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The Rise of Fungi: Evidence on the Global Scale. Old Known Silences or Mysterious Threats to the Planet

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Authors' contributions

This work was carried out in collaboration among all authors. The first author DPLJ conceived and designed or scope of the review. All other authors contributed to the improvement of the article, carrying out a careful review. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Fungi are organisms that present themselves in multicellular macroscopic and unicellular microscopic forms. They are eukaryotic, heterotrophic, reproduce asexually/sexually, cosmopolitan, achlorophyllates and are present in various climatic conditions and found in a variety of species and forms in nature.

Aims: Present the emerging evolution of fungi, their underreporting, scale and parameters that show their potential as a heterotrophic organism, decomposer and pathogen.

Methodology: In this review, we conducted a search emphasizing themes about fungi using the available databases and based on the scientific literature, we discussed a series of recent issues involving this wide realm and the constant controversies and expectations that guide the existence of fungi on the planet.

Results: The results presented show an analysis of the action of these eukaryotic organisms and their interaction with other living beings, the constant changes in taxonomy, their pathogenic potential in plants and animals, issues related to the intrinsic resistance of some species to drugs and also the potential biotechnological for which these organisms demonstrate high plasticity.

Conclusion: The expansion of fungal diseases to the fauna and flora of the planet; leads us to believe that, unless measures are taken to reinforce biosafety issues, it will be increasingly necessary to take care of the health conditions of the planet to avoid a global collapse caused by microscopic beings.

Keywords: Mycology; pathogens; fungi kingdom; tropical diseases; fauna and flora.

1. INTRODUCTION

The recent events that have occurred around the world in the face of the fatal threat of the COVID-19 pandemic have caused humanity to rethink its way of being and act before the world in which it lives and the environment around it. Emerging Infectious Diseases (EIDs) are considered a significant burden for global economies and public health [1].

Divergent from the animal kingdom for more than 1.3 billion years, distinguishable from animals by their extracorporeal and non-internal digestion; not comparable to plants by their heterotrophic nature, capable of competing with each other and with other microorganisms, fungi have developed numerous strategies [2].

Fungi are organisms that present in a macroscopic and multicellular (filamentous) and microscopic and unicellular (yeasts) form are eukaryotic, heterotrophic nutrition, can reproduce in an asexual and/or sexual form, most of the eukaryotic group are cosmopolitan, achlorophyllate, presenting rarely cellulosic cell wall, usually chitinous, aerobic par excellence, with glycogen storage and are present under various climatic conditions and found in an abundant variety of species by nature [2,3].

These macros and microorganisms have a vast colonization capacity of living organic substrates,

relating to the various environmental, taxonomic, morphological, physiological characteristics, as an ability to degrade substrates that are difficult to digest, such as cellulose, lignin and pollen, as well as nutritional and biochemical capacities; while fighting competitors using an arsenal of bioactive metabolites such as antibiotics, organic acids, ethanol and antigenicity while behaving in their lives saprophytes, decomposers and parasites, becoming pathogenic organisms that attack plantations, wildlife, domestic animals and even humans [2-6].

The diversity of life is one of the most striking aspects of our planet; therefore, knowing how many species inhabit the Earth is among the most fundamental questions of science. Recent improvements in researchers' ability to detect uncultured microbial species have made it possible to document the enormous diversity of microorganisms in animals and vegetables and reporting that when we treat the human species, we Homo sapiens, 90% of all cells are microbial [7].

For decades estimates of the number of fungi on the planet were evaluated, first by Bisby and Ainsworth [8] who estimated about 100,000, then Martin [9] estimated that this fungal biodiversity was 250,000 and reaching a magnitude of 1.5 million by Hawksworth [10], the latter being accepted for about two decades.

In 2011, a new hypothesis came into question by Blackwell [11], this estimate of 3.5 to 5.1 million worldwide. An updated estimate of fungal diversity showed that fungal species ranged from 2.2 to 3.8 million worldwide [12] with insertion of species that can infect humans and animals, especially in tropical and temperate countries. Based on more recent data generated by Chinese researchers [13] from research, the fungal species on Earth have been estimated at 12 to 13.2 million species, and it seems that these estimates will change with the new daily discoveries of the existence of these organisms on the planet.

When addressing the clustering characteristics of these fungal organisms, we cannot ignore infectious diseases, including those caused by fungal organisms, which are associated with considerable morbidity and consequent worldwide mortality, caused by pathogens in this eukaryotic group.

Human activity and global warming are intensifying behavioral changes, creating new adaptations of the species and contributing to the spread of various diseases, including fungal diseases. The action of man has modified natural environments and created new opportunities for the evolution of species.

Although human, financial, substantial and time resources are limited, in the case of infections by fungal organisms, it is not yet clear whether the resources applied to elucidate fungal diseases are effectively used in research to manage these diseases [14].

2. METHODS

In this review, we conducted a search in the literature emphasizing topics about fungi using the available databases. We examined the landscape and evolution of fungi and mycoses, discussing the current state of some fungi such as *Cryptococcus*, *Candida*, *Aspergillus*, dermatophytes and other fungi, and the future challenges facing these microorganisms, with a focus on understanding the main problems related to fungal infections, taxonomy and the current situation in which these beings are, providing a critical and rational discussion on the available knowledge to obtain a clear vision of the future on the action of these eukaryotic organisms and their importance on the planet in the global challenge of species.

3. RESULTS

After consultation and evaluation, 148 scientific papers that were available were used as relevant results for the discussion of the review. The results presented show an analysis of the action of these eukaryotic organisms and their interaction with other living beings, the constant changes in taxonomy, their pathogenic potential in plants and animals, issues related to the intrinsic resistance of some species to drugs and also the potential biotechnological for which these organisms demonstrate high plasticity. The results were grouped by themes and are presented below.

4. DISCUSSION

4.1 Fungi: Environmental Contamination?

Until recently, many fungi were considered merely contaminants of surfaces and laboratory plates due to their presence dispersed by aerial sources, many of these fungi once considered "contaminants"; currently has been modifying its "status quo". The premise that there was a division of pathogenic fungi and environmental fungi has fallen apart and some of these eukaryotic microorganisms are leaving their mark and showing themselves to what they came for and why they exist.

Changes in the taxonomy of these eukaryotic organisms have changed in recent decades and fungal phylums have taken a leap in nature from recent reports. The classification of fungi kingdom has been continuously updated, with the frequent inclusion of DNA sequence data in recent studies [15]. A new classification for the Fungi kingdom was created by Tedersoo et al. [16] based on phylogenetic studies and the time of divergence of certain taxons, establishing 18 phylums:

Ascomycota, *Aphelidiomycota*, *Basidiomycota*, *Basidiobolomycota*, *Blastocladiomycota*, *Calcarisporiellomycota*, *Caulochytriomycota*, *Chytridiomycota*, *Entomophthoromycota*, *Glomeromycota*, *Kickxellomycota*, *Monoblepharomycota*, *Mortierellomycota*, *Mucoromycota*, *Neocallimastigomycota*, *Olpidiomycota*, *Rozellomycota* and *Zoopagomycota*.

That same year, Wijayawardene et al. [17] provided a more detailed classification system of phylums and genera for the most specific clades

of fungi, in agreement with the specifications elaborated by Tedersoo et al. [16], closing its ranking in 16 taxons, leaving out the phylum ascomycota and Basidiomycota, from the previous list.

Most currently mycologists and scholars of the Fungi kingdom have established a new classification in 12 taxons:

Ascomycota, Basidiomycota, Microsporidia, Chytridiomycota, Zoopagomycota, Mucoromycota, Cryptomycota, Neocallimastigomycota, Entorrhizomycota, Aphelidiomycota, Monoblepharidomycota, Blastoclamiyocota [18].

In the same year, a large group of researchers led by Wijayawardene et al. [15] updated the classification in class, order and families by establishing 19 fungal taxons:

Aphelidiomycota, Ascomycota, Basidiobolomycota, Basidiomycota, Blastocladiomycota, Calcarisporiellomycota, Caulochytriomycota, Chytridiomycota, Entomophthoromycota, Entorrhizomycota, Glomeromycota, Kickxellomycota, Monoblepharomycota, Mortierellomycota, Mucoromycota, Neocallimastigomycota, Olpidiomycota, Rozellomycota and Zoopagocotamy.

We observed that the "dance of the chairs" in fungal taxonomy becomes constant, and often difficult to understand, this conception often leads young researchers to give up the area due to the difficulty and complexity of this group of living beings. From the moment new studies and analyses of the various groups are evaluated, we find out whether these created fiscals will be accepted or will remain established as new and more fiscal are analyzed and new discoveries being included.

Given these facts, this reality demonstrates the hidden, silent and microscopic nature of many fungi and also means that their diversity is underreported with a much higher number of species that have been formally described [11,12]. In the same decades, fungal outbreaks have appeared caused by previously rare genotypes or even new species affecting humans, mammals, amphibians [19].

Human activity is intensifying the spread of fungal diseases, modifying natural environments

and creating new opportunities for evolution. An unprecedented number of fungal diseases have recently resulted in some of the most serious deaths and extinctions ever seen in wild species [3].

Currently, emerging fungal diseases are becoming increasing all over the world, and showing themselves to be on the rise threatening to wildlife species as we can mention the *Batrachochytrium dendrobatidis* (Bd) a fungus of the order Chytridiales, phylum Chytridiomycota parasite of skin cells of wild amphibians (frogs, salamanders, caecilians) [20], which decimated populations of global amphibious biodiversity, being widely distributed in the Americas and detected in Africa, Asia and Europe [3].

A second species *B. salamandrivorans* (Bsal), discovered in 2013 [21] was considered the etiological agent for causing chytridiomycosis in salamanders in Asia and Europe. According to Ossiboff [22], morphologically the strains of these chytridiomycosis are indistinct in the tissues of the affected amphibians, being differentiated only by molecular methods. Amphibian chytridiomycosis is the "worst infectious disease ever seen among vertebrates, in terms of the number of species affected and are prone to extinction.

