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ANTIMICROBIAL AGENTS FROM DIFFERENT FUNGAL STRAINS: A COMPREHENSIVE REVIEW

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ABSTRACT

The emergence of antimicrobial resistance (AMR) has intensified the global need for novel antimicrobial agents. Fungi are prolific producers of structurally diverse secondary metabolites, many of which possess potent antibacterial, antifungal, antiviral, and antiparasitic properties. Classical antibiotics such as penicillin, cephalosporin, and griseofulvin originated from fungi, yet recent omics-driven research has revealed thousands of previously unexplored biosynthetic pathways with unprecedented therapeutic potential. This review provides a comprehensive analysis of antimicrobial compounds produced by filamentous fungi, mushrooms, yeasts, and endophytic fungal strains. It discusses the chemical classes of fungal metabolites, mechanisms of action, biosynthetic pathways, advances in discovery methods, and applications in medicine, agriculture, and biotechnology. Special emphasis is given to studies from 2020–2024, highlighting emerging compounds from marine-derived fungi, extremophiles, and endophytes. The review concludes with future prospects for fungal metabolite discovery in combatting AMR.

Keywords: Fungal metabolites, Antimicrobial agents, Biosynthetic gene clusters, Endophytic fungi, Marine fungi, Genome mining, Drug discovery.

INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most significant global health threats. As conventional antibiotics lose efficacy against multidrug-resistant (MDR) pathogens, there is an urgent requirement for new antimicrobial agents. Fungi, known for their biochemical diversity, represent one of the richest reservoirs of natural antimicrobial molecules. Many well-known antibiotics, including penicillins and cephalosporins, originated from fungal metabolites. Continued research into fungal biosynthetic pathways, especially using modern genomics and metabolomics, has revealed thousands of unexplored biosynthetic gene clusters capable of producing novel antimicrobial agents. The rise of antimicrobial resistance (AMR) has intensified the search for novel antimicrobial compounds from diverse biological sources. Fungi represent one of the most promising groups of organisms for drug discovery due to their extraordinary metabolic versatility. As decomposers in nature, fungi synthesize a wide spectrum of secondary metabolites to compete with bacteria, other fungi, and environmental stresses. Many clinically important antibiotics—including penicillin, cephalosporins, and griseofulvin—are fungal in origin, highlighting their potential as natural pharmaceutical factories. Recent advances in genomics, metabolomics, and biotechnological approaches have accelerated the identification of new antimicrobial agents from both filamentous and non-filamentous fungi (Brakhage, 2018; Keller, 2019; Huang & Jia, 2023).

Fungi represent one of the most prolific sources of natural antimicrobial compounds, contributing significantly to modern medicine and biotechnology. Their metabolic diversity enables the production of bioactive molecules effective against bacteria, fungi, viruses, and parasites (Bérdy, 2012). The global rise of antimicrobial resistance (AMR) has renewed scientific interest in fungal metabolites as alternative therapeutic sources (Ventola, 2015). Numerous fungal species—particularly filamentous fungi and endophytic strains—produce secondary metabolites such as polyketides, peptides, terpenoids, alkaloids, and phenolic derivatives that demonstrate broad-spectrum activities (Keller, 2019). As the pharmaceutical pipeline for new antibiotics faces stagnation, fungal-derived compounds offer an essential resource for next-generation antimicrobials (Newman & Cragg, 2020).

Diversity of Fungal Secondary Metabolites

Fungal secondary metabolites encompass structurally diverse compound classes synthesized through polyketide synthases (PKS), nonribosomal peptide synthases (NRPS), and hybrid PKS-NRPS pathways (Brakhage, 2013). These biosynthetic systems enable the formation of complex antimicrobial molecules such as β-lactams, macrolides, peptaibols, and quinones. The metabolic output varies widely between species and environmental conditions, making fungi valuable reservoirs for drug discovery (Keller, 2019). In nature, these metabolites serve ecological functions including defense, competition, and communication, but in therapeutic applications, they exhibit potent inhibitory effects on pathogenic microbes (Demain & Fang, 2000). Fungi produce a wide array of secondary metabolites including polyketides, non-ribosomal peptides, terpenoids, and alkaloids, each synthesized through specialized biosynthetic gene clusters (Brakhage, 2013). The structural complexity of these molecules underpins their broad spectrum of bioactivities.

