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EMERGING ANTIFUNGAL RESISTANCE IN DERMATOPHYTES: A COMPREHENSIVE REVIEW OF MECHANISMS, CHALLENGES, AND FUTURE THERAPEUTIC APPROACHES

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Abstract:
Antifungal resistance among dermatophytes is increasing, posing a significant challenge to the effective management of superficial fungal infections (SFIs). Dermatophyte species responsible for numerous cutaneous infections have developed resistance to commonly used antifungal agents, resulting in treatment failure and persistent disease. This review provides a comprehensive analysis of the mechanisms underlying antifungal resistance in dermatophytes, including genetic mutations, overexpression of efflux pumps, and biofilm formation, all of which contribute to diminished drug efficacy. Terbinafine remains the first-line therapeutic agent for dermatophyte infections; however, reports of terbinafine resistance have risen, particularly in strains of *Trichophyton rubrum* and *Trichophyton indotineae*. Resistance to azoles—especially itraconazole and fluconazole—has also emerged as a growing concern. Key resistance mechanisms involve mutations in genes such as *ERG11* (lanosterol 14α-demethylase), *CYP51*, and squalene epoxidase, which play essential roles in ergosterol biosynthesis and thus represent critical targets for antifungal therapy. Additionally, the review examines host–pathogen interactions, highlighting how immune-evasion strategies employed by dermatophytes, along with host genetic factors, contribute to increased infection severity. Potential strategies to counter antifungal resistance are also discussed, including combination therapies, the development of novel antifungal agents, and host-directed treatment approaches. Understanding the molecular basis of resistance and the dynamics of host immunity is crucial for the development of more effective and targeted therapeutic interventions. This review underscores the need for continued research and innovation in antifungal therapy to address the growing problem of dermatophyte resistance.

Keywords: Dermatophytes, Antifungal Resistance, Azoles, Host-Pathogen Interaction

Introduction:

The World Health Organisation (WHO) estimates that superficial mycotic infections affect 20-25% of the world population [1]. Dermatophytes, a class of fungi that may proliferate by penetrating the keratin of the hair, skin, and nails, are responsible for dermatophytosis, the most significant and prevalent superficial fungal infection. Dermatophytes are classified as geophilic, zoophilic, and anthropophilic species based on their native environment [2].

Azoles are typically fungistatic against yeasts and fungicidal against Aspergillus spp. but have a significant risk of medication interactions and probable hepatotoxicity [3]. Wide-spectrum antifungal azoles, such as fluconazole, efinaconazole, voriconazole, ketoconazole, and itraconazole, can be used to treat mycosis. Significantly, azole groups hinder the cytochrome P-450 enzyme 14-α demethylase, which prevents the formation of ergosterol. Furthermore, compared to other antifungal therapies,azole groups' selectivity for the cytochrome P-450 enzymes of fungi rather than mammals allows for highly selective antifungal activity with very little adverse effects [4]. Since anthropophilic dermatophytes have an evolutionary advantage over geophilic or zoophillic organisms in terms of transmission between human hosts, they are regarded as true pathogens. Dermatophyte infection happens when an infected individual transfers hyphae or arthroconidia, or keratin material that carries these fungal components, to a vulnerable host [5]. Antifungal resistance to medications began with the widespread use of antifungal treatment in immunocompromised people. Clinical or microbiological fungal resistance are also possible. Numerous fungal variables that have developed as a result of genetic changes in the fungus are responsible for microbiological resistance [6]. Drug-related or host- related variables are the cause of clinical resistance. Fungal resistance may result from any one of these variables alone or in combination. Combinational antifungal treatment is one strategy to prevent resistance, along with standardized susceptibility testing and proper medication dosage.

