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CORRESPONDENCE

Anti-inflammatory effect of amygdalin analogs following topical administration on the TPA-induced irritant contact dermatitis model in mice

In vitro studies on keratinocytes demonstrate the effect of amygdalin analogs as inflammation modulators, downregulating pro-inflammatory cytokines with the concomitant upregulation of anti-inflammatory ones.[1] They are also effective in reducing psoriatic lesions, as shown in a xenograft transplantation model.[2] However, due to their poor pharmacokinetic profile they cannot be administered systemically. Considering the good skin penetration profile exhibited by their parent compound,[3] we decided to assess their anti-inflammatory efficacy by topical administration in the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced irritant contact dermatitis model in BALB/c mice.[4,5] Accordingly, we tested compound FIB-116 (Figure S1) in a cream formulation at 3%. In addition, dexamethasone at 0.05% in an acetone/olive oil 4:1 mixture (vehicle) was also included in the study, as positive control.

We conducted a randomized controlled trial using 35 male Balb/c mice that were randomized into five different groups. Groups 1 and 2 were used to assess the efficacy of FIB-116 cream vs. placebo on the TPA model, respectively; groups 3 and 4 were used to assess the efficacy of dexamethasone solution vs. vehicle (control) on the TPA model, respectively; group 5 (blank) only received vehicle. Dermatitis was induced by topical ear administration of 12.5 μl of a 0.03% TPA solution on days 0, 2, 4, 7 and 9 (groups 1–4). During the treatment period (days 3–9), animals received daily topical administrations of the diverse treatments. Mice in the blank group were treated with acetone during the induction period (days 0–2), followed by vehicle administration during the treatment period (days 3–9). Diverse parameters were collected during the experimental procedure including clinical signs, body weight, ear thickness and ear disc weight.

Repeated topical application of TPA in the ear induced a severe inflammatory reaction characterized by erythema, dryness/scaling, erosions/ulcerations with bleeding and crust formation, induration and ear thickness increase (group 4 (control) vs group 5 (blank), Figure S2). Pruritic behaviours (e.g. scratching, head shacking) were also detected. Mice in group 2 (placebo) exhibited similar clinical signs as animals in group 4 (control), although the intensity of the inflammatory reaction to TPA was higher, as reflected by increased proportion of animals showing ear pinnae necrosis and tissue loss. Mice in group 1 (FIB-116) exhibited similar skin lesions to those described in animals from groups 2 (placebo) and 4 (control), but with clinical symptoms generally less severe, whereas animals in group 3 (dexamethasone) exhibited mild to moderate dermatitis clinical symptoms (slight erythema and dryness, small erosions on the edges of the ear).

Body weight did not experience significant changes during dermatitis progression (groups 2 (placebo) and 4 (control); Figure 1, panel A). In contrast, mice from groups 1(FIB-116) and 3 (dexamethasone) exhibited a significant reduction of body weight, suggesting both compounds presented some rate of systemic absorption.

TPA administration produced a progressive and significant increase in ear thickness in mice from groups 2 (placebo) and 4 (control) (Figure 1, panels B and C). FIB-116 cream treatment significantly attenuated the progressive increase in ear thickness induced by TPA. Moreover, dexamethasone was highly effective at preventing TPA-induced ear thickness increase.

TPA administration also produced an approximately fourfold increase in ear disc weight (groups 2 (placebo) and 4 (control) vs. group 5 (blank); Figure 1, panel D). FIB-116 cream treatment produced a significant reduction of TPA-induced ear disc weight increase as compared to groups 2 (placebo) and 4 (control), whereas dexamethasone completely prevented TPA-induced ear disc weight increase.

Present results demonstrate a significant moderate anti-inflammatory efficacy of topically administered 3% FIB-116 cream formulation on the TPA-induced irritant contact dermatitis model compared with the positive control dexamethasone, providing encouraging results to undertake further studies with more sophisticated animal models in the dermatology field.

