Infection and Drug Resistance

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REVIEW

Natural Source-Derived Compounds with Antifungal Activity Against Medically Relevant Fungi

Manuela Gómez-Gaviria, Dario A Baruch-Martínez, Héctor M Mora-Montes

Departamento de Biología, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Guanajuato, Gto, México

Correspondence: Héctor M Mora-Montes, Departamento de Biología, División de Ciencias Naturales y Exactas, Campus Guanajuato, Universidad de Guanajuato, Noria Alta s/n, col. Noria Alta, Guanajuato, Gto, C.P. 36050, México, Tel +52 473-7320006 Ext. 8193, Fax +52 473-7320006 Ext. 8153, Email hmora@ugto.mx

Abstract: Fungal infections represent a growing global public health problem, particularly in immunocompromised individuals. The availability of effective treatments is limited, and the emergence of strains resistant to conventional antifungal agents further complicates disease management. Therefore, it is essential to explore novel therapeutic alternatives. This review analyzes compounds derived from natural sources with potential antifungal activity and highlights their structural and functional diversities. These include plant primary metabolites, fatty acids, antimicrobial peptides, secondary metabolites, crude extracts, terpenoids, essential oils, flavonoids, and saponins, as well as fungal metabolites and compounds extracted from marine algae. These natural products have demonstrated activity against various fungal species through multiple mechanisms of action, making them promising candidates for the development of new antifungal therapies. Compared with synthetic molecules or novel antifungal drugs under development, natural compounds often display lower toxicity, higher availability, and greater chemical diversity, which can be strategically exploited to overcome resistance. The compilation and analysis of this information underscores the value of natural sources as valuable resources in the search for therapeutic alternatives against human mycoses, particularly in the current context of increasing antifungal resistance.

Keywords: antifungal resistance, drug discovery, fungal infections, natural products, pathogenic fungi, therapeutic alternatives

Introduction

Fungal infections are a worldwide public health problem that affect millions of people each year.[1–3] These diseases can range in severity from superficial skin and nail infections to invasive forms that are life-threatening and compromise vital organ function, especially in people with temporal or permanent immunosuppression.[4] Recent estimates indicate that invasive mycoses are responsible for more than 1.5 million deaths annually, underscoring their global impact. Moreover, the epidemiological landscape of fungal diseases is shifting, with the emergence of *Candida auris*, outbreaks of azole-resistant *Aspergillus fumigatus* strains, and the rising incidence of *Sporothrix brasiliensis* in Latin America.[1,5–8] Unlike bacterial or viral infections, mycoses are more difficult to diagnose and treat because of the limited availability of identification methods and effective antifungal drugs. The latter is aggravated by the increasing frequency of fungal strains resistant to antifungal drugs.[9] In addition, some pathogens can live in the environment without causing harm; however, under certain conditions, they can become opportunistic or primary agents of infection in immunosuppressed patients.

Human fungal infections are caused by a diverse group of pathogenic fungi that are capable of invading tissues and evading the host's immune response.[9] Among the main pathogenic fungi are *Candida* spp., responsible for mucocutaneous and systemic candidiasis; *Aspergillus* spp., agents of invasive aspergillosis, particularly in immunocompromised individuals; *Cryptococcus neoformans* and *Cryptococcus gattii*, causing cryptococcal meningitis; and fungi, such as *Histoplasma capsulatum, Coccidioides* spp., *Paracoccidioides* spp., and *Blastomyces dermatitidis*, associated with pulmonary and disseminated infections. Furthermore, *Sporothrix schenckii* and related species can cause sporotrichosis, affecting the skin and lungs, or disseminating in immunosuppressed individuals.[1,10,11]

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The treatment of mycoses depends on the type of infection and the causative agent and includes the use of antifungals classified into different groups according to their mechanisms of action. The most commonly used drugs are azoles (fluconazole, itraconazole, and voriconazole), echinocandins (caspofungin, micafungin, and anidulafungin), and polyenes (amphotericin B and nystatin). Despite their efficacy, the treatment of fungal infections faces significant challenges, such as the toxicity of some drugs, limited availability of therapeutic options, and increased antifungal resistance. Resistance has been documented for most of these causative agents, with strains being resistant to azoles and echinocandins, making the management of invasive infections difficult.[9] Factors such as prolonged use of antifungals, exposure to subtherapeutic antifungal drug doses, and fungal genetic adaptation have contributed to the emergence of resistant strains. In contrast to antibacterial and antiviral agents, the progress in antifungal development has stagnated over the last decades, largely because fungi are eukaryotic organisms that share many molecular features with human cells, which complicates the discovery of selective therapeutic targets.[12]

These limitations highlight the need to develop new therapeutic strategies and improve resistance monitoring in the clinical setting. A promising strategy is to study molecules obtained from natural sources, such as plant secondary metabolites, which have demonstrated antifungal activities against various pathogenic species.[13] Compounds, such as alkaloids, terpenoids, flavonoids, and antimicrobial peptides, have shown the potential to inhibit the growth of *Candida* spp., *Aspergillus* spp., and other clinically relevant fungi. Compared with synthetic molecules or novel antifungals under development, natural products offer several advantages, including structural diversity, ecological availability, and, in many cases, lower toxicity.[13,14] However, they also show limitations, such as variability in composition, difficulties in standardization, and the need for extensive pharmacological and clinical validation. Nevertheless, natural products represent a fundamental route for the discovery of new therapeutic strategies against mycoses.

This review aims to analyze natural-source compounds with antifungal activity, emphasizing their structural and functional diversity, and potential applications in antifungal therapy. By weighing their advantages and limitations, we highlight the relevance of natural products as strategic alternatives in the search for new antifungal agents in the current context of increasing resistance.

Etiological Agents of Human Mycosis

The increased incidence of fungal infections has raised concerns in the medical community because of the wide range of pathways in which a fungus can affect the host, some of which include cutaneous, subcutaneous, mucosal, and, in the worst cases, systemic infections, making fungal infections a public health concern.[15,16] Some reports have indicated that most fungal pathogens come from the phyla Ascomycota and Basidiomycota, and the transmission routes mostly used by fungal pathogens are direct contact and inhalation.[16,17] Some of the fungal pathogens that use direct contact to infect hosts include *Microsporum, Epidermophyton, Trichophyton, Sporothrix*, and *Malassezia*. In contrast, those that use inhalation as the transmission route include *Blastomyces dermatitidis, Paracoccidioides brasiliensis, Histoplasma capsulatum, Pneumocystis jirovecii, Aspergillus fumigatus, Aspergillus flavus, Coccidioides immitis, Cryptococcus neoformans*, and *Cryptococcus gattii*.[15,16,18] In addition, *Candida albicans* is among the most studied opportunistic pathogens owing to its high incidence in human infections.