2.Antifungal Drug Resistance in Dermatophyte and its Mechanisms

2.1Terbinafine (TRB)

Terbinafine is an allylamine-based synthetic antifungal medication. Squaleneepoxidase, a fungus enzyme necessary for ergosterol production, is inhibited by this antifungal medication. Azoles have a different method of action. Terbinafine had the greatest degree of dermatophyte sensitivity and clinical response. It is still an option of medicine for treatment of SFI. The fact that 20% of clinical dermatophytes exhibited terbinafine resistance and a comparable proportion of patients had recurrence of SFI, however, is quite concerning [7]. Since the isolates of dermatophytes resistant to terbinafine are also resistant to fluconazole and itraconazole, it may be deduced that around 20% of dermatophytes are multidrug resistant (MDR) [8]. However, terbinafine MIC90 values are increased by many magnitudes in T. rubrum and T. indotineae strains with Erg1 point mutations encoding for squalene epoxidase [9,10].Fink et al. [11] used microplate laser nephelometry to study the sporicidal effects of sertaconazole nitrate on Epidermophyton chlamydospores, Trichophyton microconidia, Scopulariopsis brevicaulis conidia and Candida blastospores. Sertaconazole nitrate may be more effective than the widely used antifungals terbinafine and ciclopirox olamine in treating recurrent dermatomycoses because it combats resting spores that remain in the tissues. Terbinafine was extremely effective against most dermatophytes and reduced the spread of "E. floccosum as well as S. brevicaulis in the 3D skin model," but greater dosages were needed to eradicate the resistant strain T. indotineae. Additionally, TRB exhibited substantially decreased treatment efficiency in infections caused by Candida spp [11–14].

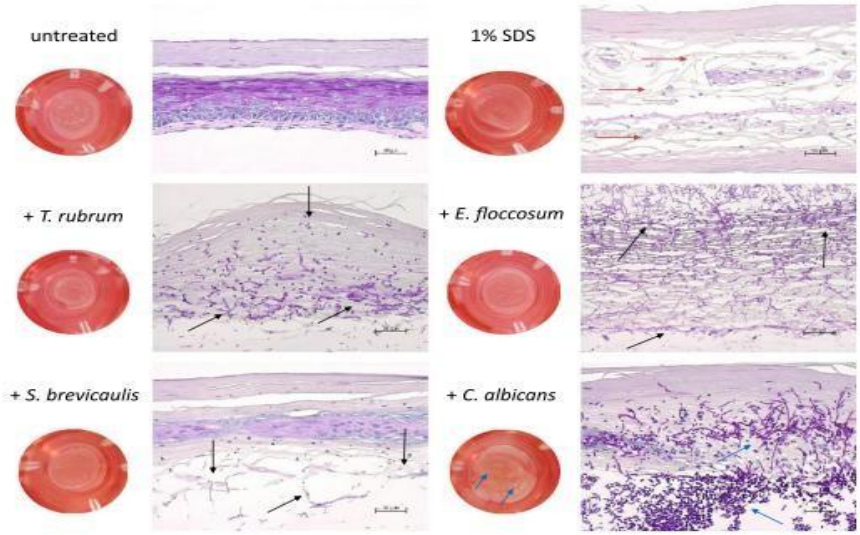

Figure 1. Microscopic and Macroscopic images of skin models infected with "T. rubrum, S. brevicaulis, C. albicans and E. floccosum at 72 h. Fungal growth is marked with black arrows, yeast spread and pseudo mycelia with blue arrows, and SDS treatment-induced damage with red arrows. SDS: Sodium dodecyl sulfate; PAS: Periodic acid–Schiff" [11]

2.2Griseofulvin (GRIS)

Griseofulvin inhibits the assembly of microtubules. It interferes with microtubule activity in dermatophytes to alter the development of the mitotic spindle. This interference ultimately suppresses mitosis in dermatophytes, as well as nucleic acid synthesis and polymerization. In addition to its progressive discontinuity and unavailability, griseofulvin is less effective than terbinafine and itraconazole [15].Griseofulvin interacts with polymerized microtubules to break the mitotic spindle, hence inhibiting fungal mitosis. The medicine is absorbed by sensitive dermatophytes through an energy-

dependent process, and resistance may arise from a reduction in this transport. Grineofulvin acts as a fungicide against Microsporum, Trichophyton, and Epidermophyton species via this mechanism [16,17].

2.3Itraconazole (ITC)

One of the primary antifungals that are provided to treat these infections is Itraconazole (ITC). The treatment, nevertheless, particularly when it comes to onychomycosis, demands extensive regimens, leaving no opportunity for medication resistance. We examined the impacts of ITC on the physiology of T. interdigitale, pathogenicity and interaction of T. interdigitale with phagocytes and mice cutaneous infection. Amazingly, several strains of T. interdigitale had a permanent partial phenotypic [18].Kraußе et al.

