A review of bioactive compounds produced by endophytic fungi associated with medicinal plants

Uma revisão de compostos bioativos produzidos por fungos endofíticos associados a plantas medicinais

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Abstract: Interest in exploring endophytic fungi has increased in recent years, especially those associated with medicinal plants, reflecting the great potential of these microorganisms for the production of bioactive substances. Medicinal plants shelter a high diversity of endophytes that represent targets for use in biotechnological processes. These fungi synthetize several compounds that can be used in pharmaceutical, agricultural and other industries. Additionally, endophytes produce many bioactive metabolites involved in host-endophyte symbiosis, such as those that increase resistance to stressful conditions, alter physiological properties, and produce phytohormones, toxins, antimicrobial compounds and medicinal substances, immunosuppressants, antitumoral agents, and other biotechnological substances of interest, such as enzymes. In this review, information regarding plant interactions with endophytes is highlighted, contributing to a better understanding of this association, benefits and potential for biotechnological utilization.

Keywords: Host-endophyte interaction. Secondary metabolites. Bioactive compounds.

Resumo: O interesse em explorar fungos endofíticos tem aumentado nos últimos anos, refletindo o grande potencial destes micro-organismos para a produção de substâncias bioativas, especialmente aqueles associados com plantas medicinais, as quais abrigam grande diversidade destes micro-organismos, alvos para utilização em processos biotecnológicos. Estes fungos sintetizam diversos compostos que podem ser usados como produtos farmacêuticos, agrícolas e industriais. Além disso, endófitos produzem diversos metabólitos bioativos envolvidos na interação simbiótica entre fungos endofíticos e seus hospedeiros, tais como aqueles que aumentam a resistência a condições de estresse; alteram propriedades fisiológicas; produzem fito-hormônios, toxinas, compostos antimicrobianos e substâncias medicinais; agentes imunossupressores, antitumorais; entre outras substâncias biotecnológicas de interesse, tais como enzimas. Nesta revisão, informações sobre interações de plantas com fungos endófitos são destacadas, contribuindo, assim, para melhor compreensão desta associação, de seus benefícios e potencial para utilização biotecnológica.

Palavras-chave: Interação endofítico-hospedeiro. Metabólitos secundários. Compostos bioativos.

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INTRODUCTION

The term 'endophyte' refers to microorganisms (primarily fungi and bacteria) colonizing the intercellular and/or intracellular regions of healthy plant tissues at a particular time, the presence of which does not interfere with or cause symptoms in the host (Stone *et al*., 2000; Strobel, 2003; Schulz & Boyle, 2006). Ubiquitous in nature, these endophyte microbes have been isolated from different plants examined to date (e.g., *Ginkgo biloba* L., *Taxus chinensis* (Pilg.) Rehder, and *Tectona grandis* L. f.), and this association can be obligate or facultative (Nair & Padmavathy, 2014). The existence of interactions between plants and fungi, especially symbiotic and parasitic interactions, is well known. Several studies have reported that plants colonized by endophytic fungi represent an important repository of microorganisms, including new species (Carvalho *et al*., 2012; Tao *et al*., 2013). Moreover, medicinal plants have been used for the isolation, characterization, and analysis of endophytic fungi that are considered an important microbial reservoir for drug discovery with antibiotic activities of immunosuppressants, anticancer agents, and biological control agents (Peixoto Neto *et al*., 2004). According to Strobel & Daisy (2003, p. 499): "Torreyanic acid, a selectively cytotoxic quinone dimer (anticancer agent), was isolated from a *Pestalotiopsis microspora* (Batista & Peres, 1966) strain". This strain was originally obtained as an endophyte associated with the endangered tree *Torreya taxifolia* (Florida torreya) (Kurz, 1938) (Lee *et al*., 1996).

The endophytic community encompasses a wide variety of microbial species, constituting a complex micro-ecosystem (El-Shatoury *et al*., 2013). Endophytes play important roles in plant adaptation to the environment, even stress conditions caused by a lack of water, conferring several benefits to plants, including protection against predators and diseases through the production of toxic substances (Tan & Zou, 2001; Arnold *et al*., 2003; Gunatilaka, 2006; Kusari *et al*., 2012). However, the ecological role of different fungal species is still not entirely clear and may even vary from symbiotic to antagonistic or slightly pathogenic (Schulz & Boyle, 2005). Some endophytes can produce substances that alter the plant phenotype and thus increase host defenses (Matiello *et al*., 1997; Higgins *et al*., 2014). Other endophytes produce useful natural compounds that can be applied in different industrial purposes (Demain, 2014). In this context, endophytic fungi present interesting biochemical capabilities for the production of different groups of compounds, including several classes of antimicrobial substances, suggesting that these microbes are important research topics for bioprospecting (Mousa & Raizada, 2013). Endophytic also are biotechnologically important due to the ample variety of their products; such as production of antibiotic, antiparasitic, antifungal, and antitumor compounds, use in agriculture and industry, especially pharmaceuticals, and can used as vectors to introduce genes of interest into plants (Lacava *et al*., 2010; Kaneko *et al*., 2010).

A classic example of the importance of endophytes is Taxol, a powerful anti-cancer substance produced by plants of the genus *Taxus* and by a fungal endophyte of *Taxus mairei* (Lemée & H. Lév.) S.Y. Hu, *Tubercularia* sp. (Wang *et al*., 2000). In the present review, we present examples of bioactive substances produced by endophytic fungi, focusing on an overview of plant-endophytic interactions.

