UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE FARMÁCIA

TRABALHO DE CONCLUSÃO DE CURSO EM FARMÁCIA

PATRÍCIA ABREU PEREIRA

DERMATOPHYTOSIS PROFILE, EPIDEMIOLOGY, VIRULENCE AND SUSCEPTIBILITY IN THE LAST TWENTY YEARS: A LITERATURE REVIEW

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Trabalho de conclusão de curso de graduação apresentado para obtenção do grau de farmacêutico (a) do curso de Farmácia da Universidade Federal do Rio Grande do Sul

Orientadora: Prof.ª Dra Adelina Mezzari

Porto Alegre, 2021

Eu tentei 99 vezes e falhei, mas na centésima tentativa eu consegui, nunca desista de seus objetivos mesmo que esses pareçam impossíveis, a próxima tentativa pode ser a vitoriosa.

Albert Einstein

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Dermatophytosis profile, epidemiology, virulence and susceptibility in the last twenty years: a literature review

Perfil das dermatofitoses, epidemiologia, virulência e suscetibilidade, nos últimos vinte anos: uma revisão de literatura

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ABSTRACT: The present study aims to review of the last 20 years of literature, between 2000 and 2020, of the epidemiological studies on superficial and cutaneous mycoses caused by dermatophyte fungi, their etiological agents, as well as the susceptibility and resistance factors to the antifungals used for their treatment. The literature review was carried out in the online databases*: PubMed, Scielo* and *Science Direct*. The selected studies presented data on the prevalence of species, the profile of patients, the most affected sites of infection, the diagnostic method used and the susceptibility profile of some species of fungi in relation to the most used antifungals. The dermatophyte fungi species: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis e Epidermophyton floccosum* were the most commonly found in cutaneous infections caused by fungi in several countries. The most prevalent sites of infection are skin, nail and hair. The antifungals tested against the most prevalent pathogen were ketoconazole, fluconazole, ciclopirox and terbinafine. The results obtained in this study point to *Trichophyton rubrum* as the most isolated species in skin infections caused by dermatophyte fungi in different regions of the world. Terbinafine, compared to most fungal isolates, was the drug that showed the greatest efficacy.

Keywords: dermatophytes, dermatomycoses, dermatophytosis, superficial mycoses, antifungals.

INTRODUCTION

Superficial mycoses are infections caused by fungi that affect tissues such as skin, hair and nails. The main causative agents of this disease are a group of keratinophilic filamentous fungi called dermatophytes, which use the keratin present in the tissues as a nutrient[1] (Peres, 2010). The dermatomycosis caused by dermatophytes are also known as dermatophytosis. Epidemiological studies indicate that superficial and cutaneous mycoses are among the most prevalent diseases in the world, affecting all age groups and generating millions of dollars in treatments every year[19](Almeida, 2009). Between mycoses, dermatophytosis are the most common fungal infections in man worldwide[9].

Dermatophytosis is caused by three genera of dermatophytes, *Trichophyton*, *Microsporum* e o *Epidermophyton*. The most isolated clinical species are *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis* e *Epidermophyton floccosum*[2] (Magagnin, 2011) It is estimated that about 10 to 15% of the world population, can be infected by dermatophytes during their lifetime.[17] (Siqueira, 2006). Climatic factors, as well as social practices, population migration, individual characteristics, including age, abnormal nail morphology, genetic factors and inadequate hygiene conditions can contribute as epidemiological factors for these infections. Some diseases as *diabete mellitus,* immunodeficiency, immunosuppression, peripheral vascular disease, skin-related disorders, such as hyperhidrosis and psoriasis, use of tight shoes and nail trauma are also risk factors that can affect the epidemiology of dermatophytosis [1,2] (Peres, 2010; Magagnin, 2011).

Dermatophytosis can affect both humans and animals [4] (Nweze, 2011) and may be asymptomatic between 30% to 70% of the adult population[2] (Magagnin, 2011). The highest incidence occurs in regions of tropical and subtropical climate, where there is a predominance of hot and humid weather, causing a relevant public health problem [3,10,17] (Souza, 2012; Dias, 2013; Siqueira, 2006). Transmission can occur through direct contact with infected humans and infected animals or by indirect contact, through contaminated fomites. Although these mycoses are not serious in terms of mortality or psychological morbidity, they have substantial clinical consequences, producing chronic skin lesions that are difficult to treat. In addition, they affect the quality of life of patients, cause disfigurement, impacting self-esteem, vanity and social discrimination [13] (Pires, 2014).

