



Therapeutic Potential of Secondary Metabolites from Endophytic Fungi in Biotechnology and Medicine

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ABSTRACT

Endophytic fungi, which reside within plant tissues without causing harm, have attracted considerable scientific attention due to their wide-ranging applications. This review delves examines key aspects of research on endophytic fungi, focusing on isolation methods, the production of natural compounds, sampling strategies, and their therapeutic potential. Techniques such as surface sterilization and the use of selective media have revealed a vast diversity of fungi within plant hosts, shedding light on their ecological roles and biotechnological importance. Endophytic fungi are known to produce a variety of natural compounds, particularly secondary metabolites with medicinal properties. Prominent examples include taxol from *Taxus* endophytes and camptothecin from *Camptotheca acuminata* endophytes, both recognized for their anticancer activities. Various sampling strategies, from random collection to host-specific approaches, are essential for uncovering the diversity of these fungi. Additionally, optimization techniques for cultivation and extraction have been developed to maximize the yield of bioactive compounds and ensure sustainable production. Beyond anticancer agents, endophytic fungi have shown potential as sources of antimicrobials, antioxidants, and immunomodulators. These bioactive metabolites offer promising alternatives for drug development, particularly in response to the growing challenge of antibiotic resistance. This review contributes to the growing body of knowledge in the understanding of endophytic fungi and their applications across medicine, agriculture, and biotechnology.

Keywords: Antimicrobials, Bioactive compounds, Endophytic fungi. Secondary metabolites,

Introduction

The prevalence of drug resistance is escalating rapidly, exacerbating the challenge of managing infectious diseases. The efficacy of existing antimicrobial drugs is increasingly compromised

due to rising resistance cases, highlighting the urgent need for innovative solutions that offer lasting efficacy (Suleiman *et al.*, 2016; Pasrija *et al.*, 2022). In response to these health concerns, it is not surprising that many individuals, particularly

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in developing countries, are turning to naturally occurring bioactive compounds for primary healthcare (Anand *et al.*, 2019). Plants produce a wide array of secondary metabolites with significant medical, pharmacological, and industrial applications, all of which are vital to human well-being. However, the growing demand for these metabolites has endangered numerous medicinal plants. The processes involved in extracting plant secondary metabolites are often time-consuming, costly, and labor-intensive (Yeshi *et al.*, 2022).

Plants form symbiotic associations with various microorganisms, leading to the term "endophytic," which has been widely discussed and defined in multiple ways. As first proposed by Anton De Bary in 1886, the term generally refers to any organism that resides within (éndon) a plant (phyton). Endophytic fungi (EF) represent a large and diverse group within endophytes, with an estimated one million different fungal taxa (Abdelaziz *et al.*, 2022). The endophytic community is further classified into two subgroups: 'obligate endophytes,' which depend critically on plant metabolism for survival, and 'facultative endophytes,' which can spend certain stages of their life cycle outside the host, often associating with plants in the surrounding soil environment (Jha *et al.*, 2023).

Endophytes engage in a variety of interactions with their host plants, ranging from symbiotic and benign commensal relationships to decomposer and latent pathogenic associations (Diagra & Nonzom, 2023). Currently, the term "endophytic" encompasses a broad range of microorganisms, including bacteria, fungi, viruses, protozoa, and even microalgae, that inhabit plant tissues without causing harm to their hosts (Noemi & Everlon, 2022). Endophytic fungi can enhance host plant growth by releasing phytohormones or by increasing the plant's resilience to various stresses. Additionally, they can produce insecticides that protect plants from herbivores (Abdelaziz *et al.*,

2022). Under stress conditions, endophytes secrete a variety of stress-responsive molecules such as gibberellins (GB), cytokinins (CIS), salicylic acid (SA), and indole-3-acetic acid (IAA), which promote plant growth, development, and induce several physiological changes (Shaffique *et al.*, 2022).

Almost every plant, particularly woody species, hosts one or more fungal endophytes. These fungal endophytes are found in diverse geographical and climatic zones, displaying a wide distribution and high species diversity. Their ubiquity, diversity, and varied ecological roles suggest that they are well-adapted to their plant hosts under global distribution and selective pressure (Singh & Kumar, 2023). The identification of the plant as a host triggers the activation of virulence mechanisms necessary for colonization and induces host defense responses. This dynamic interaction, best described as balanced antagonism, allows the fungus to thrive by utilizing nutrients from the host while providing benefits such as resistance to biotic and abiotic stresses (Noemi & Everlon, 2022; Bamisile *et al.*, 2018).

Endophytic fungi have become valuable resources in the pharmaceutical and healthcare sectors, serving as sources of novel therapeutic biomolecules. These fungi produce a variety of compounds, including immunosuppressants, anticancer agents, plant growth promoters, antimicrobial volatiles, insecticides, antioxidants, and antibiotics (Mamankey, 2024). Notable examples of medicinal endophytic fungi include *Penicillium chrysogenum*, *Taxomyces andreanae*, *Piriformospora indica*, and *Curvularia protuberata*. These fungi have been found to produce beneficial medicinal substances, such as paclitaxel (taxol) and camptothecin, both of which are anticancer agents, ergoflavin, which has anti-inflammatory properties, and cyclosporine, an antiviral compound (Eid *et al.*, 2021).

This review aims to explore the research surrounding endophytic fungi and their diverse medicinal potentials, with a focus on the isolation of endophytes, the natural production of bioactive compounds, and the optimization of sampling and media for the production of these bioactive molecules.

