International Journal of Pharmacy and Biological Sciences-IJPBS™ (2021) 11 (1): 176-187
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Superficial and Cutaneous Mycoses, Epidemiology, Virulence, Susceptibility Profile to Antifungals and Their Infections: A Literature Review of the Last Twenty Years

P. A. Pereira, E. S. Vieira, F. C. Charles, V. M. Giudice, C. G. S. Nascimento, J. S. Borges, L. P. R. Silva, G. S. Silva, S. K. Ferrão, L. Mezzomo, L. N. Calil, A. Mezzari*

Department of Clinical Analysis, Faculty of Pharmacy, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Rio Grande do Sul (RS), Brazil.

Received: 12 Oct 2020 / Accepted: 6 Nov 2020/ Published online: 01 Jan 2021
***Corresponding Author Email:** mezzari@ufrgs.br

Abstract

Introduction: Superficial and cutaneous mycoses or dermatomycoses affect keratinized tissues of humans and animals. They can be caused by dermatophyte fungi, non-dermatophytes and yeasts. Epidemiological studies indicate that superficial and cutaneous mycoses are among the fungal diseases with the highest incidence in the world, affecting all age groups and with high treatment costs. Among mycoses, dermatophytosis are the most common fungal infections in humans in the world, followed by candidiasis and pityriasis versicolor. **Objective:** This study aims to review the literature of the last 20 years (2000 to 2020) on the epidemiological studies of superficial and cutaneous mycoses, their etiological agents, as well as the susceptibility and resistance factors to antifungals used for their treatment. **Method**: A literature review was conducted in online databases. The selected studies showed data on the prevalence of species, the profile of patients, the most affected infection sites, the diagnostic method used and the susceptibility profile of some fungal species in relation to the most used antifungals. **Results:** Dermatophyte fungal species *T. rubrum, T. mentagrophytes, T. tonsurans, M. canis* and *E. floccosum* and non-dermatophytes, yeasts *Candida* spp. and *Malassezia* spp. were the most isolated in skin infections in several studies. The most prevalent sites of infection were skin, nail and hair. The antifungals tested against the most prevalent pathogens were ketoconazole, fluconazole, cyclopirox and terbinafine. **Conclusion**: The results obtained in this study point to *T. rubrum* as the most isolated species in skin infections. Terbinafine was the drug that presented the highest efficacy.

Keywords
Dermatomycoses, dermatophytosis, epidemiology, antifungal resistance.

*****

INTRODUCTION

Superficial and cutaneous mycoses or dermatomycoses affect keratinized tissues of the skin, nails and hair of humans and animals [14]. They can be caused by a group of fungi called dermatophytes, non-dermatophyte strains and yeasts. Dermatomycosis caused by dermatophytes are also called dermatophytosis. Epidemiological studies indicate that superficial and cutaneous mycoses are among the diseases with the highest incidence in the world, affecting all age groups and generating spending of millions of dollars on treatments every year [19]. Among these mycoses dermatophytosis are the most common fungal infections in humans around the world. Although candidiasis and pityriasis versicolor are also quite common [9].

Among dermatomycosis, dermatophytosis are the most frequent fungal infections in dermatological practice and caused by microorganisms of the genus *Trichophyton, Microsporum* and *Epidermophyton*. It is estimated that about 10 to 15% of the world population can be infected with dermatophytes throughout their lives [17]. Climatic factors, as well as social practices, population migration, individual characteristics, including age, morphological anomalies in the nails, genetic factors and inadequate hygiene conditions can contribute as epidemiological factors for these infections. Some diseases such as diabetes mellitus, immunodeficiency, immunosuppression, peripheral vascular disease, skin-related disorders such as hyperhidrosis and psoriasis, wearing tight shoes and nail trauma are also risk factors that may affect the epidemiology of dermatophytosis [1,2].