Despite the diversity of fungal species found in the environment, only a limited number of genera pose a significant threat to human health. Among them, *Sporothrix, Paracoccidioides, Histoplasma, Aspergillus, Cryptococcus, Candida, Coccidioides*, and *Blastomyces* are of particular concern because they are (I) among the most prevalent causes of human mycoses worldwide, (II) associated with severe and often difficult-to-treat infections. Furthermore, these are the main pathogens for which data on the activity of natural-based antifungal agents are available.[15,17–19] These fungi are responsible for infections ranging from superficial mycoses to invasive forms with high mortality rates, especially in immunocompromised patients. Despite advances in antifungal drug development, the emergence of resistance in these species has limited the effectiveness of available treatments, hindering the eradication of infections and increasing the clinical and economic burdens associated with these diseases.[9,20]

Mechanisms of Antifungal Drug Resistance

Pathogenic fungi have developed various mechanisms of resistance to antifungal agents, which represent a significant challenge in the treatment of mycoses. These mechanisms include modifications of antifungal targets, such as mutations in genes encoding enzymes essential for ergosterol synthesis, which reduce drug affinity and efficacy.[21–23] In addition, overexpression of efflux pumps of the ABC and MFS families enables active expulsion of antifungal agents, reducing their intracellular concentrations and limiting their action. Alterations in cell wall composition have also been described, particularly in echinocandin-resistant fungi, where mutations in the genes coding for the enzyme β-1,3-glucan synthase confer reduced sensitivity to these compounds.[24,25] Another key mechanism is biofilm formation, organized structures of fungal cells embedded in an extracellular matrix that protects microorganisms from attack by antifungal agents and the host immune response.[26,27] Finally, metabolic and epigenetic adaptations allow fungi to tolerate high concentrations of antifungal agents by modifying their biochemical pathways or by regulating gene expression in response to antifungal stress. These mechanisms can act simultaneously, complicating treatment and favoring the persistence of infections.[28,29]

Candida species are a major cause of fungal infections in hospitals, especially in patients with medical devices or in intensive care units. Resistance to azoles is mainly due to mutations in *ERG11* and overexpression of efflux pumps (*CDR1* and *MDR1*), whereas biofilm formation increases tolerance to antifungal drugs.[30,31] Echinocandin resistance is associated with mutations in *FKS1* and *FKS2*, which reduce drug efficacy,[16,32] and some strains have shown reduced susceptibility to amphotericin B due to changes in the plasma membrane and ergosterol production.[32,33] In *A. fumigatus*, azole resistance is linked to mutations in *cyp51A*, which reduce the affinity of the target enzyme for the drug, a problem exacerbated by the use of fungicides in agriculture.[25] Resistance to echinocandins has also been documented due to alterations in the synthesis of β-1,3-glucan.[32] In dimorphic fungi such as *H. capsulatum, C. immitis, B. dermatitidis*, and *P. brasiliensis*, which can cause severe systemic infections, antifungal drug resistance has been less studied. However, cases of decreased sensitivity to azoles and amphotericin B have been documented, probably because of alterations in ergosterol synthesis and mechanisms that favor cellular tolerance.[34,35] In *C. neoformans* and *C. gattii*, the etiological agents of cryptococcosis, fluconazole resistance is associated with changes in ergosterol synthesis, cell permeability, and epigenetic mechanisms.[16,25] Resistance to amphotericin B has also been observed because of modifications in cell membranes and ergosterol synthesis.[25,36] Finally, in *S. schenckii*, although cases of resistance are less frequent, some strains have shown decreased sensitivity to itraconazole, which could compromise standard therapy.[37]

The increasing prevalence of antifungal-resistant species underscores the urgent need to optimize the use of existing antifungal agents and develop novel therapeutic strategies. The exploration of bioactive compounds from natural sources offers a promising alternative to combat antifungal resistance and enhances the prognosis of patients affected by these emerging infections.

Methods for the Identification and Evaluation of Antifungal Compounds

When a novel compound is considered to have antifungal properties, it must be evaluated from various perspectives. Plants are often used to treat different clinical manifestations, and researchers have analyzed them to determine whether any essential oils or antimicrobial peptides (AMPs) exhibit specific antifungal activity (Figure 1). [38] The identification of a compound begins with its extraction from the organism. Techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry are useful for extraction. The homogeneity of the peaks is evaluated using the same method employed in the initial analysis to assess the purity of the compound and to identify the potential antifungal molecule. Electrophoresis and chromatography are performed to confirm the purity of the peaks. In addition, compound concentrations may be measured at each stage of the purification process. Sequencing of peptides is necessary to confirm their identity.[38,39]

Once the peaks are identified and the compounds are purified, the next step is to conduct the initial antifungal assays using a radial diffusion assay. This involves inoculating a spore/conidial suspension into the selected medium and then using a puncher to create several wells on the culture plate. A selected concentration of the compound is placed in the wells, and the plate is incubated. A control, such as amphotericin B, should also be included. The surrounding clear zones are measured to determine antifungal activity. Compounds with the highest antifungal activity are selected for further testing.[38] The next assay is the minimal inhibitory concentration (MIC) assay, in which the compound in water or DMSO

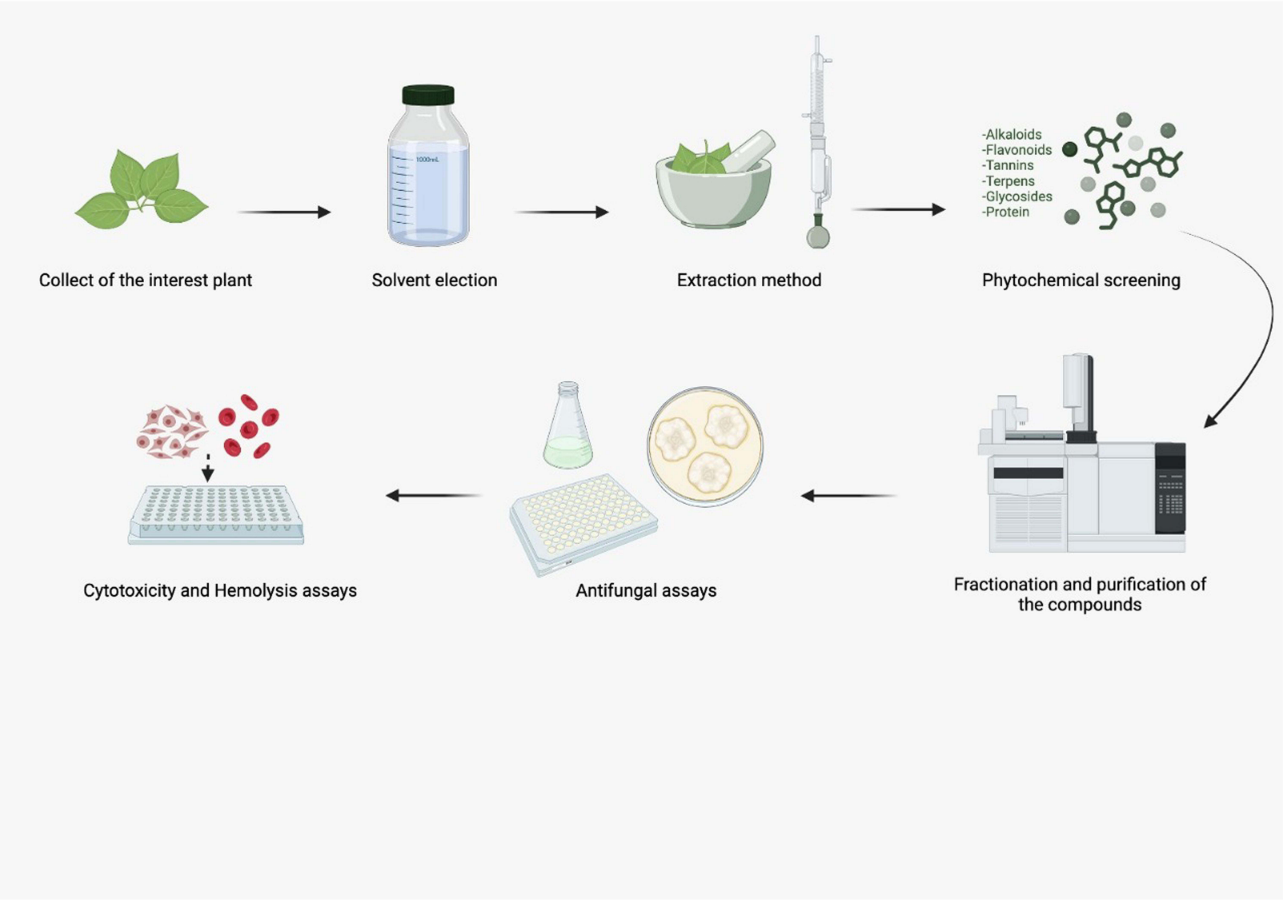

Figure 1 Process of discovery and evaluation of a novel antifungal compound from a plant.

suspension is mixed with the selected broth at different concentrations, typically in a 96-well plate. The plate is inoculated with the fungal suspension and incubated under optimal conditions. MIC is determined as the concentration at which no growth occurrs.[38] Another assay required to test a novel potential antifungal agent is the minimum fungicidal concentration (MFC). This involved inoculating 100 µL of the culture at concentrations similar to those used in the MIC assay onto SDA plates, which are then incubated under optimal conditions. The MFC is defined as the lowest compound concentration at which no growth occurs.[38,40] Temperature and pH stability assays are usually performed to evaluate these compounds. Evaluation of the cytotoxicity of a compound is crucial for the assessment of novel antifungal agents. This can be achieved by using cell lines or primary cells.

