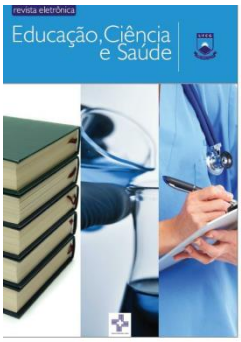

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PHARMACOLOGICAL TREATMENT OF DERMATOPHYTOSES: NARRATIVE REVIEW

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Abstract

Dermatophytoses, commonly known as "tinea" or "ringworm," are common cutaneous fungal infections caused by a group of fungi known as dermatophytes, affecting the skin, hair, and nails of a significant portion of the global population. The objective is to review the literature on the main pharmacological classes and drugs used in the treatment of tinea. This is a narrative review based on articles published between 2013 and 2023 in the Lilacs, SciELO, and PubMed databases, prioritizing publications in English. The main drugs used to treat tinea include fluconazole, ketoconazole, itraconazole, miconazole, clotrimazole, terbinafine, griseofulvin, and amorolfine. Moreover, the key resistance mechanisms to antifungal drugs marketed against dermatophytoses include enzymatic overexpression and permeability alterations. In this context, numerous molecules with anti-dermatophyte potential have been studied, with luliconazole standing out. Despite advancements in treatment, challenges remain, such as fungal resistance and the need for a personalized approach. Collaboration among dermatologists, mycologists, and pharmacists is essential to optimize therapeutic outcomes and improve the quality of life of patients affected by dermatophytoses.

Keywords: dermatophytes, infections, antifungals.

Resumo

As dermatofitoses, conhecidas como popularmente como “tinhas”, são infecções fúngicas cutâneas comuns causadas por um conjunto de fungos denominados dermatófitos, sendo responsáveis por afetar a pele, o pelo e as unhas de grande parte da população mundial. Objetiva-se realizar uma revisão da literatura sobre as principais classes farmacológicas e fármacos utilizados no tratamento das *tineas*. Revisão do tipo narrativa, com busca de artigo publicados entre 2013 a

2023, nas bases de dados Lilacs, Scielo e PubMed, priorizando-se publicações em língua inglesa. Os principais fármacos utilizados para o tratamento das tinhas são: fluconazol, cetoconazol, itraconazol, miconazol, clotrimazol, terbinafina, griseofulvina e amorolfina. Ademais, os principais mecanismos de resistência aos fármacos antifúngicos comercializados contra as dermatofitoses foram principalmente: superexpressão enzimática e alterações de permeabilidade. Nesse contexto, evidenciou-se que inúmeras moléculas com potencial anti-dermatófitos têm sido estudadas destacando-se o luliconazol. Apesar dos avanços no tratamento, desafios persistem, como a resistência fúngica e a necessidade de uma abordagem individualizada. A colaboração entre dermatologistas, micologistas e farmacêuticos é essencial para otimizar os resultados terapêuticos e melhorar a qualidade de vida dos pacientes afetados por dermatofitoses.

Palavras-chave: dermatófitos, infecções, antifúngicos.

1 Introduction

Dermatophytoses, commonly known as *ringworm*, are a group of superficial fungal infections affecting the skin, hair, and/or nails (ANDRADE JÚNIOR et al., 2020). These mycoses are caused by a group of fungi commonly referred to as dermatophytes, which are classified into three genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*. These pathogens can be geophilic, zoophilic, or anthropophilic, keratinolytic and keratinophilic, filamentous, and belong to the phylum Ascomycota, class Eurotiomycetes, order Onygenales, and family Arthrodermataceae (MOSKALUK; VANDEWOUDE, 2022).

The signs and symptoms of these infections, although not considered severe, can vary depending on the affected area and the type of fungus involved. They generally present with characteristic skin lesions such as reddish, scaly patches, intense itching, and sometimes the formation of blisters or vesicles. In the nails, dermatophytoses can cause changes such as discoloration, thickening, and brittleness (AL-KHIKANI, 2020).

Furthermore, these conditions can affect 20 to 25% of the global population during their lifetime, with the species *Trichophyton rubrum* being the most commonly associated with human infections, where up to 70% of adults are asymptomatic carriers of dermatophytes (PETRUCELLI et al., 2020), particularly in tropical and subtropical regions where environmental conditions favor the growth of these pathogens (SOARES et al., 2017).

