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Endophytic Mycoflora as a Source of Biotherapeutic Compounds for Disease Treatment

Ravindra Prasad Aharwal, Suneel Kumar, Sardul Singh Sandhu*

Fungal Biotechnology and Invertebrate Pathology Laboratory, Department of Biological Sciences, Rani Durgawati University, Jabalpur, (M.P.) India.

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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, tetralones 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.

* *Corresponding Author*
Fungal Biotechnology and Invertebrate Pathology Laboratory, Department of Biological Sciences, Rani Durgavati University, Jabalpur 482001, (M.P.) India. Email: ssandhu @ rediffmail.com

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 sustainence 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-phenaleno[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 aeroginosa* 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-enyl)-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).

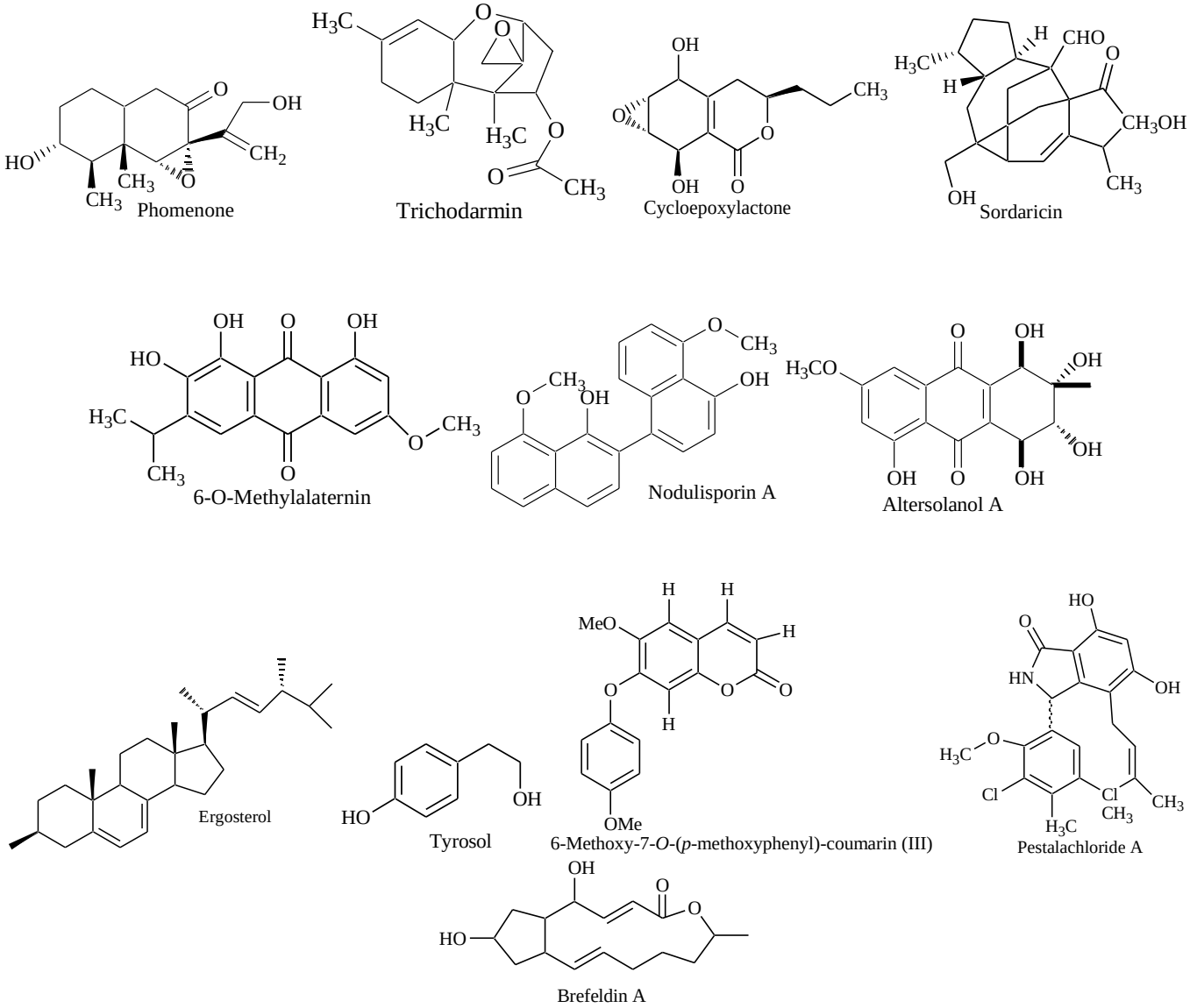


Fig. 1: Structures of several antimicrobial bioactive compounds from endophytic mycoflora.