Isolation of Endophytic Fungi

The concept of the "rhizosphere" was introduced by agronomist and plant physiologist Lorenz Hiltner in 1904, describing the area around a plant's root system that harbors a diverse microbial community. The term has since evolved, and the rhizosphere is now divided into three zones: the endo-rhizosphere, where microorganisms occupy spaces between plant cells; the rhizoplane, which is adjacent to the root epidermal cells; and the ecto-rhizosphere, which surrounds the roots and extends into the surrounding soil, housing free-living or non-symbiotic microorganisms (de Paula *et al.*, 2021).

One of the primary methods for isolating endophytic fungi involves the surface sterilization of plant tissues followed by culturing on selective media. This technique has been widely used across various plant species, revealing a rich diversity of endophytic fungi. For example, a significant number of endophytic fungi with diverse biotechnological potential have been isolated from the medicinal plant *Bauhinia forficata* (Bezerra *et al.*, 2015). Similarly, Rajakumari *et al.* (2018) isolated 25 endophytic fungi from *Calotropis procera*, demonstrating their ability to produce various chemically significant compounds with pharmaceutical importance. The outcomes of the isolation process can vary depending on the type of plant tissue used; for example, in a study by Hastuti *et al.* (2021). Various studies have highlighted the diversity of endophytic fungi across different plant species and tissues. In one study, Hussaini *et al.* (2022) isolated 35 endophytic fungi from the leaves of *Azadirachta indica* and *Mentha piperita*,

identifying genera such as *Trichoderma*, *Penicillium*, and *Aspergillus* (Table 1). Other successful isolations from the leaves and stems of *Stenochlaena palustris* have shown that these fungi produce secondary metabolites with significant antibacterial properties (Aisyah *et al.*, 2023; Mashar *et al.*, 2023).

Natural Products as Bioactive Compounds

Natural products are substances biosynthesized by living organisms, including plants, microbes, and animals (Pang, 2023). The term most commonly refers to secondary metabolites, which are distinct from primary metabolites. While primary metabolites are directly involved in essential growth and developmental processes, secondary metabolites play indirect roles in metabolism and fulfill crucial ecological functions within the organism (Dadwal, 2024). The production of secondary metabolites by fungal endophytes is strongly influenced by various factors such as the timing of sample collection, environmental conditions, the geographical location or habitat of the host plant (with extreme environments like saline habitats, high altitudes, rainforests, deserts, swamps, and marshes being particularly significant), the nutritional source of the host plant, the specific plant tissues (such as roots, leaves, or seeds), and the type of plant (whether angiosperms or gymnosperms) (Aldinary *et al.*, 2021).

Secondary metabolites are typically small organic compounds characterized by diverse chemical structures and biological functions, often possessing low molecular weight (Mosunova *et al.*, 2020). These compounds have had a profound impact on modern medicine, as evidenced by the fact that more than 52% of anti-infective small molecule drugs approved in recent decades originate from natural sources. Furthermore, approximately 42% of new drugs approved over the past 40 years are either natural products or their derivatives (Newman *et al.*, 2020).

Table 1: Functional Group and Bioactive Compounds Produced by the Endophytic Fungi- *Aspergillus fumigatus*

Endophytic Fungus	Compound(s) Produced	Functional Group	Antimicrobial Activity	Reference
<i>Aspergillus fumigatus</i>	Linoleic acid, R-glycerol monolinoleate, bisdethio-(bis-methyl-thio)-gliotoxin, fumiquinazoline F, fumiquinazoline D, deoxythymidine, cerebroside A, (Z,Z)-N,N'-[1-[(4-hydroxyphenyl)methylene]-2-[(4-methoxyphenyl)methylene]-1,2-ethanediyl]bisformamide, pyrazoline-3-one trimer, tricho-9-ene-2 α ,3 α ,11 α ,16-tetraol	Alkaloids, Terpenoids, Steroids, Polyketones, Peptides, Flavonoids, Furandiones, Quinols, Perylene derivatives, Depsipeptides xanthones	Exhibits antimicrobial effects	Sharaff <i>et al.</i> , 2022
<i>Aspergillus fumigatus</i>	Hexadecanoic acid, Hexadecanoic acid methyl ester, bisabolol oxide B, 9,12-octadecadienoic acid, octadecenoic acid, 2-hydroxy-1-ethyl ester, linoelaidic acid, glycidyl palmitate, 9,17-octadecadienal, ethyl-9,12-octadecadienoate, glycidyl oleate, linoleoyl chloride	Alkaloids, Terpenoids, Steroids, Polyketones, Peptides, Flavonoids, Furandiones, Quinols, Perylene derivatives, Depsipeptides xanthones	Exhibits antimicrobial effects	Sharaff <i>et al.</i> , 2022

Sampling and Optimization of Media for the Production of Bioactive Molecules from Endophytic Fungi

In recent years, there has been considerable interest in the sampling and optimization of media for the production of bioactive compounds from endophytic fungi. These fungi are known to generate a wide range of bioactive compounds with diverse biological activities, including antibacterial, antifungal, antioxidant, anticancer, antidiabetic, and antiparasitic properties (Abdalla & McGraw, 2018). The potential of these bioactive compounds in the pharmaceutical industry are significant (Anand *et al.*, 2023).

