

Review Article

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## Endophytes: The Producers of Important Functional Metabolites

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### ABSTRACT

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Natural product based compounds have immense impact on modern medicine. More than 50% of the new chemical products registered with FDA during 1981-2002 as anti-cancer agents, anti-migraine agents and anti-hypertensive agents were with natural products or derived thereof. Some possible sources of natural products include mostly plants, which are extensively being used by man and may lead to their permanent loss from habitat. This natural loss is important to the society for a number of reasons, including the maintenance of ecosystem, functioning and for ethical reasons and specifically important to pharmaceutical companies in their search for novel natural products. Amongst the plants being lost, will be some which have the ability to produce important, but as yet undiscovered bioactive molecules. Though efforts are on to conserve these important species involving insitu and exsitu cultivation and the search for microbial diversity associated with the plants known as endophytes. Endophytes are microorganisms (bacteria or fungi or actinomycetes) that dwell within robust plant tissues by having a symbiotic association. A large amount of bioactive compounds produced by them not only are

### Introduction

From 1981-2002, only 43% of the drugs were purely synthetic, while remaining 57% were derived from natural source (Newman *et al.*, 2003). Out of 250,000 (approx.) higher species of plants, it is estimated that only 5-15% has been investigated for natural products (Cragg and Newman, 2001a).

The world Health Organization (WHO) estimates that approximately 80% of the world relies on natural sources directly or indirectly for primary medicinal treatment and that the health care systems for the remaining 20% of the population also incorporate natural sources in their medicinal treatment (Cragg, 2002).

Also research suggests that less than 1% of bacterial species and less than 5% of fungal diversity are currently known (Cragg and Newman, 2001b). Microorganisms known as endophytes colonizing inside plant tissues usually get nutrition and protection from the host plant and in return, they confer profoundly enhanced fitness to the host plants by producing certain functional metabolites. In addition, fungal endophytic metabolites are useful resources for natural products which effectively have wide range of application in medicine, agriculture, and industry (Selim *et al.*, 2012). Endophytes have been recognized as a repository of novel metabolites of pharmaceutical

importance (Tan and Zou, 2001). Many endophytes of the same species are isolated from the same plant and only one of the endophyte will produce a highly active compound in culture (Li, *et al.*, 1996). The reason why some endophytes produce certain phytochemicals originally characteristic of the host might be related to a genetic recombination of the endophyte with the host (Tan and Zou, 2001). This is a concept that was originally proposed as a mechanism to explain why the endophytic fungus *T. andreanae* may be producing paclitaxel (Stierle *et al.*, 1993). Thus, if endophytes can produce the same rare and important bioactive compounds as their host plants, this would not only reduce the need to harvest slow-growing and possibly rare plants but also preserve the world's diminishing biodiversity.

### **Here is the List of Natural Functional Metabolites Produced by Endophytic Microbes and their Potential in the Pharmaceutical and Agrochemical Arenas.**

#### **Antimicrobial Compounds**

Natural products from endophytic microbes have been observed to inhibit or kill a wide variety of harmful disease causing agents including, bacteria fungi, viruses and protozoans that affect humans and animals. There are number of antimicrobial compounds primarily known from plants, have now being reported as metabolites of endophytic fungi, such as coumarin found in extracts of strains of *Alternaria* spp., *Penicillium* spp and *Aspergillus flavus* from the annual herb *Crotalaria pallida* (Umashankar *et al.*, 2014), a strain of *Fusarium chlamydosporum* from stem of *Tylophora indica* (Asclepiadaceae) producing kaempferol (Chaturvedi *et al.*, 2014).

Cryptocin, a unique tetrameric acid is produced by *Cryptosporiopsis quercina*. This unusual compound possesses potent activity against *Pyricularia oryzae* as well as a number of other plant-pathogenic fungi. *C. quercina* also demonstrated excellent antifungal activity against some important human fungal pathogens like *Candida albicans* and *Trichophyton sp* (Li *et al.*, 2000). A unique peptide antimycotic, termed cryptocandin, was isolated and characterized from *C. quercina*, the bioactive compound is related to the known antimycotics, the echinocandins and the pneumocandins. As is generally true not one but several bioactive and related compounds are produced by a microbe. Thus, other antifungal agents related to cryptocandin are also produced by *C. quercina*. Cryptocandin is also active against a number of plant-pathogenic fungi including *Sclerotinia sclerotiorum* and *Botrytis cinerea*. Cryptocandin and its related compounds are currently being considered for use against a number of fungi causing diseases of skin and nails (Walsh, 1992).

The ecomycins are produced by *Pseudomonas viridifolia*, which is generally associated with leaves of many grass species and is located within the tissues. The ecomycins are active against such human-pathogenic fungi as *Cryptococcus neoformans* and *C. albicans* (Miller, 1998). Another group of antifungal compounds is the pseudomycins, produced by a plant-associated pseudomonad. The pseudomycins represent a family of lipopeptides that are active against a variety of plant and human-pathogenic fungi (Harrison *et al.*, 1991, Ballio *et al.*, 1994). The molecules are candidates for use in human medicine especially after structural modification has successfully removed mammalian toxicity (Zhang *et al.*, 2001).

A strain of *Pestalotiopsis microspora* was also isolated from the endangered tree *Torreya taxifolia* which produces several compounds that have antifungal activity, including pestalosite, an aromatic  $\beta$  glucoside, and two pyrones; pestalopyrone and hydroxypestalopyrone, caryophyllene sesquiterpenes, pestalotiopsins A and B, 2-hydroxydimeninol (Lee *et al.*, 1995a, Pulici *et al.*, 1996b, 1996c, 1997).

Also Capitulatin B, hydroxycapitulatin B, antimicrobial compounds have been obtained from *Nigrospora oryzae* of *Aquilaria sinensis* (Li *et al.*, 2014), Isocaryophyllene from *Muscodor sutura* of *Prestonia trifidi* (Kudilkar *et al.*, 2012), Arundinols, arundinones from *Microsphaeropsis arundinis* of *Ulmus macrocarpa* (Luo *et al.*, 2014), Bisabolol from *Muscodor kashayum* of *Aegle marmelos* (Meshran *et al.*, 2013).

*Pestalotiopsis microspora* is a common rainforest endophyte (Strobel, 2002a). It turns out that enormous biochemical diversity does exist in this endophytic fungus, and as such there seem to be many secondary metabolites produced by this widely dispersed fungus. One such secondary metabolite is ambuic acid, an antifungal agent which has been recently described from several isolates of *Pestalotiopsis microspora* (Li *et al.*, 2001). Species of *Pestalotiopsis* namely *Pestalotiopsis jesteri* from the Sepik River area of Papua New Guinea, produces jesterone and hydroxy-jesterone, which exhibit antifungal activity against a variety of plant-pathogenic fungi (Li and Strobel, 2001).

