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A Review of Bioactive Metabolites from Endophytic Fungi

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Abstract – High potential for medicinal substances such as anticancer, antioxidant, antibacterial, antidiabetic and industrial enzymes are endophytic fungus; The presence of novel illnesses, infections, resistance to drugs and imbalances in ecosystems is now a major problem for human beings. The possible sources for novel treatments were here endophytes. Endophytes are regarded as a bioprospect treasure and help to overcome numerous difficulties in many ways. Most possible microorganisms, which are a reservoir of mostly untapped bioactive compounds, have been identified among the different endophytic bacteria. For their bioactive substances, we must look for endophytes.

Key Words – Endophytic fungi, Bioactive Compounds, Host Plants, Podophyllotoxin, Camptothecne, Vinblastine, Hypericin

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1. INTRODUCTION

Natural products are crucial in the discovery of new drug leads for the treatment of human diseases. Natural ingredients are an unrivaled source of bioactive chemicals, as well as a valuable economic opportunity for the medicinal, beauty, and food industries. Medicinal plants have a special habitat for endophytes and have been identified as a source of endophytes with novel pharmaceutically important metabolites. The exploration of natural materials relies heavily on medicinal plants and their endophytes. Microbial variation relies heavily on endophytes. Endophytes are a form of microorganism that lives in the living tissues of plants without causing any symptoms. Endophytic fungi are a significant and quantifiable part of fungal diversity, and they have been shown to influence the diversity and function of plant communities. Pharmacological potential is more probable in endophytic fungi extracted from medicinal plants. Endophytes provide a diverse range of bioactive natural products with distinct structural characteristics. These abundant natural products constitute a vast resource with tremendous potential for medical, agricultural, and industrial applications. Endophytic fungi have sparked a lot of curiosity as possible producers of novel, biologically active compounds. Endophytes connected with medicinal plants contain secondary metabolites that may be used to cure illnesses. The identification of novel endophytes, their genetics, and their possible use are all more interesting possibilities in the wild and unexplored parts of the globe.

2. ISOLATION OF ENDOPHYTES

The plant materials are thoroughly washed and surface sterilized with different surface sterilizing agents such as mercuric chloride ($HgCl_2$), ethanol, and others to remove epiphytic microbes. Cut into small pieces, these are then placed on a PDA (potato dextrose agar) plate. The hypical tips of the fungi are removed and transferred to PDA slants, where they are screened for bioactive secondary metabolite production after a significant period of incubation ranging up to several days. Isolations of these fungi from surface sterilized tissues were used to determine whether they were epiphytic or endophytic. Due to the slow growth rate of endophytes, the most difficult part of most procedures is isolating and purifying these cultures for long periods of time. A variety of stains have been used to identify these fungi in plants. To look for endophytic fungi in epidermal peels from stems, seeds, leaf sheaths, pith scrapings, and other places, Sampson used cotton blue or gentian violet, followed by Gram's iodine solution. Other researchers used lactophenol cottonblue, lactophenoltrypan blue, and aniline blue to stain mycelium. Clark et al. soaked the seeds in aniline blue-lactic acid. Recently, endophytes in seeds and plant tissue systems were detected using an enzyme-linked immunosorbent assay (ELISA). Saha et al. developed a rapid staining method for endophytes using rose bengal stains. This method was superior to trypan blue in terms of speed and safety. Since then, a large number of bioactive secondary metabolites from plant-associated endophytic fungal strains have been isolated, purified, and thoroughly characterized.

3. BIOACTIVE METABOLITES FROM ENDOPHYTIC FUNGI

[A] Anticancer drugs from endophytes:

(i) Paclitaxel (Taxol)

The first major class of anticancer agents produced by endophytes is paclitaxel and some of its derivatives. Paclitaxel is a highly functionalized diterpenoid found in yew (Taxus) species throughout the world. Its mechanism of action is to prevent tubulin molecules from depolymerizing during cell division, making it the best anti-cancer drug in the world. Taxol is used to treat a variety of human tissue proliferating diseases in addition to cancer.

