



Review article

From Plant partners to Therapeutics Champions: Endophytic Fungi of Uttarakhand Region

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Abstract

Medicinal plants have long been essential in treating various ailments, with over 75% of the global population relying on traditional Ayurveda systems. The Indian Himalayan Region, especially Uttarakhand, boasts rich biodiversity, including numerous medicinal and aromatic plants, though overexploitation threatens these species. Fungal endophytes, microorganisms living symbiotically within plants, have emerged as a promising source of bioactive compounds due to their unique metabolic interactions with host plants. These fungi produce diverse secondary metabolites, such as alkaloids, flavonoids, and terpenoids, with potent pharmacological attributes viz. anticancer, anti-inflammatory, antimicrobial and antioxidant potential. Fungal endophytes have demonstrated efficacy against a range of pathogens, including bacteria, fungi, and viruses, and show promise in tackling drug resistance. Additionally, they contribute to industrial applications through enzymes with therapeutic potential. Studies on various plant species from the Himalayas have highlighted the antimicrobial and anti-inflammatory properties of fungal endophytes, supporting their role in drug discovery and bio-prospecting. The increasing isolation and characterization of these fungi underline their potential as sustainable sources of novel therapeutic agents, offering a valuable alternative to traditional plant-derived medicines.

Introduction

Medicinal plants have long been utilized for treating various diseases and health

conditions across the world. More than 70% of the global population still relies on traditional medicine systems like Ayurveda

for their healthcare needs (Pandey et al., 2013; Dubale et al., 2025). In India, especially in rural and tribal communities, people continue to depend on the Indian System of Medicines and other established conventional healing practices for managing a wide range of health issues (Khan et al., 2004, Singh et al., 2012, Deb Roy et al., 2023). The Himalayas, known for their rich biodiversity, are one of the most ecologically diverse regions in the world (Bargali et al., 2022). Over 3,000 plant species, including medicinal plants, wild edibles, fodder, aromatic plants, and holy plants, have been recorded in the Indian Himalayan Region (Sharma et al., 2018). Uttarakhand, which forms a significant part of the western Himalayas, is home to high-altitude areas, cold deserts, and an exceptional variety of plants, including numerous medicinal and aromatic species. For centuries, these plants have been vital sources of medicine for treating various ailments. However, due to over exploitation and the destruction of their habitats, many valuable medicinal plants are becoming increasingly scarce. The rapid extinction of some species is a growing concern, with improper harvesting practices being one of the primary contributors to the loss of biodiversity and the endangerment of these plants (Kala et al., 2004, Godiyal et al., 2024). There is a need to conserve it by developing alternative sources. In recent years,

researchers have discovered one way to explore the bioactive potential of plants through microbial communities, viz. bacteria, fungi, and actinomycetes residing in the plant's inter and intracellular locations (Pimentel et al., 2011, Singh and Dubey, 2015). Among these, a specific niche of fungi known as endophytes has shown huge potential as a reservoir of bioactive substances. This potential arises from the co-evolution between endophytic fungi and their host plants, which leads to the production of bio-active compounds that play a significant role in plant-microbe interactions and provide various fitness benefits to the host plants. The presence of fungal endophytes is influenced by factors such as the plant species, the specific host plant, the type of plant tissue, and the phytochemicals found within the plant (Alam et al., 2021). Endophytic fungi interact with their host plants through metabolic exchanges. In accordance to the hypothesis of Xenohormesis under evolutionary pressure, fungi, as heterotrophic organisms, acquire the ability to detect stress-induced chemical signals from the host plants and begin producing similar chemicals. Essentially, these fungi replicate the biological functions of the host plant. Beyond producing compounds that resemble those of the host plant, endophytic fungi are also capable of synthesizing a wide array of unique secondary metabolites (Howitz et al., 2008).

