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PHARMACEUTICAL EFFECTS OF BIOACTIVE COMPOUNDS FROM ENDOPHYTES

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Abstract

Endophytes, microorganisms that reside in the internal tissue of living plants without causing any immediate overt negative effects, have been found in every plant species examined to date recognized as potential source of novel natural products for exploitation in medicine, agriculture, and industry with more bioactive natural products isolated the microorganisms. Endophytes have fascinating potential for a source of new drug leads as they have capacity to synthesize organic compound of diverse structural features. Most of the promising natural products are available only in extremely small quantities, which necessitate substantial efforts to produce required amounts for pharmacological testing. The majority of such drug candidates remains pharmacologically undeveloped due to the perceived supply problem and anticipated higher production costs. In this review, I have tried to discuss the pharmacological activities of endophytes and the Biotransformation process.

Keywords: Biotransformation, Endophytes, Pharmaceutical effects.

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INTRODUCTION

Endophytes are an endosymbiotic group of microorganisms often bacteria or fungi that colonize the inter- and/or intracellular locations of plants (Pimentel et al., 2011).Endophytes are ubiquitous with rich biodiversity, which have been found in every plant species examined to date. It is noteworthy that, of the nearly 3, 00,000 plant species that exist on the earth, each individual plant is the host to one or more endophytes (Strobel, 2003). In this view of the special colonization in certain hosts, it is estimated that there may be as many as 1 million different endophyte species. Some of the endophytes are the chemical synthesizers in inside the plants (Owen and Hundley, 2004).Many of them are capable of synthesizing bioactive compounds that can be used by plants for defense against human pathogens and some of these compounds have been proven useful for novel drug discovery. Recent studies have reported hundreds of natural products including substance of alkaloids, terpenoids, flavonoids, steroids, etc. from endophytes. Up to now, most of the natural products from endophytes are antibiotics, anticancer agents, biological control agents and other bioactive compounds by their different functional roles. Thus far, they have not been widely explored for therapeutic properties. A single endophyte may be able to produce not one but several bioactive metabolites. As a result, the role of endophytes in the production of novel structures for exploitation in medicine is receiving increased attention (Wang *et al*., 2000; Ezra *et al*., 2004a). A small amount of endophytes have been studied, recently, several research groups have been motivated to evaluate and elucidate the potential of these microorganisms applied on biotechnological processes focusing on the production of bioactive compounds. The production of bioactive substances by endophytes is directly related to the independent evolution of these microorganisms, which may have incorporated genetic information from higher plants, allowing them to better adapt to plant host and carry out some functions such as protection from pathogens, insects and grazing animals (Strobel, 2003). Endophytes are chemical synthesizer inside plants (Owen and Hundley, 2004), in other words, they play a role as a selection system for microbes to produce bioactive substances with low toxicity toward higher organisms (Strobel, 2003). Bioactive natural compounds produced by endophytes have been promising potential usefulness in safety and human health concerns, although there is still a significant demand of drug industry for synthetic products due to economic and time-consuming reasons (Strobel *et al*., 2004). Problems related to human health such as the development of drug resistance in human pathogenic bacteria**,** fungal infections and life threatening virus claim for new therapeutic

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agents for effective treatment of diseases in human, plants and animals that are currently unmet (Strobel, 2003; Zhang *et al*., 2005). 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 (Tan and Zou, 2001). Such bioactive metabolites find wide-ranging application as agrochemicals, antibiotics, immunosuppressants, antiparasitics, antioxidants and anticancer agents (Gunatilaka, 2006). Extraction from natural sources presents some disadvantages such as dependency on seasonal, climatic and political features and possible ecological problems involved with the extraction, thus calling for innovative approaches to obtain such compounds (Bicas *et al*., 2009). Hence, biotechnological techniques by using different microorganisms appear promising alternatives for establishing an inexhaustible, cost-effective and renewable resource of high-value bioactive products and aroma compounds. The biotransformation method has a huge number of applications (Borges *et al*., 2009), for instance, it has been extensively employed for the production of volatile compounds (Bicas *et al*., 2009; Bicas *et al*., 2008). These volatile compounds possess not only sensory properties, but other desirable properties such as antimicrobial (vanillin, essential oil constituents), antifungal and antiviral (some alkanolides), antioxidant (eugenol, vanillin), somatic fat reducing (nootkatone**),** blood pressure regulating (2-[E]-hexenal), anti-inflammatory properties (1,8-cineole) and others (Berger, 2009). The intent of this review is to provide insights into the biological effects of endophytes producing bioactive compounds, the importance of including endophytic microbes for novel drugs and the microbial biotransformation process as a novel alternative method to obtain bioactive compounds. This review, however, also describes these compounds by different functions and pharmaceutical potential for human use.

