# Immunomodulatory and Anti-psoriatic Effects of Herbal Formula SC-E1 on Imiquimod-induced Psoriasis in Mice

**Ju-Hee Lee**
  Dongguk University College of Oriental Medicine

**Jung Yun Ahn**
  Dongguk University College of Oriental Medicine

**Deog-Bon Koo**
  Daegu University

**Chi-Yeon Lim**
  Dongguk University College of Medicine

**Chang-Hyun Kim** ( ✉ ctlkim@hanmail.net )
  Dongguk University College of Medicine

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Research

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# Abstract

**Background:** Psoriasis is a chronic and relapsing inflammatory autoimmune skin disease. We recently reported that SC-E1 has various beneficial biological effects, including anti-inflammatory activity in an *in vitro* experimental study. Therefore, SC-E1 has been expected as complementary and alternative medicines for various inflammatory autoimmune skin diseases, including psoriasis. In this study, we investigated the potential anti-psoriatic effect of SC-E1 using an imiquimod (IMQ)-induced skin inflammation in mice and explored the mechanism underlying those actions.

**Methods:** Psoriatic dermatitis was induced by repeated challenges with IMQ on the backs of C57BL/6 mice. SC-E1 (250 mg/kg, 500 mg/kg, and 1000 mg/kg) was administered to the mice orally once a day by oral gavage needle for 5 days before and together with IMQ application for another 7 days (totally 12 days of treatment). The anti-psoriatic effects of SC-E1 were evaluated by dermatitis score, skin histology, and immunological parameters. In addition, the mechanisms responsible for the immunomodulatory effect of SC-E1 were examined using p38 MAPK, IκBα, and NF-κB.

**Results:** We found that SC-E1 (500 mg/kg) or SC-E1 (1000 mg/kg) pretreatment ameliorated the development of IMQ-induced skin inflammation in mice. Histological analysis revealed a reduction of epidermal thickening, hyperkeratosis, and inflammatory cell infiltration in SC-E1 (500 mg/kg) or SC-E1 (1000 mg/kg) pretreatment. Moreover, SC-E1 (500 mg/kg) or SC-E1 (1000 mg/kg) pretreatment effectively attenuated production of Th1 cytokines (TNF-a, IFN-g) and Th17 cytokines (IL-17A and IL-23) in the serum and dorsal skin induced by IMQ in mice. SC-E1 (500 mg/kg) or SC-E1 (1000 mg/kg) pretreatment also inhibited splenomegaly. In addition, SC-E1 inhibited the expression of inflammatory modulators, such as p38 MAPK, IκBα, and NF-κB in the skin of mice induced by IMQ.

**Conclusion:** Our present study demonstrated that the immunomodulatory mechanism underlying the anti-psoriatic effect of SC-E1 on IMQ-induced in mice may be attributed to the inhibition of production of various systemic proinflammatory mediators via a mechanism that may involve the inhibition of MAPK and NF-κB signaling pathway. Based on the results we suggest that SC-E1 could be considered as an anti-psoriatic agent for the prevention or treatment of inflammatory autoimmune skin diseases including psoriasis.

# Background

Psoriasis is a chronic and relapsing inflammatory autoimmune dermatitis characterized by erythema, scaling, and thickening due to hyperproliferation and abnormal differentiation of epidermal keratinocytes with inflammatory infiltration of leukocytes in the skin [1,2]. However, the underlying pathogenic mechanisms of psoriasis have not been fully understood. Several recent reports have demonstrated the T helper 17 (Th17) cells and Th17-inducing proinflammatory cytokines such as interleukin (IL)-17A, IL-22, and IL-23, were detected in the serum and skin lesions of patients with psoriasis [3,4]. In addition, proinflammatory cytokines, including IL-12, necrosis factor (TNF)-a, and interferon (IFN)-a induced by Th1

cells mediate the chronic symptoms of psoriasis have been recent reports [5]. Thus, Th1 and Th17 immune response and their proinflammatory cytokines are important mediators in the

pathogenesis of immune-mediated inflammatory systemic disease, including psoriasis.

Furthermore, the activation of nuclear factor kappa B (NF-kB) and mitogen-activated protein kinases (MAPK) signaling regulates various proinflammatory cytokines, and it is a crucial proinflammatory modulators in the pathogenesis of inflammatory autoimmune skin disease [6,7].

