

Review

# Patents on Endophytic Fungi for Agriculture and Bioand Phytoremediation Applications

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**Abstract:** Plant endophytic fungi spend all or part of their lives inside host tissues without causing disease symptoms. They can colonize the plant to protect against predators, pathogens and abiotic stresses generated by drought, salinity, high concentrations of heavy metals, UV radiation and temperature fluctuations. They can also promote plant growth through the biosynthesis of phytohormones and nutrient acquisition. In recent years, the study of endophytic fungi for biological control of plant diseases and pests has been intensified to try to reduce the ecological and public health impacts due the use of chemicals and the emergence of fungicide resistance. In this review, we examine 185 patents related to endophytic fungi (from January 1988 to December 2019) and discuss their applicability for abiotic stress tolerance and growth promotion of plants, as agents for biocontrol of herbivores and plant pathogens and bio- and phytoremediation applications.

Keywords: endophytic fungi; patent; abiotic stress tolerance; biocontrol; bioremediation; phytoremediation

## 1. Introduction

An endophytic fungus is any organism inhabiting plant organs that, at certain point in its lifetime, can colonize tissues without causing apparent harm [1]. Endophytic fungi have been a proven source of secondary metabolites with potential uses as anticancer, antibiotics, antivirals, anti-inflammatories, antioxidants, neuroprotective agents, insecticides and antifungals, and have multiple applications in biotechnological developments in pharmaceutical, agriculture, cosmetic, food industry and environmental processes [2]. In the last decades, studies of endophytic fungi have resulted in a number of patents linked to the production of biologically active secondary metabolites and in biotransformation processes [3].

Moreover, interaction between fungi and their hosts drives changes in the host metabolism, altering the response to environmental stress and predator attack. Additionally, this interaction leads to the production of secondary metabolites by both the fungi and the host, which further enhance the capability to respond to the environment [4–7].

The use of endophytic fungi for environmental applications such as growth promotion, relief of abiotic stress, biocontrol of pest and plant pathogens and bio/phytoremediation has gained important attention in recent years due to the concern about global climate change and contamination in soils and natural sources that increases stress in crops, limiting and reducing the production [8–11]. Furthermore, basic and applied research has been conducted to develop processes, methodologies and technologies that resulted in a considerable number of patents with new proposals to overcome some of these

challenges. Therefore, in this review, we cover patents on endophytic fungi applications related to (a) abiotic stress tolerance and growth promotion of plants; (b) biocontrol of herbivores and plant pathogens; (c) bio- or phytoremediation.

The highlighted topics in each of the patents, cited here, could inspire other researchers to take their investigation to the next level and contribute to overcome, in a more efficient way, some of the principal challenges of humanity today.

#### 2. Materials and Methods

The present review was conducted mainly through searches in the Scifinder<sup>®</sup> and Google Patents databases. The search was initially conducted in Scifinder<sup>®</sup> using the terms "endophytic fungi" and "patents" covering the period from 1988 to 2019. 12,315 references were found. After removing duplicates (those describing the same patent/endophyte), we selected those related to the aim of this review, resulting in 185 documents. The patents covered in this study are described in five tables below.

#### 3. Results

The description and analysis of patents was divided, considering the main objective of each one, into four sections; those associated to: (Section 3.1) abiotic stress tolerance and growth promotion of plants; (Section 3.2) biocontrol of herbivores and plant pathogens, and (Section 3.3) bio- and phytoremediation applications; (Section 3.4) patents where the endophyte has multiple applications. The information in tables describe the fungi, the host plant where they were isolated, and the main application of the patent. All endophytes, listed in the tables, have beneficial effects on plants, even though some of them could be considered as pathogens in previous reports.

#### 3.1. Abiotic Stress Tolerance and Growth Promotion of Plants

The principal abiotic stress factors in plants include drought, salinity, high heavy metal concentrations, UV radiation and temperature fluctuations [12]. Abiotic stress affects the cellular pathways of plants, resulting in negative changes to their physiology and morphology [12]. Endophytic fungi have been shown to help their host plant to overcome abiotic stress and promote plant growth through the biosynthesis of phytohormones (indole-3-acetic-acid, gibberellins, cytokinins, ethylene, acetoin, 2, 3-butanediol) and nutrient absorption and uptake [12–14].

Plant endophytic fungi have been patented based on their ability to improve the following in plants: (a) root and seed development; (b) nutrient uptake or absorption; (c) photosynthesis promotion; (d) growth of biomass; (e) increase chlorophyll content; and (f) abiotic stress resistance. Numerous genera have been used for such purposes, including *Acremonium, Alternaria, Aspergillus, Chaetomium, Fusarium, Penicillium,* and others (Tables 1 and 2). A specific area of application for which endophytic fungi have been widely used is in the growth promotion of medicinal plants; this includes such species as *Acanthopanax senticosus* [15], *Salvia miltiorrhiza* [16], *Rumex gmelinii* Turcz [17], *Acacia confusa* [18], *Coix lacryma-jobi* [19], *Cynanchum acuminata* [20], *Huperzia serrata* [21], *Anoectochilus roxburghii* [22], *Arnebia* sp. [23], *Saussurea* sp. [24], *Rhizoma bletillae* [25], *Salvia miltiorrhiza* [26,27], and *Eucalyptus* sp. [28–30]. Additionally, some endophytic fungi have been patented due to their capability to promote the growth of crop plants such as corn, tomato, soybean, rice, wheat, potato, and barley [31–37] as well as other useful plants such as *Casuarina equisetifolia* [38–41], fir [42–45], *Aleurites montana* [46–51], *Dendrobium* sp. [52–54], tobacco [55–58], *Schima superba* [59–61], *Bletilla striata* [62,63], and *Paphiopedilum* sp. [64].