Because of this ability to host various forms of microorganisms, the epidemic of white nose syndrome (WNS) in bats has as a catastrophic example and incriminated agent; the fungus *Pseudogymnoascus destructans* (Eurotiales, Ascomycota) [23]. This fungus, lover of the cold responsible for white nose syndrome, zoonosis that has gained the name of white ring that forms around the snouts of these winged mammals while hibernating. Affected animals are no longer able to control their body temperature during hibernation periods, deplete their reserves and starve to death [24].

The capacity of fungal pathogens such as *P. destructans* to persist outside the host, probably increases their impact on populations and increases the risk of species extinction [3]. It is known from the literature that bats are hosts of a rich diversity of microorganisms and some records point to this link between the chiropterans and fungi. Among the fungal agents stand out *Cryptococcus* spp., *Paracoccidioides* spp., *Pneumocystis* spp. and *Histoplasma* spp. [25-27].

Most emerging wildlife pathogens are of viral origin, but fungal infections have also been recognized at a wide range of taxa, including plants and still peciolothermal animals [3].

The list of fungal infections affecting wildlife, not by far is it to be finished, we can mention outbreaks and diseases by Emerging Infections Disease (EID's) in reports in the literature, occurred in recent decades, caused in bee species *Apis mellifera* decimated by a microsporide fungus of the genus *Nosema*, causing collapse and the decline of the colonies of these hymenoptera [28], nests of sea turtles *Caretta caretta*, attacked by ascomycete fungus *Fusarium solani* [29] causing poor development of future turtles and another ascomycete, causing aspergillosis by *Aspergillus sydowii*, an epizootic that affected *Gorgonia ventalina* marine corals, probably derived from global climate change and ocean warming [30].

The Lethargic Crab Disease (LCD) that has been decimated native populations since 1997 of the crab-uçá *Ucides cordatus* (Decapoda: Ocypodidae) in the Brazilian mangroves. Phylogenetic analyses confirm the diagnosis of the fungus LCD in crab tissues as an ascomycete, presenting a close relationship with members of the subphylum Pezizomycotina [31].

In Brazil, a fungal disease has worried health agencies in the South and Southeast regions of the country, where its occurrence is restricted. In the urban area, *Sporotrix brasiliensis* (the most virulent species of the complex) has been considered the predominant agent in cats (rarely observed in other mammalian hosts). The fungus is capable of producing a large amount of infectious material in feline tissues, nails and oral cavity [32], currently being considered an epidemic in the city of Rio de Janeiro/Brazil, southeast region of the country, provided by this species.

More presently, a study conducted in Belo Horizonte/Brazil associated the presence of felines and humans who have been suffering from sporotrichosis since 2015, reporting that human cases are closely linked to feline infections. The authors warned that actions include the control of the disease in cats and the search for cases of felines, focusing on diagnosis and control, close to the human cases reported [33].

Registration of another infectious agent in cats have been reported in cases of infections caused by *Aspergillus felis* in felines in Australia. This fungal entity causes fungal rhinosinusitis, invasive sino-orbital and pulmonary aspergillosis, and may be an invasive infectious agent for other mammals; dogs and humans [34]. Often these cryptic species, highly contaminating and that can cause outbreaks, have a variable degree of susceptibility and antifungal resistance, which is worrisome because they end up making their treatment difficult.

Also in this context, we can mention the various fungal organisms that attack plant species, decimating plantations promoting great losses in agricultural production, such as those reported by Fisher et al. [3], as phytopathogens with intrinsic resistance such as *Zymoseptoria tritici*, which affects wheat crop; pathogen of banana *Mycosphaerella fijiensis*; *Blumeria graminis* mold powder fungus; the emerging barley pathogen *Ramularia collo-cygni* and the apple shell fungus *Venturia equequis* and *Botrytis cinerea*, a generalist fungus that affects several crops.

When we then move to the human sphere, we consider dermatomycosis, also called cutaneous mycoses that affect skin, nails and scalp, cause esthetics problems and less serious to human health. However, the act of scratching causes injuries and may be the gateway to a group of fungi, more specialized, reaching deeper tissues and causing serious problems [35].

Other mycoses such as histoplasmosis, paracoccidioidomycosis, chromoblastomycosis, sporotrichosis and mucormycosis are associated with high mortality rates or generation of conditions that prevent the performance of professional functions and social integration. In this group are subcutaneous and systemic mycoses, where their spores or mycelial fragments are inoculated causing diseases and fungal infections predominant in people who work with the land or have contact with animals and their excretes. It is these systemic mycoses, which lead to infection throughout the human organism, and cause the greatest damage to the body system causing manifestations in the nervous, respiratory, digestive, circulatory and osteoarticular system [35].

4.2 Fungi: Neglect how Long?

Until recently fungi, they were considered harmless environmental beings, even friends,

because they were recognized as decomposers; currently this image, have been gaining importance, and become a highlight in the scientific environment and especially in medicine. Common inhabitants of the environment, present in the soil, in the air, in water, in caves, in homes and even hosts in our own bodies; these eukaryotic beings, gradually have been spreading and becoming aggressive causing serious infections, resistant to antifungals and becoming deadly to humans and animals with weakened natural defenses.

The use of the term "neglected diseases" is relatively recent and often considered controversial in its employment. According to the World Health Organization, some diseases are well known around the world, such as dengue, leishmaniasis, American trypanosomiasis, leprosy, zika, chikungunya, schistosomiasis and rabies [36]. Although they have been present on our planet for thousands of years, they still remain a challenging factor for the medical and scientific community. According to the GAFFI (Global Action Fund for Fungal Infections) fungal diseases are neglected worldwide by public health authorities, estimating that the global burden of severe fungal infections reaches 80% of the world population [37].

Neglected diseases are diseases and/or infections, which at the same time are consequences and causes of economic and social underdevelopment present in several international reports and studies such as those organized by the World Health Organization (WHO) [36] and Medecins Sans Frontieres (MSF) [38], which will propose dividing diseases into Global, Neglected and more Neglected; in this same parameter, who introduced a similar classification, dividing the diseases into Type I, II and III [39], respectively the ones proposed by the MSF.

Woolhouse et al. [40], classify these manifestations of these prokaryotic and eukaryotic microbiological agents that often present their emergence motivated largely; in addition to the socioeconomic factors already mentioned, also framing them in environmental and ecological factors.

The threats of emerging and re-emerging infectious diseases have increased globally. When we approach the themes of emerging diseases, neglected diseases, we observe how important this process is called

health/disease and the extent to which we can determine who it is; or who can be considered neglected.

Neglected Tropical Diseases (NTD), such as schistosomiasis (popularly known as water belly) or American trypanosomiasis, in Brazil called Chagas disease, attract especially low attention. In a recent enlightening paper on the subject, Furuse [14] emphasized the lack of consensus among scientific publications, demonstrating that some neglected diseases are delegated for a second, or a third plan by the researchers themselves, leaving as an example the verminosis known as hookworm (*Ancylostoma duodenale* or *Necator americanus*) and ascariasis (*Ascaris lumbricoides*); while other diseases are objects of so many studies making their research paradoxical as are the case, leprosy, Chagas disease and leishmaniasis.

In Brazil, human fungal infections are predominant, however, these conditions are not officially reportable diseases [41]. When we turn our vision and attention to fungi, we revert this questioning to the statements of Molloy et al. [42] that alerts us to cryptococcal meningitis, a deadly systemic fungal disease, of the tropics and subtropics, so neglected that it is even part of the WHO list. According to Fisher et al. [3] fungal infections were largely neglected in relation to other classes of infectious diseases, although these infections are quite ubiquitous.

In 2017, the journal Nature Microbiology published an alert on neglected fungal diseases, showing that despite being a significant threat to public health, biosecurity, ecosystem resilience and biodiversity on the planet; the funding agencies, the press, the public authorities of the countries and even the scientific community, should pay more attention, as they aim to mitigate a problem that afflicts several regions of the globe, including Brazil, inserted in this context [43].

Although many fungal diseases are neglected by public health authorities and poorly addressed, some fit the World Health Organization's (WHO) definition of Neglected Tropical Diseases (NTD). Brazilian Ministry of Health [44] in its list reports that diseases considered as neglected. We observed that no fungal organism is mentioned in this list. However, recently the World Health Organization has included mycetomas, chromoblastomycosis and "other deep mycoses" in the list of neglected tropical diseases [45].

According to GAFFI [37], among fungal diseases, mycetoma was adopted as NTD by the WHO in 2013 and chromoblastomycosis in 2017 with 'other deep mycoses'. This is a major step forward in the perspective of improving the outcomes of patients with these serious diseases, and they hope that other diseases such as sporotrichosis, paracoccidioidomycosis and fungal ceratitis will be included in the World Health Organization's Portfolio of Neglected Tropical Diseases (NTD).

Despite their alarming impact on human health, fungal diseases have been continuously neglected over the years [35]. In Brazil, estimates from the Ministry of Health suggest almost 4 million individuals suffer from some fungal disease [41]. It is estimated that cases of allergic aspergillosis, candidemias and meningitis caused by *Cryptococcus* are the main causes of death in the Brazilian population. This leads us to believe that it may be the fact that the alternatives for treating fungal infections available on the market are expensive, ineffective and often associated with undesirable side effects [46].

According to records conducted by GAFFI, global estimates suggest an annual occurrence of approximately more than 223,000 cases of cryptococcal meningitis, 750,000 cases of invasive candidiasis, 3,000,000 cases of chronic pulmonary aspergillosis mainly affecting HIV/AIDS patients, 100,000 cases of disseminated histoplasmosis infection, 500,000 cases of *Pneumocystis pneumonia*, 300,000 cases of invasive aspergillosis and even more than 6,500,000 cases of fungal asthma [37].

4.3 Dermatophytes: New Taxonomy, Old Etiological Agents

Since the studies on the identification of dermatophytes with the contributions of David Gruby (1840-1875) were recommended, who discovered the nature of skin infections to the advances proposed by Sabourraud (1870-1920), where morphological characters and clinical characteristics were requirements for the identification of keratinophilic fungi in the last decades of the twentieth century [47].

