

## **Endophytic fungi: Benefits for plants and biotechnological potential**

**Fungos endofíticos: Benefícios para plantas e potencial biotecnológico**

**Hongos endófitos: Benefícios para las plantas y potencial biotecnológico**

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### **Abstract**

Endophytic fungi are microorganisms that live inside plants, establishing a mutualistic relationship, where both benefit from this interaction. They require protection and nutrients from host plants, and in return fungi can contribute to host's growth and nutrient uptake. In addition, they can improve plant tolerance to abiotic and biotic stresses and increase plant resistance to insects and pests. Endophytic fungi produce bioactive compounds similar to those of the host plant. The economic exploitation of these bioactive compounds is much promising. These bioactive products are related to sustainable production systems and to the development of new substances with strong pharmacological properties such as antiviral, antifungal, anti-inflammatory, antitumor and antiparasitic, antidiabetic and immunosuppressant, including response to resistant microorganisms. This study is a descriptive review, having as aim to approach the main benefits of endophytic fungi for host plants, as well as the biotechnological application of the bioactive compounds produced by them. The prospection of endophytic in extreme environment could result in discovery of new bioactive compounds with surprising potential for biotechnology area. So, the development of new research frontiers in this issue is indispensable for the sustainable exploitation of the great benefits that these microorganisms could provide to the science.

**Keywords:** Endophytic; Mutualistic relationship; Antimicrobial resistance; Bioactive substances.

### **Resumo**

Fungos endofíticos são micro-organismos que vivem dentro das plantas, estabelecendo uma relação mutualista, onde ambos se beneficiam desta interação. Eles requerem nutrientes e proteção das plantas hospedeiras, e em troca os fungos

contribuem para o crescimento e captação de nutrientes dos seus hospedeiros. Além disso, eles podem melhorar a tolerância das plantas aos estresses abióticos e bióticos e aumentar a resistência das plantas aos insetos e pragas. Fungos endofíticos produzem compostos bioativos similares aos produzidos pelas plantas hospedeiras. A exploração econômica desses compostos bioativos é muito promissora. Esses produtos bioativos estão relacionados a sistemas de produção sustentáveis e ao desenvolvimento de novas substâncias com fortes propriedades farmacológicas como antiviral, antifúngico, anti-inflamatório, antitumoral, antiparasitário, antidiabético e imunossupressor, incluindo resposta a microorganismos resistentes. Este estudo é uma revisão descritiva, tendo como objetivo abordar os principais benefícios dos fungos endofíticos para as plantas hospedeiras, bem como a aplicação biotecnológica de seus compostos bioativos produzidos. A prospecção de endofíticos em ambientes extremos pode resultar na descoberta de novos compostos bioativos com potencial surpreendente para a área de biotecnologia. Assim, o desenvolvimento de novas fronteiras de pesquisa nesta temática é indispensável para a exploração sustentável dos grandes benefícios que esses microorganismos podem proporcionar à ciência.

**Palavras-chave:** Endofíticos; Relação mutualista; Resistência antimicrobiana; Substâncias bioativas.

### Resumen

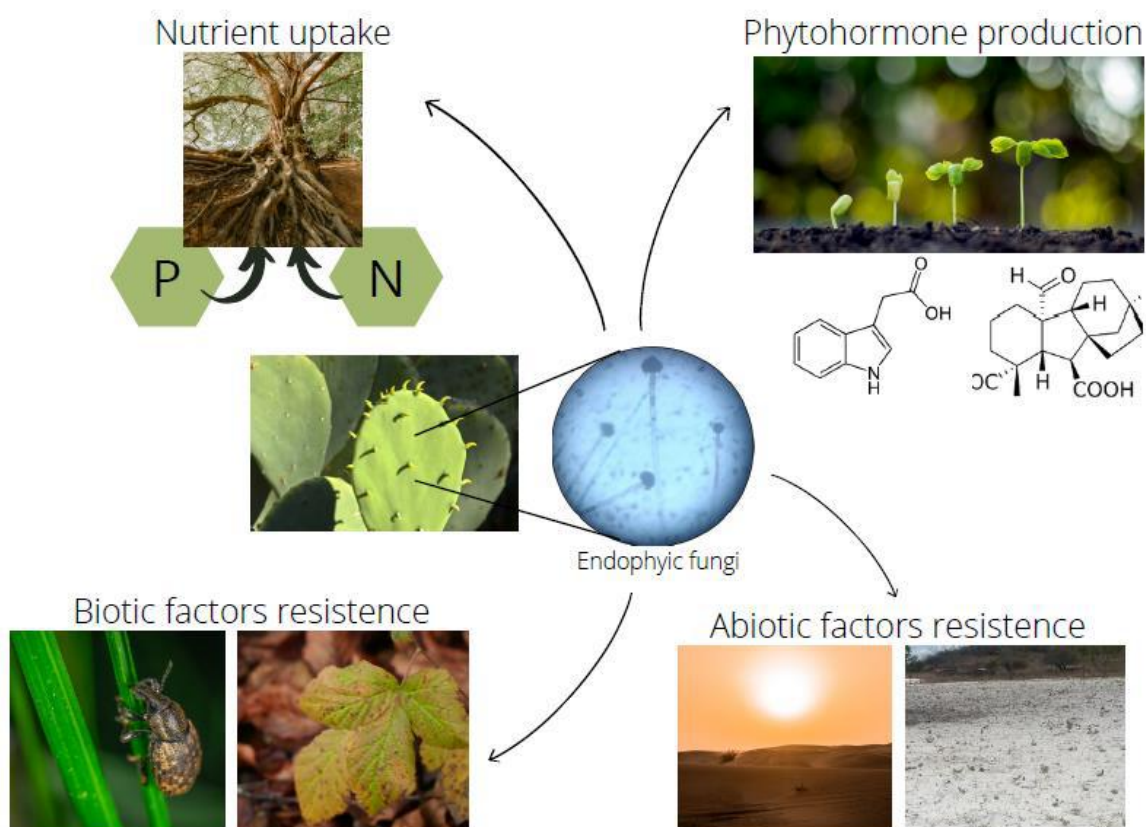
Hongos endófitos son microorganismos que viven en el interior de las plantas, estableciendo una relación mutualista, donde ambos se benefician de esta interacción. Requieren nutrientes y protección de las plantas anfitrionas y, a cambio, los hongos contribuyen al crecimiento y la absorción de nutrientes de sus anfitriones. Además, pueden mejorar la tolerancia de las plantas al estrés abiótico y biótico y aumentar la resistencia de las plantas a insectos y plagas. Los hongos endófitos producen compuestos bioactivos similares a los producidos por las plantas hospedantes. La explotación económica de estos compuestos bioactivos es muy prometedora. Estos productos bioactivos están relacionados con los sistemas de producción sostenible y el desarrollo de nuevas sustancias con una fuerte propiedades farmacológicas como antivirales, antifúngicos, antiinflamatorios, antitumorales, antiparasitarios, antidiabéticos e inmunosupresores, incluida la respuesta a microorganismos resistentes. Este estudio es una revisión descriptiva, con el objetivo de abordar los principales beneficios de los hongos endófitos para las plantas hospederas, bien como la aplicación biotecnológica de los compuestos bioactivos producidos por ellos. La prospección de endófitos en ambientes extremos puede resultar en el descubrimiento de nuevos compuestos bioactivos con un potencial sorprendente para el campo de la biotecnología. Por lo tanto, el desarrollo de nuevas fronteras de investigación en este tema es fundamental para la exploración sostenible de los grandes beneficios que estos microorganismos pueden proporcionar a la ciencia.

