Review Article

Microbial Biosystems 9(1) (2024) 2024.371458
10.21608/mb.2024.371458

Contents lists available at Egyptian Knowledge Bank
Microbial Biosystems
Journal homepage: http://mb.journals.ekb.eg/

Antifungal activity of secondary metabolites produced by fungi

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ARTICLE INFO

Article history:
Received 5 April 2024
Received revised 29 May 2024
Accepted 25 July 2024
Available online 2 August 2024

Corresponding Editors:
Balbool, BA.
Mohamed, AH.

Keywords
Egypt,
endophytic fungi,
ergosterol,
human diseases,
marine fungi,
soil fungi.

ABSTRACT

Antifungal agents, which are essential for treating various body fungal infections, have evolved significantly since the late 19th century where local antiseptics had limited effectiveness. However, the discovery of penicillin in 1928 and the subsequent realization that it was ineffective against fungi spurred the development of specific antifungals. The discovery of amphotericin B in 1955, azoles in the 1960s, and echinocandins in the 1970s made key breakthroughs. To inhibit fungal growth, each class targets different fungal components, such as the cell membrane or cell wall. Soil, marine, and endophytic fungi can yield antifungals, each contributing unique compounds. Rising resistance challenges the sustainability of antifungal agents, necessitating advanced susceptibility testing and stewardship programs. Resistance mechanisms include genetic mutations, efflux pumps, and enzymatic modifications. In Egypt, studies reveal increasing resistance, emphasizing the need for comprehensive strategies to mitigate this tendency. This article provides a comprehensive analysis of the remarkable antifungal capabilities of fungi, emphasizing their capacity to generate unique and varied antimicrobial substances that effectively combat infections affecting humans, plants, and marine organisms. This also emphasizes the important role that fungi recovered from various environmental habitats may play in our fight against human pathogenic fungi. This serves as a reason to intensify our efforts to find new and powerful antimicrobial medications.

Published by Arab Society for Fungal Conservation

Introduction

The fungal kingdom represents an extraordinary diversity of organisms with profound impacts across animal, plant, and ecosystem health (Abdel-Azeem 2010). Fungi play a dual role in supporting life, since they establish mutually beneficial relationships with plants, produce life-saving medications, and can inflict severe illnesses on humans, plants, and animals. The current challenges of climate change, rising antimicrobial resistance, global trade, environmental degradation, and emerging viruses have significantly influenced the effects of fungi on health and disease. Consequently, it is now imperative to develop innovative strategies to address the risks posed by fungi and utilize their remarkable capabilities in areas such as human health, food production, and environmental restoration (Abdel-Azeem 2010; Abdel-Azeem et al. 2016, 2019; Balbool and Abdel-Azeem 2020; Mubasher et al. 2022; Mohamed et al. 2022; Abo Nouh et al. 2024).

Secondary metabolites produced by endophytic fungi exhibit a wide range of biological activities, including antimicrobial, antiviral, anticancer, and particularly antifungal effects (Strobel & Daisy, 2003). These metabolites include alkaloids, terpenoids, steroids, quinones, phenols, and flavonoids, which often display unique structural features not found in synthetic compounds (Gupta et al. 2020). The ability of these metabolites to inhibit the growth of pathogenic fungi is attributed to various mechanisms, such as disrupting cell wall synthesis, interfering with cell membrane integrity,

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and inhibiting critical enzymatic pathways within the fungal cells.

The increasing resistance of fungal pathogens to conventional antifungal agents underscores the urgency of identifying alternative sources of effective antifungals. Endophytic fungi, particularly those isolated from native plants, are a rich source of such bioactive compounds. Studies have shown that extracts from these fungi can inhibit the growth of several phytopathogenic and clinically relevant fungal species (Ek-Ramos et al. 2019).

Since the Convention on Biological Diversity and environmental legislation restrict the gathering of medicinal plants globally, restoring their endophytic microorganisms has become a new trend in plant conservation in the last 30 years. Endophytic fungi, which live in plant tissues noninvasively, are unmatched sources of bioactive compounds e.g. antimicrobials, anticancer, antiviral, antiparasitic antitubercular compounds (Abdel-Azeem et al. 2021). This review provides a comprehensive overview of antifungal agents, including their history, mechanisms of action, resistance mechanisms, and current research efforts.