Dermatophytosis comprises an extensive variety of distinct clinical conditions. The most common were included in cutaneous mycoses under the generic name of "tinhas" (from Latin tinea = worm), and classified according to location: tinea

capitis, tinea corporis (ringworm), tinea barbae, tinea unguium (onychomycosis), tinea pedis (athlete's foot), tinea manuum and tinea cruris (jock itch) [5], an item richly addressed in the classical work of mycology – *Les Teignes*, by Raymond Jacques Andrien Sabouraud [6].

Dermatophytes is a highly specialized group of filamentous fungi capable of extracting nutrients from the hard-to-obtain keratin protein, the most abundant substance present in the epithelial cells of the upper vertebrates (mammals, birds and reptiles) is the basic component of human or animal skin, hair, hooves, nails, scales, horns, feathers, including wool.

Tissues that have the ability to produce keratin, such as keratinized layers of skin, hair and nails are highly selective for the growth of dermatophytes, which explains the fact that these fungi infect only the superficial and cutaneous tissues rich in keratin, with no invasive power [48,49]. However, records in the scientific literature show rare cases of deep dermatophytosis described in association with patients with human immunodeficiency virus (HIV) and immunosuppressed patients [50,51].

These keratinophilic agents, affect corneal extract of the skin or nail plate of normal hosts, but other forms of skin and nail mycoses can also be caused by dermatophyte fungi and/or caused by other genera that called "non-dermatophytic fungi", causing a diversity of clinical pictures. Among these fungi stand out the genera: *Fusarium*, *Aspergillus*, *Penicillium*, *Chrysosporium*, *Scopulariopsis*, *Microascus*, *Aphanoascus*, *Chaetomium*, *Alternaria*, *Curvularia* and *Scytalidium* that are related to superficial mycoses in nail lesions and interdigital foot spacings demonstrating the pathogenic capacity of these microorganisms [6,48].

These non-fungal etiologies that mimic the typical dermatophytic lesion on the skin, and produce manifestations equal to dermatophytic agents and their differential diagnosis were detailed by researchers from Belgium [52].

Traditionally, dermatophytes are classified in division, ascomycota, class, upper tons; Eurotiomycetes; Order, Onygenales, and family, Arthrodermataceae, remaining until recently a limited taxonomy and belonged there are three distinct genera: *Microsporum*, *Trichophyton* and *Epidermophyton* and their respective species.

Species belonging to these genera that reproduce sexually [5], presented according to the primary habitat and affinity for hosts, to be classified into three ecological groups: geophilic, zoophilic and anthropophilic species [6] saprophytes by nature, have the ability to colonize keratinized tissues [5,6].

The importance of recognizing, a certain species of dermatophyte, to which microecosystem it belongs is related to the response it can trigger in the human host; thus, it is believed that the more phylogenetically distant a dermatophyte of the species it parasitized, the greater the inflammatory response [53], that is, the farther from the human host the degree of infection becomes more aggressive and evident, this can be observed in more aggressive and exuberant infections caused by geophilic species, than by zoophilic and anthropophilic species, the latter, the latter can coexist with the human host and often produce manifestations without many tissue changes.

Anthropophilic species naturally colonize the human host, are easily transmitted and spread through contact between humans (schools, prisons, barracks, swimming pools and families), presenting mild and chronic skin infections, without severe inflammation. Zoophilic species are closely related to the animal reservoir, causing infections in animals mostly asymptotically, colonizing the skin and attachments, and can be transmitted to humans. The reservoir of geophilic dermatophytes is the land itself, this type of fungal agent is especially around mammalian habitats, contributing to its dissemination [5,6,47,53] (Table 1).

The distributions of these fungi vary considerably, depending on epidemiological factors and geographic area. According to ancient and current records, the species *Trichophyton rubrum* is the most predominantly isolated etiological agent of humans followed by *T. mentagrophytes* [5,6,54,55].

These days, based on advanced molecular studies (ITS, rDNA and partial LSU sequencing, ribosomal subunit 60S, β -tubulin fragments and translation 3 stretching factor), American researchers phylogenetically analyzed trees from dermatophyte groups and showed a degree of correspondence between phylogenetic groups reaching an acceptable level of stability [47].

In the work developed by de Hoog et al. [47], six new genera were suggested for this fungal group (*Nannizzia*, *Paraphyton*, *Lophophyton*, *Arthroderma*, *Ctenomyces* and *Guarromyces*) to the three genera (*Trichophyton*, *Microsporum* and *Epidermophyton*) already existing emerging new dermatophytic classification. The genus *Epidermophyton* remained an original restricted clade, as well as the genus *Trichophyton*, classifying some zoophilic and anthropophilic species. In relation to the geophilic and zoophilic species of the genus *Microsporum* were divided into the genera *Arthroderma*, *Lophophyton*, *Nannizzia* and *Guarromyces*.

In the recently proposed taxonomy, 56 species are now classified as dermatophytic. The genus *Arthroderma* now contains 21 species, *Microsporum* three species, *Ctenomyces*, *Epidermophyton*, *Lophophyton* one species, respectively, *Nannizzia* nine species and *Trichophyton* 16 species. In addition, two new genera were introduced: *Guarromyces* containing one species and *Paraphyton* three species (Table 1).

The preponderant observations were detected that the genera *Arthroderma* and *Nannizzia*, which previously denoted sexual states of dermatophytes, are now considered regular genera. Although the molecular approach has been able to address the main characteristics of the evolution of dermatophytes, it may still suffer flaws in some details. The phylogenetic tree created based on the kinship evaluation contains 7 representative clades (A-G) and two unmarked clades (Table 1).

According to Lacaz et al. [6] of healthy skin, several dermatophytes can be isolated, referring to *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Epidermophyton floccosum*, *Microsporum canis* and *M. gypseum* (currently *Nannizzia gypsea*) [47].

In 2018, Sharma and Shoushe [56] added a new species of the genus *Nannizzia* called *Nannizzia graeserae* and Borman et al. [57], isolated another species in the United Kingdom. named *Nannizzia perplicata*. More recently Dukik et al. [58], two new species were inserted in the taxonomy of the genus *Nannizzia*. With the new proposals the genus *Nannizzia* currently comprises thirteen species: *Nannizzia aenigmatica*, *N. corniculata*, *N. duboisii*, *N. fulva*, *N. gypsea*, *N. nana*, *N. incurvata*, *N. persicolor*, *N. praecox* [47] and the three new species

Table 1. Classification of fungal agent species (dermatophytes) causing Tineas and/or dermatophytosis and the relationship with their ecological types (microecosystems)

Ecological criteria/degree of infection	Taxonomic clades								
	Clade A <i>Trichophyton</i>	Clade B <i>Epidermophyton</i>	Clade C <i>Nannizzia</i>	Clade D <i>Paraphyton</i>	Clade E <i>Lophophyton</i>	Clade F <i>Microsporum</i>	Clade G <i>Arthroderma</i>	<i>Ctenomyces</i>	<i>Guaromyces</i>
Anthropophilic (mild inflammation)	<i>T. concentricum</i> <i>T. interdigitale</i> <i>T. rubrum</i> <i>T. schoenleinii</i> <i>T. soudanense</i> <i>T. tonsurans</i> <i>T. violaceum</i>	<i>E. floccosum</i>	<i>N. aenygmaticum</i> <i>N. duboisii</i> <i>N. perplicata</i> <i>N. persicolor</i> <i>N. polimorpha</i> <i>N. praecox</i>			<i>M. audouinii</i> <i>M. ferrugineum</i>	<i>A. eboreum</i> <i>A. onychocola</i>		<i>G. ceretanicus</i>
Geophilic (severe inflammation)			<i>N. corniculata</i> <i>N. fulva</i> <i>N. gypsea</i> <i>N. graeserae</i> <i>N. gipsita</i> <i>N. incurvata</i>	<i>P. cookei</i> <i>P. cookiellum</i>			<i>A. ciferrii</i> <i>A. cuniculi</i> <i>A. curreyi</i> <i>A. gertleri</i> <i>A. gloriae</i> <i>A. insingulare</i> <i>A. lenticulare</i> <i>A. melis</i> <i>A. multifidum</i> <i>A. phaseoliforme</i> <i>A. quadrifidum</i> <i>A. tuberculatum</i> <i>A. uncinatum</i>	<i>C. serratus</i> <i>C. albus</i> <i>C. obovatus</i> <i>C. peltricolor</i> <i>C. vellereus</i>	
Zoophilic (moderate inflammation)	<i>T. eriothephon</i> <i>T. benhamiae</i> <i>T. bullosum</i> <i>T. equinum</i> <i>T. erinacei</i> <i>T. mentagrophytes</i> <i>T. quinckeanum</i> <i>T. simii</i> <i>T. verrucosum</i>		<i>N. lorica</i> <i>N. nana</i> <i>N. persicolor</i>	<i>P. mirabile</i>	<i>L. gallinae</i>	<i>M. canis</i>	<i>A. amazonicum</i> <i>A. flavescens</i> <i>A. redellii</i> <i>A. silverae ?</i> <i>A. thuringiensis</i> <i>A. vespertilii</i>		

Species reported in taxonomic characteristics in research conducted by de Hoog et al. [47], Sharma and Shoushe [56], Borman et al. [57], Dukik et al. [58] and Zhang et al. [59]. The question in *A. silverae* (?) Indicates rarity of the species, due to its unknown ecology and little described in literature.

N. graeserae (India) [56], *Nannizzia perplicata* (U.K.) [57] and *Nannizzia polymorpha* (French Guiana) and the *Nannizzia lorica* strain in place of *Microsporum racemosum* [58] (Table 1).

In 2019, Chinese researchers [59] presented new morphological evidence to delimit species, circumscribing five species of the genus *Ctenomyces*, *C. serratus* type species [47], and described three new species: *C. albus*, *C. obovatus*, *C. peltricolor* and confirming *C. vallereus* as a distinct species. The five species were established and distinct from each other, based on morphological, biochemical and phylogenetic sequences (Table 1).