ENDOPHYTIC FUNGI

The term 'endophyte' was originally described in 1866 by de Bary and refers to any living organism in plant tissue or on the plant surface, with the exception of epiphytes, as well as organisms acting as plant pathogens (De Bary, 1866). In other words, endophytic fungi are organisms that colonize the internal tissues of plants without causing damage during at least one stage of their life cycle (Bacon & White, 2000; Hyde & Soytong, 2008). Regardless of the environment in which the host plant grows, including the Arctic and Antarctic, geothermal soils, deserts, oceans, forests, mangroves, and coastal forests, endophytes are ubiquitously present in their inner tissues. These microorganisms have been isolated from algae, bryophytes, pteridophytes, gymnosperms, and angiosperms (Kharwar *et al*., 2011; Chowdhary *et al*., 2012).

Recent studies suggest that fungal diversity is very high, i.e., approximately 5.1 million species (Blackwell, 2011). Although there are approximately 300,000 species of plants on the planet, few plant species have been studied with regard to their endophytic community (Strobel & Daisy, 2003). Typically, dozens of endophytic fungal species are present in a single plant (Gamboa *et al*., 2002). Consequently, there is a great opportunity to discover new and interesting endophytic microorganisms in plants from different ecosystems (Esposito & Azevedo, 2010; Kusari & Spiteller, 2011).

In most plants, colonization by endophytes occurs by natural or artificial openings, such as stomata, injuries caused by agricultural implements, or the friction between the roots and soil (Hallmann *et al*., 1997). Some endophytes colonize plant tissue via the secretion of hydrolytic enzymes, and others possess specialized structures, such as haustoria and appressoria (Esposito & Azevedo, 2010). Colonization can also occur vertically via seed colonization (Stone *et al*., 1994; Aly *et al*., 2010). Overall, the route of plant colonization varies according to the plant species. Once inside the host, some endophytes remain in a latent state throughout their life or for a prolonged period until the emergence of favorable environmental conditions. Plant-endophyte associations are complex, and abiotic conditions can influence the patterns of this ecological interaction (Saikkonen *et al*., 1998; Aly *et al*., 2011).

The fungal community present in a host plant can also differ among various tissues and organs (Moricca *et al*., 2012). The literature reports different species of fungi belonging to the genera *Alternaria*, *Colletotrichum*, *Phyllosticta*, *Diaporthe*, *Phoma*, *Guignardia*, *Cladosporium*, and *Xylaria* as endophytes of various plant tissues growing under different ecological and geographical conditions, whereas others can be occasionally found colonizing host tissue and are isolated only once or twice from several hundred samples (Verma *et al*., 2007; Siqueira *et al*., 2011; Bezerra *et al*., 2012).

MEDICINAL PLANTS

Medicinal plants are an important source of interesting bioactive compounds. Endophytes from medicinal plants have received much attention due to the production of several natural products. According to Selim *et al*. (2012, p. 36), "Yu *et al*. (2010) showed that medicinal plants and plants from special environments frequently contain endophytic fungi that produce interesting antimicrobial substances". Because of the long-term association between endophytic fungi and the host plants, the organisms may develop means to share metabolic pathways and genetic information to produce bioactive compounds (Chithra *et al*., 2014; Rai *et al*., 2014a, 2014b).

Therefore, the endophytes isolated from medicinal plants have great significance due to their ability to synthesize secondary metabolites similar to the host and show great potential for the discovery of new bioactive compounds (Kusari *et al*., 2008). When considering the exploitation of endophytic fungal metabolites in medical practices, the utilization of compounds isolated from plants that already have an ethnobotanical use, i.e., medicinal plants, is suggested.

According to Mello *et al.* (2010), plants and their derivatives have long been utilized in folk medicine, and currently, approximately 30% of the drugs used have vegetal origin. This is due, in part, to the biological properties of a wide variety of plants species. It is believed that approximately 80% of the world's population uses plants as therapeutic resources, suggesting the most important alternative in developing countries (Bannerman *et al*., 1983; Silva & Cechinel Filho, 2002; Uprety *et al*., 2012). In the last decade, economic and social factors contributing to the development of public health have led to the realization of intense studies concerning natural therapies (WHO, 2002).

Endophytes protect plants against attack by other microorganisms, insects, and herbivores due to the production of toxins (Pileggi *et al*., 2002), including the endophytic microorganisms of medicinal plants, as many species are amenable to isolation by culture. Endophytes can also produce enzymes and other chemical compounds, conferring benefits to the host plant. In many cases, these substances are produced by microorganisms and not by the host plant (Tan & Zou, 2001; Strobel, 2003; Ferrara, 2006; Almeida *et al*., 2009).

The endophyte community of a particular plant may vary according to the health of the plant, suggesting the potential protective actions of some of these microorganisms (Yang *et al*., 2001; Reiter *et al*., 2002). The protective potential of endophytes reflects competition for space and/or nutrients, the production of antimicrobial substances, and the induction of systemic resistance (Pleban *et al*., 1995; M'Piga *et al*., 1997). Gao *et al*. (2005) found that seasonality also affects the endophyte community, showing that isolates obtained from *Heterosmilax japonica* Kunth in the spring were more abundant, with a greater number of species compared to summer. This phenomenon may reflect the fact that the endophyte population depends on the physiological status of the host plant, which, in turn, is partially associated with seasonal weather variations (Gao *et al*., 2005).

Wiyakrutta *et al*. (2004) reported positive results for endophytic fungi from medicinal plants in Thailand with activities against *Mycobacterium tuberculosis* (Zopf, 1883), *Plasmodium falciparum* (Welch, 1897), herpes simplex type 1 virus, human oral squamous carcinoma cells, and breast cancer cells. Li *et al*. (2005) screened Chinese herbs in search of endophytic fungi with antitumor and antifungal activity, with 9.2% of the isolates displaying antitumor activity and 30%, antifungal activity.