The control of fungal infections depends initially on the host's immune response. The disease sets in when there is a failure in the individual's immune defenses or when the pathogen evades the host's responses, leading to the need to use fungicidal or fungistatic drugs that act specifically against the offending agent. However, this specificity is still limited due to little knowledge in several areas of pathogen biology, such as the factors responsible for the virulence and pathogenicity of fungi, as well as the mechanisms of resistance to drugs available on the market. Antifungals commonly used still have a limited number of cellular targets, such as ergosterol, the enzymes involved in their synthesis, the synthesis of nucleic acids of the cell wall and the formation of microtubules [1] (Peres, 2010).

As for epidemiology, surveys already carried out in Brazil and in the world show a high frequency of these superficial and cutaneous mycoses. There are many clinical manifestations, and may compromise the hands, feet, nails, skin fold regions, glabrous skin and others. The diagnosis is made mostly by direct microscopic examination and culture of biological material. [20] (Steiner, 2018).

The main groups of systemic antifungals that are commonly used for the treatment of superficial and cutaneous mycoses are imidazoles (ketoconazole), triazoles (fluconazole and itraconazole) and allylamine (terbinafine). Currently, there is a range of antifungals available, both topical and systemic, but the therapeutic arsenal is still quite restricted, been evident the need for new, more effective and less toxic antifungals [19](Almeida, 2009). The spectrum of activity of these antifungals is variable, and can lead to therapeutic failures, possibly due to low patient compliance, lack of drug penetration, drug bioavailability, drug interactions or resistance [2] (Magagnin, 2011).

An appropriate treatment choice is determined by the site and extent of the infection, the species involved, as well as the effectiveness, safety profile and pharmacokinetics of the available antifungals. Therapy with topical agents can be done with imidazole agents, such as tioconazole and miconazole, or with griseofulvin, whose therapeutic success is equivalent to 75% of cases. Another recommendation for topical treatment is the use of ciclopirox olamine, an alternative treatment for fungal infections, particularly when used in combination with other antifungals, such as amorolfine or ketoconazole. As

for oral therapy, terbinafine, itraconazole, ketoconazole and fluconazole are the antifungal agents, all of which are the treatment of choice for dermatophytosis when they do not respond to therapies with topical drugs. However, the use of these medications can cause undesirable effects to the patient. Terbinafine, despite having low toxicity, can cause gastrointestinal and skin side effects. The use of azoles has disadvantages, such as hepatotoxicity and hepatic metabolism via cytochrome P450 (CYP), which influences the metabolism of other drugs.[2] (Magagnin, 2011).

In an attempt to increase the cure rate, combined therapy with topical, oral antifungals and anti-inflammatory agents has been used. [13] (PIRES, Carla Andréa Avelar et al, 2014). Treatment is based on the choice of available therapeutic schemes and minimization of possible adverse effects and drug interaction. Treatment is not always simple, because there is a difficulty in choosing the available therapeutic schemes as well as their possible drug interactions and negative effects [10] (Dias, 2013).

The main biochemical and molecular mechanisms that contribute to the drug resistance phenotype in eukaryotes are the reduction of their uptake, modification or metabolic degradation by the cell. Also changes in the interaction of the drug with the target site or with other enzymes involved in the same enzyme pathway. And point mutations, overexpression of the target molecule, amplification, and gene conversion, that is, recombination and increased cell efflux, for example, greater expression of efflux pumps. Antifungals induce cell stress responses necessary to overcome their toxic effects, allowing the fungus to survive[1] (Peres, 2010).

The performance of *in vitro* sensitivity tests is extremely important to assess the susceptibility profile of the etiologic agents in relation to the antifungal drugs available for therapy. The analysis of the results of these trials allows the comparison and choice of available drugs, ensuring the effectiveness of the treatment of fungal infections[2] (Magagnin, 2011).

Among the drugs with a different mechanism of action than azoles, there is terbinafine, belonging to the class of allylamines, acting on the epoxidase enzyme of the fungal cell. It is especially indicated for superficial and skin infections caused by fungi of the dermatophyte group. Terbinafine has a fungicidal action in addition to allowing joint administration with other drugs. Its side or toxic effects are considered mild, the most common being gastrointestinal disorders and changes in taste. [28] (Hilda, 2010).

