



Endophytic Fungi: A Review on Pharmacological Activities and Its Industrial Application

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ABSTRACT

Endophytic fungi isolated from different parts of plants have a more beneficial effect and therefore endophytes can be used in various applications. As Endophytes living inside the plants increases the resistance capacity of the plant towards undesirable microbial attacks and stresses. The secondary metabolites like alkaloids, indole derivatives, steroids, terpenoids, quinones, flavonoids produced by these fungi show antimicrobial, insecticidal, cytotoxic and anticancer activities. Substances that are producing by endophytes have promising role in modern medicine, agricultural field and also in industries as like an antibiotic, anticancer and anti-diabetic compounds for the treatment of several diseases in human and animals. Nowadays researchers have unique attention on endophytic fungi because of its ability to generate an excellent number of new and interesting bioactive metabolites, which plays a significant role in pharmaceutical, industrial and agricultural importance. The present review contains a wide range of information about the application of endophytic fungi in various fields and also its implications for drug development.

Keywords: Endophytic fungi, Pharmaceutical application, Bio-active compound, Antimicrobial activity, Secondary metabolites.

INTRODUCTION

Endophyte (Greek: endo = within + phyte=plant) are microorganisms including bacteria, fungi, and actinomycetes that resist within plants for at least a part of their lifecycle without causing any harmful symptoms.¹ The endophytes studies were first carried out with host plants from temperate regions and then recent research was developed and developing in several places such as forests, mangrove swamps, pastures, agricultural field, marine etc.,^{2,3}

The secondary metabolites including alkaloids, indole derivatives, steroids, terpenoids, quinones, flavonoids, and many more, are successfully isolated from the endophytic fungi and these metabolites having different functions and benefits to humans.⁴ Endophyte enhances the plant resistance activity against biotic and abiotic stresses. Endophytic fungi produce a large number of bioactive compounds and these bioactive compounds were gradually integrated into novel therapeutic drug discovery.^{5,6} Several bioactive compounds isolated from the endophytic fungi have biological activities like antibiotic, anticancer, antioxidant, antidiabetic, anti-inflammatory etc.⁷ Endophytic fungi were able to produce enzymes such as pectinases, cellulases, lipases, amylases, lactases, and proteinases. These enzymes play a key role in the process of biodegradation and hydrolysis.¹ Historically, more than half of the compounds have been screened from the natural environment, especially plants, which are helpful in treating many diseases and illnesses. Thereby, these natural products become a potential source for drugs. Recently attention has been focus on endophytes as these microorganisms become a potential source for the new bioactive compounds production.⁸

PHARMACOLOGICAL ACTIVITIES OF ENDOPHYTIC FUNGI

Antibacterial activity

Cytochalasin D is an antibiotic compound derived from the endophytic fungi *Xylaria sp.* of Brazilian marine red alga *Bostrychiatenella* (Ceramilales) and the other compound Dicerandrol C from *Phomopsis longicolla* also exhibit antibacterial activity against *Staphylococcus aureus* and *Staphylococcus saprophyticus*.⁹ The crude extract of *Alternaria sp.* Samif01 derived from the traditional medicinal plant *Salvia miltiorrhiza*, which is used to treat cardiovascular diseases and liver diseases contains alternariol 9-methyl ether which shows strong antibacterial activity towards the *Ralstonia solanacearum*.¹⁰ The antibacterial compound Anshanmycin derived from an endophyte fungus *Aspergillus terreus* (BS001) of the medicinal herb *Sophora flavescens* is effectively active against soil microbe *actinomycete* at the higher concentration of 160µg/mL and 320µg/mL.¹¹ Endophytic *Phomopsis sp.* isolated from the stem of *Ficus pumila* had excellent antibacterial activity against Gram-positive and Gram-negative human and phytopathogenic bacteria.¹² Phomalactone, tetracycline, penicillin, emodin, (3R)-5-Hydroxymellein is the pure biologically active secondary metabolites obtained from *Phoma sp.* living inside the plant *Fucus serratus* showed antibacterial activity against Gram-positive bacterium *Bacillus megaterium*. The compound (3R)-5-Hydroxymellein has the inhibition zone of 7 mm radius for the *Bacillus megaterium*.⁵ The ethyl acetate extract of endophytic fungus *Physalospora sp.* is active against the bacterial cells *E.coli* and *Bacillus megaterium* with the inhibition zone radius of 13 and 16mm.¹³ The sponges derived *Callyspongia sp.* are host to many endophytic fungi like *Aspergillus niger*, *Aspergillus flavus*



