Endophytic Mycoflora as a Source of Biotherapeutic Compounds for Disease Treatment

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ABSTRACT

Endophytic mycoflora are ubiquitous organisms residing in the internal tissues of the plants, at least for a portion of their lives without causing apparent symptoms of infection. Endophytes serve as rich sources of novel natural compounds with a wide-spectrum of biologically active agents. This review reveals the significance of endophytic mycoflora from plants as sources of bioactive organic compounds. The bioactive compounds produced by endophytic fungi originate by various biosynthetic pathways like PKS/NRPS. These compounds belong to diverse structural groups such as alkaloids, benzopyranones, chinones, cytochalasines, depsipeptides, enniatines, flavonoids, furandiones, isocumarines, peptides, polyketones, phenols, quinols, terpenoids, tetrалones and xanthones were characterized by NMR, mass spectrometry, X-ray crystallography etc. Therefore, endophytes, represent a chemical reservoir for array of new compounds which are anti-cancerous, anti-microbial, anti-diabetic, anti-oxidant, anti-parasitical, anti-viral, anti-mycobacterium, anti-insecticidal, anti-malarial, anti-biotic, immunosuppressive & immunomodulatory agents, also in addition, other compounds were used in pharmaceutical and agrochemical industries. This paper mainly focuses on the exploration of novel and useful compounds from endophytic mycoflora, and study of their roles in cure of diseases, the recent scenario of screening approach for novel drugs and their pharmacological interest.

INTRODUCTION

Plants produce bioactive constituents capable of preventing or curing illnesses. They also provide a unique environment for endophytes (Rebecca et al., 2011). Endophytes are microorganisms that inhabit the healthy tissues of living plants without causing any apparent symptoms of disease (Strobel et al., 2004). The majority of endophytes are fungi (Kharwar et al., 2008). Sultan et al.,(2011) added that endophytic fungi have a mutualistic relationship with the host, protecting the host against pathogen and in some cases may be an opportunistic pathogen. Most of the endophytes are known to possess biosynthetic capabilities greater than the host plant due to their long co-evolution and genetic recombination (Fernandes et al., 2009). Endophytic fungi have been recognized as important and novel resources of natural bioactive products with potential application in agriculture, medicine and food industry (Verma et al., 2009). According to Hussain et al. (2009); Nithya et al. (2011) plants have been recognized as a repository of fungal endophytes with novel metabolites of pharmaceutical importance. Many endophytes have the potential to synthesize various bioactive metabolites that may directly or indirectly be used as therapeutic agents against numerous diseases (Kusari and Spiteller, 2012). Endophytes contain different bioactive compounds for commercial exploitation of vital therapeutic drugs, which mainly include different types of secondary metabolites and were reported to elicit a number of pharmacological effects (Xu et al., 2008; Joseph and Priya, 2011). Dompeipen et al.,(2011); Tenguria et al.,(2011) pointed out that above bio-therapeutic compounds are selected on the basis of their role in the treatment of various infectious diseases.

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This review focuses particularly on the role of endophytic fungi in the production of natural products, the importance of endophytic fungi in the screening approach for novel drugs as a novel alternative method to obtain such compounds. The above bio-therapeutic compounds were selected on the basis of their roles in the treatment of various infectious diseases.

**REQUIREMENTS FOR NEW MEDICINES AND PHARMACEUTICAL AGENTS**

There are many diseases and health problems that people deal with every day. Because of the development and spread of drug-resistant pathogens, infectious diseases, diabetes mellitus, rheumatoid arthritis, ischemia, cardiovascular diseases and neurodegenerative diseases remain global problems (Espinel et al., 2001; Valko et al., 2007). Worldwide, these diseases cause millions of deaths annually. According to Tran et al. (2010) global human health is threatened by cancers and various infectious diseases, where cancer is one of the major health problems in both developed and developing countries. After cancer cardiovascular diseases is the second leading cause of death (Patnaik et al., 2011). Because of high death rate associated with cancer, serious side effects of chemotherapy and radiation therapy, many cancer patients seek alternative complementary methods for treatment (Kaur et al., 2011). Novel anti-cancer drugs are also required due to the high worldwide mortality. Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by infection with human immune deficiency virus (HIV) (Sepkowitz, 2001). The ingress to the human population of diseases like AIDS and severe acute respiratory syndrome requires the discovery and development of new drugs to combat them. Sandhu et al., (2014) stated that tuberculosis and malaria represents infectious diseases which were known since extreme antiquity. These diseases remain large-scale problems not only from medical but also from social point of view. Annually, owing to tuberculosis, about 3 million people die all over the world and approximately 8 million events of first registered tuberculosis are observed every year. The endophytes have been identified as promising sources of new pharmacologically active secondary metabolites that might be suitable for medicinal and agrochemical applications (Strobel and Daisy, 2003).

**BIOACTIVE NATURAL PRODUCTS FROM ENDOPHYTIC MYCOFLORA**

Bioactive natural compounds produced by endophytes are promising potential tools useful in safety and human health concerns. However, there is still a significant demand of drug industry for synthetic products due to economic and time-consuming reasons (Strobel et al., 2004). According to Strobel, (2003); Zhang et al. (2005) problems related to human health such as the development of drug resistance in pathogenic bacteria, fungal infections and life threatening virus, claims for new therapeutic agents for effective treatment of diseases in human, plants and animals are currently unmet. Natural products are rich sources of therapeutic agents as they inspire the advancement on synthetic methodologies and to the possibility of making analogues of original bioactive compounds with improved pharmaceutical properties. Endophytic fungi are thus rich sources of novel organic compounds with interesting biological activities and high level of biodiversity (Krohn et al., 2009; Kharwar et al., 2011).

The production of bioactive compounds by endophytes, especially those exclusive to their host plants, is not only important from an ecological perspective but also from biochemical and molecular standpoints. There exist many exciting possibilities for the exploitation of endophytic fungi for the generation of a pleothera of novel biologically active secondary metabolites. The key challenge for the establishment and sustenance of in vitro biosynthetic potential of endophytes involves the task of repeated subculturing under auxenic monoculture conditions, which leads to the reduction of secondary metabolites production capabilities. This led to focus on the rediscovery of known secondary metabolites (Walsh and Fischbach, 2010; Kusari and Spiteller, 2012).

The discovery and production of secondary metabolites from endophytic fungi has emerged as an exciting field in biotechnology. Aly et al.,(2011); Sandhu et al.,(2014) stated that in the past two decades, many valuable bioactive compounds with anti-microbial, anti-insecticidal, cytotoxic & anticancer, anti-oxidant, anti-malaria, anti-viral, immunosuppressive, anti-tuberculosis etc. activities have been successfully discovered from the endophytic mycoflora. Some of these bioactive compounds are discussed with their structures and functions.

**Anti-microbial Bioactive Compounds from Endophytic Mycoflora**

The emergence of antibiotic-resistant microorganisms calls for inventive research and development strategies. Inhibition of these pathogenic microorganisms may be a promising therapeutic approach (Sadrati et al., 2013). Plants and fungi are the chief sources of natural compounds used for medicine, where medicinal plants and endophytes have attracted considerable interest for their wide variety of bioactive metabolites (Newman and Cragg, 2007). Demain and Sanchez, (2009) reported that production of bioactive secondary metabolites by medicinal plants and their endophytes have provided countless therapeutic applications. Many of these compounds are being used for the treatment of a number of diseases (Sandhu et al., 2014). The anti-microbial compounds could be used as drugs and as food preservatives in the control of food spoilage and food-borne diseases (Liu et al., 2008). So far, Tan and Zou, (2001) reported large number of anti-microbial compounds isolated from endophytes, belonging to several structural classes such as; alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids. Yu et al. (2010) isolated three compounds namely; melleolides K, L and M from Armillaria mellea which showed...
anti-microbial activities against Grampositive bacteria, yeast and fungi.