Role of Endophyte in Drug Discovery

Tropical regions are home to many plant species, for this they are known for their rich plant biodiversity, and India stands out as one of these biodiversity hotspots. It is believed that India's extensive plant genetic resources may harbor a significant diversity of endophytic fungi, which could prove to be a valuable genetic pool for exploring their bioactive properties (Singh, S. K. 2016). Endophytic fungi have been the subject of research for over a century, beginning with the isolation of the first endophytic strain from ryegrass seeds (*Lolium temulentum* L.) by Vogl et al. in 1898. The discovery of the paclitaxel-producing endophytic fungus *Taxomyces andreanae* from the Pacific yew by Stierle et al. in 1993, followed by its identification in other plant species, sparked significant interest among mycologists and pharmaceutical chemists. This breakthrough highlighted endophytic fungi as a promising source of bioactive compounds, leading to a growing interest in utilizing them as a sustainable source of plant metabolites. Numerous endophytic fungi from various plants have been found to secrete compounds with analogous bio-activity (Table 1).

The bio-active compounds produced by endophytes primarily belongs to diverse classes of organic compounds namely alkaloids, steroids, terpenoids,

flavonoids, polyketides, peptides, tannins and phenols (Xu et al., 2021). The metabolites have shown a broad spectrum of pharmacological activities, including antimicrobial, antineoplastic, anticancer, antioxidant, anti-inflammatory, antidiabetic, and antidepressant effects. In the past decade, approximately 51 % of the unknown/novel bioactive agents are harnessed from fungal endophytes, which were patented for novel therapeutic attributes, thereby paving the way to revolutionize the pharmaceutical industry, bio-remediation and bio-medicine sector (Gokhale et al., 2017, Cruz et al., 2020). Endophytes are recognized as a valuable source of various industrially relevant enzymes viz. asparaginase, amylase, laccase, cellulase, lipase and proteases with promising therapeutic potential (Gupta et al., 2023, Kapoor et al., 2018). In recent years, L-asparaginase has been studied for its antitumor activity against tumors of lymphoid precursor, acute myeloid leukemia, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia. A consistent supply of asparagine, regulated by asparagine synthetase, is essential for protein production in the cell. However, leukemic cells lack asparagine synthetase and rely entirely on the bloodstream for their L-asparagine supply (Brumano et al. 2019). On the other hand, amylases are one of the prime industrial enzymes that encompass a wide spectrum of functional

applications in pharmaceutical, food, textile and detergent industries. Approx. 30% of the total enzyme production globally accounts for amylases (Souza, 2010). Cellulolytic enzymes have been a focal point of research as a mediator of baggase degradation and second-generation ethanol production. Cellulase enzymes supplementation can improve the enzymatic hydrolysis of lignocellulosic biomass, in terms of speed and hydrolysis yield. Proteases have profound applications in bioremediation, cosmetics, silk degumming, animal cell culture, therapy, diagnosis, pharmaceutical and food industry (Singh et al. 2016).

Therapeutic Insights of fungal endophytes

The rising problem of drug resistance in pathogenic microorganisms has become a critical global issue that demands urgent attention. Infectious diseases continue to be a leading cause of death, closely followed by cardiovascular diseases and cancer. To address this issue, researchers are actively seeking new antimicrobial scaffolds that are both highly effective and have minimal side effects. In this regard, endophytic fungi have gained significant attention due to their ability to produce a wide range of bioactive secondary metabolites. The antimicrobial action of these fungal-derived metabolites involves various mechanisms, such as inhibiting cell

wall synthesis, altering plasma membrane integrity, disrupting cellular energy production, interfering with nucleic acid and protein synthesis, and modulating key metabolic pathways (Singh et al., 2021, Pancu et al., 2021, Hards et al., 2018). In addition to their antimicrobial potential, endophytic fungi possess strong antioxidant properties that help combat oxidative stress-related diseases, viz. cancer, neurodegenerative disorders, diabetes, and aging. Reactive oxygen species (ROS) and free radicals contribute to cellular damage, but fungal-derived antioxidants can counteract these harmful effects (Sharifi-Rad et al., 2020, Okagu et al., 2022). According to the literature available on the different Research platforms viz., ResearchGate, Google Scholar, Science Direct, and PubMed, etc. a significant number of antimicrobials, antioxidant, anti-obesity, and anti-inflammatory compounds have been isolated from endophytic fungi from the different sites of Uttarakhand, demonstrating their potential as valuable sources of therapeutic agents.