(*A. flavus*), *Hypocrea lixii*, *Trichoderma hypericum*, *Eurotium amstelodam*. Among these fungi, the ethyl extract of *Aspergillus flavus* showed excellent antibacterial activity against two human pathogens *Staphylococcus aureus* and *Escherichia coli* with the zone of inhibition 18mm and 31mm respectively.³ *Hibiscus subdarifa* L plant being the host of three endophytes, *Aspergillus niger*, *Corynespora cassicola*, *Glomerella acutata* and the ethanolic crude extract of these fungi *Aspergillus niger* and *Corynespora cassicola* EF14 showed the inhibition zone against bacteria cells *Klebsiella pneumonia* and *Escherichia coli* whereas *Glomerella acutata* fungus ethanolic extract showed strong antibacterial activity against *Klebsiella pneumonia* and *Escherichia coli* with clear inhibition zone radius between 18 – 22mm.¹⁴ Hybrid poplar(cottonwood) is a fast-growing tree, *Hyalodendriella* sp. *Ponipode*12 an endophytic fungus from this plant produces several compounds like botrallin (four dibenzo- α -pyrones), palmariol, TMC-264 and alternariol9-methyl ether, among these compounds botrallin and TMC-264 showed antimicrobial activity.¹⁵ An indole-3-carboxylic acid compound isolated from the ethyl acetate crude of *Epicoecum nigrum* an endophyte of *Entada abyssinica* showed the minimum inhibitory concentration of 3.12 and 6.25 against *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus cereus*, *Escherichia coli*, *Salmonella typhimurium* respectively.¹⁶ The *Cladosporium* sp. obtained from the leaves of *Rauwolfia serpentina* yields a naphthoquinone called methyl ether of fusarubin which was said to have antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus megaterium* with a zone of inhibition of 27 mm, 25 mm and 22 mm respectively at the concentration of 40 μ g/discs.¹⁷ The young stems of a yellow moonseed plant (*Arcangelisia flava*) traditionally used to treat malaria, dysentery, and fever, produces an endophytic filamentous fungus, *Coelomyces* AFKR-18 able to produce pachybasin. It exhibited antimicrobial activities against *S. aureus* and *F. oxysporum* with MIC values of 32.0 and 16.0 μ g/mL respectively and also against *E. coli*, *B. subtilis*, *M. luteus*, *S. cerevisiae*, *C. albicans*, *A. niger*, and *A. flavus*, with MIC values of 64.0 μ g/mL.⁴ *Asclepias sinaica* mostly used in traditional Bedouin medicine to treat cancer disease are the host to endophytic fungi *Penicillium chrysogenum*, *Alternaria alternate* and the fungal strain *sterile hyphae*. The crude extract of these endophytic fungi showed antimicrobial activity against gram-positive bacteria (*S.aureus* and *B.subtilis*), gram-negative bacteria(*E.coli*, *P.aeruginosa*, and *S.typhimurium*) and yeast strain (*Candida albicans*).¹ The fruits of *Melia azedarach* is the host of an endophyte *Penicillium janthinellum*, this fungus produces a polyketide citrinin compound which showed 100% antibacterial activity towards *Leishmania* sp.¹⁹

Antifungal activity

Alkaloids, terpenoids, steroids, isocoumarins, and chromones are the different metabolites produced by

