# Animal Models as Tools for Translational Research: Focus on Dermatophytosis

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More than a century ago, Bloch, a Swiss dermatologist, proposed an animal model of dermatophytosis. In the early 1950s, Sakai and colleagues reported the *antifungal properties* of *halogen phenol esters* on an animal model of dermatophytosis and opened the doors into the new horizons of chemotherapy. Animal models of dermatophytosis are used principally in the evaluation of new therapeutic agents, but are also tools for investigation of pathogenicity, immune responses, and physiopathology.

In this chapter, the translated and spontaneous animal models that were developed to study the cause, nature, and cure of human dermatophytoses that caused by zoophilic, geophilic and anthropophilic dermatophytes will be critically compared and discussed.

**Keywords** Animal model, dermatophytosis, *tinea*, antifungal activity.

"The mere intention of God from the creation of the world is human; whatever else you see is frivolous." NASSER KHOSROU (A PERSIAN POET )

## 1. Dermatophytosis: public health issues and economic importance

Dermatophytoses are common infections of keratinized tissues caused by dermatophytes that are species of fungi belonging to *Epidermophyton*, *Microsporum*, and *Trichophyton* genera that further classified as anthropophilic, zoophilic and geophilic species on the basis of their primary habitat associations [1]. Anthropophilic dermatophytes usually infect humans and rarely infect other animals, zoophilic dermatophytes usually infect animals or are associated with animals, but occasionally infect humans, and geophilic dermatophytes usually recovered from the soil but occasionally infect humans and animals. Dermatophytes colonize the keratinized outermost layer of the skin of human and animals and usually do not invade the living tissue. Generally, these infections include *tinea capitis* (infection of scalp), *tinea pedis* (infection of feet), *tinea cruris* (infection of the groin area), and *tinea unguium* or onychomycosis (infection of nails). However, the disease generally known as tinea or ringworm may be a consequence of the inflammatory reaction of the host to the materials produced by the fungus during its invasive process [1].

Unfortunately, a precise and reliable data were not reported about economics of control, prevention, diagnosis, treatment and eradication of dermatophytoses in the literature. However one report stated that over USD $500,000,000 per year is spent worldwide for chemotherapy used against dermatophytoses [2].

Reproduction of human dermatophytosis is ethically prohibited in human subjects and it is hardly difficult in the *in vitro* and *ex vivo* experiments, therefore designing experiments using translated animals is necessary for the clarification of unidentified pathogenesis and the development of noteworthy drugs for patients. In this continuum, we must follow the experiment facility guidelines or national guidelines stated in the Institutional Animal Care and Use Committees (IACUC) to limit suffering of animal models.

More than a century ago, Bloch, a Swiss dermatologist, proposed an animal model of dermatophytosis [3]. In the early 1950s, Sakai and colleagues [4] reported the *antifungal properties* of *halogen phenol esters* on an animal model of dermatophytosis and opened the doors into the new horizons of chemotherapy. In this chapter we summarize the current animal models which have been implicated in the pathophysiology and physiopharmacology of dermatophytosis.

## 2. Animal models suitable for antidermatophytic compounds

### 2.1.1. The mouse models

Dermatophytosis is caused by the *T. mentagrophytes* var. mentagrophytes in pet mice. Lesions, when present, are distributed over the face, head, neck, and tail. The lesions are including alopecia, damaged hairs, scales, erythema, and crusting with or without itching. *T. mentagrophytes* var. quinckeanum causes the most severe form of dermatophytosis especially in wild mice, known as mouse favus. Favus typically begin as thick, yellow, saucer-shaped crusted lesions called scutula that highly consist of mycelium and neurophils [5].