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN104762216A	Arthrinium sp.	Salicornia bigelovii	Plant anti-salt stress.	[65]
WO2004000017A2	<i>Curvularia</i> sp.	Dichanthelium languinosum	Conferring stress tolerance to inoculated plants (monocots and dicots).	[66]
WO2009012480A2	Fusarium sp.	Leymus mollis	Conferring stress tolerance to inoculated plants (monocots and dicots).	[67]
CN105296359A	Lecanicillium sp.	Tobacco	Reducing the absorption of heavy metals in tobacco.	[58]
CN101314760A	Neotyphodium chisosum	Festuca arundinacea	Improving the stress tolerance to drought and diseases.	[68]
CN104004665A	Papulospora sp.	Fir roots	Relieving phosphorus stress in fir.	[43]
CN105002099A	Paraconiothyrium cyclothyrioides	Myricaria root	Reducing heavy metal pollution in plants.	[69]
CN101974437A	Penicillium sp.	Eucalyptus	Relieving aluminum toxicity in <i>Eucalyptus</i> .	[30]
CN102002463A	Penicillium sp.	<i>Eucalyptus</i> roots, stems, and leaves	Improving the cold resistance of <i>Eucalyptus</i> .	[28]
CN103865806A	Phialophora oryzae	Not disclosed	Reducing the absorption of heavy metals in tobacco	[57]
CN107926549A	Piriformospora indica	Not disclosed	Improving the resistance of plants to the herbicide bensulfuron-methyl.	[70]
CN103834578A	Pyrenochaeta sp.	Tobacco	Promoting plant growth and reducing the heavy metal content in tobacco.	[55]
CN105316240A	Rhizopycnis sp.	Tobacco	Reducing the absorption of heavy metals in tobacco.	[56]
US20150366217A1	Group of several fungi <sup>2</sup>	Roots of Triticum turgidum L.	Improving seed vitality, biotic and abiotic stress resistance, and plant health and yield under both stressed and unstressed environmental conditions.	[71]

**Table 1.** Endophytic fungi applied to enhance the abiotic stress tolerance of plants.

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN105907648A	Acremonium sp.	Panax notoginseng	Root and seed development of different plants including <i>Radix</i> Ginseng, Oryza sativa L., Semen Maydis, Semen Tritici aestivi, Rhizoma Paridis, Rhizoma Solani tuberosi, etc.	[34]
CN108513990A	Alternaria alternata	Acanthopanax senticosus	Seedling-stage growth of A. senticosus.	[15]
CN104911108A	Alternaria sp.	<i>Hippophae</i> sp.	Drought resistance on turf grass.	[72]
CN104818218A	Alternaria sp.	Aleurites montana	Phosphorus uptake in A. montana.	[47]
CN102086439A	Alternaria tenuissima	Panax ginseng	Growth of corn plant.	[31]
CN103173362A	Aspergillus sp.	Casuarina sp. rhizosphere	Photosynthesis in <i>C. equisetifolia</i> .	[38]
CN103173361A	Aspergillus sp.	Casuarina sp. rhizosphere	Nutrient element absorption in Casuarina.	[39]
CN103173364A	Aspergillus sp.	Casuarina sp. rhizosphere	Casuarina biomass growth.	[41]
CN110343619A	Botryosphaeria sp.	Root of Schima superba	Schima superba seedling height and ground diameter under a low-phosphorus environment.	[61]
CN109456902A	Byssochlamys spectabilis	Rhizoma bletillae	The growth of <i>R. bletillae</i> .	[25]
CN106929436A	Cercosporella Sacc.	Rumex gmelini Turcz	Growth in <i>R. gmelinii</i> Turcz.	[17]
CN106801014A	Chaetomium globosum	Salvia miltiorrhiza	Radix root biomass, plant height, crown diameter in S. miltiorrhiza.	[73]
CN109628322A	Chaetomium nigricolor	Bletilla striata	The growth of <i>B. striata</i> .	[62]
CN110438011A	Cladosporium tenuissimum	Salvia miltiorrhiza	Synthesis of effective components (tanshinone and salvianolic acid substances) in the root system of <i>Salvia miltiorrhiza</i> .	[26]
CN104630073A	<i>Claviceps</i> sp.	Dendrobium officinale	Growth and yield in <i>D. officinale</i> .	[74]
CN104004664A	Colletotrichum sp.	Abies sp. roots	Photosynthesis of cedar.	[45]
CN106085872A	Colletotrichum sp./Fusarium sp.	Acacia sp.	Nutrient absorption in A. confusa.	[18]
CN104805019A	Coniothyrium sp.	Aleurites sp.	Nutrient element absorption in wood oil tree.	[75]
CN104004666A	Cylindrocarpon sp.	fir plant	Growth of fir.	[42]
CN110250210A	Darksidea sp.	<i>Stipa capillata</i> root	Rooting and growth of maize.	[36]

