Review Paper:

Potential of endophytic fungi as therapeutics: Antibiotics, Antiviral and Anticancer properties

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Abstract

Antibiotic resistance, an emerging threat to human health, is the world's major challenge today. Endophytic microbes found in medicinal plants aid in the resolution of these issues. It is critical to select the plant that will be used to investigate endophytes for bioactive metabolites. As a result, medicinal plants which have been used as a traditional source of medicine for centuries, are a valuable source for bioprospecting endophytes. Fungi are the most commonly reported organisms among endophytes. Endophytic fungi are a diverse group of microbes that invade plant interior tissues without creating any symptoms. Endophytic fungi represent an abundant source of novel bioactive secondary metabolites with diversified structures that can be exploited for various applications in the field of therapeutics. Endophytic fungi produce secondary metabolites such as alkaloids, enzymes, steroids, terpenoids, phenols, quinones, peptides, polyketides etc. which have a higher therapeutic value. They produce a wide range of bioactive molecules with various biological activities such as antibacterial, antiviral, antifungal, antioxidants, cytotoxic and antimalarial compounds.

The chemical diversity of endophytic fungi also serves to protect host plants from pathogens by hindering their growth and stimulating the host immune system, thereby enhancing plant defense mechanisms. Endophytic fungi synthesize metabolites that are identical to their host medicinal plant (azadirachtin, taxol, ginkgolide, jasmonic acid, camptothecin etc.) due to their specific capacity to form a symbiotic association with the host. Endophytic fungi can serve as substitutes for secondary metabolite production, aiding in biodiversity conservation.

This review discusses numerous bioactive metabolites produced by endophytic fungi that have diverse biological activities. The majority of these metabolites have the potential to be utilized as drugs to treat a wide range of diseases.

Keywords: Antagonistic activity, Antibiotics, Bioactive metabolites, Endophytic fungi, Therapeutics.

Introduction

The world's population is expanding at a rapid pace, necessitating the search for novel bioactive chemicals. Several medicinal plants were used for the exploration of new bioactive molecules. Furthermore, medicinal plants are unique that have a reduced growth rate and are found only in unusual habitats[12]. The usage of synthetic drugs has led to side effects, thus the demand for exploration and usage of drugs is also on the rise.

Hesterkamp[35] has reported that the discovery rate of novel antibiotics and novel antitumor drugs is on a decline. Henceforth, it will be significant in the future to seek out new natural sources of innovative bioactive compounds. After Alexander Fleming discovered penicillin in 1929, many scientists have been isolating novel natural bioactive molecules from fungi. Several discoveries for extracting novel bioactive molecules have led to the introduction of a distinct group of microbes called endophytes.

Endophytes comprise of bacteria, fungi, algae and actinobacteria. Endophytic fungi reside within the plants without causing any symptoms. They are present in all species of plants that are evaluated for their presence. Krings et al[49] have reported that endophytic fungi are found even in fossilized flora. This demonstrates the ancient interaction that existed between plants and endophytic fungi and their relationship is mutually beneficial for both. The host plant gives nutrition and shelter to the endophytic fungi, in turn endophytic fungi give support to the host to withstand both biotic and abiotic stress. Endophytic fungi provide this assistance to the host by the production of different classes of bioactive molecules[56].

Moreover, endophytic fungi synthesize bioactive molecules that are identical to bioactive molecules produced by the host plant and so endophytic fungi can be employed as an alternate source for secondary metabolite production with the added benefit of being of natural origin[51]. Metabolites extracted from endophytic fungi such as flavonoids, phenolic acids, steroids, alkaloids, xanthones and a few other metabolites including enzyme (L-Asparaginase) have a broad spectrum of uses in the pharmaceutical industry[39,40]. Endophytic fungi are considered to be the source of many novel metabolite products that can be used as antibiotics, antiviral, antimalarial and anticancer agents (Figure 1)[57]. The secondary metabolites obtained from endophytic fungi and their therapeutic applications are discussed in the present review.

