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# ENDOPHYTIC FUNGI: AS A SOURCE OF ANTIMICROBIALS BIOACTIVE COMPOUNDS

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## ABSTRACT

There is a need to search new ecological niches for potential of natural bioactive agents for different pharmaceutical, agriculture and industrial application; these should be renewable, eco-friendly and easily obtainable natural products discovery in the search for new drugs, and is the most potent source for the discovery of novel bioactive compounds. Therefore, a large number of bioactive compounds are isolated from the plants, bacteria, fungi and many other organisms. Endophytic fungi being the most promising of these have been a source of various such bioactive compounds. Many of these compounds are being used for the treatment of a number of diseases. The present review gives a detailed account about endophytic fungi and the antimicrobial bioactive compounds produced by them.

**Key Words:** antimicrobial, antagonism, bioactive compounds, endophytes, xenohormesis.

## INTRODUCTION

From thousands of year's mankind has used natural product, chemicals produced by plants, fungi, bacteria and other living organism in a variety of application: drugs, food and hallucinogens. Now a days large number of medicine are also prepared from fungi, plants and bacteria. But from all of these, fungi play an important role for formation of useful drugs which are used for curing number of diseases. Fungi are eukaryotic organisms that differ from bacteria and other prokaryotes in many ways. The simplest type of fungi is unicellular yeast. Depending upon the morphology, the fungi are divided into many categories. But from all of these, a huge work carried out on endophytic fungi for preparation of useful product for mankind.

The term 'endophyte' includes a family of microorganisms that grows intra and intercellular in the tissues of higher plants without causing any symptoms on the plants in which they live.

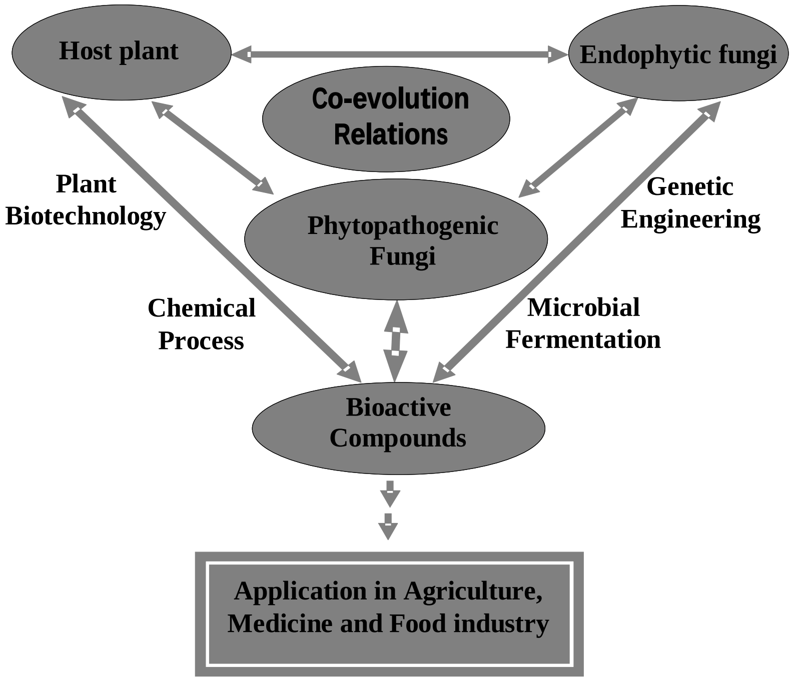


**Fig. 1. Symbiotic relationship of host and fungi and application of their produced bioactive compounds.**

These microorganism may produce a large number of novel natural products for medical, agriculture and industrial uses such as antibiotics, anticancer reagents, biological control agents and other useful bioactive compounds.[1,2] The endophytes may provide protection and survival condition to their host plant by producing a plethora of substances which once isolated and characterized, may also have potential for use in industry, agriculture and medicine.[3] Some studies show that the endophytes are not host specific a single endophyte can survive a wide range of host. A large number of fungi isolated from the different parts of the same plants which differ in their ability to utilize different substances.[4] Therefore, a number of fungi can be isolated from different plant belonging to different genera and grow under different climatic conditions. The host and endophytes relationship varies from host to host and endophytes. Some studies show that host plant and endophyte relationship also able to maintain the pathogen host antagonism.[5] Plant endophytic fungi have been found in each plant species examined, and it is estimated that there are over one million fungal endophytes existed in the nature.[6] Drefyuss and Chapala[7] have estimated that there are 1.3 millions species of endophytic fungi alone, the majority of which are likely to be found in tropical ecosystem. The greatest fungal diversity probably occurs in tropical forest, where a highly diverse population of angiosperms exist.[8] Endophytic relationship may have begun from the time, when higher plants first appeared (millions of years ago).

