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ANTICANCER, ANTIMICROBIAL AND ANTIOXIDANT BIOACTIVE FACTORS DERIVED FROM MARINE FUNGAL ENDOPHYTES; A REVIEW

T. Vijaya*

Department of Botany, Sri Venkateswara University, Tirupati, Andhra Pradesh, India.

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ABSTRACT

The marine-derived fungi has proven to be a very rich source of extremely potent compounds that have demonstrated a number of biologically active compounds with varying degrees of action such as anticancer, antioxidant, anti proliferative and anti microbial properties. These compounds are of interest as new lead structures for medicine as well as for plant and animal self defense. This review is an attempt to consolidate the latest studies in this field, and to showcase the immense competence of marine microbial flora and fauna as bioactive metabolite producers.

Corresponding author

Prof.T.Vijaya

Department of Botany,

S.V.University,

Andhra Pradesh, India.

tarttevijaya@yahoo.co.in

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INTRODUCTION

Endophytes are microorganisms that reside asymptomatically in the tissues of higher plants and are a promising source of novel organic natural metabolites exhibiting a variety of biological activities. The term "endophytes" includes a suite of microorganisms that grow intra and/or intercellular in the tissues of higher plants without causing any adverse effects to the plants in which they live, and have proven to be rich sources of bioactive natural products (1). The main emphasis of this review is on bioactive compound producing marine fungi and their biological active compounds. Approximately 3,00,000 plant species growing in unexplored area on the earth are host to one or more endophytes(2), and the presence of bio diverse endophytes in huge number plays an important role on ecosystems with greatest biodiversity, for instance, the tropical and temperate rainforests (3), which are extensively found in Brazil and possess almost 20% of its biotechnological source(4).In recent years, marine fungi have been explored more intensely to obtain novel and biologically active compounds, when compared with marine sponges and bacteria. Cephalosporin C was the first bioactive compound from *Cephalosporium acremonium* which was isolated from a sewage outlet of the Sardinian coast(5).

Previous literature shows that marine derived fungi have been recognized as one of the tapped sources for new biologically active secondary metabolites including antitumor, antibacterial, antiviral, antifungal, anti-inflammatory and anticancer activities and enzyme inhibitor compounds. Clodepsipeptide isolated from the marine fungus, *Clonostachys* sp. is having anticancer activity(5). Recent review by Newman and Cragg(6) presented a list of all approved agents from 1981 to 2006, from which a significant number of natural drugs are produced by microbes and/or endophytes. Endophytes provide a broad variety of bioactive secondary metabolites with unique structure, including alkaloids, benzopyranones, chinones, flavonoids, phenolic acids, quinones, steroids, terpenoids tetralones, xanthones, and others (7). Such bioactive metabolites find wide ranging application as agrochemicals, antibiotics, immunosuppressants, antiparasitics, antioxidants, and anticancer agents (8).

This paper focuses particularly on the role of endophytes in the production of bioactive compounds, the importance of including endophytic microbes in the screening approach for novel drugs, and the microbial biotransformation process as a novel alternative method to obtain such compounds. It also describes these compounds by different functions, including some examples that illustrate the potential for human use. The different methods to obtain bioactive compounds includes extraction from a natural source, microbial production *via* fermentation, or microbial transformation. Extraction from natural sources have few disadvantages such as dependency on seasonal, climatic and political features and possible ecological problems involved with the extraction, thus in need for innovative approaches to obtain novel compounds(9). Hence, biotechnological techniques using different microorganisms appear promising alternatives for establishing cost-effective and renewable resource of high value bioactive products and aroma compounds. The biotransformation method has a huge number of applications (10), for instance, it has been extensively used for the production of volatile compounds(9, 11, 12). These volatile compounds possess not only sensory properties, but other useful properties such as antimicrobial (vanillin, essential oil constituents), antifungal and antiviral (some alkaloids), antioxidant (eugenol, vanillin),somatic fat reducing, blood pressure regulating(2-[E]-hexenal), anti-inflammatory properties (1,8-cineole),and others (13).

Bioactive compounds from marine derived fungi

Marine derived fungal strains produce polyketide derived alkaloids, terpenes, peptides and mixed biosynthesis compounds which are representative groups of secondary metabolites produced by fungi. Miriam et al. (2012) isolated marine-derived fungal strains(14), they yielded several bioactive secondary metabolites among which are *E*)-4-methoxy-5-3-methoxybut-1-enyl)-6-methyl-2*H*-pyran-2-one, a new metabolite isolated from the *Penicillium paxilli* strain MaG)K, Norlique xanthone, also known as 1, 3,6-trihydroxy-8-methyl-9H-xanthen-9-one, was isolated from the fungus *P. raistrikii* obtained from the sponge *Axinella*cf *corrugate*. The structure and absolute stereochemistry of *S*)-8-methoxy-3,5-dimethylisochroman-6-ol, isolated from *Penicillium steckii* obtained from an algae belonging to the genus *Sargassum*, could be established by analysis of spectroscopic data and also by comparison with literature data.

A *Penicillium* sp. strain DG M3) 6'C, isolated from the ascidian *Didemnum granulatum*, yielded 13-deoxy-phomenone. Roridin A was isolated from *Trichoderma* sp. obtained from the sponge *Mucaleangulos*a and also identified by analysis of spectroscopic data and comparison with literature data. The fungal strain Ma G) K, obtained from the sponge *M. Angulosa* and identified as *Penicillium paxilli*, gave an extract which was cytotoxic against MDA-MB435 human mammalian cancer cells (HCT8 human colon), CNS 295 central nervous system cancer cells and HL60 leukemia cells. Fractionation of this crude extract yielded three 2-pyrones, belonging to Pyrenocines the class of pyrenocines, of which two were known and one was a new natural product, Pyrenocine J. B and A were first isolated from *Pyrenochaeta terrestris* and identified by spectroscopic and X-ray diffraction analysis (14). Two new indole alkaloids, 2-3, 3-dimethylprop-1-ene) costaclavine and 2-3, 3-dimethylprop-1- ene)-epicosta-clavine, together with the known compounds costaclavine, fumgaclavine A and C, were isolated from the marine-derived fungus *Aspergillus fumigates*(15). *Penicillium commune* SD-118, a fungus obtained from a deep sea sediment sample, resulted in the isolation of a known antibacterial compound, xanthocillin X, and 14 other known compounds comprising three steroids, two ceramides, six aromatic compounds and three alkaloids (Table 1).