There are also some reports suggesting that hormone rates may affect the frequency of such infections in both men and women and that the growth of these pathogens may be influenced by the presence of steroid hormones. Some species of *Trichophyton* e *Microsporum Some species of Trichophyton and Microsporum* have cytosolic proteins that specifically bind to progesterone. This, in pharmacological and physiological concentrations can inhibit the growth of dermatophytes. Thus, anthropophilic species respond better to the action of steroids, than geophilic specie [1,2].

Dermatophytosis can also affect both humans and animals [4], may be asymptomatic between 30% and 70% in the adult population [2]. The most isolated clinical species are *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum canis* and *Epidermophyton floccosum* [2]. In addition to dermatophytes, dermatomycoses caused by non-dermatophyte keratinophilic fungi and yeasts of the genera *Candida* spp. and *Malassezia* spp. [2,15]. There is a high incidence of superficial and cutaneous mycoses in tropical and subtropical climate regions, The climatic characteristics of these regions favor the growth of theses fungi, causing relevant public health problem [3,10,17]. Transmission can occur by direct contact with infected humans and animals or indirectly, by contaminated fomites [13]. 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 and social discrimination [13]. One way to control 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. One way to control 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 [1].

As for epidemiology, surveys already carried out in Brazil and in the world show a high frequency of these superficial and cutaneous mycoses. The clinical manifestations are varied and may compromise the hands, feet, nails, skin fold regions, glabrous skin, among others. The diagnosis is made mainly by direct examination and culture of the biological material collected from the clinical manifestation [20].

The main groups of systemic antifungals 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 limited, and the need for new, more effective and less toxic antifungals is evident [19]. The spectrum of activity of these antifungals is variable, possibly leading to therapeutic failures, possibly due to low patient compliance, lack of drug penetration, drug bioavailability, drug interactions or resistance [2].

The choice of appropriate treatment is determined by the location and extent of the infection, the species involved, as well as the effectiveness, safety profile and kinetics of the available antifungals. Therapy with topical agents can be performed 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 cyclopirox 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 all antifungal agents, all of which are treatments of choice for dermatophytoses when they do not respond to therapies with topical drugs [2]. 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]. 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].

Combination therapy with topical, oral antifungals and anti-inflammatory agents has been used to attempt to increase the cure rate [13]. Combination therapy with topical, oral antifungals and anti-inflammatory agents has been used to attempt to increase the cure rate [10].

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].

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]. 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].

The fungi species of medical interest have known profiles of susceptibility to antifungals, thus guiding the clinician to start therapy, when it is not possible to access the Minimum Inhibitory Concentration (MIC) [12].It is important to know the biological characteristics of the main agents, as it allows directing treatment. In the study by Almeida et al., (2009), they observed that the genus *Fusarium* spp. presented a high Minimum Inhibitory Concentration (MIC) for all drugs evaluated, fluconazole, ketoconazole, itraconazole and terbinafine. This makes it difficult to treat invasive *Fusarium* spp.. Resistance is an intrinsic characteristic of this genus, which also makes it difficult to treat superficial and skin infections, signaling the need to search for new antifungal treatment options [19].

The azole resistance of *Candida albicans* in HIV-infected patients with oropharyngeal candidiasis becomes a therapeutic problem. However, resistance has been lower in patients with other diseases, such as vaginal candidiasis and candidemia. Intrinsic or reduced susceptibility to fluconazole has also been reported for non-albicans *Candida* species such as *C. glabrata, C. krusei* and *C. lusitaniae*. The similarity in the azole structure are responsible for the cross-resistance patterns among Candida species [12]. *Candida parapsilosis* present intermediate susceptibility to echinocandins [18].

Trichosporon species show different susceptibility to antifungal agents, for example, *T. asahii* is more resistant to amphotericin B in vitro than to triazoles. Regarding the filamentous fungi of clinical interest, zygomycetes have intrinsic resistance to azoles, except for posaconazole, while *Aspergillus fumigatus* is sensitive to triazoles such as itraconazole, voriconazole, posaconazole, echinocandin and amphotericin B [18].

