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# Endophytic Fungi as Rich Sources of Naturally Occurring Bio-Active Compounds- A Review

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## Abstract

Medicinal plants are rich source of therapeutic substances and playing a good rule to curing illnesses. This review describes information that endophytic fungi are the rich source of naturally occurring bio active compounds. Endophytic fungi generally live peacefully with their host without causing any visible harm and often produce metabolites that help to protect the host plant from insects and other pathogen microorganisms. Emergence of new diseases, appearance of life threatening viruses, and development of drug resistance against the current drugs are some challenges in front of scientists to search for new drugs. In this review, we focus mainly on bioactive natural products from endophytic fungi by their different functional roles.

**Keywords**

Endophytes, Bio-active compounds, anticancer effect, antioxidant effect, Immunomodulatory effect, Antiviral effect, Antimicrobial effect, Ant diabetic effect, Anti-tubercular effect, Anti-parasitic effect, insecticidal effect

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## I. INTRODUCTION

Natural products have continued to play a significant role in the drug discovery by designing drugs against various diseases [1]. Appearance of life-threatening viruses, drug resistance against current drugs, more common advanced disease such as acute respiratory syndrome, cancers, acquired immunodeficiency syndrome, severe acute respiratory syndrome, hemagglutinin type 1 and neuraminidase type 1 ($H^1NI$) flu virus, etc. Endophytes are microorganism which are present within healthy plant tissues without causing any substantive harm to their host, are relatively unstudied and potential source of novel natural products for exploitation in medicine, agriculture and industry [2]. They play an essential role to provide protection to their host from

infectious agents and also synthesize bioactive natural products, which defense the plants against pathogens .Some of the endophytic microorganisms have been found to produce the same secondary metabolites as that of the plant thus making them a promising source of novel compounds [3]. Almost all the plant species harbour one or more endophytic organisms and these endophytic fungi have a great potential to provide metabolites such as alkaloids[4],terpenoids, cardiac glycosides, steroids, flavonoids, phenols ,tannins and peptides [5]. Endophytic fungi are also precursors of biologically active novel compounds [6]. The most important role of endophytic fungi is to carry nutrient recycling pathway by degradation of dead or dying host plants [7] .

This report concentrates on work that appeared within the literature from 1994 to July 2018.

## II. ENDOPHYTES AS NATURAL RESOURCE OF BIO ACTIVE COMPOUND

Fungi are ubiquitous occurring heterotrophic organisms having different lifestyle. They live in mutualistic, antagonistic ,or neutral symbiosis with a wide variety of autotrophic organisms [8]. It is noteworthy that, of the nearly 300,000 plant species on the earth, each individual plant is considered to host one or more types of endophytes [9] .To date, only a few plants have been extensively investigated, indicating the opportunity to find new and targeting natural products from interesting endophytic microorganisms [10] .Fungi remain rich sources of bio active metabolites which have a great potential in the field of medicine, agriculture and industry [11]. Endophytic organisms are also believed novel sources of bioactive compound and attempts are being made to isolate and identify bioactive compounds from them. They protect their host from pathogenic microorganism and resist a systemic relationship in the host plant [12,13].

