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Fungal endophytes: A modern approach to Pharmaceutical industry

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ABSTRACT

Fungal endophytes are microorganisms that grows within living plant tissues without any symptoms of infection, and develop with plants for a major part of their life cycle. There is an endophyte for almost every plant in the world. Several novel bioactive compounds which can show a revolution in industrial agricultural and pharmaceutical sectors have been recently synthesized from endophytic fungi. This review is about endophytic diversity, and synthesizes of secondary metabolites that possess antimicrobial, antiviral, anti cancerous, antibiotics and with a lot of other secondary metabolites which can be used for better results in pharmaceuticals. It also sheds light on development of certain microorganisms that can provide remedy to drug resistant microbes present in the pharamaceutical market as the synthetic drugs present in the market are drug resistant. In order to provide aid and comfort in all aspects of mankind's life it is very important to make drugs which have safe bioactive compounds which are not dangerous for human health. So, research for bioactive molecules which are new to pharmaceutical sector and have intense properties of treatment are studied upon.

***Keywords:* Bioactive compounds, Fungal Endophytes, Secondary metabolites.**

I. INTRODUCTION

In this new era requirement for latest and user friendly bioactive compounds for better cure in all relms of human life is growing everyday. Outbreak of deadly viruses, emerging diseases, organ transplant issues and development of different drug resistant microorganisms, are some of the major challenges in the field of fungal research. Therefore this present scenario requires exploration of unique natural resource to meet the challenges faced by the world.

Plants are host for endemic microbes mainly known as endophyte that live inside host tissue which do not show any visible external symptoms [1]&[2].Their certain types are fungi [3] bacteria[4]or actinomycetes[5] which colonizes internal living tissues of plants [1] either as obligate or in facultative associated with lower and higher plants without causing any immediate negative or external symptom to host [2] and shows the beneficial effects to their host plant [6]. Endophytes transfer information via interaction with higher plant and also evolved biochemical pathways resulting in the production of various novel bioactive compounds and offer opportunities for discovering products and processes with potential applications in Medicine and biotechnology [7]&[8]. Researchers are mostly intersted in the study of diversity of fungal endophytes, host microbial relationships, study of natural bioactive compounds, and by introducing genetic engineering and other measures. A lot of information has been acquired in last many years of endophytic fungal research about bioactive group which are growing day by day. In 1928 Alexander Fleming discovered penicillin from *Penicillium notatum* which was the

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first bioactive compound. So this resulted in exploration of new antimicrobial compounds from fungi. As a result, the list of potent drugs from fungal sources is increasing day by day.

Till date, only some plants are completely studied for the endophytic diversity and their ability to produce bioactive secondary metabolites. Many researches are undertaken in all most all parts of the world about the endophytic biodiversity, reproduction, taxonomy, host effect and their host ecology. In recent studies endophytes are found to be a large sources of bioactive compounds, due to their unique biological niches that grow in diverse environments.

II. HISTORY OF FUNGAL ENDOPHYTES

Attention towards fungal endophytic studies initiated during early 1900 when Freeman in 1904 has made references from a paper published in 1898, in his paper described fungus from an annual grass [6]. Afterward a series of studies on asymptomatic fungal endophytes were recorded from almost all plant inhabitants in nature from various plant parts [9] geographical locations and different environmental conditions[10][11][12]&[13]. There are mainly two major groups of endophytic fungi, reflecting differences in evolutionary relatedness, taxonomy, plant hosts, and ecological functions. They are the clavicipitaceous endophytes (C-endophytes), which infect some grasses; and the nonclavicipitaceous endophytes (NC-endophytes), which can be recovered from asymptomatic tissues of nonvascular plants, ferns and allies, conifers, and angiosperms[14].

III. RELATIONSHIP WITH HOST PLANT, OCCURRENCE AND BIODIVERSITY OF FUNGAL ENDOPHYTES

Fungal endophytes show a large number of relationships with their host like symbiotic or mutualistic or antagonistic or slightly pathogenic [6]. Ecology and evolution of fungal endophytes is influenced by their association with host plant [15]. Occurrence of fungal endophytes is not a host specific there are reports that a single endophytes may be inhabitant of different host plants [16].Fungal endophyte and host interaction is controlled at the gene level, involving genes of both partners which are modulated by the environment [17]. Diversity has multidisciplinary effects on ecosystem such as nutrient retention, enhancement of primary productivity, and flow along with the development of resistance to pathogen invasion [6]. Fungal endophytes have been isolated from almost all plant groups range from grasses11, large trees10, lichens20, medicinal plants21, palm19, sea grasses12, The diversity of fungal endophytes may vary in different geographically locations such as temperate or tropical, different plant parts and position of host plant. Most of the fungal endophyte isolated belongs to ascomycetes [18]and several may also basidiomycetes[19]. Endophytic fungi from aquatic[20],temperate [21], tropic[22] and Xerophytic[23] are reported Investigation of endophytic fungal diversity has been done on the basis of its relative frequency, isolation and colonization rates in medicinal plants