 

Close to 30 years ago, a reproducible mouse model of dermatophytosis has been established by using *Trichophyton quinckeanum* [5]. Among different inbred strains of mouse, BALB/c or BALB/K mice were more susceptible to *T. quinckeanum*. Nakamura and colleagues established a mouse Trichophytin-associated inflammation model of superficial skin mycosis in which immunological and genetic analyses can be performed [6]. To produce their model, mice were sensitized percutaneously by application of Trichophytin, an antigenic extract, on the back traumatized skin on days 0 and 7. On day 21, they were challenged percutaneously by Trichophytin on the right side of each damaged ear. Ear thickness was measured at 0 and 6 h, and 1, 2, 3, 4, and 6 days after challenge. Finally, they concluded that this Trichophyton-associated contact hypersensitivity model may facilitate studies on the defense mechanism against Trichophyton, the development of a treatment strategy for fungal infection appropriate to individual immune conditions, and development of drug discovery.

Sharma and colleagues introduced an immunocompromised mouse model of dermatophytosis that used for studying antidermatophytic potential of some phytomedicines against *T. mentagrophytes* [7]. Briefly, male Swiss albino mice (*Mus musculus*) were first immunosuppresed by subcutaneous injection of estradiol valerate [8]. After 3 days of immunosuppression, flanks of mice were shaved and the exposed area lightly abraded. Hundred microliter of standard inoculums size ($1 \times 10^6$ colony forming units/ml of *T. mentagrophytes*) was applied on the shaved site and was gently rubbed with the flat part of a sterile blade [9]. In this model, first signs of infection were observed on second and third day of inoculation and lesion reached at its maximum at the infected site on eighth and 10th day of inoculation in all animals of immunosuppresed infected animal group and infected animal group without immunosuppression, respectively. Lesion scores started decreasing as a result of spontaneous healing after 20 and 25 days of inoculation, whereas complete spontaneous recovery was observed on 26th and 32th day of inoculation in immunosuppresed group and intact group, respectively. Disease recurrence was recorded in 40% animals of both the groups during the observational period of 6 months.

Dermatophytosis is not considered as an opportunistic infection and frequently infects the integumentary system, causing superficial infections. Rarely, in immunocompromised hosts, the infection can extend into deeper skin layers and internal organs, resulting in invasive dermatophytosis [10]. Recently, Venturini and coworkers proposed a murine model of experimental invasive dermatophytosis [11]. In this model, Swiss mice were subcutaneously injected in the footpad with *T. mentagrophytes* and then were killed at 6, 24 and 48 h and 7, 14 and 30 days after the inoculation. Then, the homogenates of internal organs were cultured to detect the frequencies of fungal dissemination. The laboratory of these authors has also initiated studies using this experimental model to evaluate dermatophytic infection during a hypoinsulinemia-hyperglycemic (HH) state, a model for diabetes mellitus, as this metabolic disease is associated with a high incidence of dermatophytic infection [12]. They reported that HH mice exhibited disseminated dermatophytosis following a delay in the infection outcome [12].

*Neoscytalidium dimidiatum* (*Scytalidium dimidiatum*), as an emerging dematiaceous fungus, is a dematiaceous ascomycete belonging to the family of Botryosphaeriaceae that is known to cause superficial skin lesions and onychomycosis. Ruíz-Cendoya and coworkers have developed two murine models of disseminated infections by *Neoscytalidium dimidiatum*. Immunosuppressed mice were challenged through the lateral tail vein with fungus. *N. dimidiatum* var. dimidiatum was more virulent than the nonpigmented variety, *N. dimidiatum* var. hyalinum [13]. All mice infected with *N. dimidiatum* var. dimidiatum died within 8 days while those infected with *N. dimidiatum* var. hyalinum survived to the end of the experiment. Fungal load in tissue was also higher in animals inoculated with *N. dimidiatum* var. dimidiatum especially in spleens and kidneys.

The mouse models of *tinea corporis* has been reported in an excellent case of grafting guinea pig skin onto congenitally athymic mice [14], and mice [15]. The *in vivo* model using nude mice xenografted with guinea pig skin showed well-grown dermatophytosis on the xenograft but not on nude mouse skin [14]. Infectivity of two strains of human origin, *T. quinckeanum* NCPF309 and T. mentagrophytes MRL 81/889, were evaluated in seven inbred strain mice: BALB/c, AKR, C3H, DBA/2, (CBA×DBA/2)F1, CBA, and C57BL/6 [15]. As a result, variations were noted in susceptibility in different inbred mice strains, and BALB/c mice showed greater susceptibility to the infection from both fungal strains.

