

Unexploited Potentials of Endophytic Fungi: Patents Review on Endophytic Fungi Related to Secondary Bioactive Compounds

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ABSTRACT

Endophytic fungi are various micro-organisms that inhabit intracellular or intercellular plant tissues in symbiotic association [at certain stages of their life cycles], without causing damage or morphological changes. The endophytes from medicinal plants are important resources for discovery of natural products and secondary bioactive metabolites having the potential biotechnological applications in agriculture, medicine, and allied sectors. The endophytic fungi such as *Acremonium*, *Aspergillus*, *Fusarium*, *Trichoderma*, *Penicillium*, *Phomopsis*, *Pestalotiopsis*, *Pseudomassari*, *Quercina*, *Trichoderma* genera have been reported from different medicinal plants with potential therapeutic activity. On the other hand, the endophytic fungi can also confer profound impacts on their host plants like improvement in growth, activation of systemic tolerances towards abiotic/biotic stresses, enhancement of nutrient solubilization, biosynthesis of phytohormones and stimulating accumulation of secondary metabolites. Endophytic fungi have attracted much research interest because they have provided not only novel sources of Cytotoxic compounds, Antimicrobial agents, Bio-stimulants for essential oil biosynthesis, Anticancer agents, antioxidant agents, anti-diabetic agents, immunosuppressant and insecticidal compounds. The present review reveals the importance of endophytic fungi from medicinal plants as a source of bioactive compounds as well as landscape of patents related to the production of secondary metabolites through endophytic fungi and their application in pharmaceutical sectors.

Keywords: Endophytic fungi, Symbiotic association, Patents, Secondary metabolites, Biological activity, Phytohormones.

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INTRODUCTION

Micro-organisms are widely testified to be naturally associated with plants which ecological significance and their ability to produce metabolites that could modulate the physiology of the host plant or be of pharmacological interest.^[1] Numerous classes, their characteristics with examples of plant associated fungi are elaborated in Figure 1.

Plants have served as a potential source of medicinal bioactive compounds, in recent years, micro-organisms associated with plants rather than plants themselves have proved to offer material and bioactive secondary metabolites with high therapeutic potential which can use widely for novel drug discovery.^[2,3]

Endophytic fungi are various micro-organisms that inhabit intracellular or intercellular plant tissues in symbiotic association

[at certain stages of their life cycles], without causing damage or morphological changes. Endophytes can be categorized as,

1. Facultative
2. Obligate

Endophytic fungi are taxonomically and ecologically heterogeneous group of organisms, mainly belonging to,

1. Ascomycotina
2. Deuteromycotina.

Among these endophytic micro-organisms, endophytic fungi have attracted much research interest because they have provided novel sources of Cytotoxic compounds: anticarcinogenic molecules,^[4] Antibacterial substances,^[5] Bio stimulants for essential oil biosynthesis^[6] and different benefits of endophytic fungi enlisted in Figure 2 and examples explained in Figure 3 Metabolites isolated from endophytic fungi exhibited various pharmacological properties like, Since the dawn of industrialization, fermentation has been employed for the synthesis of a wide range of bioactive molecules from natural