Antagonistic substances against the bacteria *Helicobacter pylori* (Goodwin *et al*., 1989), *Sarcina lutea* (Cohn, 1872), *Staphylococcus aureus* (Rosenbach, 1884) and the yeast *Candida albicans* (Berkhout, 1923) were isolated from the endophytic fungi obtained from *Cynodon dactylon* (L.) Pers., another medicinal plant (Li *et al*., 2005). Sette *et al*. (2006) reported an endophytic fungus isolated from *Coffea arabica* L. and *C. robusta* L. Linden (coffee plants) with antimicrobial activity against *Salmonella choleraesuis* (Kauffmann & Edwards, 1952), *S. aureus*, *Pseudomonas aeruginosa* (Schroeter, 1872), four serotypes of *Escherichia coli* (Escherich, 1885), and one strain of *Aspergillus niger* (van Tieghem, 1867) from *C. dactylon* (a medicinal plant that produces metabolites with antitumor and antimicrobial activities) (Song *et al*., 2004). In addition, the *Alternaria* strain isolated from *Trixis vauthieri* DC., a plant with activity against *Trypanosoma*, showed up to 99% inhibition of the protozoan (Cota *et al*., 2008).

Corrado & Rodrigues (2004) isolated *Diaporthe* sp. from the petioles and leaves of the medicinal plant *Aspidosperma tomentosum* Mart. and observed antimicrobial activity in 13 fungal strains, and experiments with these extracts inhibited the growth of bacteria, yeasts and filamentous fungi, showing the great potential of this fungus as a source of bioactive compounds. Ramasamy *et al*. (2010) studied 348 endophytic fungi from 24 medicinal plants in Malaysia, verifying their efficacy against *Bacillus subtilis* (Cohn, 1872), *Micrococcus luteus* (Cohn, 1872), *S. aureus*, *E. coli* and *C. albicans*, with inhibition zones ranging from 8 to 24 mm.

Zhao *et al*. (2011) also isolated 560 endophytic fungi from medicinal plants from China and verified that many strains displayed broad-spectrum antimicrobial activity. Qin *et al*. (2009) isolated 46 endophytes from medicinal plants of tropical rainforests and showed that these plants are reservoirs of biologically active compounds. Furthermore, Carvalho *et al*. (2012) evaluated the diversity and activity of endophytic fungi associated with the medicinal plant *Stryphnodendron adstringens* (Mart.) Coville and obtained 16 taxa that exhibit activity against bacteria and fungi as well as *Leishmania amazonensis* (Laveran & Mesnil, 1903).

Rosa *et al*. (2012) evaluated the diversity of the microbial community associated with healthy *Echinacea purpurea* (L.) Moench clones, which produce bioactive compounds. Thirty-nine fungal endophytes were closely related to species of *Ceratobasidium*, *Colletotrichum*, *Cladosporium*, *Fusarium*, *Glomerella* and *Mycoleptodiscus*, and a total of 16 extracts (41%) showed antifungal properties. Other studies have shown that the endophytic fungal communities in the tissues of medicinal plant produce a range of metabolites with different types of biological activity (Chowdhary & Kaushik, 2015; Sharma *et al*., 2016; Potshangbam *et al*., 2017).

HOST-ENDOPHYTE INTERACTIONS

These endophytic microorganisms confer protection against disease by competition for resources and space in intra-tissue regions and increasing plant biomass under conditions of stress (Schulz & Boyle, 2005; Rodriguez *et al*., 2008). According to Redman *et al*. (1999), plants colonized by endophytes show improvements in defense mechanisms compared to plants that are not colonized.

Endophytic fungi may become pathogenic under conditions of plant stress (Kogel *et al*., 2006). Schulz & Boyle (2005) proposed that asymptomatic colonization is a result of a balanced antagonistic interaction between plants and fungi. Thus, there is equilibrium between fungal virulence and plant defense, and if this balance is affected, disease develops (Schulz *et al*., 2002). The opposite situation can also occur: pathogenic fungi can become endophytes during certain stages of the life cycle through mutagenic changes (Freeman & Rodriguez, 1993; Wilson, 1995). It has been suggested that the evolutionary origin of many endophytes may be the result of asymptomatic or latent pathogens (Saikkonen *et al*., 1998).

Special attention has been devoted to fungi that establish a mutualistic association with medicinal plants. Although the relationship between an endophyte and its host may vary, and the interactions between these organisms remain poorly understood, this association suggests that these microorganisms co-evolved with the host (Bacon & Hill, 1996). During the establishment of the associations, specific biosynthetic pathways are induced to produce new and diverse secondary metabolites, depending on biotic (e.g., species involved in the interaction) and abiotic (e.g., climate) factors (Khan *et al*., 2012; Chandra, 2012; Soliman *et al.*, 2013).

Many bioactive metabolites are produced by endophytic fungi from different biosynthetic pathways and belong to diverse structural groups, such as terpenoids, steroids, quinones, phenols, and coumarins (Pimentel *et al*., 2011; Kaul *et al*., 2012). Xue *et al*. (2012) elucidated eight substances (cyclopentenedione, diketopiperazine, lactone, benzophenone, terpene, anthraquinone, diphenyl ethers, and alkaloid) from endophytic *Aspergillus* sp. isolated from *Cephalotaxus mannii* Hook. f.