Table 2. Endophytic fungi applied for the growth promotion of plants	nts.
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Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN109504611A	Diaporthe spectabilis	Bletilla striata	Growth of <i>B. striata</i> .	[63]
CN103733829A	Emericella foeniculicola	Salvia miltiorrhizae	Growth of S. miltiorrhizae.	[76]
CN105624047A	Epichloë bromicola	Coix lacryma-jobi	Growth of <i>Coix lacryma-jobi</i> , <i>Arabidopsis thaliana</i> and other graminaceous plants.	[19]
CN105861334A	Filobasidium sp.	Acacia sp.	Taiwan Acacia biomass.	[77]
CN105861335A	Filobasidium sp.	Acacia sp.	Nutrient element absorption in Taiwan <i>Acacia</i> in a low-phosphorous environment.	[78]
CN106085873A	Filobasidium sp./Penicillium sp.	Acacia sp.	Phosphorous uptake in <i>A. confusa</i> under a low-phosphorus environment.	[79]
CN107432135A	Fusarium redolens	Not disclosed	Germination of Cynanchum acuminata seeds.	[20]
CN103173360A	<i>Fusarium</i> sp.	Casuarina equisetifolia	Chlorophyll content of C. equisetifolia.	[80]
CN110257259A	<i>Fusarium</i> sp.	Schima superba stems	Photosynthesis of Schima superba.	[59]
CN103114044A	Heterodera oryzae	rice	Plant growth regulation and/or plant pathogenicity.	[81]
CN103798293A	<i>Hypha</i> sp.	Salvia miltiorrhiza	The growth and improvement of <i>S. miltiorrhiza</i> hairy root tanshinone content.	[82]
CN1961631A	<i>Mycocentrospora</i> sp./ <i>Leptodontidium</i> sp.	Saussurea involucrata	Saussurea sp. growth.	[24]
CN104593274A	Nectria sp.	Dendrobium officinale	Yield in <i>Dendrobium</i> artificial planting.	[83]
US20130104263A1	Neotyphodium sp.	perennial ryegrass	Beneficial properties (phenotype) for plant.	[84]
CN104004667A	Paecilomyces sp.	Not disclosed	Phosphorus absorption in fir.	[44]
CN106010984A	Penicillium sp.	Acacia confusa	Plant biomass growth of Taiwan <i>Acacia</i> plant under low-phosphorus environment.	[85]
CN101974438A	Penicillium sp.	Eucalyptus	Phosphorus absorption in <i>Eucalyptus</i> .	[29]
CN104818219A	Penicillium sp.	Aleurites montana	Root growth of <i>A. montana</i> in a low-phosphorous environment.	[51]

## Table 2. Cont.

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN104789481A	Penicillium sp.	Aleurites montana	Growth and photosynthesis enhancement of <i>A. montana</i> in a low-phosphorus environment.	[48]
CN104762219A	Penicillium sp.	Aleurites montana	Biomass growth of <i>A. montana</i> in a low-phosphorus environment.	[49]
CN110257258A	Penicillium sp.	Schima superba leaves	Phosphorus absorption of Schima superba.	[60]
WO2016210238A1	Penicillium sp.	Not disclosed	Cultivation of agricultural plants, such as soybean and maize.	[33]
CN104818217A	Pestalotia sp.	Not disclosed	Biomass growth of A. montana.	[50]
CN105886405A	Pestalotiopsis sp.	Dendrobium officinale	Growth of <i>D. officinale</i> and change in metabolic components.	[54]
CN107988087A	Pezicula ericae	wild blueberry root	Growth effects.	[86]
CN109706084A	Phoma herbarum	Salvia miltiorrhiza	Growth of Salvia miltiorrhiza and synthesis of tanshinone compounds.	[27]
CN104593273A	Phyllachora sp.	Dendrobium officinale	Dendrobium yield.	[87]
CN103173363A	Phyllosticta sp.	Casuarina sp.	Photosynthesis of <i>C. equisetifolia</i> .	[40]
ES2500790A1	Pochonia chlamydosporia	Not disclosed	Flowering and fruiting and increased yield in crops such as tomatoes.	[32]
WO2016038234A1	Pochonia chlamydosporia	Meloidogyne spp.	Culture yield and reduction in flowering and fructification times.	[88]
CN105039172A	Pythium sp.	Huperzia serrata	Improved transplant survival rate of <i>H. serrate</i> .	[21]
CN108041078A	Rhizopycnis sp.	tobacco	Rice growth.	[89]
WO2019113255A1	Serendipita vermifera ssp. bescii	Australian orchid	Enhancement of plant performance in combination with phosphite as a phosphorous source.	[90]
CN105420119A	Schizophyllum commune	Ginseng	Host tissue culture hairy root biomass and ingredients of ginseng saponins.	[91]
CN104774771A	Thermomyces sp.	Not disclosed	Photosynthesis of A. montana under a low-phosphorus environment.	[46]
CN107046965A	Trichoderma sp.	Anoectochilus formosanus	Seedling adaptation cultivation.	[92]

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN104745482A	Trichoderma sp.	Arnebia euchroma	Growth of <i>Arnebia</i> hairy roots and improved shikonin component content in hairy roots.	[23]
CN105969672A	Trichoderma sp. Fusarium sp.	Acacia sp.	Increase in the height and ground diameter of <i>A. confusa</i> seedlings.	[93]
CN110408551A	Tulasnella calospora	Roots of <i>Paphiopedilum</i>	Growth of aseptic seedlings of <i>Paphiopedilum</i> .	[64]
CN102876584A	Xylaria striata	Oryza meyeriana	Plant growth.	[94]
CN107460133A	Zasmidium sp.	mangrove	Growth and development of D. officinale.	[95]
WO2016179047A1	Group of fungi	Not disclosed	Agronomic traits in plants.	[96]
CZ306950B6	Group of fungi	Miscanthus sp.	Growth, especially of graminaceous and Miscanthus plants.	[97]
WO2017134664A1	Acremonium sclerotigenum/ Sarocladium implicatum	Set of grass relatives of wheat	Nutrient uptake.	[98]
US20150373993A1	Group of several <sup>2</sup> fungi	A diverse type of wild relatives or ancestral landraces of maize, wheat, rice, and other seeds	Agronomic traits.	[99]
WO2018102733A1	Group of several <sup>2</sup> fungi	Agricultural plants	Modulation of the nutritional quality traits in seeds	[100]

Table 2. Cont.