An endophytic *Fusarium* sp. from the plant *Selaginella pallescens*, collected in the Guanacaste, conservation Area of Costa Rica, was screened for antifungal activity. A new antifungal agent, CR377, was isolated from the culture broth of the fungus that

showed potent activity against *C. albicans* (Brady and Clady, 2000).

Phomopsichalasin, a metabolite from an endophytic *Phomopsis* spp mainly exhibit antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. It also displays a moderate activity against the yeast *Candida tropicalis* (Horn *et al.*, 1995).

Colletotric acid is a metabolite of an endophyte, *Colletotrichum gloeosporiodes* isolated from *Artemisia annua*, a traditional Chinese herb that is well recognized for its synthesis of artemisinin (an anti-malarial drug). The *Colletotrichum* sp, found in *A. annua* produced not only metabolites with activity against human- pathogenic fungi and bacteria but also metabolites that were fungistatic to plant-pathogenic fungi (Lu *et al.*, 2000).

Antibiotics called munumbicins produced by *Streptomyces* sp possess widely differing biological activities, depending on the target organism. In general, the munumbicins demonstrate activity against gram-positive bacteria such as *Bacillus anthracis* and multidrug-resistant *M. tuberculosis* as well as a number of other drug resistant bacteria (Castillo *et al.*, 2002).

Another endophytic streptomycete (NRRL 30566) from a fern-leaved *Grevillea* tree (*Grevillea pteridifolia*) growing in the Northern Territory of Australia produces in culture novel antibiotics called kakadumycins (Castillo *et al.*, 2003). Two active ingredients identified as (i) 5, 7-dimethoxy-4-p-methoxyphenyl coumarin and (ii) 5, 7-dimethoxy-4-p-phenyl coumarin from endophytic *Streptomyces aureofaciens* isolated from root tissue of *Zingiber officinale* showed antifungal activity against *Colletotrichum musae* and *Fusarium oxysporum* (Tacchowisan *et al.*, 2005).

*Muscudor albus* is an endophytic fungus obtained from small limbs of *Cinnamomum zeylanicum* (cinnamon tree). This *xylariaceae* (non-spore-producing) fungus effectively inhibits and kills certain other fungi and bacteria by producing a mixture of volatile compounds. The ecological implications and potential practical benefits of the “mycofumigation” effects of *M. albus* are very promising, given the fact that soil fumigation utilizing methyl bromide will soon be illegal in the United States. This organism is already in the market for the decontamination of human wastes. *Muscodor roseus* obtained from the tree species growing in the Northern Territory of Australia is effective in causing inhibition and death of test microbes in the laboratory as *M. albus* (Worapong *et al.*, 2002).

In addition for the first time, a non muscodor species, *Gliocladium* spp was discovered to be a volatile antibiotic producer. The volatile components of this organism are totally different from those of either *M. albus* or *M. roseus*. In fact, the most abundant volatile inhibitor is annulene formerly used as a rocket fuel and discovered for the first time as a natural product in an endophytic fungus (Stinson and Strobel, 2003).

Another fascinating use of antibiotics products from endophytic fungi is the inhibition of viruses, two novel human cytomegalovirus protease inhibitors, cytonic acids A and B have been isolated from the solid-state fermentation of the endophytic fungus, *Cytanaema* sp. It is apparent that the potential for the discovery of compounds from endophytes, having antiviral activity is in its earliest. The main limitation for the discovery of antiviral compounds from endophytes is probably related to the absence of appropriate antiviral assay systems (Guo *et al.*, 2000).

Two compounds, pestacin and isopestacin have been obtained from culture fluids of *Pestalotiopsis microspora*, an endophyte isolated from a combretaceous plant, *Terminalla morobensis* growing in the Sepik River drainage of Papua New Guinea. Both pestacin and isopestacin display antimicrobial as well as antioxidant activity (Harper *et al.*, 2003).

Moreover, production of saponins has been recently documented for strains of *A. alternata*, *A. niger* and *Penicillium* sp. from *Loranthus* sp. (Govindappa *et al.*, 2011), dihydrocumambrin A, known as a secondary metabolite of *Glebionis coronaria* (*Chrysanthemum coronarium*), has been recently extracted as a fermentation product of a strain of *Lasiodiplodia* (= *Botryodiplodia*) *theobromae* endophytic in leaves of *Dracaena draco* [Zaher *et al.*, 2015], all possessing the antimicrobial properties.

### **Anticancer Compounds**

Numerous reviews have highlighted the importance of compounds derived from microbial sources in treating human diseases. In addition to the anti-infective area, natural products have also had a major impact on cancer therapy. Surveying the period from 1981 to 2002, Newman *et al.*, reported that > 60% of the approved drugs for cancer treatments are natural products or derivatives of natural products. The search for natural products as potential anticancer agents dates back to 1550 BC, but the scientific period of this search is much more recent. Much of nature remains unexplored, particularly the marine and microbial environments, and the interplay of these two sources, as exemplified by review of Colwell 2002, leaves no doubt that a host of novel bioactive chemotypes awaits discovery. A large number of plants, marine

and microbial sources have been tested as leads and many compounds have survived the potential leads. Several potential lead molecules such as camptothecin, vincristine, vinblastine, taxol, podophyllotoxin, combretastatins, etc. have been isolated from plant and many of them have been modified to improve activity and reduce toxicity. Several successful molecules like topotecan, irinotecan, taxotere, etoposide, teniposide, etc. have emerged as drugs upon modification of these natural leads and many more are yet to come.

The alkaloids are also commonly found in endophytic fungi. Fungal genera like *Xylaria*, *Phoma*, *Hypoxylon*, and *Chalara* spp are representative producers of a relatively large group of substances known as the cytochalasins of which over 20 are now known. Many of these compounds possess antitumor and antibiotic activities. Three novel cytochalasins have recently been reported from a *Rhinocladella* sp. as an endophyte on *Tripterygium wilfordii*. These compounds have antitumor activity (Wagenaar *et al.*, 2000).