endophytic fungi showed antifungal properties against plant pathogenic fungi.²⁰ Nystatin and Actidione are the two bioactive metabolites derived from *Phoma* sp., the endophytic fungi of *Fucus serratus* and the fungus showed clear inhibition zone of 20 and 50mm radius respectively against the *Microbotryum violaceum*.⁵ The four metabolites Mycorrhizin A, cytochalasins E, cytochalasins K, Radicinin isolated from *Plectophomella* sp., *Physalospora* sp., and *Crataegus monogyna* showed strong antifungal activity towards *Eurotium repens* and *Mycotypha microspora*.¹³ The palmitic acid is a saturated fatty acid obtained from *Alternaria* sp. of medicinal cactus *Opuntia humifusa* showed antifungal activity against *Emericella nidulans* and *Fusarium oxysporum*. Linoleic acid obtained from a crude extract of *Alternaria* sp. exhibit strong antifungal activity against several phytopathogenic fungi such as *Colletotrichum lagenarium* and *Fusarium oxysporum*.²⁰ *Fusarium* sp., *Phoma* (*Pleospora*) *betae*, and *Rhizoctonia solani* are a plant pathogenic fungus which affects the plant growth, so it is inhibited by the volatile organic compounds dimethyl disulfide, dibenzofuran, methanethiol, ketones produced from *T. gamsii* an endophyte of *Panax notoginseng* plants.²¹ Thirty fungal endophytes were isolated from the plant *Zingiber officinale* Rosc among them *Curvularia affinis* obtained from the stem and *Glomerella cingulata* from rhizome showed the highest inhibitory effect of 68.8 and 65.1 on *Fusarium oxysporum*, a pathogenic plant fungus.²² An endophytic fungus *Paecilomyces* sp. and *Penicillium* sp. produces a compound known as leucinostatin A which has an unusual functionalized peptide exhibit a antifungal activity. The famous and widely used traditional Chinese medicine was *Houtuyynia cordatathunb*, from this an endophytic fungus *H.cordata* was isolated, which has been used to treat inflammation, bronchitis infections of the upper respiratory cavity, cough, arthritis. This strain was identified as *Cheatomium globosum* based on morphological characteristic and a phylogenetic analysis of ITS sequences. The crude extract of ethyl acetate from fungus *Cheatomium globosum* showed antifungal activity against *Exserohillum turcicum*. The wide antifungal was carried out for fungal strain 28 using ethyl acetate extract which effectively inhibited 15 types (B1-15) of pathogenic fungi, among this 15 types of pathogen B6, B11 and B14 showed inhibition ratio 100% whereas B15 showed 91.67 \pm 0.24%, B7 showed 86.18 \pm 4.28% overall the inhibition ratio of B1-15 pathogenic fungi were above 50% excluding B12 showed 45.93 \pm 1.74% and B13 showed 41.67 \pm 1.27% inhibition activity.²³ The genus *Xylaria* residing in different plant host produces bioactive compounds Sordaricin and Multiplolides A and B with antifungal activity against *Candida albicans*.²⁴

Anticancer activity

Cancer can be cured by chemotherapy drug but some of the synthetic drugs cause many side effects on the patients and thus the endophytic fungi living inside the plant can be used to produce compounds with natural



anticancer activity.³³ Microbial metabolites had become the major target for developing old drugs and for discovering new drugs.⁹ Taxol is a chemotherapeutic drug used to treat lung cancer, breast cancer and many other types of cancer and it is also isolated from the endophytic fungi of the medicinal plant *Salacia oblonga*.²⁵ Taxol was first separated from the bark of *Taxus brevifolia* and this compound kills the tumor cells by interfering with the normal function of microtubule during cell division.²⁶ *Trichoderma* sp. is a common soil fungi and it is also found in association with *Taxus chinensis* produces an anticancer compound taxol.²⁷ L-Asparaginase is an enzyme which converts L-asparagine to L-aspartate and ammonia and makes L-asparagine unavailable for cancer cells. Bacterial production of L-asparaginase is very expensive and eukaryotic fungi can be used to produce the anticancer enzyme. *Ascomycota* sp obtained from plant *Oldenlandia diffusa* produced highest L-asparaginase activity of 0.025 IM⁻¹ mL⁻¹ min⁻¹ and the other fungus *Dothideo mycetes* sp. from *Cymbopogon citrate* produced 0.023 IM⁻¹ mL⁻¹ min⁻¹. L-asparaginase is a tumor controlling enzyme inhibits the growth of tumor cells. *Fusarium oxysporum* (MKS1) an endophyte of a medicinal plant *Murraya koenigii* involve in the synthesis of L-asparaginase enzyme.⁶ The compound 4,8-dihydroxy-6-methoxy-3-methyl-3,4-dihydro-1H-isochromen-1-one collected from the crude extract of *Phoma* sp. fungal isolate of *Cinnamomum mollissimum* possess inhibitory activity against murine leukemic cells(48.8%).²⁸ Quinizarin isolated from an endophyte *Epicoccum nigrum* of *Entada abyssinica* showed moderate cytotoxic effect towards the RAW 264.7 cells with an LC50 value of 21.59 µg/ml.¹⁶ An endophytic fungi isolated from *Taxus baccata* (European yew) produces a highly bioactive compound known as Leucinostatin A which shows strong anticancer activity against certain cancer cells.²⁹ The plant, *Catharanthus roseus* being the host of many endophytic fungi like *Colletotrichum* sp., *Macrophomina phaseolina*, *Nigrospora sphaerica* and *Fusarium solani* are able to produce anticancer alkaloid compounds vinblastine and vincristine. These compounds isolated from *Colletotrichum* sp of *Catharanthus roseus* leaf parts is expected to have anticancer activity.³⁰ Fungi species present in the marine ecosystem provides lots of bioactive compounds and these fungi are the potential source for discovering new pharmaceutical drugs. The enzyme protease produced from *Xylaria psidii*, an endophytic fungus of red seaweed *kappaphycus alvarezii* showed excellent anticancer activity.³¹ An endophytic fungi *Cladosporium* sp. produces bioactive secondary metabolite naphthoquinones such as anhydrofusarubin and methyl ether of fusarubin. These two compounds showed anticancer activity against human leukemia cell (K-562) with the IC50 values of 3.97µg/ml and 3.58µg/ml respectively.¹⁷ The endophytic fungi *Penicillium* sp., isolated from the plant *Sinopodophyllum hexandrum* and *Diphylleia sinensis* is able to produce Podophyllotoxin (PDT), a well-known aryltetralin lignin which has the anticancer property.¹⁸ *Diaporthe* sp. (EPSD), *Diaporthe* sp.