Polyketides constitute one of the largest classes, encompassing antibiotics like lovastatin and antifungals such as griseofulvin (Chiang et al., 2016). Non-ribosomal peptides, synthesized by multi-enzyme complexes, give rise to clinically important compounds like penicillin, cyclosporine, and echinocandins (Walsh et al., 2017). Terpenoids, derived from isoprenoid pathways, include compounds like trichothecenes and pleuromutilin, known for their antimicrobial and cytotoxic properties (Quin et al., 2014). Similarly, fungal alkaloids—such as ergotamine and psilocybin—exhibit potent neurological and pharmacological effects (Tudzynski, 2014). Advances in genomics have revealed that fungi often harbor many "silent" or cryptic biosynthetic gene clusters that remain unexpressed under standard laboratory conditions (Keller & Turner, 2012). Activation of these clusters through epigenetic modulation, co-culture techniques, or environmental stress has significantly expanded the known chemical diversity of fungal metabolites (Brakhage & Schroeckh, 2011). Moreover, endophytic fungi associated with medicinal plants have emerged as promising sources of novel metabolites with anticancer, antioxidant, and antimicrobial properties (Strobel, 2018).

Overall, the extraordinary diversity of fungal secondary metabolites underscores their immense biotechnological potential. Continued exploration using integrated omics, metabolic engineering, and synthetic biology approaches is expected to uncover even more unique compounds with significant therapeutic and industrial applications (Zhang et al., 2020).

Penicillium Species as Sources of Antibacterial Metabolites

Penicillium species have historically contributed to antibiotic discovery, most famously through the β-lactam compound penicillin isolated from *Penicillium chrysogenum* (Fleming, 1929). Recent studies reveal that Penicillium spp. also produce griseofulvin, patulin, secalonic acid, and several novel polyketides with broad antimicrobial potential (Houbraken et al., 2020). Many isolates obtained from soil and endophytic environments show activity against multidrug-resistant (MDR) pathogens such as *Staphylococcus aureus* and *Klebsiella pneumoniae* (Nicoletti & Trincone, 2016). The genus continues to provide promising leads due to its vast metabolic capacity and widespread distribution.

Species of *Penicillium* are renowned producers of diverse antibacterial secondary metabolites that play pivotal roles in pharmaceutical and clinical applications. The most iconic example is penicillin, first discovered from *Penicillium chrysogenum*, which revolutionized modern medicine due to its potent ability to inhibit bacterial cell wall synthesis (Fleming, 1929; Lobanov et al., 2017). Beyond penicillin, numerous *Penicillium* species produce additional antibacterial compounds, including patulin, citrinin, secalonic acids, and meleagrin, each showing broad-spectrum activity against Gram-positive and Gram-negative bacteria (Nielsen et al., 2017). Recent studies indicate that *Penicillium* endophytes isolated from medicinal plants exhibit significant antibacterial effects, often linked to unique polyketides and alkaloids synthesized through specialized biosynthetic gene clusters (Keller, 2019). These metabolites act through multiple mechanisms, such as disrupting membrane integrity, inhibiting protein synthesis, or generating oxidative stress in pathogenic bacteria (Brakhage & Schroeckh, 2011). With advances in genomics and metabolomics, many cryptic biosynthetic pathways in *Penicillium* are being activated, unveiling novel antibacterial molecules with promising therapeutic value (Chiang et al., 2016).

Given their metabolic versatility, *Penicillium* species remain important reservoirs for discovering new antibacterial agents, particularly in the face of rising antibiotic resistance. Continued exploration of environmental and endophytic strains is expected to yield additional bioactive compounds with significant clinical potential (Strobel, 2018).

