**UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL**

**FACULDADE DE FARMÁCIA**

**TRABALHO DE CONCLUSÃO DE CURSO EM FARMÁCIA**

# Dermatomycosis: epidemiology, virulence and susceptibility of fungal agents, a literature review of the last twenty years

**Ester da Silva Vieira**

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**Orientadora: Prof.ª Dra. Adelina Mezzari**

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*“O êxito da vida não se mede pelo caminho que você conquistou, mas sim pelas dificuldades que superou no caminho”*

*Abraham Lincoln*

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**Dermatomycosis: epidemiology, virulence and susceptibility of fungal agents, a literature review of the last twenty years**

**Dermatomicoses: epidemiologia, virulência e suscetibilidade de agentes fúngicos, uma revisão da literatura dos últimos vinte anos**

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## Abstract

**Objective:** This study aims to evaluate the epidemiology of superficial and cutaneous mycoses, their etiological agents, as well as the factors of susceptibility and resistance factors to antifungals used for their treatment, in the last 20 years, between 2000 and 2020.

**Methods and results**: A literature review was conducted in *online* databases *PubMed, Scielo* and *Scopus*. The selected studies showed data on the prevalence of the species, the profile of the patients, the most affected sites of infection, the diagnostic method used and the susceptibility profile of the fungal species in relation to the most used antifungals. The most prevalent infection sites were skin, nail and hair and the most tested antifungals, against to isolated pathogens, were ketoconazole, fluconazole, cyclopirox and terbinafine.

**Conclusion:** In recent years there has been an increase in cases of dermatomycosis caused by non-dermatophyte fungi. In this study, we observed that the most isolated non-dermatophyte fungi were the genera *Candida* spp., *Malassezia* spp., *Fusarium* spp. and *Aspergillus* spp. The drugs itraconazole and voriconazole were the most active agents against *Candida* species. *Fusarium* species demonstrated greater resistance to antifungals, with high MIC (minimal inhibitory concentration) concentrations for all antifungal agents.

**Keywords:** dermatomycoses, non-dermatophyte fungi, yeasts, superficial mycoses, resistance and susceptibility.

## INTRODUCTION

Dermatomycosis is a disease characterized by superficial and cutaneous infections in keratinized tissues, such as skin, hair, nails and mucous membranes of humans and animals, caused by a variety of fungal agents, being characterized by dermatophytes, non-dermatophytes and yeasts (Almeida et al. 2009; Hube et al. 2015).

Superficial fungal infections are a major cause of morbidity in the world, especially in the tropics, where heat and humidity provide the ideal conditions for the growth of fungi that cause skin infections. Direct contact is sufficient to transmit the infection from one contaminated or host surface to another. In superficial mycoses, fungi are confined to the epidermis and its attachments, and rarely invade the dermis. In extremely rare cases, the internal organs can also be affected. There are two categories of clinical manifestations: non-inflammatory and inflammatory (Dias et al. 2013).

Climatic factors, as well as social practices, population migration, individual characteristics, including age, morphological anomalies in the nails genetic factors and inadequate hygiene conditions and 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. (Peres et al. 2010). Among the several reasons pointed out to explain the increase in the incidence of dermatomycoses in the last decades, include the abuse of antibiotics, cytostatic drugs and immunosuppressive diseases (Oliveira et al. 2006).

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 (Almeida et al. 2009). These fungal infections caused by dermatophytes, non-dermatophytes or yeasts are frequent and can be transmissible in most cases, as these fungi remain in the outermost layer of the skin, that is, in the horny extract. The most humid areas of the body, for example, between the fingers, toes, breast folds, armpits, genital region and others are the most vulnerable to infection due to their favorable microenvironment (Vartak et al. 2020).

Its incidence has increased in recent years, as affected individuals have searched for diagnosis and treatment in dermatology outpatient clinics. Fungal diseases that affect the skin and its attachments are frequent reasons for consultation in basic health screening services and in dermatology. Its worldwide prevalence is estimated between 0,1 and 11%, with variation according to geographic areas, as well as external conditions or influences that affect the individual's life, behavior and society (Calado et al. 2011; Lemuz- Espinoza et al. 2014).

Several factors explain this fact, some of them are the environment, the climate, animals as a reservoir of microbial agents, vector insects and socioeconomic condition, together with the sum of personal habits such as the use of closed shoes, tight clothes and the frequent practice of sports that exacerbate the increase in heat and humidity, associated with a tropical climate, poor hygiene habits, playing in the sand and contact with domestic animals and the individual way of life, as determining factors of exposure to these diseases or resistance (Calado et al. 2011; Lemuz- Espinoza et al. 2014).

The most frequent fungi that cause dermatomycoses in dermatological practice, are the dermatophytes, which are divided into three genera: *Trichophyton*, *Microsporum* e o *Epidermophyton*, in addition to dermatophytes, dermatomycoses caused by non-dermatophyte keratinophilic fungi are also prevalent, as well as yeasts of the genus *Candida* spp. and *Malassezia* spp. (Peres et al. 2010).