Isolating endophytic fungi and bacteria with broad bioactivities requires careful consideration of

certain criteria, such as the ethnomedicinal history, habitat, unique biology, and endemism of the plant species. Additionally, it is generally recommended to select healthy-looking plants and young plant tissues over older materials (Yu *et al.*, 2017). Various parts of plants, including seeds, leaves, stems, and bark, serve as reservoirs for endophytes. The process of isolating endophytes involves the chopping of plant material and surface sterilization. Surface sterilization is a critical step to eliminate external materials, molds, and contaminants, thereby promoting the growth of internal microorganisms. This is typically achieved by treating plant materials with surfactants such as ethanol (70-95%) and sodium hypochlorite (NaOCl 2-10%), followed by rinsing with ethanol

and sterile water to remove residual sterilants (Anand *et al.*, 2018).

To enhance the production of bioactive molecules, endophytic fungi can be cultured in optimized media (Table 2). The optimization of media composition, including factors such as carbon and nitrogen sources, pH, temperature, and other variables, is essential for maximizing the yield of

bioactive compounds. Elicitors—biomolecules produced by endophytic fungi, such as polysaccharides, polypeptides, unsaturated fatty acids, and glycoproteins—play a role in protecting plants from pathogenic diseases and also promote the development of various phytochemicals, including alkaloids, flavonoids, terpenoids, saponins, and phenols (Singh & Kumar, 2023).

Table 2: Optimization of Culture Media and Conditions for Enhanced Production of Bioactive Compounds by Endophytic Fungi

Endophytic Fungi	Optimized Media/Conditions	Bioactive Compounds Produced	Key Findings	References
<i>Aspergillus eucalypticola</i> SBU-11AE	Potato Dextrose Agar (PDA), Potato Carrot Broth (PCB), Yeast Extract Peptone Dextrose (YEPD), Malt + Peptone; pH 5-7	Glabaridin	PCB media yielded the highest level of glabaridin (7.26 ± 0.44 mg/L), particularly at pH 6 due to starch and vitamin content supporting fungal growth and bioactive production	Parisa <i>et al.</i> , 2023
<i>Diaporthe</i> sp. GNBP-10	Potato Starch and Dextrose	Bis-anthraquinones	Optimized media with potato starch and dextrose produced the highest Bis-anthraquinones; minerals and excessive proteins had insignificant effects	Listiana <i>et al.</i> , 2023

The optimization of media composition, including carbon and nitrogen sources, pH, temperature, and other factors, plays a crucial role in maximizing the yield of bioactive molecules (Anand *et al.*, 2023).

Diverse Medicinal Potentials

The emergence of resistance among pathogenic microorganisms, the appearance of novel life-threatening viruses, and the increasing prevalence of communicable and non-communicable diseases present an urgent need to explore and utilize new resources that can provide sustainable solutions (Digra, 2023).

Historically, plants have served as a primary source of phytochemicals for the discovery and development of drugs (Adeleke & Babalola, 2021). Endophytes, microorganisms that live symbiotically within plants, and their bioactive

byproducts are promising natural sources for future therapeutics. There has been growing interest in the medicinal potential of endophytes and their metabolites as biotherapeutic agents (Xia *et al.*, 2022).

Endophytic fungi are particularly remarkable for their ability to synthesize a diverse array of compounds with significant medicinal potential, including those with antiviral, antifungal, antibacterial, and anticancer properties. Many endophytic fungi are also potential sources of hormones and plant growth factors (Morales-Vargas, 2024). Additionally, some endophytes secrete extracellular enzymes, such as phosphatases, which convert insoluble phosphates into soluble forms, making them more accessible for plant uptake. The secondary metabolites produced by endophytic fungi enhance the host plant's immune system, which has been shown to

reduce the severity of infections and mitigate damage caused by harmful microorganisms (Sharma *et al.*, 2021). The medicinal roles of endophytic fungi are detailed as follows:

A. Anticancer Compounds from Endophytic Fungi

According to the American Cancer Society (ACS), cancer ranks as the second leading cause of death worldwide. In 2020, the World Health Organization (WHO) reported that approximately 15 million people succumbed to malignant cells, and this number continues to rise. The most common cancers globally include breast, cervical, colon, prostate, oral, rectal, skin, and stomach cancers. The incidence of cancer varies significantly by region and country, with higher rates observed in more developed nations (Ali, 2024). Research is focused on developing innovative anticancer substances and treatments that specifically target cancer cells while minimizing side effects (Zayden *et al.*, 2020). Various factors, such as genetics, lifestyle choices, and access to healthcare, influence the incidence of cancer (Iqbal *et al.*, 2017). Table 3 present anticancer activity of secondary metabolites from Endophytic Fungi.

B. Antidiabetic Compounds from Endophytic Fungi

Diabetes is a metabolic disorder characterized by elevated blood glucose levels, commonly referred

to as blood sugar levels (Usman, 2024). Over time, this condition can lead to severe complications, including damage to the heart, blood vessels, eyes, kidneys, and nerves. Diabetes mellitus is particularly associated with various complications such as retinopathy, nephropathy, cardiovascular diseases, and neuropathy (Munandar, 2024). Secondary metabolites from Endophytic Fungi with Anti-Diabetic and Hypolipidemic Properties are presented in Table 4.

C. Antiviral Compounds from Endophytic Fungi

The continuous emergence of new virus serotypes, characterized by high mutation rates and low replication fidelity, complicates efforts to control these pathogens. With new viruses appearing daily, the current arsenal of vaccines and antivirals is becoming increasingly insufficient. The global challenge of drug resistance underscores the critical need for the development of novel antiviral compounds. Additionally, the growing resistance of human pathogens to existing antibiotics further highlights the urgency for alternative therapeutic strategies. Compounds derived from endophytic fungi present a vast, largely untapped reservoir of chemical structures with significant potential as sources of novel antiviral agents (Rashed, 2024) (Table 5). One of the major obstacles in developing effective antiviral drugs is the inadequacy, inappropriateness, or absence of robust antiviral screening methods.