Aspergillus-Derived Antimicrobial Compounds

Aspergillus species are equally renowned for producing antibacterial and antifungal metabolites including gliotoxin, fumagillin, helvolic acid, and terrein (Gacesa & Barlow, 2019). Endophytic *Aspergillus* strains isolated from medicinal plants often exhibit enhanced antimicrobial profiles, likely due to ecological coevolution (Strobel, 2018). Several *Aspergillus* metabolites exhibit dual antimicrobial and antiviral properties, positioning the genus as a priority group for novel drug leads. Advances in genome mining have further revealed silent biosynthetic gene clusters that may encode yet-undiscovered antimicrobials (Nielsen & Nielsen, 2017).

Species of *Aspergillus* are prolific producers of antimicrobial secondary metabolites with significant pharmaceutical relevance. These fungi synthesize structurally diverse compounds, including polyketides, non-ribosomal peptides, terpenoids, and alkaloids, many of which exhibit strong antibacterial and antifungal activities (Keller, 2019). Notable examples include aspergillomarasmine A, which inhibits metallo-β-lactamases and restores β-lactam antibiotic efficacy, and gliotoxin, known for its potent antimicrobial and immunosuppressive properties (Bok et al., 2006). Endophytic and soil-derived *Aspergillus* species also produce metabolites such as helvolic acid, fumagillin, and terrein, which demonstrate broad-spectrum activity against pathogenic bacteria and fungi (Brakhage & Schroeckh, 2011). Advances in genome mining have revealed numerous silent biosynthetic gene clusters in *Aspergillus*, indicating a far greater reservoir of antimicrobial molecules yet to be exploited (Chiang et al., 2016).

Overall, the metabolic versatility of *Aspergillus* makes it an important source for novel antimicrobial agents, particularly in the context of increasing antibiotic resistance (Nielsen et al., 2017).

Bioactive Metabolites from Trichoderma Species

Trichoderma spp. are particularly recognized for producing peptaibols—linear peptides with potent membrane-disrupting antimicrobial activity (Sood et al., 2020). These peptides, including alamethicin and trichogin, act by forming ion channels on microbial membranes, making them effective against resistant pathogens. In addition, *Trichoderma* species synthesize polyketides, terpenes, and pyrones with antibacterial, antifungal, and antiviral activity (Mukherjee et al., 2016).

Owing to their strong antagonism, *Trichoderma* strains are widely applied in agriculture as biocontrol agents. It is well-known producers of diverse bioactive secondary metabolites with significant agricultural, medical, and industrial applications. These fungi synthesize polyketides, terpenoids, alkaloids, and peptaibols, many of which exhibit strong antimicrobial, antifungal, and plant-growth-promoting activities (Vinale et al., 2008). Peptaibols such as alamethicin and trichogin form ion channels in microbial membranes, leading to cell leakage and death (Whitmore & Wallace, 2004).

Additionally, *Trichoderma* produces compounds like 6-pentyl-α-pyrone (6-PP), harzianic acid, and gliotoxin, which suppress phytopathogens including *Fusarium*, *Rhizoctonia*, and *Pythium* spp. (Maharachchikumbura et al., 2016). Many of these metabolites contribute to *Trichoderma*'s role as a biological control agent, enhancing plant defense responses and improving crop resilience (Harman, 2011).Genome mining has revealed several cryptic biosynthetic gene clusters in *Trichoderma*, indicating the potential for discovering new metabolites with antimicrobial and therapeutic relevance (Zeilinger et al., 2016).

Endophytic Fungi as Promising Antimicrobial Reservoirs

Endophytic fungi residing within plant tissues without causing disease have emerged as prolific sources of pharmacologically significant metabolites (Strobel & Daisy, 2003). Their ecological adaptation often drives unique metabolic pathways, leading to compounds such as paclitaxel, camptothecin analogues, and antimicrobial peptides (Kusari et al., 2014). Endophytes from medicinal plants show unusually high antimicrobial potency, likely due to host-derived selection pressures (Kaul et al., 2012). These strains remain a focal point of current natural-product drug discovery.

