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BIOACTIVE METABOLITES FROM ENDOPHYTIC FUNGI-APPLICATIONS AND FUTURE PROSPECTS

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ABSTRACT

Endophytes are the microorganisms which resides with symbiotic association inside the plant tissues which mimic the natural compounds produced by the plants. Endophytes are evolving for millions of the years within the plant parts. They have colonized the plant parts without any apparent harmful effects or symptoms to the host plant, rather the endosymbiotic microbes produce beneficial products which helps the host plant to increase the immunity against the biotic and abiotic stress and defence against pathogens. In return, plants also secret some chemical components which act as nutrients for endophytic microbes that helps them to grow. Endophytes may be bacteria, fungi, archea etc. Now a days, endophytic microorganisms are gaining tremendous attraction of scientific community because of the production of valuable bioactive metabolites which have pharmaceutical, agricultural and industrial importance. The fungal extracts show the pharmacologically important properties such as antimicrobial, antiviral, anticancer, anti-inflammatory, antidiabetic etc. This review emphasises on endophytic fungi and their bioprospecting potential for the production of bioactive metabolites which have medicinal and industrial values.

Keywords: Endophytic fungi, antimicrobial activity, anticancer activity, anti-inflammation activity, anti- viral activity

INTRODUCTION:

Due to very fast evolution in infectious/ pathogenic microorganisms, there is always a need of novel and useful compounds for curing the human ailments. Pathogenic microorganisms have the ability to gain resistance against the existing synthetic drugs. That's why, scientists are always under the pressure to discover new and effective drug which can compete with the pathogenic microorganisms with high efficiency **[1]**. Microbes are very important and diverse component of every ecosystem. We can perform lots of processes such as recycling, degradation of agricultural or industrial waste materials, transportation of nutrient to every ecosystem, decomposition etc with the help of microorganisms **[2]**.

In recent days, endophytic microbes are the point of attraction because of their ability to produce lots of beneficiary bioactive compounds. Endophytes are the endosymbiotic group of microorganisms which colonise in the host plant or in the plant parts with symbiotic association without any apparent harmful effect on the host plant **[3, 4]**. The components produced by the endophytes helps to increase the growth of host plant and can also give the resistance property against the biotic and abiotic stress **[5, 6]**. There is an equal benefit for both host plant and the endophytic microbes due to the mutual interaction **[7]**. Endophytes can colonise the different parts of the host plant such as root, leaves, bark, stem etc. Endophytic microbes can be bacteria, fungi, actinomycetes etc.

More than 23,000 active natural compounds produced till now from the endophytic microbes. These natural compounds may be antibiotics, antiviral, cytotoxic compounds, out of which 42% from fungi and 38% from filamentous bacteria, and rest from actinomycetes **[8]**. Endophytic fungi isolated from the medicinal plants produce so many natural products which have commercially, industrially and pharmaceutically importance **[9]**. These bioactive metabolites show immense therapeutic significance such as immune-suppressants, anti- allergic, antibiotics, anticancer agents, anti-depressants. Surprisingly, a single microbe can produce more than 50 chemical compounds **[10]**.

At present, there is an increase in the use of medicinal plants to prepare the herbal drugs to cure the human health issues. Currently, more than the 80% of the world population moving towards the phytomedicine because of the readily availability, cost- effectiveness and most common non- toxicity **[11]**. From the ancient time, natural sources such as plants, animals, microbes provide us so many bioactive compounds (also known as secondary metabolites) which enhances the life span of the human being by helping them to cure various health issues like pain, suffering, wound etc. **[8]**. Most of the bioactive compound produced by the endophytic fungi are natural as produced by the host plant.

Relation between endophytes and the host plant

Endophytes are existing within the host plant from millions of the years. By discovering their niche within the host plant, endophytic fungi established their image as a versatile inhabitant. The environmental conditions make the changes in the plants and plant parts due to which evolution occur in the endophytic microorganisms. The exact origin of the endophytes is unknown **[12]**.