Table 1. Antibacterial compounds from marine derived fungi (16).

No	Source	Metabolite	Class of compound
1	*Emericella unguis*	Guisinol	Depside
2	*Curvularia lunata* *Emericella variecolor* *E. variecolor*	Lunatin 1) Cytoskyrin A 2) Varixanthone Shamixanthone, Tajixanthone hydrate, Terrein	Anthraquinone
3	*Trichoderma virens*	Trichodermamide B	Dipeptide
4	*Paraphaeosphaeria* sp N-119	Modiolides A-B	Macrolide
5	*Cladosporium herbarum*	Sumiki's acid, Acetyl Sumiki's acid	Furan carboxylic acid
6	*Aspergillus versicolor*	Aspergillitine	Chromone derivative
7	*Stilbella aciculosa*	Fusidic acid	Steroid
8	*Ascochytasa licorniae* *Phoma sp*	Ascosalipyrrolidinone A Phomadecalins A-D, Phomadecalin A, B, D	Alkaloid
9	Unidentified marine-derived fungus	Seragikinone A	Anthracycline related pentacyclic compound
10	*Fusarium sp.* *Coniothyriumsp*isolated from the sponge Ectyplasiaperox)	Neomangicol B 2-hydroxymethyl furan)	Sesterterpenes

Xanthocillin X was isolated for the first time from a marine fungus. In the bioassay, xanthocillin X displayed significant cytotoxicity against MCF-7, HepG2, H460, Hela, Du145 and MDA-MB-231 cell lines. Meleagrin exhibited cytotoxicity against HepG2, Hela, Du145 and MDA-MB-231 cell lines. This is the first report on the cytotoxicity of xanthocillin X (17). Khouloud and Yousry (2012) isolated new biologically active metabo-lites against some virulent fish pathogens *Edwardsiella tarda*, *Aeromonas hydrophila*, *Vibrio ordalli and Vibrio angularuim*. *Aspergillus terreus var. Africanus* was identified as the most potent isolate(18). Acremolin, a novel modified base, was isolated from the culture broth of the marine fungus *Acremonium strictum*. Based on combined spectroscopic analyses, the structure of this compound was that of a methyl guanine base containing an isoprene unit. In addition, the presence of a 1H-azirine moiety is unprecedented among natural products. This compound exhibited weak cytotoxicity against an A549 cell line (19).

In investigation of new bioactive natural products from marine fungi collected from the South China Sea one terrestrial fungal metabolite, chrodrimanin B, together with five new phenolic bisabolane type sesquiterpenoids were isolated from the fermentation broth of a marine-derived fungus *Aspergillus* sp. This is the first report of the isolation of chrodrimanin B from a marine organism (20). S. metanina et al. (2011) determined that the biologically active compounds among marine isolates of microscopic fungus(21). *Myceliophthora lutea Costantin*, which was isolated from marine sediments of Sakhalin Bay Sea of Okhotsk, synthesizes compounds with antibacterial and cytotoxic activities. The new compounds isoacremine D and acremin were reported for the first time from the marine isolate of the fungus Myceliophthora lutea. It was found that acremine A in $CHCl_3$ was converted through the action of light into spiro compounds called as spiro acremines A and B (21). A new cyclopentanopyridine alkaloid, 3-hydroxy-5-methyl-5,6-dihydro-7*H* cyclopenta(*b*)pyridin- 7-one, together with 11 known aromatic compounds were isolated from the secondary metabolites of the halo tolerant fungal strain *Wallemiasebi* PXP-89 in 10% NaCl(22).

Anticancer compounds

Cancer is a group of diseases characterized by unregulatedgrowth and spread of abnormal cells, which can result in death if not controlled (23). It has been considered one of the major causes of death worldwide: 7.4 million (about13% of all deaths) in 2015 (23). The anticancer drugs show nonspecific toxicity to proliferating normal cells, possess enormous side effects, and are not effective against many forms of cancer (24, 25). Thus, the cure of cancer has been enhanced mainly due to diagnosis improvements which allow earlier and more precise treatments (25).

There are some evidences that bioactive compounds produced by endophytes could be alternative approaches for discovery of novel drugs, since many natural products from plants, microorganisms, and marine sources were identified as anticancer agents (26). The anticancer properties of several secondary metabolites from endophytes have been investigated recently. Following, some examples of the potential of endophytes on the production of anticancer agents are cited.

The isolation of Taxol producing endophyte *Taxomyces andreanae* has provided an alternative approach to obtaina cheaper and more available product *via* microorganism fermentation (27). After that, Taxol has also been found in a number of different genera of fungal endophytes either associated or not to use, such as *Taxodium distichum (28)*; *Wollemia nobilis (29); Phyllosticta spinarum (30)*; *Bartaliniaro billardoides (24)*; *Pestalotiopsis terminaliae (31)*; *Botryodiplo diatheobromae (32).*

Another important anticancer compound is the alkaloid "Camptothecin" ($C_{20}H_{16}N_2O_4$), a potent antineoplastic agent which was firstly isolated from the wood of *Camptothecaacuminata* Decaisne (Nyssaceae) in China(33). Camptothecin and 10-hydroxy camptothecin are two important precursors for the synthesis of the clinically useful anticancer drugs, topotecan, and irinote can(34). Although it's potential use in medical treatments, the unmodified Camptothecin suffers from drawback that compromises its applications due to very low solubility in aqueous media and high toxicity (35, 36). On the other hand, some Camptothecin derivatives retain the medicinal properties and can show other benefits without causing over drawbacks in some cases (37, 38). Therefore, it is desirable to develop strategies for isolation, mixture separation, and production of Camptothecin and its analogues from novel endophytic fungal sources. The anticancer properties of the microbial products Camptothecin and two analogues (9-methoxycamptothecinand 10-hydroxycamptothecin) were already reported. The products were obtained from the endophytic fungi *Fusarium solani* isolated from *Camptotheca acuminate (38)*. Several reports have described other Camptothecin (or analogues) producing endophytes (39-43). Since then, endophytes have been included in many studies purposing new approaches for drug discovery.

