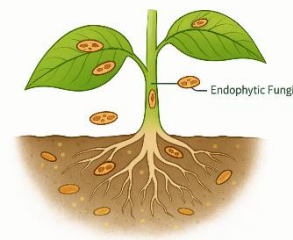


## CHAPTER 15

# Endophytic Fungi and Their Biomedical Significance

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**ABSTRACT:** Endophytic fungi are symbiotic microorganisms that inhabit healthy plant tissues without causing any apparent harm or disease to their hosts. These fungi are widely distributed across diverse plant parts, including roots, stems, leaves, bark, flowers, fruits, and scales, demonstrating their ubiquitous presence and ecological importance. In recent years, endophytic fungi have gained significant attention as a promising and sustainable source of novel bioactive compounds with minimal toxicity. These metabolites exhibit a broad spectrum of therapeutic properties, such as immunosuppressive, anticancer, antioxidant, antiparasitic, anti-inflammatory, and antimicrobial activities. Owing to their metabolic versatility, endophytic fungi offer unique advantages in the discovery and development of new pharmaceutical agents. This chapter provides an overview of the diversity of endophytic fungi, highlights key classes of bioactive compounds derived from them, and explores their biomedical significance. Emphasis is placed on the potential of endophytic fungal metabolites to contribute to drug discovery pipelines and support the development of eco-friendly therapeutic alternatives.

Endophytes exist as living organisms which inhabit healthy plant tissues without causing any disease symptoms or harm to their host plants (Wani et al., 2015). The endophytes present in plants may be bacteria or fungi and they live in plants for prolonged periods or for specified periods in their life cycle. Endophytic fungi protect plants from diseases by producing antibiotics and by activating resistance mechanisms and by competing for colonization areas and nutrients with pathogens (Heydari & Pessaraki, 2010). Endophytic fungi represent a major group of endophytes which display significant diversity with about one million different fungal species that scientists have identified (Nisa et al., 2015). Endophytic fungi support their host plants through two main methods which involve phytohormone production and enhancing plant resistance to different stress factors. The fungi also create pesticides which safeguard plants against herbivorous organisms (Badawy et al., 2021; Abdelaziz et al., 2022).

Endophytic fungi have become a focus of research because they contain diverse bioactive chemicals and some research indicates they exhibit higher metabolic activity than both soil fungi and cyanobacteria-associated fungi (Nisa et al., 2015). Endophytic fungi produce secondary metabolites which consist of terpenoids, alkaloids, quinones, isocoumarins, xanthenes, phenols, and steroids (Manganyi & Ateba, 2020). The fungi produce a wide range of chemically diverse secondary metabolites (Frisvad et al., 2008) which shows antifungal, antiviral, anticancer, antimicrobial and antiparasitic properties (Attia et al., 2022). Numerous studies have reported that endophytic fungi show promising biological effects including antituberculosis (Wijeratne et al., 2013), anti-inflammatory (Tan et al., 2020), antiprotozoal (Pina et al., 2021), antidiabetic (Agrawal et al., 2022), immunomodulatory (Rauf et al., 2022), insecticidal (Zhang et al., 2019) and anthelmintic activities (Manganyi & Ateba, 2020).