Exogenous and Endogenous are the two-hypothesis used by the scientist to justify the occurrence of endophytes inside the plants. According to exogenous hypothesis, the endophytes are entered inside the host plant parts through the contact with surface and make the channels. But, according to the endogenous hypothesis, the endophytes evolved from the mitochondria and chloroplast of the host plant. That's why, the endophytes have bio prospective similarity with their host plant. There are mainly two types of relationship between host plant and endophytes namely, mutualistic and neutralism. If the endophytic fungi is inactive throughout the life of the host plant, then the endophytes living with neutralism relationship. If both of the host plant and endophytes getting benefit from each other then it is known as mutualistic or symbiotic relationship **[13]**.

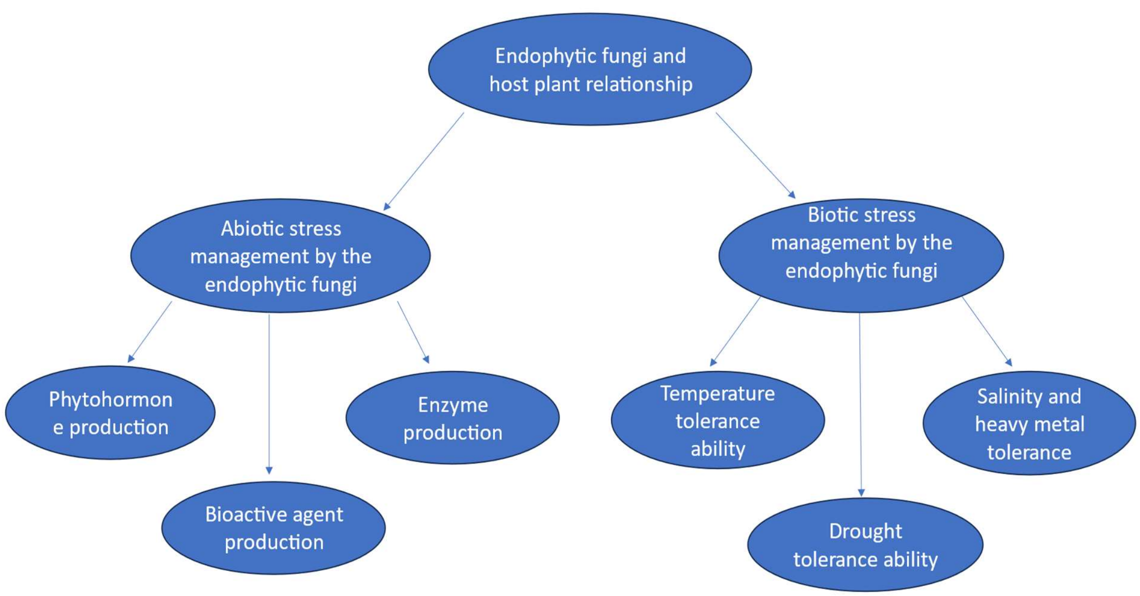

Figure 1: Benefits of the endophytic fungi to the host plant

Why endophytic fungi are becoming source of attraction-

The plant kingdom provides shelter to millions of endophytic species. Endophytes include both fungi and bacteria, but the majority of known endophytes are fungi **[14]**. The species richness and diversity of fungal endophyte depends upon the climatic conditions such as rainfall and atmospheric humidity in which the plant grows **[15]**. Endophytic fungi are an influential source of bioactive compounds that participate an important role in plant growth and also give protection to host plant from unfavourable conditions (biotic and abiotic). Bioactive metabolites isolated from endophytic fungi also mimic plant-based natural bioactive metabolites. Natural bioactive compounds with small size and less complexity are synthesised by endophytic fungi **[16]**.

Currently, there are increasing cases of antibiotics resistance among most causative agents of diseases in human beings, due to which researchers are searching for an alternative source of drug discovery using natural sources. Fungal endophytes are natural reservoir of novel bioactive compounds with pharmaceutical importance. Fungal endophytes represent themselves as a storehouse of many bioactive metabolites such as phenolic acids, alkaloids, quinones, steroids, saponins, tannins, and terpenoids which makes them a promising candidate for anticancer, antimalarial, antituberculosis, antiviral, antidiabetic, anti-inflammatory, anti-arthritis, and immunosuppressive properties among many others **[17]**.