"Phenylpropanoids" have attracted much interest for medicinal use as anticancer, antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive properties (44).Despite the phenylpropanoids belong to the largest group of secondary metabolites produced by plants, reports showed the production of such compounds by endophytes. The endophytic *Penicillium brasilianum*, found in root bark of Meliaa zedarach, promoted the biosynthesis of phenylpropanoid amides (45). Likewise, two monolignol glucosides, coniferin and syringin, are produced not only by the host plant, but were also recognized by the endophytic *Xylariaceae* species as chemical signals during the establishment of fungus-plant interactions (46). Koshino and coworkers characterized two phenylpropanoids and lignin from stromata of *Epichloetyphina* on *Phleumpretense(47).*

"Lignans" are other kinds of anticancer agents originated as secondary metabolites through the shikimic acid pathway and display different biological activities that make them interesting in several lines of research (48). Although their molecular backbone consists only of two phenylpropane units (C6-C3), lignans show enormous structural and biological diversity, especially in cancer chemotherapy (44)."Podophyllotoxin" (C22H22O8) and analogs are clinically relevant mainly due to their cytotoxicity and antiviral activities and are valued as the precursor to useful anticancer drugs like etoposide, teniposide, and etopophos phosphate(49). The aryl tetralignans, such as podophyllotoxin, are naturally synthesized by *Podophyllum*sps., however, alternative sources have been searched to avoid endangered plant.Another study showed a novel fungal endophyte, *Trameteshirsute,* that produces podophyllotoxin and other related aryltetra lignans with potent anticancer and properties (50).Novel microbial sources of Podophyllotoxin were reported from the endophytic fungi *Aspergillus fumigates* Fresenius isolated from *Juniperus communis* L. Horstmann (49), *Phialocephala fortinii* isolated from *Podophyllum peltatum(51),* and *Fusarium oxysporum* from *Juniperus recurva (37).*

"Ergoflavin" ($C_{30}H_{26}O_{14}$), a dimeric xanthene linked in position 2, belongs to the compound class called ergochromes and was described as a novel anticancer agent isolated from an endophytic fungi growing on the leaves of an Indian medicinal plant *Mimus opselengi*(Sapotaceae) (52)."Secalonic acid D" (C32H30O14), a mycotoxin also belonging to ergochrome class, is known to have potent anticancer activities. It was isolated from the mangrove endophytic fungus and observed high cytotoxicity on HL60 and K562 cells by inducing leukaemia cell apoptosis (53).

Crude Extracts of *Alternaria alternata*, an endophytic fungus isolated from *Coffea arabica* L., displayed moderate cytotoxic activity towards HeLa cells *in vitro*, when compared to the dimethyl sulfoxide (DMSO) treated cells (54). The investigation of endophytic actinomycetes associated with pharmaceutical plants in rainforest reported 41 microorganisms from the genus Streptomyces displayed significant antitumor activity against HL-60 cells, A549 cells, BEL-7404 cells, and P388D1 cells (55). The screening of endophytic fungi isolated from pharmaceutical plants in China showed that 13.4% endophytes were cytotoxic on HL-60 cells and 6.4% on KB cells (56).Finally, other compounds with anticancer properties isolated from endophytic microbes were reported such as "cytoskyrins" (57), "phomoxanthones A" and "B" (56),"photinides A-F" (58), "rubrofusarin B" (59), and "(+) epiepoxydon" (60).

Antimicrobial Compounds

Metabolites bearing antibiotic activity can be defined as low molecular weight organic natural substances made by microorganisms that are active at low concentrations against other microorganisms (61). Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites (7). So far,studies reported a large number of antimicrobial compounds isolated from endophytes, belonging to several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids (62).The discovery of novel antimicrobial metabolites from endophytes is an important alternative to overcome the increasing levels of drug resistance by plant and human pathogens, the insufficient number of effective antibiotics against diverse bacterial species, and few new antimicrobial agents in development, probably due to relatively unfavourable returns on investment (62, 63). The antimicrobial compounds can be used not only as drugs by human kind but also as food preservatives in the control of food spoilage and food borne diseases, a serious concern in the world food chain (64).

Many bioactive compounds, including antifungal agents,have been isolated from the genus *Xylaria* residing indifferent plant hosts, such as "sordaricin" with antifungal activity against *Candida albicans(65);* "mellisol" and "1,8-dihydroxynaphthol 1-O-a-lucopyranoside" with activity against herpes simplex virus-type 1 (66); "multiploides A and B" with activity against *Candida albicans(67).* The bioactive compound isolated from the culture extracts of the endophytic fungus *Xylaria* sp. YX-28 isolated from *Ginkgobiloba* L. was identified as "7-amino-4-methylcoumarin"(64). The compound presented broad-spectrum inhibitory activity against several food borne and food spoilage microorganisms including *S. aureus, E. coli, S.typhia, S.typhimurium, S.enteritidis, A.hydrophila, Yersinia* sp., *V.anguillarum, Shigella* sp., *V. parahaemolyticus, C. albicans, P.expansum,* and *A. niger,* especially to *A. hydrophila,* and was suggested to be used as natural preservative in food (64).

