**Antimicrobial activities of endophytic fungi**

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**Abstract**

Endophytic fungi live inside the plant tissues without harming the plant. These microorganisms were found to produce several bioactive compounds of medicinal importance. Endophytic fungi associated with medicinal plants were found to have bioactive compounds. Many antimicrobial substances, including tyrosol, alkaloids, terpenoids, steroids, quinones, isocoumarins, lignans, phenylpropanoids, phenols, and lactones, were isolated from endophytic fungus. Some endophytic fungi like *Nigrospora oryzae*, *Colletotrichum dematium*,*Chaetomium globosum*, *Raffaelea* sp., *Colletotrichum* sp. etc showed antimicrobial activity against several pathogenic microbes. The main aim of this chapter is to discuss the endophytic fungi associated with plants that have antimicrobial potential. Also, efforts are being adopted to discuss their isolation from host plant and extraction of bioactive compounds with antimicrobial activity from endophytic fungi.

Keywords: Anti-microbial activity; endophytic fungi; bioactive compounds; medicinal plants.

1. **Introduction**

Due to the widespread usage of antibiotics, antibiotic resistance is becoming an urgent problem. The discoveries of new antimicrobial agents have become essential to the research. Endophytes are a class of endosymbiotic microorganisms that live inside plant tissues and serve as storage units for bioactive substances (1). Endophytic fungi colonize inside the plant tissues without harming the plants and can be isolated from almost all kinds of plants (2). The diversity and concentration of fungal endophytes vary significantly in different plants and tissues of the same plant. Endophytic fungal species can also differ in seasons and ages (3). Endophytic fungal diversity and large number of species were found higher in the leaf than in the stem (4).

The research on endophytesis increasing due to their ability to produce antibacterial, antifungal, antiviral, antioxidant, antidiabetic and immunosuppressive compounds. Endophytic fungi also help plants to fight against pathogens. People all across the world utilize medicinal plants to treat a variety of illnesses (5). As these plants serve as storehouse of several important bioactive compounds and are also known as a reservoir of fungal endophytes. The endophytic fungi isolated from medicinal plants were found to produce novel bioactive compounds of pharmaceutical importance (6). There are several medicinal plants are on the way to extinction due to overuse (7). As previously, it was reported that sometimes endophytic fungi produces the same bioactive compounds which is produced by host plant (8). Therefore, instead of using plant tissue we can use endophytic fungi to extract bioactive compounds.

These microorganisms are widely known for producing beneficial secondary compounds such lignans, phenylpropanoids, lactones, terpenoids, steroids, quinones, isocoumarins, and terpenoids (9). Previously it was reported that natural compounds produced by endophytic fungi worked as an inhibitor of various animal and plant pathogens.The relationship between host-microorganisms has been reported to stimulate the production of bioactive compounds. However, understanding host–endophyte relationships is still inadequate regarding biochemistry and physiology (10).

**Endophytic fungi showed several plant growth promotion activities such as phytostimulation, biocontrol, and biofertilizations. These microorganisms were found to help in growth and development of the host plant by producing phytohormones such as Indole Acetic Acid (IAA) and gibberellic acid (11).** Some endophytic fungi were found to stimulate plant growth hormone; anti-phagocytic components that help the host resist biological feeding, develop medicinal constituents, and produce many products with biological activities (12).

It was previously reported that out of 377 isolates from five Garcinia plants, *G. atroviridis*, *G. dulcis*, *G. mangostana*, *G. nigrolineata* and *G. scortechinii*, 70 isolates were able to show antimicrobial activity against at least one pathogenic microorganism, such as *Staphylococcus aureus*, some clinical isolate of methicillin-resistant*Candida albicans* and *Cryptococcus neoformans* (13). Some endophytic fungi like *Nigrospora oryzae*, *Colletotrichum dematium* and *Chaetomium globosum*showed a great antimicrobial activity against some pathogenic microbes (4). *Raffaelea sp*. isolated from *Cocos nucifera* (L.) cotyledon also have antimicrobial properties against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, and *Candida tropicalis* (14). *Colletotrichum* sp. isolated from a medicinal plant *Houttuynia cordata* Thunb. showed an effective result in killing pathogenic microbes like *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (15).The main aim of this chapter is to discuss the endophytic fungi associate with antimicrobial activity and their isolation. Also efforts have been laid down to discuss about the bioactive compounds having antimicrobial activity extracted from endophytic fungi.