Filamentous non-dermatophyte fungi considered contaminants, are currently being observed as causal agents in cases of superficial and cutaneous mycoses, represented predominantly by genera *Alternaria, Aspergillus, Acremonium, Cladosporium, Penicillium, Scopulariopsis*, among others (Oliveira et al. 2006).

Dermatomycoses caused by non-dermatophyte filamentous fungi are rare, varying from 1 to 11% of cases. *Scytalidium dimidiatum* has been an increasingly agent present in onychomycosis, which can be explained by the fact that soil or plant material is the source of transmission of this fungus by direct contact with its propagules. This fungus has the ability to metabolize the keratin of the nails even with less intensity than the dermatophytes (Oliveira et al. 2006).

Yeasts of the genus *Malassezia* spp. and *Candida* spp. are among those that most cause skin infections. *Malassezia* spp., a superficial mycosis agent, is strictly lipophilic and is part of the normal microbiota of the skin and scalp of individuals. Although without keratinolytic activity, this fungus lives on the skin around the hair and uses epithelial debris or waste products as sources of energy for development. This agent is the cause of *pityriasis versicolor* and has been implicated in the pathogenesis of seborrheic dermatitis, has its cosmopolitan distribution, occurring mainly in temperate and tropical climates (Chiacchio et al. 2014).

Yeast produces dicarboxylic acids such as azelaic acid, which inhibits tyrosine kinase, resulting in hypopigmentation of the area involved, especially in individuals with dark skin, and also hyperchromic or erythematous lesions, hence the term versicolor (Dias et al. 2013a). It is associated with several factors, including poor health, chronic infections, excessive sweating and physiological conditions, such as pregnancy, use of contraceptives and steroid therapy, among others (Chiacchio et al. 2014).

*Candida* spp. is a normal habitant of the human microbiota, being the main responsible for candidiasis, it is considered an opportunistic yeast which compromises, individually or together, mucous membranes, skin and nails. As an agent of superficial mycoses, it has the ability to digest keratin present in the skin and its attachments, which can trigger an inflammatory response from the host. Among positive cases for *Candida* spp., patients of any age can be affected. This fungus has a worldwide distribution and affects people of all ages, with a preference for certain professionals, such as domestic workers, washerwomen, cooks and nurses (Chiacchio et al. 2014).

Among the more than 20 species of *Candida* proven to be pathogenic to man, *Candida albicans* has been the one most capable of causing infection. They are saprophytes normally present in the gastrointestinal, genital, skin and mucous membranes. In situations such as compromised immunity, obesity, use of antibiotics and corticosteroids, trigger an uncontrollable growth of yeasts in these areas, generating the symptoms of the disease. If not controlled in time, they can produce large amounts of harmful enzymes, transforming yeast cells into pseudohyphae and hyphae and even more, they can form biofilm. The virulence of yeast depends on its ability to morphological transition, to express the specific gene expression that determines the binding and invasion of yeast on cell surfaces, to secrete hydrolytic enzymes, to adapt to pH changes, to respond to stress and flexibility metabolic (Vartak et al. 2020).

There are many non-dermatophyte filamentous fungi isolated from nails but only a few species are among the causes of onychomycosis. These included the *Scopulariopsis brevicaulis, Fusarium* spp.*, Acremonium* spp.*, Aspergillus* spp., *Scytalidium* spp. and *Onychocola canadiensis.* Many other non-dermatophyte fungi and some yeasts considered saprobes can also parasitize the nail plate directly, but without causing clinical manifestation. These include some species of the genera *Alternaria, Curvularia, Penicillium, Scytalidium, Trichosporon* and *Hendersonula*. In addition, other non-dermatophyte fungi can, exceptionally, cause onychomycosis (Araújo et al. 2003; Diogo et al. 2010).

*Scopulariopsis brevicaulis* species is, among the non-dermatophyte filamentous fungi, the most frequent agent of onychomycosis of the feet, involving predominantly the nail of the hallux. Its proximal location is the most frequent and is characterized by white, yellow or orange color that appears in the lunula and extends to the distal region of the nail (Araújo et al. 2003).

*Trichosporon* spp. and *Rhodotorula* spp. are other yeast genera also considered responsible for dermatomycoses (Souza et al. 2012). The etiological diagnosis performed in the laboratory can confirm the clinical suspicion of ringworm, allowing the choice of specific treatment and its evaluation. Although clinical manifestations generally do not cause systemic complications, there is no doubt that such infections significantly affect the psychological and aesthetic condition of patients. The incidence of superficial and cutaneous mycoses can only be partially estimated, since the published data are usually from cases in which the consultation reaches the dermatologist and the latter transfers the confirmatory diagnosis to the mycologist (Lemuz-Espinoza et al. 2014).

One of the best indicators of public health importance has been implemented by the continuous and growing notification of the cases studied. However, the most present barrier is the fact that these fungi do not evoke an important response in the host because they are not very invasive. The interest in these fungal infections has arisen by observing a variety of diseases, including invasive ones, originating from fungi of the genera *Malassezia*, *Hortaea* and *Trichosporon* (Lemuz -Espinoza et al. 2014).

