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# Dermatophytoses: A short definition, pathogenesis, and treatment

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## Abstract:

Dermatophytosis is an important type of fungal skin infection caused by dermatophytes. There is actually no part of the world that can be cleared from infection with dermatophytosis. The skin, hair, and nail of all types of mammalian, including humans, are under the risk to develop dermatophytosis. The disease is mainly caused by different species of dermatophytes within the cutaneous layer of the skin. Several topical and systemic antifungal drugs are used for the treatment of dermatophytosis. This review focuses on the general features of dermatophytic treatment, epidemiology, and the risk of contact with infected animals. Animal model as a promising branch for evaluation of new drugs is also discussed to give clear vision in the management of this worldwide predominant disease.

## Keywords:

Animal model, dermatophytes, dermatophytoses, treatment

## Introduction

Dermatophytoses or tinea is predominantly in about 20%–25% of the world population.<sup>[1,2]</sup> It is usually caused by dermatophytes, which are filamentous fungi natural living on keratin materials found in soil.<sup>[3,4]</sup> This type of disease is considered a prevalent skin disease worldwide.<sup>[5]</sup> Moisture and warm conditions are the most suitable factors that encouraged the distribution of dermatophytosis in tropical countries.<sup>[1]</sup> This epidemiological distribution may change with migration, lifestyle, immunosuppressive state, drug therapy, and socioeconomic conditions.<sup>[1,6]</sup> Dermatophytosis can occur in either of the humans and animals.<sup>[7-9]</sup> Thus, the usage of animal model will consider a primary step for *in vivo* evaluation of any new drug for the treatment of dermatophytosis.<sup>[10]</sup>

## Dermatophytes

Dermatophytes are a special group of keratinous fungi which have the ability to

live on keratin-rich materials found in soil or in the human or animal tissues such as skin, hair, and nail.<sup>[3]</sup> They involve about 40 different species included within the three most important genera of *Trichophyton*, *Microsporum*, and *Epidermophyton*.<sup>[1,4,11]</sup> Based on morphological characters, all of these genera consider an anamorphic form of the class Hyphomycetes of the phylum Deuteromycota (imperfect fungi).<sup>[12]</sup> Sexual stage (teleomorph) for some of *Trichophyton* and *Microsporum* genera is also discovered to make them included within *Arthrodermataceae* of ascomycetes.<sup>[13]</sup> However, molecular assays which are depending on the analysis of rRNA sequences confirmed that all dermatophytes are a cohesive group, with no clear distinction between the three genera.<sup>[14]</sup>

The difference in macroconidia characters is the old morphological feature used to differentiate between three genera of dermatophytes. The species of *Trichophyton* genus produce smooth, thin wall, and 1–12 septum macroconidia which are borne singly or in cluster with clavate, fusiform, or cylindrical shape. Whereas, the macroconidia of *Microsporum* genus

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have a thick rough wall with asperulate, echinulate, or verrucose surface and spindle, fusiform, or egg shape with 1–15 septa. Fungal species of *Epidermophyton* genus can produce a broad clavate macroconidium with a moderately thick wall and 1–9 septa and usually borne as a single or cluster conidium.<sup>[12]</sup>

Dermatophytes can classify according to the location in the environment or route of transmission into three groups: anthropophilic (transmitted from human to human), zoophilic (transmitted from animals to human), and geophilic (transmitted from soil to human).<sup>[15,16]</sup> The phylogeny of dermatophytes is more influenced by the environment location of these fungi. Sexual reproduction is very clearly observed among geophilic group and some of zoophilic, while it is very rarely observed in anthropophilic group.<sup>[11]</sup>

## Dermatophytosis

There are approximately 100,000 species of fungi from millions of species of fungi on the earth which have the ability to cause diseases in humans and animals, especially in the temperate and tropical countries.<sup>[1]</sup> Dermatophytes are an important group of pathogenic fungi causing skin diseases worldwide.<sup>[5]</sup> They attend to infect the keratinized tissues such as cutaneous skin layer, hair, and nail.<sup>[1,5,16,17]</sup> Dermatophytoses or tinea is the name of the disease caused by dermatophytes.<sup>[4]</sup> This disease causes chronic morbidity with a high prevalence and distribution in the entire world.<sup>[17,18]</sup> The predominance of dermatophytosis is about 20%–25% of the world population.<sup>[1,2]</sup>

