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Review

# Biosynthetic Sharing of Anticancerous Natural Products by Plants and Endophytic Fungi

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## Abstract

Endophytic fungi are diverse microbes that reside within the plants without causing any harmful effect to the host. They generally have a mutualistic relation with the host plant for the nutritional requirement. By occupying within the plant metabolism of these fungi have been known to be directed towards synthesis of metabolites which are beneficial to the plant in various ways. Some of these fungi have been shown to have extreme chemical adaptation with its host plant as evidenced by the production of plant specific compounds. This biosynthetic sharing is assumed to be acquired during the long term co-evolution and exchange of genetic material between plant and fungi. Several studies have also suggested the presence of biosynthetic pathway intermediates in endophytic fungi which resemble to that present in host plant. Even though a complete understanding on the biosynthetic sharing by plant and endophytic fungi is unknown, it is indicative of presence of yet to know genetic mechanisms which might have evolved as per the adaptation requirement. However, these amazing processes can have immense promises for large scale production and purification of medicinal compounds. Current review is directed to provide insight in to complexity of this process.

## Introduction

Endophytic fungi are microorganisms that live within plants and have been characterized from wide range of plants [1-3]. They generally provide beneficial support to their host. The distribution of fungal endophytes within the plant can vary and a single species can inhabit different host plants [4]. The endophytic distribution in host plant depends upon nutritional requirement [5]. Ecological and geographical conditions can also have determining effect on fungi involved in endophytic association [26]. The interaction between host plant and endophytic fungus is considered to be controlled by various genes of both partners under the modulation of environment. Endophytic fungi have been isolated from wide range of plants ranging from grasses, lichens, medicinal plants, palm to trees [27]. Endophytic fungi generally belong to Ascomycetes and by Basidiomycetes [28] The frequently occurring endophytic fungi in leaves of medicinal climbers and grasses include *Nigrospora shaerica*, *Cladosporium cladosporioides*, *Chaetomium globosum*, *Phyllosticta* sp., *Alternaria alternata*, *Cladosporium herbarum*, *Curvularia lunata* and *Gliocladium roseum* [6].

**Colonization of fungi with in host plant :** Endophytic fungal colonization is considered to occur not by an incidental opportunity but by chemotactic interaction with host plants. The secondary metabolites produced by the plants are likely restrict the endophytic colonization. However, some of these bioactive compounds are detoxified by the endophytes and is assisted by production of enzymes like laccase, protease, cellulase and xylanase which pave the way for endophytic entry into the host plant [29], [7]. The endophytic mechanisms to interact with plant bioactive compounds can have determining effect on a certain extent to their host range for colonization[30].

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**Ecological function of endophytes in host plants:** The endophytic fungi that reside in plant tissues have important role in plant symbiosis, and plant growth under stressful environmental conditions. They are also involved in the production of secondary metabolites of to support plant growth under stress conditions together with valuable pharmaceutical substances of biotechnological interest. The duplicative production of bioactive compounds by endophytic fungi has been shown to provide protection to plants during biotic and abiotic stress. For example, taxol producing endophytic fungus, *Paraconiothyrium* sp., growing at the branch points of Yew trees (species Taxus x media ) has been reported to prevent the growth of wood decaying pathogens such as *Heterobasidion annosum, Phaeolus schweinitzii* and *Perenniporia subacida* . Here the taxol acted as a fungicide and the fungicide-containing hydrophobic barriers appears to be novel host immunity mechanism [31].

**Endophytic Fungal classification based on colonization behavior:** Based on colonization behavior, endophytic fungi can be of different types. Class I endophytic fungi includes clavicipitaceous endophytes which colonize above and below ground plant tissues like rhizosphere, endorhiza, and aerial tissues [32] [24]. Class II endophytic fungi involves those which are transmitted horizontally or vertically [8]. Class III endophytic fungi includes the members of *Dikaryomycota* (*Ascomycota* or *Basidiomycota*) which are horizontally transmitted and mainly restricted to aerial tissues of plants [25] [9]. The endophytes in class IV comprise dark, septate forms which reside inter or intracellularly in cortical cell layers and are restricted to roots [33-36].

