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A N I N T E R N A T I O N A L J O U R N A L

Endophytic Fungi as Novel Resources of natural Therapeutics

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ABSTRACT

Fungal endophytes constitute a major part of the unexplored fungal diversity. Endophytic fungi (EF) are an important source for novel, potential and active metabolites. Plant-endophyte interaction and endophyte –endophyte interactions study provide insights into mutualism and metabolite production by fungi. Bioactive compounds produced by endophytes main function are helping the host plants to resist external biotic and abiotic stress, which benefit the host survival in return. These organisms mainly consist of members of the Ascomycota, Basidiomycota, Zygomycota and Oomycota. Recently, the genome sequencing technology has emerged as one of the most efficient tools that can provide whole information of a genome in a small period of time. Endophytes are fertile ground for drug discovery. EFare considered as the hidden members of the microbial world and represent an underutilized resource for new therapeutics and compounds. Endophytes are rich source of natural products displaying broad spectrum of biological activities like anticancer, antibacterial, antiviral, immunomodulatory, antidiabetic, antioxidant, anti-arthritis and anti-inflammatory.

Key words: Endophytic fungi, Ascomycota, Natural products, Antidiabetic.

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INTRODUCTION

Endophytic fungi [EF] are organisms which live in all healthy plant tissues without signs of disease or morphological changes for at least part or the whole life cycle of the plant [1]. The existence of fungi inside the plants has been known since the end of the 19th century, and the term ‘‘endophyte’’ was first coined in 1866 by de Bary. EF has been associated with plants for over 400 million years [2]. An endophytic fungus lives in mycelial form in biological association with the living plant. EF are found in all kinds of plants, i.e. trees, grasses, algae and herbaceous plants. Endophyte and endophytic fungi have been frequently used to describe the internal mycota of living plants. EF are now considered as an important components of biodiversity [3,4].EF are highly diverse, with the reported majority being ascomycetes, also lack a of teleomorphic state [5]. In one survey it is estimated that over one million fungal endophytes exist in nature [6]. EF is an important source of novel, potential and active metabolites [7-12]. Bioactive compounds produced by EF main function are helping the host plants to resist external biotic and abiotic stress, which benefit the host survival in return. Plants lack immune response to certain pathogens, but the endophytes that reside inside the plant tissue enhance the immune response of the plants to fight against invading pathogens [13]. Plant EF has the ability to produce the same or similar kind of compounds of from their originated host plants. Fungal endophyte communities differ in species composition, host and tissue preference worldwide distribution and differ in the polyketide and synthesis and production of bioactive compounds [14]. In the last few years, considerable knowledge has been accumulated on the biology of endophytic microorganisms [15]. The study of endophytes distribution, biodiversity and their biochemical characteristics has huge importance in plant sciences to understand and to improve plant fitness [16]. Endophytes commonly increase plant biomass under stressful conditions but the cellular mechanisms involved in stress tolerance and growth enhancement are poorly characterized. EF are considered as an important components of biodiversity as the distribution of endophytic mycoflora differs with the host. The omnipresence of endophytic fungi symbiosis with the plant, the extent of their contribution to fungal biodiversity remains unclear [17]. Apart from the above mentioned myriad of activities for the protection of host plants EF play an important role to initiate the biological degradation of dead or dying host-plant, which is necessary for nutrient recycling. The ‘‘balanced antagonism’’ hypothesis [18] was initially proposed to address how an endophyte controls host defenses mechanisms to be activated against it, ensures self-resistance before being incapacitated by the toxic metabolites of the host, and manages to grow within its host without causing visible manifestations of infection or disease [19,20].

Plant-endophyte interaction

How does an endophyte manage to exist and grow within its host without causing visible disease symptoms? Is a complex and precisely controlled interaction. Endophyte-plant symbioses represent a broad continuum of interactions, from strong antagonisms to obligate mutualisms. Mutualisms are generally thought to have evolved from antagonistic interactions, mainly parasitic and the same has been assumed for fungal endophytes of grasses and woody plants. The continuum of antagonistic-mutualistic interactions for any two interacting species depends on phylogenetic and life history constraints, geography, interactions with other species in the community, and abiotic factors. Similarly, the complex microbial mutualisms with host plants vary along a continuum from pathogenic to mutualistic, even within the lifespan of the microorganism and host plant. Despite

the complexity and variability of EF-host plant interactions, evolutionary traits, Modes of reproduction and transmission to other hosts are now well recognized as important factors related to virulence and aggressiveness in disease-causing microorganisms—and ecological factors—such as condition of host, competition with other microorganisms, spatial structure of populations, and prevailing abiotic factors—permit predictions of where endophyte-plant associations are likely to fall along the continuum. Endophytes reside within plants and are continuously interacting with their hosts; it is conceivable that plants would have a substantial influence on the in plant metabolic processes of the endophytes. Although it has long been known that fungal secondary metabolites are crucial to the pathogenicity of many fungi only little experimental work has been done to study the role of secondary metabolites in the endophyte-host interaction. There are several physiological mechanisms of the endophyte-host interaction well understood and established but mechanisms that gave rise to the evolution of endophytism and the genetic basis of the endophytic habit are also poorly understood. It has been speculated that endophytic lineages have evolved several times from plant pathogenic ancestors. The 'endophytic continuum' model suggests that the outcome of the plant- fungus interaction which can range from mutualism to parasitism depends on the fungal species, the host genetic background and the environment.