The new taxonomic classification proposed by Hoog et al. [47], presupposes that in this new classification the criteria for identification of species, are simplified, although the number of genera has increased, the number of related species in a given genus has decreased, which should facilitate the proposals for identification of these keratinolytic fungi.

Using the newest identification tool, through MALDI-TOF MS, L'Ollivier and Ranque [60] analyses suggest that the mass spectrometry technique has the potential to become the gold standard in the identification of dermatophytes, showing satisfactory results.

The enormous survivability of fungi in different substrates and ecosystems result in a morphological diversity, with great capacity to adapt to the constant changes in environmental conditions, often proposed by man himself. Even with taxonomic changes, and adoption of different molecular techniques, to be used as a support in the identification of dermatophytes, we observed that the diagnosis in the laboratory routine for the identification of dermatophyte infections can still be performed using traditional methods, and in the identification of species cultivated based on their morphology, but for a more effective epidemiological action, studies are further studied.

The understanding of new studies and facts related to the biology and ecology of these pathogens, the mechanisms of pathogenesis, and the pathogen-host interaction, will allow the development of new strategies for the detection and control of dermatophytosis. As we can observe the reports of the most varied researchers there is still a lot of work ahead when it comes to dermatophytes.

4.4 *Cryptococcus*: A Fungus, Biodiversity and Host Sources

In fact, when we talk about systemic fungal infections, fungi of the genus *Cryptococcus* (Tremellales, Basidiomycota) are implicated and incriminated in most human mortality and, in Brazil, the main cause of death in immunodepressed patients affected by systemic mycoses [41].

Although *Cryptococcus neoformans* mainly infects immunocompromised patients, *C. gattii* may cause disease in immunocompetent patients. Currently, meningitis by *C. neoformans* is the second cause of morbidity and mortality in individuals with AIDS. Worldwide, the number of reported cases of meningitis caused by *C. neoformans* and *C. gattii* has increased from a few hundred to about 1 million cases per year, mainly in people with HIV/AIDS [61].

At least 70 species of *Cryptococcus* have been described for practical purposes, however, *C. neoformans* and *C. gattii* were considered pathogenic. However, other species are being considered emerging pathogens for humans and animals, isolated from human and environmental samples and considered as saprophytes. In any case, emerging pathogens were considered in immunosuppressed patients, *C. laurentii*, *C. adeliensis*, *C. macerans*, *C. albidus*, *C. uniguttulatus*, *C. humicola*, *C. luteolus*, *C. terreus* and *C. curvatus* [62]. Within the non-*neoformans* and non-*gattii* cryptococcal species, *C. laurentii* and *C. albidus* are responsible for 80% of pathogenic, non-*neoformans* and non-*gattii* infections [63].

Historically, the most prominent report of these outbreaks of this fungal entity was the one that occurred on the island of Vancouver (British Columbia, Canada), caused by *C. gattii*, which expanded from the island to the continent of British Columbia and the Pacific Northwest [64,65]. Autochthonous infections caused by this basidiomycetic yeast initially occurred almost exclusively in the Mediterranean region. Several clinical and veterinary cases of this region have been described and involved *C. gattii* infections in human and animal mammals [66-69].

The primary ecological niche of *C. neoformans* was determined in bird droppings, especially pigeon droppings and after plant species [70], but in recent decades' initial hypotheses, the advent of *C. gattii* indicated eucalyptus trees

(*E. camaldulensis* and *E. tereticornis*) [70] as the initial host of capsulated yeast and that the export of eucalyptus seeds and trees has contributed to the dispersion of the agent around the planet [71].

Researchers have discovered the capsulated fungal species, isolated in the Amazon rainforest of Brazil. However, the discovery *C. gattii* in the hollow of a native *Guettarda acreana* tree in an unaffected area in the Amazon rainforest of northern Brazil, indicated that it probably would not be eucalyptus, the host of the fungal agent but the plant material (decomposition) the niche for *C. gattii* [64,71,72].

More recently it was confirmed in the reports of African researchers [73] were recovered from rocks and hollow trees, showing that the fungal lineage can occupy trees, manure and environments both associated with the activity of mammals of the African region (*Dendrohyrax arboreus*, in trees and *Procavia capensis*, in rocks) because *Cryptococcus* has a pronounced tropism for urea as a nutritive substrate.

Modern evolutionary and virulent lines of *C. gattii* outbreaks derive from mating events of strains in South America, dispersing through temperate regions of the globe, causing severe infections in humans and animals [19] contributing to the Brazilian strains presenting an endemic character.

Phylogenetic analyses in several studies indicated that the virulence strains of *C. gattii*, is not restricted to the so-called main genotype of the Vancouver Island outbreak, other strains found in the outbreak of the Pacific Northwest present with high virulence and infection power in different hosts, but other strains found in smaller islands near vancouver island, showed low or no virulence [64,65].

Several studies reveal that *C. neoformans* in immunocompromised individuals causes meningoencephalitis, which can lead to death. *C. gattii* affects immunocompromised and immunocompetent patients [74]. During the last two decades, considerable genetic heterogeneity of these two fungal strains has been shown to occur.

Several molecular genotyping techniques have been used for the genetic identification of *C. neoformans* and *C. gattii* complexes, especially digital printing by polymerase chain

reaction (PCR) [75], Amplified Fragment Length Polymorphism (AFLP), microsatellite type [76]; study of the restriction fragment length polymorphism (PCR-RFLP) [75] and whole genome sequencing (WGS) [77]; more recently, the use of matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) can reliably identify the recognized species of *Cryptococcus* [78,79] with the objective of comparing the groups, formed by 13 different genotypes proposed for *C. neoformans* and *C. gattii*.

Previously, *Cryptococcus* strains were classified in serotypes B and C isolates for *C. gattii*, while *C. neoformans* includes all strains of serotypes A and D and hybrid AD, according to mucopolysaccharide components (MPS), glucuronoxylomanana (GXM) and galactoxylomane (GalXM) [62]. New recognition proposals proposed by Hagen et al. [78,80] within the genotypes and serotypes of *C. gattii*, this fungal group underwent a new classification passing to five genotypes: Clado A, presented the genotype AFLP6/VGII called *C. deuterogattii*; Clado B, AFLP10/VGIV/VGIIIc called *C. decagattii*; Clado C AFLP5/VGIII proposed name *C. bacillisporus*; Clado D, AFLP4/VGI with name *C. gattii*; and finally Clado E, AFLP7/VGIV called *C. tetragattii* (Fig. 1).

Within the genotypes and serotypes of *C. neoformans* var. *grubii* three genotypes were determined that can be discerned: Clado F, AFLP1/VNI; Clado G, AFLP1A/VNB and Clado H, AFLP1B/VNII currently recognized as *C. neoformans*, still genotype *C. neoformans* var. *neoformans* presents a genotype considered Clado I, AFLP2/VNIV currently named *C. deneoformans*. The intervariety considered hybrid (former serotype AD) AFLP3/VNIII proposed *C. neoformans* x *C. deneoformans* hybrid, because it presents indistinct genotypic characteristics [78,80] (Fig. 1).

Other hybrids identified interspecies were described as: *C. neoformans* var. *neoformans* x *C. gattii* AFLP4/VGI currently called *C. deneoformans* x *C. gattii* hybrid; still *C. neoformans* var. *grubii* x *C. gattii* AFLP4/VGI designated AFLP9 called *C. neoformans* x *C. gattii* hybrid and finally *C. neoformans* var. *grubii* x *C. gattii* AFLP6/VGII currently designated AFLP11 with proposed name for species *C. neoformans* x *C. deuterogattii* hybrid [78,80] (Fig. 1).

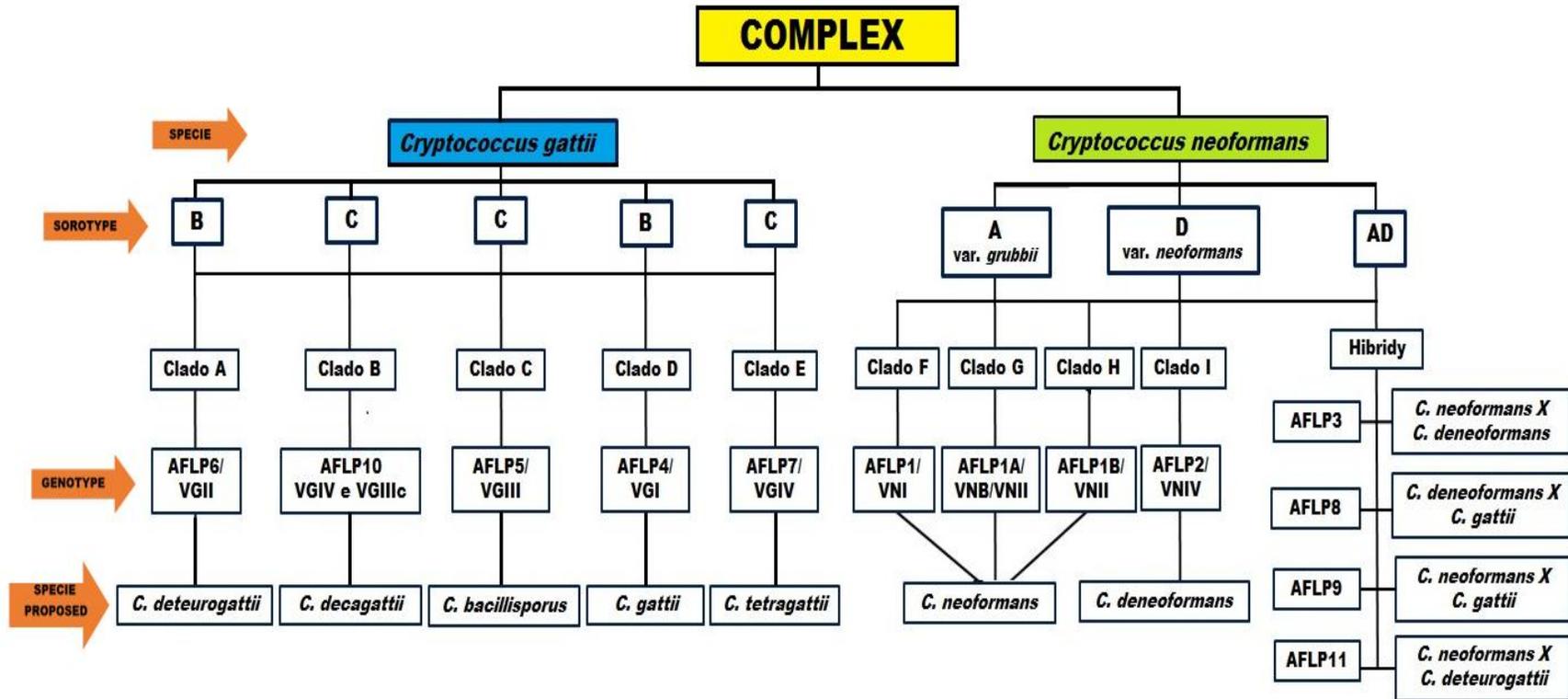


Fig. 1. Organogram of the species proposed in the *C. gattii* and *C. neoformans* species complex.

