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The Potential of Medicinal Plants in Antifungal Drug Development: Mechanisms, Synergies, and Future Directions

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Fungal infections pose a significant threat to global health, leading to considerable morbidity and mortality in humans, animals, and plants. The rise of drug-resistant fungal strains, coupled with the limitations of current antifungal therapies, such as toxicity and the potential for resistance, has prompted the exploration of alternative treatments. Medicinal plants, with their bioactive phytochemicals, have emerged as promising sources of antifungal agents. These compounds, which include phenols, alkaloids, terpenoids, and phytosterols, exhibit diverse mechanisms of action, such as disruption of fungal cell membranes, inhibition of cell wall synthesis, and induction of mitochondrial dysfunction. This review discusses the effect of various fungal pathogens, such as *Candida albicans*, *Aspergillus fumigatus*, and *Fusarium* species, highlighting their virulence factors and the diseases they cause. It also examines the antifungal properties of medicinal plants, focusing on specific species and their bioactive compounds targeting fungal cells. This study explores the mechanisms through which phytochemicals such as alkaloids, flavonoids, and saponins inhibit fungal growth and the potential for synergistic effects when combined with conventional antifungals. While acknowledging the importance of safety, standardization, and toxicity evaluations, the review also delves into the role of computational drug-discovery methods, such as molecular docking and artificial intelligence-assisted screening, in identifying potential antifungal candidates. Despite challenges such as the variability in plant composition and the need for further clinical data, this review emphasizes the significant potential of medicinal plants in addressing drug-resistant fungal infections and outlines the directions for future research, including biotechnology, nanotechnology, and the exploration of understudied plant species.

Key Words: Antifungal agents, Drug resistance, Fungal infections, Medicinal plants, Phytochemicals

INTRODUCTION

Fungal infections pose a significant challenge for global health, affecting humans, animals, and plants. These infections are a major cause of death and illness, particularly in developing countries. In humans, fungal infections such as invasive candidiasis, aspergillosis, and cryptococcosis account for substantial morbidity and mortality, with millions affected annually and approximately 1.7 million deaths reported. Immunocompromised individuals, including those with HIV/AIDS, cancer, or diabetes, are especially vulnerable. The long-term use of specific drugs further increases this risk. Fungal infections can target various parts of the body, including the brain, ears, skin, mucous membranes, and internal organs[1-4].

In animals, fungal infections can result in respiratory and generalized infections, with tissue predilection varying across species. In plants, fungi are responsible for 70~80% of agricultural losses caused by microbial diseases, reducing the

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nutritional value of crops and producing harmful mycotoxins. Genera such as *Fusarium*, *Aspergillus*, and *Penicillium* are particularly notorious for mycotoxin production, posing risks to food safety and human health[5].

The rise of drug-resistant fungal strains exacerbates the global challenge to health. Factors such as the overuse of broad-spectrum antibiotics and the prolonged use of antifungal drugs such as fluconazole have contributed to resistance. The limited availability of antifungal drugs, coupled with their toxic side effects, emphasizes the urgent need for novel therapeutic approaches[6].

There are significant limitations to the use of conventional antifungal treatments, including polyenes, azoles, echinocandins, and flucytosine. These include nephrotoxicity, the development of rapid resistance, drug interactions, and the potential for relapse. Some antifungal medications are associated with additional side effects, such as hepatotoxicity and visual disturbances, further complicating treatment strategies[7].

Medicinal plants are emerging as valuable alternatives and complementary treatments for fungal infections. These plants contain bioactive phytochemicals such as phenols, alkaloids, terpenoids, and phytosterols, which exhibit antifungal properties. These compounds act through mechanisms such as damaging fungal cell membranes, inhibiting cell wall and DNA/RNA/protein synthesis, and causing mitochondrial dysfunction. There is a long history of the use of medicinal plants in traditional medicine, with many cultures relying on them for the treatment of various ailments. Plant extracts often combine multiple compounds that work synergistically to suppress fungal growth and reduce the risk of resistance. Moreover, plant-based remedies are generally associated with fewer side effects and improved efficacy[8-13].

In this review, we examine the role of medicinal plants and their phytochemicals in combating pathogenic fungi. We also explore plant extracts and isolated compounds as potential sources of novel antifungal agents, along with *in silico* studies on the molecular interactions of plant compounds with fungal enzymes. Specific plants with demonstrated antifungal properties and their mechanisms of action are highlighted to identify potential therapeutic candidates and support the development of new drugs.

FUNGAL PATHOGENS AND THEIR IMPACT

Fungal pathogens are of significant medical importance as they cause a range of infections in humans, with some also affecting animals and plants. These pathogens can be categorized based on the type of infection they cause, such as systemic, dermatophytic, or mucocutaneous infections.

Candida albicans is a common cause of candidiasis, a fungal infection that can affect the skin, mucous membranes, and internal organs. It is a dimorphic commensal, meaning it can exist as a harmless organism but under certain conditions can become pathogenic. Candidiasis is characterized by white patches on the skin and superficial infections, particularly in moist areas of the body. *C. albicans* is a major source of nosocomial septicemia, acquired in a hospital setting. Other clinically significant *Candida* species include *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata*, which can form biofilms that contribute to antifungal resistance[7,12,14].

Dermatophytes, including *Trichophyton*, *Microsporum*, and *Epidermophyton*, cause superficial infections of the skin, hair, and nails (dermatophytoses). In particular, *Trichophyton rubrum* and *Trichophyton mentagrophytes* are associated with nail infections (onychomycosis), whereas *Microsporum canis* and *Epidermophyton floccosum* are also common dermatophytes. These fungi produce enzymes such as keratinases, proteases, and lipases that enable them to infect keratinized tissues. Dermatophyte infections are especially prevalent in tropical and subtropical areas.

Aspergillus fumigatus is a common cause of aspergillosis, a severe infection that can affect the lungs and other organs, especially in immunocompromised individuals. Some *Aspergillus* species, such as *Aspergillus niger*, produce mycotoxins, including ochratoxin A, which are harmful to both humans and animals[15].

Fusarium species can cause infections that range from superficial skin and nail infections to invasive diseases, particularly in immunocompromised individuals. These fungi can also cause plant diseases such as head blight and vascular wilt and produce mycotoxins that contaminate food, resulting in to health issues such as cancer and kidney failure.

Mucormycosis, which is caused by fungi in the order Mucorales, including *Rhizopus*, *Mucor*, and *Lichtheimia* species, is a rare but deadly infection primarily affecting immunocompromised individuals, those with uncontrolled diabetes, and organ transplant recipients. *Rhizopus oryzae* is the most common cause of mucormycosis, which can affect the brain, lungs, and sinuses. *Cryptococcus neoformans* is a significant pathogen responsible for cryptococcosis, a systemic fungal infection that affects the lungs and central nervous system, particularly in individuals with HIV/AIDS or other immunodeficiencies[2].

Other fungal pathogens, such as *Trichophyton soudanense*, *Trichophyton vaoundei*, *Trichophyton erinacei*, *Microsporum audouinii*, and *Penicillium* species, also play roles in human

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and plant infections. *Penicillium* causes blue mold rot in fruits, whereas *Botrytis* species lead to gray mold in crops, and *Pilidiella granati* causes heart rot in pomegranates.