Endophyte –Endophyte interactions

Many recent studies provide evidence that microbial interactions can play a major role in the onset of metabolite production in fungi and which may involve small, diffusible signalling molecules, such as quorum-sensing signals or other elicitors, which may trigger otherwise silent biosynthetic pathways. In microbial communities, potentially every natural product could have an impact on the metabolic profiles of the microorganisms sharing the same habitat. In endophytic communities, potentially every natural product could have an impact on the metabolic profiles of these microorganisms sharing the same habitat. The interesting fact is that, the interplay between endophytes within the plant results in significantly higher natural product diversity than what is observed in organism as individual. To study the communication and interaction between Endophyte –Endophyte we need emerging tools. Systems biology uses a multidisciplinary approach to study the multiple, complex interactions of and between organisms. The endophyte-endophyte differential gene expression can be revealed using various tools like suppression subtractive hybridization (SSH) technique, serial analysis of gene expression (SAGE), cap analysis of gene expression (CAGE) and massive parallel signature sequencing (MPSS).

General Classification

Endophytic fungi mainly consist of members of the Ascomycota [21] or their mitosporic fungi, as well as some taxa of the Basidiomycota, Zygomycota and Oomycota [22, 23] and Classification endophytic fungi and existence in plant cell (Fig.1). But there are also different ways of grouping fungal endophytes are suggested by [24] the transmission mode in particular, and distinguished between the endophytes of the Clavicipitaceae (clavicipitaceous endophytes) and the rest (non-clavicipitaceous endophytes). Several studies have demonstrated that various fungal endophytic interactions ranging from mutualistic to antagonistic, depending on host and endophyte genotype, and environmental conditions [25-29].

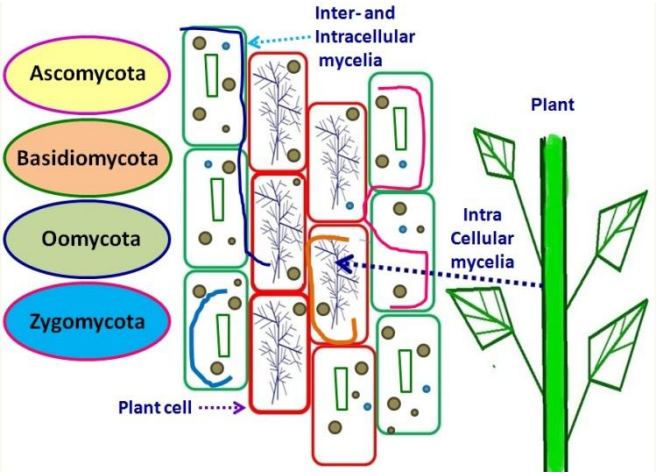

Figure. 1- Classification of endophytic fungi and existence in plant cell

Molecular studies and Phylogeny

Fungal taxonomy is traditionally based on comparative morphological features [30,31] but need take special caution for closely related or morphologically similar species. Mycologists facing tough task for to identify various EF at genera or species level because they mainly depends only on morphological characteristics and also very time-consuming process. More over significant portions of endophytic isolates consist of sterile mycelia and cannot be identified based on traditional approaches. The development of molecular biology brings a new perspective to endophyte diversity studies. Modern molecular techniques exhibit high sensitivity and specificity for identifying and classifying microbial strains at diverse hierarchical taxonomic levels [32]. Many phylogenetic studies involving fungi rely on the analysis of ribosomal DNA, in particular the internal transcribed spacer (ITS) regions, to assist in separation at the genus and species levels [33]. 18S and 28S genes are considered as identification markers in the identification of EF at high taxonomic levels [34]. The recently developed, high-throughput sequencing (pyrosequencing) enables metagenomic and metagenetic analyses and provides a powerful alternative to molecular studies of fungal community in natural environments [35]. Pyrosequencing has several advantages like inexpensive, rapid, free-cloning step and high productivity over Sanger sequencing technology [36]. This technique has been employed successfully in the study of fungal diversity in natural environments, such as phyllosphere fungi [37], clinical fungi [38], freshwater fungi [39], wood-inhabiting fungi [40], soil fungi [41] and mycorrhizal fungi [42]. DNA barcoding systems employ a short, effective and standardized gene region to identify species [43]. This method is advanced for screening of fungal endophytes, ideally, the DNA barcode region used should be a single locus for all groups of organisms across all kingdoms. ITS based DNA barcode approaches has many advantages, such as high successful amplification among all lineages of EF using universal primers, suitable fragment length, and a large number of available databases [44,45]. There are several disadvantages too in using ITS barcode like there are various inter- and intra-specific distances among the different fungal groups. There is another method which is cheap and fast simple sequence repeat (SSR) marker technique. A number of previous studies have demonstrated that ITS is insufficient for some species delimitation, especially in rapidly evolving or highly diverse genera [46].Denaturing gradient gel electrophoresis (DGGE) technique, which are capable of separating closely related sequences by their differential mobilities in a gradient of denaturants, have recently been successfully applied to document endophytic fungal

communities by excising and sequencing bands [47, 48]. (Table.1) list of endophytes isolated from host plant using Phylogeny analysis.