Several studies have demonstrated the important symbiotic interaction between endophytic fungi and their hosts. These microorganisms have a positive influence on the metabolism and physiology of the host in exchange for protection and nutrition (Douglas, 1998; Parecer & Ahmadjian, 2000; Selosse *et al*., 2004). Besides, the genetic richness of these microbial communities can play a determinant role in both the adaptation and the evolution of their hosts (Zilber-Rosenberg & Rosenberg, 2008; Tonon *et al*., 2011; Simon *et al*., 2016). Zilber-Rosenberg & Rosenberg (2008) argued for the plant-microorganism association, referred to as the Hologenomic theory, which considers the 'holobionte' animal or plant, with all its associated microorganisms, as an evolutionary unit. The hologenome is the sum of the genetic information from the host and its microbiota, and these authors proposed that the hologenome is the basic unit on which evolutionary forces act. This theory considers, from a holistic/systemic point of view, the various genetic and metabolic interactions of symbiotic microbiota with the host plants (Rosenberg *et al*., 2007; Rosenberg & Zilber-Rosenberg, 2011). Many studies have clearly demonstrated that coevolution occurs in interactions among organisms and that the genetic constitution of the holobionte is altered in response to environmental stimuli (Thornhill *et al*., 2013, 2014; Prada *et al*., 2014).

An interesting aspect of endophytic fungi is that they can produce a wide variety of secondary metabolites (Kaul *et al*., 2012; Suryanarayanan *et al*., 2012; Rönsberg *et al*., 2013), which, unlike primary metabolites, play an important role in the physiological processes of microorganisms in the environment (Braga *et al*., 1999; Conti *et al*., 2012). In addition to ecological importance, the secondary metabolites produced by endophytic fungi are a source of bioactive natural products for utilization in several areas as agricultural, medical and pharmaceutical fields (Strobel & Daisy, 2003; Suryanarayanan *et al*., 2009; Kumar & Kaushik, 2012; Rönsberg *et al*., 2013). These compounds have been exploited due to their importance to industry, especially substances such as antibiotics, pigments, toxins, pheromones, enzymes, immunomodulatory agents, pesticides, antitumor agents and plant growth promoters (Okafor, 2007).

Natural products, which are typically secondary metabolites, are produced by an organism in response to external stimuli, such as nutritional changes or infection (Strohl, 2000). Aly *et al*. (2011), De Souza *et al*. (2011) and Gutierrez *et al*. (2012) summarized the comprehensive information on compounds from endophytic fungi and described potential trends for future research, together with the botany, phytochemistry, pharmacology, and toxicology, and they discussed the possible trends and the scope for future research of endophytes. According to Gutierrez *et al*. (2012),

> modern pharmacological studies reported by theses authors demonstrated that their crude extracts and active compounds possess wide pharmacological actions, especially for anti-microbial drug discovery, with neuroprotective, antioxidant, nematicidal, antiplasmodium, anti-inflammatory activities.

The ability of endophytic fungi to synthesize the metabolites produced by the host plant is most likely due the transfer of genes from the host to the fungus, or vice-versa (Kusari *et al*., 2013). According to Selim *et al*. (2012, p. 41), quoting Moricca & Ragazzi (2007), "the type of interaction between an endophyte and a plant is controlled by the genes of both organisms and is also modulated by the environment". During co-evolution, endophytic fungi gradually adapted to specific micro-environments by genetic variation, including the uptake of some plant DNA segments into their own genomes, as well as the insertion their own DNA into the host genome. One typical example is the production of gibberellins by both fungi and plants (Perez *et al*., 2002).

Some endophytes have the ability to produce different substances, such as bioactive volatile organic compounds (VOC), including esters, lipids, alcohols, organic acids, and ketones, which can be lethal to other microorganisms and are thus useful for reducing or eliminating diseases in the preservation of seeds, fruits and flowers, and other plant parts during storage or transport (Gutierrez *et al*., 2012; Kudalkar *et al*., 2012; Kusari *et al*., 2013). The endophytic fungus *Muscodor albus* (Woropong *et al*., 2001) is often cited in the literature as a promising producer of VOC. A non-sporulating Xylariaceae isolated from the leaves of *Cinnamomum zeylanicum* Blume (Cinnamon) was found to be lethal to certain fungi and bacteria due to the production of a mixture of volatile compounds; VOC analysis by gas chromatography identified the production of 25 different volatile compounds (Strobel *et al*., 2001; Strobel, 2003).

A mixture of different volatile compounds produced by *Muscodor* sp., mainly naphthalene, 2-methyl-propanoic acid, and methyl ester, was found to inhibit many pathogenic microorganisms (Zhang *et al*., 2010). Pimenta *et al*. (2012) isolated endophytic fungi from plum (*Prunus domestica* L.) leaves and determined whether the microbes produce compounds that inhibit *Monilinia fructicola* (Honey, 1928) and *Colletotrichum gloeosporioides* (Pen.) Sacc. Compelling evidence for variation was observed in only 4 of 141 isolates of *Phaeosphaeria nodorum* (Hedjaroude, 1969), which produced antifungal volatiles inhibitory to *M. fructicola*, whereas no isolate produced volatiles inhibitory to *C. gloeosporioides.* However, these reports demonstrate the antagonistic potential of VOC produced by endophytic fungi and their acceptance for utilization in agriculture and medicine.

BIOTECHNOLOGICAL POTENTIAL OF FUNGAL ENDOPHYTES

The beneficial effects of plant endophytes are very promising, and, accordingly, these microorganisms have become an important tool for obtaining natural products with biotechnological applications. Bioprospecting is defined as the exploration and investigation of plants, animals and microorganisms to identify active ingredients useful in different areas such as biotechnology. Endophytic fungi are a huge source of bioactive substances, particularly considering that living organisms are constantly evolving (Trigueiro, 2002; Strobel & Daisy, 2003).