Plant Compounds with Antifungal Properties

Fungal infection rates have increased in recent years, causing concern in the clinical setting. In addition, the limited available therapeutic options and the rise of resistant strains represent significant challenges when facing fungal infections. Therefore, the identification of novel compounds with antifungal properties is necessary, and natural products seem to be an option for their development.[41] In this context, plant-derived primary and secondary metabolites have attracted attention as potential sources of antifungal compounds. These bioactive molecules have been evaluated against various fungal species of medical relevance and have demonstrated promising inhibitory effects. The following sections discuss the antifungal properties of these metabolites, highlighting the fungal pathogens they have been tested against, and their potential as alternative therapeutic agents (Table 1). In addition, the possible action mechanism of some of these compounds will be described, based on the available evidence (Figure 2).

Table 1 Most Relevant Fungal Diseases, Their Etiological Agents, and Potential Natural Compounds with Antifungal Activity

Disease	Etiological Agent	Natural Compound
Sporotrichosis	*Sporothrix schenckii, Sporothrix globosa*	*Rubus urticaefolius* *Combretum* *Herissantia crispa* ToAP2A, ToAP2C, ToAP2D
Pityriasis versicolor	*Malassezia spp.*	Not found
Blastomycosis	*Blastomyces dermatitidis*	Not found
Paracoccidiomycosis	*Paracoccidioides brasiliensis*	FAMEs
Histoplasmosis	*Histoplasma capsulatum*	*Tripterigeum wilfordii*
Pneumocystis pneumonia	*Pneumocystis jirovecii*	Not found
Aspergillosis	*Aspergillus spp*	*Linum usitatissimum* L. seed oil NaD1 *Thymus pulegioides* Eos *Combretum* species *Phytolacca tetramera* *Pestalotiopsis* sp
Coccidioidomycosis	*Coccidioides immitis, Coccidioides posadasii*	Not found
Cryptococcosis	*Cryptococcus neoformans, Cryptococcus gattii*	6-NDA NaD1 Tryptanthrin FK506 Cyclosporine A *Herissantia crispa* *Rubus urticaefolius Combretum* *Maclura tinctoria* *Phytolacca tetramera* *Pestalotiopsis* sp
Candidiasis	*Candida spp.*	Terpenoids from camphor and eucalyptol Cinamon oil and citronella Cascarilla bark and helichrysum oil Flavonoids Skh-AMP1 compound from *Satureja khuzistanica* MCh-AMP1 compound from *Matricaria chamomilla*

Primary Metabolites from Plants

Fungal infections caused by genera such as *Sporothrix, Paracoccidioides, Histoplasma, Aspergillus, Cryptococcus, Candida, Coccidioides*, and *Blastomyces* are a significant threat to human health, especially due to the growing problem of antifungal resistance.[5,42,43] In this context, primary plant metabolites have emerged as promising sources of bioactive compounds with the potential to develop effective treatments against these pathogens. Primary metabolites, such as sugars, fatty acids, amino acids, and vitamins, are essential for the metabolic and structural processes of fungi, and their modulation can alter cell viability and pathogenicity.[44,45] Recent studies exploring the antifungal activities of these primary metabolites in the aforementioned fungal genera are reviewed below, highlighting their therapeutic potential.

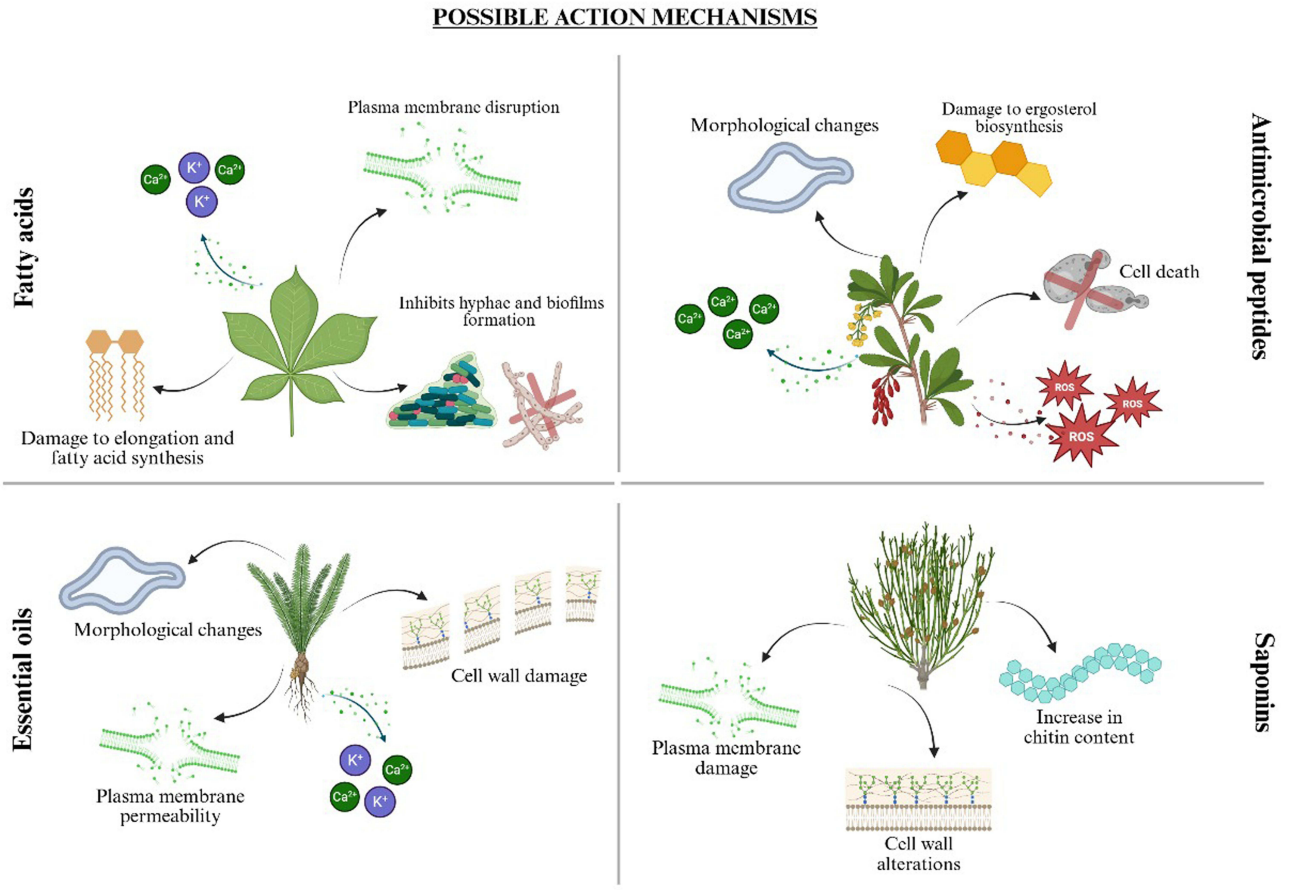

Figure 2 Proposed action mechanisms of plant-derived compounds with antifungal activity. The figure summarizes the main molecular and cellular targets of fatty acids, antimicrobial peptides, essential oils, and saponins against medically important fungi. Reported mechanisms include disruption of cell membrane integrity and permeability, inhibition of ergosterol biosynthesis, interference with biofilm formation through degradation of extracellular polysaccharides, modulation of cell wall synthesis (notably chitin synthesis), and induction of oxidative stress. These pathways illustrate the potential of natural compounds as alternative or complementary antifungal strategies.

