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ENDOPHYTIC FUNGI A REPOSITORY OF BIOACTIVE COMPOUNDS- A REVIEW

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ABSTRACT

Endophytes are microorganisms that reside asymptomatically in the tissues of higher plants and are relatively unstudied and a promising source of novel organic natural metabolites exhibiting a variety of biological activities. The intent of this review is to provide insights into the presence of endophytes in nature : their relationship with the host plants, isolation and particularly on the role of endophytes in the production of anticancer, antimicrobial, and antifungal compounds and includes examples that illustrate their potential for human use.

INTRODUCTION

Microorganisms have long served mankind by virtue of the myriad enzymes and secondary compounds that they produce (Demain, 1981). The diversity of microbial life is enormous and the niches in which microbes live are truly amazing, ranging from deep ocean sediments to the Earth's thermal pools .One specialized and unique biological niche that supports the growth of microbes is the intracellular space between cells of higher plants. It turns out that each plant supports a suite of microorganisms known as endophytes (Strobel and Daisy, 2003). Plants appear to be a reservoir of untold numbers of endophytic organisms (Bacon and White, 2000). Endophyte includes all organisms which colonize the living internal tissues of their hosts without producing symptoms of disease (Petrini, 1991). Common endophytes include a variety of bacteria, fungi and actionomycetes. The ubiquity of these symbiotic microorganisms is clear, but diversity, host-range, and geographical distributions are unknown (Arnold and Engelbrecht, 2007). Endophytic bacteria and filamentous fungi have been isolated from surface-sterilized seeds, roots, stems, leaves, needles, twigs and barks of various symptomless plant species (Stone et al. 2000; Sturz et al. 2000).

In this review we will focus on endophytic fungi, its type, their interaction with the host plants, methods for isolation of endophytic fungi and their sources of natural products on the role of endophytes in the production of bioactive compounds, the importance of including endophytic microbes in the screening approach for novel drugs, and the microbial biotransformation process as a novel alternative method to obtain such compounds. It also describes these compounds by different functions, including some examples that illustrate the potential for human use.

Endophytic fungi

Endophytic fungi, a polyphyletic group of highly diverse, primarily ascomycetous fungi defined functionally by their occurrence within asymptomatic tissues of plants, are found in above-ground tissues of liverworts, hornworts, mosses, lycophytes, equisetopsids, ferns, and seed plants from the arctic to the tropics, and from agricultural fields to the most biotically diverse tropical forests (Elizabeth Arnold 2007). Dreyfuss and Chapela, 1994 estimated that there may be one million species of endophytic fungi alone.

In general, two major groups of endophytic fungi have been recognized previously, 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 (Rodriguez et al., 2009). Transmission of C- endophytes is primarily vertical, with maternal plants passing fungi on to offspring via seed infections (Saikkonen et al., 2002). They frequently increase plant biomass, confer drought tolerance, and produce chemicals that are toxic to animals and decrease herbivory (Clay, 1988). However, the benefits conferred by these fungi appear to depend on the host species, host genotype and environmental conditions (Saikkonen et al., 1999).

Nonclavicipitaceous Endophytes (NC-endophytes) are diverse, both phylogenetically and with respect to life-history strategy. Most of them belong to the Ascomycota and colonize either inter or intracellular, localized or systemic. The majority of these isolates belonged to ubiquitous genera (Table.1) (e.g. *Acremonium, Alternaria, Cladosporium, Coniothyrium, Epicoccum, Fusarium, Geniculosporium, Phoma, Pleospora*) but some genera are common in both tropical and temperate climates (e. g. *Fusarium, Phomopsis, Phoma*) while members of the *Xylariaceace, Colletotrichum, Guignardia, Phyllosticta* and *Pestalotiopsis* predominate as endophytes in the tropics (Schulz and Boyle, 2005).

Table I. Host plants and their endophytes

S.no	***Name of the host plant***	***Name of the endophytic fungi***	***References***
1.	*Taxus brevifolia.*	*Taxomyces andreanae,*	Gary Strobel *et al*.,(1993.)
2.	*Torreya taxifolia*	*Pestalotiopsis microspore*	Lee et al,(1996)
3	*Taxus mairei*	*Tubercularia sp. strain TF5*	Jianfeng Wang et al., (2000)
4	*Tripterygium wilfordii*	*Rhinocladiella sp*	Wagenaar et al., (2000)