Many prospecting studies have identified more than 20,000 bioactive compounds (Ownley *et al*., 2010). Endophytes produce substances of different chemical classes, and those with antagonistic activity include aliphatic compounds, phenolic compounds (phenols and phenolic acids, isocoumarin derivatives, lignans, flavonoids, and quinones), alkaloids (indole derivatives, amines, and amides), peptides, polyketides, steroids, and terpenoids (primarily sesquiterpenes, diterpenes, and triterpenes) (Mousa & Raizada, 2013) (Appendix).

Yu *et al*. (2010) highlighted alkaloids as products commonly obtained via the secondary metabolism of endophytic fungi. The biological activities shown by these compounds are highly diverse and have many applications, including antimicrobial, antiparasitic, neuroprotective, antioxidant, antidiabetic, immunosuppressive, antiviral, anticarcinogenic, and cytotoxic activities (Aly *et al*., 2011; Wang *et al*., 2012).

Bioactive compounds that are co-produced by plants and their associated endophytes include the anticancer drug camptothecin, the natural insecticide azadirachtin, penicillin from *Penicillium* sp., and the immunosuppressant cyclosporine from *Tolypocladium inflatum* (Gams,1971) and *Cylindrocarpon lucidum* (Booth, 1966) (Puri *et al*., 2005, 2006; Kusari *et al*., 2012).

The most striking example of a metabolite with bioactive properties is the anticancer drug paclitaxel (Taxol®), which was originally produced from the plant *Taxus brevifolia* Nutt. (Zhou *et al*., 2010). This drug interferes with the proliferation of cancer cells, reducing or stopping their growth and spread. The production of this compound by an endophytic fungus was first demonstrated by Stierle *et al*. (1993), who showed that the endophytic fungus *Taxomyces andreanae* (Strobel *et al*., 1993) isolated from *T. brevifolia* produced Taxol *in vitro*. Subsequently, other studies have also shown that different species of endophytic fungi are able to produce Taxol. Some examples include *Pestalotiopsis microspora* isolated from *Taxus wallichiana* Zucc. (Strobel *et al*., 1996), *Tubercularia* sp. isolated from *Taxus mairei* (Wang *et al*., 2000), *Colletotrichum gloeosporioides* (Penzing & Saccardo, 1884) isolated from *Justicia gendarussa* Burm. f. (Gangadevi & Muthumary, 2008), *Pestalotiopsis terminaliae* (Agarwal & Hasija, 1961) isolated from *Terminalia arjuna* (Roxb. ex DC.) Wight & Arn. (Gangadevi & Muthumary, 2009), *Gliocladium* sp. isolated from *Taxus baccata* L. (Sreekanth *et al*., 2009), and *Guignardia mangiferae* (Roy, 1968) isolated from *Taxus media* Rehder (Xiong *et al*., 2013).

In addition to Taxol, many other secondary metabolites produced by endophytic fungi showing biotechnological activities are reported in the literature (Marinho *et al*., 2005; Borges & Pupo, 2006; Pastre *et al*., 2007; Momesso *et al*., 2008; Silva *et al*., 2010a; Budhiraja *et al*., 2013), and one of the main applications of these natural products is as inhibitors of pathogenic organisms (Idris *et al*., 2013). Some important examples of these metabolites include phomopsichalasin, a metabolite produced by the endophytic fungus *Diaporthe* sp., with important antibacterial activity (Horn *et al*., 1995); cryptocandin, a metabolite produced by the endophyte fungus *Cryptosporiopsis* cf. *quercina* (Petrak, 1924), with antifungal activity (Strobel *et al*., 1999); cercosporin, a substance with antiparasitic action produced by the endophytic fungus *Mycosphaerella* sp. (Moreno *et al*., 2011); and cytochalasins, substances produced by the endophytic fungi *Chaetomium globosum* (Kunze, 1817) (Momesso *et al*., 2008) and *Xylaria* sp. (Silva *et al*., 2010b), with many biological activities, including cytotoxic action.

Endophytic fungi have been the subject of studies aimed at identifying new bioactive natural products that can be used not only in the pharmaceutical industry but also in food and agriculture (Porras-Alfaro & Bayman, 2011; Liang *et al*., 2012; Quadri *et al*., 2013). The relationship of the food industry with fungi is longstanding and extensive. With the development of food science, it may be possible to determine the processes by which fungi modify foods (Pastore & Macedo, 2004).

In addition, extracellular fungal enzymes can confer host resistance to a particular threat and provide soluble products to the host that may be absorbed and utilized as food. Enzymes are used extensively in the textile (amylase, cellulase, and oxidoreductase), detergent (protease, lipase, cellulase, and oxidoreductase), food (pectinase, protease, cellulase, and oxidoreductase), paper (xylanase, lipase, and oxidoreductases) and leather (protease and lipase) industries (Nielsen & Oxenboll, 1998).

Torres *et al*. (2003) studied endophytic fungal producers of lipases, which can be applied in the detergent industry for the synthesis of high-value compounds (Kirk *et al*., 2002; Jaeger & Eggert, 2002; Panke & Wubbolts, 2002). Proteases are used in industrial processes, such as detergent manufacturing, brewing, and baking, and under appropriate conditions, these enzymes can catalyze the synthesis of commercially valuable peptides (Beynon & Bond, 1989). Xylanases are extracellular enzymes mainly produced by fungi (Pham *et al*., 1998) that can be used in the paper industry for the bleaching of kraft pulps. Cellulases, as well as other hydrolases, are induced in microorganisms for secretion, allowing them to grow in cellulose media (Kubicek *et al*., 1993). In the food industry, cellulases are used in many processes, mainly in the extraction of components of green tea, soy protein, essential oils, flavorings, and sweet potato starches (Mester & Tien, 2000; Hofrichter, 2002).