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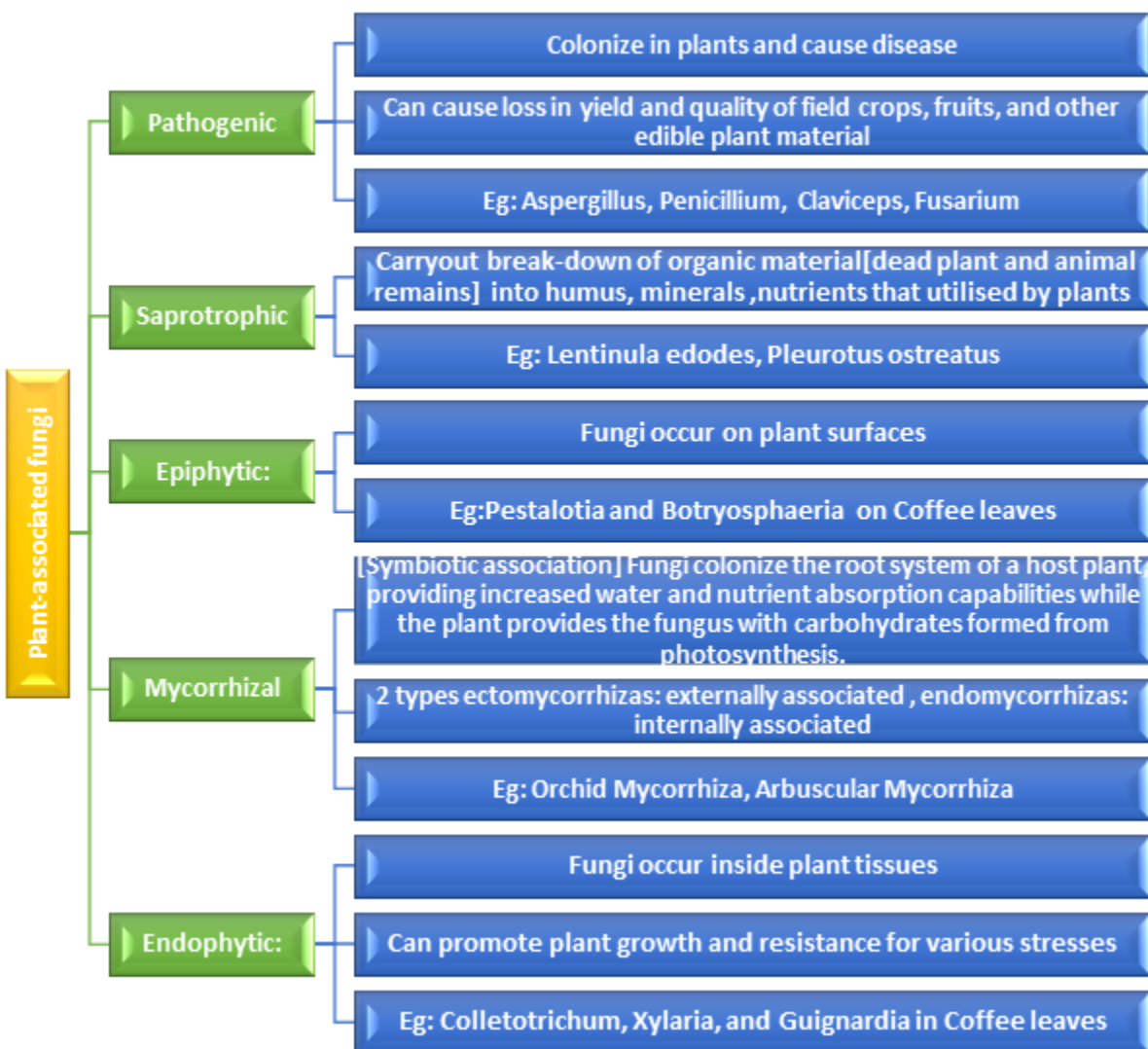


Figure 1: Plant associated fungi classification.

sources for application in a variety of industries, including the food, pharmaceutical, and chemical ones. Due to the potential for these secondary metabolites to be used on an industrial scale for their application in several fields, process conditions for the generation or extraction of secondary metabolites by endophytic fungal strains have been developed more frequently in recent years by fermentation technology. Benefiter characteristics for fermentation process as production of secondary metabolites are enlisted in Figure 4.

Plants holding pharmacological activities and its Novel bioactive metabolites are used to treat numerous health ailments, summary of review mentioned in Table 1.

