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Antimicrobial compounds isolated from endophytic fungi.

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Abstract

There is a need to search for new antimicrobial agents because infectious diseases are still a global problem because of the development and spread of drug-resistant pathogens Novel anticancer drugs are also required due to the high worldwide mortality. Many endophytic fungi were reported to produce novel bioactive metabolites such as antimicrobial, anticancer, and antiviral agents. The discovery of taxol producing fungi increased the importance of endophytes and shifted natural products research to endophytic fungi. Endophytic fungi can provide a wide variety of secondary metabolites that might be a potential source of novel bioactive compounds.

Keywords : Antimicrobial agents, bioactive compounds, drug resistance, endophyte

INTRODUCTION

Endophytes are microbes that inhabit host plants without causing disease. The isolation, culture and characterization of some endophytes have provided opportunity for discovery of novel antibiotics, antimycotics, immunosuppressants and anticancer compounds among other products. (Strobel, *et al*., 2003). The pharmaceutical and medical concerns of new drugs are the toxicity of these prospective drugs to human tissues. Since the plant tissue where the endophytes exist is a eukaryotic system, it would appear that the secondary metabolites produced by the endophytes may have reduced cell toxicity; otherwise, death of the host tissue may occur. Thus, the host itself has naturally served as a selection system for microbes having bioactive molecules with reduced toxicity toward higher organisms (Strobel, 2003).

Endophytes are universally present in all of the world's higher plants, so it was reasoned that plants might support certain endophytic microorganisms that could synthesize important phytochemicals of medicinal plants as well as the plant itself. Thus, if a microbial source of the drug was available, it could eliminate the need to harvest and extract the slow-growing and relatively rare trees. The price for the drug would also be reduced, since the drugs could be produced *via* fermentation in such the same way that penicillin is fermented (Strobel, 2003). Many reports supported this idea. It began with the discovery of taxol producing endophytes, the most potent anticancer drug, from the culture of the endophytic fungi, *Taxomyces andreanae* isolated from *Taxus brevifolia* tree, and endophytic fungus *Pestalotiopsis microspora* from medicinal plants *Taxus wallichiana* and bald cypress *Taxodium distichum* (Stierle *et al*., 1993).

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The ultimate purpose of endophytes research is to find new antibiotics or pesticides, thus the following aspects should be intensively studied: (1) to find better bioactive antimicrobial substances without any side effect to human, plant and environment; (2) To enhance the antimicrobial activity or decrease the side effects of known metabolites from endophytes by modifying their structures in order to improve the efficacy and specificity to microbes; (3) To optimize conditions of endophyte fermentation that has been found to show bioactivity in order to enhance the yield of active substances synthesized by endophyte; and (4) to search for the regulatory gene in synthesis path of antimicrobial compound, and use genetic engineering technology to increase the production of antibacterial substances. As so many antimicrobial compounds were isolated from endophytes which only occupied a small portion of total endophyte species, it is obvious that there is a great opportunity to find reliable and novel antimicrobial natural products in endophytes, which may be used as clinically effective antibiotics in future.

Antimicrobial Agents from Endophytes

Antimicrobial metabolites (Antibiotics) can be defined as low-molecular-weight organic compounds made by microorganisms that are active at low concentrations against other microorganisms, not required for its growth, produced as an adaptation for specific functions in nature, and are the most bioactive natural products isolated from endophytes (Demain,1981; Strobel and Daisy, 2003; Guo et al., 2008). Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites bearing antimicrobial activity. It is believed that screening for antimicrobial compounds from endophytes is a promising way to overcome the increasing threat of drug resistant microbes of human and plant pathogen (Tan and Zou, 2001; Yu et al., 2010). The antimicrobial compounds can be used not only as

drugs by humankind but also as food preservatives in the control of food spoilage and food-borne diseases, a serious concern in the world food chain (Liu *et al.* 2008).

