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Antifungal natural products and combination strategies: an update concerning molecular mechanisms

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Abstract

When human immune function is compromised, infections caused by pathogenic fungi are often difficult to cure, with invasive fungal diseases frequently associated with high mortality rates. Presently, the types of antifungal drugs available for clinical use are limited, and their toxicity and safety issues can lead to adverse effects for patients. The emergence of drug-resistant strains and the "super fungus" *Candida auris* has further complicated treatment. Consequently, the identification of new antifungal medications and the formulation of effective combination therapy strategies have emerged as pivotal research priorities within this discipline. Natural products are specialized small molecules that are produced in nature and play pivotal roles in numerous cellular processes and are considered to be among the most significant pharmaceutical agents in the field of human healthcare. Accordingly, the objective of this paper is to review natural products and relevant compounds that exhibit antifungal activity by targeting key components of the fungal cell walls or cell membranes. We focused on the most recent research findings from 2022 to 2025 concerning antifungal natural products derived from plants, fungi, and bacteria, and conducted a comprehensive summary of the sources and types of natural products, along with their antifungal mechanisms of action. Furthermore, we analyzed the application prospects of combining novel natural products with existing antifungal drugs from the perspective of compensatory mechanisms of fungal cell structures, thus establishing new treatment strategies for fungal infections.

Keywords: Natural products, Human pathogenic fungi, Anti-fungi, Fungal cell wall, Fungal cell membrane, Pharmacological mechanisms

1 Introduction

Fungi are a group of eukaryotic organisms characterized by their cell wall structure[1]. In the event of compromised human immunity, the presence of pathogenic fungi can lead to persistent superficial infections and invasive infections[2]. The global increase in fungal infections can be attributed primarily to the widespread prevalence of HIV/AIDS, radiation therapy and chemotherapy in cancer patients, and the implantation of medical devices[3]. A recent global epidemiological analysis has revealed that the cumulative number of individuals affected by fungal infections has surpassed 1 billion, with 150 million of these individuals experiencing severe forms of these infections (2010-2023)[4]. The annual incidence rate of invasive fungal infections is estimated to be 6.5 million, resulting in 3.8 million deaths, with approximately 2.5 million of these deaths attributable directly to fungal infections[5]. During the 2019 COVD-19 pandemic, the severity of fungal infections was revealed in the form of life-threatening secondary infections in intensive care units[6]. A statistical analysis of 99 patients infected with COVID-19 reveals that 5 of them subsequently developed fungal infections[7]. Common pathogens that cause invasive fungal diseases have been identified as *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*[8]. Despite the availability of antifungal medications in clinical practice,

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approximately half of the patients still lose their lives due to fungal infections, with a mortality rate that exceeds that of tuberculosis and malaria (2019-2021)[9].

The five antifungal medications that are currently most frequently used in clinical practice are pyrimidines, azoles, polyenes, allylamines, and echinocandins. However, a comprehensive analysis of clinical research findings indicates that the current availability of antifungal drugs is limited, and there is a broad spectrum of adverse effects associated with their use, including hepatotoxicity and nephrotoxicity[10,11]. This has resulted in a consistent increase in mortality rates from invasive fungal infections. Furthermore, the emergence of fungal strains that are resistant to existing antifungal medications, as well as the "super fungus" *Candida auris*, contributes to the complexity of effective treatment options[12]. Additionally, the presence of complex compensatory mechanisms in fungal cells has been demonstrated to be associated with fungal virulence and adaptation to adverse external factors[13]. These compensatory mechanisms are considered a significant cause of resistance and tolerance to antifungal drugs[14]. Therefore, the exploration of novel antifungal medications and combinatorial therapeutic strategies has emerged as a pivotal area of research in this context.

Given the substantial investment required for the research and development of novel antifungal medications, pharmaceutical researchers have directed their attention to the screening of natural products derived from plants, fungi, and bacteria[15,16]. A substantial number of natural products are preferred by pharmaceutical researchers due to their minimal adverse effects, low cost, and multi-targeted properties[17]. Furthermore, the semi-synthetic technology using natural sources as lead compounds has become the most used method in structural modification of antifungal drugs due to its advantages of few reaction steps and easy operation[18]. Notably, a considerable number of natural products and relevant compounds have been demonstrated to possess a broad spectrum of pharmacological activities, thus highlighting their potential for diverse clinical applications[15,19,20]. Further exploration into their potential antifungal activities and mechanisms of action will contribute to the expansion of their clinical application prospects. The novel mechanisms underlying their antifungal effects, which differ from those of existing antifungal drugs, are of particular interest.

Fungi and human cells are both eukaryotic organisms, exhibiting a high degree of similarity in metabolic pathways and cellular structure. This similarity poses significant challenges for the development of specific antifungal drugs. Given the absence of fungal cell wall components and ergosterol in human cells, the related synthesis pathways can serve as optimal targets for antifungal drug development[21]. Accordingly, this review summarized natural products targeting specific components of fungal cell walls or cell membranes in recent studies, analyzed the types of natural products and their antifungal activities and mechanisms, and looked to the application prospects of drug combinations.

2 Natural Products Targeting Fungal Cell Wall Components

Fungal cell walls are composed of polysaccharides and glycoproteins, with the polysaccharides accounting for over 90% of the cell wall's dry weight[21]. The main polysaccharides are glucan and chitin, which are covalently cross-linked to form the cell wall's three-dimensional framework[22]. As the human body does not contain fungal cell wall components and cell walls are essential for fungal cell growth, morphogenesis, and resistance to external stress factors, as well as being involved in pathogen-host interactions, inhibiting fungal cell wall synthesis is a safe and effective strategy for preventing and treating fungal infections[23].

2.1 Natural Products Targeting Glucan Synthesis

Glucan constitutes 40%~60% of the dry weight of fungal cell walls, with β-1,3-glucan being the most abundant component[24]. β-1,3-glucan is a homopolymer formed by glucose units linked via β-1,3-glycosidic bonds and is catalyzed by β-1,3-glucan synthase[25]. Echinocandins are a class of antifungal drugs used in clinical practice that exhibit inhibitory activity against various *Candida* and *Aspergillus* species. They exert their effect by non-competitively inhibiting β-1,3-glucan synthase, disrupting the synthesis of β-1,3-glucan in the fungal cell wall. Consequently, cell wall permeability is disrupted, leading to cell lysis and death[26]. Echinocandin are natural products isolated from *Aspergillus* cultures[27]. It serves as the lead compound for the development of semi-synthetic antifungal drugs, including caspofungin, micafungin, anidulafungin, and rezagfungin. Despite having a reduced adverse reaction profile compared to other antifungal medications, echinocandins are rapidly degraded when taken orally, thus necessitating intravenous administration as the prevailing delivery method[28].

Zingibroside R1, a triterpenoid saponin derived from the plant *Panax notoginseng*, has demonstrated the capacity for self-assembly into molecular hydrogels. This molecular

transformation was accompanied by the manifestation of pronounced antifungal activity, a property that was absent in its free molecular form. The glucan presents in the cell wall of *C. albicans* served as a potential target for the antifungal activity of Zingibroside R1 hydrogels. The nanomaterial's ability to adsorb to the fungal cell surface via hydrogen bonds, resulting in membrane deformation, has been demonstrated to ultimately disrupt the integrity of the fungal cell membrane[29] (Figure 1A and Table 1). Ibrexafungerp represents a novel, highly bioavailable, and orally and intravenously administrable β-1,3-glucan synthase inhibitor that has been demonstrated to exhibit in vitro antimicrobial activity against a variety of *Candida* species that are resistant to echinocandins. This compound is a semi-synthetic derivative that has been synthesized from the natural product enfumafungin, which is derived from the fungus *Hormonema carpetanum*, and belongs to the triterpenoid glycoside class[30] (Figure 1B and Table 1). Sesamin, a compound derived from *Sesamum indicum*, has been observed to bind to the Phe144-Phe258 clamp and Phe229 residues in the active site of exo-1,3-glucanase of *Candida spp*., potentially preventing the entry of the glucan chain, thereby disturbing β-1,3-glucan structure and preventing growth and morphogenetic switching[31] (Figure 1C and Table 1).