**Palabras clave:** Endófito; Relación mutualista; Resistencia antimicrobiana; Sustancias bioactivas.

## 1. Introduction

Fungi found within plant species are called endophytic fungi and have enormous potential in the production of bioactive substances (Strobel, Daisy, Castillo & Harper, 2004). They seek protection and nutrients from host plants and in return, they contribute to greater nutrient uptake and growth of host plant, improve the tolerance to abiotic and biotic stresses (Gouda, Das, Sem, Shin & Patra, 2016) (Figure 1), possibly through secondary metabolites production (Kusari et al., 2012). The bioactive products of plants have effective antimicrobial activity against resistant pathogens (Farjana et al., 2014; De Zoysa et al., 2019). However, the endophytic fungi are able to produce bioactive substances with similar antimicrobial proprieties (Kumar et al., 2017), in fact, according to Jalgaonwala et al. (2010), these microorganisms are seen as an excellent source of natural products.

**Figure 1.** Endophytes and their benefits for host plants.



Source: Authors (2022).

Similar bioactive compounds produced from endophytes, were related in many research papers: quinones (Hu et al., 2001); lignans (Puri et al., 2006); alkaloids (Yadav et al., 2014); lactones (Elfitra et al., 2014; Liu et al., 2018); isocumarins (Wu et al., 2019), steroids (Parthasarathy et al., 2020); and phenols (Yadav et al., 2014; Khiralla et al., 2015; Bhabhardwaj et al., 2015; Parthasarathy et al., 2020). These bioactive compounds showed several pharmacological activities, such as, antidiabetic (Zhang et al., 1999), antiviral (Guo et al., 2000), anti-inflammatory (Weber et al., 2004), antitumour (Li et al., 2005), immunosuppressive (Xu et al., 2020), and anticancer (Lim et al., 2021). These benefits indicate a wide applicability of bioactive compounds from endophytic fungi. This study is a review article with the aims to investigate endophytic fungi associated with host plants and their biotechnological potential.

## 2. Methodology

This study is a descriptive review (Prodanov & Freitas, 2013) focused on the main benefits of endophytic fungi for host plants and the biotechnological application of their bioactive compounds. This review aimed to answer the research questions: What are endophytic fungi? How do they interact with host plants? What are benefits of this interaction? What kind of bioactive compounds the endophytic fungi produce? How these bioactive compounds could be applied in biotechnology? The search strategy was carried out in electronic databases of the Science Direct, Periódicos Capes, Academic Google, and SciELO for scientific articles published in english and portuguese languages, no matter the publication year (eligibility criteria). The search was performed with the follow keywords: "endophytic fungi", "plant", "interaction", "bioactive compounds", "secondary metabolites", and "biotechnological potential". Dissertations, theses, conference abstracts, editorials, erratum, letters to the editor

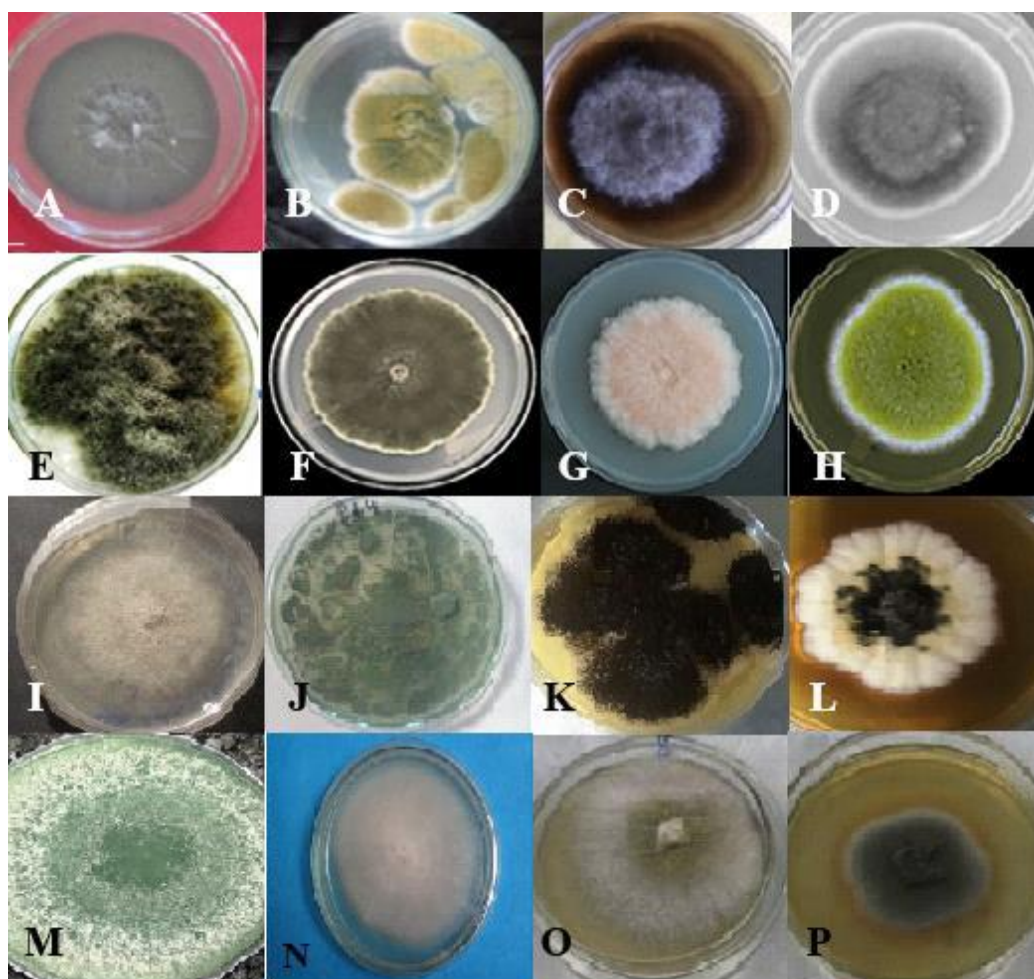
and duplicate publications were excluded. After studies selection, all papers were evaluated, being chosen those relevant for the studied theme.