Source: Hagen et al, [78,80]. Adapted Leite-Jr, D.P.

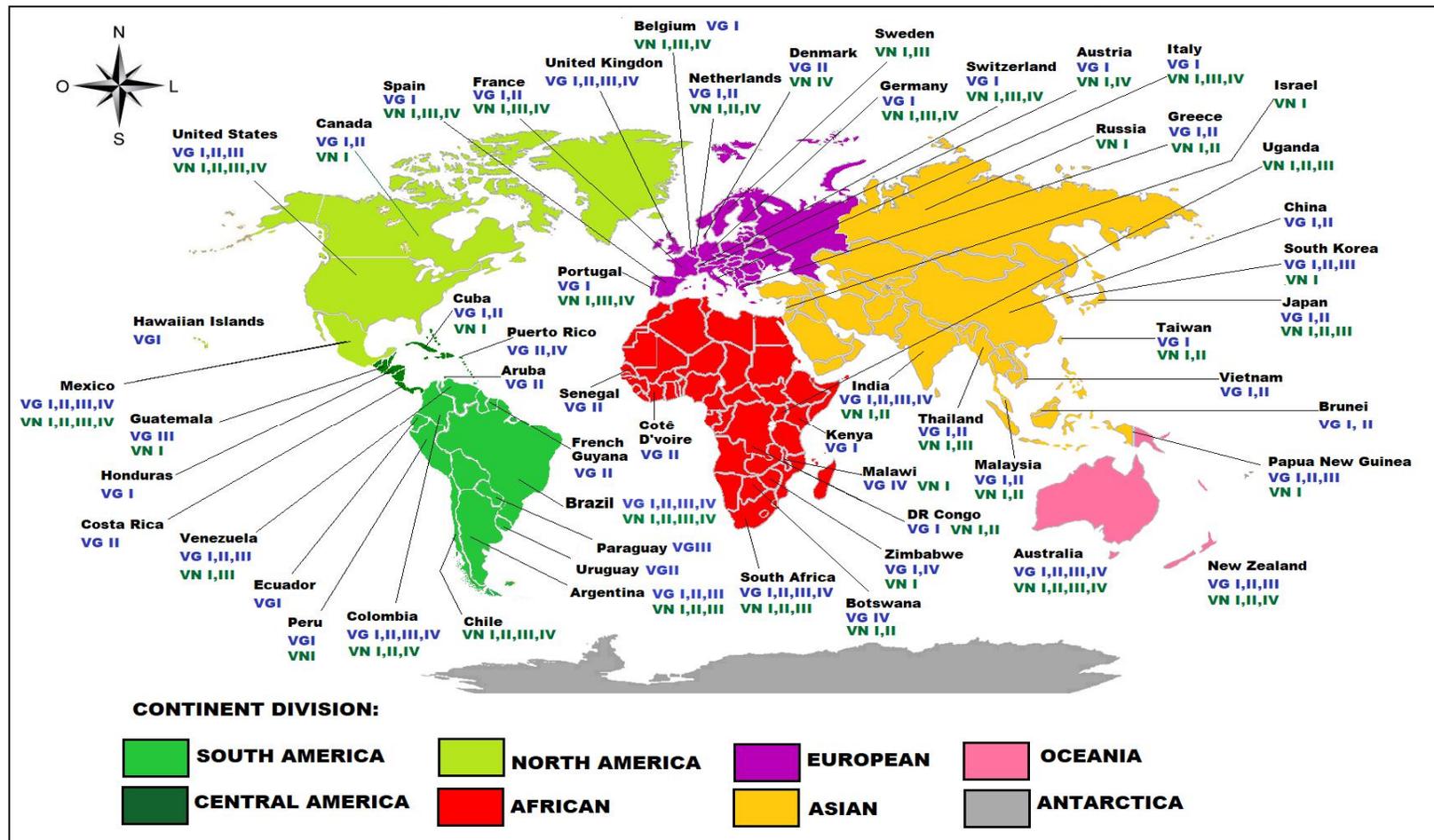


Fig. 2. Occurrence of clinical and environmental isolates of the *Cryptococcus gattii* and *Cryptococcus neoformans* species complex and their various genotypes distributed across the globe
 VG genotypes of *Cryptococcus gattii* (in blue), VN genotypes of *Cryptococcus neoformans* (in green). Sources: Cogliati [147], Chen et al. [148]. Image Adapted Leite-Jr, D.P.

Strains of *Cryptococcus gattii* and *Cryptococcus neoformans* gained worldwide distribution and their genotypes spread throughout the planet and have been identified and recognized since the historic event, which occurred on Vancouver Island (Fig. 2).

However, the taxonomy proposed by Hagen et al. [80] can currently be controversial, leading to continued nomenclatural instability. Recent discoveries of new strains of *C. gattii* provide evidence within the complex for new species divisions of the *Cryptococcus* species complex. Botswana samples revealed the existence of the strain of *C. neoformans* VNB [81], which recently proved to be deeply divided into two genetically isolated strains, VNBI and VNBII [82].

More recently, Vanhove et al. [83] isolated samples of plant substrates and animal excreta in the Zambia region, identifying the isolates as a new type of strain called VGV, however phylogenetic and genetic population analyses led to the conclusion that they were distinct and deeply divergent strains, confirming this VGV lineage (Gattii variety five). All VGV isolates were identified as serotype B, which also includes vgi, VGII, VGIIIa subgroup and rare isolates between VGIV strains [73].

Hybridization is increasingly recognized as an important matrix key that affects adaptation and evolution in many fungal strains and this characterization often, are gathered in the same cell, potentiating the adaptation and increasing genomic plasticity of many species, and this fact is very common found among the species of basidiomycotic yeasts of the genus *Cryptococcus* that potentiate these mechanisms rapidly generating genotypic and phenotypic diversity [84].

A recent study on the arsenal of antifungal drugs with action on this group of fungi was proposed by Aaron et al. [85] to combat anti-virulence therapy against cryptococcal meningitis, using lead compounds, which ruptured and blocked the action and dissemination by the blood brain barrier; since these infections maintain an intimate relationship with human cells by fungi, because they are also eukaryotes.

Another study using zinc metabolism was also characterized against this fungus, where the

authors presented the effects of gene deletion on cryptococcal virulence [86]. But recently, the synergistic effect of lactoferrin, an iron-binding glycoprotein, showed antimicrobial activity in combination with amphotericin B, increasing the efficacy of antifungal strains and showing promising results in the action against yeasts of the genus *Cryptococcus* and *Candida* [87] and also the results presented in the physiology of *C. gattii*, which had its glucuronoxylomanan capsular component decreased in the face of toxic manganese concentrations and had unbalanced stress and virulence expression [88].

The renaming of each lineage in species remains controversial and the current system increasingly needs standardization for the occurrences of hybridization, a common characteristic of the identified strains [62] applying metagenomic methods to environmental or zoonotic reservoirs with geographical scopes. Hypermuting strains of the genus *Cryptococcus*, with the potential to evolve rapidly in response to the selection of hosts and medications, have been recently reported [83].

As names are chosen and applied to recognize species in a complex this taxonomic technique requires a balance and recognition of the usefulness of names to be adopted, but also the need to clarify pathogenesis and differences when there are genetically distinct microorganisms.

Just as the changes with the genus *Cryptococcus* occurred; in 2017, another study recognized at least four species among what was the *Histoplasma capsulatum* complex. Histoplasmosis is endemic in much of Central, South America and throughout Latin America, with differences in its regional variability. Fungal disease acquired mainly by inhalation of *Histoplasma capsulatum* var. *capsulatum* or *Histoplasma capsulatum* var. *duboisii*. There is an additional variety, *H. capsulatum* var. *farciminosum*, described as an equine pathogen, but based on molecular analyses, may include infections in humans [89].

More recently, after phylogenetic analyses researchers evaluated phylogenetic and geographic patterns among isolates, and arguments for naming species, proposing a taxonomic rearrangement. The genus maintained the name *Histoplasma capsulatum* for the original strain, *Histoplasma mississippiense*,

Histoplasma ohiense, *Histoplasma suramericanum* were the new taxonomic proposals and the African Strain *H. capsulatum*

Decades of studies of the *Cryptococcus neoformans* and *Cryptococcus gattii* species complex, as well as other fungal species, have resulted in a huge accumulation of biological, geographical, morphological, clinical and fundamental knowledge and applied to the knowledge of this fungi.

The constant investigations and reports on this capsulated fungal organism, called *Cryptococcus*, demonstrate that the fungal species is still far from being elucidated and still needs understanding, until the whole concept of its global ecology and biodiversity is fully deciphered and known. What will be the next questions?

4.5 *Candida auris*: The Mysterious Fungal Infection Adapted to Global Warming

Candidiasis or candidosis is a form of mycosis caused by yeasts of the genus *Candida*, opportunistic, saprobes; which are ubiquitous in the environment, and from exogenous sources, found in several substrates: in soil, marine environments, inanimate objects, plants and animals [6].