Dermatophytosis or tinea can be found on the skin of different parts of the human body, which makes that it takes various names based on the infected area such as tinea pedis on the feet, tinea unguium on the nails, tinea capitis on the scalp, tinea cruris on the groin, and tinea corporis on the body.<sup>[15]</sup> A lesion of tinea can be caused by a single species of dermatophyte or by many species in some cases.<sup>[19]</sup> In addition, a single species of dermatophytes can cause different types of tinea.<sup>[20]</sup>

## Epidemiology of Dermatophytoses

Dermatophytosis is usually taken a different pattern of infection in the entire world and that will reflect on the variable geographic distribution of this disease.<sup>[6]</sup> Moisture and warm conditions are the most encouraged factors for the development of dermatophytoses in tropical countries.<sup>[1]</sup> Other factors, including increasing sweating, result from outdoor physical human activities in hot weather, and low degree of hygiene, are also associated with the prevalence of dermatophytosis.<sup>[20]</sup> However, epidemiology of such disease has changed due

to lifestyle, migration, socioeconomic conditions, drug therapy, and immunosuppressive state.<sup>[1,6]</sup>

Tinea corporis is the more common type of tinea which is mostly caused by *Trichophyton* species,<sup>[1,15]</sup> while tinea capitis is most frequently caused by *Trichophyton violaceum*, *Trichophyton tonsurans*, and *Microsporum canis*.<sup>[3]</sup> From all species of dermatophytes, *Trichophyton rubrum*, *M. canis*, *Trichophyton interdigitale* (*mentagrophytes* var. *interdigitale*), *T. tonsurans*, *Trichophyton verrucosum*, and *Microsporum audouinii* are the most account for dermatophytosis worldwide.<sup>[1]</sup> The investigation for these fungi is very important in diagnosis, treatment, and differentiation from other clinical skin diseases.<sup>[21]</sup> *T. rubrum* is the predominant isolate from humans followed by *Trichophyton mentagrophytes*.<sup>[20,22-24]</sup> This is clear in Europe when a high incidence of *T. rubrum* infection was recorded, while *T. mentagrophytes* was a higher incidence in Asia.<sup>[1]</sup>

## Clinical features of dermatophytoses

Dermatophytosis or tinea is usually presented with variable clinical features depending on the location of infection, type of dermatophytes, and the immune state of the host.<sup>[25]</sup> General features of tinea on infected skin of the human are represented by the presence of an annular patch with an advancing, raised, scaling border and central clearing.<sup>[15,26]</sup> These features may show variable degrees of scaling and inflammation reaction which could extend to form scarring and alopecia area.<sup>[4]</sup> Thus, inflammation and erythematous signs are clearly identified in a severe type of dermatophytosis infection.<sup>[27]</sup> Other clinical features such as itching, maceration, pain, scaling, vesicles or plaster forming, and erythematous rate are variable between mild and modern degrees.<sup>[15,17,27]</sup> The trigger to develop such clinical signs is mainly by diffusible of fungal metabolites through the Malpighian layer of skin and induces host response.<sup>[25]</sup>

Tinea corporis and tinea cruris are the most common types of tinea represented with pruritic and erythematous rash lesions and containing pustules or vesicles with an active scaly palpable edge.<sup>[17]</sup> However, these features are mostly associated with tinea cruris<sup>[15]</sup> and less common in tinea corporis.<sup>[27]</sup> Itching is an additional sign of dermatophytosis infection, which depends on the site of infection, and it usually appeared very mild in case of tinea corporis and very intense in tinea cruris.<sup>[27]</sup> Tinea pedis which is located between the fingers of the foot is characterized by the presence of scaling and maceration and less commonly with small vesicles and blisters.<sup>[17,27]</sup> However, clinical signs such as erythema, itching, scaling, margins, and size of lesion can be used as an indicator to determine the therapeutic ability of some antifungal drugs.<sup>[28]</sup>

The general clinical features of tinea on the human body are represented by the gradual appearance of the annular erythematous lesion with central healing tendency. Scaling, pustules, itching, inflammation, and hair and nail loss are also characters of most dermatophytosis infection.<sup>[5]</sup>

