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Review

Bioactive secondary metabolites produced by microorganisms associated with plants

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Abstract: In the past few decades groups of scientists have focused their study on relatively new microorganisms called endophytes. By definition these microorganisms, mostly fungi and bacteria, colonise the intercellular spaces of the plant tissues. The mutual relationship between endophytic microorganisms and their host plants, taxanomy and ecology of endophytes are being studied. Some of these microorganisms produce bioactive secondary metabolites that may be involved in a host-endophyte relationship. Recently, many endophytic bioactive metabolites, known as well as new substances, possesing a wide variety of biological activities as antibiotic, antitumor, antiinflammatory, antioxidant, etc. have been identified. The microorganisms such as endophytes may be very interesting for biotechnological production of bioactive substances as medicinally important agents. Therefore the aim of this review is to briefly characterize endophytes and summarize the structuraly different bioactive secondary metabolites produced by endophytic microorganisms as well as microbial sources of these metabolites and their host plants.

Key words: endophytic microorganisms; bioactive secondary metabolites; phytochemicals; plant hosts; therapeutics

Introduction

Natural products still remain the most important source for discovery of new and potential drug molecules. Large number of plants, microbial and marine sources have been tested for production of bioactive compounds. Number of natural products with diverse chemical structures, have been isolated as pharmaceutical agents. The search for novel secondary metabolites should be focused on endophytic microorganisms isolated from plants.

In the last few years cosiderable amount of knowledge has accumulated on the biology of endophytic microorganisms. The mutual relationship between endophytic microbes and their host plants, taxanomy and ecology of endophytes are being studied. Recent reviews by Strobel (2003), Petrini (1991), Petrini et al. (1992) deal with biology of endophytes. Tan & Zou (2001) have summarized functional metabolites produced by endophytes, covering the years 1987–2000. The aim of our review is to briefly characterize endophytic microorganisms, summarize newly discovered endophytes and their structuraly different bioactive secondary metabolites and their host plants since the year 2001.

Definiton of endophytes

Endophytes are microbial entities that occupy living tissues of plants. The term endophytes became firmly established in ecological literature when livestock toxicoses in USA and New Zeland were demonstrated to be attributed to alkaloids produced by fungal endophytes belonging to the strain *Balansiae* (Ascomycotina) in the 1970s (Saikkonen et al. 2004). Petrini et al. (1992) has expanded definition of endophytes to include all those microorganisms that during a more or less long period of their life, colonize symptomlessly the living internal tissue of their hosts.

As an endophyte, a fungus may grow within a plant in mutuality relationship. This mutuality relationship benefits the fungus through provision of energy, nutrients and shelter and manifest itself as improved growth and survival of individual host plants. In some cases an endophyte may survive as a latent pathogen, causing infections for a long period and symptoms only when physiological or ecological conditions favours virulence. Recent reports indicate, that fungal endophytes are responsible for the adaptation of plants to abiotic stresess such as light, droght and biotic stresess, such as herbivory, insect attack or tissue invading pathogens through the production of secondary metabolites (Barz et al. 1988). The question is whether bioactive phytochemicals of medicinal plants are produced by plant itself or as a consequence of a mutuality relationships with beneficial organisms in their tissue. It appears that all higher plants are host to one or more endophytic microbes. These microbes primarily reside in the tissues beneath the epidermal cell layers. An endophyte in one

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plant could be a pathogen of the other depending on the balance between pathogenicity and endophytism of the microorganism in the different hosts (Saikkonen et al. 2004).

As reported Strobel (2003), the relationship of the endophyte to the host plant may have begun to evolve from the time that higher plants first appear on the earth, hundreds of millions years ago. Evidence of plant-associated microbes has been discovered in fossilized tissues of stems and leaves. As a result of this long-held associations, it is possible to imagine that some of these endophytic microorganisms may have developed genetic systems allowing for the transfer of information between themselves and the higher plants.

It is becoming clear that host specificity is a phenomenon in endophyte-higher plant relatioship (Strobel 2003). Such plant specificity implies that complex biochemical interactions are occurring between the host and its associated microorganism. Our knowledge of such interactions can provide guidance to which endophyte might be selected in the search for novel medicinal natural products (Strobel 2003; Strobel & Daisy 2003).