JF766998 (EPSD1), *Diaporthe* sp. JF767007 (EPSD2) and *Phomaherbarum* (EPSP) are the four fungal community of endophytic ascomycetes harboured on the *Piper hispidum* and these fungi produced sufficient level of exopolysaccharides so, glucan rich exopolysaccharides act as the good antitumor agent.³² Daldinone C and Daldinone D are the two benzo fluoranthene metabolites obtained from *Hypoxylon truncatum* IFB-18, an endophyte of *Artemisia annua* showed cytotoxic activity towards human colorectal cell line SW1116 cells, with IC50 values of 49.5 and 41.0 µM. The compound taxol is a promising anticancer agent, the endophytic fungi *P. terminaliae* isolated from the *Terminalia arjuna* produced the highest amount of taxol. Camptothecin is an inhibitor of DNA topoisomerase I, 9-methoxy CPT (9-MeO-CPT) and 10-hydroxy CPT (10-OH-CPT) are produced by the endophytic fungi *Fomitopsis* sp. and *Phomopsis* sp. respectively which was isolated from *Miquelia dentate*. Vincristine used to treat different types of cancer, isolated from an endophytic fungi *F. oxysporum* from *Catharanthus roseus* and this compound interfere with microtubule formation.³³ Meleargine and chrysogine are the two bioactive compounds produced by *Penicillium* sp. obtained from the Srikaya plant (*Annona squamosa* L.) showed anticancer activity.¹⁹

Antioxidant activity

Aspergillus sp, the endophytic fungi obtained from two Sudanese medicinal plants *Calotropisprocera* and *Trigonellafoenum-graecum* showed good antioxidant potential with high phenolic content of about (77.2 ± 7.5) mg GAE/g] and (89.9 ± 7.1) mg GAE/g respectively.³⁴ *Eugenia jambolana* is an Indian medicinal plant which is also known as black plum used to treat diabetes and endophytic fungi, *Chaetomium* sp and *Aspergillus terreus* of *Eugenia jambolana* isolated from this plant showed 80% and 63% antioxidant activity.³⁵ Seven endophytic fungi *Pestalotiopsis* sp., *Pestalotiopsis* sp., *Diaporthe* sp., *Meyerozyma* sp., *Diaporthe* sp., *Pestalotiopsis* sp. and *Pseudocercospora* sp. were isolated from the tropical and subtropical evergreen tree *Elaeocarpus sylvestris*, among these fungi the crude extract of the *Pseudocercospora* sp. showed significant antioxidant activity with IC50 of (30.54 ± 0.88) mg/mL.³⁶ In DPPH assay, anthraquinone-quinizarin a compound produced by *Epicoccum nigrum* fungus of *Entadaabyssinica* showed good scavenging activity with IC50 values of 10.86 and 11.36 µg/ml.¹⁶ The secondary metabolite saponin isolated from the herbaceous plant *Panax notoginseng* showed antioxidant activity.³⁷ *Fusarium oxysporum* an endophyte living inside the *Sabina recurve* plant was able to produce a compound Podophyllotoxin (PDT) with potent antioxidant activity.¹⁸ The endophytic fungi of several medicinal plants showed high total phenolic content and also possess high antioxidant potential. The ethyl acetate extract of endophytic fungi *Chaetomium* sp, *Aspergillus niger* and *Aspergillus peyonelii* isolated from *Eugenia jambolana* showed high phenol content of about 60.13+-0.41,58.46+-0.15 and 56.83+-0.76 respectively.³⁵