Li *et al.* (2005) reported 30% of tested isolates exhibited antifungal activity, also antimicrobial activity was demonstrated for 8%-92% of endophytic extracts in other studies (Banu and Kumar, 2009; Hazalin *et al.,* 2009; Tong *et al.,* 2011).

Cryptocin and cryptocandin are antifungal metabolites obtained from the endophytic fungus *Cryptosporiopsis* cf. *quercina.* Cryptocandin demonstrated excellent antifungal activity against some important human fungal pathogens, including *Candida albicans* and *Trichophyton* spp., and against a number of plant pathogenic fungi, including *Sclerotinia sclerotiorum* and *Botrytis cinerea.* Cryptocandin and its related compounds are currently being considered for use against a number of fungi causing diseases of the skin and nails (Strobel and Daisy, 2003). Cryptocin however possesses potent activity against plant pathogens only, especially against *Pyricularia oryzae*, the causal organism of one of the worst plant diseases in the world, with minimum inhibitory concentration 0.39 µg/ml (Strobel *et al.,* 1999). The endophytic fungus *Pestalotiopsis microspora* was found to produce number of antifungal metabolites, like ambuic acid, pestaloside, and pestalotiopsins A and B. They showed activity against many of pathogenic fungi, while pestaloside possessed phytotoxic properties. Endophytic fungi *Pestalotiopsis jesteri* and *Pestalotiopsis adusta* were found to synthesize jesterone and Pestalachlorides A respectively, which exhibit antifungal activity against a variety of plant pathogenic fungi (Li *et al.,* 2008). Pestalachlorides A was proven to display significant antifungal activity against three plant pathogenic fungi, *Fusarium culmorum, Gibberella zeae* and *Verticillium albo-atrum* (Lee *et al.,* 1995; Pulici *et al.,* 1996; Li *et al.,* 2001; Li *et al.,* 2008).

Lu *et al.* (2000) isolated three metabolites from the culture of endophytic fungus *Colletotrichum* sp., residing in the medicinal *Artemisia annua.* These compounds were shown to have not only activity against human-pathogenic fungi and bacteria but also be fungistatic to plant-pathogenic fungi. Krohn *et al.* (2002) reported fusidikactones with antifungal activity from endophytic *Fusidium* species. Preaustinoid A, B isolated from *Penicillium* sp., exhibited moderate bacteriostatic effect on *Escherichia coli, Staphylo-coccus aureus, Pseudomonas aeruginosa* and *Bacillus.* Antibacterial periconicins A and B isolated from endophytic fungus *Periconia* sp. Obtained from host plant *Taxus cuspidate.* Among metabolites produced by the endophytic fungus *Aspergillus fumigatus* CY018 asperfumoid, fumigaclavine C, fumitremorgin C, physcion, and helvolic acid were shown to inhibit *Candida albicans* (Liu *et al.,* 2004).

Investigation of endophytic fungus *Rhizoctonia* sp. yielded rhizoctonic acid with anti-*helicobacter pylori* activity, the causative bacteria of peptic ulcer (Ma *et al.,* 2004). Rubrofusarin B, fonsecinone A, asperpyrone B, and aurasperone A from *Aspergillus niger* IFB-E003, an endophyte in *Cyndon dactylon*. The four metabolites exhibited growth inhibitions against the pathogenic microbes with minimal inhibitory concentra-tions (MICs) ranging in between 1.9 and 31.2 µg/ml. Another novel antibioticphomol was isolated from fermentations of an endophytic fungus *Phomopsis* species, another two antimicrobial agents cytosporone B and C were isolated from the same genus *Phomopsis* sp.; they inhibited two fungi *Candida albicans* and *F. oxysporum* with the MIC value ranging from 32 to 64 mg/ml. Investigation of endophytic *Phomopsis cassia,* ethyl 2,4-dihydroxy-5,6-dimethylbenzoate and phomopsilactone displayed strong antifungal activity against two phytopathogenic fungi, *Cladosporium cladosporioides,* and *C. sphaerospermum* (Weber *et al.,* 2004; Silva *et al.,* 2005; Huang *et al.,* 2008).

