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TROPICAL MYCOSES (L MARTINEZ, SECTION EDITOR)

New Insights in Dermatophytes: *Microsporum* spp. and *Nannizzia* spp.

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Abstract

Purpose of Review Species of the *Microsporum* and *Nannizzia* complexes are some of the etiological agents of dermatophytosis, an important cutaneous infection that affects humans and other mammals and whose incidence is increasing worldwide. This article aims to review the pertinent knowledge about dermatophytosis, specifically with these etiological agents.

Recent Findings The immunological mechanisms involved in the prevention and control of these infections are not fully understood. Many reports suggest that the mammalian immune system evolved with the interaction of these pathogens, and the infection depends directly on the virulence of the strain, geographic location, and environmental resources. As virulence factors, thermotolerance, melanin production, and cell wall components stand out. Treatment for dermatophytosis includes the use of topical or systemic drugs.

Summary These fungi present an increasing risk in human health care; studies in physiology, genetics and biochemistry, pathology of dermatophytosis, and immune response are essential for the development of new diagnostic measures, treatment protocols, and prevention strategies.

Keywords *Microsporum* · *Nannizzia* · Dermatophytosis · Infection · Virulence · Mycoses

Introduction

History and Taxonomy of Dermatophytes

The dermatophytes are fungi that belong to the Arthrodermataceae family and are related by their morphological and physiological characteristics. During their life cycle, most species present both asexual and sexual reproduction [1]. In the past, the asexual stage of the fungi, so-called anamorphic state, was taxonomically described in the genera *Trichophyton*, *Microsporum*, or *Epidermophyton*, whereas the genus *Arthroderma* comprised the sexual (or teleomorphic) stage of all dermatophytes [1]. With the recent advances of molecular biology, phylogenetic studies were carried out to classify the dermatophytes together with their main ecological characteristics and host specificities [2]. Nine groups are currently accepted as genera: *Guarromyces*, *Ctenomyces*, *Paraphyton*, *Arthroderma*, *Epidermophyton*, *Lophophyton*, *Microsporum*, *Nannizzia*, and *Trichophyton*. Although the number of dermatophyte genera has increased, the species relevant for routine diagnosis of dermatophytosis now belong to smaller groups, which facilitates their correct identification [2]. The new and previous names of species that suffered taxonomical changes after molecular studies are described in Table 1.

Regarding their physiology and morphology, dermatophytes are keratinophilic filamentous fungi that can affect the nails, hair, and skin of humans. These infections are called dermatophytoses and have a prevalence of around 19% in the general population of developing countries [4•]. Approximately 20–25% of the global human population was/is infected with some dermatophyte [5]; the prevalence of dermatophytes is variable in different regions of the world and within the same country, due to climatic factors, socioeconomic and hygienic conditions of the population, urbanization, host's immune system, fungal characteristics, and available therapeutic

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Table 1 Ecological division of dermatophyte species and host preferences, accordingly to their new taxonomic data to the most recent taxonomical changes

Anthropophilic	Previous obsolete names	*Zoophilic*	Previous obsolete names	*Geophilic*	Previous obsolete names	*Unknown*
Arthroderma eboreum	*Trichophyton eboreum*	*Arthroderma amazonicum*	*Microsporum amazonicum*	*Arthroderma ciferrii*		*Arthroderma chiloniense*
Arthroderma onychocola	*Trichophyton onychocola*	*Arthroderma flavescens*	*Trichophyton flavescens*	*Arthroderma cuniculi*		*Arthroderma silverae*
Epidermophyton floccosum	*Acrothecium floccosum* *Blastotrichum floccosum* *Dactylium floccosum* *Epidermomyces floccosus*	*Arthroderma redellii*	*Trichophyton redellii*	*Arthroderma curreyi*		*Ctenomyces bossae*
Microsporum audouinii	*Closteroaleurosporia audouinii* *Sabouraudites audouinii* *Sporotrichum audouinii* *Veronaia audouinii*	*Arthroderma tuberculatum*		*Arthroderma gertleri*		*Ctenomyces indicus*
Microsporum ferrugineum	*Arthrosporia ferruginea* *Grubyella ferruginea* *Trichophyton ferrugineum*	*Arthroderma vespertilii*	*Chrysosporium vespertilii*	*Arthroderma gloriae*		*Ctenomyces serratus*
Nannizzia aenigmatum		*Lophophyton gallinae*	*Achorion gallinae* *Closteroaleuriospora gallinae* *Epidermophyton gallinae* *Microsporum gallinae* *Sabouraudites gallinae*	*Arthroderma insingulare*		*Ctenomyces vellereus*
Nannizzia duboisii	*Sabouraudites duboisii* *Microsporum duboisii*	*Microsporum canis*		*Arthroderma lenticulare*		*Guarromyces ceretanicus*
Nannizzia praecox	*Microsporum praecox*	*Nannizzia nana*	*Microsporum gypseum var. nanum* *Microsporum nanum*	*Arthroderma melis*		*Nannizzia perplicata*
Trichophyton tonsurans	*Oidium tonsurans* *Trichomyces tonsurans*	*Nannizzia persicolor*	*Arthroderma persicolor* *Closteroaleuriosporia persicolor* *Ectotrichophyton persicolor* *Microsporum persicolor* *Sabouraudites persicolor*	*Arthroderma multifidum*		*Trichophyton eriotrephon*