**Fungal endophytes and bioactive molecules:** Endophytic fungi are important sources of biologically active natural products and hence have enormous potential for the discovery of new drugs and have important agricultural and industrial applications [37]. However, these highly diverse fungi are least explored for bioactive products. It is estimated that only about 5% of fungi have been isolated and characterized and the rest remains unexplored [38]. The potential of known endophytes are also least explored, due to unknown biosynthetic pathways and lack of expression of biosynthetic gene clusters [39]. However modification of culture techniques by coculturing, chemical induction, epigenetic modulation, media engineering and metabolite remodeling in association with fermentation technology have been used to scale up endophytic production of natural products [11]. The interaction between plant and fungi can be considerably diverse. The host metabolism may get induced by endophytes, likewise endophytic metabolism can be induced by host. Both the partners may likely to metabolize each others compounds also [40]. Bioprospecting of endophytes can remarkably offer novel ways to explore the isolated strains for the discovery of bioactive metabolites for human welfare[50].

Endophytic fungi play important role in the biosynthesis of plant secondary metabolites [23]. However, biosynthesis of same compound in both plant and fungi is scientifically impressive. The biosynthetic pathway studies have suggested the likely presence of similar but distinct pathways for secondary metabolite production in plants and fungi [12]. Also several studies have revealed similar biosynthetic pathway intermediates in host plant and endophytic fungi. But the entire biosynthetic pathway for production of compounds is not studied in detail.

The presence of biosynthetic basis for the production of phytochemicals in fungi offers novel use of endophytes to improve the existing drug and also to generate novel metabolites. These modified compounds can have promising medicinal applications [51]. Endophytic fungi isolated from *Camptotheca acuminata* have been identified to produce 9-methoxy camptothecin and 10-hydroxycamptothecin which are analogues of anticancerous compound camptothecin with potential anticancer activity and lower toxicity [21]. Hence the biosynthetic promises of endophytic fungi due to the presence of phytochemical biosynthetic machinery are tremendous. The examples discussed as follows provide deeper insight in to the presence of many fungal species in same plant with the ability to produce plant specific compounds.

**Podophyllotoxin and its analogues from endophytic fungi :** *Podophyllum* spp. (family: Berberidaceae) are remarkable for its ability to synthesize podophyllotoxin, 4-demethyl podophyllotoxin, podophyllotoxin glycoside and polyphenolic compounds that have application as anticancer, antiviral, antibacterial, immunostimulating, and antirheumatic drugs [52]. It blocks cell division by inhibiting the microtubular assembly of mitotic apparatus. *Trametes hirsute,* an endophytic fungus isolated from *Podophyllum* sp. has been described as a promising alternative source of podophyllotoxin and related aryl tetralin lignans. The endophytic ligans are biologically active and have antioxidant, anticancer and radioprotective properties [53]. From the *Phialocephala podophylli* isolated from *Podophyllum peltatum*, secoisolariciresinol dehydrogenase gene was characterized. This assist the dehydrogenation of secoisolariciresinol to form matairesinol, a mid pathway intermediate product in podophyllotoxin biosynthesis [54]. Podophyllotoxin produced by various endophytic fungi are given in the Table 1**.**