Aliphatic compounds, frequently detected in cultures of endophytes, often show biological activities. Four antifungal"aliphatic compounds" were characterized from stromata of *E. typhina*on *P. pratense(68, 69)*. Two novel ester metabolites isolated from an endophyte of the eastern larch presented antimicrobial activity. One compound was toxic to spruce budworm (*Choristoneura fumiferana Clem.*) larvae, and the other may serve as potent antibacterial agent against *Vibriosal monicida*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus(69)*.Chaetomugilin A and D with antifungal activities, were isolated from an endophytic fungus *C. Globosum* collected from *Ginkgo biloba (70)*. Cytosporone B and C were isolated from a mangrove endophytic fungus, *Phomopsis* sp. They inhibited two fungi *C. albicans*and *F. oxysporum*with the MIC value ranging from 32 to 64 mg·mL^{-1}(71). An endophytic *Streptomyces* sp. from a fern-leaved grevillea (*Grevilleap teridifolia*) in Australia was described as a promising producer of novel antibiotics, "kakadumycin A"and "echinomycin". Kakadumycin A is structurally related to echinomycin, a quinoxaline antibiotic, and presents better bioactivity than echinomycin especially against Gram positive bacteria and impressive activity against the malarial parasite *Plasmodium falciparum (72).*

Among the 12 secondary metabolites produced by the endophytic fungi *Aspergillus fumigates* CY018 isolated from the leaf of *Cynodondactylon*, "asperfumoid", "fumigaclavine C", "fumitremorgin C", "physcion", and "helvolic acid"were shown to inhibit *Candida albicans(73).* Endophyte *Verticillium* sp. isolated from roots of wild *Rehmannia glutinosa* produced two compounds "2,6-Dihydroxy-2-methyl-7-(prop-1E-enyl)-1-benzofuran-3(2H)-one", reported for the first time, and "ergosterol peroxide" with clear inhibition of the growth of three pathogens including *Verticillium* sp.*(74).*An endophytic fungus *Pestalotiopsis theae* of an unidentified tree on Jianfeng Mountain, China, was capable of producing "Pestalotheol C" with anti-HIV properties (75).Other secondary metabolites with antimicrobial properties isolated from endophytic microbes were reported like"3-O-methylalaternin" and "altersolanol A" (76), "phomoenamide"(77), "phomodione" (78), "ambuic acid" (79),"isopestacin" (2), and "munumbicin A, B, C" and "D" (80).

Antioxidant Compounds

The importance of compounds bearing antioxidant activity lays in the fact that they are highly effective against damage caused by reactive oxygen species (ROSs) and oxygen-derived free radicals, which contribute to a varietyof pathological effects, for instance, DNA damages,carcinogenesis, and cellular degeneration (81, 82). Antioxidants have been considered promising therapy for prevention and treatment of ROS linked diseases as cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/reperfusion injury, diabetes mellitus, neuro degenerative diseases (Alzheimer and Parkinson diseases),rheumatoid arthritis, and ageing (83). Many antioxidant compounds possess anti-inflammatory, antiatherosclerotic,antitumor, antimutagenic, anticarcinogenic, antibacterial, or antiviral activities in higher or lower level (84-87).

Natural antioxidants are commonly found in medicinal plants, vegetables, and fruits. However, it has been reported that metabolites from endophytes can be a potential source of novel natural antioxidants. Liu and co-workers evaluated the antioxidant activity of an endophytic *Xylaria* sp. isolated from the medicinal plant *Ginkgo biloba(88).*The results collected indicated that the methanol extract exhibited strong antioxidant capacity due to the presence of "phenolics" and "flavonoids" compounds among 41identified compounds. Huang and coworkers investigated the antioxidant capacities of endophytic fungal cultures of medicinal Chinese plants and its correlation to their total phenolic contents. They suggested that the phenolic content were the major antioxidant constituents of the endophytes (89).

"Pestacin" ($C_{15}H_{14}O_4$) and "isopestacin", 1,3-dihydroisobenzofurans, were obtained from the endophytic fungus*Pestalotiopsismicrospora*isolated from a plant growing in the Papua New Guinea, *Terminalia morobensis(90, 91).* Besides antioxidant activity, pestacin and isopestacin also presented antimycotic and antifungal activities, respectively. Pestacin is believed to have antioxidant activity 11 times greater than Trolox, a vitamin E derivative, primarily via cleavage of an unusually reactive C-H bond and to a lesser extent, O-H abstraction (91). Isopestacin possess antioxidant activity by scavenging both superoxide and hydroxy free radicals in solution, added to the fact that isopestacin is structurally similar to the flavonoids (90).

"Graphislactone A", a phenolic metabolite isolated from the endophytic fungus *Cephalosporium* sp. IFB-E001 residing in *Trachelospermum jasminoides*, demonstrated to have free radical scavenging and antioxidant activities *in vitro* strongerthan the standards, butylated hydroxytoluene (BHT) and ascorbic acid, co assayed in the study (92).For more detailed information on antimicrobial, antioxidant,and anticancer agents from microbial source, the references Newman and Cragg(6) and Fir´akov´a and coworkers(26) are recommended.

CONCLUSION

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. However, the application of microorganisms by the food and pharmaceutical industries to obtain compounds of interest is still modest, considering the great availability of useful microorganisms and the large scope of reactions that can be accomplished by them.