Plant Fatty Acids

Fatty acids are the most abundant components of oils, along with stearic, palmitic, oleic, linoleic, and linolenic acids.[46] The antifungal properties of vegetable oils have been reported previously, and this action can be attributed to the presence of fatty acids.[47,48] For many years, the antifungal potential of these molecules has attracted scientific interest owing to the growing need for substances that counteract antifungal resistance. Various fatty acids have been studied in different fungal species, with medical relevance. The 6-nonadecenoic acid (6-NDA), an acetylenic acid derived from the roots of *Pentagonia gigantifolia*, has been shown to have a strong inhibitory activity against *C. albicans* and *A. fumigatus*.[49] Using microdilution assays, the strains ATCC 90028 and ATCC 90906 of the aforementioned species were tested, and at low concentrations, a significant effect on growth reduction was observed. For *C. albicans*, strong inhibition of hyphal formation was observed at all concentrations tested (0.195–50.0 μg mL^{-1}), a strong inhibition of hyphal formation was found.[49] However, unlike other fatty acids that have been tested against *C. albicans*, such as butyric, capric, lauric, palmitoleic, oleic, and linoleic acids, 6-NDA did not demonstrate the ability to inhibit the yeast-to-hypha transition under different experimental conditions.[50] Thus, this compound may only inhibit hyphal elongation, as has been demonstrated for other fatty acids in this species. In addition to these phenotypic effects, several studies have shown that 6-NDA primarily exerts its antifungal activity by disrupting lipid homeostasis in *C. albicans*.[49] Specifically, it interferes with the synthesis and elongation of long-chain fatty acids, generating marked "lipid stress" within the fungal cell. Notably, this inhibitory effect can be reversed by the addition of exogenous oleate, confirming the central role of this metabolic pathway.[49] Furthermore, transcriptomic analyses revealed that 6-NDA downregulates eight genes involved in ergosterol

biosynthesis, suggesting a direct impact on plasma membrane integrity and functionality. This compound also inhibits hyphal development, a key virulence factor in *C. albicans*.[49,51] In addition to its activity against *C. albicans* and *A. fumigatus*, 6-NDA also showed activity against *C. neoformans*.[46,52,53]

The antifungal activity of fatty acids, such as lauric, myristic, and palmitic acids, against *Aspergillus niger* has also been investigated. Reported assays have shown that palmitic acid specifically inhibits the growth of this species.[54] The *Linum usitatissimum* L. seed oil exhibited potential antifungal activity against *Aspergillus flavus*, achieving a growth inhibition of up to 54%. The observed antifungal potency can be attributed to the abundance of linoleic and α-linolenic acids in flaxseed oil, which seems to be promising for aspergillosis treatment.[55]

Chemical characterization of the extracts obtained from *Excoecaria agallocha* showed that palmitic and lauric acids were present in a higher proportion.[56] In concentrations of 0.125–0.5 mg mL^{-1}, both acids showed antifungal activity against *C. albicans*.[56,57] Short-chain fatty acids, such as butyric acid, inhibit *C. albicans* germination and hyphal formation, thereby reducing its virulence, as well as capsule formation in *C. neoformans*.[58] Medium-chain fatty acids, including caprylic, capric, and lauric acids, destabilize the plasma membrane and cause leakage of intracellular components, in addition to inhibiting biofilm formation. Unsaturated fatty acids, such as oleic, linoleic, and palmitoleic acids, interfere with the yeast-hypha transition and modulate signaling pathways associated with virulence. In contrast, long-chain saturated fatty acids, including myristic and palmitic acids, have been linked to the inhibition of virulence factors (eg, biofilm formation), suppression of ergosterol biosynthesis, and altered gene expression in pathways related to lipid metabolism in *C. tropicalis*.[59–61] Furthermore, fatty acid methyl esters (FAME) obtained from soybean, corn, and sunflower vegetable oils are potential sources of antifungal and antioxidant activities.[62] When assessed for antifungal activity against *Paracoccidioides*, concentrations of 15.6 and 500 μg mL^{-1} were found to decrease fungal growth. *P. brasiliensis* demonstrated increased susceptibility to soybean and sunflower FAMEs, with an MIC of 15.6 μg mL^{-1}. Interestingly, these FAMEs can produce reactive oxygen species (ROS) and hydroperoxide, which may be responsible for their antifungal activities.[62] In addition, FAMEs have been reported to exert antifungal activity through several other mechanisms. These compounds can interact with the fungal plasma membrane, inserting into the lipid bilayer and disrupting membrane integrity, which leads to leakage of ions and intracellular components and compromises cellular homeostasis.[53,56] FAMEs have also been suggested to interfere with ergosterol biosynthesis, weakening the membrane and reducing fungal viability. Moreover, some studies indicate that FAMEs can modulate the yeast-to-hypha morphological transition in *Candida albicans*, a process crucial for virulence and biofilm formation. Collectively, these mechanisms, including membrane disruption, oxidative stress induction, interference with ergosterol synthesis, and modulation of morphogenesis, highlight the multifaceted antifungal potential of FAMEs, supporting their consideration as promising candidates for the development of novel antifungal therapies.[53,56,62]

Although the antifungal activity of fatty acids has not been extensively studied in all fungal species of medical relevance, available studies have suggested that they may play a promising role in treatment. These findings open the door for future research to better understand the mechanisms of action and assess their efficacy in preclinical and clinical models, which could lead to the development of new antifungal strategies based on these natural compounds.

Plant Antimicrobial Peptides

Given the emergence of fungal pathogens that are resistant to commonly used drugs, several studies have focused on the use of AMPs as therapeutic agents. AMPs represent ancient host defense effector molecules present in different organisms across the evolutionary spectrum.[63] Their action mechanism may involve membrane permeabilization and cell lysis, in addition to interactions with cytoplasmic targets. Since these peptides are likely to act on multiple targets, the development of resistance against them seems to be an evolutionary change.[64,65] Plants have evolved an extreme richness of AMPs that are often found in plant organs such as roots, seeds, flowers, stems, and leaves.[66,67]

Nodule-specific cysteine-rich peptide (NCR) families have been tested against *C. albicans*. In particular, peptides NCR192, NCR137, NCR147, NCR280, NCR183, NCR247, NCR044, NCR030, and NCR335 exhibited antifungal activity against *C. albicans*, with MIC values ranging from 10.0 to 50.0 μg mL^{-1}, which are comparable to the values used for amphotericin B.[67] NCR peptides have a dynamic structure that allows them to act on several essential cellular processes in fungi. One of the main action mechanisms is the alteration of the fungal plasma membrane integrity.[67] These

peptides interact with the lipid bilayer, inserting themselves into it and causing the leakage of ions and intracellular components, which compromises cellular homeostasis and reduces fungal viability.[67] In addition, NCR peptides can induce ROS generation and peroxide production, which produces oxidative stress that damages fungal lipids, proteins, and nucleic acids. This effect contributes significantly to the peptide's antifungal activity.[68]