Antidiabetic activity

The herbaceous plant *Panax notoginseng* is able to produce several secondary metabolites like saponins, flavones, amino acid and polysaccharide. Among these metabolites, saponins are having active constituents used for several pharmacological effects like antidiabetic, neuroprotective and other activities.²¹ The enzyme protease produced by the fungus *Biosporus* sp. isolated from *Datura stramonium* plant were used to treat diabetes.²

Antinematodal activity

Brotrallin isolated from fungi like *Botrytis alli*, *Microsphaeropsis olive*, *Hyalodendriella* sp. and TMC-264 isolated from *Phoma* sp, *Hyalodendriella* sp exhibited antinematodal activity.¹⁵

Anti-rheumatoid activity

The anti-rheumatic property was found in the compound Podophyllotoxin (PDT) which is mainly present in the genera of *Diphylleia*, *Dysosma*, *Sabina* (also called Juniperus), and *Sinopodophyllum* (also called Podophyllum).¹⁸

Enzyme productions

Endophytic fungi were recognized to be the best source for metabolites with medicinal values and that can be synthesized within 2-4 weeks by the microbes in the culture medium. *Colletotrichum* sp., *Macrophomina phaseolina*, *Nigrospora sphaerica*, *Fusarium solani* are filamentous fungi associated with the *Catharanthus roseus*, all these fungi are able to produce cellulase which helps in cellulose degradation. The endophyte *Fusarium solani* isolated from *Catharanthus roseus* had the capability to secrete cellulose, protease and amylase.³⁰ *Aspergillus* sp. isolated from the leaf of *Piper longum* has the ability to produce cellulase in the solid media in the range of 71.00k ± 0.51 and the other isolate *Mycelia sterilia* from the same host are involved in the high production of pectinase in the range of 81.00d ± 0 which cleaves the pectin. The medicinal plant *Tinospora cordifolia* being the host plant of *Fusarium* sp. are rich in species diversity and this *Fusarium* sp. produces an important *Asparaginase*(79.66e ± 0.29) which has good pharmaceutical applications.³⁸ From the seven medicinal plant like *Azadirachta indica*, *Citrus limon*, *Gossypium hirsutum*, *Sonchafa*, *Datura stramonium*, *Datura stramonium*, *Phyllanthus emblica*, and *Piper betle*, the endophytic fungi *Cladosporium* sp., *Rhizoctonia* sp., *Aspergillus* sp., *Chaetomium* sp., *Biosporus* sp., *Fuzarium* sp., *Curvularia* sp., *Cladosporium* sp., *Colletotrichum* sp. were isolated. These endophytic fungi are capable to produce enzymes like amylase, protease, cellulose and lipase whereas, the highest production of amylase (0.26U/ml) was found in *Rhizoctonia* sp and other fungi producing amylase are *Aspergillus* sp., *Fuzarium* sp., *Curvularia* sp., *Colletotrichum* sp., *Biosporus* sp.. *Cladosporium* sp. showed greater yield of lipase with

0.72U/ml, *Biosporus* sp. showed higher production of protease(11U/ml) and the better yield of cellulase (0.013U/ml) was exhibited by *Colletotrichum* sp.² Endophytic fungi *Penicillium chrysogenum*, *Alternaria alternate* and fungal strain sterile hyphae isolated from *Asclepias sinaica* produces extracellular enzymes, among these fungi *Penicillium chrysogenum* and *Alternaria alternate* showed maximum amylolytic activity and *Alternaria alternate* is the endophyte which has the ability to produce gelatinase enzyme.¹ From the plant Tulsi (*Ocimum* species) they had isolated forty fungal and tested for its enzyme production. The fungal isolates showed a positive result for amylase and protease with 50% enzyme production and for tyrosinase enzyme production 27.5% of the fungal isolates showed positive result ie, out of 40 isolates, only seven isolates are producing tyrosinase enzyme.³⁹ *Xylaria psidii* KT30 fungus from marine red seaweed *kappaphycus alvarezii* is able to produce protease an extracellular enzyme which exhibited antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* with the inhibition zone of 7±0.57mm and 8±0.57mm respectively.³¹