Evidences for plant-associated fungi has been discovered in fossilized tissues of stem and leaves.[9] As a consequence of these long term association, some of these microorganisms may have developed genetic stem that allow the exchange of information between themselves and the higher plant. This exchange would allow the fungi to cope with the environmental condition more efficiently and perhaps increase compatibility with the plant host. Moreover, the dependant evolution of endophytic fungi may have allowed them a better adaptation with the plant such that the fungi could contribute in the relationship by performing protective function against pathogen and insect.[3] [10] To make these contributions to their plant host, endophytic fungi produce bioactive secondary metabolites.[3] According to the plant-endophyte co-evolution hypothesis[11] it might be possible for endophytes to assist the plant in chemical defense by producing bioactive secondary metabolites.[12] The present review on endophytic fungi focus on novel antimicrobial bioactive compounds produced by them.

**Why only endophytic fungi?**

Environmental factors including biotic and abiotic stimuli, carbon-nutrition balance, genotype and ontogenesis usually control and regulate the biosynthesis of secondary metabolites in plants.[13] With regard to plant-microbe interactions, co-evolution between plants and their microbial partners are mediated *via* plant chemical defense.[14] Production of secondary metabolites can be the result of genetic, developmental and environmental factors.[15] Genes involved in the production of secondary metabolites appear to be clustered in fungi and bacteria.[16] and genetic screening methods have gained attention because they are rapid, economical and sensitive. Endophytes are chemical synthesizer inside plants which produce bioactive substances with low toxicity toward higher organisms.[17] They also feature diverse chemical structures and have often evolved to possess biological activities with roles as defensive compounds against competitors/parasites/predators, growth and reproduction facilitators, or as cell signaling compounds.[18] Endophytes provide a broad variety of bioactive secondary metabolites with unique structure, synthesized *via* various metabolic pathways e.g. polyketide, isoprenoid, amino acid derivation.[2] They have the ability to produce a range of secondary metabolites, providing researchers with numerous leads for compounds of pharmaceutical significance and possible development as new drugs.[3] Natural products can be divided into several classes based on assembly pathways. It is evident that a plethora of microbial secondary metabolites are polyketides and nonribosomal peptides, which are biosynthesised by polyketide synthase (PKS) and nonribosomal peptide synthetase (NRPS) systems, respectively as shown fig 2 & 3[19] [20].

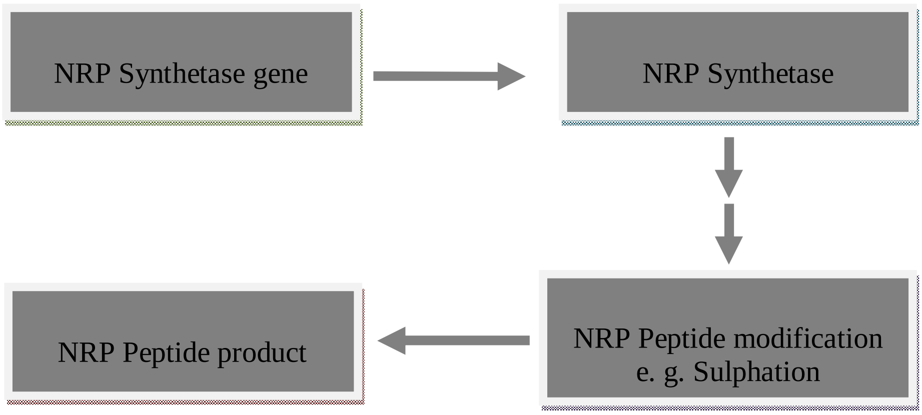


**Fig. 2. Schematic representation of enzyme involved in NRPS system.[21]**

Consequently, identification of PKS and NRPS biosynthetic pathways can be used to evaluate an organism's potential to produce bioactive compounds.[19] While screening for new bioactive secondary metabolites from endophytic fungi; it is relevant to consider that the secondary metabolites a fungus synthesizes may correspond with its respective ecological niche and continual metabolic interactions between fungus and plant which may enhance the synthesis of secondary metabolites.[20] Biotechnological techniques by using different microorganisms appear promising alternatives for establishing an inexhaustible, cost-effective and renewable resource of high-value bioactive products and aroma compounds. These compounds possess not only sensory properties, but other desirable properties such as antimicrobial (vanillin, essential oil constituents), antifungal, antiviral (some alkanolides), antioxidant (eugenol, vanillin), somatic fat reducing (nootkatone), blood pressure regulating {2-(E)-hexenal}, anti-inflammatory properties (1,8-cineole) and many others.[22]