### **3. Endophytic fungi**

Terrestrial plants and fungal endophytes interacted since approximately 400 million years ago (Krings et al., 2007). Evidence of fungal endophytes were found in fossilized tissues of stem and leaf suggesting that these fungi were present before the first vascular plants arose, facilitating the colonization of land by plants (Redecker et al., 2000). However, endophytic microorganisms were first mentioned in the early 19<sup>th</sup> century and, it was only in 1866 that the mycologist De Bary established the differences between these microorganisms and plant pathogens (Azevedo, 1999).

The word endophyte came from two greek words, "endon" meaning inside and "phyton" meaning plant (Dutta, Puzari, Gogoi & Dutta, 2014). According to Hirsch and Broun (1992), endophytes are microorganisms colonizing plant tissue without causing any immediate, evident and/or negative effects on the plant. They are generally fungi and bacteria and can be found in leaves, stems, roots and seeds (Peixoto Neto, Azevedo & Caetano, 2004), however, fungi are the most frequently isolated (Strobel & Daisy, 2003). The scientific community considers endophytic fungi as those that spend at least part of their life cycle inside plant tissues, without apparently causing any damage to their hosts (Petrini, 1991; Fouda et al., 2015). Endophytic fungi are different from phytopathogenic fungi, which are harmful to plants and also differ from epiphytic microorganisms which live on the surface of plant organs and tissues (Azevedo, 1998). The endophytic belong to a diverse polyphyletic group of microorganisms. They can thrive asymptotically in plant tissues above and below ground, including stems, leaves and/or roots (Kusari et al., 2012). Research have been showed that each of the nearly 300,000 species of plants host one or even hundreds of endophytes strains (Figure 2). However, only a few these plants have ever been completely studied relative to their endophytic biology, thus, enormous opportunities exist for the recovery of novel fungal forms, taxa, and biotypes (Strobel & Daisy, 2003; Gakuubi et al., 2021).

**Figure 2.** Some examples of Endophytic fungi.



(A) *Cladosporium delicatulum* (Venkateswarulu, Shameer, Bramhachari & Basha, 2018); (B) *Aspergillus sojae* (Elango et al. 2020); (C) *Phoma* sp. (Chen, Yang, Zou, Chen & Pang, 2019); (D) *Alternaria* sp. (Tonial et al. 2016); (E) *Botryosphaeria ramosa* (Hu et al. 2020); (F) *Alternaria* (Gopane, Tchatchouang, Regnier, Ateba & Manganyi, 2021); (G) *Fusarium* (Gopane et al., 2021); (H) *Penicillium* (Gopane et al., 2021); (I) *Thielaviopsis basicola* (Bhardwaj et al., 2015); (J) *Penicillium frequentans* (Bhardwaj et al., 2015); (K) *Aspergillus* (Manganyi, Regnier, Kumar, Bezuidenhout & Ateba, 2018); (L) *Epicoccum* (Manganyi et al., 2018); (M) *Trichoderma* (Manganyi, et al., 2018); (N) *Fusarium solani* (Chowdhury, Farjana & Sohrab , 2020); (O) *Phomopsis* sp. (Ye, Li, Yi, Zhang & Zou, 2019); (P) *Microsphaeropsis arundinis* (Ye e al., 2019).

Endophyte fungi and their plant hosts establish a mutualistic interaction, because while the plants give protection and nutrition, the fungi help with the growth and competitiveness of the host plant by protecting it against biotic: attack by herbivores, pests and phytopathogens (Azevedo, 1998) and abiotic stresses: drought, salinity, extreme temperatures, and others (Khare, Mishra & Arora, 2018). For this reason, plants infected with endophytes are usually healthier than those free from endophytes (Waller et al., 2005). One of the main factors influencing the establishment and evolution of mutualistic interrelations between fungi and plants is the fact that endophytic fungi can produce plant metabolites. They can sometimes produce bioactive compounds analogous to their hosts (Kumar et al., 2017). In reality, it is possible that several “plant metabolites” are in fact the biosynthetic products of their endophytes (Kusari et al., 2012). According to Tan and Zou (2001), the genetic recombination between endophyte and host throughout the evolutionary time could be explain the similarity between phytochemical products from both.

#### 4. Some Aspects Affecting Endophytic Fungi Diversity

The population of endophytes in a plant species is highly variable and depends on several factors such as host genotype and environmental conditions (Tan et al., 2003). The distribution and population structure of endophytic fungi depend largely on host plant characteristics and its habitat. Arnold and Lutzoni (2007) compared endophyte communities along a broad latitudinal gradient from the Canadian arctic to the lowland tropical forest of central Panama. They observed that endophyte communities from higher latitudes, are characterized by relatively few species from many different classes of Ascomycota, whereas tropical endophyte assemblages are dominated by a small number of classes with a very large number of endophytic species, showing that the distribution of endophytic fungi varies with latitude. Hoffman and Arnold (2008) examined endophytes associated with healthy photosynthetic tissues of three closely related tree species in North Carolina (*Juniperus virginiana*; *Platycladus orientalis*) and Arizona (*Cupressus arizonica* e *Platycladus orientalis*). They found that endophytes diversity differed as a function of locality and host identity, as the diversity of endophytes from hosts in North Carolina was more than twofold greater than for hosts from Arizona, and the total diversity of endophytes collected from *Juniperus* and *Cupressus* was 1.4 times greater than that from *Platycladus*. This underscores the importance of host geography and taxonomy in the formation of the endophytic community.

