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NOVEL DRUG THERAPIES IN THE TREATMENT OF DERMATOPHYTOSIS

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ABSTRACT

Dermatophytes are a major cause of fungal infections worldwide, and they are quite common in developing countries. Recent studies show that these infections have been increasing notably in India, particularly in the last few years. The rise in recurrent or chronic cases has made it clear that we need novel drug therapies for dermatophytosis treatment. Also, there is a worrying increase in resistance to the usual oral and topical antifungal medicines. Novel formulations or newer derivatives of existing drug classes and few newer drug classes are being developed by researchers for the treatment of chronic or extensive dermatophytosis. Newer topical drugs include efinaconazole, tavaborole, ciclopirox HPCH lacquer, econazole and luliconazole. Additional forms of local therapies including photodynamic therapy and laser irradiation are also recommended for dermatophytosis treatment.

Keywords: Dermatophytosis, Tinea, Novel drug, Fosravuconazole, Voriconazole, SUBA Itraconazole, Efinaconazole, Tavaborole, Sertaconazole, Laser therapy

INTRODUCTION

Dermatophytosis are superficial fungal infections resulting from dermatophytes that impact the hair, skin and/or nails, commonly known as tinea infections. They are caused by a group of keratinophilic fungi known as "dermatophytes" which includes three genera, namely, Epidermophyton, Microsporum, and Trichophyton. Dermatophytosis is categorized based on the affected body area, including conditions like tinea capitis (scalp), tinea barbae (beard region), tinea corporis (skin excluding the beard, scalp, groin, hands, or feet), tinea cruris (groin, perineum, and perineal regions), tinea pedis (feet), tinea manuum (hands), and tinea unguium (nails). [1] In dermatophyte infections, the clinical manifestations result from a combination of keratin disruption and the inflammatory responses of the host. Dermatophytosis often appears as a scaly patch with inflammation, characterized by an elevated edge that exhibits varying degrees of inflammation and common symptoms include rashes, scaling, erythema and itching. [2]

The treatment of dermatophytosis primarily involves the use of oral and topical antifungal medications. Topical anti-fungal medications are advised for localized skin infections caused by dermatophytes. In cases of more widespread

infections, systemic antifungal drugs are recommended. Combination therapy, utilizing both topical and oral antifungal agents, exhibits substantial efficacy in the treatment of dermatophytosis with better mycological and clinical cure than systemic or topical agents used alone. [1]

classification of antifungals used in dermatophytosis:

CLASS	DRUGS
1. AZOLES a) IMIDAZOLES:	Topical: Clotrimazole, Oxiconazole, Luliconazole, Econazole, Miconazole, Fenticonazole, Butoconazole Systemic: Ketoconazole
b) TRIAZOLES:	Fluconazole, Itraconazole, Voriconazole, Posaconazole, Isavuconazole
2. ALLYLAMINES	Naftifine, Terbinafine
3. BENZYLAMINE	Butenafine (topical)
4. HETEROCYCLIC BENZOFURAN	Griseofulvin (oral)
5. OTHER TOPICAL ANTIFUNGALS	Tolnaftate, Ciclopirox olamine, Undecylenic acid, Benzoic acid, Quiniodochlor, Sodium thiosulphate

We are currently witnessing a surge in challenging cases of dermatophytosis characterized by atypical clinical presentations, varying therapeutic responses, frequent recurrences and relapses. The available conventional drugs have limited options, acting on similar targets, exhibiting potential drug interactions, and presenting questionable bioavailability. Treatment decisions rely more on experience than clear evidence. A new species, Trichophyton indotineae has become a significant issue showing resistance especially against terbinafine. These challenges highlight a critical need for novel antifungal formulations and therapies. Ongoing research is exploring compounds with unique fungal targets, including other antimicrobials, natural substances, and physical treatments based on devices. The increasing prevalence of recurring or chronic dermatophytosis has resulted in a requirement for innovative treatments and novel antifungal agents. [3]

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A. NOVEL ORAL FORMULATION:

1. SUBA-Itraconazole (SUBA-ITZ):

Super Bioavailable Itraconazole (SUBA-ITZ) is a novel amorphous solid dispersion (ASD) containing itraconazole in a pH-responsive polymeric matrix (hydroxypropyl methylcellulose-phthalate, HPMC-P) to enhance its dissolution and intestinal absorption. Conventional itraconazole is not reliably absorbed by the body, with a maximum bioavailability of only 55 percent, and the absorption varies. However, the new version of itraconazole (SUBA-ITZ) is designed to release the drug specifically in the small intestine has predictable serum levels with minimum interindividual variability, which could make it a potentially useful drug in recalcitrant dermatophytosis. Conventional itraconazole (C-ITZ) have the site of absorption restricted to the stomach, while SUBA-ITZ shows intestinal absorption. The US FDA has approved a dose of 200 mg (100 mg per capsule, taken twice) for C-ITZ in the treatment of dermatophytosis. Research findings suggest that taking 50 mg of SUBA-ITZ twice a day could be equally effective as taking 100 mg of C-ITZ twice a day. [4,5]

2. FOSRAVUCONAZOLE:

Fosravuconazole L-lysine ethanolate (F-RVCZ) is a prodrug of ravuconazole, a new type of triazole antifungal medication known for its wide-ranging and potent effectiveness against fungal infections. F-RVCZ demonstrates a more favourable dosing schedule and higher effectiveness compared to existing oral antifungal treatments on the market. This suggests it could be a valuable option for treating onychomycosis, regardless of the severity of the condition. It exhibits improved hydrophilicity with oral bioavailability, and the skin and nail tissue transition as well as

tissue retention are excellent. Fosravuconazole therapy is reportedly effective for the treatment of various dermatomycoses. Drug regimen involves taking only 1 capsule per day (equivalent to 100 mg of Ravuconazole) for 12 weeks. [6,7]

3. VORICONAZOLE

Voriconazole, a new oral antifungal medication suitable for treating recurrent and resistant dermatophytosis, demonstrates high effectiveness and safety, coupled with an exceptionally low recurrence rate. Voriconazole is a recently developed second-generation triazole antifungal medication, offered in both oral and intravenous forms, known for its wide-ranging effectiveness against various fungal infections. It has received US Food and Drug Administration approval specifically for treating invasive fungal infections. It is generally administered as 200mg twice daily for 4 weeks. The terminal half-life of voriconazole is dose-dependent and the drug is rapidly and almost completely absorbed following oral administration with maximum plasma concentration being achieved 1- 2 h after dosing. The estimated amount of voriconazole that can be absorbed through oral administration is approximately 96%. The presence of high-fat food affects voriconazole absorption; oral voriconazole should be taken at least 1 hr before or after a meal. This medication undergoes metabolism via hepatic cytochrome P450 enzymes, specifically CYP2C19, CYP2C9, and CYP3A4. Around 80% of a labelled dose of voriconazole is eliminated through urine, while the remaining 20% is excreted through faeces. Common side effects associated with voriconazole include changes in vision, sensitivity to light, nausea, headaches, abdominal discomfort, skin rash, and diarrhoea. [8,9]

4. OTESECONAZOLE

Oteseconazole is an emerging orally administered tetrazole antifungal that is highly specific for the fungal cytochrome P450 51 (CYP51, lanosterol 14-α-demethylase). Oteseconazole exhibits wide-ranging effectiveness against various types of yeasts, dermatophytes, certain mucorales, and some dimorphic fungi. Clinical development for the treatment of onychomycosis is ongoing. Typically, it is given as a loading dose of 300 mg per day for two weeks, followed by a maintenance dose of 300 mg per week for ten weeks. [10]

B. NOVEL TOPICAL FORMULATION:

Topical antifungal treatments are typically the primary choice for treating simple, surface-level fungal infections due to their effectiveness and minimal risk of causing systemic side effects. These medications are formulated into different forms such as lotions, gels, creams or sprays to aid in absorption and effectiveness, tailored to the affected area. The classes of topical antifungals mainly include azoles, allylamines, polyenes and benzylamines.