These fungal pathogens contribute significantly to human health issues, ranging from superficial skin conditions to life-threatening systemic diseases. The emergence of drug resistance in many of these pathogens highlights the urgent need to develop alternative treatment strategies, including the potential use of medicinal plants.

To establish infections, fungi use various virulence factors. Key enzymes, such as proteases, keratinases, lipases, and phospholipases, facilitate tissue invasion, immune evasion, and inflammation. Proteases, including secreted aspartic proteinases (SAPs), assist with fungal morphogenesis and inhibit the immune response by digesting complement components. Keratinases allow dermatophytes to invade the skin, hair, and nails. Lipases and phospholipases hydrolyze host tissues, triggering inflammation. Some fungi, such as *Aspergillus* and *Fusarium*, produce mycotoxins such as aflatoxins and trichothecenes, causing severe health issues such as liver damage and cancer[16,17].

Other virulence factors include candidalysin, a toxin from *Candida* species that damages epithelial cells, and hemolysin, which affects red blood cells and phagocytes. Melanin production helps fungi resist environmental stress. In addition, sulfate transporters, heat shock proteins, and adenosine triphosphate (ATP)-binding cassette transporters may be targeted for antifungal therapies.

The formation of biofilm is a key immune evasion strategy. Biofilms create a protective matrix that shields fungi from antifungal drugs and immune responses, contributing to resistance. *C. albicans* uses aspartic proteases to evade the complement system, and its ability to switch between yeast and hyphal forms enhances tissue invasion and immune evasion. To develop effective antifungal therapies and combat resistance, understanding these mechanisms is essential. Fig. 1 provides a visualization of the fungal pathogens and their effects.

MEDICINAL PLANTS AS ANTIFUNGAL AGENTS

For millennia, medicinal plants have played a central role in treating fungal infections and other ailments across cultures. In ancient Egypt, herbal remedies were meticulously documented in texts such as the Ebers Papyrus, dating back to 1500 BCE, which included treatments for various conditions. Similarly, more than 5,000 years ago, the Sumerians recorded plant-based remedies, and Traditional Chinese Medicine and Ayurveda in India have long used herbs that contain bioactive compounds such as flavonoids, terpenoids, saponins, alkaloids, and polyphenols. Plant-based treatments have been developed by Indigenous and traditional systems of medicine across the globe, with knowledge often passed down orally through generations[9,11,18,19].

Historically, plants have served as effective antimicrobial agents, with many used to treat fungal infections such as ringworm, tinea, scabies, herpes, and eczema. For instance, *Calotropis procera* has been used to manage skin infections. In many developing countries, medicinal plants remain a primary source of therapy, especially where access to modern health care is limited. *Ageratum conyzoides*, *Asparagus racemosus*, *Cassia alata*, *Cassia occidentalis*, and *Ficus religiosa* are examples of plants traditionally used for treating fungal infections. These plants have demonstrated antifungal properties, and others such as *Lantana camara* and *Thymus capitatus* have demonstrated antimicrobial activity.

Medicinal plants are rich in secondary metabolites with known therapeutic properties, forming the foundation of modern pharmacologic research. These plants often contain multiple bioactive compounds that work together to inhibit fungal growth through various mechanisms, reducing the likelihood of resistance development. In many cases, they are preferred over conventional antifungal drugs due to their reduced incidence of side effects, better efficacy, and accessibility.

Recent studies have emphasized the potential of medicinal plants as sources of novel antifungal agents. Phytochemicals such as phenolics, alkaloids, terpenoids, and phytosterols found in plants demonstrate antifungal properties. These compounds can disrupt fungal cells, inhibit their growth, and prevent the production of mycotoxin. *A. conyzoides*, for example, has demonstrated antifungal action against pathogens such as *Aspergillus*, *Candida*, *Fusarium*, and *Phytophthora*. Similarly, *Syzygium aromaticum* and *Inula racemosa* exhibit significant antifungal activity against *Bipolaris oryzae*, with compounds such as ursolic acid targeting specific fungal enzymes. *Thymus capitatus*, known for its antimicrobial properties, has been studied for its pharmaceutical applications, showing potential in treating fungal infections[13,21,22].

Plants such as *Heliotropium indicum* and *Grona triflora*, which contain compounds such as indicine-N-oxide and quercetin, have demonstrated antifungal activity against *C. albicans*. *Brucea antidysenterica*, aloe vera, and *Justicia schimperiana* also exhibit antifungal effects against *C. albicans* and *A. niger*, attributed to alkaloids, flavonoids, and phenols. *Cinnamomum zeylanicum* and its relatives, including

Cinnamomum tamala and *Trigonella foenum graecum*, show antifungal potential through polyphenols such as rutin, kaempferol, and quercetin.

A. racemosus and *C. occidentalis* have proven effective against dermatophytes such as *Microsporum gypseum* and *Trichophyton mentagrophytes*, with active compounds including saponins and hydroxy anthraquinones. *Tristemma mauritianum* and *Lavigeria macrocarpa* demonstrate antifungal activity attributed to their phenolic content. *C. procera* has been shown to inhibit *Microsporum* and *Trichophyton* species completely, whereas *Vernonia amygdalina* has demonstrated activity against *Botrytis cinerea*.

Although the potential of plant-derived antifungal agents is promising, challenges to their full development remain. Current pharmacopeias often lack rigorous validation of plant-based medications, and more research is needed to isolate and characterize active compounds, elucidate their mechanisms of action, and validate their effects *in vivo*. Standardizing extraction and formulation techniques, assessing chronic toxicologic effects, and exploring interactions with existing medications are essential for ensuring the safety and efficacy of plant-derived treatments.

The synergistic use of plant extracts with conventional antifungals could enhance therapeutic outcomes and offer an attractive alternative for addressing drug resistance. With the continued investigation into novel bioactive compounds, medicinal plants offer valuable sources for discovering new therapeutic agents to tackle the growing problem of drug-resistant fungal infections. Through the expansion of our understanding of these plants and their antifungal properties, we can develop more effective and sustainable treatments for fungal infections in the future.

PHYTOCHEMICALS WITH ANTIFUNGAL PROPERTIES

Phytochemicals are bioactive plant compounds with antifungal properties, encompassing groups such as alkaloids, flavonoids, terpenoids, phenolics, saponins, and tannins. These compounds inhibit fungal growth by targeting cell walls, membranes, and metabolic pathways, offering potential as novel antifungal therapies[9,23-27].

Alkaloids, which are nitrogen-containing compounds, are known for their diverse biological activities, including antifungal effects. For example, an alkaloid from *Datura metel* has shown activity against *Candida* and *Aspergillus* species, whereas other alkaloids, such as jatrorrhizine from *Mahonia aquifolium*, exhibit antifungal potential against various fungi. Alkaloids such as β-carboline, haloxylines A and B, and piperidine from *Haloxylon salicornium* have also demonstrated antifungal properties. Alkaloids typically block enzyme activity, contributing to their antifungal efficacy. Berberine, which is found in *Berberis* species, is another alkaloid with antibacterial and antifungal properties that disrupts fungal cell membranes and inhibits growth. Quinine, derived from the *Cinchona* tree, is mainly known for its antimalarial effects but also exhibits antifungal potential, especially when combined with other therapies. Other alkaloids, such as jatrorrhizine, β-carboline, and haloxylines, inhibit fungal metabolic pathways, including cell wall biosynthesis and enzyme activity, broadening the scope of antifungal treatments.