Table 1 (continued)

Anthropophilic	Previous obsolete names	*Zoophilic*	Previous obsolete names	*Geophilic*	Previous obsolete names	*Unknown*
Trichophyton interdigitale	*Epidermophyton interdigitale* *Kaufmannwolfia interdigitalis* *Microides interdigitalis* *Sabouraudites interdigitalis* *Trichophyton mentagrophytes var. interdigitale*	*Paraphyton mirabile*	*Arthroderma mirabile*	*Arthroderma phaseoliforme*	*Trichophyton phaseoliforme*	
Trichophyton schoenleinii	*Achorion schoenleinii* *Arthrosporia schoenleinii* *Grubyella schoenleinii* *Oidium schoenleinii* *Sporotrichum schoenleinii*	*Trichophyton equinum*		*Arthroderma quadrifidum*		
Trichophyton concentricum	*Achorion concentricum* *Aspergillus concentricum* *Endodermophyton concentricum* *Lepidophyton concentricum* *Mycoderma concentricum* *Oospora concentrica*	*Trichophyton mentagrophytes*	*Ctenomyces mentagrophytes* *Ectotrichophyton mentagrophytes* *Microides mentagrophytes* *Microsporum mentagrophytes* *Spiralia mentagrophytes*	*Arthroderma uncinatum*		
Trichophyton eriotrephon		*Trichophyton simii*	*Epidermophyton simii* *Pinoyella simii*	*Arthroderma thuringiensis*	*Trichophyton thuringiense*	
Trichophyton rubrum		*Trichophyton quinckeanum*	*Achorion quinckeanum* *Closteroaleuriospora quinckeana* *Microsporum quinckeanum* *Oidium quinckeanum* *Sabouraudites quinckeanus* *Trichophyton mentagrophytes var. quinckeanum*	*Nannizzia corniculata*	*Arthroderma corniculatum*	
Trichophyton soudanense		*Trichophyton benhamiae*		*Nannizzia fulva*	*Closterosporia fulva* *Microsporum fulvum* *Sabouraudites fulvus*	

Table 1 (continued)

Anthropophilic	Previous obsolete names	*Zoophilic*	Previous obsolete names	*Geophilic*	Previous obsolete names	*Unknown*
Trichophyton violaceum	*Achorion violaceum* *Arthrosporia violacea* *Bodinia violacea* *Favotrichophyton violaceum* *Sabouraudites violaceum*	*Trichophyton erinacei*	*Arthroderma benhamiae var. erinacei* *Trichophyton mentagrophytes var. erinacei*	*Nannizzia gypsea*	*Achorion gypseum* *Closterosporia gypsea* *Gymnoascus gypseus* *Microsporum gypseum* *Sabouraudites gypseus* *Trichophyton gypseum*	
		Trichophyton verrucosum	*Ectotrichophyton verrucosum* *Favotrichophyton verrucosum*	*Nannizzia incurvata*	*Microsporum incurvatum* *Nannizzia gypsea var. incurvata*	
		Trichophyton bullosum		*Paraphyton cookei*	*Microsporum cookei*	
				Paraphyton cookiellum	*Nannizzia cookiella*	

Adapted from de Hoog et al. (2017) [2] and S. Gnat et al. (2020) [3•]

actions [1]. Dermatophytes are also classified into three ecological groups: anthropophilic (humans can be reservoirs and develop disease), zoophilic (animals are reservoirs; they can be pathogenic or not to their kind, but extremely pathogenic to humans), and geophilic (they are found in the soil; some of which are pathogenic to humans [6] (Table 1).