5	*Lycopersicon esculentum*	*Alternaria alternate, C. gloeosporioides, Penicillium sp.,cladosporium sp*	Larrun et al (2001)
6	*Cinnamomu m zeylanicum*	*Muscodor albus*	Strobel et al., (2001)
7	*Aphelandra tetragona*	*Fusarium sambucinum . Plectosporium tabacinum, Gliocladium cibotii, Chaetosphaeria sp.*	Zikmundova et al., (2002)
8	*Paullinia paullinioides*	*Muscodor vitigenus*	Bryn Daisy et al., (2002)
9	*Terminalia morobensis*	*Pestalotiopsis microspore*	Harper et al., (2003.)
10	*Acrostichum aureum*	*Acremonium sp. Trichoderma sp. Penicillium sp. Fusarium sp.*	Maria , (2005).
11	*Ocimum basilicum*	*2L-5*	Md. Aminul Haque et al., (2005)
12	*Jatropha curcas*	*Pestalotiopsis sp.*	Haiyan Li et al., (2005)
13	*Acanthus ilicifolius*	*Cumulospora marina Schmidt, Pestalotiopsis sp., Sterile isolate (MSI 1)*	Maria (2005).
14	*Calotropis gigantea*	*Marssonina sp*	Haiyan Li et al., (2005)
15	*Tectona grandis L*	*Alternaria, Colletotrichum, Schizophyllum commune Nigrospora, Phomopsis and mycelia sterilia*	Sukanyanee Chareprasert et al .,(2006)
16	*Ephedra Fasciculate*	*Chaetomium chiversii C5-36-62*	Turbyville et al.,(2006)

17	*Samanea saman Merr.*	*Phomopsis , mycelia sterilia, Colletotrichum , Penicillium, Nigrospora*	Sukanyanee Chareprasert et al .,(2006)
18	*Azadirachta indica A. Juss*	*Periconia, Stenella, and Drechslera*	Verma et al., (2007)
19	*Guazuma ulmifolia*	*Muscodor albus E-6*	Katreena Kluck et al., (2007)
20	*Acalypha indica L.*	*Chaetomium sp.,Colletotrichum falcatum and C. gloeosporioides*	Gangadevi et al.(2008)
21	*Eucryphia cordifolia*	*Gliocladium roseum (NRRL 50072)*	Gary Strobel et al., (2008)
22	*Azadirachta indica A. Juss*	*Chloridium sp.*	Kharwar et al., (2008)
23	*Piptadenia adiantoides J.F. Macbr*	*Cochliobolus sp. (UFMGCB-555)*	Campos et al., (2008)
24	*Justicia gendarussa*	*Colletotrichum gloeosporioides (strain JGC-9)*	Gangadevi and Muthumary (2008)
25	*Ginkgo biloba L.*	*Xylaria sp.YX-28*	Xiaoli Liu et al ., (2008)
26	*Salvia officinalis*	*Chaetomium sp.*	Abdessamad Debbab et al., (2009)
27	*Coffea arabica L.)*	*Alternaria alternata*	Maurette dos Reis Vieira Fernandes ***et al .,*** (2009)
28	*Dracaena*	*Fusarium sp. 1,*	Li-Juan

	cambodiana		Gong(2009)
29	*Camptotheca acuminate*	*Fusarium solani*	S. Kusari (2009)
30	*Taxus chinensis*	*Fusarium solani*	Deng, B.W. et al. (2009)
31	*Gastrodia elata*	*Armillaria mellea*	Li Wen Gao et al., (2009)
32	*Artemisia capillaris*	*Aureobasidium pullulans (AcapL1), Ephelis(AcapS8,AcapS10),Pestalotiopsis(AcapF6),* *and Pleosporaceae (AcapS4),*	Huang, (2009)
33	*Aquilaria sinensis*	*Glomerularia sp.*	Li-Juan Gong (2009)
34	*Beta vulgaris*	*Alternaria alternate, Fusarium oxysporum and penicillium species.*	Yingwu Shi et al., (2009)
35	*Plumeria acutifolia Poiret*	*Phomopsis sp*	K. Nithya(*2010)*
36	*Vitis vinifera*	*Pyrigemmula aurantiaca*	Donát Magyar et al .,(2010)
37	*Camptotheca acuminate*	*Guignardia, Zythia, Diaporthe*	T. Ding et al (2010)
38	*Ananas ananassoides*	*Muscodor crispans*	Angela Mitchell et al., (2010)
39	*Guazuma tomentosa*	*Phyllosticta sp.*	Srinivasan et al., (2010)
40	*Ginkgo biloba L.*	*Aspergillus nidulans, Aspergillus oryzae*	Min Qiu et al., (2010)