Flavonoids are phenolic compounds that have antioxidant, anticancer, and antimicrobial properties. They disrupt fungal membranes and bind to cell walls, with compounds such as quercetin, kaempferol, and rutin demonstrating antifungal activity. Other flavonoids, such as iso-piscerythrone and piscisoflavones, also demonstrate promising antifungal effects. As a result of their polyphenolic structure, flavonoids interact with fungal membranes, altering their fluidity and permeability, resulting in leakage and cell death. Quercetin, which has been widely studied for its antifungal properties, disrupts fungal membranes and enhances the activity of conventional antifungal drugs, indicating its potential for combination therapy. Kaempferol, found in cinnamon, contributes to its antifungal effects through its interaction with fungal membranes. Flavonoids such as isorhamnetin, naringenin, and hesperidin also exhibit antifungal activity by interfering with cell wall synthesis, membrane integrity, and cellular processes such as RNA/protein synthesis, offering a multitarget approach to combating fungal infections[28].

Terpenoids, including terpenes, steroids, and saponins, are another group of compounds with significant antifungal properties, especially via the disruption of fungal cell membranes. For instance, phytol, a diterpene, disrupts fungal membranes, which causes ion leakage and the wilting of hyphae. Eugenol, found in *S. aromaticum* (clove), disrupts fungal membranes, increasing permeability and causing cell death. Carvacrol, a monoterpenoid from oregano and thyme, also disrupts fungal cell membranes. Other terpenoids such as estragole and panicutine show antifungal effects, likely through their interaction with fungal membranes. Limonoids, a class of oxygenated triterpenes found in citrus fruits, also display antifungal properties by interfering with the functions of fungal cells. Sesquiterpenoids, such as drimenin, drimenol, and polygodial, exhibit potent antifungal effects through the disruption of fungal cell membranes. Trichodermin, which is produced by *Trichoderma* spp., has shown effectiveness against plant

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pathogenic fungi, further highlighting the biocontrol potential of terpenoids[18].

Phenolic compounds, such as tannins, coumarins, quinones, and stilbenoids, are abundant in plants and possess antifungal activity. Caffeic acid and ellagic acid inhibit the growth of *Candida auris* by modifying the fungal cell wall. Phenolic compounds damage fungal membranes, inhibit electron transport enzymes, and disrupt cell walls, with a correlation between increased oxidation and enhanced antifungal potency[29,30].

Saponins, which are glycosides with surface-active properties, exhibit diverse biological activities, including antifungal effects. CAY-1, a triterpene saponin from *Capsicum frutescens* (chili pepper), is potent against various fungal strains, likely due to its ability to disrupt fungal cell membranes. Tannins, which are known for their astringent properties, also exhibit antifungal activity by binding to proteins and inhibiting their synthesis, contributing to the antimicrobial effects of plants such as *Ficus vasta* and *Bersama abyssinica*.

Bioavailability plays a crucial role in the effectiveness of phytochemicals. Techniques such as nanoencapsulation enhance their absorption and bioavailability, ensuring they are more effective in combating fungal infections. Phytochemicals exert their antifungal effects through mechanisms such as membrane disruption, inhibition of cell wall synthesis, mitochondrial interference, and the production of reactive oxygen species (ROS). However, variations in the specific phytochemical composition of plants, which depend on factors such as geographical location and methods of extraction, can influence their antifungal activity[32].

One primary mechanism of antifungal action is the disruption of the cell membrane, as many phytochemicals interact with ergosterol, a crucial component for membrane integrity. Polyene antifungals bind to ergosterol, increasing membrane permeability and causing leakage of cell contents. Saponins also disrupt membrane integrity, leading to cell lysis, whereas flavonoids can alter membrane structure, cause mitochondrial malfunction, and interfere with cellular processes such as cell wall construction and division. Phenolic compounds further damage fungal membranes, inhibit electron transport enzymes, and compromise cell function.

The inhibition of cell wall synthesis is another key antifungal mechanism. Phytochemicals such as flavonoids, phenolic compounds, and certain alkaloids weaken the walls of fungal cells, preventing fungal growth and proliferation. In addition, some phytochemicals interfere with fungal metabolic pathways, targeting enzymes such as N-myristoyl transferase

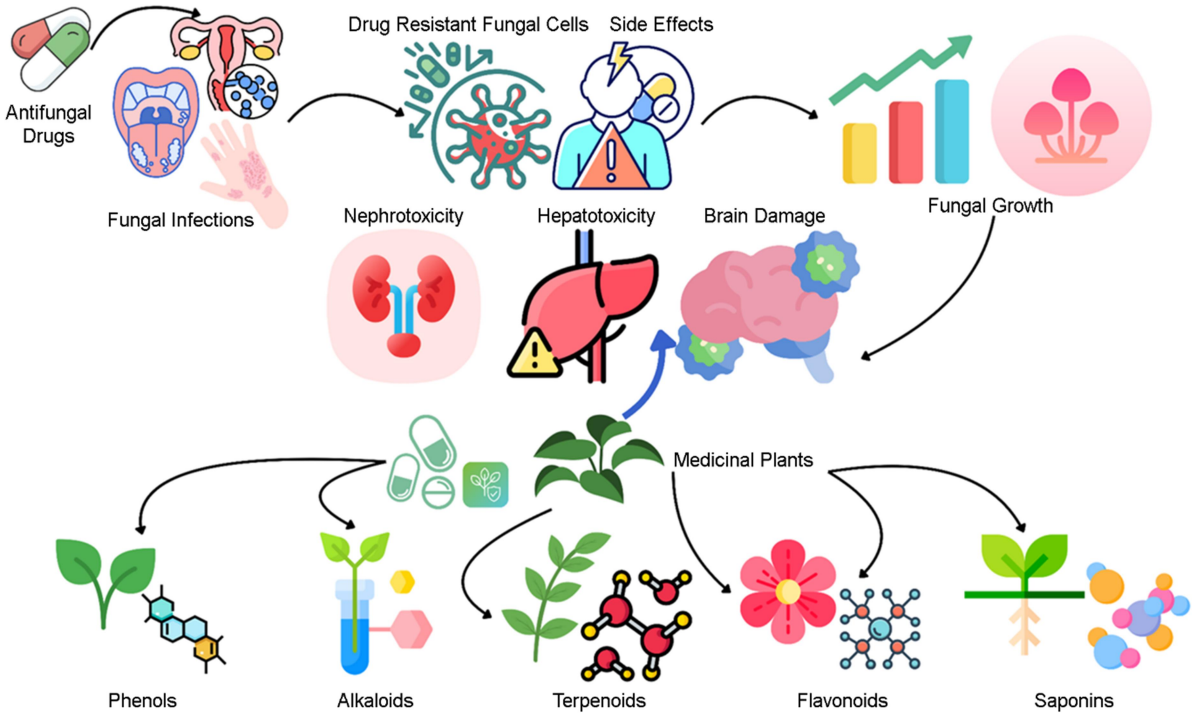

Fig. 1. Significant limitations, including toxicity (nephrotoxicity, brain damage, hepatotoxicity), rapid drug resistance, drug interactions, and side effects such as visual disturbances, hinder conventional antifungal treatments. The rise of fungal strains that are drug resistant underscores the urgent need for innovative therapeutic approaches.