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Table 3: Anticancer Activity of Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Cancer Type/Cell Line	Activity	Reference
<i>Aspergillus terreus</i> , <i>Penicillium commune</i> , <i>P. chrysogenum</i> , <i>Talaromyces piophilus</i>	<i>Taxus brevifolia</i> , Chilli plant	Taxol	MCF-7, HLK-210, HL-251	Cytotoxic activity	Kumar <i>et al.</i> , 2021
<i>Sinopodophyllum hexandrum</i> , <i>Dyosma veitchii</i>	-	Podophyllotoxin	Leukemia, testicular, prostate, lung, ovarian	Effective in treating multiple cancers	Leung & Cassimeris, 2019
<i>Aspergillus niger</i>	<i>Camptotheca acuminata</i>	Camptothecin	Colon cancer cell lines	Causes apoptosis, cell viability 11.85-65.13%	Aswani & Soundhari, 2018
<i>Fusarium oxysporum</i> , <i>Alternaria sp.</i>	<i>Catharanthus roseus</i>	Vinblastine	HepG-2	Effective at 7.48 µg/mL	Kousar <i>et al.</i> , 2022
<i>Pestalotiopsis microspora</i>	<i>Torreya taxifolia</i>	Torreyanic acid	-	-	Deshmukh <i>et al.</i> , 2019
<i>Mucor fragilis</i>	-	Kaempferol, podophyllotoxin	-	-	Deshmukh <i>et al.</i> , 2019
<i>Xylaria sp.</i> ZJWC255	-	Cytochalasin Q	SMMC-772, MCF-7, MGC80-3	Cytotoxic activity	Deshmukh <i>et al.</i> , 2019
<i>Aspergillus terreus</i> , <i>A. flavus</i>	<i>Ficus elastica</i>	-	MCF7, LS174 T, HCT29, HEPG-2	Possible anticancer properties	El-Sayed <i>et al.</i> , 2021
<i>Chaetomium globosum</i>	-	Flavipin	HT-29, A549	Effective anticancer activity	Senthil <i>et al.</i> , 2019

Table 4: Secondary Metabolites from Endophytic Fungi with Anti-Diabetic and Hypolipidemic Properties

Endophytic Fungus	Host Plant	Compound(s) Produced	Biological Activity	Reference
<i>Nigrospora oryzae</i>	<i>Combretum dolichopetalum</i>	-	Lowering fasting blood sugar levels in diabetic mice	Uzor <i>et al.</i> , 2017
<i>Xylariaceae</i> spp.	<i>Quercus gilva</i> Blume	8-hydroxy-6,7-dimethoxy-3-methyl isocoumarins, abscisic acid, 70-hydroxy abscisic acid, 4-des-hydroxyl altersolanol A	Significant glucosidase inhibitory activity	Indrianingsih & Tachibana, 2017
<i>Fusarium</i> spp., <i>Alternaria</i> spp.	<i>Rauwolfia densiflora</i> , <i>Leucas ciliata</i>	-	Anti-diabetic properties	Adeleke <i>et al.</i> , 2021
<i>Alternaria</i> spp.	-	Glycoprotein (N-acetylgalactosamine)	In vivo and in vitro antidiabetic activity	-
<i>Phoma</i> spp., <i>Aspergillus</i> spp.	<i>Salvadora oleoides</i>	-	Anti-diabetic and hypolipidemic effect in Wistar albino rats	Ezekwesili & Ogbunugafor, 2015
<i>Aspergillus</i> sp.	<i>Sonneratia apetala</i>	Aspergiamides A and F	α-glucosidase inhibitory action with IC50 values of 40 and 83 µM	Ye <i>et al.</i> , 2021
<i>Aspergillus egypticus</i> HT166S	<i>Helianthus tuberosus</i>	Polymethoxylated flavone (K-10)	Inhibition of α-amylase	Ruzieva <i>et al.</i> , 2022
<i>Zasmidium</i> sp. strain EM5-10	Mangrove	Tripalmitin	Significant inhibition of α-glucosidase activity	Lopez <i>et al.</i> , 2019