41	*Dendrobium. loddigesii Rolfe.*	*Acremonium*	Juan Chen et al., (2010)
42	*Dipterocarpus tuberculatus Roxb.*	*Pestalotiopsis sp, Nodulisporium spp, Phomopsis sp, Xylaria sp.1*	Sutjaritvorakul et al., (2011)
43	*Dalbergia oliveri Gamble*	*Phyllosticta spp., Paecilomyces sp. Xylaria sp.3, Pestalotiopsis sp*	Sutjaritvorakul et al., (2011)
44	*Shorea obtusa Wall.*	*Nodulisporium spp, Xylaria sp.1, Phomopsis sp, Penicillium sp. Daldinia sp.*	Sutjaritvorakul, et al., (2011)
45	*Shorea siamensis Miq*	*Phyllosticta spp., Fusarium sp., Penicillium sp., Phomopsis sp.*	Sutjaritvorakul, et al., (2011)

Plant-fungus interactions

In the 1970's, endophytes were considered to be neutral as they were believed to neither cause any harm nor benefit the plant. However, in the course of time, many studies revealed that endophytes play an important role in host protection against predators and pathogens (Azevedo et al., 2000). The stability or the variability of the asymptomatic interaction depends on numerous factors such as environmental stress, senescence of the hosts, virulence of the endophytes and the host defense response (Schulz and Boyle 2005). The molecular and biochemical basis for the switch from endophytic to parasitic lifestyle are characterized by an imbalance in nutrient exchange that can explain why colonization of different hosts can cause a fungus to adopt contrasting lifestyles. In this regard, *Colletotrichum magna*, a fungal pathogen which provokes anthracnose in cucurbit plants, exercises an endophytic lifestyle when growing asymptomatically on an assortment of non-cucurbit species (Hahn and Mendgen, 2001; Redman et al., 1999).

There is sufficient evidence that endophytic fungi play an important role in host plant physiology. They receive nutrition, protection and propagation opportunities from their hosts (Clay and Schardl, 2002; Thrower & Lewis, 1973). Endophytes not only can mediate interactions between host plants and herbivores and pathogens, but can also control food-web structure by disrupting the transfer of energy from plants to upper trophic levels (Omacini et al., 2001). The endophyte profits from host plant by receiving organic nutrients, shelter and guaranteed transmission to the next host generation whereas infected plants are more vigorous, drought resistant and toxic to herbivores, nematodes and pathogens than uninfected plants (Müller and Krauss, 2005; Schardl *et al*., 2004), as has been shown for the symbiotic interaction between *Neotyphodium* endophytes and certain grasses resulting in the synthesis of a number of alkaloids which defend the plants against herbivory (Salminen *et al*., 2005). Endophytes can be transmitted vertically as well as horizontally. Vertical transmission occurs through seeds and vegetative propagation of the host and horizontal transmission occurs through spores, external to host tissues (Carroll, 1988).

Endophytic fungi isolation

The rationale for the host plant selection is crucial to increase the chances of isolating novel microorganisms and new bioactive compounds. Plants should be selected mainly on the basis of their unique environmental setting, ethonobotanical history, endemism, unusual longevity, and large areas of biodiversity (Strobel and Daisy, 2003).

Generally, the isolation of endophytes is first based on the principle that the selected plant is apparently healthy. The materials are then surface sterilized by immersing them sequentially in 70% ethanol for 3min and 0.5% NaOCl for 1min and rinsed thoroughly with sterile distilled water. The surfactant and sterilizing agent concentrations required for the sterilization varies with the kind of the plant tissue (Table I1). The excess water is dried under laminar airflow chamber. The media is supplemented with streptomycin sulphate (100mg/L) to suppress bacterial growth. The plates are then incubated at 25 ± 2 ° C until fungal growth appeared. The fungi are identified on the basis of their morphological characteristics (Christensen and Raber, 1978) Nevertheless, some isolates must be cultured on different media as banana leaf pieces impregnated on PDA (Tejesvi et al., 2006), oatmeal agar (Bayman et al., 1998)**,** malt extract agar, plant-origin tissue fragments (Strobel et al., 1999) or several other industrializing media (Shen et al., 2006) to induce sporulation.