In vitro tests are essential to assess antimicrobial susceptibility for adequate antibiotic therapy. They contribute to the choice of the best treatment alternative, reducing the possibility of therapeutic failure. However, unlike bacteria and yeasts, the standardization of methods for assessing the susceptibility of filamentous fungi, dermatophytes or non-dermatophytes against antifungal agents has limitations.[19] (Almeida, 2009).

In general, the species of fungi that frequently cause infections in humans already have known profiles of susceptibility to antifungals, thus guiding the clinician to initiate therapy, when it is not possible to access the Minimum Inhibitory Concentration (MIC) [12] (Spampinato, 2013).

It is important to know the biological characteristics of the main agents, as it allows directing treatment. As an example, we have the different species of *Trichosporon* that have different susceptibility to antifungals.[18] (Tapia, 2009).

MATERIAL AND METHODS

A literature review, of the last 20 years , was carried out, through a systematic search, in the online databases *PubMed, Scielo* and *Science Direct*. The terms used in the database search were “superficial mycoses" AND “Dermatomycoses” AND "dermatophytoses", “superficial mycoses” AND “antifungal” AND “resistance”.

The articles were selected from the analysis of the title, abstract and, when necessary, the full text. The searched words followed the search criteria of the databases and quotation marks were used to make a better selection of the analyzed term, boolean operator (AND) and the filter by year of publication. Articles where the study of superficial and cutaneous mycoses and resistance to antifungals were not related to humans and to the dermatophyte species were excluded. From the selected articles were read, the summary, the parts related to the theme, making the selection of the items relevant to the study being the year of publication, superficial and cutaneous mycoses, most prevalent etiological agents, types of treatment, dermatophytosis, dermatomycoses and antifungal resistance.

The results were exported to the Zotero® management software, version 5.0.68 (Center for History and New Media, George Mason University, Fairfax, VA, USA). duplicates and triplicates were excluded.

RESULTS

To conduct this study, a search was made in three databases: *Pubmed, Scielo* and *Science direct*. After searching the databases, 128 articles were found in the Pubmed database, 17 articles in Scielo and 41 in Science Direct, totaling 186 articles. Of these, duplicates and triplicates were excluded. Reading the title and abstract allowed the exclusion of articles that did not focus on the dermatophytosis theme and / or did not fit the inclusion criteria Of the remaining 76 articles, the summary was read and epidemiological data were collected, and of these, 15 met all the eligibility criteria, being used for data extraction and analysis. These were separated by data relevant to the research, ten articles were selected to verify the epidemiological profile of the etiological agents and are shown in table 1, five articles

demonstrate the profile of susceptibility and resistance to antifungals, shown in table 2.The flowchart for the selection of articles is shown in Figure 1.

Analyzed newspaper were published between 2000 and 2020, in Senegal (DIONGUE, K. et al., 2016) [21], in Tunisia (SELLAMI, A. et al., 2008) [22], in Brazil (SILVA-ROCHA WP 2017) [23], (CHIACCHIO, N. et al., 2014) [25], (MAGAGNIN, CM et al., 2011) [2], (ALMEIDA, LMM, 2009) [19], (AZAMBUJA, CVA. et al., 2014) [27] and (DIOGO, HC 2010) [28], in Chile (CRUZ, R. et al., 2011) [24], in Iran (TAGHIPOUR S, et al., 2020) [16], in India (KAUR, R. et al., 2015) [26], and (VJEDRAN, P. et al,2019) [5], in China (WENYING, C. et al, 2016) [8] , in Italy (PANASITI, V. et al, 2007) [6] and France (COGNET, O. et al., 2016) [7].

The articles published between 2000 and 2020 about the epidemiological profile of etiological agents as can be seen in the table 1.

Table 1: Data extracted from the 10 selected articles that express epidemiological data.

Author/Year	**Country**	**Biological samples**	**Positives**	**Dermatophyte etiologic agent found**	**Clinical aspects**	**Average age of the patients**
Diongue, K. et al., 2016	Senegal	1851	633	*-Trichophyton soudanense* *-Trichophyton rubrum*	*-Tinea capitis -Tinea unguium*	31 years old
Sellami, A. et al., 2008	Tunisia	4559	2247	*-Trichophyton violaceum* *-Microsporum canis*	*-Tinea capitis* *-Tinea corporis*	<16 years old