REFERENCES

1. Pimentel MR, Molina G, Dionísio AP, Maróstica Junior MR, Pastore GM. The Use of Endophytes to Obtain Bioactive Compounds and Their Application in Biotransformation Process. Biotechnology Research International. 2011;2011:11.
2. Strobel GA. Endophytes as sources of bioactive products. Microbes Infect. 2003 May;5(6):535-44. PubMed PMID: 12758283.
3. Strobel G, Daisy B. Bioprospecting for microbial endophytes and their natural products. Microbiol Mol Biol Rev. 2003 Dec;67(4):491-502. PubMed PMID: 14665674. Pubmed Central PMCID: PMC309047.
4. Dos Banhos EF, de Souza AQ, de Andrade JC, de Souza AD, Koolen HH, Albuquerque PM. Endophytic fungi from Myrcia guianensis at the Brazilian Amazon: distribution and bioactivity. Braz J Microbiol. 2014;45(1):153-61. PubMed PMID: 24948926. Pubmed Central PMCID: PMC4059290.
5. Samuel P PL, Prabakaran P. Antibacterial Activity of Marine derived Fungi Collected from South East Coast of Tamilnadu, India. Journal of Microbiology & Biotechnology Research. 2011;1(4):p86.
6. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. J Nat Prod. 2007 Mar;70(3):461-77. PubMed PMID: 17309302.
7. Tan RX, Zou WX. Endophytes: a rich source of functional metabolites. Nat Prod Rep. 2001 Aug;18(4):448-59. PubMed PMID: 11548053.
8. Gunatilaka AA. Natural products from plant-associated microorganisms: distribution, structural diversity, bioactivity, and implications of their occurrence. J Nat Prod. 2006 Mar;69(3):509-26. PubMed PMID: 16562864. Pubmed Central PMCID: PMC3362121.
9. Bicas JL, Dionisio AP, Pastore GM. Bio-oxidation of terpenes: an approach for the flavor industry. Chem Rev. 2009 Sep;109(9):4518-31. PubMed PMID: 19645444.
10. Borges KB, Borges WdS, Durán-Patrón R, Pupo MT, Bonato PS, Collado IG. Stereoselective biotransformations using fungi as biocatalysts. Tetrahedron: Asymmetry. 2009 3/11/;20(4):385-97.
11. Bicas JL, Barros FF, Wagner R, Godoy HT, Pastore GM. Optimization of R-(+)-alpha-terpineol production by the biotransformation of R-(+)-limonene. J Ind Microbiol Biotechnol. 2008 Sep;35(9):1061-70. PubMed PMID: 18560915.
12. Krings U, Hardebusch B, Albert D, Berger RG, Marostica M, Jr., Pastore GM. Odor-active alcohols from the fungal transformation of alpha-farnesene. J Agric Food Chem. 2006 Nov 29;54(24):9079-84. PubMed PMID: 17117793.
13. Berger RG. Biotechnology of flavours--the next generation. Biotechnol Lett. 2009 Nov;31(11):1651-9. PubMed PMID: 19609491.
14. Kossuga MH, Romminger S, Xavier C, Milanetto MC, Valle MZd, Pimenta EF, et al. Evaluating methods for the isolation of marine-derived fungal strains and production of bioactive secondary metabolites. Revista Brasileira de Farmacognosia. 2012;22:257-67.
15. Zhang D, Satake M, Fukuzawa S, Sugahara K, Niitsu A, Shirai T, et al. Two new indole alkaloids, 2-(3,3-dimethylprop-1-ene)-costaclavine and 2-(3,3-dimethylprop-1-ene)-epicostaclavine, from the marine-derived fungus Aspergillus fumigatus. J Nat Med. 2012 Jan;66(1):222-6. PubMed PMID: 21792727.
16. Bhadury P, Mohammad BT, Wright PC. The current status of natural products from marine fungi and their potential as anti-infective agents. J Ind Microbiol Biotechnol. 2006 May;33(5):325-37. PubMed PMID: 16429315.
17. Shang Z LX, Meng L, Li C, Gao S, Huang C, Wang B. Chemical profile of the secondary metabolites produced by a deep-sea sediment-derived fungus Penicillium commune SD-118. Chinese Journal of Oceanology and Limnology. 2012;30(2):305-14.
18. Barakat KM, Gohar YM. Antimicrobial Agents Produced by Marine Aspergillus terreus var. africanus Against Some Virulent Fish Pathogens. Indian J Microbiol. 2012 Sep;52(3):366-72. PubMed PMID: 23997326. Pubmed Central PMCID: PMC3460127.
19. Januar LA, Molinski TF. Acremolin from Acremonium strictum is N(2),3-etheno-2'-isopropyl-1-methylguanine, not a 1H-azirine. Synthesis and structural revision. Org Lett. 2013 May 17;15(10):2370-3. PubMed PMID: 23635003. Pubmed Central PMCID: PMC3957326.
20. Mei-Yan W G-YC, Yu W, Xiu-Li Z, Chang-Yun W, Chang-Lun S. Isolation, 1H, 13C NMR Assignments, and crystal structure of Chrodrimanin B from a marine fungus Aspergillus sp.. Chemistry of Natural Compounds. 2011;47(4):571-79.
21. Smetanina OF YA, Kalinovskii AI, Berdyshev DV, Gerasimenko AV, Pivkin MV, Slinkina NN, Dmitrenok PS, Menzorova NI, Kuznetsova TA, Afiyatullov SH. Biologically active metabolites from the marine isolate of the fungus Myceliophthora lutea. Chemistry of Natural Compounds. 2011;47(3):p385.
22. Peng XP, Wang Y, Liu PP, Hong K, Chen H, Yin X, et al. Aromatic compounds from the halotolerant fungal strain of Wallemia sebi PXP-89 in a hypersaline medium. Arch Pharm Res. 2011 Jun;34(6):907-12. PubMed PMID: 21725811.
23. American Cancer Society, Cancer Facts & Figures 2015.
24. Muthumary VGaJ. Taxol, an anticancer drug produced by an endophytic fungus Bartalinia robillardoides Tassi, isolated from a medicinal plant, Aegle marmelos Correa ex Roxb. Journal of Microbiology and Biotechnology. 2008;24(5):717-24.
25. Pasut G, Veronese FM. PEG conjugates in clinical development or use as anticancer agents: an overview. Adv Drug Deliv Rev. 2009 Nov 12;61(13):1177-88. PubMed PMID: 19671438.
26. Firáková S, Šturdíková M, Múčková M. Bioactive secondary metabolites produced by microorganisms associated with plants. Biologia.62(3):251-7.
27. Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. J Am Chem Soc. 1971 May 5;93(9):2325-7. PubMed PMID: 5553076.
28. Li JY, Strobel G, Sidhu R, Hess WM, Ford EJ. Endophytic taxol-producing fungi from bald cypress, Taxodium distichum. Microbiology. 1996 Aug;142 (Pt 8):2223-6. PubMed PMID: 8760934.

