Int J Pharm Bio Sci 2015 Jan; 6(1): (B) 887 - 898

Review Article Microbiology

International Journal of Pharma and Bio Sciences

ISSN
0975-6299

ENDOPHYTIC FUNGI AS RESOURCE OF BIOACTIVE COMPOUNDS

VED PRAKASH*

Department of Biotechnology, Madhav Institute of Technology and Science,
M.I.T.S. Gwalior, Madhya Pradesh 474005, India

ABSTRACT

Endophytic fungi live inside plants, apparently do not cause any harm to their hosts and may play important roles in defense and growth promotion. Endophytes are microorganism that lives between living plant cell. Their relationship may vary with plant from symbiotic to bordening on pathogenic. Endophytes may contribute to their host plant by producing a plethora of substances that provide protection and ultimately survival value to the plant. Of all plant species on only a few grass species have had their complete complement of endophyte studied. As a result the opportunity to find new and interesting endophyte derived bioactive compound is great. Endophytes have proved to be a rich source of novel chemistry and biological molecules. The review aim at endophyte successful isolation methods , media used as well as different as well as production of secondary metabolites with special emphasis on anticancerous, anti-TB, antimicrobial, antibiotics along with a huge number of other secondary metabolites for commercial exploitation in pharmaceutical and medical field. With day to day increasing demand of drugs plant sources are proving to be able to meet the tremendous demand, endophytes can serve the purpose of mass scale production of bioactive metabolites to mitigate the increasing demand and prospect of finding new drugs that may be effective candidates for treating newly developing diseases in humans, plants, and animals are immense.

KEYWORDS: Endophyte isolation, media, bioactive compounds: anti-TB, anti-fungal, anti-cancer.

VED PRAKASH
Department of Biotechnology, Madhav Institute of Technology and Science,
M.I.T.S. Gwalior, Madhya Pradesh 474005, India
E mail address: ved.prakash2012@vit.ac.in
Mobile number: 9753529115

***Corresponding author**

INTRODUCTION

Bioactive natural products and their derivatives have historically served as a major source of therapeutic agents for treating infectious diseases[1]. Almost all plants harbour numerous fungi known as endophytes in various amounts in almost all plant tissues[2-5].Infact, a recent comprehensive study has indicated that 51% of biologically active substances isolated from endophytic fungi were previously unknown[6]. Endophytes have proven to be rich sources of novel natural compounds with a wide-spectrum of biological activities and a high level of structural diversity. The use of endophytes as biocatalysts in the biotransformation process of natural products assumes greater importance[7] and recently several novel bioactive substances have been isolated from these microorganisms[8]. However, fungi isolation in pure cultures has been limited. Of the estimated 1.5 million species that are thought to exist, less than 5% have been successfully isolated into pure cultures[9-10].Endophytic fungi represent an important and quantifiable component of fungal diversity, and are known to affect the plant community diversity and structure[11]. Endophytic fungi isolated from medicinal plants more likely exhibit pharmaceutical potentials. Plant endophytic fungi have been found in each plant species examined, and it is estimated that there are over one million fungal endophytes existed in the nature[12].

Host specificity of endophytic fungi

The term “endophyte” was introduced by De Bary and was for some applied to “any organism occurring within plant tissues”[13]. Endophytic relationships may have begun from the time that higher plants first appeared hundreds of millions of year ago. Evidence of plant associated fungi has been discovered in fossilized tissues of stems and leaves[14]. As a consequence of these long-term associations, some of these microorganisms may have developed a mechanism of genetic cross systems that allow the exchange of information between themselves and the higher plant. This exchange would allow the fungi to more efficiently cope with the environmental conditions and perhaps increase compatibility with the host plant. The dependent evolution of endophytic fungi may have allowed them to better adapt to the plant such that the fungi could contribute to the relationship by performing a protective function against pathogens and insects[15]. Plant endophytic fungi have been found in each plant species examined and it is estimated that there are over one million fungal endophytes existed in the nature[16]. During the long period of coevolution, a friendly relationship was gradually set up between each endophytic fungus and its host plant. The host plant can supply plenteous nutriment and easeful habitation for the survival of its endophytes. On the other hand, the endophytes would produce a number of bioactive compounds for helping the host plants to resist external biotic and abiotic stresses, and benefitting from the host growth in return[17]

Fungal isolation

The methods used to isolate endophytic fungi vary in technique used for surface disinfection of the host plant tissue(leaves, stems, roots, bark, flowers, fruits, and seeds) and choice of cultivation media.

Isolation by leaf cutting

Leaf and stem fragments about 1 cm long were surface-sterilized by successive dipping in ethanol 70%, hypochlorite 4%, ethanol 70%[18]. This is done in order to eliminate surface contaminating microorganisms. With a sterile scalpel, outer tissues were removed from the plant samples and the inner tissues were carefully dissected under sterile conditions & placed onto malt agar plates containing antibiotics(chloramphenicol/streptomycin). After 3 weeks of incubation at room temperature, hyphae tips of the fungi were transferred to fresh malt agar medium. Plates are prepared in duplicates to eliminate the possibility of contamination. Pure strains were isolated by repeated inoculation[19].

Isolation by mortar and pestle

A mortar was prepared with 1 ml of tap water and some sterile sand. Leaves were added to the mortar and crushed with a pestle. The leaf suspension was then filled up with tap water to a volume of 8 ml and 200 µl of the resulting suspension was spread on the seven artificial media[20].