IV. ENDOPHYTES AS A SOURCE OF BIOACTIVE METABOLITES

Fungal endophytes result in natural products that have biological activity of broad spectrum and might be grouped into many classes including; flavonoids, alkaloids, steroids, terpenoids, glycosides, xanthones, isocoumarins, quinones, phenyl propanoids, lignans, etc. [24] .Endophytic fungi is not well explored group of microorganisms and this group represents an abundant supply of bioactive molecules. Some bioactive molecules

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produced by fungal endophytes of medicinal plants are listed below. Despite the cryptic nature of their dependent existence in host plants they have gained recognition as prolific producers of secondary metabolites that have potential in medical and agricultural applications useful to human beings [25].

4.1 Antimicrobial Compounds

Natural products derived from endophytic microbes have been discovered to kill a large number of harmful disease inflicting agents as well as, bacteria viruses, fungi, and protozoans that have an effect on humans and animals. There are variety of antimicrobial compounds that were primarily identified from plants but currently reported from endophytic fungi, like coumarin found in extracts of *Alternaria* spp., from crotalaria pallid [26]. chaetoglobosin A and C, produced by the endophytic fungus *Chaetomium globosum.* The endophytic fungus Pestalotiopsis theae isolated from branches of an unidentified tree in China resulted four new metabolites namely pestalotheols A–D orpestalotheols (1–4). Among all four compounds pestalotheol C (3) suppressed HIV-1LAI replication in C8166 cells with an EC50 value of 16.1 µM [27].The endophytic fungus *Phoma sp* isolated from *Cinnamomum mollissimum* yielded a polyketide compound 5-hydroxyramulosin (63) (C10H14O4) inhibiting fungal pathogen *Aspergillus niger* was reported . Endophytic *Phoma sp.* isolated from a variety of medicinal plants has been reported to be a good source of antimicrobial compounds. *Phoma sp.* endophytic in *arisaema erubescens* produces α-tetralone derivative (3S)-3,6,7-trihydroxy- α -tetralone together with cercosporamide, b-sitosterol and trichodermin which exhibit good antifungal and bactericide activity against pathogenic fungi Fusarium oxysporum, Colletotrichum gloeosporioides, Rhizoctonia solani, and Magnaporthe oryzae as well as against 2 plant pathogenic bacteria xanthomonas campestris and Xanthomonas oryzae . Chaetoglobosin A and C isolated from nymphaea nouchali yielded chaetoglobosin A and C, chaetoglobosin A showed good antibacterial activities against Gram-positive B. subtilits (UBC 344), MRSA (ATCC 33591) and S. aureus (ATCC 43300) with MIC values of 16, 32 and 32 µg mL-1, respectively.

Table1:-List of some fungal endophytes isolated from different plants showing antimicrobial activity

Plant Source	Endophyte Isolated	Compound	Reference
Aquilaria sinensis	*Nigrospora oryzae*	Capitulatin B, hydroxycapitulatin B,	[27]
Prestonia trifidi	*Muscodor sutura*	Isocaryophyllene	[28]
Aegle marmelos	*Muscodor kashayum*	Bisabolol	[29]
Crotalaria pallida	*Alternaria* spp., *Penicillium* spp and *Aspergillus flavus*	Coumarin	[30]
Tylophora indica	*Fusarium chlamydosporum*	Kaempferol	[31]
Torreya taxifolia	*Pestallotiopsis microspora*	pestaloside,caryophyllene sesquiterpenes, pestalotiopsins A and B, 2-hydroxydimeninol	[32] [33] [34] [35]
Artemisia annua	*Colletotrichum gloeosporiodes*	Colletotric acid	[36]
Zingiber officinale	*Streptomyces aureofaciens*	5,7-dimethoxy-4-p-methoxyphenyl coumarin and 5,7-dimethoxy-4-p-phenyl coumarin	[37]
Terminalla	*Pestalotiopsis microspora*	pestacin and isopestacin	[38]