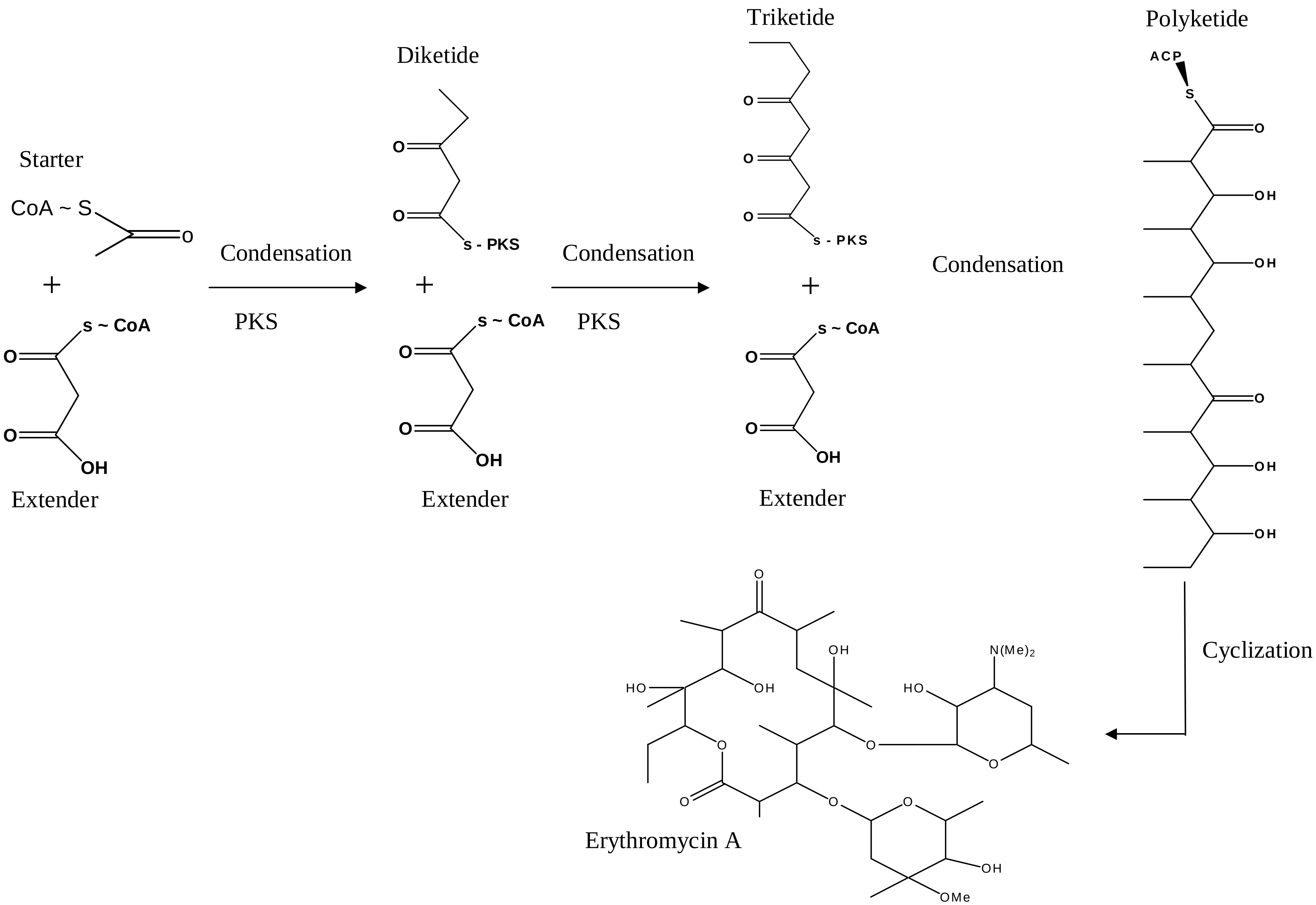


**Fig. 3 Mechanism of Polyketide Biosynthesis.**[23]

**Need for new bioactive compounds**

The need for new and useful bioactive compounds to provide assistance and relief in all aspects of the human condition is ever growing. During resistance in bacteria the appearance of life-threatening viruses, the recurring problems with disease in persons with organ transplants, and the tremendous increase in the incidence of fungal infections in the world's population each only underscore our inadequacy to cope with these medical problems. Added to this are enormous difficulties in raising enough food on certain areas of the Earth to support local human populations.