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

Endophytic fungi	Host plant	Bioactive compounds	Class of substance	Activity	References
Phomopsis sp.	*Erythrina cristagalli*	Isoflavonoids	Flavonoid	Antimicrobial	Radji *et al*., 2011
Phomopsis sp.	*Plumeria acutifolia*	Terpenoid	Terpenoid	Antimicrobial	Nithya *et al*., 2010
Xylaria sp.	*Piper aduncum*	Phomenone	Terpenoid	Antifungal	Silva *et al*., 2010
Trichoderma harzianum	*Ilex cornuta*	Trichodermin	Terpenoid	Antimicrobial	Chen *et al*., 2007
Phomopsis sp.	*Laurus azorica*	Cycloepoxylactone	Terpenoid	Antimicrobial	Hussain *et al*., 2009
Xylaria sp.	*Garcinia dulcis*	Sordaricin	Diterpenes	Antifungal	Pongcharoen *et al*., 2008
Botryosphaeria sp.MHF	*Maytenus hookeri*	Diterpene CJ-14445	Diterpenes	Antimicrobial	Yuan *et al*., 2009
Xylaria sp. YX- 28	*Ginkgo biloba*	7-amino-4 Methylcoumarin	Phinolics	Antimicrobial	Xu *et al*., 2008
2L-5	*Ocimum basilicum*	Ergosterol, Cerevesterol	Steroids	Antimicrobial	Haque *et al*., 2005
Chloridium sp.	*Azadirachta indica* A. Juss	Javanicin	Terpenoids	Antibacterial	Kharwar *et al*., 2008
Eutypella scoparia PSU-D44	*Garcinia dulcis*	Scoparasin B	Terpenoids	Antimicrobial	Pongcharoen *et al*., 2006
Alternaria sp.	*Sonneratia alba*	Xanalteric acids I and II	Polyketides	Antimicrobial	Kjer *et al*., 2009
Ampelomyces sp.	*Urospermum picroides*	6-*O*-Methylalaternin	Polyketides	Antibacterial	Aly *et al*., 2008
Nodulisporium sp.	*Juniperus cedrus*	Nodulisporins	Polyketides	Antifungal	Dai *et al.*, 2006
Chalara sp.	*Artemisia vulgaris*	Isofusidienol	Polyketides	Antifungal	Losgen *et al*., 2008
Streptomyces sp.	*Monstera* sp.	Coronamycin	Peptides	Antimicrobial	Ezra *et al*., 2004
Phoma sp.	*Taxus wallichinia*	Altersolanol A	Quinones	Antimicrobial	Liu *et al*., 2004
Penicillium janthinellum	*Melia azedarach*	Citrinin	Peptide	Antifungal	Marinho *et al*., 2005
Guignardia sp., *Phomopsis* sp. and *Pestalotiopsis guepinii*	*Spondias mombin*	Phomopsichalasin	Alkaloids	Antimicrobial	Phongpaichit *et al*., 2007
Phomopsis sp.	*Garcinia dulcis*	Phomoenamide	Alkaloids	Antimicrobial	Rukachaisirikul *et al*., 2008
Cryptosporiopsis quercina	*Tripterygium wilfordii*	Cryptocin	Alkaloids	Antifungal	Li *et al*., 2000
Xylaria sp.	*Abies holophylla*	Griseofulvin	-	Antifungal	Park *et al*., 2005
Chaetosphaeridium globosum	*Ginkgo biloba*	Chaetomugilin A and D	Alkaloids	Antifungal	Qin *et al*., 2009
Verticillium sp.	*Rehmannia glutinosa*	Ergosterol peroxide	Steroids	Antifungal	You *et al*., 2009