The species of *Candida* spp. and other non-dermatophyte agents have variable susceptibility to terbinafine. Therefore, its action profile is not predictable by the drug, and in these cases, tests for susceptibility to antifungals "in vitro" are indicated with a view to therapeutic guidance. [28].

In this way, this study aims to review the literature of the last 20 years (2000 to 2020) on the epidemiological studies of superficial and cutaneous mycoses, their etiological agents, as well as the susceptibility and resistance factors to antifungals used for their treatment.

MATERIAL AND METHODS

A literature review 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”, (filamentous) AND (yeast) AND (antifungal) AND (susceptibility).

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 were excluded. The selected articles were read, the summary, of 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, dermatophytoses, 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. The data relevant to the research of the selected articles were organized in an Excel table, after applying the eligibility criteria.

RESULTS AND DISCUSSION

After searching the databases, 276 articles were found in the Pubmed database, 20 articles in Scielo and 41 in Science Direct, totaling 337 articles. Of these, duplicates and triplicates were excluded, leaving 247 articles. Reading the title and abstract allowed the exclusion of articles that did not focus on the theme of superficial and cutaneous mycoses and / or did not fit the inclusion criteria. Of these 76 articles, 15 met all the eligibility criteria, being used for data extraction and analysis. Ten articles were selected to verify the epidemiological profile of the etiologic agents and are shown in table 1 and five articles demonstrate the profile of susceptibility and resistance to antifungals, presented in table 2. The flowchart for the selection of articles is shown in Figure 1.

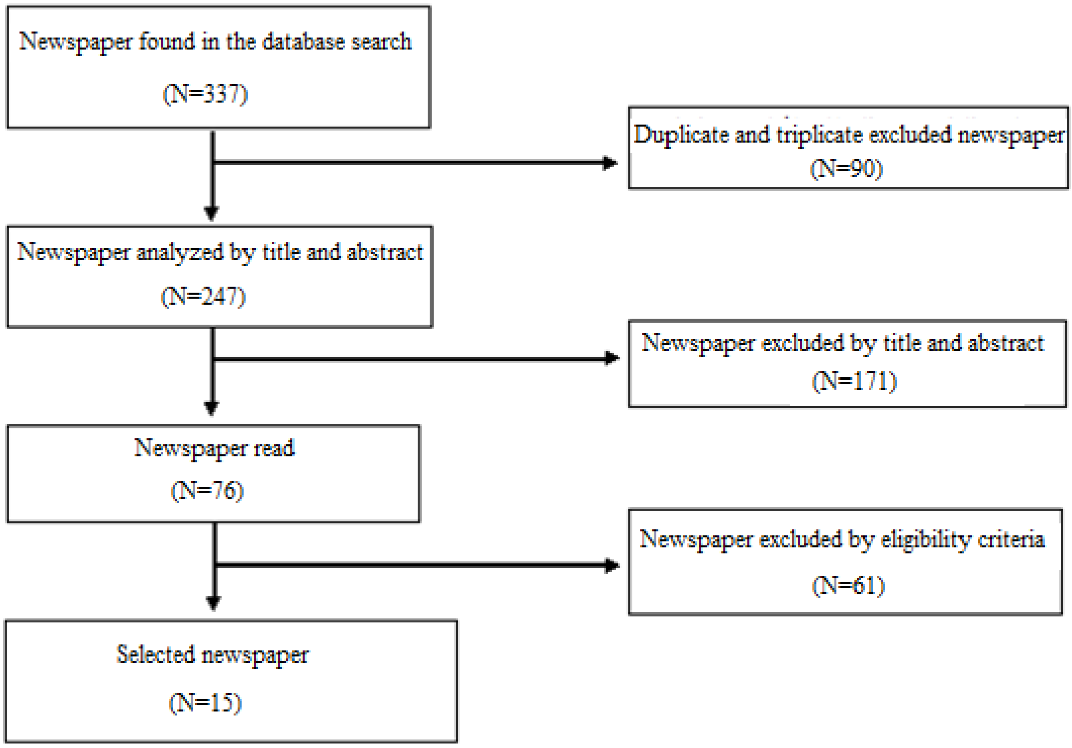

Figure 1: Scheme used for the selection of studies.