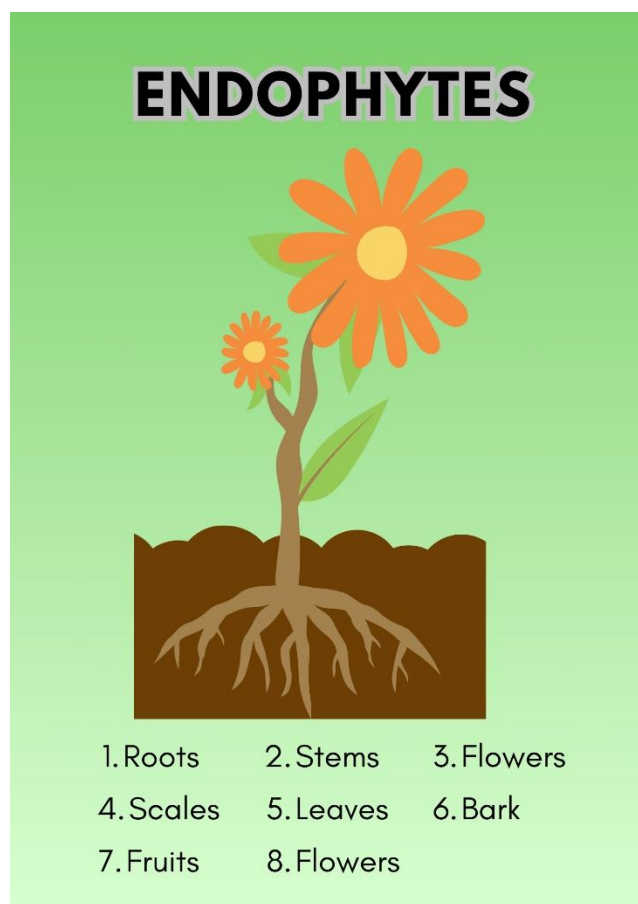
Research studies have established that these fungi function as chemical production centers within plants. Scientists proved that fungal metabolites produced in controlled environments function as alternatives to synthetic chemicals and antibiotics. Microorganisms develop resistance to synthetic chemicals and antibiotics because of their natural ability to adapt to these substances. The accumulation of these substances in the environment creates health dangers for both human beings and animal populations (Dufossé et al., 2021). The production of biologically active compounds from endophytic fungi reaches its highest levels through the application of optimization techniques together with co-culture practices and epigenetic strategies and molecular approaches (Hewage et al., 2014). The current chapter discusses the diversity, metabolites and biomedical potential of endophytic fungi in detail.

## DIVERSITY AND ECOLOGY OF ENDOPHYTIC FUNGI

Endophytes exist within almost every part of plants because they have been detected in scales, stems, leaves, bark, fruits, flowers and roots (Fig. 1) (Pirttilä et al., 2008). Plants serve as natural habitats for numerous endophytic microorganisms which exist in large populations (Abedinzadeh et al., 2019). Scientists isolate endophytes from plants which inhabit various environmental settings including tropical, semi-tropical, and temperate, cold, hot and deep ocean zone (Hashem et al., 2023). Endophytes can also be extracted from seaweeds and marine algae (Lini et al., 2020). The earth supports over 300,000 plant species which host endophytes. Endophytes make up a natural source of biological diversity because modern research has established that hundreds of endophytic fungi genera and species can be extracted from a single plant. Scientists have identified hundreds of genera and species of endophytes in single plants through current biological diversity research (Strobel & Daisy, 2003). The presence of endophytes in a large number elevates our chances to get novel types as well as strains of these microorganisms that exhibit a key role, irrespective of their diversity. Plant microorganisms exist in specific areas because their distribution and density depend on various elements which include plant components, farming methods,

environmental factors, weather conditions and their location (Hashem et al., 2023).

Endophytes establish various types of interactions with their host plants which include benign commensal, symbiotic, decomposer as well as pathogenic effects (Digra & Nonzom, 2023; Promputtha et al., 2007). An endophyte that establishes itself in the host plant tissue remains inactive throughout its life or until environmental factors become suitable for growth. Endophytes stay inactive during this time because they need to detect environmental signals which show when conditions become suitable for their growth and reproduction. The process of coevolution helps the host plant and endophyte build a relationship which benefits both parties. The host plant provides essential nutrients and protection to the endophyte which enables it to live but the endophyte returns this support by generating bioactive compounds that boost the survival prospects of the host plant. Bioactive metabolites produced by endophytes enable host plants to withstand different biotic and



**Fig 1.** The parts of plants where endophytes are present

abiotic stresses while protecting themselves from insect attacks, microbial pests and conserving water. Endophytes function as essential elements in plant symbiosis because they enable plants to defend themselves from pathogens and environmental stressors (Kusari et al., 2014; Tan et al., 2018).

Endophytes evolve continuously to survive environmental conditions which include both living and non-living factors so they form complex bi-, tri-, or multipartite relationships with their host plants. The two organisms form a mutualistic bond which leads to the production of biologically active natural compounds that show potential for medical applications. The flexible relationship between endophytes and their host plants enables them to create multiple bioactive compounds which scientists have identified as medically valuable (Aly et al., 2013; Qadri et al., 2013). Through genetic recombination with plants endophytic fungi have gained the ability to perform host biological functions which results in the production of identical biological metabolites. The metabolic capabilities of these organisms make them essential tools for researchers who want to find natural bioactive compounds (Qadri et al., 2013; Adeleke & Babalola, 2021).