The presence of paclitaxel, a highly functionalized diterpenoid in each of the world's yew (*Taxus*) species prompted the study of their endophytes (Suffness, 1995). The mode of action of paclitaxel is to preclude tubulin molecules from depolymerizing during the process of cell division. This compound is the world's first billion-dollar anticancer drug. It is used to treat a number of other human tissue-proliferating diseases as well. After several years of effort, a novel paclitaxel-producing endophytic fungus *T. andreanae* was discovered in *T. brevifolia* (Schiff and Horowitz, 1980, Strobel *et al.*, 1993), *Acremonium* sp from *Taxus globosa* (Soca *et al.*, 2011, Kusari *et al.*, 2014b), *Fusarium proliferatum* (Xiong *et al.* 2013),

*Fusarium redolens* from *Taxus wallichiana* (Garyali *et al.*, 2013). 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 mairei*) (Wang *et al.*, 2000). Three endophytes of *T. wallichiana* produce paclitaxel, including *Sporormia minima* and a *Trichothecium* sp. By the use of high-performance liquid chromatography and electrospray mass spectroscopy, paclitaxel has been discovered in *Corylus avellana*. Several fungal endophytes of filbert produce paclitaxel in culture. One of the most commonly isolated endophytic species is *P. microspore* (Stroble 2002a). An examination of the endophytes of *Taxus wallichiana* yielded *Pestalotiopsis microspore* and a preliminary monoclonal antibody test indicated that it might produce paclitaxel. Several other *Pestalotiopsis* isolates were obtained from bald cypress in South Carolina and also shown to produce paclitaxel. This was the first indication that endophytes residing in plants other than *Taxus* sp. were producing paclitaxel. Simply it appears that the distribution of the fungi making paclitaxel is worldwide and not confined to yew. From the extremely rare and previously thought to be extinct, Wollemi pine (*Wollemia nobilis*), *Pestalotiopsis* was isolated, which was shown to produce paclitaxel (Strobel *et al.*, 1997). Also quite surprisingly, a rubiaceous plant, *Maguireothamnus speciosus*, yielded a novel fungus, *Seimatoantlerium tepuiense* that produces paclitaxel. Furthermore fungal paclitaxel production has also been noted in *Periconia* sp. and in *Seimatoantlerium nepalense* another novel endophytic fungal species (Bashyal *et al.*, 1999). However that paclitaxel production by all endophytes in culture is in the range of submicrograms to micrograms per litre. Also commonly endophytic fungi will attenuate paclitaxel

production in culture. However, it is possible to recover paclitaxel production in attenuated cultures if certain activator compounds are added to the medium (Li *et al.*, 1998).

Torreanic acid, a selectively cytotoxic quinine dimmer (anticancer agent) was isolated from a *Pestalotiopsis microspora* strain. This strain was originally obtained as an endophyte associated with the endangered tree *T. taxifolia* (*Florida torreya*) (Li *et al.*, 2002).

The extract of a *Curvularia* sp. an endophytic fungus isolated from *Ocotea corymbosa* showed moderate antifungal activity against *Cladosporium sphaerospermum* and *C. cladosporioides*. Further studies of crude ethyl acetate extract afforded two new benzopyran derivatives and two known compounds which caused a potent stimulus to two mammalian cell lines. Recently fractionation of the extract of *Aspergillus niger*, an endophyte in *Cydonia oblongifolia* gave four known compounds rubrofusarin B, Biosecinone A, asperpyrone B and auasperone A which were further investigated for bioactivity and it was observed to be cytotoxic to the colon cancer cell line (Teles *et al.*, 2005).

Camptothecin, an anticancer drug molecule have also been isolated from endophytic fungi like *Entrospora infrequens* and *Neurospora crassa* isolated from *Nothapodytes foetida*, an important medicinal herb (Puri *et al.*, 2005b, Rehman. *et al.*, 2008). Furthermore, CPT production by a strain of *F. solani* from *C. acuminata* was even notably increased by supplying an ethanolic extract of leaves of *C. roseus* containing strictosidine as a precursor in CPT biosynthesis, and even by ethanol itself (Venugopalan and Srivastava, 2015).

Podophyllotoxin has been discovered from various *Podophyllum* plant species. The production of bioactive lignans by novel fungal endophytes *Trametes hirsuta* and *Fusarium oxysporum* which exhibit potent antioxidant, anticancer and radioprotective properties have also been reported (Porter and Eyberger, 2004, Puri *et al.*, 2005a, Amardeep *et al.*, 2007).

### **Immunoregulators**

The endophytic fungus *Fusarium subglutinans* isolated from *T. wilfordii* produces the non toxic immunosuppressant diterpene pyrones, subglutinol A and B. Immunosuppressive drugs are used today to prevent allograft rejection in transplant patients and in future they could be used to treat autoimmune diseases such as rheumatoid arthritis and insulin-dependent diabetes (Lee *et al.*, 1995b).

*Pestalotiopsis* species have been reported to secrete immunosuppressive compounds in culture broth. *Pestalotiopsis sp.*, isolated as an endophytic fungus from *T. brevifolia* (Yew tree) produces immunosuppressive pestalotiopsins A and B in liquid culture (Pulici *et al.*, 1996a). *Pestalotia* sp, isolated from a pea plant (*Cassia fistula*), produces immunosuppressive, cytochalasin (Burren *et al.*, 1992). *Pestalotiopsis leucothes*, an endophytic fungus from *T. wilfordii* has tremendous immunomodulatory effects especially suppression of various activities of peripheral blood mononuclear cells. Bioassay guided purification of the crude extracts of *P. leucothes* revealed three compounds that accounted for its activity (Kumar *et al.*, 2003, 2005).

The Microbiology Department at Sandoz Ltd. developed a computer-aided evaluation program to screen and evaluate fungi for bioactivity. This approach resulted in the

discovery of the fungus *Tolyocladium inflatum*, from which cyclosporine, a hugely beneficial immunosuppressant was isolated (Borel and Kis, 1991).

Caffeine, the methylxanthine alkaloid from *Coffea* sp. well known as a psychoactive drug, has been evidenced in extracts of unidentified endophytic fungi recovered from the Indian ethnomedicinal plants *Osbeckia chinensis*, *O. stellata* and *Potentilla fulgens* (Bhagobaty *et al.*, 2011). Piperine is an alkaloid of *Piper longum* and *Piper nigrum* known for its immunoregulatory and antitumor properties and this valuable compound has been extracted from liquid cultures of endophytic strains of *Periconia* sp. From *P. longum* (Verma *et al.*, 2011), and *Mycosphaerella* sp (Chithra *et al.*, 2014a) and *C. gloeosporioides* from *P. nigrum* (Chithra *et al.*, 2014b).