BIOPHARMACEUTICAL EFFECTS OF ENDOPHYTES

Effects of bioactive compounds obtained from endophytic microbes and their potential in the pharmaceutical areas.

Antimicrobial effect

Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites (Tan and Zou, 2001).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 (Guo*et al*., 2008). So far, studies reported a large number of antimicrobial compounds isolated from endophytes, belonging to

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several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines and flavonoids (Yu *et al*., 2010). 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 unfavorable returns on investment(Yu *et al*., 2010;Song, 2008). 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). Many bioactive compounds, including antifungal agents, have been isolated from the genus *Xylaria* residing in different plant hosts, such as sordaricin with antifungal activity against *Candida albicans* (Pongcharoen*et al*., 2008), mellisol and 1,8- dihydroxynaphthol 1-O-a-glucopyranoside with activity against herpes simplex virus type multiplolides A and B with activity against*Candida albicans*. The bioactive compound isolated from the culture extracts of the endophytic fungus *Xylaria* sp. YX-28 isolated from *Ginkgo biloba* L. was identified as 7-amino-4-methylcoumarin (Liu *et al*., 2008).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 (Liu *et al*., 2008). The production of Hypericin, a naphthodianthrone derivative and Emodin believed to be the main precursor of hypericin by the endophytic fungus isolated from an Indian medicinal plant was reported. Both compounds demonstrated antimicrobial activity against several bacteria and fungi including *Staphylococcus aureus* sp., *aureus*, *Klebsiella pneumoniae* sp., *ozaenae*, *Pseudomonas aeruginosa*, *Salmonella enterica* sp., *Enteric* and *Escherichia coli* and fungal organisms *Aspergillus niger* and *Candida albicans* (Kusari*et al*., 2008). Metabolites produced by the endophytic fungi *Aspergillus fumigatus* CY018 isolated from the leaf of *Cynodon dactylon*, asperfumoid, fumigaclavine C, fumitremorgin C, physcion and helvolic acid were shown to inhibit *Candida albicans* (Liu *et al*., 2004). 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., (You *et al*., 2009). Another fascinating use of antibiotic products from endophytic fungi is the inhibition of viruses. Two novel human cytomegalovirus protease

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inhibitors, cytonic acids A and B have been isolated from the solid-state fermentation of the endophytic fungus *Cytonaema* sp., Their structures as p-tridepside isomers were elucidated by mass spectrometry and NMR methods (Guo*et al*., 2000). An endophytic fungus *Pestalotiopsis theae* of an unidentified tree on Jianfeng Mountain, China, was capable of producing Pestalotheol C with anti-HIV properties (Li *et al*., 2008). It is apparent that the potential for the discovery of compounds, from endophytes, having antiviral activity is in its infancy. The fact, however, that some compounds have been found is promising. The main limitation in compound discovery is probably related to the absence of appropriate antiviral screening systems in most compound discovery programs (Strobel, 2003).

Antioxidant effect

Many antioxidant compounds possess anti-inflammatory, antiatherosclerotic, antitumor, antimutagenic, anticarcinogenic, antibacterial, or antiviral activities in higher or lower level (Owen *et al.,* 2000; Sala *et al.,* 2002). 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 *et al.,* 2007) evaluated the antioxidant activity of an endophytic *Xylaria* sp., isolated from the medicinal plant *Ginkgo biloba*. The results collected indicated that the methanol extract exhibited strong antioxidant capacity due to the presence of phenolics and flavonoids compounds among 41 identified 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 (Huang *et al.,*2007). Pestacin and isopestacin, 1, 3-dihydro isobenzofurans, were obtained from the endophytic fungus *Pestalotiopsis microspora* isolated from a plant growing in the Papua New Guinea, *Terminaliamorobensis* (Harper *et al.,* 2003; Strobel *et al.,* 2002). 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 (Harper *et al.,* 2003). 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 (Strobel *et al.,* 2002). Liu *et al.* (2009) reported for the first time, the capacity of endophytic microorganisms to produce polysaccharides with antioxidant. The bacterium endophyte *Paenibacillus polymyxa* isolated from the root tissue

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of *Stemona japonica* Miquel, a traditional Chinese medicine, produced exopolysaccharides (EPS) that demonstrated strong scavenging activities on superoxide and hydroxyl radicals. 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* stronger than the standards, Butylated Hydroxytoluene (BHT) and ascorbic acid, coassayed in the study (Song *et al.,* 2005).

