



**EXPLOITING ENDOPHYTIC FUNGI FROM MEDICINAL
PLANTS FOR NEW ANTIMICROBIAL AGENTS AGAINST
RESISTANT PATHOGENS**

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ABSTRACT

Amidst the escalating global health challenge of antibiotic resistance, this review underscores the critical need for novel antimicrobials. It showcases endophytic fungi as a largely untapped reservoir of bioactive secondary metabolites, capable of yielding novel antibiotics to combat multidrug-resistant bacteria. These fungi, through symbiosis with host plants, produce an array of bioactive compounds, including alkaloids, terpenoids, polyketides, peptides, and phenolic compounds, exhibiting potent antimicrobial properties. This synthesis of evidence highlights the synergistic interplay between endophytic fungi and medicinal plants, advocating for intensified research into their unique chemical structures and bioactivities. Such efforts promise sustainable strategies to address antibiotic resistance.

Introduction

The World Health Organization (WHO) has identified antibiotic resistance as a top ten global public health threat to humanity, highlighting an urgent demand for novel antimicrobial agents [1]. Among the most promising avenues of research are endophytic fungi—microorganisms residing within plant tissues that have garnered attention for their potential to produce a wide array of bioactive secondary metabolites with antimicrobial capabilities[2,3]. These symbiotic organisms coexist with their plant hosts, synthesizing compounds that are sometimes analogous to plant-derived substances and at other times entirely unique, offering a new frontier in the battle against multidrug-resistant pathogens.

The diversity and symbiotic nature of endophytic fungi facilitate the production of secondary metabolites, including alkaloids, terpenoids, polyketides, peptides, and phenolic compounds, with demonstrated antimicrobial efficacy [3,4]. The cultivation of these fungi under controlled laboratory conditions has proven to be an effective strategy for the discovery and analysis of novel bioactive compounds, positioning endophytes as critical players in the development of alternative therapies to counteract antibiotic resistance.



The global escalation of infections caused by antibiotic-resistant bacteria, fungi, and viruses poses a significant challenge, especially in regions with limited healthcare resources [5,6]. Traditional use of medicinal plants, known for their repertoire of natural bioactive substances such as essential oils, alkaloids, and phenolic compounds, has played a pivotal role in treating infectious diseases. The continuing emergence of multidrug-resistant pathogens underscores the imperative need to explore natural sources, like endophytic fungi, for new antimicrobial agents.

This article aims to delve into the symbiotic relationships, metabolic diversity, and promising antimicrobial properties of endophytic fungi. Through a comprehensive exploration of their role in antimicrobial discovery, we underscore the critical importance of leveraging these natural resources to address the burgeoning global challenge of antibiotic resistance, illuminating pathways to innovative antimicrobial solutions and reinforcing the significance of endophytic fungi in enhancing global health and infectious disease management.

Endophytic microorganisms, including bacteria such as *Bacillus megaterium*, *Micrococcus luteus*, *Pseudomonas sp.*, and *Acinetobacter calcoaceticus*, isolated from various medicinal plants, have also demonstrated significant antimicrobial activities [7]. These findings further support the broad antimicrobial potential of endophytes and underscore the necessity for continued research and development of new therapies derived from these unique symbiotic relationships.

The urgent need to combat antibiotic resistance has led to increased scrutiny of the rich biodiversity within medicinal plants such as *Peganum harmala*, the *Ferula* genus, and *Ajuga turkestanica*, and their endophytic fungi. These entities have been identified as significant sources of bioactive compounds with broad therapeutic applications, underscoring the critical role of natural products in drug discovery.

Peganum harmala:

Peganum harmala, a perennial herb indigenous to the arid regions of Asia, is renowned in traditional medicine for its multifaceted therapeutic applications, including its analgesic, diuretic, antithrombotic, antiseptic, and abortifacient properties. Its seeds are rich in alkaloids such as harmaline and harmine, which exhibit potent pharmacological effects, including anti-mutagenic and abortifacient activities [8,9]. Furthermore, β -carbolines derived from *P. harmala* have demonstrated a spectrum of pharmacological activities, including antitumor, antiviral, antimicrobial, and antiparasitic effects, highlighting the plant's significant medicinal value [10].

Ajuga turkestanica:

Native to Central Asia, *Ajuga turkestanica* has been traditionally valued for its muscle strength enhancement and cardiovascular disease treatment capabilities. The plant's bioactive constituents, such as phytoecdysteroids, iridoids, and flavonoids, contribute to its antioxidant, anti-inflammatory, antidiabetic, and antimicrobial properties [11]. Notably, phytoecdysteroids like turkesterone and ecdysterone are recognized for their protein synthesis stimulation and hepatoprotective activities, suggesting potential applications in liver therapy and muscle development [12,13].

The Ferula Genus:



The *Ferula* genus, encompassing over 180 species, is distinguished by its diverse array of secondary metabolites, including coumarins, sesquiterpene lactones, and sulfur-containing compounds. These metabolites exhibit a wide range of biological activities, such as antioxidant, anti-inflammatory, antimicrobial, and antitumor effects, indicating the genus's extensive pharmacological potential [14,15]. The therapeutic versatility of *Ferula* species underscores the necessity for in-depth research to unlock their full drug development and therapeutic application potential.

In conclusion, the symbiotic relationship between endophytic fungi and medicinal plants, such as *Peganum harmala*, *Ajuga turkestanica*, and species of the *Ferula* genus, holds significant potential for discovering novel antimicrobial agents and therapeutic compounds. This collaboration highlights the role of natural products in combating drug resistance while advocating for deeper research into bioactive mechanisms, optimized extraction methods, and clinical applications. Further exploration of these plant-endophyte associations, through multidisciplinary approaches like genomics and metabolomics, promises innovative, sustainable solutions for pressing health challenges. Preserving biodiversity and ecological integrity is essential as we advance in this pursuit of new pharmacological breakthroughs.

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