Anticancer agents from endophytes

Cancer is a major leading cause of death. The total worldwide mortality rate causing by cancer is about 7.6 million and this number is predicted to increase to 13.1 million in 2030 [14]. Due to this cause, research on novel anti-cancer drugs is today's need. Among anticancer compounds, taxol, the most famous and fascinating compound in the history of secondary metabolites is isolated from endophytic fungi *Taxomyces andreanae* [15] .The diterpenoid Paclitaxel (**I**) interferes with normal function of microtubule break down. Specifically ,taxol binds to the β-subunit of tubulin and thereby interrupt the dynamic rearrangement of this important component of the cytoskeleton .This adversely affects cell function because the shortening and lengthening of microtubules is necessary for their function as a mechanism to cells, especially fast dividing ones like cancer cells [16]. Other than fungus *Taxomyces andreanae,* the endophytic species which produce taxol are *Pestalotiopsis microspora*[17], *Pestalotiopsis guepini* [18] and *Tubercularia* [19]. Camptothecin ($C_{20}H_{16}N_2O_4$) (**II**) an alkaloid isolated from endophytic *Entrophospora* infrequence ,a potent antineoplastic agent inhabiting *Nothapodytes foetida* [20]. More recently, endophyte BT2 isolated from old inner bark of tree *Taxus chinnsis var.mairei* was found capable of producing taxol and its precursor *taxane baccatin* III was shown to have strong toxicity to liver and lung cancer cells [21]. Torreyanic acid (**III**), a potent anticancer agent is isolated from endophyte *Pestalotiopsis microsporum* strain. Torreyanic acid showed 5-10 times more potent cytotoxicity against several cancer cell lines particularly those that are sensitive to protein kinase C agonists, and caused cell death via apoptosis [22]. One more compound namely ergoflavin (C30H26O14) (**IV**), a novel and effective anticancer agent was isolated from the leaf endophytes an Indian medicinal plant *Mimusops elengi* belonging to family *Sapotaceae*. It is a dimeric of xanthene connected at position-2, having a place with the ergochrome category of compounds [23]. The compound Asperazine (**V**), an unusual unsymmetrical diketopiperazine dimer isolated from the saltwater culture of the fungus Aspergillus niger obtained from Hyrtios proteus sponge showed selective cytotoxicity towards leukemia cells and gymnastatins (**VI**) which has been isolated from *Gymnascella dankaliensi* having significant cytotoxicity against P388 lymphocytic leukemia cells [24].

Antioxidant agents from endophytes

Reactive oxidant species (ROS, e.g., O2– and OH–) and free radical-meditated reactions creating oxidative stress, which could lead to cell injury and death. Damage of biomolecules by oxidative stress leading various diseases like cancer, atherosclerosis, coronary heart ailment, diabetes, Alzheimer's disease and other neurodegenerative disorders [25].The free radicals which are main causative of diseases occur in the body during an imbalance between reactive oxygen species and antioxidants [26]. Antioxidants are thought to be highly profitable in the management of reactive oxygen species-mediated tissue impairments. The search for naturally occurring antioxidants especially from

plants and fungi origin had increased greatly in the past decades [27].Pestacin (**VII**) and Isopestacin (**VIII**) which were isolated from *Pestalotiopsis microspora*, have the antioxidant property[28]. Pestacin occurs naturally as a racemic mixture and acts by cleaving an unusual reactive C–H bond and through O–H abstraction to a lesser extent [29]. Isopestacin behaves as an antioxidant by scavenging both superoxide and hydroxyl free radicals [30]. Endophytic fungus *Corynespora cassiicola* L36 produce corynether A (**IX**), which have a potent antioxidant activity [31]. The natural antioxidant cajaninstilbene acid (**X**)has been reported from *Fusarium* an endophyte of Pigeon pea, Cajanus cajan [32]. Similarly, a strong antioxidant activity was exhibited by *Xylaria* sp. isolated from *Ginkgo biloba* [33]. *Chaetomium sp.* from *Nerium oleander* can be a potential antioxidant resource as the flavonoids and phenolic acid derivatives of this fungus exhibit strong antioxidant activity [34]. Graphislactone A (**XI**) was isolated from *Cephalosporium* sp. a fungus isolated from the root of *Trachelospermum jasminoides*. This phenolic compound was confirmed to have stronger free radical–scavenging and antioxidant activity [27].