Chaetomugilin A and D with anti-fungal activities were also isolated from an endophytic fungus Chaetosphaeridium globosum collected from Ginkgo biloba plant (Qin et al., 2009). Kjer et al. (2009) added that two new anti-microbial compounds; 10-oxo-10H-phenalen[1,2,3-de]chromene-2-carboxylic acids, xanalteric acids I and II and 11 were known as secondary metabolites. These were obtained from extracts of the endophytic fungus Alternaria sp., isolated from the mangrove plant Sonneratia alba collected in China (Table 1). They showed antibacterial activities against Enterococcus faecalis, Pseudomonas aeruginosa and Staphylococcus epidermidis.

A Diaporthe helianthi strain isolated from Luehea divaricata has been employed in current researches. An investigation of the secondary metabolites from D. helianthi by CC and NMR of $^1$H and $^{13}$C yielded the separation of 10 fractions and the identification of the phenolic compound 2-(4-hydroxyphenyl)-ethanol (Tyrosol) (Fig 1). Its anti-microbial potential was tested and the ensuing antagonistic effects on the human pathogenic bacteria and phytopathogenic fungi were recorded. Results showed that bioactive compounds and Tyrosol produced by D. helianthi had an anti-microbial potential (Specian et al., 2012). A new anti-microbial compound 3,1'-didehydro-3[2''(3''″,3″′-dimethyl-prop-2-etyl)-3″-indolylmethylene]-6-methyl pipera-zine-2,5-dione), a known secondary metabolite was obtained from extract of the endophytic fungi Penicillium chrysogenum (MTCC 5108), recovered from mangrove plant Porteresia coarctata (Roxb.). The metabolites of P. chrysogenum showed significant activity against Vibrio cholerae (MCM B-322), a bacterial pathogen causing cholera in humans (Devi and Wahab, 2012).

![Fig. 1: Structures of several antimicrobial bioactive compounds from endophytic mycoflora.](image-url)
Anti-cancerous Bioactive Compounds from Endophytic Mycorrhiza

Table 1: List of some Anti-microbial bioactive compounds from endophytic mycorrhiza.

| Endophytic fungi | Host plant | Bioactive compounds | Class of substance | Activity | References |
|------------------|------------|---------------------|--------------------|----------|------------|
| Phomopsis sp.    | Erythrina cristagalli | Isolavonoids | Flavonoid | Antimicrobial | Radji et al., 2011 |
| Phomopsis sp.    | Plumeria acutifolia | Terpenoid | Terpenoid | Antimicrobial | Nithya et al., 2010 |
| Xylaria sp.      | Piper aduncum | Phenomenone | Terpenoid | Antifungal | Silva et al., 2010 |
| Trichoderma harzianum | Ilex cornuta | Trichodermin | Terpenoid | Antimicrobial | Chen et al., 2007 |
| Phomopsis sp.    | Laurus azoric | Cyclophosphylactone | Terpenoid | Antimicrobial | Hussain et al., 2009 |
| Xylaria sp.      | Garcinia dulcis | Sordarinic | Diterpenes | Antifungal | Pongcharoen et al., 2008 |
| Botryosphaeria sp. | Maytens hooker | Diterpenes CI-14445 | Diterpenes | Antimicrobial | Yuan et al., 2009 |
| Xylaria sp. YX-28 | Ginkgo biloba | 7-amino-4 Methylcoumarin | Flavonoid | Antimicrobial | Xu et al., 2008 |
| 2L-5 | Ocimum basilicum | Ergostanol, Cereverstol | Steroids | Antimicrobial | Haque et al., 2005 |
| Chlorodid sp.    | Azadirachta indica A. Juss | Javaninc | Terpenoids | Antibacterial | Khawar et al., 2008 |
| Eupolypogonopsis PSU-D44 | Gericcia dulcis | Scoparasin B | Steroids | Antimicrobial | Pongcharoen et al., 2006 |
| Alternaria sp.   | Sonnerata alba | Xanatorial acids I and II | Polyketides | Antibacterial | Kjer et al., 2009 |
| Ampelomyces sp.  | Urosepermum picroides | 6-O-Methylalaterratin | Polyketides | Antibacterial | Aly et al., 2008 |
| Nodaliposphorium sp. | Juniperus cedrus | Nodafilsporin | Polyketides | Antibacterial | Dai et al., 2006 |
| Chatulara sp.    | Artemisia vulgaris | Isotufudanol | Polyketides | Antibacterial | Lang et al., 2008 |
| Streptomycses sp. | Monstera sp. | Coronamycin | Peptides | Antimicrobial | Ezra et al., 2004 |
| Phoma sp.        | Taxus sallwichina | Altersolanol A | Peptide | Antifungal | Liu et al., 2004 |
| Penicillium janthinellum | Melia azedarach | Citrinin | Antifungal | Peptide | Marinho et al., 2005 |
| Gignardia sp. Phomopsis sp. | Spindias mombin | Phomopsischalasin | Alkaloids | Antimicrobial | Phongpaichit et al., 2007 |
| Pestalotips sp.  | Gericcia dulcis | Phompomenaedine | Alkaloids | Antimicrobial | Rukhasaisri et al., 2008 |
| Cryptosporisorps quisicina | Tripertysium woldford | Cryptacin | Alkaloids | Antimicrobial | Li et al., 2000 |
| Xylaria sp.      | Abies holophylla | Griselofulvin | - | Antifungal | Park et al., 2005 |
| Chaeosporidium globosum | Ginkgo biloba | Chaetomugin A and D | Alkaloids | Antifungal | Qin et al., 2009 |
| Verticillium sp. | Rehmannia glutinoso | Ergosterol peroxide | Steroids | Antifungal | You et al., 2009 |
| Pichia guillermondii Ppt9 | Paris polyphylla var. yunnanensis | Helvolic acid | Triterpenoids | Antibacterial | Zhao et al., 2010 |
| Aspergillus niger IFB-E003 | Cydon dactylon | Rubrofasarin B, fonsecinone A, asperpyrone B and aurasperone A | - | Antimicrobial | Song et al., 2004 |
| Aspergillus clavatunianus | Torreyya mairei | Clavatol | - | Antimicrobial | Huang et al., 2008 |
| Auremonium zeae | Zea maize | Pyro-cidines A and B | Alkaloids | Antimicrobial | Wicklow et al., 2005 |
| Penicillium sp. | Acrostichum aureum | Cyclo(Pro-Thr) | Peptides | Antibacterial | Cui et al., 2008 |
| Nodaliposphorium sp. | Juniperus cedrus | Alternariol, alternariol methyl ether and tennazamic acid | Steroids | Antimicrobial | Dai et al., 2006 |
| Alternaria alternate | Euphoria helioscelia | Alternariol, alternariol methyl ether and tennazamic acid | - | Antimicrobial | Ashour et al., 2011 |
| Diaporthella helianthi | Luehea divaricata | 2-4-dihydroxybenzaldehyde-1H-indene and 3-Cyano-1,2-dimethylindole | Phenolics | Antimicrobial | Specian et al., 2012 |
| Alternaria sp. | Trizys vasshierti | Podophylothanox | Phenolics | Antimicrobial | Cota et al., 2008 |
| Aspergillus fumigates | Juniperus communis L. | 3-(3-azido-propyl)-1H-indene and 3-Cyano-1,2-dimethylindole | Phenolics | Antimicrobial | Kasali et al., 2009 |
| Penicillium sp. | Camelia sinensis | - | - | Antibacterial | Devi and Wahab, 2012 |
| Phoma her-barum | Aegle marmelos | 1,7-dihydroxy-3-methoxyanthraquinone | - | Antimicrobial | Kharwar et al., 2013 |
| Fungal strain AL-2 | Aquiliaria malaccensis Lank | 1,7-dihydroxy-3-methoxyanthraquinone (I), Propyl p-methoxy-phenyl ether (II), 6-Methoxy-7-O-(p-methoxyphenyl)-coumarin (III) | - | Antimicrobial | Shueb et al., 2010 |
| Phomopsis sp. | Allamanda cathartica | Tepene | Terpenoids | Antibacterial | Nithya et al., 2011 |
| Endophytic fungus | Hypericum perforatum | Hypercin | - | Antibacterial | Kasali et al., 2008 |
| NFU/HF/KF/34B | Cassia spectabilis | Ethyl 2,4-dihydroxy-5,6-dimethylbenzoate and “Phomopsilactone” | - | Antifungal | Silva et al., 2005 |
| Phomopsis cavia | Quercus variabilis | Brefeldin A | Aliphatic | Antimicrobial | Wang et al., 2007 |
| Curvularia geniculata | Catunaregam tomentosa | Curvularine B | Peptide | Antimicrobial | Chomchon et al., 2010 |
| Pestalotasip sp. | Rhizophora maccronata | Pestalotiopepsone | Pestalotiopepsone | - | Beckman et al., 2013 |
| Unidentified | Ipomea psycrapaces Lin. | Tetrahdroaurolugain and Flavoglaucin | - | Antimicrobial | Chiapackdee et al., 2013 |
| Trichothecium sp. | Phyllanthus amarus | Trichotheclin-A | - | Antifungal | Taware et al., 2014 |
| Chaetomium globosus HYML55 | Hypericum myrsnere | Cytochalan | - | Antimicrobial | Samaga et al., 2014 |