[19] attempted to assess how incubation temperature, medium composition, and spore concentration influence ITC susceptibility tests across distinct dermatophyte species. The results of IC50 were strongly influenced by temperature and medium composition. Erg11B point mutations linked to resistance and genomic amplifications in T. indotineae were validated by genotypic screening. In order to effectively treat superficial mycosis, Subedi et al. [20] suggested a stable and highly skin- permeable topical administration method for ITC.

The safety profiles, relapse rates, cure rates, and treatment durations of ITC 400, 200, and 100 mg/d for the treatment of ITC were compared by Khurana et al. [21]. The most common empirical dosage of itraconazole used by medical professionals is 200 mg [22]. All three treatment failures' MICs were less than

0.5 μg/mL, which was previously suggested as the top limit of the wild-type MIC of the common Indian strain [23, 24]. A total of 55 individuals (47.4%) relapsed following therapy. Treatment with the 400 mg a 120% higher cost and 200-mg dosage entailed a 63% higher cost over 100 mg in attaining cure [25].

2.4Fluconazole (FLC)

As itraconazole, fluconazole, a member of the azoles family, depletes ergosterol by blocking the cytochrome p450 enzyme 14 alpha-demethylase, which demethylates lanosterol. Yassin et al. [25] assessed the effectiveness of various concentrations at twelve combinations of nano-zinc or mineral zinc and FLC antifungal, as well as the "interaction between zinc in its two forms and the fluconazole antifungal on a biomass dry weight of colony (mg) on grown liquid sabouraud dextrose broth" media. On the ninth day of incubation, however, Microsporum canis produced significantly more keratinase than T. rubrum. Chitin building activity is impacted by azole chemicals, resulting in an uneven distribution of chitin inside the cell wall. This finding is consistent with a study by Suchodolski et al. [26] on the impact of the antifungal FLC on the plasma membrane of Candida albicans, which found that azole compounds prevent the production of arctrolytes by blocking the ERG11 gene-encoded enzyme 14 methyl sterol demethylase (P450 cytochrome). The frequency of dermatophyte species in the specific research region and their sensitivity to fluconazole, terbinafine, and itraconazole were investigated by Vernekar et al. [27]. Nevertheless, they have little fungicidal effect, and long-term fluconazole use causes resistant strains of Candida albicans to develop during therapy [28, 29]. The functions of major facilitator superfamily (MFS1) in dermatophytes' inherent resistance to CYH and chloramphenicol (CHL), which are frequently employed to isolate these fungi, as well as the degree to which MFS1 influences susceptibility to azole antifungals were examined by Yamada et al. [30]. To confirm the antifungal activity of the six isolates in vitro, Song et al.tested the antifungal susceptibility of five medications: amphotericin B, caspofungin, voriconazole, itraconazole, and fluconazole. While the original susceptible strain and the end resistant strain had low adhesion, hyphal development, and biofilm formation, four drug-intermediate strains have improved biofilm potential. The capacity for generating biofilms was not directly correlated with the level of fluconazole resistance.

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2.5Voriconazole (VRC)

Voriconazole (VRC), a second-generation triazole derivative, has demonstrated potential in the treatment of fungal infections. Compared to the control VRC hydrogel formulation (10.67 ± 0.03%) at 25°C (60% RH), the VRC in oil/PEG formulation (93.44 ± 1.59%) was stable for three months. In contrast with the formulation without the permeation enhancer, VRC penetration was nine times greater in the formulation containing Transcutol® P [32]. As 53.3% of the ITC group, 70% of the ITC/isotretinoin group, and 83.3% of the VRC group showed complete clinical cure, according to Khattab et al. [33]. Of the ITC group, 56.7% had a mycological cure, 83.3% had an ITC/isotretinoin group, and 86.7% had a VRC group. The three groups differed statistically significantly in favour of VRC, followed by the combined group. No notable negative consequences were noted. When compared to the other two groups, the voriconazole group's recurrence rate was noticeably lower. One potential future therapy option for resistant dermatophytosis is voriconazole.

