

# Innovations in Topical Antifungal Therapy: A Comprehensive Review of Natural Compounds, Nanotechnology, and Delivery Systems

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## Abstract

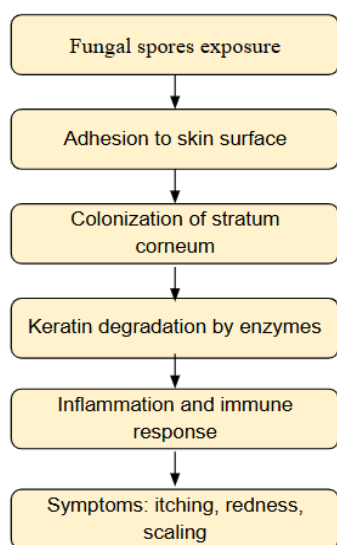
Fungal infections represent a widespread global health concern, ranging from superficial skin conditions to more severe systemic infections, particularly among immunocompromised individuals. Conventional antifungal therapies, although widely used, are often associated with several limitations, including poor aqueous solubility, inadequate skin penetration, low bioavailability, and potential adverse effects. These challenges can lead to suboptimal therapeutic outcomes and reduced patient compliance. In recent years, there has been growing interest in the development of advanced topical antifungal strategies aimed at overcoming these limitations. This review highlights recent progress in topical antifungal therapy, with a particular focus on the use of natural bioactive compounds, nanotechnology-based drug delivery systems, and innovative formulation approaches. Emerging systems such as liposomes, ethosomes, solid lipid nanoparticles, and emulgels have demonstrated significant potential in enhancing drug stability, permeability, and controlled release. Furthermore, the incorporation of essential oils, plant-derived compounds, biopolymers, and probiotic-based systems offers a promising avenue for improving antifungal efficacy while minimizing toxicity and enhancing patient acceptability. Overall, these integrated approaches provide a novel and effective platform for the management of fungal infections. Continued research and clinical validation are essential to translate these advancements into routine therapeutic applications and improve patient outcomes.

**Keywords:** Topical antifungal therapy; Nanotechnology; Drug delivery systems; Emulgel; Antifungal resistance; Skin infections

## I. Introduction

Fungal infections such as athlete's foot, yeast infections, and seborrheic dermatitis are common skin disorders affecting a large proportion of the global population, particularly among immunocompromised individuals [1,3]. These infections are primarily caused by dermatophytes, yeasts, and non-dermatophytic molds, and are associated with significant morbidity, discomfort, and reduced quality of life (Figure 1). The prevalence of superficial mycoses has been increasing in recent years due to factors such as rising diabetes incidence, immunosuppressive therapies, poor hygiene conditions, and climatic variations that favor fungal growth [1,2]. Traditional antifungal creams remain the primary treatment option; however, their effectiveness is often limited. These limitations arise due to poor skin penetration, development of antifungal resistance, and inadequate retention of the drug at the site of infection [2,4]. Additionally, many conventional antifungal agents exhibit low aqueous solubility and stability issues, which further compromise their therapeutic performance. Prolonged treatment duration and associated side effects may also reduce patient compliance, ultimately affecting treatment outcomes [4,5]. In response to these challenges, significant research efforts have been directed toward the development of advanced drug delivery systems and novel formulation strategies. Recent advancements in drug delivery and formulation strategies have shown promising potential in overcoming these limitations. Approaches such as nanocarrier-based systems, essential oils, emulgels, and other natural agents are being increasingly explored to enhance therapeutic efficacy and improve patient outcomes [5-7]. Nanotechnology-based delivery systems, including liposomes, ethosomes, transfersomes, and solid lipid nanoparticles, have demonstrated the ability to improve drug solubility, enhance skin permeation,

and provide controlled and targeted drug release. Similarly, natural compounds such as essential oils and plant extracts have gained attention due to their inherent antifungal properties, biocompatibility, and reduced risk of adverse effects. In parallel, innovative formulation approaches such as emulgels and hydrogels have been developed to optimize drug delivery and patient acceptability. This review aims to provide a comprehensive overview of recent advancements in topical antifungal therapy, with a particular focus on natural compounds, nanotechnology-enabled drug delivery systems, and modern formulation strategies. Furthermore, the review highlights current challenges, evaluation methods, and future prospects to provide insights into the development of more effective and patient-friendly antifungal treatments.



