



Emerging Trends in Antifungal Treatment: Role of Gels, Natural Products, and Innovative Targets

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Abstract

Growing medication resistance limits the efficacy of traditional antifungal treatments, making fungal infections a major worldwide health problem, especially among immunocompromised people. This review focuses on new molecular targets, gel-based drug delivery methods, and drugs derived from natural products as developing trends in antifungal therapy. Due to their biocompatibility, capacity to improve drug stability, and enhanced patient compliance, gels have drawn interest as topical delivery systems that provide localised therapy with less systemic side effects. Natural products, such as marine chemicals, plant-derived metabolites, and microbial bio actives, are highlighted as a possible source of novel antifungal medicines with a variety of actions, including enzyme inhibition and membrane disruption. In order to address the present problems with resistance, novel therapeutic targets are being investigated, including fungal cell wall production, biofilm formation, hyphal morphogenesis, mitochondrial function, and heat shock proteins. Optimising treatment approaches is further aided by developments in pharmacokinetics and pharmacodynamics, as well as better diagnostic instruments and antifungal stewardship. All things considered, combining innovative drug delivery strategies with targeted treatments and natural substances presents a potential path toward the creation of safer and more potent antifungal treatments.

Keywords: Antifungal therapy, Antifungal resistance Gel-based drug delivery, Natural products, Fungal biofilms, Novel molecular targets, Topical drug delivery, Drug repurposing

1. Introduction

Gels are semi-solid systems in which particle interactions or the capacity of big molecules to dissolve in the dispersed phase regulate the dispersing medium's consistency^{1,2}. Gels are cross-linked, much diluted systems that don't flow steadily. They are made up of a two-component, highly liquid, semi-solid system. Gels' continuous structure, which gives them solid-like qualities, is one of their main characteristics. Because of its network structure, biocompatibility, and the molecular stability of the bioactive chemicals they contain, gels are becoming more and more popular for drug delivery formulations. Improving systemic absorption or offering localised treatment are the primary objectives of drug delivery via the skin.

Intravenous injection is invasive, but it avoids gastrointestinal side effects. Topical barrier treatments, on the other hand, increase patient compliance and are frequently self-administered³⁻⁵. The two main categories of fungus are yeasts and moulds. Yeasts are typically single, small, oval cells, whereas mould colonies are

composed of fibrous strands called hyphae. Some fungi are dimorphic, which means that depending on their surroundings, such as temperature, they can live as yeasts or moulds^{4,5}. Despite the fact that fungi are ubiquitous in the environment, only a few species are commonly associated with humans and have the potential to be harmful.

A few fungi that cause sickness in healthy individuals are referred to as genuine pathogens (*Histoplasma* and *Paracoccidioides*), whereas the majority of fungi that cause illness only in immunocompromised people are classified as opportunistic pathogens *Candida* and *Cryptococcus*⁶. However, it is evident that certain opportunistic fungal infections, like *Cryptococcus gattii* outbreaks or *Candida vaginitis*, can potentially infect otherwise healthy individuals^{7,8}. For a systemic effect, cutaneous fungal infections are typically treated intravenously or orally. (Figure 1) Among the many negative effects it might cause are gastric irritation, diarrhoea, nausea, vomiting, stomach discomfort, headache, fever, renal impairment, and anaemia.