Table-1- list of endophytes isolated from host plant using Phylogeny analysis

Entophyte	**Host plant**	**Ref**
Muscodor albus	*Cinnamomum zeylanicum*	[49]
Alternaria, Cladosporium, Chaetomium, Curvularia, Drechslera ,Scopulariopsis,Acremonium, Aspergillus, C olletotrichum, Fusarium, Paecilomyces,Penicillium.	*Glycine max*	[50]
Alternaria sp., Colletotrichum sp., Phomopsis sp., Xylaria sp.,	*Artemisia capillaris, A. indica, and A. lactiflora*	[51]
Cladosporium sp., Acremonium sp., Trichoderma sp., Monilia sp., Fusarium sp., Spicaria sp., Humicola sp., Rhizoctonia sp., Cephalosporium sp., Botrytis sp., Penicillium sp., Chalaropsis sp. and Geotrichum sp.,	*Cephalotaxus mannii*	[52]
Fusarium solani	*Taxus baccata*	[53]
Stemphylium sedicola SBU-16	*Taxus baccata*	[54]
Fusarium sp., Nectria rigidiuscula	*Annona squamosa*	[55]
Fusarium oxysporum, Emericella nidulans	*Ipomea batatas*	[56]
Paraconiothyrium sp	*Capsicum annuum, Cucumis sativus, Glycine max*	[57]
Phomopsis sp.,, Diaporthe sp.,, Dothideomycete sp., Cordyceps sp.,	*Trichilia elegans*	[58]
Alternaria sp., Cladosporium sp., Curvularia sp., Fusarium sp., Phaeoacremonium sp., Trichoderma sp.,	*Aquilaria malaccensis*	[59]
Trichoderma sp.,	*Coffea arabica*	[60]
Trichothecium sp.,	*Phyllanthus amarus*	[61]
,Glomerella spp.,Diaporthae/Phomopsis sp., Alternaria spp., Cochliobolus sp., Cladosporium sp., Emericella sp.,	*Aegle marmelos, Coccinia indica , Moringa oleifera*	[62]
Acremonium sp., Colletotrichum sp., Cochliobolus sp., Fusarium, Hypocrea sp., Nemania sp.	*Lycium chinense*	[63]
Colletotrichum sp., Curvularia sp., Fusarium sp., Phomopsis sp., Verticillium sp., Fusarium sp., Phomopsis sp.	*Tabernaemontana heyneana*	[64]
Alternaria sp., Phomopsis magnoliae	*Artemisia argyi.*	[65]
Acremonium *sp.,* Penicillium *sp.,*	*Gossypium hirsutum*	[66]
Trichoderma brevicompactum	*Allium sativum*	[67]
Sporidiobolus sp., Rhodotorula sp., Pilidium concavum, Corynespora cassiicola, Neodeightonia subglobosa, Aspergillus awamori, Aspergillus sp.	*Fragaria x ananassa*	[68]
Epichloë festucae	*Festuca rubra*	[69]
Pestalotiopsis fici	*Camellia sinensis*	[70]
Aspergillus niger , Bipolaris maydis, Meyerozyma guilliermondii, Fusarium verticillioides	*Ocimum sanctum*	[71]
Aspergillus sp., Penicillium sp., Unidentified Eurotiomycete belong to Eurotiomycetes sp., Acremonium sp., Colletotrichum sp., Fusarium sp., Nodulisporium sp., Pestalotiopsis	*Marchantiapolymorpha*	[72]
Fusarium proliferatum, Fusarium sp., *F. solani, Curvularia lunata, Trichoderma atroviride, Calonectria gracilis, Rhizoctonia solani, Bionectria ochroleuca*	*Musa acuminata*	[73]
Penicillium chrysogenum, P. chrysogenum, Fusarium oxysporum, F. nygamai	*Tamarix nilotica, Cressa cretica*	[74]

Diaporthe sp.,, Colletotrichum sp.,, Nigrospora sp., Botryosphaeria sp., Aspergillus sp., Penicillium sp., Neofusicoccum sp., Cercospora sp., Rhizoctonia sp., Alternaria sp., Curvularia sp.,	*Artemisia lavandulifolia, A. tangutica, A. brachyloba, A. subulata, A. argy A. scoparia*	[75]
Penicillium polonicum	*Huperzia serrata*	[76]
Diaporthe ampelina	*Commiphora wightii*	[77]
Emericella qaudrilineata (RS-5):	*Pteris pellucida*	[78]
Chaetomium globosum	*Nymphaea nouchali*	[79]
Aspergillus sp., Chaetomium sp., Curvularia sp., Dreschelara sp., Fusarium sp., Penicillum sp., Colletotrichum sp., Nigrospora sp., Pestalotiopsis sp. and Phyllosticta sp.	*Hugonia mystax*	[80]
Aspergillus nidulans, Aspergillus oryzae.	*Ginkgo biloba*	[81]
Phomopsis theicola	*Litsea hypophaea*	[82]
Fusarium sp.,	*Honeysuckle*	[83]
Aspergillus flavus	*Solanum nigrum*	[84]
Pestalotiopsis clavispora,	*Dendrobium officinale*	[85]
Trichoderma-Hypocrea, Penicillium Phialemonium.	*Balanophora japonica*	[86]
Trichoderma sp., Aspergillus sp., Rhizopus sp., Cladosporium sp., Alternata sp., Penicillium sp., Chepalosporium sp.	*Toona sinensis*	[87]
Cladosporium cladosporioides, Aspergillus ochraceus, Aspergillus niger, Aspergillus flavus, Penicillium citrinum, Monascus ruber, Fusarium semitectum, Fusarium sp., Fusarium sp.	*Corn cob*	[88]
Fusarium solani	*Phaius tankervilleae, Dendrobium lancifolium, Calanthe triplicata*	[89]
Talaromyces amestolkiae	*Kandelia obovata*	[90]

Proteomic analysis

Proteins secreted by fungal hyphae play an important role in the plant cell during symbiosis these molecules used in establishing and maintaining a successful symbiotic relationship among them. Proteomics appears as a powerful tool (Fig.2) to gain a global picture and our perception of plant–microbe interactions. 2-Dimentional Electrophorisis (2-DE) is a tool used to compare infected and noninfected plant proteomes it also provides a way of identifying plant and fungal proteins differentially regulated in this symbiosis [91]. Proteins were extracted from *Undifilum oxytropis* and analysed using 2-DE and liquid chromatography tandem mass spectrometry (LC-MS/MS) [92] and found large group proteins were related to stress and heat shock proteins. EST-based approach was used for identification of proteins from filamentous fungal endophyte based on [93]. Protein extraction was followed according to [94] and further 2-DE analysis was done for the proteins of *Piriformospora indica* [95].