(NMT) and cytochrome P450 14α-demethylase, which are essential for fungal metabolism. Compounds such as myristicin and rutin hinder the synthesis of critical components such as DNA, RNA, and proteins. Fig. 1 shows the types of phytochemicals in medicinal plants.

MECHANISMS OF ACTION OF MEDICINAL PLANTS AND PHYTOCHEMICALS

Phytochemicals derived from medicinal plants can disrupt the walls of fungal cells and membranes through various mechanisms, ultimately inhibiting fungal growth and preventing infections. These compounds target key components and processes that are essential for the integrity of the fungal cell wall, membrane stability, and metabolic function[33].

Echinocandins, semisynthetic cyclic lipopeptides, block the formation of cell walls by inhibiting the (1,3)-β-D-glucan synthase complex, an enzyme on which fungi rely but that is absent in humans, ensuring their safety for therapeutic use. Other plant extracts inhibit the synthesis of chitin and glucan, which are vital components of the fungal cell wall. Some compounds, such as coumarins, damage fungal cells through the formation of pores in the cell wall, causing cytoplasmic leakage and necrosis. Meanwhile, saponins disrupt cell membranes, increasing wall permeability. Phenolic compounds, along with other phytochemicals, can also damage the cell walls and alter fungal structures. For instance, *V. amygdalina* extract causes the twisting and folding of fungal mycelia, creating jagged edges and shrinking conidia[34].

Certain plant extracts directly target the cell membrane, which has an indirect effect on cell wall function. For example, the seed extract of *Cassia fistula* damages the membrane of *C. albicans*, harming yeast cells. Extracts from *Piper nigrum* (pepper) containing limonene, sabinene, and β-caryophyllene disrupt the fungal cell walls and membranes, coagulating the cytoplasm and damaging organelles. Chitosan also plays a role via the inhibition of gene expression crucial for maintaining cell wall integrity. In addition, flavonoids such as isopiscerythrone, piscisoflavones, quercetin, and hesperidin show antifungal activity by binding to fungal cell walls. Some plant extracts can even prevent fungal growth by inhibiting the formation of germ tubes, which are essential for hyphal development[35-38].

Phytochemicals can also disrupt the membranes of fungal cells, compromising their function. Many antifungal compounds, including polyenes, target ergosterol, a key fungal sterol, reducing membrane fluidity and causing pore formation, ultimately leading to cell death. Eugenol abolishes membrane permeability, resulting in electrolyte loss, whereas saponins perforate lipid bilayers, increasing permeability. Lipophilic flavonoids and terpenoids, such as β-caryophyllene, also disrupt membranes. Other compounds, such as sesquiterpenes, reduce ATP reserves and intracellular pH, contributing to cell death. In addition, certain compounds such as silymarin increase oxidative stress and membrane permeability, whereas others such as coumarins and specific terpenoids cause structural changes in the membrane[39].

Alkaloids, which are another class of phytochemicals, can block enzyme activity, disrupting essential cellular processes. For instance, myristicin inhibits fatty acid translocation, which is vital for membrane modification. High concentrations of squalene disturb fungal membranes and impair essential functions, leading to cell death via mechanisms such as apoptosis, necrosis, or autophagy. These compounds' effectiveness depends on the fungal species, compound concentration, and environmental conditions. Plant extracts often contain multiple antifungal compounds, which can have synergistic effects, enhancing their overall efficacy.

Phytochemicals can also target and inhibit fungal enzymes critical for growth and survival, such as chitinase and proteases. The ethanolic extract of *F. vasta*, for example, has demonstrated strong inhibition of α-glucosidase and α-amylase, outperforming synthetic drugs such as acarbose. Fungal proteases, such as the SAPs (SAP1, SAP2, and SAP3), are virulence factors that contribute to fungal pathogenicity by aiding in adhesion and damaging host tissues. Some plant extracts inhibit fungal growth by preventing the formation of germ tubes, an essential step for hyphal development. For instance, curcumin modulates proteolytic enzyme activity in *C. albicans*, enhancing antifungal effects.

Phytochemicals also inhibit enzymes involved in ergosterol biosynthesis, a critical pathway for fungal growth. Compounds such as rutin, quercetin, and myristicin bind to fungal enzymes such as 14-alpha demethylase (CYP51), inhibiting ergosterol synthesis and affecting membrane integrity. Other compounds inhibit enzymes such as squalene epoxidase, which is involved in the same pathway. Furthermore, compounds such as α-copaene, cis-calamenene, β-caryophyllene, and caryophyllene oxide inhibit NMT, an enzyme involved in membrane fatty acid translocation[36,40].

Some phytochemicals can even block fungal enzymes by binding to their active sites, either competitively or allosterically. For instance, phenolic compounds can oxidize into quinones, inactivating fungal enzymes, whereas alkaloids from *B. antidysenterica* exhibit antimicrobial effects by blocking enzyme activity. Flavonoids also contribute to antifungal activity via

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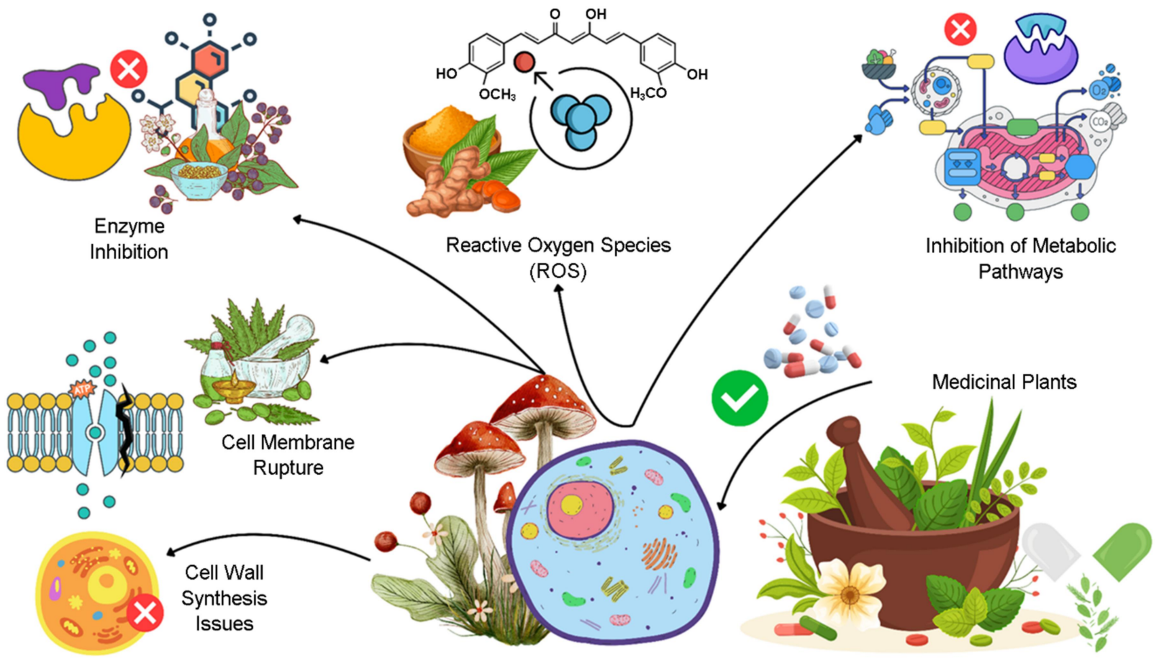