Chemical investigations of corn endophyte *Acremonium zeae* led to the discovery of two antibiotics pyrrocidines A and B , which displayed significant antifungal activity against *Aspergillus flavus* and *Fusarium verticillioides* (Wicklow *et al.,* 2005). More than 50% of endophytic fungal strains residing in *Quercus variabilis* possessed growth inhibition against at least one pathogenic fungus or bacterium. *Cladosporium* sp., displaying the most active antifungal activity, was investigated and found to produce a secondary metabolite known as brefeldin A with antibiotic activity (Wang *et al.,* 2007). The antimicrobial agents Hypericin and Emodin were produced by *Hypericum perforatum.* Both compounds possessed antimicrobial activity against several bacteria and fungi, including *Staphylococcus aureus* ssp. *aureus*, *Klebsiella pneumoniae* ssp. *ozaenae*, *Pseudomonas aeruginosa*, *Salmonella enterica* ssp. *Enteric,* and *Escherichia coli*, and fungal and candidal pathogens *Aspergillus niger* and *C. albicans* (Kusari *et al.,* 2008). Chaetoglobosins A and C with antifungal activities were characterized from the culture of an endophytic *Chaetomium globosum* isolated from the leaves of *Ginkgo biloba.* In agar diffusion method, these two metabolites were shown antimicrobial activity against *Mucor miehei* (Qin *et al.,* 2009). The endophytic genus *Xylaria* was investigated as producers of many antifungal agents; species also produce griseofulvin which is used for the treatment of human and veterinary animals mycotic diseases. Sordaricin and multiplolides had antifungal activity against *Candida albicans*,7-amino-4-methylcoumarin showed broad-spectrum inhibitory activity against several food-borne and food spoilage

microorganisms. It was suggested for use as natural preservatives in food. *In vitro* and *in vivo* antifungal activity of endophyte-produced griseofulvin against plant pathogenic fungi were effective for controlling effectively the development of various food crops diseases (Boonphong *et al.*, 2001; Cafµu *et al.*, 2005; Liu *et al.*, 2008; Pongcharoen *et al.*, 2008).

Curvularide B was isolated from the endophyte *Curvularia geniculata* and showed antifungal activity with increase in inhibition zone in the presence of fluconazole (example of currently used azol drug), which indicated the synergistic effect of both drugs against *Candida albicans*. The minimum inhibitory concentrations (MIC) values that produced no visible growth (MIC-0) for fluconazole and curvularide B were 26.1 and 782.8µM, respectively. While in combination, the MIC-0 values decreased to 3.2 and 48.9µM, respectively. Curvularide B did not exhibit cytotoxicity towards ten human cancer cell lines even at a concentration of 50µg/ml, which indicates positive results for using it to improve activity of azol antifungal drugs (Chomcheon et al., 2010). The mangrove derived endophytic fungus *Talaromyces* sp. produced the antimi-crobial metabolites (7-epiaustdiol, stemphy-perylenol and secalonic acid A). 7-epiaustdiol displayed significant inhibitory activity against *Pseudomonas aeruginosa*, a multidrug resistant opportunistic pathogen, with MIC value of 26.48µM. Stemphy-perylenol inhibited *Sarcina ventriculi* with MIC value of 8.86µM, which is lower than that of ampicillin (35.81µM), while secalonic acid A exhibited high activities against all tested organisms. Furthermore, the three compounds showed moderate to strong cytotoxicity against KB and KBv200 cell lines (Liu et al., 2010).