Some NCR peptides also interfere with the ergosterol biosynthesis, a key component of the fungal plasma membrane. The reduction of ergosterol levels weakens the membrane and increases its permeability, enhancing the toxic action of the peptides and compromising cell integrity.[69] Another relevant effect of these peptides is the modulation of *C. albicans* dimorphism. By interfering with this transition, NCR peptides reduce the fungus's invasive capacity and resistance to treatment.[70] Finally, NCR peptides can enhance the host's immune response. For example, some peptides have been shown to increase the *C. neoformans* phagocytosis by murine macrophages, suggesting a synergistic effect between direct antimicrobial action and stimulation of innate immunity.[68] In the *Sporothrix* genus, different AMPs, such as ToAP2A, ToAP2C, and ToAP2D have also been tested, and MIC assays have shown that ToAP2A has high antifungal activity against *Sporothrix globosa*. In addition, it exhibited low hemolytic and cytotoxic activities, indicating that this peptide has great potential for the development of new antifungal drugs.[71,72] Through in vivo studies, it has also been shown that the ToAP2D peptide inhibits *S. globosa* infection, and its efficacy is comparable to that of itraconazole.[72] The antifungal activity of ToAP2D has been associated with a multifactorial mechanism that combines structural alteration and the induction of programmed cell death pathways.[72] Treatment with this peptide causes cell deformation, surface irregularities, vesicle formation, and rupture, indicating direct damage to the cell wall and plasma membrane of the fungus. In parallel, ToAP2D promotes the accumulation of ROS and the loss of mitochondrial membrane potential, triggering the activation of fungal metacaspases.[72] These processes culminate in apoptosis-like cell death, characterized by nuclear condensation, DNA fragmentation, and increased membrane permeability. Taken together, these findings indicate that ToAP2D exerts its antifungal effect by both compromising fungal cell integrity and activating mitochondria-dependent apoptotic pathways, positioning it as a promising candidate for antifungal therapy against *Sporothrix* species.[72]

The *Heuchera sanguinea* HsAFP1 peptide is a defensin obtained mainly from seeds.[73] In vitro analyses showed that this peptide inhibited the growth of a wide variety of fungi, including *C. albicans* and *A. flavus*.[74] Several studies have elucidated the mechanism of action of this AMP, and it has been found that HsAFP1 can permeabilize fungal cells by interacting with its high-affinity target on the membrane. In addition, it was also shown that it binds to various membrane lipids, specifically phosphatidic acid.[75,76] In *C. albicans*, it was shown that HsAFP1 produces intracellular ROS, leading to fungal death and inducing changes in the expression of genes encoding proteins, such as those anchored to glycosylphosphatidylinositol (GPI) or those involved in cation homeostasis.[75] On the other hand, NaD1, Psd1, and RsAFP2 AMPs have also been tested against different fungal species.[77–79] The NaD1 peptide extracted from *Nicotiana alata* flowers was produced by the plant, mainly at the beginning of flower development.[78] It has been determined that NaD1 possesses antifungal activity against *C. albicans, C. neoformans*, and *Aspergillus* spp.[80] In addition, it can cross the fungal cell wall and bind to its molecular target, phosphatidylinositol 4,5-bisphosphate (PIP2). Subsequently, AMP was internalized via endocytosis. Once in the cytoplasm, ROS can alter membrane permeability and induce ROS production, which generates oxidative stress and leads to membrane disruption and cell death.[81–83] The plant defensin Psd1, isolated from *Pisum sativum* seeds, has high affinity and specificity towards ergosterol and does not interact with cholesterol-rich membranes, making it attractive because its toxicity towards mammalian cells is negligible.[84] It is reported that this peptide exhibits activity against *A. niger* and *C. albicans* at a concentration of 20 μM. Furthermore, in murine infection models, a decrease in *C. albicans* growth rate was observed.[77,83,84] Finally, the RsAFP2 peptide found in the seeds of radish (*Raphanus sativus*) possesses broad antifungal activity against *C. albicans*, inhibiting biofilm formation and affecting the hypha-to-yeast transition.[79] RsAFP2 exerts its antifungal effect mainly through a specific interaction with membrane glycosphingolipids, particularly glucosylceramides (GlcCer), present in numerous medically important fungal species. This binding causes plasma membrane disorganization, loss of permeability, and ionic imbalance, with a marked influx of $Ca^{2}+$.[85] As a result, ROS and oxidative stress are generated, damaging essential cellular components, while triggering programmed cell death pathways with apoptotic characteristics, such as the activation of metacaspases and loss of mitochondrial potential.[86,87] Additionally, RsAFP2 interferes with growth and morphogenesis processes, affecting hyphae formation and cell wall organization, which compromises virulence and the ability to form biofilms.[86,87]

Together, these multiple effects explain the strong fungicidal activity of RsAFP2, while its specificity for fungal lipids makes it less toxic to host cells.

Investigations of plant-derived AMPs as an antifungal strategy have focused primarily on *Candida* and *Aspergillus* genera, with multiple studies showing their ability to inhibit the growth and virulence of these species. However, the potential of these compounds can be extended to other pathogenic fungi of medical importance, thereby offering a promising alternative against antifungal resistance.

Plant Secondary Metabolites

Several natural compounds from vegetal and microbial secondary metabolites have antifungal properties.[88] The reports indicate that the total number of secondary metabolites isolated or produced by superior organisms is approximately 20,000, most of which have been used as antimicrobial agents.[89] For example, the natural alkaloid tryptanthrin, isolated from indigo, has been reported as a potential compound against *C. neoformans, C. gattii, C. deuterogattii*, and *Trichophyton rubrum*. In addition, it has shown synergy with other compounds, such as FK506 and cyclosporine A.[90] In *C. neoformans*, its mode of action is directly related to cell cycle arrest.[90] Research on plant secondary metabolites is constantly growing, and new alkaloids, terpenoids, essential oils, saponins, and flavonoids have been identified. Therefore, information regarding these metabolites and their potential antifungal properties is discussed here.

Plant Crude Extracts

The leaves of some plants have been directly tested against pathogenic fungi using solvents, such as ethanol (EtOH), dichloromethane (DCM), ethyl acetate (AcOEt), hexane, acetone, and water. These solvents generate fractions that may contain secondary metabolites such as flavonoids or terpenoids, which can be used in susceptibility assays. This initial mixture is known as the crude extract.