An endophytic Hyphomycetes *Anguillospora longissima*, isolated from a riparian pteridophytic plant *Equisetum sp.*, from Nainital, Uttarakhand exhibited antibacterial activity against five bacterial strains, namely, *Bacillus subtilis*, *Agrobacterium tumefaciens*, *Escherichia*

coli, *Erwinia chrysanthemum*, and *Xanthomonas pseudomonas* (Sati et al., 2014). Apart from this, Bhardwaj et al. 2015 isolated 17 endophytic fungi including *Alternaria alternata*, *Geptrichium albida*, *Penicillium frequentans*, and *Thielaviopsis basisola* from spikes of *Pinus roxburghii* plant in Pauri, Garhwal region of Uttarakhand, and demonstrated antimicrobial activity against *E. coli*, *S. aureus*, *Salmonella typhimurium*, *Candida albicans*, *Rhizoctonia solani*, and *Cladosporium herbarum* by agar well diffusion assay. Furthermore, A total of six different endophytic fungi which morpho typically and genotypically identified as *Alternaria alternata*, *Daldinia sp.*, *Penicillium oxalicum*, and *Pestalotiopsis neglecta* were isolated from the leaf of *Cupressus torulosa* D. Don. The fungus *P. neglecta* BAB-5510 was potent because the methanolic and ethyl acetate extract of crude showed antimicrobial activity against bacteria such as *S. typhimurium*, *E. coli*, *S. aureus* and *B. subtilis*. Further the extracts also showed the good cytotoxic effect on HEK cell line after 48 h of treatment (Sharma et al., 2016). Another systematic study on *Cupressus torulosa* D. Don plant was conducted in Govind Ballabh Pant Engineering College Campus, Pauri Garhwal, Uttarakhand for the evaluation of their extracellular enzyme production and its role in

biocontrol activity. A total of eight endophytic fungi were isolated from the leaves of *C. torulosa* D. Don by using different media. The Majority of the isolated endophytes belongs to the phylum Ascomycota. The Endophytic fungi PCTS25, WCTS33 and PCTS21 identified as *Penicillium oxalicum*, *Pestalotiopsis versicolorand* and *Alternaria alternata* respectively exhibited antifungal activity against *Aspergillus niger*, and *Fusarium solani* (Mahfooz et al., 2017).

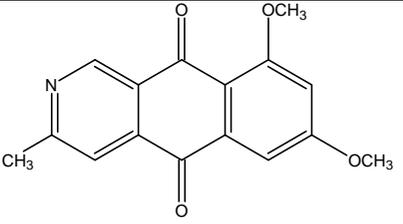
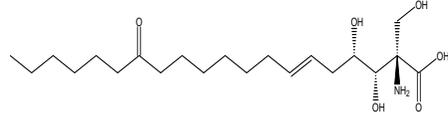
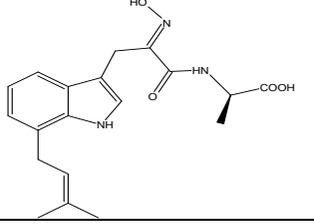
In a similar line, An endophytic fungus, *Alternaria alternata* was isolated from *Picrorhiza kurroa* Royale ex Benth., a member of the *Scrophulariaceae* family, commonly known as "Kutki". This herb, which is an important angiospermic species, naturally grows across the Western to Eastern Himalayan regions of the Indian subcontinent. The antimicrobial properties of methanolic and ethyl acetate extracts from *Alternaria alternata* were tested. The ethyl acetate extract showed activity against three bacterial species, with the highest effectiveness against Gram-positive bacteria, including *Bacillus subtilis* and *Staphylococcus aureus*. However, no antimicrobial effects were observed against *Escherichia coli* or *Serratia marcescens*. The methanolic extract exhibited lower antimicrobial activity compared to the ethyl acetate