29. Strobel GA, Hess WM, Li J-Y, Ford E, Sears J, Sidhu RS, et al. <i>Pestalotiopsis guepinii</i>, a Taxol-producing Endophyte of the Wollemi Pine, <i>Wollemia nobilis</i>. Australian Journal of Botany. 1997;45(6):1073-82.
30. Senthil Kumaran R, Muthumary J, Hur BK. Production of Taxol fromPhyllosticta spinarum, an endophytic fungus ofCupressus sp. Engineering in Life Sciences. 2008;8(4):438-46.
31. Gangadevi V, Muthumary J. Taxol production by Pestalotiopsis terminaliae, an endophytic fungus of Terminalia arjuna (arjun tree). Biotechnol Appl Biochem. 2009 Jan;52(Pt 1):9-15. PubMed PMID: 18254723.
32. Pandi M, Manikandan R, Muthumary J. 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. Biomed Pharmacother. 2010 Jan;64(1):48-53. PubMed PMID: 19762199.
33. Wall ME, Wani MC, Cook CE, Palmer KH, McPhail AT, Sim GA. Plant Antitumor Agents. I. The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumor Inhibitor from Camptotheca acuminata1,2. Journal of the American Chemical Society. 1966 1966/08/01;88(16):3888-90.
34. S. R. Uma BTR, G. Ravikanth, P. G. Rajesh, R. Vasudeva, and K. N. Ganeshaiah. Chemical profiling of N. nimmoniana for camptothecin, an important anticancer alkaloid: towards the development of a sustainable production system. Bioactive Molecules and Medicinal Plants. 2008;7(6):197-213.
35. Li QY, Zu YG, Shi RZ, Yao LP. Review camptothecin: current perspectives. Curr Med Chem. 2006;13(17):2021-39. PubMed PMID: 16842195.
36. Kehrer DF, Soepenberg O, Loos WJ, Verweij J, Sparreboom A. Modulation of camptothecin analogs in the treatment of cancer: a review. Anticancer Drugs. 2001 Feb;12(2):89-105. PubMed PMID: 11261892.
37. Kusari S, Zuhlke S, Spiteller M. An endophytic fungus from Camptotheca acuminata that produces camptothecin and analogues. J Nat Prod. 2009 Jan;72(1):2-7. PubMed PMID: 19119919.
38. Jew S, Kim HJ, Kim MG, Roh EY, Hong CI, Kim JK, et al. Synthesis and in vitro cytotoxicity of hexacyclic camptothecin analogues. Bioorg Med Chem Lett. 1999 Nov 15;9(22):3203-6. PubMed PMID: 10576688.
39. Puri SC, Verma V, Amna T, Qazi GN, Spiteller M. An endophytic fungus from Nothapodytes foetida that produces camptothecin. J Nat Prod. 2005 Dec;68(12):1717-9. PubMed PMID: 16378360.
40. Amna T, Puri SC, Verma V, Sharma JP, Khajuria RK, Musarrat J, et al. Bioreactor studies on the endophytic fungus Entrophospora infrequens for the production of an anticancer alkaloid camptothecin. Can J Microbiol. 2006 Mar;52(3):189-96. PubMed PMID: 16604115.
41. Rehman S, Shawl AS, Verma V, Kour A, Athar M, Andrabi R, et al. An endophytic Neurospora sp. from Nothapodytes foetida producing camptothecin. Prikl Biokhim Mikrobiol. 2008 Mar-Apr;44(2):225-31. PubMed PMID: 18669267.
42. Liu K, Ding X, Deng B, Chen W. 10-Hydroxycamptothecin produced by a new endophytic Xylaria sp., M20, from Camptotheca acuminata. Biotechnol Lett. 2010 May;32(5):689-93. PubMed PMID: 20112128.
43. Shweta S, Zuehlke S, Ramesha BT, Priti V, Mohana Kumar P, Ravikanth G, et al. Endophytic fungal strains of Fusarium solani, from Apodytes dimidiata E. Mey. ex Arn (Icacinaceae) produce camptothecin, 10-hydroxycamptothecin and 9-methoxycamptothecin. Phytochemistry. 2010 Jan;71(1):117-22. PubMed PMID: 19863979.
44. Korkina LG. Phenylpropanoids as naturally occurring antioxidants: from plant defense to human health. Cell Mol Biol (Noisy-le-grand). 2007;53(1):15-25. PubMed PMID: 17519109.
45. Fill TP, da Silva BF, Rodrigues-Fo E. Biosynthesis of phenylpropanoid amides by an endophytic Penicillium brasilianum found in root bark of Melia azedarach. J Microbiol Biotechnol. 2010 Mar;20(3):622-9. PubMed PMID: 20372037.
46. Chapela IH, Petrini O, Hagmann L. Monolignol glucosides as specific recognition messengers in fungus-plant symbioses. Physiological and Molecular Plant Pathology. 1991 10//;39(4):289-98.
47. Koshino H, Terada S-I, Yoshihara T, Sakamura S, Shimanuki T, Sato T, et al. Three phenolic acid derivatives from stromata of Epichloe typhina on Phleum pratense. Phytochemistry. 1988 //;27(5):1333-8.
48. Gordaliza M, Garcia PA, del Corral JM, Castro MA, Gomez-Zurita MA. Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. Toxicon. 2004 Sep 15;44(4):441-59. PubMed PMID: 15302526.
49. Kusari S, Lamshoft M, Spiteller M. Aspergillus fumigatus Fresenius, an endophytic fungus from Juniperus communis L. Horstmann as a novel source of the anticancer pro-drug deoxypodophyllotoxin. J Appl Microbiol. 2009 Sep;107(3):1019-30. PubMed PMID: 19486398.
50. Puri SC, Nazir A, Chawla R, Arora R, Riyaz-Ul-Hasan S, Amna T, et al. The endophytic fungus Trametes hirsuta as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. J Biotechnol. 2006 Apr 20;122(4):494-510. PubMed PMID: 16375985.
51. Eyberger AL, Dondapati R, Porter JR. Endophyte fungal isolates from Podophyllum peltatum produce podophyllotoxin. J Nat Prod. 2006 Aug;69(8):1121-4. PubMed PMID: 16933860.
52. Deshmukh SK, Mishra PD, Kulkarni-Almeida A, Verekar S, Sahoo MR, Periyasamy G, et al. Anti-inflammatory and anticancer activity of ergoflavin isolated from an endophytic fungus. Chem Biodivers. 2009 May;6(5):784-9. PubMed PMID: 19479845.
53. Zhang JY, Tao LY, Liang YJ, Yan YY, Dai CL, Xia XK, et al. Secalonic acid D induced leukemia cell apoptosis and cell cycle arrest of G(1) with involvement of GSK-3beta/beta-catenin/c-Myc pathway. Cell Cycle. 2009 Aug;8(15):2444-50. PubMed PMID: 19571678.
54. Fernandes MdRV, Silva TACe, Pfenning LH, Costa-Neto CMd, Heinrich TA, Alencar SMd, et al. Biological activities of the fermentation extract of the endophytic fungus Alternaria alternata isolated from Coffea arabica L. Brazilian Journal of Pharmaceutical Sciences. 2009;45:677-85.