Anticancer effect

Taxol is a highly functionalized diterpenoid which is widely used as anticancer drug (Wani*et al*., 1971). It was first isolated from the bark of western yew, *Taxusbrevifolia*. During the cell division, taxol prevent the depolymerization of tubulin. Production of taxol from different genus of endophytes by fermentation is a cheaper method (Page *et al.,* 1999). The anticancer drug, taxol has been found in many genera of endophytic fungi (*Alternaria, Fusarium, Monochaetia, Pestalotia, Pestalotiopsis, Pithomyces* and *Taxomyces*) (Strobel et al. 1996). More than 15 fungi genera were produced paclitaxel and its analogues (Zhao *et al.,*2010).

Pandi*et al*., (2011) reported that taxol isolated from *Lasiodiplodiatheobromae* showed activity against breast cancer cell line. Alternariol 9-methyl ether is a major mycotoxin produced by fungi of the genus *Alternaria*. It can induce mitochondrial apoptosis in human colon carcinoma cells, and induce DNA strand breaks, micronuclei and gene mutations in various cultured mammalian cells (Meng*et al*., 2012). Giridharan*et al*., (2012) reported that sclerotiorin isolated from *Cephalothecafaveolata* showed anti-proliferative activity against cancer cells and also it induces apoptosis in colon cancer cells. Extracts from endophytes, *Fusarium* sp., and *Aspergillusfumigatus* exhibited inhibitory activity against HeLa cervix cancer cell lines (Ruma*et al,*. 2013). The endophytic fungi, *A. terreus* showed cytotoxic effect against HepG2 cancer cell line (Suja*et al*., 2014). Polyketide compounds produced by *Phoma* sp., had high inhibitory activity against murine leukemia cells. The anticancer activity was noticed in ethyl acetate extract of *Alternariaalternata* against human breast cancer cell lines and it also showed good cytotoxicity (Arivudainambi*et al*., 2014). Chen *et al*., (2015) reported that cytochalasins from endophytic fungi, *Phomamutirostrata* exhibited moderate anticancer activity against SMMC-7721 (hepatocellular carcinoma cell line), SK-BR-3 (breast cancer cell line), PANC-1 (pancreatic cancer cell line), HL-60 (human myeloid leukemia cell line) and A-549 (lung cancer cell line).

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Antidiabetic effect

The nature has provided abundant natural resources which can be explored for their medicinal uses. Diabetes, often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both (Ushasri and Anusha, 2015). Nowadays diabetes is growing as important serious public health problem, particularly in developed countries as a major threat to global development. We need to find natural and effective antidiabetic drugs. Several researchers are investigated antidiabetic and hypolipidemic activity of Endophytic fungi. (Dhankhar*et al*., 2013) isolated antidiabetic peptide from Endophytic fungi Aspergillusawamori from medicinal plant Acacia nilotica and its purified compound was further identified using HPLC. Lectin (N-acetylgalactosamine, 64 kDa) was isolated from Endophytic fungi, Alternaria species from plant Viscum album tested for In vitro and in vivoantidiabetic activity on rats (Govindappa*et al*.,2015).

Antiarthritis and Anti-inflammatory activities

Historically, the best resources for novel scaffolds have always been natural products. Immune system of our body plays a crucial role, as an overactive immune system may lead to certain fatal disease like arthritis. Rhematoid arthritis(RA) is chronic, inflammatory, and systemic autoimmune disease, symptoms include pain, swelling, and destruction of cartilage and bone as a result of which permanent disabilities occur but the exact etiology is unknown. Nowadays, researcher shows a great interest in those finding medicinal agents that are derived from microbial source because of the currently available drugs are either have certain side effects or are highly expensive (Manjusha*et al*.,2015). Endophytic fungi *Talaromyceswortmannii* isolated from medicinal plant *Aloe vera* and further seperated as several pure substances and out of that component C showed potent anti-inflammatory activity and this ability was gained for this metabolite is due to inhibition of IL-8 release by blocking NF-κB and AP-1 activation (Pretsch*et al*., 2014). Compound Mutolide was isolated from the coprophilous fungus*Lepidosphaeria*sp. (PM0651419) and showed good anti-inflammatory activity and in future it can be used as druggable candidate for the treatment of inflammatory diseases like RA. The primary purpose for such broad-based screening of endophytic fungi was to identify novel inhibitors of pro-inflammatory cytokines involved in various immunological pathways. Ergoflavin a pigment isolated from EF which is growing on the leaves of an Indian medicinal

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plant *Mimosopselengi* (bakul) showed good anti-inflammatory activity (Sunil Kumar *et al*., 2009).