Isolation by blender shaft

Leaves were added to 250 ml of sterile tap water in a beaker and shredded with an ethanol-sterilized blender shaft. For the cultivation of endophytes, 200 µl of the leaf suspension including the sediment was spread on the artificial media.[20]

Media used

Media	Composition
SAB[21]	Peptone 10 g/L, dextrose 10 g/L, agar 15 g/L
PDA[21]	Potato 200 g/L, dextrose 20 g/L,agar15 g/L
YNBD agar[22]	6.7 g/L yeast nitrogen base, 1g/L glucose, 15 g/L agar
MMK2[23]	Mannitol 40 g/L, yeast extract [Becton Dickinson] 5 g/L, Murashuge & Skoog salts [Sigma M5524] 4.3 g/L
YES[24]	sucrose 150 g/L; yeast extract 20 g/L; MgSO4.7H_2O 0·5 g/L; $CuSO_4.5H_2O$ 0·005 g/L; $ZnSO_4.7H_2O$ 0·01 g/L
SMYA[25]	neopeptone 10 g/L, maltose 40 g/L, yeast extract 10 g/L, agar 4 g/L
YM agar[25]	malt extract 10 g, yeast extract 2 g agar 20 g
CYA agar[26]	K_2HPO_4 1 g/L, Czapek concentrate 10 mg/L, yeast extract 5 g/L, sucrose 30 g/L, agar 15 g/L
Malt extract agar[27]	malt extract, 30.0 g/L; mycological peptone, 5.0 g/L; agar, 15.0 g/L; chloramphenicol, 0.1 g/L
Wickerham medium[28]	Malt extract (3 g/l); Yeast extract (3 g/l); Peptone (5 g/l); Glucose 10 g/l; pH-7.2–7.4

Endophytic fungi as a source of bioactive natural products

It is of great relevance in this context that the number of secondary metabolites produced by fungal endophytes is larger than that of any other endophytic microorganism class.[29] Indeed, endophytic fungi are a very promising source of novel biologically active compounds, and have proven to yield a considerable hit-rate of novel compounds when screening larger strain numbers for biological activities.[30] In the following part examples including novel bioactive secondary metabolites from endophytic fungi are listed according to their indications. So far, only a small percentage of these metabolites have been carried forward as natural product drugs, nevertheless they represent interesting structures which indicate the great chemical diversity and pharmaceutical potential of endophytic fungi as sources for novel drug lead compounds

Endophyte as source of natural product Anti-Tuberculosis

Tuberculosis (TB) is a potentially deadly infectious disease caused by Mycobacterium sp., mainly Mycobacterium tuberculosis. Often infecting the lungs, it can also attack the central nervous system, the lymphatic system, as well as skeletal tissue. Common symptoms of TB include chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. TB is transmitted through the air when infected individuals cough, sneeze, or spit, spreading the bacteria from their throat or lungs. One–third of the world's current populations have been infected with M.tuberculosis.[31] there were approximately8.8 million reported cases of active TB in 2010, 5.7 million of which are new or relapsed cases. The disease caused approximately 1.5 million deaths[32] .

Compound	Endophytic Fungus
Phomoenamide[33]	Phomopsis sp. PSU-D15
Bisdethiobis(methylsulfanyl) apoaranotin[34]	Aspergillus terreus BCC 4651
Calpinactam[35]	Mortierella alpine FKI-4905
Cordycommunin[36]	Ophiocordyceps communis BCC 16475
Nocardithiocin[37]	Nocardia pseudobrasiliensis IFM 0757
Trichoderin A[38]	Trichoderma sp. 05F148
Trichoderin B[38]	Trichoderma sp. 05F148
Ramiferin[39]	Kionochaeta ramifera
Sansanmycin A[40]	Streptomyces sp. SS
Sansanmycin F[40]	Streptomyces sp. SS
Sansanmycin G[40]	Streptomyces sp. SS
Biscogniazaphilone A[41]	Biscogniauxia formosana
Chaetoviridine E[42]	Chaetomium cochloides
Mollicellin K[43]	Chaetomium brasiliense
Ramariolide A[44]	Ramaria cystidiophora W179

Endophyte as source of natural product: Anti-Fungal

New organisms and many novel natural products from endophytic fungi inhibit or kill a wide variety of harmful microorganisms like bacteria, fungi, viruses and protozoans that affect humans and animals[45]. Endophytes do produce secondary metabolites in culture, but the temperature, composition of the medium and the degree of aeration will affect the amount and kind of compounds produced[46], including steroids, xanthones, phenols, isocoumarins, perylene derivatives, quinines, furandiones, terpenoids, depsipeptides and cytochalasins [45-49]. Here we are covering the metabolites obtained from endophytic fungi, belonging to various classes of fungi along with unidentified fungi and their potential as