Pharmacological treatment of dermatophytoses is a constant area of interest in dermatology and medical microbiology. Proper selection of the antifungal agent and therapeutic regimen is essential to ensure therapeutic efficacy, minimize drug resistance, and prevent potential adverse effects

(SOARES et al., 2021). Additionally, the complexity of these infections, coupled with the diversity of dermatophyte species involved, makes treatment a challenging task for healthcare professionals (LANA et al., 2016; SANTOS et al., 2022; SILVA, 2022). Moreover, clinical factors such as the extent of infection, presence of comorbidities, and patient immunocompetence influence treatment response and efficacy (ANDRADE JÚNIOR et al., 2020; MADUREIRA, 2018; CECONI et al., 2018).

This study aims to conduct a literature review on the main pharmacological classes and drugs used in the treatment of ringworm infections.

2 Methodology

2.1 Study Type

This study consists of a narrative bibliographic analysis (ANDRADE JÚNIOR et al., 2021).

2.2 Search Strategy

To search for articles, the following keywords were used: 1) Fungi; 2) Filamentous fungi; 3) Pharmacological treatment; 4) Pharmacotherapy; 5) Antifungals; 6) Dermatophytes; 7) Drug interactions; 8) Resistance phenomena; 9) Fungos; 10) Hongos filamentosos; 11) Tratamiento farmacológico; 12) Farmacoterapia; 13) Antifúngicos; 14) Dermatofitos; 15) Asociación entre drogas; 16) Fenómenos de resistencia. To allow for various combinations, different terms were combined using the boolean operator "AND" to define the search relationship (ANDRADE JÚNIOR et al., 2021).

2.3 Inclusion and Exclusion Criteria

The selected studies addressed concepts, mechanisms of action of antifungal medications, combinations of these medications, resistance phenomena, and their adverse effects. The search was based on scientific articles published in English, Portuguese, and Spanish, covering publications from 2013 to 2023. Monographs, dissertations, theses, and editorials were excluded from the study.

2.4 Information Sources

Articles were retrieved from the following databases: Lilacs (Latin American and Caribbean Center on Health Sciences), Scielo (Scientific Electronic Library Online), and PubMed.

3 Literature Review

3.1 Current Treatment of Dermatophytoses

In the context of pharmacological treatment of dermatophytoses, various drugs and pharmacological classes are utilized to achieve therapeutic efficacy and minimize adverse effects. The main drugs employed include azoles, allylamines, griseofulvin, and amorolfine, each with its specific action characteristics and therapeutic indications (Table 1) as well as specific mechanisms of resistance (Table 2) (ANDRADE JÚNIOR et al., 2020; SILVA et al., 2022).

Table 1: Drugs Used in the Treatment of Dermatophytoses.

Author and Year	Drug(s) Used	Therapeutic Indication	Adverse Effects
Silva et al., 2022; Rakhshan et al., 2023	Fluconazole	Deep dermatophytosis in immunocompromised patients	Hepatic injury.
Ardeshna et al., 2016	Itraconazole	*Tinea corporis* and *tinea cruris*	Gastric disturbances, headache, altered taste, jaundice, and rarely, hypokalemia, torsades de pointes, and heart failure.
Rakhshan et al., 2023	Ketoconazole	Superficial mycoses and invasive infections	Headache, dizziness, itching, nausea, vomiting, abdominal pain, diarrhea, constipation, abdominal distention, increased liver enzymes, hepatotoxicity, and

			gynecomastia.
Rakhshan et al., 2023	Miconazole	Superficial mycoses and invasive infections	Hepatic injury.
Rakhshan et al., 2023	Clotrimazole	Micoses superficiais	Hepatic injury.
Majid et al., 2016	Terbinafine	*Tinea corporis* and *tinea cruris*	Gastric disturbances, headache, altered taste, changes in liver function tests, and rash; rarely, it can cause blood dyscrasias and hepatitis.
Chen et al., 2016	Griseofulvin	Onychomycosis and *tinea capitis*	Itching, abdominal discomfort, headache, and nausea.
Olson; Troxell, 2023	Amorolfine	Onychomycosis	Photosensitivity, fixed drug eruption, petechiae, itching, and urticaria.

Source: Author (2024)

In the treatment of dermatophytoses, various classes of drugs are employed, each with its specific mechanism of action and therapeutic potential. It is crucial to understand how these drug classes are used, which types of tinea they are indicated for, and the resistance mechanisms associated with each.