#### 2.1.2. The rat models

Rats are not very susceptible to dermatophytosis [16], however rat model of *tinea corporis* has been reported [17, 18]. In this context, *T. mentagrophytes* could be cultured from the skin of nude rats (rnu/rnu) for 90 days and euthymic rats (rnu/+) for 35 days [17] after experimental infection induced by the same strain of *T. mentagrophytes*. The difference in the infection period between nude mice and nude rats was not due to the organism and may involve the different structures of the skin beside different response of immune system. Because involvement of immunity on sustainability of the lesion in nude rats (rnu/rnu) was clear from the difference in the duration of complete healing using euthymic rats (rnu/+). In sum, rats were not considered as animal model of dermatophytosis compared to other conventional laboratory animals.

### 2.1.3. The guinea pig models

The guinea pig model has been used to investigate all aspects of dermatophytosis, including pathogenesis, diagnostics, pharmacotherapeutics and vaccines [19]. Since early studies indicated that guinea pigs could be reliably infected with multiple dermatophytes, including *T. mentagrophytes, M. canis,* and *E. floccosum*, studies have attempted to optimize these protocols [20]. The guinea pig model of infection with both *T. mentagrophytes* and *M. canis* has been characterized.

The guinea pig model has primarily been used to assess topical and systemic treatments for superficial fungal infections. As a classic example, we characterized guinea pig model of various dermatophytosis [21,22]. Lengthily, a strain of *T. verrucosum* was grown on sabouraud dextrose agar (SDA) slants at 37 °C for 1 week. The conidia were scraped from the plates, centrifuged and washed twice in normal saline solution. The suspension was adjusted with the aid of haemocytometer to a concentration of $1.0\times 10^7$conidia/ml. The working solution was prepared fresh in normal saline solution and 0.1 ml was used to inoculate the guinea pigs. The male albino guinea pigs were anaesthetised by intramuscular administration of ketamine and xylazine cocktail and their middle back was clipped and shaved, and a 2.5 cm × 2.5 cm (6.25 $cm^2$) area was abraded with sandpaper. In this regards, guinea pigs are usually shaved with electric clippers, and then the area is abraded prior to inoculation with the aid of pumice stone, sandpaper, hand razor, roughened glass pestle, razor blades, or even repeated application of tape. A suspension (0.1 ml, $1.0 \times 10^7$cells) of *T. verrucosum* conidia was applied to the marked area using a sterile pipette-tip and rubbed thoroughly. Studies have also evaluated the optimal concentrations of *T. mentagrophytes* and *M. canis* for induced infection and found the severity of infection was associated with the inoculum concentration for *T. mentagrophytes* but not *M. canis*. The pharmacotherapeutic formulations were applied topically to the infected area beginning 72 h postinfection once a day and continued for 1 week. At the end of pharmacotherapy, the inoculated areas were compared with negative control animals. In this sense, the infected area on the back of each guinea pig was divided into four equal quadrants. Each quadrant 1.25 cm × 1.25 cm (2.5 $cm^2$) was scored as follows: 0 - no signs of infection, hair was fully re-grown, 1- few slightly erythematous areas on the skin, no scaling, 2 - well-defined redness, swelling with bristling hairs, bald patches, little scaling, 3 - large areas of marked redness, incrustation, little scaling, hair started to re-grow, bald patches, ulcerated in places, 4 - partial damage to the integument, loss of hair, and 5 - extensive damage to the integument and complete loss of hair at the site of infection.