Patent Overview

1. The indenone derivative and its preparation method and application in a kind of marine fungi source. CN106434361B 2019:^[16]

The invention discloses the indenone derivatives and its preparation method and application in a kind of marine fungi source. Indenone derivative is isolated from mangrove endophytic fungus [CCTCC M 2016217] *Ascomycota* sp. SK2YWS L which cultivated to obtain thallus using solid rice fermentation culture medium, further methanol used for extraction, column chromatography used for separation. DPPH radicals scavenging experiment and FRAP total antioxidant activity methodology used to determine antioxidant activity of Indenone derivatives. Indenone derivative showed external reduction ferric ion ability, removed DPPH (hexichol for bitter taste hydrazine) free radical and hydroxyl radical free radical activity, good application prospect in terms of the preparation of anti-oxidation medicine or health care product.

2. A kind of polyketide in sea paint endogenetic fungus source and its application in preparing anti-inflammatory drug CN108315264A 2018.^[17]

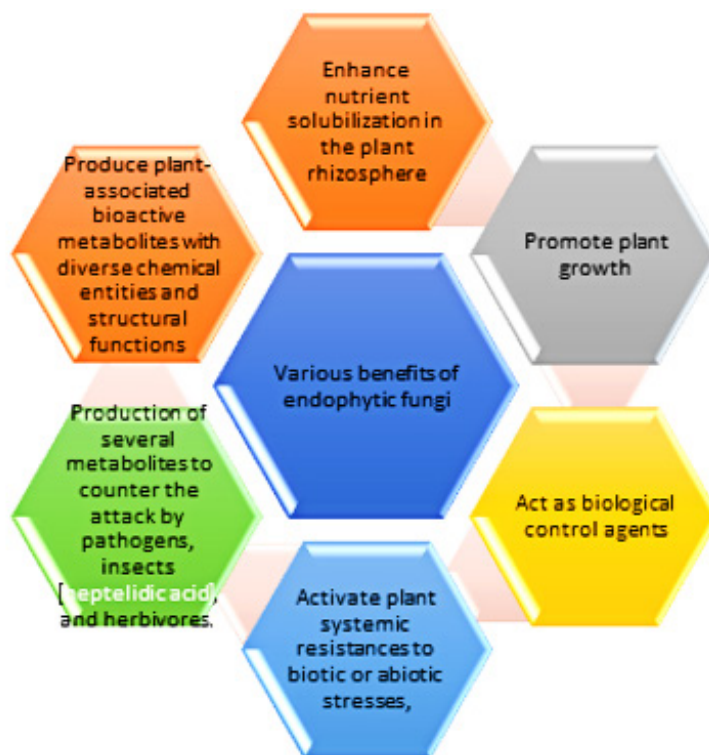


Figure 2: Various benefits of endophytic fungi.^[7-11]

The invention disclosed a kind of polyketide in sea paint endogenous fungus source and its applications in preparing anti-inflammatory drug. The present invention patents endogenous fungus from one plant of sea *Diaporthe* sp. The isolated polyketides in SYSU HQ3. Sea paint endogenous fungus *Diaporthe* sp. SYSU-HQ3 was inoculated in Potato glucose water culture medium further solid rice fermentation culture medium used for fermentation for 1 month. Fermentation media extracted by methanol, ethyl acetate. Gel column chromatography, gel Sephadex LH-20 used for separation of polyketide compound. Characterization of separated polyketide compound carried out by NMR which further used for anti-inflammatory study.

3. A kind of indene derivatives derived from endophytic fungi in *Excoecaria agallocha* and its application in preparing anti-inflammatory drugs CN108277164B 2019.^[18]

Indene derivatives derived from endophytic fungi in *Excoecaria agallocha* sea plant which fermented and used for extraction for isolation of indene derivatives by column chromatographic techniques. Further isolated Indene found potentiality of anti-inflammatory treatment, it can be used for preparing anti-inflammatory drug.