Amylases occur widely in animals, plants, and microorganisms. However, due to advantages such as reduced production time, the amylases produced by fungi have preference in the enzyme market (Reddy *et al*., 2003). The genus *Mucor* represents a group of microorganisms responsible for the production of amylases that are widely used in industry (Zare-Maivan & Shearer, 1988; Petruccioli & Federici, 1992). Pectinases are a group of enzymes with applications in the food industry (Castilho *et al*., 2000; Jayani *et al*., 2005). Fungi have also been directly implicated in environmental recovery, involving the recycling of agricultural and agro-industrial waste and the biodegradation of lignocellulosic materials (made of cellulose and lignin), especially wood (Ferraz, 2010). These degradation processes are usually catalyzed by oxidative enzymes, especially laccase and peroxidase enzymes (Dúran, 2004).

Another use for the products obtained from fungi is biological control in agriculture. Endophytes can also reduce disease symptoms caused by plant pathogens or various environmental stresses (Aravind *et al*., 2010; Shimizu, 2011). Until recently, the control of pests, diseases, and weeds has largely been based on crop spraying with many synthetic chemical pesticides (Cook, 2000). However, this practice increased the use of toxic and carcinogenic chemicals due to the increased agricultural demand to sustain population growth, which may severely compromise the health of the plant and the consumer (Montesinos, 2003).

Overall, the ability of endophytes to produce substances that inhibit the growth of other species of microorganisms has stimulated much research (Arnold, 2008). The effectiveness of endophytes as biological control agents depends on many factors, including the specificity of the host plant, the dynamics of the population and degree of plant colonization, the ability to move within plant tissue, and the ability to induce systemic resistance (Azevedo *et al*., 2002). The first researcher to report biological control using an endophytic fungus was most likely Webber (Webber, 1981). At the time, the fungus *Phomopsis oblonga* (Traverso, 1906) produced toxic compounds with repellent effects and the ability to protect host plants against attack by the beetle *Physocnemum brevilineum* (Say, 1824), the vector of the pathogen *Ceratocystis ulmi* (Moreau,1952), which causes Dutch elm disease (Azevedo *et al*., 2000; Dutta *et al*., 2014).

Currently, fungal species, such as *Metarhizium anisopliae* (Sorokin, 1883) and *Beauveria bassiana* (Vuillemin, 1912), among others, are often used in agriculture as insect pest controllers. When inhabiting plants as endophytes, these microorganisms may control insect attacks and can be artificially inoculated into the hosts. The production of toxins by endophytic fungi is related to their ability to repel insects, inducing weight loss and decreased growth and delaying development, thereby reducing the pest population (Azevedo *et al*., 2000).

As demonstrated by Carroll (1988), the mechanism underlying fungal activity is based on the ability to make the host unpleasant to various plant pests, such as aphids, beetles, and grasshoppers. *Muscodor vitigenus* (Strobel *et al*., 2002), isolated from *Paullinia paullinioides* Radlk. in the Peruvian Amazon, is capable of producing naphthalene, which acts as an insect repellent (Daisy *et al*., 2002). Additionally, the endophytic fungus *Neotyphodium coenophialum* (Morgan-Jones & Gams, 1982), which colonizes *Festuca arundinacea* Schreb., reduces the aphid population, affecting the reproductive process (Bultman & Bell, 2003). *Muscodor albus*, isolated from the *Cinnamomum zeylanicum* stem, has both fungicidal and bactericidal activities (Worapong *et al*., 2001). The endophytic fungus *Diaporthe* sp., isolated from *Aspidosperma tomentosum* leaves and the petioles of the medicinal plant *Spondias mombin* L., shows great potential as a bioactive producer, with extracts that inhibit the growth of bacteria, yeasts, and filamentous fungi (Corrado & Rodrigues, 2004).

Metabolites obtained from a *Diaporthe helianthi* (Mihaljcevic & Petrov, 1981) strain inhibited the growth of *Moniliophthora perniciosa* (Aime & Phillips-Mora, 2005), an important plant pathogen, *in vitro*. Assante *et al*. (2004) highlighted the biological control of plant pathogens through mycoparasitism. The endophyte *Cladosporium tenuissimum* (Cooke, 1878) grows inside the spore pathogen *Uromyces appendiculatus* (Strauss, 1833), filling its interior with mycelia and forming conidiophores and conidia that emerge from the spore. The species *Trichoderma viride* (Persoon, 1794), *T. harzianum* (Rifai, 1969), *T. stromaticum* (Samuels & Pardo-Schultheiss, 2000), and *T. virens* (Miller *et al*., 1957) were reported to control the phytopatogenic fungus *Rhizopus stolonifer* (Ehrenberg, 1818), the causal agent of floral passion fruit rot (Bomfim *et al*., 2010). Moreover, the endophytic fungi present in the tropical plant *Theobroma cacao* L. (Malvaceae) in Panama improved plant defense against one of its primary pathogens, *Phytophthora* sp. (Arnold *et al*., 2003).

Thus, biological control programs should be based on the selection of antagonistic microorganisms, and testing can be performed *in vitro* or *in vivo* (Mariano, 1993). As biological control agents, endophytes should demonstrate good colonization and growth, combined with antagonism to the target pathogen (Mejía *et al*., 2014). Much remains unknown about the microbial ecology and antagonism of plant pathogens in different agricultural systems (Kerry, 2000). Thus, research to identify new endophytic fungi and develop more efficient application processes are essential for the development of effective biological control strategies in agriculture (Tjamos *et al.*, 2010).