## SECONDARY METABOLITES OF ENDOPHYTIC FUNGI

Endophytic fungi exhibit a wide variety of innovative as well as eco-friendly bioactive plants that show very low toxicity. Natural phytochemicals or bioactive compounds are classified on the basis of their structural properties. These drugs show many biological effects including antioxidant,

immunosuppressive, anti-inflammatory, anticancer, antiparasitic and antimicrobial properties (Omomowo et al., 2023). These substances demonstrate superior antimicrobial effectiveness and economic value when compared to standard antimicrobials while showing reduced potential for bacterial resistance development. The approach serves as an effective method to solve the major problems that public health systems must deal with. The economic evaluation shows that industrial production of fungal endophytes for bioactive compound extraction creates major financial advantages for medical applications (Manganyi & Ateba, 2020). Table 1 demonstrates medicinal properties of metabolites obtained from endophytic fungi.

## ANTICANCER COMPOUNDS FROM ENDOPHYTIC FUNGI

Endophytes generate bioactive substances which mimic the chemical compounds that plants produce during their symbiotic relationships with their hosts (Jia et al., 2016). Endophytic fungi from *Camptotheca acuminata*, *Podophyllum hexandrum*, *Catharanthus roseus* and *Taxus chinensis var. mairei* produce drugs against cancer including podophyllotoxin, camptothecin, vincristine and taxol (Palem et al., 2015; Qiao et al., 2017; Ran et al., 2017).

Endophytes produce unique secondary metabolites that contain novel chemical structures (Pang et al., 2018). The understanding of novel structures present in endophytic fungal metabolites has played a key role in the development of new drugs. The majority of approved small molecule

**Table 1.** Medicinal actions of metabolites from endophytic fungi

Medicinal Action	Metabolites from Endophytic Fungi	Reference
Antimicrobial	2-hydroxyl-6-methyl benzoic acid, Altersolanol A, guignardic acid, colletotric acid, jesterone, xylarenone B, viridicatol, rutin, and pestacin	Gouda et al., 2016
Antifungal	Streptomyces spp. TQR12-4 (isolated from <i>Citrus nobilis</i> )	Singh et al., 2017
Anticancer	Podophyllotoxin (obtained from <i>Trametes hirsute</i> , <i>Phialocephala fortini</i> and <i>Juniperus communis</i> )	Ardalani et al., 2017
Antioxidant	Metabolites from <i>Xylaria</i> and <i>Chaetomium</i> species that are associated with <i>Ginkgo biloba</i> and <i>Nerium oleander</i> plants	Gunasekaran et al., 2015
Antidiabetic	Metabolites from <i>Aspergillus awamori</i>	Singh & Kaur, 2016
Antiviral	Cytonic acid A and cytonic acid B	Omomowo et al., 2023
Immunosuppressive	Colutellin A and subglutinol A	Adeleke & Babalola, 2021

drugs consist of natural substances or synthetic compounds that duplicate natural biological functions or synthetic versions of natural substances (Patridge et al., 2016). The two main reasons these organisms become useful for drug discovery stem from their diverse genetic makeup and their active biological processes (Xiao et al., 2016). Biomolecules are produced by endophytes which increase their adaptability, and they co-evolve with their host plant. This association results in the synthesis of natural compounds. For instance, *Neotyphodium coenophialum* is an endophytic fungus that resides inside *Festuca arundinacea* and synthesizes toxic alkaloids that aid in plant protection from herbivores via fescue toxicosis (Lyons et al., 1986). These alkaloids contain therapeutic properties which scientists investigate for treating multiple medical conditions.

Torreyanic acid is a biologically active substance known for its anticancer potential. It was found in *Pestalotiopsis microspore*, an endophytic fungus which inhabits *Taxus taxifolia*. Reportedly, torreyanic acid triggers programmed cell death in cancer cells through its impact on protein kinase C agonist-sensitive cancer cell types (Lee et al., 1996). Cytochalasins serve as anticancer agents which function as alkaloids produced by 20 species of endophytic fungal genera that include Phoma, Xylaria, Hypoxylon and Chalara (Wagenaar et al., 2000). Camptothecin serves as a powerful antineoplastic agent which is extracted from multiple endophytic fungi including *Entrophospora infrequens* that inhabit *Nothapodytes foetida* (Puri et al., 2005). Scientists discovered irinotecan and topotecan from *Fusarium solani* which lives as a fungus inside *Camptotheca acuminata* plants. Clinical studies have shown these compounds demonstrate effective anticancer drug properties (Kusari et al., 2009a). The endophytic fungi *Colletotrichum gloeosporioides*, *Phomopsis vaccinia*, *Fusarium nematophilum* and *Alternaria alternate* which are associated with *Cyanea acuminata* produce camptothecin (Su et al., 2014).