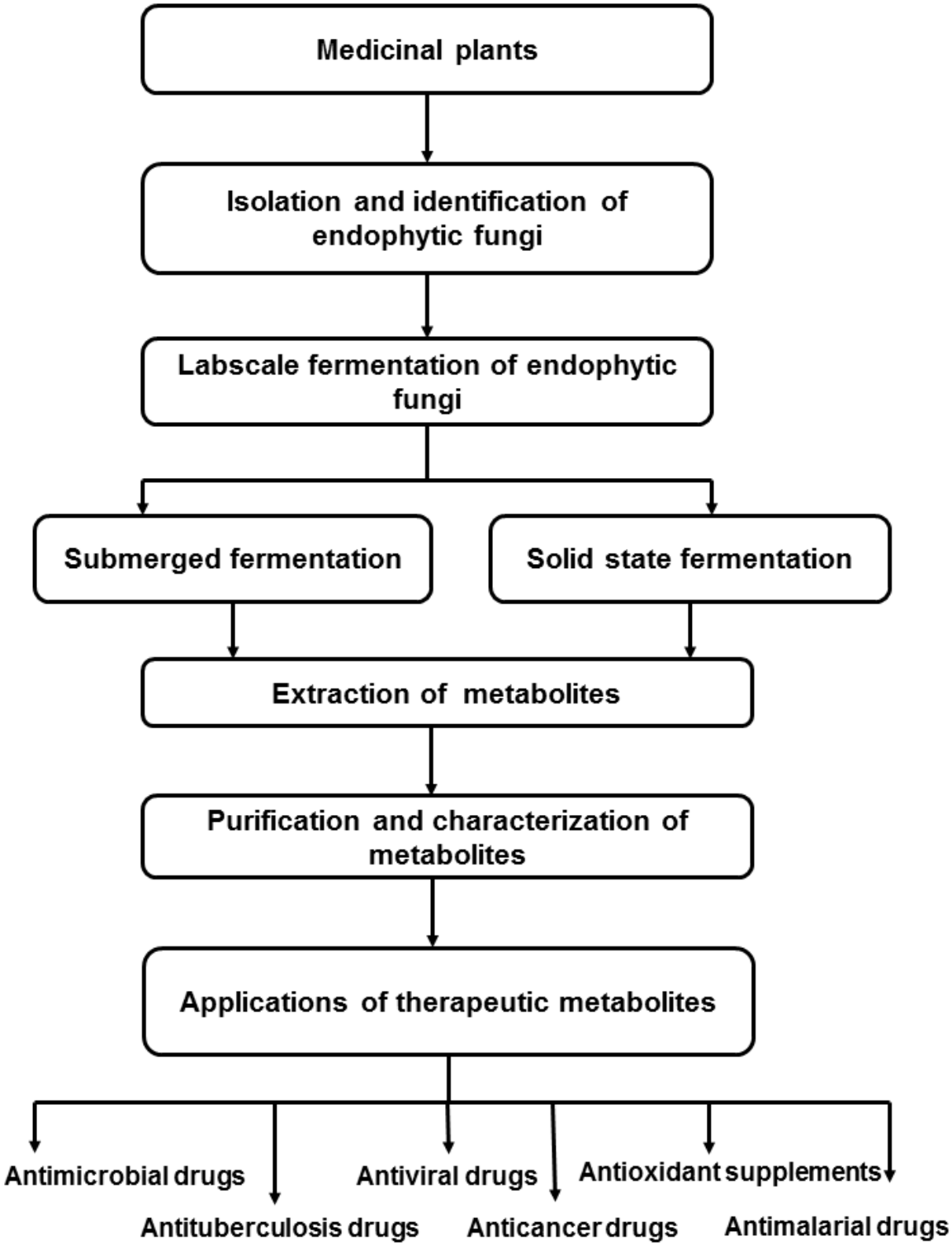

Fig. 1: Steps involved in the isolation, extraction, purification and application of bioactive metabolites from endophytic fungi

Diversity of endophytic fungi: Endophytic fungi reside both in apoplastic and symplastic areas of plant tissues[5]. There are about three major classes to which endophytic fungi belong, they are ascomycetes, basidiomycetes and zygomycetes. It is estimated that approximately a million species of endophytic fungi are yet to be discovered, based on angiospermic plants to endophytic fungi proportion of 1:4 or 1:5[85]. According to Rodriguez et al[85], endophytic fungi are classified into two classes on account of ecology, diversity and functional roles. They are clavicipitaceous and nonclavicipitaceous. Clavicipitaceous endophytic fungi are monophyletic while nonclavicipitaceous are polyphyletic. The former class has a restricted range of hosts while the latter has a diversified range of hosts. In endophytic fungi,

there are two modes of transmission, they are horizontal and vertical transmission. Horizontal transmission takes place with the help of the spores while vertical transmission takes place from parent to the offspring of the host. Traditionally the endophytic fungi are identified using the spores but some fungal cultures do not sporulate. In such cases, molecular tools like fungal PCR primers are employed for phylogenetic identification. Sometimes additional protein-coding gene regions are also employed to identify fungal endophytes[85].