### **Antidiabetic Compounds**

A nonpeptidal fungal metabolite (L-783, 281) was isolated from an endophytic fungus (*Pseudomassaria* sp.) collected from an African rainforest. This compound acts as insulin mimetic and unlike insulin is not destroyed in the digestive tract and may be given orally. Oral administration of L-783, 281 to two mouse models of diabetes resulted in significant lowering of blood glucose level (Zhang *et al.*, 1999). Berberine is a cardioprotective and antidiabetic product known from several unrelated medicinal plants (Sun *et al.* 2009), which has been recently found as a secondary metabolite of a strain of *F. solani* from roots of the medicinal liana *Coscinium fenestratum* (Vinodhini *et al.*, 2013).

### **Anti-insect Compounds**

As the world becomes wary of ecological damage done by synthetic insecticides,

endophytic research continues for the discovery of powerful, selective and safe alternatives. Several endophytes are known to have anti-insect property. Nodulisporic acids, novel indole diterpenes exhibit potent insecticidal properties against the blow fly. The first Nodulisporic compounds were isolated from an endophyte, a *Nodulisporium* sp. from the plant *Bontia daphnoides* (Demain, 2000). Insect toxins have also been isolated from an unidentified endophytic fungus from wintergreen (*Gaultheria procumbens*). The two new compounds, 5-hydroxy-2-p-hydroxy-5'-methyl-4'-hexenyl benzofuran and 5-hydroxy-2-(P-oxo-5'-methyl-4'-hexenyl benzofuran both show toxicity to spruce budworm (Findlay *et al.*, 1997). Another endophytic fungus, *Muscodor vitigenus*, isolated from a *Paullina paullinioides* yields naphthalene as its major product. Naphthalene, the active ingredient in common mothballs is a widely exploited insect repellent. *M. vitigenus* shows promising preliminary results as an insect deterrent and exhibits potent insect repellency against the wheat stem sawfly (*Cephus cinctus*) (Daisy *et al.*, 2002a, 2002b). Terpenes from *Copaifera* demonstrated *in vitro* antiparasitic and synergic activity (Izumi *et al.*, 2012). Azadirachtins A and B have been recently extracted from cultures of a strain of *Penicillium* (*Eupenicillium*) *parvum* endophytic in the neem plant (*Azadirachta indica*) possessing insecticidal activity (Kasuri *et al.*, 2014a).

Plant hormones are undoubtedly among the main secondary metabolites that can influence plant fitness and enhance development when exogenously administered. Many fungal species have been reported to be able to produce compounds such as indole-3-acetic acid (IAA) and gibberellins (GAs), particularly

species inhabiting rhizosphere which are presumed to exert a consistent effect on plant development (Manici *et al.*, 2015). The interaction of crop plants with endophytic fungi producing gibberellins could be exploited as a strategy to overcome the adverse effects of abiotic stresses, considering the increased plant growth and biomass production that have been documented even in extreme environmental conditions (Khan *et al.*, 2015).

Production of IAA by fungi establishing a mutualistic relationship with plants was first evidenced by a few mycorrhizal species recovered from pine and orchid roots (Ek and Ljungquid 1983). Afterwards it has been reported by strains of *Colletotrichum* sp. from *Artemisia annua* (Lu *et al.*, 2000), *Talaromyces verruculosus* (= *Penicillium verruculosum*) from roots of *Potentilla fulgens* (Bhagobaty *et al.* 2009), and *Penicillium glabrum* from pomegranate (*Punica granatum*) fruits (Hammerschmidt *et al.*, 2012). IAA is also produced by *Piriformospora indica* (Sirrenberg *et al.*, 2007), the quite famous Basidiomycetes species and later found to be widespread and able to colonize roots of many host plants, disclosing a potential for applications in crop production [Qiangetal *et al.*, 2012].

Other endophytic fungi have been found to produce both IAA and GAs, such as two strains of *Fusarium* sp. from *Euphorbia pekinensis* Dai and Yu, 2008]. Moreover, a strain of *Galactomyces geotrichum* isolated from the aquatic plant *Trapa japonica* produced IAA and biologically active GAs (GA1, GA4, and GA7) (Waqas *et al.*, 2014), while two strains from cucumber roots (*Phoma glomerata* and *Penicillium* sp.) were found to produce gibberellic acid (GA3) along with GA1, GA4, GA7, and IAA (Waqas *et al.*, 2012), Similar effects resulted in the evaluation of another

cucumber endophytic strain (*Paecilomyces formosus*) by the same research group (Khan *et al.*, 2012).

The production of IAA, GA, abscisic acid and jasmonic acid in several combinations was observed by a pool of unidentified endophytic fungi recovered from five plants used in Indian ethnomedicine, *Camellia caduca*, *Osbeckia chinensis*, *Osbeckia stellata*, *Potentilla fulgens*, and *Schima khasiana* (Bhagobaty and Joshi, 2011).

**Enzymes:** Very few microorganisms living in plants, e.g., the ericoid mycorrhizal fungus *Hymenoscyphus ericae* were reported to be xylenase producers (Burke and Cairney, 1997). Manabu *et al.*, (2002) isolated one hundred and sixty-nine endophytic fungi and eighty one endophytic bacteria from 14 plants in total. Among them, 155 fungi (91.7%) and 52 bacteria (64%) were found to produce xylenase. Like other microorganisms invading plant tissues, endophytes produce extracellular hydrolyases as a resistance mechanism to overcome attack by the host against pathogenic invasion and/or to get nutrition from the host.

Such enzymes including pectinases, esterases, cellulases and lipases, (Pettrini *et al.* 1992) proteinase, (Reddy *et al.*, 1996)  $\alpha$ 1, 4-glvcan lyase (Nielsen *et al.*, 2000) and phosphatases (Maccheroni and Azevedo, 1998) have been documented from different endophytes. In addition to above mentioned enzymes endophytes also produce laccase, two isolates of *Fusarium proliferatum* and *F. proliferatum* strains produce laccases during infection of wheat seedlings (Kwon and Anderson, 2001).

## Conclusion

Endophytes are not only the interesting

Class of microorganisms but may also play a significant role in their utilization in industry, agriculture, medicine, food, textiles, bioremediation, natural cycling as biofertilizers and many other ways. Microorganisms occupying virtually every living and non-living niche on earth have proven to be a very rewarding source of bioactive and structurally diverse natural products

It could be realized that plants may serve as a reservoir of unimaginable numbers of microorganisms known as endophytes which have typically gone unnoticed for centuries. Many more endophytes may produce unusual secondary metabolites of tremendous importance. In fact a comprehensive study has indicated that 51% of biologically active substances isolated from endophytic fungi were previously unknown. New pharmaceutical compounds, secondary metabolites, agents for biological control of insect-pests and plant diseases besides other useful characteristics could be found, by further exploration of endophytic microorganisms. This is a broad field of investigation that is almost entirely open to new findings. It is expected that new ways of interactions between endophytes and their hosts will be found. It is expected also that new drugs of biotechnological importance produced by endophytes will be described with the increasing knowledge focusing on these microorganisms. There is a need of world wide scientific effort to isolate endophytes and study their secondary metabolism.