Immunomodulatory agents

Immunosuppressive medication area unit is the main agent to stop graft rejection in transplant patients and conjointly to treat reaction diseases similar
to endocrine dependent polygenic
disease and arthritis. As a result of this, researchers have in the main centered on the assembly of those medications from the choice supply and one in all them may well be endophytes. Endophytic fungi might prove a helpful supply for the production of those medications as a result of possessing the capability to supply novel compounds that would be doubtless active immunomodulatory substances. Phenylpropanoids have a place with the biggest gathering of optional metabolites created by plants, reports demonstrated the generation of such compounds by endophytes. The endophytic *Penicillium brasilianum*, found in root bark of *Melia azedarach*, advanced the biosynthesis of phenylpropanoid amides [35]. Phenylpropanoids have attracted much enthusiasm for restorative use as anticancer, cell reinforcement, antimicrobial, mitigating and immunosuppressive properties [36]. Another two important immunosuppressive compounds Subglutinol- A (**XII**) and Subglutinol-B (**XIII)** are noncytotoxic diterpene pyrones. These compounds were isolated from the plant endophyte *Fusarium subglutinans*, inhabiting *Tripterygium wilfordii* [37]. Another fungal metabolite cyclosporine-A (**XIV)** a vital immunosuppressive drug, was 104 times more intense in the TP measure and generally as strong in the murine spleen lymphocytes examine. Mycophenolic acid (**XV)** as well a strong immunosuppressive parasitic metabolite utilized for the treatment of immune system maladies and organ transplantations [38] .

Antiviral agents from endophytes

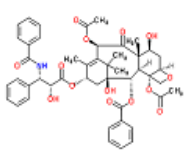
Microbial natural products have been distinguished as a standout amongst the most vital source and the motivation for medicate revelation. Among them, fungal auxiliary metabolites are a standout amongst the most imperative hotspots for finding new medications or lead compounds [39]. The fungal secondary metabolite Brefeldin A (**XVI**) ,as a novel antiviral specialist against dengue infections [40]. Another two human cytomegalovirus protease inhibitors, cytonic acid A (**XVII**) and cytonic acid B (**XVIII**) have been isolated from the endophytic fungus *Cytonaema* [41].

Antimicrobial agents derived from endophytes

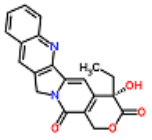
Fungi as hotspots for novel antifungal agents have been screened and among the numerous compounds confined from fungi. The compounds are present into several chemical structural groups like alkaloids ChaetoglobosinsA and C (**XIX**), Ergosterol and 5α, 8α-epidioxyergosterol (**XX**) as steroidal, 3-o-methylalaternin and Altersolanol A, as quinines (**XXI**). These compounds shows a promising antimicrobial activity[13].The echinocandins and the pneumocandins are produced by *Aspergillus nibulans* which are inhibitory to B-1,3 glucan combination, having action against both candida and pneumocytis carinii, which is the causal specialist of pneumonia in immunocompromised (particularly AIDS) patients [42]. (-)Mycorrhizin-A (**XXII**) was isolated from *Plectophomella* sp. while cytochalasins (**XXIII**) E and K were confined from *Physalospora* sp. reflects good antimicrobial activities. Additionally, radicinin (**XXIV**) were also reported from endophytic fungi which having antimicrobial activity.

Up until this point, an expansive number of metabolites showing antimicrobial action have been isolated from endophytic organisms. The compounds are characterized into a few substance basic gatherings, for example, alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids. They incorporate compounds demonstrating antibacterial, antifungal and antiviral activities. Cases of antimicrobial specialists with antifungal action incorporate cryptocandin, cryptocin, ecomycins, pseudomycins, pestaloside, and pestalopyrone cases of antimicrobial operators

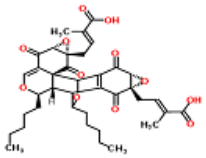
with antibacterial action incorporate periconicins A and B, phomopsichalasin and javanicin; and cases of antimicrobial agents with antiviral movement incorporate cytonic acid A and B. A portion of the antimicrobial operators from endophytic fungi are dynamic against human pathogens as well as against plant pathogens, prompting their application in farming fields [13].