Ecology and occurence of endophytes

Almost all vascular plant species examined to date were found to harbor endophytic bacteria and/or fungi. Moreover, the colonization of endophytes in marine algae, mosses and ferns has been also recorded. Endophytes are present in virtually all organs of a given plant host, and some are seed-borne. The endophytes are transferred from plant to plant via seed. The mycelium of the fungus then grows into the sheath, stem, leaf tissues and finally enters the flowering stem and seed (www.uri.edu/ce). The endophyt is passed to the next generation of plants through the seed. For instance asexual *Acremonium* grass endophytes are dispersed exclusively through the seeds of their hosts (Read et al. 2000; Tan & Zou 2001).

In general, it can be expected that environmental conditions, in which the host plant growth influence the number and variety of endophytic populations. Generally plants growing in unique environmental settings, having special ethnobotanical uses, having extreme age or interesting endemic locations produce novel endophytic microorganisms which can supply new leads. About 51% of biologically active substances isolated from endophytic fungi were previously unknown. Many modern drugs have origin currently in traditional medicine and ethnopharmacology (Strobel 2003; Strobel & Daisy 2003).

Host-specific strain formation can be interpreted as a form of ecological adaptation. It can be excepted that morphologically indistinguishable strains of the same species will exhibit different physiological traits that may be host-related (Petrini 1991). For example *Pestalotiopsis microspora* is one of the most commonly found endophytes of the world's yews. Extracts of 15 isolates of *Pestalotiopsis microspora,* obtained from at least four continents, were examined and observed that no two chromatograms were identical. In author's respect (Strobel 2002) it appears that *Pestalotiopsis microspora* is a microbial factory of bioactive secondary metabolites. There is an indication that such enormous variability must exist in this organism, arising through mutation, genetic crossing, or yet unsubstantiated mechanisms such as genetic exchange with its hosts.

Significance of endophytic microorganisms

Presence of endophytic microorganisms in the plant host is in the most cases benefitial for the plant. Secondary metabolites produced by endophytes provide a variety of fitness enhancements such as increased resistance to herbivora, parasitism, drought, as well as growth enhancements. Endophytic actinobacteria isolated from healthy cereal plants were assessed for their ability to control fungal root pathogens of cereal crops both *in vitro* and *in planta*. Strains belonging to the genera *Streptomyces*, *Microbispora*, *Micromonospora*, and *Nocardioidies* were assayed for their ability to produce antifungal compounds *in vitro* against *Gaeumannomyces graminis* var. *tritici* (*Ggt*), the causal agent of take-all disease in wheat, *Rhizoctonia solani* and *Pythium* spp.. The results of Coombs et al. (2004) study indicate that endophytic actinobacteria may provide an advantage as biological control agents for use in the field, where others have failed, due to their ability to colonize the internal tissues of the host plant. Endophytic microorganisms have been also tested as potential biological fumignats of fresh fruit. *In vitro* tests showed that *Muscodor albus* volatiles inhibited and killed a wide range of storage pathogens belonging to species of *Botrytis*, *Colletotrichum*, *Geotrichum*, *Monilinia*, *Penicillium* and *Rhizopus*. Since *M. albus* is a sterile mycelium and does not require direct contact with the crops to be treated, it could be an attractive biological fumigant for controlling postharvest diseases (Mercier & Jiménez 2004).

Endophytes usually produce the enzymes necessary for the colnization of plant tissues. It was demonstrated that most endophytes are able to utilize, at least *in vitro*, most plant cell components. Most of investigated endophytes utilize xylan and pectin, show lipolytic activity and produce non-specific peroxidases and laccases (Sieber et al. 1991; Leuchtmann et al. 1992), chitinase (Li et al. 2004) and glucanase (Moy et al. 2002). Endophyte may be a novel and good producer of xylanase (Suto et al. 2002). Production of extracellular cellulase and hemicellulases other than xylanases are widespread but usually limited to organisms derived from selected hosts or even host tissues (Leuchtmann et al. 1992). Nowadays, thermostable amylolytic enzymes are investigated to improve industrial processes of starch degradation. *Streptosporangium* sp. an endophytic actinomycete isolated from leaves of maize (*Zea mays* L.) showed glucoamylase production. The isolated enzyme exhibited thermostable properties (Stamford et

Table 1. Overview of the endophytic secondary metabolites predominantly with anticancer or antibacterial activity isolated in the last years. If more metabolites are produced by one endophytic microorganism, metabolite marked with * has shown its structure.