History of antifungal agents and their mechanism

Antifungal agents are drugs that are used to treat fungal infections, which can affect various parts of the body, such as the skin, nails, mouth, lungs, and blood (Smith 1990). The history of antifungal agents dates to the late 19th century, when the first topical antiseptics, such as phenol and iodine, were used to treat superficial fungal infections. However, Odds et al. (2003) reported that these agents were not very effective and had limited spectrum of activity. The discovery of penicillin in 1928 by Fleming opened a new era of antimicrobial therapy, but it was soon realized that penicillin and other antibiotics had no activity against fungi. Therefore, the search for specific antifungal agents began in the mid-20th century. One of the first breakthroughs in antifungal therapy was the discovery of amphotericin B in 1955 (Gallis 1996), which was isolated from a soil bacterium.

Amphotericin B is a polyene macrolide that binds to ergosterol, a sterol component of the fungal cell membrane, and forms pores that disrupt the membrane integrity and cause cell death (Cuervo et al. 2016).

Another important class of antifungal agents is the azoles, which were discovered in the late 1960s (Mares et al. 1996). The azoles are synthetic compounds that inhibit the enzyme lanosterol 14-alpha-demethylase, which is involved in the biosynthesis of ergosterol. By blocking this enzyme, the azoles impair the synthesis and function of the fungal cell membrane and cause cell death. The azoles have a wide spectrum of activity against many fungi, including *Candida*, *Aspergillus*, *Cryptococcus*, and *Dermatophytes* (Du et al. 2023). The azoles can be divided into two generations: the first-generation azoles, such as ketoconazole, miconazole, and clotrimazole, which have a lower potency and selectivity, and the second-generation azoles, such as fluconazole, itraconazole, voriconazole, and posaconazole, which have a higher potency and selectivity (Scorzoni et al. 2017). A newer class of antifungal agents is the echinocandins, which were discovered in the late 1970s. The echinocandins are cyclic lipopeptides that inhibit the enzyme beta-1,3-D-glucan synthase, which is involved in the synthesis of beta-glucan, a major component of the fungal cell wall (Scorzoni et al. 2017). Other antifungal agents include allylamines, such as terbinafine, which inhibit the enzyme squalene epoxidase, another enzyme involved in the ergosterol biosynthesis pathway; flucytosine, which is a pyrimidine analog that interferes with the fungal DNA and RNA synthesis; and griseofulvin, which is a natural product that binds to the microtubules and disrupts the fungal mitotic division.

Types of antifungal agents and their chemical structure

Fungal infections can pose significant health challenges, but diverse classes of antifungal agents offer effective treatments. This overview explores the primary types of antifungals, their chemical structures, and mechanisms of action.

Main types of antifungal agents

Polyenes

These naturally derived or synthetic compounds bind to ergosterol, a vital component of the fungal cell membrane, creating pores and disrupting its integrity, ultimately causing cell death. Despite their broad spectrum, polyenes may be limited due to potential human cell toxicity. Examples include Amphotericin B and nystatin (Hamilton-Miller 1973).

Azoles

These synthetic agents target lanosterol 14-alpha-demethylase, an enzyme critical for ergosterol synthesis. By inhibiting this enzyme, azoles compromise the fungal

cell membrane, leading to cell death. While offering a broad spectrum, azoles may interact with other medications and cause side effects. Examples include ketoconazole, fluconazole, itraconazole, and voriconazole (Singh et al. 2023).

Allylamines

These synthetic agents target squalene epoxidase, another enzyme involved in ergosterol synthesis. By inhibiting this enzyme, allylamines decrease ergosterol levels in the fungal cell membrane, ultimately causing cell death. They possess a narrower spectrum, primarily targeting dermatophytes, fungi that infect skin, hair, and nails. Examples include terbinafine and naftifine (Cross et al. 1995).

Echinocandins

These semi-synthetic agents target beta-1,3-D-glucan synthase, an enzyme responsible for synthesizing beta-glucan, a crucial component of the fungal cell wall. By inhibiting this enzyme, echinocandins prevent cell wall formation and maintenance, leading to cell death. They have a narrower spectrum, primarily effective against *Candida* and *Aspergillus*, fungal species known to cause invasive infections. Examples include caspofungin, micafungin, and anidulafungin (Cross et al. 1995).

It is important to note that these are the most common types, and others exist with distinct mechanisms of action and spectrums. Selection of an appropriate antifungal agent depends on various factors, including the type and severity of the infection, fungal susceptibility, pharmacokinetics, and potential for drug interactions and side effects.

Chemical Structure and Significance

The chemical structure of antifungal agents varies across classes, but commonalities exist within each class. Below some important classes will be discussed.