To obtain the metabolite from the plant sources, we have to depend on the season, climatic conditions and for the approval from the government. Extraction of bioactive metabolite from the plants also have lengthy and laborious procedure and in return a small quantity of metabolite will be obtained.

Thus, endophytic fungi become a source of attraction for microbiologists, ecologists, agronomists, and chemists for discovering novel compounds that will help to confront the growing medical and environmental problems of mankind. Also, the bioactive compounds produced by the endophytic fungi are natural in nature, easily available, affordable and non-toxic to the human body. Over 300 endophytes with the potentials to synthesize secondary metabolites with therapeutic values have been isolated and successfully cultured in laboratory conditions in the last 5 years **[18]**.

Bioactive Compounds from Endophytic Fungi

Endophytic fungi are known to produce lots of bioactive metabolites such as quinones, terpenoids, alkaloids, benzopyrones, phenolic acid, steroids, xanthones and many other bioactive metabolites. These metabolites show various important physiological activity such as immunosuppressive, antiviral, antimicrobial, anticancer, antioxidant, antidiabetic etc. These metabolites can also be used as phytohormones and agrochemicals. The metabolites extracted from the endophytic fungi by using various biological techniques. To obtain the bioactive metabolite from the endophytic fungi include microbial production via fermentation, extraction of bioactive compounds via several purification techniques and microbial transformation to enhance the metabolite production. Endophytic fungi are good alternative for the cost effective and high value bioactive metabolite production.

'Torreyanic acid' is a dimeric quinone first isolated and by Lee *et al*. **[19]** in 1996 from an endophyte, *Pestalotiopsis microspora* strain. Terroyanic acid is the analogue of ambuic acid and can be formed by the oxidation, cyclization and Diels-Alder dimerization of ambuic acid. Torreyanic acid show the cytotoxic effect and little bit antimicrobial activity. It follows the apoptosis with high potency by arresting the cells in G1 phase. It kills the tumour cells which are sensitive to the protein kinase C antagonist **[20, 21, 22]**.

'Taxol' is a part of medication class called taxanes **[23]** and highly functionalised polycyclic diterpenoid which is used to treat various human cancer **[24]**. Paclitaxel (taxol) is the world's first billion-dollar anticancer drug which is a natural product derived from endophytic fungi *Phoma medicaginis*, isolated from the yew tree *Taxus wallichiana* **[25, 26]**. Paclitaxel arrests the mitotic cell cycle in the G0 /G1 and G2 /M phase of the animal tumor cells and cell culture **[27, 28]**. Paclitaxel is an anti-microtubule which prevent depolymerisation of microtubule and stabilise the living cells due to which the cancer cell undergoes for apoptosis **[29, 30, 31]**. Taxol is used to treat gastroesophageal, endometrial, cervical, prostate, and head and neck cancers, sarcoma, lymphoma, leukemia, breast, ovarian, non-small-cell lung carcinoma (NSCLC), Kaposi's sarcoma, head, and leucopenia cancers **[32, 33, 34]**.

'Camptothecin' is a pentacyclic indole alkaloid which was first isolated from the endophytic fungi of *Camptotheca acuminata*, was found to kill cancer cells **[35, 36]**. An endophytic fungi *Fusarium solani*, isolated from the *Camptotheca acuminata* show a potential for the production of camptothecin **[37]**. In 1966, Wall ME and Wani MC first identified camptothecin during screening of natural herbal products for anticancer potential **[38]**. Camptothecin targets the topoisomerase which facilitate the DNA replication process. Topoisomerase 2 cause the double stranded break and topoisomerase 1 cause the single strand break. Camptothecin inhibit the topoisomerase 1 **[39]** and causes the apoptosis of the cell. It may cause the hydrolysis or removal of lactones which are important for the binding of topoisomerase 1 and initiate the activity of topoisomerase 1 **[40]**. Camptothecins can be used for the treatment of colorectal cancer, small-cell lung cancer, and ovarian cancer **[41, 42]**.