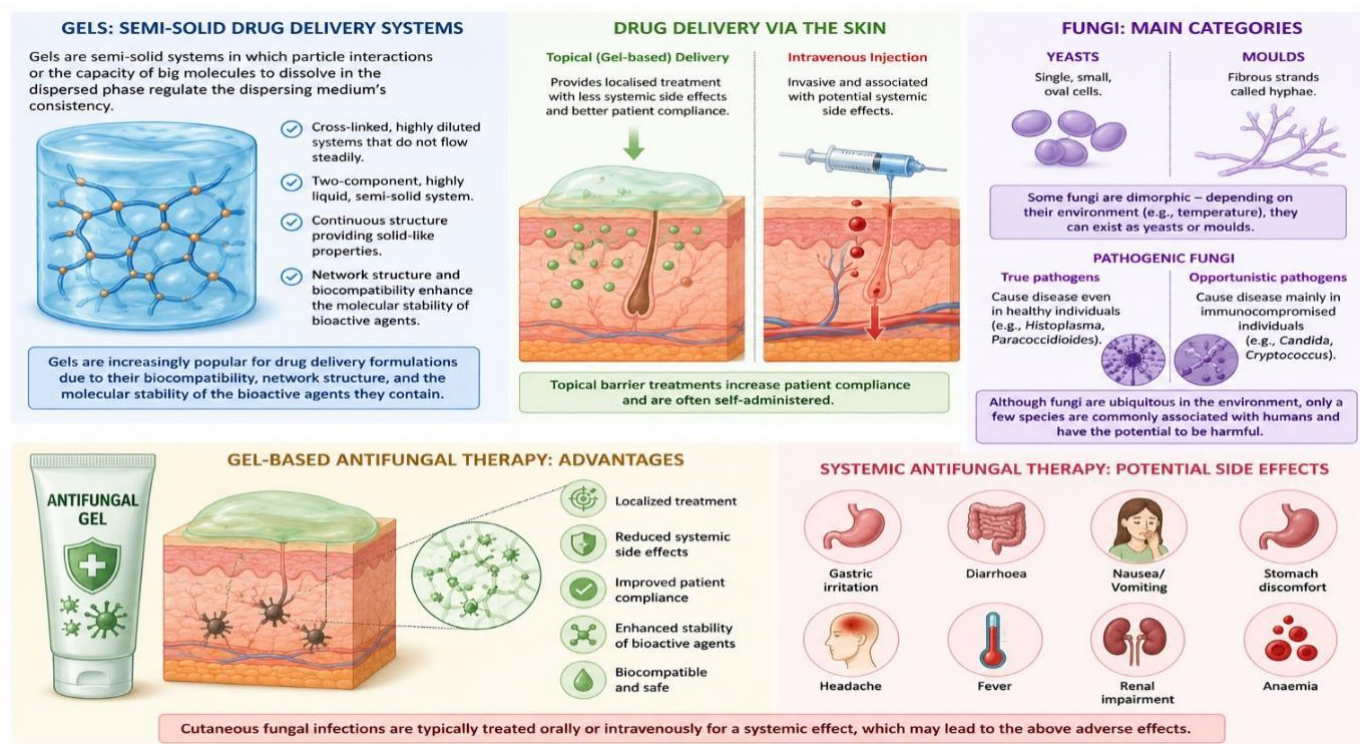


Figure 1: Drug delivery from various dosage form

Therefore, the best method for administering medications that go through first-pass metabolism is topical drug delivery. In general, it works well against fungal infections⁹. In order to administer medications topically to the skin, ointments, lotions, and gels are spread and rubbed directly onto an external body surface. The medication must penetrate and distribute throughout the skin in order to have a therapeutic impact^{10,11}. The drug's molecular characteristics and the biologic tissue's characteristics determine the rate and degree of transport. Targeting the infection site, improving treatment efficacy, lowering the risk of systemic adverse effects, and increasing patient compliance are all benefits of topical treatment for fungal infections¹².

Azoles, allylamines, echinocandins, griseofulvin, and flucytosine are the five main types of antifungal drugs that are commonly used in clinical settings to treat fungal infections. Azole resistance is well known, despite the fact that the path to modern treatment has not been

without issues and complications, especially drug resistance, which has not significantly affected the now used antifungals with the exception of superficial Candidiasis bacterial infections¹³.

2. Fungal Infections of the Skin and Their Causes

Fungal exposure can cause tissue necrosis of the epidermal layers as well as superficial, systemic, and subcutaneous mycosis¹⁴. With the exception of yeast and non-dermatophytes producing protease enzymes, dermatophytes, yeast, and non-dermatophytes all follow the same pathogenic pathway. They always affect the keratin found in human and animal skin, nails, and hair because they use keratin as a source of nutrients, which eventually causes tissue necrosis¹⁵. Dermatophytes can be divided into three main groups based on natural epidemiology: anthropophilic, zoophilic, and geophilic (Table 1).

Table 1. Dermatophytes based on Natural habitat and infection site¹⁶⁻¹⁷

Habitat Group	Fungal Species	Common Infection Site
Anthropophilic	<i>Microsporum audouinii</i>	Scalp
Anthropophilic	<i>Trichophyton concentricum</i>	Body
Anthropophilic	<i>Microsporum ferrugineum</i>	Scalp
Anthropophilic	<i>Trichophyton interdigitale</i>	Foot, groin, nails
Anthropophilic	<i>Trichophyton megninii</i>	Scalp, beard
Anthropophilic	<i>Trichophyton rubrum</i>	Foot, nails, body
Anthropophilic	<i>Trichophyton schoenleinii</i>	Scalp
Anthropophilic	<i>Trichophyton soudanense</i>	Scalp
Anthropophilic	<i>Trichophyton tonsurans</i>	Scalp, body
Anthropophilic	<i>Trichophyton violaceum</i>	body, nails

Zoophilic	Microsporum canis	Scalp, body
Zoophilic	Microsporum distortum	Scalp
Zoophilic	Trichophyton equinum	Scalp
Zoophilic	Microsporum nanum	Scalp, body
Zoophilic	Trichophyton verrucosum	Exposed areas
Geophilic	Microsporum fulvum	Scalp, body

3. Mechanisms of Action and Pharmacodynamics

3.1. Classes of Antifungals and Their Targets

Important classes of antifungals include polyenes, azoles, echinocandins, allylamines like terbinafine 18, and antimetabolites like flucytosine. Polyenes such as amphotericin B (AmB), nystatin, and natamycin were discovered in the 1950s. AmB destabilises and creates pores by binding to ergosterol, an essential component of the fungal cell membrane. It comes in lipid (ABLC lipid complex, liposomal L-AmB) and conventional (deoxycholate, AmB-d) formulations. Lipid formulations have been developed to reduce the toxicity of AmB, particularly the nephrotoxicity associated with the deoxycholate formulation. A meta-analysis found that lipid formulations significantly reduced nephrotoxicity as compared to conventional formulations¹⁹.

