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Review Article

Unlocking the Potency of Endophytic Fungi: Connecting Discovery Endophytic Fungi for Bioactive Compound

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ABSTRACT

Endophytic fungi have engrossed the most attention owing to their prospect of being a source of many bioactive compounds. These fungi are regarded as effective producers of valuable metabolites, such as antibacterial, antifungal, anticancer and antiviral substances, which are crucial in the fight against the growing global healthcare problem of antimicrobial resistance. Also, new DNA sequencing technologies, metagenomics, and LCMS require searching for new fungi and their bioactive substances though isolation is still useful. Additionally, these compounds can also be produced using co-cultivation or genetic manipulation techniques. Reports stress the fact that endophytic fungi possess the ability to produce a considerable array of unique compounds from terpenes to alkaloids to peptides, with applications as anti-microbials, anticancer, and anti-inflammatory agents. The work done here emphasizes the importance of endophytic fungi in the development of green and eco-friendly medicines for the treatment of chronic diseases and infections.

Keywords: Anticancer, Anti-Inflammatory, Antimicrobial Properties, Bioactive compounds, Endophytic Fungi.

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INTRODUCTION

The rampant emergence of pathogen resistance, the emergence of new life-threatening viruses, and increase in both infectious and noninfectious ailments present major challenges to contemporary health care systems globally. These growing health risks also underline the critical need for novel and environmentally responsible strategies to address global health challenges (Gupta *et al*., 2023). Traditional therapeutics, especially antibiotics, provide less and less effectiveness in face of AMR, whereas the increasing ecological burden of synthetic drugs emphasizes a demand towards less hazardous, naturally derived alternatives. In this context, natural products-bioactive metabolites sourced from plants, animals, and microorganisms-have long been regarded as a cornerstone in the development of therapeutic agents. These molecules have specific structures and show widespread biological activities, thus they are potential interests of drug discovery. Notably, more than 50% of drugs approved for clinical use over the past three decades have been derived from natural products, and 58% of newly approved drugs have been inspired by these compounds, underscoring their continuing relevance in modern medicine (Gupta *et al*., 2023).

Among the diverse sources of natural products, endophytic fungi-fungi that reside within the tissues of living plants in a mutualistic relationship-emerge as a particularly rich yet underexplored resource (Gupta *et al*., 2023). These fungi have adapted to synthesize a large number of secondary metabolites (e.g., alkaloids, terpenoids, phenolic compounds, steroids, peptides), many of which exhibit potent bioactivities, including antimicrobial, anticancer, antioxidant, anti-inflammatory and immunosuppressing properties (Ujam *et al*., 2021). Endophytic fungi, because of their metabolic uniqueness and close association with plant cells, have been known to synthesize a higher number of bioactive compounds than do soil fungi (Hasen *et al*., 2023). The distinctive metabolic substrates of these fungi, and structural resemblance of their compounds to those of their host plants, make these an interesting source for the identification of potential therapeutic molecules. Given their enormous potential, endophytic fungi represent an invaluable resource for developing novel drugs that can address pressing healthcare challenges, including the rise of antibiotic resistance and the need for more effective treatments.

Historically, plants have been the main source of bioactive phytochemicals employed in drug discovery and a variety of plant-derived compounds have yielded therapeutic revolutions.

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On the other hand, serendipitous discovery of penicillin by *Penicillium chrysogenum* in 1928 represented a turning point in drug development, where the role of microorganisms (and fungi) as potent contributors to modern medicine became realized. Fungal-derived agents, i.e., lovastatin (a hypolipidemic drug from *Aspergillus terreus*) and cyclosporine (an immunosuppressant from *Tolypocladium inflatum*) have dramatically changed the pharmaceutical sector changing it from plant-derived drugs to microorganism-derived drugs. However, although they play a critical role in drug discovery, fungi are still an understudied resource, as the majority of species are still not comprehensively characterized. This under exploration is mainly due to the complexity of the fungal biosynthetic pathways, which represent an important challenge of exploiting their full potential.