Collado et al. (1999) evaluated the importance of geographical and seasonal factors in fungal communities after the collection of plant material from eight trees per site, and differences were observed in the population of endophytic fungi according to the sample season and geographic distribution of host plants. Medians of fungal species per tree were significantly different among the sites and the degree of endophytic infection, and the diversity of fungal species were significantly higher in the spring. Souza et al. (2018) evaluated the population of endophytic fungi, associated with the leaves of plant *Kalanchoe pinnata* (in rainy and dry season) and observed greater richness and diversity of endophytic fungi in rainy season compared to dry season. Jiang et al. (2013) isolated endophytic fungi from different parts of *Angelica sinensis* in four different periods and found that the colonization of endophytic fungi depends on environmental conditions, because several communities varied seasonally, being more abundant in September and October at each site.

Endophytic microorganisms may also prefer specific organs and tissues because of their adaptation to different physiological conditions in plants (Deng & Cao, 2016), e.g when Jiang et al. (2013) confirmed a greater diversity of endophytic fungi in root tissues rather than in stem and leaf tissues. González and Tello (2011) examined the composition of the endophytic fungal communities within the plant tissues of several cultivars of *Vitis vinifera* from the Madrid region and verified that fungal diversity was shown to be different according to the tissue analyzed. Results have shown that a greater percentage of fungal taxa were recovered from both woody tissues and leaves. Sieber (2007) showed that species composition of the endophyte community differs between tissue types and the age, something also demonstrated by Nascimento et al. (2015). They analyzed the community of endophytic fungi of *Calotropis procera* leaves, at different stages of maturation, and observed that the rate of endophyte colonization increased with the leaf age/development.

The methodology used to isolate endophytic fungi affects the community composition and diversity of these microorganisms. Sun et al. (2011) isolated endophytic fungi from *Acer truncatum* using two methods. Results indicated that the composition and diversity obtained differed in both isolation methods, confirming that the entire endophyte community cannot be revealed by a single technique. Gamboa et al. (2002) compared the number of fungi isolated from 400 mm<sup>2</sup> leaf pieces that were divided into increasingly small fragments and observed that cutting leaf pieces into smaller fragments significantly increased the number of fungal morphospecies recovered.

The production of endophyte metabolites is also affected by several factors, such growth and fermentation conditions and habitat of the host. Supratman et al. (2021) found that modification of the culture media enhanced the production of secondary metabolites by endophytic fungus *Clonostachys rosea* B5-2. Ariantari et al (2019) isolated *Bulgaria inquinans* from

*Viscum album*, when the fungus was fermented in solid Czapek medium and later in the same media supplemented with a mixture of MgSO<sub>4</sub>, NaNO<sub>3</sub> and NaCl salt. They identified compounds from the cultures grown in salt-supplemented Czapek media that were not detectable in cultures grown in normal Czapek media. Jadulco et al. (2002) isolated two strains of the fungus *Cladosporium herbarum*, from the marine sponge *Aplysina aerophoba*, in the Mediterranean sea and *Callyspongia aerizusa*, in Indonesia, respectively, and the same fungus produced different metabolites in their different hosts.

## 5. Fungi and Their Host Specificities

Endophytic fungi are mainly host-specific, causing little or no risk to non-target organisms or beneficial insects, such as pollinators (Carvalho et al., 2020). This specificity towards the host requires a close adaptation between the host plant and its fungal partner, suggesting a mutual influence resulting from co-evolution. In the long run, this association remains imprinted in the genetic makeup of both partners, who start to develop complementary genetic systems (Moricca & Ragazzi, 2008). Soares et al. (2017) reported that during co-evolution, endophytic fungi gradually adapted to specific microenvironments, including the uptake of some plant DNA segments into its genomes, as well as the insertion its DNA into the host genome.

The specificity of fungi for their hosts has been demonstrated in some studies. Higgins, Arnold, Miadlikowska, Sarvate and Lutzoni (2007) surveyed endophytic fungi from healthy tissues of three plant species (*Picea mariana*, *Dryas integrifolia* e *Huperzia selago*) collected in two forests in the Canada: Québec e Nunavut. They found that endophyte communities were more similar among *P. mariana* from different localities than those associated with *D. integrifolia* and *H. selago*, in the same and different locations. Among all genotypes obtained from *Picea*, 66.7% were found only in that host, 66.7% found in *Huperzia* were recovered only from that host species, and 60% from *D. integrifolia* were unique to that host. González and Tello (2011), investigated the diversity of fungal endophytes in many varieties of grapevines distributed along the Madrid regions. They observed that most taxa obtained could be considered as frequent species, suggesting that the majority of endophytic mycota of grapevine plants analyzed could be dominated by a group relatively constant species, rather than rare or occasional fungal taxa. Sun, Ding, Hyde and Guo (2012) investigated the endophytic fungi associated with *Betula platyphylla*, *Quercus liaotungensis* and *Ulmus macrocarpa* surveyed in Mount Dongling. Their results indicated that the host effect on the endophyte community was significant, showing 30.1% of variance in endophyte composition explained by host. The fungi *Disculina vulgaris*, *Melanconis stilbostoma* and *Myxocyclus polycystis* were strongly correlated with *B. platyphylla*. The fungi *Fusicoccum* sp., *Microsphaeropsis arundinis* and *Phomopsis archeri* were strongly correlated with *Q. liaotungensis*. They also reported that the fungi *M. stilbostoma* and *M. polycystis* have been found as endophytic fungi of *Betula pubescens* and *Betula pendula* in some European countries, suggesting that these two species significantly prefer *Betula* plants.

## 6. Endophyte and Host Plant Interaction

The interaction plants-endophytic fungi results in the production of metabolites by both (Kusari et al., 2014), and this interaction of plant metabolism and its endophytes can occur in five ways: (a) endophyte induces the metabolism of host, (b) host induces the metabolism of endophyte, (c) host and endophyte share parts of a specific metabolic pathway and contribute partially, (d) host can metabolize endophyte products and vice versa (e) endophyte can metabolize secondary compounds of host (Ludwig-Muller, 2015). Endophytes can not only produce bioactive substances, but also induce or promote their host plants to synthesize or accumulate more secondary metabolites (Jiang et al., 2013). These secondary metabolites obtained by endophytes, associated with the metabolites from the plant itself, can increase resistance of the plant and ensure that it can be more easily adapted to its habitat (Gomes & Luiz, 2018).