55. Li J, Zhao GZ, Chen HH, Wang HB, Qin S, Zhu WY, et al. Antitumour and antimicrobial activities of endophytic streptomycetes from pharmaceutical plants in rainforest. Lett Appl Microbiol. 2008 Dec;47(6):574-80. PubMed PMID: 19120929.
56. Huang Y, Wang J, Li G, Zheng Z, Su W. Antitumor and antifungal activities in endophytic fungi isolated from pharmaceutical plants Taxus mairei, Cephalataxus fortunei and Torreya grandis. FEMS Immunol Med Microbiol. 2001 Aug;31(2):163-7. PubMed PMID: 11549424.
57. Brady SF, Singh MP, Janso JE, Clardy J. Cytoskyrins A and B, new BIA active bisanthraquinones isolated from an endophytic fungus. Org Lett. 2000 Dec 14;2(25):4047-9. PubMed PMID: 11112640.
58. Ding G, Zheng Z, Liu S, Zhang H, Guo L, Che Y. Photinides A−F, Cytotoxic Benzofuranone-Derived γ-Lactones from the Plant Endophytic Fungus Pestalotiopsis photiniae. Journal of Natural Products. 2009 2009/05/22;72(5):942-5.
59. Klemke C, Kehraus S, Wright AD, Konig GM. New secondary metabolites from the marine endophytic fungus Apiospora montagnei. J Nat Prod. 2004 Jun;67(6):1058-63. PubMed PMID: 15217297.
60. Song YC, Li H, Ye YH, Shan CY, Yang YM, Tan RX. Endophytic naphthopyrone metabolites are co-inhibitors of xanthine oxidase, SW1116 cell and some microbial growths. FEMS Microbiol Lett. 2004 Dec 1;241(1):67-72. PubMed PMID: 15556711.
61. Guo B, Wang Y, Sun X, Tang K. Bioactive natural products from endophytes: a review. Prikl Biokhim Mikrobiol. 2008 Mar-Apr;44(2):153-8. PubMed PMID: 18669256.
62. Yu H, Zhang L, Li L, Zheng C, Guo L, Li W, et al. Recent developments and future prospects of antimicrobial metabolites produced by endophytes. Microbiol Res. 2010 Aug 20;165(6):437-49. PubMed PMID: 20116229.
63. Song JH. What's new on the antimicrobial horizon? Int J Antimicrob Agents. 2008 Dec;32 Suppl 4:S207-13. PubMed PMID: 19134521.
64. Liu X, Dong M, Chen X, Jiang M, Lv X, Zhou J. Antimicrobial activity of an endophytic Xylaria sp.YX-28 and identification of its antimicrobial compound 7-amino-4-methylcoumarin. Appl Microbiol Biotechnol. 2008 Feb;78(2):241-7. PubMed PMID: 18092158.
65. Pongcharoen W, Rukachaisirikul V, Phongpaichit S, Kühn T, Pelzing M, Sakayaroj J, et al. Metabolites from the endophytic fungus Xylaria sp. PSU-D14. Phytochemistry. 2008 6//;69(9):1900-2.
66. Pittayakhajonwut P, Suvannakad R, Thienhirun S, Prabpai S, Kongsaeree P, Tanticharoen M. An anti-herpes simplex virus-type 1 agent from Xylaria mellisii (BCC 1005). Tetrahedron Letters. 2005 2/21/;46(8):1341-4.
67. Boonphong S, Kittakoop P, Isaka M, Pittayakhajonwut D, Tanticharoen M, Thebtaranonth Y. Multiplolides A and B, new antifungal 10-membered lactones from Xylaria multiplex. J Nat Prod. 2001 Jul;64(7):965-7. PubMed PMID: 11473437.
68. Pimentel MR, Molina G, Dionisio AP, Marostica Junior MR, Pastore GM. The use of endophytes to obtain bioactive compounds and their application in biotransformation process. Biotechnol Res Int. 2011;2011:576286. PubMed PMID: 21350663. Pubmed Central PMCID: PMC3042614.
69. Findlay JA, Li G, Johnson JA. Bioactive compounds from an endophytic fungus from eastern larch (Larixlaricina) needles. Canadian Journal of Chemistry. 1997 1997/06/01;75(6):716-9.
70. Qin JC, Zhang YM, Gao JM, Bai MS, Yang SX, Laatsch H, et al. Bioactive metabolites produced by Chaetomium globosum, an endophytic fungus isolated from Ginkgo biloba. Bioorg Med Chem Lett. 2009 Mar 15;19(6):1572-4. PubMed PMID: 19246197.
71. Huang Z, Cai X, Shao C, She Z, Xia X, Chen Y, et al. Chemistry and weak antimicrobial activities of phomopsins produced by mangrove endophytic fungus Phomopsis sp. ZSU-H76. Phytochemistry. 2008 May;69(7):1604-8. PubMed PMID: 18343465.
72. Castillo U, Harper JK, Strobel GA, Sears J, Alesi K, Ford E, et al. Kakadumycins, novel antibiotics from Streptomyces sp NRRL 30566, an endophyte of Grevillea pteridifolia. FEMS Microbiol Lett. 2003 Jul 29;224(2):183-90. PubMed PMID: 12892881.
73. Liu JY, Song YC, Zhang Z, Wang L, Guo ZJ, Zou WX, et al. Aspergillus fumigatus CY018, an endophytic fungus in Cynodon dactylon as a versatile producer of new and bioactive metabolites. J Biotechnol. 2004 Nov 9;114(3):279-87. PubMed PMID: 15522437.
74. You F, Han T, Wu J-z, Huang B-k, Qin L-p. Antifungal secondary metabolites from endophytic Verticillium sp. Biochemical Systematics and Ecology. 2009 7//;37(3):162-5.
75. Li E, Tian R, Liu S, Chen X, Guo L, Che Y. Pestalotheols A-D, bioactive metabolites from the plant endophytic fungus Pestalotiopsis theae. J Nat Prod. 2008 Apr;71(4):664-8. PubMed PMID: 18303847.
76. Aly AH, Edrada-Ebel R, Wray V, Muller WE, Kozytska S, Hentschel U, et al. Bioactive metabolites from the endophytic fungus Ampelomyces sp. isolated from the medicinal plant Urospermum picroides. Phytochemistry. 2008 May;69(8):1716-25. PubMed PMID: 18400237.
77. Rukachaisirikul V, Sommart U, Phongpaichit S, Sakayaroj J, Kirtikara K. Metabolites from the endophytic fungus Phomopsis sp. PSU-D15. Phytochemistry. 2008 Feb;69(3):783-7. PubMed PMID: 17950385.
78. Hoffman AM, Mayer SG, Strobel GA, Hess WM, Sovocool GW, Grange AH, et al. Purification, identification and activity of phomodione, a furandione from an endophytic Phoma species. Phytochemistry. 2008 Feb;69(4):1049-56. PubMed PMID: 18070629.
79. Li JY, Harper JK, Grant DM, Tombe BO, Bashyal B, Hess WM, et al. Ambuic acid, a highly functionalized cyclohexenone with antifungal activity from Pestalotiopsis spp. and Monochaetia sp. Phytochemistry. 2001 Mar;56(5):463-8. PubMed PMID: 11261579.
80. Castillo UF, Strobel GA, Ford EJ, Hess WM, Porter H, Jensen JB, et al. Munumbicins, wide-spectrum antibiotics produced by Streptomyces NRRL 30562, endophytic on Kennedia nigriscans. Microbiology. 2002 Sep;148(Pt 9):2675-85. PubMed PMID: 12213914.