Table 1: Some of the endophytic fungi producing paclitaxel are:

S. No.	Host plant	Paclitaxel-producing endophytic fungus
1	Taxus baccata	Botryodiplodia theobromae, Fusarium lateritium, Monochaetia sp., Pestalotia bicilia, Gliocladium sp.
2	Taxus wallachiana	Pestalotiopsis microspora.
3	Taxus cuspidate	Alternaria sp., Botrytis sp., Pestalotiopsis microspora.
4	Taxus brevifolia	Taxomyces andreanae
5	Taxus media	Cladosporium cladosporioides
6	Taxus celebica	Fusarium solani
7	Taxus sumatrana	Fusarium solani

(ii) Camptothecin

The two most effective anti-influenza drugs are Camptothecin and its analogue hydroxycamptothecin. Camptothecin is a quinoline alkaloid of pentacyclic origin that had been originally discovered by Wall et al in 1966 from Camptotheca (Nyssaceae) wood. Camptothecin mechanism of actions is inhibited by the intranuclear enzyme topoisomerase-1, which is needed during molecular processes for DNA replication and transcription. In order to produce camptothecine and related compounds, excessive cultivation of the wild trees Camptotheca Acuminata and Nothapodytes Nimmoniana (Icacinaceas) found in Indian and Chinese have made it essential that alternatives for the obtaining of these products are obtained and natural resources not further utilised. With this view, various researchers attempted to isolate endophytes from these plants and finally, many endophytes like Entrophospora infrequens, Neurospora sp., Fusarium solani, etc., producing camptothecin and its analogues were successfully isolated from the above mentioned tree species.

Table 2: Some of the endophytic fungi producing camptothecin:

S. No.	Host plant	Camptothecin-producing endophytic fungus
1	Nothapodytes foetida	Entrophospora infrequens, Neurospora sp.
2	Camptotheca acuminata	Fusarium solani
3	Apodytes dimidiate	Fusarium solani

(iii) Podophyllotoxin

Podophyllotoxin is an excellent anti-cancer, antiviral and Antioxidant chemical that is primarily isolated from Podophyllum (Sinopodophyllum) plants, antibacterial, Immunostimulation and anti-rheumatic plants. This lignan is an aryltetraline and is utilised as a precursor for chemical production of anticancer medicines like etoposide. Other genera in which this compound occurs include Diphylleia, Dysosma and Sabina (Juniperus). Yet, supply of this compound proves to be insufficient although the plants used for its synthesis are now being declared endangered due to excessive exploitation. Thus, increasing demand and lack of resources make it very important to find an alternate source for drug production and this is where the use of endophytes steps in. Researchers have now successfully isolated podophyllotoxinproducing endophytic fungi like Sinopodophyllum hexandrum, Diphylleia sinensis, Dysosma veitchii, Alternaria sp, Sabina vulgaris, Phialocephala fortinii, Trametes hirsuta, Fusarium oxysporum, etc. from the above mentioned plant species and attempts are now being targeted towards increasing production of this novel compound and its derivatives.

Table 3: Some of the endophytic fungi producing podophyllotoxin:

S. No.	Host plant	Podophyllum-producing endophytic fungus
1.	Sinopodophyllum hexandrum (Podophyllum hexandrum)	Trametes hirsuta, Penicillium sp., Alternaria sp., Alternaria neesex.
2.	Sinopodophyllum peltatum	Phialocephala fortinii.
3.	Sabina recurva (Juniperus recurva)	Fusarium oxysporum.
4.	Dysosma veitchii Monilia sp.,	Penicillium sp.

(iv) Vinca alkaloids - Vinblastine & Vincristine

The two most common anti-cancer medicines are vinblastine and vincristine. The plants are generated from field leaves from cell culture and tissue Catharnthus roseus, callus culture, cell suspension culture, cultivation of the firefighters, cultures of hair roots, semi-synthesis and synthesis.

[B] Antimicrobial compounds from endophytes

Metabolites with anti-biotic properties are low-molecular-weight natural organic compounds synthesized by microorganisms which are active at low concentrations against other microorganisms. These secondary endophytes generated metabolites are classified as alkaloids, peptides, steroids, phenols, flavonoids, quinines, terpenoids, diterpenoids, etc. The growing levels of drug resistance shown by plant or human pathogen are worldwide, leading researchers to explore endophytes for the creation of new antimicrobial metabolites that can not only be utilised as medicines, but also to other uses, such as food preservation, anti-food and food illnesses, etc.