The interactions between plant and endophytes are complex, involving multi-species communications and vary from host to host and from endophyte to endophyte (Gupta et al., 2018). This interaction is preceded by a physical encounter between

a plant and a fungus, followed by several physical and chemical barriers that must be overcome to establish the association (Kusari et al., 2012). The plant then produces different types of secondary metabolites, as mechanism of resistance to pathogens that are likely harmful for the endophytic fungi. As these metabolites become obstacles to the colonization of endophytic fungi, they protect themselves by secreting enzymes to break down these secondary metabolites before they penetrate the defense systems of host plants (Jia et al., 2016). The colonization of endophytic fungi on host plants can begin with production of these hydrolytic enzymes, that facilitate colonization (Dutta et al., 2014) or with the penetration of the microorganism in the plant through stomata or wounds (Azevedo, 1998). The colonization of endophytic fungi can occur inter or intra-cellularly and involves several stages, including recognition of the host, spore germination, penetration of the epidermis and tissue multiplication (Dutta et al., 2014). Once inside the tissues of a host plant, endophytic fungi assume a quiescent state, either for the life of the host plant or until the environmental conditions are favorable (Sieber, 2007).

Most endophytes infect plants by airborne spores, in a type of transmission is termed horizontal transmission. On the other hand, some endophytes can also be transmitted vertically to the next generations of plants through seeds (Hartley & Gange, 2009). The transmission mode may moderate the endophytic-plant interactions, as studies have shown that vertically transmitted (systemic), growing inside the seeds are more likely to be mutualistic, while transmitted horizontally via spores (non-systemic), to be more antagonistic to the host (Saikkonen et al., 1998). So, the interaction fungi-plant must be considered as a flexible, whose directionality is determined by small differences in the fungal expression gene like an answer to host, or inversely by the recognition of host and response to fungus. Thus, small genetic differences in the genomes of both partners control the relationship result, positive, negative or neutral (Moricca & Ragazzi, 2008).

Different from pathogen-host interaction, that causes disease to the host, the endophyte-host interaction maintains a balanced antagonism without development of disease. The endophytes play a mutualistic role within its host, by increasing the concentration of defense metabolites potentially activated against pathogens, by excreting phytohormones and/or by increasing the general metabolic activity of plant host (Schulz et al., 1999).

The idea of a balanced antagonism means that the endophyte acts preventing the activation of the host defenses, before being disabled by the host's toxic metabolites. In this way, the endophytic can grow inside the host without causing visible manifestations of infection or disease, and the balance of antagonism between plant and host is established and this association remains apparently asymptomatic and no virulent. If the plant defense mechanisms counteract fungal virulence factors, the fungus will die, but on the other hand, if the plant succumbs to the fungus virulence, a plant pathogen relationship is established and would lead to plant disease. Many endophytes can be latent pathogens, in other words, they can be influenced by certain intrinsic or environmental conditions to express the factors that lead to pathogenicity (Pamphile et al., 2017).

Schulz et al. (2015) suggested that to grow asymptotically within their plant hosts, fungal endophytes would need to not only maintain a balanced antagonism with their plant host, but also with other bacterial and fungal communities in the host. This would explain the synthesis of antibacterial and antifungal metabolites by fungal endophytes.

The factors responsible for fungal transition from endophyte to pathogen are not fully understood. For better understanding the dynamics of endophytes, comparative studies must be undertaken to work out conditions and gene expressions, in both plants and endophytes, under which the same microbe behaves as mutualist or pathogen (Khare et al., 2018). However, the existence of endophytic microorganisms in the plant host is in most cases advantageous since the secondary metabolites produced by endophytes provide many benefits for plants (Tanvir et al., 2017). These benefits include resistance to abiotic and biotic stress, nutrient uptake, among others.



## 7. Plant Resistance to Abiotic Factors Provided by Endophytic Fungi

Endophytic fungi produce different bioactive compounds, such as alkaloids (Yadav et al., 2014; Bhardwaj et al., 2015; Xu et al., 2020), diterpenes (Bhardwaj et al., 2015; Parthasarathy et al., 2020), and flavonoids (Yadav et al., 2014; Bhardwaj et al., 2015; Mollaei et al., 2019) that increase the resistance to abiotic stress in their host plants (Jia et al., 2016). They can also modulate the abscisic acid (ABA) biosynthesis and ABA mediated signaling, phytohormone that regulates stomatal closure in plants, and thus, contribute to the plant growth enhancement under salt stress conditions (Khare et al., 2018).

Bayat et al. (2009) demonstrated that endophytic fungi *Neotyphodium coenophialum* in *Festuca arundinacea* Schreb considerably contributes to host's water stress tolerance, compared to grasses without the endophytic fungi. These results can help finding more compatible endophyte–grass combinations to breed grass cultivars more tolerant to drought stress. Ghaffari et al. (2019) analyzed the contribution made by *Piriformospora indica* colonization in barley root to the host plant's ability to tolerate drought stress. The fungal endophyte increased host biomass and its ability to overcome abiotic stresses. The evidence is that the presence of the endophyte redirects protein synthesis towards nitrogenous compounds, especially under more severe stress conditions. According to them, this may function in both biotic and abiotic stress resistance mechanisms which can enhance plant adaptation in field conditions in face face both biotic and abiotic stresses. Kham, Hussain, Al-Harrasi, Al-Rawahi and Lee (2013) and Kham et al. (2011a, 2011b) demonstrated that plants inoculated with endophytic fungi are more resistant to abiotic stresses, when compared to uninoculated plants (control). Thus, the association of endophytes with the target cultures, would make possible to grow plants in certain places where plants without association with the endophytic agent could have difficulties to developing (Fontana et al., 2021).

## 8. Plant Resistance to Biotic Factors Provided by Endophytic Fungi

After colonizing the plant and establishing itself, endophytes can induce the plant resistance to pathogens and insects (Deng & Cao, 2016), as the endophytic colonization occupies an ecological niche and leaves no room for pathogens, showing how fungal endophytes inhibit plant infection by pathogens (Dutta et al., 2014). Endophytic fungi can also inhibit plant pathogens through other mechanisms: competing for space and nutrients, parasitizing, producing secondary metabolites (such as enzymes and antibiotics) and inducing resistance in the plant by activation of its own defense system (Zabalgoceazcoa, 2008). The result of these interactions, such as antibiosis, competition, defense induction and parasitism, leads to biological control of plant diseases (Howell, 2003).

Several natural products from endophytic fungi have antimicrobial activity and are involved in protecting the host plant against phytopathogenic microorganisms (Gunatilaka, 2006). A screening of fungal isolates for biologically active secondary metabolites (antibacterial, antifungal or herbicide) showed that the proportion of endophytic isolates that produce active herbicidal substances is three times higher when compared to the proportion produced by fungi isolated in the soil, and twice as high as that the proportion produced by phytopathogenic fungi (Schulz et al., 1999).