Chiacchio, NDI et al., 2014	Brazil	9042	3022	-*Trichophyton rubrum* -*Trichophyton mentagrophytes* -*M. gypseum* -*T. tonsurans* -*E. floccosum* -*M. canis*	-Onychomycosis -*Tinea pedis*	48 years old
Silva-Rocha, WP. 2017	Brazil	235	113	-*Trichophyton rubrum* -*Trichophyton tonsurans*	-Glabrous skin -Onychomycosis	Not informed
Cruz, CR et al., 2011	Chile	1004	1004	-*Trichophyton rubrum* - *Trichophyton mentagrophytes* - *Microsporum canis*	-*Tinea capitis* -Onychomycosis	All ages
Vijendran, P. et al., 2018	India	200 (100) HIV negative patients (100) HIV positive patients	21 HIV negative patients and 57 HIV positive patients	**HIV negative patients:** -*Trichophyton rubrum* - *Trichophyton mentagrophytes* **HIV positive patients:** -*Trichophyton rubrum* -*Trichophyton tonsurans* -*Epidermophyton floccosum*	Dermatomycosis	Not informed
Kaur, R. et al., 2015	India	351	215	-*Trichophyton rubrum*	Dermatomycosis	All ages
Wenying, C. et al., 2016	China	3385	697	-*T. rubrum* -*T. mentagrophytes* -*M. canis*	Dermatomycosis	Not informed

Panasiti, V. et al., 2007	Itália	3160	1275	-*Microsporum canis* -*Trichophyton rubrum* -*Trichophyton mentagrophytes*	-*Tinea corporis* -*Tinea cruris* -*Tinea capitis* -T*inea ungueum* pés -*Tinea pedis* -*Tinea ungueum* mãos	30 years old
Cognet, O. et al., 2015	France	5470	1984 (92,6% were dermatophytes)	-*Trichophyton rubrum* -*Trichophyton mentagrophytes* var. *interdigitale* -*Trichophyton tonsurans*	Dermatomycosis	Not informed

The five selected newspaper who focused on "*in vitro*" antifugal susceptibility tests are described in Table 2.

Table 2: Selected studies on "in vitro" susceptibility test.

Autor/Ano	**País**	**Amostra**	**Agentes etiológicos**	**Antifúngicos testados**	**Método**	**Resultados**

Magnanin, CM. et al., 2011	Brazil	26 clinical isolates of dermatophytes	*Microsporum canis* (4) -*Microsporum gypseum* (7) *Trichophyton mentagrophytes* var. *interdigitale* (4) *Trichophyton mentagrophytes* (8) *Trichophyton rubrum* (3)	Ketoconazole Ciclopirox olamine Fluconazole Griseofulvin Itraconazole Miconazole Piroctona olamine Terbinafine Tioconazole	Microdilution in broth according to protocol *Clinical and Laboratory Standards Institute* (CLSI M38-A_2002), ,adapted for dermatophytes..	Terbinafine and tioconazol: obtained the best sensitivity results. Fluconazole: showed low activity, especially for samples of the species *M. gypseum.* Ciclopirox olamine: although less effective than terbinafine, also showed satisfactory results.
Almeida, LLMM, 2009	Brazil	80 clinical isolates agentes of cutaneous superficial mycoses.	*Trichophyton mentagrophytes* (35) *Trichophyton rubrum* (21) *Trichophyton tonsurans* (06) *Trichophyton raubitscheki* (03) *Microsporum canis* (08) *Microsporum gypseum* (02) *Microsporum ferrugineum* (01)	Fluconazol Ketoconazole Itraconazole Terbinafine	Microdilution in broth according to protocol M38-A (2002) *Clinical Laboratory Standards Institute* (CLSI)	Of the 80 samples of filamentous fungi identified, the genus *Trichophyton* represented 81%. The four drugs analyzed showed great variation in the genera *Trichophyton and Microsporum.* Terbinafine was the most effective antimycotic against most fungal isolates. (Almeida, LLMM, 2009)
Diogo, HC. 2010	Brazil	53 dermatophyte isolates	*Trichophyton mentagrophytes* (34) *Trichophyton rubrum* (18) *M. gypseum* (1)	Itraconazole Terbinafine Ketoconazole	Microdilution in broth according to protocol M38-A2 (CLSI) 2008	*T. mentagrophytes* isolates were more susceptible to itraconazole and ketoconazole compared to terbinafine.