Analyzed newspaper were published between 2000 and 2020, in Senegal (DIONGUE, K. et al., 2016) [21], in Tunísia (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 newspaper selected to verify the epidemiological profile of etiological agentes are presented in Table 1.

Table 1: Selected newspaper expressing epidemiological data.

Author/Year	Country	Samples	Positive for dermatomycosis	Etiological agent	Middle age
Silva-Rocha 2017	Brazil	235	113	*Trichophyton rubrum* *T. tonsurans* *Candida parapsilosis*	Not informed
Chiacchio. et al 2014	Brazil	9042	3022	*Trichophyton rubrum* *T. mentagrophytes* *T. tonsurans* *Epidermophyton. floccosum* *Microsporum gypseum* *M. canis*	48 years old
Cruz et al. 2011	Chile	1004	1004	*Trichophyton rubrum* (78,9% dos dermatófitos) *T. mentagrophytes* (14,9%) *Microsporum canis* (5,4%) *Candida* spp. (95,4% of yeasts)	All ages
Wenying et al. 2016	China	3385	697	*Trichophyton rubrum* (56,24%) *T. mentagrophytes* (13,35%) *Microsporum canis* (10,19%)	Not informed
Cognet et al. 2015	France	5470	1984	*Trichophyton mentagrophytes* var. *interdigitale* *T. tonsurans*	Not informed
Vijendran. et al. 2018	Índia	200 (100) HIV negative patients (100) HIV positive patients	21 HIV negative patients and 57 HIV positive patients	HIV negative patients: *Trichophyton rubrum* (69,23%) *T. mentagrophytes* (30,76%) *Candida albicans* HIV positive patients: *Trichophyton rubrum* *T. tonsurans* *Epidermophyton floccosum* *Candida albicans and non-albicans*	Not informed
Kaur et al. 2015	Índia	351	215	*Aspergillus niger* (9%) *Trichophyton rubrum* (4,6%) *Candida* non-*albicans* (6%)	All ages
Panasiti et al. 2007	Itály	3160	1275	*Microsporum canis* *Trichophyton rubrum* *T. mentagrophytes*	30 years old
Diongue et al. 2016	Senegal	1851	633	*Candida albicans* (26,9%) *Trichophyton soudanense* (24,9%) *T. rubrum* (13,7%)	31 years old
Sellami et al. 2008	Tunísia	4559	2247	*Trichophyton violaceum* (54,1% of dermatophytosis) *Microsporum canis* (24,5%) of dermatophytosis) *Malassezia* spp. (71% of yeast infection)	<16 years old

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

Table 2: Selected studies on antifungal susceptibility test.

Autor/Ano	País	Amostra	Agentes etiológicos	Antifúngicos	Método	Resultados
Diogo 2010 (34)	Brazil/SP	53 dermatophyte isolates	*Trichophyton mentagrophytes* (34) *T. rubrum* (18) *Microsporum 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.
Almeida 2009	Brazil/PR	26 clinical isolates of dermatophytes 80 clinical isolates agentes of cutaneous superficial mycoses.	*Trichophyton mentagrophytes* (35) *T. rubrum* (21) *T. tonsurans* (06) *T. raubitscheki* (03) *Microsporum canis* (08) *M. gypseum* (02) *M. ferrugineum* (01) *Fusarium oxysporum* (01) *F. solani* (01) *F. incarnatum* (01) *F. verticillioides* (01)	FluconazoleK Ketoconazole Itraconazole Terbinafine	Microdilution in broth according to protocol M38-A (2002)	80 positive samples were found for filamentous fungi, being Trichophyton spp. 81% of the samples. The clinical isolates of Trichophyton and Microsporum. presented different susceptibility to the antifungals tested. All clinical isolates of Fusarium spp. the drugs tested were resistant. Terbinafine was the most effective antimycotic against fungal isolates. (Almeida, LLMM, 2009)
Magnanin, et al. 2011	Brazil/RS	26 clinical isolates of dermatophytes	*Microsporum canis* (4) *M. gypseum* (7) *Trichophyton mentagrophytes* var. *interdigitale* (4) *T. mentagrophytes* (8) *T. rubrum* (3)	Ketoconazole Ciclopirox olamine Fluconazole Griseofulvin Itraconazole Miconazole Piroctona olamine Terbinafine Tioconazole	Microdilution in broth according to protocol CLSI M38-A_2002), adapted for dermatophytes.	Terbinafine and thioconazole: obtained the best sensitivity results, followed by cycloprox olamine Fluconazole: showed low activity, especially for samples of the species M. gypseum.