Environmental degradation, loss of biodiversity and spoilage of land and water also added to problems facing mankind. Endophytes, microorganism that reside in the tissue of living plants, are relatively understudied and potential source of novel natural products for exploitation in medicine, agriculture and industries.

The discovery of novel anti-microbial metabolites from endophyte is an important alternative to overcome the increasing levels of drug resistance by plants and human pathogens.[24] More than 20,000 bioactive metabolites of microbial origin are known.[25]

**Bioactive natural products overview**

Plants and microorganisms constitute a major source of natural products with desirable bioactive properties. Fungi are among the most important groups of eukaryotic organisms that are being explored for metabolites for clinical applications. Existing drugs of fungal origin include β-lactam anti-biotics, griseofulvin, cyclosporine A, taxol, ergot alkaloids, and lovastatin; however increasingly more new natural products of varied chemical structures are reported to be produced by fungi.[26] [27] The discovery of novel antimicrobial metabolites from endophytes is an important alternative to overcome the increasing levels of drug resistance by plant and human pathogens, the insufficient number of effective antibiotics against diverse bacterial species and few new anti-microbial agents in development, probably due to relatively unfavorable returns on investment. Many bioactive compounds, including antifungal agents, have been isolated from the genus *Xylaria* residing in different plant hosts, such as "sordaricin" with antifungal activity against *candida albicans.*[26] "mellisol" and "1, 8-dihydroxynaphthol 1-O-a glucopyranoside" with activity against herpes simplex virus-type 1 multiplolides A and B" with activity against *Candida albicans.*[27] Endophytes provide a broad variety of bioactive secondary metabolites with unique structure, including alkaloids, benzopyranones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, and others.[2] Such bioactive metabolites find wide-ranging application such as antimicrobial, agrochemicals, antibiotics, immunosuppressant and anti-parasitic.[3] *Aloe vera* has reported huge number of endophytes, that have been systematically characterized, taxa of *Alternaria*, *Colletotrichum*, *Phoma*, *Phomopsis*, *Xylariales* and *Mycelia sterilia* were the dominant endophytes found in *Aloe vera*.[28]

**Fungi as source of bioactive compounds**

Fungi are ubiquitous occurring, eukaryotic, heterotrophic organisms. Beside the well-known mushrooms, fungal life is found worldwide, in soil samples as well as deep sea vents and arctic ice and often reveals symbiotic traits. Similar to plants, there is a long history of the utilization of fungi by mankind as remedies and in everyday life. Nearly 3000 years ago the *Mayans* used fungi to treat intestinal ailments.[3] Without deeper knowledge about the mode of action the transformation by fungi has been used for food production since Neolithic times.

The earliest types of fermented food were beer and leavened bread, followed by the early Chinese who produced fermented soy foods. Since Pasteur's discovery that fermentation is caused by living cells, investigation of microbes as natural products resources sprung up. But it was not until the discovery of penicillin isolated from *Penicillium notatum* by Sir Alexander Fleming in 1928 which resulted in a breakthrough in the treatment of bacterial infections, that fungi became an important source of drugs for the treatment of a variety of diseases. Since then, especially fungi isolated from soil samples have been identified as a rich source of biologically active secondary metabolites.

Beside other well known antimicrobial agents like fusidic acid and griseofulvin, novel semi-synthetic anti-fungal drugs like anidulafungin (Eraxis) and caspafungin (Cancidas) are likewise derived from fungal metabolites. With the discovery of cyclosporine (also known as ciclosporin or cylosporin) isolated from *Tolypocladium inflatum* in 1971, an important step in immuno-pharmacology was made because this substance prevents rejection after organ or tissue transplantations. Fungal metabolites are, however, not only indispensable for medicine but are also important for plant protection as demonstrated by the discovery of the strobilurines, that were first isolated from *Strobilurus* sp. and served as lead compounds for synthetic fungicidal such as trifloxystrobin .