Azambuja, CVA. et al., 2014	Brazil	Nail sample of 100 patients	*Trichophyton rubrum*	Ciclopirox (32 a 0,0625 µg / mL) Terbinafine (0,5 a 0,0001 µg / mL) Fluconazole (64 a 0,125 µg / mL) Itraconazole (0,5 a 0,0001 µg / mL)	Microdilution in broth according to protocol CLSI M38-A2 (2002) for filamentous fungi in duplicate	High MICs values for fluconazole were found for clinical isolates of *T. rubrum* itraconazole, ciclopirox and terbinafine showed good in vitro activity against *T. rubrum.*
Taghipour, S. et al., 2020	Iran	141dermatophyte isolates	96 isolates of *T. mentagrophytes* var. *interdigitale* and 45 *T. mentagrophytes*	Terbinafine Itraconazole Griseofulvin Clotrimazole Efinaconazole Luliconazole Amyrofillin hidrochloride Ciclopirox olamine	Microdilution in broth according to protocol CLSI M38-A2 (2008) and sequencing of the squalene epoxidase gene (SQLE) to check mutations for isolates that exhibited elevated MICs for terbinafine.	Five *T. mentagrophytes* type VIII isolates with terbinafine MIC ≥32 µg / mL were found. These clinical isolates contained two variants of the SQLE gene.all terbinafine-resistant strains can be inhibited by luliconazole and efinaconazole. Taghipour, S. et al., 2020)

DISCUSSION

The results obtained in the present literature review study are of scientific and epidemiological importance. The aim of this study was to highlight the etiological agents, the diagnostic method, the treatment used and the profile of susceptibility and resistance to antifungal agents most used in superficial and cutaneous mycoses in various regions of the world.

In relation to the sample size of the studied population, ten studies evaluated the epidemiological profile of the etiologic agents of dermatophytosis, with a great variation in the number of biological samples between the studies, with VIJENDRAN, P. et al., (2019) being the smallest with 200 samples and CHIACCHIO, R. et al., (2014) the largest with 9042 samples. Of the studies analyzed, all evaluated both genders. Five studies did not specify the age of the individuals (CRUZ, R. et al., 2011), (KAUR, R. et al., 2015), (WENYING, C. et al., 2016), (COGNET, O. et al., 2016) and (SILVA-ROCHA WP, 2017). Two studies delimited age, (DIONGUE, K. et al., 2016), age between two months and 81 years and (SELLAMI, A. et al., 2008), under 16 years. Two studies determined an average age between 30 and 48 years old (PANASITI, V. et al., 2007) and (CHIACCHIO, N. et al., 2015), respectively.

From the ten articles analyzed regarding the epidemiology of dermatophytoses worldwide, the majority point to *Trichophyton rubrum* and *T. mentagrophytes* as the main etiological agents in the world. The most used diagnostic method was direct microscopic examination and culture, Table 1.

In Brazil, were isolated the dermatophyte fungal agents *Trichophyton rubrum, T. tonsurans* by Silva-Rocha (2017), *Trichophyton rubrum, T. mentagrophytes, Microsporum gypseum, T. tonsurans, Epidermophyton floccosum* and *M. canis* in the Chiacchio et al., (2014) studies. In Chile, *Microsporum canis, Trichophyton rubrum, T. mentagrophytes* were the most isolated agents according to Cruz, R. et al., (2011), Tabela 1.

In the study conducted by Diongue et al, (2016), in Senegal, the most isolated dermatophyte agents were *Trichophyton soudanense and T. rubrum.* . In Tunisia, the fungi isolated were *Trichophyton violaceum e Microsporum canis* according to Sellami, A. et al., (2008), Table 1.

In India, the fungal agents *Trichophyton rubrum, T. mentagrophytes, T. tonsurans* and *Epidermophyton floccosum* were the most frequently the dermatophytes found according to the findings in the study of Kaur et al., (2015). In China, *Trichophyton rubrum, T. mentagrophytes* and *Microsporum canis* according Wenying et al., (2016), table 1.

In Italy, *Microsporum canis, Trichophyton rubrum, T. mentagrophytes* and *Microsporum audouinni,* have been appointed by Panasiti et al., (2007) as the most isolated fungi. In France, *Trichophyton rubrum, T. mentagrophytes* var. *interdigitale* and *T. tonsurans* were reported by Cognet et al. (2016), Table 1.

In all the studies described, the sites of infection were mostly skin, hair, scalp, nails, feet, hands and inguinal region. . The main form of laboratory diagnosis was made from direct examination, after collection of the biological sample and subsequently observed by an experienced professional taking care of conservation, transportation and handling of the material in order to obtain a reliable mycological diagnosis. Fungal cultivation was carried out in Sabouraud dextrose agar medium containing inhibitors such as chloramphenicol (inhibits contaminant bacteria) or cycloheximide (inhibits the growth of yeasts and opportunistic saprofitas fungi). The cultures were incubated in a bacteriological greenhouse at a temperature between 25-30°C [14] (Martinez et al. 2020).