Table 4: Endophytic fungi have been isolated from different plant species worldwide which produce novel anti-microbial compounds: (1, 53, 74, 104, 106)

S. No.	Endophytic fungi	Anti-microbial Compounds Synthesized
1	Xylaria sp.	Sordaricin, 7-amino-4-methylcoumarin, Griseofulvin, 2-hexyl-3-methyl-butanodioic acid, Cytochalasin D.
2	C. globosum	Chaetomugilin A, Chaetomugilin D.
3	Pezicula sp.	(−)-mycorrhizin A, (+)- cryptosporiopsin .
4	Pestalotiopsis adusta	Pestalachloride A, Pestalachloride B.
5	Cladosporium sp.	Brefeldin-A.
6	Penicillium janthinellum	Citrinin.
7	Phomopsis cassiae	ethyl 2,4-dihydroxy- 5,6-dimethylbenzoate, phomopsilactone.
8	Pestalotiopsis theae	Pestalotheol C (anti-HIV).
9	Aspergillus fumigatus	Asperfumoid, Fumigaclavine C, Fumitremorgin C, Physcion, Helvolic acid.
10	Verticillium sp.	2,6-Dihydroxy-2-methyl-7- (prop-1E-enyl)-1-benzofuran-3(2H)-one.

[C] Antioxidants from endophytes

Compounds for the production of anti-oxidants are very efficient against damage produced by free radicals and reactive oxygen species (ROS) from oxygen and contribute to a variety of adverse consequences including cell degeneration, membrane breakdown, damage to DNA, carcinogenesis, etc. These characteristics make antioxidants extremely promising to effectively cure a large number of ROS-related disorders, such as atherosclerosis, high blood pressure, ageing, RH, Alzheimer's and Parkinson's, Diabetes mellitus, cardiovascular disease, many kinds of malignancies, etc.

Table 5: Metabolites from endophytes are used as potentail source of novel natural antioxidants

Plant name	Isolated endophytic fungi	Anti-oxidants synthesized
Terminalia morobensis	*Pestalotiopsis microspora*	Pestacin, Isopestacin, 1,3-dihydro isobenzofurans.
Trachelospermum jasminoides	*Cephalosporium* sp.	Graphislactone A

[D] Ergot alkaloids from endophytes

Ergot-alkaloids are confined to the sclerotium of the fungus while alkaloids on the other hand can be isolated from whole parts of the plant symbiotic with endophytes. Although, ergot powder obtained from dried sclerotia of the fungus Claviceps purpurea parasitic on rye, was used to hasten childbirth by midwives for thousands of years, its use in modern medicine was first reported by German physician Lonicer in 1582.

Table 6: Endophytic fungi and Ergot alkaloids synthesized

Endophytic fungi	Ergot alkaloids synthesized
Claviceps purpurea	Ergometrine, Ergometrinine, Ergotamine, Ergosine, Ergocryptine, Ergocrystine.
Balansia claviceps	Chanoclavine , Ergonovine, Ergonovinine.
Balansia epichloe'	Agroclavine, Chanoclavine, Elymoclavine, Ergonovine, Ergonovinine, Isochanoclavine- I, Panniclavine, 6,7-Secoagroclavine.
Balansia henningsiana	Chanoclavine, Dihydroelymoclavine, Ergonovine, Ergonovinine.
Balansia strangulans	Chanoclavine, 6,7-Secoagroclavine.

[E] Antiviral compounds from endophytes

Drug resistance cases in viruses have grown frequent and global researchers are seeking a method to fight against this problem. In such a case, drugs isolated from endophytic fungi may come to rescue as these belong to a new and improved class of therapeutic agents. Guo et.al recently discovered, via solid-state fermenting of the endophytical fungus Cytonaema sp, two new inhibitors of CMV protease, cytonic acido A and B. Thus, although in its infancy, the potential of endophytic fungi to produce novel anti-viral compounds cannot be sidetracked and has tremendous scope for discovery, and treatment of various viral diseases like AIDS, poliomyelitis, chicken pox, swine flu, mumps, etc.

[F] Antibiotics from endophytes

A sudden surge in the number of people worldwide facing health problems due to cancers, parasitic protozoans, drug-resistant bacteria, life threatening viruses, and fungi have caused a red-alert. Recurring problems with diseases in patients who have undergone organ transplants and are immunocompromised, emergence of new diseases like AIDS and severe acute respiratory syndrome, presence of naturallyresistant organisms, and development of resistance in pathogenic microorganisms like species of *Staphylococcus*, *Mycobacterium*, *Streptococcus,* etc. call for an immediate development in the variety of drugs being produced and advent of newer and stronger derivatives to tackle these utmost serious issues.