'Podophyllotoxin' is an important bioactive natural compound and has derivatives such as etoposide and teniposide, which have been used as therapies for cancers and venereal wart **[43]**. Podophyllotoxin is an aryl-tetralin-type lignan isolated from the endophytic fungi *Phialocephala fortinii* of *Podophyllum peltatum* and *Alternaria tenuissima* of *Sinopodophyllum hexandrum* **[44, 45, 46]**. Podophyllotoxin cause the arrest of cell cycle in the G2/M phase and initiate apoptosis through the p38 MAPK signaling pathway by upregulating ROS in colorectal cancer HCT116 cells **[47]**. It is used for the treatment of lung cancer, testicular cancer, leukemia, and other solid tumors **[48]**.

'Vinca alkaloids' play a major role to fight against the cancer. Vinca alkaloids are the second-most used medication group of cancer drugs which is used in original cancer therapies **[49]**. Vinca alkaloids (Vinblastine and vincristine) are asymmetric dimeric compounds which are isolated from endophytic fungi, *Fusarium oxysporum* present in the leaves of the Madagascar periwinkle plant, *Catharanthus roseus*, formerly known as Vinca rosea **[50]**. Vinca alkaloids are cell cycle specific anti-microtubule compound which arrests cell cycle in metaphase and disrupt the mitotic apparatus after binding to the tubulin **[50, 51]**. Vinca alkaloids are approved to treat the lung cancer, breast cancer, colon cancer, stomach cancer **[52]**, acute leukaemia, rhabdomyosarcoma, neuroblastoma, wilm's tumor, Hodgkin's disease **[49]**.

'Ergoflavin', was first reported in 1912 by Freeborn **[53]**. Ergoflavin was also isolated as the major secondary metabolite from *Claviceps purpurea*, but no pharmacological activity was reported **[54, 55]**. Firstly, anti-inflammatory and anti- cancer activity was reported by Deshmukh et. al (2009). Endophytic fungus isolated from the leaves of the Indian medicinal plant named as *Mimusops elengi* is also have ability to synthesize Ergoflavin **[55]**. Besides its anticancer properties, it was reported as a potent anti-inflammatory compound as it markedly inhibits lipopolysaccharide (LPS)-induced IL-6 and TNF-α production in human monocytic cell line (THP1) with an IC50 value of 1.2 ± 0.3 and 1.9 ± 0.1 μM, respectively. This compound inhibits the production of proinflammatory cytokine production in THP1 and peripheral blood mononuclear cells (PBMC) stimulated by toll-like receptor (TLR) or CD28/B7 co-stimulation pathway. This compound was also isolated from several endophytic fungi like *Aspergillus* sp., *Penicillium oxalicum*, *Pyrenochaeta terrestris*, and *Phoma terrestris* **[55]**.

'Hypericin' (4,5,7,4′,5′,7′-hexahydroxy-2,2′-dimethylnaphtodiant hrone) is a natural compound which can be isolated from some species of the genus *Hypericum* **[56]**. The first detailed report of Hypericin (commonly known as St. John's wort) isolation from *Hypericum perforatum* L. was given by Brockmann *et al*., 1939. In the last three decades, hypericin is used for medicinal purposes because of its lots of pharmaceutical properties **[57]**. Antidepressive, antiviral, antiretroviral, antineoplastic, antitumor, photodynamic and photo diagnostic activities of hypericin properties of Hypericin are under clinical trials **[56, 57]**. According to some clinical studies, high doses of hypericin may show phototoxic skin reaction without showing any observing antiviral and antiretroviral activity **[58]**.