In addition to the conventional routine, some studies have also used the polymerase chain reaction (PCR), susceptibility and resistance tests to antifungals by diffusion disc or microdilution, urea hydrolysis, chlamydoconidia production and carbohydrate assimilation [11,19,28] (SAUL-GARCIA, Yotsabeth et al. 2015; ALMEIDA, Lívia Maria Martins de et al. 2009; DIOGO, Hilda Conceição et al. 2010) and molecular typing by ITS ribosomal region [16] (Taghipour, S. et al. 2020).

In the study conducted in Senegal by Diongue, K. et al., (2016), it was conducted with 1851 patients, of these 633 were positive for superficial and cutaneous mycoses. Mycological diagnosis was made through direct microscopy and culture examination, from skin, nails and scalp. The age of the patients evaluated was from 2 months to 81 years. Of these, 70.3% were women and 29.7% were men. The isolated agents causing mycoses, 58.0% were dermatophytes, 36.7% yeasts and 5.3% non-dermatophyte fungi. The most isolated species were 24,9% *Trichophyton soudanense* and 13,7% *T. rubrum*. The presence of these fungi showed different clinical aspects,isolated or associated. Among the clinical aspects observed, those that affected the pelo, tinea capitis were the most prevalent with 44.8%, followed by tinea unguium, 34.5%. Unlike other studies where the fungus *T. rubrum* was the most isolated agent of the genus *Trichophyton* in this study, T. *soudanense* was isolated in 91 (24.9%) samples, probably due to the geographic region studied. In the research in question, no drug therapy was evaluated, Table 1.

According to Sellami et al., (2008), in Tunisia, 4559 children under of 16 years old were evaluated. The diagnosis of superficial and cutaneous mycoses was confirmed in 49.4% of the cases. Dermatophytes were the most prevalent fungal agents and responsible for 1865 cases (80.6%), with54.1% *Trichophyton violaceum* predominant and 24.5% *Microsporum canis.* As previously described in the research by Diongue, K. et al., (2016), no drug therapy was evaluated in this study, table 1.

In Brazil, Silva-Rocha, WP. (2017) evaluated 205 patients, of which 235 clinical samples of skin and nails were collected, analyzed by direct examination by optical microscopy and petri dish culture. a total of 113 (55.1%) samples were positive for dermatophytosis. Of these, 64.6% were female and 35.4% were male. Glabrous skin was the major source of dermatomycosis (30.1%), followed by toenails (27.4%) and fingernails (17.7%). *Trichophyton rubrum* was the most isolated species, the presence of *T. tonsurans* is also observed in many cases among the isolates. Drug therapy was not evaluated, table 1.

According to Cruz. (2011) in Chile, 1004 patients diagnosed with superficial and cutaneous mycoses were evaluated. All ages and both genders were included. The study was carried out through direct microscopic examination with 20% KOH and culture of the lesions. The identification of fungi was made by morphophysiological evaluation. Of the 1004 patients studied, 609 were women and 87.7% were 15 years old or younger. Nail onychomycosis was the most frequent lesion (58.1%), followed by *Tinea pedis* interdigital (16.3%). In patients under 8 years old, the *tinea capitis* by *Microsporum canis* was the most frequent mycosis. Among dermatophytes, *Trichophyton rubrum* (78.9%), predominated in most affected sites, followed by *T. mentagrophytes* (14.9%) and *Microsporum canis (*5.4%).

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Chiacchio, NDI. (2014), also in Brazil, conducted a survey of 9,042 patients with suspected superficial and cutaneous mycoses. After direct microscopic examinations and cultures of the lesions, 2,626 (29.0%) were positive for dermatophytes, 205 (2.3%) for *Malassezia* spp., and 191 (2.1%) were positive for other types of yeasts, 48 (0.5%) were positive for bacteria and 5972 (66.0%) were negative. The average age of the patients was 48 years old. Of the patients evaluated, 77.0% were female and 23.0% were male. Of the dermatophytes isolated, the species found were 96,2% *Trichophyton rubrum*, 2,3% *T. mentagrophytes*, 0,6% *Microsporum gypseum*, 0.3%, *T. tonsurans*, 0,3% *Epidermophyton floccosum*, and 0.2% *M. canis*, Table 1. The most affected site was the nail and foot in adults and the scalp in children, with a predominance of females, table 1.