Azoles have been divided into two categories since their introduction in the 1960s: Imidazoles like Miconazole and Ketoconazole which are primarily used topically or have limited systemic usage, and Triazoles such as Fluconazole, Itraconazole, Voriconazole, Posaconazole, and Isavuconazole, which are widely used systemically. They stop ergosterol from being formed by blocking the

cytochrome P450-dependent enzyme lanosterol 14 α -demethylase. Membrane function is altered as a result of the accumulation of dangerous methylated sterols and the depletion of ergosterol. Azoles are frequently fungicidal against *Aspergillus* species and fungistatic against yeasts, despite their high risk of drug interactions and potential hepatotoxicity. Isavuconazole is a more contemporary triazole that has been licensed to treat mucormycosis and invasive aspergillosis. It is delivered as the pro-pharmaceutical isavuconazole sulphate. (Figure 2)

Echinocandins such as caspofungin, micafungin, and anidulafungin were introduced in the early 2000s. They function by inhibiting the production of β -(1,3)-D-glucan, an essential structural component of the fungal cell wall, by blocking the enzyme β -(1,3)-D-glucan synthase. They are generally well tolerated, have a better drug interaction profile than azoles, are fungicidal against *Aspergillus* species and fungistatic against *Candida* species, however there have been reports of potential hepatotoxicity. Echinocandins are the first-line treatment for invasive candidiasis, according to most current guidelines.²¹

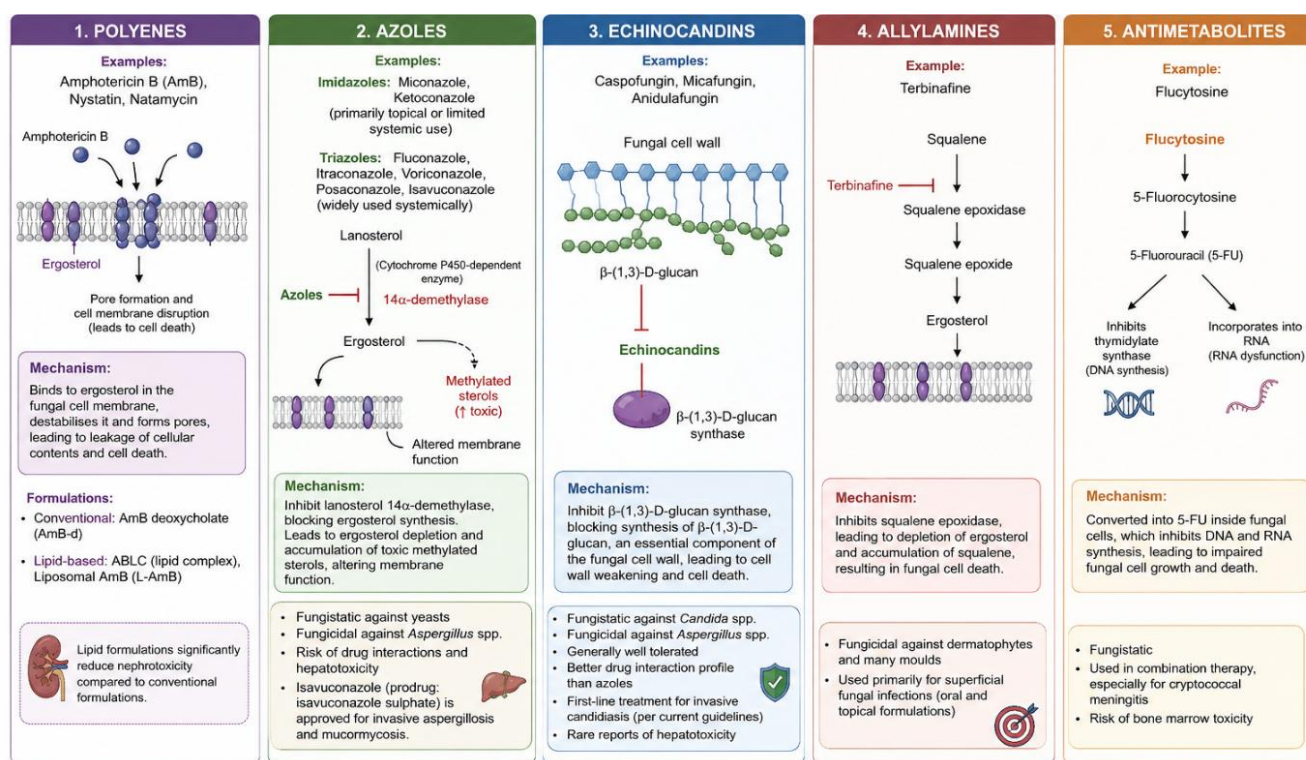


Figure 2: Major classes of antifungal agents: mechanisms of actions, key examples, and clinical consideration

The pyrimidine analogue flucytosine (5-FC) inhibits the synthesis of DNA and RNA after being absorbed by the fungal cell and converted into 5-fluorouracil. It is virtually exclusively used in combination therapy, typically with AmB, to treat cryptococcal meningitis and severe *Candida* infections. However, the potential for myelotoxicity and the rapid development of resistance when taken alone limit its use²².

