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Targeted Nanomedicines for the Treatment of Fungal Infections: Advances, Mechanisms, and Clinical Prospects

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ABSTRACT

Invasive and superficial fungal infections represent a growing global health challenge, particularly among immunocompromised individuals, critically ill patients, and those receiving chemotherapy or organ transplantation. Despite the availability of antifungal agents such as polyenes, azoles, echinocandins, and allylamines, therapeutic outcomes remain suboptimal due to drug toxicity, poor solubility, limited tissue penetration, emergence of resistance, and biofilm-associated refractoriness. Targeted nanomedicine has emerged as a promising strategy to enhance antifungal efficacy while minimizing systemic toxicity. Nanocarriers—including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, metallic nanoparticles, and Nano emulsions—offer improved pharmacokinetics, controlled drug release, enhanced bioavailability, and site-specific targeting. Surface functionalization with ligands such as antibodies, peptides, and carbohydrates enables active targeting toward fungal cell wall components and infected tissues. Additionally, nanosystems demonstrate superior penetration into fungal biofilms, overcoming a major barrier to conventional therapy. This review discusses the pathophysiology of fungal infections, limitations of current antifungal therapy, design principles of antifungal nanomedicines, targeting strategies, anti-biofilm approaches, translational progress, safety concerns, and future directions. Targeted nanomedicine represents a transformative approach that may redefine antifungal pharmacotherapy in the coming decade.

Keywords: Antifungal resistance; Targeted drug delivery; Nanocarriers; Liposomal amphotericin B; Fungal biofilm; Nanotechnology; Mycosis therapy.

1. INTRODUCTION

Fungal infections range from superficial cutaneous conditions to life-threatening systemic mycoses. Opportunistic fungal pathogens such as *Candida albicans*, *Candida auris*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* are increasingly responsible for morbidity and mortality in hospitalized and immunocompromised patients. Individuals with diabetes, malignancies, HIV infection, neutropenia, organ transplantation, or prolonged corticosteroid use are particularly susceptible.

The global incidence of invasive fungal infections has risen significantly due to:

- Increased survival of immunocompromised patients
- Widespread use of broad-spectrum antibiotics
- ICU-related device-associated infections
- Emerging multidrug-resistant strains

Mortality rates in invasive candidiasis and aspergillosis may reach 30–60%, and higher in disseminated infections.

Despite therapeutic advancements, conventional antifungal drugs suffer from serious drawbacks including nephrotoxicity, hepatotoxicity, poor aqueous solubility, erratic oral bioavailability, and limited penetration into sanctuary sites such as the central nervous system and biofilms. These limitations highlight the urgent need for improved drug delivery strategies.

Nanomedicine offers innovative solutions by enabling targeted delivery, sustained release, improved solubility, and reduced toxicity. Over the past two decades, antifungal nanocarriers have evolved from simple liposomal systems to highly engineered multifunctional platforms capable of active targeting and biofilm disruption.

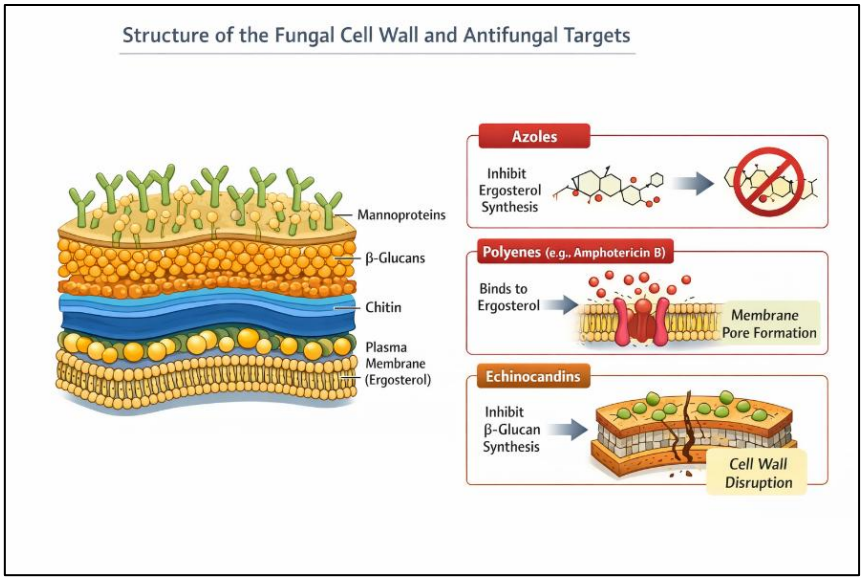

Fig 1: Structure of the Fungal Cell Wall and Antifungal Targets

2. Pathogenesis of Fungal Infections and Therapeutic Barriers

2.1 Structure of the Fungal Cell Wall

The fungal cell wall is a dynamic and complex structure primarily composed of:

- β-glucans
- Chitin
- Mannoproteins
- Glycoproteins

This unique composition provides selective targets for antifungal therapy but also contributes to drug resistance.