#### 3.2. Biocontrol of Herbivores and Plant Pathogens

Crop plant diseases represent a major threat in agriculture [101]. The number of chemicals that can be effectively used to control pathogens has been reduced due to the emergence of fungicide resistance along with an increased awareness of the negative associated ecological and public health impacts [101]. Due to these problems, study of the biological control of plant diseases with endophytes has intensified in recent years [101]. Endophytes have been shown to protect their hosts against diseases, reducing infection levels and inhibiting the growth of pathogens [102,103]. The proposed mechanisms used by endophytes are the production of antimicrobial and structural compounds, niche competition, and the induction of plant immunity [104].

Several patents describe the biocontrol of herbivores and plant pathogens using endophytic fungi (Table 3). Species of the genus Acremonium have been described to control Verticilium wilt [105]; Argentine stem weevil (*Listronotus bonariensis*) [106]; plant diseases caused by banana root nematode and different pathogenic microbes such as Bipolaris oryzae, Colletotrichum falcatum, Colletotrichum gloeosporioides, Corynespora cassiicola, Corynespora sp., Drechslera sp., Fusarium oxysporum, Gloeosporium *musarum*, and *Magnaporthe grisea* [107]; and to prevent fescue toxicosis [108]. Species of *Alternaria* can control the growth of different pathogens such as Rhizoctonia solani, Fusarium oxysporum, Botrytis cinerea, Phytophthora capsici, Pseudomonas aeruginosa, Proteus hauseri, and Plasmopara viticola [109–115]. Members of the genus Aspergillus have been applied to limit the growth of nematodes in soil [116]; the plant pathogenic fungi Sclerotinia sclerotiorum, Rhizoctonia solani, and Thanatephorus cucumeris [52,117,118]; as well as grass fungi [119]. Several strains of the genus Chaetomium have been reported to enhance plant disease resistance in Anoectochilus roxburghii cultivation [16], to control different plant pathogenic fungi [120–122], to inhibit *Erwinia* causing soft rot and *Ralstonia solanacearum* causing bacterial wilt [123], to inhibit anthracnose apple pathogens [124], in the preparation of an anti-plant pathogen fermentation liquid broth [125], and in the production of chaetoglobosin A with antagonistic activity against Exserohilum turcicum, Coniothyrium diplodiella, and Rhizopus stolonifer [126]. Species of Fusarium can prevent and treat black spot and fungal diseases in Panax notoginseng [127,128], control five plant pathogenic fungi (Fusarium oxysporum, Cytospora mandshurica, Colletotrichum gloeosporioides, Venturia pyrina, and Fusarium graminearum) [129], and control rice blast disease [130,131] and bacterial wilt of ginger [132]. Species of *Neotyphodium* can decrease the mildewing rate of *Elymus sibiricus* seeds at the germination stage [133] and improve fungicide and pest resistance in plants [134,135]. Species of *Penicillium* can restrain the effects of *Panax notoginseng* anthracnose, root rot [136–138], and Alternaria panax [139]; control different harmful pathogenic fungi [140,141] and litchi downy blight [142]; and prevent plant diseases such as *Sclerotinia* rot of colza and tobacco blackleg [53]. Species of Rhexocercosporidium can control the fungal pathogens Colletotrichum gloeosporioides, Fusarium solani, and Alternaria panax Whetzel on Panax notoginseng [143–145].

Endophytic fungi of different genera such as *Beauveria*, *Cladosporium*, *Metarhizium*, *Muscodor*, *Trichoderma*, and others have also been described in patents to control pests or different plant diseases (Table 3).

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN103897992A	Acremonium alternatum	cotton	Verticillium wilt.	[105]
US93951A0	Acremonium coenophialum	Not disclosed	Fescue toxicosis.	[108]
AU639084B2	Acremonium lolii	French perennial ryegrass ecotype	Argentine stem weevil ( <i>Listronotus bonariensis</i> ) by production of compound peramine.	[106]
CN101235355A	Acremonium strictum	Brachiaria brizantha	Banana root-knot nematode and different pathogenic microbes.	[107]
WO2012174585A1	Acremonium sp.	Brachiaria/Urochloa	Fungal plant diseases.	[146]
CN108192832A	Acrocalymma sp.	Sinomenium acutum	Plant diseases caused by pathogenic bacteria.	[147]
CN108085259A	Arcopilus aureus	Dendrobium sp.	The plant pathogenic fungus Botrytis cinerea.	[148]
CN102204570A	Alternaria alternata	Cinnamomum camphora	Rhizoctonia solani, Fusarium oxysporum, and Botrytis cinerea.	[111]
CN102191184A	Alternaria alternata	Cinnamomum camphora	Plant pathogenic fungi such as <i>Rhizoctonia solani</i> , <i>Fusarium oxysporum</i> , and <i>Botrytis cinerea</i> .	[110]
CN110373331A	Alternaria alternata	Huperzia serrata	Gray mold of crops.	[115]
ES2696982A1	Alternaria alternata and Fusarium acuminatum	Artemisia thuscula and Austrian Artemisia	Plant pathogenic fungi with the production of antifungal compounds.	[114]
CN103232942A	Alternaria sp.	<i>Spiraea</i> sp.	The plant pathogenic fungus Phytophthora capsici.	[112]
CN106520572A	Alternaria mali	Toona sinensis	The pathogens Pseudomonas aeruginosa or Proteus hauseri.	[113]
WO2008007251A2	Alternaria alternata	Not disclosed	Plasmopara viticola.	[109]
CN108441426A	Aspergillus niger	Aquatic plant	Plant parasitic nematodes in soil.	[116]
CN104560735A	Aspergillus oryzae	Tephrosia purpurea	Plant pathogenic fungi such as <i>Sclerotinia</i> rot of colza and tobacco black shank disease.	[52]
CN102191185A	Aspergillus restrictus	Allium sativum	Plant pathogenic fungi such as <i>Rhizoctonia solani</i> and <i>Thanatephorus cucumeris.</i>	[117]
CN109504610A	Aspergillus sp.	Epiphyte	The pathogenic fungus rhizoctonia solani.	[118]
CN108342328A	Aspergillus versicolor	seaweed	Grass fungi.	[119]