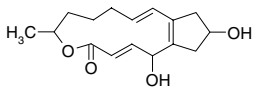
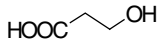
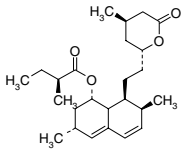
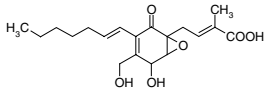
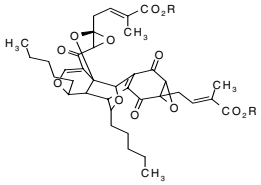
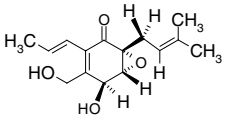
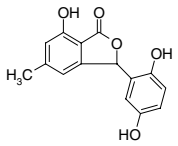
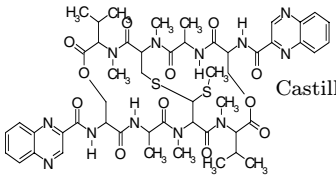
MICROBIAL PRODUCER		METABOLITE			REFERENCES
NAME OF MICRO-ORGANISM	PLANT SOURCE	NAME OF METABOLITE	BIOLOGICAL ACTIVITY	STRUCTURE	
Phoma medicaginis	*Medicago sativa* *Medicago lupulina*	BREFELDINE A	Antibiotic activity, initiation of apoptosis in cancer cells		Weber et al. (2004a)
Phomopsis phaseoli *Melanconium betulinum*	*Betula pendula* *Betula pubescens* Leaf of a tropical tree	3-HYDROXY-PROPIONIC ACID	Nematicidal activity against *Meloidogyne incognita, Caenorhabditis elegans*		Schwarz et al. (2004)
Phomopsis spp.	*Erythrina cristagalli*	PHOMOL	Antifungal, antibacterial, anti-inflammatory and weak cytotoxic activity	Polyketide lactone	Weber et al. (2004b)
Phomopsis spp.	*Erythrina cristagalli*	MEVINIC ACID	Antiinflammatory activity		Weber et al. (2004b)
Pestalotiopsis microspora *Monochaetia* sp.	*Torreya taxifolia*	AMBUIC ACID	Antifungal agent		Li et al. (2001)
Pestalotiopsis microspora	*Torreya taxifolia*	TORREYANIC ACID	Selectively cytotoxic activity		Li et al. (2001)
Petalotiopsis jesteri	*Fragraea bodenii*	JESTERONE*, HYDROXY-JESTERONE	Antimycotic activity against the oomycetous fungi		Li & Strobel (2001)
Pestalotiopsis microspora	*Terminalia morobensis*	ISOPESTACIN*, PESTACIN	Antimicrobial and antioxidant effect		Harper et al. (2003), Strobel et al. (2002)
Streptomyces NRRl 30566	*Grevillea pteridifolia*	KAKADUMYCIN A (chemically related to echinomycin*)	Wide spectrum antibiotic activity, especially against Gram-positive bacteria, impressive activity against the malarial parasite		Castillo et al. (2003)
Streptomyces sp. Is9131	*Maytenus hookeri*	DIMERIC DINACTIN, DIMERIC NONACTIN, CYCLOHOMONONACTIC ACID, CYCLONONACTIC ACID	Strong antineoplastic activity and antibacterial activity	Macrolides	Zhao et al. (2005)

Table 1. (continued).