**Table 1 :** Endophytic fungi producing podophyllotoxin and its host plant

| Endophytic fungi | Plant secondary metabolite | Host plant | References |
|---|---|---|---|
| *Alternaria* sp. | Podophyllotoxin | *Sinopodophyllum hexandrum* | Yang *et al.*, 2003 |
| *Monilia* sp. | Podophyllotoxin | *Dysosma veitchii* | Yang *et al.*, 2003 |
| *Penicillium* sp. | Podophyllotoxin | *Sinopodophyllum hexandrum* | Yang *et al.*, 2003 |
| *Penicillium* sp. | Podophyllotoxin | *Diphylleia sinensis* | Yang *et al.*, 2003 |
| *Penicillium* sp. | Podophyllotoxin | *Dysosma veitchii* | Yang *et al.*, 2003 |
| *Penicillium implicatum* | Podophyllotoxin | *Diphylleia sinensis* | Zeng *et al.*, 2004 |
| *Penicillium implicatum* | Podophyllotoxin | *Dysosma veitchii* | Guo *et al.*, 2004 |
| *Phialocephala fortinii* | Podophyllotoxin | *Sinopodophyllum peltatum* | Eyberger *et al.*, 2006 |
| *Trametes hirsuta* | Podophyllotoxin | *Sinopodophyllum peltatum* | Puri *et al.*, 2006 |
| *Alternaria* sp. | Podophyllotoxin | *Sabina vulgaris* | Lu *et al.*, 2006 |
| *Alternaria neesex* | Podophyllotoxin | *Sinopodophyllum hexandrum* | Cao *et al.*, 2007 |
| *Fusarium oxysporum* | Podophyllotoxin | *Juniperus recurva* | Kour *et al.*, 2008 |
| *Aspergillus fumigatus* | Podophyllotoxin | *Juniperus communis L.* | Kusari *et al.*, 2009 |
| *Alternaria tenuissima* | Podophyllotoxin | *Sinopodophyllum emodi* | Liang *et al.*, 2015 |
| *Phialocephala podophylli* | Podophyllotoxin | *Podophyllum peltatum* | Sonja *et al.*, 2015 |
| *Alternaria tenuissima* | Podophyllotoxin | *Sinopodophyllum emodi* | Zizhen *et al.*, 2016 |

**Taxol producing endophytic fungi :** Taxol (Paclitaxal) reported from all species of Taxus is an anticancerous drug which act as a microtubule inhibitor. The endophytic origin of taxol was first reported from *Taxomyces andreanae*, an endophyte of *Taxus brevifolia*. The gene involved in taxol biosynthetic pathway was identified from an endophytic fungus *Clasdosporium cladosporiodes* isolated from *Taxus media* (yew species). The gene responsible for taxol production, 10-deacetylbaccatin-III-10-O-acetyl transferase gene shared 99 % identity with with *Taxus media* and 97 % identity with *Taxus wallichiana var. marirei* [13]. Paclitaxel biosynthetic gene candidate in endophytic fungus *P. aurantiogriseum* has also been reported. But it was different from the host *C. avellana* and *T. baccata* in terms of aminoacid sequences [55]. Taxol producing endophytic fungi mostly belonging to ascomycetes and imperfect fungi. These include the genera *Fusarium, Pestalotia, Truncatella, Pestalotiopsis, Alternaria, Seimatoantlerium, Sporormia, Trichothecium, Tubercularia, Pithomyces, Monochaetia*, and *Penicillium* amongst others [20]. Both Taxus and non Taxus species have the ability to produce taxol which implies host and placlitaxel producing fungi have biological diversity. Paclitaxel produced by endophytic fungi and respective host plants are represented in Table 2 and genes responsible for taxol biosynthesis are represented in Table 3.