Table II. Recently employed methods for endophytic fungi isolation

Washing	Rinse with ethanol solution	Surface disinfection	Rinsed with ethanol solution	Rinsed in sterile distilled water	Incubation days, temperature	Reference
Running tap water (RTW)	70%	3%, 3 min in sodium hypochloride solution	70%	twice	3-15, 28^{o}C	Rubini *et al*., 2005
Water and detergent the material was dried with sterile filter paper	70%, 1 min	15%, 1 min in hydrogen peroxide solution	70%, 1 min	not informed	not informed	Gao *et al*., 2005
RTW air-dried	70%, 1 min	5%, 5 min in sodium hypochloride solution	Not informed	twice, 1 min	30^{o}C' cultivated on banana leaf agar the fungi developed conidia,	Chomcheon *et al*., 2005
RTW	75%, 1 min	6%, 3 or 5 in in sodium hypochloride solution	75%, 0.5 min	three times	30, 25^{o}C	Raviraja *et al*., 2006
RTW	70%, 1 min	5.3%, 5 min in sodium hypochloride solution	75%, 0.5 min	not informed	Several days, 27^{o}C	Agusta *et al*., 2005
RTW air-dried	70%, 1 min	6%, 5 min in sodium hypochloride solution	Ni	twice, 1 min	30^{o}C	Chomcheon *et al*., 2006

RTW	95%, 1 min	6%, 5 min in sodium hypochloride solution	95%, 0.5 min	three times	4-5, 25°C	Seena and Sridhar 2004
Water and detergent	70%, 1 min	3%, 4 min in sodium hypochloride solution	70%, 0.5 min	once	3-8, 18°C	Souza *et al*., (2004)
RTW technique used for seeds	75%, 1 min	34%, 10 min	75%, 0.5 min	not informed	22°C	Bayman *et al*., 1998

Secondary metabolites from endophytes

Environmental factors including biotic and abiotic stimuli, carbon-nutrition balance, genotype and ontogenesis usually control and regulate the biosynthesis of secondary metabolites in plants (Mary Ann Lila, 2006). With regard to plant-microbe interactions, co-evolution between plants and their microbial partners are mediated via plant chemical defense (Lu and Shen, 2004). Production of secondary metabolites can be the result of genetic, developmental and environmental factors**.** (Pieters and Vlietinck, 2005). Genes involved in the production of secondary metabolites appear to be clustered in fungi and bacteria (Keller et al., 2005) and genetic screening methods have gained attention because they are rapid, economical and sensitive.

Endophytes are chemical synthesizer inside plants which produce bioactive substances with low toxicity toward higher organisms (Owen and Hundley, 2004). They also feature diverse chemical structures and have often evolved to possess biological activities with roles as defensive compounds against competitors/parasites/predators, growth and reproduction facilitators, or as cell-signalling compounds (Vining, 1990). Endophytes provide a broad variety of bioactive secondary metabolites (Table III) with unique structure, synthesized via various metabolic pathways e.g. polyketide, isoprenoid, amino acid derivation. These belong to diverse structural groups including alkaloids, benzopyranones, chinones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, and others (Tan and Zou 2001). They have the ability to produce a range of secondary metabolites, providing researchers with numerous leads for compounds of pharmaceutical significance and possible development as new drugs (Strobel, 2003). Some of them represent novel structural groups, for example the palmarumycins and a new benzopyroanone. According to Schulz et al (2002) fungal endophytes has the ability to produce novel metabolites with new structures than soil isolates.

Natural products can be divided into several classes based on assembly pathways. It is evident that a plethora of microbial secondary metabolites are polyketides and nonribosomal peptides, which are biosynthesised by polyketide synthase (PKS) and nonribosomal peptide synthetase (NRPS) systems, respectively. Consequently, identification of PKS and NRPS biosynthetic pathways can be used to evaluate an organism's potential to produce bioactive compounds (Sauer, et al. 2002). Such bioactive metabolites find wide-ranging application as agrochemicals, antibiotics, immunosuppressants, antiparasitics, antioxidants, and anticancer agents (Gunatilaka 2006). Attempts are being made to isolate and identify bioactive metabolites from endophytic fungi to screen them for antibiotics, antiviral and anticancer, antioxidants, insecticidal and immunomodulatory compounds. While screening for new bioactive secondary metabolites from endophytic fungi;it is relevant to consider that the secondary metabolites a fungus synthesizes may correspond with its respective ecological niche and continual metabolic interactions between fungus and plant which may enhance the synthesis of secondary metabolites (Rakshith Devaraju et al, 2010).

Biotechnological techniques by using different microorganisms appear promising alternatives for establishing an inexhaustible, cost- effective and renewable resource of high-value bioactive products and aroma compounds. These compounds possess not only sensory properties, but other desirable properties such as antimicrobial (vanillin, essential oil constituents), antifungal and antiviral (some alkanolides), antioxidant (eugenol, vanillin), somatic fat reducing (nootkatone), blood pressure regulating (2-[E]-hexenal), anti-inflammatory properties (1,8-cineole) and others (Berger 2009).