### Pathogenesis of dermatophytes

The ability of dermatophytes to produce various proteins or enzymes plays an important role to invade keratinous skin layers.<sup>[29]</sup> An important enzymes, including Keratinases, adhesins, lipases, phosphatases, DNAses and non-specific proteases are supporting dermatophytes to perform several pathogenic activities such as attachment and penetration the stratum corneum of the skin, overcome the host immune system and scavenge nutrients.<sup>[29]</sup> Keratinase and phospholipase found to be produced by 96% of 234 clinical dermatophytes isolates, while gelatinase and elastase produced from 14% and 23% of isolates, respectively.<sup>[30]</sup> The acidic nature of the skin stimulates dermatophyte to produce sensing transcription factors such as PacC and Hfs1 to raise fungi adapting to this acidic pH and give the time to increase pH value after keratin degradation for elevated protease enzyme activity.<sup>[29]</sup> Dermatophytosis is often initiated from the contact of viable fungal arthrospores or hyphae with the skin surface of the human which later encourage to adhesion and germinate to form infection by the presence of suitable conditions.<sup>[25]</sup> The incubation period on the human skin for the development of dermatophytosis is usually from 1 to 2 weeks.<sup>[26]</sup> Humidity and warm temperature are the most effective factors for infection development.<sup>[27]</sup> However, dermatophytosis infection can be increased in the presence of several conditions such as overcrowding, dressing of occlusive cloths, increased urbanization, low socioeconomic status, contact with animals, and poor hygiene.<sup>[31]</sup>

### Dermatophytosis in animal

Dermatophytes have the ability to cause dermatophytoses in different types of animals (domestic and wild) as well as in the human.<sup>[7-9,32]</sup> The zoophilic group of dermatophytes that mainly infected animals can easily cause infection in the human with a progressive lesion than that caused by anthropophilic members of dermatophytes.<sup>[32]</sup> Otherwise, the human can sometimes become a source for infecting other farm or wild animals as noted in the laboratory or other workplaces.<sup>[8]</sup> Dermatophytoses in animals may have a significant correlation with the age of the animal but not with the gender or with the season even though that dog is highly infected in winter and spring compared with cats that mostly infected in autumn, summer, and spring.<sup>[7]</sup> A single or multiple follicular lesions are the most clinical features of dermatophytoses in animals

that may associate with hair loss, crusting, scaling, and erythema.<sup>[9]</sup>

*T. mentagrophytes* and *M. canis* are the common causative zoophilic agents of dermatophytoses in animals.<sup>[32]</sup> Rabbits and guinea pigs are mostly infected by *T. mentagrophytes* as observation of a positive culture in 72.3% and 91.6% of them, respectively.<sup>[33]</sup> Therefore, the great number of infected rabbits (15 from 19 rabbits) with *T. mentagrophytes* can consider a risk factor to their owners, particularly children.<sup>[34]</sup> Otherwise, adult rabbits can become a carrier to dermatophytes.<sup>[8]</sup> However, the lesion of dermatophytoses in rabbits revealed alopecia with crusts or yellowish-white dry scales chiefly on the head and can spread to other parts of the rabbit body.<sup>[8,34]</sup> *M. canis* is the most causative agent of dermatophytoses in cats and dogs compared with *T. mentagrophytes*.<sup>[7,35]</sup> From 15 cats with dermatophytoses, 13 revealed positive results for *M. canis*, while only 2 with *T. mentagrophytes*.<sup>[35]</sup> Meanwhile, fivefold infected dogs than cats are frequently caused by *T. mentagrophytes*.<sup>[7]</sup>

The development of dermatophytosis on the animal body may require 1 week, while clinical signs need 2–4 weeks, as shown by the infected animal with *M. canis*.<sup>[26]</sup> Animals consider the main reservoir of zoophilic dermatophytes.<sup>[17,36]</sup> These zoophilic and even geophilic dermatophytes can easily transmit to the human.<sup>[26]</sup> Thus, the human in contact with infected animals which may be pets, domestic animals, or wild animals is always at risk to get dermatophytic infection.<sup>[4,26,37]</sup> The pet population has been increased in the last years due to raise interesting of people to have this small animal and spend most of the time with them, especially children.<sup>[36]</sup> Three of 11 cases of children were acquired dermatophytosis from infected rabbits which are used as pets by their family.<sup>[34]</sup> Thus, an individual who is in contact with animals during his works as a farmer or even when he works at home will be at risk to get dermatophytosis.<sup>[38]</sup>