**Table 2 :** Endophytic fungi producing Paclitaxel and its host plant

| Endophytic fungi | Plant secondary metabolite | Host plant | Bioactive properties of secondary metabolites | References |
|---|---|---|---|---|
| *Taxomyces andreanae* | Paclitaxel | *Taxus brevifolia* | Antitumor | Stierle *et al.*, 1993 |
| *Taxomyces* sp. | Paclitaxel | *Taxus yunnanensis* | Antitumor | Qiu *et al.*, 1994 |
| *Pithomyces* sp.<br>*Alternaria* sp. | Paclitaxel<br>Paclitaxel | *Taxus sumatrana*<br>*Taxus cuspidata* | Antitumor | Strobel *et al.*, 1996<br>Strobel *et al.*, 1996 |
| *Pestalotiopsis microspora* | Paclitaxel | *Taxus wallichiana* | | Strobel *et al.*, 1996 |
| *Pestalotiopsis guepinii* | Paclitaxel | *Wollemia nobilis* | Antitumor | Strobel *et al.*, 1997 |
| *Periconia* sp. | Paclitaxel | *Torreya grandifolia* | | Li *et al.*, 1998 |
| *Alternaria* sp. | Paclitaxel | *Ginkgo biloba* | | Kim *et al.*,1999 |
| *Phyllosticta citricarpa* | Paclitaxel | *Citrus medica* | Antitumor | Kumaran *et al.*, 2008 |
| *Botryodiplodia theobromae*<br>*Fusarium lateritium, Monochaetia* sp., *Pestalotia bicilia* | Paclitaxel | *Taxus baccata* | Antitumor | Venkatachalam *et al.*, 2008 |
| *Aspergillus fumigatus* | Paclitaxel | *Podocarpus* sp. | Antitumor | Sun *et al.*, 2008 |
| *Fusarium solani* | Paclitaxel | *Taxus celebica* | Antitumor | Chakravarthi *et al.*, 2008 |
| *Ozonium* sp.<br>*Alternaria alternata*<br>*Botrytis* sp.<br>*Ectostroma* sp.<br>*Fusarium mairei*<br>*Papulaspora* sp.<br>*Tubercularia* sp. | Paclitaxel | *Taxus chinensis* var. *mairei* | Antitumor | Guo *et al.*, 2009 |
| *Pestalotiopsis terminaliae* | Paclitaxel | *Terminalia arjuna* | Antitumor | Gangadevi and Muthumary, 2009 |
| *Phyllosticta dioscoreae* | Paclitaxel | *Hibiscus rosa-sinensis* | Antitumor | Kumaran *et al.*, 2009 |
| *Fusarium solani* | Paclitaxel | *T. chinensis* | | Deng *et al.*, 2009 |
| *Guignardia mangiferae*<br>*Fusarium proliferatum*<br>*Lasiodiplodia theobromae*<br>*Phoma medicaginis*<br><br>*Aspergillus fumigatus, Alternaria tenuissima*<br><br>*Grammothele lineata*<br>*Cladosporium sp.* | Paclitaxel<br><br>Paclitaxel<br>Paclitaxel<br><br>Paclitaxel<br><br><br>Paclitaxel<br>Paclitaxel | *Taxus x media*<br><br>*Salacia oblonga*<br>*Taxus wallichiana* var. *mairei*<br><br>*Taxodium distichum*<br>*Terminalia arjuna*<br>*Corchorus olitorius*<br>*Taxus baccata* | Antitumor<br><br>Antitumor<br>Antitumor<br><br>Antitumor<br><br><br>Antitumor<br>Antitumor | Xiong *et al.*, 2013<br><br>Roopa *et al.*, 2015<br>Jian *et al.*, 2017<br><br>Ahmed *et al.*, 2017<br><br><br>Das *et al.*, 2017<br>Abdollah *et al.*, 2017 |

**Table 3 :** Taxol biosynthetic genes of endophytic fungi

| Endophytic fungi | Genes in taxol biosynthesis | Host plant | References |
|---|---|---|---|
| *Cladosporium-cladosporoides* | 10-Deacetylbaccatin III-10-O-Acetyl Transferase (DBAT) | *Taxus x media* | Zhang *et al*., 2009 |
| *Aspergillus candidus* | 10-Deacetylbaccatin III-10-O-Acetyl Transferase (DBAT) | *Taxus x media* | Zhang *et al*., 2009 |
| *Mucor rouxianus* | Taxadiene Synthase (TS) | *Taxus chinensis* | zhou *et al*., 2007 Miao *et al*., 2009 |
| *Taxomyces andreanae* | Taxadiene Synthase (TS) | *Taxus brevifolia* | Staniek *et al*., 2009 |
| *Gibberella intermedia* | Taxadiene Synthase (TS) | *Taxus x media* | Xiong *et al*., 2013 |
| *Taxomyces andreanae* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus brevifolia* | Staniek *et al*., 2009 |
| *Colletotrichum -gloeosporioides* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus x media* | Xiong *et al*., 2013 |
| *Guignardia mangiferae* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus x media* | Xiong *et al*., 2013 |
| *Fusarium redolens* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus baccata sub* sp. *wallichiana* | Garyali *et al*., 2013 |
| *Fusarium tricinctum* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus baccata sub* sp. *wallichiana* | Garyali *et al*., 2014 |
| *Fusarium avenaceum* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus baccata sub* sp. *wallichiana* | Garyali *et al*., 2014 |
| *Paraconiothyrium -brasiliense* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus baccata sub* sp. *wallichiana* | Garyali *et al*., 2014 |
| *Microdiploidia* sp.<br><br>*Lasiodiplodia theobromae*<br>*Cladosporium sp.,*<br>*Alternaria sp.,*<br>*Fusarium sp.* | Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT)<br>10-deacetylbaccatin III-10-*O*-acetyl transferase<br>Baccatin III Aminophenylpropanoyl-13-O-Transferase (BAPT) | *Taxus baccata sub* sp. *wallichiana*<br>*Piper nigrum*<br><br>*Taxus baccata* | Garyali *et al*., 2014<br><br>Balendra *et al*.,2017<br>Abdollah *et al*., 2017 |