Their unique ecological niche drives the production of structurally diverse compounds, including polyketides, terpenoids, alkaloids, peptides, and phenolic derivatives, many with potent antibacterial and antifungal properties (Strobel & Daisy, 2003). Endophytes associated with medicinal plants often mirror or enhance the host's bioactive chemistry, producing metabolites such as taxol, camptothecin analogs, and antimicrobial xanthones (Kusari et al., 2012). These fungi exhibit strong activity against multidrug-resistant pathogens, making them valuable in the search

for new antibiotics (Gunatilaka, 2006). Advances in genome mining and metabolomics have revealed numerous silent biosynthetic gene clusters in endophytes, suggesting a vast unexplored reservoir of antimicrobial molecules (Keller, 2019). Given their metabolic diversity and adaptability, endophytic fungi hold considerable potential for pharmaceutical applications and represent a promising frontier in natural product-based drug discovery.

Marine Fungi as Novel Antimicrobial Sources

Marine-derived fungi, exposed to unique environmental stresses, produce chemically distinct metabolites absent in terrestrial species (Rateb & Ebel, 2011). Marine *Aspergillus*, *Penicillium*, and *Fusarium* species frequently yield halogenated compounds, macrolides, alkaloids, and peptides active against MDR bacteria (Carroll et al., 2020). Because less than 1% of marine fungi have been cultured, the ocean represents a largely untapped reservoir of novel antimicrobial substances (Imhoff, 2016). Their adaptation to extreme conditions—such as high salinity, pressure, and limited nutrients—drives the synthesis of structurally unique polyketides, peptides, terpenoids, and alkaloids with potent bioactivities (Rateb & Ebel, 2011). Several marine-derived *Aspergillus*, *Penicillium*, and *Fusarium* species have yielded compounds like citrinin analogs, terretonin derivatives, and fusaric acid, many of which demonstrate strong antibacterial and antifungal activity, including against drug-resistant pathogens (Imhoff, 2016).

Endophytes from marine sponges, seagrasses, and algae also produce metabolites with broad-spectrum antimicrobial properties, expanding the chemical diversity available for drug discovery (Blunt et al., 2018). Advances in genome mining and fermentation optimization have revealed numerous silent biosynthetic gene clusters in marine fungi, suggesting substantial untapped potential (Zhang et al., 2019). Overall, marine fungi represent a promising frontier for discovering structurally novel antimicrobial compounds with significant pharmaceutical relevance.

Mechanisms of Antimicrobial Action

Fungal metabolites act via diverse mechanisms, including inhibition of cell-wall synthesis (e.g., β-lactams), disruption of membrane integrity (peptaibols), interference with protein synthesis (fumagillin), and generation of oxidative stress (gliotoxin) (Walsh, 2003). Some compounds also target nucleic acid synthesis or interfere with quorum sensing, reducing virulence rather than killing pathogens outright (LaSarre & Federle, 2013). Understanding these mechanisms is essential to optimizing fungal metabolites for

therapeutic design.

One of the most common mechanisms is the inhibition of cell wall synthesis, as demonstrated by β-lactam antibiotics such as penicillin, which block peptidoglycan cross-linking in bacteria (Kohanski et al., 2010). Many fungal metabolites also disrupt cell membrane integrity; for example, peptaibols and polyenes create pores that cause ion leakage and cell lysis (Whaley et al., 2017). Other metabolites interfere with protein synthesis by binding to ribosomal subunits, leading to impaired translation and inhibited microbial growth (Wilson, 2014). Additionally, certain compounds inhibit nucleic acid synthesis by targeting DNA topoisomerases or RNA polymerases, thereby blocking replication and transcription (Poole, 2012). Some fungal metabolites, such as reactive oxygen–generating polyketides, induce oxidative stress, resulting in cellular damage and apoptosis in pathogens (Keller, 2019). Overall, the multifaceted mechanisms of fungal antimicrobials make them powerful tools against pathogenic bacteria and fungi.

Genomic and Metabolomic Advances in Drug Discovery

The integration of genome mining, metabolomics, and synthetic biology has transformed fungal natural-product discovery. Bioinformatic tools identify silent biosynthetic gene clusters that can be activated through genetic or environmental manipulation (Nielsen & Nielsen, 2017). Metabolomic profiling allows rapid identification of novel compounds, while CRISPR-Cas tools facilitate pathway engineering to enhance antimicrobial yield (Zhang et al., 2020). These innovations significantly accelerate the discovery pipeline.