4. An endophytic fungus of the genus *Fusarium* with the function of producing huperzine A and its application CN106497803A 2017.^[19]

Wild *Huperzia serrata* (*Huperzia serrata*, Huperaceae) used as a host plant for isolation of *Fusarium verticillioides* NSH-5 which genetic stability after passage for 20 generations in the laboratory,

and its amino sequence is shown in SEQ ID NO: 1. Isolated endophyte use for treating vascular dementia and senile dementia. Its excellent huperzine A-producing high-efficiency expression gene is transferred into other model strains, and more excellent characters can be obtained through genetic modification. Further optimization of the strain is achieved by mutagenesis breeding.

5. One plant of paclitaxel produced *Aspergillus flavus* BP6T2 and its application CN106967622A 2019.^[20]

Tissue of taxaceae Bashan Mountain *Chinese torreyia* plant root, stem, leaf, bark, used for isolation of *Aspergillus flavus* BP6T2 endophytic fungi [deposit number: CCTCC NO:M2016318] by use of PDA solid medium. Isolated endophytic fungi used for colonial morphologies identification such as colony edge, colony growth rate and chromogenic element. Bacteriostatic activity of endogenous fungus were determined with agar block method for *Staphylococcus aureus* and *Escherichia coli*. Isolated endophytes used for fermentation process by use of PDA liquid medium for 7-10 days further used for ethyl acetate extraction [3 times counter current extraction] and rotary evaporator which provided fat soluble extract. HPLC is found in extract containing basically identical with Taxol Standard retention time, LC-MS instrument (HPLC-MS) determines the structure of paclitaxel analogs in metabolism extract which found extract that BP6T2 is produced is taxol. *Aspergillus flavus* BP6T2 proved inhibitory action of the fermentation broth extract to Hela tumour cells, inhibiting rate can reach 66.20%.