Fumigants are produced by many of endophytes. *Muscodor* is a novel endophytic fungal genus that produces bioactive volatile organic compounds (VOCs). This fungus, as well as its VOCs, has enormous potential for uses in agriculture, industry and medicine. Endophytic *Muscodor albus* and the most recently discovered *Muscodor crispans* produce a mixture of VOCs that act synergistically to kill a wide variety of plant and human pathogenic fungi and bacteria. It is also effective against nematodes and certain insects. This mixture of gases consists primarily of various alcohols, acids, esters, ketones and lipids. Artificial mixtures of the VOCs mimic the biological effects of the fungal VOCs when tested against a wide range of fungal and bacterial pathogens. Potential applications for mycofumigation by this genus are currently used for treating various plant diseases, buildings, soils, agricultural produce and human wastes. Another promising option includes its use to replace methyl bromide fumigation as a means to control soil-borne plant diseases (Strobel 2006, 2011).

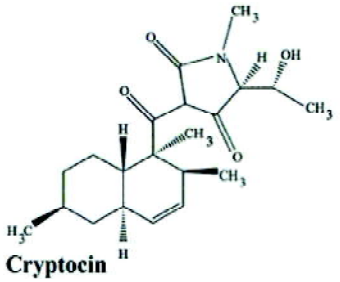
Recently, tuberculosis inhibitors were found among endophytes, some of the endophytes were found to inhibit *Mycobacterium aurum* and *Mycobacterium tuberculosis*, the causative organisms of tuberculosis. Rukachaisirikul *et al.* (2008) isolated phomoenamide which exhibited *in vitro* antimycobacterial activity against *M. tuberculosis* H37Ra. The screening of endophytic extracts, lead to isolation of endophytic isolate from *Vaccinium myrtillus* which showed MIC 8 µg/ml against *M. aurum*, and endophytes from *Calluna vulgaris*, *Empetrum nigrum*, *Vaccinium vitis-idaea* and *V. myrtillus* which show 90 to 96% inhibition at 100 µg/ml against *M. tuberculosis* (Gordien *et al.*, 2010). Chemical analysis of mangrove endophytes *Fusarium* sp. led to the isolation of fusaric acid is which used for the synthesis of a variety of metal complexes of fusaric acid. Antimyco-bacterial assays showed that cadmium (II) and copper (II) complexes exhibited potent inhibitory activity against *M. bovis* BCG strain with MIC 4 µg/mL and *M. tuberculosis* H37Rv strain with MIC 10 µg/ml (Pan et al., 2011). Verma et al., (2011) reported the endophytic fungus *Periconia* sp. produced piperine with strong antimycobacterial activity against *M. tuberculosis* and *M. smegmetis* with MIC 1.74 and 2.62 µg/ml, respectively.

Yu *et al.* (2010) published a remarkable review of antimicrobial metabolites belonged to several classes, including: alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids, which were isolated from endophytes. They concluded that as so many antimicrobial compounds were isolated from endophytes which only occupied a small portion of total endophyte species and it is obvious that there is a great opportunity to utilize endophytes as a new source for production of reliable and novel antimicrobial agents. They also stated that this could be a promising way to solve the problem of microbial resistance to commonly used drugs and meet the emergency demand of discovering highly effective, low toxicity, and environmentally friendly antibiotics, which may be used as clinically effective antibiotics in future.

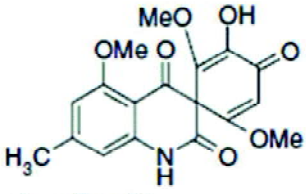
CONCLUSION

Fungi are remains a rich source of many therapeutic substances. Many antimicrobial substances have been isolated and identified by fungi. Endophytic fungi are also believed to be a potential source of novel bioactive compounds. Attempts are being made to isolate and identify bioactive metabolites from endophytic fungi. Endophytic fungi have been screened for antibiotics, antiviral and anticancer agents, antioxidants, insecticidal, and immunomodulatory compounds.