Generally, the gradual process of infection in the host is similar among dermatomycosis species, however, the specific ability of the species to cause a reaction in the host after infection is different. Yeasts like *Candida albicans* cause a relatively low level of damage and inflammation in host tissue during pathogenicity, while dermatophytes can induce a higher level of tissue damage and show an inflammatory reaction (Hube et al. 2015).

According to (Chiacchio et al. 2014), *Malassezia* spp. most cases of infection occur in young adulthood. One possible explanation is that, due to the lipophilic nature of this yeast and the post-puberty hormonal stimulation inherent in this age group, there is stimulation of the sebaceous glands accompanied by an increase in the fat content of the skin, which serves as a substrate for the fungus (Chiacchio et al. 2014).

Onychomycosis is considered the most difficult cutaneous mycosis (dermatomycosis) to diagnose and treat. The most common clinical form of onychomycosis caused by non-dermatophyte filamentous fungi is the proximal, associated with inflammation of the proximal fold, which can be limited to the region of the lunula or affect the entire nail. The presence of inflammation suggests onychomycosis by a non-dermatophyte fungus, which is almost never seen in dermatophyte onychomycosis. Onychomycosis due to *Acremonium* spp., on the other hand, is not associated with peculiar clinical characteristics (Araújo et al. 2003).

To confirm the etiology of non-dermatophyte onychomycosis, the standard criteria for mycological diagnosis must be well applied. The diagnosis of onychomycosis must always be based on fundamental points such as the clinical aspect, the patient's origin, the history of other infections correlated with onychomycosis and possible previous specific treatments. The mycological diagnosis is definitive, being based on direct examination, culture and identification of the etiological agent, whether morphological and / or with the aid of biochemical tests (Araújo et al. 2003).

The finding of a hypha in a nail lesion is a diagnosis of *tinea unguium*, even if the fungus cannot be isolated in the culture medium. The isolation of a non-dermatophyte fungus or yeast can be the result of environmental contamination, originating from the patient's normal microbiota, or the agent of a real infection. The direct positive examination of non-dermatophyte filamentous fungus and the number of colonies corresponding to the number of inoculated points are indicative, but it is necessary to request further samples to prove the initial diagnosis. The patient's origin, his contact with possible outbreaks, such as other sick people or animals, the occupation that favors the development of mycoses and the region of the country where he comes from, tend to guide on the value of the cultivation of unusual species (Araújo et al. 2003).

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, salicylic acid or ketoconazole. As for oral therapy, terbinafine, itraconazole, ketoconazole and fluconazole are all antifungal agents, all of which are treatments of choice for dermatophytosis when they do not respond to therapies with topical drugs (Magagnin et al. 2011).

The effectiveness of topical agents in cutaneous mycoses depends not only on the type of lesion but on the drug's own mechanism of action, and also on the viscosity, hydrophobicity and acidity of the formulation. Regardless of the type of formulation, the penetration of topical agents in hyperkeratotic lesions is usually precarious. Products used for cutaneous application tend to be made in creams or solutions. Ointments are heavy and excessively occlusive for use in macerated or fissured intertriginous lesions. The use of powders, applied in the form of a spray or aerosol, is largely limited to the area of the feet and injuries in moist intertriginous areas. Cutaneous formulations are not suitable for oral, vaginal or ocular use (Dias et al. 2013b).

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. However, this specificity is still limited due to little knowledge in several areas of the biology of pathogens, 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. Commonly used antifungals 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 (Peres et al. 2010).

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 (Almeida et al. 2009). The spectrum of activity of these antifungals is variable, leading to therapeutic failures, possibly due to low patient compliance, lack of drug penetration, drug bioavailability, drug interactions or resistance (Magagnin et al. 2011).

Topical antifungal drugs are the first-line treatment for infections by *Malassezia* spp. and ketoconazole (KTZ) is one of the most effective agents. KTZ is a fungistatic imidazole that inhibits lanosterol 14α-demethylase, an enzyme that regulates the synthesis of ergosterol. The interruption of ergosterol biosynthesis alters the cell membrane structure, compromising its integrity and permeability and, consequently, interfering with cell growth and reproduction (Mussin et al. 2019).

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, changes in the interaction of the drug with the target site or with other enzymes involved in the same enzyme pathway, 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 (Peres et al. 2010).

Among the drugs with a different mechanism of action than azoles is terbinafine, belonging to the class of allylamines, acting on the epoxidase enzyme of the fungal cell. It is especially indicated for dermatomycoses caused by fungi from the group of dermatophytes. 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 (Diogo et al. 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 (Magagnin et al. 2011).

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 (Diogo et al. 2010).

## MATERIAL AND METHODS

A literature review was carried out on non-dermatophyte dermatomycosis agents, more isolated in different parts of the world, through a systematic search in the *online* databases *PubMed, Scielo* and *Scopus*. The terms used in searching the databases were “superficial mycoses" AND ‘’ yeast ’’ AND “Dermatomycoses” AND “nondermatophyte molds”.