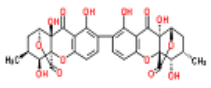
Paclitaxel (I)



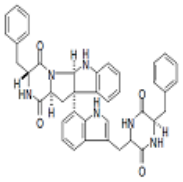
Camptothecin (II)



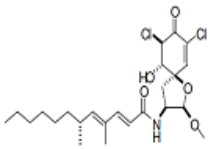
Torreyanic acid (III)



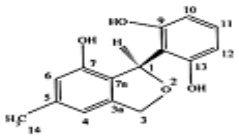
Ergoflavin (IV)



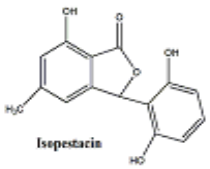
Asperazine (V)



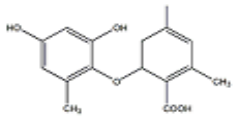
Gymnastatin B (VI)



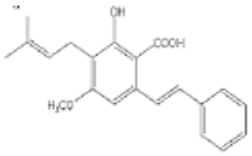
Pestacin
(VII)



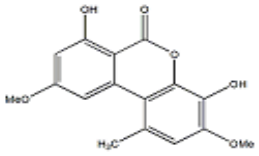
Isopestacin
(VIII)



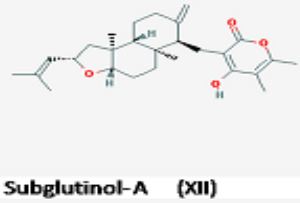
Corynether A
(IX)



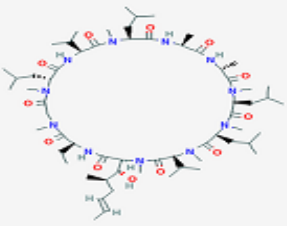
Cajaninstilbene acid
(X)



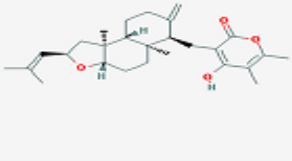
Graphislactone A
(XI)



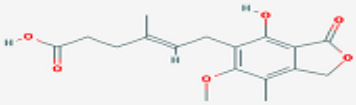
Subglutinol-A (XII)



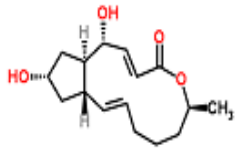
Cyclosporine-A (XIV)



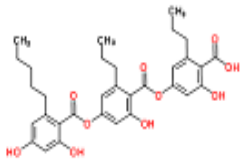
Subglutinol-B (XIII)



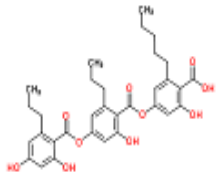
Mycophenolic acid (XV)



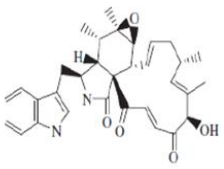
Brefeldin -A (XVI)



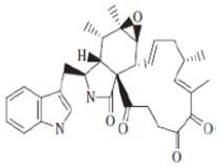
Cytonic acid -A (XVII)



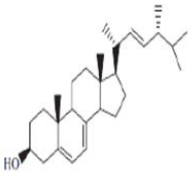
Cytonic acid- B (XVIII)



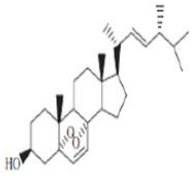
Chaetoglobosin A (XIX)



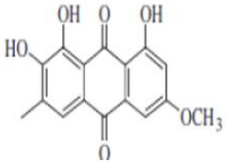
Chaetoglobosin C



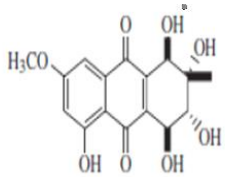
Ergosterol



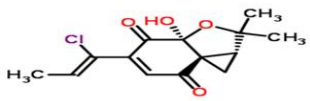
5α, 8α-epidioxyergosterol (XX)



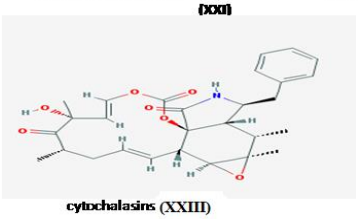
3-o-methylalatemin (XXI)



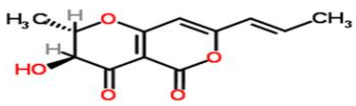
Altersolanol A



Mycorrhizin A (XXII)