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morobensis			
Dracaena draco	*Lasiodiplodia theobromae*	dihydrocumambrin A	[39]

4.2. Anticancer Compounds

Since the discovery of million dollar drug Taxol ($C_{47}H_{51}NO_{14}$) from the endophytic fungi *Taxomyces andreanae* there are many studies on endophytic fungi as a source of anticancer agents [40]. *Rhinocladella* sp. an endophyte of *Tripterygium wilfordii* produces three novel cytochalasins have antitumor activity[41]. Paclitaxel also known as taxol isolated for the first time, from the bark of the *Taxus brevifolia* is a very potent anticancer agent. In USA the Food and Drug Administration (FDA) allowed to use paclitaxel for the treatment of ovarian and breast cancer. The fractionation extract of *Aspergillus niger*, an endophyte on *Cyndom dacivion* results in four known compounds rubrofusarin B, Biosecinone A, asperpytone B and auasperone A which were further investigated for bioactivity and it was observed to be cytotoxic to the colon cancer cell line [42]. After several years of effort, a novel paclitaxel-producing endophytic fungus *T. andreanae* was discovered in *T. brevifolia* [43] [44] *Acremonium* sp *from Taxus globose* [45] [46], *Fusarium proliferatum* [47], *Fusarium redolens* from *Taxus wallichiana* [48]. Other investigators have also made observations on paclitaxel production by endophytes, including the discovery of paclitaxel production by a *Tubercularia* sp. isolated from southern Chinese yew (*Taxus mairel*) [49]. A new isobenzofuranone derivative 4,6-dihydroxy-5-methoxy-7-methylphthalide alongwith three known compounds:4,5,6-trihydroxy-7-methyl-1,3 dihydroisobenzofuran; 4,6-dihydroxy-5-methoxy-7-methyl-1,3-dihydroisobenzofuran and 4,5,6-trihydroxy-7-methylphthalide with antioxidative activity were obtained from Cephalosporium sp.AL031 endophytic in Sinarundinaria nitida. A few studies showed that endophytes associated with non taxol producing plants have also been found to produce taxol. A novel endophytic taxol-producing fungus *Colletotrichum gloeosporioides* was isolated from the leaves of a medicinal plant, *Justicia gendarussa*, and it produced 163.4 µg/l of taxol [8]. Endophytic fungus *Fusarium oxysporum* isolated from the Indian *Catharanthus roseus* produces the anti-cancer drugs vinblastine and vincristine in 76 mg/lit and 67 mg/lit concentrations respectively, with properties similar to that of the plant derived vinblastine and vincristine [50]. Due to the continuous growing market, current industrial production of taxol by semi-synthesis that consumes large amount of *Taxus* trees cannot meet the requirement of the market. Scientists all over the world have studied taxol production on various platforms including chemical synthesis, plant cell and tissue culture [51], endophytic fungi microbial fermentation, and so on.

Table 1: Some important endophytes reported from different host plants and their compounds

Host Plant	Endophytic Fungi	Compound	Reference
Taxus brevifolia	*Taxomyces andreanae*	Paclitaxel	[40]
Taxus wallichiana	*Pestalotiopsis*	Paclitaxel	[52]
Taxus chinensis	*Fusarium solani*	Tax-3	[53]
Taxus wallichiana	*Seimatoantlerium nepalense*	Taxol	[54]

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Taxus chinensis var. mairei	*Isolate BT2*	Taxol	[55]
Taxus cuspidata	*Alternaria alternata*	Taxoids type III	[56]
Taxus wallichiana	*Pestalotiopsis microspora*	Taxol	[52]
Taxus mairei	*Tubercularia sp.*	Taxol	[51]
Taxodium distichum	*Pestalotiopsis microspora*	Taxol	[57]
Torreya grandiflora	*Periconia sp.*	Taxol	[58]
Wallemia nobilis	*Pestalotiopsis guipini*	Taxol	[59]
Stegolepis guianensis	*Stegolerium kukenani*	Taxol	[60]
Taxus cuspidata	*Pestalotiopsis versicolor*	Taxol	[61]
Capsicum annuum	*Colletotrichum capsici*	Taxol	[61]
P. hexandrum	*Fusarium solani,*	Taxol	[62]
Catharanthus roseus.	*Fusarium oxysporum*	Vinblastine and Vincristine	[50]

4.3. Antioxidant Compounds

Antioxidants are substances that may protect cells from the damage caused by unstable molecules known as free radicals. 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 Free radical mediated reactions are associated with degenerative human diseases like diabetes mellitus, cancer, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, atherosclerosis, ageing and inflammatory diseases. There are only a few antioxidants that are approved for clinical use. So there is a need to search new sources for antioxidants.