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

## RESULTS

In order to carry out this study, a search was made in three databases: 120 articles were found in the *Pubmed* database, 8 articles in *Scielo* and 38 in *Scopus*, totaling 166 articles. Of these, duplicates and triplicates were excluded, leaving 110 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 the remaining 56 articles, the summary was read and epidemiological data were collected, and of these, 16 met all the eligibility criteria, being used for data extraction and analysis. These were separated by data relevant to the research, 12 articles were selected to verify the epidemiological profile of the etiologic agents, Table 1. To assess the profile of susceptibility and resistance to antifungals, Table 2. The article selection flowchart is represented in Figure 1.

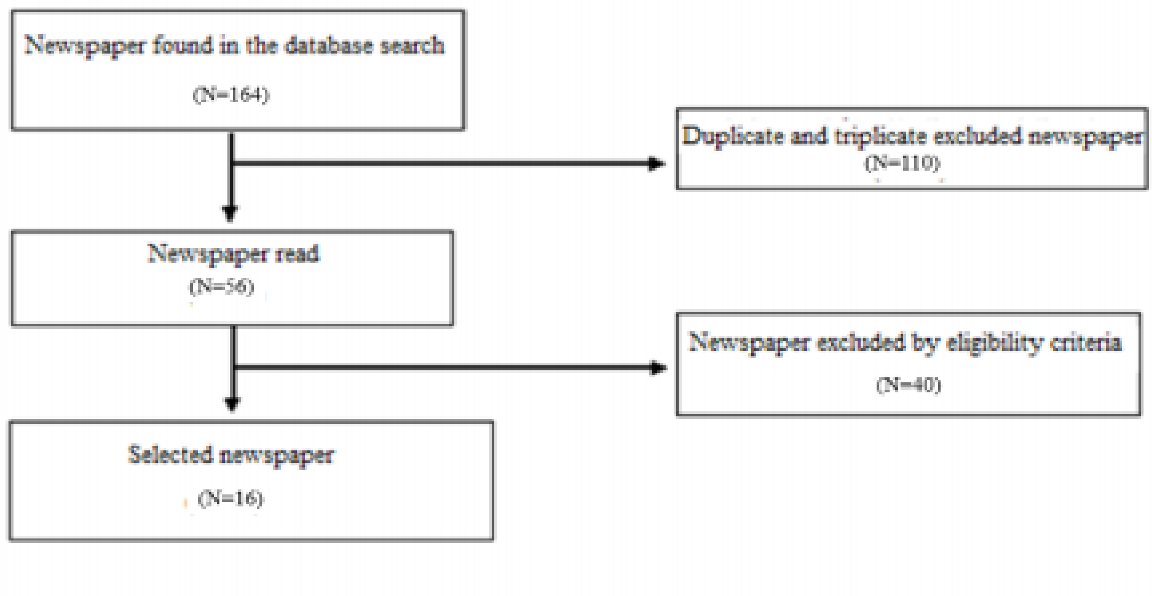


**Fig. 1.Flowchart of study selection**

Analyzed newspaper were published between 2000 and 2020, in Senegal (Diongue et al. 2016), in Tunísia (Sellami et al. 2008), in Brazil (Silva-Rocha et al. 2017), (Almeida et al. 2009), (Petry et al. 2011), (Diogo et al. 2010) and (Vasconcellos et al. 2013), in Colombia (Estrada-Salazar et al. 2016), (Bueno et al. 2010) and (Grosso et al. 2009), in Chile (Cruz et al. 2011), in India (Kaur et al. 2015), (Vijedran et al. 2019), in Greece (Nasr et al. 2015), in Turkey (Gulgun et al. 2013) and in Iran (Pakshir et al. 2015).

Twelve articles were selected to verify the epidemiological profile of the etiological agents, which are represented in Table 1.

**Table 1: Data extracted from the 12 selected articles that express epidemiological data**

| Author/Year | Country | Biological samples | Positives | Dermatophyte etiologic agent found | Clinical aspects | Average age of the patients |
|---|---|---|---|---|---|---|
| Diongue et al. 2016 | Senegal | 1851 | 633 | *Candida albicans* | Dermatomycosis | 31 years old |
| Sellami et al. 2008 | Tunisia | 4559 | 2247 | *Malassezia* spp. | Dermatomycosis | <16 years old |
| Cruz et al. 2011 | Chile | 1004 | 1004 | *Candida* spp,<br>*Fusarium* spp. | Dermatomycosis | All ages |

