

Review Article

Secondary metabolites of endophytic fungi -source of bioactive compounds

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Article Info

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Abstract

Endophytic fungi, dwelling harmoniously within the internal tissues of plants, have emerged as a veritable treasure trove of bioactive secondary metabolites with diverse pharmacological properties. This article delves into the fascinating world of endophytic fungi, exploring their impressive diversity and the multitude of bioactive compounds they produce, such as alkaloids, terpenoids, polyketides, peptides, and phenolic compounds. Notably, many of these secondary metabolites exhibit potent antimicrobial and antifungal activities, making them promising candidates for drug development. This review draws on compelling examples from scientific literature to shed light on the potent pharmacological potential of endophytic fungi's secondary metabolites and their promising applications in combating infectious diseases.

As we unveil the myriad of opportunities that endophytic fungi offer for modern medicine, we also recognize their integral role in promoting ecological balance and sustainable practices. By delving into the synergistic relationship between plants and these enigmatic fungi, we unlock nature's pharmacy and harness its potential for the betterment of human health and environmental sustainability.

Keywords: endophytic, fungi, alkaloids, terpenoids, polyketides, peptides, and phenolic compounds.

Introduction

Endophytic fungi, a diverse group of microorganisms, quietly establish a mutualistic relationship with plants, residing in their internal tissues without causing obvious symptoms of disease. These enigmatic fungi, present in a variety of plant species including medicinal plants, have recently attracted the attention of researchers due to their potential as a source of bioactive secondary metabolites. These diverse metabolites hold great promise as potential sources of pharmacologically effective drugs with remarkable antimicrobial and antifungal properties. In this article, we explore the fascinating world of endophytic fungal secondary metabolites, highlighting the diverse classes and bioactivities that position them as potential revolutionaries in the search for new therapeutics[1].

It is widely documented that endophytic fungi are important contributors to the complex plant microbiome, forming intimate relationships with their host plants. Unlike pathogens, these fungi coexist peacefully within plant tissues, offering numerous benefits to their hosts. Studies have indicated that endophytic fungi contribute significantly to plant growth, nutrient uptake, stress tolerance, and disease resistance. Their presence in medicinal plants has piqued the curiosity of scientists, as these fungi have the potential to biosynthesize various bioactive compounds of pharmacological import [2].

Endophytic fungi are prolific producers of secondary metabolites, which are chemical compounds not directly involved in the primary processes of growth and development. These metabolites often serve specialized functions such as defense against predators, pathogens, and environmental stressors. The vast diversity of endophytic fungi enables each species to synthesize a unique set of secondary metabolites, offering an extensive reservoir of bioactive compounds for exploration [3].

Secondary metabolites produced by endophytic fungi have garnered considerable attention due to their remarkable biological activities. Among the diverse spectrum of bioactive

compounds, those with potent antimicrobial and antifungal properties are particularly noteworthy. These compounds present exciting opportunities for drug discovery, as they may be key in combating drug-resistant bacteria and emerging fungal infections [4].

To understand the potential of endophytic fungi as sources of pharmacologically potent drugs with antimicrobial and antifungal properties, extensive research has been conducted to isolate, identify, and characterize these bioactive secondary metabolites.

Diversity of secondary metabolites of endophytic fungi

Alkaloids: Alkaloids, nitrogen-containing compounds, are known for their significant biological activity, including antimicrobial properties. For instance, the study by Du et al. [5] isolated Securinega-type alkaloids from endophytic fungi (*C. globosum* and *Fusarium sp.*) associated with *Securinega suffruticosa*, demonstrating strong antimicrobial activity.

Similarly, Xie et al. [6] identified three novel secondary metabolites, including rotational isomers of brasylamide J-a, brasylamide J-b, and penicillic acid from the endophytic fungus *Penicillium janthinellum* isolated from notoginseng, with notable antibacterial activity against drug-resistant bacteria.