Table III. List of biological activities and bioactive compounds isolated from endophytic fungi

S.no	***Name of the host plant***	***Name of the endophytic fungi***	***Chemical compound Reported***	***Biological activities***	***References***
1	*Tripterygium wilfordii*	*Fusarium subglutians*	Subglutinol A and B	Immuno-suppressive	Lee et al. (1995)
2	*Torreya taxifolia*	*Pestalotiopsis microspore*	Torreyanic acid	Anti-cancer agent	Lee, et al,(1996)
3	*Tripterygium wilfordii*	*Rhinocladiella sp*	22-oxa-(12)-cytochalasins	Anticancer	Wagenaar, et al 2000
4	*Taxus mairei*	*Tubercularia sp. strain TF5*	Taxol	Anticancer agent	Jianfeng Wang et al (2000)
5	*Cinnamomum zeglanicum*	*Muscodor albus*	1-butanol ,3-methyl-, acetate	Antimicrobial	Strobel, et al. (2001)
6	*Paullinia paullinioides*	*Muscodor vitigenus*	Naphthalene	Insect repellent	Bryn Daisy et al (2002)
7	*Aphelandra tetragona*	*Fusarium sambucinum* *Plectosporium tabacinum, Gliocladium cibotii, Chaetosphaeria sp.*	N-(2-hydroxyphenyl) acetamide N-(2-hydroxyphenyl)malonamic acid.	Bio-remediation	Zikmundov et al (2002)
8	*Terminalia*	*Pestalotiopsis*	1,3-dihydro	Antioxidant	Harper et al

	morobensis	*microspora*	isobenzofurans	activity	, (2003.)
9	*Trachelospermum jasminoides*	*Cephalosporium sp. IFB-E001*	"Graphislactone A",	Antioxidant activity	Song,et al (2005)
10	*0cimum basilicum*	*2L-5*	Ergosterol, Cerevesterol	Antimicrobial activity	Md. Aminul Haque et al (2005)
11	*Nothapodytes foetida*	*Entrophospora infrequens*	camptothecin	Anticancer	Puri et al.,(2005)
12	*Ephedra fasciculata*	*Chaetomium chiversii C5-36-62*	Radicicol	Cytotoxic	Turbyville, et al. (2006)
13	*Erythrina crista-galli*	*Phomopsis sp.*	isoflavonoids	Antimicrobial activity	Redko et al (2006)
14	*Podophyllum hexandrum*	*Trametes hirsute,*	Podophyllotoxin	Anticancer agent	Puri et al., 2006
15	*Azadirachta indica A. Juss*	*Periconia, Stenella, and Drechslera*	Pestasol	Insect repellent	Verma, et al (2007)
16	*Ocimum basilicum,*	*Phyllosticta sp.6,*	Taxol	Anticancer	Gangadevi (2007)
17	*Guazuma ulmifolia*	*Muscodor albus E-6*	Caryophyllene, phenylethyl alcohol, 2-phenylethyl ester, bulnesene	Antibiotic activity	Gary Strobel, Katreena Kluck et al (2007)
18	*Justicia gendarussa*	*Colletotrichum gloeosporioides (strain JGC-9)*	Taxol	Anticancer	Gangadevi & Muthumary (2008)
19	*Piptadenia adiantoides J.F.*	*Cochliobolus sp.*	cochlioquinone A,	Anti-	Campos

	Macbr	*(UFMGCB-555)*	isocochlioquinone A.	parasitical Properties	et al. (2008)
20	*Ginkgo biloba L.*	*Xylaria sp.YX-28*	7-amino-4-methylcoumarin	Antimicrobial	Xiaoli Liu et al (2008)
21	*Azadirachta indica A. Juss*	*Chloridium sp.*	Javanicin	Antibacterial activity	Kharwar et al (2008)
22	*Eucryphia cordifolia*	*Gliocladium roseum (NRRL 50072)*	2,6-dimethyl, 3,3,5-trimethyl; cyclohexene, 4-methyl; decane, 3,3,6-trimethyl; and undecane, 4,4-dimethyl(Volatile hydrocarbons)	Biofuel	Gary A. Strobel et al (2008)
23	*Salvia officinalis*	*Chaetomium sp.*	Cochliodinol, isocochliodinol.	Cytotoxic activity	Abdessamad Debbab et al (2009)
24	*Camptotheca acuminate*	*Fusarium solani*	Camptothecin, (9-methoxycamptothecin, 10-ydroxycamptothecin	Anticancer properties	S. Kusari (2009)
25	*Taxus chinensis*	*Fusarium solani*	Taxol	Anticancer	Deng, et al. (2009)
26	*Gastrodia Elata*	*Armillaria mellea*	Sesquiterpene aryl esters	Antimicrobial activity	Li Wen Gao et al (2009)
27	*Meliotus dentatus*	*unidentified Ascomycete*	5-methoxy-7-hydroxyphthalide, (3R,4R)-cis-4-hydroxymellein	Antifungal	Hidayat Hussain et al (2009)
28	*Meliotus*	*unidentified*	4-	Antialgal	Hidayat