Dermatophytoses (*Tineas*)

Among the genera cited above, about 50 species are of medical interest around the world. Their distribution is influenced by geographic and climatic factors, population habits, among others [3•]. Their nutrition is based on the absorption of nutrients, mainly keratin, which makes them a pathogen of keratinized superficial tissues of men and animals, affecting adults, children, and the elderly [6]. The infection occurs through contact with the fungal spores or propagules existing in the environment, or by direct contact with humans, animals, and soil harboring a dermatophyte [1]. Dermatophytes can infect skin, hair follicle, or nails, causing mechanical damage that results in scaling of the epithelial surface [1]; in the nails, the fungi infect the viable matrix and then damage it, making it hyperkeratotic and thickened, followed by highlighting and distortion [7]. In the hair, there is a common rupture with an inflammatory reaction and hypersensitivity in the scalp, responsible for the development of the lesions, and this may present with alopecia plaque or in an area with broken or toned hairs that pierce the vivacity of hair strands [8]. The tonsurant form can be differentiated by clinical manifestation, by the type of parasitism, and etiologic agent [9]. A magnetic microscope shows extensive and unique lesions, with ectotrix parasitism, being detected by zoophilic or geophilic dermatophytes such as *Microsporum canis* and *Nannizzia gypsea*. During parasitism, dermatophytes present as hyphae and arthroconidia [8]. The clinical presentation is diverse; as general clinical signs, they usually present asymmetrical lesions, with variable itching that causes trauma to the skin due to itching [10]. The classic lesion in the scalp is characterized by a circular, irregular, or diffuse alopecia, and centrifugal expansion, usually without pruritus, growing from the center of the lesion to the circular shaped borders, areas of alopecia, erythematous, and vesicular borders with intense peeling [11]. In the skin, dermatophytes cause circular or ring-shaped changes, with sizes usually ranging from 1 to 5 cm, reddish, and with flaking at the edges [12]. Larger lesions and confluence of lesions can also occur [10]. The progression of the margins with simultaneous central scarring is characteristic, and itching is frequently observed. Deep infections can occur with massive inflammatory reactions [10]. Dermatophytoses are also classified according to the site of infection, using the word *tinea* followed by the Latin term for the particular location of the body (Table 2). Tinea imbricata is another manifestation of dermatophytosis that is usually caused by *Trichophyton concentricum*. It features concentric annular and diffuse rings of scaly lesions, often accompanied by pruritus [36]. Its name is given by the Latin word "imbrex" which means "an

Table 2 *Tineas*, clinical presentations, and the most common species

Tinea	Clinical presentation	More isolated species	Reference
Barbae	Inflammatory, pustular lesions on the beard area of men, with erythematous, scaly plaques, opaque hair, and folliculitis	*Trichophyton verrucosum* *T. mentagrophytes* *T. rubrum*	[13, 14]
Capitis	Scalp lesions in skin, hair, eyebrows, and eyelashes. Inflammatory, scaly areas, and folliculitis formation may occur	*Microsporum audouinii* *M. canis* *M. ferrugineum* *Nannizzia gypsea* *Trichophyton tonsurans* *T. verrucosum* *T. violaceum*	[15–17]
Corporis	Lesions located in the upper body (trunk, shoulder, armpit, chest, and back). They have defined erythematous borders, slightly elevated, sometimes with vesicles	*Epidermophyton floccosum* *Trichophyton rubrum* *T. mentagrophytes* *T. tonsurans* *T. verrucosum* *T. interdigitale* *Microsporum audouinii* *M. canis*	[18–24]
Cruris	Erythematous lesions in the inguinal, genital, pubic, perineal, and perianal regions, sometimes with pruritus, secondary bacterial infection, and pain	*Trichophyton rubrum* *T. mentagrophytes* *T. tonsurans* *Epidermophyton floccosum*	[25–28]
Faciei	Lesions almost always pruritic, erythematous annular, or serpiginous patches with an active border composed of papules, vesicles, and/or crusts	*Trichophyton tonsurans* *T. mentagrophytes* *T. verrucosum* *Microsporum canis*	[29, 30]
Manuum and *Pedis*	They involve the interdigital and plantar/palmar regions. The intertriginous form is more commonly associated with maceration, desquamation, fissure, and erythema	*Trichophyton rubrum* *T. mentagrophytes* *T. erinacei* *T. violaceum* *Epidermophyton floccosum* *Microsporum canis* *Nannizzia gypsea*	[31–34]
Unguium	Affect nails and surrounding tissue, periungual folds, leaving brittle, friable, or irregular	*T. rubrum* *T. mentagrophytes* *Epidermophyton floccosum* *T. interdigitale*	[35]

overlapping roof tile" being used for the first time by the British explorer William Dampier in 1686 on the island of Mindanao, Philippines [36]. The most common infections in prepubertal children are *tinea corporis* and *tinea capitis*, whereas adolescents and adults are more likely to develop *tinea cruris*, *tinea pedis*, and *tinea unguium* (onychomycosis) [1].

The diagnosis of dermatophytoses can be made based on anamnesis, clinical examination, fungal culture, direct examination with 10 to 20% potassium hydroxide solution, histopathology, polymerase chain reaction (PCR), or demonstration of the fungal infection using the Wood lamp, which is a device that uses transillumination to detect bacterial or fungal skin infections and skin pigment disorders or irregularities [4•]. Eventually, histopathology and immunohistochemistry are essential for the correct diagnosis of dermatophytosis [37].