Genomic and metabolomic advancements have significantly accelerated the discovery of novel drug candidates, particularly from fungi and other microorganisms. Genome sequencing and mining tools enable the identification of biosynthetic gene clusters (BGCs), many of which encode previously unknown secondary metabolites with potential therapeutic value (Keller, 2019). These BGCs often remain silent under standard laboratory conditions, but genomic analysis allows their targeted activation through genetic engineering or environmental manipulation (Ziemert et al., 2016). Metabolomics complements genomics by providing comprehensive profiling of metabolites using advanced analytical techniques such as LC-MS, GC-MS, and NMR spectroscopy (Wolfender et al., 2015). This approach facilitates the rapid detection,

characterization, and quantification of bioactive molecules, enabling researchers to link specific metabolites to their corresponding gene clusters.

Integrating genomics, metabolomics, and bioinformatics enhances pathway elucidation, supports metabolic engineering, and accelerates the identification of antimicrobial, anticancer, and immunomodulatory compounds. Consequently, these technologies represent powerful tools driving modern natural-product-based drug discovery (Rutledge & Challis, 2015).

Industrial and Clinical Applications

Fungal metabolites are widely used in pharmaceuticals, agriculture, and food preservation. Antibiotics such as cephalosporins, statins, and echinocandins remain clinically indispensable (Newman & Cragg, 2020). In agriculture, fungal biocontrol agents like *Trichoderma* reduce chemical pesticide dependence (Sood et al., 2020). Fungal-derived preservatives such as natamycin are applied in food systems for antifungal protection (Pitt & Hocking, 2009). These applications highlight the broad societal significance of fungal antimicrobials.

Clinically, these metabolites have led to the development of major antibiotic classes, such as β-lactams (e.g., penicillin) and echinocandins, which are widely used to treat bacterial and fungal infections (Keller, 2019). Immunosuppressants like cyclosporine, produced by *Tolypocladium inflatum*, revolutionized organ transplantation by preventing graft rejection (Bentley, 2016). In industry, fungal metabolites serve as biocontrol agents, food preservatives, pigments, and enzymes that enhance fermentation, textile processing, and biotransformation (Meyer et al., 2016).

Additionally, fungi-derived statins such as lovastatin have substantial applications in cardiovascular therapy by reducing cholesterol levels (Manzoni & Rollini, 2002). Industrial biotechnology also harnesses fungal fermentation for large-scale production of organic acids, enzymes, and pharmaceuticals. Overall, the versatility of fungal metabolites underscores their continued relevance in healthcare, agriculture, and biomanufacturing.

Challenges and Limitations

Despite their promise, fungal metabolites face challenges including low yield, complex purification, and difficulty in culturing rare species (Bérdy, 2012). Some strains harbor toxic metabolites requiring careful screening. Additionally, rediscovery of known compounds remains

common, necessitating new strategies such as co-culturing and epigenetic modulation to stimulate novel metabolite production (Brakhage, 2013). It also include low metabolite yield, toxicity, and difficulty culturing rare fungi. Future research will focus on synthetic biology, metagenomics, bioreactor optimization, and exploration of extremophilic fungi. (Brakhage, 2018; Keller, 2019; Huang & Jia, 2023).

Despite the tremendous potential of fungal secondary metabolites, several challenges limit their large-scale discovery, characterization, and application. One major constraint is the silent or cryptic nature of many biosynthetic gene clusters (BGCs), which remain unexpressed under standard laboratory conditions, resulting in low or undetectable metabolite yields (Keller, 2019). Cultivation challenges further complicate research, as many fungi—especially marine and endophytic species—are slow-growing or unculturable using traditional methods, limiting access to their metabolites (Imhoff, 2016). Additionally, metabolite extraction and purification often require labor-intensive and costly procedures due to the structural complexity and low natural abundance of many compounds (Wolfender et al., 2015).