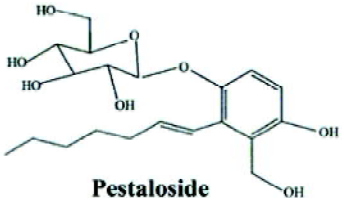
Structure of Some Antimicrobial Metabolites from Endophytes



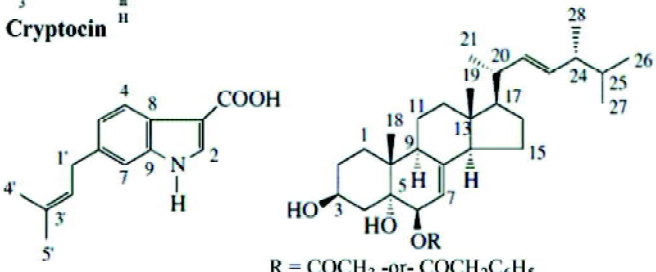
Cryptocin



Asperfumoid

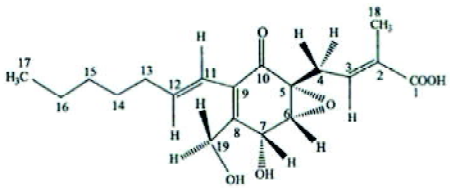


Pestaloside

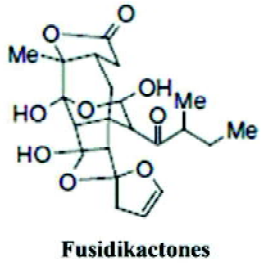


R = $COCH_3$ -or- $COCH_2C_6H_5$

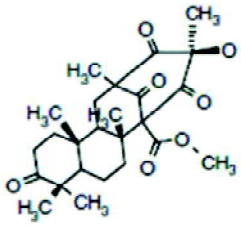
Three metabolites from the culture of endophytic *Colletotrichum* sp.