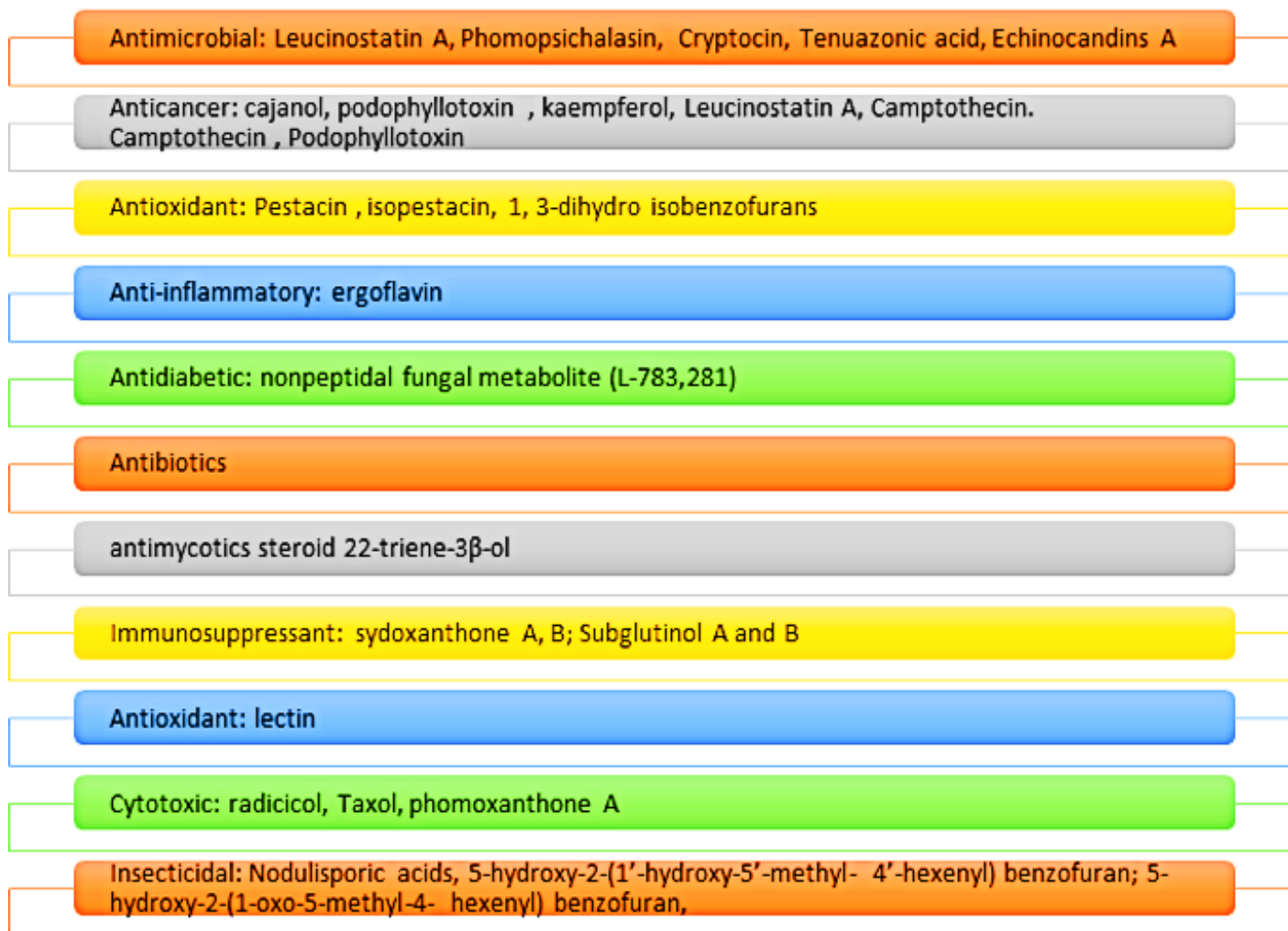


Figure 3: Reported compounds isolated from endophytic fungi.^[12-15]

6. One plant production bearing taxanes Bakating III *Aspergillus niger* and its application CN106967623A.

The invention discloses the endophyte *Aspergillus niger* BP12 ± 3 separated from the tissue of taxaceae Bashan Mountain Chinese torreyia, The bacterial strain has the activity of anti-*Staphylococcus aureus* and *Escherichia coli*, the crude extract content of paclitaxel analogs is up to 120mg/L in zymotic fluid, wherein the percentage contents of bearing taxanes Bakating III are 10.5%, and yield is 12.6 mg/L, higher than the published yield of prior art; Using L phenylalanines as precursor, the yield of Bakating III can increase by 129.84%. Inhibitory action of the fermentation broth extract to HeLa tumour cells of *Aspergillus niger* BP12 ± 3 is demonstrated using the reagent methods of CCK 8, inhibiting rate can reach 62.91%.^[21]

7. One plant height effect taxol-producing endophytic fungi micro-organism *Aspergillus aculeatus* Tax 6 and its application CN107058118A.^[22]

Aspergillus aculeatus Tax-6 endophytic fungi used for production of paclitaxel showed yield of taxol 334.92 µ g/L.

8. Can liquid fermentation production pectin *Solidago Canadensis* endogenetic fungus and its application.^[23]

Solidago canadensis endogenetic fungus, i.e *Epicoccum* L1 (*Epicoccum* sp.L1) [deposit number is CCTCC NO: M 2016365] isolated from Canada Chrysanthemum. *Solidago canadensis* endogenetic fungus *Epicoccum nigrum* L1 used for energy liquid fermentation production of pectin which it provided new method to produce pectin.

9. The tunning and its acetic acid ethyl acetate extract of compound E1011 and the preparation method and application thereof, potato endogenetic fungus.^[24]

The present invention relates to a kind of compound E1011 and the preparation method and application, the tunning and its