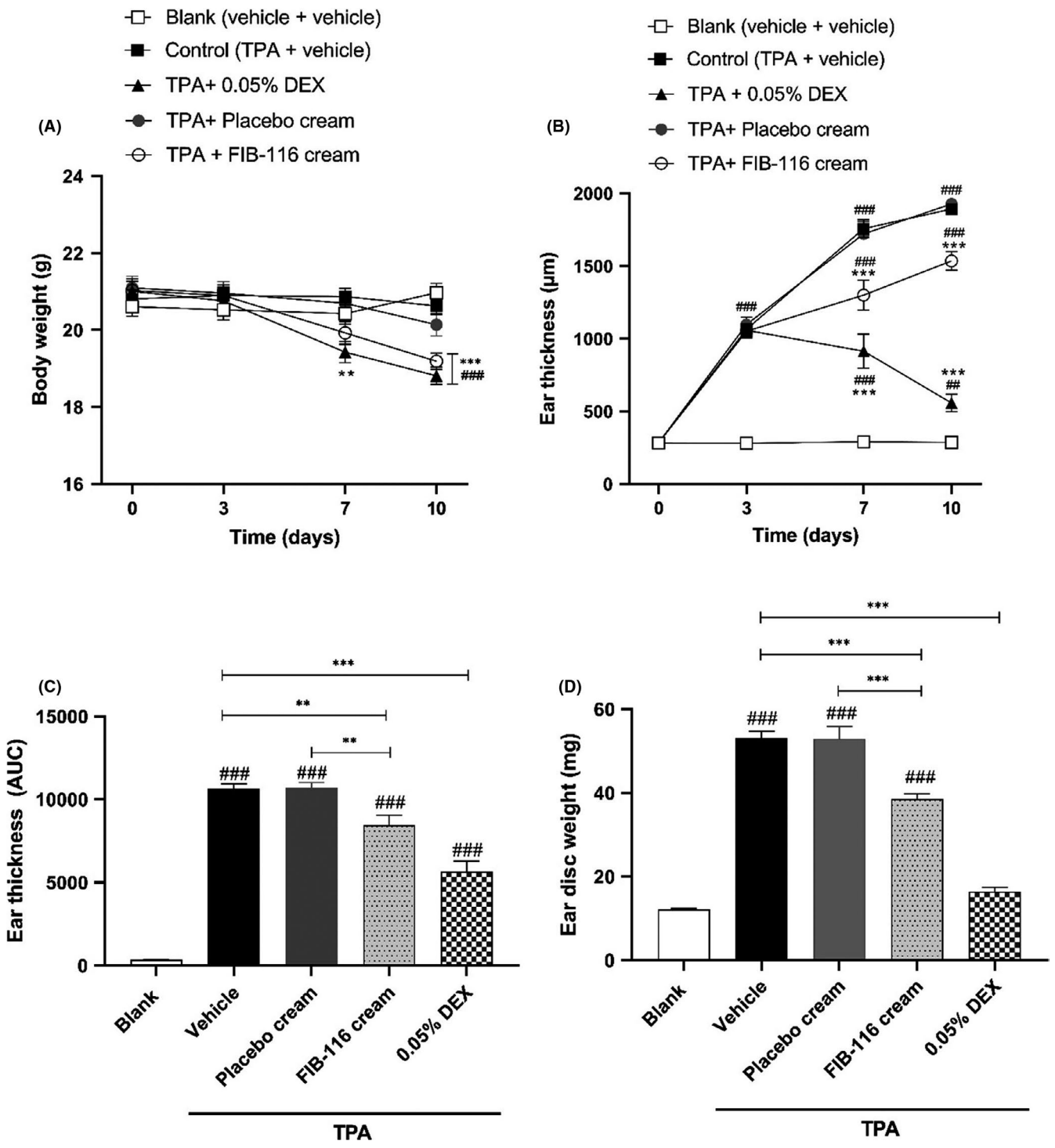

FIGURE 1 Panels A-D. Attenuation of TPA-induced irritant contact dermatitis in mice by topical application of FIB-116 cream. Dermatitis was induced by topical application of TPA to the right ear of Balb/c mice on days 0, 2, 4, 7 and 9. Placebo cream (20 mg), 3% FIB-116 cream (20 mg), 0.05% dexamethasone (25 µl) or vehicle (25 µl) were topically administered from day 3 to 9. Animals in the blank group received exclusively vehicle. Body weight (A) was measured throughout the study as an indicator of general well-being condition. Skin inflammation was assessed by measuring ear thickness (B, C) and ear disc weight (D). Data are expressed as mean ± SEM ($n = 7$). $^{**}p < 0.01$, $^{***}p < 0.001$ vs. control group. $\#\#p < 0.01$, $\#\#\#p < 0.001$ vs. blank group (A and B, two-way ANOVA; C and D, one-way ANOVA)

KEYWORDS

amygdalin analogs, skin Inflammation, TPA-induced dermatitis model

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LAG carried out the experimental design; MP carried out experiments; JJP wrote the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1. Individual Animal Body Weight.
Table S2. Individual Ear Thickness Data.
Table S3. Individual Ear Weight Data.
Figure S1. Chemical structure of the amygdalin analog FIB-116.
Figure S2. TPA-induced irritant dermatitis model in mice. Representative photographs of the right ear from Balb/c mice challenged with TPA on days 0, 2, 4, 7 and 9 and treated with 3% FIB-116 cream (group 1), placebo cream (group 2), 0.05% dexamethasone (group 3) or vehicle (control, group 4). Animals in the blank group received exclusively vehicle.

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