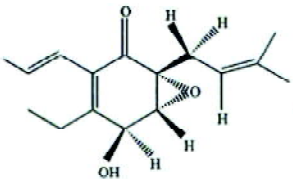
Ambuic acid



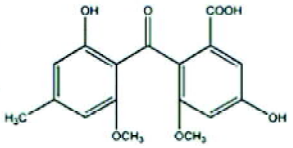
Fusidikactones



Preaustinoid

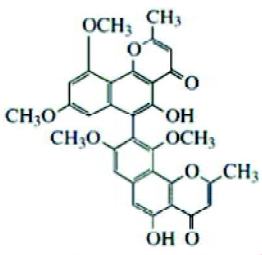


Jesterone

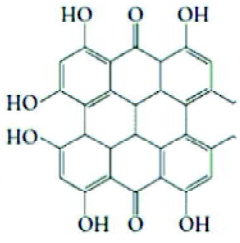


Rhizoctonic acid

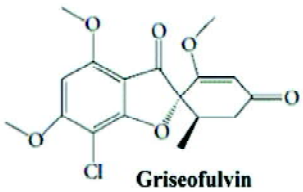
Fonsecinone A



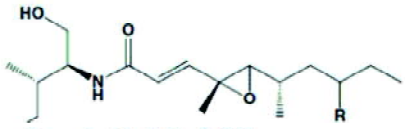
Asperpyrone B



Hypericin



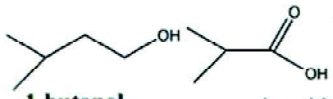
Griseofulvin



Curvularide B R= β-OH

7-epiaustdiol R=H

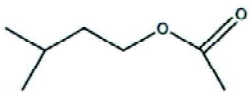
Secalonic acid A



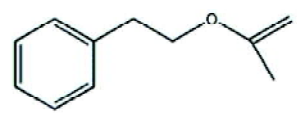
1-butanol, 3- methyl

propanoic acid, 2-methyl

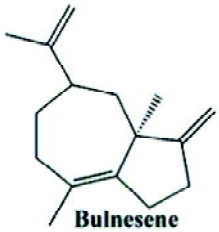
propanoic acid, 2-methyl ester



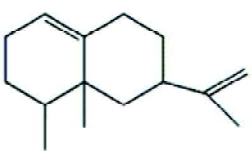
1- butanol,3 methyl, acetate



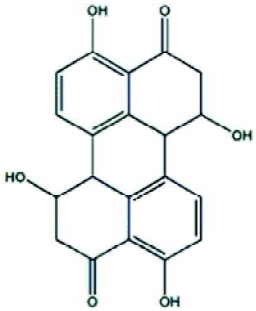
Acetic acid, 2-phenylethyl ester



Bulnesene

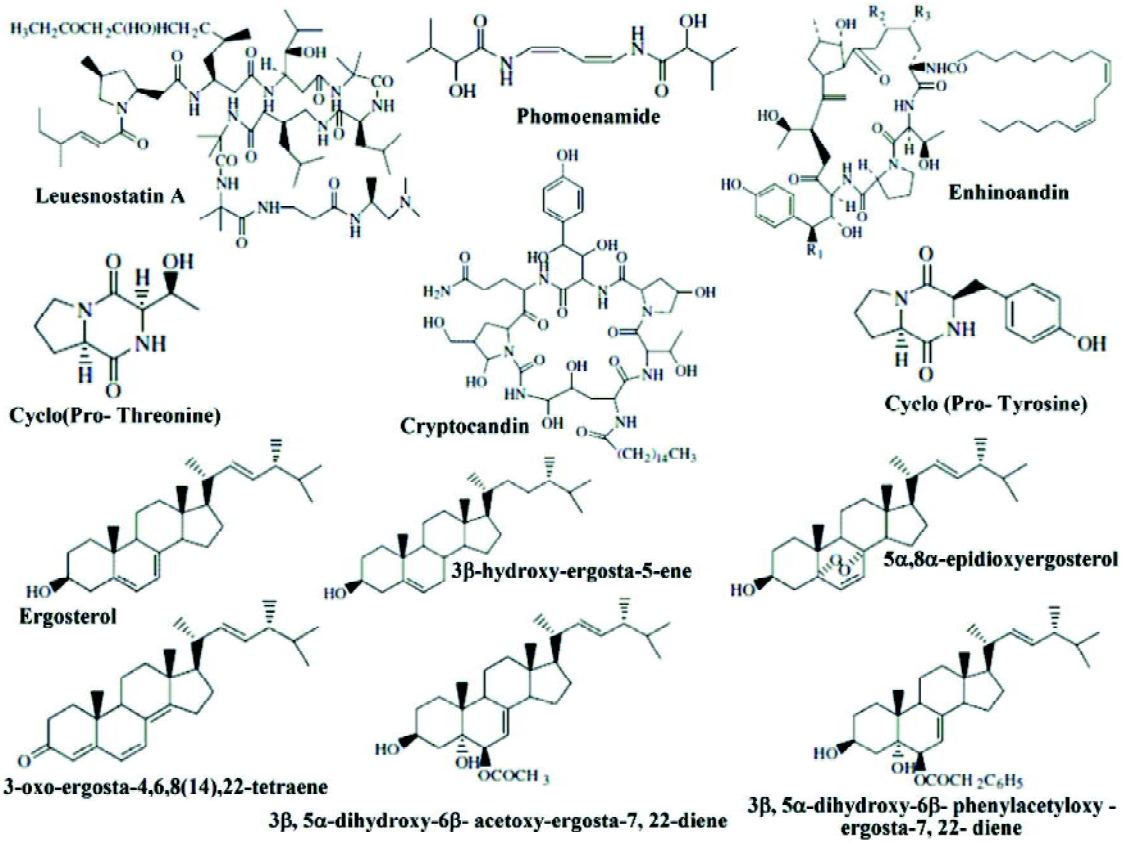


+/- Valencene



Stemphyperylenol

Structure of Some Antimicrobial Metabolites from Endophytes that reported in Yu *et al.*, 2010



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