Endophytic fungi, especially, provide a potential but unexploited source of bioactive compounds. Not only those fungi secrete a vast library of bioactive metabolites, such as antibacterial, antifungal, anticancer, and antiviral molecules, but also, they are a green source of alternative to synthetic drugs. With the growing concerns over antibiotic resistance and environmental effects of chemical pharmaceuticals, endophytic fungi have attracted much attention for the yield of new compounds with the potential of used as powerful therapeutics for the treatment of chronic diseases and infections.

In order to achieve the maximum potential of endophytic fungi, an integrative and multi-level research framework is needed. This encompasses the aim to exploit novel and underexploited ecological niches, and to utilize sophisticated methods such as high-throughput DNA sequencing, metagenomics and Liquid Chromatography-Mass Spectrometry (LC-MS) to isolate and recover new fungal species and their potentially bioactive components. Furthermore, exposure to co-cultivation and genetic engineering tools can induce valuable metabolite yields. Optimizing cultivation strategies and drug screening can help to fully exploit the promise of endophytic fungi as a sustainable drug discovery resource. Specifically, this study seeks to leverage natural products from endophytic fungi for the existing pressing health challenges of modern medicine, in providing novel solutions for the discovery of new, effective and environmentally friendly therapeutics.

What are endophytic fungi and its types

Endophytes are microbes (bacteria, fungi, and actinomycetes) that reside within plant tissues without expressing macromorphological symptoms (Wilson, 1995). They have been around for more than 400 million years, with their evolutionary origin in the Devonian period, and were first described in the year 1904, in Eurasian darnel ryegrass (Gupta *et al*., 2023). These microorganisms occur in a wide variety of environments, ranging from rainforests to deserts and even extreme environments, such as the Arctic and the Antarctic (Gupta *et al*., 2023). Endophytes establish symbiotic, commensal, or, in rare cases, latent pathogenic associations with their host plants (Jha *et al*., 2023).

To provide shelter and nutrition, endophytes synthesize bioactive metabolites which assist plants in resisting biotic and abiotic stresses, such as resistance to pathogens and pests. These metabolites also contribute to the plant's overall health (Chaudhary *et al*., 2022). The coevolution of plants and endophytes leads to the production of valuable natural compounds with significant therapeutic potential. Such bioactive molecules, which often are also acting like the plant back as their function, are important in drug discovery (Gupta *et al*., 2023).

Endophytes represent many microorganisms, including more than 200 genera of endophytic bacteria from Actinobacteria, Proteobacteria, and Firmicutes (Gouda *et al*., 2016). Interestingly, bacteria, such as Streptomyces, are responsible for 76% of bioactive molecules, including antibacterials and anticancer agents (Del Carratore *et al*., 2022). Actinomycetes, morphologically resembling fungi, also generate pharmaceuticals, e.g., paclitaxel, for anticancer therapy (Khalifa *et al*., 2019). *Clavicipitaceous* and *non-clavicipitaceous* fungi play an important role in drug development by synthesizing, e.g., taxol and penicillenols, which exhibit antimicrobial and anticancer activities (Gouda *et al*., 2016). Individually, endophytes are an underutilized, but potentially rich, source of therapeutic agents (Gupta *et al*., 2023).

Diversity of Endophytic Fungi in Different Plant Species

Endophytic fungi are very flexible organisms that are able to both grow within the internal tissues of a large number of plant species in a broad range of environments (Wen *et al*., 2022). These fungi have the ability to colonize many plant types, ranging from tree's to grasses, shrubs, small plants and to exist in a variety of habitats, from forests to grasslands, wetlands to aquatic habitats (Wijesekara & Xu, 2023). This plasticity in being able to live in a variety of different habitats illustrates the extraordinary adaptability and survival tactics of the fungi. They have been detected in all terrestrial plants examined to date, with genera *Penicillium, Alternaria, Fusarium, Colletotrichum, Aspergillus* and *Xylaria* being frequently isolated. Other genera such as *Gibberella, Glomerella* and *Phoma* have also been reported. The isolation frequency of such fungi can differ depending on considerations, including the host plant's genotype, the plant material collected, geographical region, plant age and sampling season (Hyde *et al*., 2024).