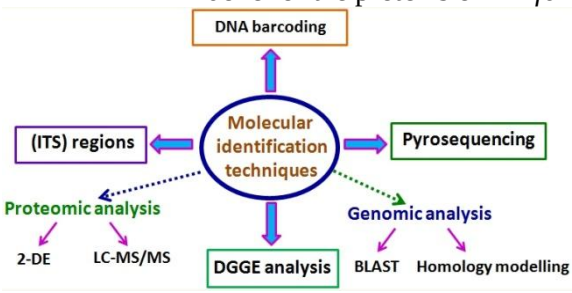

Figure. 2- Proteomic and genomic tools for analysis of endophytic fungi

Genomic analysis

The field of fungal genomics and with that of eukaryotic genomics, started with the report on the complete sequence of the yeast *S. cerevisiae* [96]. Recently, the genome sequencing technology has emerged as one of the most efficient tools that can provide whole information of a genome in a small period of time. Identification of genes expressed during different phases of endophytism such as pre-penetration, plant tissue penetration and plant colonization is important task for the fungal genomics. The rapid development in molecular biology and genomics in the recent advances offers a lot of scope for unraveling the various facets of the ecology and phylogenetics for the horizontally transmitted endophytes. Now a day's Genomic analysis was done by BLAST search, Homology modeling tools.

Fungal sources as natural products

Endophytes constitute a major part of the unexplored fungal diversity. Natural products derived particularly from medicinal plants have been exploited for human use for thousands of years to make human life easy. Endophytes are fertile ground for drug discovery. Establishment of fungal repositories from various ecological niches is an important step towards tapping their potential values for novel drug discovery. EF are considered as the hidden members of the microbial world and represents an underutilized resource for new therapeutics and compounds. Fungal Secondary metabolites are defined as low molecular weight compounds not required for growth but they are produced as an adaptation for specific functions in nature. There is an ongoing need for novel drugs that are highly effective in the treatment of cancer, drug resistant bacteria, and fungal infections. Reviews, patents, and original research articles on isolation and identification of metabolites from EF are rapidly growing in this modern field of drug discovery [97].Recently, several studies have led to the discovery of important plant secondary metabolites from EF thus raising the prospect of using such organisms as alternative sources of these metabolites [98].

Endophytes are rich source of natural products displaying broad spectrum of biological activities. They produce diverse groups of metabolites such as (Fig.3) steroids, xanthones, phenols, isocoumarines, perylene derivatives, quinones, furandiones, terpenoids, depsipeptides and cytochalasine, polyketides, alkaloids, peptides, proteins, lipids, shikimates, glycosides, isoprenoids [99].The secondary metabolites produced by endophytes associated with medicinal plants can be exploited for curing many diseases. EF are a poorly investigated group of microorganisms that represent an abundant and dependable source of bioactive and chemically novel compounds. Several attempts have been made to isolate and identify various bioactive metabolites from endophytic fungi. EF can grow in small to large fermenters to provide sufficient supply of bioactive compounds and thus can be exploited commercially. Presently there is a huge potential for endophytes biologically active natural products which are useful not only in medical but extended to agricultural and industrial application. Now a day's these enzymes are used in energy, food, paper, textile, cosmetics, fine chemicals, biomaterials, leather, cellulose and detergent industries. Bioprospecting of microbes is carried out from every possible source, including extreme environments like ocean beds, geothermal vents, cold desserts etc., in search of novel strains with promising bioactivities [100, 101]. Endophytes produce low molecular weight and volatile organic compounds (VOCs) [102] such as alcohols, ketones, esters, acids, and hydrocarbons typically derived from either biosynthetic or degradative pathways. VOCs attracted interest for a variety of

potential applications, including use as characteristic markers of fungal growth in the built environment (e.g., workspaces and residential structures) [103] and volatile antibiotics [104,105].