*Trametes hirsute* functions as an endophytic fungus which produces podophyllotoxin, a nonalkaloid lignin with strong anticancer properties (Puri et al., 2006). Podophyllotoxin and its analogues are also produced by various endophytic fungi i.e., *Phialocephala fortinii*, *Fusarium*

*oxysporum*, and *Aspergillus fumigates* isolated from *Podophyllum peltatum*, *Juniperus communis* and *J. recurve* (Kusari et al., 2009b; Kour et al., 2008; Eyberger et al., 2006). The production of podophyllotoxin and its analogues by these fungi shows that *Trametes hirsute* does exclusively produce these compounds. The research shows that Endophytic *Podophyllum hexandrum* produces three types of lignans (cholagogue, cathartic, and emetic) that display anticancer effects. *P. emodi* produces resins which contain teniposide and etoposide compounds that exhibit strong anticancer properties (Gouda et al., 2016). The plant *Huperzia serrata* produces Huperzine A which functions as a cholinesterase inhibitor (Nair & Padmavathy, 2014). The endophyte *Mycelia sterilia* which is associated with *Catharanthus roseus* generates vincristine, a strong bioactive substance that is used to treat acute lymphoblastic leukemia and neuroblastoma (Yang et al., 1994).

Endophyte characterization has garnered significant attention following the discovery that medicinal plants harbor diverse microorganisms capable of producing bioactive compounds within their tissues and organs (Hassan & Ullah, 2019). Hence, research in medicinal plants may provide valuable information regarding the usage of medicinal plants as alternative sources of medications. The exploration of endophytic communities within medicinal plants leads to the discovery of previously unknown bioactive metabolites which possess substantial pharmacological benefits (Nivetha & Kharwar, 2019). Scientists are conducting research to understand all structural elements and new biological activities of plant-derived endophytic compounds which show medicinal potential for therapeutic use.

## ANTI-INFLAMMATORY EFFECTS OF ENDOPHYTIC FUNGI

The bioactive compounds found in endophytic fungi demonstrate anti-inflammatory effects. Research shows that terpenoids and polyphenols from these substances modify inflammatory pathways which results in decreased development of chronic inflammation. They lower the risk of multiple diseases induced by inflammation (Chen et al., 2018). Endophytic compounds contain

substances that decrease inflammation and also regulate cellular response. The substances help balance immune system responses by blocking the generation of pro-inflammatory molecules which cause inflammation. The body uses this precise control system to manage stress and keep internal balance alongside its function to stop diseases (Deshmukh et al., 2009).

The anti-inflammatory properties help produce various advantages which support both physical health and mental wellness. The substances inhibit chronic inflammation, protect against diseases and also control various medical conditions. *P. brefeldianum*, an endophytic fungus which is isolated from *A. hispida* leaves, produce significant anti-inflammatory effects in the carrageenan-provoked paw-edema model. The research observed changed histological tissue patterns and immunohistochemical markers in paw skin sections together with reduced levels of oxidative stress as well as inflammatory biomarkers (Saleh et al., 2023). Animal studies have shown that decreasing inflammation and tissue damage via endophytic fungi creates opportunities for their human medical applications.

## ANTIVIRAL EFFECTS OF ENDOPHYTIC FUNGI

Fungal endophytes may become a good choice as antiviral agents due to the presence of biologically active substances. In most metabolites discovered, the significant issues in finding antiviral metabolites are ineffective processes. The following antiviral agents have been detected within fungal endophytes: cyclosporin U, podophyllotoxin, cytonic acid A and B, and sequoiatones C-F (Gupta et al., 2020).