The distribution of endophytic fungi is, however, not only dictated by plant taxonomy, but also by geographical and environmental factors. Plants from different regions and ecosystems harbor distinct endophytic communities, reflecting complex interactions between the fungi and their host plants (Hu *et al*., 2024). So, the diversity and composition of endophytic fungi in a given plant species is influenced by factors like soil type, climate and its proximity to the neighbor plants (Wijesekara & Xu, 2023). This widespread distribution highlights the dynamic, symbiotic relationship between plants and their endophytes, where fungi contribute to plant health by enhancing nutrient uptake, improving water efficiency, and helping plants cope with environmental stresses such as drought and pathogen attacks. As a reward, the plants offer the fungi a protective home and nutrition for mutualism (Sena *et al*., 2024).

Endophytic fungi have demonstrated great therapeutic utility owing to their capacity to produce a broad spectrum of bioactive metabolites (Varghese *et al*., 2024). These phytokramich substances possibly or not similar to compounds elaborated by the host plant consist in alkaloid, terpenoid, polyketide, flavonoid and steroid (Huang *et al*., 2022). These metabolites also possess diverse remarkable pharmacological activities including antimicrobial, anticancer, antioxidant, anti-inflammatory, and antidiabetic activities. Examples of such are paclitaxel, an anticancer compound originally obtained from the fungus *Taxomyces andreanae*, that has been isolated from the Pacific yew tree, and resveratrol, an antioxidant and anticancer compound (Nobili *et al*., 2009). Among the other significant compounds yielding from endophytic fungi, camptothecin, vinca alkaloids, and huperzine A showing different potentials for treating different kinds of diseases.

The potential of endophytic fungi goes beyond medicine (Tiwari *et al*., 2023). These fungi also produce enzymes like amylase, catalase, laccase, lipase, and proteases, which have valuable applications in industrial and clinical settings. The increasing amount of research on endophytic fungal species has led to new possibilities for drug discovery, and in particular because these fungi secrete bioactive compounds that are likely to play a crucial role in tackling worldwide health problems, including resistance to antibiotics and cancer (Bhadra *et al*., 2022).

In addition, endophytic fungi are present in all plant tissues (root, stem, leaf, fruit, flower, bark), with more than 300,000 plant species homes these microorganisms. They have been isolated from plants in temperate, tropical, and even harsh environments, including cold, hot, and deep-sea environments, which illustrate their vast diversity and adaptability (Zheng *et al*., 2016). The bioactive metabolites isolated from these fungi are extractible by several approaches such as solvent extraction, chromatography, and more sophisticated methods such as mass spectrometry and Nuclear Magnetic Resonance (NMR) spectroscopy for the characterization of their chemical structures (Pai *et al*., 2022).

The expanding search in endophytic fungi, and the development in biotechnological approaches have promised an overload of new therapeutic agents. These fungi are an immense untapped resource for the biopharmaceutical and agrochemical fields, with their bioactive molecules having tremendous promise for the discovery of new drugs, therapeutics, and industrial applications. As research progresses, endophytic fungi have a great potential to play a significant role to healthcare, agriculture, and other industries and are a thrust of future innovation (Wen *et al*., 2022).

Fungal endophytes as a treasure for bioactive compounds

The discovery of new drugs from microbes, especially from fungi, has a rich and evolutionary history. A milestone in this journey occurred in 1928 when Alexander Fleming discovered Penicillium notatum, leading to the development of penicillin, the first antibiotic (Gaynes, 2017). This finding changed medicine, by offering a potent tool against bacterial infections. Nevertheless, the isolation of Taxol (paclitaxel) from the endophytic fungus *Taxomyces andreanae* in the 1990s was another breakthrough moment (Vélëz *et al*., 2022). Taxol, originally isolated from the Pacific yew (*Taxus brevifolia*), was previously identified as being synthesized by endophytic fungi that colonize the tissues of species in the genus Taxus (Zhang *et al*., 2024). This discovery showed the tremendous future of endophytic fungi in drug discovery thereby, reigniting interest in endophytic fungi as a source of new therapeutics (Tiwari & Bae, 2022).