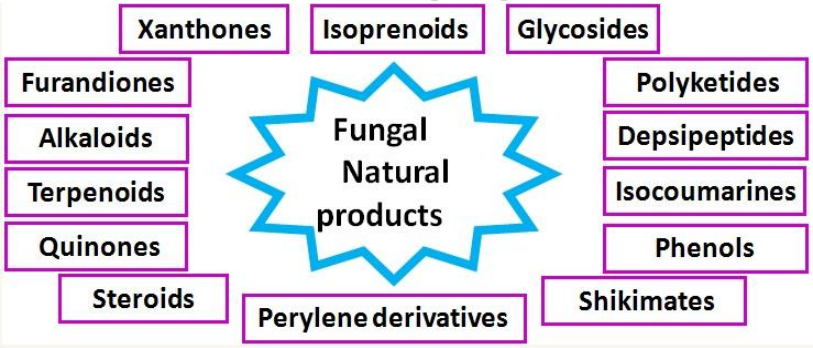

Figure. 3- Different groups of fungal metabolites

Antibacterial substances of endophytic origin

Emergence of multidrug-resistant (MDR) microorganism infections has generated considerable attention in recent decades [106, 107]. The problem of drug-resistant pathogens and infectious diseases are growing enormously. Antibiotic resistance is one of the greatest challenges facing modern medicine [108]. New problems demand the discovered of novel antibiotics from fungal source. *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus faecium* (VREF), have developed resistance toward current antibiotics. Antibiotics that lose their effectiveness for treating human disease through antibiotic resistance in this scenario old therapeutics must be replaced with new drugs [109].Metabolites produced from endophytes were reported to inhibit the growth of micro-organisms in host. The world recognized that fungal endophytes with novel metabolites biologically active against various resistant human pathogens. The World Health Organization (WHO) estimated that one-third of the world's human population is infected with *Mycobacterium tuberculosis* (MT) [110].Due to the emergence of multi-drug resistant of *M. tuberculosis* bacteria there is an urgent need to discover and develop new and non-toxic therapeutic agents from natural sources. Phomapyrrolidones A-C isolated from Phoma sp. NRRL 46751 showed antitubercular activity[111]. [112]Isolated Alterporriol-type dimers from the mangrove endophytic fungus, *Alternaria* sp. (SK11) and the compound Atropisomer 2 exhibited strong inhibitory activity against MT. [113] Investigated natural compounds from *Annulohypoxylon ilanense* of medicinal plant Cinnamomum species against MT. Recently, there have been an increasing number of articles on the research of EF producing antimicrobial substances [114]. Since the discovery of penicillin saved billions of lives and played an important role in human history. There are numerous reports on antimicrobial activity of EF isolated from various plant sources are presented in (Table.2).

Table-2- list of endophytes isolated from host plant against bacterial species

Host plant	Endophyte	Target bacteria	Ref
Camptotheca acuminata	*Nigrospora, Diaporthe, Alternaria, Colletotrichum, Pestalotiopsis, Sordariomycete, Guignardiai, Penicillium, and Zythia*	*P, solanacearum and Ralstonia solanacearum*	[115]
Smallanthus sonchifolius (yacón)	*Papulaspora immersa* and *Arthrinium* state of *Apiospora*	*S, aureus , Kocuria rhizophila P, aeruginosa*	[116]

	montagnei Sacc *Pichia guilliermondii*		
Paris polyphylla var. yunnanensis		*B. sublitis, Clavibacter michiganensis, E. coli, H. pylori, Micrococcus lysoleikticus, P. aeruginosa, Sarcina lutea, Staphylococcus aureus, Streptococcus lactis, fungi (i.e. Alternaria brassicae, Botrytis cinerea, C. albicans, Colletotirchum gloeosporioides, F.graminearum, Phytophthora capsici* and *Valsa mali*	[117]
Sesbania grandiflora (L.) Pers., .	*Fusarium* sp, *Phaeoacremonium* sp., *Acremonium* sp., *Cladosporium* sp	*Staphylococcus aureus, B. subtilis, E.coli, Pseudomonas, Aeruginosa, C. albicans* and *Cryptococcus neoformans*	[118]
Vitex negundo Linn,	*Colletotrichum gloeosporioides Penz., Phomopsis archeri B. Sutton, A. flavus gr., Nigrospora sphaerica(Sacc.)Mason, Colletotrichum gloeosporioides Penz., Phomopsis sp. aff. P. archeri B. Sutton, Alternaria raphani JW Groves &skolko, Mucor hiemalis Wehmer, Monodictys paradoxa (Corda) Hughes, Mucor hiemalis Wehmer, Nigrospora state of Khuskia oryzae H.J. Hudson*	*B. subtilis S. aureus, B. Cereus, E. coli, Klebsilla pneumoniae* and *S. typhimurium*	[119]
Ricinus communis (Aurundi)	*A. fumigates, A. japonicas, A. niger, Fusarium semitectum, Curvularia pallescens, Phoma hedericola, Alternaria tenuissima, F, solani, Drechslera australien and A. repens*	*B,subtilis, Enterococcous sp., K, pneumoniae, E, coli, S. typhimurium and S. aureus*.	[120]
Achyranthes aspera, Adhatoda zeylanica, Aegle marmelos, Leucas aspera, Azadirachta indica	*Aspergillus flavus, Cladosporium sp., Xylaria sp. Adhatoda zeylanica Aspergillus sp., Chaetomium spirale, Curvularia clavata, Penicillium sp. Alternaria alternata, Aspergillus fumigatus, Aspergillus niger, Chaetomium globosum, Cladosporium sp.,*	*Bacillus cereus, Bacillus subtilis , Escherichia coli, Klebsiella pneumoniae, Proteus sp, Pseudomonas sp, ,Salmonella typhi, Staphylococcus aureus, Streptococcus pyogens*	[121]

	Fusarium oxysporum, Nigrospora oryzae, Penicillium sp., Pestalotia macrotricha, Phomopsis sp., Rhizoctonia sp., Stenella agalis, Trichoderma sp., Verticillium sp., Acremonium sp., Cladosporium sp., Curvularia lunata, Fusarium oxysporu, Fusarium solani, Nigrospora oryzae, Pestalotiopsis sp., Phoma eupyrena, Phyllostica sp., Trichoderma sp., Verticillium albo-atrum Alternaria sp., Colletotrichum sp., Fusarium sp., Spicaria sp., Stemphylium sp		
Baccharis trimera .	*Epicoccum* sp., *Pestaloti opsis* sp. , *Cochliobolus lunatus,* and *Nigrospora* sp	Not specified	[122]

Antifungal activity

Little-studied groups of fungi are considered to be potential sources of novel natural products for medicine and agriculture [123]. The function of invasive fungal infections has increased significantly during cancer organ transplantation, chemotherapy and bone marrow transplantation. Endophytes are presumably ubiquitous in plants, with populations dependent on host species and location. During long research only a few numbers of antifungal agents are available for the treatment of various life threatening fungal infections. The search for new antifungal agents to overcome the growing human problems of drugs resistance in microorganisms is growing. Ongoing global efforts to discover new compounds from EF of medicinal plants are yielding valuable results [124]. Compounds produced by EF are being recognized as a versatile arsenal of antifungal agents. Many EF have been reported to have fungicidal activity are listed (Table.3).