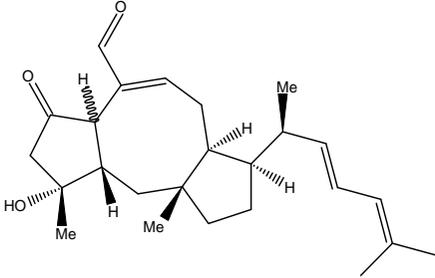
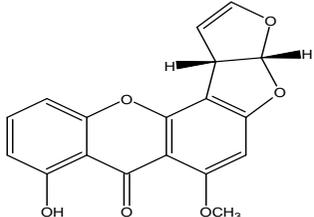
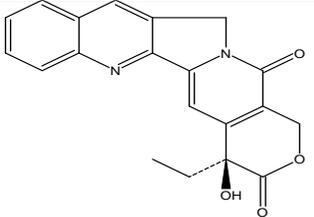
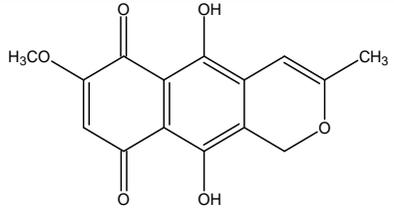
extract, with the greatest inhibition of growth observed for *B. subtilis* and *S. aureus*. Additionally, when compared to broad-spectrum antibiotics like gentamicin and amoxicillin-clavulanate, the ethyl acetate fraction showed comparable antibacterial activity against *Staphylococcus spp.* and *B. subtilis* (Chandra et al., 2021).

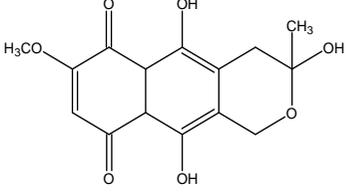
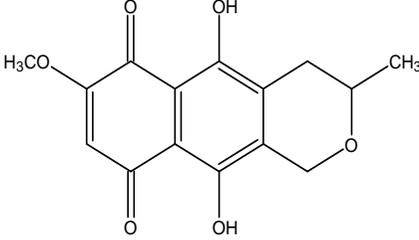
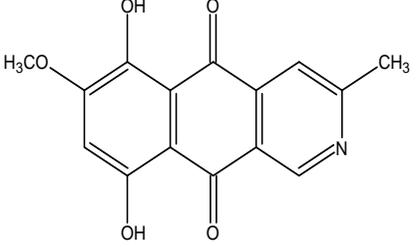
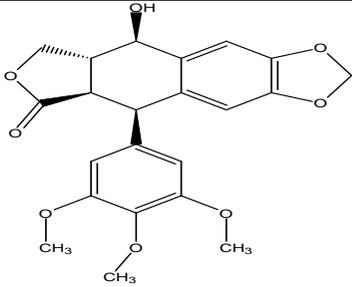
Throughout the ages, *Curcuma longa L.* commonly known as turmeric has a renowned nutritional and therapeutic importance. Each part of the turmeric like rhizome, roots, stems, and leaves has its own medicinal properties. A study was conducted to optimize techniques used in the surface sterilization method for isolating fungal endophytes associated with different parts (rhizome, roots, stem, and leaves) of *Curcuma longa L.* and their antibacterial activity. A total of 38 endophytic fungi of different genera and species were isolated from the different parts of healthy plants. Out of 38, only 11 fungal isolates viz. *Aspergillus sp.*, *Penicillium sp.*, *Cladosporium sp.*, and *Fusarium sp.*, showed antimicrobial activity. Three species of *Aspergillus*, one sterilia mycelia, and two unidentified species showed broad spectrum activity by inhibiting pathogens, i.e., *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus cereus*. *Cladosporium sp.* showed potential