Although the systemic or topical medication of corticosteroid and calcineurin inhibitors has represented the mainstay of anti-inflammatory and immunosuppressive therapy for psoriasis, the use of such agents can be hampered by long-term toxicity and inadequate response [8,9]. Therefore, complementary and alternative therapeutic strategies that are more efficacious and safer need to be identified. Some studies have suggested that natural herbs or oriental herbal medicines present anti-inflammatory and anti-allergic effects in various immune system-mediated disease models, including atopic dermatitis (AD) and psoriasis [10,11]. We recently reported that SC-E1, which is a novel herbal formula consisting of five oriental medicinal herbs, has various beneficial biological effects, including anti-oxidant and anti-inflammatory activity in an *in vitro* experimental study [12]. However, no research is available on the role of SC-E1 on imiquimod (IMQ)-induced psoriasis in mice.

In this study, based on above mentioned effects of SC-E1, we investigated SC-E1 pretreatment has potential anti-psoriatic effects on IMQ-induced skin inflammation in mice, a recently recognized murine model of psoriasis [13] and further explored its possible mechanisms of action.

# Materials And Methods

# Animals

Eight-week-old female C57BL/6 mice were purchased from Orient Bio (Seongnam, Korea). The mice were adapted for one week before the start of experiments. During the experiment, animals were maintained under specific pathogen-free conditions in the animal facilities at Dongguk University School of Medicine. The animal care and use committee of the research institute at Dongguk University Hospital approved all studies used in this investigation.

# Chemicals and reagents

Primary antibodies against p38 MAPK, p-p38 MAPK, p-IκBα, p-NF-κB p65, and β-actin and horseradish peroxidase-linked anti-rabbit IgG secondary antibody were supplied by Cell Signaling Technology (Danvers, MA, USA). IMQ cream (5%) (Aldara; 3M Health Care, UK) was purchased from Dong-A Pharmaceutical Co. (Seoul, Korea).

# Preparation of herbal formula SC-E1

All herbal medicines of SC-E1 were purchased as dried herbs from Omniherb (Daegu, Korea) and prepared according to our previous study [12]. Briefly, A mixture of *Gypsum*, *Gardenia jasminoides*, *Glycyrrhiza uralensis*, *Pueraria lobata*, and *Platycodon grandiflorum* at 16:6:2:6:3 ratios was macerated with 800 ml of 70% ethanol, stirred for 24 h at room temperature (RT), and filtered twice using 8 μm pore size Whatman filter paper. After rotary evaporation at 40 ~ 45 °C, the concentrate was lyophilized, yielding 15.9 g of dried power (yield ratio 15.9%). All constituents of SC-E1 have been recognized as standard products by the Korea Food and Drug Administration (KFDA).

# Induction of psoriasis and the administration with SC-E1

IMQ cream was used to induce psoriasis-like skin symptoms in mice as previously described [14]. Briefly, hair on the backs of the C57BL/6 mice was shaved using an electric shaver, after which they were treated with a skin-hair-remover (Niclean, Ildong, Korea). The experimental scheme is shown in Fig. 1. The mice were then randomly divided into five groups (n=5/group): (1) Normal group (vehicle cream; Petrolatum), (2) IMQ/distilled water (DW) control group, (3) IMQ/SC-E1 (250 mg/kg), (4) IMQ/SC-E1 (500 mg/kg), and (5) IMQ/SC-E1 (1000 mg/kg). On day 0, SC-E1 (250 mg/kg, 500 mg/kg, and 1000 mg/kg) was administered to the mice orally once a day by oral gavage needle for 5 days before and together with IMQ application for another 7 days (totally 12 days of treatment). For the control IMQ group, distilled water (DW) was administered instead of SC-E1. The normal group was treated with only a vehicle cream (Petrolatum).

# Scoring severity of dermatitis

The extent of: (1) erythema, (2) scaling, and (3) thickening was scored as 0 (none), 1 (slight), 2 (moderate), and 3 (marked). The cumulative dermatitis score (erythema plus scaling plus thickening) was used to indicate the severity of dermatitis of the back skin (scale 0-9).