The clinical manifestations of the disease can be presented in a mucocutaneous, cutaneous and or severe systemic form and may involve multiple organs, after hematogenous dissemination of the agent [6] in the case of immunodepressed and immunosuppressed patients. Lesions by *Candida albicans*, a species most commonly isolated in clinical studies [91,92], being an important member of the endogenous microbiota of the human body, oral mucosa, gastrointestinal tract, being responsible for vaginal candidiasis (or vulvovaginal) originating erythema, intense rashes and genital discomfort.

These infections are common often during pregnancy, diabetes, hormone therapy, immunosuppressive therapy, cancer patients and exceptionally in individuals infected with human immunodeficiency virus (HIV) [6].

In addition to *Candida albicans*, the most commonly isolated species clinically isolated are: *C. parapsilosis*, *C. tropicalis*, *C. guilliermondii*, *C. glabrata* and *C. krusei*, being part of

var. duboisii, still awaits confirmation to become the fifth species, as it is probably a separate species of *H. capsulatum* [90].

components of the human microbiota [91,92]. However, other emerging species have been described as etiological agents of candidiasis and still causing fungemia, namely: *C. lusitanae*, *C. lipolytica*, *C. kefyri*, *C. inconspicua*, *C. norvergensis*, *C. catenulata*, *C. ciferrii*, *C. inconspicua*, *C. fermentati*, *C. famata*, *C. haemulonii*, *C. lipolitica*, *C. viswanathii* among others [93-95].

With the fall of immunity, yeasts of the genus *Candida* begin to invade the corneal layer of the skin or nail lamina of normal hosts, but there are other forms of skin and nail mycoses [6].

As well as phenotypic and genotypic characteristics similar to those of *C. albicans*. The species *C. dubliniensis* differs from *C. albicans* in terms of isolation frequency, pathogenic characteristics and resistance to antifungals, besides presenting greater capacity for adherence to oral mucosal cells [96]. The similarities between these two species hinder their rapid differentiation and may lead to results that underestimate their prevalence. Since the discovery of *C. dubliniensis* by Sullivan et al. [97] this species attracted considerable attention from researchers, due to its almost exclusive association with individuals with HIV/AIDS and oral manifestations, showing that this is an adaptive factor.

With the advent of genetic analyses, sample species believed to be a single species became distinct species with different levels of drug resistance. This is the case of *Candida parapsilosis*, reclassified into three species: *C. parapsilosis sensu stricto*, *C. orthopsilosis* and *C. metapsilosis* [98].

In the clado Nakaseomyces, which belongs to *Candida glabrata* (Sensu Stricto), two new species, *C. nivariensis* and *C. bracarensis*, were reported as emerging pathogens. The differentiation of these species of *C. glabrata* is of great importance to understand their clinical and epidemiological role in candidiasis [99].

The *Candida haemulonii* species complex is currently known as groups *C. haemulonii* I and II. Phenotypic, chemotaxonomic and phylogenetic analyses indicated an affiliation to the genus

Candida, with a close relationship with other unusual species, such as *C. haemulonii*, *C. pseudohaemulonii*, *C. duobushaemulonii*, *C. haemulonii* var. *vulnera* [100]. In recent years, two species related to *C. haemulonii* have been described receiving highlights, *C. pseudohaemulonii* and *C. auris*, which are phylogenetically closely related to *C. haemulonii* in the clade Metschnikowiaceae [62].

Given this large group of species and complex, we will use *C. auris* to illustrate these leveduriform agents. *Candida* spp. infections are one of the main causes of morbidity and mortality in critically ill patients. *C. auris* is an emerging multidrug resistant fungus that is spreading rapidly worldwide [101].

C. auris is a new species of drug-resistant yeast fungus that was first isolated in 2009 from the auditory canal of a female patient at the Metropolitan Geriatric Hospital in Tokyo, therefore, called "auris" that comes from the Latin meaning ear [102]. This fungal species colonizes the skin and not the gastrointestinal tract and is extremely resistant to the environment. This resilience led the fungus to be associated with health outbreaks, which were extremely difficult to control due to the remarkable difficulty in eradicating the fungus from both patients and the environment [103].

Now, this fungal entity is being considered an emerging multidrug-resistant nosocomial pathogen and has since spread to other countries around the world, including east and south Asia, southern Africa and South America [104]. In recent years, this infectious agent has reached a neonatal unit in Venezuela, committed a hospital in Spain, reached the ICU of a British medical center and left a trace of its trace in Pakistan, India, and South Africa [103,104].

These records revealed that the isolates recovered from these continents constituted genetically different clades, which led to researchers being questioned and unexplained facts of how *C. auris* manifested itself in three geographically distant regions [103].

Outbreaks have been reported in various parts of the world, and recent research suggests that higher temperatures caused by global warming may have led to an increase in the number of cases [104]. This yeast has been responsible for rapidly increasing invasive infections in hospitals and considered a fungus resistant to all existing

clinical antifungals, representing a global threat to intensive care units, as yeast can survive disinfection and decontamination protocols [104,105].

Candida auris is a yeast that belongs to the class of ascomycetes and a close relative of the *C. haemulonii* species complex, which includes occasionally pathogenic species in humans and animals and demonstrates a high level of resistance to antifungal drugs at baseline, conferring pathogenic potential and virulence attributes [100]. Because it belongs to the group of ascomycetes is, therefore, a characteristic that this group can grow at higher environmental temperatures [106].

Based on the principle of adaptation as mentioned in *C. albicans*/*C. dubliniensis* in response to temperature, researchers support the hypothesis that *C. auris* was the first pathogenic fungus emerging from man-induced global warming, that this species of *Candida* was an environmental fungus and that it recently suffered thermal tolerance breaking the thermal barrier of mammals forcing *C. auris* to adapt to climatic and human conditions [107-109].

Another line of reasoning refers to the fact that if there is any evidence that *C. auris* or close relatives in these environments, have jumped from avian hosts to humans following mechanisms similar to those operating for influenza viruses [105,107] because fungi that grow at a temperature between 40 or 42°C can infect avian fauna, especially seabirds, direct or indirect contact with migratory birds and from wildlife trafficking [110].

Following this premise, this may have facilitated the development of this species of fungus for the human body, which is hot, with temperatures around 36°C and 37°C. These observations are in line with current events and reports on conditions transmission similarities of COVID-19, which may be associated with seasonality (temperature, humidity, climate, etc.), suggesting that climate may be an important factor for the spread of the virus and that bats are likely primary reservoirs, recognized by several studies.

These probable genetic modifications in yeasts of the genus *Candida* may have favored the mechanism of resistance to antifungal drugs such as polyenes, azoles and echinocandins have been described mainly in *C. glabrata*

and, more recently, in *C. auris* [101,105, 107,110].

The selective pressure exerted on fungi by antifungals (fungistatic and fungicide) that inhibit certain action on their metabolism, may result in adaptations that over the years has contributed to the selection of fungal species. The parallel evolution of resistance extends to clinical and pathogenic fungi, with the same key resistance mechanisms occurring independently in both [3]. More recently, this selective pressure of *Candida* species and their resistance mechanisms presented combined antifungal action for biofilm-related infections produced by these fungal entities in the oral and vulvovaginal mucosas, reported by Tits et al. [111] who associated Miconazole and domyphene bromide resulting in the control and reduction of biofilm cells of isolates *C. auris*, *C. albicans* and *C. glabrata* resistant mainly to azoles.

In 2017; report described by Graham et al. [112] showed the efficiency of a protein produced by *Enterococcus faecalis* as a potent inhibitor of the ability of *C. albicans* to form biofilms, reducing fungal virulence and raising the hypothesis of becoming an antifungal agent. More recently, in vitro clinical trials have shown promising results against *C. auris*, where Barreto et al. [113] used the drug miltefosine, used in the treatment of leishmaniasis and infections by amebas, exhibiting inhibitory effects in the formation of biofilm of this emerging species.

According to the Centers for Disease Control and Prevention (CDC); Reported cases were recorded with unique isolates of *C. auris* in Austria, Belgium, Chile, Costa Rica, Egypt, Greece, Italy, Iran, Norway, Poland, Switzerland, Taiwan, Thailand and the United Arab Emirates. Records of several cases of *C. auris* reported in Australia, Bangladesh, Canada, China, Colombia, France, Germany, India, Israel, Japan, Kenya, Kuwait, Malaysia, Netherlands, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sudan, United Kingdom, United States and Venezuela; in some of these countries, extensive transmission of *C. auris* has been documented in more than one hospital. And yet the records of cases of infections caused by this fungal entity found in patients who have had recent stays in health units in India, Kenya, Kuwait, Pakistan, South Africa, South Korea, the United Arab Emirates and Venezuela. Other countries not highlighted on the map (Fig. 3) may have

occurred *C. auris* cases, but so far not detected or have not yet been reported [104].

According to the reports observed, there are several records of the occurrence of this fungal species of yeast emerging worldwide. Previous reports of *C. auris* in Brazil may not be accurate, since yeast can be easily confused with other species of yeast, such as *Candida haemulonii* and *Saccharomyces cerevisiae*, as reported by ANVISA [114].

Recently, in Brazil, a possible registration of this eukaryotic organism in a catheter tip sample and urine sample from patients admitted to the ICU (Intensive Care Unit) and a hospital in the State of Bahia/Brazil, for the treatment of complications COVID-19 [114] (Fig. 3).

Given the current situation in which they are a yeast species, we observe that it will be necessary, standards and techniques recommended for the health system to be prepared, with emergency actions, creating a surveillance system, based mainly on epidemiological control and actions in sentinel hospitals, in each region of the planet to face this new villain called *C. auris*, otherwise we will be caught by surprise again, as was the case with the SARS-Cov-2 pandemic (COVID-19).

4.6 Fungal Infections X SARCoV-2

The changes that occur on the planet often end up modifying the behavior of microorganisms, and often causing them to share their form of manifestation associated with other microorganisms of different taxons, interacting clinically presenting evidence in which they often culminate in death of the host.

