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ORIGINAL ARTICLE

Asiatic acid exerts an anti-psoriatic effect in the imiquimod-induced psoriasis model in mice

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ABSTRACT

Background: Psoriasis is a common skin disorder related to inflammation and immune response. However, many treatment modalities are present in the clinics, and drug conformity halts chronic treatment. Therefore, novel treatment options are still needed. In this study, the possible protective effect of asiatic acid is one of the active compounds present in *Centella Asiatica*, was investigated in the imiquimod-induced psoriasis murine model.

Methods: Imiquimod (62.5 mg) was administered dorsal skin of the mice for 6 days. Animals were co-treated with low-dose (25 mg/kg, p.o.) and high-dose (100 mg/kg, p.o.) asiatic acid. The dorsal skin of the animals was daily scored for erythema, thickness, and scaling. At the end of the treatments, serum levels of IL-17A and IL-23 were determined by ELISA. Additionally, the dorsal skins of animals were histopathologically evaluated.

Results: Asiatic acid (high-dose) prevented imiquimod-induced skin lesions and protected dermal integrity in addition decreasing mast cell infiltration due to the imiquimod. Furthermore, asiatic acid (high-dose) suppressed the imiquimod-induced increase in serum levels of IL-17A and IL-23.

Conclusion: These results indicate that asiatic acid showed an anti-psoriatic effect in the imiquimod-induced psoriasis model *via* mediating IL-17A and IL-23 pathways. Because wound healing properties of asiatic acid are described, further investigations should be carried out to understand deeper mechanisms and possible use in dermatological pathologies such as psoriasis.

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Introduction

Psoriasis is a debilitating chronic inflammatory disorder which is affecting nearly 10% of the world population [1]. Although several risk factors are related to disease tendency and prevalence, epidemiological studies failed to show a significant relationship between sex, age, gender, or other factors. Besides ongoing inflammation, itch in psoriasis is nearly 80%, and this makes many patients consider itch to be the most bothersome symptom [2]. Psoriasis is characterized by sharply demarcated, red, scaly plaques on elbows, knees, scalp, and lumbar areas. Scaling, itching, erythema, and even bleeding are frequently seen in psoriasis patients [3]. Several lines of evidence indicate that psoriasis is the result of cell-mediated adaptive immune system disease [4]. Systemic and transdermal corticosteroids, vitamin D3 analogs, calcineurin inhibitors are used for mild psoriasis currently. Additionally, phototherapy, methotrexate, cyclosporin, and acitretin are extensively used in severe psoriasis while the frequently seen systemic side effects.

Imiquimod-induced mice model of psoriasis was described and extensively used to demonstrate possible anti-psoriatic compounds [5]. Additionally, topical 5% imiquimod application to mice skin results with plaque psoriasis and IL-17/23 response very similar to humans, and it is a helpful tool to investigate drug candidates. Several mechanisms are suggested as responsible for disease progression [6]. However, TH17 cytokine response emerged one step further in these mechanisms because TH17 is strongly related to other autoimmune diseases [7]. One of the cytokines released from TH17, IL-17A, is strongly associated with psoriasis [8]. IL-23 is mainly produced by macrophages and dendritic cells and is frequently found in psoriatic skin lesions [9]. Therefore, in the context of psoriasis, treatment compounds that could decrease levels of IL-17A and IL-23 could show a protective effect against psoriasis.

Asiatic acid is an aglycone of ursane type of pentacyclic triterpenoids and is abundantly present in many edible plants. Asiatic acid is known to possess potent anti-inflammatory and wound healing abilities [10]. Additionally, regulatory effects on apoptosis make the way to investigate effects of asiatic acid in several chronic diseases such as neurodegeneration, cancer, and hypertension [11]. Interaction between asiatic acid and different enzymes and cytokines has already been shown. Additionally, owing to favorable pharmacokinetic properties, asiatic acid is accepted as adjuvant and

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currently for the treatments of various chronic diseases [12]. Although effects of Asiatic acid on different systems and diseases were investigated, knowledge about the effects of Asiatic acid on psoriasis is still missing. Therefore, this study aimed to show a possible protective effect of asiatic acid on the imiquimod-induced psoriasis model. Based on the available anti-inflammatory and wound healing properties of asiatic acid, our results will provide proof for further investigation about the possible use of Asiatic acid for human health.