# Assay of cytokines production

To measure cytokine levels, mice serum was collected at 24 h after the final administration and stored at -70°C until analysis. To measure the cytokine levels in skin tissue, the dorsal skin of mice was removed and stored at -80°C. For analysis, skin was homogenized using a Bullet Blender $^{TM}$ Blue (Next Advance, Averill Park, NY) at 4°C, after which the supernatants were at -30°C. The concentration of TNF-a, IFN-g, IL-17A, and IL-23 in the mouse serum and skin tissue was measured using the Quantikine mouse IL-17A (R&D system, Minneapolis, MN, USA), TNF-a, IFN-g, and IL-23 (eBioscience, San Diego, CA, USA). ELISA (enzyme-linked immunosorbent assay) was performed in accordance with the manufacturer's instructions.

# Histological analysis

Paraformaldehyde-fixed and paraffin-embedded back skin samples from the mice were sliced and then stained with hematoxylin and eosin (H&E). Based on the histological finding, the several representative symptoms of dermatitis were assessed in a blind manner on the epidermis or dermis (epidermal thickening, stratum corneum, and inflammatory cell infiltration). The inflammatory cells were counted per 5 high-power fields (X400) for each section under the microscope.

# Spleen weight and size

The spleen of each mouse was removed, weighed and sized at the time of sacrifice.

# Western blotting analysis

Total proteins of skin lesion tissues were extracted by homogenization in radioimmunoprecipitation assay (RIPA) buffer (Thermo Fisher Scientific, Rockford, IL, USA) containing protease and phosphatase inhibitor cocktails (GenDEPOT, Barker, TX, USA). Briefly, equal amounts of protein (40 µg) were separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride membranes (EMD Millipore, Bedford, MA, USA). The membranes were blocked in PBST containing 5% skim milk (BD Diagnostic Systems, Sparks, MD, USA) for 1 h and incubated with primary antibodies against p38 MAPK (1:1000), p-p38 MAPK (1:1000), p-IκBα (1:1000), anti-p-NF-κB p65 (1:1000), and β-actin (1:2000) overnight at 4°C. After three washes with PBST, membranes were incubated with horseradish peroxidase-linked anti-rabbit IgG secondary antibody (1:3000) for 1 h at room temperature. After washing three times with PBST, detection was performed using an enhanced chemiluminescence solution (Amersham™ ECL™ Prime Western Blotting Detection Reagent; GE Healthcare, Buckinghamshire, UK). Bands were visualized using a Fusion Solo 2M chemiluminescence imaging system (Vilber Lourmat, France) and the intensity of each band was analyzed using ImageJ 1.48v software (NIH, Bethesda, MD, USA).

# Statistical analysis

All groups were compared by one-way analysis of (ANOVA), followed by the Duncan test. The results were expressed as the means ±S.D. A $p < 0.05$ was considered significant.

# Results

# Effect of SC-E1 on IMQ-induced psoriasis in mice

To examine whether the SC-E1 pretreatment on IMQ-induced skin inflammation in mice has an anti-psoriatic effect, IMQ-induced mice were orally administered with SC-E1 (250, 500, or 1000 mg/kg) on a daily basis for 12 days, and the several representative symptoms was measured by cumulative score (erythema plus scaling plus thickening). As shown in Fig. 2a, repeated application of IMQ showed prominent erythema, scaling, and thickening on the back skin. However, the SC-E1 (500 or 1000 mg/kg) pretreatment significantly ameliorated or resolved the IMQ-induced psoriasis-like dermatitis in mice with reduced symptoms severity scores including erythema, scaling, and thickening. Although SC-E1 (250 mg/kg) pretreatment also slightly alleviate the psoriasis-like symptoms compared with the control IMQ mice, this difference was not statistically significant. Representative clinical features of IMQ-induced psoriasis-like inflammation in mice are shown in Fig. 2b.

# Effects of SC-E1 on skin histopathological changes

To understand the role of SC-E1 on the skin hypertrophy of IMQ-induced skin inflammation in mice, the dorsal skin samples of mice were employed for histopathological analysis by H&E staining. As shown in Fig. 3a, the control IMQ mice skins showed thickened epidermis (parakeratosis and hyperkeratosis) with inflammatory cell infiltration, which is similar to human psoriatic skin. However, the SC-E1 (500 or 1000 mg/kg) pretreatment showed much smoother epidermis, less parakeratosis and epidermal thickening with decreased inflammatory cell infiltration than the control IMQ mice. Moreover, epidermal thickness was significantly reduced by SC-E1 (500 or 1000 mg/kg) pretreatment as compared to the control IMQ mice (Fig. 3b). However, the SC-E1 (250 mg/kg) pretreatment showed little effect on these histopathological characteristics.