| | | | | | | |
|---|---|---|---|---|---|---|
| Salazar- Estrada et al. 2016 | Colombia | 255 | 255 | *Candida albicans,*<br>*Trichosporon* spp.,<br>*Penicillium* spp.,<br>*Fusarium* spp. | Dermatomycosis | <15 to > 61 years old |
| Grosso et al. 2009 | Colombia | 53 | 53 | *Fusarium* spp.,<br>*Cryptococcus* spp.<br>*C. parapsilosis,*<br>*S.hyalinum, C.krusei,*<br>*S. dimidiatum, C. rugosa, C. tropicalis* | Onychomycosis<br>Dermatomycosis | All ages |
| Vijendran et al. 2018 | Índia | 200 (100 pac/( HIV -) e 100 pac/ (HIV +) | 21 pat/ (HIV -) and 57 pat/ (HIV +) | (HIV -) patients: *C. albicans* (HIV +) patients:*Candida albicans and non-albicans* | Dermatomycosis | Not informed |
| Kaur et al. 2015 | India | 351 | 215 | *Aspergillus niger* (9%)<br>*Candida* non-*albicans* (6%) | Dermatomycosis | All ages |
| Petry et al. 2011 | Brazil | 87 | 87 | *M. sympodialis,*<br>*M. furfur, M. globosa,*<br>*M. restricta,*<br>*M. obtusa,*<br>*M slooffiae* | Dermatomycosis | >16 years old |
| Silva-Rocha et al. 2017 | Brazil | 235 | 113 | *Candida parapsilosis* | Onicomycosis | Not informed |
| Vasconcellos et al. 2013 | Brazil | 35 | 18 | *Candida guilliermondii,*<br>*C. parapsilosis,*<br>*C. glabrata,*<br>*Trichosporon asahii,*<br>*Fusarium* spp.<br>*Aspergillus* spp. *and*<br>*Neoscytalidium* spp. | Onychomycosis<br>Dermatomycosis | 65-98 years old |
| Nasr et al. 2015 | Greece | 503 | 222 | *C. parapsilosis, C. albicans*, *Fusarium* spp., *Acremonium* spp. | Dermatomycosis | All ages |

| | | | | | | |
|---|---|---|---|---|---|---|
| Gulgun et al. 2013 | Turkey | 8122 | 152 | *C. glabrata, C. parapsilosis, Trichosporon* spp., *Rhodotorula* spp. | Onychomycosis | 5-16 years old |

To assess the susceptibility profile and resistance to antifungals, 4 articles were selected and are described in Table 2.

**Table 2: Data extracted from the 4 selected studies on "in vitro" susceptibility testing**

| **Author/ Year** | **Country** | **Biological samples** | **Etiological agents** | **Antifungal tested** | **Methods** | **Results** |
|---|---|---|---|---|---|---|
| Diogo et al. 2010 | Brazil (SP) | 53 isolates of non-dermatophyte and dermatophyte fungi | *S. hyalinum, F. oxysporum, Cladophialophoa carrionii, Candida spp and Trichophyton spp.* | Itraconazole Terbinafine Ketoconazle | Microdilution in broth according to protocol M38-A2 (CLSI) 2008 | *S. hyalinum, C. parapsilosis* and *Fusarium* spp. were considered sensitive to terbinafine, however presenting a 12 mm halo with a 2 µg disc. |
| Almeida et al. 2009 | Brazil (PR) | 80 clinical isolates agentes of cutaneous superficial mycoses | *Dermatófitos (76) Fusarium oxysporum* (01); *F. solani* (01); *F. incarnatum* (01); *F. verticillioides* (01). | Fluconazole Ketoconazole Itraconazole Terbinafine | Microdilution in broth according to protocol M38-A2 (CLSI) 2008 | 80 positive samples were found for filamentous fungi, being Trichophyton spp. 81% of the samples. . All clinical isolates of Fusarium spp. the drugs tested were resistant. Terbinafine was the most effective antimycotic against fungal isolates. |
| Pakshir et al. 2015 | Ira | 97 *Candida* spp. isolates | *C.parapsilosis(44), C. albicans (23), C. tropicalis(13), C. glabrata (7), C. krusei (6), C.guilliermondi (3) C. dubliniensis (1)* | fluconazole, voriconazol and clotrimazole | Microdilution in broth according to protocol M38-A2 (CLSI) 2008 | All isolates were susceptible to CLT (clotrimazole). VRC (voriconazole) had lower values of minimal inhibitory concentration (MIC) for the isolates compared to FLC (fluconazole). |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bueno et al. 2020 | Colombia | 103 fungal isolates | *Candida spp (58), Fusarium spp. (10), Fusicoccum dimidiatum ( 4), Scytalidium hyalinum ( 1) dermatófitos (30)* | terbinafine, itraconazol voriconazole and fluconazole | CLSI M38-A (2002) and AFST-EUCAST | Itraconazole and voriconazole were the most active agents against *Candida* species, while terbinafine and voriconazole were the most potent against dermatophytes. *Fusarium* species showed the highest values of minimum inhibitory concentration (MIC) with all antifungal agents. |

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.

Regarding the sample size of the studied population, twelve studies evaluated the epidemiological profile of the etiological agents, non-dermatophytes, with a great variation in the number of biological samples between the studies, being (Vasconcellos et al. 2013) the smallest with 35 samples and (Gulgun et al. 2013) the largest with 8122 samples. Of the studies analyzed, all evaluated both genders. Four studies did not specify the age of the individuals (Grosso et al. 2009), (Vijedran et al. 2019), (Cruz et al. 2011), (Silva-Rocha et al. 2017). The other eight studies delimited age (Gulgun et al. 2013) (5-16 years), (Vasconcellos et al. 2013) (65-98 years), (Kaur et al. 2015) (0-60 years), ( Nasr et al. 2015) (2-85 years), (Petry et al. 2011) (> 16 years), (Estrada-Salazar et al. 2016) (15-61 years), (Diongue et al. 2016) ( 2 months - 81 years) and (Sellami et al. 2008) (<16 years).