### Dermatophytosis in animal model

Dermatophytosis can be developed in both humans and animals, with some differences in clinical features.<sup>[7-9,32]</sup> Zoophilic group of dermatophytes is the most causative agents of dermatophytosis in humans and animals.<sup>[31]</sup> The human can easily get dermatophyte agents from contact with different types of animals such as cats, dogs, guinea pigs, and rabbits.<sup>[1]</sup> Thus, choosing of the animal as a model to infect with dermatophytes will elevate the success rate of the process to develop a new drug and also to prevent use by the human as an experiment model.<sup>[39]</sup> Scientific ethics and safety requirements are always focused on preventing usage of the human as a preliminary experimental subject to evaluate the new drug or to determine the pathogenesis of any disease like dermatophytosis.<sup>[40]</sup>

Dermatophytosis animal model is so important in evaluating new drug to manage dermatophytes, increasing our knowledge regarding dermatophytes pathogenesis and more understanding about host immune mechanisms.<sup>[10]</sup> *In vitro* microbiological experiments are usually shown poor predictors of clinical outcome because the host immune response has a predominant role in disease resolution and also due to the lack of accurate correlation between *in vitro* testing and *in vivo* outcomes.<sup>[41]</sup> These animal models demonstrate a good correlation with the mammalian model for testing of new antifungal agents,<sup>[39]</sup> and they have a crucial role in pathogenic diseases.<sup>[42]</sup> Dermatophytosis can occur in either of the humans and animals.<sup>[7-9]</sup> Thus, the usage of animal model will consider a primary step for *in vivo* evaluation of any new drug for the treatment of dermatophytosis.<sup>[10]</sup>

### Treatment of Dermatophytosis

Several different drugs are used today for topical treatment of dermatophytosis infection. Itraconazole of azole group and terbinafine of allylamine group are the most common types of topical treatment of dermatophytosis.<sup>[43]</sup> Long duration periods of treatment, drug resistance, and even the cost are the most problems associated with the usage of known antifungal agents.<sup>[29]</sup> Thus, the discovery of a new antifungal agent will take the priority for enhancement treatment of various fungal infections, including dermatophytosis.

Dermatophytosis is usually needed at least 2–4 weeks to be cured in approximately all of its types and may reach 6 months in cases of tinea capitis and onychomycosis.<sup>[38,43,44]</sup> Actually, there are always differences between the results of *in vitro* and *in vivo* exterminates. These differences may be related to either of the host conditions, such as immune response, site of infection, and underlying illness or to the fungal characters as with virulence, or to the antifungal agent, such as dose, pharmacodynamics, pharmacokinetics, and drug interaction.<sup>[31]</sup>

New development forms of drugs for topical usage are recommended for the treatment of dermatophytosis. There are many advantages of using antifungal as a topical treatment of dermatophytosis. First, discover a new topical drug or modification old one will participate to increase the available list of antifungal drugs.<sup>[29]</sup> Second, topical preparations are much less costly than orally administered antifungal drugs and cause minimal adverse side effects.<sup>[44,45]</sup> Third, the application of topical formulation of amphotericin B (AmB) considers more safety to use and will not produce clinically relevant serum levels of AmB.<sup>[44,46]</sup> Forth, the failure of other antifungal agents to treat cutaneous fungal

infection will be resolved as noticed when used topical AmB (0.1% w/w) against sporotrichosis.<sup>[47]</sup> Fifth, the quality of patient life will increase if the new drug improved to cure infectious lesions in short time.<sup>[29]</sup>

Superficial mycosis has usually shown a low tendency to self-limitation.<sup>[27,42]</sup> For dermatophytosis, most of the healthy humans or animals tend to be self-limiting within weeks to months.<sup>[25,48]</sup> Treatment can shorten the course of the disease to prevent spread to other animals and peoples.<sup>[25,42,48]</sup> Thus, poor medical care will increase the epidemic spread of skin mycoses.<sup>[27]</sup> A combination of different drugs may show better efficiency.<sup>[49]</sup> The primary experiments provide promising results about the efficiency of topical drugs as AmB against fungi and to reduce the adverse effects of intravenous usage.<sup>[50]</sup>

### Conclusion

In spite of that, there is no population in the world clear from dermatophyte infections; there are few studies *in vivo* to test new drugs. Thus, using an animal model is necessary to learn more about dermatophyte pathogenesis, host immune response, and treatment efficiency. Dermatophyte revolutions appeared strongly as a significant rising trend of this infection, especially in the last years. The usage of animal model will consider a fundamental step for *in vivo* evaluation of any new drug for the management of dermatophytosis.

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### Conflicts of interest

There are no conflicts of interest.

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