**Camptothecin producing endophytic fungi:** Camptothecin (CPT), the third largest anticancer drug is mainly produced by *Camptotheca acuminata* and *Nothapodytes foetid*a. This natural DNA topoisomerase I inhibitor is commonly used as a model hydrophobic compound for anticancer drug and is also known for its activity against human immunodeficiency virus (HIV). Now a day chemically converted forms such as 10- hydroxyl camptothecin, topotecan and irinotecan were used for lung cancer and refractory ovarian cancer [56], [14]. Several attempts have been made to enhance camptothecin production from plant cell and tissue culture but the yield has been found to be too low to support the heavy demand from the global market as camptothecin itself is the starting material for clinical purpose. Camptothecin producing endophytes are represented in Table 4

**Vincristine And Vinblastine from endophytic fungi :** Vincristine and vinblastine are the major vinca alkaloids used in chemotherapy of cancer. They inhibit cell proliferation by binding to microtubules which leads to mitotic block and apoptopsis [16]. The only source of vinca alkaloids are the green glossy leaves of *Catharanthus roseus* (*Vinca rosea*) , a short lived perennial plant of the Apocyanaceae family. In 2004, Xianzhi et al, have reported the production of vincristine from *Fusarium oxysporum,* an endophyte of *Catharanthus roseus. The endophytic fungus such as Colletotrichum gloeosporioides, Alternaria tenuissima , Aspergillus niger, Colletotrichum kahawae, Flavodon flavus, Dothideomycetes sp., Eutypa sp., Talaromyces radicus [15], Eutypella sp. [15] Chaetomium globosum, Nigrospora sphaerica*[22]**,** *Fusarium solani, Fusarium oxysporum* [17] *and Alternaria sp. [19] identified from Catharanthus roseus were also reported to produce vinca alkaloids.* Talaromyces radicus was found to have constitutive expression of tryptophan decarboxylase gene responsible for vinca alkaloid production [16]. This example further proves endophytic competency to autonomously synthesize vinca alkaloids similar to those of host plants.

**Table 4 -** Camptothecin producing endophytes and host plants

| Endophytic fungi | Plant secondary metabolite | Host plant | Bioactive properties of secondary metabolites | References |
|---|---|---|---|---|
| *Entrophospora-infrequens*<br><br>*Entrophospora-infrequens* | Camptothecin<br><br>Camptothecin | *Nothapodytes foetida*<br><br>*Nothapodytes foetida* | Antitumor<br><br>Antitumor | Puri *et al.*, 2005<br><br>Amna *et al.*, 2006 |
| *Neurospora crassa* | Camptothecin | *Nothapodytes foetida* | Antitumor | Rehman *et al.*, 2008 |
| *Fusarium solani*<br><br>*Nodulisporium* sp. | Camptothecin<br><br>Camptothecin | *Camptotheca acuminate*<br><br>*Nothapodytes- foetida* | Antitumor<br><br>Antitumor | Kusari *et al.*, 2009<br><br>Rehman *et al.*, 2009 |
| *Fusarium solani*<br><br>*Botryosphaeria-parva*<br>*Aspergillus sp.*<br>*Trichoderma-atroviride* | Camptothecin<br><br>Camptothecin<br><br>Camptothecin | *Apodytes-dimidiate*<br>*Nothapodytes-nimmoniana*<br><br>*Camptotheca-acuminate* | Antitumor<br><br>Antitumor<br><br>Antitumor | Shweta *et al.*, 2010<br>Gurudatt *et al.*, 2010<br><br>Xiang *et al.*, 2013 |
| *Botryosphaeria-dothidea*<br><br>Colletotrichum-gloeosporioides<br>Fusarium solani | 9-Methoxycamptothecin<br><br>10-hydroxycamptothecin<br><br>Camptothecin | Camptotheca- acuminate<br><br>Camptotheca- acuminate<br><br>Camptotheca- acuminate | Antitumor<br><br>Antitumor<br><br>Antitumor | Xiaowei Ding *et al.*, 2013<br><br>Hao *et al.*, 2014<br><br>Xueqin *et al.*, 2017 |