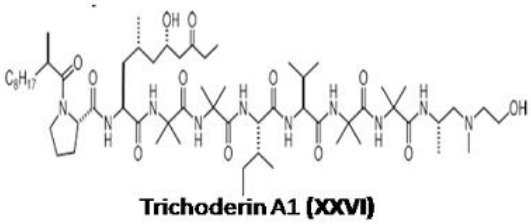


cytochalasins (XXIII)

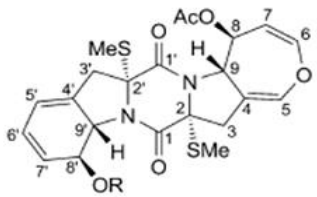


Radicinin (XXIV)

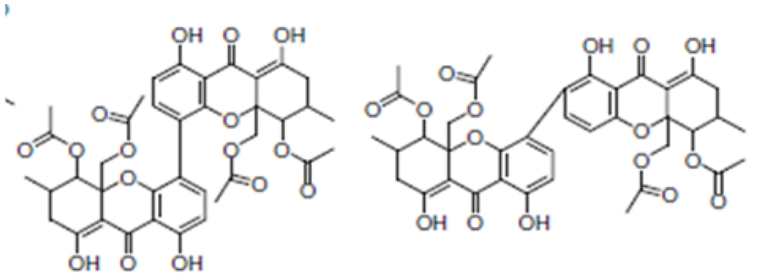
Phomoenamide (XXV)



Trichoderin A1 (XXVI)



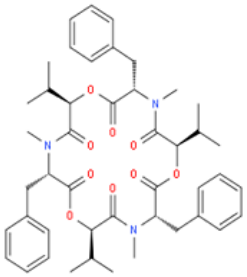
Bisdethiobis(methylsulfanyl) apoaranotin (XXVII)



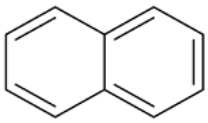
Phomoarcherins A (XXVIII)



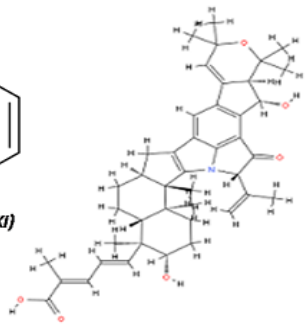
Phomoarcherins C (XXIX)



***Beauvericin* (XXX)**



***Naphthalene (XXXI)***



***Nodulisporic acid* (XXXII)**

**Hypoglycaemic agents from endophytic fungi**

Diabetes is a worldwide medical issue. As of late, an expected 3.4 million individuals died because of danger of diabetes. The WHO predicts that the quantity of passing because of diabetes will be multiplied by 2030. Diabetes mellitus is a metabolic issue portrayed by significant deformity in hyperglycaemia or glucose digestion [43]. It for the most part influences the nerves and veins. It influences because of imperfection in insulin discharge or activity of insulin which persistently prompts unending diabetics which indicates auxiliary appearances by influencing eyes, kidneys and heart. It likewise prompts the reason for different illnesses to different parts of our body. This requires treatment and a few changes in human ways of life. It has been reported that extract of endophytic fungus *Nigrospora oryzae* have antidiabetic activity and number of compounds have been isolated from it [44] . A non peptidal flora substance (L-783,281) having antidiabetic activity was isolated from endophytic plant (*Pseudomassaria* sp.). This compound goes about as an insulin mimetic and dissimilar to insulin, is not pulverized in the stomach related tract and might be given orally [45].

Anti-tubercular agents

Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that almost all typically have an effect on the lungs. Around 33% of the total populace has dormant TB, which implies individuals have been contaminated by TB microorganisms however are not (yet) sick with infection and can't transmit the ailment. Individuals infected with TB mycobacterium have a lifetime danger of falling sick with TB of 10%. After development and spread of Mycobacterium tuberculosis safe strains to different drugs, the search for new anti-mycobacterial agents is opportune. Endophytic organisms are great hotspot for investigating the possibility of new anti-mycobacterial drugs like phomoenamide (**XXV**) from Phomopsis sp.[46], Trichoderin A1 (**XXVI**) from Trichoderma sp.[47] and Bisdethiobis (methylsulfanyl) apoaranotin (**XXVII**) from Aspergillus terreus [48].