COVID-19, respiratory disease caused by the SARS-Cov-2 virus, a virus belonging to the Coronaviridae family, is characterized by mild symptoms, many asymptomatic and in some cases presenting similar to common influenza and has been an emergency event of global public health [115,116]; however, secondary infections may be associated with severe respiratory manifestations such as invasive aspergillosis (IA), caused by fungal species of the genus *Aspergillus*, is considered a disease that mainly affects immunocompromised individuals with neutropenia, presenting a difficult and challenging diagnosis in Intensive Care Units (ICU) [117,118].

About 20% of patients may progress to severe pneumonia and sepsis, requiring intensive support, and are prone to complications caused by Severe Acute Respiratory Syndrome (SARS) [115,116,117]. In addition to damage to the bronchial tree and diffuse alveolar structures with the presence of severe inflammatory exudation, patients affected by COVID-19 always have immunosuppression, with high levels of pro-inflammatory cytokines (IL-1, IL-2, IL-6), alpha and anti-inflammatory tumor necrosis (IL-4, IL-10) with decreased TCD4 + and TCD8 + cells [116-119] and are the most likely to develop severe fungal co-infections, such as invasive pulmonary aspergillosis, invasive candidiasis or pneumonia caused by *Pneumocystis jirovecii*.

In a multicenter study conducted by Chinese researchers [115] comorbidities by COVID-19 were 48% hypertension being the most common among those surveyed, followed by 30% by patients with diabetes mellitus and 8% with heart disease. Lu et al. [118] found in their records six comorbidities showing significant associations with the outcome of the disease, with malignancy exhibiting the highest risk of death, followed by chronic kidney diseases, cerebrovascular diseases, hypertension as the most prevalent comorbidity 32.9%, followed by Diabetes Mellitus with 15.6% in his sample.

Also in China, other researchers performed fungal culture tests in patients affected by COVID-19, finding cases of fungal co-infection, including case of *Aspergillus flavus* and cases associated with *Candida albicans*, *C. glabrata*, *C. dubliniensis*, *C. parapsilosis*, *C. tropicalis*, *C. krusei* [119] and also co-infections associated with the *Mucor* and *Cryptococcus* genera [116]. And more recently in Brazil, a case of a patient interned in the Intensive Care Unit with COVID 19 presented co-infection with *Candida auris* [114].

German researchers [112] found invasive pulmonary aspergillosis associated with COVID-19 in their sample in patients with severe respiratory problems. The most common *aspergillus* species associated with invasive infections are *Aspergillus flavus* and *Aspergillus fumigatus*; however, in a study carried out in Brazil, researchers confirmed invasive aspergillosis associated with COVID-19, isolating as the casuistry agent, *Aspergillus penicillioides* xerophilic species that occurs in dry habitats and domestic powder; responsible for human and animal allergies [117,120].

The main fungal pathogens for fungal co-infections in critically ill patients with COVID-19 are the genera *Aspergillus* and *Candida*, other less frequent opportunists need to be considered, such as *Mucor* and *Cryptococcus*. Infections in patients with COVID-19 will require early detection through a comprehensive diagnostic intervention (histopathology, direct microscopic examination, culture, (1.3) - β -D-glucan, galactomannan, assays based on PCR and MALDI-TOF technology, etc.) to ensure effective treatments [116].

In Brazil, more recently, a case of dimorphic fungus co-infection of the onygenaceae family has been reported. The reported case of nosocomial infection by SARS-CoV-2 in a patient with acute juvenile Paracoccidioidomycosis. These researchers highlight that patients with PCM are considered vulnerable populations suffering from severe endemic mycoses and severe risk for COVID-19, reinforcing the need for more attention to NTD's the context of the pandemic [121].

Interactions and disputes of eukaryotes and prokaryotes, ubiquitous organisms found in many environments and that are part of the human microbiota, were recorded by American researchers [122] in dispute for hosts. The fungus *Aspergillus fumigatus* and the bacterium *Pseudomonas aeruginosa* compete with each other for nutrients and survival in natural environments and have been widely studied because of their intermicrobial interactions in the human microbiome. This record draws attention to concern for immunocompromised patients, especially neutropenic patients.

Deficient treatment through the available antifungals and becoming even more difficult in the face of the COVID-19 pandemic, this synergistic association between virus and fungus, has become a herculean challenge to the medical community in the face of these infections. However, regarding fungal co-infection in patients with COVID-19, few studies report it, which may have been neglected, and it is extremely important to pay attention to the probability of COVID-19 accompanied by fungal infections [116].

4.7 Fungal Biotechnology: Yesterday, Today and Tomorrow

Fungi are an understudied group of organisms, with several mechanisms of survival and biotechnologically valuable and incalculable.

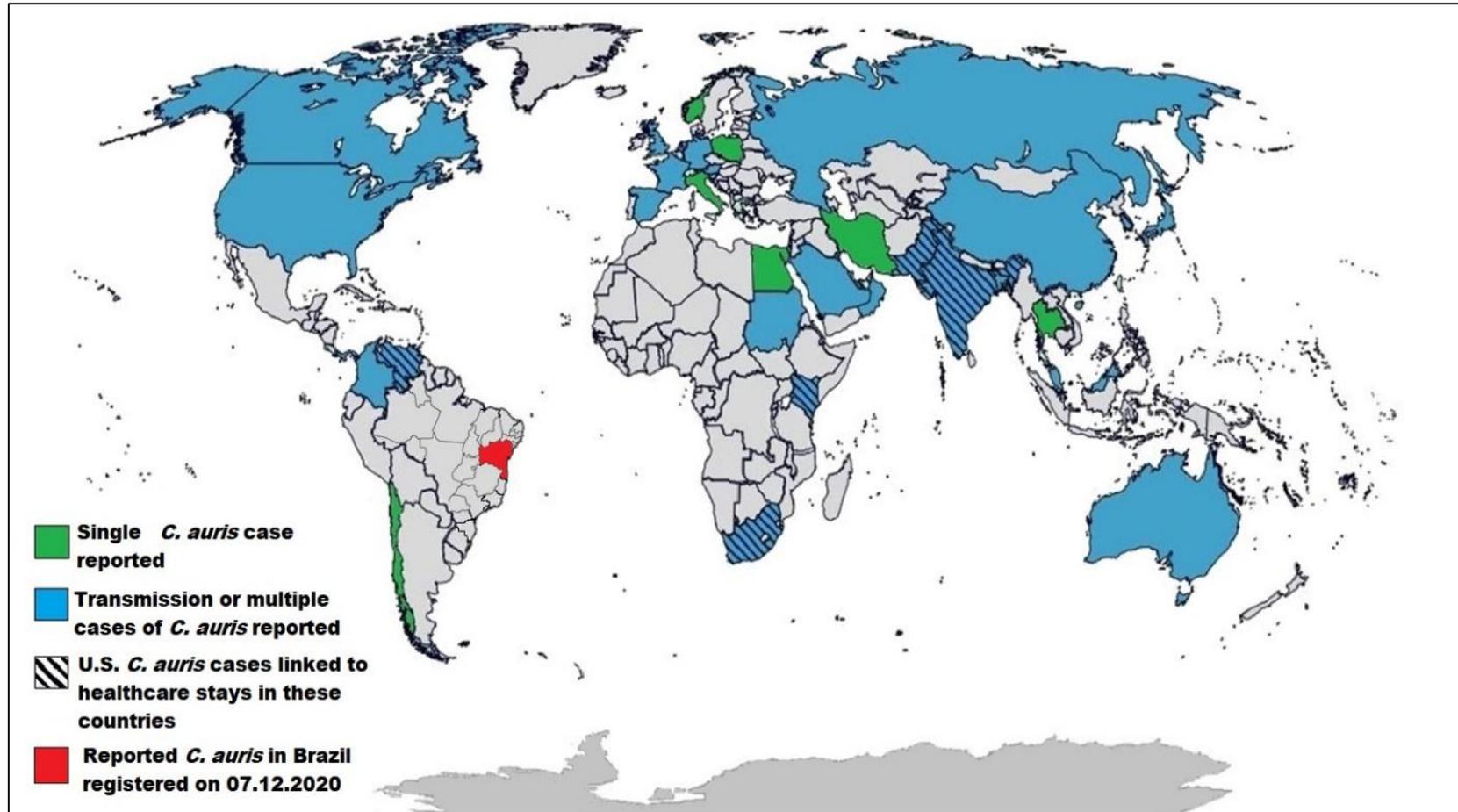


Fig. 3. Geographic map representing the worldwide distribution of the respective countries from which single or multiple infections by the pathogen *Candida auris* were registered, reported until December 2020

Source: Image World map. CDC [104]. Anvisa (map of Brazil, highlighted in red for the State of Bahia) Brasil [114]. Adapted Leite-Jr, D.P.

From the point of view of Ecology, fungi are considered the garbage men of the world, because they degrade all kinds of organic remains, regardless of origin, transforming them into elements assimilated by plants. Although they are often left out or simply relegated to environmental decomposers, or simply "dumpsters" of fauna and flora, they outperform themselves, while they are left there is a background, each day they renew themselves, evidencing or reborn from the ashes, as new phoenixes and showing the world the purpose and why they exist.

Since the discovery of penicillin (*Penicillium chrysogenum*), by Alexander Fleming [123], which was instrumental during World War II for the control of infection by *Staphylococcus aureus* and *Haemophilus influenzae* bacteria, thus marking the beginning of the antibiotic era [124]. From the economic point of view, the biotechnological applications of fungi present implicit actions and several areas: pharmaceutical, nutritional, human and veterinary medicine, phytopathology, among others; with surprising results are being used in the secretion of secondary metabolites, source of new drugs for the pharmaceutical industry, biocontrol, mycoparasitism, production of industrial enzymes and improvement of new species.

Taking an approach to the vast arsenal of antiviral, antibacterial, anti-parasitic, antitumor, anti-hypertensive, anti-atherosclerotic, hepatoprotective, anti-diabetic, anti-inflammatory and immune system modulating substances [125]; fungi in the scientific literature; are referenced due to the action of these heterotrophs in the production of substances that contribute to sporulation or production of mycotoxins, one of the genera most targeted by researchers is *Aspergillus*, being *Aspergillus nidulans*, *A. flavus*, *A. parasiticus*, *A. fumigatus* the most mentioned [126].