**Table 1: Structure of some important Anti-microbial compounds.**[29] [30]

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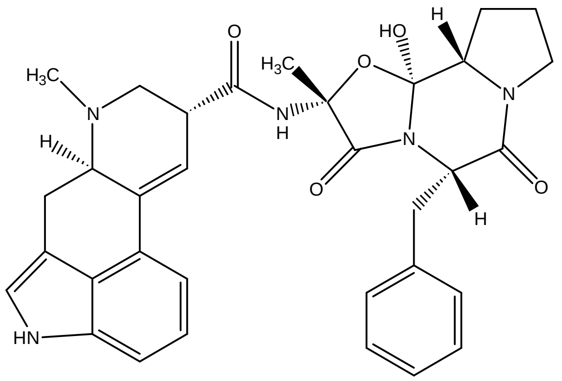
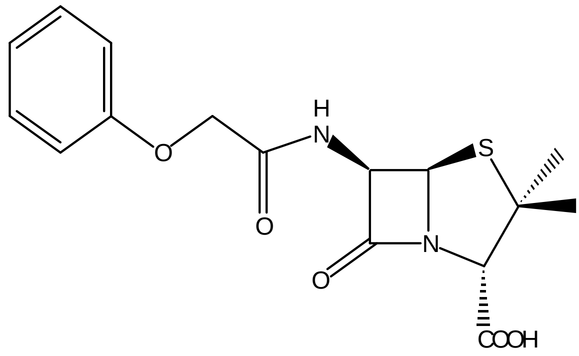
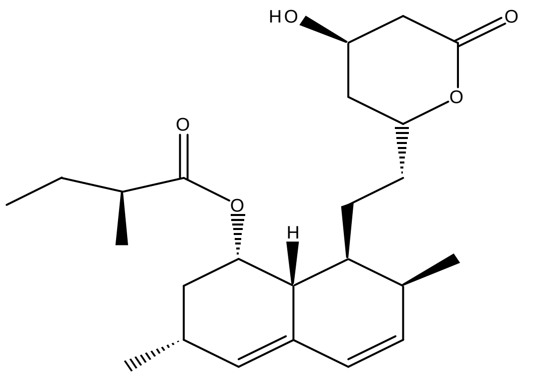
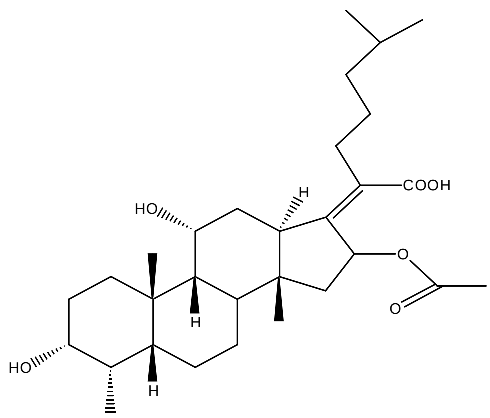
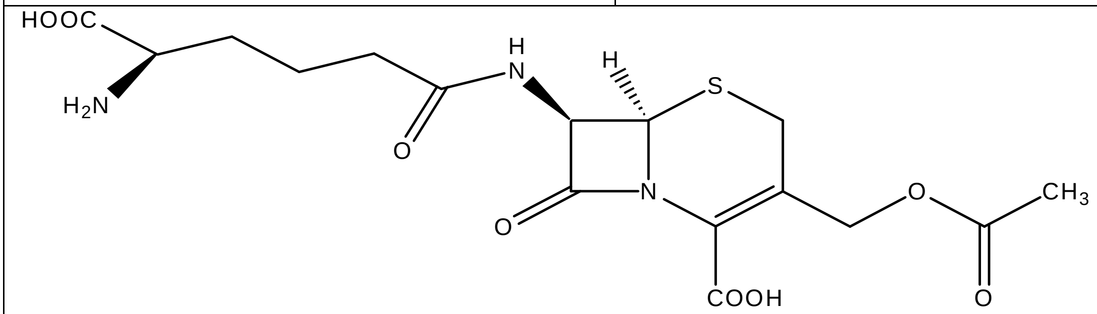
| <br>Ergotamine | <br>Penicillin V |
| <br>Lovastatine | <br>Fusidic acid |
| <br>Cephalosporine C | |

The demand for new highly effective agricultural agents to control farm pests and pathogens is enormous, and partly arises from the removal of synthetic compounds from the market because of their toxicity towards the environment, but also from the rising need for food due to a stringent population growth.

**Pharmaceutical application of endophytic bioactive compounds**

Endophytes are the chemical synthesizers inside plant.[17] Many of them are capable of synthesizing bioactive compounds that can be used as potential sources of pharmaceutical leads. Endophytic fungi have been proven useful for novel drug discovery as suggested by the chemical diversity of their secondary metabolites. Many endophytic fungi have been reported to produce novel anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, anti-tumor and many other compounds belonging to the alkaloids, steroid, flavenoid and terpenoids derivatives and other structure types.[31] [32] [33] [34] The pharmaceutical and medical concerns of new drugs are the toxicity of these prospective drugs to human tissues.