**Figure 1. Basic progression of superficial fungal infection on the skin.**

## II. Natural Compounds as Antifungal Agents

Essential oils and herbal extracts, such as tea tree, clove, thyme, sage, and palmarosa, are widely recognized for their potent antifungal properties [8–10]. These bioactive compounds exert their effects primarily by disrupting fungal cell membranes and inducing oxidative stress through the generation of reactive oxygen species [9,10]. For instance, clove oil has been reported to inhibit the growth of *Trichophyton mentagrophytes* in a dose-dependent manner [11]. Similarly, palmarosa oil-based formulations have demonstrated significant efficacy against *Candida albicans* in experimental studies [10]. Polyherbal and plant-based formulations have also gained considerable attention in antifungal therapy. Medicinal plants such as *Ocimum sanctum* (Tulsi), *Azadirachta indica* (Neem), and *Alpinia galanga* have been incorporated into topical formulations showing notable antifungal activity [12,13]. Another promising natural product is Dragon’s Blood, derived from *Dracaena cinnabari*, which exhibits broad-spectrum antifungal properties when formulated in suitable delivery systems [10]. These natural agents are often preferred due to their enhanced biocompatibility and better patient acceptability compared to synthetic drugs [8]. Furthermore, probiotic-based antifungal formulations are emerging as a novel therapeutic approach. Preparations containing *Lactobacillus plantarum* have demonstrated the ability to inhibit fungal growth and reduce mycotoxins such as aflatoxin M1 [14]. In addition, these formulations contribute to maintaining the skin microbiome and are generally well tolerated, making them suitable for sensitive skin applications [14]. A comparative analysis between natural antifungal compounds and conventional synthetic agents is summarized in Table 1.

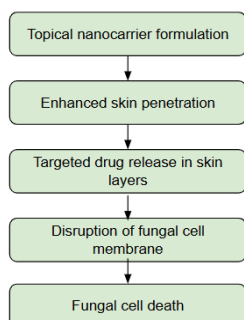
**Table 1. Comparison between natural antifungal compounds and conventional synthetic antifungal agents**

Parameter	Natural Compounds (e.g., Essential Oils, Plant Extracts)	Synthetic Antifungal Agents (e.g., Azoles, Allylamines)
Source	Plant-derived (e.g., tea tree, clove, neem)	Chemically synthesized
Mechanism of Action	Membrane disruption, oxidative stress induction	Inhibition of ergosterol synthesis
Efficacy	Moderate to high (varies with compound and formulation)	High and well-established

Safety Profile	Generally safer, fewer side effects	May cause irritation, toxicity with prolonged use
Resistance Development	Lower risk due to multi-target action	Increasing resistance reported
Stability	Often less stable (volatile, sensitive to light/heat)	More stable and predictable
Standardization	Difficult (variation in composition)	Highly standardized
Cost	Generally low to moderate	Moderate to high
Patient Acceptability	High (natural origin, better tolerance)	Moderate (depends on formulation)
Clinical Evidence	Limited clinical trials	Extensive clinical validation

### III. Nanotechnology-Enabled Drug Delivery

Nanotechnology has emerged as a promising approach in modern drug delivery, particularly for improving the therapeutic efficacy of antifungal agents [5–7]. It is especially beneficial for drugs such as clotrimazole and fluconazole, which exhibit poor solubility and limited skin penetration. Nanocarrier-based systems enhance drug permeation, stability, and targeted delivery at the site of infection [15,16]. Liposomes, composed of phospholipid bilayers, are widely used nanocarriers capable of encapsulating both hydrophilic and lipophilic drugs. Liposomal formulations of antifungal agents such as econazole have demonstrated improved skin retention and enhanced therapeutic efficacy [17]. Ethosomes, which are modified liposomes containing high concentrations of ethanol, facilitate deeper penetration into the skin layers. Ethosomal delivery of fluconazole (Figure 2) has shown promising results, particularly in the treatment of resistant fungal infections [18].



**Figure 2. Nanocarrier-Based Topical Antifungal Delivery**

Transfersomes are highly deformable vesicular systems that can traverse narrow intercellular spaces within the skin. These carriers have been effectively utilized for delivering drugs such as griseofulvin, improving their penetration into deeper skin layers [19]. Niosomes, composed of non-ionic surfactants, offer advantages such as improved stability and cost-effectiveness compared to conventional liposomes. Clotrimazole-loaded niosomes have demonstrated enhanced bioavailability and prolonged drug retention [20]. Solid lipid nanoparticles (SLNs), prepared using solid lipid matrices, provide controlled and sustained drug release. SLN-based formulations of fluconazole have been reported to improve therapeutic outcomes by extending drug action [21]. Additionally, nanoliposomes incorporating natural oils such as tea tree and clove oil have shown enhanced antifungal activity [10]. Nanosponges, particularly those loaded with essential oils like palmarosa, improve solubility and enable controlled drug delivery [15]. Overall, nanotechnology-based delivery systems represent a significant advancement in topical antifungal therapy by enhancing drug efficacy, stability, and patient compliance [5,16]. A comparative overview of commonly used nanocarrier systems in topical antifungal therapy is presented in Table 2.

