei; Aspergillus fumigates; Botryodiplodia theobromae; Fusarium solani; Aspergillus niger; Mucor rouxianus; Fusarium solani; Metarhizium anisopliae*	Angiosperms; *Taxus wallichiana; Ginkgo biloba; Taxus mairei; T. wallichiana; Taxus chinensis; Taxus chinensis* var. *mairei; Taxus chinensis* var. *mairei; Taxus chinensis* var. *mairei; Podocarpus* sp.; *Taxus baccata; Taxus celebica; Taxus cuspidate; Taxus chinensis; Taxus chinensis; Taxus chinensis*	Paclitaxel	93 – 102, 44 – 49
Taxomyces andreanae; Pestalotiopsis spp.; *Alternaria* sp., *and Monochaetia* sp.; *Pestalotiopsis guepinii; Seimatoantlerium tepuiense*	*Taxus brevifolia; Taxus wallichiana; Taxus cuspidate and Taxus baccata; Wollemia nobilis; Maguireothamnus speciosus*	Paclitaxel	29 – 32, 7
P. microspora; Periconia sp.	*Taxodium distichum; Torreya grandifolia*	Paclitaxel	103 -104
Bartalinia robillardoides Tassi; *P. terminaliae*	*Aegle marmelos; Terminalia arjuna*	Paclitaxel	8, 33
Phyllosticta spinarum; Phyllosticta citricarpa; Phyllosticta dioscoreae	*Cupressus* sp.; *Citrus medica; Hibiscus rosa sinensis*	Paclitaxel	34 – 36
Pestalotiopsis microspora	*Torreya taxifolia*	Torreyanic acid	63
Rhinocladiella sp.	*T. wilfordii*	Cytochalasins	105
Alternaria sp. & *Fusarium oxysporum*	*Catharanthus roseus*	Vinblastine & Vincristine	106, 107
Alternaria sp., *Monilia* sp., *Penicillium* sp., *Penicillium* sp. & *Penicillium* sp. Respectively; *Penicillium implicatum; Alternaria* sp.; *Trametes hirsute; Phialocephala fortinii; Alternaria neesex; Fusarium oxysporum; Aspergillus fumigates*	*Sinopodophyllum hexandrum, Dysosma veitchii, Sinopodophyllum hexandrum, Diphylleia sinensis & Dysosma veitchii* Respectively; *Diphylleia sinensis; Sabina vulgaris; Sinopodophyllum hexandrum; Sinopodophyllum peltatum; Sinopodophyllum hexandrum; Juniperus recurva; Juniperus communis*	Podophyllotoxin	108 – 111, 55, 112, 53, 54
Entrophospora infrequens; Neurospora sp.; *Fusarium solani; Fusarium solani; Xylaria* sp.	*Nothapodytes foetida; Nothapodytes foetida; Camptotheca acuminate; Apodytes dimidiate; Camptotheca acuminate*	Camptothecine and its analogues	113, 60, 114, 59, 58
Penicillium brasilianum	*Melia azedarach*	phenylpropanoid amides	115

Table 3: Anti-oxidant from fungal endophytes

Endophytic Fungus	Source	Bioactive compound	Ref.
Xylaria sp.	*Ginkgo biloba*	Antioxidant	116
Paenibacillus polymyxa	*Stemona japonica*	Exopolysaccharides (antioxidant)	117
Cephalosporium sp. IFB-E001	*Trachelospermum jasminoides*	Graphislactone A (free radical-scavenging & antioxidant activities)	118
Penicillium brasilianum	*Melia azedarach*	phenylpropanoid amides (antioxidant)	114

Table 4: Products of endophytes with insecticidal activities

Endophytic Fungus	Host plant	Active against/ Anti-insect agent	Ref.
Phomopsis oblonga	elm trees	Beetle *Physocnemum brevilineum*	73
-	perennial ryegrass *Lolium perenne*	Sod webworms	119
Cladosporium sphaerospermum	*Adelges abietis* (L.)	*Adelges abietis*	120
Balansia cyperi	Grasses	*Spodoptera frugiperda*	121, 122
Muscodor vitigenus	*Paullina paullinioides*	Naphthalene (insect repellent)	123
Hypoxylon pulicicidum	-	Pantropical insecticide	124