Anti-cancerous Bioactive Compounds from Endophytic Mycorrhiza

Novel anti-cancer drugs are also required due to high worldwide mortality rate (Pisani et al., 1999). Cancer is a disease characterized by unregulated cell proliferation and leads to the spread of abnormal cells and uncontrolled tissue growth (American Cancer Society, 2009). It has been considered as one of the major causes of death worldwide (about 13% of all deaths) in 2004 (WHO, 2009). Guo et al. (2008); Debab et al. (2011) reported some evidences that bioactive compounds produced by endophytes could be used as alternative approach for the discovery of novel anti-cancer drugs. Thus, the cure of cancer has been enhanced mainly due to diagnosis improvements which allow earlier and more precise treatments (Pasut and Veronese, 2009). Endophytic fungi are rich sources of novel organic compounds with interesting biological activities and high levels of biodiversity (Krohn et al., 2007). Taxol, a diterpenoid, also called paclitaxel, have gained interest, possibly due to its unique mode of action compared to other anti-cancer agents (Gangadevi and Muthumary, 2008). This compound interferes with the multiplication of cancer cells, reduces or interrupts their growth (Firakova et al., 2010). FDA (Food and Drug Administration) had approved Taxol for the treatment of advanced breast cancer, lung cancer, and refractory ovarian cancer (Cremasco et al., 2009). Wani et al. (1971)
previously reported that Taxol (C_{47}H_{51}NO_{14}) was firstly isolated from the bark of trees belonging to Taxus family (Taxus brevifolia), which was its most common source. Several reports about Taxol anti-cancer properties were published since its discovery (Lu et al., 2006), in addition, other sources for production of Taxol have been investigated in the last decade. The isolation of Taxol producing endophyte Taxomyces andreanae (Table 2) has provided an alternative approach to obtain cheaper and more available products via microbial fermentation (Stierle and Strobel, 1993). Pestalotiopsis terminaliae fungus isolated from the Terminalia arjuna plant produced the highest amount of Taxol (Gangadevi and Muthumary, 2009).

Camptothecin is another important alkaloid anticancer compound (Fig 2), a potent anti-neoplastic agent which was firstly isolated from the wood of Camptotheca acuminata Decaisne (Nyssaceae) in China (Wall et al., 1966). The important precursors for clinically useful anticancer drugs, such as topotecan, irinotecan, camptothecin and 10-hydroxycamptothecin (Uma et al., 2008). The products obtained from the endophytic fungus Fusarium solani, recovered from Camptotheca acuminata were camptothecin and two analogues (9-methoxycamptothecin and 10-hydroxycamptothecin) which Kusari et al.,(2009) reported to have anticancer properties.

The anticancer drugs like etoposide and etopophosphosphate have precursor’s podophyllotoxin and their analogues, due to their properties of cytotoxicity and antiviral activities (Kour et al., 2008). These podophyllotoxin are aryl tetralin lignans which were naturally synthesized by Podophyllum spp. A novel anticancer agent Ergoflavin, a dimeric xanthenes linked in position 2 was isolated from endophytic fungi recovered from the leaves of an Indian medicinal plant Mimusops elengi (Sapotaceae) (Deshmukh et al., 2009). Secalonic acid D, a mycotoxin, isolated from mangrove endophytic fungus ZSU44, belongs to ergochrome class known to have potent anti-cancer activities and induction of leukemia cell apoptosis. Moreover, it showed high cytotoxicity on HLA60 and K562 cells (Zhang et al., 2009).

\[
\begin{align*}
\text{Paclitaxel} & \\
\text{Sclerotiorin} & \\
\text{Ergoflavin} & \\
\text{Citrinin} & \\
\text{Podophyllotoxin} & \\
\text{Toosendanin} & \\
\text{Camptothecian} & 
\end{align*}
\]

Fig. 2: Structures of Anti-cancerous Bioactive Compounds from Endophytic Mycoflora.
Table 2: List of some Anti-cancerous bioactive compounds from endophytic Mycoflora.

| Isolated fungus | Host Plant | Compound | Class of substance | References |
|-----------------|------------|----------|--------------------|------------|
| Taxomyces andreanae | Taxus brevifolia | Taxol (Paclitaxel) | Diterpenoid | Siterle and Strobel, 1993 |
| Phoma sp. | Aloe vera | Taxol | Diterpenoid | Rebecca et al., 2011 |
| Alternaria sp. | Ginkgo biloba | Taxol | Diterpenoid | Kim et al., 1999 |
| Alternaria alternata TPF6 | Taxus chinensis var. mairei | Taxol | Diterpenoid | Tian et al., 2006 |
| Aspergillus fumigatus EPTP-1 | Podocarpus sp. | Taxol | Diterpenoid | Sun et al., 2008 |
| Phyllosticta sp.6 | Ocimum basilicum | Taxol | Diterpenoid | Gangadevi, 2007 |
| Aspergillus niger var. taxi HD86-9 | Taxus cuspidata | Taxol | Diterpenoid | Zhao et al., 2009 |
| Botryodiplodia theobromae BT115 | Taxus baccata | Taxol | Diterpenoid | Venkatachalam et al., 2008 |
| Cladosporium cladosporioides MD2 | Taxus media | Taxol | Diterpenoid | Zhang et al., 2009 |
| Fusarium mairei YH117 | Taxus chinensis var. mairei | Taxol | Diterpenoid | Cheng et al., 2007 |
| Fusarium mairei UH23 | Taxus chinensis var. mairei | Taxol | Diterpenoid | Dai et al., 2008 |
| Fusarium solani | Taxus celebica | Taxol | Diterpenoid | Chakravarthi et al., 2008 |
| Fusarium solani Tax-3 | Taxus chinensis | Taxol | Diterpenoid | Deng et al., 2009 |
| Oxytropis sp. BT2 | Taxus chinensis var. mairei | Taxol | Diterpenoid | Guo et al., 2006 |
| Pestalotiopsis terminaliae TAP-15 | Terminalia arjuna | Taxol | Diterpenoid | Gangadevi et al., 2009 |
| Phellosticta disciosorae No.605 | Hibiscus rosa-sinensis | Taxol | Diterpenoid | Kumaran et al., 2009 |
| Bartalinia robillardodites | Aegle marmelos | Taxol | Diterpenoid | Gangadevi et al., 2009 |
| Lasiodiplodia theobromae | Morinda citrifolia | Taxol | Diterpenoid | Pandi et al., 2011 |
| Fusarium oxysporum | Rbizyphora annamalayana | Camptothecin | Alkaloid | Elavarasi et al., 2012 |
| Fusarium solani | Camptotheca acuminate | Camptothecin | Alkaloid | Kusari et al., 2009 |
| Entrophospora infrequens RJMEF 001 | Nothapodytes foetida | Camptothecin | Alkaloid | Pun et al., 2005 |
| Entrophospora infrequens 5124 | Nothapodytes foetida | Camptothecin | Alkaloid | Annma et al., 2006 |
| Fusarium solani MTCC 9667 | Apodytes dimidiate | Camptothecin | Alkaloid | Shweta et al., 2010 |
| Neorospora sp. ZP5SE | Nothapodytes foetida | Camptothecin | Alkaloid | Rehman et al., 2008 |
| Aspergillus fumigatus | Juniperus communis L. | Podophyllotoxin | Alkaloid | Kusari et al., 2009 |
| Phialocephala fortunii | Podophyllum peltatum | Podophyllotoxin | Lignin | Amy et al., 2006 |
| Fusarium oxysporum JRE1 | Sabina recurva | Podophyllotoxin | Lignin | Kour et al., 2008 |
| Penicillium sp. | Diphylliea sinensis | Podophyllotoxin | Lignin | Yang et al., 2003 |
| Penicillium implicatum SJ21 | Diphylliea sinensis | Podophyllotoxin | Lignin | Zeng et al., 2004 |
| Trametes hirsute | Sinosopodophyllum hexandrum | Podophyllotoxin | Lignin | Puri et al., 2006 |
| Penicillium expansum | Exsoccaria agallocha | Expansols A, B | - | Lu et al., 2010 |
| Penicillium janthinellum | Melia azedarach | Citrinn | - | Marinho et al., 2005 |
| Paeclomyces sp. | Paris polyphylla var. yunnanensis | Diosgenin | - | Cao et al, 2007 |
| Aspergillus niger | Cydon dactylon | Rubefusarin B | - | Song et al., 2004 |
| Cephalothea faveolata | Eugenia jambolana Lam. | Scelentoxin | - | Girdharan et al., 2012 |
| Fusarium proliferatum | Syzygium cordatum | Eergosta-5,7,22-trien-3β-ol, 9-O-methyl fusarubin, Bostrycoerdin, 4-naphtoquinone | - | Dame et al., 2016 |