In India, Vjendran, P. et al., (2019), evaluated 200 patients, 100 patients with immunodeficiency virus (HIV) and 100 HIV negative patients. The samples collected from the skin, inguinal region and tongue. The diagnosis was made by direct microscopic examination, culture in Petri dishes, susceptibility tests, antifungal resistance by diffusion disc and E-test. In the HIV-negative individuals, only *Trichophyton rubrum*, 69.2% and *T. mentagrophytes*, 30.7% were the dermatophytes isolated. HIV-positive patients were also isolated, *Trichophyton tonsurans* 13.6%, *Epidermophyton floccosum* 4.5%, and *Trichophyton rubrum* 81.9%, Table 1.

According to Kaur *et al.* (2015) in a study conducted in the Department of Microbiology of the Maulana Azad School of Medicine, New Delhi (India), in the period of two years (2012-2013), three hundred and fifty-one (351) clinical samples of skin, hair and nails were evaluated. Direct microscopic examination and culture in Petri dish were performed. Two hundred and fifteen samples (61.2%) were positive. The most frequent isolates were non-dermatophyte fungi in 36.1%, followed by dermatophytes, 13.8% and yeasts 8.6%. Among dermatophyte fungi, *Trichophyton rubrum*, was isolated in 4.6% of cases. Of these 351 samples evaluated, 236 (67.2%) were male and 115 (32.7%) female. In this study most patients were male, unlike the other studies previously described. The most prevalent age group was between 21 and 30 years (23.3%), followed by 31 to 40 years (20.5%) and the least common over 60 years of age (5.6%), Table1.

In a study conducted in Guangzhou (China) between 2004 and 2014 by Wenying, C. et al., (2016) evaluating 3,367 patients and a total of 3,385 biological samples of skin lesions, hair and nails. The laboratory diagnosis was performed for direct examination and culture. This material resulted in 697 (20.6%) positive samples. Dermatophytes were the most isolated, 84.4% of the cases. In 56,2% of the cases, the isolated agent was *Trichophyton rubrum (83.9% cases of Tinea unguium, 71.2% Tinea pedis, 71.2%, 91.7% Tinea cruris, 91.8% Tinea corporis* and *65.0% Tinea manum), Trichophyton mentagrophytes* (13.4%) and *Microsporum canis* (10.2%), were the predominant species when associated with cases of *Tinea faciei*, 54.5% and *Tinea capitis*, 54.1%, respectively, Table 1.

In Italy, the study by Panasiti (2007) with the support of the Department of Dermatology at La Sapienza University, in Rome, from 2002 to 2004, evaluated 3160 individual, these, 1275 (40, 3 %) were positive for fungal infection, but only 252 (19.7%) had caused by dermatophytes The biological samples were processed by direct examination and culture of skin and nail. The most frequently isolated dermatophytes were *M. canis*, *T. mentagrophytes*, *T. rubrum* and *M. audouinii*. O *M. canis* was the most frequent dermatophyte in *tinea corporis* and *tinea capitis*. In this study from Rome, it was found that T. mentagrophytes had a higher prevalence in relation to T. rubrum, and in previous studies it was the second most prevalent species. The study also isolated *M. audouinii* not found in the studies previously described. The age of the patients evaluated was on average 30 years old and of both genders, table 1.

In France, the study conducted by Cognet et al., (2015), in Grenoble, from 2001 to 2011, evaluated 5.470 biological samples collected from skin, nails and hair from 3,740 patients of both sexes to confirm dermatomycosis. For laboratory diagnosis, direct examination and culture were performed. Between 1984 (36.3%) positive cultures, 1348 (67.9%) dermatophytes were identified and 636 (32.1%) non-dermatophytes, yeasts were positive in 24.4% and molds in 7.7%. The most isolated dermatophytes were *Trichophyton rubrum*, *T. mentagrophytes* and *T. tonsurans*, with *T. rubrum* isolated 78.6% of the time. In this study, drug therapy was not evaluated, Table 1.

Table 2 describes the selected journals about *in vitro* tests to evaluate the susceptibility of antifungal agents in relation to the species most found as causing dermatophytosis. The drugs most used for the treatment of these mycoses were imidazole derivatives. Among the drugs tested, terbinafine showed satisfactory results in relation to most fungal isolates in two studies (Magnanin CM. et al., 2011) e (Almeida, LMM, 2019).