2.2 Fungal Biofilms

Biofilms are structured microbial communities embedded in an extracellular polymeric substance (EPS). They are commonly formed on:

- Catheters
- Prosthetic devices
- Implants
- Mucosal surfaces

Biofilm-associated fungal cells may demonstrate up to 1000-fold increased resistance to antifungal drugs compared to planktonic cells.

3. Limitations of Conventional Antifungal Therapy

Table 1. Major Classes of Antifungal Drugs and Their Limitations

Drug Class	Examples	Mechanism of Action	Major Limitations
Polyenes	Amphotericin B	Binds ergosterol → membrane pore formation	Nephrotoxicity, infusion reactions
Azoles	Fluconazole, Itraconazole	Inhibit ergosterol synthesis	Resistance, hepatotoxicity
Echinocandins	Caspofungin	Inhibit β-1,3-glucan synthesis	Poor oral bioavailability
Allylamines	Terbinafine	Inhibit squalene epoxidase	Limited systemic use

Key problems:

- Poor water solubility
- Frequent dosing
- Toxicity to host cells
- Emergence of resistant strains
- Inadequate biofilm penetration

4. Rationale for Nanomedicine in Antifungal Therapy

Nanocarriers typically range from 10–200 nm in size. Their advantages include:

- Enhanced solubility of hydrophobic drugs
- Prolonged systemic circulation
- Reduced off-target toxicity
- Controlled and sustained drug release
- Passive and active targeting capabilities
- Improved penetration into infected tissues

5. Types of Nanocarriers in Antifungal Therapy

5.1 Liposomes

Liposomes are phospholipid vesicles capable of encapsulating hydrophilic and hydrophobic drugs. Liposomal amphotericin B has significantly reduced nephrotoxicity compared to conventional formulations.

Advantages:

- Biocompatibility
- Reduced renal toxicity
- Enhanced macrophage uptake

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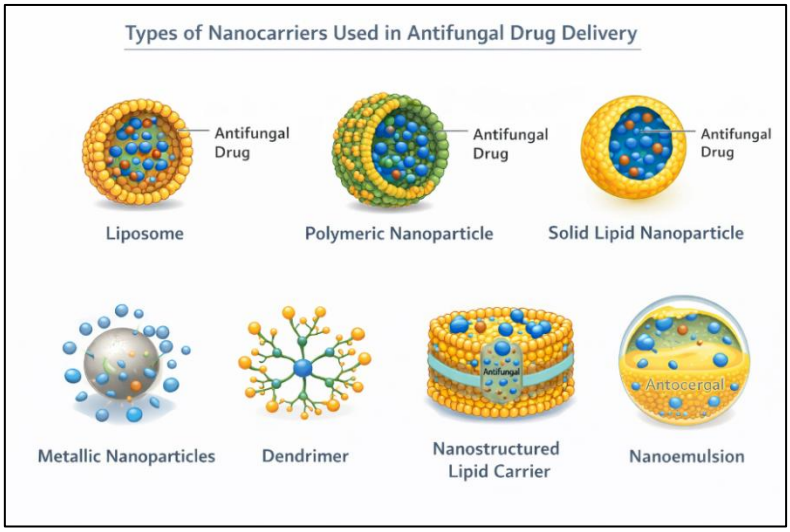

Fig 2: Types of Nanocarriers Used in Antifungal Drug Delivery

5.2 Polymeric Nanoparticles

Common polymers:

- PLGA
- Chitosan
- PEGylated polymers

Benefits:

- Sustained release
- Surface modification for targeting
- Enhanced stability

Applications include fluconazole-loaded and itraconazole-loaded nanoparticles for systemic and topical therapy.

5.3 Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

These are particularly useful for dermal and transdermal delivery.