	dentatus	*Ascomycete*	hydroxyphthalide, -5-methoxy-7-Hydroxyphthalide, (3R,4R)-cis-4-hydroxymellein		Hussain et al (2009)
29	*Plumeria acutifolia Poiret*	*Phomopsis sp*	Terpenoid	Antimicrobial activity	Nithya(2010)
30	*Ananas ananassoides*	*Muscodor crispans*	propanoic acid, methyl ester, 2-methylbutyl ester, ethanol.	Antibiotic activity	Angela M. Mitchell et al, (2010)

Antimicrobial compounds

Metabolites bearing antibiotic activity can be defined as low-molecular-weight organic natural substances made by microorganisms that are active at low concentrations against other microorganisms (Guo et al., 2008). Some endophytic fungi possess antimicrobial activity that may be involved in a symbiotic association with a host plant (Yang et al., 1994). Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites (Tan and Zou 2001). The antimicrobial compounds can be used not only as drugs by humankind but also as food preservatives in the control of food spoilage and food-borne diseases, a serious concern in the world food chain (Liu et al., 2008). So far, studies reported a large number of antimicrobial compounds isolated from endophytes, belonging to several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids_ (Yu, Zhang, Li et al.,2010, Momose et al. 2000) isolated three compounds, melleolides K, L and M. from *Armillaria mellea* which showed antimicrobial activity against grampositive bacteria, yeast and fungi.. Previously these antibacterial sesquiterpenoids, melleolides B-D, were yielded from A. *mellea* were isolated by (Arnone et al., 1986). A compound polyketide citrinin, produced by endophytic fungus *Penicillium janthinellum* from fruits of *Melia azedarach*, presented 100% antibacterial activity against *Leishmania sp.*(Marinho et al., 2005). Donnelly et al., (1985) isolated two new sesquiterpene aryl esters, 4-O-methylmelleolide and judeol, both of strong antibacterial activity against gram positive bacteria. Armillaric acid also exhibited marked inhibitory activity against gram positive bacteria and yeast (Obuchi et al., 1990). Bioactive compound 7-amino-4-methylcoumarin isolated from the culture extracts of the endophytic fungus *Xylaria sp*. YX-28 isolated from *Ginkgo biloba L*. by Liu, Dong et al., 2008 having an activity against several food-borne and food spoilage microorganisms including *Staphylococcus aureus, Escherechia coli, S. typhia, S.typhimurium, S. enteritidis, A. hydrophila, Yersinia sp., V. anguillarum, Shigella sp., V. parahaemolyticus, C. albicans, P. expansum, and A. niger, especially to A. hydrophila,* and was suggested to be used as natural preservative in food .

The production of Hypericin (C30H16O8), a naphthodianthrone derivative, and Emodin (C15H10O5) believed to be the main precursor of hypericin, by the endophytic fungus isolated from an Indian medicinal plant, having an antimicrobial activity against several bacteria and fungi, including *Staphylococcus aureus sp, Klebsiella pneumoniae sp. ozaenae, Pseudomonas aeruginosa, Salmonella enterica sp. Enteric, and Escherichia coli, and fungal organisms Aspergillus niger and Candida albicans* (Kusari et al., 2008)**.** Three steroids namely, ergosta-5,7,22-trienol , 5α,8α-epidioxyergosta-6,22- dien-3β-ol , ergosta-7,22-dien-3β,5α,6β-triol and one nordammarane triterpenoid helvolic acid were isolated for the first time from the endophytic fungus *Pichia guilliermondii Ppf9* from the medicinal plant *Paris polyphylla var. yunnanensis* showing the strongest antibacterial activity against all test bacteria (Jianglin Zhao et al., 2010).