Fig. 2. Phytochemicals combat fungal infections through multiple mechanisms: disrupting cell membranes, inhibiting cell wall synthesis and metabolic pathways, blocking key enzymes, inducing oxidative stress, and preventing the formation of biofilm. These diverse actions highlight the potential of plant-based compounds as effective antifungal agents.

the disruption of plasma membranes, inducing mitochondrial dysfunction, and by inhibiting cell division, wall construction, RNA, and protein synthesis. By targeting these enzymes, plant-derived compounds disrupt critical fungal metabolic processes, reducing fungal growth and survival.

Beyond the direct inhibition of fungal growth, phytochemicals can enhance the immune response of the host. They act as immunomodulators, stimulating the immune system to better combat fungal infections. In addition, by scavenging free radicals, antioxidants in plants help protect the immune system from oxidative stress, thus supporting the integrity of cell membranes and macromolecules. Certain vitamins, such as vitamin D, regulate biochemical pathways that are essential for immune function. Phytochemicals may also help overcome antifungal resistance. Some plant extracts have demonstrated synergistic effects with conventional antifungal drugs, enhancing their efficacy. For example, by boosting ROS production, curcumin has been shown to increase the effects of itraconazole, co-trimoxazole, and amphotericin B. In addition, phytochemicals can disrupt fungal biofilms, which protect fungi from antifungal drugs, and can modulate fungal gene expression associated with resistance mechanisms[41-43].

By targeting multiple pathways in fungi, including cell walls, membranes, and metabolic processes, plant-derived compounds provide a promising solution for counteracting antifungal drug resistance. These compounds not only offer a safe, low-toxicity alternative to synthetic antifungal medications but also hold potential for preventing fungal growth and mycotoxin contamination in food. However, to fully understand their mechanisms and optimize their clinical use, further research is needed. Fig. 2, Table 1 provides a visualization of these mechanisms.

SYNERGISTIC EFFECTS OF MEDICINAL PLANTS AND PHYTOCHEMICALS

Combination therapy that involves the use of medicinal plant extracts alongside conventional antifungal drugs offers a promising strategy for combating drug resistance and improving treatment outcomes. This approach leverages the synergistic effects of plant-derived compounds and conventional antifungals, making it more challenging for fungi to develop resistance and enhancing the overall efficacy of treatment[25,27,44].

Numerous studies have demonstrated that combining plant extracts with conventional antifungals results in synergistic effects, in which the combined action is greater than the

Table 1. A nonexhaustive list of phytochemicals extracted from plants with their mechanism of actions against various fungal pathogens

Phytochemical	Mechanism of action	Pathogen (s)
Rutin	Inhibition of fungal 14-alpha demethylase (CYP51) and nucleoside diphosphokinase (NDK)	Various fungal pathogens
Kaempferol	Inhibition of fungal 14-alpha demethylase (CYP51) and nucleoside diphosphokinase (NDK)	Various fungal pathogens
Quercetin	May inhibit fungal growth through various mechanisms including plasma membrane disruption, inhibition of cell wall and DNA/RNA/protein synthesis, and mitochondrial dysfunction and by binding to the active site of Candidapepsin-2	*Candida albicans*
Indicine-N-oxide	Binds to the active pockets of target protein Candidapepsin2 (PDB ID: 3PVK) and forms hydrogen bonds with TYR84 and ASP86 residues	*Candida albicans*
Saponins	Antifungal activity against dermatophytes	*Microsporum gypseum*, *Microsporum nanum*, *Trichophyton mentagrophytes*, *Trichophyton terrestre*
Hydroxy anthraquinone	Antifungal activity against dermatophytes	*M. gypseum*, *M. nanum*, *T. mentagrophytes*, *T. terrestre*
Ellagic acid	Modifies the fungal cell wall	*C. auris*
Caffeic acid	Modifies the fungal cell wall	*C. auris*
Curcumin	May enhance reactive oxygen species production; modulates proteolytic enzyme activity	*C. albicans*, various fungal pathogens
Myricetin	Exhibits antifungal effects	*C. albicans*, *Saccharomyces cerevisiae*
Naringenin	Exhibits antifungal effects	*C. albicans*, *S. cerevisiae*
3-O-methylviridicatin	Antifungal activity	*Alternaria brassicae*, *Botrytis cinerea*, *Venturia mali*
Viridicatol	Antifungal activity	*A. brassicae*, *A. alternata*, *B. cinerea*
Fusaripeptide A	Antifungal activity	*C. glabrata*, *C. albicans*
Trichothecinol A	Antifungal activity	*Cryptococcus albidus*
Cytochalasin Z28	Fungicidal activity	*Gaeumannomyces saubinetti*
2-amino-3	4-dihydroxy-2-25-(hydroxymethyl)-14-oxo-6	12-eicosenoic acid
Myriocin	Antifungal activity	*Cryptococcus neoformans*, *Cryptococcus gattii*
Botryosphaerin H	Antifungal and nematicidal	*Gaeumannomyces graminis*, *Fusarium solani*, *Pyricularia oryzae*, *Fusarium moniliforme*, *Fusarium oxysporum*

sum of individual effects. These combinations can enhance the effectiveness of antifungal treatments and potentially overcome resistance mechanisms. For example, extracts of *T. mauritianum*, *L. macrocarpa*, and *Crassocephalum boughe-*

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yanum showed synergistic effects with ketoconazole against drug-resistant *Candida* species. Similarly, *L. macrocarpa* extract showed synergistic effects with both ketoconazole and fluconazole. In addition, *Nigella sativa* seed extract demonstrated synergistic effects with ciprofloxacin, whereas curcumin exhibited synergistic effects with itraconazole, cotrimoxazole, and amphotericin B, primarily by enhancing ROS production. Furthermore, aqueous extract of *Hibiscus sabdariffa* combined with antibiotics showed *in vitro* synergistic effects against *Helicobacter pylori*[45,46].

Other studies have reported additive effects when plant extracts are combined with conventional antifungals. For instance, *Murraya koenigii* and other plant extracts showed synergistic antiplasmodial activity when combined. In addition, combinations of *Carica papaya* and *V. amygdalina* demonstrated synergistic effects in reducing the *Plasmodium* parasite load in mice. These findings suggest that plant extracts not only have independent antifungal activity but can also enhance the effects of conventional drugs, making them valuable partners in combination therapy.