The production of alkaloids by endophytes results in the reduction of herbivory by insects and mammals (Bush et al., 1997). Toxicoses induced in domestic herbivores by ingesting certain plants are related to endophytic microorganisms, mainly fungi. Cattle that feed on forage grasses containing endophytes may develop symptoms such as weight reduction, increased body temperature and gangrene, and even die (Azevedo, 1998). For example, the endophytic fungus *Epichloë typhina* causes "fescue toxicity", a syndrome suffered by cattle fed on *Festuca arundinacea* grass pastures (Bacon, Porter, Robbins & Luttrell, 1977). It was found that these infected plants contained several toxic alkaloids and that *Epichloë* (asexual forms = *Neotyphodium* spp.) could be beneficial to host plants, increasing their tolerance to stresses caused by biotic and abiotic factors (Schardl et al., 2004).

Metabolites produced by endophytic fungi *Phomopsis oblonga* have a repellent effect against the beetle *Physocnemum brevilineum*, disease vector in plants of the genus *Fagus* (Webber, 1981). Wilkinson et al. (2000) affirmed that alkaloids produced

by endophytic fungi are toxic or unpleasant for insects, protecting host plants from their attacks. Another example is the fungi *Colletotrichum tropicale*, that influences leaf chemistry and makes leaves less appealing to leaf-cutting ants and changed the host metabolism in a way that leaf-cutting ants prefer non-colonized plants (Estrada et al., 2013).

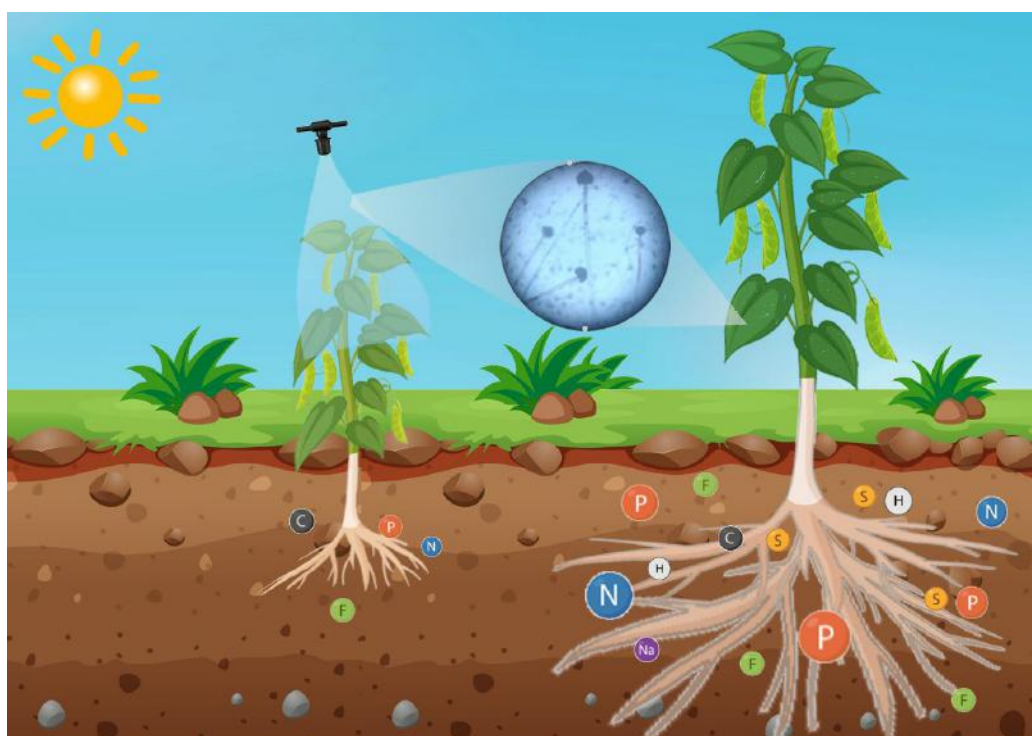
Fungi can be pathogens for insects, attacking the plant pathogen insects by different mechanisms, such as parasitism, competition for habitat and nutrients, and production of secondary bioactive metabolites (Jaber & Ownley, 2017). In a study, Ownley et al. (2008) demonstrated that application of conidia of the entomopathogenic fungus *Beauveria bassiana* on seed cotton and tomato results in endophytic colonization and protection against plant pathogenic *Rhizoctonia solani* and *Pythium myriotylum*. With these evidences, endophytes have been recognized for their ability to protect their hosts from pathogens and can be used as biocontrol agents (Fontana et al., 2021).

## 9. Nutrient uptake and growth promotion mediated by endophytic fungi

Endophytic microorganisms facilitate nutrient uptake for plant growth through modification of root morphology, alteration of nitrogen accumulation and metabolism (Figure 3). They also help to use water efficiently through osmotic adjustment and stomatal regulation (Lata et al., 2018) and can also increase the host fitness and competitive skills, increasing the rate of germination and growth or improving the absorption of nutritional elements by the host (Aly et al., 2011). Yang et al., (2021) evaluated the role of endophytic fungus *Piriformospora indica* in plant growth and nutrient acquisition especially phosphorus (P), into trifoliolate orange (*Poncirus trifoliata*). Compared with the non-inoculated treatment, *P.indica* inoculation significantly increased root N (Nitrogenous), P (Phosphorus), K (Potassium). Inoculation of this fungus also improved stem diameter, plant height, leaf number, stem, and root biomass.

The ability to stimulate plant growth can also be attributed to the production of phytohormones (Luz, Silva, Silveira & Cavalcante, 2006). Endophytic fungi are directly related to the production of phytohormones in plants, mainly in the production of auxins and gibberellins that provide vital functions for plants. Some endophytic fungi can increase the fitness and growth of host plants, increasing hormones such as indole-3-acetic acid, indole-3-acetonitrile and cytokinins (Jia et al., 2016). White Junior et al. (2002) related those fungi producing growth hormone for plants modify the plant physiology and structure, to better extract nutrients for themselves. This ability to stimulate plant growth is extremely important and can be explored in modern agricultural practices, increasing the production and contributing to sustainability (Luz et al., 2006).

**Figure 3.** Nutrient uptake mediated by endophytic fungi.



Source: Authors (2022).