Discovery of pestacin and isopestacin as antioxidant compounds from *Pestalotiopsis microspora* from *Terminalia morobensis* led to the exploration of antioxidant potential of this less explored group of fungi [38] [63]. *Trachelospermum jasminoides* produces an endophytic fungi *Cephalosporium sp.* IFB-E001 produces Graphislactone A. Graphislactone A has strong antioxidant activity in vitro as compared to positive control, butylated hydroxytoluene and ascorbic acid [64]. *Xylaria sp.* isolated from *Ginkgo biloba* exhibit a strong antioxidant activity and that was due to the presence of flavonoids and phenolics [65]. Another antioxidant compound phenylpropanoid amide has been isolated from endophytic fungus Penicillium brasilianum that reside in Melia azedarach [66]. Cajaninstilbene acid (46) ($C12H22O4$) (CSA), 3-hydroxy-4-prenyl-5-methoxystilbene-2-carboxylic acid, a natural antioxidant has been reported from Fusarium an endophyte of *Pigeon pea, Cajanus cajan* . *Penicillium spp*. and *Aspergillus spp*., isolated from *Calotropis procera* were found to possess antioxidant potential with % inhibition value of 81.16% and 80.97% in the DPPH radical scavenging assay. The phytochemical screening of the methanolic extracts showed the presence of phenolics and flavonoids. These metabolite produced by endophytic fungi from *C. procera* need to be explored further as potential source of

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novel natural antioxidant compound [67]. *Pseudocercospora sp.* ESL 02 an endophytic fungi from *Elaeocarpus sylvestris*, exhibit antioxidant activity due to the presence of terreic acid (1) and 6-methylsalicylic acid (2) [68].

4.4. Antidiabetic Compounds

Pseudomassaria sp. isolated from an African rainforest exhibit a nonpeptidal fungal metabolite (L-783, 281) and oral administration of L-783, 281 to two diabetic mouse models resulted in significant lowering of blood glucose level [69]. Berberine is a cardioprotective and antidiabetic product known from several unrelated medicinal plants [70] , Berberine has been recently found as a secondary metabolite from *F. solani* which was isolated from roots of the medicinal plant *Coscinium fenestratum* [71]. The endophytic fungi *Aspergillus awamori* obtained from *Acacia nilotica* produces a peptide with alpha glycosidase inhibitory activity. This peptide is proteinaecous in nature with an approximate molecular mass of 22 KDa. This peptide possess both inhibitory activity and low IC_{50} values and is highly stable under extreme conditions of temperature and pH. So this can be commercially exploited for better management of diabetes [72].

4.5. Immunosuppressive Compounds

Immunosuppressive drugs are used today to prevent allograft rejection in transplant patients, and in the future they could be used to treat autoimmune diseases such a rheumatoid arthritis and insulin-dependent diabetes. Subglutinol A and B immunosuppressive non toxic bioactive agent were identified from endophytic fungus *Fusarium subglutinans* propose to have an active role in allograft rejection in transplant which could be utilized to treat autoimmune diseases like rheumatoid arthritis and insulin dependent diabetes [6].Study of fungal endophytes from western Himalayas offers an opportunity to investigate and extraction of novel natural products having immunomodulatory activities for use in medicine and industry.

V. CONCLUSION

Endophytic fungi are a acceptable and reliable antecedent of atypical natural compounds with a high level of biodiversity and results in several important compounds of pharmaceutical significance, which is currently alluring scientific investigations worldwide. In nature, endophytic fungi assume to be in a close interaction with plants. The production of bioactive compounds by endophytes, notably those restricted to their host plants, are important both from the biochemical and molecular point of view. Secondary metabolites produced by fungal endophytes nurtures expectations of utilizing them as another and acceptable sources of these compounds. However, the commercial implication of assembly of adorable compounds by endophytic fungi still remains a future prospect. A deeper knowledge of host–endophyte relationships at the molecular and genetic levels and the effects of ecology changes and culture conditions on gene expression will be helpful for optimizing secondary metabolite assembled by endophytic fungi in laboratory conditions. Endophytic biodiversity and the regulation of fungal secondary metabolism at advanced molecular level may offer better insights in future research.

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