## References

Ballio, A., Bossa, F., DiGioglio, P., Ferranti, P., Paci, M., Pucci, P., Scaloni, A., Segre, A., Strobel, G, A. 1994. Structure of the pseudomycins, new lipodepsipeptides produced by

*Pseudomonas syringae* MSU 16H. *FEMS Lett.*, 355: 96-100.

Bashyal, B., Li, J.Y., Strobel, G.A., Hess, W.M. 1999. *Seimatoantlerium nepalense*, an endophytic taxol producing coclomycete from Himalayan yew (*Taxus wallichiana*), *Mycotaxon.*, 72: 33-42.

Bhagobaty, R.K., Joshi, S.R. 2009. Promotion of seed germination of green gram and chick pea by *Penicillium verruculosum* RS7PF, a root endophytic fungus of *Potentilla fulgens* L. *Adv. Biotechnol.*, 8: 7-15.

Bhagobaty, R.K., Joshi, S.R. 2011. Metabolite profiling of endophytic fungal isolates of five ethnopharmacologically important plants of Meghalaya, India. *J. Metabolomics Syst. Biol.*, 2: 20-31.

Borel, J.F., Kis, Z.L. 1991. The discovery and development of cyclosporine. *Transplant. Proc.*, 23(2): 1867-1874.

Brady, S.F., Clardy, J. 2000. CR377, a new pentaketide antifungal agent isolated from an endophytic fungus. *J. Nat. Prod.*, 63: 1447-1448.

Burke, R.M., Cairney, J.W.G. 1997. Purification and characterization of a p-14-endoxylanase from the ericoid mycorrhizal fungus *Hymenoscyphus ericae*. *New Phytol.*, 135: 345-352.

Burres, N.S., Premachandran, U., Humphrey, P.E., Jackson, M., Chen, R.H. 1992. A new immunosuppressive Cytochalasin isolated from a *Pestalotia* sp. *J. Antibiotics*, 45: 1367-1369.

Castillo, U.F., Harper, J.K., Strobel, G.A., Sears, J., Alesi, K., Ford, E., Lin, J., Hunter, M., Maranta, M., Fe, H., Yaver, D., Jensen, J.B., Porter, H., Robison, R., Millar, D., Hess, W, M., Condrón, M., Teplow, D. 2003. Kakadumycins, novel antibiotics from *Streptomyces* sp. NRRL 30566, an

- endophyte of *Grevillea pteridifolia*. *FEMS Lett.*, 224: 183-190.
- Castillo, U.F., Strobel, G.A., Ford, E.J., Hess, W.M., Porter, H., Jensen, J.B., Albert, H., Robison, R., Condrón, M, A., Teplow, D, B., Stevens, D., Yaver, D. 2002. Munumbicins, wide-spectrum antibiotics produced by *Streptomyces NRRL 30562*, endophytic on *Kennedia nigriscans*. *Microbiol.*, 148: 2675-2685.
- Chaturvedi, P., Gajbhiye, S., Roy, S., Dudhale, R., Chowdhary, A. 2014. Determination of kaempferol in extracts of *Fusarium chlamydosporum*, an endophytic fungi of *Tylophora indica* (Asclepeadaceae) and its anti-microbial activity. *J. Pharm. Biol. Sci.*, 9: 51–55.
- Chithra, S., Jasim, B., Anisha, C., Mathew, J., Radhakrishnan, E.K. 2014a. LC-MS/MS based identification of piperine production by endophytic *Mycosphaerella* sp. PF13 from *Piper nigrum*. *Appl. Biochem. Biotechnol.*, 173: 30–35.
- Chithra, S., Jasim, B., Sachidanandan, P., Jyothis, M., Radhakrishnan, E.K. 2014b. Piperine production by endophytic fungus *Colletotrichum gloeosporioides* isolated from *Piper nigrum*. *Phytomedicine*, 21: 534–540.
- Colletotrichum* sp., an endophytic fungus in *Artemisia annua*. *Plant Sci.*, 151: 67–73.
- Colwell, R.R. 2002. Fulfilling the promise of biotechnology. *Biotechnol. Adv.*, 20: 215–228.
- Cragg, G.M. 2002. Natural Product Drug Discovery and Development, The United States National cancer Institute Role. *Puerto Rico Health Science Murnal*, 21: 97-111.
- Cragg, G.M., Newman, D.J. 2001b. Cytotoxic alkaloids from the marine sponge Thorectandra. *J. Nat. Prod.*, 67: 232-244.
- Cragg, G.M., Newman, D.J., 2001a. Natural Product Drug Discovery in the Next Millennium. *Pharma. Biol.*, 39: S8-17.
- Dai, C.C., Yu, B.Y., Li, X. 2008. Screening of endophytic fungi that promote the growth of *Euphorbia pekinensis*. *Afr. J. Biotechnol.*, 7: 3505–3510.
- Daisy, B., Runyon, J.B. 2002b. Naphthalene, an insect repellent, is produced by *Muscodor vitigenus*, a novel endophytic fungus. *Microbiol.*, 148: 3737-3741.
- Daisy, B., Strobel, G., Ezra, D., Castillo, U., Baird, G., Hess, W.M. 2002a. *Muscodor vitigenus* anam. Sp. Nov., an endophyte from *Paullinia paullinioides*. *Mycotaxon*. 84:39-50.
- Daisy, B.H., Strobel.G.A., Castillo, U., Ezra, D., Sears, J., Weaver.
- Demain, A.L. 2000. Microbial natural products: a past with a future, p. 3-16. In S. K. Wrigley, M. A. Hayes, R. Thomas, E. J. T. Chrystal, and N. Nicholson (ed.), *Biodiversity: new leads for pharmaceutical and agrochemical industries*. The Royal Society of Chemistry, Cambridge, United Kingdom.
- Ek, M., Ljungquist, P.O., Stenström, E. 1983. Indole-3-acetic acid production by mycorrhizal fungi determined by gas chromatography-mass spectrometry. *New Phytol.*, 94: 401–407.
- Findlay, J.A., Bothelezi, S., Li, G., Sevek, M. 1997. Insect toxins from an endophyte fungus from wintergreen *J. Nat. Prod.*, 60:1214-1215.
- Garyali, S., Reddy, M.S. 2013. Taxol production by an endophytic fungus, *Fusarium redolens*, isolated from Himalayan yew. *J. Microbiol. Biotechnol.* 23, 1372–1380.
- Govindappa, M., Channabasava, R.,