Table -3 list of endophytic fungal activity against fungi

Endophyte	Host plant	Target fungi	Ref
Hormonema sp.	*Juniperus communis*	*Aspergillus fumigates* and *Candida* sps	[125]
Alternaria sp.		*Paracoccidioides brasiliensi* and *Schizosaccharomyces pombe*	[126]
Phaeosphaeria nodorum	*Prunus domestica*	*Monilinia fructicola, Colletotrichum gloeosporioides*	[127]
Chaetomium globosum No.04	*Ginkgo biloba*	*Rhizopus stolonifer Coniothyrium diplodiella.*	[128]
Colletotrichum truncatum, Nigrospora	*Jatropha curcas*	*Fusarium oxysporum, Sclerotinia sclerotiorum*	[129]

oryzae, Fusarium proliferatum, Guignardia cammillae, Alternaria destruens, and *Chaetomium sp*			
Pestalotiopsis mangiferae	Mangifera indica	*Candida albicans*	[130]
Trichoderma brevicompactum	*Allium sativum*	*Fusarium oxysporum, Colletotrichum lindemuthianum, C. ampelinum, Rhizoctonia solani, Botrytis cinerea*	[66]
Colletotrichum gloeosporioides	*Michelia champaca*	*Cladosporium cladosporioides, C. sphaerospermum*	[131]
Botryosphaeria dothidea	*Melia azedarach*	*Alternaria solani*	[132]
Chaetomium, Zopfiella, Fusarium, Purpureocillium, Arthrinium, Nigrospora, Eurotium, Aspergillus, Penicillium, Neosartorya, Talaromyces, Alternaria, Curvularia, Leptosphaerulina, Bipolaris, Periconia	*Tephrosia purpurea*	*Sclerotinia sclerotiorum, Phytophthora parasitica var. nicotianae, Phytophthora melonis, Botrytis cinerea, Colletotrichum gloeosporioides, Rhizoctonia solani*	[133]
Phomopsis quercella	*Cephalotaxus hainanensis*	*Rhizoctonia solani, Fusarium oxysporum*	[134]
Alternaria alternate, Aspergillus flavus, A.terreus , A.niger	*Suaeda maritima , Suaeda monoica.*	*Trichophyton rubrum*	[135]
Not specified	*Ocimum sanctum, Aloe vera*	*Rhizoctonia solani, Fusarium oxysporum, Colletotrichum falcatum and Helminthosporium maydis.*	[136]
Curvularia lunata	***Cymbopogon caesius***	*Candida albicans , Trichophyton rubrum*	[137]
Xylaria sp. strain PB3f3	*Haematoxylon brasiletto*	*Alternaria solani, Fusarium oxysporum*	[138]
Alternaria solani	*Heptacodium miconioides*	*Rhizoctorzia solani, Valsa mali*	[139]
Alternaria, Aureobasidium,	*Cactus Opuntia*	*Opuntia humifusa*	[140]

Cladosporium, Cryptococcus, Curvularia, Diaporthe, Epicoccum, Paraconiothyrium, Pestalotiopsis and *Phoma*	*humifusa*

Antiviral compounds

The discovery of the potential antiviral compounds from EF is still in its infancy. There is only limited number of compounds reported as antiviral agents from fungal endophytes. The main limitation to antiviral compound discovery is most probably related to the absence of antiviral screening systems. Altertoxins was isolated [141] from *Alternaria tenuissima* QUE1Se have HIV-1 virus activity. Several hundred endophytic fungal extracts were evaluated on HIV-1 replication in T-lymphocytes, and out of that four extracts are non-toxic and exhibited inhibitory with the range of 75% to 99% and out of three of these extracts were fractionated and fraction DB-2 completely inhibited HIV-1 replication at concentration that was also found it is not cytotoxic [142] . In antiviral activity was reported against influenza A viral (H_1N_1) [143] for the compounds emerimidine (A, B) ,emeriphenolicins (A,D), aspernidine (A , B) austin, austinol, dehydroaustin, and acetoxy dehydroaustin for *Emericella* sp.(HK-ZJ) which is isolated from of plant *Aegiceras corniculatum.* A source of several natural products has been in the endophytic fungi that live within desert plants. [144] purified coumarins from Alternaria Species in *Calophyllum inophyllum.* Endophytes *Aspergillus, Curvularia, Fusicoccum, Guignardia, Muscodor, Penicillium, Pestalotiopsis,* and *Phomopsis spp* isolated [145] from Garcinia plants and evaluated against Herpes simplex virus type 1 (HSV-1 ATCC VR-260) and most of fungi exhibited weak to moderate antiviral activity against. EF isolated [146] from 81 thai medicinal plant species out of 582 pure isolates obtained 40 species have strong anti-viral activity against HSV-1.