Pichia guilliermondii Ppf9	*Paris polyphylla* var. *yunnanensis*	helvolic acid	Tritepanoid	Antibacterial	Zhao *et al*., 2010
Aspergillus niger IFB-E003	*Cyndon dactylon*	Rubrofusarin B, fonsecinone A, asperpyrone B and aurasperone A	-	Antimicrobial	Song *et al*., 2004
Aspergillus clavatonanicus	*Torreya mairei*	Clavatol	-	Antimicrobial	Huang *et al*., 2008
Acremonium zeae	*Zea maize*	Pyrro- cidines A and B	Alkaloids	Antifungal	Wicklow *et al*., 2005
Penicillium sp.	*Acrostichum aureurm*	Cyclo(Pro-Thr)	Peptides	Antibacterial	Cui *et al*., 2008
Nodulisporium sp.	*Juniperus cedre*	Ergosterol and 5α, 8α-epidioxyergosterol	Steroids	Antimicrobial	Dai *et al*., 2006
Alternaria alternate	*Euphorbia helioscopia*	Alternariol, alternariol methyl ether and tenuazonic acid	-	Antimicrobial	Ashour *et al*., 2011
Diaporthe helianthi	*Luehea divaricata*	2(-4 hydroxyphenyl)-ethanol (Tyrosol)	Phenolics	Antimicrobial	Specian *et al*., 2012
Alternaria sp. UFMGCB55	*Trixis vauthieri*	Altenusin	Phenolics	Antimicrobial	Cota *et al*., 2008
Aspergillus fumigates	*Juniperus communis* L.	Podophyllotoxin	Phenolics	Antimicrobial	Kusari *et al*., 2009
Penicillium sp.	*Camellia sinensis*	3-(3-azidopropyl)-1H-indene and 3-Cyano-1,2-dimethylindole	-	Antibacterial	Devi and Wahab, 2012
Phoma her-barum	*Aegle marmelos*	1-iodo-naphthalene	-	Antimicrobial	Kharwar *et al*., 2013
Fungal strain AL-2	*Aquilaria malaccensis* Lamk	1,7-dihydroxy-3-methoxyanthraquinone (I), Propyl *p*-methoxy-phenyl ether (II), 6-Methoxy-7-*O*-(*p*-methoxyphenyl)-coumarin (III)	-	Antibacterial	Shoeb *et al*., 2010
Phomopsis sp.	*Allamanda cathartica*	Terpene	Terpenoids	Antibacterial	Nithya *et al*., 2011
Endophytic fungus NFU/Hp/KF/34B	*Hypericum perforatum*	Hypericin	-	Antimicrobial	Kusari *et al*., 2008
Phomopsis cassia	*Cassia spectabilis*	Ethyl 2,4-dihydroxy-5,6-dimethylbenzoate" and "Phomopsilactone	-	Antifungal	Silva *et al*., 2005
Cladosporium sp.	*Quercus* v*ariabilis*	Brefeldin A	Aliphatic	Antimicrobial	Wang *et al*., 2007
Curvularia geniculata	*Catunaregam tomentosa*	Curvularide B	Peptide		Chomcheon *et al*., 2010
Pestalotiopsis sp.	*Rhizophora mucronata*	Pestalotiopsones	-	Antimicrobial	Beekman *et al*., 2013
Unidentified	*Ipomoea pescaprae* Linn.	Tetrahydroauroglaucin and Flavoglaucin	-	Antimicrobial	Chaipackdee *et al*., 2013
Trichothecium sp.	*Phyllanthus amarus*	Trichothecinol-A	-	Antifungal	Taware *et al*., 2014
Chaetomium globosum HYML55	*Hypericum mysorense*	Cytochalasan	-	Antimicrobial	Samaga *et al*., 2014