# Effect of SC-E1 on IMQ-induced systemic immunological factors

We investigated the anti-psoriatic effect of SC-E1 is associated with changes in pro-inflammatory cytokine profiles. As shown in Fig. 4a and 4b, the production of various proinflammatory cytokines such as Th1 cytokines (TNF-a, IFN-g) and Th17 cytokines (IL-17A and IL-23) in the control IMQ mice were significantly enhanced in the serum and skin than in the normal mice. However, the SC-E1 (500 or 1000 mg/kg) pretreatment was shown to obviously suppressive the production of these proinflammatory cytokine in the serum and skin. Conversely, there was no significant difference between the SC-E1 (250 mg/kg) pretreatment and the control IMQ mice. Furthermore, the weight and size of the spleen were significantly increased in the in the control IMQ mice compared with the normal mice (Fig. 5a and 5b). However, such splenomegaly was significantly reduced in the SC-E1 (500 or 1000 mg/kg) pretreatment, although not to the level of the normal mice. However, there were no changes in the SC-E1 (250 mg/kg) pretreatment.

# Effect of SC-E1 on IMQ-induced proinflammatory modulators

Based on the results, we studied to further elucidate the mechanisms underlying the immunomodulatory effects of SC-E1. NF-κB and MAPK are essential proinflammatory modulators in the pathogenesis of psoriasis. Therefore, we examined the effects of SC-E1 on the protein expression of NF-κB and MAPK signal pathways involving p38 MAPK, p-IκBα, and p-NF-κB using Western blotting analysis. As shown in Fig. 6a and 6b, the protein expressions of p38 MAPK, p-IκBα, and p-NF-κB in the skin were markedly increased in the control IMQ mice compared to the normal mice. By contrast, as compared to the control IMQ mice, SC-E1 (250, 500 or 1000 mg/kg) pretreatment could markedly suppress the protein expressions of those elevated skin proinflammatory modulators.

## Discussion

The anti-psoriasis treatments are currently used as various topical or systemic immunosuppressive agents such as FK-506 and cyclosporine A (CsA) [15]. However, these conventional agents for psoriasis are limited by their propensity to cause serious adverse effects. Therefore, patients with psoriasis often search other alternative treatment option, and natural herbs or oriental herbal medicines are used as complementary and alternative medicines for psoriasis immunomodulation based on their potent anti-psoriatic activity with few adverse effects. We have recently reported that SC-E1, an herbal formula consisting of five oriental medicinal herbs, could display potent anti-oxidant and anti-inflammatory activities and reduced the protein expression of NF-κB and MAPK signal pathways leading to a decrease of various proinflammatory cytokines in an *in vitro* study using cell line [12]. Based on these data, we investigated the potent anti-psoriatic effect and immunomodulatory mechanism of SC-E1 on IMQ-induced psoriasis in mice closely resembles human psoriatic lesions.

Topical treatment of IMQ on the dorsal skin of mice results in induced epidermal keratinocytes proliferation and subsequently leads to erythema, scaling, and thickening of the skin and increased inflammatory cell infiltration as well as parakeratosis [16]. Consistent with those finding, IMQ-induced mice in the present study showed clinical symptoms, including erythema, skin thickening, and scaling, as well as histological phenotypes, including inflammatory cell infiltration, acanthosis, and parakeratosis. We found that the pretreatment of SC-E1 (500 or 1000 mg/kg) improved the development of IMQ-induced psoriasis in mice, but pretreatment of SC-E1 (250 mg/kg) had no impact. Prereatment of SC-E1 (500 or 1000 mg/kg) significantly reversed the histological characterization of skin lesions, including smoother epidermis, less parakeratosis, and mild lymphocytes infiltration. Moreover, epidermal thickness was reduced in the SC-E1 (500 or 1000 mg/kg) pretreatment when compared to the control IMQ group. These results amply indicated that SC-E1 had noticeable potent anti-psoriatic effect on IMQ-induced psoriasis in mice.