CONCLUSION

This review highlights the importance of studying endophytic fungi associated with medicinal plants, since the sampling effort is considerably reduced as these plants are already used as medication. Substances present in these plants can either be produced by the plant itself, by the endophytic fungi alone, or by the plant and the endophytic fungi together. The possibility of utilizing substances of microbial origin is far more viable than of vegetable origin. It is worth noting that with endophytis fungi the time needed for production is shorter, and the area of cultivation is smaller, and this preserves native plant species in nature.

Therefore, we conclude that the study of endophytic fungi associated with medicinal plants should gain more attention as it reduces technological risks once the samples are previously directed.

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Appendix. Promising reports of some medicinal plants and their endophyte fungi as sources of bioactive compounds.

(Continue)

Endophytic fungus	Medicinal plant	Secondary metabolite	Activity	Reference
Aspergillus parasiticus (Speare, 1912)	*Sequoia sempervirens* (D. Don) Endl.	Sequioatones a	Anticancer	Stierle *et al*. (1999)
Penicillium janthinellum (Biourge, 1923)	*Melia azedarach* L.	Polyketide citrinin, 1,6,8-trihydroxy-3 hydroxymethylanthraquinone and janthinone	Antileishmanicidal	Marinho *et al*. (2005)
Pestalotiopsis guepinii (Steyaert, 1949)	*Virola michelii* Heckel	Isosulochrin and chloroisosulochrin	Antimicrobial	Oliveira *et al*. (2011)
Curvularia sp.	*Ocotea corymbosa* (Meisn.) Mez	Benzopyrans	Antifungal	Teles *et al*. (2006)
Phoma sorghina (Boerema *et al*., 1973)	*Tithonia diversifolia* (Hemsl.) A. Gray	Dendryol e and dendryol f	Antimicrobial	Borges & Pupo (2006)
Penicillium sp.	*Melia azedarach* L., *Murraya paniculata* (L.) Jack	Azaphylones, citrinin and citrinin h-1	Antibacterial	Pastre *et al*. (2007)
Taxomyces andreanae (Strobel *et al*., 1993)	*Taxus brevifolia* Nutt.	Taxol	Anticancer	Stierle *et al*. (1993)
Pestalotiopsis microspora (Batista & Peres, 1966)	*Torreya taxifolia* Arn.	Torreyanic acid	Anticancer	Lee *et al*. (1996)
Entrophospora infrequens (Ames & Schneid, 1979)	*Nothapodytes foetida* (Wight) Sleumer	Camptothecin	Anticancer	Puri *et al*. (2005)
Trametes hirsute (Pilát, 1939), *Aspergillus fumigatus* (Fresenius, 1863), *Phialocephala fortinii* (Wang & Wilcox, 1985), *Fusarium oxysporum* (Schlechtendal, 1824)	*Podophyllum hexandrum* Royle, *Juniperus communis* L., *Podophyllum peltatum* L., *Juniperus recurve* Buch.-Ham. ex D. Don	Podophyllotoxin	Anticancer	Puri *et al*. (2005), Kusari *et al*. (2009), Eyberger *et al*. (2006), Kour *et al*. (2008)
Curvularia lunata (Boedijn,1933)	*Niphates olemda* (de Laubenfels, 1954)	Citosquirines	Antifungal	Brady *et al*. (2000), Ohzeki & Mori (2003)
Rhinocladiella sp.	*Tripterygium wilfordii* Hook. f.	Cytochalasin h, cytochalasin j, epoxycytochalasin h and cytochalasin e	Anticancer	Wagenaar *et al*. (2000)
Chaetomium globosum (Kunze ex Fries, 1829)	*Imperata cylindrical* (L.) Raeusch.	Cytochalasan based alkaloid chaetoglobosin u, four analogues chaetoglobosin c, chaetoglobosin f, chaetoglobosin e and ponochalasina	Anticancer	Ding *et al*. (2006)
Pestalotiopsis microspora	*Terminalia morogorensis* Engl.	Pestacin, 1, 3-dihydro isobenzofuran) and isopestacin	Antioxidant	Harper *et al*. (2003), Strobel *et al*. (2002)

Appendix. (Continue)