Antifungal activity

A potent antifungal strain of *Serratia marcescens* was recovered from *R. penicillata* which produces oocydin A, a novel antioomycetous compound having the properties of a chlorinated macrocyclic lactone. Oocydin A is being considered for agriculture use to control the ever-threatening presence of oomyceteous fungi such as *Pythium and Phytophthora*.,(Strobel et al., 1999). Pestalachlorides A (C21H21Cl2NO5 and B(C20H18Cl2O5), from the endophytic fungus *Pestalotiopsis adusta*, display a significant antifungal activity against three plant pathogenic fungi, *Fusarium* *culmorum,Gibberella zeae, and Verticillium albo-atrum* (Li et al., 2008). An endophytic strain of *Muscodor albus* produces volatile organic compounds which has both antibacterial and antifungal activity (Atmosukarto et al., 2005).

Chaetomugilin A and D with antifungal activities, were isolated from an endophytic fungus *Chaetomium globosum* collected from *Ginkgo biloba* (Qin et al., 2009). A new, highly functionalized compound, ambuic acid, an antifungal compound was isolated from both *Pestalotiopsis sp. and Monochaetia sp*. (Li et al., 2001). Cytosporone B and C were isolated from a mangrove endophytic fungus, *Phomopsis sp*. which inhibits the activity of two fungi *C. albicans* and *F. oxysporum*. Two new bioactive metabolites, ethyl 2,4-dihydroxy- 5,6-dimethylbenzoate and phomopsilactone were isolated from an endophytic fungus *Phomopsis cassiae* from *Cassia spectabilis* and displayed strong antifungal activity against two phytopathogenic fungi, *Cladosporium cladosporioides, and C. sphaerospermum* (Silva et al 2005).

Anticancer compounds

Novel anti-cancer drugs are also required due to the high worldwide mortality rate (Pisani et al., 1999). Many antitumor compounds possess a cytostatic activity and act by inhibiting microtubule assembly, and eventually inducing programmed cell death. (Rosario Nicoletti Elisabetta Buommino et al., 2008). Taxol, a powerful antimitotic agent with excellent activity against a range of cancers, was originally isolated from Taxus brevifolia (Wani et al. 1971). It can kill tumor cells by enhancing the assembly of microtubules and inhibiting their depolymerisation. (Schiff et al., 1979). This compound is the world’s first billion dollar anticancer drug and it is used to treat breast, lung, ovarian cancer and other human tissue proliferating disease. Taxol is a white to off white crystalline power contains 11 sterocenters and with the empirical formula C47H51NO14 (molecular weight 853.9). It is highly lipophillic, insoluble in water and melts at around 216-217ºC. The isolation of Taxol-producing endophyte *Taxomyces andreanae* has provided an alternative approach to obtain a cheaper and more available product *via* microorganism fermentation . (Stierle etal., 1993). Some endophytic fungi belonging to different genera such as *Taxomyces. andreanae Pestalotiopsis microspora, Alternaria alternata, Periconia* sp., *Pithomyces* sp., *Chaetomella raphigera*, *Monochaetia* sp. and *Seimatoantlerium Nepalense, Botryodiplodia theobromae, Bartalinia robillardoides* are reported to produce Taxol. *Pestalotiopsis terminaliae* isolated from the *Terminalia arjuna* plant produced the highest amount of Taxol (Gangadevi & Muthumary 2009).

An another important anticancer compound is the alkaloid Camptothecin a potent antineoplastic agent which was firstly isolated from the wood of Camptotheca acuminata Decaisne (Nyssaceae) in China (Wall et al., 1966). Similarily SW1116. *Entrophospora infrequens* associated with *Nothapodytes foetida*, a medicinal plant native to the Western Ghats, India, was found to produce camptothecin (Puri et al.,2006). *Entrophospora infrequens*, an endophyte isolated from *Nothapodytes foetida*, was able to produce camptothecin (Puri *et al*., 2005), chemotherapeutic agent efficient against lung, ovarian and uterine cancer, which was first isolated from *Camptotheca acumina* (Amna *et al*., 2006)**.** The anticancer properties of the microbial products Camptothecin and two analogues (9-methoxycamptothecin and 10-hydroxycamptothecin) were obtained from the endophytic fungi *Fusarium solani* isolated from *Camptotheca acuminata* (S. Kusari etal 2009). Wagenaar et al.,(2000)**,** identified three novel cytochalasins, bearing antitumor activity from the endophyte *Rhinocladiella sp*. Torreyanic acid is an unusual dimeric quinone isolated from the endophytic fungus *Pestalotiopsis microspora* from *T. taxifolia* (Florida torreya) and was proven to have selective cytotoxicity 5 to 10 times more potent in cell lines that are sensitive to protein kinase C agonists and causes cell death by apoptosis (Lee et al., 1996). Jiao et al., (2006) reported that Chaetominine an alkaloid with a new framework, was produced by *Chaetomium sp. IFB-E015*, an endophytic fungus from *Adenophora axiliflora*. Chaetominine showed cytotoxicity against the human leukemia K562 and colon cancer SW1116 cell lines higher than the drug 5-fluorouracil. Bioactive compound named Phaeosphoramides A and B, two new carbon skeleton derivatives, were isolated from the endophytic fungus *Phaeosphaeria avenari*. Phaeosphoramide A was found to be an inhibitor of the signal transducer and activator of transcription (STAT)-3, which plays a vital role in regulating cell growth and survival, constituting a target for anticancer therapy (Maloney et al., 2006). A novel fungal endophyte, *Trametes hirsute*, produced podophyllotoxin and other related aryl tetralin lignans with potent anticancer properties (Puri, et al., 2006).