The mechanisms underlying these synergistic effects are diverse. Plant extracts can disrupt fungal cell membranes, inhibit efflux pumps, and modulate proteolytic enzyme activity. By targeting multiple pathways, plant extracts complicate the development of resistance by fungi. Furthermore, these extracts can enhance the effectiveness of antifungal drugs by increasing drug penetration, inhibiting biofilm formation, and acting as immunomodulators, all of which boost the host's immune response. This multifaceted approach may help combat fungal infections that are difficult to treat using conventional antifungal agents alone[47].

Combining different plant-derived compounds often leads to stronger antifungal effects than individual compounds alone as a result of synergistic interactions. This approach enhances the therapeutic potential of plant extracts and helps overcome some of the limitations associated with single-compound treatments. Combining various bioactive molecules found in plants allows for a more robust and comprehensive approach to combating fungal infections. Phytochemicals such as rutin and quercetin, for example, have been shown to enhance the antifungal activity of amphotericin B and fluconazole, whereas curcumin enhances the effectiveness of itraconazole, co-trimoxazole, and amphotericin B.

Moreover, synergistic combinations can help overcome mechanisms of fungal resistance. Fungi often develop resistance to antifungal treatments via the alteration of their metabolic pathways or the expulsion of drugs through efflux pumps. By targeting multiple pathways simultaneously, synergistic plant combinations can help reverse or bypass these resistance mechanisms. Some phytochemicals interfere with efflux pumps, disrupt cell wall synthesis, and inhibit biofilm formation, all of which contribute to overcoming drug resistance.

In addition to combining plant extracts with conventional drugs, some plant extracts can act synergistically when used together. For example, the combination of *M. koenigii* leaf, *Artocarpus altilis* stem bark, *A. altilis* root, and *Enantia chlorantha* stem bark extracts has exhibited a synergistic effect. Likewise, *C. papaya* and *V. amygdalina*, when combined, resulted in enhanced antifungal activity[35].

One of the main advantages of synergistic combinations is their broad-spectrum activity. Combining different plant extracts increases the range of fungal species targeted and allows for lower concentrations of individual compounds, reducing the risk of toxicity. This is particularly important because many synthetic antifungal drugs are associated with adverse side effects, whereas plant-based treatments tend to have lower toxicity profiles. The improved efficacy of synergistic combinations also results in greater effective control of fungal growth and infections, engaging multiple mechanisms of action to address fungal infections from various angles. By combining compounds with different mechanisms of action, synergistic combinations can delay the development of resistance, reducing the likelihood of fungi adapting to treatment.

From an environmental perspective, plant-based treatments are more sustainable and eco-friendly than synthetic drugs are, making them a promising natural alternative to chemical antifungals. However, depending on factors such as the specific plant species, compounds, extraction methods, and the fungal species targeted, the effectiveness of these treatments can vary. Further research is needed to identify optimal combinations and understand their underlying mechanisms of action.

Standardized extraction and formulation techniques are essential to achieve consistent and reliable results. These techniques help ensure that plant extracts used in combination therapies are potent and effective across different settings.

TOXICITY AND SAFETY OF MEDICINAL PLANTS

Although medicinal plants have a long history of use in traditional medicine, their safety and efficacy must be evaluated rigorously before they can be widely adopted in modern health care. Although many plant-based remedies have been used for centuries with apparent safety, not all plant-derived

compounds are safe. Some plants contain toxic compounds that may cause adverse effects, particularly when used in high doses or for prolonged periods. A significant challenge to the use of medicinal plants is the lack of standardization in their preparation, which can result in variability in the concentration of bioactive compounds. Factors such as plant genetics, environmental conditions, and harvesting methods influence the chemical composition of the plant[12,48-50].

Certain plant families, such as the Asteraceae family, which includes *A. conyzoides*, may contain hepatotoxic pyrrolizidine alkaloids (PAs), which can be harmful. However, the presence of PAs varies by region. Before clinical use, it is crucial to conduct thorough toxicologic assessments of natural products and their isolated compounds. Studies on *A. conyzoides* extracts and compounds suggest they are safe within specific dosing parameters. Mycotoxin contamination also poses a concern, as plant materials with medicinal properties can become contaminated, raising questions about their safety. Herb-drug interactions also require further study to better understand the potential risks of combining medicinal plants with pharmaceutical drugs.

To ensure the safety and effectiveness of plant-derived products, stringent quality control measures are essential. Variations in the concentration of bioactive substances or impurities can affect the reliability and safety of herbal remedies. The pharmacokinetics of plant-derived substances, including their absorption, distribution, metabolism, and elimination within the body, can also vary greatly. Understanding these properties is essential for developing medications that exhibit consistent and predictable therapeutic effects. To determine the appropriate doses of plant-based medicines to ensure both efficacy and safety, more research is needed. Clinical studies are crucial for validating ethnomedicinal claims and establishing the safety and efficacy of these preparations in humans[51].

Some phytochemicals found in medicinal plants can be toxic at high doses or with prolonged use, which makes it important to understand their specific properties and potential risks before they are used. Traditional knowledge accumulated over generations often serves as the foundation for modern drug development. Traditional pharmacopeias, based on the wisdom of native societies, typically rely on plant-based substances rich in secondary metabolites. The ethnopharmacological approach, which draws from traditional medicine systems, is frequently used to select plants for pharmacological studies. Due to their higher likelihood of containing bioactive molecules, plants that have a long history of use in traditional medicine are often prioritized for research.

Although traditional use provides a useful starting point, the scientific validation of the efficacy of medicinal plants is necessary through rigorous testing and clinical trials. Modern science aims to identify the active components of medicinal plants and understand their mechanisms of action, which can help determine the most effective and safe ways to use these plants. There is a growing need for clinical trials to confirm the efficacy and safety of plant-derived medicines. These trials are essential for validating the ethnomedicinal claims and determining the safe, effective doses. Modern methods of drug development are also being used to standardize herbal remedies and identify analytical marker biomolecules. Standardized extracts are especially important when the pharmacologic effect results from the synergistic action of multiple compounds.

The World Health Organization has developed policies, guidelines, and strategies to promote the safe use of plant-derived drugs globally. The therapeutic effects of medicinal plants are largely attributed to their chemical constituents, such as secondary metabolites including flavonoids, alkaloids, tannins, saponins, phenols, and glycosides. However, if consumed in high doses or for extended periods, some phytochemicals can exhibit toxic effects, making it crucial to understand their potential toxicity. The concentration of bioactive compounds can vary based on the plant species, growing conditions, and processing methods. In some cases, whole plant extracts may be more effective than isolated compounds, indicating a synergistic effect of multiple compounds.

COMPUTATIONAL DRUG DISCOVERY AND VIRTUAL SCREENING FOR ANTIFUNGAL DRUG DEVELOPMENT

Using a variety of methods such as virtual screening, molecular docking, and molecular modeling, computational drug discovery has revolutionized the identification of potential drug candidates, including antifungal agents. These computational techniques help streamline the drug discovery process by predicting how compounds interact with biological targets, optimizing lead compounds, and assessing drug-likeness early in the development stage[9,39,52,53,16,54,53].

