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Review Article

Navigating Effective Therapeutic Strategies for Dermatophytosis

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ABSTRACT

Dermatophytosis, a common fungal skin infection, is a pressing global health issue, especially in underdeveloped regions where resistance to all antifungal classes is prevalent. While tinea infections are superficial, they can spread extensively, leading to significant socio-economic burdens and decreased quality of life. Early diagnosis and intervention are vital to combat resistance and recurrence. However, traditional topical antifungal therapies face challenges in penetrating and being retained by the skin, reducing their effectiveness. This review aims to explore innovative therapeutic strategies to enhance drug delivery for the treatment of dermatophytosis. Nanocarrier systems have emerged as a promising approach, with the potential to facilitate targeted delivery of antifungal drugs through the skin's natural barrier. Various nanocarriers, such as liposomes, niosomes and polymeric nanoparticles, have significant potential for delivering drugs with unstable physiochemical characteristics. Additionally, formulations combining antifungals with hydrating agents may significantly enhance topical therapy efficacy, particularly for recalcitrant infections associated with compromised skin barrier function. This comprehensive review will delve into the epidemiology and pathogenesis of dermatophytosis, with an emphasis on the potential of novel nanocarrier systems and optimized formulations to address the growing challenge of antifungal resistance in resource-limited settings. By exploring these advanced strategies, we can work towards improving treatment outcomes for dermatophytosis and alleviating the burden of these persistent infections.

Keywords: Dermatophytes, Nanocarriers, Diagnosis, Drug resistance, Luliconazole.

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INTRODUCTION

The skin serves as a formidable barrier, protecting the body from various environmental threats, including the invasion of pathogens.[1] The skin comprises three primary layers: the epidermis, dermis and subcutaneous tissue. The epidermis, which forms the outermost layer, consists of multiple cell types, including keratinocytes, which form a protective barrier against pathogens. Beneath the epidermis lies the dermis, composed of connective tissue, blood vessels and appendages such as hair follicles and sweat glands. The subcutaneous tissue, situated beneath the dermis, helps in maintaining skin health and sensation.[2] Despite these defense mechanisms, the skin remains susceptible to fungal infections, particularly those caused by a group of keratinophilic fungi called dermatophytes. While internal factors can predispose individuals to dermatophytosis, like compromised immunity due to underlying medical conditions (e.g., diabetes) or medication use (e.g., corticosteroids), external factors also play a significant role. The dryness of the outermost skin layer (stratum corneum) or a damp environment can favor fungal growth. Additionally, poor hygiene practices, such as sharing personal items with infected individuals or neglecting proper skin and nail care, can increase the risk of transmission. Direct contact with infected individuals or animals further facilitates the spread of dermatophytes.[3]

The most important factors contributing are under-diagnosis, a poor treatment regimen, an increased number of immuno-compromised patients and most importantly geographic distribution.[4] The pathogenesis of dermatophytosis still remains unclear, but studies revealed the pathogenesis in four ways, adherence, penetration, development of host immune response and keratin degradation. 1. Dermatophytes compete with the

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normal flora and sphingosines (produced by keratinocytes) and the fatty acids (produced by the sebaceous glands), then the arthroconidia (infecting element) adhere to the keratinized tissue. 2. An arsenal of proteases is accessible to dermatophytes, with the goal of breaking down the keratin network into absorbable oligopeptides or amino acids. Once established, the spores need to proliferate and break through the stratum corneum more quickly than they desquamate. The various serine-subtilisins and metallo-endoproteases (fungalysins), formerly known as keratinases and found virtually exclusively in dermatophytes, that are released by these organisms overlap with penetration. 3. The invasion of dermatophytes triggers an immune response characterized by the activation of innate and adaptive immune mechanisms. Immune cells, such as neutrophils, macrophages and T lymphocytes, are recruited to the site of infection to combat the fungal invaders. Inflammatory mediators, including cytokines and chemokines, are released, contributing to the clinical manifestations of dermatophytosis, such as erythema, scaling and pruritus. 4. Dermatophytes produce an array of enzymes, including keratinases, proteases and lipases, which degrade the structural proteins present in the skin, particularly keratin. Keratin is a tough protein that forms the outermost layer of the skin, hair and nails. By breaking down keratin, dermatophytes can penetrate the skin's barrier and access deeper layers of tissue.[5]