Table 3: List of some Anti-diabetic bioactive compounds from endophytic mycoflora.

| Endophytic fungi | Host plant | Bioactive compound | References |
|-----------------|------------|--------------------|------------|
| Swietenia macrophylla | Undetected | α-glucosidase | Ramdas et al., 2012 |
| Dendrophthony nanum | Ficus religiosa | Naphthaquinones | Mishra et al., 2013 |
| Aspergillus sp. JPY1 | Salvadora oleoides Decone | 2, 6-di-tet butyl-p-cresol and Phenol, 2, 6-bis [1, 1-dimethylthyl]-4-methyl | Dhanakhar and Yadav, 2013 |

Anti-diabetes Bioactive Compounds from Endophytic Mycoflora

Diabetes mellitus (DM) or simple diabetes is a metabolic disorder resulting from a defect in insulin secretion, insulin action or both. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism. It is the most common endocrine disorder and by the year 2010, it was estimated that it affected more than 200 million people worldwide (ADA, 2009). This disease can cause wide range of heterogeneous complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulcerations due to tissues or vascular damages (Bastaki, 2005).

Domeipen et al. (2011), pointed that endophytic microbe’s ability to produce bioactive compounds in association with its host plants is an opportunity to get sources of anti-diabetic drugs, which as they are natural, inexpensive and ecofriendly. The α-glucosidation inhibitors were the most common oral agents used to decrease postprandial hyperglycemia, since they can decrease glucose intake with low hypoglycemic effect (Hanefeld and Schaper, 2007). In addition, Elya et al., (2011) showed that some natural products from various medicinal plants and microorganisms had potencies such as α-glucosidase inhibitors. Methanolic extract of seeds of Swietenia macrophylla had hypoglycemic effects in both aloxion and streptozotocin induced diabetic rats (Maiti et al., 2009). Ramdanis et al., (2012) isolated and characterized of α-glucosidase anti-diabetic bioactive compound from endophytic fungus of Swietenia macrophylla (Table 3). Moreover, Dhanakhar and Yadav, (2013) added that anti-diabetic drug from Aspergillus sp. Phoma sp. reduced blood glucose level identified by GC-MS analysis as having constituents of 2, 6-di-tet butyl-p-cresol and Phenol, 2, 6-bis [1, 1-dimethylthyl]-4-methyl.
Anti-malaria Bioactive Compounds from Endophytic Mycoflora

Malaria is a disease caused by single cell obligate intracellular parasite from *Plasmodium. Plasmodium falciparum* is the most dangerous species for humans because it can cause acute infection that leads to death. This parasite infects humans by female anopheles mosquito (Aryanti et al., 2006). Endophytic fungi were also known as producers of many natural products of anti-malarial activities. Kongsaeere et al. (2003) also reported three novel dihydroisoucumarin derivatives with anti-malarial, anti-tuberculosis and anti-fungal activities. They have been isolated by bioassay guided fractionation from an endophytic fungus, *Geotrichum sp.*, recovered from *Crasseocapum crepidioides.* Structures were established as 7-butyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one (A), 7-butyl-5-enyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one (B) and 7-butyl-6,8-dihydroxy-3(R)-pentylisochroman-1-one (C) using NMR spectroscopic data. Isaka et al. (2007) reported isolation of pullarins A, B and C (Fig 3) from culture of endophytic fungus *Pullularia sp.*

![Structure of Anti-malaria active compound Pullarins A, B and C from endophytic Mycoflora.](image)

These compounds showed strong anti-malarial activities as they inhibited the activity of *Plasmodium falciparum* K1 with IC$_{50}$ 3.6, 3.3, and 9.8 µM values respectively. Romero et al. (2008) isolated lactones from endophytic *Xylaria* sp. BCC21097 (Table 4), with potential activity against *Plasmodium falciparum*, which could be used as leads for anti-malarial drugs. Haritakun et al. (2010), added that Butyro lactone V compound had also been isolated from endophytic *A. terreus*, showing anti-malarial activity with an IC$_{50}$ 17.95 µM. Isaka et al. (2010) also isolated sesquiterpenoids compounds eremophilane-type, with anti-malarial activity with IC$_{50}$ values ranging between 8.1-13.0 µM, from endophytic *Xylaria* sp. BCC 21097. Two alkaloids had been isolated from endophytic fungi of brotowali plant. These compounds were determined as: 7- hydroxy- 3,4,5-trimethyl-6-on- 2,3,4,6-tetrahydroisoquinoline-8-carboxylic acid and 2,5-dihydroxy-1-(hydroxymethyl) pyridin-4-on. They had anti-malarial activities against *Plasmodium falciparum* 3D7 (Elfita et al., 2011).

### Anti-tuberculosis Bioactive Compounds from Endophytic Mycoflora

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* which remains a major public health problem and cause ill-health among millions of people each year. The resistance of bacteria to different drugs is still increasing. Therefore, findings of new anti-tuberculosis agents are an important issue (Sittikornpaiboon et al., 2014). From the endophytic fungus *Phomopsis* sp. PSU-D15, three metabolites named as phomoenamide, phomonotreoster and deacetyl phomoxanthone B, were isolated together with three known compounds, dicarandol A, (1S,2S,4S)-p-methane-1,2,4-triol and uridine. Phomoenamide exhibited moderate *in vitro* anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rva (Rukachaisirikul et al., 2007).

The endophytic mitosporic *Dothideomycete* sp. LRUB20 fungus isolated from Thai medicinal plant *Leuca rubra* produced dothideopyrones A–D (Pyrene derivatives) together, with seven known compounds. These compounds include questin, asterric acid, methyl asterrate, sulochrin, eugenitin, 6-hydroxymethyljuglinit, cis, trans-muconic acid, 3-nitropropionic acid (Fig 4), asterric acid, a novel compound 2-hydroxymethyl-3-methylcyclopentene-2-enone (synthetically known), cis-2-hydroxymethyl and 3-methylcyclopentanone which were inhibiting *Mycobacterium tuberculosis* H37Ra (Chomcheun et al., 2010). Gordin et al. (2010) added that Cladonia arbuscula, endophytic fungus isolated from *Vaccinium myrtillus* and endophytes isolated from *Carлина vulgaris, Empetrum nigrum* and *Vaccinium vitis-idaea* showed inhibitory activities against *M. tuberculosis*. *Muscodor crisps* is recently described as novel endophytic fungus of *Ananas ananassoides* grown in Bolivia having potential to inhibit drug resistant strains of *M. tuberculosis*. Mitchell et al. (2010), *Muscodor crisps* metabolites have mixtures of volatile organic compounds (VOC’s) such as: ester propanoic acid, 2-methyl-, methyl ester; propanoic acid, 2-methyl-; 1-butanol, 3-methyl; 1-butanol, 3-methyl, acetate; propanoic acid, 2-methyl, 2-methylbutyl ester and ethanol.