Table 5: Antiviral Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Target Virus(es)	Biological Activity	Reference
4894 <i>Cytonaema</i> spp.	-	Cytonic acid A, Cytonic acid B	Human cytomegalovirus (HCMV)	Protease inhibition	Gupta <i>et al.</i> , 2020
<i>Trichoderma harzianum</i>	<i>Kadsura angustifolia</i>	Nigranoic acid	HIV-1	Inhibits reverse transcriptase	Wang <i>et al.</i> , 2019
<i>Pestalotiopsis theae</i>	-	Pestalothol-C	HIV	Anti-HIV activities	Wang <i>et al.</i> , 2019
<i>Curvularia papendorffii</i>	<i>Vernonia amygdalina</i>	Crude extract	Coronavirus	Reduces cytopathogenic effects by 40% at low MOI	Khiralla <i>et al.</i> , 2020
<i>Phoma</i> sp.	<i>Aconitum vilmorinianum</i>	Phomanolide	-	-	Liu <i>et al.</i> , 2019
<i>Jishengella endophytica</i>	-	2-(furan-2-yl)-6-(2S, 3S, 4-trihydroxybutyl) pyrazine	Influenza A (H1N1)	Inhibits viral spread	Fadiji & Babalola, 2020
<i>Alternaria</i> sp. QUE1Se	-	Altertoxins	HIV-1	Strong anti-HIV-1 effects	Raekiansyah <i>et al.</i> , 2017
<i>Emericella</i> spp. (HKZJ)	-	Emerimidine (A, B), Dehydroaustin, Austinol, Aspermidine (A, B), Austin, Emeriphenolicins (A, D), Acetoxydehydroaustin	Influenza A (H1N1)	Antiviral activity against influenza A virus	Raekiansyah <i>et al.</i> , 2017
<i>Alternaria alternata</i>	-	Alternariol, Alternariol 9 Methyl Ether	Hepatitis C virus (HCV)	Inhibits HCV NS3/4a protease	El-Kassem <i>et al.</i> , 2019
<i>Cytonaema</i> spp.	-	Cytonic acid A, Cytonic acid B	Human cytomegalovirus (HCMV)	Protease inhibition	Gupta <i>et al.</i> , 2020
<i>Trichoderma harzianum</i>	<i>Kadsura angustifolia</i>	Nigranoic acid	HIV-1	Inhibits reverse transcriptase	Wang <i>et al.</i> , 2019
<i>Pestalotiopsis theae</i>	-	Pestalothol-C	HIV	Anti-HIV activities	Wang <i>et al.</i> , 2019
<i>Curvularia papendorffii</i>	<i>Vernonia amygdalina</i>	Crude extract	Coronavirus	Reduces cytopathogenic effects by 40% at low MOI	Khiralla <i>et al.</i> , 2020
<i>Phoma</i> sp.	<i>Aconitum vilmorinianum</i>	Phomanolide	-	-	Liu <i>et al.</i> , 2019
<i>Jishengella endophytica</i>	-	2-(furan-2-yl)-6-(2S, 3S, 4-trihydroxybutyl) pyrazine	Influenza A (H1N1)	Inhibits viral spread	Fadiji & Babalola, 2020
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<i>Alternaria alternata</i>	-	Alternariol, Alternariol 9 Methyl Ether	Hepatitis C virus (HCV)	Inhibits HCV NS3/4a protease	El-Kassem <i>et al.</i> , 2019

D. Antimicrobial Compounds from Endophytic Fungi

The growing issue of antibiotic resistance among pathogenic bacteria necessitates an urgent search for new antimicrobial agents that are both effective and have fewer or milder side effects. Endophytic fungi, which can reside within plant tissues without causing any apparent harm to their hosts (Sharaf *et al.*, 2022), have emerged as promising sources of such agents (Table 6). These fungi are capable of synthesizing a wide range of secondary metabolites, including alkaloids, terpenoids, flavonoids, and polyketides, which hold significant potential as antimicrobial compounds (Awad, 2024).

E. Immunosuppressive Compounds from Endophytic Fungi

Immunosuppressive drugs are essential for preventing, suppressing, or minimizing organ rejection in transplant patients. They also play a crucial role in effectively managing autoimmune conditions such as lupus, psoriasis, insulin-dependent diabetes, and rheumatoid arthritis (Renda *et al.*, 2021). Despite their importance, these drugs are often associated with significant side effects, underscoring the need for safer alternatives that can provide effective immune modulation with fewer adverse effects (Mohammedsaleh, 2022). Table 7 present a summary of immunosuppressive activity of Secondary Metabolites from Endophytic Fungi.

F. Antiparasitic Compounds from Endophytic Fungi

Protozoan parasites, such as *Trypanosoma cruzi*, *Plasmodium berghei*, *Plasmodium falciparum*, and *Leishmania amazonensis*, are responsible for a range of diseases, including Chagas disease, malaria, and leishmaniasis (Joselin *et al.*, 2021). These vector-borne illnesses are transmitted to humans through the bites or feeding processes of infected mosquitoes or flies. Predominantly

affecting low-income countries, these diseases are classified by the WHO as neglected tropical diseases, receiving limited attention in terms of research and development. The treatments for these conditions face significant challenges, including low efficacy, toxicity, drug resistance, and high cost. Consequently, there is a pressing need to discover new drugs that are effective, safe, and affordable. To address these challenges, efforts are being directed toward various approaches, such as repurposing existing drugs, screening chemical libraries, and developing new candidates using targeted or natural product-based strategies (Table 8) (Capela *et al.*, 2019).

G. Antioxidant Compounds from Endophytic Fungi

Free radicals are unstable molecules generated either naturally through metabolic processes in the body or from external sources such as UV light, pesticides, medications, smoking, and alcohol (Dahan, 2023). These free radicals can damage cells, leading to various diseases, including cardiovascular disorders, diabetes, Down's syndrome, degenerative diseases, Alzheimer's disease, and Parkinson's disease (Saxena *et al.*, 2021). Antioxidant compounds protect cells from damage by neutralizing free radicals, preventing them from causing cellular harm. These antioxidants are also crucial in cancer prevention, as they can interact with and neutralize the free radicals that contribute to the formation of cancer cells (Zhu *et al.*, 2023).