The burden of dermatophytosis is significant. Fungal diseases, in general, pose a substantial health concern, with their annual incidence in India exceeding even that of tuberculosis. This burden is particularly high in tropical and subtropical regions, where factors like climate favor fungal growth. A decade ago, a report by the Centers for Disease Control and Prevention (CDC) in the United States revealed that over 4.9 million patients visited outpatient dermatology departments for dermatophytosis, highlighting the prevalence of this condition.[6] The increased incidence of fungal infections in 2024 may be attributed to several factors: resistance developed against antifungal agents, changes in the growth patterns of dermatophytes favoring their survival, genetic evolution enhancing fungal virulence and the rapid emergence of drug-resistant species due to inadequate dosing of potent antifungals. In particular, a sudden increase in the incidence of recurrent and chronic dermatophytosis has been presented in India as a significant issue.

Research has shown that the dermatophytes isolated from Tinea infection, *T. rubrum* is the primary causal organism in Western India that lately switched to *T. mentagrophytes* complex and *M. audounii*. A growing percentage of the *T. mentagrophytes* complex, has been seen in recent investigations. Additionally, these species displayed higher minimal inhibitory concentrations for the widely used antifungal products. The most common kind of infection in India was *Tinea* corporis (infection on the skin), followed by *Tinea cruris* (infection on the jock) and *Tinea capitis* (infection on the scalp).[5] Indeed led to an increase in India's topical drug delivery market size to US$0.81bn (survey rate up to 2024) and its annual growth rate of 9.58% (CAGR 2024-2029). In 2024, India's per-person revenues amount to US$0.56 revealing antifungals are the most commonly prescribed and most selling drug in India. Within the OTC Pharmaceuticals market, there has been a notable increase in demand for natural and Ayurvedic skin treatment products in the country.[7]

Diagnosis

Traditionally, diagnosing fungal infections like dermatophytosis relies on conventional methods like direct microscopic examination and fungal culture. However, these methods have limitations. Microscopy offers limited sensitivity and can't differentiate between different dermatophyte species. Culturing the fungus, although considered the gold standard, can be slow (taking weeks to grow), susceptible to contamination and may not detect non-viable fungi.[8] Molecular diagnostic techniques, like Polymerase Chain Reaction (PCR), offer significant advantages in diagnosing dermatophytosis. PCR provides a reliable and faster method for identifying the causative agent compared to cultures. It can detect a broader range of dermatophyte species and even yield positive results when cultures are negative. Additionally, PCR boasts a quicker turnaround time, allowing for more rapid treatment decisions. While PCR comes with a potentially higher initial setup cost and requires specialized expertise, the long-term cost-effectiveness and improved diagnostic value make it a valuable tool in mycology laboratories.[9]

CLASSIFICATION OF ANTI-FUNGAL AGENTS

There are many classes of antifungal medications that work in different ways. Azoles prevent the production of ergosterol, which is the primary sterol found in fungi.[10] Polyenes interact physically and chemically with the sterols found in fungal membranes. Lastly, 5-fluorocytosine prevents the creation of macromolecules.[11] There are approximately 23 antifungal azoles available on the market at present, with the most commonly used ones being clotrimazole, ketoconazole, miconazole, fluconazole, itraconazole and voriconazole. The antifungal susceptibility of *Trichophyton* spp. to terbinafine worldwide indicated a change in MICs to terbinafine in India, underscoring India's significant role in the growing drug resistance pandemic. From the year 2015 and 2021 in India, the major pathogen responsible for more than 65% of all cases was *T. mentagrophytes*/*T. interdigitale* complex.[12]

CONVENTIONAL METHODS USED TO TREAT DERMATOPHYTOSIS

In the past, the mainstay of dermatophytosis treatment consisted of topical formulations like creams, gels, solutions, lotions and ointments. Topical delivery aims to localize the drug's effect to the skin surface or within the upper layers, maximizing drug availability at the infection site and minimizing systemic exposure.