Endophytic Fungus	Host Plant	Compound
Pestalotiopsis microspore	*Terminalia morobensis*	Pestacin[50]
Pestalotiopsis jesteri	*Fragraea bodenii*	Hydroxyjesterone[51]
Dothiorella sp., strain HTF3	*Avicennia marina*	Cytosporone B[52]
Phomopsis sp.	*Costus* sp.	Phomoxanthone A[53]
Phoma sp.	*Saurauia scaberrinae*	Phomodione[54]
Colletotrichum gloeosporioides	*Artemisia mongolica*	Colletotric acid[55]
Exophiala sp.	*Adenocarpus foliolosus*	Exochromone[56]
Cryptosporiopsis quercina	*Tripterigeum wilfordii*	Cryptocandin A[57]
Cryptosporiopsis quercina	*Phleum pratense*	Cryptocin[58]
Hormonema sp. (ATCC 74360)	*Juniperus communis*	Enfumafungin[59]
Epichloe typhina	*Phleum pratense*	Epichlicin[60]
Aspergillus niger	*Cynodon dactylon*	Fonecinone A[61]
Periconia sp.	*Taxus cuspidata*	Periconicin A[62]
Trichoderma harzianum	*Llexcornuta Lindl*	Trichodermin[63]
PSU-N24	*Garcinia nigrolineata*	Griseofulvin[64]
Edenia gomezpompae	*Callicarpa acuminata*	Preussomerin EG1[65]
Cladosporium sp.	*Quercus variabilis*	Brefeldin A[66]
Xylaria sp. F0010	*Abies holophylla*	7-dechlorogriseofulvin[67]
Chaetomium globosum	*Ginkgo biloba*	Chaetoglobosin A[68]
Dinemasporium strigosum	*Calystegia sepium*	Dinemasone A[69]
Botryosphaeria rhodina	*Bidens pilosa*	Botryorhodine A[70]

Endophyte as source of natural product: Anti-cancer

Plant-derived compounds have played an important role in the development of several clinically useful anti-cancer drugs. Vinblastine, vincristine, the camptothecin(CPT) derivatives, topotecan and irinotecan, etoposide derived from epipodophyllotoxin and taxol are some of the clinically useful drugs[71]. Taxol (paclitaxel) is an attractive invention from an endophytic fungus generated more attention in the treatment of various cancers because of its unique mode of action as compared to other anticancer agent. Podophyllotoxin is an aryltetralin Lignan have been used as a precursor for synthesis of anticancer drug and with antimicrobial and antioxidative properties, mainly occurs in genera of an endangered species Sinopodophyllum. Camptothecin, a pentacyclic quinoline alkaloid, and its analogue10-hydroxycamptothecin have been identified as effective antineoplastic agents and important precursors of anticancer drug topotecan, and irinotecan[72]. Vinblastine and vincristine, the terpenoid indole alkaloids act as anticancer agents, interfere with microtubule and mitotic spindle.[73]