## 10. Prospecting and Biotechnological Potential of Endophytic Fungi

Some features from plant communities have been chosen to optimize the selection of advantageous endophytes, like plants from peculiar environments, plants with unusual biology and survival strategies; plants with an ethnobotanical history, that is, those traditionally used as a medicine; endemic plants, with unusual longevities or located in ancestral environments; plants from environments with high diversity (Strobel & Daisy 2003), growing in hot spots and that are in threatened categories. Habitats that have not yet been explored may also contain new isolates of fungal endophytes of pharmaceutical interest (Gupta et al., 2018).

Endophytic fungi are frequently isolated from medicinal plants to obtain bioactive compounds for therapeutic activities (Rana et al., 2020). For Gomes and Luiz (2018), the use of medicinal plants for the isolation of endophytes is one of the most viable options, as many compounds are already obtained from plants.

Ecosystems with higher biodiversity are also those with higher quantity of endophytes, implying higher chemical diversity (Ferrara, 2006), which is totally associated with biological diversity due to the constant chemical innovation existing in ecosystems (Strobel & Daisy, 2003). Tropical, semi-arid and humid forests are rich in endophytes due to their enormous diversity of plants (Oita et al., 2021). That is why many mycologists agree that in tropical forests the fungal diversity is maxima (Arnold et al., 2000). According to Redell and Gordon (2000), it's likely that tropical forests are a source of new molecular structures and biologically active compounds. Jia et al. (2016) showed that some species of endophytic fungi were found only in extreme conditions, as observed in *Cactus* sp. from savanna deserts and with *Saussurea involucreta*, *Sinopodophyllum hexandrum* and *Pedicularis* sp., in high altitude. Thus, there is an excellent possibility to explore new biomolecules among countless plants in various niches and ecosystems (Gupta et al., 2018).

Many endophytes are able to produce the same substances as the host plant, given that plants and microorganisms have a similar primary metabolism (Gomes & Luiz, 2018). This makes possible obtaining bioactive products directly from microorganisms without the host plant (Milke et al., 2018). The production of biologically active substances by endophytic fungi

is related to their ability to survive and colonize a distinct microenvironment, subject to constant metabolic and environmental interactions, which are often hostile (Ferrara, 2006). So, if endophytes can produce the same bioactive compounds such as their host plants, it's possible to reduce the harvest of slow-growing plants or rare plants, preserving biodiversity (Strobel & Daisy 2003). Thereby, these compounds would be obtained from fermentative processes, in contrast to traditional extractive processes, with advantages related to regularity and uniformity of production and environmental gains (Ferrara, 2006).

Endophytic fungi are advantageous because they have short generation time, high biomass production due to high growth rates and good handling features in bioreactors (Ludwig-Müller, 2015). According to Gomes and Luiz (2018), this method of obtaining such products is quite advantageous, since many of them are already known and can be obtained from isolated endophytic fungi. Two important aspects must be considered: the biotechnological potential of endophytic fungi, and the possibility of obtaining new substances that have never been isolated from plant tissues.

In addition, it is recognized that a microbial source of an evaluated product can be easier and more economical in terms of its production, effectively reducing its market price (Strobel & Daisy 2003). This could lead to a cost-effective, sustainable, continuous, and reproducible yield, compliant to commercial scale-up. This production process would then be independent of the variable quantities produced by plants, that are influenced by environmental conditions (Kusari et al., 2012). For example, the Taxol was the first anticancer drug that reached a world market of a billion dollar (Strobel, 2002), which is found in small quantities (0.001% to 0.01% of the dry bark weight) in *Taxus* sp., slow growing trees found in the Pacific regions (Kathiravan et al., 2013). From this plant species, the endophytic fungus *Taxomyces andreanae* was isolated, capable of producing Taxol were isolated, opening the possibility of obtaining it through fermentation, with lower costs and greater quantity (Stierle, Strobel & Stierle, 1993). This result shows that substances with known therapeutic activities can be obtained from endophytic fungi in a sustainable way, highlighting the need for further research on these microorganisms (Gomes & Luis, 2018).

The ability of endophytic fungi to produce biocompounds represent an important resource for biotechnological advancement and sustainable economic development (Oliveira et al., 2006). They are efficient producers of several bioactive compounds (Gunatilaka, 2006; Kumar et al., 2017). These bioactive compounds have biotechnological proprieties, such as, antimicrobial, antidiabetic, antiviral, anti-inflammatory, anticancer, antifungal, antiparasitic, and immunosuppressive (Table 1). Endophytic fungi isolation and selection have applications in several segments such as health, agriculture, industry and the environment protection (Oliveira et al., 2006).

**Table 1.** Some examples of endophytic fungi and their host plant, local, pharmacologic property, produced bioactive compounds and authors.

Fungus Species	Host plant	Local	Property	Bioactive compounds	Authors
<i>Alternaria alternata</i> , <i>Drechslera dematiodea</i> , <i>Phomopsis archeri</i> , <i>Mycelia Sterilia</i>	<i>Lippia sidoides</i>	Pernambuco, Brazil	Antimicrobial activity	Not identified	Siqueira, Conti, Araújo & Souza-Motta 2011
<i>Chaetomium</i> sp., <i>Aspergillus</i> sp., <i>Aspergillus peyronelii</i> , <i>Aspergillus niger</i>	<i>Eugenia jambolana</i>	Haryana, India	Antioxidant activity	Alkaloids, phenols, flavonoids, saponins and terpenes	Yadav et al., 2014
<i>Alternaria alternate</i> , <i>Aspergillus flavus</i> , <i>A. terreus</i> , <i>A. niger</i> , <i>Cladosporium</i> sp., <i>Fusarium</i> sp., <i>Penicillium</i> sp., <i>Sterile mycelium</i> , <i>Meyerozyma</i> sp.	<i>Suaeda maritima</i> and <i>Suaeda monoica</i>	Vellar Estuary, India	Antimicrobial and antifungal activity	Not identified	Kalyanasundaram, Nagamuthu, & Muthukumaraswamy, 2015
<i>Aspergillus</i> sp.	<i>Trigonella foenum-graecum</i>	Khartoum, Sudan	Antioxidant activity	Phenolic compounds	Khiralla et al., 2015
<i>Aspergillus niger</i> , <i>Corynespora cassicola</i> , <i>Glomerella acutata</i>	<i>Hibiscus subdarifa</i> L.	Assam, India	Antimicrobial activity	Not identified	Nath and Joshi, 2015
<i>Alternaria alternate</i> , <i>Thielaviopsis Basicola</i> , <i>Geotrichium Albida</i> , <i>Penicillium Frequentans</i>	<i>Pinus roxburghii</i>	Uttarakhan, India	Antimicrobial activity	Alkaloids, flavonoids phenols, tannins, terpenoids and saponins	Bhardwaj et al., 2015
<i>Penicillium chrysogenum</i> , <i>Sterile hyphae</i> , <i>Alternaria alternata</i>	<i>Asclepias sinaica</i>	South Sinai, Egypt	Antimicrobial activity	Not identified	Fouda et al, 2015
<i>Curvularia pallescens</i>	<i>Calotropis procera</i>	Pernambuco, Brazil	Antimicrobial activity	Not identified	Nascimento et al., 2015
<i>Trichoderma longibrachiatum</i>	<i>Cereus jamacaru</i>	Pernambuco, Brazil	Antimicrobial activity	Not identified	Pires et al., 2015
<i>Colletotrichum</i> sp., <i>Aspergillus</i> sp., <i>Pestalotiopsis</i> sp., <i>Scedosporium</i> sp., <i>Phomopsis</i> sp., <i>Paecilomyces</i> sp., <i>Xylaria</i> sp., <i>Exserohilum rostratum</i>	<i>Bauhinia guianensis</i>	Amazônia, Brazil	Antimicrobial activity	Monocerin	Pinheiro et al., 2017
<i>Aspergillus</i> sp., <i>A. niger</i> , <i>Penicillium expansum</i>	<i>Pelargonium sidoides</i>	Pretoria, Hercules; Cape Town, Klein Karoo; Port Elizabeth, Uitenhage; Bloemfontein, Danhof; South Africa	Antimicrobial activity	Not identified	Manganyi et al., 2018
<i>Fusarium tricinctum</i>	<i>Lithospermum officinale</i> L.	Tabriz, Iran	Antioxidant activity	Shikonin	Mollaei et al., 2019