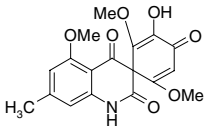
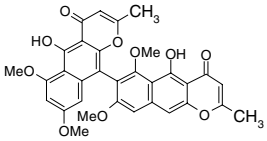
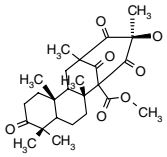
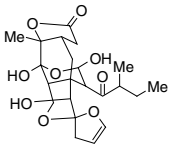
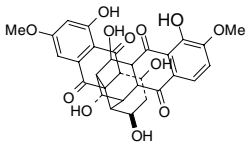
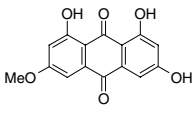
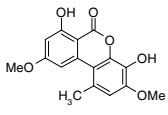
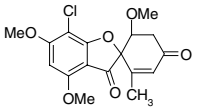
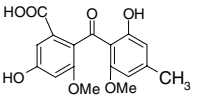
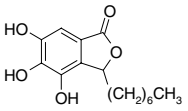
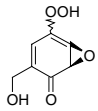
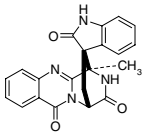
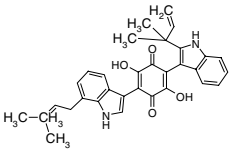
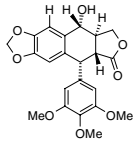
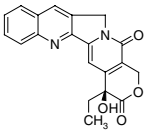
MICROBIAL PRODUCER		METABOLITE			REFERENCES
NAME OF MICRO-ORGANISM	PLANT SOURCE	NAME OF METABOLITE	BIOLOGICAL ACTIVITY	STRUCTURE	
Streptomyces sp.	*Monstera sp.*	CORONAMYCIN	Activity against pythiaceous fungi and the human fungal pathogen *Cryptococcus neoformans*, active against the malarial parasite – *Plasmodium falciparum*	Peptide structure	Ezra et al. (2004)
Streptomyces NRRL 30562	*Kennedia nigriscans*	MUNUMBICIN A, B, C and D	Effective against methicillin-resistant strain of *Staphylococcus aureus, Bacillus anthracis, Mycobacterium tuberculosis, Plasmodium falciparum*	Peptide structure	Castillo et al. (2002)
Aspergillus fumigatus CY 018	*Cynodon dactylon*	ASPERFUMOID*, ASPERFUMIN, PHYSCION	Inhibit growth of *Candida albicans*		Liu et al. (2004)
Aspergillus niger IBF-E003	*Cynodon dactylon*	RUBROFUSARIN B, AURASPERONE A*	Strong co-inhibitors on xantin oxidase, colon cancer cell and some microbial pathogens		Song et al. (2004)
Penicillium sp.	*Melia azedarach*	PREAUSTINOID A, B	Exhibit moderate bacteriostatic effect on *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus sp.*		Dos Santos & Rodrigues-Fo (2003)
Fusidium sp.		FUSIDILACTONES	Antifungal activity		Krohn et al. (2002)
Curvularia lunata	*Niphates olemda*	CYTOSKYRINS	Antibacterial activity, potential anticancer agent		Brady et al. (2000), Jadulco et al. (2002)
Curvularia lunata	*Niphates olemda*	LUNATIN	Active against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Cladosporium herbarum*		Jadulco et al. (2002)
Cephalosporium sp. IFB-E001 *Microsphaeropsis olivacea*	*Trachelospermum jasminoides Pilgerodendron uviferum*	GRAPHISLACTONE A	Antioxidant effect		Hormazabal et al. (2005), Song et al. (2005)

Table 1. (continued).

MICROBIAL PRODUCER		METABOLITE			REFERENCES
NAME OF MICRO-ORGANISM	PLANT SOURCE	NAME OF METABOLITE	BIOLOGICAL ACTIVITY	STRUCTURE	
Xylaria sp. F0010	*Abies holophylla*	GRISEOFULVIN*, DECHLORO-GRISEOFULVIN	Antifungal antibiotic		Park et al. (2005)
Rhizoctonia sp.	*Cynodon dactylon*	RHIZOCTONIC ACID	Anti-*Helicobacter pylori* activity		Ma et al. (2004)
Cytospora sp. *Diaporthe* sp.	Endophytic fungi from Guanacaste Conservation Area of Costa Rica	CYTOSPORONE	Antibacterial activity		Brady et al. (2000), Ohzeki & Mori (2003)
Apiospora montagnei	*Polysiphonia violacea*	(+)-EPIEPOXY-DON	Exhibited significant cytoxicity against human cancer cell lines		Klemke et al. (2004)
Eupenicillium spp.	*Murraya paniculata*	ALANTRY-PHENONE, ALANTRY-PINENE*, ALANTRY-LEUNONE	Insecticide		Fábio et al. (2005)
Pseudomassaria sp.	Leaves collected near Kinshasa, Democratic Republic of Congo	DEMETHYL-ASTERRIQUI-NONE B-1	Insulin-mimetic compound		Salituro et al. (2001), Strobel (2002)
Trametes hirsuta	*Podophyllum hexandrum*	PODOPHYLLO-TOXIN*, ARYL TETRALIN LIGNANS	Anticancer activity		Puri et al. (2006)
Fungal endophytic isolate	*Nothapodytes foetidafrom*	CAMPTO-THECIN	Anticancer activity		Puri et al. (2005)

al. 2002). A more novel application of endophytes is in the area of phytoremediation (plant assisted removal of xenobiotics from soil). From the poplar rhizosphere diesel degrading endophytic strains were isolated and identified by 16S rRNA gene sequencing (Tesar et al. 2002; Germaine et al. 2004).