Material and methods

Animals and chemicals

Twenty-eight male Balb/C mice (25–32 g, 8–10 week old) were procured from Ondokuz Mayıs University Vivarium. Ethical approval was obtained from Ondokuz Mayıs University Experimental Ethical Committee (2021/11). Animals were maintained 4–5 per cage under standard conditions ($22^{\circ}C \pm 0.5$, 55% humidity, and 12/12 day and night cycle) and fed *ad libitum*. All drug treatments and experiments were employed between 10 and 12 am each day for 6 days. All efforts were made to reduce animal suffering and reported according to the ARRIVE guidelines [13]. The number of animals was determined by power analysis to observe the effects with 95% power. The analysis was performed with G-power. Asiatic acid and vaseline were purchased from Sigma Aldrich (Missouri, USA). Aldaraâ was obtained from a local pharmacy. Asiatic acid was freshly dissolved in PEG400 at the days of the treatment period. The asiatic acid dose was selected according to the previous studies [14,15].

Imiquimod-induced psoriasis model and evaluation

Animals were randomly divided into four equal groups. The back skin and ears of animals were depilated 2 days before the treatment. Psoriasis was induced by daily imiquimod treatment Aldara (containing 5% imiquimod) consecutively for 6 days [5]. The back skin and ears of the control group were treated with vaseline. Imiquimod (IMI, 62.5 mg) was applied back skin and ears of the IMI and low dose (LD, 25 mg/kg, p.o.) and high dose (HD, 100 mg/kg, p.o.) asiatic acid groups once a day for 6 days. Animals were observed daily for the daily assessment of the psoriasis index. Each animal was placed to the separate cages to avoid skin-mouse contact interaction. Disease severity was evaluated with a scoring system considering scaling, erythema, and skin thickness, like the human Psoriasis Area and Severity Index, but not taking the area into account because the experimenter defines it. Additionally, cumulative scores were generated from these parameters. Erythema and scaling were scored from 0 to 4, with 0 indicating no severity and 4 indicating high severity. The thickness of the skin was scored based on the increase in the thickness compared with day 1 (1 for 20–40%, 2 for 40–60%, 3 for 60–80%, and 4 for >80%). Additionally, because ear thickness is used to indicate the extent of epidermal proliferation and inflammation, thickness measurements were performed through the experimental period.

Biochemical analysis

Serum levels of IL-17a and IL-23 were evaluated by ELISA. Just before the dorsal skin isolation, animals have sacrificed with high dose ketamine:xylazine (100:12.5 mg/kg, i.p.). Blood was collected and centrifuged for serum analysis. IL-17a (201-11-0117, Sunred, Wuhan, China) and IL-23 (201-11-0126, Sunred, Wuhan, China) levels were determined by commercially available ELISA kits strictly following the manufacturer's instructions.

Histology

After scarification, the dorsal skins of the animals were carefully removed and fixated in the 4% paraformaldehyde solution. Following routine tissue tracking, all samples were embedded in paraffin or OCT compound and sectioned 5–6 μm thickness with a rotary microtome (Leica, Wetzlar, Germany). Sections were dried overnight and washed with tap water before staining. Samples were stained with hematoxylin-eosin and 0.05% toluidine blue solution (pH 4.1). Following staining samples were washed and subjected for visualization. Sections were acquired in the same orientation under a microscope and mast cells were counted as previously described [16]. At least six fields of view were blindly selected, and average of these fields was used as the mast cell counts for comparison. All samples were observed under a microscope using a digital camera system.

Statistical analysis

All experimental data were analyzed with SPSS v21.0 (Illinois, US). Data distribution was assessed with Shapiro-Wilk's test. Differences between experimental groups were evaluated with one-way ANOVA and Kruskal-Wallis tests. Multiple comparisons were employed by Mann-Whitney U and Tukey's tests. p Values $<.05$ were considered significant.