<i>Alternaria</i> sp., <i>Chaetosphaeronema achilleae</i> , <i>Fusarium tricinctum</i> , <i>Mucor hiemalis</i> , <i>Trichoderma harzianum</i>	<i>Lithospermum officinale</i> L.	Tabriz, Iran	Antimicrobial and antioxidant activity	Polyphenols and flavonoids	Mollaei et al., 2019
<i>Aspergillus cejpaii</i>	<i>Nelumbo nucifera</i>	Pathumthani, Thailand	Antimicrobial activity	5- (1H-Indol-3-il) -4,5-dihydro- [1,2,4] triazin-3-ilamina (C <sub>11</sub> H <sub>11</sub> N <sub>5</sub> )	Techaoei, Jirayuthcharoenku, Jarmkom, Dumrongphuttidecha & Khobjai, 2020
<i>Diaporthe phaseolorum</i> , <i>Penicillium</i> sp., <i>Periconia igniari</i> , <i>Colletotrichum</i> sp	<i>Stephania dielsiana</i>	Laibin, Guangxi, China	Antimicrobial activity	Not identified	Wu et al., 2020
<i>Penicillium chrysogenum</i>	<i>Chaetomorpha antennina</i>	Kovalam, Chennai, South India	Antimicrobial and anticancer activity	Terpenoids, steroids, phenolics, flavones, anthraquinone and cinnamic acid	Parthasarathy et al., 2020
<i>Aspergillus fumigatus</i>	<i>Rhizophora mucronata</i>	Dong Zhai Gang- Hainan Island, China	Immunosuppressive activity	Alkaloids and polyketides	Xu et al., 2020
<i>Penicillium decumbens</i>	<i>Sonneratia</i> sp.	Morib, Malaysia	Anticancer activity	Polyphenolic	Lim et al., 2021
<i>Trichoderma longibrachiatum</i>	<i>Juniperus lutchuensis</i> Koidz	Alpine Sanctuary, Sikkim, Himalayas	Antifungal activity	Hydrocarbons, alcohols, ketones, aldehydes, esters, acids, ethers and different classes of terpenes	Rajani, Rajasekaran, Vasanthakumari, Olsson & Ravikanth, 2021

Source: Authors.

These applications have been demonstrated previously, e.g., when Farhat et al. (2019) isolated *Cephalosporium acremonium* and *Fusarium solani* from healthy plants, and these fungi have showed strong activity against common laboratory bacteria (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Bacillus subtilis* and *Escherichia coli*). They identified twenty-one different volatile compounds of *Cephalosporium*, of which eleven are new compounds from this source. Elango et al. (2020) isolated and investigated endophytic fungi and its metabolites as a biocontrol agent pesticide-resistant insect pest, isolating the fungus *Aspergillus sojae* from the plant *Plectranthus amboinicus*. The produced metabolites demonstrated potent activities against cotton leaf worm *Spodoptera litura*. Cruzzi, Link, Vilani and Onofre (2011) evaluated the capacity of species of endophytic fungi isolated from *Baccharis dracunculifolia* to produce extracellular enzymes. Endophytic fungi showed lipolytic, amylolytic and proteolytic activity. The fungi *Cylindrocladium* sp. and *Penicillium* sp., showed higher production of lipases and enzyme production proteolytic, respectively. Pietro-Souza et al. (2020) evaluated the capacity for mercury bioremediation in vitro mediated by endophytic fungi. The fungi *Aspergillus* sp., *Curvularia geniculata*, *Lindgomycetaceae* and *Westerdykella* sp. removed up to 100% of mercury from the culture medium. Based on this studies, endophyte-assisted phytoremediation is a promising technology for the remediation of contaminated soils.

Endophytic fungi represent an inexhaustible source of important metabolites with a wide biological activity, and the discovery that these endophytic fungal can produce plant-associated molecules raises the prospects of exploiting such fungi as an alternative source of valuable compounds. According to Gakuubi et al. (2021), this may offer the possibilities for production of other useful bioactive compounds that are produced in unsustainable quantities in plants.

## 11. Final Considerations

The endophytic fungi are able to produce bioactive substances similar to their hosts and could be widely explored for the sustainable development of bioactive substances more effective and more ecological friendly. Also, they have a biotechnological potential to produce large amounts of biomass, due to their high productivity in fermentation processes. Therefore, endophytic fungi could be used in different fields like industry, health, agriculture and the environment.

The prospection of endophytic in extreme environment could result in discovery of new bioactive compounds with surprising biotechnology potential. So, the development of new research frontiers in this issue is indispensable for the sustainable exploitation of the great benefits that these microorganisms could provide.

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## Conflict of Interest

No conflict of interest declared.

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