By inhibiting the enzyme squalene epoxidase, allylamines like terbinafine cause squalene buildup and ergosterol depletion, which changes the function of fungal cell membranes. With a restricted role in invasive fungal infections, their usage is mostly limited to the treatment of dermatophytoses²³.

3.2 Principles of PK/PD Applied to Antifungals

The capacity to attain and sustain sufficient drug concentrations at the infection site long enough to produce the intended effect is just as important to the efficacy of antifungal therapy as the selection of a medication that is effective against the pathogen *in vitro*²⁴.

PK/PD studies aim to identify which pharmacokinetic parameters typically evaluated in serum or plasma best correspond with clinical or microbiological outcome in relation to the pathogen's *in vitro* susceptibility. The lowest medication concentration that, under regulated laboratory circumstances, inhibits apparent fungal growth is known as the Minimum Inhibitory Concentration²⁴. (Figure 3)

Preclinical and clinical studies have identified the most relevant PK/PD indicators for a number of antifungal classes. fAUC is often taken into account because only the free part is active. The AUC/MIC ratio is usually the best indicator of azole efficacy; for fluconazole in candidiasis, a target fAUC/MIC > 25 is linked to a positive outcome²⁵. Since azole activity is time-dependent and concentration-independent once the MIC is exceeded, cumulative exposure (AUC) is a critical consideration. The C_{max}/MIC ratio is believed to be more indicative of the effectiveness of Amphotericin B (AmB), a member of the polyenes, since it shows concentration-dependent fungicidal activity. A higher chance of therapeutic response with liposomal AmB has been associated with a C_{max}/MIC > 40.^{25 26}

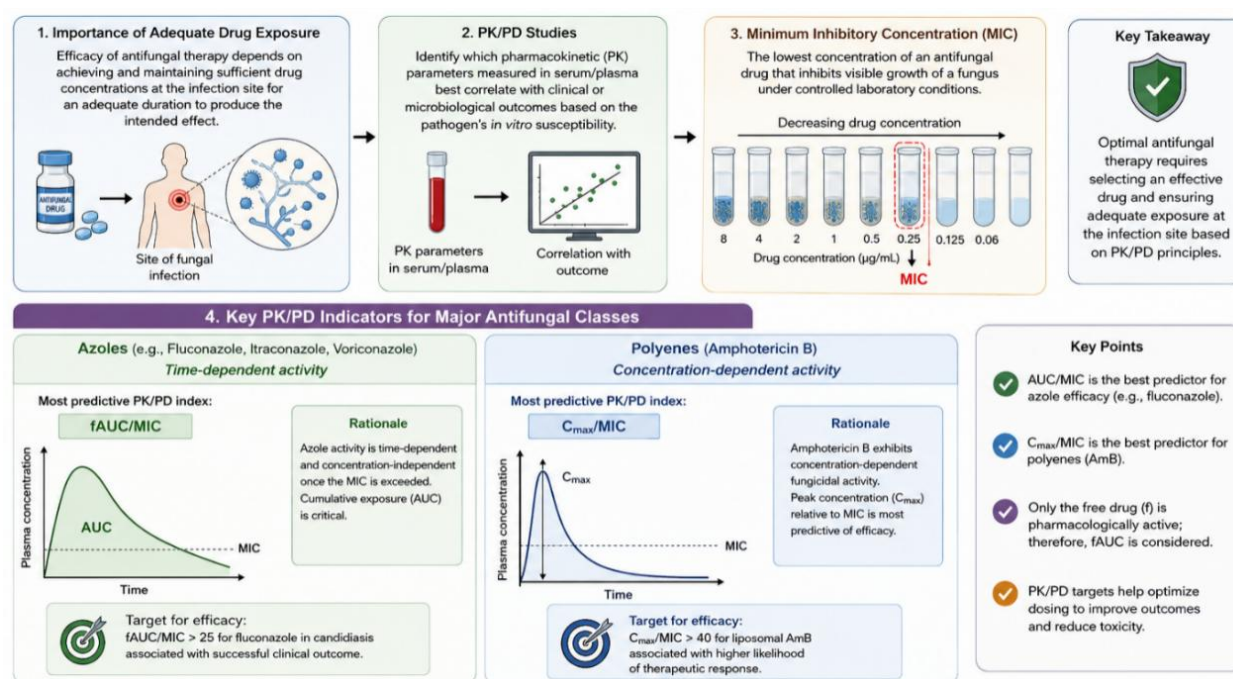


Figure 3: PK/PD principles and key pharmacokinetics/pharmacodynamics (PK/PD) indications in antifungal therapy