In addition to β-1,3-glucan, the cell walls of common pathogenic fungi also contain β-1,6-glucan. Although certain pathogenic fungi, such as *Neurospora crassa* and *A. fumigatus*, lack β-1,6-glucan components in their cell walls, gene knockout studies have demonstrated that *C. albicans* and *C. neoformans* lacking β-1,6-glucan exhibit significantly diminished pathogenicity[32]. Additionally, α-glucan is commonly found in *Basidiomycota*, such as pathogen *C. neoformans*. Interestingly, *C. neoformans* could regulate the construction of cell walls by modulating the α-glucose production, thereby adapting to host conditions[33]. Consequently, the screening and identification of natural products and their compounds that target β-1,6-glucan and α-glucan will facilitate the development of novel antifungal drugs.

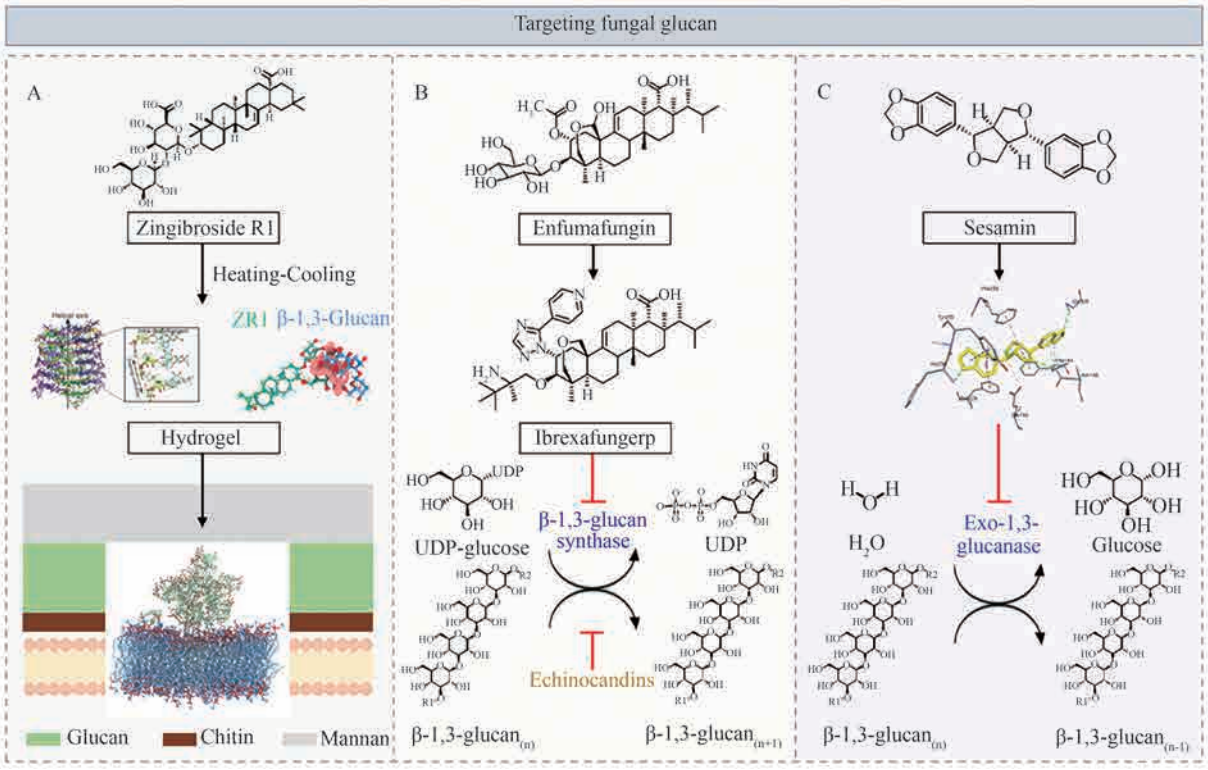

Figure 1 Antifungal mechanisms of natural products targeting glucan. (A) Zingibroside R1 spontaneously self-assembles into a hydrogel made up of helical nanofibrils with a complex hydrogen-bonding network, which could bind glucan of *C. albicans* and damage its membrane integrity. (B) By employing enfumafungin as the lead product, ibrexafungerp is created by eliminating the unstable hemiacetal at position C25, substituting a hydrophilic nitrogen-containing aromatic heterocyclic ring for the acetoxy group at position C2, and partially substituting an amino ether for the C3 glycoside. Ibrexafungerp exhibits antifungal properties by blocking β-1,3-glucan synthase. (C) Sesamin targets the active site of exo-1,3-glucanase by binding at the Phe144-Phe258 clamp and Phe229 residues, thus potentially inhibiting the growth of *Candida* species.

Table 1 Natural products targeting fungal glucan.

Name	Source	Antifungal mechanisms	Antifungal spectrum	Safety evaluation	References
Zingibroside R1	*Panax notoginseng*	The hydrogen-bonding interface between ZR1 gel and glucan compromises fungal membrane integrity	*Candida albicans*	No adverse effects	[29]
Ibrexafungerp	*Hormonema carpetanum*	Disrupting cell wall integrity by inhibiting β-1,3-glucan synthase	*Candida spp.*	Low toxicity	[30]
Sesamin	*Sesamum indicum*	Disrupting cell wall integrity by inhibiting exo-1,3-glucanase	*Candida spp.* (MIC and MFC of 16 and 32 g/mL, respectively)	Low toxicity	[31]

2.2 Natural Products Targeting Chitin Synthesis

Chitin is a homopolysaccharide composed of N-acetylglucosamine units that are linked by β-1,4-glycosidic bonds and synthesized by chitin synthases (*CHS*). While chitin constitutes a relatively minor proportion of the dry weight of fungal cell walls (e.g., 2%-10% in *C. albicans* and 7%-15% in *A. fumigatus*), chitin builds the primary septum and chitin synthases play a crucial role in regulating the processes of cell proliferation and pathogenicity[34]. Existing chitin synthase inhibitors, such as nikkomycins and polyoxins, are nucleopeptide antibiotics with strong antifungal activity in vitro[35]. These inhibitors are found in the fermentation broth of the bacteria *Streptomyces ansochromogenes* and *S. cacaoi* var. *asoeinsis*, respectively, and competitively inhibit chitin synthase activity. However, they have been reported to degrade rapidly in vivo, reducing their inhibitory efficacy[36]. Currently, there are no effective antifungal medications targeting chitin available for clinical use. The structure of *C. albicans* chitin synthase and its co-crystal structure with the inhibitors nikkomycin and polyoxin have been characterized[36]. Cryo-electron microscopy has been used extensively to reveal the crystal structures of chitin synthase from the plant pathogen *Phytophthora sojae* and the yeast *S. cerevisiae*[36]. By elucidating the structure of chitin synthases and the catalytic mechanism of chitin synthase, these studies have provided an important foundation for the discovery of natural products that target chitin.

Citronellal is a volatile, colorless-to-yellowish liquid with an aroma reminiscent of lemon, lemongrass, and rose. It is soluble in ethanol and the least volatile oils, slightly soluble in volatile oils and propylene glycol, and insoluble in glycerin and water. The substance occurs naturally in lemongrass oil and eucalyptus oil. Recent studies have demonstrated that citronellal could impair the cell wall of the plant pathogenic fungus *Magnaporthe oryzae* and interfere with its chitin synthesis, which prevents mycelium growth and effectively protects rice from rice blasts[37].

2.3 Fungal Cell Wall Disruptors

Recent studies have demonstrated that baicalin could promote the recognition and clearance of macrophages by affecting the expression of cell wall synthesis-related genes in *C. albicans*. This effect led to the exposure of cell wall components such as β-1,3 glucan and chitin deposition[38]. The natural product enterotoxin CHQS, derived from the bacterium *Enterococcus faecalis*, exerted a substantial effect on the β-1,3-glucan and chitin components of the *C. albicans* cell wall, resulting in defects such as impaired cell wall integrity, cell wall rupture, and intracellular vacuolization[39]. However, the mechanism by which these natural products disrupt fungal cell wall remains unclear and requires further investigation.