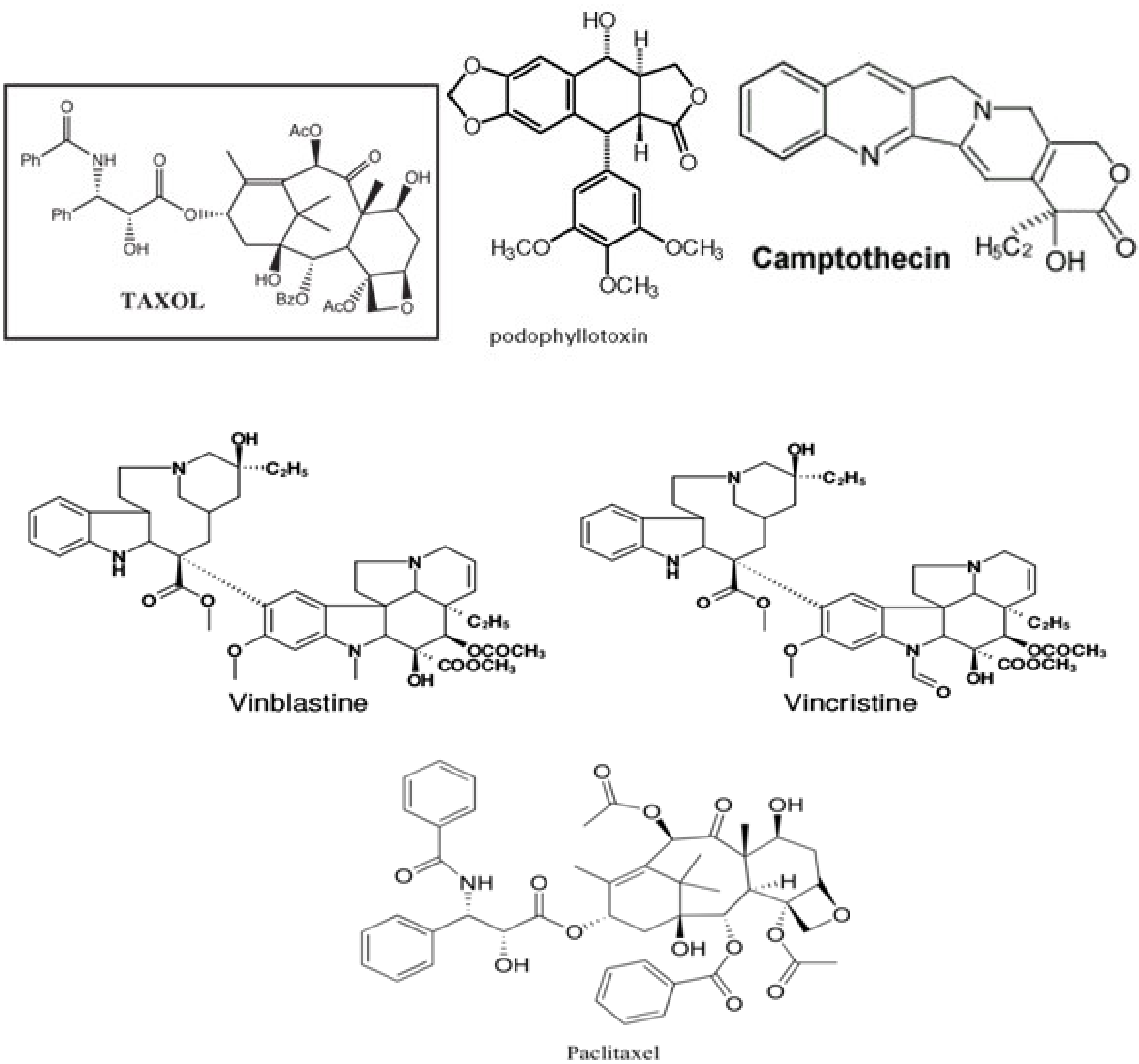

Figure. Showing molecular structure of anti-cancer compound

Host Plant	Endophytic fungus	Compound
Taxus chinensis	*Fusarium solani*	Taxol[74]
Pestalotiopsis versicolor	*Taxus cuspidata*	Taxol[75]
Taxus chinensis var. mairei.	*EFY-21(Ozonium sp.)*	Taxol[76]
Taxus globosa	*Nigrospora sp.*	Taxol[77]
Morinda citrifolia linn.	*Botryodiplodia theobromae*	Taxol[78]
Morinda citrifolia	*Lasiodiplodia theobromae*	Taxol[79]
Aloe vera	*Phoma species*	Taxol[80]
Taxus baccata	*Gliocladium sp.*	Taxol[81]
Capsicum annuum	*Collectotrichum capsici*	Taxol[82]
Taxus x media	*Cladosporium cladosporioides*	Taxol[83]
Sabina vulgaris	*Alternaria sp.*	Podophyllotoxin[84]
Sinopodophyllum hexandrum	*Alternaria neesex*	Podophyllotoxin[84]
Sabina recurva	*Fusarium oxysporum*	Podophyllotoxin[85]
Dysosma veitchii	*Monila sp.*	Podophyllotoxin[86]
Diphylleia sinensis	*Penicillium sp.*	Podophyllotoxin[86]
Dysosma veitchii	*Penicillium implicatum*	Podophyllotoxin[87]
Sinopodophyllum peltatum	*Phialocephala fortinii*	Podophyllotoxin[86]
Sinopodophyllum hexandrum	*Trametes hirsuta*	Podophyllotoxin[88]
Nothapodytes foetida	*Entrophospora infrequens*	Camptothecin[89]
Camptotheca acuminata	*Fusarium solani*	Camptothecin[90]
Apodytes dimidiata	*Fusarium solani(*MTCC 9667)	Camptothecin[91]
Apodytes dimidiata	*Fusarium solani(*MTCC 9668)	Camptothecin[91]
Nothapodytes foetida	*Neurospora sp.*	Camptothecin[92]
Catharanthus roseus	*Fusarium oxysporum*	Vinblastine[93]
Catharanthus roseus	*Alternaria sp.*	Vinblastine[94]
Catharanthus roseus	*Fusarium oxysporum*	Vincristine[95]
Phyllosticta spinarum; Phyllosticta citricarpa;	*Cupressus sp.; Citrus medica;*	Paclitaxel[96]
Podocarpus sp	*Aspergillus fumigatus*(EPTP-1)	Paclitaxel[97]
Taxus cuspidata	*Aspergillus niger var. taxi*(HD86-9)	Paclitaxel[98]
Taxus baccata	*Botryodiplodia theobromae*	Paclitaxel[99]
Taxus media	*Cladosporium cladosporioides*	Paclitaxel[100]
Taxus celebica	*Fusarium solani*	Paclitaxel[101]
Taxus chinensis	*Metarhizium anisopliae*	Paclitaxel[102]
Taxus chinensis	*Mucor rouxianus*	Paclitaxel[102]
Wollemia nobilis	*Pestalotiopsis guepinii*	Paclitaxel[104]
Pestalotiopsis sp.	*Wollemia nobilis*	Paclitaxel[104]
Pestalotiopsis pauciseta	*Cardiospermum helicacabum*	Paclitaxel[105]
Phyllosticta citricarpa	*Citrus medica*	Paclitaxel[106]
Taxomyces sp.	*Taxus yunnanensis*	Paclitaxel[107]
Phyllosticta spinarum	*Cupressus sp*	Paclitaxel[108]

CONCLUSION

The recent spurt in demand for natural medicine has made the discovery of alternate production methods the need of the hour. Fermentation, with its wide array of application and immense benefits, has proved to be a main contender to fill this void. However, due to the variations among different fermentation techniques, a lot of work still needs to be done in terms of comparison of these techniques. Also, a lot of exploration still needs to be carried out to identify sustainable substrates and processes to maintain productivity and quality. These can help in increasing production and reducing the cost of these compounds. The plants with ethanobotanical history and their use by indigenous people for healing and medicinal purposes may provide guidance for further the study.