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**Table 4: List of Anti-malaria bioactive compounds from endophytic Mycoflora.**

| Endophytic fungi | Host plant | Bioactive compound | Class of substance | References |
|------------------|------------|--------------------|--------------------|------------|
| *Phomopsis* sp.  | -          | Phomoxanthones A and B | Phenolics          | Isaka et al., 2001 |
| *Streptomyces* sp. | Monstera sp. | Coronamycin | -                | Ezza et al., 2004 |
| *Pullularia* sp. BCC8613 | Quercus cocifera | Pullarins A-C | Peptides          | Isaka et al., 2007 |
| *Xylaria* sp. BCC21097 | Licuala spinosa | 1α-10α-Epoxy-7α-hydroxyeremophil-11-en-12,8-β-olide | Terpenoid          | Isaka et al., 2010 |
| PSU-N24 | *Garcinia nigrolineata* | Griseofulvin | Polyketides       | Sommart et al., 2008 |
| *Phomopsis archeri* | Vanilla alibindia | Phomoxanthones A-C | Sesquiterpenes    | Hemtasi et al., 2011 |
| *Fusarium* sp. | Mentha longifolia L. | Integracides F and G | Triterpenoids      | Ibrahim et al., 2016 |

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![Structure of Anti-malaria active compound Pullarins A, B and C from endophytic Mycoflora.](image)
Table 5: List of some Anti-tuberculosis bioactive compounds from endophytic Mycoflora.

| Endophytic fungi | Host plant | Bioactive compound | Class of substance | References |
|------------------|------------|--------------------|--------------------|------------|
| Phomopsis sp.    | Garcinia sp. | Phomoxanthone A and B | Phenolics | Isaka et al., 2001 |
| Eutypella scoparia | Garcinia atroviridis | Cytochalasins | Diterpenes | Pongcharoen et al., 2006 |
| Phomopsis sp. PSU-D15 | Garcinia dulcis | Phoemoamide | Polypeptides | Rukachaisirikul et al., 2007 |
| PSU-N24 | Garcinia nitrolineata | Hydronaphthalenones, Dihydroramulosin, griseofulvin desoxybostrycin and austrocortin | Polypeptides | Sommart et al., 2008 |
| Fusarium solani | Hypericum perforatum | Hypericin | Alkaloids | Kusari et al., 2008 |
| Periconia sp. Piper longum L. | Piper (5-(3, 4-methylenedioxyphenyl)-1-piperidinopent-2, 4-dien-1-one) | Piperine | Peptides | Sonaimuthu et al., 2011 |
| Alternaria alternate | Indigofera eneaaphylla | Tenuazonic acid | Polyketides | Prince et al., 2011 |
| Phomopsis stipata | Styrac camparum | Koninginins | - | Flores et al., 2013 |
| Phomopsis longicolla | Trichilia elegans A. JUSS sp. Elegans | 3-nitropropionic acid | - | |

Fig. 4: Structures of some anti-tuberculosis bioactive compounds from endophytic mycoflora.

The endophytic fungus *Periconia* sp. (Table 5) produces piperine (5-(3, 4-methylenedioxyphenyl)-1-piperidinopent-2, 4-dien-1-one) under liquid culture. This highly functionalized fungus-derived piperine exhibits strong anti-mycobacterium activities against *Mycobacterium tuberculosis* and *Mycobacterium smegmetis*. Piperine compound was crystallized and its structure was elucidated by single-crystal X-ray crystallography (Rukachaisirikul et al., 2004).

**Anti-viral Bioactive Compounds from Endophytic Mycoflora**

Another charming use of antimicrobial products from endophytic fungi is the inhibition of viruses. Many reports demonstrated the importance of endophytic fungi in the production of anti-viral agents. Two novel human cytomegalovirus (hCMV) protease inhibitors, cytonic acids A and B (Fig 5) have been isolated from solid-state fermentation of the endophytic fungus *Cytonaema* sp. Their structures isomers were elucidated by mass spectrometry and NMR methods as p-trydepside (Guo et al., 2000). Exploration of endophytes associated with leaves of *Quercus coccifera* led to the isolation of endophyte with the ability to synthesize hinnumulinquone, a potent inhibitor of human immunodeficiency virus type 1 (HIV-1) protease (Singh et al., 2004). Moreover, Mellisol and 1,8- dihydroxynaphthol 1-O-a-glucopyranoside were isolated from the fungus *Xylaria mellisii* (BCC 1005) and showed inhibitory activities against herpes simplex virus-type 1 (Pittayakhaonwut et al., 2005).

An endophytic fungus *Pestalotiopsis theae* (Table 6) of an unidentified tree on Jianfeng Mountain, China, was capable of producing Pestalothecol C with anti-HIV properties (Li et al., 2008). Arunpanichlert et al.,(2010) investigated the secondary metabolites of endophytic fungus *Penicillium sclerotiorum* and isolated the known compound (+)-Sclerotiorin. (+)-Sclerotiorin exhibited effects on human immunodeficiency virus HIV-1 integrase and protease, with IC₅₀ values of 45.88 and 198.41μM, respectively.

Moreover, Zhang et al. (2011) reported the isolation and structure elucidation of Emerimidine A and B from culture of the endophytic fungus *Emericella* sp. Both of them showed moderate inhibition of Influenza virus H1N1 with IC₅₀ values of 42.07 mg/mL and 62.05 mg/mL, respectively.
CONCLUSION

In the present scenario, human beings are suffering from various health problems due to infectious diseases, drug resistance, neurodegenerative diseases, cardiovascular diseases etc. in their daily life. There is an urge to investigate novel compounds for the treatment of these diseases. Therefore, endophytic fungi provide a broad variety of secondary metabolites with their unique structures like flavonoids, terpenoids, alkaloids, phenolic acid etc. Such bioactive metabolites find wide range of application against infectious diseases, autoimmune, enteric, cardiovascular, and other diseases. The potential of finding new drugs that may be effective candidates for treating newly developing diseases in humans is remarkable. Hence, we concluded that the endophytic mycoflora are novel and important microbial resources for producing bioactive compounds, and have attracted attention of many researchers for their potential applications and studies. However, future studies include various biosynthetic pathways responsible for the production of novel bioactive metabolites from the endophytic mycoflora. Also, molecular biology based studies can be used to isolate and identify the different types of genes found in biosynthetic pathways and used for the large scale production of novel bioactive compounds in laboratory as well as at commercial level. However, genetic engineering techniques can be carried out further for the gene transfer leading to the development of more efficient species.

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REFERENCES

Aly AH, Debbab A, Proksch P. Fungal endophytes: unique plant inhabitants with great promises. Appl Microbiol Biotechnol, 2011; 90: 1829-1845.
Asian Pac J Trop Biomed

Aryanti, Ermayanti TM, Prinadi KL, Dewi RM. Test power antimalarial Aktiniaspora spp. against Plasmodium falciparum. Indonesia J Pharm, 2006; 17: 81-84.

Asimov, Hany M, Yehia PP. Utilization of Agro-industrial byproducts for production of bioactive natural products from endophytic fungi. J Nat Prod, 2011; 10: 108-114.

Bastaki S. Diabetes mellitus and its treatment. Int J Diabetes Metab, 2005; 13: 111-34.

Beekman AM, Barrow RA. Stereochemical assignment of the fungal metabolites pestalotiopsones D and E through enantiopure 

Bunyapaiboonsri T, Yoiprommarat S, Srikitikulchai P, Barrow RA. Stereochemical assignment of the fungal metabolites pestalotiopsones D and E through enantiopure

Cui HB, Mei WL, Miao CD, Lin HP, Hong K, Dai HF. Identification and screening of α-glucosidase inhibitory activity from some plants of apocynaceae, Clusiaeceae, euphorbiaceae and rubiaceae. J Biomed Biotechnol, 2011; 2: 1-6.