In this context, azoles such as fluconazole, itraconazole, and ketoconazole are widely used in the treatment of dermatophytoses due to their effectiveness against fungi. They work by inhibiting the enzyme lanosterol 14-α-demethylase, which is essential for the synthesis of ergosterol, a crucial sterol in the fungal cell membrane. This action compromises the membrane's integrity. Azoles are frequently prescribed for superficial tinea infections, such as tinea corporis, tinea cruris, and tinea pedis (FONSECA, 2018).

Allylamines, represented by terbinafine, are another important group of antifungals used in the treatment of dermatophytoses. Terbinafine inhibits squalene epoxidase, an enzyme involved in ergosterol biosynthesis. By blocking this step, the drug compromises the integrity of the fungal cell

membrane, leading to fungal death. Allylamines are often prescribed for tinea corporis, tinea cruris, and tinea pedis, as well as deeper infections like tinea capitis (SILVA et al., 2022).

Table 2: Main Drugs Used Against Dermatophytosis and Their Resistance Mechanisms.

Author and Year	Drug	Mechanism of Resistance
Madureira et al., 2018	Griseofulvin	Resistance mechanisms to griseofulvin are not fully elucidated but include reduced drug entry into fungal cells due to permeability changes or alterations in affinity for cellular targets.
Santos et al., 2022	Amorolfine	Resistance mechanisms to amorolfine are still poorly understood but may include alterations in ergosterol biosynthesis pathways, enzyme overexpression, or changes in fungal cell membrane permeability.
Silva et al., 2022	Terbinafine	Resistance mechanisms to allylamines are associated with mutations in the target gene, causing structural modifications in the enzyme squalene epoxidase or its overexpression.
Fonseca, 2018	Azoles	The most common resistance mechanism associated with azoles is changes in the expression or structure of the target enzyme, reducing drug affinity and decreasing efficacy.

Source: Author (2024)

Griseofulvin, a classic antifungal, is used in the treatment of dermatophytoses, especially in cases of chronic or resistant infections. Its mechanism of action involves interference with fungal mitosis by inhibiting the formation of the mitotic spindle and preventing cell division, making it indicated for tinea capitis and tinea corporis (MADUREIRA et al., 2018). In contrast, amorolfine is a broad-spectrum antifungal that inhibits ergosterol biosynthesis, similar to allylamines. However, its antifungal activity is more focused on filamentous fungi like dermatophytes. This active ingredient is frequently used in the topical treatment of tinea pedis and tinea unguium (SANTOS et al. 2022).

In severe cases of dermatophytoses, treatment becomes even more crucial due to the increased risk of complications and infection spread.

Therapeutic approaches in these situations often require the use of more potent and prolonged antifungal agents to effectively control the infection and prevent recurrences (SOARES et al., 2017).

A significant example is deep dermatophytosis in immunocompromised patients caused by *Trichophyton rubrum*, as reported by Silva et al. (2022). In these cases, the fungal infection may spread to deeper tissues, such as muscles and internal organs, presenting significant morbidity and mortality risks. The study highlighted the use of fluconazole as an effective therapeutic option, showing an 85% therapeutic success rate after treatment. These results underscore the importance of aggressive treatment in severe cases of dermatophytoses to prevent serious complications.

Another atypical situation is when atopic dermatitis is associated with fungal infection, which can present a more severe clinical course with extensive and recurrent skin lesions. The use of griseofulvin, despite its potential adverse effects, may be necessary to control both the fungal infection and the symptoms of dermatitis, improving the patient's quality of life (FONSECA, 2018).

Similarly, in individuals with hypercortisolism, as reported by Santos et al. (2022), dermatophytosis can become more severe due to cortisol-induced immunosuppression. In these cases, appropriate treatment is crucial not only to control the fungal infection but also to avoid additional complications related to the underlying condition. The case report highlighted the use of amorolfine as an effective therapeutic option, resulting in complete remission of clinical signs in 95% of treated cases.

Furthermore, when considering combination therapy for dermatophytoses, it is crucial to assess the synergy between different classes of antifungal drugs. Combining antifungal agents can offer therapeutic advantages such as increased efficacy, reduced microbial resistance, and expanded action spectrum (ANDRADE JÚNIOR et al., 2019; FOLEY et al., 2020; LIRA et al., 2020).