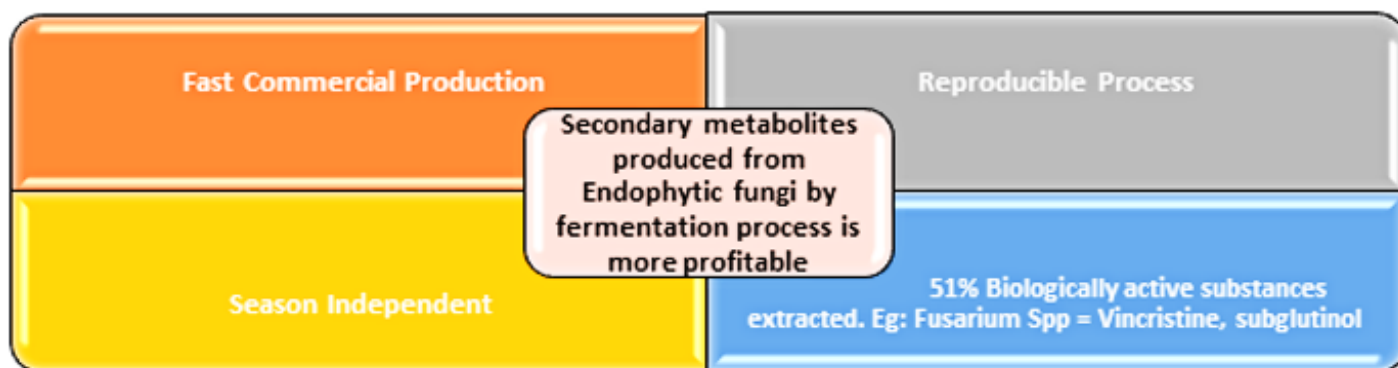


Figure 4: Benefits of Secondary metabolites produced from Endophytic fungi.

acetic acid ethyl acetate extract of potato endogenetic fungus, belong to chemical field.

10. The hexichol phenolic acid compound in a kind of santal endogenetic fungus source and preparation method thereof and the application in preparation antibacterials CN 109206337 A, 2019.^[25]

Hexichol phenolic acid compounds extracted with support of santal endogenetic fungus source *Fusarium* sp, preparation method and the application in preparation antibacterials explained in mentioned invention. The structural formula of the hexichol phenolic acid compound extracted from fermentation media with methanol and ethyl acetated which showed good bacteriostatic activity against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus albus*, *Micrococcus luteus*, *Bacillus cereus* or *salmonella* etc. MIC value found between 3.0-12.5µG/mL can be used for preparing antibacterials.

11. Metabolite product of ginkgo endophytic fungi and application of metabolite product in antibiosis. CN109082445B 2020.^[26]

A metabolite product of Ginkgo biloba host endophytic fungi i.e *Fusarium (Fusarium proliferatum)* DZHQ1 [preservation number of CGMCC No.14983], obtained by fermentation culture, extraction and separation methods used for purification of metabolites. The metabolite showed potential inhibitory effect against resisting *Escherichia coli* and/or *Staphylococcus aureus*, and has a potential application in preparing a new antibacterial product.

12. Endophytic fungus from ginkgo, metabolite product and use thereof US20210238538A1 August 2021.^[27]

An endophytic fungus from ginkgo plant bark, i.e *Fusarium proliferatum* DZHQ1 proved antitumor and antibacterial activity. The endophytic identification carried out by the combination of colonial morphology and 18 sRNA sequencing, folled by anti-cervical cancer activity and antibacterial activity of extract was detected by MTT. Finally, a secondary were isolated by semi-preparative HPLC, which promotes the further screening of individual compounds with anti-tumor activity.

13. One plant of ginkgo endogenous fungus and its application CN108102928B 2019.^[28]

The present study invented ginkgo endogenous fungus layer (*Fusarium proliferatum*) DZHQ1 with anti-tumor activity from ginkgo bark, which use for anti-cervical cancer activity of mtt assay detection bacterial strain crude extract is utilized, the method for finally preparing HPLC using half, the secondary metabolite of bacterial strain to inhibiting rate greater than 50% separates, and helps further to screen compound monomer with anti-tumor activity.