Espinel MA, Laszlo A, Simonens L, Boulaibhal F, Kim SJ, Rozga AM, Hoffner S, Rieder HL, Binkin N, Dye C, Williams R, Raviglione MC. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med, 2001; 344: 1294-1303.

Ezra D, Castillo UF, Strobel GA, Hess WM, Porter H, Jensen JB, Condron MA, Teplov DB, Sears J, Maranta M, Hunter M, Weber B, Yoyer D. Coronamycins, peptide antibiotics produced by a verticillate fungus.

Elavarasi A, Gnanaprakash SR, Murugaiyan K. Taxol producing endophytic fungus Fusarium oxysporum from Rhizophora annamalayana. Asian Pac J Trop Biomed, 2012; 2: 1081-1085.

Elfitia, Muharni, Munawar, Leoni L, Darwati. Antimalarial Compounds from Endophytic Fungi of Brotowali (Tinaspora crispa L). Indonesien J Chem, 2011; 11: 53-58.

Elya B, Basak K, Munim A, Yuliatusti W, Bangun A, Septiana EK. Screening of a-glucosidase inhibitory activity from some plants of apocynaceae, Clusiaeceae, euphorbiaceae and rubiaceae. J Biomed Biotechnol, 2011; 2: 1-6.

Espinel MA, Laszlo A, Simonens L, Boulaibhal F, Kim SJ, Renjero A, Hoffner S, Rieder HL, Binkin N, Dye C, Williams R, Raviglione MC. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med, 2001; 344: 1294-1303.

Ezra D, Castillo UF, Strobel GA, Hess WM, Porter H, Jensen JB, Condron MA, Teplov DB, Sears J, Maranta M, Hunter M, Weber B, Yoyer D. Coronamycins, peptide antibiotics produced by a verticillate Streptomyces sp. J Med Sci, 2004; 150: 785-793.

Fernandes MRV, Silva TAC, Pfenning LH, da Costa-Neto CM, Heinrich TA, de Alencar SM, de Lima MA, Ikegaki M. Biological activities of the fermentation extract of the endophytic fungus Alternaria alternata isolated from Coffea arabica L. Braz J Pharm Sci, 2009; 45: 677-685.

Firakova S, Sturdikova M, Muckova M. Bioactive secondary metabolites produced by microorganisms associated with plants. Biolica, 2007; 62: 251-257.

Flores AC, Pamphile JA, Sarragottho MH, Clemente E. Production of 3-nitropropionic acid by endophytic fungus Phomopsis longicolla isolated from Trichilia elegans A. JUSS sp. elegans and evaluation of biological activity. World J Microbial Biotechnol, 2013; 29: 923-932.

Gangadevi V, Muthumary J. Antimicrobial activity of the fermentation extract of the endophytic fungus Alternaria alternata isolated from Coffea arabica L. Braz J Pharm Sci, 2009; 45: 677-685.

Firakova S, Sturdikova M, Muckova M. Bioactive secondary metabolites produced by microorganisms associated with plants. Biolica, 2007; 62: 251-257.

Flores AC, Pamphile JA, Sarragottho MH, Clemente E. Production of 3-nitropropionic acid by endophytic fungus Phomopsis longicolla isolated from Trichilia elegans A. JUSS sp. elegans and evaluation of biological activity. World J Microbial Biotechnol, 2013; 29: 923-932.

Gangadevi V, Muthumary J. Endophytic fungal diversity from young, mature and senescent leaves of Ocimum basilicum L. with special reference to Taxol production. Indian J Sci Technol, 2007; 1: 1-12.

Gangadevi V, Muthumary J. Taxol production by Pestalotiopsis terminaliae, an endophytic fungus of Terminalia arjuna (arjun tree). Biotechnol Appl Biochem, 2009; 52: 9-15.

Gangadevi V, Muthumary J. Taxol, an anticancer drug produced by an endophytic fungus Bartallorinia robillarioides Tassi.
isolated from a medicinal plant, "Aegle marmelos" Correa ex. Roxb. World J Microbiol Biotechnol, 2008; 24: 717-724.

Giridharan P, Verekar SA, Khanna A, Mishra PD, Deshmukh SK. Anticancer activity of scelorotin, isolated from an endophytic fungus Cephalotheca favelata Yaguchi, Nishim and Udagawa. Indian J Exp Biol, 2012; 50: 464-468.

Gordien AY, Gray A, Ingleby K, Franzblau SG, Seidel V. Activity of Scottish Plant, Lichen and Fungal Endophyte Extracts against Mycobacterium aurum and Mycobacterium tuberculosis. Phytother Res, 2010; 24: 692-698.

Guo B, Dai JR, Ng S, Huang Y, Leong C, Ong W, Carte BK. Cytotoxic acids A and B and novel tridepside inhibitors of ICAMV protease from the endophytic fungus Cytospora species. J Nat Prod, 2000; 63: 602-604.

Guo B, Wang Y, Sun X, Tang K. Bioactive Natural Products from Endophytes: A Review. Appl Biochem Microbiol, 2008; 44: 136-142.

Guo BH, Wang YC, Zhou XW, Hu K, Tan F Milo ZQ, Tang KX. An endophytic Taxol producing fungus BT2 isolated from Taxus chinesis var. mairei. Afr J Biotechnol, 2006; 5: 875-877.

Hermans C, Kanommedahkul S, Kanommedahkul K, Hahnyajanawong C, Soyongan K, Prabpai S, Kongsaeeree P. Cytotoxic Pentacyclic and tetracyclic aromatic sesquiterpenes from Phomopsis archeri. J Nat Prod, 2011; 74: 609-613.

Huang Z, Cai X, Shao C, She Z, Xia X, Chen Y, Yang J, Zhou S, Lin Y. Chemistry and weak antimicrobial activities of phomopsins produced by mangrove endophytic fungus Phomopsis sp. ZSU-H76. Phytochem, 2008; 69: 1604-1608.

Hussain H, Akhtar N, Draeger S, Schulz B, Pescitelli G, Salvadori P, Antus S, Kurtan T, Massarilactones E, G. New metabolites from the endophytic fungus Coniothyrium sp., associated with the Plant Artimisia maritime. Chirality, 2007: 19; 464-470.

Kumaras RM, Muthumary J, Kim, E.K.; Hur, B.K. Production of taxol from Phyllosticta dioecorea, a leaf spot fungus isolated from Hibiscus rosa-sinensis. Biotechnol Bioprocess Eng, 2009; 14: 76-83.

Kusari S, Lamsht S, Speltizer M. Aspergillus fumigatus Fresenius, an endophytic fungus from Juniperus communis L. Horstmann as a novel source of the anticanicer pro-drug deoxycytophlobotoxin. J Appl Microbiol, 2009; 107: 1019-1030.

Kusari S, Lamphoet M, Zhuhike S, Speltizer M. An endophytic fungus from Hypericum perforatum that produces hypericin. J Nat Prod, 2008; 71: 159-162.

Kusari S, Speltizer M. 2012. Metabolomics of endophytic fungi producing associated plant secondary metabolites: progress, challenges and opportunities. In Metabolomics. Roesnesser, ed. Rijeka, Croatia: InTech, 241-266.

Kusari S, Zhuhike S, Speltizer M. An endophytic fungus from Cuntotheca acuminata that produces camptothecin and analogues. J Nat Prod, 2009; 72: 2-7.

Li E, Tian R, Liu S, Chen X, Guo L, Che Y. Pestalothoels A-D, bioactive metabolites from the plant endophytic fungus Pestalotiopsis theae. J Nat Prod, 2008; 71: 664-668.

Li JY, Strobel GA, Harper JK, Lobkovsky E, Clardy J. Cryptocin, a potent tetramic acid antiyomicot from the endophytic fungus Cryptosporiopsis sp. cf. querica. Org Lett, 2000; 2: 767-770.

Liu JY, Song YC, Zhang Z, Wang L, Gao ZJ, Zon WX, Tan RX. Aspergillus fumigatus CY018, an endophytic fungus in Cynodon dactylon as a versatile producer of new and bioactive metabolites. J Biotechnol 2004; 114: 279-287.