Terpenoids: Terpenoids, a class of compounds derived from isoprene units, have been extensively researched for their antifungal potential. For example, research has indicated that terpenoids produced by the endophytic fungus associated with *Cinchona ledgeriana* exhibit antifungal properties. In a study by Sobhy et al. [7], terpenoids isolated from an endophytic fungus in *Cinnamomum camphora* demonstrated significant antifungal activity against various pathogenic fungi. In contrast, Xie et al. [6] reported that a combination of botriospherin H and 13,14,15,16-tetranorlabd-7-ene-19,6 β :12,17-diolide showed strong antifungal activity against pathogens including *Gaeumannomyces graminis* and various *Fusarium species*.

Polyketides: Polyketides, complex compounds synthesized from acetyl and propionyl

subunits, have garnered attention for their antimicrobial properties. For instance, Flewelling et al. [8] isolated a polyketide from the endophytic fungus *Aspergillus fumigatus* with inhibitory effects on *Mycobacterium tuberculosis* and significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

Ola et al. [9] isolated the antimicrobial polyketide palitantin from *Aspergillus fumigati*affinis, which was effective against multidrug-resistant pathogens such as *Enterococcus faecalis* UW 2689 and *Streptococcus pneumoniae* 25697.

Polypeptides: Bioactive polypeptides and peptides have emerged as promising candidates for antimicrobial therapy. Endophytic fungi from plants like *Hordeum vulgare* have been found to produce bioactive enniatins with antimicrobial properties. Zaher et al. [10] reported the isolation of trichosetin and beauvericin A from the endophytic fungus *Fusarium sp. TP-G1*, which exhibits potent antibacterial activity against strains including *Staphylococcus aureus* and MRSA.

Phenolic compounds:

Phenolic compounds, characterized by aromatic rings bearing hydroxyl groups, display a range of biological activities, including antimicrobial and antifungal effects. Subban et al. [11] isolated a novel phenolic compound, 4-(2,4,7-trioxabicyclo[4.1.0]heptan-3-yl)phenol, from the endophytic fungus *Pestalotiopsis mangiferae* associated with *Mangifera indica L.*, which showed significant antimicrobial and antifungal activity against a variety of pathogens. A transmission electron microscopy study of the compound's mode of action revealed the destruction of bacterial cells, evidenced by cytoplasmic agglutination and the formation of pores in cell wall membranes.

Endophytic fungi have become a significant source of bioactive secondary metabolites with diverse pharmacological properties. Besides their potential as antimicrobial and antifungal agents, these microorganisms are also

promising in antiviral and antioxidant therapies.

Biological activities of the secondary metabolites of endophytic fungi

Antiviral properties.

Influenza is a persistent global health challenge. Studies have investigated the production of antiviral metabolites by endophytic fungi targeting influenza viruses. Liu et al. [12] identified a novel 14-nordrimane sesquiterpenoid from the endophyte *Phoma sp.*, isolated from the roots of *Aconitum vilmorinianum*, which inhibited the growth of influenza A virus (A/Puerto Rico/8/34, H1N1). Zhao et al. [13] discovered a novel compound, APL-16-5, from *Aspergillus sp.*, which exhibited potent in vivo activity against the influenza A virus (IAV), suggesting its potential as a therapeutic agent.

HIV remains a critical medical issue, with the need for novel antiviral agents being imperative. Endophytic fungi have shown potential in producing anti-HIV metabolites. Nzimande et al. [14] found a novel compound from the endophytic fungus *Alternaria alternata* from *S. birrea* and *Hypoxis species* with potential as an anti-HIV agent.

Antimicrobial activities.

The escalating global challenge of antimicrobial resistance necessitates an unrelenting quest for novel and efficacious antimicrobials. Secondary metabolites from endophytic fungi are emerging as a promising avenue in drug discovery due to their rich repertoire of bioactive compounds that exhibit significant antibacterial and antifungal properties. The diversity inherent in these metabolites presents unprecedented opportunities to identify innovative antimicrobials to counteract drug-resistant pathogens. Silva et al. [15] underscored the capability of endophytic fungi to synthesize compounds with antimicrobial efficacy against multidrug-resistant bacteria, heralding a new frontier in antibiotic development.