**Table 3.** Endophytic fungi applied as biocontrol agents of herbivores and plant pathogens.

## Table 3. Cont.

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
US8709399B2	Beauveria bassiana	maize stem borer Busseola fusca	Herbivorous insects and/or plant pathogens.	[149]
CN105462892A	Burkholderia sp.	Sophora tonkinensis	Panax notoginseng black spot.	[150]
CN105838613A	Chaetomium globosum	Cajanus cajan	Fungal plant diseases with the production of flavipin.	[151]
CN107475123A	Chaetomium globosum	Anoectochilus roxburghii	Plant disease in Anoectochilus roxburghii cultivation.	[16]
CN102742605A	Chaetomium globosum	Ginkgo biloba	Plant pathogenic fungi.	[122]
CN102690759A	Chaetomium globosum	Solidago canadensis	Plant pathogenic fungi propagation	[121]
CN101280320A	Chaetomium globosum	Not disclosed	Plant fungal diseases with the production of antibiotic substances	[120]
CN106754396A	Chaetomium globosum	Toona sinensis	Erwinia and Ralstonia solanacearum	[123]
CN104877919A	Chaetomium globosum	Phellopterus littoralis	Anthracnose pathogens of apples and certain inhibitory actions against other plant pathogens	[124]
CN103255065A	Chaetomium globosum	Camptotheca acuminata	Plant pathogens with broth culture of the endophytic fungi	[125]
CN102754652A	Chaetomium globosum	Ginkgo biloba	Exserohilum turcicum, Coniothyrium diplodiella, and Rhizopus stolonifer	[126]
CN105368720A	Chaetomium sp.	Healthy cotton plant	Cotton Verticillium wilt.	[152]
CN109749938A	Cladosporium tenuissimum	Healthy Panax notoginseng	Panax notoginseng rot.	[153]
CN110172408A	Clonostachys rosea	Podophyllum hexandrum	Diseases and pests of Podophyllum hexandrum.	[154]
CN110272829A	Colletotrichum boninense	Huperzia serrata	Sclerotinia sclerotiorum of crops.	[155]
WO2014136070A1	Epichloë	Elymus mutabilis	Pests on <i>Secale</i> spp. plants.	[156]
CN105483022A	Fusarium solani	Sophora tonkinensis	Panax notoginseng black spot.	[127]
CN105483021A	Fusarium solani	Sophora tonkinensis	Panax notoginseng fungal diseases.	[128]
CN103194490A	Fusarium solani	Ginkgo biloba	Five plant pathogenic fungi.	[129]
CN105087386A	Fusarium sp.	Yinchuan Phragmites communis	Rice blast disease.	[130]
CN108624527A	Fusarium sp.	Ginkgo sp.	Bacterial wilt in ginger.	[132]

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN110558337A	Fusarium oxysporum	Ginkgo biloba	Rice blast disease.	[131]
CN102174416A	Fusella sp.	Angelica sinensis	Plant pathogenic bacteria.	[157]
WO2016034751A1	Guignardia mangiferae	Persea indica	Phytopathogens and plant pests.	[158]
WO2013081448A2	Hendersonia sp.	Not disclosed	Basal stem rot disease and <i>Ganoderma</i> disease in oil palms.	[159]
CN109536390A	Hypoxylon sp. nov	Midvein of citrus leaves	Citrus black spot disease.	[160]
CN103642704A	Leptosphaeria sp.	cotton	Cotton Verticillium wilt.	[161]
CN103289906A	Metarhizium sp.	Gentiana manshurica	G. manshurica leaf blight.	[162]
CN110229758A	Mortierella elongata	Atractylodes macrocephala	Atractylodes macrocephala root rot.	[163]
CN101691541A	Muscodor sp.	Not disclosed	Pathogenic fungi.	[164]
US20040141955A1	Muscodor albus and Muscodor roseus	Not disclosed	Organisms such as microbes, insects, and nematodes with volatile compounds.	[165]
WO2002082898A1	Muscodor albus and Muscodor roseus	Not disclosed	Plant pathogens, bacteria, nematodes, and insects with volatile antibiotics.	[166]
WO2010115156A2	Muscodor strobelii	Not disclosed	Pests and pathogenic microbes, including Ganoderma boninense.	[167]
WO2004034785A2	Muscodor vitigenus	Paullinia paullinioides	Insects with the production of repellents by a novel endophytic fungus.	[168]
CN106893678A	Myrothecium verrucaria	grapes	Grape gray mold.	[169]
CN104774768A	Nectria haematococca	Fritillaria wabuensis	Bacteria such as <i>S. aureus</i> and <i>P. aeruginosa</i> and pathogenic fungi.	[170]
CN106538108A	Neotyphodium sp.	gramineous plants	Mildewing rate of <i>Elymus sibiricus</i> seeds in the germination stage.	[133]
WO2007021200A1	Neotyphodium sp.	Not disclosed	Plant pathogenic fungi.	[134]
CA2319847C	Neotyphodium sp.	Festuca arundinacea	Pests and reduce ergopeptine alkaloid levels.	[135]
CN102191186A	Nigrospora oryzae	Allium sativum	Plant pathogenic fungi such as <i>Rhizoctonia solani, Colletotrichum lindemuthianum,</i> and <i>Botrytis cinerea</i> .	[171]
CN104789482A	Nigrospora sp.	Magnolia officinalis	Wheat disease.	[172]