Liu L, Niu S, Lu X, Chen X, Zhang H, Gao L, Che Y. Unique metabolites of Pestalotiopsis fici suggests a biosynthetic hypothesis involving a Diels-Alder reaction and then mechanistic diversification. Chem Commun, 2010; 46: 460-462.

Liu X, Dong M, Chen X, Jiang M, Lv X, Zhou J. Antimicrobial activity of an endophytic Xylaria sp.XY-28 and identification of its antimicrobial compound 7-amino-4-methylcoumarin. Appl Microbiol Biotechnol, 2008; 78: 241-247.

Lösken S, Magull J, Schulz B, Draeger S, Zeeck A. Isofusidienols: novelchromone-3- oxepines produced by the endophytic fungus Chalara sp. Eur J Org Chem, 2008; 4: 698-703.

Lu F, Lu Z, Bie X, Yao Z, Wang Y, Lu Y, Gao Y. Purification and characterization of a novel anticoagulant and fibrinolytic enzyme produced by endophytic bacterium Paenicibacillus polysmyxa EJS-3. Thromb Res, 2010; 126: 349-355.
Lu H, Li B, Kang Y, Jiang W, Huang Q, Chen Q, Li L, Xu C. Paclitaxel nanoparticle inhibits growth of ovarian cancer xenografts and enhances lymphatic targeting. Cancer Chemother Pharmacol, 2006; 59: 175-181.

Maiti A, Dewanjee S, Jana G, Mandal SC. Hypoglycemic effect of *Swietenia macrophylla* seeds against type II diabetes. Int J Green Pharm, 2009; 2: 224-227.

Marinho MR, Rodrigues-Filho E, Motinho MDLR, Santos LS. Biologically active polyketides produced by *Penicillium janthinellum* isolated as an endophytic fungus from fruits of *Melia azedarach*. J Braz Chem Soc, 2005; 16: 280-283.

Mishra PD, Vetekar SA, Kulkarni-Almeida A, Roy SK. Anti-inflammatory and anti diabetic naphthaquinones from an endophytic fungus *Dendrophyion nanum* (Nees) S. Hughes. Indian J Chem, 2013; 52: 565-567.

Mitchell AM, Strobel GA, Moore E, Robison R, Sears J. Volatile antimicrobials from *Miracidor crispans*, a novel endophytic fungus. Microbiol, 2010; 156: 270-277.

Newman DJ, Cragg MG. Natural products as source of new drugs over the last 25 years. J Nat Prod, 2006; 69: 1177.

Nithya K, Muthumary J. Bioactive Metabolite Produced by *Phomopsis* sp., an Endophytic Fungus in *Allamanda cathartha* Linn. Rec Res Sci Tech, 2011; 3: 44-48.

Nithya K, Muthumary J. Secondary Metabolite from *Phomopsis* sp. isolated from *Plumeria acutifolia*. Rec Res Sci Tech, 2010; 2: 99-103.

Pandi M, Rangarajulu SK, Yong-Keun C, Hyung JK, Johnpal M. Isolation and detection of taxol, an anticancer drug produced from *Lasiodiplodia theobromae*, an endophytic fungus of the medicinal plant *Morinda citrifolia*. Afr J Biotechnol, 2011; 10: 1428-1435.

Park JH, Choi GJ, Lee HB, Kim KM, Jung HS, Lee S, Jang KS, Cho KY, Kim J. Griseofulvin from *Xylaria citrifolia*. Tetrahedron Lett, 2005; 46: 1341-1344.

Park J, Keun C, Hyung JK, Johnpaul M. Isolation and detection of taxol, an anticancer drug produced from *Lasiodiplodia theobromae*, an endophytic fungus of the medicinal plant *Morinda citrifolia*. Afr J Biotechnol, 2011; 10: 1428-1435.

Pongcharoen W, Rukachaisirikul V, Phongpaichit S, Sakayaroj J, Silva GH, Teles HL, Trevisan HC, Bolzani VS, Young MCM, Costa KH, Cesar FH, Silva CM, Moraes AL, Batistella M, Costa LF. Anti cancer activity of some natural products against breast cancer cell lines. World J Sci Tech, 2011; 1: 23-31.

Rehanm M, Shafaa S, Kaur A, Andarbi R, Sudan P, Sultan P, Verma V, Qazi GN. An endophytic *Neurospora* sp. from *Nothapodytes foetida* producing camptothecin. J Nat Prod, 2008; 44: 203-209.

Romero JC, Barria OE, Arnold AE, Rios CL. Activity against *Plasmodium falciparum* of lactones isolated from an endophytic fungus *Xylaria sp*. Pharm Biol, 2008; 46: 1-4.

Rukachaisirikul T, Sirirawanatikit P, Sukcharoenphol K, Wongvein C, Ruttanaweang P, Wongwatanaavuch P, Suksamrarn A. Chemical constituents and bioactivity of *Piper sarmentosum*. J Ethnopharmacol, 2004; 93: 173-176.

Rukachaisirikul V, Sommart U, Phongpaichit S, Sakayaroj J, Kirtikara K. Metabolites from the endophytic fungus *Phomopsis* sp. PSU-D15. Phytochem Lett, 2008; 69: 783-787.

Rukachaisirikul V, Sommart U, Phongpaichit S, Sakayaroj J, Kirtikara K. Metabolites from the endophytic fungus *Phomopsis* sp. PSU-D15. 2007; 69: 783-787.

Sadrazi N, Harzallah D, Amin Z, Saliha D, Saddek B. Screening of antimicrobial and antioxidant secondary metabolites from endophytic fungi isolated from wheat (*Triticum durum*). J Plant Prot Res. 2013; 53: 128-136.

Samaga PV, Vittal RR, Kuriya MLR. Production of an antimicrobial cytochalasin by an endophytic *Chaetomium globosum* HYML55 from *Hypericum myosorum* and its RNA secondary structure analysis. Chem Ecol, 2014; 30:01-13.

Sandhu SS, Kumar S, Aharwal RP, Shukla H, Rajak RC. Endophytic Fungi: As A Source of Antimicrobials Bioactive Compounds. World J Pharma Pharma Sci, 2014; 3: 1179-1197.

Sekpowitz KA. AIDS-the first 20 years. N Engl J Med, 2001; 344:1764-1772.

Shoeb M, Shahanara B, Nilufar N. Study of an endophytic fungus from *Aquilaria malaccensis* Lambk. Bangladesh J Pharmcol, 2010; 5: 21-24.

Shweta S, Zaheilc S, Ramesha BT, Priti V, Mohana Kumar P, Ravikanth G, Spiteller M, Vasudeva, R, Uma SR. Endophytic fungal strains of *Fusarium solani*, from *Apodytes dimidiata* E. Mey. ex Arn (Icacinaceae) produce camptothecin, 10-hydroxycamptothecin and 9-methoxycamptothecin. Phytochem, 2010; 71: 117-122.

Silva GH, de Oliveira CM, Teles HL, Pauletti PM, Castro-Gamboa L, Silva DHS, Bolzani VS, Young MCM, Costa, Neto CM, Pfennig, LH, Berlinck RGS. Sesquiterpenes from *Xylaria sp.*, an endophytic fungus associated with *Piperaceae* (*Piperaceae*). Phytochem Lett, 2010; 3: 164-167.

Silva GH, Teles HL, Trevisan HC, Bolzani VS, Young MCM, Pfennig, LH, Eberlin MR, Haddad R, Costa, Neto CM, Arahao RR. New bioactive metabolites produced by *Phomopsis cassiae*, an endophytic fungus in *Cassia spectabilis*. J Braz Chem Soc, 2005; 16: 1463-1466.

Singh SB, Ondeyka JG, Tsipouras N, Ruby C, Sardana V, Schulman M, Pellez F, Stahlhut MW, Munshi S, Olsen DB, Lingham RB. Hinnuliquinone, a C2-symmetric dimeric non-peptide fungal metabolite inhibitor of HIV-1 protease. Biochem Biophy Res Comm, 2004; 324: 108-113.