Results

Asiatic acid alleviated imiquimod-induced psoriasis

Psoriatic behavior assessed with evaluating erythema, scaling, thickness, and cumulative scores. Our results demonstrate that IMI caused significant increase in erythema (2.41 ± 1.39, Figure 1(A)), scaling (1.62 ± 1.53, Figure 1(B)), thickness (1.38 ± 1.62, Figure 1(C)) and cumulative (5.02 ± 4.46, Figure 1(D)) scores compared to control (0.0 ± 0.0, Figure 1), as expected. Low dose treatment of asiatic acid did not show any significant effect on erythema (2.12 ± 1.43, Figure 1(A)), scaling (1.36 ± 1.46, Figure 1(B)), thickness (1.38 ± 1.62, Figure 1(C)) and cumulative (4.88 ± 4.53, Figure 1(D)) compared to IMI ($p > .05$, Figure 1). In contrast, Asiatic acid at the high dose significantly prevented IMI-induced increase in erythema (1.17 ± 0.88, Figure 1(A)), (0.90 ± 0.87, Figure 1(B)),

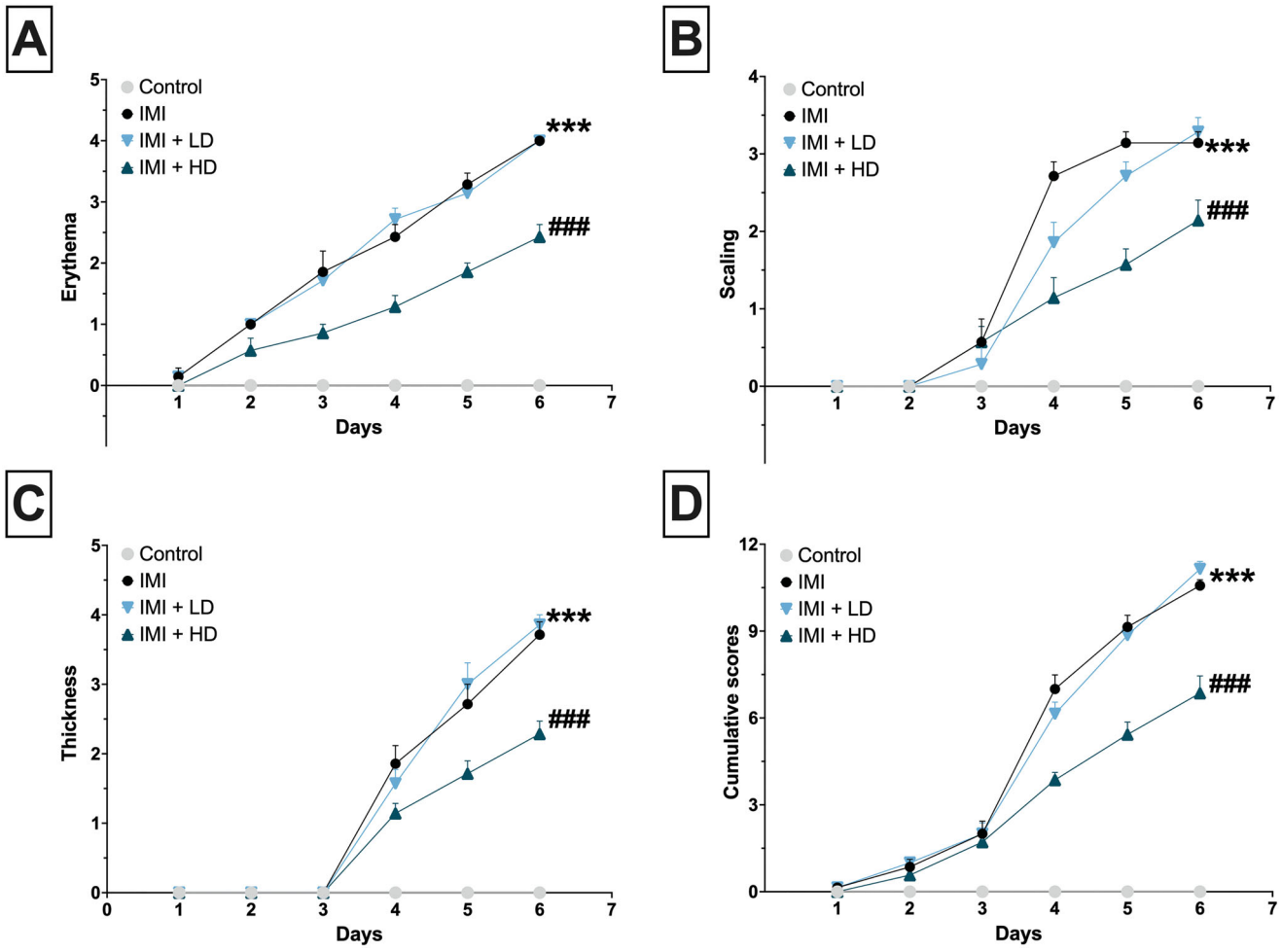


Figure 1. Erythema (A), scaling (B), thickness (C), and cumulative scores (D) of all experimental groups for 6 days. Imiquimod-induced increase in all parameters was prevented by high-dose asiatic acid treatment. Data expressed as mean ± SEM. Each group had eight animals. ***$p < .001$ versus control, ###$p < .001$ versus imiquimod.