Additionally, echinocandins' efficacy against *Candida* species is concentration-dependent²⁶. AUC/MIC and C_{max}/MIC are relevant indices, and efficacy for *Candida albicans* is associated with an f-AUC/MIC ratio of approximately 20 (or 7 for less virulent species). MEC (Minimum Effective Concentration) is occasionally used in place of MIC because *Aspergillus* is fungi-static²⁴. AUC/MIC is linked to the efficacy of flucytosine (5-FC). Establishing clinical susceptibility breakpoints, or MIC

values that distinguish curable from resistant microorganisms, and optimising dosages are made possible by an understanding of these PK/PD indicators. Tissue distribution and plasma protein binding are two pharmacokinetic factors that are essential to the effectiveness of antifungals^{23,24,22}.

A comparative summary of the main characteristics of the antifungal classes is given in Table 2.

Table 2. Antifungal classes, Targets Mechanism and resistance²⁵⁻³¹.

Antifungal Class	Mode of Action	Activity	Primary PK/PD Index	Resistance Mechanisms
Azoles	Blocks ergosterol synthesis leading to defective cell membrane	Fungistatic: <i>Candida</i> , <i>Aspergillus</i> , <i>Cryptococcus</i> (variable)	AUC/MIC	Target enzyme mutation, increased efflux pumps
Polynes	Binds ergosterol and forms pores in membrane	Fungicidal: Broad spectrum including <i>Candida</i> , <i>Aspergillus</i>	Cmax/MIC	Reduced ergosterol content, rare resistance
Echinocandins	Inhibits cell wall synthesis	Fungicidal vs <i>Candida</i> , static vs <i>Aspergillus</i>	AUC/MIC, Cmax/MIC	FKS gene mutations
Allylamines	Blocks ergosterol synthesis, increases squalene	Fungicidal: Dermatophytes	Not clearly defined	Enzyme mutation or overexpression
Flucytosine	Converted to active form inhibiting nucleic acid synthesis	Fungistatic: <i>Candida</i> , <i>Cryptococcus</i>	Time > MIC	Mutation in metabolic enzymes

4. Clinical Applications

The treatment of invasive fungal infections especially invasive candidiasis necessitates a prompt and focused strategy based on the pathogen's identification, evaluation of its antifungal susceptibility, and the clinical features of the patient, including the infection site, immune status, comorbidities, and concurrent treatments. Antifungal selection is greatly influenced by prompt and precise diagnosis. In addition to facilitating the quick start of the right treatment, early detection of the fungal infection and its susceptibility profile lowers toxicity, minimises needless exposure to broad-spectrum medications, and aids in preventing the formation of resistance. Empirical decisions are based on host risk factors and epidemiological data in the absence of microbiological proof, but therapy can frequently be de-escalated or modified appropriately once diagnostic information is available ³².

Evidence-based recommendations for the treatment of major clinical syndromes are provided by the Infectious Diseases Society of America and other international guidelines. For most adult patients with candidaemia, echinocandins are recommended as empirical and targeted first-line therapy due to their fungicidal activity against most *Candida* species, including *C. glabrata*, which is often resistant to fluconazole, and their favourable tolerability profile. Rezafungin is a new generation echinocandin that is given once a week and was recently approved for the treatment of invasive candidiasis. It may have benefits in terms of less frequent administration and has demonstrated efficacy comparable to that of caspofungin.³⁴

Fluconazole is the preferred medication for de-escalation once the isolate is found to be susceptible, and it continues to be a first-line treatment for clinically stable individuals who have not recently been exposed to azoles and have a low chance of infection with resistant species. Amphotericin B lipid formulations are advised for infections of the central nervous system, endocarditis, osteomyelitis, and species resistant to

azole and echinocandin, as well as in situations where the other classes are ineffective or intolerable. If the isolate is susceptible, voriconazole can be used as a de-escalation treatment for some infections or for some less prevalent species.

The frequent multiresistance of *Candida auris* infections makes managing them difficult. Although echinocandins are typically thought of as the first-line treatment for invasive infections, susceptibility testing is crucial due to the emergence of resistance. An alternative is amphotericin B in lipid formulations. Research is being done on combination treatments and novel medications such fosmanogepix and ibrexafungerp. Oral triterpenoid ibrexafungerp has demonstrated in vitro efficacy against isolates of *C. auris* that are resistant to echinocandin ³⁵. Phase 2 studies have demonstrated the therapeutic efficacy of fosmanogepix in patients with *Candida auris* ³⁶. In the absence of metastatic foci, the course of treatment for invasive candidiasis typically lasts two weeks following the first negative blood culture and the remission of symptoms and signs of infection. It is very advised to remove central venous catheters.