Endophyte and host relationship: The relationship between the plant (host) and endophytic fungi is mutually beneficial. Endophytes protect their hosts and in return, they obtain nutrients from them. The primary desirable outcomes of the host plant endophyte relationship are as follows: (i) increased plant growth, (ii) increased host plant resilience to biotic and abiotic stress and (iii) increased deposition of secondary metabolites[41]. Genes of both organisms and environmental conditions regulate the type of interaction that takes place between the host and the endophyte. This variation in interaction between them results in some endophytic fungi being able to produce secondary metabolites similar to their host while some produce distinct metabolites from its host. These distinct compounds are critical for enhancing the adaptability of endophytic fungi and their host by increasing tolerance to biotic and abiotic stress. Furthermore, these compounds can stimulate the production of a multitude of recognized and unrecognized bioactive compounds[85].

Endophytic fungi and medicinal plant: Around 80% of people in underdeveloped nations utilized medicines made from medicinal herbs. Medical herbs have been used as a vital source of medicinal goods for a long time. Medicinal plants are prized for their abundance of natural compounds and for their ability to prevent diseases and ailments[69,114]. Different chemicals of medicinal plants have applications in the pharmaceutical business such as anticancer agents, contraceptives, analgesics, antibiotics, diuretics, laxatives and so on[82]. Since the endophytic fungi can produce compounds similar to their host, medicinal plants were and are currently used for isolating endophytic fungi to obtain the metabolite of interest.

The advantage in using endophytic fungi obtained from medicinal plants for metabolite production helps in conserving the medicinal plants as well as in increased production of metabolites in a short period. According to research conducted by Chowdhary et al[16], around 18% of secondary metabolites derived from plants can also be derived from its related endophytic fungi. Table 1 represents the bioactive secondary metabolites produced by endophytic fungi isolated from medicinal plants.

Therapeutic applications of endophytic fungi: Endophytic fungi are capable of producing a diverse spectrum of secondary metabolites that have the potential to be used as therapeutic agents for a variety of ailments[53]. According to Strobel and Daisy[95], roughly 51% of bioactive compounds produced from endophytic fungi are unique and were not previously known. Secondary metabolites can be obtained from endophytic fungi at a higher level since they can be cultivated in bioreactors and utilized in the pharmaceutical industry.

Endophytic fungi act as a producer of a variety of bioactive compounds within the plants that can be used as novel sources of pharmaceutical leads. The main concern in the discovery of new drugs in the pharmaceutical field is the level of toxicity that can cause harm to humans. The presence of endophytic fungi within plant tissue and their ability to synthesize secondary bioactive compounds without affecting the host demonstrates that the secondary metabolites produced by endophytic fungi are minimal or non-toxic to the tissue[91]. The following are various bioactive compounds produced from endophytic fungi that demonstrate the potential of endophytic fungi as a therapeutic reservoir.

Table 1
Bioactive compounds from endophytic fungi associated with medicinal plants

Endophytic fungi	Compound	Medicinal plant	Bioactivity
Rhizoctonia solani	Solanioic acid[84]	*Cyperus rotundus*	Antibacterial
Fusarium oxysporum	Fusarubin 3-O-methylfusarubin Javanicin[90]	*Glycyrrhiza glabra*	Antitubercular
Pleospora tarda	Alternariol Alternariol-(9)-methyl ether[89]	*Ephedra aphylla*	Antiviral
Aspergillus niger 58	Flavasperone Aurasperone A[99]	*Terminalia catappa*	Antimalarial
Nigrospora sphaerica	2,4-Di-tert-butylphenol[29]	*Euphorbia hirta*	Antioxidant
Fusarium oxysporum	Vincristine Vinblastine[50]	*Catharanthus roseus*	Anticancer

Antimicrobial: Endophytic fungi exhibit a variety of bioactivities, the most important of which is antimicrobial activity, as endophytic fungi benefit host plants in their growth and survival. Antimicrobial activity includes both antibacterial and antifungal activity. Alexander Fleming paved the stepping stone for the discovery of antibiotics. Since then antibiotics are significantly used which has led to the mutations in pathogens resulting in the incidence of antibiotic resistance[62]. Antibiotic resistance in both gram-positive and negative pathogens has increased which leads to the grave threat for the management of contagious diseases[7]. The discovery of novel metabolites is needed to reduce the emergence of antibiotic resistance in pathogens[74].

Vallabhaneni et al[103] reported that fungal diseases cause a high rate of morbidity and mortality all over the world. Fuentefria et al[27] have reported that fungal diseases are difficult to treat as they have side effects, a limited spectrum of activity and resistance to drugs which indicated a high priority need to discover new therapeutics.