- Sowmya, D.V., Meenakshi, J., Shreevidya, M.R., Lavanya, A., Santoyo, G., Sadananda, T.S. 2011. Phytochemical screening, antimicrobial and *in vitro* anti-inflammatory activity of endophytic extracts from *Loranthus* sp. *Pharmacognosy J.*, 3, 82–90.
- Guo, B., Dai, J., Ng, S., Huang, Y., Leong, C., Ong, W., Carte, B.K. 2000. Cytotoxic acids. A and B, novel tridepside inhibitors of hCMV protease from the endophytic fungus *Cytonaema species*. *J. Nat. Prod.* 63:602-604.
- Hammerschmidt, L., Wray, V., Lin, W., Kamilova, E., Proksch, P., Aly, A.H. 2012. New styrylpyrones from the fungal endophyte *Penicillium glabrum* isolated from *Punica granatum*. *Phytochem. Lett.* 5, 600–603.
- Harper, J. K., Ford, E, J., Strobel, G, A., Arif, A., Grant, D.M., Porco, J., Tomer, D.P., Oneill, K. 2003. Pestacin a 1, 3-dihydro isobenzofuran from *Pestalotiopsis microspora* possessing antioxidant and antimycotic activities. *Tetrahedron.* 59:2471-2476.
- Harrison, L., Teplow, D., Rinaldi, M., Strobel, G, A. 1991. Pseudomycins, a family of novel peptides from *Pseudomonas syringae*, possessing broad spectrum antifungal activity. *J. Gen. Microbiol.*, 137:2857-2865.
- Horn, W, S., Simmonds, M, S, J., Schwartz, R, E., Blaney, W, M. 1995. Phomopsichalasin, a novel antimicrobial agent from an endophytic *Phomopsis* sp. *Tetrahedron.* 14:3969-3978.
- Izumi, E., Ueda-Nakamura, T., Veiga V.F., Jr., Pinto, A.C., Nakamura, C.V. 2012. Terpenes from *Copaifera* demonstrated *in vitro* antiparasitic and synergic activity. *J. Med. Chem.* 55, 2994–3001.
- Khan, A.L., Hamayun, M., Kang, S.M., Kim, Y.H., Jung, H.Y., Lee, J.H., Lee, I.J. 2012, Endophytic fungal association via gibberellins and indole acetic acid can improve plant growth under abiotic stress: An example of *Paecilomyces formosus* LHL10. *BMC Microbiol.* 12, 3.
- Khan, A.L., Hussain, J., Al-Harrasi, A., Al-Rawahi, A., Lee, I.J. 2015. Endophytic fungi: Resource for gibberellins and crop abiotic stress resistance. *Crit. Rev. Biotechnol.* 35, 62–74.
- Kour. A., Abdul, S.S., Suriya. R., Phaliseen, S., Parvaiz, H.Q., Pankaj, S., Ravi, K.K and Vijeshwar ,V. 2007. Isolation and identification of an endophytic strain of *Fusarium oxysporum* producing podophyllo toxin from *Juniperus recurva* *World Journal of Microbiology and Biotechnology* 24: 1115-1121.
- Kudalkar, P., Strobel, G., Riyaz-Ul-Hassan, S., Geary, B., Sears, J. 2012. *Muscodor sutura*, a novel endophytic fungus with volatile antibiotic activities. *Mycoscience* 53, 319–325.
- Kumar, S, S, D., Lau, C, S., Chan, W, K., Yang, D., Cheung, H, Y., Chen, F., Hyde, K, D., 2003. Immunomodulatory activity of an endophytic fungus from *Tripterygium wilfordii*. Proceeding of the 2<sup>nd</sup> International Conference on Medicinal Mushroom and the International Conference on Biodiversity and Bioactive Compounds, 367-373.
- Kumar, S, S, D., Lau, C, S., Chan, W, K., Yang, D., Cheung, H, Y., Chen, F., Hyde, K, D., 2005. Immunomodulatory compounds from *Pestalotiopsis leucothes* an endophytic

- fungus from *Tripterygium wilfordii*. *Life science* 72(2): 147-156.
- Kusari, S, Verma, V.C., Lamshoeft, M., Spiteller, M. 2014a. An endophytic fungus from *Azadirachta indica* A. Juss. that produces azadirachtin. *World J. Microbiol. Biotechnol.* 2012. 28, 1287–1294.
- Kusari, S. Singh, S. Jayabaskaran, C.. 2014b. Rethinking production of Taxol® (paclitaxel) using endophyte biotechnology. *Trends Biotechnol.* 32, 304–311.
- Kwon, S, L., Anderson, A, J. 2001, Laccase isozyme production by an opportunistic pathogen, a *Fusarium proliferatum* isolate from wheat. *Physiol. Mol. Plant Pathol.*, 59: 235-242.
- Lee, J, C., Yang, X., Schwartz, M., Strobel, G., Clardy, J. 1995a. The relationship between an endangered North American tree and an endophytic fungus. *Chem. Biol.* 2:721-727.
- Lee, J., Lobkovsky, E., Pliam, N, B., Strobel, G, A., Clardy, J. 1995b. Subglutinols A and B, immunosuppressive compounds from the endophytic fungus *Fusarium subglutinans*. *J. Org. Chem.* 60:7076-7077.
- Li, C., Johnson, R, P., Porco, J, A. 2002. Total synthesis of the quinine epoxide dimmer (+)-torreyanic acid, application of a biomimetic oxidation/electrocyclization/Diels-Alder dimerization cascade. *J. Am. Chem. Soc.* 125: 5059-5106.
- Li, D., Chen, Y., Pan, Q., Tao, M., Zhang, W. 2014. A new eudesmane sesquiterpene from *Nigrospora oryzae*, an endophytic fungus of *Aquilaria sinensis*. *Rec. Nat. Prod.* 8, 330–333.
- Li, J, Y., Harper, J, K., Grant, D, M., Tombe, B, O., Bashyal, B., Hess, W, M., Strobel, G, A. 2001b. Ambuic acid, a highly functionalized cyclohexenone with antifungal activity from *Pestalotiopsis spp* and *Monochaetia spp*. *Phytochemistry.* 56: 463-468.
- Li, J, Y., Sidhu, R, S., Ford, E., Hess, W, M., Strobel, G, A. 1998. The induction of taxol production in the endophytic fungus *Periconia sp.* from *Terreya grandifolia*. *J. Ind. Microbiol.* 20: 259-264.
- Li, J, Y., Strobel, G, A. 2001a. Jesterone and hydroxy-jesterone antioomycete cyclohexenone epoxides from the endophytic fungus *Pestalotiopsis jesteri*. *Phytochemistry* 57: 261-265.
- Li, J, Y., Strobel, G, A., Harper, J, K., Lobkovsky, E., Clardy, J. 2000. Cryptocin, a potent tetramic acid, antimycotic from the endophytic fungus *Cryptosporiopsis cf. quercina*. *Org. Lett.* 2:767-770.
- Li, J, Y., Strobel, G, A., Sidhu, R., Hess, W, M., Ford, E. 1996. Endophytic taxol producing fungi from Bald Cypress *Taxodium distichum*, *Microbiology.* 142:2223-2226.
- Lu, H., Zou, W.X., Meng, J.C., Hu, J., Tan, R.X. 2000. New bioactive metabolites produced.
- Luo, J., Liu, X., Li, E., Guo, L., Che, Y. 2013. Arundinols A-C and arundinones A and B from the plant endophytic fungus *Microsphaeropsis arundinis*. *J. Nat. Prod.* 76, 107–112.
- Maccheroni, W., Azevedo, J, L. 1998. Synthesis and secretion of phosphatases by endophytic isolates of *Colletotrichum musae* grown under conditions of nutritional starvation. *J. Gen. Appl. Microbiol.* 44: 381.
- Manabu, S., Takebayashi, M., Katsuichi, S., Michiko, T., Atsushi, Y., Fusao, T. 2002. Endophytes as producers of xylanase. *Journal of Bioscience and Bioengineering.* 93(1): 88-90.
- Manici, L.M., Kelderer, M., Caputo, F.,