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN110178857A	Paecilomyces variotii	Hippophae rhamnoides	Plant virus. Induces plant endogenous salicylic acid accumulation and enhances the plant RNA silencing efficiency.	[173]
CN105462854A	Penicillium citrinum	Sophora tonkinensis	Panax notoginseng anthracnose.	[136]
CN105462850A	Penicillium citrinum	Sophora tonkinensis	Panax notoginseng root rot.	[137]
CN105462855A	Penicillium citrinum	Sophora tonkinensis Gagnep	Alternaria panax.	[139]
CN104531543A	Penicillium griseofulvum	Tephrosia purpurea	Plant diseases such as <i>Sclerotinia</i> rot of colza, tobacco blackleg, and others with a fermentation product.	[53]
CN105255742A	Penicillium sp.	Malus hupehensis	Harmful pathogens such as <i>Fusarium solani</i> , F. proliferatum, F. moniliforme, and F. oxysporum.	[140]
CN108546651A	Penicillium sp.	Kandelia candel	Plant pathogenic fungi such as <i>Fusarium graminearum</i> , <i>Phytophthora sojae</i> , and <i>Colletotrichum musae</i> with a fermentation product.	[141]
CN109112069A	Penicillium sp.	Panax notoginseng root	Panax notoginseng root rot.	[138]
CN103773699A	Penicillium purpurogenum	Litchi	Litchi downy blight.	[142]
CN103627643A	Penicillium simplicissimum	Healthy cotton plant	Cotton Verticillium wilt.	[174]
CN104161049A	Pestalotiopsis uvicola	Artemisia japonica	Kiwifruit <i>Sclerotinia sclerotiorum, Phytophthora capsici,</i> and other plant pathogenic fungi with a fermentation product.	[175]
CN110511878A	Pezicula neosporulosa	Fir	The pathogenic fungus Fusarium oxysporum.	[176]
CN109769535A	Phialophora oryzae	Wild rice root	Bacterial blight of rice.	[177]
CN102154116A	Phomopsis wenchengensis	Not disclosed	Plant pathogenic fungi by antifungal compounds.	[178]
CN105462853A	Rhexocercosporidium sp.	Sophora tonkinensis	Colletotrichum gloeosporioides on Panax notoginseng.	[143]
CN105462851A	Rhexocercosporidium sp.	Sophora tonkinensis	Fusarium solani on Panax notoginseng.	[144]
CN105462848A	Rhexocercosporidium sp.	Sophora tonkinensis	Alternaria panax Whetzel on Panax notoginseng.	[145]
CN102234618A	Rhizopus and Trichoderma	Not disclosed	Soft rot disease of the orchid family <i>Dendrobium</i> plants.	[179]
CN110452290A	Sarocladium brachiariae	Brachiaria brizantha	Plant disease and pests.	[180]

## Table 3. Cont.

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	
CN110468057A	Seimatosporium sp.	Rosa multiflora Tobacco powdery mildew caused by <i>Erysiphe cichoracearum</i> .		[181]
CN106167767A	Schizothecium sp.	Not disclosed Banana wilt.		[182]
CN110558336A	Spirillum roseum	Not disclosed Lettuce <i>sclerotinia</i> rot.		[183]
CN103834580A	Talaromyces flavus	Not disclosed Cotton Verticillium wilt		[184]
CN106119134A	Talaromyces flavus	Not disclosed Fruit rot		[185]
CN109593658A	Talaromyces sp.	<i>Fructus corni</i> Fungal diseases of wheat		[186]
CN105211105A	Trichothecium roseum	strawberries	Powdery mildew of wheat	[187]
US20120108425A1	Trichoderma atroviride	healthy tea leaves	Foliar disease in tea plantations caused by Cercospora theae	
CN108179115A	Zopfiella sp.	Chrysanthemum morifolium	Plant pathogens such as <i>Fusarium moniliforme, F. oxysporum,</i> <i>Curvularia lunata,</i> and <i>Pythium</i>	
WO2018119419A1	Group of several <sup>2</sup> fungi	cotton	Nematodes, aphids, flea hopper, lygus bug, stink bug, soy looper, cabbage looper, or fungi	
US9469836B2	Not disclosed	Pinus strobus	Pinus strobus Pests in Pinus strobus	

#### 3.3. Bio- and Phytoremediation

Bioremediation is a process that uses microorganisms, plants or enzymes to detoxify contamination in natural sources. In phytoremediation, plants and their own metabolic system can extract toxic chemicals from water, soil and air. This chemicals or contaminants include metals and metalloid pollutants, carcinogenic agents, industrial organic waste material, inorganic pesticides and herbicides, chlorinated products, excess nutrients and radionuclides [10,11,192].