3 Natural Products Targeting Fungal Cell Membrane

The fungal cell membrane serves as both a structural barrier separating the intracellular environment from the extracellular milieu and a crucial platform for numerous metabolic processes, including substance transport, energy metabolism, and signal transduction. Therefore, maintaining the integrity and functional stability of the membrane is vital for fungal viability, proliferation, and pathogenicity[40]. In the yeast *S. cerevisiae*, the plasma membrane primarily consists of three major lipid classes: phospholipids (including glycerophospholipids and sphingolipids), glycolipids (such as inositol phosphorylceramide, mannosyl-inositol-phosphorylceramide, and their disubstituted derivatives), and ergosterol[41]. These lipid species are organized into dynamic, spatially regulated domains that govern membrane fluidity, permeability, and compartmentalization. Through intricate interactions, they confer to the fungal membrane its unique physicochemical properties and biological functions. Given the central role of the fungal membrane in cellular processes, natural products that disrupt membrane integrity or target key membrane components have emerged as promising antifungal agents.

The following sections provide a comprehensive overview of natural products that target fungal membranes, focusing on those that affect ergosterol, sphingolipids, and membrane integrity.

3.1 Natural Products Targeting Ergosterol

Ergosterol, the principal sterol in fungal cell membranes, differs from cholesterol, the dominant sterol in animal cell membranes, by possessing a unique system of double bonds and methyl side chains. This distinctive structure is essential for maintaining membrane fluidity, structural integrity, and the functional microenvironment of the fungal membrane[42,43]. The biosynthesis of ergosterol is a complex multistep pathway involving at least 23 enzymatic reactions catalyzed by approximately 25 enzymes, beginning from acetyl-CoA through the mevalonate pathway and farnesyl pyrophosphate intermediate, ultimately leading to ergosterol formation via the *ERG* gene cluster[43,44]. Lanosterol 14α-demethylase, encoded by the *ERG11* gene, acts as a key rate-limiting enzyme and has long served as the primary target of azole antifungals such as fluconazole and voriconazole. Inhibition of Erg11 impairs the 14α-demethylation step, resulting in decreased ergosterol production and accumulation of the toxic sterol 14,24-dimethylcholesta-8,24(28)-dien-3β,6α-diol (DMCDD), further compromising membrane function[45]. Additionally, squalene monooxygenase *ERG1* is targeted by allylamine antifungals like terbinafine, while morpholine drugs such as amorolfine interfere with sterol maturation by inhibiting downstream enzymes *ERG2* and *ERG24*[46]. Polyene natural antifungals, including amphotericin B, natamycin, and nystatin, bind directly to ergosterol in the fungal membrane, forming transmembrane channels that lead to leakage of intracellular contents and fungal cell death. However, due to the structural similarity between ergosterol and cholesterol, these agents may exhibit non-specific interactions with human cell membranes, resulting in significant nephrotoxicity, particularly in patients with impaired glomerular filtration[47,48]. In contrast, azole drugs, although generally safer, have encountered clinical resistance linked to target enzyme mutations, *ERG11* overexpression, or activation of the high-osmolarity glycerol (HOG) signaling pathway[49,50]. Overall, antifungal agents targeting the ergosterol biosynthesis pathway, including polyenes, azoles, allylamines, and morpholines, have proven effective therapeutic strategies. Nonetheless, limitations remain due to host toxicity, conservation of target enzymes, and emerging resistance mechanisms. Therefore, the development of novel natural products with unique structures and mechanisms continues to be a crucial focus in antifungal research (Figure 2A).

3.1.1 Thymol, a monoterpenoid phemiaceae plant *Zataria multiflora* Boiss., exhibited broad-spectrum antifungal activity against both fluconazole-resistant and -sensitive *Candida glabrata*. Its mechanism primarily involved direct inhibition of key enzymes in the ergosterol biosynthesis pathway, including *ERG1*, *HMG1*, and *ERG11*, thereby blocking the mevalonate pathway and the sterol cyclization cascade. Thymol also significantly downregulated the expression of related genes *HMG1* and transcription factor *UPC2*. Additionally, it synergistically inhibited the chitin synthase *CHS6* and activates the HOG1-MAPK signaling pathway to induce oxidative stress, achieving multi-target damage to fungal cell membranes and cell walls[51].

3.1.2 Isoflavaspidic acid PB, derived from the *Dryopteris fragrans* (L.) Schott, exhibited potent inhibitory effects against dermatophytes such as *Trichophyton rubrum*. Its antifungal mechanism included simultaneous inhibition of *ERG1* and *ERG11*, blocking ergosterol biosynthesis and causing squalene accumulation. Concurrently, it disrupted membrane permeability through direct membrane binding, inducing organelle dissolution and nucleotide leakage, thus exerting a dual mechanism of synthesis inhibition and membrane damage. This compound was also effective against multiple dermatophytes including *Microsporum canis*[52].

3.1.3 Novel imidazole derivatives, Eugenol-imidazole, based on natural phenols eugenol and dihydroeugenol coordinate the imidazole ring with the heme iron of *ERG11* and insert a chlorophenyl ring into the hydrophobic cavity of the enzyme active site, blocking the conversion of lanosterol to ergosterol. This resulted in ergosterol depletion and accumulation of toxic intermediates. These compounds exhibited broad-spectrum and potent inhibition against *C. albicans*, multidrug-resistant *C. auris*, and *Cryptococcus gattii*, with higher targeting efficiency and lower toxicity compared to miconazole[53].

3.1.4 Pachysamine M, a pregnane alkaloid from the medicinal plant *Pachysandra axillaris*, effectively blocked ergosterol biosynthesis by downregulating multiple key genes (*ERG1, ERG4, ERG7, ERG9,* and *ERG24*). It reduced ergosterol content by 74.7% and showed sustained antifungal activity against fluconazole-resistant *C. albicans* in vitro. In murine models, pachysamine M reduces fungal burden and inflammation, demonstrating multi-target effects, low resistance potential, and favorable in vivo safety[54].