Polyenes

Polyene antibiotics are composed of a macrolactone ring made up of polyunsaturated carbons. The presence of hydroxyl groups gives the molecule its amphipathic nature. These medications consist of a series of four to eight connected double bonds inside the macrolactone structure (Ganis et al. 1971) as shown in figure (1). The hydrophobic chain is thought to play a crucial role in one of the suggested mechanisms of action. It is believed to be responsible for the interaction between antimycotics and sterols, leading to the creation of transmembrane pores (Haro-Reyes et al. 2022)

Amphotericin B ($C_{47}H_{73}NO_{17}$) is a crucial polyene macrolide antibiotic. It is a heptaene compound that includes a macrolactone ring, which is β-glycosylated to a mycosamine group at the C19 position (Fig. 2) (Ganis et al. 1971). The macrolactone ring is a nearly flat chromophore with seven double bonds in a trans configuration, forming the hydrophobic area.

Additionally, it includes a hemiketal ring at positions C13 and C17. Furthermore, it possesses a polyol subunit that is more adaptable and serves as the hydrophilic portion of the polyene compound. The amphoteric nature of AmB is determined by the existence of a carboxyl group at the C16 position and an amino group situated on the mycosamine head group (Ganis et al. 1971).

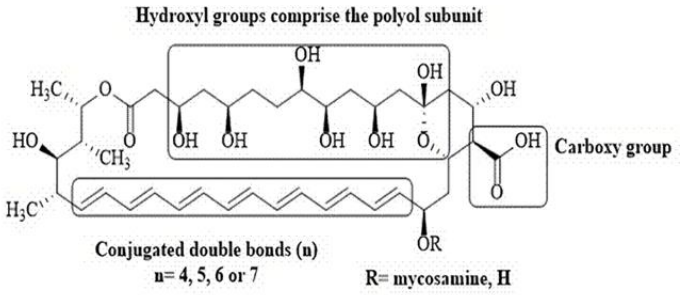

Fig1. General structure of polyenes.

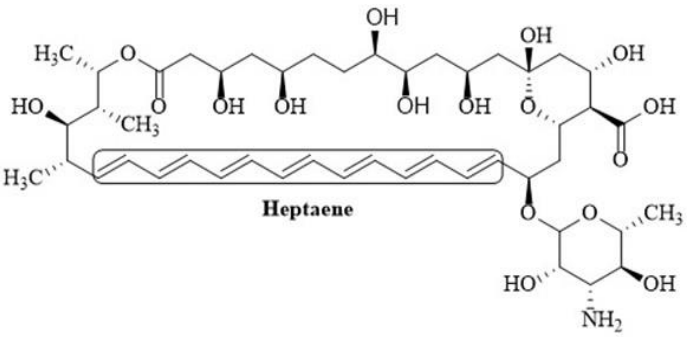

Fig 1. Structure of Amphotericin B 1.

Azoles

Heterocyclic compounds with a five-membered ring containing at least one nitrogen atom and a functional group attached. Further classified as imidazoles (e.g., ketoconazole, Ketoconazole is an imidazole derivative that was synthesized and developed by Janssen Pharmaceuticals in 1977 (Heeres et al. 1979). It is an antifungal compound that can be taken orally. It is often regarded as the most reliable and effective among the antifungal medications derived from azole. Thus far, it has demonstrated itself to be the most effective and extensively utilized azole derivative for combating fungal infections. Ketoconazole (Fig. 3) is recommended as the preferred treatment for blastomycosis, disseminate

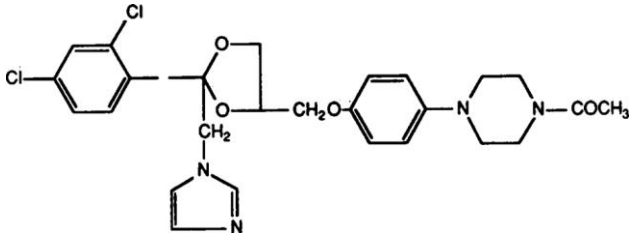

Fig3. Ketoconazole chemical structure.