Table 7: Some of the endophytic fungi producing antibiotics:

Host plant	Antibiotic-producing endophytic fungus	Antibiotics synthesized
Tripterigeum wilfordii	Cryptosporiopsis quercina	Cryptocandin, Cryptocin
Torreya taxifolia (endangered)	Pestalotiopsis microspora	Pestaloside, β glucoside, Pestalopyrone, Hydroxypestalopyrone, Pestalotiopsins A and B, 2-α-hydroxydimeninol, Humulane.
Selaginella pallescens	Fusarium sp.	Pentaketide antifungal agent-CR377.
Artemisia mongolica	Colletotrichum gloeosporioides	Colletotric acid.
Artemisia annua	Colletotrichum sp.	Artemisinin
Mangifera indica (mango), Psidium guajava (guava).	Pestalotiopsis sp., Monochaetia sp.	Ambuic acid
Fragraea bodenii	Pestalotiopsis jesteri	Jesterone, hydroxy-jesterone.

[G] Volatile Antibiotics from endophytes

A new cinnamon tree isolated endophytic fungus Muscodor album was shown to be effective to suppress or eliminate some fungal and bacterial substances by generating a combination of volatile chemicals. Most of the chemicals that were generated by this xylariaceous fungus have been detected, synthesised or acquired independently via gas chromatography and mass spectrometry and have ultimately become an artificial combination which mimics the antibiotic properties that the fungus generates. This go to say that fungus alone, via a simple and eco-friendly way is producing complex volatile anti- biotics which otherwise takes in a lot of our efforts, time and money to fabricate. As soil fumigation utilizing methyl bromide will soon be illegal in several countries worldwide, mycofumigation effects of *M. albus* and similar fungi to treat soil, seeds, fruits, vegetables, cereals, bulbs, tubers and plants would have potential practical benefits and be safe to the environment and associated flora and fauna.

Table 8: Some of the endophytic fungi producing volatile antibiotics:

Host plant	Volatile antibiotic producing endophytic fungus
Cinnamomum zeylanicum (cinnamon tree)	Muscodor albus
Ananas ananassoides (wild pineapple)	Muscodor crispans
Erythophelum chlorostachys (ironwood)	Muscodor roseus
Grevillea pteridifolia (fern-leafed grevellia)	Muscodor roseus

[H] Insecticidal compounds from endophytes

Due to the eco-friendly non-hazardous nature of the bioinsecticides market, its effectiveness and pesticide toxicity are becoming more and more popular in the area of insecticides. Bioinsecticides are being investigated as a selective, safe and strong alternative as the world becomes aware of the ecological harm done by synthetic insecticides and plant protection agents. Various endophytic fungi have shown anti-insect characteristics. As a resistance mechanism, endophytes produce mild toxic chemicals and secondary metabolites so as to keep away grazing animals, pathogens, insects and ensure fitness and survival of the host. Nodulisporic acids are novel indole diterpenes which exhibit potent insecticidal properties against blowfly larvae. These compounds work by activating the insect's glutamate-gated chloride channels and were first derived from the endophyte *Nodulisporium* sp. isolated from the plant *Bontia daphnoides*. Eversince, intensive research has been carried out to produce more potent analogues of nodulisporic acid and explore more fungal species which produce them and other important insect repellants.

Table 9: Some of the endophytic fungi producing insecticides

Host plant	Insecticide producing endophytic fungus	Pest species affected
Bontia daphnoides	Nodulisporium sp.	Aedes aegypti (mosquito larvae), Lucilia sericata (blowfly larvae).
Paullina Paullinioides	Muscodor vitigenus.	Cephus cinctus (wheat stem sawfly).
Festuca arundinacea	Acremonium coenophialum	Diuraphis noxia, Sipha flava, Rhopalosiphum padi, Schizaphis graminum, Acheta domesticus (house cricket), Sitobion fragariae (strawberry aphid), Tribolium castaneum (flour beetle).
Lolium perenne	Acremonium lolii	The chetocnema pulicaria, listronotus bonariensis and sphenophorus sp. (billbug), oncopeltus fasciatus (dairy weed bug), lystronotus bonariensis (argentine stem weevil).