Metabolites produced by endophytic fungi exhibit potential efficacy against various viruses i.e., influenza A virus, HIV, human cytomegalovirus and dengue virus (Farooq et al., 2016; Liu et al., 2019). *Cytonaema* species generate two unique substances known as cytonic acid A and B which show promise as antiviral agents (Kumar et al., 2017). New human cytomegalovirus protease inhibitors are discovered from pteridines isomers through mass spectrometry and NMR analysis. Moreover, Hinnuliquinone, produced by a fungus that is present in *Quercus coccifera* leaves,

functions as an antiviral agent which inhibits HIV-1 protease (Kumar et al., 2017). *Pullularia* spp. BCC 8613 produces the metabolite Pullularins A-D which demonstrates antiviral activity against Herpes simplex virus (HSV). *Pestalotiopsis theae* produces Pestalothol-C which shows anti-HIV activity (Kumar et al., 2017).

*Alternaria tenuissima* produces antiviral metabolites which demonstrate activity against HIV-1. *Emericella* species secretes multiple emergent compounds emerimidine (A and B) which show antiviral activity against influenza viruses. *Emericella* also produces emeriphenolicins (A and D), austinol, acetoxyldehydroaustin, dehydroaustin, aspernidine (A and B) and austin which demonstrate antiviral properties against influenza A virus (Raekiansyah et al., 2017). Some actinomycetes also possess antiviral capabilities (Fadji & Babalola, 2020). Scientists discovered *Streptomyces* species GT2002/1503 produces substances which inhibit R5 tropic HIV (Liu et al., 2019). Moreover, 2-(furan-2-yl)-6-(2S, 3S, 4-trihydroxybutyl) pyrazine, a metabolite obtained from *Jishengella endophytica*, inhibits Influenza A virus (Fadji & Babalola, 2020).

## CHALLENGES AND FUTURE DIRECTIONS

Recent years have seen endophytic fungi emerge as key players for natural drug discovery because they produce secondary metabolites which serve as novel medical compounds with reduced toxicity to treat multiple human diseases (Bedi et al., 2018). Despite the significant advancements made in endophytic fungi research, only a few endophytes have been studied yet and most of these organisms still remain uncharacterized. Therefore, there is still a great potential for discovering novel compounds from endophytic fungi (Manganyi & Ateba, 2020; Adeleke & Babalola, 2021). For an effective isolation of endophytes, having notable biological activity, the selection of a specific host plant and its ecological niche is mandatory. Plants that are present in areas with high biodiversity, especially those with endemic species, are more likely to exhibit endophytes with unique chemical properties. Endophyte isolation requires selecting host plants which demonstrate medicinal properties according to standard selection protocols. This method aids in

finding endophytes which produce bioactive substances that benefit human health (Deshmukh et al., 2015). Genome analysis can be used to study plant biosynthetic routes for fungal metabolites. This will provide us the understanding of metabolite production based on verified scientific facts instead of theoretical assumptions (Caruso et al., 2022; Strobel, 2018).

Moreover, advanced cutting-edge methods including epigenetic modifiers and CRISPR-Cas9, exhibit the potential to increase the production of bioactive compounds (Agrawal et al., 2022). Integration of bioinformatics and molecular approaches also provide potential solutions in finding specific fungal strains at species level, so bioactive compounds specific to species can be detected (Meshram & Gupta, 2019). Furthermore, machine learning and artificial intelligence (AI) based techniques can also be used for studying endophytic fungi based bioactive compounds. AI tools have shown their potential in finding hidden patterns, classifying objects and clustering compounds based on their properties (Li et al., 2022). Therefore, with the application of AI, the therapeutic potential of bioactive compounds may be enhanced as it improves the efficiency as well as accuracy of the process via increasing the speed of identification as well as development (Li et al., 2022).

## CONCLUSION

In conclusion, endophytic fungi are a prominent source of bioactive compounds with potential pre-clinical and clinical applications. They possess a variety of metabolites that have antimicrobial, anticancer, antifungal, antidiabetic, antioxidant, antiviral, and immunosuppressive properties. Some endophytic fungi based are used in clinical practice for their significant therapeutic efficiency. Hence, there are still challenges in the identification and isolation of bioactive compounds from endophytic fungi. These problems can be solved via using advanced genomic techniques as well as AI and ML. Till now, further research is needed to determine the exact medicinal potential of endophytic fungi and the compounds obtained from them.

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