Owen & Hundley (2004) reported endophytes as the chemical synthesizers inside plants. Among the first secondary metabolites isolated from grass endophytes were alkaloids (peramine, ergovaline, ergotamine, lolitrem) (Schardl 2001; Scott 2001, Janssen et al. 2000; Kunkel et al. 2004; Wang et al. 2004). In various studies, was demonstrated that crude extracts from culture broth of endophytic microorganisms displayed antibacterial, antifungal, antiviral, antiinflammatory and antitumor activity. In the past few years endophytes as a source of secondary metabolites were isolated predominantly from exotic plants and/or with ethnobotanical usage. For example, endophytic fungi and bacteria were isolated from surface disinfected leaf tissues of several citrus rootstocks. The predominant bacterial species isolated were *Alcaligenes* sp., *Bacillus* spp., *Bulrkholderia cepacia*, *Curtobacterium flaccumfaciens*, *Enterobacter cloacae*, *Methylobacterium extorquens*, and *Pantoea agglomerans*. The most abundant fungal species were *Colletotrichum gloeosporioides*, *Guignardia citricarpa*, and *Cladosporium* sp. (Araújo et al. 2001). From 81 Thai medicinal plant species were obtained 582 pure isolates of endophytes with 360 morphologically distinct fungi. Extracts of 92 isolates could inhibit *Mycobacterium tuberculosis*, while 6 extracts inhibited *Plasmodium falciparum*. Strong anti-viral activity against *Herpes simplex* virus type 1 was observed in 40 isolates (Wiyakrutta et al. 2004).

Some of compounds produced by endophytes could be candidates for discovery of new drugs. Worldwide cancer is the second major cause of the deaths after cardiovasular diseases. This disease is characterized by unregulated proliferation of cells. Large number of plants, microorganisms and marine sources of natural products have been isolated and identified as producers of anticancer compounds. Probably no new drug has generated as much public attention and interest as has taxol in the last 25 years. It is maily for ist excellent clinical activity against brest and ovarian cancers (Kingston 2001). New possibility for the production of this anticancer drug could be biotechnological production using endophytes as producers, because after several years of effort, a novel taxol producing endophytic fungus, *Taxomyces andreanae*, was discovered in *Taxus brevifolia* (Strobel et al. 1993). The endophytic fungus *Pestalotiopsis leucothes* isolated from *Trypterygium wilfordii* was found to produce three compounds which have variable effects on T- and B-cells and monocyte. They may represent a new source of immunomodulatory compounds or treatment of human immune mediated diseases (Kumar et al. 2005). The papers published last year reported two other useful anticancer drugs podophyllotoxin and camptothecin before isolated from plants, as a products of endophytic fungi. Fungal endophyte *Trametes hirsuta* isolated from plant *Podophyllum* species, produces lignans with anticancer activity. Derivatives of podophyllotoxin, etoposide and teniposide are currently used in frontline cancer chemotherapy against various cancer diseases (Puri et al. 2005a). The fungus, which belongs to the family *Phycomycetes*, isolated from inner bark of plant *Nothapodytes foetida* (India), produces the known anticancer drug camptothecin (Puri et al. 2005b).

Substances isolated by Schulz et al. (2002) from endophytic fungi originate from different biosynthetic pathways and belong to diverse structural groups: terpenoids, phenols, xanthones, steroides, isocoumarins, cytochalasines, tetralones, benzopyranes and enniatines.

Table 1 presents the overview of bioactive secondary metabolites isolated from endophytes in the last five years. The endophytic production microorganisms, the plant source as well as the structure and bioactivity of metabolites are shown in this table.

To conclude, the herbal traditional medicine existed in different cultures such as south Asia (Chinese, India, Japan) hundreds years ago. Many modern drugs have origin in traditional medicine and in the past years there has been a rapidly increasing interest in plant secondary metabolism. Production of metabolites useful in pharmaceutical industry is widespread, mostly among endophytic fungi. In the recent years research of endophytic microorganisms has opened a new promising perspectives for improved poduction of plant medicinally agents. Numerous reports including our review show that endophytes produce a wide variety of chemical substances, many of which show biological activity. Thus for the biotechnological production of natural compounds endophyte seems to be the most interesting alternative and they are likely to play more significant role in the years to come.

Efforts continue to characterize endophytic microorganism diversity with the potential utility of these microorganisms as a source of useful products for biotechnology.

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