Antioxidants from fungal endophytes

Several endophytic fungi have been identified to show antioxidant activity. Pestacin (1,3-dihydroisobenzofuran) and isopestacin (isobenzofuranone) bioactive compound obtained from an endophytic fungus such as *P. microspora* from *Terminalia morobensis* is able to scavenge superoxide and hydroxyl free radicals. The antioxidant activity of Isopestacin believes to based on its structural similarity to flavonoids and is of pestacin is due to of cleavage of an unusually reactive C-H bond and to a lesser extent, though O-H abstraction.[71,72]

Insecticidal activities from fungal endophytes

Several dedicated literature published on endophytic fungi are known to show anti-insect property to the host plant against herbivore insects. The mechanisms involve production of toxic repellent compound by endophytic fungus.[73]

Antidiabetic agents from fungal endophytes

An antidiabetic compound L-783,281 was identified from an endophytic fungus *Pseudomassaria sp.* originally isolated from African rainforest acts as insulin mimetic and does not destroy in the digestive tract as insulin destroyed in the digestive tract. Their administration to mouse model shows significant lowering in blood glucose level make it an efficient substitute in the place of costly and unstable insulin and open new door in diabetes therapy. Antidiabetic drug from *Aspergillus* sp., *Phoma* sp. Reduce blood glucose level identified as having constituents of 2, 6-di-tert-butyl-p-cresol and Phenol, 2, 6-bis [1, 1- dimethylethyl]-4-methyl by GCMS analysis.[74,75]

Immunosuppressive compounds from fungal endophytes

Immunosuppressive non toxic bioactive agent subglutinol A and B identified from endophytic fungus *Fusarium subglutinans* propose to have an active role in allograft rejection in transplant which could be utilized to treat autoimmune diseases like rheumatoid arthritis and insulin dependent diabetes.[76,6] Study of western Himalayas fungal endophytes offers an opportunity to investigate and extraction of novel natural products having immuno-modulatory activities for use in medicine and industry. A significant modulation of lymphocytes was observed by extracts of 17 fungal endophytes. Extracts from *Petriella* sp. and *Ulocladium* sp. from *Pinus roxbergii*, *Cochliobolus spicifer* from *Cedrus deodara* and *Sordaria superba* and *Fusarium redolens* from *Artemisia* sp. were found to have immunosuppressive properties.[13]