Topical azole and allylamine antifungals are preferred for dermatophytosis due to their effectiveness against these fungi.[13] Previously, topical agents like clotrimazole and ketoconazole were commonly used in various forms such as powders, shampoos and soaps. Terbinafine was another option, available in both topical cream and oral formulations. However, these conventional treatments have limitations. Many antifungal drugs are highly lipophilic (fat-soluble), leading to several drawbacks such as poor skin retention due to which the medication doesn't stay on the skin effectively, reducing its duration of action. The lipophilic nature can irritate the skin, especially with prolonged use. Also, the photo-stability issues where some drugs degrade in sunlight, rendering them ineffective. These limitations can hinder the overall effectiveness of conventional topical treatments for dermatophytosis.[14] Alternatively, lipid-based nanovesicles offer a versatile platform for drug encapsulation and lead to the clinical translation of several formulations. The vesicles-based formulation can sustain drug release by depot formation, enhanced drug stability, targeting infected tissue, reduction of off-target side effects, prolongation of residence time in the blood, improved drug efficacy and exhibits high kinetic stability, great surface area, which renders them highly satisfactory for the application of lipophilic substances promoting a homogeneous drug release. Among the former topical formulation gel-based therapies in dermatology have gained a higher cosmetic appeal, patient-friendly and are more convenient in application.[15] The topical delivery with gels improves the delivery and release of the substance by increasing the residence time at the injection site as well as less sticky, less oily and easily washable.[16] Oral administration stands as the predominant method for drug delivery, favored by patients for its widespread acceptance. In comparison to traditional intravenous administration, a successful and safe oral dosage holds the potential to significantly lower medical expenses, minimize side effects and enhance the quality of life for patients. Unfortunately, oral antifungals are only effective in high doses compared to topical formulations. Prolonged usage of oral antifungals can lead to renal toxicity. Among oral antifungals, drug fluconazole and Itraconazole were mostly prescribed.

Individuals undergoing organ transplants, cancer treatments, COVID-19 management and those with HIV/AIDS often receive intensive care involving broad-spectrum antibiotics and/or immune-suppressants, heightening their susceptibility to infections.[17] As mentioned in the introductory section, Favus (*Tinea favosa*), is called to be a severe and long-lasting inflammatory fungal infection of the skin usually triggered by *Trichophyton schoenleinii*[18] and needs the systemic route of treatment. IV administration of terbinafine, itraconazole and fluconazole can inhibit the fungal growth and cure the infection. However, no clinical trials for the systemic route of administration incorporating newer antifungals are available.[19] The treatment of systemic fungal infections in clinical practice therefore poses a major challenge.

ALTERNATIVE METHODS TO CONVENTIONAL METHODS USED FOR TREATING DERMATOPHYTOSIS

The topical/transdermal treatment options for localized fungal infections (*Tinea corporis, Tinea cruris, Tinea facie* and *Tinea pedis*) always remain as an alternative approach.[20] Regardless of the mode of treatment, whether conventional or novel, topical