Patients with impaired immune systems, such as those undergoing transplantation or neutropenia, are more vulnerable to invasive aspergillosis (AI), which is mostly caused by *Aspergillus fumigatus*. Voriconazole is the first-line treatment for invasive pulmonary aspergillosis and has been shown to be effective in treating disseminated infections of the central nervous system ³⁷. Isavuconazole is a first-line substitute that has been demonstrated to be noninferior to voriconazole and may have a superior tolerability profile with fewer side effects. Another first-line approach is lipid formulations of AmB (L-AmB), particularly in environments where azole resistance or azole contraindications/intolerance are highly prevalent ³⁸.

While echinocandins alone are not advised for the primary treatment of AI, they may be useful in combination or in some situations. For resistant strains, novel agents like fosmanogepix and olorofim show

promise. Posaconazole is advised for prevention in high-risk individuals, such as those with GVHD following allogeneic transplantation or acute myeloid leukaemia induction. In certain situations, micafungin or voriconazole may also be utilised. Immunocompromised individuals or diabetics with ketoacidosis are frequently afflicted with mucormycosis, an aggressive infection brought on by fungus of the order Mucorales ³⁹.

Empirical, pre-emptive, and targeted therapies are therapeutic options for IFIs that are tailored to host variables, clinical suspicion, and diagnostic certainty. Table 3 summarises suggested first-line and alternate treatments for severe invasive fungal infections. Empiric treatment is initiated before microbiologic confirmation of fungal infection in high-risk patients, including those with persistent febrile neutropenia. Echinocandins (such as caspofungin) are often used for suspected

candidiasis, whereas voriconazole, isavuconazole, or liposomal amphotericin B, for example, are used for suspected aspergillosis. Research has demonstrated that in patients with persistent fever during neutropenia, empiric treatment can lower the prevalence of reported fungal infections ^{40,41}.

Using biomarkers like galactomannan and β D-glucan in conjunction with imaging methods, pre-emptive therapy aims to detect IFI early and start treatment before microbiological confirmation. With the benefit of lowering the needless use of antifungals, this approach has demonstrated efficacy comparable to empiric therapy ⁴². Targeted therapy, which is guided by antifungal susceptibility testing and enables optimised drug selection, dose modifications, or less toxic drugs, becomes the preferred strategy once a fungal pathogen has been identified ^{43 44 45}.

Table 3. Key invasive fungal infections, suggested first-line therapy, and alternative (backup) treatments are reviewed.

Infection	Preferred Initial Treatment	Alternative Therapeutic Options
Crypto coccal meningitis	Induction therapy with Amphotericin B conventional or lipid formulation plus Flucytosine followed by Fluconazole for consolidation and maintenance	Fluconazole alone when Flucytosine is unavailable, or Amphotericin B monotherapy in selected situations
Invasive candidiasis	An echinocandin such as Caspofungin or Micafungin is generally recommended as the initial treatment	Fluconazole for clinically stable patients with susceptible isolates or Liposomal Amphotericin B when echinocandins cannot be used
Invasive aspergillosis	Voriconazole is preferred, with Isavuconazole as another recommended first-line option	Liposomal Amphotericin B when azoles are unsuitable Posaconazole for salvage therapy
Mucormycosis	Liposomal Amphotericin B is regarded as the treatment of choice	Posaconazole or Isavuconazole when Amphotericin B is unsuitable or for step-down therapy
Pneumocystis jirovecii pneumonia	Trimethoprim Sulfamethoxazole (TMP-SMX) is the standard therapeutic regimen	Pentamidine, Atovaquone, or Dapsone plus Trimethoprim for patient's intolerant to TMP-SMX
Disseminated histoplasmosis	Initial treatment with Liposomal Amphotericin B followed by oral Itraconazole	Amphotericin B deoxycholate if lipid formulations are unavailable; Fluconazole may be considered despite lower efficacy

5. Antifungal Agents from Natural Products

Compounds found in plants, bacteria, fungi, and other natural sources are known as natural antifungals ^{46,54}. These substances have developed to defend their host organisms from harmful microorganisms, such as fungus, and have demonstrated promise as treatments for fungal infections in humans. The identification of novel antifungal chemicals from nature has been made easier by recent developments in genomics, molecular

biology, and natural product chemistry. Lower toxicity, less of an impact on the environment, and the ability to target numerous fungus species at once are just a few benefits of using natural antifungals. Certain chemicals have been reported to have activity against phytopathogens and amphibian pathogens, despite the fact that the majority of research in this field has concentrated on human fungal pathogens. Table 4 lists some of the possible natural antifungals' sources.

Table 4. Natural materials may be used to generate antifungal compounds with various antifungal mechanisms ^{46,55}.