Antimicrobial compounds from fungal endophytes

Pavithra *et al.*[77] assess the antimicrobial activity of endophytic fungi from the leaves and branches of *Ocimum* species (Tulsi) against different pathogenic microorganisms such as *Candida albicans, Penicillium chrysogenum, Pseudomonas aeroginosa*, *Salmonella typhimurium* and *Mycobacterium smegmatis.* A number of endophytic fungi of different taxon belong to Species of *Phyllosticta* spp. (15 isolates), *Nodulisporium* spp. (13 isolates) and *Xylaria* sp.1 (10 isolates) isolated from Dipterocapous trees were reported to produce bioactive compounds having antimicrobial activity against *Staphylococcus aureus, Pseudomonas aerogenosa, Bacillus subtilis* and *Escherichia coli*.[10] Asperfumin a new metabolite produced by an endophytic fungus *Aspergillus fumigatus* CY018 inhibit *Candida albicans*.[78] Endophytic fungus from *Lithocarpus* sp. inhibits *Staphylococcus aureus*.[79] *Xylaria* sp.1 a common inhabitant of tropical plants found to produce bioactive compound having a broad spectrum of antimicrobial activity.[80] Taxol also has anti-fungal properties which could utilize by host plant to protect themselves and other endophytic fungus from pathogenic fungi.[7] Antifungal compound sordaricin[81], multiplolides A and B[82] are active against *Candida albicans* isolated from *Xylaria*. Hypericin and Emodin production by the endophytic fungus isolated from an Indian medicinal plant evaluated as an antimicrobial agent against several bacteria includes *Klebsiella pneumoniae* ssp. *ozaenae*, *Staphylococcus aureus* ssp. *aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and fungal pathogen *Candida albicans, Aspergillus niger*.[52] *Cynodon dactylon* leaf endophytic fungi *Aspergillus fumigatus* CY018 produces several metabolites such as fumigaclavine C, asperfumoid, fumitremorgin C, helvolic acid and physcion active against *Candida albicans*.[78] Antibacterial, antialgal and antifungal bioactive compounds identified as polyketide metabolites (7-hydroxyphthalide, 4-hydroxyphthalide, 5-methoxy-7-hydroxyphthalide, 5,7-dihydroxy phthalide, (3*R*,4*R*)-*cis*-4-hydroxymellein and (3*R*,4*R*)-*cis*-4-hydroxy-5-methylmellein) and steroids (ergosterol and 5α, 8α -epidioxyergosterol) from an unidentified endophytic fungus strain 6650 of group Ascomycete, originally isolated from *Meliotus dentatus* from the coastal area of the Baltic Sea, Ahrenshoop, Germany.[83] Endophytic fungus from the western Himalayan region was characterized for their antimicrobial activity against bacterial and fungal pathogen with bioactive compound extracted from their fermented broth and their IC50 were determined to evaluate their potentiality. Altogether 29 fungal endophytes showed an IC50 of less than 100 µg/ml against different pathogens. Extracts from the fermented broth of fungal endophytes *Trichophaea abundans* from *Pinus* sp., *Diaporthe phaseolorum* from *Picrorhiza* sp. and *Fusarium redolens* from *Artemisia* sp. inhibited *S. aureus* strongly with an IC50 of 18, 31 and 25, respectively. Extracts of *Chaetomium globosum* from *Artemisia* sp. and *Phomopsis* sp. from *Nothapodytes* sp. showed an IC50 of around 50 µg/ml against *E. coli* and *S. aureus*. While the fungus pathogen *Candida albicans* were inhibited by the fermented broth extracts of endophytic fungus *Fusarium tricinctum*, *Gibberella avenacea* and *Alternaria sp.* all isolated from *Artemisia annua* with an IC50 of 50, 15 and 50 µg/ml, respectively.[13] Several endophytic fungi from western Himalayas were investigated for their antimycotic activity against seven plant pathogen belongs to the genera *Talaromyces* sp., *Giberella* sp., *Cochliobolus* sp., *Fusarium* sp. and *Alternaria* sp.[13] Ethnomedicinal *Garcinia mangostana* inhabiting endophytic fungal isolate *Microdiplodia hawaiiensis* CZ315 active against gram-positive bacteria such as *S. aureus* (MIC 25 µg/ml), *B. subtilis* (MIC 50 µg/ml), *M. luteus* (MIC 25 µg/ml), *E. coli* (MIC 200 µg/ml), *S. typhi* (MIC 200 µg/ml) and *P. aeruginosa* (MIC 100 µg/ml).[84] Entomopathogenic endophytic fungus genera *B. bassiana* and *Clonostachys rosea* were active against the coffee berry borer.[85]