3.1.5 Fruitless Wolfberry Bud Tea Extract (FWE), rich in flavonoids such as quercetin, significantly inhibited

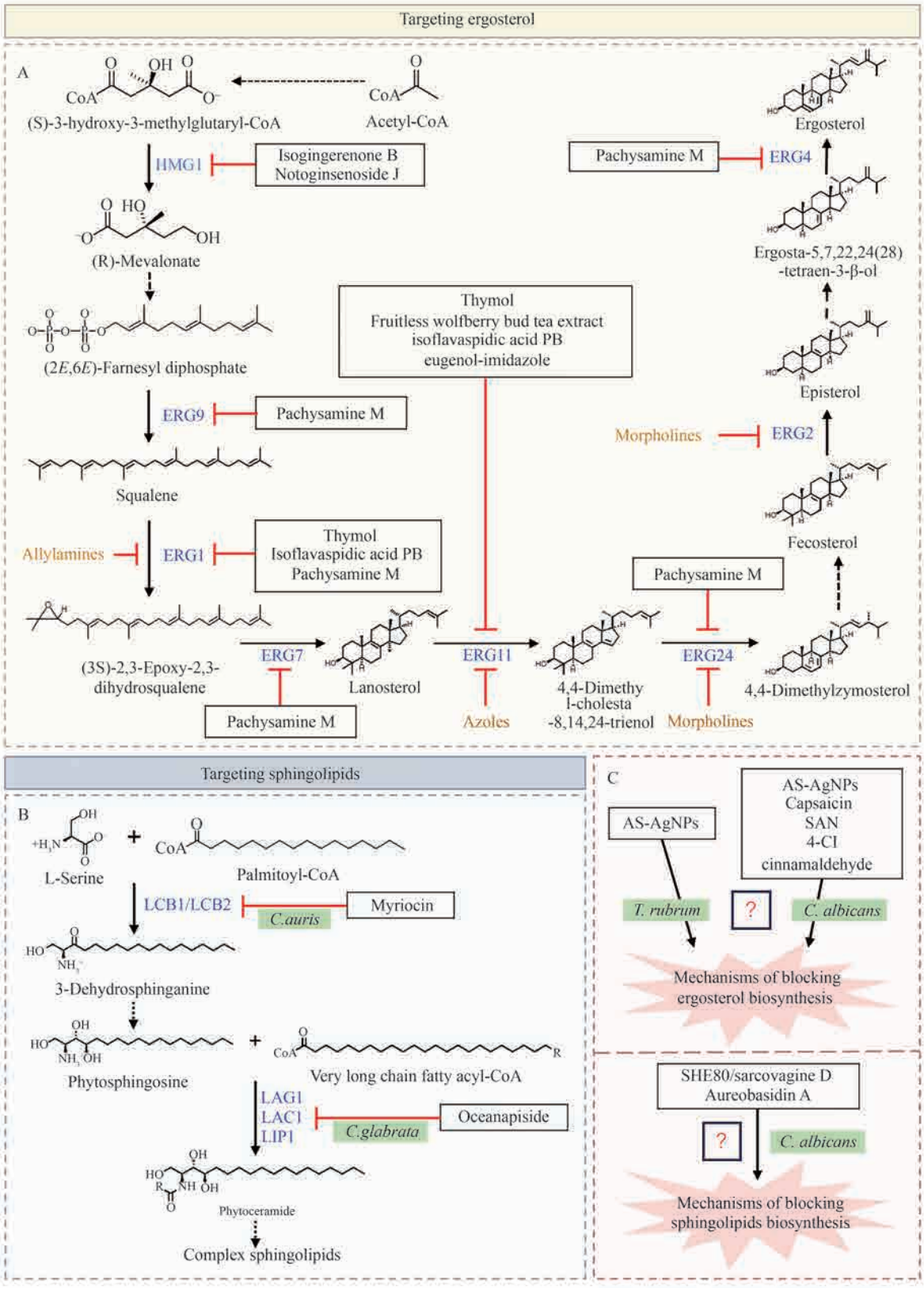

Figure 2 Antifungal mechanisms of natural products targeting cell membrane components. (A) Fungal ergosterol production pathway blocking by various natural product activities. (B) Natural products inhibit serine palmitoyltransferase LCB1/LCB2 and ceramide synthase LAC1/LAG1/LIP1 activity and intracellular sphingolipids production. (C) The mechanisms by which natural products block ergosterol biosynthesis are still unknown.

ERG11 enzyme activity in *C. glabrata* and downregulated the encoding gene *ERG11*, blocking ergosterol biosynthesis at both transcriptional and enzymatic levels, thereby impairing fungal membrane function. Furthermore, FWE suppressed the expression of efflux pump genes *CDR1* and *CDR2*, enhanced the efficacy of azole drugs, and reduced biofilm formation. Combination treatment of FWE with azoles exhibited significant synergistic inhibition against resistant strains, indicating potential clinical application value[55].

3.1.6 The lyophilized supernatant of *Streptomyces albidoflavus* strain Q contains active compounds such as isogingerenone B and notoginsenoside J, which effectively inhibit the rate-limiting enzyme HMG-CoA reductase in ergosterol biosynthesis. This resulted in a significant reduction of ergosterol content in yeast membranes and disruption of membrane structure. The compounds also demonstrated good safety profiles in the *Galleria mellonella* in vivo model[56].

In summary, although these natural products originate from diverse sources, they all disrupt fungal cell membrane integrity by targeting key enzymes involved in ergosterol biosynthesis. They effectively inhibit the growth of various pathogenic fungi, with some exhibiting advantages such as activity against resistant strains, synergistic effects, and favorable safety profiles, highlighting their promising potential as novel antifungal drug candidates (Figure 2A and Table 2).

3.1.7 Capsaicin, a natural compound extracted from chili peppers (genus *Capsicum*), exhibited potent antifungal activity primarily against *C. albicans* involved in oral and endodontic infections. Its antifungal mechanism involved a dose-dependent reduction of ergosterol content in the fungal cell membrane, inhibition of hyphal formation and biofilm maturation, and disruption of membrane permeability, leading to intracellular content leakage. Capsaicin demonstrated significant efficacy against both clinical isolates and standard strains of *C. albicans*, and shows synergistic effects with fluconazole, thereby reducing the risk of resistance development[57].

3.1.8 4-chloro-cinnamaldehyde(4-Clcinnamaldehyde), a chlorinated derivative of cinnamaldehyde, exhibited enhanced activity against fluconazole-resistant strains. It disrupted cell membrane structure by interfering with ergosterol biosynthesis, induced membrane potential imbalance, and markedly inhibited biofilm formation, overcoming drug resistance barriers. This compound showed strong therapeutic efficacy and favorable safety in animal models and exerted an additive effect when combined with nystatin, highlighting its potential in multi-target antifungal strategies[58].

3.1.9 Sanguinarine (SAN), a natural benzophenanthridine alkaloid, significantly reduced ergosterol content in the fungal membrane, disrupted the integrity of the cell membrane and wall, and induced fungal structural damage and death. In a murine model of candidiasis, SAN significantly reduced fungal burden and improved survival, emphasizing its promise as a small-molecule natural product targeting ergosterol biosynthesis[59].

3.1.10 Silver nanoparticles (AS-AgNPs) synthesized using an aqueous extract of the Asteraceae plant *Achillea santolina* also exerted antifungal activity by disrupting ergosterol biosynthesis and membrane permeability. These nanoparticles concurrently inhibited key cell wall synthases and induced ROS accumulation in fungal cells, leading to apoptosis. AS-AgNPs exhibited significant inhibitory effects against *Trichophyton rubrum* and achieved a favorable balance between antifungal potency and biocompatibility[60].

Although derived from diverse plant sources and including nanomaterials, these compounds share a common mechanism: disruption of ergosterol biosynthetic enzymes and membrane structures, ultimately compromising membrane stability and function. Consequently, they effectively inhibit the growth of various pathogenic fungi, including *C. albicans*, drug-resistant strains, and dermatophytes (Figure 2C and Table 2).

Ergosterol shares significant structural similarity with human cholesterol, which raises concerns about potential cytotoxicity to host cells, the safety profile of ergosterol-targeting compounds remains a critical issue requiring further investigation through comprehensive pharmacokinetic and toxicological studies[61]. Nevertheless, natural products offer a diverse array of chemical scaffolds and bioactive leads with high modifiability. Through rational structural optimization and targeted modifications, it is possible to retain antifungal efficacy while improving selectivity and biocompatibility. This provides a solid molecular foundation and design strategy for the development of next-generation ergosterol synthesis inhibitors with enhanced efficacy and reduced toxicity.

3.2 Natural Products Targeting Sphingolipids

In recent years, natural products have emerged as a promising avenue in antifungal drug development by targeting sphingolipid metabolism in fungal cell membranes.

Table 2 Natural products targeting fungal ergosterol and sphingolipids.