Immunosuppressive Compounds from Endophytes

Immunosuppressive drugs are used today to prevent allograft rejection in transplant patients, and in the future they could be used to treat autoimmune diseases such a rheumatoid arthritis and insulin-dependent diabetes. The endophytic fungus *Fusariumsubglutinans*, isolated from *T. wilfordii*, produces the immunosuppressive but noncytotoxicditerpenepyronessubglutinol A and B **(**Lobkovsky*et al*., 1995)**.**Subglutinol A and B are equipotent in the mixed lymphocyte reaction assay and thymocyte proliferation assay, with a 50% inhibitory concentration of 0.1 μM. In the same assay systems, the famed immunosuppressant drug cyclosporine is roughly as potent in the mixed lymphocyte reaction assay and 10^4 more potent in the thymocyte proliferation assay. Still, the lack of toxicity associated with subglutinols A and B suggests that they should be explored in greater detail **(**Lobkovsky et al., 1995). The discovery of the fungus *Tolypocladiuminflatum*, from which cyclosporine, a hugely beneficial immunosuppressant, was isolated (Borel and Kis, 1991). This example perfectly depicts the current aim of many investigators to seek out rare endophytes from interesting and uncommon hosts and environments.

Enzyme Production

Many commercially important enzymes are produced by several soil micro-organisms. The hunt for other potential sources had led to the discovery of a few vital enzymes being produced by endophytes. Endophytic fungi like *Acremonium terricola, Aspergillus japonicas, Cladosporium cladosporioides, Cladosporium sphaerospermum, Fusarium lateritium, Monodictys castaneae, Nigrospora sphaerica, Penicillium aurantiogriseum, Penicillium glandicola, Pestalotiopsis guepinii, Phoma tropica, Phomopsis archeri, Tetraploa aristata, and Xylaria* sp. and many other unidentified species in Opuntia ficus-indica Mill. have indicated their promising potential for deployment in biotechnological processes involving production of pectinases, cellulases, xylanases, and proteases (Bezerra*et al*.,2012). An endophyte, *Acremonium zeae*, isolated from maize produced the enzymehemicellulaseextracellularly (Bischoff *et al*., 2009). This hydrolytic enzyme from *A. zeae* may be suitable for application in the bioconversion of lignocellulosic biomass into fermentable sugars.

BIOTRANSFORMATION PROCESS

Biotransformation can be defined as the use of biological systems to produce chemical changes on compounds that are not their natural substrates (Borges *et al*., 2008). The microbial growth,

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sustenance, and reproduction depends on the availability of a suitable form of reduced carbon source, used as chemical energy, which under normal conditions of culture broth are the common sugars. Nevertheless, microorganisms are believed to have no limit to adapt to new environments and to metabolize various foreign substrates to carbon and nitrogen sources (Doble*et al*., 2004). A molecule can be modified by transforming functional groups, with or without degradation of carbon skeleton. Such modifications result in the formation of novel and useful products not easily prepared by chemical methods (Borges *et al*., 2008). The biotransformation process provides a number of advantages over chemical synthesis. The process can be carried out under mild conditions like ambient temperature and without the need of high pressure and extreme conditions, thus reducing undesired byproduct, energy needs, and cost (Suresh *et al*., 2006). The region-and stereo-selectivity of the process allows the production of enantiomerically pure compounds, eliminating the need for complicated separation and purification steps (Borges *et al*., 2008).Besides, the reactions occur under ecologically acceptable conditions, with lower emission of industrial resides and production of biodegradable resides and products, thus reducing the environmental problems (Aleu and Collado, 2001). Finally, the products obtained by biotransformation process can be labeled as "natural." On the other hand, chemical synthesis often result in environmentally unfriendly production processes and lacks substrate selectivity, possibly causing the formation of undesirable reaction mixtures, and reducing process efficiency and increasing downstream cost (Longo and Sanroman, 2006). Therefore, biotransformation is a useful method for production of novel compounds; enhancement in the productivity of a desired compound; overcoming the problems associated with chemical analysis; leading to basic information to elucidate the biosynthetic pathway (Suresh *et al*., 2006). For this reason, biotransformation using microbial cultures and/or their enzymatic systems alone has received increasing attention as a method for the conversion of lipids, monoterpenes, diterpenes, steroids, triterpenes, alkaloids, lignans, and some synthetic chemicals, carrying out stereospecific and stereoselective reactions for the production of novel bioactive molecules with some potential for pharmaceutical and food industries (Borges *et al*., 2009; Pimentel *et al*., 2010).

CONCLUSION

Endophytes are a poorly investigated group of microorganisms that represent an abundant and dependable source of bioactive and chemically novel compounds with potential for exploitation in a wide variety of medical, agricultural and industrial areas. Although work on the utilization of

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this vast resource of poorly understood microorganisms has just begun, it has already become obvious that an enormous potential for organism, product and utilitarian discovery in this field holds exciting promise. This is witnessed by the discovery of a wide range of products and microorganisms that already hold inkling for future prospects as mentioned in this report. 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.

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