This antifungal specifically inhibits the demethylation of 14- alpha-lanosterol, which lowers ergosterol. Voriconazole's pharmacokinetics are distinct due to its saturable, nonlinear metabolism, which is believed to be closely linked to its metabolic clearance [34]. Although VRC is a broad-spectrum antifungal medication, topical drug administration can reduce its severe systemic side effects. At skin pH (5.5), the optimised formulation exhibited a prolonged release of VRC up to 24 hours through a diffusion-based mechanism. The deposition of VRC in skin layers was validated by ex vivo permeability and skin retentivity tests. Potential antifungal efficacy against Aspergillus flavus and Candida albicans was demonstrated by the finished formulation [35]. Genes related to protease inhibitor activity and terminal epithelial development are down-regulated by voriconazole [36]. Regulating the FOXM1 tumorigenesis pathway, which is essential

for cell proliferation and frequently overexpressed in many epithelial malignancies, is a key component of voriconazole's mode of action [37, 38].

2.6Ketoconazole (KTC)

Ketoconazole (KTC) is an azole antifungal that inhibits the 14α- demethylase enzyme, which is necessary for fungi to produce ergosterol. It is frequently applied topically to treat dermatophyte infections, but its systemic usage has decreased because of liver toxicity concerns. Factors influencing C. albicans tolerance and resistance to ketoconazole were examined by Xu et al. [39]. Deletion investigation of known efflux pump genes revealed that MDR1 and CDR2 were expendable, whereas CDR1 was partly necessary for azole tolerance.Tao et al., [40] employed a high- throughput DNA sequencing approach to assess the cutaneous microbial populations of individuals with Seborrhoeic dermatitis before and after topical ketoconazole therapy. To determine the degree of KTC penetration into the skin, Ramzan et al. [41] conducted an in vivo dermatokinetics investigation in rats. The optimised, spherical KTZ-SLN formulation (KOF1) had a high EE of 88.5% with a particle size of 293 nm. Ex vivo penetration characteristics were much higher in KTC-SLNs than in free drug suspension (KTC-SUS) and commercial product (Nizral®; 2% KTC w/v), but in vitro release was gradual and persistent. Morteza et al. [42] sought to examine the properties, cellular safety, and antifungal efficacy of ketoconazole-loaded niosomes (ketosomes) with the highest cholesterol:surfactant ratio and the quickest drug release. The optimised ketoconazole-loaded niosome may be utilised as a potential nanovesicle for ketoconazole medication administration, according to the study's findings, which might lead to novel approaches for the treatment of cutaneous candidiasis symptoms.

2.7Posaconazole (POS)

Posaconazole (POS) is a relatively new, “broad- spectrum triazole antifungal active ingredient” that works against a variety of bacteria, including Aspergillus species, Candida species, Cryptococcus gattii, Cryptococcus neoformans, Fusarium oxysporum and Scedosporium apiospermum. Trichophyton tonsurans and Trichophyton rubrum are among the dermatophytes that it is effective against. The main purpose of POS is to prevent and cure invasive fungal infections, especially in individuals with weakened immune systems. It exhibits its antifungal effect by blocking the enzyme lanosterol 14α-demethylase, consequently interrupting ergosterol production and affecting fungal cell membrane integrity [43,44]. Consequently, research was done to determine if the chemical may be used in formulations meant for topical cutaneous application.Dual-cross-linked alginate hydrogels could enhance the effectiveness of posaconazole in treating antifungal infections, making it a promising dermatological formulation [45]. In order to enhance medication delivery and antifungal activity, Dutta et al. [46] set out to create a Posaconazole microemulsion-loaded chitosan transdermal film. The optimised microemulsion (MEP3) revealed the drug's encapsulation efficiency (94.81%), zeta potential (-2.77 mV), and globule size (20.52 nm). The created transdermal film had strong antifungal efficacy on a 29 mm zone of inhibition against Aspergillus niger and demonstrated a sustained drug release with a cumulative release of 77.91% in 48 hours. According to the current findings, the POS-chitosan film has the potential to improve aspergillosis management by improving the drug's bioavailability, reducing the frequency of doses, and releasing it gradually.