Ding et al[20] reported two new isocoumarin analogues derived from the endophytic fungi *Trichoderma harzianum* Fes1712 that showed strong antagonistic activity against *E.coli*. Gao et al[28] have elucidated seven compounds from the endophytic fungus *Aplosporella javeedii*. Among the seven compounds, five compounds were found to be sesterterpenes. Compound six and seven were found to be new and known macrolide derivative. The new macrolide derivative (compound six) showed antibacterial activity against *Staphylococcus aureus* with a minimum inhibitory concentration (MIC) of 100 µM. Widjajanti et al[111] isolated *Fusarium* sp. and *Dematophora* sp. from *Paederia foetida* L. which showed strong antibacterial activity against *Staphylococcus aureus* with MIC about 250 µg/ml and 125 µg/ml respectively. Alkaloid and tannin metabolites were found in *Fusarium* sp. extracts while phenolic and alkaloid metabolites were found in *Dematophora* sp. extract using chromatographic techniques. *Nigrospora sphaerica*, an endophytic fungus isolated from the mangrove plant *Bruguiera gymnorrhyza*, yielded nigronapthaphenyl, a novel chemical. With MIC values of 2 and 4 g/mL, nigronapthaphenyl showed antibacterial activity against *Bacillus cereus* TISTR 688 and *Bacillus subtilis* TISTR 088 respectively[101]. Antimicrobial bioactivity profiles were found in extracts of fungal endophytes, *Annulohypoxylon multiforme* (TC2-046), from the medicinal plant *Juniperus communis*, with particularly strong activity against *Staphylococcus aureus*. 3R,5R-dihydroxyhexanote polymers were isolated via bioassay-guided fractionation and showed strong and specific suppression of *S. aureus*[67]. *Mortierella alpina* is an endophytic fungal strain that produces large quantities of polyunsaturated fatty acids (PUFAs) like y-(gamma) linolenic acid and arachidonic acid. Fungal extracts had high antibacterial action against the microorganisms *Escherichia coli* (MIC: 26.9 µg mL^{-1}), *Pseudomonas aeruginosa* (MIC: 107 µg mL^{-1}) and *Enterococcus faecalis* (MIC: 107 µg mL^{-1})[64].

Hussain et al[36] reported colletonoic acid, a secondary metabolite derived from *Colletotrichum* sp. that is effective against *Microbotryum violaceum.* Nine new diphenyl ethers (Epicoccethers A - I) were isolated by Zhu et al[120] from the endophytic fungus *Epicoccum sorghinum* that exhibited strong antifungal activity against *Fusarium oxysporum* and *Colletotrichum musae*. The bioactive secondary metabolites isolated from endophytic fungi that show antibacterial and anti-fungal activity, are listed in tables 2 and 3.

Table 2
Antibacterial compounds obtained from endophytic fungi

Fungal source	Antibacterial compound	Effective against
Armillaria mella	Melleolides K, L and M[115]	Gram-positive bacteria
Muscodor albus	1-butano,3-methyl-acetate[95]	*Staphylococcus aureus* *Micrococcus luteus* *E. coli*
Phomopsis sp.	Isoflavonoids[80]	*Bacillus subtilis* *Staphylococcus aureus*
Xylaria sp. YX-28	7-amino-4-methylcoumarin[61]	*Salmonella typhi* *E. coli* *Staphylococcus aureus*
Mortierella alpina	Linolenic acid Arachidonic acid[64]	*Pseudomonas aeruginosa* *Enterococcus faecalis*
Pichia guilliermondii Ppf9	Ergosta - 5,7 Ergosta – 7[118]	*E. coli* *Bacillus subtilis*
Annulohypoxylon multiforme (TC2 – 046) KP1 – 131DD	3R, 5R – Dihydroxyhexanote polymers[67]	*Staphylococcus aureus*
Nigrospora sphaerica	Nigronapthaphenyl[101]	*Bacillus subtilis* TISTR 088 *Bacillus cereus* TISTR 688
Aplosporella javeedii	Macrolide derivative[28]	*Staphylococcus aureus*