A series of processes is done to isolate endophytic fungi from different plant parts. Surface sterilization plays a cruicial role in isolating endophytic fungi. Sterility test showed the success of isolation of endophytic fungi after every experiment.

Sandhu et al.(2014) isolated endophytic fungi from plant materials, which were first washed in water to remove dust and particles after collecting plant materials, followed by cutting them into small pieces witha sterile blade. The surface sterilization step was performed by using 70% alcohol for one minute. The plants parts were then dipped in sodium hypochlorite for 30seconds to one minute, followed by immediately washing the samples in sterile distilled water for one minute. The plant parts were then dried in sterile filter paper followed by inoculation in PDA media supplemented with tetracycline antibiotic and incubated at 28±1⁰C. After 5-7 days, pure colonies were transferred on PDA slants and preserved at 4⁰C. In the study, the researchers used leaves, stems and roots. A total of ten fungi were isolated: five of Ascomycetes, one belongs to Ulovophycetes, two belongs to class Hypomycetes and one belongs to Ascomycota (16).

Mbilu et al.(2018) isolated endophytic bacteria from the medicinal plant *Warburgia ugandensis*. In this method the authors washed plant material in water to remove dust and soil particles. For surface sterilization, 75% ethanol was used for one minute followed by treatment in 12% Sodium hypochlorite for one minute and washed in sterile distilled water twice. The plant material was dried in sterile filter paper and cut into small pieces (3-3.5 cm) using sterile scalpel. Then the plant material was inoculated in agar plate and incubated at 26⁰C -27⁰C for 4 days (17).

Zihad et al. (2022) isolated antimicrobial compounds from *Aspergillus fumigatus*: an endophytic fungus from a mangrove plant of the Sundarbans. In this study, the researchers collected the plant parts and washed in sterile distilled water to remove dust and soil particles. Then the plant parts were dipped in 75% ethanol for oneminute followed by treating in 0.5% sodium hypochlorite for 3 minutes and washed in sterile distilled water for three times. Finally, the plant materials were cut into small pieces using sterile sharp blade, inoculated in Sabouraud dextrose agar (SDA) medium supplemented with 200µg/ml streptomycin, and incubated at room temperature for 1-3 weeks. Pure culture was obtained by inoculating a tiny pinch from distinct colony into new SDA medium amended with streptomycin. In this study the authors found three bioactive compounds named fumigaclavine C, azaspirofuran B and fraxetin extracted from *A*. *fumigatus* which was isolated from the leaves of *C*. *decandra* (18).

Mao et al. (2021) isolated endophytic fungi from healthy branches and fruits of *E. exserta* were collected and washed under running water. After that surface sterilization was performed using ethanol and mercuric chloride for. At last samples were rinsed in sterile distilled water for three times and dried in sterile filter paper. The epidermis was removed with sterile scalpel, inoculated on PDA media supplemented with 500mg/L streptomycin sulfate, and incubated in the dark for 7-30 days. The pure culture was obtained by sub culturing. In this study bioactive compound named Scorpinone which contains antimicrobial properties was isolated (3).

1. **Bioactive compounds showing antimicrobial activites**

Bioactive compounds have been isolated from different phyla and their respective genera of endophytic fungi ranging from ascomycetes, aspergillus, fusarium etc. The compounds isolated from aspergillus genera include1,1′-Bislunatin and 2,2′- epicytoskyrin A which has been extracted from *Diaporthe* sp. found in the host plant *Uncaria gambier*. It could be seen that both compounds exhibit anti-tubercular activities, notably against *Mycobacterium tuberculosis* (19). 2,1-Acetoxycytochalasin, a compound obtained from *Diaporthe* sp. residing in *Sophora tonkinensis* was seen to possess activity against *Bacillus anthracis* and *E. coli* (20). Another compound with antibacterial properties is Diaporone A isolated from *Diaporthe* sp. Found in the plant *Pteroceltistatarinowii,* the compound proved effective in activity against *Bacillus subtilis* (21) *Xylariaellisii*belonging to the genera Xylaria under phylum Ascomycetes produced Ellisiiamide which worked against *E. Coli*.