Azambuja, et al. 2014	Brazil/RS	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. Ciclopirox and terbinafine showed good in vitro activity against t. rubrum
Taghipour, et al. 2020	Iran	141 dermatophyte 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. isolados que exibiam CIMs elevadas para terbinafina.	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)

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.
A large variation in the sample number was found in studies evaluating the epidemiological profile of etiological agents of superficial and cutaneous mycoses. The smallest sample number is composed of 200 biological samples in the study conducted by VIJENDRAN et al., (2019) and the largest sample number, in the study by CHIACCHIO et al., (2014) has 9042 samples.
Of the analyzed studies, 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 (SELLAMI, A. et al., 2008), under 16 years old. Two studies determined by mean age between 30 and 48 years (PANASITI, V. et al., 2007) e (CHIACCHIO, N. et al., 2015), respectively.
The main etiological agents of dermatomycosis in the world are *Trichophyton rubrum* and *T. mentagrophytes* causing dermatophytosis. *Candida* spp yeasts. and *Malassezia* spp. were the main causative species of superficial and cutaneous mycoses caused by non-dermatophyte fungi. The most used diagnostic method was direct microscopic examination and culture, Table 1.
In Brazil, the fungal agents *Trichophyton rubrum, Candida parapsilosis* and *T. tonsurans* by Silva-Rocha, WP., (2017), Trichophyton *rubrum, T. mentagrophytes, Microsporum gypseum, T. tonsurans, Epidermophyton floccosum, M. canis, Malassezia* spp. *and Candida* spp., in the Chiacchio, NDI. et al., (2014) studies. In Chile, *Microsporum canis*, *Trichophyton rubrum*, *T. mentagrophytes*, *Candida* spp. and *Fusarium* spp., were the most isolated agents according to Cruz, R. et al., (2011), Tabela 1.
In the study conducted in Senegal by Diongue, K. et al., (2016), the most isolated agents were *Candida albicans, Trichophyton soudanense* and *T. rubrum.* In Tunisia, the fungi isolated were *Trichophyton*

violaceum, Microsporum canis, Malassezia spp. and *Candida albicans* according to Sellami, A. et al., (2008), Table 1.

In India, the most isolated fungal agents were *Candida albicans, C.* não-*albicans*, *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans* and *Epidermophyton floccosum*, in the study of Kaur et al., (2015). In China, *Trichophyton rubrum, T. mentagrophytes* and *Microsporum canis* according Wenying et al., (2016), In Italy, *Microsporum canis, Trichophyton rubrum, T. mentagrophytes* and *Microsporum audouinni,* have been appointed by Panasiti et al., (2007). 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 skin, hair, scalp, nails, feet, hands and inguinal region. The laboratory diagnosis was made from the direct examination, after the collection of the biological sample and, later, observation under optical microscope. In the analysis, the criteria for conservation, transport and manipulation of biological material were observed 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]. 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, chlamydoconidium production and carbohydrate assimilation [11,19,28] and molecular typing by ITS ribosomal region [16].