Endophytic fungi have the capability to degrade small and large organic compounds by enzymatic reactions, decompose environmental contaminants, and improve the soil microenvironment [193]. They can also increase the ability of host plants to remove contaminants from soil, water, sediment, and air [194], and to modulate morphological and physiological functions in the host plant improving its resistance to metals and providing different detoxification routes such as extracellular scavenging and complexation, compartmentalization and volatilization [14,195]. Figure 1 shows different bioremediation techniques involving endophytic fungi.

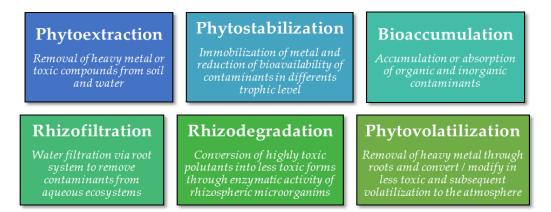


Figure 1. Bio- and phytoremediation approaches involving endophytic fungi.

Some patents describe the use of endophytic fungi for bioremediation and phytoremediation (Table 4). Strains of the genus *Fusarium* have been reported to induce phytoremediation in heavy metal-contaminated soil [196], repair uranium-polluted water bodies [197], and decontaminate and decompose human and animal waste [198]. Additionally, the endophytic fungi Y2R14 and RWDL4-1 can be used to treat wastewater polluted by cadmium [199]. Heavy metals such as mercury, cadmium, arsenic, chromium, and lead are toxic at low concentrations. They can be accumulated in the ecosystem inside living organisms and are capable of entering the food chain [200]. The functions of several organs of the human body can be affected by heavy metals, and some of these substances can cause cancer by long-term exposure [200]. Uranium is a radioactive substance and is also harmful for the environment and human beings [197]. The use of microorganisms to repair large areas of farmland pollution can reduce costs, the use of large amounts of chemicals, and secondary pollution [196].

Species of *Phomopsis* and *Xylaria* have been reported to degrade the herbicide MCPA (2-methyl-4-chlorophenoxyacetic acid) in water and soil [201,202]. Additionally, several genera of fungi can be used to produce high-laccase content for soil bioremediation [203].

#### 3.4. Patents that Claim Multiple Applications

A small number of patents comprised more than one possible application (Table 5); this is the case of the applications for *Neotyphodium uncinatum* to induce insect resistant and drought tolerance in plants [204]; *Phoma* sp. can improve salt stress resistance, promote the growth and increase biomass in crop plants such as wheat and rice [205]; *Clonostachys rosea* promotes plant growth, stress resistance and reduces dependency on chemical pesticides [206,207]; *Fusarium* sp. stimulates plant growth and reduces heavy metal absorption in tobacco [208], and *Rhizoctonia* sp. fosters plant growth and stress resistance in *Anoectochilus roxburghii* [22].

Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	Ref.
CN105733958A	Fusarium oxysporum	Not disclosed	Phytoremediation of heavy metal-contaminated soil	[196]
CN106340337A	Fusarium sp.	mangrove	Repair of uranium-polluted water body	[197]
WO2005116272A2	Fusarium culmorum and Muscodor albus	Not disclosed	Decontamination and decomposition of human and animal waste	[198]
CN106947697A	Phomopsis sp.	Not disclosed	Degradation of the herbicide MCPA (2-methyl-4-chlorophenoxyacetic acid) in water or soil	[201]
CN107177511A	Xylaria sp.	Not disclosed	Degradation of the herbicide MCPA in water and soil	[202]
CN107900098A	Group of several fungi <sup>2</sup>	Not disclosed	Production and application of a high-laccase content soil remediation agent	[203]
CN108751424A	Not disclosed	wild soybean	Treatment of wastewater polluted by the heavy metal cadmium	[199]

<b>Tuble 1.</b> Encopriy de tangi applied in biotenicalation and phytorenicalation.	Table 4	. Endophytic f	ungi applied in bior	emediation and phytoremediation.	
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<sup>1</sup> Some patents just provided a common name for the host organism. <sup>2</sup> A list of the group of fungi is in Table S1.

Table 5. Patents th	hat claim	multiple	applications.
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Patent No.	Endophyte	Host <sup>1</sup>	Patent Application	
WO2000062600A1	Neotyphodium uncinatum	meadow fescue	Import desired traits: include no adverse effects on herbivore, insect resistance drought tolerance and improved persistence in the plants.	
CN104293681A	Phoma sp.	Not disclosed	Improving salt stress resistance in rice and wheat. Promotion of growth in rice seedling, delaying salt damage of wheat in saline and alkaline land. Increasing biomass accumulation in wheat.	
US20160007613A1	Clonostachys rosea	Not disclosed	Promotion of plant vigor, health, growth, yield, and resistance to competitive stress.	
WO2007107000A1	Clonostachys rosea	Not disclosed	Enhanced plant vigor, health, growth, yield, reducing environmental stress and reduction of dependency on chemical pesticides for pest control.	
CN103849572A	Fusarium sp.	Not disclosed	Promoting plant growth and reduction of heavy metal absorption in tobacco.	
CN101953261A	<i>Rhizoctonia</i> sp.	Anoectochilus roxburghii	<i>Growth of A. roxburghii, improved the reproductive rate, survival rate and stress resistance.</i>	
WO2019115582A1	Group of several fungi <sup>2</sup>	Hordeum murinum	Increased yield and biomass in cereal crops, and promotes biotic and abiotic stress resistance in cereal crops	
WO2016030535A1Group of several fungi 2Hordeum murinumsubsp. murinum			Improving dry shoot weight, mean dry grain weight and suppression of seed-borne infection in a cereal crop.	[35]

We found two patents, whose applications implicated the use a plural number of fungi (genus/species); one of them claims the capability to increase biomass and promote biotic and abiotic stress resistance in cereal crops [37], the other claims to improve dry shoot weight, mean dry grain weight and suppression of seed-borne in cereal crops [35].