Table 3
Antifungal compounds obtained from endophytic fungi

Fungal source	Antifungal compound	Effective against
Acremonium zeae	Pyrrocidines A and B[21]	*Aspergillus flavus* *Fusarium verticilloides*
Pestalotiopsis adusta	Pestalachlorides A, B and C[57]	*Fusarium culmorum* *Gibberella zeae*
Colletotrichum sp.	Colletonoic acid[36]	*Microbotryum violaceum*
Colletotrichum gloeosporioides	2-phenylethyl 1H-indol-3-yl-acetate[11]	*Cladosporium cladosporioides* *C. sphaerospermum*
Cladosporium cladosporioides	Cladosporin Isocladosporin[105]	*Colletotrichum acutatum* *Colletotrichum fragariae* *Colletotrichum gloeosporioides* *Phomopsis viticola*
Xylaria feejeensis	Xyolide[4]	*Pythium ultimum*
Chaetomium globosum	Chaetoglobosin A, B, E, F Penochalasin G[58]	*Phoma herbarum*

Table 4
Antitubercular compounds obtained from endophytic fungi

Fungal source	Antitubercular compound	Effective against
Phomopsis sp. BCC 1323	Phomoxanthones A and B[38]	*Mycobacterium tuberculosis* (H37 Ra strain)
Phomopsis sp. USIA5	Nitropropionic acid[15]	*Mycobacterium tuberculosis*
Dothideomycete sp. LRUB20	2,4 – dinitrophenyl hydrazone derivative[14]	*Mycobacterium tuberculosis*
Diaporthe sp. P133	Diaportheone A and B[8]	*Mycobacterium tuberculosis*
Chaetomium globosum IFB – E036	Chaetoglocins A and B[30]	*Mycobacterium smegmatis*
Biscogniauxia formosana	Biscogniazaphilone A and B N - trans - feruloy - 3 - O - methyldopamine 5 – hydroxy – 3,7,40 – trimethoxyflavone 4 – methoxycinnamaldehyde 4 – methoxy – trans – cinnamic acid[13]	*Mycobacterium tuberculosis*
Nigrospra sp.	Nigrosporin 4 – deoxybostrycin[106]	*Mycobacterium tuberculosis* (MDR strain) *Mycobacterium bovis* *Mycobacterium avium*
Nodulisporum sp.	$C_{12}H_{12}O_5$[76]	*Mycobacterium tuberculosis*
Penicillium sp.	Penialidin A, B and C Citromycetin Brefeldin A[42]	*Mycobacterium smegmatis*
Chaetomium globosum	Chetomin[63]	*Mycobacterium tuberculosis*
Chaetomium globosum 7s – 1	Epipolythiodioxopiperazines 4,5 and 6[98]	*Mycobacterium tuberculosis*
Gliocladium sp. MR41	Ergosterol-5,8-peroxide[100]	*Mycobacterium tuberculosis*
Aplosporella javeedii	Sesterterpenes 3,4 and 7[28]	*Mycobacterium tuberculosis* H37Rv

Antituberculosis: Mycobacterium belongs to the genus actinobacteria and the family mycobacteriaceae. This genus includes *Mycobacterium tuberculosis* and *Mycobacterium leprae* which causes life-threatening diseases in humans[86]. Nearly one-third of the world's population has been infected with tuberculosis. In countries with large populations and weak health care system, diagnosing tuberculosis is challenging. 10.4 million new cases were estimated in 2016 but only 6.3 million were detected. Half of the undetected 4.1 million cases are accounted for India, Indonesia and Nigeria[109]. The major challenge faced by the researchers is that Mycobacterial infections are difficult to treat due to the emergence of resistant strains[31].

Bioactive substances derived from natural products are important in the treatment of Mycobacterial infections, according to a study conducted by Alvin et al[2]. Plants are an important source of drugs[25] and the numerous endophytes found within plants can be used as a possible source of secondary metabolites[102]. Nearly three hundred novel anti TB drugs were characterized in three years i.e. 2003 to 2005[17] while between 2006 and 2009, four hundred and fifty novel compounds were identified. Between 2008 and 2012, twenty eight novel secondary metabolites were isolated from microbial sources[24]. Thus plants are a vital source of drugs[25].

Four compounds were isolated from the ethyl acetate extracts of endophytic fungi *Gliocalidium* sp MR41. The compound Ergosterol-5,8-peroxide exhibited antitubercular property against *Mycobacterium tuberculosis* with MIC of 0.78 µg mL^{-1} [100]. Gao et al[28] elucidated seven compounds from the endophytic fungus *Aplosporella javeedii*. Among the seven compounds, sesterterpenes (3, 4 and 7) exhibited antitubercular activity against *Mycobacterium tuberculosis* with a MIC of 100 µM. Tantapakul et al[98] reported ten compounds isolated from the endophytic fungus *Chaetomium globosum* 7s-1. Among the ten compounds, six compounds were tested against *Mycobacterium tuberculosis*. Of these six compounds, three compounds (Epipolythiodioxopiperazines 4, 5 and 6) showed antitubercular activity with MIC of 0.55, 4.06 and 8.11 µM respectively. A compound called Chetomin that belongs to epipolythiopiperazines was isolated from the endophytic fungus *Chaetomium globosum* which exhibited antitubercular activity against *Mycobacterium tuberculosis* with MIC of 0.78 µg mL^{-1} [63]. The bioactive secondary metabolites isolated from endophytic fungi that show anti TB activity, are listed in table 4.