Reports have shown that *Schinus terebinthifolius* Raddi extract leaves have potential antifungal activity against *C. albicans* and *S. schenckii*, with MIC values of 30.0 μg mL^{-1}. In addition, the EtOH extract of the same plant showed an MIC of 15.0 μg mL^{-1} against *S. schenckii*.[91] *Baccharis dracunculifolia* extracts have been evaluated against pathogens, such as *C. neoformans*. Saponins, flavonoids, and alkaloids were qualitatively identified in the hexane extract, and the MIC against *C. neoformans* was 30.0 μg mL^{-1}. In contrast, hexane and DCM extracts of *Piper regnellii* inhibited growth at 30.0 and 60.0 μg mL^{-1}, respectively. *Rubus urticaefolius* and *Herissantia crispa* extracts were tested against *S. schenckii* and *C. neoformans*, respectively, at an MIC of 125.0 μg mL^{-1}.[91] Acetone extracts from several plants, including *Acokanthera oppositifolia, Apodytes imidiate, Artemisia afra, Bauhinia galpinii, Brachylaena discolour, Breonadia salicina, Combretum caffrum, Kirkia wilmsi, Maytenus undata, Milletia grandis, Mystroxylon aeththopicum, Solanum aculeastrum*, and *Spirostachys*, inhibited *A. flavus* growth at an MIC of 0.16 mg mL^{-1}. In addition, phytochemical analysis of *Curtisia dendata* and *Markhamia obtusifolia* revealed compounds, such as terpenoids, terpenes, essential oils, alkenes and alkanes, alkaloids, fatty acids, and vitamins, which could be related to their antifungal activity.[92] However, studies involving single compounds are necessary to confirm this hypothesis.[92] Several crude extracts from *Combretum* species have been evaluated to determine their antifungal activity against some strains of *S. schenckii, C. neoformans, M. canis, A. fumigatus*, and *C. albicans*. It was found that mainly the acetone extracts from *Combretum molle* and *C. celastroides* ssp. orientale was the most active compound against all the strains (MIC of 0.19 and 0.13 mg mL^{-1}, respectively).[93]

Plant Terpenoids

Terpenoids can be found in crude extracts of plants and have been reported as potential antimicrobials. The antifungal activity of camphor and eucalyptol was evaluated against different *Candida* species. Camphor showed more antifungal activity than eucalyptol, with a MIC of 0.125–0.35 mg mL^{-1} and 2.0–23.0 mg mL^{-1}, respectively. Some of the strains that were most sensitive to camphor were *C. albicans* 475/15 and *C. albicans* 527/14 (MIC 0.125 mg mL^{-1}). Reduction in biofilm biomass was observed by more than 50% in their MIC concentrations for both compounds in three *C. albicans* strains (*C. albicans* ATCC 10231, 475/15, and 27/14). This anti-biofilm activity has been reported to be related to the downregulation of the adhesion-related genes *HWP1, RBT1*, and *EED1*.[41,94] Reduction of hypha growth was observed at

a concentration of 0.125 mg mL^{-1} for camphor and 23.0 mg mL^{-1} for eucalyptol, and this effect was related to *ECE1* downregulation.[41,94] In addition, camphor was observed to reduce ROS production by 52%, a promising result because when an active infection exists, epithelial cell damage is linked to high ROS production.[41] Beyond these effects, both compounds were found to interfere with efflux pump regulation: camphor upregulated *CDR1* and downregulated *CDR2*, while eucalyptol upregulated both genes, suggesting that their antifungal activity may trigger compensatory resistance mechanisms.[41] Interestingly, none of these compounds significantly affected *ERG11* expression, indicating that their action is not directly linked to ergosterol biosynthesis inhibition. Finally, cytotoxicity assays showed that camphor exerts its antifungal activity at concentrations that are not harmful to mammalian cells, while eucalyptol displayed cytotoxicity closer to its antifungal range, highlighting camphor as the more promising candidate for therapeutic development.[41]

Plant Essential Oils

Essential oils (EO) give plants a distinctive smell or taste and are defined as volatile secondary metabolites. These compounds have been used in several industrial fields, including pharmaceuticals, for the discovery of novel antimicrobial compounds.

Cinnamon and citronella EOs produced by *Cinnamon cassia* and *Cymbopogon winterianus*, respectively, were evaluated for antifungal activity. The MIC concentrations were 0.065 mg mL^{-1} for cinnamon EOs and 0.25 mg mL^{-1} for citronella EOs. They showed an anti-biofilm effect linked to cinnamaldehyde and citronellal, which are membrane disruptors that degrade extracellular polysaccharides in biofilms.[95] In addition, their antifungal effects have been associated with severe structural damage to fungal cells. Both oils disrupt the integrity of the cell wall and plasma membrane, resulting in leakage of intracellular components and collapse of hyphal morphology.[96] Microscopic studies of *A. flavus* treated with these EOs revealed deformation, shrinkage, and ruptures on the hyphal surface, supporting the hypothesis that their mechanism of action involves direct compromise of membrane stability and cell envelope integrity. Although further studies are needed to clarify specific molecular targets, current evidence indicates that these compounds act through combined disruption of biofilm matrix and essential cellular structures, ultimately inhibiting fungal growth and viability.[96] In another study, six EOs from cascarilla bark, helichrysum, coriander, lemon eucalyptus, lemongrass, and lime were found to exhibit anti-biofilm properties against *C. albicans*. Cascarilla bark and helichrysum EOs showed major anti-biofilm and anti-hyphal activities, with efficiency in biofilm reduction from 87 to 92% at a concentration of 0.001%.[94] The chemical analysis of the EOs indicated that α-pinene and α-longipinene were the most abundant compounds, and the latter was found to be responsible for the anti-biofilm properties of the EOs.[94] Complementarily, mechanistic studies have shown that coriander EO (*Coriandrum sativum*) disrupts plasma membrane integrity in *C. albicans*, leading to leakage of intracellular contents and inhibition of hyphal growth and biofilm formation.[97] Similarly, lemongrass EO (*Cymbopogon citratus*), rich in citral and citronellal, destabilizes fungal membranes, impairs yeast-to-hypha transition, and inhibits biofilm development in *C. tropicalis* and *C. neoformans*.[98,99] Lime and lemon EOs, mainly composed of limonene, have been associated with alterations in membrane permeability and inhibition of growth in *Candida* spp.[100] Although fewer studies exist for cascarilla bark and helichrysum, available evidence suggests that their activity also relies on membrane disruption and interference with adhesion and biofilm-related processes. The *Thymus pulegioides* EOs showed antifungal activity against *Candida, Aspergillus, Microsporum canis*, and *Epidermophyton floccosum* strains by disrupting ergosterol biosynthesis.[101] The MIC values ranged from 0.16 to 0.32 µL mL^{-1} for *Aspergillus* and dermatophytes and 0.32 to 0.64 µL mL^{-1} for *Candida* strains.[101] In the same way, *Origanum vulgare* EO has been identified as a potential antifungal option against *Candida* species, evaluating six clinical isolates. The MIC varied from 2.10 to 3.54 µL mL^{-1}, and inhibition of fungal growth was associated with 4-terpineol, γ-terpinene, thymol, and carvacrol.[102]

Plant Flavonoids

Flavonoids, which are plant secondary metabolites, represent an option for the search of new alternatives for the treatment of fungal infections. They have a diphenyl propane skeleton and multiple biological activities, in addition to being common constituents of the human diet.[103] A study focused on the evaluation of flavonoids, such as flavone aglycones (luteolin and apigenin), a flavone glycosylated derivative (apigetrin), flavonol (quercetin), and its glycosylated derivatives (quercitrin, isoquercitrin, and rutin), showed that luteolin, quercitrin, isoquercitrin, and rutin have antifungal activity, with MIC of 37.5 µg mL^{-1}.[104] Biofilm formation was also evaluated, and isoquercitrin showed a 75% inhibition

of this cell consortium.[104] Hyphal growth was also affected by some of the compounds, with both apigenin and apigenin being major inhibitors of this fungal growth.[104] Gene expression analyses showed that *ERG11* was downregulated by apigenin, which places it as a potential candidate for the development of novel antifungal drugs.[104]

Chemical analysis of leaves from *Maclura tinctoria* leaves identified five new flavonoids (chalcones), which were tested in an inhibitory assay against *C. albicans* and *C. neoformans* at different concentrations. Only 2',4',4-trihydroxy-3′-[3″-methylbut-3″-enyl]chalcone (isobavachalcone) showed inhibitory activity, with IC50 values for *C. albicans* and *C. neoformans* of 15.0 and 7.0 μg mL^{-1}, respectively.[105]