Extracts of *Curvularia sp.,* an endophytic fungus isolated from *Ocotea corymbosa*, yielded two new benzopyran derivatives, (2′S)-2-(propan-2′-ol)-5-hydroxybenzopyran- 4-1 induced a potent antiproliferative stimulus in two mammalian cell lines (Teles et al., 2005). Li et al., (2006)**,** reported that *Aspergillus niger IFB-E003,* an endophyte from *Cynodon dactylon* was found to produce rubrofusarin B which is cytotoxic to the colon cancer cell line. An endophytic fungus from leaves of *Catharanthus roseus* was reported to biosynthesize the potent antileukemia agent vincristine (Yang et al., 2004).

Insecticidal activity

The use of agrochemicals, although decreasing the attack of insects and phytopathogenic microorganisms, still represents a high risk to field workers and consumers. In addition, their use is, in certain cases, economically unviable. The control of pests and diseases by means of biological processes i.e., use of entomopathogenic microorganisms or those that inhibit / antagonise other microorganisms pathogenic to plants, is an alternative that may contribute to reduce or eliminate the use of chemical products in agriculture. In the early 80's it was demonstrated that the presence of endophytic microorganisms *Phomopsis oblonga* protected elm trees against the beetle *Physocnemum brevilineum* which is the potential causative agent for the Dutch disease *Ceratocystis ulmi* due to the toxic compounds produced by the endophytic fungi (Webber, 1981). In 1985**,** Claydon et al. showed that endophytic fungi belonging to the Xylariacea family synthesize secondary metabolites in hosts of the genus Fagus which affect the beetle larvae. Gaynor and Hunt (1983) observed in several ryegrasses having high endophytic fungal infection is correlated with a decrease in the attack frequency of the Argentine stem weevil, Listronotus bonariensis. Pike et al. (1986) described in oak (Quercus sp.), the role of the endophytic fungus Rhabdocline parkeri against the insect Contarinia sp. Saha et al. (1987) studied endophytes Acremonium in fine fescue associated with host resistance to Blissus leucopterus hirtus. Kanda et al. (1994) reported the preference of larvae from the bluegrass webworm *Parapediasia teterrella* for diets with endophyte-free plants of *Lolium perenne* and *Festuc .arundinacea*, to a point that the larvae would starve to death if only plants infected with *Acremonium* were available. In the field, endophyte-free species were severely attacked by insects, whereas those infected with *Acremonium* stayed almost free of insect larvae Recently, Miles et al. (1998) showed that endophytic isolates of *Neotyphodium* sp. produce N-formilonine and a paxiline analogous in the host *Echinopogum ovatus*. These compounds show insecticidal activity against *Listronotus bonariensis* and other insects.

CONCLUSION

Understanding the ecology, evolution, and importance of fungal endophytes is a daunting prospect given the tremendous number of fungi capable of forming endophytic associations and their unique relativeness to other plant-associated microbes. Further research in endophytes is required at the molecular level for a better understanding of host–endophyte interactions and secondary metabolism biosynthesis. This will afford the rapid recognition of the genetic potential of endophytes and facilitate the natural product discovery process. Comprehensive efforts are needed to culture or clone the genomic potential of the endophytes of medicinally important plants.

In future, by integrating endophytes into comparative genomics and related areas of research, we will begin to address the mechanisms of virulence in evolutionarily relevant comparisons. Uniting these steps forward is an interdisciplinary approach that will rely on the interplay of surveys, hypothesis-driven research, and classical training in mycology. Taken as a whole, endophytes promise to be a significant prospect for scientific discovery in the future.

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