REFERENCES

1. Newman, David J., Gordon M. Cragg, and Kenneth M. Snader. Natural products as sources of new drugs over the period 1981-2002. *Journal of natural products,* 66(7): 1022-1037, (2003)
2. Schulz, Barbara, and Christine Boyle. The endophytic continuum. *Mycological research* 109(6): 661-686, (2005)
3. Rodriguez, R. J., et al. Fungal endophytes: diversity and functional roles. *New Phytologist* 182(2): 314-330 (2009)
4. Peršoh, Derek. Factors shaping community structure of endophytic fungi–evidence from the Pinus-Viscum-system. *Fungal Diversity* 60(1): 55-69 (2013)
5. Rajala, Tiina, et al. Endophyte communities vary in the needles of Norway spruce clones. *Fungal biology* 117(3): 182-190 (2013)
6. Strobel, Gary A. Rainforest endophytes and bioactive products. *Critical reviews in biotechnology* 22(4):315-333 (2002)
7. Pimentel, Mariana Recco, et al. The use of endophytes to obtain bioactive compounds and their application in biotransformation process. *Biotechnology research international* 2011 (2010).
8. Nuclear, Paulwatt, et al. Butenolide and furandione from an endophytic Aspergillus terreus. *Chemical and Pharmaceutical Bulletin* 58(9), 1221-1223 (2010)
9. Hawksworth DL .The magnitude of fungal diversity: the 1.5 million species estimate revisited. *Mycol Res* 105: 1422–1432, (2001)doi:10.1017/S0953756201004725.
10. O'Brien, Heath E., et al. Fungal community analysis by large-scale sequencing of environmental samples. *Applied and Environmental Microbiology* 71(9): 5544-5550, (2005)
11. Krings, Michael, et al. Fungal endophytes in a 400-million-yr-old land plant: infection pathways, spatial distribution, and host responses. *New Phytologist* 174(3): 648-657, (2007)
12. Petrini, Orlando. Fungal endophytes of tree leaves. *Microbial ecology of leaves.*Springer New York, 179-197, (1991)
13. de Bary, Anton. *Neue Untersuchungen über Uredineen,* (1866)
14. Taylor, J. E., K. D. Hyde, and E. B. G. Jones. Endophytic fungi associated with the temperate palm, Trachycarpus fortunei, within and outside its natural geographic range. *New Phytologist*, 142(2): 335-346 , (1999)
15. Gunatilaka, AA Leslie. Natural Products from Plant-Associated Microorganisms: Distribution, Structural Diversity, Bioactivity, and Implications of Their Occurrence⊥. *Journal of Natural Products* 69(3): 509-526, (2006)
16. Petrini, Orlando. Fungal endophytes of tree leaves. *Microbial ecology of leaves.*Springer New York, 179-197, (1991)
17. Firáková, Silvia, Mária Šturdíková, and Marta Múčková. Bioactive secondary metabolites produced by microorganisms associated with plants. *Biologia* 62(3): 251-257, (2007)
18. Collado, J., G. Platas, and F. Peláez. Fungal endophytes in leaves, twigs and bark of Quercus ilex from Central Spain. *Nova Hedwigia* 63(3): 347-360, (1996)
19. Ashour, Mohamed, Hany M. Yehia, and Peter Proksch. Utilization of Agro-industrial by-products for production of bioactive natural products from endophytic fungi. *Journal of Natural Products* 4: 108-114 , (2011)
20. Prior, René, et al. New isolation method for endophytes based on enzyme digestion. *Mycological Progress*, 1-8 (2014)
21. de Siqueira, Virginia Medeiros, et al. Endophytic fungi from the medicinal plant Lippia sidoides Cham. And their antimicrobial activity. *Symbiosis,* 53(2): 89-95, (2011)
22. Bills, G. F., et al. Enhancement of antibiotic and secondary metabolite

detection from filamentous fungi by growth on nutritional arrays. *Journal of applied microbiology* 104(6): 1644-1658, (2008)
23. Bills, Gerald F., et al. Discovery of the parnafungins, antifungal metabolites that inhibit mRNA polyadenylation, from the Fusarium larvarum complex and other Hypocrealean fungi. *Mycologia,* 101(4): 449-472, (2009)
24. Frisvad, Jens C., and Robert A. Samson. Polyphasic taxonomy of Penicillium subgenus Penicillium.A guide to identification of food and air-borne terverticillate Penicillia and their mycotoxins. *Studies in Mycology* 49(1): C174, (2004)
25. Bills, G. F., et al. Enhancement of antibiotic and secondary metabolite detection from filamentous fungi by growth on nutritional arrays. *Journal of applied microbiology* 104(6): 1644-1658, (2008)
26. HemaMoorthy, T., and V. Prakasam. First Report of Penicillium expansum Causing Bulb Rot of Lilium in India. *American-EurasianJournal of Agricultural & Environmental Sciences,* 13(3): 293-295, (2013)
27. Jung, Chan, and A. Elizabeth Arnold. The Effects of Endohyphal Bacteria on Anti-Cancer and Anti-Malaria Metabolites of Endophytic Fungi. (2012)
28. Kumar, Susheel, and Nutan Kaushik. Endophytic fungi isolated from oil-seed crop Jatropha curcas produces oil and exhibit antifungal activity. *PloSone,* 8(2): e56202, (2013)
29. Zhang, Hua Wei, Yong Chun Song, and Ren Xiang Tan. Biology and chemistry of endophytes. *Naturalproductreports,* 23(5): 753-771, (2006)
30. Schulz, Barbara, et al. Endophytic fungi: a source of novel biologically active secondary metabolites. *Mycological Research* 106(09): 996-1004, (2002)
31. Koul, Anil, et al. The challenge of new drug discovery for tuberculosis. *Nature* 469, no. 7331: 483-490, (2011)
32. World Health Organization. Global tuberculosis control. Geneva: World HealthOrganization; (2011)
33. Rukachaisirikul, Vatcharin, et al. Metabolites from the endophytic fungus< i> Phomopsis</i> sp. PSU-D15. *Phytochemistry,* 69(3):783-787, (2008)
34. Rukachaisirikul, Vatcharin, et al. Metabolites from the endophytic fungus< i> Phomopsis</i> sp. PSU-D15. *Phytochemistry,* 69(3):783-787, (2008)
35. Koyama, Nobuhiro, et al. Calpinactam, a new anti-mycobacterial agent, produced by Mortierella alpina FKI-4905. *The Journal of antibiotics,* 63(4): 183-186, (2010)
36. Haritakun, Rachada, et al. An antimycobacterial cyclodepsipeptide from the entomopathogenic fungus Ophiocordyceps communis BCC 16475. *Journal of natural products,* 73(1): 75-78, (2009)
37. Mukai, Akira, et al. Nocardithiocin, a novel thiopeptide antibiotic, produced by pathogenic Nocardia pseudobrasiliensis IFM 0757. *The Journal of antibiotics,* 62(11): 613-619, (2009)
38. Pruksakorn, Patamaporn, et al. "Trichoderins, novel aminolipopeptides from a marine sponge-derived< i> Trichoderma</i> sp., are active against dormant mycobacteria." *Bioorganic & medicinal chemistry letters,* 20(12): 3658-3663, (2010)
39. Bunyapaiboonsri, Taridaporn, et al. "Ramiferin, a bisphenol-sesquiterpene from the fungus< i> Kionochaeta ramifera</i> BCC 7585." *Phytochemistry Letters,* 1(4): 204-206, (2008)
40. Xie, Yunying, et al. Two novel nucleosidyl–peptide antibiotics: Sansanmycin F and G produced by Streptomyces sp SS. *The Journal of antibiotics,* 63(3): 143-146, (2010)
41. Cheng, Ming-Jen, et al. Secondary metabolites from the endophytic fungus< i> Biscogniauxia formosana</i> and their antimycobacterial activity.*Phytochemistry Letters* 5(3): 467-472, (2012)