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 26.9% of *Candida albicans*, 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 was 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.* The yeast infections totaled 442 (19.4%) cases and *Malassezia* spp predominated (71.0%) of the isolates. In *Candida* spp infections. the most isolated was *Candida albicans* (58.0%), Table 1. Diongue et al., (2016), in this study did not evaluate any drug therapy.

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 superficial and cutaneous mycosis. 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. Another observed fact was that *Candida parapsilosis* was the most prevalent species of the genus and the presence of *T. tonsurans* was also observed in many cases among the isolates, Table 1. Drug therapy was not evaluated.

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%). As for Candida spp. (95.4%) prevailed among the yeasts that cause onychomycosis, Table 1. In this study, as well as in others no drug therapy was mentioned.

DChiacchio (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 lesions. 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. Both Candida spp. like Malassezia spp. were the most prevalent yeasts in adult women, the first most commonly affecting the interdigital region and the nails and the second the chest and neck.

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. The yeast *Candida albicans* was the only species isolated in HIV negative individuals, while in HIV positive patients was 80.5%, and in the rest, e19.5% were *Candida* non-*albicans* species. In the HIV-negative individuals, only *Trichophyton rubrum*, 69.2% and *T. mentagrophytes*, 30.7% were the dermatophytes isolated. In HIV-positive patients, *Trichophyton tonsurans* 13.6%, *Epidermophyton floccosum* 4.5%, and *Trichophyton rubrum* 81.9%, Table 1. The yeast *Candida albicans.*

Acoording 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%. The most prevalent fungus was the non-dermatophyte *Aspergillus niger* (non-dermatophyte) 9.0% followed by *Trichophyton rubrum* (dermatophyte) 4.6%. In yeasts, *Candida* non-*albicans* were the most isolated, 6.0%. Of these 351 samples evaluated, 236 (67.2%) were male and 115 (32.7%) females. 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. The laboratory diagnosis was performed by direct examination and culture. This material resulted in 697 (20.6%) This material resulted in 697 (20.6%) positive samples. positive samples.

Dermatophytes were the most isolated, 84.4%, followed by yeasts, 14.9% and non-dermatophyte fungi, 0.7%. Dermatophytes were the most isolated, 84.4%, followed by yeasts, 14.9% and non-dermatophyte fungi, 0.7%. *Trichofiton rubrum* (56.2%) *Trichofiton rubrum* (56.2%) it was the most isolated dermatophyte (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). it was the most isolated dermatophyte (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, 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 *T.rubrum* was the most frequent, unlike previous studies. The incidence of *T.mentagrophytes* increased, mainly in the cases of *tinea unguium* and *tinea pedis*. The study also isolated *M.audouinii* not fouind in the studies previously described. The age of the patients evaluated was on average 30 years old and of both genders.

In France, the study conducted by Cognet et al., (2015), in Grenoble, evaluated 5,470 biological samples collected from skin, nails and hair from 3,740 patients of both sexes to confirm dermatomycosis. The samples were collected from 2001 to 2011. For laboratory diagnosis, direct examination and culture were performed. 1984 (36.3%). positive cultures. In these, 1348 (67.9%) dermatophytes were identified and 636 (32.1%) non-dermatophytes. The most isolated dermatophytes were *Trichophyton rubrum*, *T. mentagrophytes* and *T. tonsurans*, with *T. rubrum* isolated 78.6% of the time, Table 1. In this study, drug therapy was not evaluated.

Table 2 describes the selected journals on in vitro tests to evaluate the susceptibility of antifungal agents in relation to the species most found as causing superficial and cutaneous mycoses. The drugs most used for the treatment of these mycoses were imidazole derivatives. and the best results were obtained with terbinafine, which showed satisfactory results in relation to most fungal isolates (Magnanin, CM. et al., 2011; Almeida, LMM., 2019).

In 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, olamina cyclopirox, 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*. Table 2.