Similarly, Xylaria endophytic fungi *Xylaria sp.* isolated from *S. tonkinensis* produced 6-Heptanoyl-4-methoxy-2H-pyran-2-one. These highlight the capabilities of endophytic fungi having action against a diverse plethora of microbials.

**Table 1: Bioactive compounds isolated from different endophytic fungi**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sl No. | Bioactive Compound | Endophytic Fungi | Host Plant | Author |
|  | (+)-1,1′-Bislunatin and (+)-2,2′- epicytoskyrin A | *Diaporthe* sp. | *Uncaria gambier* | Oktavia et al., 2020 |
| 2 | 21-Acetoxycytochalasin J3 | *Diaporthe* sp. GDG-118 | *Sophora tonkinensis* | Huang et al., 2021 |
| 3 | Pyrrolocin A | *Diaporthales* sp. E6927E | *Ficus sphenophyllum* | Patridge et al., 2015 |
| 4 | 3-Hydroxy-1-(1,8- dihydroxy- 3,6-dimethoxynaphthalen-2-yl)propan-1-one, 3-hydroxy-1-(1,3,8-trihydroxy-6-methoxynaphthalen-2-yl)propan-1-one and 3-hydroxy-1-(1,8-dihydroxy3,5-dimethoxynaphthalen-2-yl) propan-1-one | *Phomopsis fukushii* | *Paris polyphylla var. yunnanensis* | Yang et al., 2017 |
| 5 | 1-[2-Methoxy-4-(3-methoxy-5-methylphenoxy)-6-methylphenyl]-ethanone (**9**) and 1-[4-(3-(hydroxymethyl)-5-methoxyphenoxy)-2-methoxy-6-methylphenyl]-ethanone | *Phomopsis fukushii* | *Paris polyphylla var. yunnanensis* | Yang et al., 2019 |
| 6 | 4-(3-Methoxy-5-methylphenoxy)-2-(2-hydroxyethyl)-6-methylphenol, 4-(3-Hydroxy-5-methylphenoxy)-2-(2-hydroxyethyl)-6- methylphenol and 4-(3-methoxy-5-methylphenoxy)-2-(3-hydroxypropyl) -6-methylphenol | *Phomopsis fukushii* | *Paris polyphylla* var. *yunnanensis* | Gao et al., 2019 |
| 7 | 1-(4-(3-Methoxy-5-methylphenoxy)-2-methoxy-6-methylphenyl)-3-methylbut-3-en-2-one (**14**), 1-(4-(3-(hydroxymethyl)-5-methoxyphenoxy)-2-methoxy-6- methylphenyl)-3-methylbut-3-en-2-one (**15**), 1-(4-(3-hydroxy-5-(hydroxymethyl)phenoxy)-2-methoxy-6- methylphenyl)-3-methylbut-3-en-2-one | *Phomopsis fukushii* | *Paris polyphylla* var. *yunnanensis* | Li et al., 2018 |
| 8 | (2*Z*)-2-(1,4-dihydro-2-hydroxy-1-((*E*)-2-mercapto-1 (methylimino)ethyl) pyrimidine-4-ylimino)-1-(4,5-dihydro-5-methylfuran-3-yl)-3-methylbutane-1-one | *Phomopsis*/*Diaporthe* sp. GJJM 16 | *Vitex negundo* | Ibrahim et al., 2020 |