2.8Luliconazole (LUC)

Luliconazole (LUC), a broad-spectrum antifungal azole derivative, effectively inhibits the cytochrome P450 14- α-demethylase (CYP45014M) enzyme responsible for the production of the fungal outer cell membrane [47]. The partition coefficient (Log P) of LUC is 4.07, and its molecular weight is 354.28 Daltons. Luliconazole's dermal availability is restricted by its solubility, which is a rate-limiting step for its penetration into the lipid section of the stratum corneum [48-50].Using the broth microdilution technique, Das et al. [51] established the in vitro susceptibility profile of several dermatophyte isolates to eight antifungal medications. The MIC values for griseofulvin (0.125–8 μg/mL) and terbinafine (0.06–16 μg/mL) varied greatly; 13.1% and 52.6% of isolates, respectively, demonstrated resistance (MIC > 4 μg/mL) to both drugs. The antifungal effectiveness of luliconazole-loaded nanostructured lipid carriers (LUC-NLCs) against a panel of resistant fungus strains was assessed in vitro by Nosratabadi et al. [52]. All isolates of T. rubrum, T. tonsurans, and T. mentagrophytes were well inhibited by LUC, POS, VRC, ITC, and KTC. Tahiliani et al. showed that LUC displayed the lowest mean MIC values across several areas, notably Delhi and Kolkata [53,54]. As a topical treatment, LUC is now favoured due to its superior activity against filamentous fungus [55].

2.9Ciclopirox

Ciclopirox is a hydroxypyridone derivative that inhibits fungal metal-dependent enzymes by chelating polyvalent cations such as Fe3+, which is necessary for the enzymatic breakdown of hazardous metabolites. Ciclopirox works on a wide range of organisms, including bacteria, yeasts, dermatophytes, and some NDMs. Numerous research have looked into ciclopirox olamine as a potential sporicidal agent. It works by chelating polyvalent metal cations, which alters the fungal plasma membrane and inhibits a variety of cellular functions [56]. Compared to sertaconazole nitrate, ciclopirox olamine showed strong antifungal activity, but it required larger doses and was less effective in infected 3D skin models, particularly against yeast [11].

3.Host-Pathogen Interaction Genes

In invasive dermatophytosis, host vulnerability to dermatophytes is largely determined by immunological state and genetic variables [57]. Anthropophilic species typically cause chronic infections with mild inflammation, while geophilic and zoophilic species result in acute infections with severe inflammation. Keratinocyte responses to different dermatophyte species are key in the host-dermatophyte interaction. Genetic factors, including mutations in the CLEC7A gene and signalling pathways like STAT3 and CARD9, may increase susceptibility to dermatophyte infections [58-60. When "keratinocytes were incubated with the zoophilic dermatophyte T. benhamiae, the expression of genes encoding various proinflammatory chemokines and cytokines (IL-1A, IL-1β, IL-6, TNF, IL-23A, IL-8, and CXCL1), peptides with antimicrobial activity (HBD3, HBD2, RNASE7 and S100A7), and the pattern recognition receptor TLR2. Moreover, onychomycosis is linked to mutations in the HLA-DR8 haplotype, while invasive dermatophytosis is linked to mutations in the caspase recruitment domain-containing protein gene (CARD9) [61, 62]. In reaction to the dermatophyte invasion of the host tissue, which is linked to fungal species, certain cytokines will be produced. It has been demonstrated by Hau and associates that anthropophilic creatures would produce fewer cytokines. For instance, Trichophyton tonsurans will primarily cause keratinocytes to secrete IL-8, IL-6, and IL-1b [63]. Pro- inflammatory interleukins like IL-17, IL-6, IL-1β and TNF-α are often the interleukins that are researched since they are in charge of the immune response [64,65]. The immune response against dermatophytes was also observed to have high amounts of TGF-β and IL-22. However, dermatophytosis brought on by zoophilic species, such as IL-6,
IL-8, IL-10, IL-1b, IL-15, IL-2, and TGF-b," exhibits a far wider range of released cytokines. This results in more clinically significant lesions, driven by a substantial increase in inflammatory cells at the infection site, which are essential for fungal clearance, tissue healing, and remodelling [66]. The flow diagram for antifungal drugs and host-pathogen interactions in dermatophytes is displayed in Figure 2.