For example, combining fluconazole with terbinafine may be a promising strategy in treating severe or resistant cases of dermatophytoses. While azoles work by inhibiting ergosterol synthesis in the fungal cell membrane, allylamines interfere with the same pathway, providing a synergistic antifungal effect that may enhance the eradication of the infecting fungus (SOARES et al., 2021).

Additionally, combination therapy may be particularly beneficial in cases of recurrent or chronic dermatophytoses, where monotherapy may not be sufficient to control the infection effectively. This approach can help overcome microbial resistance and reduce the risk of reinfection, providing a more comprehensive and effective treatment strategy (FOLEY et al., 2020; ANDRADE JÚNIOR et al., 2023; ANDRADE JÚNIOR et al., 2024).

However, it is important to highlight that combining antifungal drugs can increase the risk of adverse effects and drug interactions, requiring careful and individualized monitoring throughout the treatment course. Thus, a thorough evaluation of the therapeutic benefit versus potential risks is essential when considering combination therapy for dermatophytoses.

3.2 Resistance Phenomena

It is important to emphasize that irrational use of antifungals can lead to the development of resistance and toxicity, compromising treatment effectiveness and patient safety. Therefore, the choice of drug and the duration of treatment must be carefully evaluated by healthcare professionals, taking into account factors such as the type of infection, the severity of the clinical picture, and the susceptibility of the etiological agent to available drugs (RABAAN et al., 2023). Pharmacological treatment of dermatophytoses generally involves the use of topical antifungals, and in more severe or resistant cases, systemic antifungals (LANA et al., 2016).

At this point, it is crucial to discuss the resistance mechanisms that dermatophytes can develop in response to the continuous use of antifungal drugs currently employed in the treatment of dermatophytoses (Table 2).

Increased antifungal resistance can compromise treatment effectiveness, making it difficult to control the infection and contributing to the spread of the disease. Studies have highlighted the emergence of azole-resistant dermatophyte strains, such as those resistant to fluconazole, and allylamine-resistant strains, such as those resistant to terbinafine, posing a significant challenge in managing cutaneous fungal infections (CECONI et al., 2018). Resistance to antifungals can occur due to various mechanisms, including changes in cell wall composition, overexpression of efflux pumps, and

mutations in the target genes of antifungal drugs, thereby reducing their therapeutic efficacy (SILVA et al., 2022; SOARES; SÉRVIO, 2022).

Additionally, it is necessary to emphasize that resistance to antifungals is not limited to dermatophytes isolated from human patients but can also be observed in dermatophytes from companion animals, such as dogs and cats. The spread of resistant strains among animals can represent a potential reservoir of resistance, increasing the risk of transmission to humans and further complicating the control of dermatophytoses (SANTOS et al., 2022).

Given this scenario, it is essential to closely monitor antifungal resistance and implement effective infection control strategies, including rationalizing antifungal use, developing new therapeutic agents, and adopting prevention and control measures in environments with high prevalence of dermatophytoses (COWEN et al., 2014).

One of the primary forms of resistance of dermatophytes to antifungals is modification of cell wall composition, which can reduce the permeability of antifungals, preventing their entry into the fungal cell and thus their effectiveness (LANA et al., 2016). Additionally, drug efflux activity, where dermatophytes actively pump antifungals out of the cell, is another commonly observed resistance mechanism (Andrade Júnior et al., 2020).

Another resistance mechanism of dermatophytes to antifungals is the mutation or overexpression of antifungal target genes. For example, changes in the gene encoding the enzyme 14-α-demethylase, a target of azoles, can reduce the affinity of the antifungal for the binding site, making dermatophytes less sensitive to azoles (ANDRADE JÚNIOR et al., 2020).

Furthermore, dermatophytes' ability to form biofilms on both biotic and abiotic surfaces contributes to resistance to antifungals, as biofilms provide a protective environment that hinders antifungal penetration and promotes fungal survival (ROCHA, 2022).

These resistance mechanisms of dermatophytes to antifungals highlight the need for alternative therapeutic strategies and the development of new antifungal agents with different targets and mechanisms of action. Approaches such as combination therapy, which uses multiple antifungals with different modes of action, and the development of antifungal agents targeting new

molecular targets in dermatophytes, are promising research areas to address the growing challenge of antifungal resistance (MADUREIRA et al., 2018).