'Polyketides' are the structurally diverse bioactive natural products produced by the lots of microorganisms. Polyketides play an important role in survival of producing organism and also serve as a chemical defence agent **[59]**. Polyketides have the properties to act as anticancer, antifungal, and anti-cholesteric agents; antibiotics; parasiticides and immunomodulators **[60, 61]**. Polyketides are synthesized by polyketide synthases (PKSs) which are multi-domain enzymes which helps in the biosynthesis of polyketides by loading the starter unit acyl-Coenzyme A (CoA) on the acyl carrier protein (ACP) catalysed by the AT domain of PKS enzyme **[61]**.

'Cladosporine' is a naturally occurring fungal metabolite mainly isolated from the endophytic fungus *Cladosporium cladosporioides* and *Aspergillus flavus*. Cladosporine have significant antibacterial, antifungal, insecticidal, and anti-inflammatory activities, as well as plant growth regulatory effects **[62]**. Cladosporine exhibit selective nano-molar activity against malarial parasite *Plasmodium falciparum* which is main causative pathogen for malaria. Cladosporine have the ability to cease the parasitic protein biosynthesis in the parasitic cell through inhibition of cytosolic lysyl-tRNA synthetase (PfKRS) **[63]**.

'Colletotric acid' are the type of antimicrobial compound which was isolated from the endophytic fungi *Colletotrichum gloeosporioides*, an endophytic fungus colonised *Artemisia mongolica* plant parts. Colletotric acid is a type of organic acids. It exhibits antimicrobial activity against the phytopathogenic fungus, *Helminthosporium sativum* **[64]**.

