FUNGAL ENDOPHYTES IN ETHNOMEDICINAL PLANTS: THE GOLD MINE FOR DRUG DISCOVERY

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Keywords: Endophyte, gold mine, ethnomedicinal plants, secondary metabolites

Contents

Summary

Endophytes are microorganisms that reside in internal tissues of living plants without causing any negative effect. Endophytes in general and fungal endophytes (mycoendophytes) in particular are the gold mines for the drug discovery. Endophytic fungi are novel source of bioactive compounds and hence it is need of hour to screen them for new and more effective metabolites useful from mankind. Fungal endophytes offer tremendous potential to exploit novel and eco-friendly secondary metabolites in medicine, pharmaceutical and in agricultural products. This chapter is mainly focused on diversity of endophytes from different ethnomedicinal plants used by tribal people. We also discussed the bioactive compounds of endophytes, which would be useful for the development of new drug molecules.

1. Introduction

Endophytes are microorganisms that live within the host plant tissues without causing any symptoms of disease. There has been a crescent interest in the prospecting of these microorganisms as sources of novel and bioactive natural products. These are relatively less studied and offer potential of novel secondary metabolites for their exploitation in medicine, pharmaceutical and agriculture industry. Fungal endophytes have been found in healthy tissues of all the plant taxa studied to date and it is due to their chemical diversity rather than biological diversity which is mainly responsible for the interest in these organisms. Vanessa and Christopher (2004) reported that endophytes invade the tissues of living plants and cause unapparent and asymptomatic infections entirely within plant tissues without appearance of any symptoms of disease.

Endophytes reside in the tissues between living plant cells, forming a mutually beneficial relationship with plants from symbiotic to bordering pathogens. This kind of relationship may refer to as mutualism or symbiosis. Petrini *et al*. (1992) reviewed that there are chances of more than one type of endophytic fungi in one plant.

Herre *et al*. (2007) demonstrated that endophytic fungi play a potentially important mutualistic role by augmenting host defense responses against pathogens. Endophytes could contribute to host protection increasing the expression of intrinsic host defense mechanisms and providing additional sources of defense; extrinsic to those of the host. The production of antibiotics from *Pseudomonas* such as 2-4-diacethylphloroglucinol, phenazines, pyrrolnitrin, pyoluteorin and hydrogen cyanine antibiotics show antifungal, antibacterial, antihelminthic and phytotoxic activity.

There has been an immense interest in the prospecting of these microbial endophytes as source of novel bioactive natural products. Endophytes have the ability to show much chemical diversity, including alkaloids, peptides, steroids, terpenoids, isocoumarins, quinones, phenylpropanoids and lignans, phenols, phenolic acids, aliphatic compounds, lactones, and others. After the discovery of *Taxomyces andreanea*, the producer of taxol from *Taxus brevifolia*, the interest in endophyte research has increased with fast pace. Endophytic fungi are an interesting group of microorganisms associated with the healthy tissues of plants. Endophytic fungal diversity was found to be higher in tropical and subtropical plants than other climatic zones (Banerjee, 2011). Tropical and subtropical rainforests are found nearer to north or south of the equator. They are common in Asia, Australia, Africa, South America, Central America, Mexico (Banerjee, 2011).

These metabolites might exhibit a broad range of biological activities. In fact, natural products have played a fundamental role in drug discovery and development processes for a long time (Pupo *et al*., 2006). In addition, the structural complexity of the natural products have inspired synthetic organic chemists and also provided useful research tools for the understanding of several biochemical pathways. However, one crucial aspect to be considered for a successful discovery of useful novel natural products is the selection of the source of the compounds to be studied.

Increasing global health concern due to failure of currently used antibiotics to many super resistant strains have necessitated the search for new and effective antimicrobial agents. Natural products from microorganisms have been the primary source of antibiotics, but with the increasing acceptance of herbal medicine as an alternative form of health care, screening of medicinal plants for active compounds has become very popular. In fact, many common prescribed drugs, anticancer and antimicrobial agents that are in current use are of plant origin. However, indiscriminate exploitation of these plant resources have led to the rapid decline of their populations and threatened their existence. It is now known that plants serve as a reservoir of some untold number of endophytes. Some of these endophytes have produced important bioactive metabolites for therapeutic applications. More recently it has also been found that endophytes colonizing medicinal plants could produce same bioactive natural products or derivatives that are more bioactive than those of their respective hosts.

This chapter deals with different aspects of endophyte research and mainly focused on endophytes as source of natural products, and importance of endophytic metabolites in medicine.