42. Phonkerd, Nutchanat, et al. Bis-spiro-azaphilones and azaphilones from the fungi Chaetomium cochliodes VTh01 and C.cochliodesCTh05. *Tetrahedron,* 64(40): 9636-9645, (2008)
43. Khumkomkhet, Primmala, et al. Antimalarial and cytotoxic depsidones from the fungus Chaetomium brasiliense. *Journal of natural products,* 72(8): 1487-1491, (2009)
44. Centko, Ryan M., et al. Ramariolides A–D, antimycobacterial butenolides isolated from the mushroom Ramaria cystidiophora. *Journal of natural products,* 75(12): 2178-2182, (2012)
45. Tan, R. X., and W. X. Zou. Endophytes: a rich source of functional metabolites. *Natural product reports,* 18(4): 448-459, (2001)
46. Strobel, Gary, et al.Natural Products from Endophytic Microorganisms. *Journal of Natural products,* 67(2): 257-268, (2004)
47. Zhang, Hua Wei, Yong Chun Song, and Ren Xiang Tan. Biology and chemistry of endophytes. *Natural product report* 23(5): 753-771, (2006)
48. Gunatilaka, AA Leslie. Natural Products from Plant-Associated Microorganisms: Distribution, Structural Diversity, Bioactivity, and Implications of Their Occurrence⊥. *Journal of Natural Products* 69(3): 509-526, (2006)
49. Guo, B., et al. Bioactive natural products from endophytes: a review. *Applied Biochemistry and Microbiology* 44(2): 136-142, (2008)
50. Brotzu, G. I. U. S. E. P. P. E. Ricerche su di un nuovo antibiotico. *Lav. Inst. Igiene Cagliari*, 1-11, (1948)
51. Benz, Fritz, et al. Stoffwechselprodukte von Mikroorganismen 143. Mitteilung. Echinocandin B, ein neuartiges Polypeptid-Antibioticum aus Aspergillus nidulans var. echinulatus: Isolierung und Bausteine. *Helvetica Chimica Acta,* 57(8): 2459-2477, (1974)
52. Newman, David J., and Gordon M. Cragg. Natural Products as Sources of New Drugs over the Last 25 Years⊥.*Journal of natural products* 70(3): 461-477 (2007)
53. Schulz, B., et al. Endophytes from herbaceous plants and shrubs: effectiveness of surface sterilization methods. *Mycological Research* 97(12): 1447-1450, (1993)
54. Xu, Qing-yan. Purification, elucidation and activities study of cytosporone B. *JOURNAL-XIAMEN UNIVERSITY NATURAL SCIENCE.* 44(3): 425, (2005)
55. Zhang, Wen, et al. Diversity of antimicrobial pyrenophorol derivatives from an endophytic fungus, Phoma sp. *European Journal of Organic Chemistry*2008(25): 4320-4328, (2008)
56. Strobel, Gary A., et al. Cryptocandin, a potent antimycotic from the endophytic fungus Cryptosporiopsis cf. quercina.*Microbiology* 145(8):1919-1926, (1999)
57. Noble, H. Mary, et al. An echinocandin from an endophytic Cryptosporiopsis</i> sp. and Pezicula sp. in Pinus sylvestris and Fagus sylvatica. *Mycological Research* 95(12): 1439-1440 , (1991)
58. Köpcke, Bärbel, Roland WS Weber, and Heidrun Anke. Galiellalactone and its biogenetic precursors as chemotaxonomic markers of the Sarcosomataceae(Ascomycota). Phytochemistry 60(7): 709-714 , (2002)
59. Abdou, Randa, et al. Botryorhodines A–D, antifungal and cytotoxic depsidones from Botryosphaeria rhodina, an endophyte of the medicinal plant Bidens pilosa, *Phytochemistry* , 71(1): 110-116 (2010)
60. Krohn, Karsten, et al. "Dinemasones A, B and C–New Bioactive Metabolites from the Endophytic Fungus Dinemasporium strigosum." *European Journal of Organic Chemistry* 2008(33): 5638-5646, (2008)
61. Gorman, Jessica A., et al. Ascosteroside, a new antifungal agent from Ascotricha amphitricha. I. Taxonomy, fermentation and biological activities.*The Journal of antibiotics* 49(6): 547-552, (1996)
62. Mitchell, Angela M., et al. Volatile antimicrobials from Muscodor crispans, a novel endophytic fungus. *Microbiology,* 156(1): 270-277, (2010)