Source	Compound Class	Representative Compounds	Antifungal Activity/Mode of Action	Main Fungal Targets
Marine ecosystems	Alkaloids	Zamamidine D, Theonellamide G	Combines with ergosterol in the fungus membrane, causing damage and integrity loss.	<i>Candida albicans</i> , <i>Aspergillus niger</i>
Marine ecosystems	Polyketides	Dicitrinone E, Plakortide F Acid	Disrupts vital cellular functions necessary for fungal development by altering the intracellular calcium balance.	<i>Candida albicans</i>
Marine ecosystems	Peptides	Rhodopeptins	Causes fungal cell death by damaging membranes and impairing mitochondrial activity.	<i>Cryptococcus neoformans</i>
Terrestrial plants	Essential oils	Cymbopogon (lemongrass), <i>Cyperus</i> species	decreases the growth of biofilms and jeopardises the integrity of fungal cell membranes	<i>Aspergillus flavus</i>
Terrestrial plants	Secondary metabolites	<i>Arcangelisia flava</i>	Suppresses fungal growth by inhibiting key metabolic enzymes	<i>Candida</i> species
Amphibian skin microbiome	Bacterial metabolites	Violacein produced by <i>Janthinobacterium lividum</i>	Prevents normal fungal cell wall formation, thereby restricting fungal proliferation	<i>Batrachochytrium dendrobatidis</i>

6. Novel Therapeutic Approaches and New Antifungal Targets

6.1 The Cell Barrier as a Basis for the Development of Antifungals

6.1.1. Standard Mannosidases and Cell Wall Integrity

The fungal cell wall is a desirable target for antifungal medications since it is an essential component for preserving fungal integrity and virulence which are produced by the *C. albicans* mannosidases genes Dfg5 and Dcw1 and are crucial for preserving cell wall integrity and normal hyphal development. These enzymes play a role in the covalent bonding of cell wall glycoproteins and contribute to hyphal formation, a critical pathogenic feature of *Candida albicans*. According to recent research, faulty cell wall assembly caused by mutations in dfg5 and dcw1 makes fungal cells vulnerable to antifungal medications ⁵⁶.

6.1.2. Chitin Synthases

Chitin synthases (Chs) produce chitin, a crucial part of the fungal cell wall. The several chitin synthases (Chs1, Chs2, Chs3, and Chs8) found in *Candida albicans* cooperate to preserve the integrity of the cell wall. Because chitin synthases are crucial to fungal survival, they are a prospective target for antifungal research. Fungal growth is inhibited when chitin synthase inhibitors disrupt chitin production, opening the door for new antifungal drugs.⁵⁷ Nikkomycin showed some in vitro efficacy against *Blastomyces dermatitidis*, but its performance mostly depended on its synergistic actions with echinocandins, especially for *A. fumigatus* and *Candida albicans*. For *Candida albicans*, *Candida*

immitis, and *Candida neoformans*, polyoxins are often ineffective or fungistatic ^{58,59,60,61}.

6.2 Biofilm Inhibition

One of the main virulence factors of fungal infections, especially *Candida albicans*, is biofilm development. By creating protective extracellular matrices and decreasing the effectiveness of antifungal medications, biofilms provide resistance to antifungal therapies. As a result, preventing biofilm development has become a cutting-edge antifungal tactic. A unique class of diazaspiro-decane structural analogues that can prevent *C. albicans* biofilm formation without impairing fungal growth was discovered by Pierce et al. These substances are antivirulence agents that target the structure of biofilms and stop fungi from colonising surfaces like medical equipment. To increase the effectiveness of conventional antifungals, biofilm inhibitors can be added. For instance, using small compounds to interfere with the production of biofilms can enhance medication penetration ⁶².

6.3. Suppression of Hyphal Morphology

For *Candida albicans*, hyphal morphogenesis is a crucial virulence mechanism that promotes biofilm development. Romo *et al.* created a number of small compounds that effectively lessen the pathogenicity of *Candida albicans* by selectively blocking the yeast-to-hypha transition. By inhibiting filamentation and decreasing biofilm formation, these compounds target the signalling pathways that regulate hyphal growth, such as the cAMP and MAPK pathways. N-[3-(allyloxy)-phenyl]-4-methoxybenzamide, the lead drug, showed in vivo effectiveness in invasive candidiasis models in mice ⁶³. These compounds provide a novel antifungal strategy

that lessens fungal pathogenicity without encouraging treatment resistance by focusing on virulence factors including hyphal development.