(0.85 ± 1.01, Figure 1(C)), (3.07 ± 2.76, Figure 1(D)) compared to control ($p < .001$, Figure 1).

Imiquimod-induced increase of IL-17a and IL-23 was inhibited by asiatic acid treatment

Serum levels of IL-17a and IL-23 were evaluated by ELISA. Imiquimod significantly increased serum levels of IL-17a (230.0 ± 13.0, Figure 2(A)) and IL-23 (611 ± 36.3, Figure 2(B)) compared to control (61.8 ± 5.37 and 186.0 ± 16.0, $p < .001$, respectively, as expected, Figure 2). Similar to behavioral results, low dose asiatic acid treatment did not affect IL-17a (235 ± 19.8, Figure 2(A)) and IL-23 (676.0 ± 39.2, Figure 2(B)) levels significantly ($p > .05$, Figure 2). However, the high dose asiatic acid treatment significantly suppressed IMI-induced increase in IL-17a (145 ± 9.09, Figure 2(A)) and IL-23 (320.0 ± 31.5, Figure 2(B)) levels compared to IMI ($p < .001$, Figure 2).

Asiatic acid improved psoriasis-like skin lesions and

Histopathological analysis was performed on dorsal skin with hematoxylin-eosin staining. IMI treated dorsal skin was found to be in line with the phenotypical observations and behavioral scores. H&E staining demonstrated that IMI caused significantly increased acanthosis, hyperkeratosis of the epidermis (Figure 3(A), ii). Although low dose asiatic acid treatment did not significantly affect dorsal skin structure (Figure 3(B), iii), high dose asiatic acid treatment significantly alleviated IMI-induced hyperplasia of epidermal and subcutaneous tissue with minimal inflammatory reaction (Figure 3(C), iv). Mast cell counts were investigated and found that imiquimod caused significant increase in the counts (533.50 ± 14.20) compared to the control (219.30 ± 76.94, Figure 3(D), $p = .004$). However low dose of asiatic acid (502.70 ± 30.83) did not affect mast cell count significantly (Figure 3(D), $p > .05$), asiatic acid treatment at the high dose (326.30 ± 22.54) significantly suppressed imiquimod-induced increase in mast cell count (Figure 3(D), $p = .040$).

Discussion

Our results demonstrated that asiatic acid suppressed imiquimod-induced psoriasis severity. The asiatic acid treatment prevented the imiquimod-induced increase in skin parameters and protected skin integrity. Additionally, asiatic acid also inhibited imiquimod-induced IL-17A and IL-23 increase, which are well-known mediators of psoriasis. Therefore, our