The study of Magnanin et al., (2011), in Brazil, at the Federal University of Rio Grande do Sul, evaluated the susceptibility profile of some species of dermatophytes isolated from patients with chronic renal failure considering as antifungal agents ketoconazole, cyclopirox olamine fluconazole, griseofulviin, itraconazole, miconazole, pyrokone olamine, terbinafina and thioconazole. The *in vitro* test was performed by the broth microdilution method according to the protocol of the Institute of Clinical and Laboratory Standards (CLSI M38-A -2002) with alterations for dermatophytes. According to this study, terbinafine and thioconazole showed the best sensitivity results, followed by cyclopirox olamine. Fluconazole showed low activity, especially for samples of the species *M. gypseum*. Cyclopirox olamine, although less effective than terbinafine, also showed satisfactory results, table 2.

In another study, also from Brazil, from the State University of Maringá in Paraná by Almeida, L., (2009) the susceptibility of filamentous fungi to fluconazole, ketoconazole, itraconazole and terbinafine was evaluated using the broth microdilution method according to the CLSI M38-A protocol (2002). Eighty samples of filamentous fungi are analyzed and of these, 81.0% represented the genus

Trichophyton. According to the study, the drugs analyzed showed great variation in sensitivity and resistance between the dermatophyte genera, *Trichophyton* and *Microsporum*. Terbinafine was the drug that was most effective compared to fungal isolates, Table 2.

In Brazil, Azambuja et al., (2014), evaluated the susceptibility of cyclopirox antifungals (32 to 0.0625 μg/mL), terbinafine (0.5 to 0.0001 μg/mL), fluconazole (64 to 0.125 μg /mL) and itraconazole (0.5 to 0.0001 μg/mL) against clinical isolates of *Trichophyton rubrum* by duplicate microdilution according to the protocol of the Clinical and Laboratory Standards Institute (CLSI M38-A - 2002). The results showed that the antifungals itraconazole, cyclopirox and terbinafine showed good in vitro activity against the pathogen, while the antifungal fluconazole presented high values of MICs, Table 2.

Diogo HC (2010) evaluated the efficacy of terbinafine in vitro against filamentous fungi and yeasts that cause mycoses. The species evaluated were the dermatophytes: *Trichophyton rubrum, T. mentagrophytes* (ATCC 05533) *T. tonsurans, Microsporum gypseum, M. canis, Epidermophyton floccosum* and non-dermatophyte fungi *Scytalidium hyalinum*, *Fusarium oxysporum* and *Cladophialophora carrionii* and also yeasts *Candida parapsilosis* (ATCC 22019). The disc-diffusion protocols recommended by CLSI M44-A (2004) and CLSI M38-A (2002) were used. The results showed that terbinafine showed good in vitro action against dermatophyte fungi and lower action against yeasts, Table 2.

However, Taghipour et al., (2020) described, for the first time in Iran, the resistance to terbinafine in isolates of *T. mentagrophytes* and *T. mentagrophytes interdigitale.* The same study points out as recent data from India and some Asian and European countries, *T. mentagrophyte*s and *T. mentagrophytes* var. *interdigitale* present non-synonymous point mutations in the SQLE gene, generating clinical resistance to terbinafine. This study also proposed alternative treatments for cases of terbinafine resistance, evidencing that resistant strains can be inhibited by luliconazole and efinaconazole, Table 2.

CONCLUSION

This work presents epidemiological data from various regions of the world through the study of articles published in the last twenty years. The most prevalent species of dermatophytes present in cutaneous mycoses found in the present literature review study are *Trichophyton rubrum, T. mentagrophytes, Microsporum canis, Epidermophyton floccosum* and *T. tonsurans.*

The results obtained in this same study indicate that the human sites of greatest contamination are hair, scalp, skin, fingernails, feet and inguinal region. The most used mycological diagnostic method

was direct examination and culture, and eventually other tests such as biochemical and molecular tests, like PCR (*Polymerase Chain Reaction*).

As for treatment, the most used drugs are those of the imidazole class. Regarding susceptibility tests, the antifungals tested were ketoconazole, fluconazole, cyclopirox olamine, itraconazole and terbinafine. The antifungals itraconazole, cyclopirox and terbinafine showed good *in vitro* activity on the face of the most prevalent pathogen, *Trichophyton rubrum*. Fluconazole presented elevated MICs for this pathogen.

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CONFLICT OF INTEREST

The Authors declares that there is no conflict of interest.

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