Antiviral: Viral diseases are one of the infectious diseases that cause increased concerns in humans. Novel antiviral agents are an immediate requirement to solve drug resistant issues. The hindrance of viral growth by the secondary metabolites obtained from endophytic fungi is of great interest nowadays. Recently novel coronavirus is claiming millions of lives. Potential antiviral compounds from endophytic fungi are worth evaluating against the SARS-CoV-2 virus. The major problem in discovering novel antiviral compounds from endophytic fungi is the lack of suitable screening methods[33].

Three new chromanones obtained from *Phomopsis* sp. CGMCC no. 5416. Among them, Phomochromanone A and B showed inhibitory action against human immunodeficiency virus type 1 (HIV-1) with IC50 values of 20.4 and 32.5 µg mL^{-1} respectively[112]. Peng et al[72] isolated a compound called Ergocytochalasin A, a novel merocytochalasan with a fused octacyclic ring structure consisting of one cytochalasin and one ergosterol moiety from the endophytic fungus *Phoma multirostrata* XJ-2-1. Ergocytochalasin A was evaluated for antiviral activity against Human Dengue Virus Type 3 (DV3), Influenza A Virus (H1N1) and Respiratory Syncytial Virus (RSV), with EC50 values of 12.50, 40.92 and 6.49 µM respectively.

Crude ethyl acetate extract of *Curvularia papendorfii*, an endophytic fungus isolated from *Vernonia amygdalina*, had a significant antiviral impact against two viral infections, the human coronavirus HCoV 229E and a norovirus surrogate, the feline coronavirus FCV F9. The extract was subjected to various spectroscopic studies and a compound called kheiric acid was elucidated[46].

Table 5
Antiviral compounds obtained from endophytic fungi

Fungal source	Antiviral Compound	Effective against
Cytonema sp.	Cytonic acids A and B[32]	Human cytomegalovirus
Emericella sp.	2 isoindolone derivatives[116]	Influenza A(H1N1)
Hypericum perforatum	Hypericin[54]	HIV-1 Herpes Simplex Virus type 1(HSV-1)
Phoma sp.	Phomanolide (-)-6- methyoxymellein[60]	Influenza A virus (A/ Puerto Rico/ 8/ 34, H1N1)
Pullaria sp.	Pullarin A[6,37]	HSV- 1
Rhizopus sp.	Cannabifolactone A[117]	Influenza virus endonuclease PAN inhibitor
Phomopsis sp.	Phomopchromanone A Chromanone (compound 2)[112]	HIV-1
Phoma multriostrata	Ergocytochalasin[72]	DV3 Influenza A virus

Zhang et al[117] were the first to report the compound Cannabifolactone A from the endophytic fungus *Rhizopus* sp. that can act as an influenza virus endonuclease PAN inhibitor. The bioactive secondary metabolites isolated from endophytic fungi that showed anti-viral activity, are listed in table 5.

Antimalaria: Malaria is an infectious disease that is widespread in tropical and subtropical regions caused by *Plasmodium* sp. Malaria is a vector-borne disease that is spread by the bite of an infected female *Anopheles mosquito*[110]. Nearly 215 million people are affected by this disease especially in Africa. *Plasmodium falciparum* is the one that infects people with a high mortality rate[108]. Nowadays drug resistant strains are observed in all four species of *Plasmodium*.

Nosten et al[68] reported a *Plasmodium falciparum* strain that is highly resistant to chloroquine in malaria affected areas and sulfadoxine/pyrimethamine resistant strain worldwide. White[108] reported that the *Plasmodium vivax* strain is resistant to sulfadoxine/pyrimethamine. Due to this increased development of resistant strains, the venture for the discovery of new more efficient drugs that can solve the resistance problem, is very much needed. As a result, novel bioactive secondary metabolites obtained from endophytic fungi may offer a viable solution to this problem.