- Mazzola, M. 2015. Auxin-mediated relationships between apple plants and root inhabiting fungi: Impact on root pathogens and potentialities of growth-promoting populations. *Plant Pathol.* 64, 843–851.
- Meshram, V., Kapoor, N., Saxena, S. 2013. *Muscodor kashayum* sp. nov.—A new volatile anti-microbial producing endophytic fungus. *Mycology* 4, 196–204.
- Miller, J. D., Laflamme, A. M., Sobol, Y., Lafontaine, P., Greenhalgh, R. 1998. Fungi and fungal products in some Canadian houses. *Int. Biodeterior.* 24:103-120.
- Newman, D.J., Cragg, G.M., and Snader, K.M., 2003. Natural Products as Source of New Drugs over the Period 1981-2002. *J. Nat. Prod.* 66: 1022-1037.
- Nielsen, J. E., Yu, S. K., Bojko, M., Marcussen, J. 2000. A-1, 4- Glecans lyase-producing endophyte of *Gracilariopsis* spp (Rhodophyta) from China. *Eur. J. Phycol.* 35:207-212.
- Petrini, O., Sieber, T. H., Toti, L., Viret, O., 1992. Ecology, metabolite production and substrate utilization in endophytic fungi-Natural Toxins. 1: 185-196.
- Porter, J. R., Folsom, P. A., Eyberger, A. L. 2004. (Newark, DE). Endophytes for production of podophyllotoxin. US patent 20040248265.
- Pu, X., Qu, X.; Chen, F., Bao, J., Zhang, G., Luo, Y. 2013. Camptothecin-producing endophytic fungus *Trichoderma atroviride* LY357: Isolation, identification, and fermentation conditions optimization for camptothecin production. *Appl. Microbiol. Biotechnol.* 97, 9365–9375.
- Pulici, M., Sugawara, F., Koshino, H., Okada, G., Esumi, Y., Uzawa, J., Yoshida, S. 1997. Metabolites of *Pestalotiopsis* spp endophytic fungus of *Taxus brevifolia*. *Phytochemistry* 46: 313-319.
- Pulici, M., Sugawara, F., Koshino, H., Uzawa, J., Yoshida, S., Lobkovsky, E., Clardy, J., 1996a. Pestalotiopsin-A and pestalotiopsin-B, new caryophyllenes from an endophytic fungus of *Taxus brevifolia*. *J. Org. Chem.* 61: 2122-2124.
- Pulici, M., Sugawara, F., Koshino, H., Uzawa, J., Yoshida, S., Lobkovsky, E., Clardy, J. 1996b. A new isodiminol from *Pestalotiopsis* sp. *J. Nat. Prod.* 59: 47-48.
- Puri, S. C., Nazir, A., Chawla, R., Arora, R., Riyaz-ul-Hasan., Amina, T., Ahmed, B., Verma, V., Singh, S., Sagar, R., Sharma, A., Kumar, R., Sharma, R. K. Qazi, G. N. 2005a. The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans, *Journal of Biotechnology*.
- Puri, S. C., Verma, V., Amna, T., Qazi, G. N., Spitteller, M. 2005b. An Endophytic fungus from *Nothapodytes foetida* that Produce Camptothecin. *J. Nat. Prod.* 68(12): 1717-1719.
- Qiang, X., Weiss, M., Kogel, K.H., Schäfer, P. 2012. *Piriformospora indica*—A mutualistic basidiomycete with an exceptionally large plant host range. *Mol. Plant Pathol.* 13, 508–518.
- Reddy, P. V., Lam, C. K., Belanger, F. C. 1996. Mutualistic fungal endophytes express a proteinase that is homologous to proteases suspected to be important in fungal pathogenicity. *Plant Physiol.*, 111: 1209-1218.
- Rehman, S., Shahl, A., S., Kour, A., Andrabi, R., Sultan, P., Sudan, P and Qazi, G. N. 2008. An Endophytic *Neurospora* sp. from *Nothapodytes foetida* producing Camptothecin. *Applied Biochemistry and Microbiology*, 44(2). 203–209.