The Former Genus *Microsporum*

The genus *Microsporum* was first described in 1843 by David Gruby. This author described its species as presenting colonies with a cottony or powdery aspect, with a color that varies from white to yellow, but also may have a dark brown color [38]. Microscopically, the most common characteristic of *Microsporum* species for decades was the presence of branched, hyaline, and septate hyphae, with spindle-shaped multicellular macroconidia [38]. As described before, recent studies reclassified some species of the former *Microsporum* genus to the genera *Nannizzia* and *Paraphyton*. Most species are isolated from the soil and can cause infections in mammals [39]. In recent years, there has been a significant change in the epidemiology, etiology, and clinical pattern of infections caused by members of the former *Microsporum* genus worldwide, requiring appropriate diagnostic and

treatment strategies [40]. These species can cause infections in humans and animals, with *Microsporum canis* and *Nannizzia gypsea* standing as the most frequent agents of mammalian infections [4•, 41].

Microsporum canis

This species has velvety white colonies with the reverse showing yellow to orange pigmentation when grown in vitro on most mycological media; microscopically, it presents fast-growing and numerous spindle-shaped macroconidia, with thick, rough cell walls with septations that can vary from five to nine [38]. This zoophilic fungus can be found in asymptomatic cats, which are its main reservoir, together with some other mammal species [42]. *M. canis* is frequently isolated from their hair, even in the absence of lesions. *M. canis* is more commonly found in puppies, more frequent in cats than in dogs, especially in asymptomatic cases [42]. In humans the most frequent clinical manifestation associated with *M. canis* are *tinea capitis tinea corporis*, *tinea pedis*, and *tinea unguium*. In North Africa, Europe, Asia, and South America, *tinea capitis* has medical importance because it frequently affects children within school age range [29, 43]. Other manifestations include infection on the face (*Tinea faciei*) arms, legs abdomen, trunk, shoulder, armpit, chest, and back (*Tinea corporis*), often in the form of family microepidemics [44]. *M. canis* is responsible for most infections by dermatophytes in children. In adults, unusual clinical presentations of *M. canis* infection have been described such as severe and inflammatory tinea barbae and very atypical *Tinea faciei* [42]. In addition, transplant recipients, patients with cancer or immunosuppressive conditions, especially due to the acquired immunodeficiency syndrome (AIDS), are at risk for infection by this species [45]. This dermatophyte can cause heterogeneous disease in different hosts showing variable clinical manifestations. In recent decades, there has been a high incidence of animals with asymptomatic forms of dermatophytosis, increasing the chances of infection for humans in contact with these animals [43].

Nannizzia gypsea

Formerly known as *Microsporum gypseum*, this is a geophilic species that can infect humans and animals. This dermatophyte usually affects the skin and, on rare occasions, scalp [1, 15]. The colonies have a powdery aspect, which resembles sand, with a color that can vary from orange to brownish yellow. In microscopy, it is possible to visualize symmetrical macroconidia that have no more than six thin-walled cells with rounded ends [46]. *N. gypsea* is the main geophilic dermatophyte worldwide and has different degrees of pathogenicity, being less frequent than those dermatophytes harbored by animals [47]. Usually, only the most virulent strains are capable to cause infection. However, immunocompromised hosts are more likely to be affected [48, 49]. Environmental factors, such as soil composition, temperature, and atmospheric humidity may be related to the endemicity of certain dermatophytes in specific regions. There are few reports of isolation of *N. gypsea* from the environment [50]. When this task is successful, *N. gypsea* is frequently isolated from soils with abundance of organic matter [50]. This species may cause unusual lesions, refractory to treatments or in patients with some underlying disease [51], and can cause micro-epidemics with very different clinical forms [48]. Atypical clinical manifestations that are refractory to topical or systemic treatments have already been described in the literature in patients with HIV, being epidemiologically related to the source of geophilic infection [52].

Virulence Factors

Dermatophytes invade their hosts in a process that can be split, for academic purposes, in three stages: adhesion, invasion, and growth [52], all of them dependent on some fungal virulence factors. The first step is dependent on glycoproteins found in the cell wall [53], followed by germination of conidia, a process that lasts about 3 h. Invasion depends on the penetration of hyphae into the skin and nutrient spoilage driven by extracellular enzymes such as proteases, caseins, elastases, permeases, lipases, and keratinases and finally hyphae growth with formation of arthroconidia [54]. The skin is the host's greatest defense barrier against pathogenic fungi. The skin has specialized cells such as keratinocytes and Langerhans cells, which trigger the innate immune response, in addition to a particular microbiota that competes for space and nutrients with pathogens. [7]. To overcome this barrier, dermatophytes also produce β-lactam antibiotics and fusidans, which help them to fight the skin microbiota [7, 55]. Dermatophytes are capable of using various substrates for their growth, with proteins being their main source of nutrients during parasitism. These fungi require carbon and nitrogen, and, taking into account their development in keratinized substrates, sulfur metabolism becomes equally important [56].