Endophytic fungi are increasingly recognized as important agents in drug discovery because they are known to synthesize a huge variety of bioactive metabolites (Gupta *et al*., 2023). These metabolites have high antimicrobial, anticancer and antioxidant activities and thus are good candidates to treat diseases. Specifically, endophytic fungi provide a possible approach to address the increasing problem of antimicrobial resistance that will render a large number of traditional antibiotics ineffective (World Health Organization, 2024). Biosynthesis of bioactive compounds is affected by several parameters, notably the plant species from which fungi are extracted, environmental factors and the plant tissues taken into consideration. Extreme environments (e.g., saline areas, high altitude and rainforests) and specialized plant tissues (e.g., roots, leaves and seeds) are, not infrequently, very concentrated with this useful metabolites (Hasen *et al*., 2023).

Of the various bioactive compounds that are synthesized endogenously by endophytic fungi, *Aspergillus fumigatus* has been reported to produce alkaloids, terpenoids, and ρ-terphenyls with promising antibacterial and antifungal activities (Mamangkey *et al*., 2024). Such compounds may be either produced by the fungi themselves or imported from the host plant, resulting in a complicated crosstalk between the host and fungal metabolome (Gonçalves *et al*., 2017). The identification of Taxol is one of the best illustrations of the potential of fungal bioprospecting (Stadler & Kolarik, 2024). Despite a considerable body of research, a synthetic analogue to paclitaxel has not yet been successfully developed, and this clearly demonstrates the relevance of natural sources, such as endophytes, in drug discovery (Stadler & Kolarik, 2024).

Other bioactive molecules present in endophytic fungi are cytotoxic molecules from Alternaria species, antifungal molecules from *Berkleasmium* species, and antiviral molecules from fungal species like *Cytonaema* species which yield cytonic acid with HIV and influenza inhibitory activity (Tiwari & Bae, 2022). Additionally, due to the ability of certain endophytes to treat diabetes, some like *Aspergillus awamori* have been found to have antidiabetic activity. These fungi also contribute to the protection of agriculture from disease and of crops from pathogens (Burragoni & Jeon, 2021).

Current investigations have already uncovered the great promise that endophytic fungi hold as a natural, green and sustainable reservoir of new therapeutics (Wen *et al*., 2022). Their capacity to synthesize diverse bioactive molecules including numerous broad-spectrum activities with low toxicity, and lack of conventional drug resistance makes them an excellent resource in the war against global health threats such as antimicrobial resistance (World Health Organization, 2024). With the advancement of research, endophytes are expected to become increasingly central to pharmaceuticals development, presenting new approaches to human health and disease control (Alvin *et al*., 2014)

Biomedical Applications of Fungal Endophytes: Harnessing Nature's Potential for Drug Discovery

Fungal endophytes, the microorganisms living in plant tissues without damaging their host plants, are well known for their symbiotic interaction with plants (Nair & Padmavathy, 2014). These fungi synthesize a wide range of bioactive molecules and possess promising bioactivities that could be used in a variety of fields of biomedical uses, such as antimicrobial, antiviral, antioxidant, anticancer, anti-inflammatory, antidiabetic, antiprotozoal activities (Conrado *et al*., 2022). The development of antimicrobial resistance alongside the rise of disease (cancer, diabetes, viral infections) causing burden has made it more urgent to seek new, sustainable sources of therapeutic agents (World Health Organization, 2024). At this point in time, the search for novel bioactive compounds among fungal endophytes is of greater interest than not (Sharma *et al*., 2016).

Antimicrobial Properties

The emergence of Antimicrobial Resistant (AMR) infection has emerged to be one of the most pressing global health crises of the 21st century, resistant infections are associated with longer hospital length of stays, morbidity, and mortality (World Health Organization, 2024). In response to this threat, natural products have gained renewed attention as alternative therapeutic agents, particularly those derived from endophytic fungi. These fungi harbour numerous secondary metabolites and have been shown to exhibit ratcheting strong antimicrobial activity against many bacterial, fungal, and viral pathogens (Akpotu *et al*., 2017).