Synthesis of silver nanoparticles

The antibiotics are not effective towards the antibiotic resistance bacterial strains, this problem can be solved by using silver particle as the antimicrobial agent. Silver metal has the antimicrobial activity against both antibiotic resistance and sensitive bacterial cells. *Guignardia mangiferae* isolated from *Citrus* sp. are capable to synthesis silver nanoparticles and this nanoparticle has the strong antibacterial activity against *P. mirabilis*, *K. pneumoniae*, *P.aeruginosa* and *S. aureus* with the inhibition zone radius of 16mm and showed good antifungal property at the concentration of 1mg/ml against *Colletotrichum* sp. (12.63 mm), *R. solani* (12.03 mm) and *C. lunata* (11.23 mm).⁴⁰ The *Citrus* sp. associated fungus *Guignardia mangiferae* are able to synthesis silver nanoparticle which showed high cytotoxic effect against MCF-7 cells and HeLa cells at 23.84µg/mL and 27.54 µg/mL respectively.⁴⁰ Silver nanoparticles can easily penetrate into bacterial cell membrane and damages the cells, therefore silver nanoparticles can be biosynthesized by the fungi *Aspergillus tamarii*, *Aspergillus niger* and *Penicillium ochrochloron* isolated from the plant *Potentilla fulgens* L. *Aspergillus tamarii* were able to biosynthesize silver nanoparticles with the average size of 3.5 ± 3.3 nm and this nanoparticle is effective against antibiotic resistance microbes.⁴¹ Silver nanoparticles synthesized by an endophytic *Colletotrichum* sp. ALF2-6 isolated from an herb *Andrographis paniculata* that is used to treat the common cold. This silver nanoparticle has antimicrobial activity against *E. coli* and *S. aureus* with a minimum inhibitory concentration of 25µg/ml and 12.5 µg/ml respectively.¹⁷

Bioactive compounds

The bioactive compounds present in the *Callyspongia* sp associated fungi *Aspergillus flavus* are Desmethyl



nomifemine (27.72%), 2-Butenoic acid(12.29%), 2-Benzoic acid (8.62%) and 7H-Furofuro xanthan-7-one(6.86%).³ The Cyclohexadepsipeptide beauvericin is an active compound with pharmacological properties produced by the *Fusarium oxysporum* of *Smalanthus sonchifolius* and this compound can be used for discovering new antimicrobial and anticancer drugs.⁴² *Pulu Mandoti* is an aromatic rice variety which showed high diverse in endophytic fungi and the fungus KN10 isolated from the leaf of rice plant gave high yield of indole acetic acid of (2.651mg⁻¹) and this indole acetic acid can be used to promote plant growth.⁴³ Alkaloids are the nitrogenous organic compounds produced from microbes, plants and animals that can be used for the pharmaceutical application. Ergot alkaloids, lolines and indole-terpenes are some of the alkaloids produced from the endophyte *Clavicipitaceae* species which can be further analyzed to produce a new drug.⁴⁴ 5-hydroxy-4-hydroxymethyl-2H-pyran-2-one and (5-hydroxy-2-oxo-2H pyran-4-yl)methyl acetate are the lactone derivatives separated from the ethyl acetate extract of *Trichoderma* sp, isolated from *Tinaspora crispa*.²⁷ Botrallin and TMC-264 are the active constituents with various bioactivities like antineoplastic, acetylcholin esterase inhibitory activities produced from the endophyte of polyploid hybrid, *Hyalodendriella* sp. Ponipodefin and its production were enhanced by the addition of metal ions Zn²⁺, Cu²⁺ and Mg²⁺ in the culture medium.¹⁵ The bioactive compounds produced from the endophytes of *Panax notoginseng* act as a biological control agent for the root-rot disease of the host plant.³⁷ Polyketides like 4-hydroxymellein and 1-(2,6-dihydroxyphenyl) ethanone are synthesized by fungal isolate *Phoma* sp. CB007 of *Cinnamomum mollissimum* exhibit activities as antibiotic, antifungal, anticancer, antiparasitic, and immunosuppressant.²⁸ Terreic acid and 6-methylsalicylic acid are the compounds obtained from the extract of *Pseudocercospora* sp. ESL 02 where these compounds possess antioxidant activity with inhibitory concentration IC₅₀ of (0.22 ± 0.02) and (3.87 ± 0.27) mmol/L, respectively.³⁶ Beauvericin and indole-3-carboxylic acid are the compounds derived from the crude extract of *Epicoccumnigrum* associated with *Entada abyssinica* by silica gel column chromatography and these compounds inhibited the growth of *Staphylococcus aureus*, Gram-negative strains with MIC values of 3.12 µg/ml and 6.25 µg/ml respectively.¹⁶ Pachybasin is an anthraquinone derivative released from the *Coelomyces* AFKR-18 fungus of *Arcangelisia flava* showed a MIC value of 16.0 µg/mL against *F. oxysporum*.⁴ Endophytic fungus G324-4 from *Huperzia serrata* produced two compounds and these compounds were identified as a nuclear plexus of penicillin and pencolide, the nuclear plexus of penicillin had anti-acetylcholinesterase activity and S5 compound isolated from the fungus *Penicillium* sp. (LQ2F02) of *Huperzia serrata* had shown best anti-acetyl cholin esterase activity.⁴⁵ Bioactive compound Paclitaxel (Taxol) a highly functionalized tetracyclic diterpenoid basically found in the bark of *Taxus brevifolia* (1971), which has been