The development of new antioxidant compounds is vital for improving human health and preventing degenerative and other diseases by stabilizing free radicals and reducing cellular damage. The demand for natural antioxidants has surged in recent years due to the growing market for nutritional supplements free from synthetic antioxidants (Gulchin, 2020). While antioxidants are found in various medicinal plants, vegetables, and fruits, the metabolites of fungal endophytes

have also been identified as promising sources of new natural antioxidants (Sharaf *et al.*, 2022). Studies have shown that endophytic fungi can produce a wide range of substances with potent antioxidant properties (Table 9). Some of these

compounds, including phenolic acids, xanthenes, flavonoids, terpenoids, and polyketides, have been successfully isolated and characterized (Mishra *et al.*, 2020).

Table 6: Antimicrobial Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Target Pathogens	Biological Activity	Reference
<i>Aspergillus</i> sp. ASCLA	<i>Callistemon subulatus</i>	Isoshamixanthone	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumonia</i> , etc.	Antibacterial activity	Kamel <i>et al.</i> , 2020
<i>Aspergillus flavus</i>	<i>Ocimum basilicum</i>	-	<i>Staphylococcus aureus</i> , <i>Bacillus cereus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Salmonella typhimurium</i> , <i>Candida albicans</i> , etc.	Antibacterial and antifungal properties	Sharaf <i>et al.</i> , 2022
<i>Aspergillus nidulans</i>	<i>Ocimum basilicum</i>	-	Various resistant microbes	Antibacterial properties	Elkhouly <i>et al.</i> , 2021
<i>Aspergillus fumigatus</i>	<i>Albizia lucidior</i>	-	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Micrococcus luteus</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i>	Antibacterial properties	Hussein <i>et al.</i> , 2022
<i>Aspergillus niger</i> , <i>Emericella</i> sp.	-	Cristatumin B, quiannulatic acid, dihydroauroglaucin	Multidrug-resistant <i>Staphylococcus aureus</i> (MDRSA), <i>Enterococcus faecalis</i> , <i>Klebsiella pneumonia</i> , <i>Pseudomonas aeruginosa</i>	Broad-spectrum antibacterial activity	Elkady <i>et al.</i> , 2022
<i>Athelia rolfsii</i>	<i>Coleus amboinicus</i>	Aromatic molecule with methoxy, hydroxyl, and methyl groups	<i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus mutans</i>	Potent antibacterial action	Astuti <i>et al.</i> , 2020
<i>Aspergillus fumigatus</i>	<i>Ceriops decandra</i>	Fumigatin, fraxetin	<i>Escherichia coli</i> , <i>Micrococcus luteus</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i>	Strong antibacterial activity	Zihad <i>et al.</i> , 2022
<i>Alternaria</i> spp.	<i>Artemisia annua</i>	Altersetin, n-butanol, ethylacetate	Various pathogenic gram-positive bacteria, phytopathogenic organisms	Strong antibacterial action, growth inhibition of phytopathogens	Fadji & Babalola, 2020
<i>Aspergillus tubenginsis</i>	-	Anofinic acid	Gram-positive bacteria, gram-negative bacteria, unicellular fungi	Antibacterial activity, biofilm prevention	Mohamed <i>et al.</i> , 2020
<i>Aspergillus versicolor</i>	<i>Pulicaria crispa</i> (Forssk)	Aspergillethers A and B	<i>Staphylococcus aureus</i> , <i>Bacillus cereus</i> , <i>Escherichia coli</i> , <i>Candida albicans</i> , <i>Geotrichium candidum</i>	High antibacterial action	Maliehe <i>et al.</i> , 2022
<i>Penicillium</i> sp.	<i>Stephania dielsiana</i>	-	Various pathogenic bacteria	Potential antibacterial activity	Wu <i>et al.</i> , 2020
<i>Penicillium citrinum</i>	<i>Azadirachta indica</i>	-	Human pathogenic bacteria and fungi	Potential antibacterial action	Kumari <i>et al.</i> , 2021

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Endophytic Fungus	Host Plant	Compound(s) Produced	Target Pathogens	Biological Activity	Reference
<i>Penicillium ochrochloron</i>	<i>Taxus medium</i>	-Pyrone derivatives	Various pathogenic bacterial and fungal strains	Antibacterial activity (MICs 12.5-100 µg/ml)	Zhao <i>et al.</i> , 2019
<i>Aspergillus alternata</i>	-	Ethyle acetate crude extract	<i>Escherichia coli</i> ATCC 11229, <i>Bacillus subtilis</i> RCMB 015, <i>Staphylococcus aureus</i> ATCC 25923, <i>Candida albicans</i> ATCC 90028	Promising antimicrobial activity	-
<i>Aspergillus destruens</i>	<i>Calotropis gigantea</i>	-	Wide variety of pathogenic bacteria strains	Suppressive activity	Elghaffar <i>et al.</i> , 2022
<i>Fusarium spp.</i>	-	-	Various bacterial and fungal strains	Antibacterial action	Elghaffar <i>et al.</i> , 2022
<i>Trichoderma harzianum</i>	<i>Rosmarinus officinalis</i>	-	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumonia</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i>	Growth inhibition	Abdulhadi <i>et al.</i> , 2020
<i>Trichoderma virens</i>	<i>Artemisia argyi</i>	Trichocadinins B–G, cadinane-type sesquiterpene derivatives	-	Antibacterial properties	Shi <i>et al.</i> , 2019
<i>Chaetomium globosum</i>	-	Equisetin	Drug-resistant microorganisms	Antibacterial effectiveness	Zhao <i>et al.</i> , 2019
<i>Xylaria ellisii</i>	-	Ellisiamide A	<i>Escherichia coli</i>	Bacterial activity	Ibrahim <i>et al.</i> , 2020
<i>Diaporthe terebinthifolii</i>	<i>Schinus terebinthifolius</i>	Orthosporin, diaporthin	-	Antibacterial properties	de Medeiros <i>et al.</i> , 2018