In table 1, of the twelve articles analyzed regarding the epidemiology of dermatomycosis caused by non-dermatophyte fungi, the yeast *Candida* spp. was the most isolated. Only the study by (Petry et al. 2011), which was interested in evaluating just *Malassezia* spp., did not isolate *Candida* spp. The second most isolated pathogen in the studies was. *Malassezia* spp., followed by *Fusarium* spp. and *Aspergillus* spp. In Brazil, the most isolated non-dermatophyte fungi were: *Candida parapsilosis* by (Silva-Rocha et al. 2017), *Malassezia sympodialis, M. furfur, M. globosa, M. restricta, M. obtusa and M. slooffiae* by (Petry et al. 2011) and *Candida guillermondii, C. parapsilosis, C. glabrata, Trichosporon asahii, Fusarium* spp.*, Aspergillus* spp., and *Neoscytalidium* spp. in the study by (Vasconcellos et al. 2013), Table 1.

In Chile, the isolated non-dermatophyte fungi were: *Fusarium oxysporum, Scopulariopsis brevicaulis*, *Acremonium strictum*, *Acremonium kiliense, Aspergillus fumigatus, Aspergillus niger, Alternaria alternata, Candida* spp, *Trichosporon* spp., *Rhodotorula* spp. and *Cryptococcus laurentii* in the (Cruz et al. 2011) studies, Table 1.

In Colombia, *Candida albicans, Trichosporon* spp., *Penicillium* spp. and *Fusarium* spp., were non-dermatophyte fungi isolated by (Estrada-Salazar et al. 2016) and *Fusarium* spp., *Cryptococcus* spp., *Candida parapsilosis*, *Scytalidium hyalinum*, *S. dimidiatum*, *Candida krusei*, *C. rugosa, C. tropicalis*, *C. guillermondi, Fusarium oxysporum* and *Fusarium* spp., in the study by (Grosso et al. 2009), Table 1.

In the study conducted in Senegal by (Diongue et al. 2016), the most isolated agent was *Candida albicans.* In Tunisia, the fungi isolated were *Malassezia* spp. and *Candida albicans* according to (Sellami et al. 2008). In India, the most isolated fungal agents were *Candida albicans* and *Candida* não-*albicans*, in the study (Kaur et al. 2015) and were also the same isolates according to the study by (Vijendran et al. 2019), Table 1.

The study carried out in Greece by (Nasr et al. 2015), the fungal isolates were, *Candida parapsilosis, C. albicans, Fusarium* spp. and *Acremonium* spp. In Turkey the most isolated fungi were *Candida glabrata, C. parapsilosis, Trichosporon spp., Rhodotorula* spp. in the study by (Gulgun et al. 2013), 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, observed by an experienced professional taking care with the conservation, transport 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, that inhibits contaminant bacteria or cycloheximide, that inhibits the growth of yeasts and opportunistic saprofitas fungi. The cultures were incubated in a bacteriological greenhouse at a temperature between 25-30°C (Pakshir et al. 2015), Table 1.
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.

In addition to the conventional routine for direct examination and culture of lesions for the diagnosis of dermatomycoses, some studies have also used the polymerase chain reaction PCR (Polymerase Chain Reaction, susceptibility and resistance tests to antifungals by diffusion disc or microdilution, urea hydrolysis and biochemical tests (Almeida et al. 2009; Grosso et al. 2009; Pakshir et al. 2015).

## DISCUSSION

In the study conducted in Senegal (Diongue et al. 2016) by it was conducted with 1851 patients, of these 633 (34,19%) 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 yeast *Candida albicans* was isolated in (26,9%), followed by the dermatophyte fungus *Trichophyton soudanense* (24,9%). The presence of these fungi showed different clinical aspects, isolated or associated. The prevalence of mycoses in this study is caused by dermatophytes, with non-dermatophyte agents still representing few cases, Table 1.

According to (Sellami et al. 2008), in Tunisia, 4559 children under 16 years old were evaluated. The diagnosis of superficial and cutaneous mycoses was confirmed in (49.3%) of the cases. Dermatophytes were the most prevalent fungal agents and responsible for 1865 cases (80,6%). 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 albican*s (58,0%). As previously described in the research by (Diongue et al. 2016), the prevalent fungi that cause superficial and cutaneous mycoses were dermatophytes, Table 1.

In Brazil, (Silva-Rocha et al. 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 dermatomycoses. Of these, (64,6%) were female and (35,4%) were male. Of the positive cases, infections caused by non-dermatophyte fungi were observed in 45 (39,8%), while dermatophyte fungi in 68 (60,2%). *Candida parapsilosis* was the most isolated yeast with (15,1%), followed by the dermatophyte fungus *Trichophyton tonsurans* with (13,4%). Dermatophyte fungi also prevailed in this study, Table 1.