Anti-cancerous Bioactive Compounds from Endophytic Mycoflora

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); Debbab *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*., 2007). 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 etopophos phosphate 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).

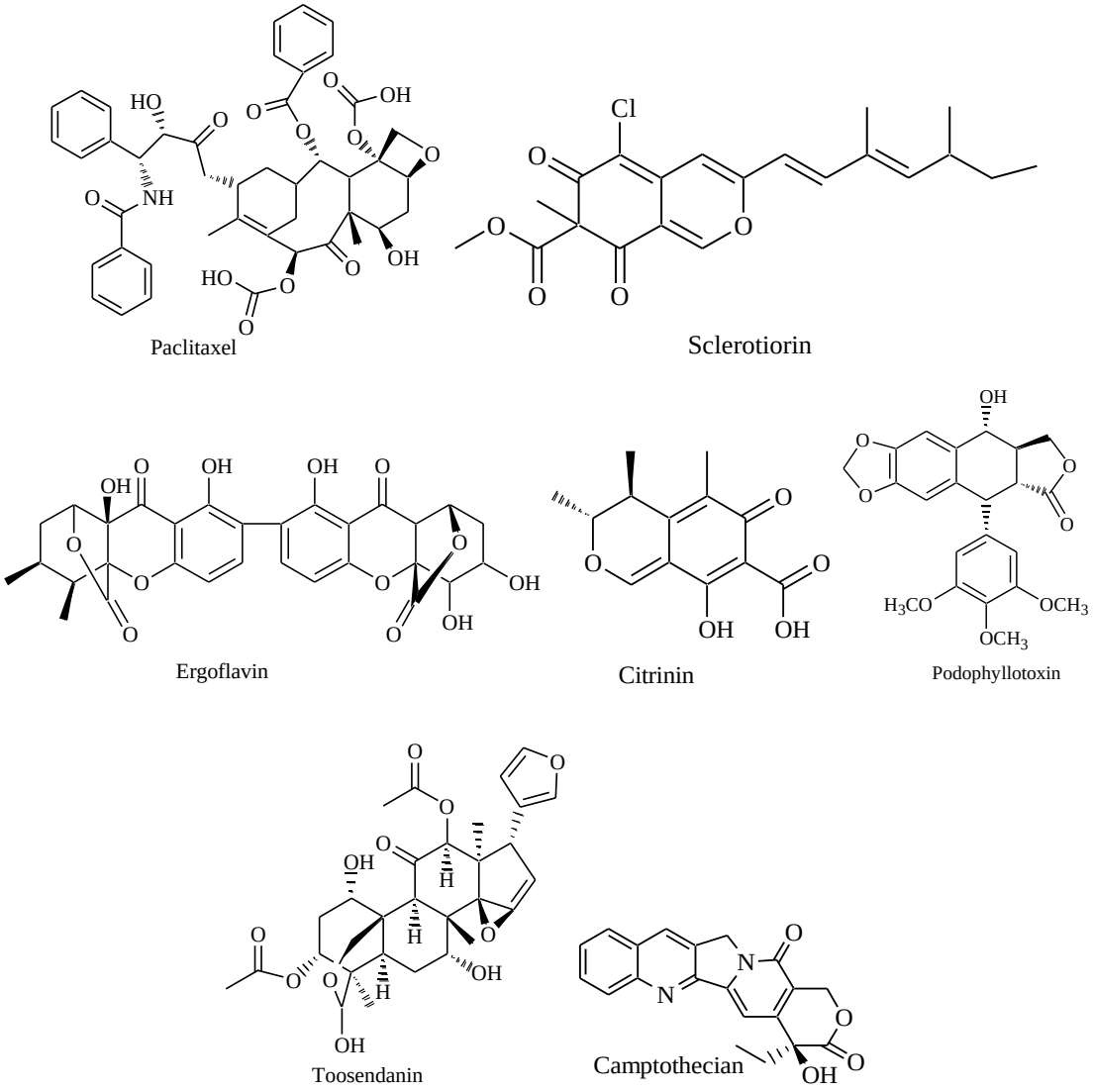


Fig. 2: Structures of Anti-cancerous Bioactive Compounds from Endophytic Mycoflora.

Table 2: List of some Anti-cancerous bioactive compounds from endophytic Mycoflora.