Anti-parasitic compounds from endophytes

A parasitic illness is an irresistible ailment caused or transmitted by a parasite. These parasitic contaminations are caused by two primary kinds of life forms protozoa and helminths. Intestinal sickness, a tropical disease caused by protozoan parasites of the class *Plasmodium*. *Plasmodium falciparum,* the most pervasive species over the globe, may cause cerebral intestinal sickness that is frequently lethal [49].As the anti-malarial drugs are the valuable and financially savvy general wellbeing asset . Like all medications for irresistible infections, they have a restricted valuable life and, in the end, require supplanting because of rise of multidrug resistance. In this way, endophytes would go about

as a wellspring of novel antimalarial medications and in this manner have an enormous effect on the wellbeing and monetary circumstance of individuals and networks influenced by intestinal sickness. *Phomopsis archeri* an endophytic growth of *Vanilla albindia* produces fragrant sesquiterpenes-phomoarcherins A–C which indicate antimalarial movement against P. falciparum [50].

Natural insecticidal agents from endophytes

With the increasing number of cases of pesticide resistance and the ecological damage done by synthetic insecticides, utilization of safe elective techniques is picking up the pace. Consequently, endophytic search into proceeds for the disclosure of particular, intense and safe choices. A few endophytes are known to have insecticidal properties. In this field, bio-insecticides have not contributed much but rather their utilization in the market is expanding step by step [51]. Production of natural insecticides, azadirachtin A and B, from endophytic fungus *Eupenicillium parvum* be one of the best alternative which are implicated to reduce the agricultural damage done by insects [52]. A number of insecticidal agents have been isolated from the endophytic fungi which exhibits insecticidal activities like as *Beauvericin* (**XXX**) [53], *Naphthalene (***XXXI***)* [54] and *Nodulisporic acid* (**XXXII**) [55].

## III. CONCLUSIONS

Natural products and natural product derived metabolites or by-products from microorganisms, plants or animals play an important role in modern healthcare. They continue to be an abundant source of novel bioactive metabolites and have profuse impact on modern medicine. Natural products and their derivatives represent more than 68 % of antibacterial compounds and 34% of products used in cancer therapy. Among all microorganisms, bacteria and fungi have raised special attention, mainly for the productions of natural products are highly effective, possess low toxicity and have a minor environmental impact. Microorganisms, mainly fungi, have been existing on earth for millions of years, representing an important increasing resource of novel new secondary metabolites. Endophytes have ended up being a rich wellspring of novel common compounds with a wide range of natural exercises and a high state of basic decent variety. Presently, the interest in wellbeing administrations is developing drastically, especially in creating developing countries, because of the rise of drug resistance by pathogenic microorganisms. Moreover, the highly increased repeat of cancer and different irresistible diseases makes the circumstance a more noteworthy disaster. Henceforth, it is desperately important to research new bioactive compounds compelling drug-resistant pathogens for the cure of the previously aforementioned diseases. Bioactive natural compounds isolated from endophytes have demonstrated promising potential and helpfulness in security and human wellbeing concerns. Exploiting present day biotechnology, for example, hereditary designing, metabolic innovation and microbial aging procedure, we can better comprehend and control this vital microorganism asset and make it more advantageous for the humanity. We can also state that the endophytic growths could be a solid hotspot for pharmaceutically and mechanically imperative compounds that can be utilized as a part of the treatment of different hazardous maladies alongside different modern applications. Numerous novel and important bioactive compounds with antimicrobial, insecticidal, immunomodulatory, antiviral, anticancer exercises have been effectively gotten from the endophytic growths. Consequently, we can reason that the endophytic growths are a novel and critical microbial asset for delivering bioactive compounds and has pulled in consideration of numerous scientists on their hypothetical examination and also their potential applications. Plenty of bioactive metabolites isolated by endophytic growths possessing the novel specialty i.e. plants are surely a concealed shrouded treasure worth investigating.

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