Name	Source	Antifungal mechanisms	Antifungal spectrum	Safety evaluation	References
Thymol	*Zataria multiflora* Boiss	Inhibition of ergosterol synthesis: 1 Downregulation of HMG1 gene expression leads to inhibition of mevalonate production; 2. High affinity binding with ERG1, HMG1, and ERG11, interfering with enzyme activity; 3. Inhibit the expression of transcription factor UPC2 and block ergosterol biosynthesis	*Candida glabrata* (MIC: 32~128 μg/mL)	–	[51]
Isoflavaspidic Acid PB	*Dryopteris fragrans* (L.) Schott	1. Similar to amphotericin B, it directly binds to ergosterol in fungal cell membranes, disrupting membrane integrity, leading to nucleotide leakage and intracellular solute efflux; 2. Inhibit the activity of ERG1 and ERG11, and block the conversion of squalene to ergosterol	*Trichophyton rubrum* (MIC: 20 μg/Ml, MFC: 40 μg/mL)	–	[52]
Eugenol-imidazole	Eugenol、Dihydroeugenol	Targeting ERG11 enzyme to inhibit ergosterol synthesis	*Candida albicans*、*Candida tropicalis*、*Candida parapsilosis*、*Cryptococcus gattii*	Low cytotoxicity to healthy rat cardiomyocytes (H9c2)	[53]
Pachysamine M	*Pachysandra axillaris*	Targeting the ergosterol biosynthesis pathway significantly inhibits the expression of key genes, leading to the accumulation of squalene, lanosterol, and yeast sterols, resulting in a decrease in ergosterol content and disruption of fungal cell membrane integrity	*Candida albicans* (MIC: 4 μg/mL, MFC: 16 μg/mL). In a mouse skin infection model, pachysamine M (15 mg/kg) significantly improved fungal infections	Low cytotoxicity to healthy rat	[54]
Fruitless wolfberry bud tea extract (FWE)	*Lycium barbarum* L.	1. Inhibit ERG11 and block the biosynthesis of ergosterol. 2. Inhibit efflux pump activity: downregulate the expression of ABC transporter genes (CDR1, CDR2), reduce drug efflux, and reverse azole resistance; 3. Inhibit biofilm formation: downregulate the expression of adhesins and reduce fungal colonization.	*Candida glabrata*	High bioavailability and low toxicity	[55]
Isogingerenone B, Notoginsenoside J	*Streptomyces albidoflavus* strain Q	Blocking ergosterol synthesis by inhibiting HMG1	*Candida spp.*	In the Galleria mellonella model, no toxicity was observed at a test dose of 2000 mg/kg	[56]
Capsaicin	*Capsicum annuum* L.	Reduce the content of ergosterol in the cell membrane, induce changes in cell membrane permeability, lead to leakage of intracellular substances, interfere with hyphae formation, inhibit biofilm maturation	*Candida albicans* (MIC: 12.5~50 μg/mL).	High dose (97 mg/kg) capsaicin showed oral toxicity in mice and rats	[57]
4-Cl Cinnamaldehyde	Cinnamon essential oil	Inhibition of ergosterol synthesis, inhibition of biofilm formation, induction of oxidative stress	*Candida albicans* (MIC = 25 μg/mL, MFC = 50 μg/mL)	Long term toxicity and metabolic stability need further evaluation	[58]
Sanguinarine	*Macleaya cordata*	Blocking ergosterol synthesis by inhibiting ERG11	*Candida albicans*	In mouse in vivo administration experiments, doses of 1.5 and 2.5 mg/kg effectively inhibited systemic fungal infections, improved survival rates and body weight, and had no significant serious side effects.	[59]

(To be continued)

Table 2 Continued.

Name	Source	Antifungal mechanisms	Antifungal spectrum	Safety evaluation	References
AS-AgNPs	*Achillea santolina*	1. Inhibit spore germination and hyphal growth of Trichophyton rubrum. 2. Damaging fungal cell membranes, increasing membrane permeability, leading to leakage of cellular contents. 3. Inhibit ERG11 and block the synthesis of ergosterol.	*Trichophyton rubrum, Candida albicans, Candida tropicalis, Candida parapsilosis*	Low toxicity to human skin fibroblasts (HDF). Local medication in rats has no significant toxic side effects.	[60]
SHE80/sarcovagine D	*Sarcococca hookeriana* var. digyna	Inhibit the synthesis of ceramides (Cer) and glucose ceramides (GlcCer), disrupt fungal cell membrane integrity and biofilm formation, and block yeast-to-hyphae transition	*Candida albicans* (In vitro: The MIC of SHE80 is 16 μg/mL, and the MFC is 64 μg/mL; The MIC of sarcovarine D is 4 μg/mL, and the MFC is 16 μg/mL; In vivo: In a mouse skin infection model, SHE80 (20~40 mg/kg) significantly reduces fungal burden and promotes wound healing)	Low toxicity in a mouse model	[62]
Aureobasidin A (AbA)	*Aureobasidium pullulans*	Inhibiting the structure and function of fungal cell membranes by disturbing sphingolipid biosynthesis	*Candida spp., Cryptococcus neoformans*	–	[63]
Oceanapiside (OPS)	*Oceanapia phillipensis*	Blocking sphingolipid biosynthesis by inhibiting ceramide synthase (encoded by LAG1/LAC1/LIP1)	*Candida glabrata* (MIC = 10 μg/mL)	–	[64]
Myriocin	*Isaria sinclairii*	Blocking sphingolipid biosynthesis by inhibiting serine palmitoyltransferase LCB1/LCB2	*Candida auris*	High cytotoxicity	[65]

Unlike ergosterol, sphingolipids are not unique to fungi but are also widely present in mammalian cell membranes, where they play critical roles in maintaining membrane structure, signal transduction, cell differentiation, and apoptosis[61]. This highlights the importance of achieving target selectivity when designing sphingolipid-directed therapies. Studies have shown that some natural compounds can effectively inhibit key enzymes in the sphingolipid biosynthesis pathway-particularly inositol phosphoceramide synthase (IPCS)-leading to the disruption of sphingolipid synthesis and impairment of fungal membrane integrity[61]. These findings provide new molecular targets and natural scaffolds for the development of antifungal agents with novel structures and unique mechanisms of action.

Sarcococca hookeriana var. *digyna* is a traditional medicinal plant commonly used by the Miao ethnic group in southwestern China. Its 80% ethanol extract (SHE80) and the major active component, the steroidal alkaloid sarcovagine D, exhibited significant antifungal activity against fluconazole-resistant *C. albicans.* Both SHE80 and sarcovagine D disrupted the sphingolipid biosynthetic pathway, leading to reduced levels of ceramide (Cer) and glucosylceramide (GlcCer), disruption of membrane homeostasis, and inhibition of sphingolipid-associated signaling molecules such as MAPK14 and PRKCA. This ultimately resulted in increased membrane permeability, decreased membrane fluidity, mitochondrial dysfunction, and ROS-induced apoptosis. In a murine skin infection model, SHE80 significantly reduced fungal burden, promoted wound healing, and suppressed the release of inflammatory cytokines, without exhibiting evident toxicity, indicating favorable in vivo safety and therapeutic potential[62]. Aureobasidin A (AbA), a cyclic non-ribosomal peptide derived from *Aureobasidium pullulans*, has been demonstrated to specifically inhibit the sphingolipid biosynthetic pathway in fungi. AbA effectively inhibited the growth of various *Candida* species, particularly clinical drug-resistant strains, and interfered with biofilm formation and colonization. Its mechanism involved reducing chitin synthesis, inducing oxidative stress, and exacerbating damage to the cell membrane and mitochondria. Moreover, AbA inhibited multidrug efflux pumps such as CDR2 and MDR1, enhancing the efficacy of antifungal drugs like fluconazole and exhibiting synergistic effects. In both *Caenorhabditis elegans* and murine infection models, AbA significantly improved host survival without observable toxicity, supporting its in *vivo* efficacy and safety[63]. However, the molecular mechanism through which these natural products inhibit sphingolipid biosynthesis remains unclear (Figure 2C and Table 2).

Due to the unique characteristics of marine ecosystems, including limited oxygen, high salinity, and high pressure. Marine microorganisms routinely produce bioactive secondary metabolites, becoming an important source of natural products. As shown in Figure 2B and Table 2, oceanapiside (OPS), a marine-derived sphingolipid analog, was isolated from the marine sponge *Oceanapia phillipensis* and represents the first antifungal agent of marine origin known to target the sphingolipid metabolic pathway. OPS exerts its antifungal activity by inhibiting ceramide synthase (encoded by *LAG1/LAC1/LIP1*), thereby blocking the conversion of phytosphingosine (PHS) to phytoceramide (PHC). This leads to intracellular accumulation of PHS, which disrupts actin cytoskeleton assembly, inhibits polarized growth and ATP production, and ultimately induces fungal cell death. OPS exhibits potent fungicidal activity against fluconazole-resistant *Candida glabrata,* but shows limited efficacy against *C. albicans* and *Candida krusei*. Its fungal-specific target suggests potential safety advantages[64]. Myriocin, a fungal-derived sphingolipid synthesis inhibitor, acts by targeting serine palmitoyltransferase LCB1/LCB2, thereby blocking the initial step in sphingolipid biosynthesis. It demonstrates significant activity against multidrug-resistant *C. auris* and can synergistically enhance the antifungal efficacy of amphotericin B, resulting in markedly reduced MICs in clinical resistant strains. Although Myriocin exhibits broad eukaryotic cytotoxicity, which limits its direct clinical use, the successful development of its derivative Fingolimod highlights the potential for structural optimization and therapeutic translation[65]. Nevertheless, despite their promising in vitro antifungal potential, these natural products still lack comprehensive in vivo safety evaluations, underscoring the need for further investigation.