Since the plant tissue where the endophytes exist is a eukaryotic system, it would appear that the secondary metabolites produced by the endophytes may have reduced cell toxicity; otherwise, death of the host tissue may occur. Thus, the host itself has naturally served as a selection system for microbes having bioactive molecules with reduced toxicity toward higher organisms[3] *Gentiana macrophylla* is a traditional Chinese medicinal plant. Its dominant active constituents are secoiridoids, mainly gentiopicrin. The biological and pharmacological effects of its active principles include choleretic, anti-hepatotoxic, anti-inflammatory, antifungal and anti-histamine activities. Endophytic fungal strain QJ18 was found to produce the bioactive compound gentio-picrin like its host plant *G. macrophylla*.[35] Thus, endophyte production of natural metabolites may help to protect the natural resources and to satisfy the requirement of drugs via production of plant-derived pharmaceutical leads by fermentation.

The following agent shows effects of bioactive compounds obtained from endophytes and their potential in the pharmaceutical and agrochemical areas.

**Antimicrobial agents from endophytes**

Metabolites bearing antibiotic activity can be defined as low-molecular-weight organic natural substances made by microorganisms that are active at low concentration against other microorganisms.[31] Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites bearing antimicrobial activity. It is believed that screening of antimicrobial compound from endophytes is a promising way to overcome the increasing threat of drug resistant microbes of human and plant pathogen.[2] [32]

So far, studies reported a large number of anti-microbial compounds isolated from endophytes, belonging to several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids.[32] The three isolated compounds, melleolides K, L and M. from *Armillaria mellea* which showed anti-microbial activity against gram positive bacteria, yeast and fungi. Previously these antibacterial sesquiterpenoids, melleolides B-D, were yielded from *Armillaria mellea* were isolated by Arnone.[36] A compound polyketide citrinin produced by endophytic fungus *Penicillium janthinellum* from fruits of *Melia azedarach*, presented 100% antibacterial activity against *Leishmania* sp.[37]

Armillaric acid also exhibited marked inhibitory activity against gram positive bacteria and yeast.[38] Bioactive compound 7-amino- 4-methylcoumarin isolated from the culture extracts of the endophytic fungus *Xylaria* sp. YX-28 isolated from *Ginkgo biloba* L.[39] having an activity against several food-borne and food spoilage microorganisms including *Staphylococcus aureus, Escherechia coli, S. typhia, S. typhimurium, S. enteritidis, A. hydrophila, Yersinia* sp., *V. anguillarum, Shigella* sp., *V. parahaemolyticus, C. albicans, P. expansum*, and *A. niger, especially to A. hydrophila,* and was suggested to be used as natural preservative in food.

Yunianto[40] isolate various endophytic fungi especially *Penicillium sp.* from Srikaya plant(*Annona squamosa L.*) which produce very active bioactive compounds meleargrine and chrysogine that tested for antibacterial and anticancer activity. An endophytic strain ITA1-CCMA 952 was isolated from a moss *Schistidium antractici* found in Admirality Bay (King George Island) that produced potent unsaturated fatty acid like linolenic acid and arachidonic acid.[41] These bioactive compounds show a very strong antibacterial activity against human pathogenic bacteria (*Pseudomonas aureginosa*, *Enterococcus facalis*). Endophytic fungi isolated from the different parts of a plant *Ipomea pes-carprae Linn.* show antimicrobial activity against 5 microorganisms; *B. subtilis, S. aureus, P. aureginosa and C. albicans*.[42]

The endophytic fungus *D. helianthius* produced a large amount of bioactive compound which can be used against large number of bacteria like *E. coli, S.aureus, S. typhi and E. hirae* etc.[43] The production of Hypericin ($C_{30}H_{16}O_8$), a naphthodianthrone derivative, and Emodin ($C_{15}H_{10}O_5$) believed to be the main precursor of hypericin, by the endophytic fungus isolated from an Indian medicinal plant, having an antimicrobial activity against several bacteria and fungi including *Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa,* *Salmonella enteric and Escherichia coli, and fungal organisms Aspergillus niger and Candida albicans.*[44]

Three steroids namely, ergosta-5,7, 22-trienol, 5α,8α-epidioxyergosta-6, 22- dien-3β-ol, ergosta-7, 22-dien-3β,5α,6β-triol and one nordammarane triterpenoid helvolic acid were isolated for the first time from the endophytic fungus *Pichia guilliermondii* from the medicinal plant *Paris polyphylla var. yunnanensis* showing the strongest anti-bacterial activity against all test bacteria.[45]