**Cinchona alkaloids:** Cinchona alkaloids such as quinine, quinidine, cinchonidine, and cinchonine are antipyretic, antimalarial, analgesic and anti-inflammatory compounds isolated from endophytes like *Phomopsis* sp., *Diaporthe* sp., *Schizophyllum* sp., *Penicillium* sp., *Fomitopsis* sp., *and Arthrinium* sp. of *Cinchona ledgeriana[57]*. Huperzine A has been characterized from endophytes of *Phlegmariurus cryptomerianus like Blastomyces* sp., and *Botrytis* sp. [18]. Other anticancerous compounds produced by endophytic fungi are represented in Table 5.

**Table 5 :** Other anticancerous compounds produced by endophytic fungi

| Endophytic fungi | Plant secondary metabolite | Host plant | Bioactive properties of secondary metabolites | References |
|---|---|---|---|---|
| | | | | |
| *Periconia atropurpurea* | Periconicin | *Xylopia aromatica* | Anticancerous | Stierle *et al.*, 1993 |
| | | | | Lee *et al.*, 1995 |
| *Rhinocladiella* sp. | *Cytochalasin 1*<br>*Cytochalasin 2*<br>*Cytochalasin 3* | *Tripterygium wilfordii* | Anticancerous | |
| | *Cytochalasin E* | *Torreya taxifolia* | | Lee *et al.*, 1995 |
| *Pestalotiopsis microspora* | *Torreyanic acid* | | Anticancerous | |
| *Acremonium sp.* | | *Taxus baccata* | | Strobel *et al.*, 1999 |
| | Leucinostatin A | | Anticancerous | Stierle *et al.*, 1999 |
| *Aspergillus parasiticus* | | *Sequoia sempervirens* | | |
| | Sequoiatones A | | Anticancerous | |
| *Cytospora* sp. | Cytoskyrin A | *Conocarpus erectus* | Anticancerous | Brady *et al.*, 2000 |
| *Phomopsis longicolla* | Dicerandrol A | *Dicerandra frutescens* | Anticancerous | Wagenaar and Clardy, 2001 |
| *Xylaria* sp. | Phomoxanthone A | *Licuala spinosa.* | Anticancerous | Isaka *et al.*, 2001 |
| *Phomopsis* sp. | Phomoxanthone B | *Tectona grandis* | Anticancerous | Isaka *et al.*, 2001 |
| *Aspergillus niger* | Rubrofusarin B | *Cynodon dactylon* | Anticancerous | Song *et al.*, 2004 |
| *Apiospora montagnei* | Epiepoxydon | *Polysiphonia- violacea* | Anticancerous | Klemke *et al.*,2004 |
| *Chaetomium globosum* | *Globosumone A*<br>*Globosumone B* | Ephedra fasciculata | Anticancerous | Bashyal *et al.*, 2005<br>Turbyville *et al.*, 2006 |
| *Chaetomium chiversii* | Radicicol | *Ephedra fasciculata* | Anticancerous | |
| Chaetomium globosum | Chaetoglobosin U<br>Chaetoglobosin C<br>Chaetoglobosin F<br>Chaetoglobosin E<br>Penochalasin A | Imperata cylindrica | Anticancerous | Ding *et al.*, 2006 |
| *Chaetomium. globosum* | Chaetopyranin | *Polysiphonia- urceolata* | Anticancerous | Wang *et al.*, 2006 |
| *Emericella nidulans* | Emindole DA | *Mediterranean- green alga* | Anticancerous | Kralj *et al.*, 2006 |