3.3 Fungal Cell Membrane Disruptors

Fungal cell membrane disruptors exert their antifungal effects by directly targeting the lipid bilayer, leading to structural damage, increased membrane permeability, and subsequent leakage of intracellular contents, ultimately resulting in cell death. In contrast to conventional antifungal agents that inhibit ergosterol biosynthesis, membrane-disrupting agents often exhibit multi-target activity, broad-spectrum efficacy, and a lower risk of inducing resistance[61]. In recent years, a wide variety of natural products, including plant extracts, bioactive compounds from edible and medicinal fungi, and green-synthesized nanoparticles, have been identified as potent fungal membrane disruptors. These agents act via non-specific mechanisms such as perturbing membrane integrity, collapsing transmembrane potential, and inducing reactive oxygen species (ROS) accumulation, which collectively trigger apoptotic or necrotic cell death. While these natural compounds show promising in vitro and in vivo antifungal activity, concerns regarding toxicity and safety profiles remain, highlighting the need for further systematic evaluation[66]. Nevertheless, fungal membrane disruptors represent a promising class of antifungal candidates with the potential to overcome limitations associated with current therapeutics.

The natural compound 2-chloro-1,3-dimethoxy-5-methylbenzene (CDM), derived from *Hericium erinaceus* (lion's mane mushroom), acted by disrupting fungal cell membranes. It significantly damaged the integrity of the cytoplasmic and mitochondrial membranes, leading to excessive reactive oxygen species (ROS) generation, mitochondrial dysfunction, and induction of apoptosis in *C. albicans*. CDM showed no toxicity to normal human gastric mucosal epithelial cells at 125 μg/mL in vitro, and significantly reduced tissue damage and improved survival in animal infection models, indicating good safety and therapeutic potential[67].

Silver-Carthamus nanoparticles (Ag-Carth-NPs), synthesized under green conditions from *Carthamus tenuis* aqueous extract and silver ions, could significantly disrupt fungal cell membrane integrity. Their antifungal activity was achieved by increasing membrane permeability, inducing leakage of intracellular contents, and causing cell death. In vitro, Ag-Carth-NPs effectively inhibited *C. albicans* and *Candida tropicalis*, and showed no significant toxicity to normal human skin cells, demonstrating good biocompatibility[68].

Baicalein (BE), a natural flavonoid compound from *Scutellaria baicalensis* (Chinese skullcap), exhibited significant fungicidal activity against multidrug-resistant *C. auris*. Its mechanism centers on inducing excessive ROS production and collapse of mitochondrial membrane potential, leading to increased membrane permeability and cell death, while synergistically inhibiting efflux pumps to reverse drug resistance. In a porcine skin colonization model, BE markedly disrupted biofilm structure. In a *Galleria mellonella* infection model, it improved survival rates, confirming good in vivo antifungal efficacy and safety[69].

The n-hexane (CCHE) and methanol (CCME) extracted from the leaves of the leguminous plant *Centrosema coriaceum* both exhibited inhibitory effects on *C. glabrata*. Their mechanism involved disruption of cell membrane structure, and molecular docking studies confirmed high

affinity for membrane-related targets. In vitro experiments showed that both extracts have no significant toxicity to mouse peritoneal macrophages and possess anti-inflammatory and antioxidant activities, supporting their development as multifunctional natural drugs[70].

Eugenol from *Syzygium aromaticum* (clove) and citral from *Cymbopogon citratus* (lemongrass) exerted antifungal activity by embedding into the lipid bilayer of fungal membranes, altering membrane fluidity, inducing depolarization, and increasing membrane permeability. These effects led to ionic imbalance and cytoplasmic leakage in *C. albicans*. At sub-inhibitory concentrations, both compounds also inhibited hyphal formation and biofilm development, with a reported additive effect when used in combination[71].

The leaves of the traditional Chinese medicinal plant *Rumex japonicus* Houtt. are rich in anthraquinones (e.g., rhein, aloe-emodin), polyphenols, and flavonoids, which disrupted fungal membrane integrity and function, resulting in nucleic acid and protein leakage. These compounds exhibited inhibitory activity against various pathogenic fungi, including dermatophytes (*Trichophyton* spp.) and *C. albicans*, and also suppressed spore germination and biofilm formation. Notably, anthraquinones downregulated the expression of the adhesion gene ALS1, thereby interfering with biofilm maturation[72,73].

Ethanolic extracts of propolis from Chihuahua, Mexico, contain diverse phenolic compounds, flavonoids, and fatty acids, and demonstrated potent antifungal activity by compromising the membrane integrity of *C. albicans*, leading to increased permeability and cytoplasmic disintegration. Saturated fatty acids might mimic quorum sensing molecules to inhibit hyphal development, while unsaturated fatty acids likely embedded into fungal membranes to increase ion and protein leakage. These multi-target mechanisms, along with the extract's low in vivo toxicity, underscored its antifungal potential[74].

Low molecular weight peptides secreted by *Streptomyces* TRM43335, isolated from Taklamakan Desert soil, disrupt *C. albicans* hyphal morphology and extracellular matrix, destabilizing biofilm formation and integrity[75]. These effects suggested membrane disruption as a core antifungal mechanism, with potential to overcome biofilm-associated resistance.

The whole extract of *Withania somnifera*, a traditional Indian medicinal plant, exhibited antifungal activity against resistant *Sporothrix globosa* by reducing ergosterol content and damaging the fungal membrane, leading to pore formation and intracellular leakage. It also interfered with cell wall biosynthesis, particularly β-glucan and chitin metabolism. Active polyphenols such as withanone and withaferin A contribute to these effects and may help reduce the risk of resistance development, with favorable safety profiles reported[76].

Although these natural products exhibit significant in vitro antifungal activity, most lack comprehensive and systematic safety evaluations, especially regarding in vivo toxicology and pharmacokinetics. In summary, these compounds primarily act as fungal cell membrane disruptors through non-specific membrane damage, possess broad-spectrum antifungal activity, and in some cases demonstrate promising in vivo safety, making them valuable candidates for the development of novel antifungal therapeutics.

4 Natural Products That Act On Other Targets

Mitochondria, as the central hub for energy metabolism and apoptosis regulation in fungal cells, play a critical role in maintaining basic cellular processes such as ATP synthesis, oxidative phosphorylation, and metabolite production. They also serve as key regulators of stress responses and programmed cell death[77]. Additionally, antimetabolites are a class of compounds that act by mimicking or interfering with key metabolic intermediates within fungal cells, thereby blocking the synthesis of DNA, RNA, or proteins. These natural products typically exert their effects by competitively binding to fungal metabolic enzymes or substrates, disrupting critical biosynthetic reactions and ultimately leading to metabolic disorders and cell death[79].

4.1 Natural Products Targeting Mitochondria

In recent years, mitochondria have emerged as promising antifungal targets due to their essential functions in fungal physiology. Natural products, with their diverse structures, biological activities, and multi-target characteristics, represent valuable sources for the development of novel mitochondria-targeting antifungal agents. Numerous studies have shown that natural compounds can interfere with fungal growth and viability by damaging mitochondrial structures, disrupting membrane potential, impairing the electron transport chain, inducing ROS accumulation, or activating mitochondrial-dependent apoptotic pathways (Figure 3A-3C and Table 3). Naphthoquinone compounds such as naphthazarin, derived mainly from plants and microorganisms, exhibited potent