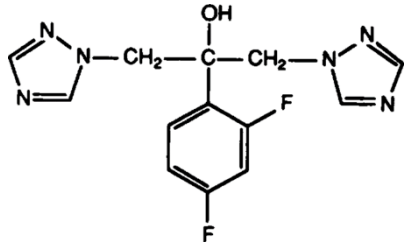

Fig 4. Fluconazole chemical structure

histoplasmosis in stable non-immunocompromised individuals, chronic cavitary histoplasmosis, paracoccidioidomycosis, and chronic mucocutaneous candidiasis. In certain instances of chromoblastomycosis and subcutaneous pseudallescheriosis, as well as specific subgroups of coccidioidomycosis, it may be utilized. This includes cases involving soft-tissue and cutaneous lesions, draining sinus tracts, and potentially osteomyelitis and synovitis (Fromtling, 1988)and triazoles (e.g., fluconazole, $C_{13}H_{12}F_2N_6O$) based on the number of nitrogen atoms in the ring (Fig. 4).

Fluconazole, also known as UK-49,858, is a triazole antifungal drug that is taken by mouth. It is currently being developed by Pfizer U.K. This compound exhibits a significant level of systemic bioavailability and is currently undergoing development for its potential use as a once-daily oral, intravenous, and topical treatment against both systemic and superficial fungal infections (Fromtling 1988). Ongoing Phase III clinical trials are currently taking place in the United States, and thus far, positive outcomes have been reported for the treatment of several systemic fungal diseases. This includes the successful treatment of cryptococcal meningitis in patients with weakened immune systems. According to Sochynsky and Hardcastle's book "Pharma Projects" from May 1987, fluconazole has demonstrated effectiveness in treating vaginal and cutaneous candidiasis, as well as superficial fungal infections.

Allylamines

Unsaturated compounds with an allyl group and an amine group e.g. ($C_{21}H_{25}N$) (Fig. 5).

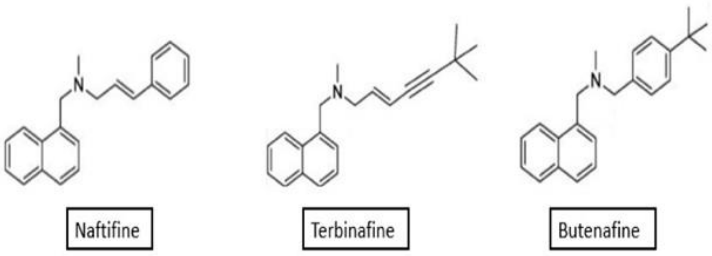

Fig 5. Chemical structures of some allylamines.

Echinocandins

These are cyclic peptides that have a large ring structure composed of amino acids. They also have a lipid tail attached to the ring, which makes them lipopeptides. The echinocandins can be further divided into caspofungins, micafungins, and anidulafungins, depending on the structure of the amino acids and the lipid tail. An example of echinocandins antifungal is caspofungin (Fig. 6), which has the following chemical structure ($C_{52}H_{88}N_{10}O_{15}$).

Mycosources of antifungal agents from different habitats

Antifungal agents are drugs used to treat fungal infections that affect various parts of the body such as skin, nails, mouth, lungs and blood. Antifungal agents can be obtained from various sources, such as soil, marine and endophytic fungi. Below are some examples of each source.

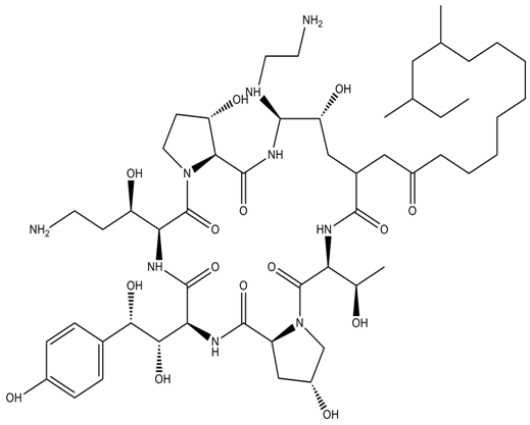

Fig 6. Chemical structures of caspofungin.

Soil fungi

These are fungi that live in the soil and produce secondary metabolites that have antifungal properties. Some of the most famous antifungal agents from soil fungi are the polyenes, such as amphotericin B and nystatin, which bind to ergosterol in the fungal cell membrane and cause cell death. Another example is griseofulvin, which is produced by *Penicillium griseofulvum* and disrupts the fungal mitosis (Giddings & Newman 2022).