**Table 2. Comparison of Nanocarrier-Based Drug Delivery Systems in Antifungal Therapy**

Nanocarrier System	Example Drug	Key Advantages	Limitations
Liposomes	Econazole	Biocompatible, enhances skin retention, suitable for both hydrophilic and lipophilic drugs	Stability issues, high production cost
Ethosomes	Fluconazole	Deep skin penetration due to ethanol, improved drug permeability	Skin irritation possible, ethanol-related instability
Transfersomes	Griseofulvin	Highly deformable, penetrates deeper skin layers effectively	Expensive formulation, complex preparation
Niosomes	Clotrimazole	Cost-effective, improved stability, enhanced drug retention	Lower penetration compared to ethosomes
Solid Lipid Nanoparticles (SLNs)	Fluconazole	Controlled drug release, improved stability, good biocompatibility	Limited drug loading capacity
Nanostructured Lipid Carriers (NLCs)	Miconazole	Higher drug loading, reduced drug expulsion, better stability than SLNs	Complex formulation process
Nanosponges	Essential oils (e.g., Palmarosa oil)	Improved solubility, controlled release, enhanced stability	Limited clinical data
Nanoliposomes (with natural oils)	Tea tree oil, Clove oil	Enhanced antifungal activity, synergistic effects	Stability and scalability challenges

#### IV. Topical Formulation Strategies

Topical formulation approaches play a crucial role in enhancing the therapeutic effectiveness of antifungal agents. Various advanced strategies have been developed to improve drug delivery, stability, and patient compliance [22,23]. One such approach is emulgel technology, which combines the properties of emulsions and gels to effectively deliver hydrophobic drugs, including azole antifungals. Emulgels enhance drug spreadability, provide controlled and sustained release, and improve patient acceptability compared to conventional formulations [22]. Clotrimazole-loaded emulgels (Figure 3), for instance, have demonstrated improved antifungal efficacy and better patient compliance [22]. Another promising strategy involves the use of hydrogels and conventional cream bases. These formulations, often prepared using polymers such as polyethylene glycol (PEG) and Carbopol, exhibit excellent moisture retention and controlled drug release properties.

They have been widely used in the treatment of dermatomycosis and onychomycosis, particularly with antifungal agents like miconazole and sertaconazole [23]. Combination topical formulations incorporating antifungal agents with non-steroidal components are also gaining attention. Although steroid-antifungal combinations are effective in reducing inflammation and pruritus, their long-term use may lead to adverse effects. Consequently, newer steroid-free formulations containing multifunctional agents such as bisabolol and piroctone olamine have been developed, offering both anti-inflammatory and antifungal benefits with improved safety profiles [24]. Overall, these advanced formulation strategies contribute significantly to improving therapeutic outcomes, patient adherence, and overall management of fungal skin infections [22,24].

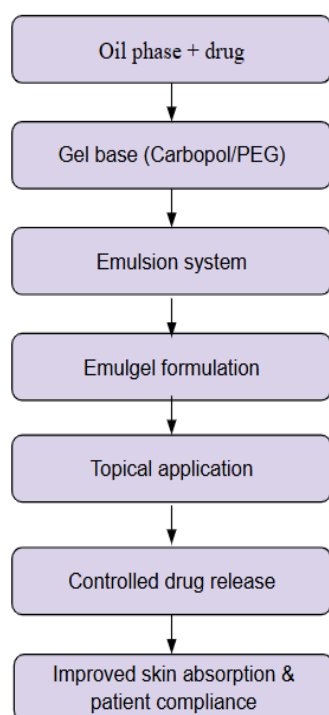


Figure 3. Simple schematic of emulgel formulation used for antifungal drug delivery.

## V. Clinical and Real-World Applications

Recent advancements in antifungal therapy have demonstrated significant potential across clinical and applied domains. In the management of skin infections, nanocarrier-based topical formulations such as nanostructured lipid carriers (NLCs), niosomes, and ethosomes have shown enhanced efficacy against fungal pathogens including dermatophytes and *Candida* species [25,26]. Formulations containing antifungal agents such as clotrimazole and miconazole have been reported to improve therapeutic outcomes, particularly in diabetic and immunocompromised patients, by accelerating symptom relief and reducing recurrence rates [25]. Beyond clinical applications, antifungal strategies have also been explored in agriculture and food preservation. Chitosan-based edible coatings and neem oil emulsions have demonstrated effectiveness in inhibiting the growth of *Aspergillus flavus* in food products such as corn, thereby preventing aflatoxin contamination [27]. These biopolymer-based systems contribute to extending shelf life and maintaining food safety during storage [27]. In environmental applications, green-synthesized zinc oxide nanoparticles have shown promising antifungal and antimicrobial properties. In addition

to inhibiting fungal growth, these nanoparticles are capable of degrading organic dyes and controlling microbial contamination in various environmental settings [28]. Collectively, these applications highlight the versatility of advanced antifungal strategies and their potential to address challenges in healthcare, food safety, and environmental sustainability [25–28].