Anticancer substances

Cancer is a group of diseases that can affect various organs of the body, and is characterized by the uncontrolled growth of abnormal cells and lead to death. It is a major cause of death worldwide. So far chemical inhibitors of carcinogenesis are mostly kinase inhibitors in the form of small molecules, antibodies and organic chemicals. The research and development of anticancer drugs is expensive which places a high financial burden on individual healthcare costs and government budgets. Medicinal plants are being reduced significantly due to over-harvesting, illegal exploitation and destruction of ecological habitat [147] to conserve endangered medicinal plants and need to develop new alternative resources for harvesting anticancer compounds from plants. Anti-cancer drugs of natural products from EF are of are cheap and great value. The EF has been recognized as a possible useful source of bioactive secondary metabolites, especially in anticancer application [148]. More than 60% of the anticancer and 70% of the antimicrobial drugs and compounds are currently in clinical use are natural products or natural product derivatives. There is an increase in need for a universal natural bioactive compound that can be used to suppress carcinogenic growth potential [149]. Likewise, there are large numbers of anticancer agents produced by fungal endophytes inhabiting different medicinal plants. For the sake of convenience, some of the endophytic fungi showed anticancer activity against cell lines are presented in the form of a table (Table.4).

Table- 4 list of endophytic fungi against Cell lines

Plant and Endophytic fungi	Targeted Cell lines	Ref
Xylopia aromatic/Periconia atropurpurea	HeLa and CHO	[150]
Cynodon dactylon/Aspergillus fumigates	K562	[151]
Terminalia arjuna/Pestalotiopsis terminaliae	BT220, H116, Int 407, HL 251 and HLK 210	[152]
Morinda citrifolia* Linn/*Botryodiplodia theobromae	Breast cancer	[153]
Aquilaria sinensis (*3087095)*	human -HepG2, MCF7, SKVO3, HL-60, and 293-T	[154]
Cephalotheca faveolata	Colon cancer HCT-116	[155]
Undaria pinnatifida/ Guignardia sp	KB	[156]
Sonneratia caseolaris/ Bionectria ochroleuca	L5178Y	[157]
Barringtonia acutangula/ Colletotrichum gloeosporioides	HT29	[158]
Astragalus lentiginosus /Emericella sp. AST003	SF-268 and MDA-MB-231	[159]
Ocimum tenuiflorum/Penicillium citrinum	L5178Y	[160]
Taxus chinensis/Perenniporia tephropora	HeLa, SMMC-7721and PANC-1	[85]
Dysoxylum binectariferum/Fusarium proliferatum	HCT-116 and MCF-7	[161]
Cinnamomum mollissimum	P388	[162]
Artemisia lactiflora	HL-60 , MCF-7 and COLO205	[163]
Ajuga decumbens/Myrothecium roridum	HepG2	[164]
Bacopa monnieri	HCT-116, MCF-7, PC-3 and A-549	[165]
Pongamia pinnata/Phomopsis glabrae	Not specified	[166]
Phyllanthus amarus/Trichothecium sp	HeLa and B16F10	[61]
Morinda citrifolia Linn.	LU-1 (lung), PC-3 (prostate), and MCF-7 (breast)	[167]
Catharanthus roseus/Talaromyces radicus	HeLa cells	[168]
Pogostemon cablin/Bipolaris sorokiniana A606	MCF-7, NCI-H460, SF-268 and HepG-2	[139]

Immune suppressive drugs

Large number of novel immunomodulatory compounds has been isolated from endophytic fungi. Since long years intensive search is going for the identification of effective agents to deal with immunological disorders related to mainly graft rejection and various other autoimmune diseases. The modulation of immune response with the aid of various bioactives in order to alleviate certain diseases is an active area of interest. There is a huge potential for production of these drugs from the alternative source and one of them could be endophytes. Microbial endophytes mimic the bioactive compounds as produced by the plant itself thus making them a promising source of novel compounds. *Entrophospora infrequens* isolated from *Nothapodytes foetida* (Wight) Sleumer and their chloroform (CEEI) and methanolic extracts showed delayed type hypersensitivity (DTH) reaction [169], and further screened for plaque forming cell phagocytic response and haemagglutination antibody titre (IgM and IgG). Three were compounds isolated from *Pestalotiopsis leucothës* from plant *Tripterygium wilfordii*, and evaluated and found variable effects on T- and B-cells and monocytes [170]. Out of several isolates and their extracts of *Pestalotiopsis leucothës*, *Muco*r sp. *Verticillium* sp. and *Pestalotiopsis disseminate* from *Tripterygium wilfordii* Hook stimulated proliferation of human peripheral blood mononuclear cells (PBMC) was reported by [171]. [172] Isolated fractions from root fungal endophytic of Tulsi (*Ocimum sanctum* Linn.) and screened for *In vitro* immunomodulatory activities on the functions of human polymorphonuclear (PMN) cells such as phagocytosis.

Tripterygium wilfordii, produces subglutinol A and diterpene pyrones with showed immunosuppressive activity [173]. Taxol (paclitexel) is an important anticancer drug used widely in the clinical field isolated from EF of *Pestalotiopsis microspora*, bark of Himalayan yew *Taxus brevifolia* [174, 175]. .

Antidiabetic activity

The nature has provided abundant natural resources which can be explored for their medicinal uses. Diabetes, often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both [176]. Nowadays diabetes is growing as important serious public health problem, particularly in developed countries as a major threat to global development. We need to find natural and effective antidiabetic drugs. Several researchers are investigated antidiabetic and hypolipidemic activity of EF [177, 178]. [179] isolated antidiabetic peptide from EF Aspergillus awamori from medicinal plant Acacia nilotica and its purified compound was further identified using HPLC. Lectin (N-acetylgalactosamine, 64 kDa) was isolated from EF, Alternaria species from plant Viscum album tested for In vitro and in vivo antidiabetic activity on rats [180].14 endophytic fungi isolated from Taxus sumatrana and tested for alpha-glucosidase inhibitor activity[181].