Advantages:

- Occlusive properties
- Improved skin hydration
- Enhanced penetration

5.4 Metallic Nanoparticles

Examples:

- Silver nanoparticles

- Gold nanoparticles
- Zinc oxide nanoparticles

Mechanism:

- Generation of reactive oxygen species
- Disruption of fungal membranes
- Protein denaturation

These nanoparticles show promising anti-biofilm activity.

5.5 Dendrimers

Highly branched macromolecules with multiple functional groups.

Advantages:

- High drug loading
- Multivalent interactions
- Targeted functionalization

5.6 Nanoemulsions

Useful in:

- Ocular fungal infections
- Topical candidiasis

Benefits:

- Increased solubility
- Improved penetration
- Enhanced stability

6. Targeting Strategies in Antifungal Nanomedicine

6.1 Passive Targeting

Based on enhanced permeability at infected sites due to inflammation.

6.2 Active Targeting

Surface ligands attached to nanoparticles improve specificity.

Table 2. Ligand-Based Targeting Strategies

Ligand	Target	Therapeutic Benefit
Mannose	Macrophage receptors	Enhanced uptake
Antibodies	Fungal surface antigens	Selective targeting
Lectins	Biofilm matrix	Biofilm disruption
Chitin-binding peptides	Fungal cell wall	Increased specificity

7. Nanomedicine Against Fungal Biofilms

Nanoparticles can:

- Penetrate EPS matrix
- Deliver high local drug concentration
- Disrupt quorum sensing
- Generate ROS

Chitosan nanoparticles and silver nanoparticles demonstrate strong anti-biofilm effects.

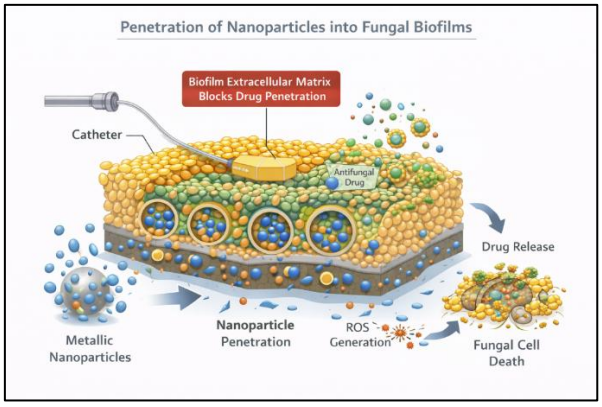

Fig 3: Penetration of Nanoparticles into Fungal Biofilms

8. Stimuli-Responsive Nanocarriers

These release drugs in response to:

- pH changes
- Enzymes
- Temperature
- Redox environment

Infected tissues often exhibit acidic pH, enabling pH-sensitive drug release.

9. Clinical and Commercial Progress

Table 3. Approved and Advanced Nanomedicine Formulations

Formulation	Drug	Status	Advantage
Ambisome	Amphotericin B	Approved	Reduced nephrotoxicity
Abelcet	Amphotericin B lipid complex	Approved	Improved safety
Fungisome	Amphotericin B liposome	Marketed (India)	Cost-effective

Clinical translation is ongoing for polymeric and metallic nanoparticle systems.

10. Safety and Toxicological Considerations

Potential concerns:

- Reticuloendothelial system accumulation
- Long-term tissue deposition
- Immunogenic reactions
- Manufacturing scale-up challenges

Thorough in vivo and clinical studies are necessary before widespread clinical adoption.

11. Regulatory and Translational Challenges

Challenges include:

- Complex manufacturing
- Batch reproducibility
- Regulatory approval pathways
- Long-term toxicity data
- High production costs

Regulatory agencies require comprehensive characterization of nanoparticle size, charge, stability, and biodistribution.

12. Future Perspectives

Future directions include:

- AI-driven nanoparticle design
- CRISPR-based antifungal gene targeting
- Theranostic nanoparticles (diagnosis + therapy)
- Combination therapy nanocarriers
- Personalized antifungal nanomedicine

Integration of nanotechnology with immunotherapy may further enhance outcomes.

6. CONCLUSION

Targeted nanomedicine represents a transformative strategy in antifungal therapy. By overcoming solubility limitations, reducing toxicity, improving tissue penetration, and enabling active targeting, nanocarriers address many shortcomings of conventional antifungal drugs. Anti-biofilm activity and stimuli-responsive systems further enhance therapeutic potential. Although regulatory and safety challenges remain, continued research and translational efforts are expected to expand the clinical utility of antifungal nanomedicine in the near future.

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