(Petry et al. 2011), a study conducted in Brazil, aimed to determine which species of *Malassezia* are more prevalent in patients with pityriasis versicolor. Collections were performed by scraping the lesions in patients with clinical suspicion of pityriasis versicolor and subsequent mycological and cultural examination for final identification of the species. Samples were collected from 87 patients, 51 (58,6%) female and 36 (41,4%) male. The evaluated patients were older than 16 years. Sixty-seven patients (77,0%), with clinical suspicion, presented positive direct mycological examination and sixty-six (75%) positive cultural mycological examination. As for cultures, 30.0% were from *Malassezia sympodialis,* (25,7%) from *M. furfur*, (22,7%) from *M. globosa,* (12,1%) from *M. restricta,* (7,6%) from *M. obtusa* and (1,5%) of *M. slooffiae.* The prevalence of pityriasis versicolor was higher in female and young patients (with a mean age of 31 years), Table 1.

In the study by (Vasconcelos et al. 2013), in Brazil, aimed to isolate and identify agents of onychomycosis in institutionalized elderly (60 years +). Thirty-five patients aged 65 to 98 years, of both sexes, were evaluated. Of the clinical samples collected (nail scrapes), after direct examination and culture, 18 (51,4%) were positive. The most isolated fungi in this study were non-dermatophytes (to which yeasts are included) in (55,60%) of the cases, followed by dermatophytes in (44,40%). The fungal findings were: *Candida guillermondii* (16,67%), *C. parapsilosis* (11,11%), *C. glabrata* (5,56%), *Trichosporon asahii* (5,56%), *Fusarium* spp., *Aspergillus* spp. e *Neoscytalidium* spp., (5,56%) each. Of the dermatophytes, the most isolated was *Trichophyton rubrum* with (27,78%). The infection rate was 11 women / 7 men, among the 18 cases of onychomycosis confirmed in this study. In this study, there was a prevalence of non-dermatophyte fungi among the isolates, Table 1.

According (Cruz et al. 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 10% KOH and culture of the lesions. The identification of fungi was made by morphophysiological evaluation. Of the 1004 patients studied, 609 were women and 395 were men. The most isolated non-dermatophyte fungi in this study were Fusarium solani, Fusarium oxysporum, Scopulariopsis brevicaulis and Acremonium strictum, Acremonium kiliense, Aspergillus fumigatus, Aspergillus niger and Alternaria alternata with 1 isolate each. Candida spp. prevailed among yeasts that cause onychomycosis with (95,3%) of infections, Trichosporon spp. (3,4%), Rhodotorula spp. (0,9%) and Cryptococcus laurentii (0,3%). In this study, there was also a prevalence of dermatophyte fungi, Table 1.

According to (Estrada-Salazar et al. 2016), a study carried out in Colombia, aimed to determine the frequency of dermatomycoses in people from different social assistance institutions in the city of Manizales between (2011-2012). For a descriptive study, 255 people (146 men and 109 women) were recruited from different institutions serving vulnerable populations. After collecting samples such as nail scrapes, scalp and body, direct analysis was performed with 10% KOH and culture on Sabouraud and Mycosel agar medium. One hundred and forty-six (146) samples were positive for dermatomycoses, with 30 samples of dermatophyte fungi, 76 of yeasts, 12 of non-dermatophytes and 28 mixed samples (more than one fungus on the same plate).

The isolated fungi were *Candida* spp., *Trichosporon* spp., *Penicillium* spp., *Fusarium* spp. and *Trichophyton* spp. Among yeasts, *Candida* spp. was the most prevalent with (53,3%) followed by *Trichosporon* spp. (12,0%). In this study, mycoses were caused mainly by non-dermatophyte fungi represented by non-dermatophyte filamentous fungi (NDFF) and by yeasts, Table 1.

According to (Grosso et al. 2009), a study conducted in Colombia, carried out in 2007 in the city of Tunja, evaluated 53 elderly people with lesions suggestive of superficial and cutaneous mycosis. One hundred and forty-nine samples of skin, hair and nails from the participating adults were obtained. The samples were subjected to direct microscopic examination, using 10% potassium hydroxide, then cultured on Sabouraud Glucose Agar, pH 5.6 with chloramphenicol and the urease test was also performed. The most isolated fungi were non-dermatophytes such as *Candida albicans* (30,0%), *Candida parapsilosis* (11,11%), *Scytalidium hyalinum* (7,41%) *Scytalidium dimidiatum* (5,56%), *Candida krusei, Candida rugosa, Candida tropicalis* (3,70%) each, respectively, *Fusarium oxysporum* (3,0%), *Cryptococcus* spp (3,3%) and the genus *Trichophyton* spp. com (28,52%). In this study, the most prevalent fungi that cause mycoses were non-dermatophytes, Table 1.