Table 7: Immunosuppressive Activity of Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Immunosuppressive Activity	IC50/Effect	Reference
<i>PGS1, NLL3</i>	<i>Psidium guajava</i> , <i>Newbouldia laevis</i>	Citrinin, nidulalin, p-hydroxybenzoic acid, cyclophenin	Linked to immunosuppressive effects	-	Ujam <i>et al.</i> , 2021
<i>Mycosphaerella nawae</i> ZJLQ129	-	Mycousnine enamine	Specifically decreases T-cell proliferation	Blocks expression of CD25 and CD69	Wang <i>et al.</i> , 2017
<i>Penicillium sp.</i> ZJ-SY2	<i>Sonneratia apetala</i>	Peniphenone, methyl peniphenone, seven xanthenes	Strong immunosuppressive effects	IC50: 5.9 to 9.3 µg/mL	Liu <i>et al.</i> , 2016

Table 8: Antiplasmodial Activity of Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Plasmodium Strain	IC50 Value (µg/mL)	Reference
<i>Aspergillus terreus</i>	<i>Artemisia annua</i>	-	<i>Plasmodium falciparum</i>	35.0	Kumarihamy <i>et al.</i> , 2019
<i>Penicillium commune</i>	<i>Artemisia annua</i>	-	<i>Plasmodium falciparum</i>	1.1	Kumarihamy <i>et al.</i> , 2019
<i>Penicillium chrysogenum</i>	<i>Artemisia annua</i>	-	<i>Plasmodium falciparum</i>	3.3	Kumarihamy <i>et al.</i> , 2019
<i>Talaromyces piophilus</i>	<i>Artemisia annua</i>	-	<i>Plasmodium falciparum</i>	7.6–9.9	Kumarihamy <i>et al.</i> , 2019
<i>Nemania</i> sp. UM10M	-	Epoxychothalasin C	<i>Plasmodium falciparum</i>	Relatively weak	Kumarihamy <i>et al.</i> , 2019
Endophytic fungal strains IP-2 & IP-6	<i>Artemisia annua</i>	-	<i>Plasmodium falciparum</i>	30.0, 42.0	Kumarihamy <i>et al.</i> , 2019
<i>Penicillium citrinum</i> AMrb11	-	-	<i>Plasmodium falciparum</i> (Pf3D7 & PfINDO/PfDd2)	0.84–0.93	Ujam <i>et al.</i> , 2022
<i>Neocosmospora rubicola</i> AMb22	-	-	<i>Plasmodium falciparum</i> (Pf3D7 & PfINDO/PfDd2)	0.39–1.92	Ujam <i>et al.</i> , 2022
<i>Neocosmospora rubicola</i>	<i>Azadirachta indica</i>	-	<i>Plasmodium falciparum</i>	Dose-dependent	Ujam <i>et al.</i> , 2022
<i>Aspergillus versicolor</i>	-	-	<i>Plasmodium falciparum</i>	-	Toghueo <i>et al.</i> , 2019
<i>Trichoderma afroharzianum</i>	-	-	<i>Plasmodium falciparum</i>	-	Toghueo <i>et al.</i> , 2019
<i>Fusarium</i> sp.	-	-	<i>Plasmodium falciparum</i>	-	Toghueo <i>et al.</i> , 2019

H. Antifungal Compounds from Endophytic Fungi

Pathogenic fungi are responsible for millions of deaths annually, as well as significant damage to agricultural products. The increasing resistance of these fungi to existing antifungal medications further exacerbates the issue (Almeida *et al.*,

2019). This growing problem underscores the urgent need for new bioactive compounds that are effective against resistant fungal strains. Among the promising candidates are bioactive compounds produced by endophytic fungi, including triterpenoids, sesquiterpenes, and diterpenoids, which have shown potential in combating plant fungal infections (Xu *et al.*, 2021).

Table 9: Antioxidant Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Biological Activity	Reference
<i>Epicoccum nigrum</i>	<i>Acanthus ilicifolius</i> L.	Bioactive substances	Antioxidant and α -glucosidase inhibitory action	Yan <i>et al.</i> , 2020
<i>Aspergillus oryzae</i> DK7	<i>Mangifera casturi</i> Kosterm	-	Antioxidant activity (IC50: 142.96 μ g/mL)	da Silva <i>et al.</i> , 2020
<i>Aspergillus minisclerotigens</i> AKF1	<i>Mangifera casturi</i> Kosterm	-	Antioxidant activity (IC50: 145.01 μ g/mL)	da Silva <i>et al.</i> , 2020
<i>Penicillium</i> spp.	-	Ferulic acid, cinnamic acid, quercetin, rutin	Antioxidant activity	Nischitha <i>et al.</i> , 2021
<i>Curvularia</i> sp.	-	Antioxidants	Antioxidant activity	Kalimuthu <i>et al.</i> , 2022
<i>Curvularia lunata</i>	-	Antioxidants	Antioxidant activity	Ye <i>et al.</i> , 2021
<i>Colletotrichum</i> sp.	-	Antioxidants	Antioxidant activity	Palupi <i>et al.</i> , 2021
<i>Cladosporium tenuissimum</i>	-	Antioxidants	Antioxidant activity	Fadhillah <i>et al.</i> , 2019
Various endophytic fungi	Medicinal plants from Central Sulawesi	-	High antioxidant and antibacterial activities	Raunsai <i>et al.</i> , 2018
Fungal endophytes ZA 163, MO 211, LO 261, FE 082, FE 084	<i>Albizia zygia</i> , <i>Millettia thonningii</i> , <i>Alchornea cordifolia</i> , <i>Ficus exasperata</i>	Pyrogallol, dl-alpha-tocopherol, Alpha tocospino, Linoleic acid, 9-octadecenamide, lupeol, 9-octadecenoic acid (Z)	Antioxidant activity	Ibrahim <i>et al.</i> , 2021
<i>Alternaria alternata</i>	<i>Azadirachta indica</i>	-	Antioxidant activity (IC50: 38 μ g/mL)	Chatterjee <i>et al.</i> , 2019
<i>Penicillium citrinum</i>	<i>Azadirachta indica</i>	-	Antioxidant activity (IC50: 52.13 μ g/mL)	Chatterjee <i>et al.</i> , 2019
<i>Chaetomium</i> sp., <i>Colletotrichum</i> sp., <i>Curvularia</i> sp., <i>Trichoderma</i> sp.	Related host plants	Antioxidants	Antioxidant activity (31-69%)	Kumaresan <i>et al.</i> , 2015