**Table: 2 Some important antimicrobial agents from endophytic fungi.**

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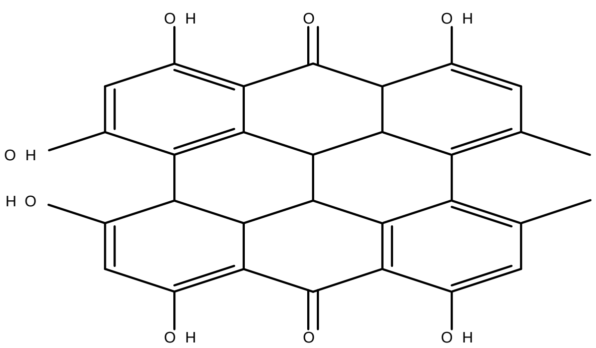
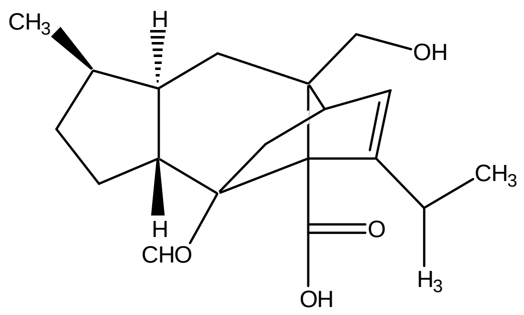
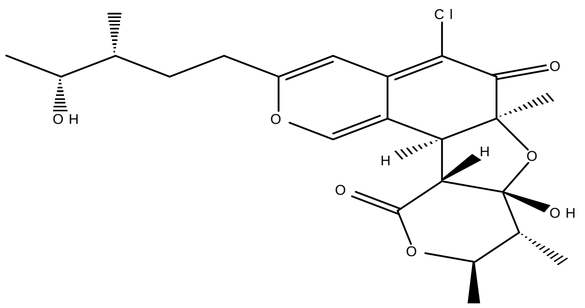
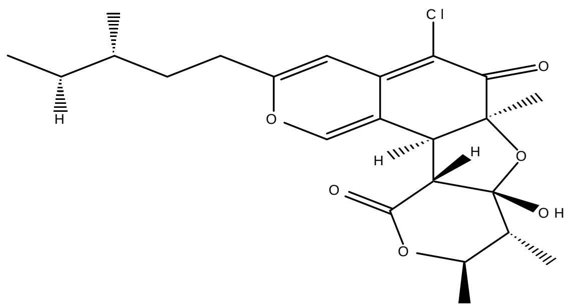
|  Hypericin |  Sordacirin |
|  Chaetomugilin A |  Chaetomugilin D |

**Antifungal compounds from Endophytic fungi**

Altomare[46] isolated two alpha pyrones antifungal compounds named as fusapyrone and deoxyfusapyrone from *Fusarium semitectum* which have very high potential against a number of pathogenic or mycotoxogenic filamentous fungi (*Alternaria alternate,Aspergillus flayus, Botrytis cinerea,Cladosporum cucumerinum, Phoma tracheiphila and Penicillium verrucosum)*. Culture extract of *P. guepinii*, *Phomopsis* sp. and *Guignardia* sp. show very active antifungal activity against *S.cervisae, Geotrichum* sp., *Cladosporium elatum, Mycotypha* sp., *Penicillium canadensi.*[47] *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigates* are the major pathogenic fungi which cause disease in human beings. *Streptomyces* sp. produce a bioactive compound polyenes have a broad spectrum activity against a number of fungi *Aspergillus* sp. and *Candida* sp. etc.[48] Amphotericin B, nystatin and natamycin are main polyenes which are widely used for the treatment of diseases like coccidiodal meningitis, cutaneous dermatophytes and histoplasmosis and in the treatment of mycotic disease.[49] [50] [51] [52] Important systemic pathogenic fungi on humans are *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus.*

The polyenes derived from *Streptomyces* sp. have a broad *in vitro* spectrum activity against a wide range of fungi including the *Aspergillus* sp. and *Candida* sp. The main polyenes are amphotericin B, nystatin, and natamycin. They are widely used for the treatment of candidiasis, coccidiodal meningitis, cutaneous dermatophytes and histoplasmosis. Wide spread use of the limited number of antifungal agents for control of mycotic diseases has led to the development of drug resistance. Much attention has been focused to overcome resistance but the development of new classes of antifungal drugs are likely to have the most significant future impact. [49] [50] [51] [52]