63. Liu, J. Y., et al. Aspergillus fumigatus CY018, an endophytic fungus in Cynodon dactylon as a versatile producer of new and bioactive metabolites. *Journal of biotechnology.* 114(3): 279-287, (2004)
64. Dai, Jingqiu, et al. New Naphthalene-Chroman Coupling Products from the Endophytic Fungus, Nodulisporium sp. from Erica arborea. *European Journal of Organic Chemistry* 2009(10): 1564-1569, (2009)
65. Qin, Jian-Chun, et al. Bioactive metabolites produced by Chaetomium globosum, an endophytic fungus isolated from Ginkgo biloba. *Bioorganic & medicinal chemistry letters,* 19(6): 1572-1574, (2009)
66. Teles, Helder Lopes, et al. Aromatic compounds produced by Periconia atropurpurea, an endophytic fungus associated with Xylopia aromatica. *Phytochemistry,* 67(24): 2686-2690, (2006)
67. Wang, Jianfeng, et al. Brefeldin A, a cytotoxin produced by Paecilomyces sp. and Aspergillus clavatus isolated from Taxus mairei and Torreya grandis. *FEMS Immunology & Medical Microbiology* , 34(1): 51-57, (2002)
68. Albaugh, David, et al. Cell wall active antifungal compounds produced by the marine fungus Hypoxylon oceanicum LL-15G256. III. Biological properties of 15G256 gamma. *The Journal of antibiotics* 51(3): 317-322, (1998)
69. Vijayakumar, E. K. S., et al. Arthrichitin. A new cell wall active metabolite from Arthrinium phaeospermum. *The Journal of organic chemistry* 61(19): 6591-6593, (1996)
70. Cafêu, Mariana C., et al. Antifungal compounds of Xylaria sp., an endophytic fungus isolated from Palicourea marcgravii (Rubiaceae). *Quimica Nova,* 28(6): 991-995, (2005)
71. Chandra, Sheela. Endophytic fungi: novel sources of anticancer lead molecules. *Applied microbiology and biotechnology* 95(1): 47-59, (2012)
72. Uma, S. R., et al. Chemical profiling of N. nimmoniana for camptothecin, an important anticancer alkaloid: towards the development of a sustainable production system. *Bioactive Molecules and Medicinal Plants,* 198-210, (2008)
73. Zhao, J., et al. Endophytic fungi for producing bioactive compounds originally from their host plants. *Curr Res, Technol Educ Trop Appl Microbiol Microbial Biotechnol* 1, 567-576, (2010)
74. Deng, Bai Wan, et al. Fusarium solani, Tax-3, a new endophytic taxol-producing fungus from Taxus chinensis. *World Journal of Microbiology and Biotechnology* 25(1): 139-143, (2009)
75. Kumaran, Rangarajulu Senthil, Hyung Joo Kim, and Byung-Ki Hur. Taxol promising fungal endophyte, Pestalotiopsis species isolated from Taxus cuspidata. *Journal of bioscience and bioengineering,* 110(5): 541-546, (2010)
76. Wei, Yamin, et al. An efficient transformation system of taxol-producing endophytic fungus EFY-21 (Ozonium sp.). *African Journal of Biotechnology,* 9(12): (2010)
77. Rivera-Orduña, Flor N., et al. Diversity of endophytic fungi of Taxus globosa (Mexican yew). *Fungal Diversity* 47(1): 65-74, (2011)
78. Pandi, M., et al. A fungal taxol from< i> Botryodiplodia theobromae Pat., attenuates 7, 12 dimethyl benz (a) anthracene (DMBA)-induced biochemical changes during mammary gland carcinogenesis. *Biomedicine& Preventive Nutrition,* 1(2): 95-102, (2011)
79. Pandi, M., R. Manikandan, and J. Muthumary. Anticancer activity of fungal taxol derived from Botryodiplodia theobromae Pat., an endophytic fungus, against 7, 12 dimethyl benz (a) anthracene (DMBA)-induced mammary gland carcinogenesis in Sprague dawley rats. *Biomedicine & Pharmacotherapy,* 64(1): 48-53, (2010)
80. Mukesh Kumar, D. J., et al. Isolation Of Phoma Species From Aloe Vera: An Endophyte And Screening The Fungus