Marine fungi

These are fungi that inhabit marine environments, such as seawater, sediments, algae, corals, sponges, and other marine organisms. Marine fungi are exposed to extreme conditions, such as high salinity, pressure, temperature, and light, which may stimulate them to produce novel and diverse antifungal compounds. Some examples of antifungal agents from marine fungi are the azaphilones, such as chaetoviridin A and B, which are produced by *Chaetomium globosum* and inhibit the fungal lanosterol 14-alpha-demethylase. Another example is the indole alkaloid, aspergillazine A, which is produced by *Aspergillus versicolor* and has activity against *Candida albicans*.

Endophytic fungi

These are fungi that live inside plant tissues without causing any harm to the host (Jha et al. 2023). Endophytic fungi can benefit from the plant's nutrients and protection, and in return, they can produce antifungal compounds that protect the plant from pathogens. Some examples of antifungal agents from endophytic fungi are the terpenoids, such as taxol and podophyllotoxin, which are produced by *Taxomyces andreanae* and *Fusarium solani*, respectively, and have activity against various cancers. Another example is the peptaibol, trichogin GA IV, which is produced by Trichoderma virens and has activity against Aspergillus fumigatus (Hosseyni-Moghaddam & Soltani 2014).

Susceptibility of antifungal agents

The susceptibility of antifungal agents is a topic that concerns the effectiveness and availability of drugs that treat fungal infections. Fungal infections can be serious and life-threatening, especially for immunocompromised patients. However, some fungi can develop resistance to antifungal drugs, making them harder to treat. Antifungal resistance can also limit the options for prophylaxis and treatment of invasive fungal infections. Therefore, it is important to monitor and prevent antifungal resistance, as well as to develop new and improved antifungal agents. Some of the key points related to the sustainability of antifungal agents are antifungal susceptibility testing and antifungal stewardship.

Antifungal susceptibility testing (AFST)

This technique measures the ability of an antifungal drug to inhibit or kill a fungal isolate. AFST can help guide clinical decisions, optimize antifungal therapy, and detect antifungal resistance. However, AFST methods have some limitations, such as high turnaround time, variability, and lack of standardization. Several innovative methods are being developed to improve AFST, such as Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF), flow cytometry, computed imaging, and molecular detection of resistance mutations (Berkow et al. 2020).

Antifungal stewardship (AFS)

A strategy that aims to optimize the use of antifungal drugs to improve patient outcomes, reduce adverse effects, and prevent antifungal resistance. AFS involves the coordination of multidisciplinary teams, the implementation of evidence-based guidelines, the monitoring of antifungal consumption and resistance, and the education of health care professionals and patients (Hart et al. 2019; Johnson et al. 2020).

Resistance of antifungal agent

Antifungal resistance is a serious problem that affects the treatment of fungal infections. Fungal infections can be caused by different types of fungi, such as *Candida*, *Aspergillus*, and *dermatophytes*. Some of these fungi are naturally resistant to certain antifungal drugs, while others can develop resistance over time due to exposure to

antifungal drugs or fungicides. Antifungal resistance can limit the options and effectiveness of antifungal therapy and increase the risk of complications and death. It occurs when antifungal medicines can't stop the growth of a fungal infection. People with weak immune systems are most at risk. Superbugs like *Candida auris* don't respond to antifungals, which limits treatment options (Li et al. 2015). You can lower the risk of antifungal resistance by taking medicine as prescribed. Some species of fungi are naturally resistant to certain types of antifungal drugs, for example, the drug fluconazole does not work against infections caused by the fungus *Aspergillus*, a type of mold found throughout the environment. Resistance can also develop over time when fungi are exposed to antifungal drugs. This resistance can occur when antifungal drugs are used to treat sick people, especially if the drugs are used improperly (for example, when dosages are too low or when treatment courses are not long enough). Use of fungicides in agriculture to prevent and treat fungal diseases in crops can also contribute to resistant disease in people. Fungal infections pose a significant global health burden, and the emergence of resistance to antifungal therapies presents a growing threat. In Egypt, research suggests a concerning rise in antifungal resistance among prevalent fungal pathogens, highlighting the need for immediate action and comprehensive strategies (Zaki & Denning, 2017).

Mechanisms of Antifungal Resistance

Fungal resistance to antifungal agents arises from various mechanisms employed by the pathogen to evade the drug's effect. These mechanisms include **genetic mutations** within genes encoding drug targets can hinder the antifungal agent's ability to bind effectively, rendering it ineffective (Kanaf et al. 2016), **efflux pumps** when the fungal cells develop mechanisms to actively pump antifungal agents back out of the cell, decreasing their intracellular concentration and reducing their impact (Singh et al. 2015), and **enzymatic modification** by which some fungi possess enzymes that can modify the structure of antifungal agents, rendering them inactive (Odds 2003).