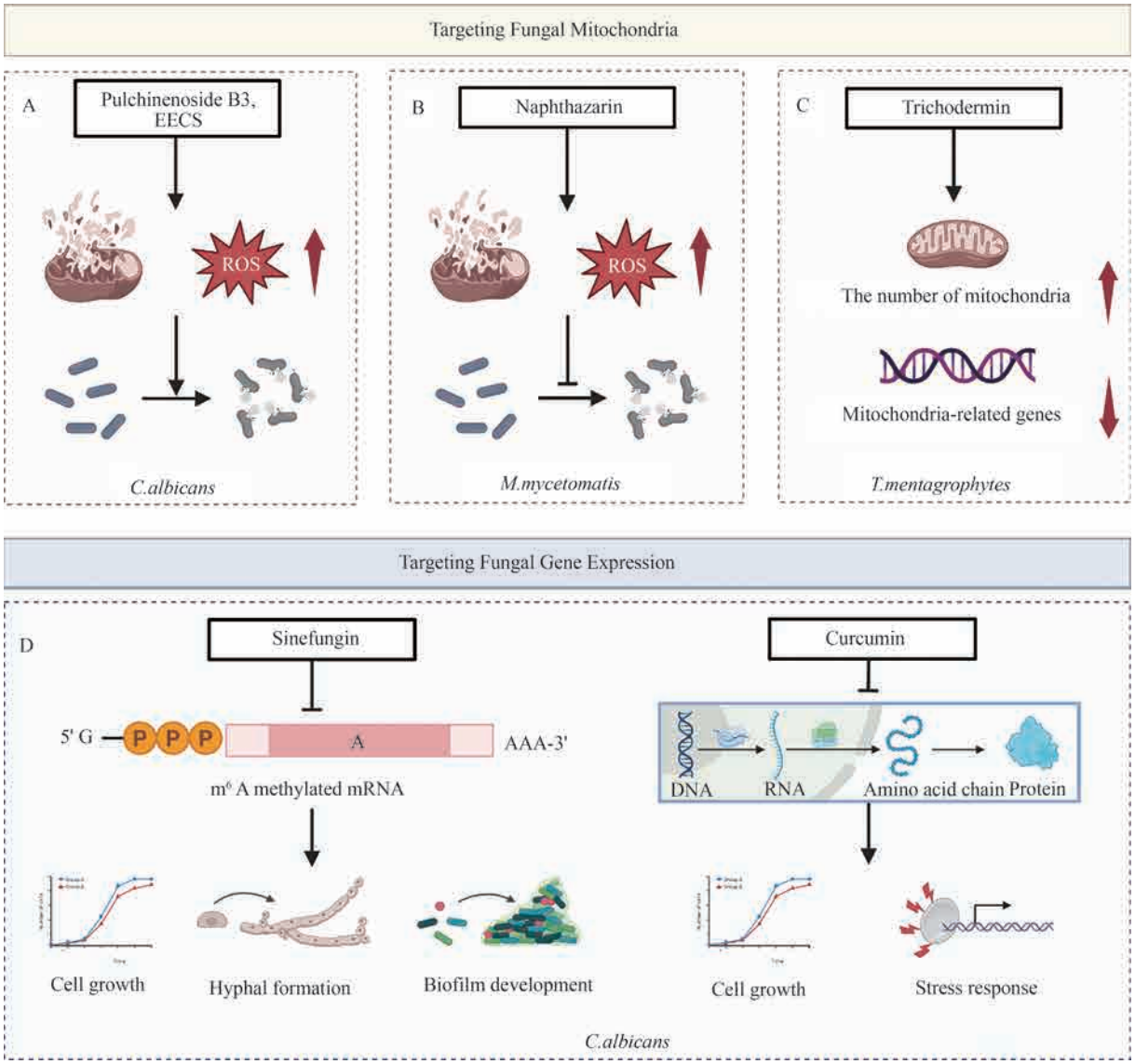

Figure 3 Antifungal mechanisms of natural products targeting mitochondria and gene expression system. Natural products lead to mitochondrial dysfunction in *C. albicans* (A), *M. mycetomatis* (B), and T. mentagrophytes (C). (D) Natural products interference with gene expression in *C. albicans*.

antifungal activity against *Madurella mycetomatis* (which causes human mycetoma). The mechanism of action was thought to involve mitochondrial damage, ROS generation, and disruption of the fungal electron transport chain, ultimately leading to cell death. In terms of safety, naphthazarin demonstrated low acute toxicity in *Galleria mellonella* models at concentrations below 0.152 μg/kg, though caution was warranted at high doses[78]. The triterpenoid natural product trichodermin, isolated from the endophytic fungus *Trichoderma taxi*, showed strong inhibitory effects against the zoonotic fungus *Trichophyton mentagrophytes*. Its antifungal activity was attributed to mitochondrial dysfunction and regulation of related metabolic gene expression. Trichodermin was considered safe for topical use at low doses in rabbit skin infection models and has been shown to promote healing, although high doses posed a risk of dermal toxicity[79]. Pulchinenoside B3, an oleanolic acid-type saponin derived from the traditional Chinese medicine *Pulsatilla chinensis*, effectively inhibited *C. albicans* biofilm formation and disrupted mature biofilms by inducing oxidative stress and activating mitochondria-mediated apoptotic pathways[80]. Ethanol extract of *Ceratonia siliqua* seeds (EECS) also demonstrated strong antifungal activity against *C. albicans*. The mechanism involved excessive ROS generation, mitochondrial membrane potential disruption, cytochrome c release, and activation of caspase-dependent apoptotic pathways, ultimately inducing fungal programmed cell death. EECS exhibited low hemolytic toxicity to mammalian cells at effective antifungal concentrations,

Table 3 Natural products targeting fungal mitochondria and gene expression system.

Name	Source	Antifungal mechanisms	Antifungal spectrum	Safety evaluation	References
Naphthazarin	Naphthoquinone derived from plants or microorganisms	Disrupting the mitochondrial function of fungi, inducing the production of reactive oxygen species, leading to metabolic disorders and death of fungal cells	*Madurella mycetomatis* (IC_{50} = 1.4 μM)	In the *Galleria mellonella* model, this compound (<0.152 μg/kg) has low toxicity, but there is some toxicity when administered multiple times at high doses	[78]
Trichodermin	*Trichoderma taxi*	1. Inhibit growth and spore development. 2. Mitochondrial damage. 3. Interference with multiple metabolic pathways, mainly including carbohydrate metabolism, secondary metabolite synthesis, glycolysis/gluconeogenesis, and carbon metabolism	*Trichophyton mentagrophytes*	At low concentrations (1 mg/mL), it significantly promotes healing of fungal infection lesions on rabbit skin. But at high concentrations (20 mg/mL), it may have toxic effects on the skin.	[79]
Pulchinenoside B3	*Pulsatilla chinensis*	1. Inhibition of biofilm formation by downregulating the expression of key transcription factors (such as BCR1, EFG1, NDT80, BRG1, ROB1, TEC1) and adhesion related genes (such as HWP1, ALS1, ALS3) involved in biofilm formation; 2. Destruction of mature biofilms by inducing oxidative stress and mitochondrial mediated apoptosis pathways	*Candida albicans* (MIC = 12.5 μg/mL)	–	[80]
Sinefungin	*Streptomyces*	1. Inhibit m6A methylation modification of fungal mRNA. The main target of inhibition may be adenosine methyltransferase	*Candida albicans*	–	[81]
Curcumin	*Curcuma longa*	Inhibit the expression of *HSP90*, thereby suppressing the expression or activity of downstream effector proteins such as *HOG1* and *CDR1*	*Candida albicans*	Low bioavailability	[82]

suggesting good therapeutic potential. This highlights the multifaceted antifungal and immunoregulatory properties of natural components within traditional Chinese herbal formulas, however, its specific antifungal spectrum and systemic safety require further investigation.