Plant Saponins

Saponins are compounds with surfactant properties that form soap-like foams when shaken in aqueous solution.[88] Three saponins, phytolaccoside B, E, and F, were identified in the dried berries of *Phytolacca tetramera*. These results indicated that phytolaccoside B had the highest antifungal activity, likely because of the presence of sugar residues in its structure.[106] The most affected species by phytolaccoside B were *T. mentagrophytes, T. rubrum, M. gypseum, A. flavus*, and *C. neoformans*.[106] Phytolaccosides exert their antifungal activity mainly through alterations in fungal cell wall homeostasis. In particular, phytolaccoside B has been shown to markedly increase both basal and maximal activity of chitin synthase 1, resulting in a significant rise in chitin content and a doubling of cell wall thickness in treated cells.[107] These structural modifications are associated with morphological alterations, resembling those produced by β-1,3-glucan synthase inhibitors, although phytolaccoside B does not inhibit this enzyme directly. At MIC, partial plasma membrane damage has also been detected, despite the absence of binding to ergosterol or hemolytic effects on erythrocytes.[108] In contrast, aglycone derivatives, such as phytolaccagenin, can disrupt membranes through ergosterol interaction, while phytolaccoside B mainly acts via modulation of chitin synthesis, highlighting a distinctive mechanism of action among plant-derived saponins.[107,108] In another study, ten steroid saponins were isolated from the plant *Tribulus terrestris*. Compounds TTS-12 and TTS-15 showed major activity against *C. albicans* and *C. neformans*. These compounds contain a carbonyl group at C-12 that is thought to be essential for their antifungal effects.[109]

Research into the discovery and isolation of new secondary metabolites with antifungal activity has provided new therapeutic options for fungal infections. However, further studies are needed to elucidate the mechanism of action of most compounds, as well as cytotoxicity assays. In addition, focusing on testing these compounds in a wide range of pathogenic fungi could help expand the exploration of these new alternatives.

Fungal Metabolites with Antifungal Properties

Alkaloids can be isolated from plant endophytic fungi, such as *Aspergillus*, in which many of these compounds have been identified, but only a few have been reported as antifungal compounds.[110] Two cytochalasans compounds, named 1 and 2, isolated from *Aspergillus micronesiensis* from *Phyllantus glacus*, showed antifungal activity against *C. albicans* with MIC of 89.9 and 100.0 mg mL^{-1}.[111] A quinoline alkaloid, identified as an asperfumoid discovered in *A. fumigatus* CY018 in the plant *Cynodon datylon* was also evaluated against *C. albicans* with an MIC of 75.0 mg mL^{-1}, making it a promising new alternative for the treatment of fungal infections caused by this pathogen.[112]

Five new compounds [(4S,6S)-6-[(1S,2R)-1,2-dihydroxypentyl]-4-hydroxy-4-methoxytetrahydro-2H-pyran-2-one (1), (6S,2E)-6-hydroxy-3-methoxy-5-oxodec-2-enoic acid (2), LL-P880γ (3), LL-880α (4), Ergosta-5,7,22-trien-3b-ol (5)] were isolated from the culture broth of the endophytic fungus *Pestalotiopsis* sp. DO14, which increases the production of these metabolites upon interaction with *Dendrobium officinalis*.[113] Compounds were identified by nuclear magnetic resonance, and the results showed that compounds 1 to 4 have a high antifungal activity against *C. albicans* (MIC from 6.25 to 12.5 mg mL^{-1}), *C. neoformans* (MIC from 3.13 to 50.0 mg mL^{-1}), *T. rubrum* (MIC from 6.25 to 50.0 mg mL^{-1}), and *A. fumigatus* (MIC from 3.13 to 50.0 mg mL^{-1}). Compound 5 showed antifungal activity at concentrations > 200.0 mg mL^{-1}.[113] Metabolites 1 and 2 are compounds with major efficacy against fungi, which can be explained by the fact that they are classified as monoterpenoids, and their mechanism of action involves the inhibition of cell wall compound synthesis.[113]

Two compounds isolated from the fungal *Scleroderma* UFSMSc1, sclerodol A and B, associated with *Eucalyptus gradins*, were tested against *C. albicans* (MIC of 50.0 and 25.0 mg mL,[113] respectively). Its antifungal activity may be

associated with its triterpene classification, and it is believed that more compounds can be found in the crude extract of this fungus.[114]

Aspergillus species produce metabolites against other pathogens. In this context, two new compounds isolated from *A. terreus* were found to have antifungal activity against *C. neoformans*: (22E,24R)-stigmasta-5,7,22-trien-3-β-ol and aspernolides F, with MIC values of 4.38 and 5.19 mg mL^{-1}, respectively.[115] Two more compounds with antifungal activity against *C. neoformans* and *C. gatti* were found in the endophytic fungus, *Mycosphaerella* sp. UFMGCB 2032 was isolated from the plant *Eugenia bimarginata*.[116] Compounds were identified and classified as eicosanoic acids. Compound 1 showed a MIC of 1.3 and 2.5 mg mL^{-1} for *C. neoformans* and *C. gatti*, respectively, and compound 2 showed a MIC of 0.5 mg mL-^{1} for both species, representing new alternatives against these pathogens.[116] However, further research is required to evaluate these effects in vivo.

A cryptocandin isolated from the fungus *Cryptosporiopsis quercina*, an endophytic fungus of the medicinal plant *Tripterigeum wilfordii*, showed antifungal activity against the pathogens *C. albicans* (MIC of 0.03 mg mL^{-1}), *C. neoformans* (MIC >20.0 mg mL^{-1}), *A. fumigatus* (MIC >20 mg mL^{-1}), and *H. capsulatum* (MIC of 0.01 mg mL^{-1}). The exceptional activity against *C. albicans* and *H. capsulatum* awakened the interest in knowing the precise role of this compound, but it can be attributed to the structural characteristics of several amino acids with two hydroxy functionalities (see Figure 2). [117]

Antifungal Compounds from Marine Algae

In recent years, marine algae have been studied as a potential source of novel antifungal agents. The red alga *Symphyocladia latiuscula* is a rich source of such compounds.[118] Four new brominated polyphenol compounds were isolated, identified, and named based on their chemical characteristics (Compounds 1–4). The antifungal activity of the compounds was tested against *C. albicans*, and only compounds 3 and 4 showed activity with MIC values of 25.0 and 12.5 μg mL^{-1}, respectively.[118]

The red alga *Laurencia papillosa* was studied, and three new compounds derived from cholestane and aldehyde derivatives were identified and tested against *C. albicans, A. fumigatus*, and *A. flavus*.[119] Molecular formulas were obtained by electron ionization mass spectrometry, and compound 2 was already identified in another red alga, *Hypnea musciformis*, which suggests that these compounds can be found in diverse algal species.[119] Antifungal assay results showed antifungal activity in the compound 1 against *C. albicans* (MIC of 2000 μg mL^{-1}) and compound 3 against *A. fumigatus* and *A. flavus* (MIC of 200 and 1000 μg mL^{-1}), although values seemed to be elevated in comparison with other compounds. Nevertheless, it would be interesting to elucidate the precise mechanisms of action.[119]