2. Ethnomedicinal Plants and Endophytic Fungi

In developing countries, the aboriginal communities have been using medicinal plants in diverse ways for the treatment of various diseases, which resulted in to scientific discoveries, with richness of literature on plant extracts and their biological activities. Strobel *et al*. (2002) reported that fungal endophytes residing within these plants could also produce metabolites similar to or with more activity than that of their hosts. Therefore, it is believed that search for novel compounds should be directed towards plants that commonly serve indigenous populations for medicinal purposes (Strobel and Daisy, 2003).

Many researchers reported diversity of fungal endophytes from different medicinal plants but little contribution has been made on screening of these endophytes for their bioactive metabolites. Gangadevi and Muthumary (2007) isolated endophytic fungi like *Bartalinia robillardoides* from *Aegle marmelos*, *Pestalotiopsis pauciseta* from *Cardiospermum helicacabum*, *Colletotrichum gloeosporioides* from *Justicia gendarussa*, *P. terminaliae* from *T. arjuna* and *Phomopsis arnoldiae* from *Rauwolfia tetraphylla* and screened for the extraction of taxol. Banerjee *et al*. (2009) recovered 103 different endophytes from three medicinal plants viz. *Ocimum sanctum*, *O. bacilicum* and *Leucas aspera* and studied the diversity of endophytic fungi occurring on these plants. Bhagobaty *et al*. (2010) isolated fungal endophytes from ethnomedicinal plant *Potentilla fulgens* L. of ethnic tribes of Meghalaya in the Eastern Himalayan range of India. Traditionally, pieces of tap roots of *P. fulgens* (laniang kynthei in Khasi) are chewed along with raw areca nut (*Areca catechu* L.) and betel leaves (*Piper betel* L). Raviraja (2005) reported eighteen species of endophytic fungi recovered from five medicinal plant species of the Kudremukh range in the Western Ghats of India. Further, they reported *Curvularia clavata*, *C. lunata*, *C. pallescens* and *Fusarium oxysporum* as dominant endophytic fungal species.

Herbal medicines are in great demand in both developed and the developing countries in primary healthcare because of their great efficacy and little or no side effects. In India, the indigenous systems of medicine, namely, Ayurvedic, Siddha and Unani, have been in existence for several centuries.

These traditional systems of medicine together with homoeopathy and folklore medicine continue to play a significant role largely in the health care system of the population. The tribals and rural population of India are highly dependent on medicinal plant therapy for meeting their health care needs. This attracted the attention of several botanists.

3. Fungal Endophytes: Gold Mine of Bioactive Compounds

The number of bioactive metabolites produced by mycoendophytes is large as compared to endophytic bacteria. Natural compounds from fungal endophytes can be grouped into several categories, including alkaloids, steroids, terpenoids, isocoumarins, quinones, phenylpropanoids and lignans, phenol and phenolic acids, aliphatic metabolites, lactones, etc. Yang *et al*. (2006) reported two new 12-membered ring lactones isolated from the mycelial extracts of *Cladosporium tenuissimum*.

Another alkaloid, chaetominine produced by endophytic *Chaetomium* species isolated from *Adenophora axiliflora* was reported. It showed the cytotoxic effect against the human leukemia K562 and colon cancer SW1116 cell lines, which was higher than the commonly used drug 5-fluorouracil (Jiao *et al*. 2006). Phaeosphoramides and two new carbon skeleton derivatives were isolated from the endophytic *Phaeosphaeria avenaria*. Phaeosphoramide was found to be a potential inhibitor of the signal transducer and activator of transcription. It plays a vital role in regulating cell growth and survival, constituting a target for anticancer therapy (Maloney *et al*. 2006).

Sumarah *et al*. (2010) recovered fungal endophytes from *Picea rubens* (red spruce) needles and isolated the active principles for the, evaluation of their cytotoxicity against cancer cell lines. *P. rubens* is a species of spruce native to eastern North America (Pimentel *et al*. 2011). Crude extracts of endophytic fungus *A. alternata*, isolated from *Coffea arabica* L., showed moderate cytotoxic activity to HeLa cells *in vitro*, when compared with dimethyl sulfoxide treated cells (Fernandes *et al*. 2009).

Alkaloids are useful anticancer agents that are often found in endophytic fungi. Wagenaar *et al*. (2000) isolated three novel cytochalasins from endophytic *Rhinocladiella* species which showed antitumor activity. Kopcke *et al*. (2002) reported lactones from an unidentified ascomycete endophyte recovered from *Cistus salviifolius* in Chile. Naturally occurring antioxidant compounds are commonly found in vegetables, fruits and medicinal plants.