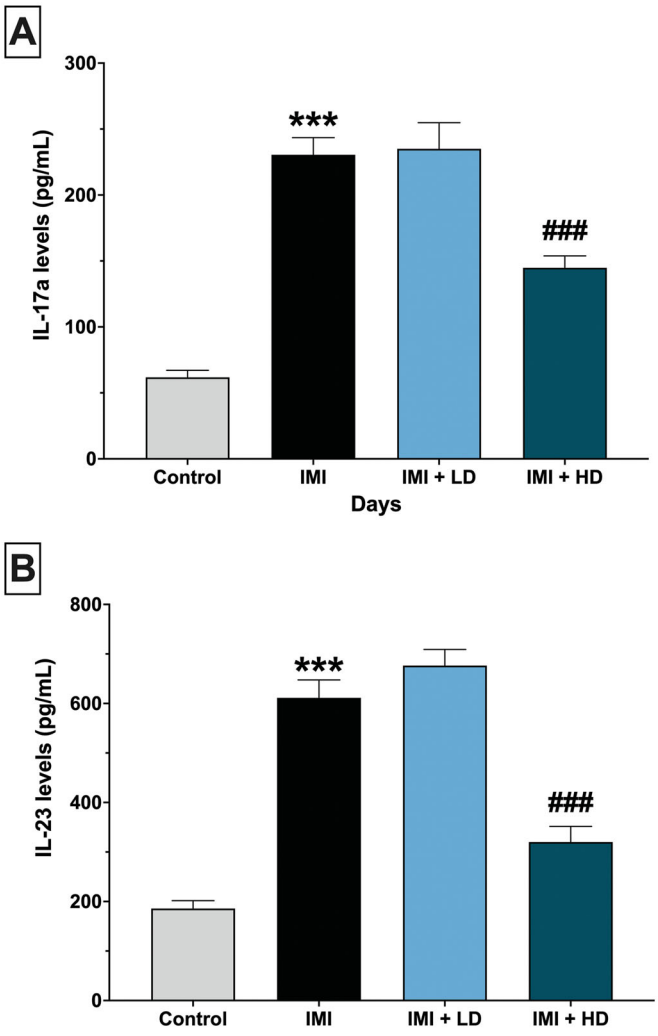
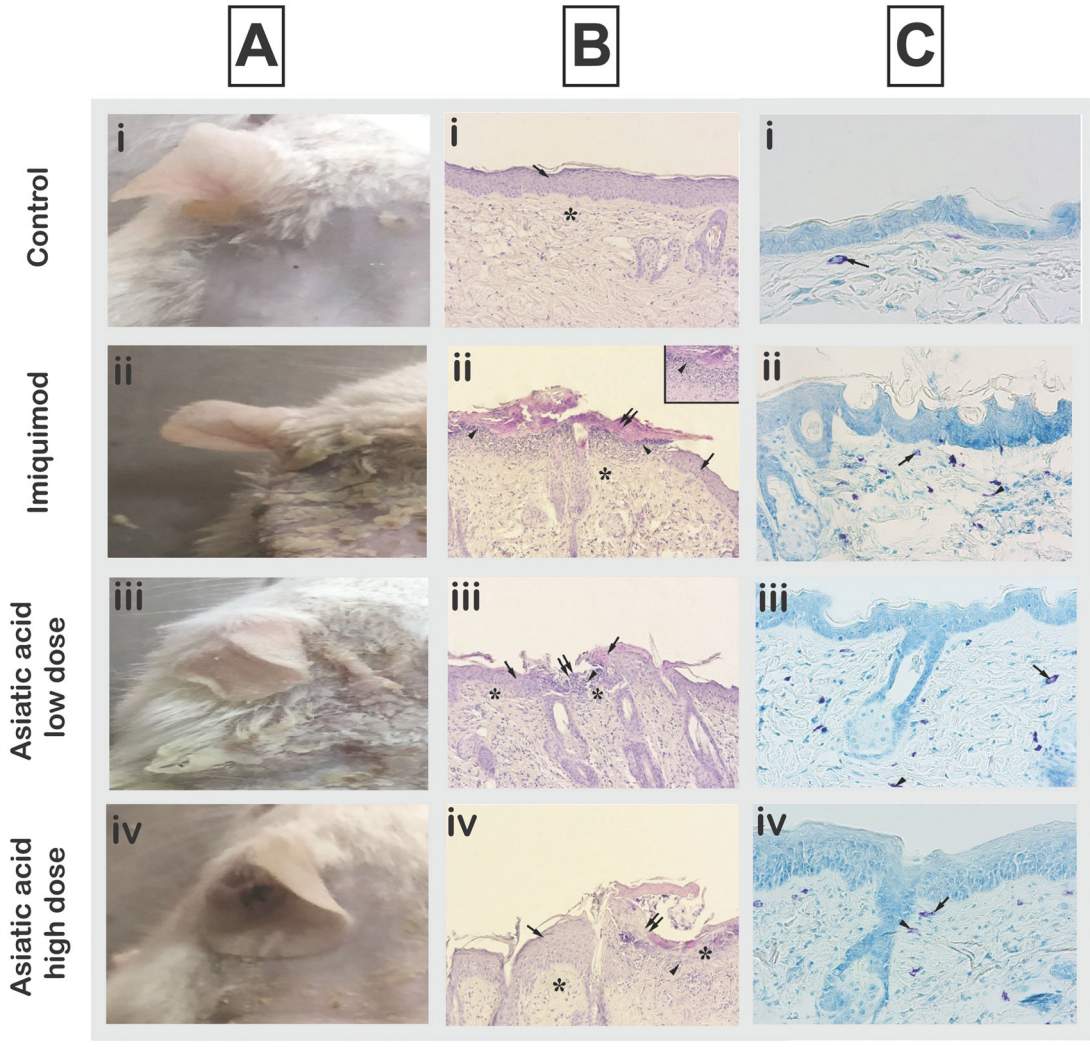