[I] Immunosuppressive compounds from endophytes:

In transplant patients, immunosuppressive compounds like cyclosporin A and FK506 are being used to prevent allograft rejection. In future, these approved immunosuppressive agents may also be used to treat autoimmune diseases such as insulin-dependent diabetes, rheumatoid arthritis, etc. However, although beneficial, these drugs do produce some undesirable side effects. Thus, efforts are now being focused towards employing endophytic fungi for the production of safe and improved immunosuppressive agents.

[J] Antidiabetic compounds from endophytes

Autoimmune disorders like insulin-dependent diabetes or *diabetes mellitus* are difficult to cure mainly because of the degradation of the peptidal drug insulin once inside the digestive tract. Thus Pseudomassaria sp., endophytic fungus from an African rain forest, was used as an insulin mimic molecule for the synthesis of a non-peptidal fungal metabolite, and unlike insulin, this substance does not breakdown in the digestive system. Moreover, it can be orally administered, sparing the patients of painful syringe shots on a daily basis. This discovery has prompted researchers to further extend the horizons of employing endophytes for the production of various life-saving drugs and other valuable compound

[K] Possible plant based bioactive metabolites which can be targeted from endophytes

The use of endophytes is not limited to the variety of compounds mentioned so far. Infact, looking at the manner in which these studies are progressing, that day is not far away when endophytes will become independent alternative sources of innumerable metabolites, sparing the parent plants and becoming an inexhaustible source of valuable compounds being produced by simple fermentation processes. Medicinal and aromatic plants of indigenous origin would be screened for their endophytes and evaluated for their true potential to manufacture several life-saving compounds required on a day-to-day basis by plants, animals and humans.

Endophytes will find applications in the synthesis of compounds required in the treatment of almost all problems faced by mankind including malaria, filaria, tuberculosis, kala-azar, arthritis, hypertension, depression, atherosclerosis, memory degeneration, various allergies, respiratory disorders, gastric ulcers, kidney problems, regulation of menses, GIT (gastro-intestinal tract) dysfunction, osteoporosis, posorosis, Parkinsonism, etc. and will provide a cheap reliable source of safe, eco- friendly drugs.

[L] Biotransformation process using endophytes

The ability to produce a wide range of novel compounds using the biotransformation method has proven to be extremely useful. Lipids, steroids, lignins, alkaloids, triterpines, and other bioactive molecules with pharmaceutical and food industry applications are synthesized using the whole cell of the fungus or an enzyme purified from it. Biotransformation has previously been carried out by a variety of microorganisms, but using endophytic fungi for the same is a more recent development. A two-stage fermentation procedure that lasts about 2-3 weeks isolates and purifies various drugs such as taxol, vinblastine, vincristine, camptothecin, podophyllotoxin, and others from the culture filtrate. If endophytic fungi are cultured in the precursors of these medicines, they may be identified in very little time. For example, if a taxol precursor is incubated by an endophytic fungus, phenylisoserine + 10 deacetylbaccatin, obtained from the Taxus baccata, taxol is generated in a matter of hours and not for a period needed for the two-stage fermentation.

4. CONCLUSION

Natural product discovery relies heavily on medicinal plants and their endophytes. Endophytes play a crucial role in microbial diversity. Endophytes are a type of microorganism that lives asymptomatically within the tissues of living plants. Polysaccharides, proteins, fats, and nucleic acids are examples of primary metabolites that are required for an organism's growth. The basic metabolic process of all species is identical. Secondary metabolites are metabolites which utilise primary metabolites as building blocks but are not necessary for the general function of the organism. Examples of secondary metabolites include terpenes, alkaloids, polyketides, and colours. Although secondary metabolites are not required for an organism's growth and health, they can give it a competitive advantage over other species competing for nutrients by inducing biological activity. The secondary metabolites produced, as well as their quantities, are thought to be species-specific. Chemotaxonomy is the concept of using secondary metabolites to distinguish between fungal species. The aim of this study is to isolate bioactive compounds from endophytic fungus and describe them. The aim of this research is to isolate and identify efficient Taxus baccata endophytic fungus. This research examined fungal extracts for antibacterial, anti-cancer and antioxidant activité and investigated antioxidant activities and the discovery by efficient endophytic fungi of various bioactive substances. Also it focuses on the thermal tolerance and thermal stability enzymes produced by endophytic fungi.

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