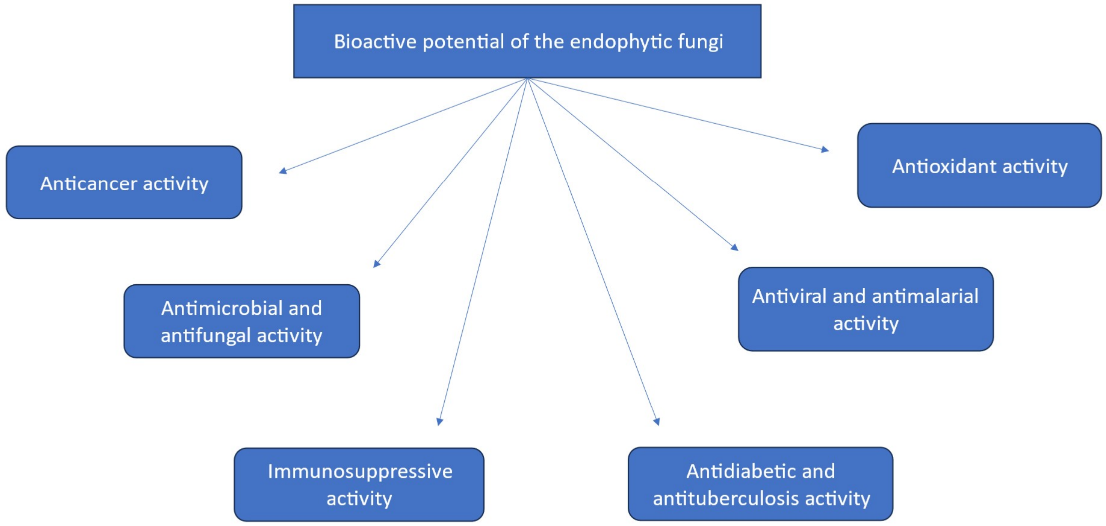

Figure 2: Bioactive potential of endophytic fungi

Table 1: Bioactive Compounds isolated from the endophytic fungi

Endophytic fungi	Host plant	Bioactive compound name	Biological activity	References
Arthrinium sp.	*Phaeurus antarcticus*	Polyketides	Photoprotective and antioxidant	[65]
Streptomyces spp.	Paddy crops	pseudopyronine A	Anti- phytopathogens	[66]
Hypoxylon investiens	*Fridericia chica*	Pigments	Antioxidant and antimicrobial activity	[67]
Aspergillus cejpii	*Hedera helix*	γ-butenolide, spiculisporic acid	Antimicrobial activity	[68]
Diaporthe sp.	*Mangroov plants*	oxygen-bridged cyclooctadienes	Cytotoxic activity	[69]
Penicillium sp	Macrozamia *com munis*	mycophenolic acid methyl ester	Antimicrobial and cytotoxic activity	[70]
Neurospora terricola	Pseudotsuga *gau ssenii*	terricoxanthones A–E (polyketides)	Antimicrobial activity	[71]
Linnemania elongata, Trichoderma sp. and *Fusarium* sp.	*Panicum virgatum*	Saponins and diterpenoids	Antifungal activity	[72]
Chaetomium sp.	*Panax notoginseng*	Dichlororesorcinols	Antitumor activity	[73]
Streptomyces sp.	*Panax notoginseng*	anthraquinone derivatives	antidiabetic, antioxidant, antitumor agent	[74]
Aspergillus niger	Haliyal region plants	dibutyl phthalate, e-5-heptadecanol, and 2,4-ditert-butylphenol	antimicrobial, antifungal and anticancer	[75]
Aspergillus carneus	Achanakmar Biosphere Reserve	trans- 1,3-dimethyl-Cyclohexane	antibacterial and anti-proliferative activity	[76]
Nigrospora chinensis	Gannan navel orange pulp	Sesquiterpene	Antibacterial and cytotoxic activity	[77]
Daldinia eschscholtzii	Mangrove plant	Polyketides	Anti-inflammatory	[78]
Cladosporium sp.	*Paris polyphylla*	aspulvinone analogues	Anti-inflammatory and antiviral activity	[79]
Penicillium citrinum	*Codonopsis pilosula (Franch) Nannf.*	bisabolane-type sesquiterpenes	Anti-inflammatory	[80]

Comoclathris	*Andalusia arid plants*	Comoclathri, sorbicillin analogue, violapyrone	Anti- tyrosinase (anti-cancer)	[81]
Aspergillus fumigatus	*Ceriops decandra*	fumigaclavine C, azaspirofuran B, and fraxetin	Antibacterial activity	[82]
Aspergillus terreus	*Moringa oleifera*	Fatty acids	Antifungal activity	[83]
Penicillium citrinum	Achanakmar Biosphere Reserve	(E)-9-Octadecenoic acid ethyl ester	antioxidant, antimicrobial, antiaging, and antiproliferative activity	[84]
Chaetomium globosum	Wheat straw	Polysaccharides	Antioxidant activity	[85]
Aspergillus luchuensis, Xylaria feejeensis	Mangrove plants	alkaloids, tannins and coumarins	antioxidant and anti-mutagenic activities	[86]
Penicillium sp., *Aspergillus* sp.,	*Chaenomeles speciosa*	Esters and phathalates	Antibacterial activity	[87]
Emericella sp.	mangrove-rhizosphere	emericelactone E	Cytotoxic activity	[88]
Aspergillus sp.	mangrove-rhizosphere	Alkaloids and polyketides	Immunosuppressive activity	[89]

CONCLUSION AND FUTURE OUTLOOK:

Endophytes show the potential to produce lots of bioactive metabolites which have pharmaceutical and agricultural importance. There is a large microbial population exist in the medicinal plants which retain the capability to defeat the deadly pathogens. Fungal endophytes produce lots of secondary metabolites like antifungal, antiviral, antimicrobial, anticancer, anti-inflammatory and so on. These metabolites have the ability to fight against the pathogens which are resistant to the existing drugs. Fungal endophytes produce novel and natural compounds which can be used medicinal purpose. The secondary metabolites synthesised by the fungal endophytes show the similar herbal properties as the metabolites from medicinal plant retain and this property is sufficient to fulfil the current demand of herbal or natural drugs from the human beings. There is very less investigation on fungal endophytes and production of lots of valuable metabolites attract the attention scientific community. Hence, we can say that there is a very bright future in the research field of fungal endophytes.

CONFLICT OF INTEREST:

All authors conclude that there is no conflict of interest.

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