demonstrated with a potent action in contrast to prostate, ovarian, breast and lung cancers. Successfully in 1993, a paclitaxel producing endophytic fungus *Taxomyces andreanae* were discovered from the *Taxus brevifolia* (Pacific yew). The research study has found at least 19 genera of endophytic fungi (i.e. *Alternaria*, *Aspergillus*, *Botryodiplodia*, *Botrytis*, *Cladosporium*, *Ectostroma*, *Fusarium*, *Metarhizium*, *Monochaetia*, *Mucor*, *Ozonium*, *Papulaspora*, *Periconia*, *Pestalotia*, *Pestalotiopsis*, *Phyllosticta*, *Pithomyces*, *Taxomyces*, *Tubercularia*) were exhibited to have the ability to produce paclitaxel.¹⁸ Endophytic fungi *Penicillium*, *Phoma* sp., *Colletotrichum* and *Fusarium* are the well-known producers of bioactive compounds like alkaloids and antibiotics.⁶

Plant growth promotion

Microbes like fungi are capable to solubilize phosphate and promote plant growth. The endophytes KN2, KN6, KN11 isolated from the stem of *Pulu mandoti* and KN9, KN13 from the leaf of the this plant solubilized phosphate in the range of 0.005 – 3.719 mg⁻¹ and promotes the plant growth.⁴³ *Clavicipitaceae* species is an endophyte which gives protection to the host plant against the herbivores and insects by releasing the alkaloids and gives the plant a healthy normal growth.⁴⁴ *Trichoderma gamsii* lives in association with *Panax notoginseng* can tolerate 20% of chemical fertilizers like ammonium chloride, potassium nitrate and ammonium dihydrogen phosphate and protect the host plant from its root rot disease-causing pathogens.²¹ *Piriformospora indica*, isolated from *Sebacinales* has the ability to promote the *Zea mays* growth during the stress condition by upregulating the drought-related genes DREB2A, CBL1, ANAC072, and RD29A in this plant with decreasing the accumulation of malondialdehyde (MDA).⁴⁶ Endophytic fungi present inside the host plant not only increases the tolerance level towards biotic and abiotic stresses but also enhances the plant's growth. The metabolites produced by these endophytes are the novel biologically active compounds which has the strong application in the agricultural and medicinal field. The rhizome of *Paris polyphylla* is used for treating inflammation in Chinese medicine; the fungal diversity and the saponin level are increased as the plant ages.⁴⁷

Biotransformation

Biotransformation is defined as the chemical modification of chemical compounds by the microorganisms. An endophytic fungus *Phomopsis* sp. isolated from *Viguiera arenaria* able to biotransform tetrahydrofuran lignin to as “3,4-dimethyl-2- (4- hydroxy-3,5 -dimethoxyphenyl)-5-methoxy-tetrahydro- furan”, and this compound has trypanocidal activity towards Chagas disease.⁴⁸ *Coelomyces* AFKR-3 is a fungus associated with the Yellow moonshed plant (*Arcangelisiaflava*(L.) are capable to biotransform berberine into 7-N-oxide derivative and this biotransformed product also showed antimicrobial properties similar to berberine.⁴⁹