Isolated fungi	Host Plant	Compound	Class of substance	References
Taxomyces andreanae	*Taxus brevifolia*	Taxol (Paclitaxel)	Diterpenoid	Stierle 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 Y1117	*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
Ozonium sp. BT2	*Taxus chinensis* var. *mairei*	Taxol	Diterpenoid	Guo *et al*., 2006
Pestalotiopsis terminaliae TAP-15	*Terminalia arjuna*	Taxol	Diterpenoid	Gangadevi *et al*., 2009
Phyllosticta dioscoreae No.605	*Hibiscus rosa-sinensis*	Taxol	Diterpenoid	Kumaran *et al*., 2009
Bartalinia robillardodies	*Aegle marmelos*	Taxol	Diterpenoid	Gangadevi *et al*., 2009
Lasiodiplodia theobromae	*Morinda citrifolia*	Taxol	Diterpenoid	Pandi *et al*., 2011
Fusarium oxysporum	*Rhizophora annamalayana*	Taxol	Diterpenoid	Elavarasi *et al*., 2012
Fusarium solani	*Camptotheca acuminat*	Camptothecin	Alkaloid	Kusari *et al*., 2009
Entrophospora infrequens RJMEF 001	*Nothapodytes foetida*	Camptothecin	Alkaloid	Puri *et al*., 2005
Entrophospora infrequens 5124	*Nothapodytes foetida*	Camptothecin	Alkaloid	Amna *et al*., 2006
Fusarium solani MTCC 9667	*Apodytes dimidiate*	Camptothecin	Alkaloid	Shweta *et al*., 2010
Neurospora sp. ZP5SE	*Nothapodytes foetida*	Camptothecin	Alkaloid	Rehman *et al*., 2008
Aspergillus fumigates	*Juniperus communis* L.	Podophyllotoxin	Lignin	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.	*Diphylleia sinensis*	Podophyllotoxin	Lignin	Yang *et al*., 2003
Penicillium implicatum SJ21	*Diphylleia sinensis*	Podophyllotoxin	Lignin	Zeng *et al*., 2004
Trametes hirsute	*Sinopodophyllum hexandrum*	Podophyllotoxin	Lignin	Puri *et al*., 2006
Penicillium expansum	*Excoecaria agallocha*	Expansols A, B	-	Lu *et al*., 2010
Penicillium janthinellum	*Melia azedarach*	Citrinin	-	Marinho *et al*., 2005
Paecilomyces sp.	*Paris polyphylla* var. *yunnanensis*	Diosgenin	-	Cao *et al*., 2007
Aspergillus niger	*Cyndon dactylon*	Rubrofusarin B	-	Song *et al*., 2004
Cephalotheca faveolata	*Eugenia jambolana* Lam.	Sclerotiorin	-	Giridharan *et al*., 2012
Fusarium proliferatum	*Syzygium cordatum*	Eergosta-5,7,22-trien-3β-ol, 9-*O*-methyl fusarubin, Bostrycoidin, 4-naphthoquinone	-	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	Unidentified	α-glucosidase	Ramdanis *et al*., 2012
Dendryphion nanum	*Ficus religiosa*	Naphthaquinones	Mishra *et al*., 2013
Aspergillus sp. JPY1	*Salvadora oleoides* Decne	2, 6-di-tert-butyl-p-cresol and Phenol, 2, 6-bis (1, 1-dimethylethyl)-4-methy	Dhankhar 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 heterogenous complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulcerations due to tissues or vascular damages (Bastaki, 2005).

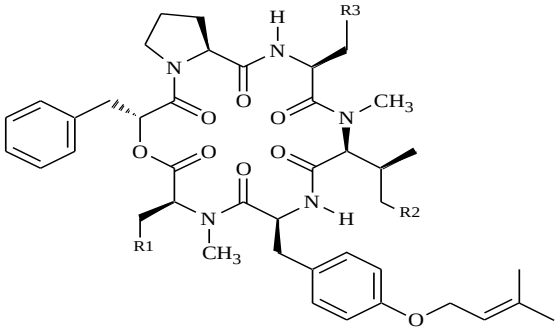
Dompeipen *et al.* (2011), pointed that endophytic microbe's ability to produce bioactive compounds in association with its host plants is an opportunity to get sources of anti-diabetic drugs, which as they are natural, inexpensive and ecofriendly. The α-glucosidation inhibitors were the most common 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 aloxon 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, Dhankhar 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-tert-butyl-p-cresol and Phenol, 2, 6-bis [1, 1-dimethylethyl]-4-methyl.

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	-	Ezra *et al*., 2004
Pullularia sp. BCC8613	*Quercus coccifera*	Pullularins 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 albindia*	Phomoarcherins A–C	Sesquiterpenes	Hemtasin *et al*., 2011
Fusarium sp.	*Mentha longifolia* L.	Integracides F and G	Triterpenoids	Ibrahim *et al*., 2016

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 human because it can cause acute infection that leads to death. This parasite infects human by female anopheles mosquito (Aryanti *et al.,* 2006). Endophytic fungi were also known as producers of many natural products of anti-malarial activities. Kongsaeree *et al.* (2003) also reported three novel dihydroisocoumarin 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 *Crassocephalum crepidioides*. Structures were established as 7-butyl-6,8-dihydroxy- 3(*R*)-pent-11-enylisochroman-1-one (A), 7-but-15-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 pullularin A, B and C **(Fig 3)** from culture of endophytic fungus *Pullularia* sp.