Endophytic fungi produce a variety of bioactive metabolites including alkaloids, terpenoids and flavonoids which display strong antimicrobial activity. For example, *Aspergillus flavus*, recovered from *Ocimum basilicum*, has demonstrated both strong antibacterial and antifungal activity against some of the most prevalent pathogens including Staphylococcus aureus and Candida albicans. Similarly, *Penicillium citrinum*, derived from *Azadirachta indica*, displays notable antibacterial activity against multiple strains, including those resistant to conventional antibiotics. In all these fungal endophytes, besides the antibacterial and antifungal activities, some fungal endophytes (e.g., *Acremonium* and *Chaetomium* spp. from *Avicennia marina*) display antiviral activity including activity against hepatitis C virus. *Curvularia papendorfii*, isolated from Vernonia amygdalina, has shown activity against coronaviruses, with this including the human coronavirus HCoV229E, revealing endophytic fungi as a source of antiviral agents (Usman *et al*., 2024).

The antimicrobial activity of these fungi is particularly relevant in light of the increasing problem of multi-drug resistant organisms (Gow *et al*., 2022). The ability to target new microbial pathways and mechanisms of action by fungal metabolites offers a promising route to effective treatments for infection diseases not responding Viruses, known and capable of rapidly mutating and evolving, pose an ongoing threat to the creation of highly effective therapeutics (Uddin *et al*., 2021). The global reach of viral illnesses, such as HIV, influenza, and now coronaviruses, emphasizes the critical importance of new antiviral therapeutics. Conventional antiviral therapies are frequently hampered by drug resistance and toxicity, thereby demanding new sources for novel antiviral therapy (Shyr *et al*., 2021). Fungal endophytes through their mutualistic association with plants, synthesize a variety of bioactive compounds rich in antiviral activity (Chandra *et al*., 2024).

An example of this is *Trichoderma harzianum*, isolated from *Kadsura angustifolia* producing nigranoic acid, an anti-HIV-1 reverse transcriptase compound, a crucial enzyme of the viral replicative cycle (Yao *et al*., 2023). Other fungal species, e.g., *Curvularia papendorfii* from *Vernonia amygdalina* with antiviral effect on coronaviruses, *Phoma sp*., from *Aconitum vilmorinianum* with production of *phomanolide* revealing its high antiviral effect on influenza A virus. These data indicate that the fungal endophytes, which have been largely disregarded in the past, could contain a treasure of novel antivirals with the potential to be invaluable in the containment of viral pandemics and the treatment of chronic infections (Siddique, 2020).

Antioxidant Activity

Oxidative stress, characterized by the imbalance between Reactive Oxygen Species (ROS) and antioxidant defenses, is one of the main factors implicated in the onset of numerous chronic conditions such as cancer, cardiovascular diseases, neurodegenerative diseases and diabetes (Dash *et al*., 2024). Natural antioxidants, able to scavenge the ROS and alleviate oxidative stress, are thus of great concern in health research. Endophytic fungi, found inside plant tissues, have been identified to synthesize diverse array of antioxidants such as polyphenols, flavonoids, and terpenoids, capable of neutralizing oxidative stress (Liu *et al*., 2018).

For example, antioxidant activity has been shown by Aspergillus species, e.g., *A. flavus, A. fumigatus*, and *A. nidulans*, having an IC5θ value between 68.4 and 347.1 µg/mL. Another species, *Penicillium roqueforti* and *Penicillium pinophilum*, yields very active antioxidants such as ferulic acid and *quercetin* that not only function as antioxidants, but also possess antimicrobial activity (Arora & Chandra, 2011). Other fungi, including *Fusarium* species (e.g., *F. tricinctum* and *F. oxysporum*) and *Chaetomium cruentum*, are also known to possess antioxidant properties, showing how a variety of fungal genera can produce these molecules.

Antioxidant metabolites from endophytic fungi can detoxify free radicals, inhibit inflammation, and prevent cytolysis (Toghueo, 2020). Through alleviation rendering oxidative stress, these metabolites present potential therapeutic effects for prevention and treatment of aging, cancer, and cardiovascular diseases. In addition, the isolation of novel antioxidants from endophytes may pave the way to novel natural antioxidant solutions with reduced side effects compared to synthetic antioxidants (Wang & Kang, 2020).