Virtual screening is one of the primary techniques used in computational drug discovery. It involves screening large databases of chemical compounds to identify those that may interact with a specific biological target. Virtual screening is often used for antifungal drug discovery to search chemical libraries for compounds that may bind to key fungal enzymes involved in processes such as ergosterol biosynthesis. This is

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critical for the integrity and growth of the fungal cell membrane, and enzymes such as sterol 14α-demethylase (CYP51) play a crucial role in this pathway.

Through virtual screening, researchers can narrow down large chemical libraries and identify potential inhibitors that are likely to interact with the target protein. For example, virtual screening of a dataset of 880 molecules identified more than 600 compounds with good affinity toward CYP51, among which ZINC95486139 and ZINC33833639 stood out as potential inhibitors. These compounds demonstrated favorable druglike properties and high binding affinities, which highlights the potential of virtual screening in discovering novel antifungal agents.

By predicting the binding interactions between a ligand (drug candidate) and its target protein, molecular docking further enhances virtual screening. It simulates how the ligand binds to the protein, exploring various orientations and conformations within the binding site. The binding affinity of each orientation is scored, with compounds that show stronger binding affinity being prioritized for further study. For instance, compounds derived from plants such as *F. vasta* and *Dodonaea angustifolia* have shown promising docking results with fungal enzymes, such as CYP51 and BMK-1[3,28,38,55,56].

Docking software, such as AutoDock Vina, PyRx, and CB-Dock2, is commonly used to perform these simulations, and the results provide valuable insights into the nature of ligand-target interactions. These interactions can include hydrogen bonds, hydrophobic interactions, and electrostatic forces, which are essential for ensuring the stability of the ligand-protein complex. The success of docking predictions is often validated by redocking the co-crystallized ligand into the binding site of the target protein. If the docking simulation returns a low root mean square deviation compared with the experimental structure, it indicates that the docking protocol is accurate and reliable.

After identifying potential drug candidates through virtual screening and docking, it is crucial to evaluate their pharmacokinetics and toxicity. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling plays an essential role in this evaluation. By predicting how a compound behaves in the human body, ADMET analysis helps researchers identify compounds with favorable druglike properties and those that may exhibit toxicity[57].

Tools such as SwissADME are used to assess the pharmacokinetics of compounds, including their bioavailability and ability to cross cell membranes. A compound with poor drug-likeness may have poor absorption, which limits its potential as an effective drug. In addition, predicting toxicity early in the discovery process can help eliminate compounds with harmful effects, streamlining the selection of safe and effective drug candidates.

Although molecular docking provides valuable insights into the binding affinity and interactions of compounds, it assumes that the protein-ligand complex is rigid, which may not always be the case in a biological environment. Molecular dynamics (MD) simulations address this limitation by modeling the movement and flexibility of the protein-ligand complex over time. These simulations provide a more realistic view of the stability of the binding interaction and the dynamic behavior of the complex.

MD simulations complement docking studies by confirming the stability of protein-ligand complexes, ensuring that the binding interactions that are observed during docking are maintained over time. Although rigid protein assumptions and computational limitations are challenges, MD simulations remain a powerful tool in the validation of docking predictions and further understanding of the mechanisms of drug action[11,55,58,59,59-63].

In addition to traditional computational methods, artificial intelligence (AI) and machine learning (ML) techniques are becoming increasingly important in drug discovery. AI and ML algorithms can analyze vast datasets, identifying patterns and relationships between chemical structures and biological activity. This analysis enables the prediction of novel compounds with antifungal activity and the optimization of lead compounds for better efficacy.

Quantitative structure-activity relationship (QSAR) models establish mathematical relationships between a compound's chemical structure and its biological activity. These models are invaluable in the prediction of the antifungal potential of untested compounds based on their structural features. By analyzing chemical descriptors, QSAR models can help researchers design compounds with improved antifungal activity and druglike properties.

Network pharmacology is an emerging field focusing on the interactions between drugs and multiple targets within biological networks. This approach helps improve drug efficacy and reduce side effects by considering the holistic effects of a compound on cellular pathways rather than focusing on a single target. In antifungal drug discovery, network pharmacology can identify key proteins and pathways involved in fungal growth and survival, guiding the design of multitarget drugs. Fragment-based drug discovery (FBDD) is another promising strategy that identifies small molecular fragments that bind to the target protein. These fragments can be optimized and developed into full-fledged drugs. By targeting enzymes critical for fungal survival, such as CYP51 and NMT, FBDD can be particularly useful in discovering new antifungal agents.

Although progress has been made in computational antifungal drug discovery, several challenges must be addressed. Fungal pathogens are eukaryotic organisms that share many similarities with host cells, making it difficult to design selective antifungal agents that do not target human proteins. In addition, fungal strains exhibit genetic diversity, which necessitates the development of broad-spectrum agents or combination therapies.

Resistance mechanisms, such as mutations in target enzymes and the formation of biofilms, add complexity to the development of antifungal drugs. Moreover, because many docking protocols treat proteins as rigid structures, the structural flexibility of fungal proteins can result in inaccuracies in docking predictions. In addition, compounds that exhibit good efficacy *in vitro* may not always perform well *in vivo* because of issues such as poor pharmacokinetic properties or off-target effects[20,64].

Emerging technologies such as AI, deep learning, and multiomics integration offer promising solutions to these challenges. AI and deep learning algorithms can process vast amounts of data, which helps researchers identify patterns and predict antifungal activity more efficiently. Multiomics approaches, which integrate genomics, transcriptomics, proteomics, and metabolomics, provide a more comprehensive understanding of fungal biology and reveal new potential drug targets.

Another promising strategy for accelerating drug discovery is drug repurposing. Computational methods can help identify new uses for existing drugs, saving time and resources compared with developing new compounds from scratch. By screening approved drugs for antifungal activity, researchers may uncover new treatments for fungal infections.

CHALLENGES AND LIMITATIONS IN THE USE OF MEDICINAL PLANTS

Although medicinal plants hold great promise for antifungal drug discovery, their use is accompanied by several challenges and limitations. A primary issue is the variability in plant composition. The chemical makeup of plant extracts can differ significantly as a result of various factors, including geoecological variations (such as altitude, latitude, and temperature), the specific part of the plant used (whole plant, roots, leaves, etc.), and the timing of sample collection. Environmental factors, including climate, soil composition, and humidity, also influence the ratio of bioactive compounds in plant extracts. In addition, genetic variations within a plant species contribute to this variability. This inconsistency in chemical composition can give rise to unreliable potency and efficacy of plant-based remedies. Furthermore, the presence of multiple compounds in plant extracts may result in synergistic, antagonistic, or unpredictable effects, complicating the development of consistent treatments[39-42].

The lack of standardization in plant extract preparation and dosages presents another significant challenge. Although standardization is crucial to ensure consistent therapeutic effects, current pharmacopeias often discourage the use of plant-derived medications without established medicinal efficacy. Variations in the concentration of bioactive substances or the presence of impurities can compromise the reliability and safety of herbal remedies. This lack of standardized extraction methods is also a barrier to the use of botanicals in managing plant diseases. The solvent and extraction methods used significantly affect the quality and variety of chemicals with antifungal properties. Moreover, depending on the source plant and the quantities used, the allelopathic effect of botanical fungicides on crops can vary. To ensure the safety and effectiveness of plant-based products, there is an urgent need for standardization and quality control.