The search for effective solutions to overcome dermatophyte resistance to antifungals is not limited to the development of new therapeutic agents. Complementary strategies, such as preventing the spread of fungal infections, improving personal and environmental hygiene practices, and educating on the proper use of antifungals, are equally important for controlling the spread of dermatophytoses and reducing selective pressure on existing antifungal agents (REDDY; PADMAVATHI; NANCHARAIAH, 2022).

Moreover, implementing epidemiological surveillance measures to monitor the prevalence of antifungal resistance and identify resistance patterns in different geographic regions is crucial for guiding public health policies and directing resources to areas with the greatest need for intervention (LANA et al., 2016).

3.3 Promising New Molecules Against Dermatophytes

Luliconazole is a new promising drug for the treatment of skin fungal infections. However, its current therapy is limited by slow skin absorption, requiring prolonged use and repeated doses for effective treatment due to its low solubility (MOUSAVI et al., 2023). This substance can be used to treat skin fungal infections such as athlete's foot (tinea pedis), jock itch (tinea cruris), and fungal skin infections caused by dermatophytes, yeasts, and other fungi. It belongs to the azole class, classified as an imidazole, which works by inhibiting ergosterol synthesis, an essential component of the fungal cell membrane, leading to fungal death (KHANNA; BHARTI, 2014).

This drug is available in the form of a cream or topical solution for application to the affected skin. It is generally applied once a day, for a period determined by the physician, varying according to the severity of the infection. Common side effects include itching, irritation, burning, or redness at the application site. Rarely, severe allergic reactions may occur. It is important to consult a physician if persistent or severe side effects occur (KHANNA; BHARTI, 2014).

Recent studies have explored the potential of natural compounds, such as riparin 2 and its homologues nor-2 and dinor-2, in combating dermatophytes.

Research indicates that these compounds exhibit antibiofilm activity in vitro and ex vivo against dermatophytes, suggesting their potential as therapeutic alternatives for treating these infections (JARTARKAR et al., 2022). The underlying mechanism of these compounds' therapeutic potential is related to their ability to destabilize and prevent biofilm formation, making dermatophytes more susceptible to conventional treatments and facilitating their elimination (ROCHA, 2022).

However, it is important to recognize that the development of new antifungal agents and the enhancement of therapeutic strategies face significant challenges, including the cost and time required for research and development, as well as regulatory and access issues for innovative treatments in developing countries (NOCUA-BÁEZ et al., 2020).

In this context, collaboration between academic institutions, the pharmaceutical industry, and regulatory agencies is essential to drive progress in antifungal therapy and ensure that patients affected by dermatophytoses have access to effective and safe treatments (MIETHKE et al., 2021). Additionally, it is crucial to promote awareness of the importance of early diagnosis and appropriate treatment of dermatophytoses among healthcare professionals and the general population to reduce morbidity and improve the quality of life of patients affected by these fungal infections (JARTARKAR et al., 2022).

3.4 Non-Pharmacological Measures

It is recommended to wash the affected area with water and neutral soap, dry it completely, and avoid sharing towels or personal hygiene items. Moreover, keeping the skin dry and well-ventilated is crucial, especially in sweat-prone areas such as feet and groin, by wearing light clothing, changing socks regularly, and avoiding tight footwear. Additionally, sharing personal items should be discouraged to prevent fungal transmission, and moist environments should be regularly disinfected to prevent infections. Furthermore, for cases of dermatophytosis on the scalp or nails, it is important to keep the hair clean and dry, avoid excessive use of hair products, and regularly trim the nails (ANDRADE JÚNIOR et al., 2020; AL-KHIKANI, 2020).

4 Conclusion

Antifungal agents have been the cornerstone of dermatophyte infection treatment, with azoles, allylamines, and morpholine derivatives being the most widely used classes. Furthermore, the primary mechanisms of resistance to marketed antifungal drugs for dermatophytoses have been mainly enzymatic overexpression and permeability changes. In this context, numerous molecules with potential anti-dermatophyte activity have been studied, with luliconazole being particularly noteworthy.

In conclusion, pharmacological treatment of dermatophytoses continues to evolve, with new therapeutic options and promising strategies being developed. However, an integrated and individualized approach to managing these infections is essential, with a focus on treatment adherence, clinical monitoring, and prevention of fungal resistance. Collaboration among dermatologists, mycologists, and pharmacists is crucial to optimizing therapeutic outcomes and improving the quality of life for patients affected by dermatophytoses.

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