Anticancer Activity

Cancer is one of the leading causes of death in the world, and despite advances in treatment, existing therapies often come with severe side effects and limited effectiveness. The need for new, targeted anticancer agents is urgent (Burmeister *et al*., 2022). Fungal endophytes have emerged as a promising source of such compounds, producing a wide variety of bioactive metabolites with potent anticancer properties. These compounds exert various modes of action, such as anti-proliferative effects, apoptosis-inducing activity, and prevention of metastasis. Of these, Aspergillus species are the most-studied for anticancer activity (Sajer *et al*., 2024).

For instance, from *Tabebuia rosea*, Aspergillus TRL1 was extracted to produce *pulchranin*, which inhibits cancerous human liver Hep-G2 and breast cancer cells MCF-7 (Sawong *et al*., 2022). *Aspergillus terreus* and *Aspergillus flavus*, isolated from *Ficus elastica*, also display anticancer activity against various cancer cell lines (El-Sayed *et al*., 2021). *Penicillium* species such as *Penicillium ochrochloron*, isolated from *Taxus media*, and *Penicillium* vsp. ct-28 produce xanthone compounds that induce apoptosis in human hepatoma (HepG2) cells, further validating the anticancer potential of fungal endophytes. Taxol (paclitaxel), a diterpenoid originally obtained from the *Taxus brevifolia* tree, is perhaps the most famous anticancer agent derived from fungal endophytes (Azar *et al*., 2023). Taxol affects the mitotic spindle; consequently, it prevents cell division by disrupting its formation, but it also possesses antiangiogenic action by inhibiting the release of Vascular Endothelial Growth Factor (VEGF) (Yvon *et al*., 1999). Taxol is used widely against breast, ovarian, lung, and testicular cancers. Besides Taxol, fungal endophytes have also led to other drugs that are valuable anticancer agents: Vinblastine and Vincristine isolated from the *Madagascar periwinkle, Catharanthus roseus*, and *Camptothecin*, predominantly extracted from *Camptotheca acuminata* (Weaver, 2014). Such compounds, isolated from fungal species that are not as much recognized, may open novel possibilities for targeted cancer drugs with fewer side effects (Shakya & Naik, 2022).

Anti-inflammatory Effects

Chronic inflammation is one of the key contributors to heart disease, autoimmune disorders, and some cancers (Furman *et al*., 2019). Inflammation management is therefore critical for disease prevention, and bioactive compounds from fungal endophytes are increasingly being recognized for their anti-inflammatory properties (Wijesekara & Xu, 2023). Compounds such as polyphenols, terpenoids, and alkaloids reduce inflammation but also modulate immune responses, making them valuable for treating chronic inflammatory conditions (Gonfa *et al*., 2023). For example, *Pestalotiopsis brefeldianum*, isolated from Aegle hispida leaves, has exhibited effective anti-inflammatory action through the inhibition of inflammatory biomarkers and oxidative stress (Saleh *et al*., 2023). Similarly, *Lasiodiplodia theobromae*, producing *Lasiodiplactone A*, has inhibited nitric oxide production and has strong anti-inflammatory potential. Other fungi such as *Botryosphaeria* sp., *Trichoderma* sp., and *Penicillium* sp. have exhibited anti-inflammatory activity by inhibiting key enzymes such as COX-1, COX-2, and 5-lipoxygenase in the process of inflammation (Chen *et al*., 2017). These fungal metabolites may, therefore provide novel therapies for chronic inflammatory diseases, such as rheumatoid arthritis, cardiovascular diseases, and neurodegenerative disorders by reducing inflammation and regulating immune responses (Hanlon *et al*., 2022).

Antidiabetic Compounds

With prevalence increasing, diabetes mellitus stands as one of the prominent global health issues worldwide with a variety of complications through cardiovascular diseases, nephropathy, and neuropathy, among others (World Health Organization, 2024). New searches into the treatment of the condition have been shown using fungus-based endophytes; a natural compound produced for such fungi has been suggested for enzyme-based inhibition of carbohydrate metabolizers, such as alpha glucosidase and amylase (Tousif *et al*., 2023). These enzymes break down carbohydrates during digestion, and their inhibition slows the absorption of glucose into the bloodstream, helping to control blood sugar levels. For example, Nigrospora oryzae produces compounds like S (+)-2 cis 4-trans *abscisic acid* (Uzor *et al*., 2017).