The cumulated scores for quadrants on each animal (maximum possible score per animal was 20) were calculated and used in the clinical assessment of efficacy of the different treatments and control regimens [21]. Accordingly, percent efficacy = 100 - (T × 100／C) where, T = total score of treatment group and C = total score of untreated control. The total score for any group denotes the average clinical score from the different animals in the same group. The severity of dermatophytosis also was numerically scored according to the Ghannoum and coworkers [23] as follows: 0, none, 1, insignificant, 2, slight, 3, moderate and 4, severe. Serial typical photographs have been also taken to show the course of disease and pharmacotherapy (see Figure 1).

In addition to the clinical scores of the lesion that employed as endpoint, microscopic mycology, culture, histopathology, and the hair root invasion test are also considered after any challenges and pharmacotherapeutic regiments [24].

Guinea pigs were used as models of *tinea pedis* [25] and onychomycosis [26]. Briefly, the plantar parts of the hind feet were cleaned with a cotton swab dipped with 80% v/v ethanol. Adhesive tape was dampened with 0.1 mL of the conidial suspension ($1 \times 10^8$ conidia/ml), fixed on to the plantar part of the foot by covering with adhesive elastic tape and allowed to remain for 7 days to develop local infection. Once-a-day topical application of pharmacotherapeutic preparations was commenced on week 2 postinfection and continued for three or four consecutive weeks. Two days after the last treatment, all animals were killed using ether anaesthesia and the skin of the infected sites was excised. The skin blocks yielding fungal growth in SDA plates were regarded as culture-positive, and the infected site with more than one culture-positive skin block was considered fungus-positive. In addition, the intensity of infection was given a score of 10 to zero according to the number of culture-positive skin blocks amongst the ten skin blocks studied.

In addition to, systemic dermatophytosis has been induced in albino guinea pigs [27]. In this sense, albino guinea pigs were inoculated intravenously (i.v.) with various strains of Zoophilic dermatophytes and human isolates of *Trichophyton mentagrophytes* var. granulare. After i.v. inoculation, the fungus was reisolated from skin samples from a considerable number of animals with and without clinical ringworm lesions, and also from lungs, liver, and kidneys. Some strains produced generalized dermatophytosis affecting all parts of the skin and internal organs. *T. mentagrophytes*, selected for further study, was inoculated i.v. in the guinea pig, rabbit, rat, mouse, and chicken. Ringworm lesions occurred in the guinea pig and rabbit; in the mouse, rat, and chicken other organs were involved.

 