Figure 2. IL-17A (A) and IL-23 (B) levels were determined by ELISA. Imiquimod caused a significant increase in both IL-17A (A) and IL-23 (B) levels. Although low dose asiatic acid treatment did not affect these cytokines, high dose asiatic acid treatment inhibited imiquimod-induced increase. Data expressed as mean ± SEM. Each group had eight animals. $^{***}p < .001$ versus control, $^{###}p < .001$ versus imiquimod.

results indicate that asiatic acid ameliorated imiquimod-induced psoriasis *via* inhibiting IL-17A and IL-23 response.

Imiquimod-induced psoriasis is a frequently used model to mimic psoriasis pathology in murine. Imiquimod is a toll-like receptor-7/8 agonist and is currently used to treat actinic keratosis, genital warts, and superficial basal cell carcinoma [17]. Recent studies demonstrated that imiquimod mimics psoriasis-like dermatitis by activating IL-23/IL-17 pathway [18]. Imiquimod-induced psoriasis model is accepted as the closest murine model that imitates human plaque-type psoriasis with inflammatory infiltration, redness, thickening, and skin scaling. Therefore, imiquimod is a valuable pharmacological tool to investigate compounds that might protect against psoriasis. In this study, we used the imiquimod-induced psoriasis model due to the properties mentioned above. In line with previous studies, imiquimod caused psoriasis-like dermatitis and increased serum levels of IL-17A and IL-23, which indicates its successful model development according to the previous studies [19]. However, several treatment options present in the clinics, their serious side effects and intolerance because of long-term treatment deter their use and show the urgent need for novel treatment options with fewer side effects. So, compounds derived from natural sources are accepted as ideal candidates. Therefore, we investigated the effect of asiatic acid, a well-known compound present in the *Centella Asiatica*. The recent works that showed wound healing and anti-inflammatory properties of *Centella Asiatica* and its ingredients led us to think that asiatic acid might be an effective natural compound to alleviate psoriasis pathology [20,21].

In our study, asiatic acid noticeably improved skin integrity and improved skin scaling at higher doses. Increase in the number of infiltrated mast cells is well-known inflammatory reaction in psoriasis [16]. Because contribution mast cells to pruritus in psoriasis is accepted as predominant in atopic dermatitis also [22]. Therefore, we investigated mast cell count and dorsal skin tissue integrity. Additionally, we also looked for the ear thickness as a gross pathological indicator to understand ongoing epidermal proliferation and inflammation. Our results demonstrated that asiatic acid prevented psoriasis-induced mast cell infiltration at the high treatment dose. Increase in ear thickness to the imiquimod was also alleviated by high dose asiatic acid treatment. It has already been demonstrated that Th17 and IL-17A are involved in many cellular processes and inflammatory diseases [23]. This Th17 response is maintained by IL-23, which is a crucial cytokine in murine and humans [24]. Intradermal administration of IL-23 stimulated keratinocyte proliferation and epidermal hyperplasia, which play a role in psoriasis-like dermatitis [21]. Because IL-17A and IL-23 showed to be increased in serum levels of psoriatic patients, we also investigated the possible effect of asiatic acid on these cytokines. Our results indicated that asiatic acid prevented imiquimod-induced IL-17A and IL-23 response, which we believe primary mechanism behind the ameliorative effect on psoriasis-like skin dermatitis. TNF-alpha stimulation and STAT3 expression are accepted as significant mediators behind IL-17A and IL-23 response [25]. Although it is one of our limitations which we were not able to investigate changes in TNF and STAT expression. Both proteins are related with the cellular and systemic inflammatory response and their expression on protein and mRNA levels are widely used to investigate mechanisms behind inflammatory diseases like in our case, psoriasis [26]. Especially, demonstration of changes in the gene expression will also give useful information about effect of asiatic acid treatment on the cellular level which will also contribute to understand anti-psoriatic effect of asiatic acid more deeply. But as mentioned above, we were unable to investigate possible changes in the gene expression which should be investigated in the further studies. Current knowledge about asiatic acid indicates that asiatic acid potently represses TNF and STAT expression, which is also one of the claimed anti-inflammatory mechanisms [15]. So, it led us to think that asiatic acid suppressed TNF and STAT expression induced by imiquimod treatment, and that is the mechanism behind inhibited IL-17A and IL-23 levels. Thus, our results are in line