| 9 | Diaporone A (19) | *Diaporthe* sp. | *Pteroceltistatarinowii* | Guo et al., 2020 |
| 10 | 4-(3-Methoxy-5-methylphenoxy)-2-(2-hydroxyethyl)- 6-(hydroxymethyl)phenol (**25**), 4-(3-Hydroxy5-methylphenoxy)-2-(2-hydroxyethyl)-6-(hydroxymethyl)phenol | *Phomopsis asparagi* | *Paris polyphylla* var. *yunnanensis* | Hu et al., 2019 |
| 11 | Ellisiiamide | Xylariaellisii | Blueberry (Vaccinium angustifolium) | Ibrahik et al., 2020 |
| 12 | 6-Heptanoyl-4-methoxy-2H-pyran-2-one (**53**) | Xylaria sp. (GDG-102) | Leaves of S. tonkinensis | Zheng et al., 2018 |
| 13 | Chaetocochin C, chetomin A, and chetomin | Chaetomium sp. SYP-F7950 | Panax notoginseng | Peng et al., 2019 |
| 14 | Chamiside A | Chaetomium nigricolor F5, | Mahonia fortune | Wang et al., 2019 |
| 15 | Equisetin | C. globosum | Salvia miltiorrhiza | Yu et al., 2018 |
| 16 | 6-Formamidochetomin | Chaetomium sp. M336 | Huperzia serrata | Yu et al., 2018 |
| 17. | Pinophol A | Talaromycespinophilus XL-1193 | Salvia miltiorrhiza | Zhao et al., 2016 |
| 18. | (1S,5S,7S,10S)-dihydroxyconfertifolin | Talaromycespurpureogenus | Panax notoginseng | Bingyang et al., 2017 |
| 19 | Alkaloids | Talaromyces sp. LGT-2 | Tripterygium wilfordii. | Zhao et al., 2016 |
| 20 | Euphorbol | Rhytidhysteron sp. BZM-9 | Leptospermum brachyandrum | Zhang et al., 2016 |
| 21 | Stagonosporopsin C | Stagonosporopsisoculihominis | Dendrobium huoshanense. | Wang et al., 2021 |
| 22 | Eutyscoparin G | Eutypella scoparia SCBG-8 | Leptospermum brachyandrum | Zhang et al., 2021 |
| 23 | Cyclo(L-Pro-L-Phe) | Paraphaeosphaeriasporulosa | Fragaria x ananassa | Carrieri et al., 2020 |
| 24 | Aspergillone A | *Aspergillus cristatus* | *Pinelliaternata* | Wang et al., 2021 |
| 25 | Aspergillether B | *Aspergillus versicolor* | Roots of *Pulicariacrispa* | Mohamed et al., 2020 |
| 26 | 3-O-β-D-Glucopyranosyl stigmasta-5(6),24(28)-diene | *Aspergillus ochraceus* SX-C7 *eus* SX-C7 | *Setaginellastauntoniana* | Luo et al., 2020 |
| 27 | Dihydroauroglaucin | *Aspergillus amstelodami* | *Ammi majus* | Fathallah et al., 2019 |
| 28 | Methylsulochrin | *A. niger* | *Acanthus montanus* | Mawabo et al., 2019 |
| 29 | 3-(5-Oxo-2,5-dihydrofuran-3-yl) propanoic acid | *Aspergillus tubingensis* | stem of *Decaisnea insignis* | Yang et al., 2019 |