In another study from Brazil, from the State University of Maringá in Paraná de 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). We analyzed 80 samples of filamentous fungi 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*. The isolates of *Fusarium* spp. were resistant to all drugs tested. Terbinafine was the drug that was most effective compared to fungal isolates, Table 2.

Also 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 (2010) in a study conducted in Brazil, 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 e o *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.

CONCLUSIONS

The most prevalent species of superficial and cutaneous mycoses found in the present literature review study were dermatophytes *Trichophyton rubrum, T. mentagrophytes, Microsporum canis, Epidermophyton floccosum*, *T. tonsurans* and yeasts *Candida* spp. e *Malassezia* spp.

The results obtained in this same study indicate that the human sites of greatest contamination are hair, scalp, skin, fingernails and 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 the 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. Terbinafine was the most effective drug against most fungal isolates,

ACKNOWLEDGMENTS
The Federal University of Rio Grande do Sul (UFRGS) and its Pro-Rectory of Extension (PROREXT) for financial support through scholarships and material resources for the realization of this project.

CONFLICT OF INTEREST
The Authors declares that there is no conflict of interest.

REFERENCES

1. Peres, Nalu Teixeira de Aguiar et al. Dermatófitos: interação patógeno-hospedeiro e resistência a antifúngicos. An. Bras. Dermatol., Rio de Janeiro. 85 (5): 657-667, (2010)
2. Magagnin, Cibele Massotti et al. Perfil de susceptibilidade a antifúngicos de dermatofitos isolados de pacientes com insuficiência renal crônica. An. Bras. Dermatol., Rio de Janeiro. 86 (4):694-701, (2011)
3. Souza, Paulo Ricardo Martins et al. Concordance between direct microscopy and fungical culture for the diagnostic of feet's onychomycosis. An. Bras. Dermatol., Rio de Janeiro. 87(1): 157-159, (2012)
4. Nweze EI. Dermatophytoses in domesticated animals. Rev. Inst. Med. Trop. São Paulo. 55: 95-99, (2011)
5. Vijendran P, Verma R, Hazra N, et al. A comparative study of the various patterns of oro-cutaneous fungi and their sensitivity to anti fungals between HIV patients and normal healthy individuals. *Med J Armed Forces India*. 75(1):50-57, (2019)
6. Panasiti V, Devirgiliis V, Borroni RG, et al. Epidemiology of dermatophytic infections in Rome, Italy: a retrospective study from 2002 to 2004. *Med Mycol*. 45(1):57-60, (2007)
7. Faure-Cognet O, Fricker-Hidalgo H, Pelloux H, Leccia MT. Superficial Fungal Infections in a French Teaching Hospital in Grenoble Area: Retrospective Study on 5470 Samples from 2001 to 2011. *Mycopathologia*. 181(1-2):59-66, (2016)
8. Cai W, Lu C, Li X, et al. Epidemiology of Superficial Fungal Infections in Guangdong, Southern China: A Retrospective Study from 2004 to 2014. *Mycopathologia*. 181(5-6):387-395, (2016)
9. Dias, Maria Fernanda Reis Gavazzoni et al . Update on therapy for superficial mycoses: review article part I. An. Bras. Dermatol., Rio de Janeiro. 88(5): 764-774, (2013)
10. Dias, Maria Fernanda Reis Gavazzoni et al . Treatment of superficial mycoses: review - part II. An. Bras. Dermatol., Rio de Janeiro. 88(6): 937-944, (2013)