Another significant limitation is cytotoxicity and narrow therapeutic windows, as some fungal metabolites exhibit toxicity to human cells, hindering clinical applicability without structural modification (Bérdy, 2012). Regulatory and biosafety considerations also slow the translation of fungal metabolites into clinical use, requiring extensive toxicity testing and pharmacokinetic evaluation (Newman & Cragg, 2020). Finally, antimicrobial resistance continues to evolve rapidly, meaning newly discovered compounds may soon face reduced efficacy, emphasizing the need for continuous discovery, structural optimization, and combinatorial biosynthesis (Brakhage, 2018). Addressing these challenges will be essential for maximizing the biomedical and industrial potential of fungal-derived antimicrobials.

Future Prospects

Advancements in high-throughput screening, metagenomics, and machine learning will significantly expand the discovery of fungal antimicrobials (Zhang et al., 2020). The exploration of extreme environments, synthetic-biology-based pathway refactoring, and microbiome-guided fungal isolation are expected to generate new antimicrobial scaffolds. Fungal metabolites hold immense potential for combating AMR and shaping the next era of drug development.

The future of fungal-based antimicrobial discovery is highly promising, driven by rapid technological advancements and expanded exploration of previously inaccessible fungal niches. Integrated multi-omics—combining genomics, transcriptomics, metabolomics, and proteomics—will enable more precise identification and activation of silent biosynthetic gene clusters, significantly increasing the rate of novel metabolite discovery (Keller, 2019). Synthetic biology and CRISPR-Cas genome editing are expected to revolutionize pathway engineering, allowing enhanced production, structural diversification, and heterologous expression of valuable antimicrobial compounds (Zhang et al., 2020). Metagenomics will further facilitate access to metabolites from unculturable fungi by reconstructing pathways directly from environmental DNA (Ziemert et al., 2016).

Exploration of extreme environments—including deep-sea ecosystems, polar regions, mangroves, and geothermal sites—offers exciting opportunities, as fungi from these habitats often produce structurally unique metabolites with potent bioactivities (Imhoff, 2016). Co-culture strategies, microbiome studies, and advanced fermentation technologies will help overcome low-yield limitations and stimulate expression of previously inaccessible metabolites. The integration of artificial intelligence (AI) and machine learning into natural product research will accelerate compound prediction, dereplication, and drug-likeness assessment, reducing the rediscovery problem and guiding efficient screening pipelines. Overall, future research is expected to unlock vast chemical diversity from fungi, supporting the development of next-generation antimicrobials urgently needed to combat AMR.

CONCLUSION

Fungi remain unparalleled producers of bioactive compounds with potent antimicrobial activity. Their metabolic diversity, ecological adaptability, and genomic potential make them vital to the development of future antimicrobial agents. As global AMR continues to escalate, fungal-derived compounds offer a sustainable and innovative pathway for therapeutic discovery. It remain one of the most productive and underexplored sources of antimicrobial agents. Advances in genomics, metabolomics, and synthetic biology promise significant future breakthroughs, particularly against multidrug-resistant pathogens.

Fungi are one of the most promising biological sources of novel antimicrobial agents. Emerging studies (2020–2024) continue to reveal new compounds with activity against MDR bacteria, fungi, viruses, and parasites. Advances in genomics, metabolomics, and synthetic biology hold immense

potential to unlock thousands of silent biosynthetic pathways. Continued exploration of terrestrial, marine, and endophytic fungi is crucial for developing next-generation antimicrobial drugs and addressing the global challenge of antimicrobial resistance. It represent one of the most prolific and versatile sources of natural antimicrobial agents, producing structurally diverse secondary metabolites with broad clinical, agricultural, and industrial relevance. Their metabolites—including polyketides, peptides, terpenoids, and alkaloids—play crucial roles in modern medicine, from β-lactam antibiotics and immunosuppressants to statins and antifungal drugs. Recent genomic and metabolomic advances have revealed thousands of previously unexplored biosynthetic pathways, expanding the potential for discovery of novel compounds effective against multidrug-resistant pathogens. Despite challenges such as low yields, toxicity, and cultivation difficulties, emerging tools in genome mining, synthetic biology, and advanced fermentation continue to overcome these limitations. The exploration of marine, endophytic, and extremophilic fungi further broadens the scope for discovering unique antimicrobial scaffolds. Overall, fungal metabolites remain indispensable in the fight against infectious diseases, and continued interdisciplinary research holds great promise for developing innovative solutions to global antimicrobial resistance.

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