## VI. Emerging Applications

In addition to conventional therapeutic uses, advanced topical antifungal systems are gaining attention in emerging areas such as transdermal drug delivery, wound healing, and cosmetic dermatology. Nanocarrier-based antifungal formulations are being explored for use in chronic wound management, particularly in diabetic ulcers, where fungal infections can delay healing. Furthermore, the incorporation of antifungal agents into cosmeceutical products, such as anti-dandruff shampoos and medicated skincare formulations, represents a growing commercial application. The integration of antifungal nanomaterials into smart textiles and biomedical coatings is also being investigated to prevent microbial contamination and hospital-acquired infections.

## VII. Evaluation Methods and Regulatory Considerations

Evaluation of topical antifungal formulations involves a series of physicochemical, biological, and clinical assessments to determine their efficacy and stability. Physicochemical characterization includes parameters such as pH, viscosity, spreadability, and stability, which are essential for ensuring formulation quality and patient acceptability [29]. Biological evaluation is performed using *in vitro* and *in vivo* assays to assess antifungal activity. Common methods include determination of minimum inhibitory concentration (MIC), zone of inhibition studies, and animal models to evaluate therapeutic efficacy [30]. In clinical settings, standardized assessment tools such as the Investigator Global Assessment (IGA) and Visual Analog Scale (VAS) are widely used to evaluate treatment outcomes and symptom improvement [31]. Despite these advancements, several challenges remain. Limited long-term safety data for novel nanoformulations continues to be a concern. Additionally, the high cost of production and scalability issues associated with nanotechnology-based systems pose significant barriers to commercialization. Furthermore, there is a pressing need for well-defined regulatory frameworks to

ensure the safety, efficacy, and quality of these advanced delivery systems [5,16].

### VIII. Limitations and Future Prospects

Despite promising outcomes demonstrated in in vitro and in vivo studies, robust clinical evidence supporting the widespread use of advanced antifungal formulations remains limited [25,26]. The translation of these novel systems from laboratory research to clinical application continues to face significant challenges. Future research directions include the development of stimuli-responsive or “smart” drug delivery systems capable of releasing therapeutic agents in response to specific physiological or environmental triggers [32]. Additionally, personalized antifungal therapies based on individual microbiome composition and pathogen-specific characteristics represent an emerging area of interest [33]. There is also a growing emphasis on the development of green nanomaterials that are environmentally sustainable, cost-effective, and scalable for industrial production [28]. Furthermore, the integration of natural bioactive compounds with synthetic drugs and probiotic-based approaches may offer synergistic effects, leading to improved therapeutic outcomes [14,32]. Overall, continued research and well-designed clinical studies are essential to fully realize the potential of these innovative antifungal strategies and to facilitate their successful translation into clinical practice [25,33]. Moreover, the application of artificial intelligence and machine learning in formulation design and drug delivery optimization is expected to accelerate the development of more efficient antifungal therapies. Advances in 3D skin models and organ-on-chip technologies may further improve preclinical evaluation, reducing reliance on animal studies and enhancing translational success.

### IX. Conclusion

In conclusion, the integration of nanotechnology, natural bioactive compounds, and advanced formulation strategies has significantly transformed the landscape of topical antifungal therapy. These innovations address many of the limitations associated with conventional treatments, including poor drug solubility, limited skin penetration, and inadequate therapeutic efficacy. The incorporation of plant-derived oils and extracts, along with nanocarrier-based delivery systems such as liposomes, ethosomes, and solid lipid nanoparticles, has demonstrated enhanced antifungal activity, improved drug stability, and better patient compliance. Moreover, the development of

multifunctional formulations, including emulgels, hydrogels, and combination therapies, has further optimized drug delivery and therapeutic outcomes while minimizing adverse effects. These advancements not only improve the effectiveness of treatment but also contribute to increased safety and user acceptability. Despite these promising developments, several challenges remain, particularly in terms of large-scale production, cost-effectiveness, regulatory standardization, and the availability of long-term clinical data. Addressing these issues through rigorous clinical trials and well-defined regulatory frameworks will be essential for translating these innovations into routine clinical practice. Future research should continue to focus on the development of targeted and personalized antifungal therapies, as well as environmentally sustainable and scalable nanotechnology-based systems. Overall, the convergence of natural compounds, nanotechnology, and innovative formulation approaches holds substantial promise for advancing the management of fungal skin infections and improving patient outcomes worldwide. These advancements also open new avenues for interdisciplinary research, bridging pharmaceuticals, nanotechnology, and biomedical sciences to develop next-generation antifungal therapies.

### Statements and Declarations

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#### Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

#### Ethical Approval

Not applicable.

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