Antifungal activity of alexidine dihyrochloride in a novel diabetic mouse model of dermatophytosis

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ABSTRACT

- Dermatophytosis is one of the most prevalent fungal infections and a major public health problem worldwide. Recent years have seen a change in the epidemiological patterns of the infecting fungi, corresponding to an alarming rise in the prevalence of the drug recalcitrant dermatophyte infections.
- In patients with diabetes mellitus, dermatophytosis is more severe and recurrent. The potency of promising new antifungal drugs in the pipeline must be expanded to include dermatophytosis.
- The Diabetic mice model was optimized as a simple and robust system for stimulating dermatophytosis in diabetic patients. The outcome of Infection was measured using clinical and mycological parameters.
- Infected mice with fungal lesions were treated with oral and topical formulations of terbinafine or topical administration of FDA approved and repurposed pan antifungal drug Alexidine dihydrochloride (AXD). In this model, AXD was found to be highly effective with outcomes comparable to those of the standard of care drug terbinafine.

INTRODUCTION

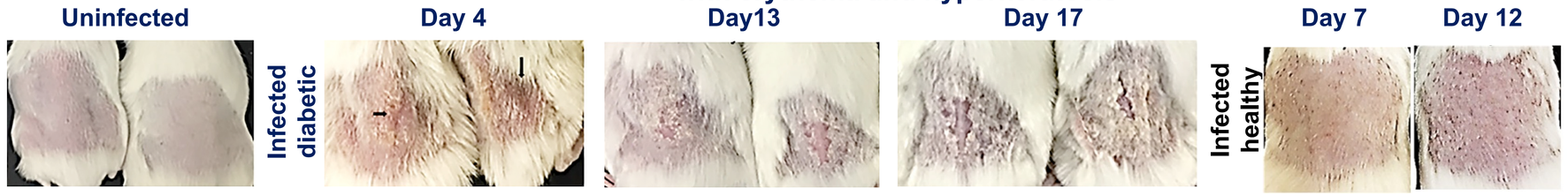
Dermatophytes are the group of fungi that cause superficial infections limited to the stratum corneum of the epidermis or to the hair or nail. *Trichophyton*, *Microporum*, and *Epidermatophyton* are the most common causes of dermatophytosis. Dermatophytes are the foremost cause of cutaneous mycoses worldwide, prevalent in 20%-25% of the global population. Poor glycemic control and obesity are top reasons for higher rates of infection in diabetic patients.

METHODS

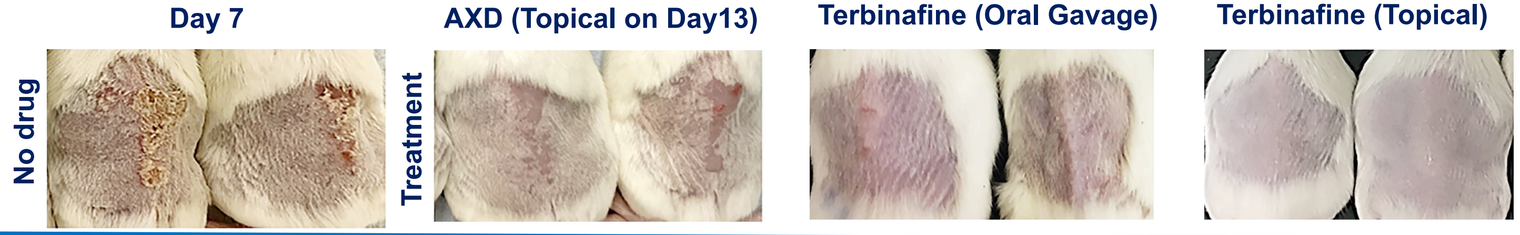
- **Fungal strain and growth conditions:** The dermatophyte strain *Trichophyton mentagrophytes* ATCC 26323 was grown on Sabouraud's agar (0.4g/L cycloheximide and 0.5g/L chloramphenicol); and then on oatmeal agar for conidiation @ 35° C.
- **Diabetes and infection:** Mice were made diabetic with a single dose of streptozotocin 210mg/kg of body weight in 0.2ml of citrate buffer which was administered intraperitoneally. Diabetes was checked using keto-diastix strip.The back of the mice was shaved, abrased with a sand paper and infected topically with 5X10^{7}cells/ml.
- **Treatment.** After 7 day of infection, mice were treated either with terbinafine 75mg/kg by oral gavage, 1% topical terbinafine or AXD topical thermos sensitive gel 20 ug. Treatment was continued once daily for Wilcoxon rank-sum test. A *p* value < 0.05 was considered significant at 6 days.

RESULTS

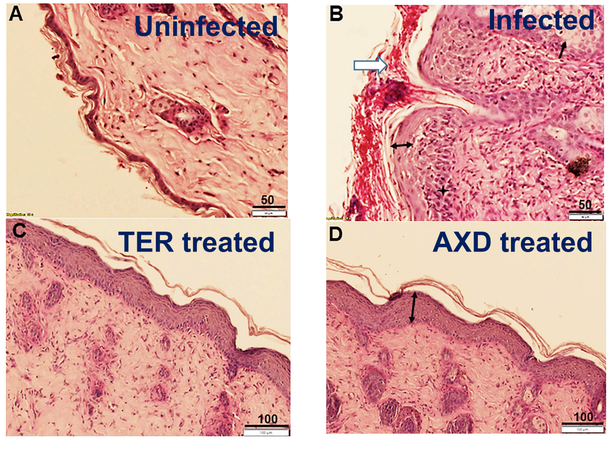
When compared to normal (infected) mice, diabetic mice show severe *T. mentagrophyte* infection with erythema and hyperkeratosis



The new drug Alexidine dihydrochloride (AXD) was as efficacious as terbinafine in clearing the disease



Dense fungal hyphae (B, arrow) showing acanthosis, spongiosis of the epidermis. Fungi clear completely after AXD and TER drug treatment (C,D)



Clinicomycological assessments

Infection in diabetic mice

Days	MICE	Erythema	Hyp. ker	%Culture+
4	20	2.7	0.3	88
7	20	1.85	2.4	100
13	20	0.45	2.8	100
17	20	0.15	2.6	60
21	20	0	1.8	40

3.0 being the max score

Efficacy of AXD and TER

Drugs	% reduced erythema	P value	% mycological efficacy	P value
Vehicle (gel)	0%	X	0	1
AXD(T)	83.33%	0.0003	100%	<0.0001
TER(T)	91.66%	0.0002	100%	<0.0001
TER(O)	87.5%	0.0002	100%	<0.0001

CONCLUSIONS

The Diabetic Mouse model is a robust, clinically relevant system to evaluate efficacy of new antifungal drugs against dermatophytosis

- M., Golim, M. A., et al. (2017)- Gugnani, H. et al. (2020)- Souza et al. (2014)-Chorilli et al (2020).

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