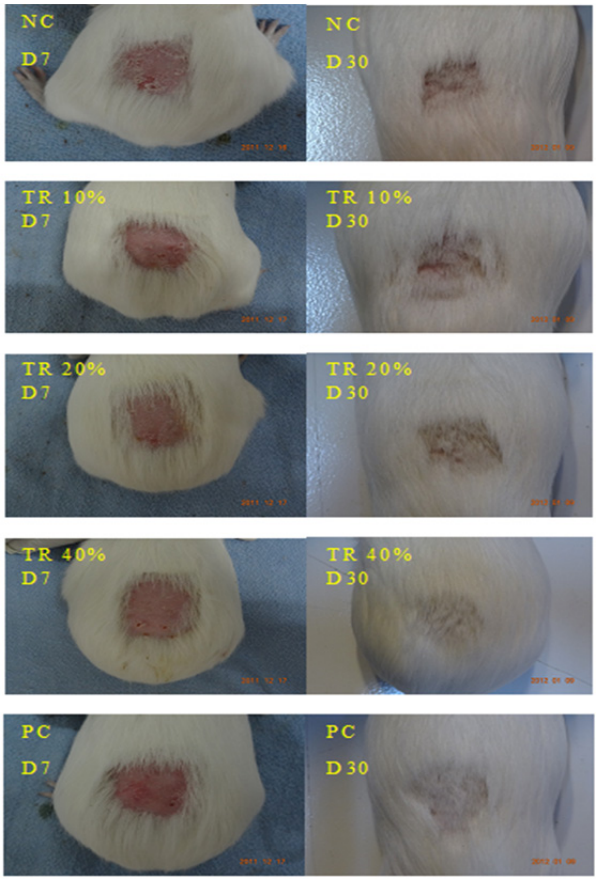


**Fig. 1** Efficacy of aqueous extract of *Tamarix ramosissima* compared with untreated (NC) and terbinafine-treated (PC) controls in the treatment of dermatophytoses caused by *Trichophyton verrucosum* in guinea pigs on one week of treatment (D7) and one month postinfection (D30). TR10%, TR20%, TR40% groups received 0.1 ml of 10, 20 and 40 percent aqueous extract of *Tamarix ramosissima*. Adopted from our recent unpublished work [22].

#### 2.1.4. The rabbit models

Rabbits are physiologically susceptible to dermatophytosis. *T. mentagrophytes* is the most common dermatophytes isolated from rabbits and some researchers consider rabbits as asymptomatic carriers of this organism [16]. Sporadic infections with *M. canis*, *M. gypseum*, *M. audouinii*, *T. verrucosum* and *T. schoenleinii* have been reported in rabbits. Dermatophytic lesions consist of patchy alopecia, broken hairs, erythema, and yellowish crusting over head. These pruritic lesions may spread to the paws, toenail beds and to the rest of the body. Like other animals, dermatophytosis in rabbits is self-limiting.

The natural fungal pathogens of laboratory animals such as rabbits and guinea pigs are mainly dermatophyte species, most commonly *T. mentagrophytes* and also, less frequently *M. gypseum* and *M. canis*. However, the incidences of infection and clinical disease are low in well-managed animal facilities. Young or immunocompromised rabbits are thought to be most susceptible [28]. Dermatophytes infect the epidermis and adnexal structures, including hair follicles and shafts, usually on or around the head, and cause pruritus, patchy alopecia, erythema and crusting. Histopathological changes in the underlying skin occur and these changes could confound histological studies involving the skin.

Faergemann proposed a rabbit-model of pityriasis (tinea) versicolor-like lesions caused by *Pityrosporum orbiculare* (*P. ovale*) [29]. He inoculated on the insides of both ears of rabbits in an area measuring 1 by 1.5 cm. The areas were occluded for 7 days with plastic wrap (1 by 1.5 cm) held in place by Scanpor tape covered with Leukoplast tape. After 7 days, the inoculated areas were investigated clinically, under Wood's light, and microscopically, and skin scrapings were taken with a curette for culturing. The criteria for positive microscopy included round and budding cells and the presence of hyphae. The rabbits were examined at weekly intervals for 3 weeks. Due to spontaneous healing properties of this induced infection like other experimental infections, a prophylactic infection model was thought to be most relevant. This model opens possibilities for screening new antimycotics for their activity against *P. orbiculare*.

There are few reports of the animal model of *tinea unguium*. One study used guinea pigs [30, 31], and the other used rabbits [32]. Shimamura and colleagues [33] introduced a rabbit model of *tinea unguium* useful to detect drug efficacy. In brief, the nails of rabbits that were immunosuppressed with injections of methylprednisolone acetate intramuscularly prior to application of fungal suspension of *T. mentagrophytes* at a site between the lunula and the proximal nail fold. Then nail plates of the hind paw were wrapped together with a gauze patch and finger cot, and 0.5ml of sterile water was injected into the finger cot to prepare suitable media for fungal growth and maintained for 2 weeks with no other intervention. The finger cot and the gauze patch were removed after 2 weeks of exposure, and this condition was maintained during for 0, 2, or 6 weeks that considered as postinfection period. Some of the infected nails became cloudy on gross appearance similar to the human onychomycosis. In this invasive fungal disease, hyphae of *T. mentagrophytes* penetrated the nail plate and even reached the nail bed.