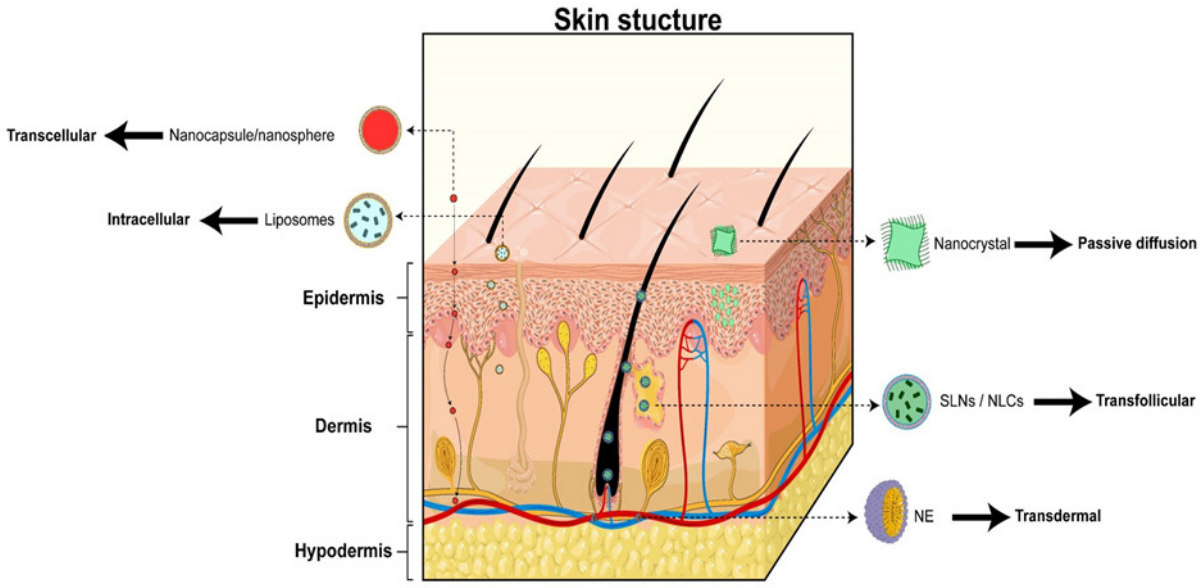

Figure 1: Skin structure and possible routes of nanoparticle penetration. A schematic diagram showing the structure of the skin and the possible routes of nanoparticle penetration. The three main layers of skin are the epidermis, dermis and hypodermis. Nanoparticles can enter the skin through passive diffusion, the hair follicles, or transdermal delivery.

application is the gold standard therapy. Topical dosage forms give more cosmetic appeal and improve patient compliance. The application of medication directly on the affected area helps to achieve higher drug concentration, resulting in faster recovery but conventional formulation would not modulate the release of drug reproducibly even though it could offer other advantages.[21] Furthermore, within the Viable Epidermis, the Stratum corneum, the outermost sub-layer, hosts keratin cells serving as a barrier against drug permeation. However, the keratinocytes, composed of lipid substances such as triglycerides, fatty acids and cholesterol, impart a lipophilic characteristic to this layer.[22] Modification of the formulation to improve the biocompatible with the layer may enhance drug penetration through the skin. Initially, simple techniques were tried to improve the formulation solubility, permeability and thereby bioavailability of the drug. With the advancement of nanotechnology, nanocarriers were developed wherein the drugs may be incorporated within the structure or deposited on the surface, thereby augmenting their efficacy in attaining the intended objectives. Nanocarriers help to target specific sites and avoid untoward effects associated. It also prevents the drug from degradation due to the external environment thereby improving the stability of the compound. Additionally, Nanocarriers facilitate the transportation of drugs across diverse biological barriers, extend half-life, boost the physicochemical and biological stability of drugs and oligonucleotides and enhance cell internalization, among other benefits. NCs can be categorized into three primary groups based on their primary composition: Lipid-based, Polymer-based, or Inorganic-based NCs. Lipids based are (liposomes, ethosomes, trans-ethosomes, nano-emulsions and lipid nanoparticles, which include solid lipid nanoparticles, nanostructured lipid carriers, lipid-polymer hybrid nanoparticles, polymer-based nanocarriers (polymeric nano micelles and polymeric nanoparticles, including polymeric nano-capsules and polymeric nanospheres and inorganic based nanocarriers are (gold nanoparticles, silver nanoparticles, iron nanoparticles and porous silica nanoparticles, respectively.[23] The routes of permeation of the nanocarriers through the skin is pictorially represented in Figure 1.