Pronflammatory mediators such as Th1 cytokines (TNF-a and IFN-g) and Th17 cytokines (IL-17A and IL-23) are thought to be crucial role in the amplification and development of inflammatory or autoimmune

disease including psoriasis [17,18]. Elevated levels of theses proinflammatory cytokines are reported in both patients with psoriasis and in IMQ-induced mice [19,20]. Activated IL-17A cytokine initiated IL-23-mediated inflammation and induced keratinocytes proliferation as well as epidermal hyperplasia [21]. IL-23 cytokine produced mainly by multiple cell types including macrophage and dendritic cell, impacting IFN-g production of Th1-mdeiatied cells [22]. In addition, TNF-a has a key role in skin inflammatory processes and proinflammatory cytokines [23]. Thus, regulation of Th1- and Th17-associated cytokines of immune responses is necessary to modulate inflammatory skin disease including psoriasis. Concordant with these findings, we observed higher production of Th1 cytokines (TNF-a and IFN-g) and Th17 cytokines (IL-17A and IL-23), in IMQ-induced mice than in normal mice. However, these various proinflammatory cytokines in serum and dorsal skin tissue were suppressed in SC-E1 (500 or 1000 mg/kg) pretreatment. These results suggest that the potential of SC-E1 treatment for attenuating immune responses by controlling various proinflammatory factors including Th1 cytokines (TNF-a and IFN-g) and Th17 cytokines (IL-17A and IL-23).

It is known that splenomegaly indicates activation of various inflammatory immune responses and plays an important role in the pathogenic mechanism associated with inflammatory skin diseases including psoriasis [19]. In our study, enlargement of spleen weight and size was induced by IMQ through systemic inflammatory immunoreactions, whereas they significantly decreased in the SC-E1 (500 or 1000 mg/kg) pretreatment. These results indicated that SC-E1 may be involved in the modulation of immune system status. The weight gain in IMQ-induced mice during the experiment was not disturbed by SC-E1.

The intracellular signaling molecules such as NF-κB and MAPK are regulatory element in inflammatory pathways [24,25]. The activation of NF-κB and MAPK signaling has been observed in psoriatic lesional skin of psoriasis patients, and these are an essential inflammatory mediator in the pathogenesis of psoriasis [26,27]. Moreover, the inhibition of MAPK could reduce the production of proinflammatory cytokines and suppress the activation of NF-κB [28]. According to our previous report, SC-E1 suppressed the production of various proinflammatory cytokines by inhibiting the NF-κB and MAPK signal pathways in stimulated cell line *in vitro.* In our study, we showed that protein expressions of p38 MAPK, p-IκBα, and NF-κB p65 were significantly increased in the skin tissue of IMQ-induced mice. However, SC-E1 pretreatment significantly suppressed the increase in phosphorylation of p38 MAPK, p-IκBα, and NF-κB p65, which consistent with previous study [12]. It is likely that these findings were closely linked with inhibitory effects of SC-E1 on the development of IMQ-induced psoriatic mice.

## Conclusion

SC-E1 pretreatment was able to exert potential anti-psoriatic effects on IMQ-induced psoriasis in mice. SC-E1 pretreatment not only significantly suppressed the production of proinflammatory cytokines but also inhibited epidermal alteration. The immunomodulatory mechanism underlying the anti-psoriatic effect of SC-E1 on IMQ-induced psoriasis in mice was closely associated with inhibition of the activation of NF-κB and MAPK signaling. Overall, SC-E1 could provide an effective alternative therapeutic strategy for the treatment of psoriasis

## Abbreviations

IMQ: imiquimod

AD: atopic dermatitis

NF-kB: nuclear factor kappa B

MAPK: mitogen-activated protein kinases

ELISA: enzyme-linked immunosorbent assay

H&E: hematoxylin and eosin

CsA: cyclosporine A

RIPA: radioimmunoprecipitation assay

## Declarations
## Acknowledge

Not applicable.

## Authors' contributions

## Funding

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Animal experiments were approved beforehand by the Institutional Animal Care and Use Committee of Dongguk University.

# Consent for publication

Not applicable.

# Competing interests

The authors declare that they have no competing interests.

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