14. Plant endophytic fungus *Echinospora terrestris* D2G24 and application thereof CN112094760B 2022.^[29]

Strain of *Echinospora terrestris* (A) *Setophoma terrestris*) molecularly identified and is utilized for bioremediation of heavy metals like lead, zinc and cadmium. The selected endophytic fungi can promote the growth of plants, transfer capacity of the plants to heavy metals, has strong accumulation capacity to the heavy metal cadmium and zinc, and is suitable for *in-situ* remediation of large-area heavy metal cadmium and zinc pollution. Endophytic fungus phomopsis D2G7 and application thereof CN112280694A 202.^[30]

A plant endophytic fungus phomopsis (*A. phomopsis*) *Phomopsis columnaris*) utilized in bioremediation of heavy metal pollution of lead, zinc and cadmium. Isolated endophyte identified by morphological characteristics and the molecular identification. Further inoculating the separated endophytic strain on PDA plate, and inoculating the block to the plate containing Pb^{2+} , Zn^{2+} , Cd^{2+} in PDA medium (with $Pb(NO_3)_2$, $2ZnSO_4 \cdot 7H_2O$ and $CdSO_4 \cdot 8H_2O$ prepared separately) and a PDA plate containing no heavy metal- as control group, were cultured at 25, the colony diameter was measured every other day, which used for calculating tolerance index, MTI.

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, were the most

Table 1: Patent landscape.

Patent title	Patent No.	Endophytic fungi	Host plant	Media used for fermentation	Compound isolate	Pharmacological activity	Separation/ isolation method for compound	Identification method for compound	Year of publication
One plant of ginkgo endogenous fungus and its application.	CN108102928B	Fusarium proliferatum	Ginkgo	-	-	Anti-cervical	Ethyl acetate extraction	HPLC chromatogram.	2019
Endophytic fungus from ginkgo, metabolite product and use thereof.	US20210238538A1	Fusarium	Ginkgo bark	-	-	Anti-tumor and antibacterial	Ethyl acetate extraction	HPLC chromatogram.	2021
Metabolite product of ginkgo endophytic fungi and application of metabolite product in antibiosis.	CN109082445B	Fusarium (Fusarium proliferatum) DZHQ1	<i>Ginkgo biloba</i>	PDA liquid culture medium	-	Antibacterial	Ethyl acetate extraction	-	2020
The hexichol phenolic acid compound in a kind of santal endogenous fungus source and preparation method thereof and the application in preparation antibacterials.	CN109206337A	Santal endogenous fungus <i>Fusarium</i> sp.	-	Solid rice fermentation culture medium	Hexichol phenolic acid compounds	Antibacterial, bacteriostatic test, minimal inhibitory concentration	1. Methanol, ethyl acetate extraction 2. Column chromatography	NMR	2019
The tunning and its acetic acid ethyl acetate extract of compound E1011 and the preparation method and application thereof, potato endogenous fungus.	CN 109180635 A,	Xylaria	Potato (<i>Solanum tuberosum</i> L.)	5.0 wt % Glucose, the pork protein peptone of 0.15 wt%, the yeast powder of 0.5 wt%, 0.05wt% KH2PO4	Compound E1011	-	1. Acetic acid ethyl acetate extraction 2. chromatography 3. Centrifugal filtration	Nuclear magnetic resonance measuring, high resolution mass spectrum (HRESIMS), ultraviolet determination and infrared analysis.	2019