Several nanocarriers utilized for incorporating antifungal drugs based on the physiochemical properties are described below. Voriconazole and Sertaconazole loaded microemulsions were developed by Moammal S. Qurt *et al.* (2018)[24] The findings demonstrated that microemulsions serve as promising carriers for delivering both substances through the skin, owing to their exceptional solubilization capacity and ability to enhance permeation. In microemulsion, the presence of the oil phase helps in solubilizing the drug. The components of ME decrease the barrier presented by the stratum corneum and elevate the concentration gradient towards the skin and the dispersed phase functions as a reservoir, facilitating the maintenance of a consistent concentration in the continuous phase.[25] Sandy Vrignaud *et al.* in the review provide an overview of the methods established to encapsulate hydrophilic molecules in polymer-containing nanoparticles, such as nanospheres and nanocapsules. Within polymer nanospheres, drugs are loaded either through entrapment within the structure or via adsorption onto the surface of the nanosphere. This ensures effective protection against degradation and facilitates faster drug release.[26] Nanocapsules typically feature an aqueous core encapsulated by a thin polymer layer. Hydrophilic molecules are solubilized directly within the internal water of the core, ensuring their entrapment within the nanocapsule and providing both drug protection and sustained release.

NEW DRUGS AND DELIVERY SYSTEMS FOR DERMATOPHYTOSIS

Given the limitations of conventional treatments and the growing demand for patient-friendly topical options, several antifungal agents hold high potential for the treatment of dermatophytosis, particularly when combined with nanotechnology advancements.[27] Newer azole derivatives are being developed with improved potency against dermatophytes and potentially fewer side effects compared to older azoles like ketoconazole. Novel allylamines are being explored, offering the potential advantages associated with the class (fungicidal activity, low side effects) while addressing limitations like shorter duration of action seen with some current allylamines (e.g., terbinafine). While currently used primarily for systemic infections, research suggests that certain echinocandins might be effective for topical dermatophytosis treatment, especially when formulated in nanocarriers to improve skin penetration and localized delivery.[28] Nanotechnology offers a revolutionary approach to topical antifungal delivery. By encapsulating these promising antifungal agents within lipid-based nanovesicles, we can achieve several benefits including improved skin penetration and sustained release of the drug at the infection site, the potential for targeting specific tissues, minimizing systemic exposure and enhancing treatment efficacy and improved patient experience.[29,30]

Studies have reported that Fluconazole has been utilized to produce voriconazole, which was approved in 2002 to treat systemic fungal infections like *Aspergillus* and candidiasis. Lately, it's being promoted in India for "resistant dermatophytosis".[31,32] Ravuconazole, another fluconazole derivative, demonstrated wide-ranging antifungal effectiveness and increased potency. A prodrug of ravuconazole, fosravuconazole bis (L-lysine), was formulated and approved for treating nail dermatophyte infection in Japan in 2018.[13] In 2006, posaconazole, a derivative of itraconazole exhibiting a broad spectrum of antifungal activity, received approval.[14] Additional second-generation triazoles comprise albaconazole, efinaconazole and isavuconazole. For the management of tinea infections, 1% cream luliconazole was initially licensed in Japan in 2005. It was then approved in India in 2009 and the US in 2013.[15] SUBA