Table 5: Antimicrobial compounds from fungal endophytes

Endophytic Fungus	Source	Bioactive compound	Ref.
Muscodor albus	*Cinnamomum zeylanicum*	Antimicrobials	125, 126
Xylaria sp. YX-28	*Ginkgo biloba* L.	7-amino-4 methylcoumarin (Antimicrobial)	80
Penicillium janthinellum	*Melia azedarach*	citrinin (antibacterial)	127
Verticillium sp.	*Rehmannia glutinosa*	2,6-Dihydroxy-2-methyl-7- (prop-1E-enyl)-1 benzofuran-3(2H)-one and ergosterol peroxide (antimicrobial)	128
Phyllosticta spp., *Nodulisporium* spp. & *Xylaria* sp.	Dipterocapous trees	antimicrobial	10
Pestalotiopsis jesteri	-	Jesterone and hydroxy-jesterone (antifungal)	129
C. globosum	*Ginkgo biloba*	Chaetomugilin A and D (antifungal)	130
Pestalotiopsis adusta	_	Pestalachlorides A-C, antifungal metabolites	131
B. pumilus	Cassava	pumilacidin (antifungal)	132
Xylaria sp.	*Palicourea marcgravii*	butanodioic acid & cytochalasin D (antifungal)	133
Phomopsis cassiae	*Cassia Spectabilis*	ethyl 2,4-dihydroxy-5,6-dimethylbenzoate and phomopsilactone (antifungal)	134
Pestalotiopsis microspora	*Terminalia morobensis*	Pestacin & isopestacin (antioxidant & antifungal)	72, 71
Chaetomium globosum	*Hypericum perforatum*	Hypericin, Emodin (Antimicrobial)	52
Pestalotiopsis spp. and *Monochaetia* sp	Rainforests	Ambuic acid (Antifungal)	135
Phomopsis sp.	Mangrove	Cytosporone B and C (Antimicrobial)	136
Penicillium brasilianum	*Melia azedarach*	phenylpropanoid amides (antimicrobial)	115

Table 6: Other Bioactive Compounds from Endophytes

Metabolite	Endophyte	Host	Function	Ref.
Naphthopyrone metabolites	*Aspergillus niger*	*Cyndon dactylon*	Co-inhibitors of xanthine oxidase, Cancer cell line and some microbial pathogens	64
Pectin lyase	*Paenibacillus amylolyticus*	*Coffea Arabica*	Pectin lyase activity	137
Subglutinols A and B	*Fusarium subglutinans*	*T. wilfordii*	Immunosuppressive	76
phenylpropanoid amides	*Penicillium brasilianum*	*Melia azedarach*	anti-inflammatory and Immunosuppressive	115
Diosgenin	*Cephalosporium* sp., *Paecilomyces* sp.	*Paris polyphylla* var.*yunnanensis*	Synthesis of steroid	138, 139
Acremonium sp.	*Huperzia serrata*	Huperzine A	Acetylcholinesterase inhibitor	20
Blastomyces sp., *Botrytis* sp.	*Phlegmariurus cryptomerianus*	Huperzine A	Acetylcholinesterase inhibitor	140
Penicillium chrysogenum	*Lycopodium serratum*	Huperzine A	Acetylcholinesterase inhibitor	141

CONCLUSION

Endophytic fungi are a good and reliable source of novel natural compounds with a high level of biodiversity and may also produce several compounds of pharmaceutical significance, which is currently attracting scientific investigations worldwide. In nature, plants seem to be in a close interaction with endophytic fungi. The production of bioactive compounds by endophytes, particularly those restricted to their host plants, are significant both from the biochemical and molecular point of view. Secondary metabolites produced by endophytes (including those produced by plants) nurtures expectations of utilizing them as alternative and sustainable sources of these compounds. However, the commercial implication of production of desirable compounds by endophytic fungi still remains a future goal. A deeper understanding of host–endophyte relationships at the molecular and genetic levels, of biogenetic gene cluster regulation, and the effects of environmental changes and culture conditions on gene expression will be helpful for optimizing secondary metabolite production by endophytic fungi under laboratory conditions. Further research at advanced molecular level may offer better insights into endophyte biodiversity and the regulation of fungal secondary metabolism.

Acknowledgment: Authors are thankful to the honorable Vice- Chancellor of the Central Agricultural University for encouragement and providing necessary facilities. Financial grant from Department of Biotechnology (DBT) Govt. of India for the Project Establishment of Institutional Biotechnology Hub is great fully acknowledged.

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Source of Support: Nil, **Conflict of Interest:** None.

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