Can liquid fermentation production pectin Solidago Canadensis endogenetic fungus and its application.	CN 107118972 A	Epicoccum L1	Canada <i>Chrysanthemum</i>	Martin's fluid nutrient medium, <i>fructus hordei germinatus</i> juice fluid nutrient medium.	Pectin	freeze-drying, Precipitation by addition of ethyl alcohol, gel electrophoresis	IR	
One plant height effect taxol-producing endophytic fungi micro-organism <i>Aspergillus aculeatus</i> Tax 6 and its application.	CN107058118A	<i>Aspergillus aculeatus</i>	-	PDA liquid medium	Paclitaxel	dichloromethane extraction and Rotary Evaporation 2. HPLC, 3. LC-MS		2017
One plant production bearing taxanes Bakating III <i>Aspergillus niger</i> and its application.	CN106967623A	<i>Aspergillus niger</i>	Bashan Mountain <i>Chinese torreyia</i>	PDA liquid medium	Taxol	HPLC, LC-MS	HPLC-MS	2019
The indenone derivative and its preparation method and application in a kind of marine fungi source.	CN106434361B	Ascomycota sp. SK2YW5-L	Mangrove	Fermentation: solid rice fermentation culture medium	Indenone derivative	silicagel column Chromatography technology, gel filtration chromatography	Compound detection: NMR	2019
A kind of polyketide in sea paint endogenetic fungus source and its application in preparing anti-inflammatory drug.	CN106434361B	Ascomycota sp. SK2YW5-L	Sea Diaporthe sp. SYSU-HQ3,	Fermentation: solid rice fermentation culture medium; sea water	Polyketide	1.Extraction solvent: Ethyl acetate 2. Separation by: column chromatography, gel Sephadex LH-20	Compound detection: NMR	2017
A kind of indene derivatives derived from endophytic fungi in <i>Excoecaria agallocha</i> and its application in preparing anti-inflammatory drugs.	CN108277164B	Diaporthe sp.SYSU-HQ3,	<i>Excoecaria agallocha</i>	Fermentation: solid rice fermentation culture medium;	Indene derivatives	1. Extraction solvent: Ethyl acetate 2. Separation by: column chromatography, gel Sephadex LH-20	Compound detection: NMR	2019

An endophytic fungus of the genus <i>Fusarium</i> with the function of producing huperzine A and its application	CN106497803A	<i>Fusarium</i>	Wild <i>Huperzia serrata</i>	PDA liquid medium	Huperzine A		1. high performance liquid chromatography 2. agarose gel electrophoresis	HPLC	2019
One plant of paclitaxel produced <i>Aspergillus flavus</i> BP6T2 and its application	CN106967622A	<i>Aspergillus flavus</i>	Bashan Mountain <i>Chinese torreyia</i> plant	PDA liquid medium	Taxol	Anti-tumour Activity	HPLC	HPLC-MS	2019
Plant endophytic fungus <i>Echinospora terrestris</i> D2G24 and application thereof.	CN112094760B	<i>Echinospora terrestris</i> (A) <i>Setophoma terrestris</i>	<i>Arabidopsis thaliana</i> (A. <i>thaliana</i>)	PDA culture medium containing 0.5g/L streptomycin sulfate and 0.5g/L penicillin, culturing for 40-50 days at 24-26 °C		Phytoremediation (phytoremediation)	-	-	2022
Endophytic fungus <i>Phomopsis D2G7</i> and application thereof.	CN112280694A	<i>Phomopsis columnaris</i>	<i>Chenopodium ambrosioides</i>	PDA medium		Phytoremediation (phytoremediation)			2021

patentable applications concerning bio- and phytoremediation, 8 patents were recorded for pharmacological activity and 3 were reported for phytoremediation for last 5 year.

CONCLUSION

Endophytes are most promising substitutes since they have proved a vast capacity for manufacturing novel bioactive primary and secondary metabolites. For this reason, endophytes have gripped the attention of natural product researchers around the globe as promising production techniques with huge benefits. Altogether, endophytes signify a largely unexploited resource for the discovery and synthesis of novel bioactive compounds with potential applications in drug discovery processes by various approaches like genome minning, computational tools, bioengineering methodologies, culture-based methods, extraction methods after fermentation etc. In this review, we analyzed patents related to the production of secondary metabolites and biotransformation processes through endophytic fungi and their fields of application. We examined 15 patents related to secondary metabolite production methodology and their pharmacological activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PDA: Potato Dextrose Agar; **Pb²⁺:** Lead (II) ion; **Zn²⁺:** Zinc ion; **Cd²⁺:** Cadmium; **HPLC:** High Performance Liquid Chromatography.

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