Extracellular Enzymes

Fungi degrade organic matter, and a series of extracellular enzymes help them in this task. These enzymes also play an important role in virulence [7]. The production of enzymes secreted by dermatophytes is related to fungal survival, clinical evolution, but possibly also to the triggering and modulation of the immune response [5]. For the degradation of proteins, an alkaline environment is necessary to break and remove disulfide bonds by proteases.

Dermatophytes can survive in the absence of keratin [57], but they need keratinase, proteinase, DNAses, phospholipase, lipase, and elastase to break down proteins and other skin constituents [58]. Keratin, collagen, and elastin constitute 25% of the mass of mammals, making these enzymes essential for infection, advantageous in terms of colonization [57]. The synthesis and secretion of enzymes are important metabolic activities for these fungi. Proteolytic enzymes such as keratinases, collagenases, and elastases act in several processes, having been implicated in the pathogenesis of some fungal diseases [53]. Hydrolytic enzymes, such as proteinases, lipases, and phospholipases, are also secreted and play a central role in fungal metabolism, being responsible for the pathogenesis of the infection, which causes damage to host cells and provides nutrients in a restricted environment. In addition, extracellular proteinases act on the adhesion and survival of the pathogen on mucous surfaces and invasion of host tissues [53]. Regarding the *Microsporum* genus, there are few studies in the literature on this subject. Keratinases are proteases capable of degrading keratinous substrates; however, the exact nature of keratinolysis is still unknown [7, 59]. Strains of *Microsporum audouinii* and *Nannizia gypsea* produce keratinolytic activity in greater amounts [59]. It has been demonstrated that keratinases represent the most important virulence factors for dermatophytes in the first stage of infection. However, the spectrum of enzymes secreted by these fungi is broader, and the duration and intensity of enzyme production differ among the strains [5]. *M. canis* produces Ekase, an extracellular keratinase that directly affects the epidermis and is capable of destroying the squamous cells of the epidermis. It is an antigenic enzyme, which can be found in the epidermal layer and in the dermatophyte, itself, through an enzyme immunoassay (ELISA), with polyclonal anti-Ekase antibody [60]. Recently, *M. canis* has been shown to produce aspartic protease, hemolysin, urease, and catalase [61]. Dermatophytes produce keratinase, proteinase, phospholipase, and lipase, but only *Trichophyton mentagrophytes*, *Trichophyton verrucosum*, *M. canis*, and *N. gypsea* were described as containing elastase [58]. Elastase is a keratinase that influences tissue reactions in dermatophytosis [62]. The enzymatic activity of strains of *M. canis* is known for the presence of keratinases, lipases, elastases, and DNAses. Another important factor is that arthroconidia are responsible not only for propagation and resistance in the environment, but also for infection [62]. Dermatophytes have a certain degree of similarity in clinical signs of human and animal patients and enzyme production; these are probably linked to host immunity or to other enzymes and virulence factors not evaluated in published studies. Therefore, a standardization of methods to determine the virulence factors of dermatophytes is strongly needed.

Melanin Production

Melanin is a dark brown to black pigment formed by the oxidative polymerization of phenolic compounds or indole precursors, with stable free radicals. It is synthesized by various organisms from all Kingdoms of life, negatively charged, and generable insoluble in aqueous solutions and organic solvents [63]. Due to their biophysical properties, melanins provide protection against several harsh conditions, including resistance to microbial attacks and protection against ionizing radiation, which increases survival and longevity of fungi in the environment [64]. This pigment is considered a major virulence factor in several pathogenic fungi, such as *Cryptococcus neoformans* [65], *Aspergillus fumigatus* [66], *Sporothrix schenckii* [67], *Histoplasma capsulatum* [68], and *Talaromyces marneffei* [69]. Dermatophytes produce melanin or melanin-like compounds, which are expected to play a role in virulence based on the known role of melanins in other pathogenic fungi. *T. mentagrophytes*, *Trichophyton rubrum*, *Epidermophyton floccosum*, and *N. gypsea* synthesize melanin when cultured in vitro, and during parasitism, this pigment is present in the septate hyphae from infected patients [69]. A study from Thailand reports melanin production by *N. gypsea*. The fungus was cultured on potato dextrose agar for 4 weeks, and melanin particles were isolated and purificated from the conidia. Purified melanin was characterized by electron spin resonance spectroscopy and immunofluorescence. In addition, laccase activity was detected in this dermatophyte [69]. Laccase was previously purified and characterized in *N. gypsea* and *M. canis* [69]. Dermatophytes can synthesize melanin or melanin pigments in vitro and in vivo. Although this is a well-known virulence factor in several fungal pathogens, there are few data available to suggest that melanin plays a critical role in the pathogenesis of dermatophytes. Further studies are needed in order to understand the mechanisms of infection of these pathogens.