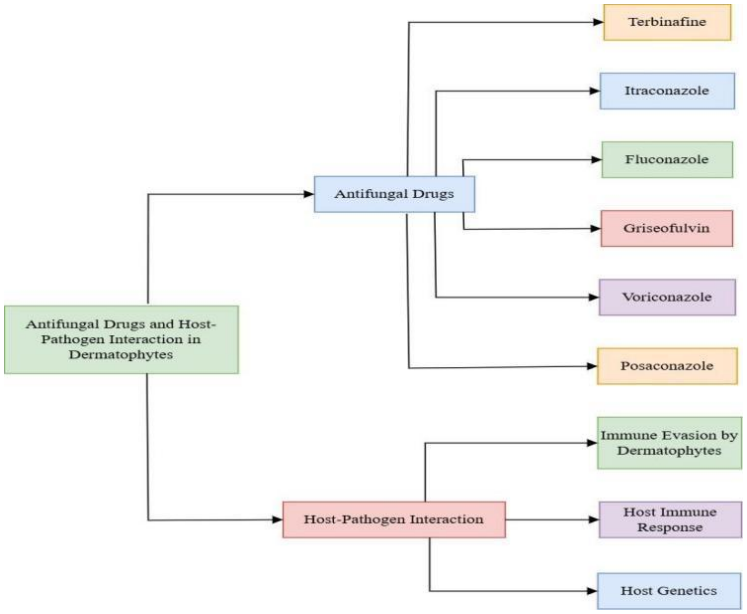

Figure 2. Antifungal Drugs and Host-Pathogen Interaction in Dermatophytes

4. Discussion

Drug resistance is a growing issue that impacts azoles and all other antifungal medications. A growing number of drug-resistant fungal species are being reported [67–70]. Therefore, utilising a range of strains linked to dermatomycoses, it is crucial to examine the sporicidal effects as well as the sensitivity of developing cells to both novel and ancient antifungal drugs [9,10]. According to Tahiliani et al. [71], griseofulvin had the lowest mean MIC among their isolates, while terbinafine's mean MIC was higher than the reference range, but itraconazole's was within the range. Terbinafine was the most successful antifungal drug in the Maharashtra trial by Ghuse et al. [72]. Terbinafine was also identified as the most effective antifungal medication by a small number of additional trials [69,70,73].

The antifungal resistance patterns of dermatophytes isolated from dermatophytosis patients were assessed by Siddiqui et al. [74]. They also looked at the resistance patterns of dermatophytes to commonly used antifungal medications (itraconazole, fluconazole and terbinafine) in patients with dermatophytosis. T. rubrum was the most prevalent dermatophyte species (69.44%) among the 120 patients. Fluconazole resistance was highest in T. rubrum (32%), followed by terbinafine (16%) and itraconazole (20%). Fluconazole resistance reached 36% in Trichophyton mentagrophytes, which had similar resistance patterns. Epidermophyton floccosum and Microsporum canis showed decreased resistance.

Increased resistance was observed to be significantly correlated with previous antifungal therapy. Table 1 illustrates the common antifungal medications for dermatophytes and their resistance.

Table 1: Common Antifungal Drugs for Dermatophytes and Their Resistance Status

Drug / Antifungal Agent	Class	Mode of Action (Target / Pathway)	Reported Resistance in Dermatophytes	Drug Dosage	Administration Route	Resistance Mechanism	Clinical Implications	Alternative Treatments	References
Terbinafine	Allylamine	Inhibits squalene epoxidase → blocks ergosterol synthesis	Yes — increasing reports, particularly in Trichophyton species	250 mg daily (oral)	Oral / Topical	Point mutations in squalene epoxidase gene (e.g., L393F, F397L)	Common first-line treatment for dermatophytosis	Itraconazole, fluconazole (oral treatment)	[75], [76], [77]
Itraconazole	Triazole	Inhibits lanosterol 14-α-demethylase → disrupts ergosterol synthesis	Rare / Emerging	100-200 mg daily (oral)	Oral	Mutation in lanosterol 14-α-demethylase gene, efflux pumps	Effective for systemic dermatophytosis; potential for resistance	Terbinafine, griseofulvin (alternative)	[78], [79], [80]
Fluconazole	Triazole	Inhibits ergosterol biosynthesis via lanosterol 14-α-demethylase	Yes — frequently reported reduced susceptibility	150-200 mg weekly (oral)	Oral	Altered binding site of 14-α-demethylase, efflux pumps	Often less effective than other azoles for dermatophytes	Itraconazole, posaconazole	[79], [81], [82]
Griseofulvin	Benzofuran derivative	Disrupts fungal mitosis by interfering with microtubules	Rare, but documented resistance	500 mg daily (oral)	Oral	Microtubule inhibition and resistance due to cell membrane transport mutations	Use is less common due to newer drugs, but still effective for hair and scalp infections	Terbinafine, fluconazole	[82], [83]
Voriconazole	Triazole	Inhibits ergosterol synthesis by blocking lanosterol 14-α-demethylase	Emerging	200 mg twice daily (oral)	Oral	Cross-resistance with itraconazole due to similar mechanism of action	Limited evidence for dermatophyte infections, used off-label	Itraconazole, posaconazole	[84], [85]
Posaconazole	Triazole	Inhibits ergosterol biosynthesis via lanosterol 14-α-demethylase	Emerging	100 mg twice daily (oral)	Oral	Resistance via mutation in lanosterol 14-α-demethylase	Considered for resistant dermatophytes, with limited studies for dermatophytes	Voriconazole, itraconazole	[86]
Ciclopirox	Hydroxypyridone	Inhibits ergosterol synthesis and interferes with fungal cell membrane integrity	No	1-2 applications per day (topical)	Topical	Resistance is extremely rare	Used topically for various dermatophyte infections, including onychomycosis	Terbinafine, imidazoles (e.g., clotrimazole)	[87]
Amorolfine	Morpholine	Inhibits fungal ergosterol synthesis by blocking squalene epoxidase	No	1-2 applications per week (topical)	Topical	No known resistance reported	Used topically for onychomycosis, effective against dermatophytes	Terbinafine, ciclopirox	[88]