Egypt as a case study

Studies such as the one carried by Zaki and Denning (2017) offer valuable insights into the current state of antifungal resistance in Egypt. Their research investigated the prevalence of resistance among various fungal pathogens isolated from clinical specimens collected in Egyptian hospitals. The study observed a significant rise in resistance rates for commonly used antifungal agents, such as fluconazole and itraconazole, against *Candida albicans*, a highly prevalent fungal pathogen.

Resistance to newer antifungal agents, like voriconazole, was also detected, suggesting the potential for a broader resistance problem in the future.

Zaki and Denning (2017) have found many variables that are likely to contribute to the increase of antifungal resistance in Egypt. These factors include:

1- The extensive use of antifungal agents in both human and veterinary medicine can exert selective pressure on fungal populations, favoring the emergence of resistant strains (Gudlaugsson et al. 2003).
2- The lack of robust antifungal stewardship programs, which promote the appropriate use of these medications, can contribute to misuse and overreliance on certain antifungal agents (Bader et al. 2019).
3- The application of antifungal agents in agriculture can also contribute to the development of resistance in environmental fungal pathogens, potentially impacting human health (Fisher et al. 2013).

Development of antifungal research

Antifungal research is a field of study that aims to discover and develop new drugs that can treat or prevent fungal infections. Fungal infections are caused by various types of fungi that can affect different parts of the human body, such as the skin, nails, hair, lungs, brain, and blood. Some fungal infections are superficial and can be easily treated, while others are invasive and can be life-threatening, especially for people with weakened immune systems. According to our research results, one of the most important current topics and challenges in antifungal research is the emergence of antifungal resistance, which reduces the effectiveness of existing drugs and limits the treatment options for patients. Antifungal resistance can occur due to genetic mutations, biofilm formation, efflux pumps, or altered drug targets in the fungi (Vitiello et al. 2023). Also, the limited number and diversity of antifungal drugs, which are mainly classified into four classes

polyenes, azoles, echinocandins, and allylamines. These drugs have different mechanisms of action, but they also have drawbacks such as toxicity, side effects, drug interactions, or narrow spectrum of activity. The difficulty and cost of antifungal drug discovery and development, which involves screening of natural or synthetic compounds, identification and validation of novel drug targets, optimization of drug properties, and evaluation of drug efficacy and safety in preclinical and clinical trials.

Antifungal drug development also faces regulatory and economic hurdles, such as low market incentives, high failure rates, and lack of funding. The need new antifungal strategies and approaches, such as exploiting natural antifungal compounds, designing structure-based drugs, combining drugs with synergistic effects, harnessing genomic and proteomic technologies, and developing novel delivery systems and formulations. These strategies and approaches aim to overcome the limitations of current antifungal drugs and to enhance their activity, specificity, and bioavailability.

Antifungal research is a vital and dynamic area of science that contributes to the improvement of human health and the prevention of fungal diseases. This study aims to search for metabolites produced from endophytic fungi which acting as antifungal and antimicrobial agents.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

The first author would like to thank his family for their unwavering support, patience, and understanding. Their constant encouragement has been a source of strength and motivation. Both authors are deeply appreciated to the Arab Society for Fungal Conservation for covering the publication fees of their work.

References

Abdel-Azeem AM. (2010). The history, fungal biodiversity, conservation, and future perspectives for mycology in Egypt. IMA Fungus 1(2): 123–142.

Abdel-Azeem AM, Zaki SM, Khalil WF, Makhlouf NA, Farghaly LM. (2016). Anti-rheumatoid Activity of Secondary Metabolites Produced by Endophytic *Chaetomium globosum*. Frontiers in Microbiology, 7 (1477): 1-11.

Abdel-Azeem AM, Abdel-Azeem MA, Khalil WF. (2019). Endophytic Fungi as a New Source of Antirheumatoid Metabolites. In Watson, R. R. and Preedy, V. R. edition. Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases (pp. 355-384), Elsevier, Amsterdam. https://doi.org/10.1016/B978-0-12-813820-5.00021-0

Abdel-Azeem MA, El-Maradny YA, Othman AM, Abdel-Azeem AM. (2021). Endophytic Fungi as a Source of New Pharmaceutical Biomolecules. In: Abdel-Azeem, A.M., Yadav, A.N., Yadav, N., Sharma, M. (eds) Industrially Important Fungi for Sustainable Development. Fungal Biology. Springer, Cham. https://doi.org/10.1007/978-3-030-85603-8_3

Abo Nouh F, Abu-Elsaoud AM, Abdel-Azeem AM. (2024). Induction of abiotic stress tolerance in plants by endophytic fungi hosted wild plants. Microbial Biosystems, 9(1):38-50.