Sittikornpaiboon P, Leartsakulpanich U, Thongpanchang C, Toochinda P, Lawtrakul L. Molecular Modeling Investigations of Pyrimethamine Analogues Binding to *Mycobacterium tuberculosis*
Dihydrofrolate Reductase. Pure and Applied Chemistry International Conference, NMC-OR-01, 2014.

Sommat U, Rukachaisirikul V, Sukpondy M, Phongpachit S, Sakayaro J, Kirtikara K. Hydropnaphthalenones and a dihydroaromulosin from the endophytic fungus PSU-N24. Chem Pharm Bull, 2008; 56: 1687-1690.

Sonaimuthu V, Parihar S, Thakur JP, Lugman S, Saikia D, Chinotiya CS, Jhompaul M, Negi AS. Tenuazonic acid: a promising antitubercular principle from Alternaria alternate. Microbiol Res, 2011; 2: 63-65.

Song YC, Li H, Ye YH, Shan CY, Yang YM, Tan RX. Endophytic naphthopyrone metabolites are co-inhibitors of xanthine oxidase, SW1116 cell and some microbial growths. FEMS Microbiol Lett, 2004; 241: 67-72.

Specian V, Maria HS, João AP, Edmar C. Chemical Characterization of Bioactive Compounds from the Endophytic Fungus Diaephorina helianthi Isolated from Lactea divaricata. Braz J Microbiol, 2012; 43: 1174-1182.

Sterle G, Strobel GA. Taxol and taxane production by Taxomyces andreanae, an endophytic fungus of Pacific yew. Science, 1993; 260: 214-216.

Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. J Nat Prod, 2004; 67: 257-268.

Strobel G, Daisy B. Bioprospecting for microbial endophytes and their natural products. Microbiol Mol Biol Rev, 2003; 67: 491-502.

Strobel G. Endophytes as sources of bioactive products. Microbes and Infec, 2003; 5: 535-544.

Sultan S, Syed AAS, Lin S, Ramaami K, Cole A, Blunt J, Murray Munro HG, Weber JP. Bioactive Fungal metabolites of 9PR2 isolated from roots of Calpophilium furgium. Int J Pharm Pharma Sci, 2011; 3: 7-9.

Sun D, Ran X, Wang J. Isolation and identification of a Taxol producing endophytic fungus from Podocarpus. Acta Microbiol Sin, 2008; 48: 589-595.

Tan RX, Zhou WX. (2001) Endophytes: a rich source of functional metabolites. Nat Prod Rep, 18; 4: 448-459.

Taware R, Prasad A, Deepak P, Rajamohananan R, Raja R, Soundararajan G, Kudun GC, Ahmad A. Isolation, purification and characterization of Trichothecinol-A produced by endophytic fungus Trichothecium sp. and its anti fungal, antitumor and antimetastatic activities. Nutr Chem Proc, 2014; 2: 01-09.

Tenguria RK, Firoz NK, Sadaf Q. Endohytes - Mines of Pharmacological Therapeutics. World J Sci Tech, 2011; 1: 127-149.

Tian R, Yang Q, Zhou G, Tan J, Zhang L, Fang C. Taxonomic study on a Taxol producing fungus isolated from bark of Taxus chinensis var. maiirei. J Wuhan Bot Res, 2006; 24: 541-545.

Tran HBO, McClare JM, Lynch F, Palombo EA. Identification and bioactive properties of endophytic fungi isolated from phyllodes of Aegiceras corniculatum. J Res Tech Edu Topics App Microbiol Biotech, 2010; 377-382.

Uma SR, Ramesha BT, Ravikathan G, Rajesh PG, Vasudeva R, Ganeshaiha KN. 2008. Chemical profiling of N. nimmoniana for camptothecin, an important anticancer alkaloid: towards the development of a sustainable production system, in Bioactive Molecules and Medicinal Plants, Ramawat KG, Merillion J. ed. Springer Berlin, Germany 198-210.

Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol, 2007; 39: 44-88.

Venkatachalam R, Subban K, Paul MJ. Taxol from Botryodiplodia theobromae (BT 115)-an endophytic fungus of Taxus baccata. J Biotechnol, 2008; 136: 189-190.

Verma VC, Kharmar RN, Strobel GA. Chemical and functional diversity of natural products from plant associated endophytic fungi. Nat Prod Comm, 2009; 4: 1511-1532.

Verma VC, Lokkovsky E, Gange AC, Singh SK, Prakash S. Piperine production by endophytic fungi Periconia sp. isolated from Piper longum L. J Antibiot, 2011; 64: 427-431.

Wall MEM, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA. Plant antitumor agents. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from Camptotheca acuminata. J Am Chem Soc, 1966; 88: 3888-3890.

Walsh CT, Fischbach MA. Natural products version 2.0: connecting genes to molecules. J Am Chem Soc, 2010; 132: 2469-2493.

Wang FW, Jiao RH, Cheng AB, Tan SH, Song YC. Antimicrobial potentials of endophytic fungi residing in Quercus variabilis and brefeldin A obtained from Cladosporium sp. World J Microbiol Biotechnol, 2007; 23: 79-83.

Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents VI: the isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J Am Chem Soc, 1971; 93: 2325-2327.

WHO. Mortality Database, Fact sheet No. 297, February, 2009.

Wicklow DT, Roth S, Deyrup ST, Gierer JB. A protective endophyte of maize: Acremonium zeae antibiotics inhibitory to Aspergillus flavus and Fusarium verticillioides. Mycol Res, 2005; 109: 610-618.

Xu L, Zhou L, Zhao J, Jiang W. Recent studies on the antimicrobial compounds produced by plant endophytic fungi. Nat Prod Res Develop, 2008; 20: 731-740.

Yang X, Guo S, Zhang L, Shao H. Selection of producing podophyllotoxin endophytic fungi from podophyllin plant. Nat Prod Res Develop, 2003; 15: 419-422.

You F, Han T, Wu JZ, Huang BK, Qin LP. Antifungal secondary metabolites from endophytic Verticillium sp. Biochem Sys Ecol, 2009; 37: 162-165.

Yu HL, Zhang L, Li Zheng C, Guo L, Li W, Sun L. Recent developments and future prospects of antimicrobial metabolites produced by endophytes. Microbiol Res, 2010; 165: 437-449.

Yuan L, Zhao PJ, Ma J, Lu CH, Shen YM. Labdane and tetrnorlabdane diterpenoids from Botryosphaeria sp. MHF, an endophytic fungus of Maytenushookeri. Helv Chim Acta, 2009; 2: 1118-1125.

Zeng S, Shao H, Zhang L. An endophytic fungus producing a substance analogous to podophyllotoxin isolated from Diphylllea sinensis. J Microbiol, 2004; 24: 1-2.

Zhang G, Sun S, Zhu T, Lin Z, Gu J, Li D, Gu Q. Antiviral isodololone derivatives from an endophytic fungus Emericella sp. associated with Aegiceras corniculatum. Phytochem, 2011; 72: 1436-1442.

Zhang JY, Tao LY, Liang YJ, Yan YY, Dai CL, Xia XK, She, ZG, Lin YC, Fu LW. Socalic acid D induced leukemia cell apoptosis and cell cycle arrest of G1 with involvement of GSK-3β/p-catenin/c-Myc pathway. Cell Cycle, 2009; 8: 2444-2450.

Zhang L, An R, Wang J, Sun N, Zhang S, Hu J, Kuai J. Exploring novel bioactive compounds from marine microbes. Curr Opin Microbiol, 2005; 8: 276-281.

Zhang P, Zhou P, Yu L. An endophytic taxol-producing fungus from Taxus media, Cladosporium cladosporoides MD2. Curr Microbiol, 2009; 59: 227-232.

Zhao J, Mou Y, Shan T, Li Y, Zhou L, Wang M, Wang J. Antimicrobial Metabolites from the Endophytic Fungus Picha guilliermondii isolated from Paris polyphylla var. yunnanensis. Molecules, 2010; 15: 7961-7970.

Zhao K, Ping W, Li Q, Hao S, Zhao L, Gao T, Zhou D. Aspergillus niger var. taxi, a new species variant of taxol-producing fungus isolated from Taxus cuspidata in China. J Appl Microbiol, 2009; 107: 1202-1207.