1. EFINACONAZOLE 10% SOLUTION

Efinaconazole is a topical azole antifungal drug suitable for treating toenail onychomycosis. It was approved by the US Food and Drug Administration (USFDA) in 2014 for the treatment of toenail onychomycosis caused by dermatophytes such as Trichophyton rubrum and Trichophyton mentagrophytes. It inhibits lanosterol 14α - demethylase in the ergosterol pathway through trans ungual and sub ungual penetration. The recommended dosage is once a day application of Efinaconazole 10% solution for 48 weeks topically on nail beds, hyponychium and nail ridges. It shows high clinical efficacy with no systemic drug-drug interactions and low adverse events profile. [11]

2. TAVABOROLE

Tavaborole is a benzoxaborole antifungal medication used to treat fungal infections of the toenails and fingernails. It is the first oxaborole antifungal agent approved by FDA in July 2014. It works by inhibiting the synthesis of fungal proteins, which are essential for the growth and survival of the fungus causing the infection. It specifically targets an enzyme called leucyl-tRNA synthetase, which is involved in the production of proteins necessary for fungal cell growth. Tavaborole 5.0% nail solution is applied once a day for 48 weeks. Fewer side effects such as ingrown toenail, dermatitis and erythema are observed in about 1% patients. [12,13]

3. CICLOPIROX 8% HYDROXYPROPYL CHITOSAN (HPCH) LACQUER

Ciclopirox 8% HPCH is considered to be the first topical nail lacquer crafted using the innovative HPCH drug formulation technology. It is suggested for the treatment of mild to moderate fungal infections affecting the nails, which are typically caused by dermatophytes. The newer formulation exhibited greater penetration and proved to be more efficient compared to the traditional version. Ciclopirox 8% HPCH is intended for onychomycosis treatment by once daily application for 48 weeks. It was found to be well tolerated in patients without any treatment related adverse events. [14]

4. ECONAZOLE NITRATE FOAM 1%

Econazole nitrate is a topical antifungal agent effective against a diverse range of fungi, including dermatophytes and yeasts. It is recommended for the treatment of Tinea pedis which is approved by US Food and Drug Administration (USFDA). This novel therapy utilised Proderm Technology based on a water-lipid formulation which is easy for application and disperses quickly. The recommended dosage is once daily topical application for 4 weeks. [15]

5. SERTACONAZOLE NITRATE MICROEMULSION BASED HYDROGEL

Sertaconazole hydrogel is an effective imidazole antifungal agent used in treatment of dermatophytosis. It was discovered to improve permeation of the sertaconazole to treat fungal infections. It mainly inhibits the ergosterol production. A hydrogel containing sertaconazole microemulsion (HSM) was developed by including 0.75% w/w of Carbopol 940, which was permitted to expand with a small quantity of water over a 24-hour period. [16]

6. LULICONAZOLE

Luliconazole 1% cream is an azole antifungal drug used to treat various fungal infections, especially dermatophytosis. It was approved by USFDA in November 2013. The potent antifungal activity of luliconazole is possibly attributable to a combination of strong in vitro antifungal activity and favourable pharmacokinetic properties in the skin. The advised dosage of luliconazole involves applying it once daily for 1 week in Tinea cruris or Tinea corporis, and for 2 weeks in Tinea pedis. Luliconazole exhibits only fewer local side effects such as pruritus, erythema and mild application site dermatitis. [17]

C. OTHER NOVEL THERAPIES:

1. LASER IRRADIATION THERAPY

Laser therapy used as a novel method to treat dermatophyte infections caused by Trichophyton Rubrum. The Trichophyton rubrum species includes xanthomegnin as its primary diffusing red pigment, which can be effectively targeted by laser irradiation at wavelengths of 532nm and 598nm. Increasing the laser power will inhibit the growth of fungal colonies. [18]

2. PHOTODYNAMIC THERAPY (PDT)

Photodynamic therapy involves using a light source of a particular wavelength to activate a photosensitive substance. This activation initiates a series of photochemical and photobiological processes that result in permanent alterations in the targeted cells. It is used to treat onychomycosis caused by tinea rubrum species. PDT produces Reactive species of oxygen (ROS) and Reactive species of nitrogen (RNS) which are capable of destroying the fungal cells. [19,20]

CONCLUSION

Emergence of newer drug therapies presents promising avenues for the treatment of dermatophytosis. As the prevalence of fungal infections, particularly in regions like India, continues to rise and resistance to traditional antifungal agents becomes more prevalent, the need for innovative treatments becomes increasingly urgent. The exploration and development of these newer drugs offer hope for more effective and efficient management of dermatophytosis, ultimately improving outcomes for patients worldwide. Continued research and clinical trials will be crucial in further advancing our understanding and utilization of these therapies in the fight against dermatophytosis. Overall, this review underscores the importance of ongoing innovation and research in improving the care and outcomes of patients with dermatophytosis.

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