Potential Applications in Health and Medicine

The endophytic fungi, which live in a symbiotic relationship within the plant, have emerged as one of the promising sources of novel bioactive compounds of therapeutic interest (Gupta *et al*., 2023). These fungi produce a variety of bioactive molecules that can be used to treat diseases ranging from antibiotic-resistant infections to chronic inflammatory conditions (Gupta *et al*., 2023). Their unique evolutionary relationship with plants has led to the development of compounds with potent biological activities, making them attractive candidates for drug development (Gupta *et al*., 2023). Research on endophytic fungi has shown their potential to combat diseases that are not amenable to treatment by conventional therapies. For example, fungi such as *Aspergillus fumigatus* produce antimicrobial agents like linoleic acid and *fumiquinazoline* derivatives, which possess potent antimicrobial activity against resistant pathogens (Shaaban *et al*., 2013). Endophytic fungi thus provide targeted therapies directed to the cause of disease and less harm to healthy cells, which aligns with the trend toward personalized medicine (Wijesekara & Xu, 2023). However, the process of transforming these natural compounds into a viable drug is not without challenges such as rigorous testing, dose optimization, and a deep understanding of their interactions with the human body (Vora *et al*., 2023). Still, the therapeutic potential of endophytic fungi remains vast, with growing evidence supporting their use in drug discovery (Varghese *et al*., 2024). History regarding the quest for microbial-based medicines dates from 1928 where penicillin was produced from the Penicillium notatum, or more lately, paclitaxel Taxol from the *Taxus brevifolia* that was later supplemented by Taxomyces Andreanna endophyte fungal connections. That was a catalyst for hunting for natural source medicine in general (Kho, 2018). There's recent great interest about the role played by endophytes in eradicating various infections and medical conditions beyond conventional remedies (Choudhary *et al*., 2023).

Prospects and Challenges

Endophytic fungi have emerged as a promising source of bioactive secondary metabolites. They have the potential to treat a wide range of human diseases (Azeem *et al*., 2024). However, only around 1% of endophytic fungi have been explored so far, with a vast reservoir of untapped compounds (Manganyi & Ateba, 2020). Unlocking this potential requires selection of the right host plants, particularly those with high biodiversity or medicinal properties (Davis & Choisy, 2024). Advances in plant genomics and fungal metabolite production have contributed to drug discovery. If the biosynthetic pathway involved in compound production is well understood, it can be maximized for yield and minimized in the discovery process (Chaachouay & Zidane, 2024). Techniques such as CRISPR-Cas9, epigenetic modifications, and coculture fermentation, where fungi grow alongside other microorganisms, have been promising in increasing yields of metabolites by imitating the natural interaction of fungi with their plant hosts (Mohamed *et al*., 2021). Other than this, drug discovery has also accelerated further with the development of molecular tools like bioinformatics, phylogenetic studies, and AI-driven platforms (Mak *et al*., 2024). Biosynthetic gene clusters could be identified, as well as simulated compound-protein interactions, to further guide in designing optimized therapeutic compounds, further accelerated with platforms like ANtiSMASH and AutoDock (Crits-Christoph *et al*., 2021). By integrating these advanced approaches with conventional bioprospecting, the discovery of endophytic fungi is on the cusp of revolutionizing pharmaceutical discovery, opening exciting new vistas for drug discovery and therapeutic innovation (Tiwari & Bae, 2022).

CONCLUSION

In conclusion, bioactive compounds from fungal endophytes offer great potential for future medicine. With rising challenges from ineffective and expensive antimicrobial therapies, endophytic fungi provide a promising alternative. These fungi produce a variety of potent metabolites, including terpenes, alkaloids, and peptides, with antimicrobial, anticancer, and anti-inflammatory effects. Their microbial diversity harbors novel compounds with unique chemical structures, making them valuable for treating infections, chronic diseases, and cancer. Advances in molecular techniques and bioinformatics enable better isolation and understanding of these compounds and, therefore, open up new avenues for drug discovery in the fight against antibiotic resistance and global health challenges.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMR: Antimcrobial Resistance; **LCMS:** Liquid chromatography-mass spectrometry; **DNA:** Deoxyribonucleic acid.

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