The genus *Aspergillus*, in particular, has been used very successfully for the production of protein sources such as glycoamylase (starch hydrolysis), chymosin (coagulator), lactoferrin (iron transporter), interleukin (immunosuppression activator) and taumatine (sweetener). *Monascus ruber* and *Aspergillus terreus* produce commercially used substances as a potent hypocholesterolemiante inhibitor, Lovastatin (Mevinoline) and other unsaturated fatty acids. *Monascus* still has antibiotic and also hypotensive effects, nephrotoxic, teratogenic

and suppressor growth of tumors "in vivo" [127-129].

Other fungal genera *Penicillium*, *Trichoderma*, *Phoma*, *Gymnoascus*, *Hypomyces*, *Doratomyces* and *Eupenicillium* have been studied in the use for inhibition of biosynthesis of plasma cholesterol levels in humans and animals, with promising results [127-129]. It is also possible to cite as examples as asperlicina (*A. alliaceus*), echinocandine B (*A. nidulans*) and fumagilin (*A. fumigatus*) substances that are used as antifungal, angiogenesis inhibitor and anti-parasitic, respectively [130].

In genetic manipulation and metabolism of organisms, in addition to Penicillin, known historically and extracted from *Penicillium chrysogenum*; another antibiotic produced by an important filamentous fungus, cephalosporin, a secondary metabolite produced exclusively by *Acremonium chrysogenum*, which achieves effectiveness against Gram-positive and Gram-negative bacteria [131,132].

But in addition to antibiotics, fungi can be used to produce immunosuppressive drugs, such as cyclosporine studies produced by *Tolypocladium nivenum*, a medicine used to reduce the action of the immune system, to prevent rejection of transplanted organs [133]. Recent studies with other commercially cultivated species in Brazil such as *Pleurotus* spp. (shimeji and hiratake) and *Lentinula edodes* (shiitake), which produce lentinan, polysaccharide with antitumor action and *Agaricus brasiliensis* (= *A. blazei*) that has been highlighted due to the medicinal, antitumor properties that have aroused great interest on the part of the medical and scientific communities [134].

Since the beginning of our existence, we have always sought to overcome the challenges that physical fragility posed to forestry communities. Anthropological reports, which refer to the Indigenous populations of the Brazilian, Colombian and Peruvian Amazons, have been using fungi as folk medicine for decades, especially the Brazilian indigenous tribes [135].

The Indians of the Amazon and Mato Grosso/Brazil use certain species of fungi as remedies for the treatment of their diseases, a practice that is learned, apparently, with the canoe Indians (Rikbaktsa) from the top of the Juruena River [136]. Brazilian indigenous tribes such as the Yanomâmis, Nambiquara, Caiabi,

Tucano, Txicão and Txucurramãe who used wood decomposer fungi, *Pycnoporus sanguineus* (red-stilted ear), saprophyte, family Poliporaceae, phylum basidiomycota, common in the most open areas of forests, were used against hemoptysis and for wound healing [135,136].

Another report refers to Australian aboriginal Indians who used this same fungal genus, used in Brazilian indigenous folk medicine, to treat and heal oral wounds, small ulcerations in the oral cavity and also treat oral candidiasis in newborns [137].

Given this great information and prospecting of the use of fungi; it is necessary to emphasize the importance of biotechnology to obtain various substances through the manipulation of fungi and obtaining new technologies for the benefits of human health and environmental balance.

4.8 Fungal Miscellany: Monsters or Biological Alternatives

From the ashes of Chernobyl, researchers have discovered new functions for these isolated eukaryotes organisms in the ruins of the Chernobyl nuclear power plant in Ukraine, which suffered an accident in 1986. Historical accounts from the 1980s announce that the Chernobyl nuclear reactor exploded affecting the cities of Ukraine, Belarus and Russia (former Soviet Union/USSR) resulting in the deaths of more than 50,000 people, and still affecting the local ecosystem and food chain, in the region [138]. Many of these evacuated areas remain abandoned to this day.

Fungi are organisms of extreme skill produce a wide range of remarkable natural products, which we call secondary metabolites, some deleterious (mycotoxins) and others extremely beneficial (antibiotics) [126]. The Chernobyl accident led to a major resurgence of radioecological studies for post-accident analyses [138]. Based on this premise, many studies have emerged to evaluate local radioecology and the consequences of the Chernobyl accident.

Studies proposed by Blachowicz et al. [139] and Dadachova et al. [140] analyzed the chemical properties of the melanin of fungi identified in chernobyl reactors. The fungi that grew around the reactor were analyzed *Cryptococcus neoformans*, *Cladosporium sphaerospermum* and *Wangiella dermatitidis*, showed increased metabolic activity of melanized cells, raising

intriguing questions about the potential role of melanin in the capture and use of energy by these eukaryotic organisms.

Studies conducted today, researchers believe that these discovered extremophile organisms, which survive radiation exposure (radiosynthesis), could be used to benefit cancer patients undergoing chemotherapy and still be used as protectors for people who expose themselves to radiation, such as engineers at nuclear power plants and astronauts [139].

Investigative analyses on fungal properties in absorbing radioactive components had already been studied by Zhdanova et al. [141] where these Ukrainian researchers analyzed about 200 species from 98 genera of fungi isolated around the Chernobyl Atomic Energy Station. These researchers have proven that the melanotic fungus *C. cladosporioides* manifests radiotropism by growing in the direction of radioactive particles (positive radiotropism) becoming widely distributed in the radioactive region. More presently, Blachowicz et al. [139] found this phenomenon of radiotropism in fungal strains of *Cladosporium herbarum*, *C. sphaerospermum*, *C. cladosporioides* and *Acremonium murorum*.

Melanin biosynthesis has also been well studied in pathogenic fungi, where the pigment not only contributes to the survival of the fungus spore by protecting against harmful ultraviolet light, but is also an important virulence factor [126] *Cladosporium sphaerospermum* has recently been the focus of space studies, where researchers from NASA [142] have evaluated the fungus's ability to attenuate the ionizing radiation tested aboard the International Space Station (ISS) on the surface of Mars. These initiatives show the strength, genomic plasticity and adaptive evolution with which these organisms present themselves, no more than being mere decomposers.

Here on planet Earth, research conducted by Brazilian and Chilean researchers also found responses to radioactive effects in yeast species. Research developed in the Atacama Desert, Chile conducted by Gonçalves et al. [143] found the filamentous fungi *Cladosporium halotolerans*, *Penicillium chrysogenum* and *Penicillium citrinum* more often and two species of light fungi *Exophiala* spp. (melanin) and *Rhodosporidium toruloides* (carotenoids) evaluating the ability to resist ultraviolet radiation from the sun in these fungi, as a model of studies of the possibility of

life on the planet Mars, since the desert presents an environment similar to that of the red planet.

Other species, isolated from a volcano named Sairecabur, located between Bolivia and Chile, found *Exophiala* sp., *Rhodosporidium toruloides*, *Cryptococcus friedmanii* and *Holtermanniella waticus* species that presented high resistance to UV radiation. Even though they were white-colored yeasts (*C. friedmanii* and *H. waticus*), devoid of pigments, these characteristics left the researchers puzzled, with their multiplying power in the face of excessive heat, desert adaptation and resistance [144].

Not only heat survives the fungi; in the cold they also develop, and go very well, thank you! This is what Gonçalves et al. [145] described when they isolated fungi from the genera *Acremonium*, *Byssochlamys*, *Cladosporium*, *Debaryomyces*, *Penicillium* and *Rhodotorula* from extremely cold and dry Antarctic rocks and environments. These researchers suggested that these cryptic fungi are phylogenetically close to pathogenic and mycotoxin opportunistic taxa, which live among living beings and animals, as they have compatible virulence characteristics.

In 2019, in this same Arctic region of the globe, Menezes et al. [146] characterized the fungal community found in the seasonal winter snow of the Antarctic Peninsula. *Phenoliferia glacialis*, was the one that presented wide distribution, also isolating the opportunistic fungi *Debaryomyces hansenii*, *Rhodotorula mucilaginosa*, *Penicillium chrysogenum*. The researchers presented a concern because the isolated environmental specimens showed resistance to agricultural and clinical antifungal tests, showing the virulence potential of these fungi in humans and animals, which evidences that we still have much to know about these eukaryotic beings and that are present in our lives and in our daily lives.

5. CONCLUSION

This review, based on several studies, related to the fungal sphere comes to affirm the enormous capacity of the filamentous and yeast-like fungi to adapt to the most varied environmental conditions, many of them extreme and develop in a wide variety of ecological niches, adapting to the pressures changes imposed by man-made changes.

Due to this immense adaptability, genetic and phenotypic plasticity, fungi are thriving in niches

that until then seemed uninhabitable and impossible to believe would survive in these inhospitable environments. Nature has given these eukaryotic and heterotrophs organisms a capacity for resilience, adaptability and high plasticity power to remain in extreme conditions, and these physiological characteristics were shaped by the varied environmental strains found in every corner of the planet.

General arguments on fungal infections in human populations, or even in animals; are causing a growing wear and tear of the planet's biodiversity, in fact, the direct and indirect effects of climate change induced by exponential growth and with broader implications for human health, ecosystems and biomes are being driving factors of the evolution of fungi, as recent discoveries and updates of these organisms should become an intense area of research for the present day and decades.

The expansion of the geographical distribution of pathogenic fungi and the acquisition of virulence characteristics in non-pathogenic environmental fungi, thermotolerant fungi or not, are reshaping the 21st century, making the expansion of fungal diseases for the fauna and flora of the planet a new era; this leads us to believe that unless measures are taken to strengthen the biosafety and health of the planet in order to avoid a global collapse; it is necessary that more accurate studies in the administration of chemical components and antifungal discoveries that can control with greater efficacy and capacity of fungal infections and their action on environments, because fungi are out there and will continue there.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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