Cell Wall

The cell wall is one of the main components of the fungal cell structure, which has several biological functions related to morphology, integrity, pathogenicity, and virulence [62]. It is a rigid, permeable three-dimensional structure, with polysaccharides, which interact with their hosts, and proteins, which are important for the growth and signaling of fungi [62]. It is mainly composed of specific carbohydrates. In nature or during parasitism, fungi must adapt to nutrient availability, osmolarity, pH, temperature, and exposure to toxic compounds; thus, the cell wall represents the first line

of defense for these microorganisms [62]. The main class of cell wall proteins is glycosylphosphatidylinositol (GPI); they mediate cell-cell interactions and wall biosynthesis by enzymatic activity and have a structural role [70]. In some species, melanization of the cell wall can occur through the deposition of the pigment melanin [62]. The fungal cell wall is a complex, dynamic, and multilayered structure, located externally to the plasma membrane, which participates in the initial interaction between the microorganism and the environment. It is also a permeable barrier, with functions related to nutrition and protection of the protoplasm against physical or osmotic injuries [62]. It participates on the fungal secretory system, releasing proteins, metabolites, organic acids, mycotoxins, and enzymes [62]. The cell wall also has a resistance function, producing fungicides and influencing its metabolism, which is why the agricultural and pharmaceutical industries are specialized in the study of this structure [71].

Like other eukaryotic cells, dermatophytes have nuclei and organelles, including mitochondria and vacuolar compartments involved in the storage, distribution, and recycling of metabolites. The plasma membrane contains ergosterol, which replaces the specific cholesterol of animal cells, which is the target of most antifungal treatments [62]. Components and thickness of fungal cell walls vary between species. The largest cell wall components are β-glucans and chitin, which ensure resistance to lysis by phagocytosis [7]. Besides chitin and β-glucans, dermatophyte cell walls can also present proteins, mannans, and galactomannans [62]. Mannan is also involved in suppressing the inflammatory response, leading to a less intense lymphoproliferation during infection by *M. canis* [72]. This structure is also a determinant of the pathogenicity of fungi, chitin, and β-1,3-glucans known to trigger immune responses in hosts. After these events, the pathogens neutralize the recognition of the host [73]. Dermatophytes produce several cell wall components that prevent them from being recognized by the host, such as the LysM binding domains and several chitinase-encoding gene domains that favor the growth of pathogens on a wide variety of substrates, including soil and human skin [53]. It is known that the cell wall constituents of the dermatophyte *Trichophyton rubrum* determine the virulence of the pathogen. However, little is known about the relationships between dermatophyte pathogenesis, cell wall biosynthesis, and cell wall morphology [63]. Changes in the environment and external stresses continually remodel the cell wall [62]. Cell wall modulation in response to stressors may reveal putative targets for antifungal drug development [53].

Biofilm

Biofilms are associations of one or more microorganisms that form a dynamic, organized, and persistent community for survival in adverse conditions such as extreme temperatures in harsh environments, such as those with extreme acidity or different levels of humidity [74]. This is relevant because of the role it plays in human infections, especially its relationship with chronicity of some diseases [74]. Therefore, the ability to form biofilms is considered an important virulence factor as it creates an environment favorable to colonization, infection, and evasion [75]. The phenotypic characteristics expressed by cells within a biofilm are different from the planktonic form. Usually, drug tolerance is increased, and greater protection against host defenses is expected [76]. Microorganisms in biofilms produce an exopolymeric matrix that acts as an impermeable barrier, hindering the penetration and diffusion of antimicrobial substances [74]. In addition, the cells inside are in a dormant state, which allows them to survive stress conditions and prevent cell death [74]. Biofims have already been described in bacteria, yeasts, dimorphic, and filamentous fungi, including dermatophytes [74, 77, 78], such *T. mentagrophytes*, *Trichomyces tonsurans*, *T. rubrum*, *M. canis*, and *N. gypsea*, under in vitro, in vivo and ex vivo conditions [77–80]. It was demonstrated abundant fungal adhesion and growth, microconidia, macroconidia, and hair perforation, based on qualitative analyses. Cat hair was more favorable for biofilm formation by *N. gypsea*, *M. canis*, and *T. mentagrophytes*, with *M. canis* and *N. gypsea* as strong biofilm producers [79, 81, 82]. The ecological niche determines which will be the preferred substrate of the fungus and the degradation mechanisms produced. This involves the secretion of keratinolytic enzymes and expression of virulence factors, such us the production of biofilm. These steps are crucial for the establishment of infection and should be better elucidated, as they directly influence the mechanisms of adhesion, penetration, and germination of dermatophytes. These factors are directly linked to the persistence of infection.