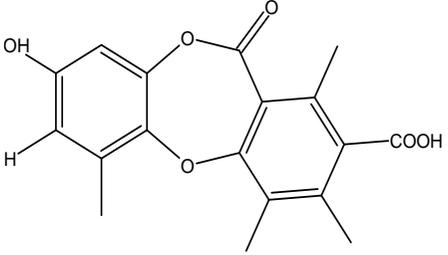
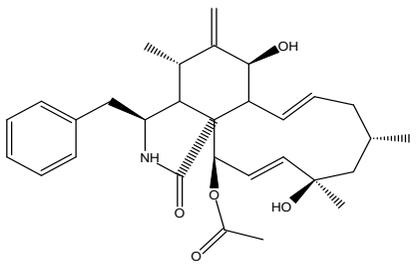
inhibitory activity against *E. coli*, while *Fusarium sp.* was able to inhibit only gram-positive bacteria (Deepak et al., 2022). Furthermore, A study conducted in 2023 to explore the bio-prospection of endophytic fungi from high-altitude medicinal plants viz. *Eclipta prostrata*, *Myrica esculenta*, *Vitex negundo*, and *Withania somnifera* to assess their antibacterial and anti-inflammatory properties. A total of 33 endophytic fungi were isolated, with the highest colonization observed in the leaves of *Myrica esculenta*. Notably, this is the first study to report endophytic fungal colonization in *Eclipta prostrata* and *Myrica esculenta*. The fungal isolates were evaluated for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Proteus vulgaris*. Among them, four isolates #50MEBUKLG, #28(a)MEBUKLG, #42EPCUKLG, and #39WSCUKLG exhibited strong antibacterial effects.

Table 1 Showing details of endophytic fungi secreting compounds analogous to their host plants

| S. No | Endophytic fungi | Host plant | Compound | Structure | Activity | Reference |
|-------|---------------------------|-----------------------------|------------|--|---|----------------------|
| 1. | <i>Lophiostoma</i> sp. | <i>Eucalyptus exserta</i> | Scorpinone |  | Antibacterial | Mao et al., 2021 |
| 2. | <i>Mycosphaerella</i> sp. | <i>Myrciaria floribunda</i> | Myriocin |  | Antifungal | Pereira et al., 2015 |
| 3. | <i>Mucor</i> sp. | <i>Centaurea stoebe</i> | Terezine E |  | Antiproliferative and antifungal activity | Abdou et al., 2020 |

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|----|--------------------------------|--------------------------------------|------------------------------------|--|--|-------------------------------|
| 4. | <i>Aspergillus calidoustus</i> | <i>Acanthospermum australe</i> | Ophiobolin K 6-epi-ophiobolin K |  | Antifungal and Cytotoxic activity | Carvalho et al., 2016 |
| 5. | <i>Aspergillus nidulans</i> | <i>Nyctanthes arbor-tristis</i> Linn | Sterigmatocystin |  | Anticancer activity | Sana et al., 2019 |
| 6. | <i>Phyllosticta elongata</i> | <i>Cipadessa baccifera</i> | Camptothecin |  | Cytotoxic activity | Dhakshinamoorthy et al., 2021 |
| 7. | <i>Fusarium solani</i> | <i>Cassia alata</i> | Anhydrofusarubin |  | Antibacterial, antioxidant, and Cytotoxic activity | Khan et al., 2018 |

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|----|------------------------|------------------------------------|------------------|--|--|---------------------|
| | <i>Fusarium solani</i> | <i>Cassia alata</i> | Fusarubin |  | Antibacterial, antioxidant, and Cytotoxic activity | Khan et al., 2018 |
| | <i>Fusarium solani</i> | <i>Cassia alata</i> | 3-deoxyfusarubin |  | Antibacterial, antioxidant, and Cytotoxic activity | Khan et al., 2018 |
| | <i>Fusarium solani</i> | <i>Cassia alata</i> | Bostrycoidin |  | Antibacterial, antioxidant, and Cytotoxic activity | Khan et al., 2018 |
| 8. | <i>Fusarium solani</i> | <i>Podophyllum hexandrum</i> Royle | Podophyllotoxin |  | Anticancer activity | Nadeem et al., 2012 |

| | | | | | | |
|-----|------------------------------|-----------------------------------|-----------------|---|---|--------------------|
| 9. | <i>Corynespora cassicola</i> | <i>Gongronema latifolium</i> | Corynesidone D |  | Anti-inflammatory and anticancer activity | Okoye et al., 2013 |
| 10. | <i>Phomopsis</i> sp. | <i>Garcinia kola</i> (Heckel) nut | Cytochalasins H |  | Cytotoxic and antibacterial activity | Jouda et al., 2016 |