Pullularins A: R1= H, R2= CH_3, R3= OH
Pullularins B: R1= CH_3, R2= CH_3, R3= OH
Pullularins C: R1= H, R2= H, R3= OH

Fig. 3: Structure of Anti-malaria bioactive compound Pullularins A, B and C from endophytic Mycoflora.

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 µg/mL 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 Butyrolactone 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, phomonitroester and deacetyl phomoxanthone B, were isolated together with three known compounds, dicerandrol A, (1S,2S,4S)-p-menthane-1,2,4-triol and uridine. Phomoenamide exhibited moderate *in vitro* anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Ra (Rukachaisirikul *et al*., 2007).

The endophytic mitosporic *Dothideomycete* sp. LRUB20 fungus isolated from Thai medicinal plant *Leea rubra* produced dothideopyrones A–D (Pyrone derivatives) together, with seven known compounds. These compounds include questin, asterric acid, methyl asterrate, sulochrin, eugenitin, 6-hydroxymethyleugenitin, cis, trans-muconic acid, 3-nitropropionic acid **(Fig 4)**, asterric acid, a novel compound 2-hydroxymethyl-3-methylcyclopent-2- enone (synthetically known), cis-2-hydroxymethyl and 3-methylcyclopentanone which were inhibiting *Mycobacterium tuberculosis* H37Ra (Chomcheon *et al*., 2010). Gordien *et al.*,(2010) added that *Cladonia arbuscula*, endophytic fungus isolated from *Vaccinium myrtillus* and endophytes isolated from *Carlina vulgaris*, *Empetrum nigrum* and *Vaccinium vitis-idaea* showed inhibitory activities against *M. tuberculosis*. *Muscodor crispans* 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 crispans* 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.

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*	Phomoenamide	Alkaloid	Rukachaisirikul *et al*., 2007
PSU-N24	*Garcinia nigrolineata*	Hydronaphthalenones, Dihydroramulosin, griseofulvin desoxybostrycin and austrocortinin	Polyketides	Sommart *et al*., 2008
Fusarium solani	*Hypericum perforatum*	Hypericin	-	Kusari *et al*., 2008
Periconia sp.	*Piper longum* L.	Piperine (5-(3, 4-methylenedioxyphenyl)-1-piperidinopent-2, 4-dien-1-one)	Alkaloid	Verma *et al*., 2011
Alternaria alternate	*Indigofera enneaphylla*	Tenuazonic acid	Peptides	Sonaimuthu *et al*., 2011
Phomopsis stipata	*Stryap camparum*	Koninginins	Polyketides	Prince *et al*., 2011
Phomopsis longicolla	*Trichilia elegans* A. JUSS ssp. Elegans	3-nitropropionic acid	-	Flores *et al*., 2013

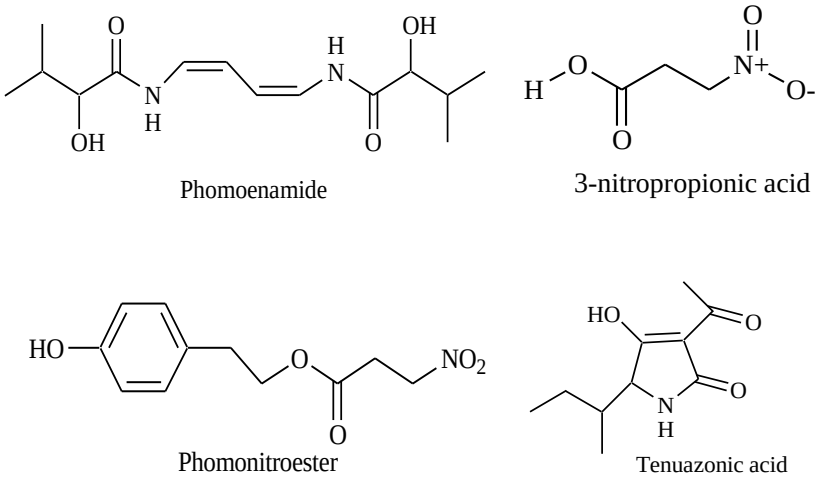


Fig. 4: Structures of some anti-tuberculosis bioactive compounds from endophytic mycoflora.