An endophytic fungi *Serratia marcescens* was isolated from *R. penicillata* which produces oocydin A, a novel antioomycetous compound having the properties of a chlorinated macrocyclic lactone. Oocydin A is being considered for agriculture use to control the ever-threatening presence of oomyceteous fungi such as *Pythium and Phytophthora*.[53]

**Anti-viral Activities of Endophytes**

Many reports demonstrated the importance of endophytic fungi in production of antiviral agents, such as, cytonic acids A and B, novel human cytomegalovirus (hCMV) protease inhibitors, which had been isolated from solid-state fermentation of the endophytic fungus *Cytonaema* sp.[31] Investigation of endophytes associated with leaves of *Quercus coccifera* lead to isolation of the endophyte with the ability to synthesize hinnuliquinone, a potent inhibitor of human immunodeficiency virus type 1 (HIV-1) protease. [54]

Florke *et al*.[55] reported anti-hepatitis C virus (HCV) activity of dihydroiso-coumarin (R)-(-)-mellein. The aryl tetralin lignans, such as podophyllotoxin and its analogs showed anti-viral and cytotoxicity activities and used as the precursor for many drugs for treatment cancer and viral infections, like etoposide, teniposide, and etopophos phosphate. Podophyllotoxin was found to produce by many endophytes: *Trametes hirsute, Aspergillus fumigates Phialocephala fortinii* and *Fusarium oxysporum.*[56] [57] [58]

**Table 3: List of biological activities and bioactive compounds isolated from endophytic fungi.**

| S.N. | Name of the host plants | Name of the endophytic fungi | Chemical compound Reported | Biology activities | Reference |
|---|---|---|---|---|---|
| 1 | *Cinnamomum zeglanicum* | *Muscodor albus* | 1-butano,3-methyl-acetate | Anti-microbial | [3] |
| 2 | *0cimum basilicum* | 2L-5 | Ergosterol, Cerevesterol | Anti-microbial | [59] |
| 3 | *Ephedra fasciculate* | *Chaetomium chiversii* C5-36-62 | Radicicol | Cytotoxic | [60] |
| 4 | *Erythrina crista-galli* | *Phomopsis* sp. | isoflavonoids | Anti-microbial | [61] |
| 5 | *Ginkgo biloba.* | *Xylaria* sp. YX-28 | 7-amino-4-Methylcoumarin | Anti-microbial | [62] |
| 6 | - | *Pestalotiopsis adusta* | Pestalachlorides | Anti-fungal | [63] |
| 7 | *Plumeria acutifolia* | *Phomopsis* sp. | Terpenoid | Anti-microbial | [64] |
| 8 | *Ananas ananassoides* | *Muscodor crispans* | propanoic acid, methyl ester, 2-methylbutyl ester, Ethanol. | Anti-biotic | [65] |
| 9 | *Aegiceras corniculatum* | *Emericella* sp. | Aegiceras corniculatum | Anti-viral | [66] |
| 10. | *Hypericum perforatum* | | hypercin | Anti-viral | [44] |
| 11. | *Guazuma ulmifolia* | *Muscodor albus* E-6 | Caryophyllene, phenylethyl alcohol, 2-phenylethyl ester, bulnesene | Antibiotic | [67] |
| 12. | *Urospermum picroides* | *Ampelomyces* sp. | 3-Omethyl alaternin & altersolanol A | Anti-microbial | [68] |
| 13. | *Azadirachta indica* A. Juss | *Chloridium* sp. | Javanicin | Antibacterial | [69] |
| 14. | *Kennedia nigriscans* | *Streptomyces* NRRL 30562 | Munumbicin A,B,C and D | Anti-microbial | [70] |
| 15. | *Cryptosporiopsis quercina* | *Cryptosporiopsis* sp. | Cryptocandin | Anti-microbial | [31] |

## CONCLUSION

The need for new bioactive compounds to overcome the growing problems of drug resistance in microorganisms and the appearance of new diseases is of increasing importance. The capability of fungi to produce bioactive metabolites has encouraged researchers to isolate and screen fungi from diverse habitat and environments to search for novel bioactive metabolites. Some endophytes produce phytochemical that were originally thought of as characteristic of the host plant. It appears that genetic interaction between the endophyte and the host has occurred over evolutionary time. In the past two decades, scientists mainly focused on the investigation of endophytic fungal diversity, relationships between endophytic fungi and their host plants, seeking for natural bioactive compounds originated from the endophytic fungi, and improving the productivity of some potential candidates by taking advantage of genetic engineering, microbial fermentation projects and other measures.

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