However, it has been observed that endophytes are also a potential source of novel natural antioxidants. Endophytic *Xylaria* species isolated from the medicinal plant *Ginkgo biloba*, contain compounds showing antioxidant activities (Liu *et al*. 2007). Endophytic *Muscodor albus* was isolated from *Cinnamomum zeylanicum* (Strobel 2006). Endophytic *M. albus* produces a mixture of volatile compounds such as alcohols,

acids, esters, ketones, and lipids which kill to plant and human pathogenic fungi and bacteria.

4. Ethnomedicinal Plants and Their Fungal Endophytes

4.1. Azadirachta indica

Neem is an evergreen tree of the tropics and sub-tropics belonging to the family Meliaceae. It is widely used in Indian traditional medicine for various therapeutic purposes as well as the source of agrochemicals for many centuries. It is used as antipathogen, immunomodulator, anticancerous, antiviral, antifungal, antiallergen, antidiabetic plant and useful in wound healing, skin diseases, antihemorrhoids, anti-pyretic, anti-bacterial, burns, ulcers etc. Based on the recent claims endophytic microbes may play a key role in therapeutic properties of these plants. It is assumed that the healing properties may be due to the secretion of metabolites from the endophytes residing in the bark. Mahesh *et al.* (2005) recovered 77 endophytic fungi belonging to 15 genera from the inner bark of *A. indica*. Verma and Kharwar (2006) studied the effect of efficacy of *neem* leaf extract against the endophyte *Curvularia lunata*, isolated from the *neem*. Total of 55 isolates were obtained from *A. indica*, some of them showed inhibitory activity against pathogenic fungi (Verma *et al*., 2009). Verma *et al*. (2007) reported 233 endophytic fungi representing 18 fungal taxa from segments of bark, stem, and leaves of *A. indica*. Recently, Tenguria and Khan (2011) reported diversity of endophytic fungi isolated from leaves of *A. indica* collected from Panchmarhi biosphere reserve. Further, they reported *Trichoderma* as dominant species followed by *Pestalotiopsis* sp. and *Penicillium* species.

4.2. *Taxus* plant (Yew)

Yew plant is a highly medicinally important plant which produces an anticancer drug Taxol. Yew plants are the source of paclitaxel or taxol, a chemotherapeutic drug used in breast and lung cancer treatment. Over harvesting of the Pacific Yew plant for drug has resulted in it becoming an endangered species and going to vanish from earth. Unfortunately, the concentrations of taxol in this species are too low to be of much value commercially, though it is being used for research purposes. Therefore, by isolating endophytic fungi like *Taxomyces andreney* which produce taxol from Yew we can save the existence of Yew plant on earth. All parts of the plant, except the fleshy fruit, are antispasmodic, cardiotonic, diaphoretic, emmenagogue, expectorant, narcotic and purgative. The leaves are used in the treatment of asthma, bronchitis, hiccup, indigestion, rheumatism and epilepsy.

Traditionally, the bark is used for preparing beverages locally called *Namkin Chay*, medicines and its wood is used as a timber in various regions of the Himalaya (Purohit *et al*., 2001). The leaves have been used in a steam bath as a treatment for rheumatism. A homeopathic remedy is made from the young shoots and the berries. Apart from this it is also used in the treatment of diseases like cystitis, eruptions, headaches, heart and kidney problems, etc. Deng *et al*. (2009) reported taxol producing endophytic fungus *Fusarium solani* recovered from barks of *Taxus chinensis* from Qinba mountains, China. Huang *et al*. (2001) reported endophytic fungi such as *Paecilomyces* species.,

Cephalosporium species and *Tubercularia* species isolated from inner barks of *Taxus mairei, Cephalataxus fortunei* and *Torreya grandis* collected from Fujian province, China. Further, they studied antitumor and antifungal activity and the genus *Paecilomyces* sp. was showed highest positive rate of antitumor and antifungal activity. Rivera-Orduña *et al*. (2010) studied diversity of endophytic fungi from *T. globosa* at the Sierra Alta Hidalguense, Mexico. The authors reported endophytes from different parts of plant and identified on the basis of morphology and molecular markers. Recently, Soca-Chafrea *et al*. (2011) studied the endophytic mycoflora associated with *T. globosa*, the Mexican yew plant.