The most potent activity against *S. aureus* was observed in #50MEBUKLG, while #28(a)MEBUKLG demonstrated the highest inhibition against *E. coli*. Additionally, #28(a)MEBUKLG exhibited the strongest inhibitory effect against *B. subtilis* and *P. vulgaris*. Also, the extract of 28(a)MEBUKLG also shows potent anti-inflammatory activity by the maximum denaturation of albumin with 81.4% denaturation inhibition (Tyagi et al., 2023).

In a similar line, A total of 5 fungal endophytes were isolated from the leaves and stem of *Hibiscus rosa-sinensis*, collected from Dehradun, Uttarakhand. Out of 5 fungal endophytes, *Collectotrichum gloeosporioides* recovered from the stem demonstrated potent antifungal and antibacterial activity against *Klebsiella pneumoniae*, and *Staphylococcus aureus* respectively (Juyal et al., 2023). In line with previous work, five endophytic fungi GBPITWR_F1 (*Penicillium sp.*), GBPITWR_F1 (*P. daleae*), GBPITWR_F1 (*Penicillium sp.*), GBPITWR_F1 (*Aspergillus versicolor*), and GBPITWR_F1 (*Aspergillus sp.*) were isolated from the roots of *T. wallichiana*. Solvent extraction was carried out using four different solvents: hexane, chloroform, ethyl acetate, and methanol. All the isolated endophytes exhibited antibacterial activity against several bacterial species, including *Bacillus subtilis*, *Bacillus megatherium*, *Escherichia coli*, *Serratia marcescens*,

Pseudomonas chlororaphis, and *P. palleroniana*. The Endophytic fungi *Penicillium sp.*, and *Aspergillus versicolor* show the lowest Minimum inhibitory concentration (MIC) against *Pseudomonas chlororaphis*, and *P. palleroniana* with the MIC value of 300 µg/mL (Adhikari et al., 2024). In the same year, a total of 15 endophytic fungi were isolated from the leaves, inflorescence, and stem of *Nardostachys jatamansi* and screened for their anti-obesity and anti-inflammatory potential. Among these, the highest albumin denaturation inhibitory activity of 74.8% was recorded in isolate -22JTM(I), which was later identified as *Fusarium sp.* through morphological and taxonomical analysis. Additionally, six isolates exhibited anti-obesity properties, with four isolates 6(b)JTM (L), -7JTM (S), -23JTM (I), and -25JTM (I) showing complete (100%) lipase inhibition (Kapoor et al., 2024).

Conclusion

The present study has focused on the therapeutic insights of fungal endophytes residing in plants of the Uttarakhand region. Endophytic fungi, which are microorganisms living within plant tissues, have emerged as a promising source of bioactive compounds with significant therapeutic potential. These fungi produce a wide variety of secondary metabolites, including alkaloids, terpenoids, flavonoids,

and polyketides, which exhibit potent antimicrobial, antioxidant, anti-inflammatory, anticancer, and antidiabetic properties. Studies have identified numerous endophytes from medicinal plants, particularly from the Indian Himalayan region, that show promising activities against various pathogens, including bacteria, fungi, and viruses. Additionally, these fungi contribute to plant fitness by producing compounds that enhance plant defense mechanisms. With the growing issue of drug resistance, endophytic fungi are increasingly recognized as sustainable sources of novel therapeutic agents. The exploration of these fungi offers valuable opportunities for the development of new pharmaceuticals and biotechnological applications, including drug discovery and bioremediation, making them crucial to the advancement of medicine and industrial applications.

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