#### 4. Discussion

In the present review, we highlight a wide number of endophytic fungi that have been patented for developing processes, methodologies, or new techniques in applications that include but are not restricted to (a) alternatives to overcome biotic and abiotic stress and to reduce the use of chemicals associated with environmental toxicity in agricultural practices, (b) the degradation of harmful compounds, and (c) improvement in the ability of plants to remove contaminants from soil, water, and air. Abiotic stress tolerance and growth promotion of plants, and biocontrol of herbivores and plant pathogens, were the most patentable applications of endophytic fungi with 88 and 90 patents, respectively; concerning bio- and phytoremediation, 7 patents were recorded for the period 1988–2019 (Figure 2). The most representative genera of these applications belong to *Alternaria, Aspergillus, Chaetomium, Fusarium, Penicillium* and *Muscodor*.

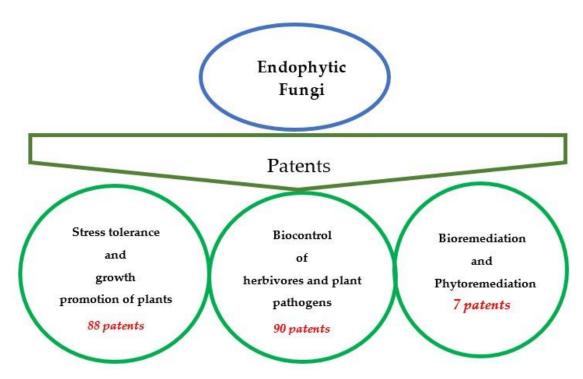
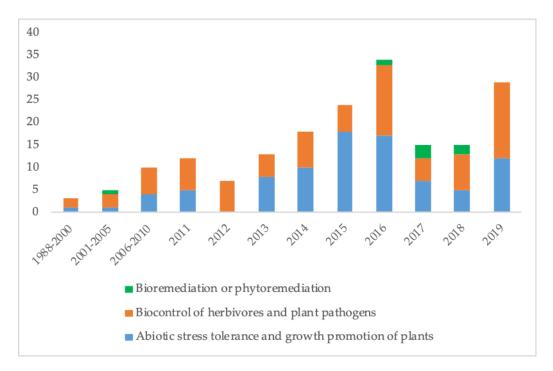
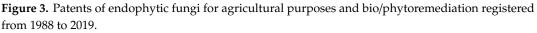


Figure 2. Total number of patents for area of application in the period 1988 to 2019.

Studies of endophytic fungi ecology have allowed the understanding of the multiple interactions they develop with their host, other endophytes, as well with herbivores and pathogens that put the host under abiotic stress. Nonetheless, it is evident that one individual or group of endophytes can be used for mitigation stresses from different origins. Due to the concerns about global climate change and its implications in food security, there are an increased interest to develop applications for the use of endophytic fungi in abiotic stress tolerance and growth promotion of important food crops [209], as well as the use for biocontrol of herbivores and plant pathogens. This increment can be noted since 2011 as shown in Figure 3. The loss of growing areas due to contamination and the recovery of spaces contaminated by heavy metals, organic and inorganic compounds will lead the focus of research on endophytic fungi for bio- and phytoremediation applications.





Considering the abundance of endophytic fungi under study, the development of patentable applications like those reviewed here, and other applications still unexplored like fungal pigments [210], has become a prominent research area for this class of microorganisms.

#### Future Perspectives

The use of endophytic fungi to improve the nutrients absorption in plants can change the optimum usage of organic and inorganic fertilizers [211]. The capability of endophytic fungi to increase biotic and abiotic stress tolerance in plant hosts is an unexplored area for agricultural purposes; the control of pests and diseases under climate change conditions [211]; studies in fungal species related to develop resistance to changes in their environment could lead their application in food production in limited resources areas and as an important alternative for crop production for human sustainability. Many endophytes are now often recognized as symbionts with unique and intimate interactions with the plant host [10]. The genetic engineering of fungi is an easier process than in plants. The genetic modification of endophytic fungi with useful genes could contribute, with new traits, to the inoculation of plants [212].

The use of endophytic fungi on remediation of contaminated ecosystems is an interesting prospect for further studies. Fungi that could increase the capacity of  $CO_2$  absorption by plants, degradation and biotransformation of waste, enhance food production without altering its quality or those that provided drought resistance/nutrient absorption capability to plant species related to human or animal feeding could be areas of significance to develop new applications and patents. The investigations applied in these fields are forwarded by the advance in the techniques used for the characterization of endophytic fungi and also by the technological advances in analytical techniques for carrying out studies of chemical processes at the cellular level. **Supplementary Materials:** The following are available online at http://www.mdpi.com/2076-2607/8/8/1237/s1, Table S1: List of patens grounded in the use of several endophytic fungi to develop applications.

**Author Contributions:** H.E.O. and D.T.-M. performed the data search and organized and analyzed the data, visualized and wrote the manuscript; L.C.-R. conceptualized, visualized, supervised, wrote and reviewed the manuscript. All authors read and approved the final manuscript.

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