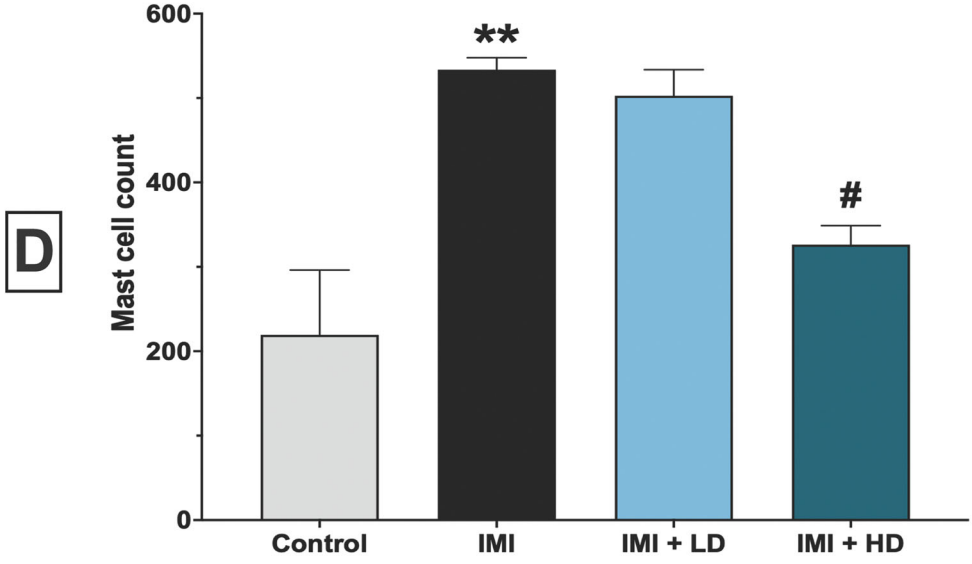


Figure 3. Illustration of left hair and part of the dorsal skins of animals from each group (A). H&E staining was performed to evaluate tissue integrity (B) and toluidine blue staining was also demonstrated (C). Imiquimod causes flaky crust, acanthosis, and hyperkeratosis in the epidermis in dorsal skin tissue (A). Intact epithelia (arrow) and steady reticular layer of dermis in connective tissue (asterisk) in control group (i,iv). In addition to large areas of damaged epithelium (double arrows) that have lost their integral structure in a part of the epidermis, undamaged epithelial tissue in a small area (arrow), inflammatory cell condensation in the reticular layer of the dermis (star) (arrowhead) in imiquimod group (i,iv). In a small part of the epidermis, undamaged epithelial tissue (arrow) in a large area, in addition to areas of epithelium that have lost their integral structure (double arrow), a small number of inflammatory cells (arrowhead) in the reticular layer of the dermis (asterisk) in low dose asiatic acid treatment group (i,iv). Additionally, areas of damaged epithelium (double arrow) as well as undamaged epithelial tissue in a large area (arrow), a small number of inflammatory cells (arrowhead) in the reticular layer of the dermis (asterisk) and reduced number of granular (arrow) and degranulated mast cells (arrowhead) in the dermis in high dose asiatic acid treatment group (i,iv). For all images A: Staining hematoxylin-eosin with $\times$100 microscope magnification; B: Staining toluidine blue with $\times$200 microscope magnification. Data expressed as mean $\pm$ SEM. Each group had eight animals. $^{**}p < .01$ versus control, $\#p < .05$ versus imiquimod.

with previous studies that asiatic acid suppressed TNF and cytokine response *in vivo*.

In conclusion, as far as we have known, this is the first study indicating the anti-psoriatic effect of asiatic acid. Nevertheless, further studies are needed to understand better the mechanism of action and possible candidacy as a treatment option.

Disclosure statement

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