For Taxol Production. *World Journal of Science and Technology,* 1(11), (2011).
81. Sreekanth, D., et al. Molecular and morphological characterization of a taxol-producing endophytic fungus, Gliocladium sp., from Taxus baccata. *Mycobiology,* 39(3): 151-157, (2011)
82. Kumaran, Rangarajulu Senthil, Heehoon Jung, and Hyung Joo Kim. In vitro screening of taxol, an anticancer drug produced by the fungus, Colletotrichum capsici. *Engineering in Life Sciences,* 11(3): 264-271, (2011)
83. Zhang, Peng, et al. Agrobacterium tumefaciens-mediated transformation of a taxol-producing endophytic fungus, Cladosporium cladosporioides MD2. *Current microbiology,* 62(4): 1315-1320 (2011)
84. Zhao, J., et al. Plant-derived bioactive compounds produced by endophytic fungi. *Mini reviews in medicinal chemistry,* 11(2): 159-168, (2011)
85. Guerram, Mounia, Zhen-Zhou JIANG, and Lu-Yong ZHANG. Podophyllotoxin, a medicinal agent of plant origin: past, present and future. *Chinese Journal of Natural Medicines* 10(3): 161-169, (2012)
86. Zhao, J., et al. Endophytic fungi for producing bioactive compounds originally from their host plants. *Curr Res, Technol Educ Trop Appl Microbiol Microbial Biotechnol* 1, 567-576, (2010)
87. Pandey, Pramod Kumar, et al. Fungal Endophytes: Promising Tools for Pharmaceutical Science. *International Journal of Pharmaceutical Sciences Review & Research,* 25(2), (2014)
88. Huang, Jian-Xin, et al. Mucor fragilis as a novel source of the key pharmaceutical agents podophyllotoxin and kaempferol. *Pharmaceutical biology* 0, 1-7, (2014)
89. Amna, Touseef, et al. Bioreactor studies on the endophytic fungus Entrophospora infrequens for the production of an anticancer alkaloid camptothecin. *Canadian journal of microbiology,* 52(3): 189-196, (2006)
90. Kusari, Souvik, Sebastian Zu□hlke, and Michael Spiteller. Effect of artificial reconstitution of the interaction between the plant Camptotheca acuminata and the fungal endophyte Fusarium solani on camptothecin biosynthesis. *Journal of natural products,* 74(4): 764-775, (2011)
91. Shweta, S., et al. Endophytic fungal strains of Fusarium solani, from Apodytes dimidiata E. Mey. ex Arn (Icacinaceae) produce camptothecin, 10-hydroxycamptothecin and 9-methoxycamptothecin. *Phytochemistry* 71 (1): 117-122, (2010)
92. Rehman, S., et al. An endophytic Neurospora sp. from Nothapodytes foetida producing camptothecin. *Applied biochemistry and microbiology,* 44(2): 203-209, (2008)
93. Kumar, Ashutosh, et al. Isolation, Purification and Characterization of Vinblastine and Vincristine from Endophytic Fungus Fusarium oxysporum Isolated from Catharanthus roseus. *PloS one* 8(9): e71805, (2013)
94. Kharwar, Ravindra N., et al. Anticancer compounds derived from fungal endophytes: their importance and future challenges. *Natural product reports,* 28(7): 1208-1228, (2011)
95. Kumar, Ashutosh, et al. Isolation, Purification and Characterization of Vinblastine and Vincristine from Endophytic Fungus Fusarium oxysporum Isolated from Catharanthus roseus. *PloS one* 8(9): e71805, (2013)
96. Kumaran, Rangarajulu Senthil, et al. Production of taxol from Phyllosticta dioscoreae, a leaf spot fungus isolated from Hibiscus rosa-sinensis. *Biotechnology and Bioprocess Engineering,* 14(1): 76-83, (2009)
97. Sun, D., X. Ran, and J. Wang. Isolation and identification of a taxol-producing endophytic fungus from Podocarpus. *Wei sheng wu xue bao= Acta microbiologica Sinica* 48(5): 589-595, (2008)
98. Zhao, K., et al. Aspergillus niger var. taxi, a new species variant of taxol-producing fungus isolated from Taxus cuspidata in China. *Journal of applied microbiology,* 107(4): 1202-1207, (2009)

99. Venkatachalam, Raja, Kamalraj Subban, and Muthumary John Paul. Taxol from Botryodiplodia theobromae (BT 115)—An endophytic fungus of Taxus baccata, *Journal of Biotechnology* 136, S189-S190, (2008)
100. Zhang, Peng, Peng-Peng Zhou, and Long-Jiang Yu. An endophytic taxol-producing fungus from Taxus media, Cladosporium cladosporioides MD2. *Current microbiology,* 59(3): 227-232, (2009)
101. Chakravarthi, B. V. S. K., et al. Production of paclitaxel by Fusarium solani isolated from Taxus celebica. *Journal of biosciences,* 33(2): 259-267, (2008)
102. Liu, Kaihui, et al. Isolation and characterization of endophytic taxol-producing fungi from Taxus chinensis. *Journal of industrial microbiology & biotechnology,* 36(9): 1171-1177, (2009)
103. Miao, Z., et al. A new endophytic taxane production fungus from Taxus chinensis. *Applied biochemistry and microbiology,* 45(1): 81-86, (2009)
104. Strobel, Gary A., et al. Pestalotiopsis guepinii, a taxol-producing endophyte of the wollemi pine, Wollemia nobilis. *Australian Journal of Botany,* 45(6): 1073-1082, (1997)
105. Gangadevi, V., M. Murugan, and J. Muthumary. Taxol Determination from Pestalotiopsis pauciseta, a Fungal Endophyte of a Medicinal Plant. *Chinese Journal of Biotechnology,* 24(8): 1433-1438, (2008)
106. Kumaran, Rangarajulu Senthil, Johnpaul Muthumary, and Byung-Ki Hur. Taxol from Phyllosticta citricarpa, a leaf spot fungus of the angiosperm Citrus medica. *Journal of bioscience and bioengineering,* 106(1): 103-106, (2008)
107. Wu, Jianyong, Chuangui Wang, and Xingguo Mei. Stimulation of taxol production and excretion in Taxus spp cell cultures by rare earth chemical lanthanum. *Journal of biotechnology,* 85(1): 67-73, (2001)
108. Senthil Kumaran, R., J. Muthumary, and B. K. Hur. Production of Taxol fromPhyllosticta spinarum, an endophytic fungus ofCupressus sp. *Engineering in Life Sciences,* 8(4): 438-446, (2008).