Fungal infections present a considerable threat to human health, particularly among immunocompromised populations. The current antifungal pharmacopeia is limited in efficacy and compromised by increasing drug resistance. Secondary metabolites from endophytic fungi offer a novel paradigm to bolster antifungal strategies. These biologically active compounds have demonstrated remarkable efficacy against a spectrum of pathogenic fungi, inclusive of drug-resistant strains. Huang et al. [16] illustrated the capacity of endophytic fungi to generate antifungal agents, marking a significant stride towards innovative antifungal therapies.

Kouipou Toghueo and Boyom [17] exhibited the antifungal promise of compounds sourced from endophytic fungi against *Candida albicans*, heralding new prospects for developing ground-breaking antifungal treatments.

Anticancer properties.

Cancer continues to impose a heavy global health burden, underscoring the imperative for novel anticancer agents. Endophytic fungi have been recognized for their production of bioactive compounds with anticancer properties. These diverse compounds have been observed to selectively exert cytotoxic effects on cancer cells, prompting apoptosis and cell cycle arrest. Na et al. [18] revealed the proficiency of endophytic fungi in synthesizing polyketides with significant anticancer activity against various cancer cell lines, instigating a revival of interest in natural products within cancer therapy. Further, Lai et al. [19] shed light on the anticancer potential of polyketides derived from endophytic fungi, illustrating their promise in the innovation of cancer treatment modalities.

Antioxidant properties. Phenolic compounds from endophytic fungi are notable for their robust antioxidant properties, scavenging free radicals, and reducing oxidative stress. Danagoudar et al. [20] identified phenolic compounds from an endophytic fungus

Aspergillus austroafricanus in *Zingiber officinale* with significant antioxidant activity. Endophytic fungi produce other antioxidants like flavonoids, alkaloids, and polyphenols. These contribute to the host plant's antioxidant defenses and may have therapeutic applications against oxidative stress-related diseases. Huang et al. [21] reported that rutin, a flavonoid glycoside, was produced by *Xylaria sp.* from *Ginkgo biloba* and *Chaetomium sp.* from *Nerium oleander*, showing potent antioxidant and potential neuroprotective properties. Liu et al. [22] discovered flavonoids from an endophytic fungus associated with *Ginkgo biloba*, exhibiting strong antioxidant effects.

Conclusion

The exploration of secondary metabolites produced by endophytic fungi has catalyzed a symphony of discovery, revealing potential applications in both pharmaceuticals and ecology. By identifying novel antimicrobials, strengthening antifungal strategies, and uncovering new anticancer therapeutics, we pave the way for a future of advanced medicine enriched with bioactive compounds from endophytic fungi. Additionally, the ecological impact of these compounds supports a holistic strategy for promoting sustainable agriculture and environmental stewardship. With ongoing research and interdisciplinary collaboration, the diverse world of endophytic fungi promises to address global health challenges and enhance ecological sustainability.

Although often eclipsed by their more conspicuous counterparts, endophytic fungi have emerged as a promising source of pharmacologically active drugs. The vast array of secondary metabolites they produce, particularly those with antimicrobial and antifungal attributes, opens new avenues for drug discovery and development. These metabolites are at the forefront of efforts to combat infectious diseases and the escalating issue of drug resistance, while also improving overall human health. Moreover, a deeper understanding of the critical role of endophytic fungi in ecological balance and sustainable

development underscores the need for their study and conservation.

Endophytic fungi harbor a remarkable diversity of secondary metabolites that could serve as a repository of pharmacologically effective drugs. These metabolites, as gateways to new therapeutics, offer a promising alternative to conventional antibiotics and antifungals, particularly in the fight against drug-resistant pathogens.

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