6.4. Targeting Fungal Mitochondrial Function

Mitochondria are a promising target for antifungal therapy because they are essential for the production of energy and the control of metabolism in fungal cells. Fungal bioenergetics can be disrupted and cell death can be induced by targeting mitochondrial activity. Apart

from T-2307 (refer to Section 2.2), it has been demonstrated that isothiocyanates, specifically benzyl isothiocyanate (BITC), have a promising antifungal action by either disrupting the fungal mitochondrial membrane potential or inhibiting mitochondrial oxidative phosphorylation^{64,65,66}. Fungal infections can be successfully treated while lowering the risk of harm in humans by focusing on mitochondrial processes unique to fungi⁶⁶. (Figure 4)

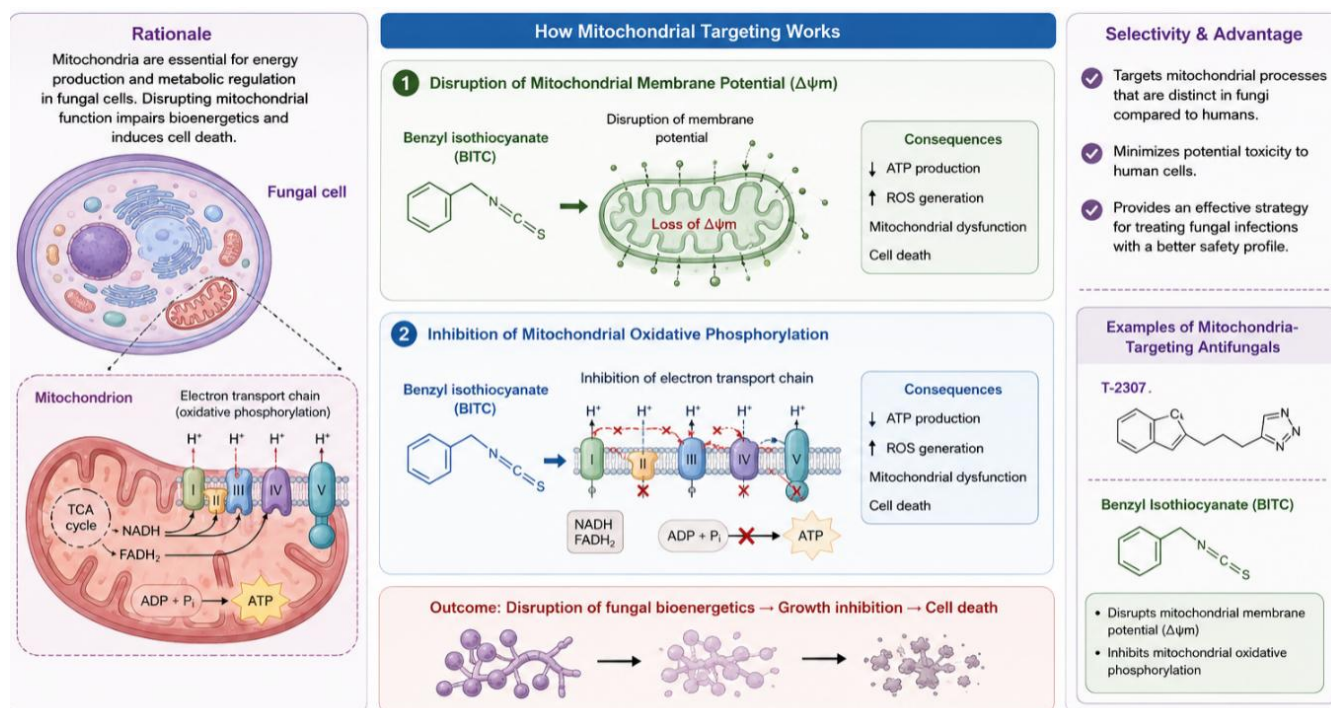


Figure 4: Targeting Fungal Mitochondria: A Promising Strategy for Antifungal Therapy

6.5. Inhibition of Heat Shock Protein (Hsp90)

A molecular chaperone called heat shock protein 90 controls antifungal resistance pathways and fungal stress reactions. Hsp90 is a good target for overcoming resistance since blocking its function makes fungal cells more susceptible to antifungal medications. It has been demonstrated that Hsp90 inhibitors increase the effectiveness of azoles and echinocandins, especially against drug-resistant strains of *Aspergillus fumigatus* and *Candida albicans*. Hsp90 inhibitors decrease fungal cell viability under drug-induced stress by interfering with fungal stress tolerance^{67,68}.

Conclusion

Due to growing antifungal resistance, a lack of medication variety, and side effects from systemic treatments, managing fungal infections remains extremely difficult. This review emphasises how crucial it is to use cutting-edge tactics to improve treatment results. Gel-based formulations show promise as a topical antifungal delivery method that minimises systemic toxicity while offering localised activity, enhanced drug penetration, and increased patient adherence. Concurrently, natural products help the development of alternative or supplemental therapies by providing a rich and mostly unexplored reservoir of

bioactive chemicals with distinct antifungal actions. There are new strategies to fight resistant fungal strains by focusing on unique pathways such cell wall integrity, biofilm formation, hyphal transition, mitochondrial function, and stress response systems. Programs for antifungal stewardship are also essential for maximising medication use and halting the emergence of resistance. In conclusion, a multidisciplinary strategy that incorporates cutting-edge drug delivery methods, natural product research, and novel molecular targets has great potential to enhance the effectiveness, safety, and long-term viability of antifungal treatments.

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