Limited clinical data further impedes the widespread adoption of medicinal plants for antifungal treatments. Although many plants have been used traditionally for centuries, there is often a lack of scientific evidence to support these claims. To validate ethnomedicinal claims and establish the safety and efficacy of plant-based preparations in humans, clinical studies are essential. Many plant-based remedies are still being researched for their therapeutic potential, but additional *in vivo* studies are required to evaluate their efficacy in controlled environments. Rigorous clinical trials are necessary to assess their therapeutic potential and safety. Plant extracts often contain complex mixtures of phytochemicals, which can act individually or synergistically, or sometimes antagonistically, leading to varying bioactivities. This complexity highlights the need for more comprehensive studies to fully understand their pharmacologic potential[6].

Regulatory and ethical issues also present significant obstacles in the development and commercialization of plant-based antifungal agents. The regulation of plant-derived medications is complex and varies by region. Regulatory bodies often require extensive safety and effectiveness testing, which increases the time and cost of the development process. In addition, the commercialization of traditional knowledge and plant resources raises concerns about intellectual property rights and fair compensation for indigenous communities. The overextraction of plant species is a significant concern, as it can lead to resource depletion, threaten plant species, and damage ecosystems. Unsustainable collection practices may

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also disrupt biodiversity. Ethical considerations must include ensuring the responsible sourcing of plant materials and minimizing the environmental impact of plant harvesting. Furthermore, the safety, toxicity, and quality of plant extracts must be carefully monitored, as some studies have reported mycotoxin contamination or the presence of toxic and mutagenic compounds. The lack of control over herbal drug quality may lead to adverse effects, including toxicity, allergic reactions, or exposure to harmful bioactive compounds such as cytotoxins or estrogenic agents.

A multidisciplinary approach is needed to address these challenges. To prevent overextraction and preserve biodiversity, conservation initiatives and sustainable harvesting practices are essential. Stringent quality control standards must be established to ensure the safety and effectiveness of plant-based products. Harmonizing regulations across regions would improve the accessibility to plant-derived antifungals, while ethical considerations should ensure that indigenous knowledge is respected and environmental impacts minimized. Standardizing the extraction and formulation techniques will improve reproducibility and consistency in plant-based antifungal products. Additional research is required to identify promising plants with fungicidal properties, and plant-breeding techniques could enhance the concentration of bioactive compounds in specific species. Identifying the optimal environments for growing certain plant species and developing synthetic analogues of active ingredients could also help maintain quality standards. Regulatory procedures and pricing strategies should be developed to facilitate the timely market introduction of plant-based drugs. To better characterize the chemical composition of medicinal plants, advanced analytical techniques, such as gas chromatography-mass spectrometry and high-performance liquid chromatography, should be used. *In silico* studies could complement *in vivo* experiments to better understand the mechanisms of action of plant-derived compounds[31,35,36,41]. Collaborative efforts between researchers, regulatory agencies, and industry stakeholders are critical in overcoming the challenges associated with medicinal plant-based antifungal drug discovery.

FUTURE DIRECTIONS IN RESEARCH

Future research into the discovery of novel antifungal compounds from unexplored plant species offers vast potential across multiple areas. A key focus is the identification of phytochemicals as drug leads as well as the application of biotechnology and nanotechnology to enhance plant-based antifungal research.

Many plant species, particularly those from tropical or remote regions, remain understudied and could serve as a rich source of new antifungal compounds. Endophytic fungi and bacteria, which reside within plant tissues, are gaining attention as reservoirs of bioactive compounds, including antifungals. These microorganisms produce metabolites that often mimic those of their host plants, and genetic modifications may enhance the production of desirable compounds. Traditional knowledge of the uses of plants can guide the selection of plants likely to possess antifungal properties, while targeted screening for specific fungal enzymes or pathways may uncover compounds with precise modes of action. A multidisciplinary approach that combines ethnopharmacology, phytochemistry, botany, and analytical chemistry is essential to discovering novel plant-based antifungals. Geographic diversity, especially in regions with neglected tropical diseases, also presents opportunities to uncover new chemical entities.

Several plant compounds have exhibited significant antifungal activity, which makes them promising drug leads. Polyphenols, including flavonoids, tannins, and phenolic acids, have shown antifungal, antibacterial, and antiviral properties. For example, rutin, kaempferol, and quercetin have demonstrated the ability to inhibit fungal growth by interacting with fungal proteins. Other bioactive compounds, such as terpenoids, saponins, anthraquinones, alkaloids, and glycosides, have also demonstrated potential in antifungal therapy. The identification of specific fungal enzymes as targets for plant polyphenols and the exploration of the combined effects of plant-derived chemicals with traditional medications could enhance treatment outcomes and help address drug resistance.

Biotechnology offers promising approaches in enhancing the production of plant-based antifungal agents. Genetic and metabolic engineering of plants or endophytes can increase the synthesis of desired bioactive metabolites. By manipulating the biosynthetic pathways of secondary metabolites, researchers can create novel analogs that have improved activity. *In vitro* culture techniques also allow for testing specific compounds as antifungal agents. Nanotechnology can complement these efforts through improvements in delivery and activity of plant-based compounds. For instance, the plant-mediated synthesis of nanoparticles, such as zinc oxide nanoparticles, can enhance the antifungal activity of plant extracts and offer eco-friendly solutions to control postharvest spoilage. Nanoencapsulation can improve the bioavailability and stability of phytochemicals, protecting them from degradation and enhancing their solubility.

Nanoformulations, such as liposomes, polymeric nanoparticles, and nanosponges, can also serve as drug-delivery systems. These formulations improve stability, target delivery,

and control the release of plant-derived compounds, potentially reducing toxicity and enhancing efficacy. Advanced bioinformatics tools, such as molecular docking studies, can predict the binding affinity of bioactive compounds to fungal proteins, aiding in the identification of potent molecules. High-throughput screening methods can rapidly assess the secondary metabolites of plants for their antifungal potential, whereas "omics" technologies, such as genomics and metabolomics, offer deeper insights into the genetic pathways responsible for producing bioactive compounds, assisting in uncovering new therapeutic candidates.

CONCLUSION

Medicinal plants hold significant promise as a source of novel antifungal agents, addressing the urgent challenge of drug-resistant fungal infections. Unlike current antifungal treatments that face limitations such as toxicity and resistance, the bioactive phytochemicals in medicinal plants, including alkaloids, flavonoids, terpenoids, and phenolics, offer diverse and potent mechanisms of action, such as the disruption of fungal cell membranes, inhibition of metabolic pathways, and induction of oxidative stress. In addition, the combination of plant-based compounds with conventional antifungals can enhance treatment efficacy and reduce resistance risks. However, translating these compounds into clinical therapies requires overcoming challenges such as variability in plant composition, lack of standardization, and limited clinical data. Future efforts should focus on improving extraction and formulation techniques, exploring understudied plant species, and leveraging biotechnology to optimize the development of plant-based antifungals. By addressing these barriers, medicinal plants can provide sustainable and effective solutions to combat drug-resistant fungal diseases.

CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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