1. **Extraction of bioactive compounds**

Bioactive compounds were extracted from fungal endophytes in different methods. In ethyl Acetate Extract was prepared from Fermentation Assay in Liquid Medium. In this method, the fermented culture after fourth weeks was filtered in vacuum filter using a no.3 Buchner funnels. Solvent-solvent extraction was used to separate the culture filtrates in a separating funnel and extract them with ethyl acetate (9).

An example for extraction of bioactive compounds from endophytic fungi described by Safwan et al.,(2021). Here, the fermented broth went through filtration and partitioning five times using equal volumes of ethyl acetate. The resulting mixture was then concentrated under a vacuum. The crude extract was dissolved in methanol to separate into a MeOH layer and sediment (22).

**Table2: Some examples of Bioactive compounds having anti-microbial ability**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sl no | Bioactive compound | Properties | Endophytic fungi | Host plant | Reference |
| 1 | Myriocin | Antifungal | Mycosphaerella sp. | Myrciaria floribunda | Pereira C.B. et al., 2015 |
| 2 | Terezine E | Antifungal and cytotoxicity properties | Mucor sp. | Centaurea stoebe | Abdou R. et al*.,* 2020 |
| 3 | Ophiobolin K, 6-epi-ophiobolin K | Antifungal, trypanocidal and cytotoxicity properties | Aspergillus calidoustus | Acanthospermum australe | Carvalho C.R.D. et al*.,* 2016 |
| 4 | Cytochalasins H | Antibacterial and cytotoxicity properties | Phomopsis sp | Garcinia kola | Jouda J.B. et al*.,* 2016 |
| 5 | Sterigmatocystin |  | *Aspergillus nidulans* | Nyctanthes arbor-tristis Linn | Sana T. et al*.,* 2019 |
| 6 | 4b-hydroxy-12,13-epoxytrichothec-9-ene |  | Trichoderma asperellum,Trichoderma brevicompactum | Vinca herbacea plant | Sahar L., et al*.,* 2018 |
| 7 | Camptothecin | Anticancer | Phyllosticta elongate | Cipadessa baccifera | Dhakshinamoorthy M. et al*.,* 2021 |
| 8 | Huperzine A | treatment of Alzheimer’s disease | *Fusarium verticillioides* | *Huperzia serrata* | Han W.X. et al*.,* 2017 |
| 9 | Napthaquinones, Azaanthraquinones | Cytotoxicity, antimicrobial andantioxidant | Fusarium solani fungi | Cassia alata | Khan N., et al*.,* 2018 |
| 10 | Antimicrobial | 1-butano,3-methylacetate | *Muscodor albus* | *Cinnamomum Zeylanicum* | Strobel et al*., 2004* |
| 11 | Radicicol | Cytotoxic | *Chaetomium chiversii* C5-36-62 | *Ephedra Fasciculata* | Strobel et al*., 2003* |
| 12 | Isoflavonoids | Antimicrobial | *Phomopsis sp*. | *Erythrina crista-galli* | Turbyville, et al*.,* 2006 |
| 13 | 7-amino-4-Methylcoumarin | Antimicrobial | *Xylaria sp*. YX-28 | *Ginkgo biloba* | Maksum et al*.,* 2011 |
| 14 | Terpenoid | Antimicrobial | *Phomopsis sp*. | *Plumeria acutifolia* | Fang Xu et al*.,* 2008 |
| 15 | propanoic acid, methyl ester, 2- methylbutyl ester, Ethanol | Antibiotic | *MuscodorCrispans* | *Ananas Ananassoides* | Nithya et al*., 2010* |
| 16 | Emerimidine A, Emeriphenolicins B, Aspernidine A and B, Austin, Austinol, Dehydroaustin, Acetoxydehydroaustin | Antiviral | *Emericella sp*. | *Aegiceras corniculatum* | Angela et al*.,* 2006 |
| 17 | Caryophyllene, phenylethyl alcohol, 2-phenylethyl ester, bulnesene | Antibiotic | *Muscodor albus* | *Guazuma ulmifolia* | Zhang et al*.,* 2011 |

1. **Conclusions**

Fungal endophytes from medicinal plants can be a great source of novel bioactive compounds like that of medicinal plants. These endophytic fungi have unexplored variety of functional fungal association. The bioactive compounds extracted from endophytic fungi can be used especially against human pathogenic microbes. Previously, it was reported that 51% of the bioactive substances made by endophytic fungi were previously unknown. 15. Talukdar et al (2021) reported *Colletotrichum* *sp*. isolated from *Houttuynia cordata* Thunb, a medicinal plant was found to produce tyrosol which showed strong growth inhibition activity against *Staphylococcus aureus*. Here in this chapter, we have mentioned several endophytic fungi which showed anti-microbial properties. We also mentioned some bioactive compounds extracted from different endophytic fungi having anti-microbial property. Exploring the endophytic fungi especially from medicinal plant becomes an essential part of research. Exploration of endophytic fungi from several medicinal plants is not done yet. The study on endophytic fungi has augmented the search of novel bioactive compounds. As drug resistance against pathogenic microbes is a current challenge occurring worldwide, discovering new antimicrobial agents become important to fight against these pathogens. Several antimicrobial bioactive compounds were already isolated from endophytic fungi. More research in this field can give us essential bioactive compounds with antimicrobial activity.

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