5. Challenges in Managing Antifungal Resistance in Dermatophytes

Antifungal resistance in dermatophytes is quite complicated to manage in relation to many factors, such as limitations of diagnostics, glacial speed of antifungal drug development, and environmental and clinical factors that contribute to

resistance. The insufficiency of diagnostic devices is one of the main barriers that complicate the timely or accurate identification of the resistant strain of dermatophytes and the primary causes of delayed or incorrect treatment, and the further deepening of the progression of the infection. Moreover, the rate of development of antifungal drugs has been slow, and this has created a vacuum in the provision of new and effective therapeutic agents, thereby making it difficult to effectively control resistant infections. The resistance has also been increased by factors in the environment,

6. Conclusion and Future Therapeutic Strategies

The rising rate of antifungal resistance in dermatophytes demonstrates the necessity of novel treatment modalities to overcome the problem of treating the superficial fungal infections (SFIs). The conventional antifungal drugs like terbinafine and itraconazole are still at the centre of the management of dermatophyte infections. Nevertheless, the emergence of resistance to these drugs is a reason why it is important to develop new antifungal drugs that act against new pathways and mechanisms in dermatophytes, which provide a chance to overcome the current resistance. Moreover, combination therapy, which is the combination of the use of several drugs with dissimilar action mechanisms, is a promising approach in terms of improving the effect of treatment, as well as reducing the chances of resistance. This method enables synergistic activity, and this may prevent or postpone the emergence of resistance since it targets other stages of the life cycle of the fungus.

Moreover, host-directed treatments can be considered the future of treating dermatophytes. These treatments are to regulate the body's immune response, which improves the body's own defence, fighting the infections without attacking the pathogen directly and therefore minimising the possibility of resistance. Simultaneously, the prospects of immunotherapy and creating vaccines provide the long- range results of preventing the recurrence of the infection in particular, particularly in patients with a predisposition to chronic dermatophytosis. Nanotechnology-based

including the massive use of antifungal agents in agriculture and in the clinical field. This has enhanced resistance due to inappropriate antifungal drug use, such as over-prescription, misuse, and inappropriate dosage, especially among the immunocompromised population. All these along with long periods of medication contribute to the development of adaptation and survival of dermatophytes, which increases the risk of treatment failure. Antifungal resistance has a significant effect on health globally as it results in increased healthcare expenditure, disease-related complications, and treatment failure, which is overwhelming healthcare systems across the world. Addressing these challenges would require a development of diagnostic capacity, expediting drug development, and advancing rational use of antifungal drugs in clinical practice and agricultural practice, taking into consideration the overall environmental factors or trends that lead to the resistance problem.

therapeutics is another strategy that is emerging, and this enhances the ability to penetrate the site of the infection with the drugs to improve drug efficacy and minimise systemic side effects. These innovations in drug delivery are vital with regard to realising the pharmaceutical potential of the available use of current and emerging antifungal agents.

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