Another red alga studied was *Laurencia composita* Yamada, in which 23 new compounds were isolated and characterized. Most of them were classified as sesquiterpenoids, some of them preintricatro, pacifenediol, helianthol B, grossonorol, and obtusane, and the rest as halosesquiterpenoids that include laurecomposins A and B, one halonerolidol, and compositacins L, M, and N.[120] Antifungal activity was tested against *Microsporum gypseum* (Cmccfmza), *T. rubrum* (Cmccftla), *C. albicans* (Y0109), *C. albicans* (SC5314), *C. neoformans* (32609), and *A. fumigatus* (07544). The results showed that laurecomposins A and B, preinctricatrol, and grossonorol had potential antifungal activities against *M. gypseum* (Cmccfmza) (MIC values of 4.0, 8.0, 8.0, and 4.0 μg mL^{-1}, respectively). Laurecomposin A and preintricatol showed activity against *C. albicans* (SC5314) (MIC of 16.0 and 32.0 μg mL^{-1}, respectively), whereas compositacin N and pacifenediol showed antifungal activity against *M. gypseum* (Cmccfmza) (MIC of 32.0 and 16.0 μg mL^{-1}, respectively) and *T. rubrum* (Cmccftla) (MIC of 64.0 μg mL^{-1} for both), while the remaining compounds were considered inactive.[120]

Two new prenylated paraxylenes, named caulerprenyols A and B, were identified in the green alga *Caulerpa racemosa* by NMR and MS. Their antifungal activity against *T. rubrum* (Cmccftla) and *C. neoformans* (32609) showed activity against compound B with MIC80 values of 16.0 and 4.0 μg mL^{-1}, respectively, whereas against *A. fumigatus* (07544), the activity of this compound was over 65.0 μg mL^{-1}.[121]

The antifungal activities of eight new compounds [laurepoxyene (1), 3β-Hydroperoxyaplysin (2), 3α-Hydroperoxy-3-epiaplysin (3), 8,10-Dibromoisoaplysin (4), (5S)-5-Acetoxy-β-bisabolene (5), 10-Bromoisoaplysin (6), Laurokamurene C (7), and Laurokamurene A (8)], which are sesquiterpenes isolated from the red alga *Laurencia okamurai* were tested against *C. neoformans* (32609), *T. rubrum* (Cmccftla), and *A. fumigatus* (07544).[122] Compounds 2, 3, 5, and 8 showed great antifungal

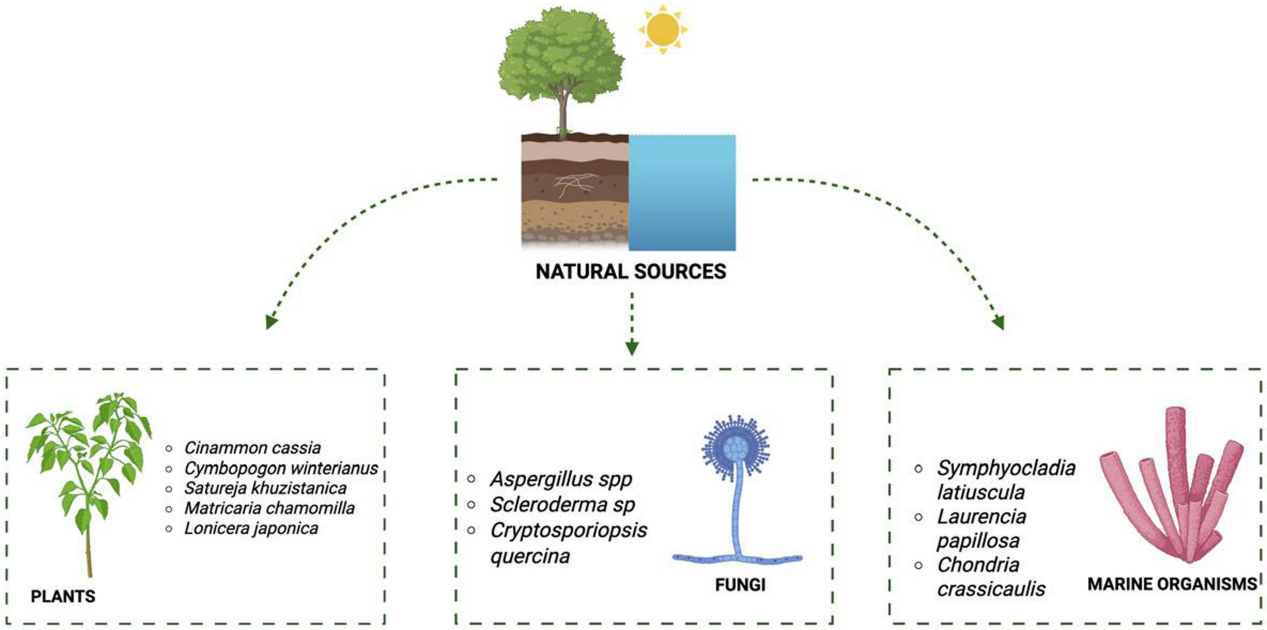

Figure 3 Diverse natural sources of bioactive compounds with antifungal potential. The figure illustrates the contribution of different organisms and biological structures in obtaining novel antifungal compounds.

activity against *C. neoformans* (32609) (MIC80 values of 4.0, 8.0, 64.0 and 32.0 μg mL^{-1}, respectively) whereas against *T. rubrum* (Cmccftla) compounds 1, 2, 6, and 8 were the most active (MIC80 values of 32.0, 16.0, 32.0 and 32.0 μg mL^{-1}, respectively).[122] In the same way, the antifungal activity of the crude extract of the red alga *Asparagopsis taxiformis* was evaluated against *A. terreus, A. flavus*, and *A. fumigatus*.[123] Results showed good antifungal activity, with MCI values from <0.15 mg mL^{-1} to >5.0 mg mL^{-1}.[123]

Metabolites of the red alga *Chondria crassicaulis* have also been studied. Two racemic lipids were identified in this alga by NMR: (±)-4,7-dihydroxy-4-methyl-2,5-heptanedione (1) and (±)-7-butoxy-4-hydroxy-4-methyl-2,5-heptanedione (2).[124] Antifungal activity of the compounds was tested against the pathogenic fungi *M. gypseum* (Cmccfmza), *T. rubrum* (Cmccftla), *C. albicans* (SC5314), *C. albicans* (Y0109), *C. neoformans* (32609), and *A. fumigatus* (07544). Unfortunately, only compound 1 showed antifungal activity against *C. neoformans* (32609), with an MIC80 value of 32.0 μg mL^{-1}, but not against any of the other pathogens, whereas compound 2 did not show antifungal activity against any strain (Figure 3). [124]

Concluding Remarks

With the growing impact of fungal infections and increasing resistance to conventional antifungal drugs, exploration of plant-derived compounds has attracted significant interest in biomedical research. Natural sources represent an abundant reservoir of bioactive metabolites with therapeutic potential, offering alternatives that could complement current pharmacotherapy with fewer adverse effects. Several studies have reported antifungal activities of primary and secondary metabolites, including essential oils, against medically relevant fungal species. Compared with synthetic antifungal drugs, natural compounds have several advantages, such as structural diversity, multiple mechanisms of action, and a lower probability of generating resistance. Some compounds also exhibit synergistic effects with conventional antifungals, which could enhance the efficacy of existing treatments. However, important limitations remain, including variability in the composition of natural extracts, limited mechanistic understanding, lack of clinical evidence for safety and efficacy, challenges in standardization and large-scale production, and a disproportionate focus of available studies on *Candida* and *Cryptococcus*. For many other clinically relevant fungal genera, data on natural compounds are scarce, highlighting significant gaps in the literature. Critically, while these limitations highlight the early stage of this field, they also define clear directions for future research. Systematic characterization, optimization, and standardization of natural compounds, coupled with rigorous preclinical and clinical studies, will be essential to translate these molecules into clinically useful antifungal agents. By integrating mechanistic

insights, structure–activity relationships, and careful evaluation of efficacy and safety, natural-based compounds have the potential to inform the next generation of antifungal therapeutics, addressing current gaps in treatment and providing innovative strategies to combat the growing problem of antifungal resistance.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare no conflict of interest.

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