Balbool BA, Abdel-Azeem AM. (2020). Diversity of the culturable endophytic fungi producing L-asparaginase in arid Sinai, Egypt. Italian Journal of Mycology, 49: 8-24.

Berkow EL, Lockhart SR, Ostrosky-Zeichner L. (2020). Antifungal Susceptibility Testing: Current Approaches. Clinical Microbiology Reviews 33, e00069-19. https://doi.org/10.1128/CMR.00069-19

Cross JT Jr, Hickerson SL, Yamauchi T. (1995). Antifungal Drugs. Pediatrics In Review 16, 123–129. https://doi.org/10.1542/pir.16-4-123

Cuervo G, Garcia-Vidal C, Nucci M, Puchades F, Fernández-Ruiz M, Obed M, Manzur A, Gudiol C, Pemán J, Aguado JM, Ayats J, Carratalà J. (2016). Breakthrough candidaemia in the era of broad-spectrum antifungal therapies. Clinical Microbiology and Infection 22, 181–188. https://doi.org/10.1016/j.cmi.2015.09.029

Du L, Haldar S, King JB, Mattes AO, Srivastava S, Wendt KL, You J, Cunningham C, Cichewicz RH. (2023). Persephacin Is a Broad-Spectrum Antifungal Aureobasidin Metabolite That Overcomes Intrinsic Resistance in Aspergillus fumigatus. Journal of Natural Products 86, 1980–1993. https://doi.org/10.1021/acs.jnatprod.3c00382

Ek-Ramos MJ, Gomez-Flores R, Orozco-Flores AA, Rodríguez-Padilla C, González-Ochoa G, Tamez-Guerra P. (2019). Bioactive Products From Plant-Endophytic Gram-Positive Bacteria. Frontiers in

Microbiology 10, 463. https://doi.org/10.3389/fmicb.2019.00463

Fromtling RA. (1988). Overview of medically important antifungal azole derivatives. Clinical Microbiology Reviews 1, 187–217. https://doi.org/10.1128/CMR.1.2.187

Gallis HA. (1996). Amphotericin B: A Commentary on Its Role as an Antifungal Agent and as a Comparative Agent in Clinical Trials. Clinical Infectious Diseases 22, S145–S147.

Ganis P, Avitabile G, Mechlinski W, Schaffner CP. (1971). Polyene macrolide antibiotic amphotericin B. Crystal structure of the N-iodoacetyl derivative. Journal of the American Chemical Society 93, 4560–4564. https://doi.org/10.1021/ja00747a037

Giddings LA, Newman DJ. (2022). Extremophilic Fungi from Marine Environments: Underexplored Sources of Antitumor, Anti-Infective and Other Biologically Active Agents. Marine Drugs 20, 62. https://doi.org/10.3390/md20010062

Gudlaugsson O, Gillespie S, Lee K, Berg JV, Hu J, Messer S, Herwaldt L, Pfaller M, Diekema D. (2003). Attributable Mortality of Nosocomial Candidemia, Revisited. Clinical Infectious Diseases 37, 1172–1177. https://doi.org/10.1086/378745

Gupta S, Chaturvedi P, Kulkarni MG, Van Staden J. (2020). A critical review on exploiting the pharmaceutical potential of plant endophytic fungi. Biotechnology Advances 39, 107462. https://doi.org/10.1016/j.biotechadv.2019.107462

Hamilton-Miller JMT. (1973). Chemistry and Biology of the Polyene Macrolide Antibiotics. Journal of the American Chemical Society 37.