| | | | | |
|---|---|---|---|---|
| *Mycelia sterilia* | SpiromamakoneA | *Knightia excelsa* | Anticancerous | van der Sar *et al.*, 2006 |
| *Periconia atropurpurea* | Periconicin B | *Xylopia aromatica* | Anticancerous | Teles *et al.*, 2006 |
| *Fusarium oxysporum* | Bikaverin | *Cylindropuntia-echinocarpa* | Anticancerous | Zhan *et al.*, 2007 |
| *Hypoxylon truncatum* | Daldinone | *Artemisia annua* | Anticancerous | Gu *et al.*, 2007 |
| *Phyllosticta spinarum* | Tauranin | *Platycladus- orientalis* | Anticancerous | Wijeratne *et al.*, 2008 |
| *Alternaria* sp. | Alternariol | *Polygonum- senegalense* | Anticancerous | Aly *et al.*, 2008 |
| *Thielavia-subthermophila* | Emodin | *Hypericum- perforatum* | Anticancerous | Kusari *et al.*, 2009 |
| *Pestalotiopsis photiniae* | Photinides A | *Roystonea regia* | Anticancerous | Ding *et al.*, 2009 |
| *Chaetomium* sp. | Cochliodinol | *Salvia officinalis* | Anticancerous | Debbab *et al.*, 2009 |
| *Phomopsis* sp. | Oblongolide Y | *Musa acuminata* | Anticancerous | Bunya *et al.*, 2010 |
| *Halorosellinia* sp. | Anthracenedione | *Avicennia germinans* | Anticancerous | Zhang *et al.*, 2010 |
| *Guignardia* sp. | Anthracenedione | *Avicennia germinans* | Anticancerous | Zhang *et al.*, 2010 |
| *Aspergillus clavatus*<br><br>*Cephalotheca faveolata* | *Brefeldin A*<br><br>Sclerotiorin | *Taxus mairei*<br><br>*Eugenia jambolana* | Anticancerous<br><br>Anticancerous | Kharwar *et al.*, 2011<br><br>Giridharan *et al.*, 2012 |
| *Aspergillus sp.*<br><br>*Chaetomium globosum*<br>*Polyporales sp.*<br><br>*Pestalotiopsis microspora*<br><br>*Diaporthe sp.*<br><br>*A.alternate,*<br>*C. taiwanense* | 6-Methyl-1,2,3-trihydroxy-7, 8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide<br><br>Chaetoglobosin A<br>Emodin<br><br>7-epi-10-deacetyltaxol<br><br>Trichalasin<br><br>5,7-dihydroxy flavone | *Gloriosa superba*<br><br>*Ginkgo biloba*<br>*Rheum emodi*<br><br>*Taxodium Mucronatum*<br><br>*Taxus baccata*<br><br>*Passiflora incarnata* | Anticancerous<br><br>Anticancerous<br><br><br>Anticancerous<br><br>Anticancerous<br><br>Anticancerous | Budhiraja *et al.*, 2012<br><br>Li *et al.*, 2014<br>Refaz *et al.*, 2017<br><br>Kamalraj *et al.*, 2017<br><br>Vasundhara *et al.*, 2017<br><br>Seetharaman *et al.*, 2017 |

## Conclusion

Endophyic fungi exhibit complex interaction with the host and live inside the plant without causing any apparent symptoms of disease. They develop significant and novel characteristics during the long term coexistence or coevolution. For maintaining stable symbiosis, they secrete various enzymes. The functioning of these enzymes such as laccase, protease, cellulase and xylanase decides the colonization range and growth of fungal endophytes. During the coevolution of endophytes and host plants the endophytes might have adapted to their environment by genetic variation resulting in the ability to synthesis some metabolites produced by host plant. Even the commercial productions of metabolic compounds by using endophytic fungi are emerging. This demands deeper understandings on host and endophytic interaction at the molecular level. The use of fungal endophytes for improving existing drug is becoming a new way to generate bioactive compounds.

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