### 2.2. Nonconventional domesticated animal models of dermatophytosis

Small domesticated cats and dogs seem to be potential model of dermatophytosis. However, we are not ethically permitted to translate dermatophytosis in these animals because of the serious zoonotic potential of dermatophytosis. In this regards, over 90% of feline dermatophytosis cases worldwide are caused by *M. canis* [34]. Others are caused by infection with *M. gypseum, T. mentagrophytes, T. quinckeanum, T. verrucosum* or other agents. With the exception of *M. gypseum,* all produce proteolytic and keratolytic enzymes that enable them to utilize keratin as the sole source of nutrition after colonization of the dead, keratinized portion of epidermal tissue (mostly stratum corneum and hairs, sometimes nails). Predisposing factors for feline ringworms include young age (first 2 years of life), immunosuppression (including immunosuppressive treatment), other diseases like feline immunodeficiency disease, nutritional deficits (especially proteins and vitamin A), high temperature and high humidity [34]. Any skin trauma

resulting from increased moisture, injury by ectoparasites or scratches due to pruritus, playing or aggressive behaviour, clipping etc. is important for facilitating infection. In general, poor hygiene is a predisposing factor. In overcrowded feline groups, social stress may play a role. Thus in catteries or shelters infected with *M. canis,* eradication of ringworm may be difficult. In highly controlled laboratory, cats and dogs may use as animal models of dermatophytosis.

Bovine trichophytosis, or ringworm, caused by *T. verrucosum* is one of the most common mycoses in cattle. In the light of the several investigations [35, 36], the prevention of ringworm in cattle by means of vaccination appears possible but the results are as yet uncertain. However, cattle are suitable animal model for producing efficient vaccines against dermatophytosis. For example, Faldyna and colleagues [37] proposed an experimental design to study vaccination against bovine trichophytosis. They induced immunity against trichophytosis by twice intramuscularly injection of a prophylactic dose of the live freeze-dried commercial vaccine with an interval of 13 days. 50 days after revaccination, all calves were challenged epicutaneously by virulent *T. verrucosum* culture to prove the protective immunity induced by the vaccination. Results showed that the vaccinated calves developed a full protection either without clinical skin trichophytic changes or with only minute superficial scales or papullae. Interestingly, all non-vaccinated control calves given the same challenge dose developed clinical trichophytosis showing extensive clinical skin trichophytic lesions persisting for 34 days.

In veterinary medicine, we also need animal model to simplify our open questions. We need animal models of dermatophytosis to simulate ringworms in farm animals because of expense, limiting access to the target animal, the logistics of maintaining an adequate number of the target animals, cost of treatment of induced infection and public health issues of dermatophytoses as very contagious diseases. In this sense, we induced tricophytosis caused by *T. verrucosum*, as a leading cause of bovine dermatophytosis, in male albino guinea pigs [21] based on the methodology mentioned above in 2.1.3 section. Beside its economical impact on leather industry, animal dermatophytosis is responsible for high economical losses especially in cattle farming because of decrease in milk and meat production. Therefore, a huge body of research is requested to find appropriate small or laboratory animals for dermatophytosis in farm animals.

### 2.3. Miscellaneous

In a seminal review, various kinds of dermatophytoses have been reported in exotic animals [16]. Dermatophytosis occured naturally in these animals (hamsters, chinchillas, ferrets, hedgehogs, cockscomb) [16, 38] therefor we can induce dermatophytosis in this animals. More epidemiological and experimental studies are requested to define sylvatic dermatophytosis and pathophysiology of dermatophytosis in exotic animals and find new reliable animal model of dermatophytosis.

## 3. Conclusions and remarks

This chapter shows that our knowledge about all aspects of dermatophytosis is still in its infancy. To response to many open questions of human dermatophytosis, confidential animal models are needed. Most of the methodologies reported regarding human dermatophytosis should be revised and standardized. Present animal models were found to be useful to screen antimycotic agents, however efforts should be focused in particular on developing animal models of antimycotic drug-resistant dermatophytosis especially onychomycosis. The translation of pathophysiology of dermatophytosis needs animal models with high fidelity to human dermatophytosis and more in-depth molecular and cellular biological studies to produce genetically engineered animal models.

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