Table 10: Antifungal Secondary Metabolites from Endophytic Fungi

Endophytic Fungus	Host Plant	Compound(s) Produced	Target Fungus	Biological Activity	Reference
<i>Xylaria</i> sp.	<i>Paullinia cupana</i> (Guarana plant)	Cytochalasin D	<i>Colletotrichum gloeosporioides</i>	Fungistatic action	Elias <i>et al.</i> , 2018
<i>Mucor</i> sp.	<i>Centaurea stoebe</i>	14-hydroxyterezine D, Terezine E	<i>Aspergillus terreus</i>	Weak antifungal activity (MICs: 127.8 µg/ml and 111.2 µg/ml, respectively)	Abdou <i>et al.</i> , 2018
<i>Trichoderma koningiopsis</i> YIM PH 30002	<i>Panax notoginseng</i>	Koningiopisin C	<i>Plectosphaerella cucumerina</i>	Antifungal activity (MIC: 57.1 µg/ml)	Liu <i>et al.</i> , 2016
<i>Drechslera</i> sp. strain 678	<i>Neurachne alopecuroidea</i> (Australian grass)	-	Various plant pathogens	Broad-spectrum potency against plant diseases	d'Errico <i>et al.</i> , 2020
<i>Colletotrichum gloeosporioides</i>	<i>Artemisia mongolica</i>	Colletotric acid	Various fungi	Antifungal properties	Li <i>et al.</i> , 2019
-	-	Roridoxins A and C	<i>Alternaria tenuissima</i> , <i>A. niger</i> , <i>Pyricularia grisea</i> , <i>Fusarium oxysporum</i>	Significant antifungal effects	Li <i>et al.</i> , 2019
-	-	Trichobreols	Pathogenic yeast-like fungi	Effective antifungal efficacy	Yamazaki <i>et al.</i> , 2020
<i>Aspergillus</i> spp., <i>Penicillium</i> spp., <i>Trichoderma viride</i>	-	Synthetic griseofulvin derivatives	Various fungi	More effective than bifonazole and ketoconazole (3–16 fold and 7–42 times, respectively)	Kartsev <i>et al.</i> , 2019
<i>Aspergillus</i> sp.	<i>Brassica napus</i> (Oilseed rape plant)	Penicillither, Methyl dichloroasterrate	<i>Botrytis cinerea</i> , <i>Monilinia fructicola</i> , <i>Sclerotinia sclerotiorum</i> , <i>S. trifoliorum</i>	Inhibitory effects (EC50s: 21.7 to 151.2 µg/ml)	Qin <i>et al.</i> , 2019
<i>Phomopsis</i> sp. YE3250	<i>Paeonia delavayi</i> (Medicinal plant)	Phomopoxides B, C, D, F, G	<i>Candida albicans</i> , <i>Aspergillus niger</i> , <i>Pyricularia oryzae</i> , <i>Fusarium avenaceum</i> , <i>Hormodendrum compactum</i>	Antifungal activity (MICs: 46.5-372.1 µg/ml)	Huang <i>et al.</i> , 2018

Conclusion

Endophytic fungi represent a promising and largely untapped source of bioactive compounds with significant therapeutic potential. This review has highlighted the broad spectrum of medicinal compounds produced by endophytic fungi, including anticancer, antidiabetic, antiviral, antimicrobial, immunosuppressive, antiparasitic, antioxidant, and antifungal agents. The ability of these fungi to synthesize novel and potent bioactive molecules positions them as invaluable resources in the discovery and development of new therapeutic agents.

Despite the promising in vitro activities demonstrated by these compounds, transitioning from laboratory research to clinical applications remains a substantial challenge. Future research should focus on optimizing extraction and purification processes, elucidating mechanisms of action, and conducting comprehensive in vivo studies to establish the safety and efficacy of these compounds. Additionally, advancements in biotechnology and synthetic biology could be leveraged to enhance the production and scalability of these bioactive compounds, potentially accelerating their integration into clinical practice.

Endophytic fungi hold great promise as sustainable sources of new pharmaceuticals. Continued exploration and development of these fungi could lead to innovative solutions to some of the most pressing health challenges, potentially revolutionizing future therapeutic practices.

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