In India, (Vijendran  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. From the retropositive patients, (69%) presented fungal infection and from the retronegative (24%). *Candida albicans* was the only species of *Candida* cultivated among HIV negative individuals, while it constituted

(80,55%) among HIV positive patients, with the remaining (19,45%) species of *Candida non-albicans.* Only the dermatophyte of the genus *Trichophyton* was grown among HIV negative individuals, while others such as *Trichophyton* spp. and *Epidermophyton floccosum* were grown among HIV positive patients. Among the fungal isolates in retro positive patients, the species *Candida* spp. was the most isolated with (63%), followed by dermatophytes with (37%). Regarding retronegative patients, the fungal isolates were (61,9%) dermatophytes (9,5%) *Candida* spp. and (27,8%) *Malassezia* spp. In this study, as well as, seen in (Estrada-Salazar et al. 2016) and (Vasconcelos et al. 2013), the most prevalent fungi that cause mycoses were non-dermatophytes, Table 1.

According (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 (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 *Aspergillus flavus* (8,1%), *Penicillium* spp. (3,5%), *Mucor* spp. (3,2%), *Rhizopus* spp. (2,7%) and *Alternaria alternata* (2,4%), 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%) female. There was a prevalence of non-dermatophyte fungi as the causative agents of mycoses. Table 1.

In Greece, a study by (Nasr et al. 2015) aimed to evaluate the data on dermatomycoses of patients mainly from the Macedonian region, northern Greece, between January 2010 and January 2014. They included samples from 438 patients (146 males and 292 females) with an age range of 2 to 85 years. Five hundred and thirty six samples of skin, hair and nail lesions were collected, which were analyzed by direct examination and culture. Of a total of two hundred and twenty-two positive cultures, 50 were considered to produce clinically non-significant isolates (saprophytes). Among the others (172), dermatophytes were the most prevalent isolates (102) followed by yeasts (51) and non-dermatophyte molds (19). The yeast *Candida parapsilosis* and *Candida albicans* were the most isolated and *Fusarium* spp. and *Acremonium* spp. among non-dermatophyte fungi. In this study, the prevalence of mycoses occurred by dermatophyte fungi, Table 1.

In Turkey, a study by (Gulgun et al. 2013), aimed to assess the pathogens and predominant risk factors for onychomycosis in schoolchildren living in Kayseri, Turkey, 8122 schoolchildren aged (5-16 years) were evaluated. The clinical diagnosis was verified in 152 (0,18%) children. Nail samples were collected and analyzed by direct examination and culture, and the mycological diagnosis of onychomycosis was verified in only 27/152 children (17,8%). Among fungal isolates, dermatophytes added (62,9%) and yeasts (37,1%). The causative agents were of the genus *Trichophyton* spp. and the yeasts *Candida glabrata, Candida parapsilosis, Trichosporon* spp. and *Rhodotorula* spp. again in another study, the prevalence of dermatophyte fungi was found to be the main cause of dermatomycoses, Table 1.

Table 2 describes the selected articles that refer to *in vitro* tests, with the objective of evaluating the susceptibility of antifungal agents in relation to the species most commonly found as agents that cause cutaneous mycoses. The most used drugs for the treatment of dermatomycoses were imidazoles.

In a study from performed in Brazil, from the State University of Maringá in Paraná (Almeida et al. 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). Were 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.

(Diogo et al. 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.

In a study by (Pakshir et al. 2015), in Iran, the in vitro susceptibility of 97 isolates comprising seven species of *Candida* against antifungals, fluconazole (FLC), voriconazole (VRC) and clotrimazole (CTL) was evaluated. The strains of *Candida albicans* (ATCC 10261) and *C. parapsilosis* (ATCC 4344) were used as controls. The techniques used were the Clinical and Laboratory Standards Institute CLSI-M27-A (2008), using the microdilution method with minor modifications. The results showed that clotrimazole was susceptible to all isolates and that voriconazole was active against (79,3%) and only (7,2%) had low susceptibility to fluconazole, Table 2.

(Bueno et al. 2010), a study carried out in Colombia, evaluated the efficacy of the antifungals terbinafine, itraconazole, voriconazole and fluconazole in relation to 103 fungal isolates being they (58) isolated from *Candida* spp*.,* (14) from *Fusarium* spp., (1) isolated from Sc*ytalidium hyalinum* and (30) dermatophytes. The samples were evaluated according to the methods described in the protocols of the Antifungal Susceptibility Testing Subcommittee of the European Committee for Antimicrobial Susceptibility Testing (AFST-EUCAST) and the Clinical and Laboratory Standards Institute CLSI M38-A (2002). Itraconazole and voriconazole were the most active agents against *Candid*a species, while terbinafine and voriconazole were the most potent against dermatophytes. *Fusarium* species showed the highest values of (MIC) minimum inhibitory concentration with all antifungal agents, Table 2.

The majority of cutaneous mycoses are caused by dermatophyte fungi. However, in recent years, there has been an increase in the number of cases of dermatomycosis caused by non-dermatophyte fungi. In the present study, in order to verify the epidemiology of such mycoses, twelve articles were evaluated and of these, six studies had dermatophyte fungi as prevalence, with *Trichophyton rubrum* being the most isolated and in the other six studies, the prevalence of the most isolated fungi was non-dermatophytes, of the genera Candida spp., *Malassezia* spp., *Fusarium* spp. and *Aspergillus* spp.

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, itraconazole and terbinafine.

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## CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

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