Metwaly et al[66] obtained two compounds (monocerin and fusarentin) from *Alternaria phragmospora* that showed inhibition of chloroquine sensitive and resistant strain of *Plasmodium falciparum*. From the extracts of *Diaporthe miriciae*, Ferreira et al[26] fractionated the compound Epoxycytochalasin H which had potent antimalarial activity against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains with IC50 values of 52 and 39 ng mL^{-1} respectively.

Kumarihamy et al[52] isolated three cytochalasins (19, 20-epoxycytochalasins C and D and 18-deoxy-19, 20-epoxycytochalasin C) compounds from the ethyl acetate extract of the endophytic fungus *Nemania* sp. All three compounds exhibited antimalarial activity when tested against *Plasmodium falciparum.* The bioactive secondary metabolites isolated from endophytic fungi that show antimalarial activity, are listed in table 6.

Antioxidant: Antioxidants are substances are substances that protect cells from the damage caused by free radicals[113]. Antioxidants are otherwise known as oxidation inhibitors[73]. Free radicals can be released by the natural metabolism during aerobic respiration. Khan et al[45] reported that extracts from endophytic fungi have antioxidant activity due to the production of phenolic and flavonoid compounds which act as reducing agents and hydrogen donors.

It is important to explore new antioxidant substances because free radicals not only damage cells but they also lead to cancer. The antioxidant activity found in endophytic fungal extracts can be used in the food industry as natural antioxidants[83].

Table 6
Antimalarial compounds obtained from endophytic fungi

Fungal source	Antimalarial compound	Effective against
Pullularia sp. BCC 8613	Cyclohexadepsipeptides Pullularins A-D[37]	*Plasmodium falciparum* (k1, multi drug resistance strain)
Geotrichum sp.	3-(R)- 7- butyl- 6, 8-dihydroxy- 3- pent- 11-enylisochroman- 1- one[47]	*Plasmodium falciparum* (k1)
Xylaria sp. PBR- 30	2- chloro- 5- methoxy- 3-methylcyclohexa- 2,5- diene-1,4- dione[97]	*Plasmodium falciparum* (k1)
Exserohilum vostratum	11(R) – hydroxymonocerin Monocerin[87]	*Plasmodium falciparum* (k1)
Pestalotiopsis sp.	Pestalacham A and B[19]	*Plasmodium falciparum* (Chloroquine resistant)
Phomatospora bellaminuta	Pestalopyrone[10]	*Plasmodium falciparum* (Dd2)
Diaporthe sp.	Dicerandrol D[9]	*Plasmodium falciparum* (3D7)
Diaporthe miriciae	Epoxycytochalasin H[26]	*Plasmodium falciparum* (Chloroquine resistant)
Nemania sp.	19,20 – Epoxycytochalasin C 19,20 – Epoxycytochalasin D[52]	*Plasmodium falciparum* (Chloroquine sensitive and resistant strain)
Alternaria phragmospora	Monocerin Fusarentin[66]	*Plasmodium falciparum* (Chloroquine sensitive and resistant strain)
Alternaria pluriseptata *Eurotium pseudoglaucus*	Crude extract[65]	*Plasmodium falciparum* (Chloroquine sensitive and resistant strain)

Da Rosa et al[18] have isolated two antioxidant compounds (Hexahydropyrrolizin-3-one and (2-methyl propyl) ether) from the endophytic fungi *Botryosphaeria dothidea*. Four resveratrol producing endophytic fungi were tested for their antioxidant activity. The endophytic fungi *Arcopilus aureus* showed strong antioxidant activity in five antioxidant assays such as nitric oxide radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydrogen peroxide, Trolox equivalent antioxidant capacity and metal ion chelating[23]. Fourteen compounds were isolated from the endophytic fungus *Chaetomium globosum*. Among them, five compounds (flavipin, epicoccone,3-methoxyepicoccone, epicoccolides A and B) showed antioxidant activity when subjected to DPPH assay[58]. The bioactive secondary metabolites isolated from endophytic fungi that showed anti-oxidant activity, are listed in table 7.