Haro-Reyes T, Díaz-Peralta L, Galván-Hernández A, Rodríguez-López A, Rodríguez-Fragoso L, Ortega-Blake I. (2022). Polyene Antibiotics Physical Chemistry and Their Effect on Lipid Membranes; Impacting Biological Processes and Medical Applications. Membranes 12, 681. https://doi.org/10.3390/membranes12070681

Hart E, Nguyen M, Allen M, Clark CM, Jacobs DM. (2019). A systematic review of the impact of antifungal stewardship interventions in the United States. Annals of Clinical Microbiology and Antimicrobials 18, 24. https://doi.org/10.1186/s12941-019-0323-z

Heeres J, Backx LJJ, Mostmans JH, Van Cutsem J. (1979). Antimycotic imidazoles. Part 4. Synthesis and antifungal activity of ketoconazole, a new potent orally active broad-spectrum antifungal agent. Journal of Medicinal Chemistry 22, 1003–1005. https://doi.org/10.1021/jm00194a023

Hosseyni-Moghaddam MS, Soltani J. (2014). Bioactivity of endophytic Trichoderma fungal species from the plant family Cupressaceae. Annals of Microbiology 64, 753–761. https://doi.org/10.1007/s13213-013-0710-1

Jha P, Kaur T, Chhabra I, Panja A, Paul S, Kumar V, Malik T. (2023). Endophytic fungi: hidden treasure chest of antimicrobial metabolites interrelationship of endophytes and metabolites. Frontiers in Microbiology 14.

Johnson MD, Lewis RE, Dodds Ashley ES, Ostrosky-Zeichner L, Zaoutis T, Thompson GR, Andes DR, Walsh TJ, Pappas PG, Cornely OA, Perfect JR, Kontoyiannis DP. (2020). Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium. Journal of Infectious Diseases 222, S175–S198. https://doi.org/10.1093/infdis/jiaa394

Li Y, Chang W, Zhang M, Li X, Jiao Y, Lou H. (2015). Synergistic and drug-resistant reversing effects of diorcinol D combined with fluconazole against Candida albicans. FEMS Yeast Research 15. https://doi.org/10.1093/femsyr/fov001

Mares D, Romagnoli C, Vicentini CB, Sacchetti G, Bruni A. (1996). Antifungal screening of seven new azole derivatives. Microbios 86, 185–193.

Mohamed AH, Abd El-Megeed FH, Hassanein NM, Youseif SH, Farag PF, Saleh SA, Abdel-Wahab BA, Alsuhaibani AM, Helmy YA, Abdel-Azeem AM. (2022). Native Rhizospheric and Endophytic Fungi as Sustainable Sources of Plant Growth Promoting Traits to Improve Wheat Growth under Low Nitrogen Input. Journal of Fungi 8, 94. https://doi.org/10.3390/jof8020094

Moubasher HA, Balbool BA, Helmy YA, Alsuhaibani AM, Atta AA, Sheir DH, Abdel-Azeem AM. (2022). Insights into Asparaginase from Endophytic Fungus Lasiodiplodia theobromae: Purification, Characterization and Antileukemic Activity. International Journal of Environmental Research and Public Health 19, 680. https://doi.org/10.3390/ijerph19020680

Odds FC, Brown AJP, Gow NAR. (2003). Antifungal agents: mechanisms of action. Trends in Microbiology 11, 272–279. https://doi.org/10.1016/S0966-842X(03)00117-3

Scorzoni L, de Paula e Silva ACA, Marcos CM, Assato PA, de Melo WCMA, de Oliveira HC, Costa-Orlandi CB, Mendes-Giannini MJS, Fusco-Almeida AM. (2017). Antifungal Therapy: New Advances in the Understanding and Treatment of Mycosis. Frontiers in Microbiology 8.

Singh A, Singh K, Sharma A, Kaur K, Chadha R, Bedi PMS. (2023). Recent advances in antifungal drug development targeting lanosterol 14α-demethylase (CYP51): A comprehensive review with structural and molecular insights. Chemical Biology & Drug Design 102, 606–639. https://doi.org/10.1111/cbdd.14266

Smith EB. (1990). History of antifungals. Journal of the American Academy of Dermatology 23, 776–778. https://doi.org/10.1016/0190-9622(90)70286-Q

Strobel G, Daisy B. (2003). Bioprospecting for Microbial Endophytes and Their Natural Products. Microbiology and Molecular Biology Reviews 67, 491–502. https://doi.org/10.1128/MMBR.67.4.491-502.2003

Vitiello A, Ferrara F, Boccellino M, Ponzo A, Cimmino C, Comberiati E, Zovi A, Clemente S, Sabbatucci M. (2023). Antifungal Drug Resistance: An Emergent Health Threat. Biomedicines 11, 1063. https://doi.org/10.3390/biomedicines11041063

Zaki SM, Denning DW. (2017). Serious fungal infections in Egypt. European Journal of Clinical Microbiology & Infectious Diseases 36, 971–974. https://doi.org/10.1007/s10096-017-2929-4