Endophytic fungus	Medicinal plant	Secondary metabolite	Activity	Reference
Cephalosporium sp.	*Sinarundinaria nitida* (Mitford ex Bean) Nakai	Isobenzofuranone derivative 4,6-dihydroxy-5-methoxy-7-methylphthalide alongwith three known compounds: 4,5,6-trihydroxy-7-methyl-1,3-dihydroisobenzofuran; 4,6-dihydroxy-5-methoxy-7-methyl-1,3-dihydroisobenzofuran and 4,5,6-trihydroxy-7-methylphthalide	Antioxidant	Huang *et al*. (2012)
Cephalosporium sp.	*Trachelospermum jasminoides* (Lindl.) Lem.	Graphislactone a	Antioxidant	Song *et al*. (2005)
Fusarium sp.	*Cajanus cajan* (L.) Huth	Cajaninstilbene acid, 3-hydroxy-4-prenyl-5-methoxystilbene-2-carboxylic acid	Antioxidant	Zhao *et al*. (2012a, 2012b)
Xylaria sp.	*Ginkgo biloba* L.	Phenolics and flavonoids 7-amino-4-methylcoumarin	Antioxidant, antibacterial and antifungal	Liu *et al*. (2007, 2008)
Chaetomium sp.	*Nerium oleander* L.	Flavonoids and phenolic	Antioxidant	Huang *et al*. (2007a, 2007b)
Fusarium subglutinans (Nelson *et al.,* 1993)	*Tripterygium wilfordii* Hook. f.	Subglutinol-a ($c_{27}h_{38}o_4$) and subglutinol-b	Immunomodulatory	Lee *et al*. (1995)
Colletotrichum dematium (Grove, 1918)	*Pteromischum* sp.	Collutelin a	Immunomodulatory	Ren *et al*. (2008)
Phomopsis archeri (Sutton, 1980)	*Vanilla albida* Blume	Sesquiterpenes phomoarcherins a-c	Antimalarial	Hemtasin *et al*. (2011)
Exserohilum rostratum (Leonard & Suggs, 1974)	*Stemona* sp.	11-hydroxymonocerin, ofmonocerin and 12-hydroxymonocerin	Antimalarial	Sappapan *et al*. (2008)
Cochliobolus sp.	*Piptadenia adiantoides* (Spreng.) J.F. Macbr.	Cochlioquinone a and isocochlioquinone a	Antileishmanial	Campos *et al*. (2008)
Edenia sp.	*Petrea volubilis* L.	Preussomerin eg1, palmarumycin cp2, palmarumycin cp17, palmarumycin cp18, cj-12,37, palmarumycin cp19 and 5-methylochracin	Antileishmanial	Martinez-Luis *et al*. (2012)
Mycosphaerella sp.	*Psychotria horizontalis* Sw.	Cercosporin	Trypanocidal, antimalarial, antileishmanial	Moreno *et al*. (2011)
Phomopsis sp.	*Viguiera arenaria* Baker	3,4-dimethyl-2-(40-hydroxy-30,50-dimethoxyphenyl)-5-methoxy-tetrahydrofuran	Trypanocidal	Verza *et al.* (2009)
Phoma sp.	*Arisaema erubescens* (Wall.) Schott	a-tetralone derivative (3s)-3,6,7-trihydroxy-a-tetralone and cercosporamide, b-sitosterol and trichodermin	Antimicrobial	Wang *et al.* (2012)

Appendix. (Conclusion)

Endophytic fungus	Medicinal plant	Secondary metabolite	Activity	Reference
Phoma sp.	*Cinnamomum mollissimum* Hook. f.	Polyketide compound 5-hydroxyramulosin	Antifungal	Santiago *et al.* (2012)
Phomopis cassiae (Saccardo, 1880)	*Cassia spectabilis* DC.	Cadinane sesquiterpenes 3,9,12-trihydroxycalamenenes; 3,12-dihydroxycalamenene; 3,12-dihydroxycadalene and 3,11,12-trihydroxycadalene	Antimicrobial	Silva *et al.* (2006)
Xylaria sp.	*Piper aduncum* L.	Presilphiperfolane sesquiterpenes	Antifungal	Silva *et al*. (2010a)
Pichia guillermondii (Wickerham, 1966)	*Paris polyphylla* Sm.	Ergosta-5,7,22-trienol, 5a,8a-epidioxyergosta-6,22-dien-3b-ol, ergosta-7,22-dien-3b,5a,6b-triol and helvolic acid	Antibacterial	Zhao *et al.* (2010)
Fusarium solani (Saccardo, 1881)	*Taxus baccata* L.	1-tetradecene, 8-octadecanone, 8-pentadecanone, octylcyclohexane and 10-nonadecanone	Antifungal, antibacterial	Tayung *et al*. (2011)
Aspergillus fumigatus	*Cynodon dactylon* (L.) Pers.	Asperfumoid and asperfumin	Antifungal	Liu *et al.* (2004)
Pestalotiopsis jesteri (Strobel *et al*., 2000)	*Fagraea bodenii* Wernham	Jesterone and hydroxy-jesterone	Antimicrobial	Li & Strobel (2000)
Colletotrichum gloeosporioides	*Artemisia mongolica* (Fisch. ex Besser) Nakai	Colletotric acid	Antimicrobial	Zou *et al*. (2000)
Edenia gomezpompae (Gonzaléz *et al*., 2007)	*Callicarpa acuminate* Kunth	Napthaquinone spiroketals and palmarumycin: preussomerin eg1, eg2 and eg3	Antimicrobial	Macias-Rubalcava *et al.* (2008)
Pestalotiopsis theae (Steyaert, 1949)	*Pinus taeda* L.	Pestalotheol-c	Antiviral	Li *et al.* (2008a, 2008b)
Phomopsis sp.	*Garcinia* sp.	Phomoxanthone a and b	Antitubercular	Isaka *et al*. (2001)
Diaporthe sp.	*Pandanus amaryllifolius* Roxb.	Benzopyranones diaportheone a and b	Antitubercular	Bungihan *et al*. (2011)
Fusarium oxysporum	*Catharanthus roseus* (L.) G. Don	Vincristine	Anticancer	Arnold (2007)
Trametes hirsuta, *Phialocephala fortinii*	*Podophylum* sp.	Podofilotoxin	Anticancer	Jalgaonwala *et al*. (2011)
Cytospora sp.	*Conocarpus erecta* L.	Cytoskyrin a	Anticancer	Brady *et al*. (2000)
Apiospora montagnei (Saccardo, 1875)	*Polysiphonia violacea* (Greville, 1824)	Epiepoxydon	Anticancer	Klemke *et al*. (2004)
Cephalotheca faveolata (Yagushi *et al*., 2006)	*Eugenia jambolana* Lam.	Sclerotiorin	Anticancer	Giridharan *et al*. (2012)
Aspergillus sp.	*Gloriosa superba* L.	6-methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide	Anticancer	Budhiraja *et al*. (2013)