Table 7
Antioxidant compounds obtained from endophytic fungi

Fungal source	Antioxidant compound
Cladosporium velox	4 phenolic compunds[93]
Paecilomyces variotii	Crude ethyl acetate extract[92]
Phyllosticta sp.	Phenolic and flavonoid compounds[94]
Aspergillus nidulans *Aspergillus oryzae*	Flavonoid compounds[79]
Cephalosporium sp.	Graphislactone A[88]
Chaetomium globosum	Flavipin Epicoccone Epicoccolide A and B[58]
Arcopilus aureus *Fusarium* equiseti *Xylaria psidii* *Fusarium solani*	Resveratrol[23]
Penicillium oxalicum	Partially purified ethyl acetate extract[44]

Table 8
Antitumor compounds obtained from endophytic fungi

Fungal source	Antitumor compound	Effective against/ Cell line name
Lasiodiplodia theobromae	Taxol[43,70,78]	Prostate, Ovarian, Breast and Lung cancer
Aspergillus aculeatinus		
Cladosporium sp.		
Fusarium solani	Camptothecin[55,81,96]	PC3
Alternaria alternate		-
Fusarium nematophilum		-
Fusarium oxysporum	Podophyllotaxin[1,48,77]	Lung and testicles cancer
Trametes hirsuta		
Phialocephala fortinii		
Botryotinia fuckeliana	Cytochalasins[59,75,104]	7221
Eutypella scoparia		HepG2
Rhino cladiella sp		MCF- 7
Chaetomium globosum	Chaetoglobesin X[107]	MFC H22
Fusarium oxysporum	Vincristine[50]	-
Aspergillus glaucus	2,14- dihydrox- 7- drimen- 12 11- olide[3]	MCF- 7
Penicillium janthinellum	Penicillic acid[119]	LOVO HepG2 HL- 60 MKN 45
Penicillium chrysogenum	Haenamindole[34]	Colon – 38 cancer cells
Curvularia verruculosa	Vinblastine[71]	HeLa cells
Rhizopus sp.	Emodin 8 – O – methyl ether[117]	HeLa cells

Anticancer: WHO has reported that nearly 8.8 million people die due to different types of cancers all over the world. Cancer is a group of diseases that involves the uncontrolled division of cells. Though there are different types of cancer each with its distinct features, the basic process by which they produce cancer is similar to all forms of the disease. Cancer starts with a single cell that loses its ability to control its very own growth. It divides rapidly to form tumors that invade and kill the adjacent cells. Chemotherapy used in the treatment of cancer is becoming difficult due to an increase in drug resistance and non-target specific activity of the chemotherapeutic drugs. Thus bioactive compounds obtained from endophytic fungi can be employed in the treatment of cancer.

Taxol was the first compound to be isolated from endophytic fungi that have anticancer properties. Camptothecin (potent anticancer compound) has been isolated from the endophytic fungi *Fusarium solani* S-019[22]. Gao et al[28] isolated sesterterpene and its acetyl derivatives as well as macrolide derivative from the endophytic fungus *Aplosporella javeedii.* Sesterterpene and its acetyl derivatives showed cytotoxic activity against lymphoma (Ramos) and human leukemia (Jurkat 16) cell lines. Macrolide derivative showed strong cytotoxic activity against thymic, lymphoma and human leukemia cell lines with IC50 values of 0.4, 4.4 and 5.8 µM respectively. Ergocytochalasin A, a novel merocytochalasan isolated by

Peng et al[72] from the endophytic fungus *Phoma multirostrata* XJ-2-1 showed moderate cytotoxic activity against human lung carcinoma (A549), human colon cancer (HCT116), human hepatocellular carcinoma (HepG2), human breast adenocarcinoma (MCF-7), human colon carcinoma (HT-29) and strong cytotoxic activity against murine colon carcinoma (CT26) with IC50 value of 6.92 µM. Two compounds called chetoseminudins B and C were isolated from the endophytic fungus *Chaetomium globosum* which exhibited strong cytotoxic activity when tested against lymphoma cell line with EC50 of 0.26 and 0.82 µM respectively[63]. The bioactive secondary metabolites isolated from endophytic fungi that showed anticancer activity, are listed in table 8.

Conclusion

Endophytic fungi provide an infinite supply of unique bioactive compounds that are of great value to both humans and plants. These novel bioactive compounds with profound biological activities have huge applications in the field of the pharmaceutical industry. It is advantageous for mankind to better understand and utilize the incredible ability of endophytic fungi to produce new compounds. Despite the discovery of such metabolites from endophytic fungi, still there is no industrial process for large scale production. Several endophytic fungi are frequently being reported which have potential of synthesizing similar bioactive molecules as their host plants or novel compounds; however, commercial application of metabolites are lacking. As a result, strategies for commercially producing secondary metabolites in a cost-effective manner must be developed. Thorough studies are required to know about the effect of environmental conditions such as climate, altitude and host on the production of secondary metabolites by the endophytic fungi. The employment of the latest biotechnological tools and techniques are required for further explaining the host - endophytic fungi communication along with State of an Art genomic approach will aid in the maximum utilization of endophytic fungal bioactive compounds.

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