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-tridepside (Guo *et al*., 2000). Exploration of endophytes associated with leaves of *Quercus coccifera* led to the isolation of endophyte with the ability to synthesize hinnuliquinone, 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 (Pittayakhajonwut *et al*., 2005).

An endophytic fungus *Pestalotiopsis theae* **(Table 6)** of an unidentified tree on Jianfeng Mountain, China, was capable of producing Pestalotheol 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 IC_{50} 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 H1 N1 with IC_{50} values of 42.07 mg/mL and 62.05 mg/mL, respectively.

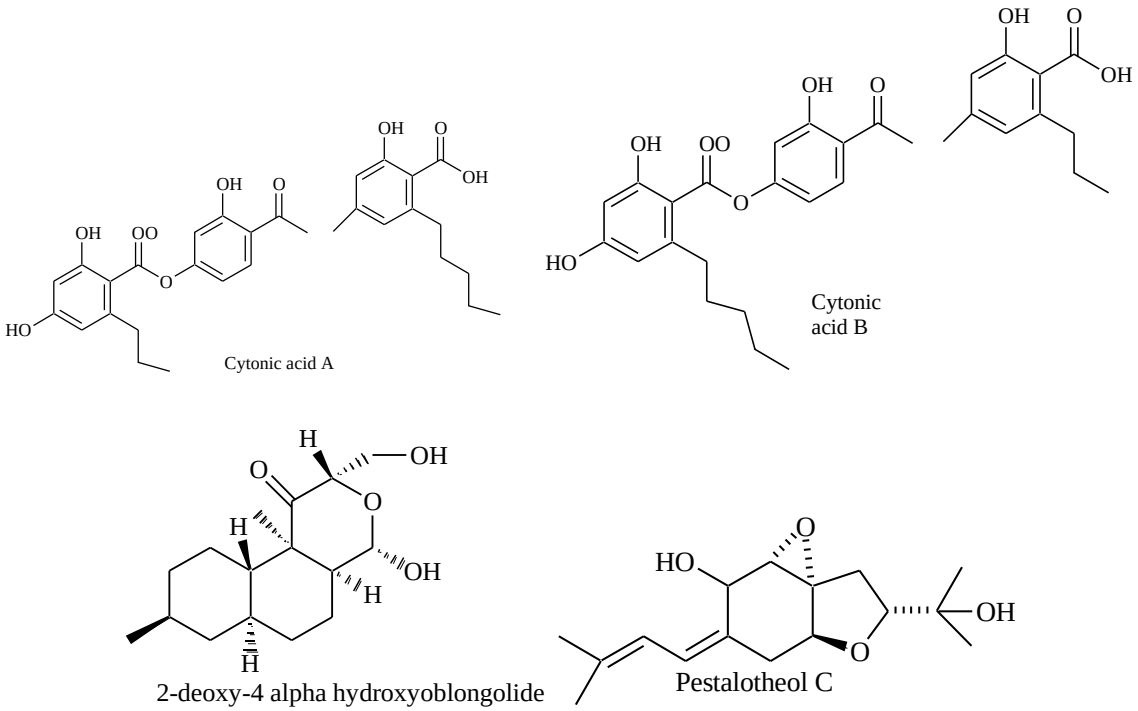


Fig. 5: Structure of some Anti-viral bioactive compounds from endophytic mycoflora

Table 6: List of some Anti-viral bioactive compounds from endophytic Mycoflora.

Endophytic fungi	Host plant	Bioactive compound	Activity	References
Cytonaema sp.	Unidentified	Cytonic acids A and B	Antiviral	Guo *et al*., 2000
Pestalotiopsis theae	Unidentified	Mellisol and 1,8- dihydroxynaphthol 1-O-a-glucopyranoside	Antiviral	Pittayakhajonwut *et al*., 2005
Pullularia sp. BCC 8613	Unidentified	Pullularin A	Antiviral	Isaka *et al*., 2007
Fusarium solani	*Hypericum perforatum*	Hypericin	Antiviral	Kusari *et al*., 2008
Pestalotiopsis theae	Unidentified	Pestalotheol C	HIV	Li *et al*., 2008
Pestalotiopsis fici	Unidentified	Chloropupukeanolides	HIV	Liu *et al*., 2010
Phomopsis sp.	*Musa acuminate*	Oblongolides Z and 2-deoxy-4α-hydroxyoblongolide X	Antiviral	Bunyapaiboonsri *et al*., 2010

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 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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