("super-bioavailability")-itraconazole, an orally administered azole, seemed to enhance both the bioavailability and interpatient variability of the current antifungal medication, itraconazole. The Food and Drug Administration (FDA) in the United States approved its use in treating blastomycosis, histoplasmosis and aspergillosis.[16] In India, clinical trials on its usage for dermatophytosis have been conducted and found to be effective.[17] In the discourse concerning efficacious anti-fungal agents, it is notable that luliconazole stands out as the sole molecule demonstrating an absence of resistance against fungal strains, consequently mitigating the likelihood of infection recurrence.[18] Luliconazole cream markets is projected to reach USD million in 2022, at a CAGR of percent during 2023 and 2028. Analysis of the patent literature shows that more and more interest is being shown in another type of novel topical vehicle for luliconazole.[33] Studies have been carried out to combine luliconazole with other antifungals and/or also steroids to improve its efficacy. When these formulations are applied to the skin surface, they readily penetrate the stratum corneum with rapid improvement in inflammatory components, but no significant difference rate in mycological cure was observed.[27] To effectively circumvent drug resistance in the future, one strategy involves investigating novel formulations of existing drugs, or discovering new derivatives for existing molecules while maintaining their inherent properties intact. Topical film-forming spray incorporated luliconazole enhances permeability and absorption, with the possibility of a once-a-day dosage by using a transparent thin film.[34] The hydrogel incorporating Luliconazole-loaded Nanocrystals (LNC) demonstrated a 5-fold improvement in solubility, a 4-fold improvement in dissolution rate, increased skin retention and enhanced antifungal efficacy overall.[35] Formulated nanosponges using luliconazole act as a carrier to transport the drugs for better antifungal activity, improved skin retention and permeation. Vesicular delivery of luliconazole is also tried to improve the permeation and retention of the drug in the stratum corneum.[36] According to Daisuke Todokoro *et al.*, (2019), antifungals such as voriconazole and luliconazole bearing low molecular weight and lipophilicity demonstrate effective penetration into the deep corneal stroma and anterior chamber. Hence author suggests it as another option for treating ophthalmic fungal infection.[37] However, to the author's understanding the lacrimal fluid is primarily aqueous which hinders the solubility of highly soluble drugs hence lowering the absorption and thereby poor bioavailability.

Despite the development and utilization of various nanocarriers, their therapeutic effectiveness remains suboptimal due to constraints associated with the physicochemical characteristics of the drug, scalable optimization, stability and biocompatibility.[38] The integration of nanotechnology and Artificial Intelligence holds the potential to address numerous challenges in formulation development. Regularly checking dermatophytes and their susceptibility to antifungal treatments is important because these profiles can change over time.[39] The combination of antifungal agents with hydrating agents is currently viewed as one of the most promising methods for improving cutaneous drug penetration and efficacy in topical antifungal therapy.[40] Currently, in the market, we have no product to the best of our knowledge with an anti-infective agent in combination with a hydrating agent. The current clinical practice suggests the use of two separate anti-infective products and moisturizers asked to be applied alternatively. Furthermore, the use of only an antifungal topical product lead to the occurrence of antimicrobial resistance. Thus, the present invention is beneficial to the patient with the convenience of applying a single product and avoidance of resistance to the infection. Recalcitrant tinea infections are associated with abnormal barrier function and trans-epidermal water loss; this formulation is likely to be beneficial in such cases.

CONCLUSION

The dermatophyte spectrum is unstable and has been displayed to change over time and in different parts of the globe. Dermatophytosis is linked to significant morbidity and socioeconomic distress. This review also explained a higher sensitivity of luliconazole compared to other azole antifungals used against superficial dermatophytosis. Despite the availability of sensitive antifungals, administering this drug presents challenges. While advancements in nano-carrier research are ongoing, the bioavailability of prepared formulations remains inadequate. Superficial fungal infections should be prioritized, because they often present as chronic, recurrent and resistant cases, overall lowering the quality of life.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PCR: Polymerase Chain Reaction; **CDC:** Centers for Disease Control and Prevention; **NC:** Nanocarriers; **LNC:** Luliconazole-loaded Nanocrystals; **FDA:** Food and Drug Administration; **SUBA:** Super-Bioavailability.

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