81. Wu-Yang H, Yi-Zhong C, Jie X, Harold C, Sun M. A Potential Antioxidant Resource: Endophytic Fungi from Medicinal Plants. Economic Botany. 2007;61(1):14-30.
82. Seifried HE, Anderson DE, Fisher EI, Milner JA. A review of the interaction among dietary antioxidants and reactive oxygen species. J Nutr Biochem. 2007 Sep;18(9):567-79. PubMed PMID: 17360173.
83. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44-84. PubMed PMID: 16978905.
84. Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. Eur J Cancer. 2000 Jun;36(10):1235-47. PubMed PMID: 10882862.
85. Cozma LS. The role of antioxidant therapy in cardiovascular disease. Curr Opin Lipidol. 2004 Jun;15(3):369-71. PubMed PMID: 15166796.
86. Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet. 1994 Sep 10;344(8924):721-4. PubMed PMID: 7915779.
87. Mitscher LA, Telikepalli H, McGhee E, Shankel DM. Natural antimutagenic agents. Mutat Res. 1996 Feb 19;350(1):143-52. PubMed PMID: 8657175.
88. Liu X, Dong M, Chen X, Jiang M, Lv X, Yan G. Antioxidant activity and phenolics of an endophytic Xylaria sp. from Ginkgo biloba. Food Chemistry. 2007 //;105(2):548-54.
89. Khiralla A, Mohamed I, Thomas J, Mignard B, Spina R, Yagi S, et al. A pilot study of antioxidant potential of endophytic fungi from some Sudanese medicinal plants. Asian Pacific Journal of Tropical Medicine. 2015 9//;8(9):701-4.
90. Strobel G, Ford E, Worapong J, Harper JK, Arif AM, Grant DM, et al. Isopestacin, an isobenzofuranone from Pestalotiopsis microspora, possessing antifungal and antioxidant activities. Phytochemistry. 2002 May;60(2):179-83. PubMed PMID: 12009322.
91. Harper JK, Arif AM, Ford EJ, Strobel GA, Porco Jr JA, Tomer DP, et al. Pestacin: a 1,3-dihydro isobenzofuran from Pestalotiopsis microspora possessing antioxidant and antimycotic activities. Tetrahedron. 2003 3/31/;59(14):2471-6.
92. Song YC, Huang WY, Sun C, Wang FW, Tan RX. Characterization of graphislactone A as the antioxidant and free radical-scavenging substance from the culture of Cephalosporium sp. IFB-E001, an endophytic fungus in Trachelospermum jasminoides. Biol Pharm Bull. 2005 Mar;28(3):506-9. PubMed PMID: 15744078.

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