INDUSTRIAL APPLICATION OF ENDOPHYTIC FUNGI

Bioremediation

Bioremediation is the process of partial or complete removal of harmful contaminants from the environment using the microorganisms. Endophytic fungi are the novel source of microbes with many industrial applications and these microbes can be used for bioremediation process. *Phomopsis liquidambar* B3 is a fungus spends its complete life time or some duration of time in association with plant *Bischofia polycarpa* are capable to survive in the indole contaminated soil. This fungus also able to decompose 99.1/ indole in the concentration of 100mg /l within 60 h.⁷ Increased concentration of cadmium in the soil may result in the abnormal physiology of the plant whereas the fungal microbes detoxify the heavy metals and reduce the metal stress on the host plant. *Paraphaeosphaeria* sp. SR46, an endophyte of *Salix variegata* is more tolerant to cadmium and the uptake value of cadmium was 2.65–7.29 mg g⁻¹ with a minimum inhibitory concentration of 0.39 mg ml⁻¹, this fungus helps in the phytoremediation.⁵⁰

Decomposition

Soybean (*Glycine max*) is said to have medicinal properties for high cholesterol, diabetes and it also has good anticancer activity. The endophytic fungi from soybean leaves includes the genera such as *Alternaria* sp., *Cladosporium* sp., *Curvularia* sp., *Nigrospora* sp., *Phomopsis* sp. and *Colletotrichum* sp., among these the endophyte *Colletotrichum* sp are important fungus which is able to produce enzymes during the final stage of leaf production and these enzymes take part in degradation of plant materials.⁵¹ The hydrolytic enzyme cellulase had released by *Macrophomina Phaseolina* and *Nigrospora sphaerica* isolated from the plant *Catharanthus roseus* were involved in the decomposition of organic matters and also protects the host plant from pathogens.³⁰

Resin production

Pinus massoniana Lamb is a plant produces resin for many industrial applications, the yield of resin can be increased by using the endophytic fungi of this plant itself. The strain ZI41155 *Paecilomyces* isolated from leaves of the host showed highest increase in resin yield of 34.12%, an average resin yield of a tree with the application of the endophyte *Paecilomyces fungus* was 37gram per day.⁵² The endophytic fungi *Bionectric* strain BS4787 of *Pinus massoniana* promotes the photosynthetic process in plant and increases the resin yield at the rate of 32.07%.⁵²

Other Bioactive Compounds Produced by Endophytic Fungi

Taxus baccata is small coniferous shrubs able to produce an interesting bioactive peptide Leucinoastatin A and thus the endophyte *Acremonium* sp from this plant can also able produce the phytotoxic component.²⁹ The fungal endophytes contain many different phytochemicals which

can be isolated individually and further can be used to produce many different drugs. Alkaloids, phenols, amino acids, tannins, terpenes and carbohydrates are some phytochemical compounds produced from endophytic fungi. *Trichoderma longibrachiatum*, *Penicillium spinulosum* and *Coprinopsis cinerea* are the fungal endophytes of *Eugenia jambolana* contain alkaloids, amino acids, phenols, terpene and flavanoids which has good medicinal properties.³⁵ volatile organic compounds like alcohols, ketones, alkanes, furanes, pyrones, and terpenes produced from *Trichoderma* species of *Panax notoginseng* has an antagonistic effect towards the root rod plant pathogens.²¹

CONCLUSION

The overall review of the present study concludes that the endophytic fungi were able to produce some of the secondary metabolites similar to their host plants. The isolation of fungi from plants and separation of fungi produced bioactive compounds can be done by simple producers. The protocols for metabolite isolation of endophytes from plants are cost-effective and thus they can be used in many numbers of fields for their valuable applications. Endophytes are the group of microorganisms that are inadequately investigated which are capable of producing biologically active compounds that can be used to treat several diseases. Endophytic fungi isolated from plants serve as a novel and significant resources for exhibiting biologically active compounds from their host, which attracted several researchers' attention on their theoretical study as well as in practical application. Additionally, the best proved active isolates should be identified using existing methods to place these fungi in the fungal kingdom.

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