4.3. Calotropis procera

Calotropis procera is a species of flowering plant in the dogbane family, Apocynaceae native of India. It also used as antidote substance and for abortive purposes. The latex of *C. procera* has been used in leprosy, eczema, inflammation, cutaneous infections, syphilis, malarial and low hectic fevers, and as abortifacient (Kumar and Basu, 1994). Traditionally the plant is used in rheumatism, as an anti-inflammatory and antimicrobial, hepatoprotective agents, against colds and coughs, syphilis and elephantiasis, as an analgesic, antimalarial and antimicrobial. Moreover, the flowers are used in the treatment of cytostatic, abortion, malaria, asthma, piles and pyrexias. The dry latex (DL) of *C. procera* shows potential anti-diarrheal activity. Dried leaves are used to promote sexual health including penile dysfunctions and also for treatment in skin disorders and liver problems. Khan *et al*. (2007) reported many mycoendophytes such as *Aspergillus flavus, A. niger, Aspergillus* sp., *Penicillium sublateritium, Phoma chrysanthemicola, P. hedericola, Phoma* sp., and *Candida albicans* from *Calotrophis procera.*

4.4. Artemisia annua

Artemisia annua L. member of family Asteraceae is a traditional Chinese medicinal herb. It is well recognized for its synthesis of artemisinin (an antimalarial drug), is a widespread species that can flourish in many geographical areas. Artemisinin from the aerial parts of *A. annua* is a promising and potent antimalarial drug which showed remarkable activity against chloroquine resistant and chloroquine sensitive strains of *Plasmodium falciparum*. It is also useful in treatment of Cerebral malaria (Liu *et al*., 2006). Liu *et al*. (2001) reported endophytes from *A. annua* and further studied the antifungal activity against crop-threatening fungi *Gaeumannomyces graminis* var. tritici, *Rhizoctonia cerealis, Helminthosporium sativum, Fusarium graminearum, Gerlachia nivalis* and *Phytophthora capsici*. The extract of endophytes showed potential activity against these plant fungi. Zhao *et al*. (2010) reported *Colletotrichum* species from *A. annua* and studied its active secondary metabolites. Lu *et al*. (2000) also found an endophytic *Colletotrichum* species from *A. Annua.* . Further they characterized three new antimicrobial metabolites from the culture extract of *Colletotrichum* species. Guo *et al.* (2008) studied the new antimicrobial metabolites isolated and extracted from the culture of *Colletotrichum* species from *A. annua.*

4.5. Catharanthus roseus

Traditionally, *Catharanthus roseus*, the 'Madagascar periwinkle' or 'sadabahar' belongs to Apocynaceae family. It is used as a folk remedy to cure diabetes and high blood pressure. As an antidiabetic remedy, it was believed to promote insulin production or increase utilisation of sugars from food. *C. roseus* is well known for production of a number of anticancerous vinca alkaloids such as vincristine, vindesine, vinorelbine, vinblastin, and the recently discovered vinflunine. Kharwar *et al*. (2008) reported endophytic fungi from leaf, stem and root tissues of *C. roseus*. Moreover, they found that leaf tissues showed a greater diversity of endophytes including *Drechslera*, *Curvularia*, *Bipolaris*, *Alternaria* and *Aspergillus* species. Yang *et al*. (2004) reported an anticancerous drug vincristine from the extract of *Mycelia sterilia*, an endophyte isolated from *C. roseus*. Zhang *et al*. (2000) isolated an endophytic *Fusarium oxysporum* from the phloem of *C. roseus* which produces vincristine.

4.6. Spondias mombin

Spondias mombin L. (Anacardiacae) is a tree growing in the rain forest and in the coastal area of Africa. The fruit decoction is used as diuretic and febrifuge. Decoction of the bark and leaves is used as an emetic, anti-diarrheal, for haemorrhoids in gonorrhoea and leucorrhoea. A tea of the flowers and the leaves is taken to relieve stomachache (Ayoka *et al*., 2005).

Rodrigues and Samuels (1999) reported endophytic *Colletotrichum gloeosporioides*, *Guignardia* species and *Phomopsis* species from leaf blades and bark of *S. mombin* collected from Pará and Rio de Janeiro states of Brazil. Further, they studied the antimicrobial activity of extract of *Guignardia* sp., *Phomopsis* sp. and *Pestalotiopsis guepinii* against pathogenic bacteria like *E. coli* and *S. aureus*. Rodrigues *et al*. (2000) isolated endophytic *Guignardia* species, *Phomopsis* species and *Pestalotiopsis guepinii* from *Spondias mombin* and evaluated their antimicrobial activity against *E. coli*, *S. aureus*, *S. cerevisiae*, *Geotrichum* species, *Penicillium canadensis Cladosporium elatum* and *Mycotypha* species. Further also studied the extracts of fungal inhibited growth of actinomycete. Enophytic *Guignardia* species showed vigorous activity against *E. coli*, *S. aureus*, *S. cerevisiae*, *Geotrichum* species and *Penicillium canadensis*. Moteover extracts of *P. guepinii* showed activity against *S. cerevisae*, similarly *Phomopsis* species showed a prominent antifungal consequence against *Cladosporium elatum*, *Mycotypha* sp. and *S. cerevisae*.

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