4.2 Natural Products Targeting Gene Expression

In antifungal research, antimetabolite-type natural products have emerged as promising drug candidates due to their unique mechanisms and multi-target characteristics. They not only interfere with the genetic and protein expression processes of pathogens but also provide valuable tools for exploring fungal metabolic regulatory networks (Figure 3D). Sinefungin is a natural analog of S-adenosylmethionine (SAM) derived from *Streptomyces*, which can significantly inhibited *C. albicans* hyphal formation, adhesion, biofilm development, and epithelial invasion at low micromolar concentrations, while exerting little effect on the growth of its yeast form, indicating a phase-selective mode of action. Its antifungal mechanism was attributed to interference with the N6-methyladenosine (m6A) modification of fungal mRNA, possibly through inhibition of methyltransferase (MTase) activity, thereby affecting the post-transcriptional stability and expression of genes involved in hyphal development. This RNA modification-targeting strategy represents a non-traditional antifungal pathway, expanding the scope of research on antimetabolite-based therapeutics[81]. Curcumin, a polyphenolic natural compound derived from the rhizome of *Curcuma longa*, exerted antifungal activity by post-transcriptionally suppressing the expression of heat shock protein 90 (HSP90), thereby disrupting the proper folding and function of multiple HSP90-dependent fungal proteins. This inhibition was primarily achieved through downregulation of HSP90 transcription and promotion of its mRNA degradation, which indirectly led to dysregulation of the HOG1 MAPK signaling pathway and decreased expression of multidrug resistance pumps such

as CDR1[82]. These effects collectively caused metabolic disturbances in protein stability and functional maintenance. Natural products can interfere with fungal nucleic acid and protein metabolism at multiple levels, highlighting the mechanistic diversity and therapeutic potential of antimetabolite-like natural products in antifungal research. This provides valuable insights and structural templates for the development of novel antifungal agents with unconventional mechanisms. However, the toxicity and safety of such drugs in clinical practice cannot be ignored.

5 Fungal Compensatory Resistance Mechanisms And NP-Based Combination Strategies

The unique components of fungal cell walls and cell membranes are ideal targets for antifungal drugs. However, the diverse and complex compensatory mechanisms present in fungal cells reduce the effectiveness of single-target drugs and often lead to the emergence of resistant strains[83].

5.1 Fungal Compensatory Resistance Mechanisms

Fungi have retained functionally redundant cell wall synthase genes during evolution, resulting in a compensatory role in cell wall synthesis. Research has demonstrated that under conditions with single or multiple dysfunctions of chitin synthases, there is a compensatory effect among other chitin synthases. In *C. albicans*, chitin synthase *CHS1* builds the primary septum. When *CHS1* was inhibited, the expression of other chitin synthases were upregulated and produced different types of compensatory septa through varying combinations, thereby maintaining cell growth and division[84]. For instance, the compensatory septa formed by the combinations of *CHS2* and *CHS3* or *CHS2* and *CHS8* were more biased toward the daughter cell side, while those formed by *CHS3* alone or in combination with *CHS8* exhibited a distinctly thickened characteristic. In *C. neoformans*, the deletion of *CHS3* caused the upregulation of *CHS5* and *CHS7* expression[85]. However, the mechanism and function of this process require further investigation. In addition to mutual compensation among chitin synthases, the functions of *C. albicans* α-1,2-mannosyl transferases *MNT1* and *MNT2* were partially redundant, and the individual deletion of *MNT1* or *MNT2* only resulted in partial shortening of O-mannan[86]. Additionally, the two *C. albicans* β-1,6-glucan synthase homologs, *KRE6* and *SKN1*, are functionally redundant. *C. albicans* β-1,6-glucan synthesis defects only occur when both KRE6 and *SKN1* were deleted, leading to multiple virulence-related phenotypic defects[87].

A compensatory effect also exists between different polysaccharides in fungal cell walls. In *C. albicans*, echinocandins have been shown to induce upregulation of chitin synthases expression, thereby increasing chitin content in the cell wall to compensate for defects in β-1,3-glucan synthesis, consequently reducing sensitivity to this class of drugs[88]. Deletion of both *CHS2* and *CHS8*, or deletion of *CHS3*, resulted in increased sensitivity to echinocandins[89]. Furthermore, mutations in specific amino acid residues at certain sites of the *C. albicans* β-1,3-glucan synthase *GSC1* are one of the key mechanisms contributing to the emergence of drug-resistant strains[90]. Studies have shown that drug-resistant point mutations in *GSC1* were associated with increased chitin content in the cell wall[50]. In *A. fumigatus*, echinocandins increased the amount of chitin in the cell wall via *CHSG*-dependent mechanisms, thereby reducing sensitivity to these drugs[91]. Deletion of *CSMA* or *CSMB* significantly enhances *A. fumigatus* sensitivity to echinocandins[92]. However, the roles of *CSMA* and *CSMB* in chitin compensatory upregulation remain unclear. In *C. neoformans*, echinocandins caused compensatory upregulation of the expression of chitin synthases *CHS1*, *CHS2*, *CHS4*, *CHS7*, and chitin deacetylase *CDA1*, as well as the content of chitin and chitosan in the cell wall, despite no significant changes in the expression of the major chitin synthase *CHS3*. However, the lack of *CHS3* resulted in a notable rise in sensitivity to echinocandins[93]. The regulation of chitin synthases expression is associated with the HOG, PKC or Ca^{2+}/calcineurin pathways. The absence of key factors in these pathways could affect chitin synthase expression in *C. albicans* and *A. fumigatus* to varying degrees, increasing sensitivity to cell wall stress agents[94,95]. Besides, when *C. albicans* exhibited defects in β-1,6-glucan synthesis in its cell wall, this led to various defects related to virulence, but the cells could still grow slowly. This was due to the fact that *C. albicans* activated CHS3 through post-transcriptional regulation via Ca^{2+}-calcineurin-mediated PKC signaling pathway, thereby increasing the content of chitin in the cell wall to maintain cellular viability, thus exerting a compensatory effect on β-1,6-glucan synthesis defects[96].

There is also a compensatory effect between the different components of the cell membrane. One study showed that *C. albicans* could upregulate sphingolipid biosynthesis genes and altered the composition of sphingolipids, especially substantially increasing levels of several mannosylinositolphosphoceramides with shorter fatty-acid chains, thereby enhancing resistance to azole drugs[97].

5.2 NP-Based Combination Strategies

Previous studies have demonstrated that the combination of curcumin derivatives and fluconazole could synergistically suppress intracellular ATP production of *C. albicans*, thereby disrupting cell membrane permeability[98]. Additionally, sodium houttuyfonate was found to be a potential synergist to enhance the antifungal *in vitro* activity of fluconazole in *C. albicans* resistant isolates, and the underlying mechanism may be associated with β-1,3-glucan synthesis and transportation[99]. Overall, given the vital role of key factors in fungi's compensatory mechanisms, screening and identifying natural products and relevant compounds that target these key molecular factors through molecular docking methods can facilitate the development of novel, effective, and safe drug combinations. Compared with conventional single-target antifungal medications, multi-target characteristics of natural products combined with existing antifungal drugs enhance not only antifungal efficacy but also effectively inhibit fungal compensatory mechanisms. This reduces the risk of drug resistance and tolerance. This opens up a new approach to the development of natural drugs for treating fungal infections.

6 Conclusion

Natural products are a fundamental resource in the drug discovery process which exhibit structural and biological activity diversity, low resistance, and abundant resources, rendering them a primary focus for the development of antifungal drugs. However, the clinical effects of natural products are often limited by their poor solubility and bioavailability. Fungal cell walls and cell membranes are dynamic structures that play a crucial role in regulating various processes, including fungal cell proliferation, morphological transformation, and interactions between the fungus and its host. As the components of the cell wall and ergosterol in the cell membrane are not present in the human body, they are often targeted as key targets for antifungal therapy, making them an important direction for the development of novel antifungal therapies. However, the majority of research on natural compounds that exhibit antifungal properties is restricted to in vitro and animal model studies, which remains uncertain whether they possess antifungal benefits for humans. In addition, the toxicity of novel natural products in the human body needs further evaluation.

Further research on natural products in the area of antifungal drug development will continue to prioritize the identification of natural products with antifungal activity and the elucidation of their mechanisms of action. The specific research directions that have been outlined include: (1) Screening and discovery of natural products targeting the synthesis pathways and related signaling pathways of unique components in fungal cell walls and cell membranes. (2) Elucidation of the crystal structures and mechanisms of action of key molecular targets of pathogenic fungi in humans, to provide a structural basis for targeted screening of natural products. (3) Utilization of antifungal natural products as lead compounds, along with the employment of semi-synthetic technology to amplify their antifungal properties, thereby addressing challenges such as inadequate bioavailability and suboptimal safety. (4) Exploration of new, effective, and safe pharmaceutical combination strategies based on the molecular mechanisms of natural products and relevant compounds is imperative.

Ethical Approval

Not applicable.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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