Host Immune Response

The immune system of mammals evolved to fight possible pathogens that are able to grow at body temperature, to penetrate into deeper tissues and organs, and to digest tissue cells for nutrient absorption [83••]. The host's immune response in dermatophyte infections depends on some factors, which are fungal species involved, virulence of the strain, location of the infection in the body, and environmental characteristics. The fungus remains in contact with the keratinous tissues and ends up stimulating the growth of keratin layers. In addition, sweat, alkaline pH, and temperatures higher than the environment provide the perfect habitat for their development [2, 7]. The main mechanisms of immunity to dermatophytes are the production of antibodies and development of late hypersensitivity, followed by inflammation in the form of erythema, peeling, and infiltration of the skin,

a process that varies from species to species, with a possibility that within the same species, there may also be a difference in the host/fungus interaction [7]. Dermatophyte metabolites induce host cells to create an immune response to pathogens. This response is linked to the degree of infection of the fungus and can lead to a mild to acute inflammatory response. Humoral and cellular immunity involve the activation of lymphocytes, macrophages, neutrophils, and mast cells at the infection site [84]. The immune response depends on the type of metabolite, the enzymes released by the agent, and the immunosuppression caused by the dermatophyte. This fungus causes a skin reaction of type Th1 or delayed type IV, and the immediate hypersensitivity response is associated with recurrent chronic infections that produce high levels of IgE, IgG4, and Th2 cytokines by mononuclear leukocytes. Late type hypersensitivity is associated with acute dermatophytosis. Previous studies report that IgG, IgA, and IgM antibodies do not seem to protect against infections by dermatophytes because uninfected humans have low levels of these antibodies [85]. Few studies explore the humoral response, cellular mechanisms, receptors, and pathways involved in dermatophyte infections in human and animal models. However, much remains to be discovered about these mechanisms, especially in innate immunity. Future studies should focus on epidermis models that mimic infection by comprehensively identifying specific cell types and host factors.

Treatment

Although not lethal, dermatophytoses can compromise the patient's quality of life [86]. There are some antifungal drugs available for the treatment of dermatophytoses, including topical and oral formulations [4•]. Due to the evolutionary relationship between fungi and animals, there is a limited number of antifungals for therapy [86]. Their most common target is the cell wall, as it is present in fungi and absent in animals. Another site of action is the cell membrane where, as different from animal cells, ergosterol is present instead of cholesterol [1]. The genus *Microsporum* is commonly treated with griseofulvin [87–90], fluconazole [41, 91], itraconazole [41, 92], ketoconazole [93, 94]· and terbinafine [41, 95]. Regarding disseminated infections, griseofulvin is used orally and indicated exclusively for infections caused by dermatophytes, as it penetrates the fungal cell and interacts with the microtubules, breaking the mitotic spindle. Griseofulvin is fungistatic and is quickly eliminated from the body requiring prolonged administration for effective treatment. This longer treatment duration may also contribute to a higher level of adverse events experienced compared to other antifungal agents [18]. Griseofulvin is more efficient to treat *Microsporum* than *Trichophyton* infections [96]. Azole derivatives (fluconazole, itraconazole, and ketoconazole) are also used, which are fungistatic due to the inhibition of ergosterol biosynthesis, alternating membrane permeability [86]. Moreover, they inhibit enzymes related to oxidative metabolism, causing the accumulation of peroxides that are toxic for the fungus [86]. Fluconazole is equally effective in treating infections by *Microsporum* and *Trichophyton*, and itraconazole is more effective in treating *Trichophyton* in *Tinea capitis* [18]. Terbinafine are synthetic allylamines that can be used topically or orally acting to inhibit the squalene-epoxidase enzyme that blocks the biosynthesis of ergosterol and promotes the accumulation of squalene, which interferes with membrane functions and synthesizes the cell wall [86]. They need to be administered for *Microsporum* infections for a longer period (6 to 8 weeks), compared to 4 weeks for *Trichophyton* infections [18]. Azole antifungals (itraconazole and fluconazole) and allylamine (terbinafine) have a high affinity for keratinized tissues; they remain in keratin and hair for a period, which means that the dosing periods may be shorter than those of griseofulvin. In combination, continuous itraconazole and terbinafine have the highest rates of mycological cure, griseofulvin and terbinafine have the highest rates of clinical cure, and griseofulvin and terbinafine have the highest rates of complete cure [18]. In animals for topical treatment, there are antifungal solutions containing miconazole, clotrimazole, and enylconazole, in the form of shampoos, spray, lotions, and creams, in addition to the use of sulfur lime, which is effective in the treatment. In the systemic treatment, itraconazole, ketoconazole, terbinafine, and griseofulvin are the most used [94]. Knowledge about dermatophyte infections should be widely disseminated in order to educate patients on preventive measures to be taken in conjunction with appropriate antifungal treatment to limit relapse and reinfection. Studies that track strains resistant to antifungals traditionally used in the treatment are of paramount importance, but the discovery of possible new drugs is also valuable, as they may help in future studies and treatments of this important mycosis.