Antioxidant activities

Antioxidants have become the topic of interest recently. The field of free radical chemistry is gaining more attention now a days. Free radicals are reactive oxygen and nitrogen species which are generated by various physiological processes in the body. Uncontrolled generation of free radicals leads to attack on membrane lipids, proteins, enzymes and DNA causing oxidative stress and ultimately cell death. These ROS are responsible for many degenerative human diseases like neurodegenerative disorders, cancer, Alzheimer's disease, ageing, Parkinson's disease, diabetes mellitus, atherosclerosis, and inflammatory diseases. Protection against free radicals can be enhanced by taking sufficient amounts of exogenous antioxidants. An antioxidant is a stable molecule which donates an electron to a rampaging free radical and terminates the chain reaction before vital molecules are damaged. Dietary antioxidants, including polyphenolic compounds, vitamin E and C are believed to be the effective nutrients in the prevention of oxidative stress related diseases. Fungal endophytes represent an abundant and dependable source of novel antioxidant compounds [182-184]. Lot of studies were conducted as antiviral, anticancer, antidiabetic and antimicrobial effects to test the potential effects of fungal endophytes, but very few scientists worked on their antioxidant capacity [185,186]. [187] was conducted antioxidant properties using EF *Phyllosticta* sp. which is isolated from medicinal plant *Guazuma tomentosa* and also quantified phenol and flavonoid content. Antioxidant was screened [188] with the 2,2'-azinodi(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) decolorization assay and 2,2'-diphenyl-1-picrylhydrazyl (DPPH) found this EF have potential novel source of natural antioxidants. Antioxidant was screened for EF in medicinal plants *Rhodiola crenulata, R. angusta, and R. sachalinensis* [189]. DPPH, FRAP, and Iron chelating activity are conducted using endophytes *Asperigillus niger , Penicillium sp.* and *Trichoderma sp.* [190]. Antioxidant compounds isolated from *Acremonium sp* identified as sesquiterpene 3,5-dihydroxy-2,5-dimethyltrideca-2,9,11-triene- 4,8-dione findings based on spectroscopic data, including 1 H-NMR, 13C-NMR, HMQC, HMBC, and COSY [191].

Antiarthritis and Anti-inflammatory activities

Historically, the best resources for novel scaffolds have always been natural products. Immune system of our body plays a crucial role, as an overactive immune system may lead to certain fatal disease like arthritis. Rhematoid arthritis(RA) is chronic, inflammatory, and systemic autoimmune disease, symptoms include pain, swelling, and destruction of cartilage and bone as a result of which permanent disabilities occur but the exact etiology is unknown. Nowadays, researcher shows a great interest in those finding medicinal agents that are derived from microbial source because of the currently available drugs are either have certain side effects or are highly expensive [192]. Endophytic fungi *Talaromyces wortmannii* isolated from medicinal plant *Aloe vera* and further seperated as several pure substances and out of that component C showed potent anti-inflammatory activity and this ability was gained for this metabolite is due to inhibition of IL-8 release by blocking NF-κB and AP-1 activation[193]. Compound Mutolide was isolated from the coprophilous fungus *Lepidosphaeria* sp. (PM0651419) and showed good anti-inflammatory activity and in future it can be used as druggable candidate for the treatment of inflammatory diseases like RA[194]. The primary purpose for such broad-based screening of endophytic fungi was to identify novel inhibitors of pro-inflammatory cytokines involved in various immunological pathways. Ergoflavin a pigment isolated from EF which is growing on the leaves of an Indian medicinal plant *Mimosops elengi* (bakul) showed good anti-inflammatory activity [195]. Endophytes alternative to chemical comounds which are shown excellent anti-inflammatory and various biological activities (Figure. 4).

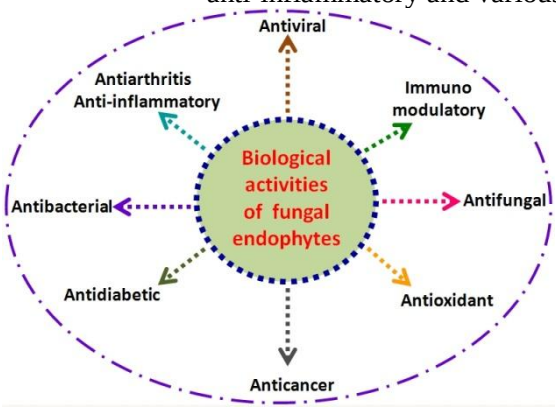

Figure. 4 Biological activities of fungal endophytes

CONCLUSION

Endophytic fungi can produce same or similar compounds originated from their host plants. Endophytic microorganisms are a huge reservoir of genetic diversity. Insights gained into endophyte-endophyte and plant-endophyte communication can be beneficial to biomedical community and the endophyte synthesized and secreted chemicals can be of importance to the society for the development of novel antibiotics against deadly pathogens. However, only a few numbers of antifungal agents are now available for the treatment of various life threatening fungal infections. There is an ongoing need for novel drugs that are highly effective in the treatment of cancer, drug resistant bacteria, and fungal infections. However, the application of microorganisms by the pharmaceutical and food industries to obtain different compounds of interest is still modest. Antioxidants have become the topic of interest recently. Fungal endophytes represent an abundant and dependable source of novel antioxidant compounds. There has been

increasing interest in systematics, evolutionary biology, ecology and applied research of endophytic fungi. A number of previous studies have demonstrated that ITS based is insufficient for some species delimitation, especially in rapidly evolving or highly diverse genera so we need more advanced techniques to solve these kinds of challenges. During the developments of modern biotechnology and taking advantage of genetic engineering, metabolic technology and their better use to manipulate this important microbial resource, and to make benefit of mankind.

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