11. SAUL-GARCIA, Yotsabeth; HUMBRIA-GARCIA, Leyla; HERNANDEZ-VALLES, Rosaura. Distribución de especies y susceptibilidad antifúngica de Candida spp. causantes de micosis superficiales. Coro, estado Falcón, Venezuela. Invest. clín, Maracaibo. 56(3): 276-283, (2015).
12. Spampinato C, Leonardi D. Candida infections, causes, targets, and resistance mechanisms: traditional and alternative antifungal agents. *Biomed Res Int*. 2013.
13. PIRES, Carla Andréa Avelar et al . Clinical, epidemiological, and therapeutic profile of dermatophytosis. An. Bras. Dermatol., Rio de Janeiro. 89(2): 259-262, (2014)
14. Martinez et al. Identificação do perfil dos agentes etiológicos causadores de micoses superficiais cutâneas no sul do Brasil. Sci. Elec. Arch. 13(9) (2020)
15. Costa MC, Pereira de Sá N, Johann S, Santos DA. Social, environmental, and microbiologic aspects of endemic mycoses in Brazil. New Microbes and New Infections, 2019
16. Taghipour S, Shamsizadeh F, Pchelin IM, Matehhkolaei AL, Mahmoudabadi AL, Valadan R, Ansari S, Katiraee F, Pakshir K, Zomorodian K, Abastabar M. Emergence of Terbinafine Resistant *Trichophyton mentagrophytes* in Iran, Harboring Mutations in the Squalene Epoxidase (*SQLE*) Gene. Infect. Drug. Resist. (13): 845-850 (2020)
17. SIQUEIRA, Emerson Roberto et al . Ocorrência de dermatófitos em amostras de unhas, pés e mãos coletadas de estudantes universitários. Rev. Soc. Bras. Med. Trop., Uberaba. 39(3): 269, (2006)
18. TAPIA P, Cecilia V. An update on antifungal susceptibility testing. Rev. chil. infectol., Santiago. 26 (2): 144-150, (2009)
19. ALMEIDA, Lívia Maria Martins de et al . Resposta in vitro de fungos agentes de micoses cutâneas frente aos antifúngicos sistêmicos mais utilizados na dermatologia. An. Bras. Dermatol., Rio de Janeiro. 84(3): 249-255, (2009)
20. Steiner D, Vaidergorn R. Superficial mycosis. Atualidades Médicas 2: 2-8, (2018)
21. Diongue K, Diallo MA, Ndiaye M, et al. Champignons agents de mycoses superficielles isolés à Dakar (Sénégal) : une étude rétrospective de 2011 à 2015 [Causative agents of superficial mycoses isolated in Dakar, Senegal: Retrospective study from 2011 to 2015]. J *Mycol Med,* 26(4):368-376, (2016)
22. Sellami A, Sellami H, Makni F, et al. Childhood dermatomycoses study in Sfax Hospital, Tunisia. *Mycoses*.51(5):451-454, (2008)
1. 23.Silva-Rocha WP, de Azevedo MF, Chaves GM. Epidemiology and fungal species distribution of superficial mycoses in Northeast Brazil. *J Mycol Med*. 27(1):57-64, (2017)
23. Cruz Ch R, Ponce E E, Calderón R L, Delgado V N, Vieille O P, Piontelli L E. Micosis superficiales en la ciudad de Valparaíso, Chile: Período 2007-2009 [Superficial mycoses in the city of Valparaiso, Chile: period 2007-2009]. *Rev Chilena Infectol*. 28(5):404-409, (2011)
24. CHIACCHIO, Nilton Di, Superficial mycoses at the Hospital do Servidor Público Municipal de São Paulo between 2005 and 2011. An. Bras. Dermatol., Rio de Janeiro. 89(1): 67-71, (2014)

25. Kaur R, Panda PS, Sardana K, Khan S. Padrão Mycological de Dermatomicoses em um Hospital de Atenção Terciária. J Trop Med . 2015.
26. AZAMBUJA, Christiane Venske de Almeida et al . Onychomycosis: clinical, mycological and in vitro susceptibility testing of isolates of Trichophyton rubrum. An. Bras. Dermatol., Rio de Janeiro. 89(4): 581-586, (2014)
27. DIOGO, Hilda Conceição et al . Avaliação do método de disco-difusão para determinação da eficácia da terbinafina in vitro em agentes de micoses superficiais e subcutâneas. An. Bras. Dermatol., Rio de Janeiro. 85(3): 324-330, (2010)