Antifungal Resistance

In the vast majority of cases, dermatophytoses are considered easy to treat, but due to the increase in cases, persistent infections, and relapses, there is concern about understanding the pharmacokinetic and pharmacodynamic properties of antifungals [97]. There was a considerable increase in the number of patients with resistant infections and/or with relapses; this can be related to drug interactions, low patient adherence, difficult to access infection site, incorrect medication administration, disorder that interferes with the immune system, and lack of environmental control [86]. Cases of antifungal tolerance, clinical failure, and relapse are more frequently observed in

other groups of fungi [86]; some cases of dermatophytes presenting tolerance or resistance have been reported and verified in *T. rubrum* [98], *T. mentagrophytes* [99], *T. tonsurans* [99], *M. canis* [86, 100, 101], *M. auduoinii* [101], and *N. gypsea* [101]. *Microsporum canis* resistant to terbinafin was isolated in China from a feline (female, 2 years old and hair); the same sample was susceptible to itraconazole [102]. More recently, strains of *M. canis* and *M. auduoinii* patients with onychomycosis are successive to itraconazole, and resistance to terbinafine and griseofulvin has been described [101]. Existing antifungals have restricted cell targets and may exhibit tolerance or resistance [100]. Cellular stress caused by antifungal drugs promotes compensatory responses, such as the overexpression of genes involved in detoxification, drug efflux, and signaling pathways, which are among the various mechanisms [86, 103]. Mutations in the genes that encode target enzymes can lead to substitutions of amino acids involved in the binding of antifungal agents, hindering their performance and leading to treatment failure. In dermatophytoses, research on antifungal resistance is precarious, since minimal inhibitory concentration data are limited [103]. Combined treatments of topical and oral drugs with anti-inflammatory drugs have been used in an attempt to increase the cure rate [6]. The combination of antifungals with topical steroids provides a protective action on the membrane, decreasing their action [86, 100]. In addition, dermatophytoses are favorable to self-medication, leading to the resistance of these fungi [86]. Currently, in addition to these concerns, agricultural environments have been shown to be possible contributors to the ability to develop resistance to antifungal agents [104]. Fungi are responsible for yield losses of 20% worldwide, with a further 10% loss after harvest, with which the chemical control of fungal pathogens has progressed [104]. Most fungicides, both for human and plant diseases, aim to alter mitochondrial function and biosynthesis of the cytoskeleton or ergosterol. Azole antifungals are the dominant chemicals in the treatment of fungal infections in crops, humans, and animals, which generates resistance and concerns, especially for geophilic dermatophytes [105]. Antifungal susceptibility tests in dermatophytes are able to detect when there is clinical resistance to standardized treatment. Although dermatophytes are a very difficult group of fungi to test in vitro, standardized procedures have been validated, thus facilitating antifungal susceptibility testing and monitoring of these strains. With the incidence of resistance increasing annually in countries like India, the advancement of dermatophytosis can be faster and more infectious, thus demonstrating that tests that seek to know the susceptibility of these fungi against already known drugs and possible new treatments will always be of paramount importance.

Conclusions

Fungi from the genera *Microsporum* and *Nannizzia* pose a growing threat to human health, with a global increase in fungal infections. In recent years, there has been significant progress in knowledge and understanding of the immune interaction between the host and *Microsporum* pathogenic species. Much of the immune response during dermatophytosis is still unknown, but many virulence factors of the fungus are already known, information that helps to control the infection so far. Studies in physiology, genetics, and biochemistry, pathology of dermatophytosis, and immune response are essential for the development of new diagnostic measures, treatment protocols, and prevention strategies. Laboratory diagnosis is necessary before treatment, although suspicion may be strong based on clinical signs. New antifungals with alternative modes of action must be developed. Resistance mechanisms should be further studied, as they have been shown to be increasingly present, generating worldwide concern. This review article demonstrated aspects of *Microsporum* and *Nannizzia* infection with different parameters. Taken together, the review increases the relevance of dermatophyte infections in human health and well-being and suggests the need for continuous monitoring of changing epidemiological aspects of this group of fungi.

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Declarations

Conflict of Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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