- Schiff, P. B., Horowitz, S. B. 1980. Taxol stabilizes microtubules in mouse fibroblast cells. *Proc-Natl. Acad. Sci. USA* 77: 1561-1565.
- Selim K.A.1., El-Beih, A.A.1., AbdEl-Rahman T.M., El-Diwany A.I. 2012. Biology of endophytic fungi. *Curr. Res. Environ. Appl. Mycol.*, 2 (1) 31–82.
- Sirrenberg, A., Göbel, C., Grond, S., Czempinski, N., Ratzinger, A., Karlovsky, P., Santos, P., Feussner, I., Pawlowski, K. 2007. *Piriformospora indica* affects plant growth by auxin production. *Physiol. Plant.* 131, 581–589.
- Soca-Chafre, G. Rivera-Orduña, F.N. Hidalgo-Lara, M.E. Hernandez-Rodriguez, C. Marsch, R. Flores-Cotera, L.B. 2011. Molecular phylogeny and paclitaxel screening of fungal endophytes from *Taxus globosa*. *Fungal Biol.* 115, 143–156.
- Stierle, A., Strobel, G. A., Stierle, D. 1993. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of pacific yew. *Science* 260:214-216.
- Stinson, M., Ezra, D., Strobel, G. 2003. An endophytic *Gliocladium* sp. of *Eucryphia cordifolia* producing selective volatile antimicrobial compounds. *Plant Sci.* 165:913-922.
- Strobel, G. A. 2002a. Microbial gifts from rain forests. *Can. J. Plant Pathol.* 24: 14-20.
- Strobel, G. A., Ford, E., Worapong, J., Harper, J. K., Arif, A. M., Grant, D.M., Fung, P. C. W., Chan, K. 2002b. Ispoestacin, an isobenzofuranone from *Pestalotiopsis microspore*, possessing antifungal and antioxidant activities. *Phytochemistry.* 60: 179-183.
- Strobel, G. A., Stierle, A., Stierle, D., Hess, W. M. 1993. *Taxomyces andreanae* a proposed new taxon for a bulbiferous hyphomycete associated with Pacific yew. *Mycotaxon.* 47: 71-78.
- Strobel, G. A. 1997. Rainforest endophytes and bioactive products. *Crit. Rev. Biotechnol.* 22:315-333.
- Suffness, M. 1995. Taxol. Science and applications CRC Press, Boca Raton. Fla.
- Sun, Y., Xun, K., Wang, Y., Chen, X. 2009. A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. *Anti-Cancer Drugs* 20, 757–769.
- Tacchowisan, T., Lu, C., Shen, Y., Lumyong, S. 2005. Secondary metabolites from endophytic *Streptomyces aureofaciens* and their antifungal activity. *Microbiology.* 151: 1691-1695.
- Tan, R. X., Zou, W. X. 2001. Endophytes; a rich source of functional metabolites *Nat. Prod. Rep.* 18: 448-459.
- Teles, H. L., Silva, G. H., Castro, G., Mida, S., Pereira, J. O., Costa, C. M., Haddad, R., Eberilu, M. N., and Young, M. C. M., Aranjó, A. R. 2005. Benzopyrans from *Curvularia spp* an endophytic fungus associated with *Ocotea corymbosa* (Lauraceae). *Phytochemistry* 66(18): 2363-2367.
- Umashankar, T., Govindappa, M., Ramachandra, Y. L. 2014. *In vitro* antioxidant and antimicrobial activity of partially purified coumarins from fungal endophytes of *Crotalaria pallida*. *Int. J. Curr. Microbiol. Appl. Sci.* 3, 58–72.
- Verma, V.C., Lobkovsky, E., Gange, A.C., Singh, S.K., Prakash, S. 2011. Piperine production by endophytic fungus *Periconia* sp. isolated from *Piper longum* L. *J. Antibiot.* 64, 427–431.
- Vinodhini, D., Agastian, P. 2013. Berberine

- production by endophytic fungus *Fusarium solani* from *Coscinium fenestratum*. *Int. J. Biol. Pharm. Res.* 4, 1239–1245.
- Wagenaar, M., Corwin, J., Strobel, G, A., Clardy, J. 2000. Three new Cytochalasins produced by an endophytic fungus in the genus *Rhanocladiella*. *J. Nat. Prod.* 63: 1692-1695.
- Walsh, T, A. 1992. Inhibitors of B-glucan synthesis In J.A. Sutcliffe and N. H. Georgopapadakou (ed.). Emerging targets in antibacterial and antifungal chemotherapy. Chapman and Hall, London, United Kingdom. 349-373.
- Wang, J., Li, G., Lu, H., Zheng, Z., Huang, Y., Su, W. 2000. Taxol from *Tubercularia* sp. Strain TF5, an endophytic fungus of *Taxus matrel*. *FEMS Microbiol. Lett.* 193: 249-253.
- Waqas, M., Khan, A.L., Kamran, M., Hamayun, M., Kang, S.M., Kim, Y.H., Lee, I.J. 2012. Endophytic fungi produce gibberellins and indoleacetic acid and promotes host-plant growth during stress. *Molecules* 17, 10754–10773.
- Waqas, M., Khan, A.L., Kang, S.M., Kim, Y.H., Lee, I.J. 2014. Phytohormone-producing fungal endophytes and hardwood-derived biochar interact to ameliorate heavy metal stress in soybeans. *Biol. Fertil. Soils*, 50, 1155–1167.
- Worapong, J., Strobel, G, A., Daisy, B., Castillo, U., Baird, G., Hess, W, M. 2002. *Muscodor roseaus* an endophyte from *Grevillea pteridifolia*. *Mycotaxon.* 81: 463-475.
- Xiong, Z,Q., Yang, Y,Y., Zhao, N., Wang, Y. 2013. Diversity of endophytic fungi and screening of fungal paclitaxel producer from Anglojap yew, *Taxus x media*. *BMC Microbiol.* 13, 71.
- Zaher, A.M., Moharram, A.M., Davis, R., Panizzi, P., Makboul, M.A., Calderón, A.I. 2015. Characterisation of the metabolites of an antibacterial endophyte *Botryodiplodia theobromae* Pat. of *Dracaena draco* L. by LC–MS/MS. *Nat. Prod. Res.* 29, doi:10.1080/14786419.2015.1012715.
- Zhang, B., Salituro, G., Szalkowaki, D., Li, Z., Zhang, Y., Royo, I., Vilella, D., Dez, M., Pelacz, F., Ruby, C., Kendali, R, L., Mao, X., Griffin, P., Calaycay, J., Zieruth, J, R., Heck, J, V., Smith, R, G., Moller, D, E. 1999. Discovery of small molecule insulin mimetic with antidiabetic activity in mice. *Sci.*, 284: 974-981.
- Zhang, Y.Z., Sun, X., Zechner, D., Sachs, B., Current, W., Gidda, J., Rodriguez, M., Chen, S, H. 2001. Synthesis and antifungal activities of novel 3-amido bearing pseudomycin analogs. *Bioorg. Med.Chem.*, 11: 903-907.

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