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Original Article

Saccharina japonica Attenuates the Allergic Inflammation *in vivo* and *in vitro*

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Saccharina japonica (SJ), a brown algae, exerts various pharmacological effects, including anti-oxidant, immune-modulating and anti-cancer properties. This study aimed to determine the pharmacological mechanism of SJ on atopic dermatitis *in vivo* and *in vitro*. We investigated the pharmacological effects of SJ on 2, 4-dinitrochlrobenzene (DNCB)-induced atopic dermatitis clinical symptoms in mice. Additionally, we evaluated the effects of SJ on the inflammatory cytokine production and nuclear factor-κB (NF-κB) activation in HaCaT cells. The findings of this study demonstrated that SJ reduced the clinical symptoms of atopic dermatitis, such as skin dryness, erythema and eczematous, and serum histamine and IgE level in DNCB-induced atopic dermatitis model. Additionally, SJ inhibited the NF-κB activation in atopic dermatitis-like skin lesion and HaCaT cells. Collectively, this result suggests that SJ could be used as a therapeutic agent for skin inflammation, including atopic dermatitis.

Key Words: *Saccharina japonica*, Atopic dermatitis, Nuclear factor-κB, HaCaT cells

INTRODUCTION

Atopic dermatitis is a common skin inflammatory disease characterized by excoriation, erythema, skin thickening and itching (Buske-Kirschbaum et al., 2001). The main hallmark of atopic dermatitis is immune imbalance, and defective skin barrier function. The pathogenesis and progression of atopic dermatitis are influenced by genetic, environmental, and immunological factors. To date, steroid therapy is crucial in the treatment of atopic dermatitis, but long term and continuous usages cause various side effects including skin thinning, atrophy, and epidermal barrier dysfunction (Berke et al., 2012). Therefore, there is a development necessity for anti-atopic agent with less side effects.

Keratinocytes are main epidermal cells and, play a critical role in atopic dermatitis development (Liu et al., 2019; Eichenfield et al., 2012). In response to various factors, keratinocytes generate various inflammatory mediators, including interleukin (IL)-6 and IL-8 (Homey et al., 2006). These cytokines contribute to the infiltration of immune cells to lesion of inflammation in the skin. In patients with atopic dermatitis, the expression of the atopic dermatitis-related cytokines increased in keratinocytes (Vestergaard et al., 2000). Nuclear factor-kappa B (NF-κB) exerts a crucial function by controlling the expression of immune-related genes (Chung et al., 2014). NF-κB activation is a key step in the progression of atopic dermatitis. It was reported that NF-κB signaling induce atopic dermatitis through the expression of various inflammatory-related genes (Nam et al.,

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2014). Therefore, inhibition of NF-κB may represent a strategy for treatment of atopic dermatitis.

Studies have demonstrated that marine product has various pharmacological applications (Wang et al., 2014). Hence, they are used in various ways as healthcare agents including food, cosmetics, and medical products. *Saccharina japonica* (SJ), an edible brown algae, exerts various pharmacological effects, including anti-oxidative, anti-viral, anti-cancer and immune-modulating properties (Bouga and Combet, 2015; Ye et al., 2020). SJ contains plenty of active ingredient, including fucoidan, mannitol, and laminarian. Previous studies have reported that fucoidan isolated from SJ has a variety of bioactivities, such as neuroprotective, antioxidant, immunomodulatory, and atherosclerosis mitigation (Cao et al., 2016; Jin et al., 2013; Zhao et al., 2018). However, information on the precise mechanism action of SJ on skin inflammatory response remains limited.

This study aimed to investigate whether SJ alleviate atopic dermatitis *in vivo* and *in vitro*. To provide experimental evidence that SJ may be a useful therapeutic agents for AD, we determined the beneficial effect of SJ on atopic dermatitis clinical symptoms induced by 2,4-dinitrochlrobenzene (DNCB) in murine model. In addition, we investigated the effect of SJ on the expression of inflammatory mediators in atopic dermatitis-like skin lesions and tumor necrosis factor (TNF)-α plus interferon (IFN)-γ-stimulated HaCaT cells.

MATERIALS AND METHODS

Reagents

The following chemicals were purchased from Sigma (St. Louis, MO, USA): 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), phosphate-buffered saline (PBS), eosin and hematoxylin, dimethylsulfoxide (DMSO), DNCB, avidin peroxidase (AP) and other reagents. Iscove's Modified Dulbecco's Medium (IMDM) was procured from Gibco BRL (Grand Island, NY, USA). The ELISA assay kits for mouse IgE and human IL-6/ IL-8 were purchased from BD Biosciences (San Diego, CA, USA). Nuclear extraction reagent kit and bicinchoninic acid (BCA) and enhanced chemiluminesence (ECL) were obtained from Pierce Thermo Scientific (Rockford, IL, USA). Specific antibodies against NF-κB Abs were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA).

Animals

Male ICR mice (male, 6-weeks-old) was obtained from Hyochang Science (Daegu, Korea). Animals were housed 7 heads per cage, allowed spontaneous take in food and water. Animals were kept under a 12-h light/dark cycle (light on 08:00-20:00) at room temperature (22 ± 2℃) and humidity (56 ± 10%). All animal procedures and experiments were conducted in accordance with the internationally accepted principles as found in Daegu Haany university guidelines (DHU2020-074).

Preparation of SJ extract

The dried of SJ (100 g) was pulverized and extracted in 1 L of a 70% aqueous ethanol solution for 24 h, and then concentrated under vacuum. The extract was filtered, freeze drying and kept at 4℃ (yield, 10.1%). The samples were dissolved in PBS and filtered.

Induction of atopic dermatitis-like Skin lesions and SJ treatment

DNCB was dissolved in vehicle (acetone-olive oil, 3:1) and used as a sensitizer for inducing AD-like skin lesions in mice (Yoon et al., 2015). Backs of mice were shaved with a clipper and gauzed a day before sensitization. Mice were divided into 4 groups with 7 mice per group: vehicle, DNCB, and DNCB plus treatment of SJ (10 mg/kg or 100 mg/kg). Exposed skin was treated with vehicle or with 200 μL of a 1% DNCB three times per week. After sensitization, the skin was challenged, with 200-μL of a 0.3% DNCB solution every day for 2 weeks. The normal group was treated with vehicle. SJ was orally administrated for 2 weeks prior to the end of the experiment. After sacrifice, blood samples and dorsal skin were collected for molecular analysis.

Skin dermatitis severity

The severity of dermatitis was determined according to the Eczema Area and Severity Index scoring system: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The severity of dermatitis was evalu-

ated by the naked eye of three blind examiners. The sum of the individual scores was evaluated as the dermatitis score for erythema/haemorrhage, oedema, excoriation/erosionand scaling/dryness (Hanifin et al., 2001).

Cell culture

Human immortalized keratinocytes (HaCaT cells) were cultured in IMDM (100 IU/mL penicillin, 100 μg/mL, streptomycin, and 10% heat-inactivated FBS) at 37℃, 5% CO_2 and 95% humidity.

Cell viability test

To investigate the cell viability at various concentrations of SJ, the MTT colorimetric assay was conducted. Briefly, Cells were treated with various concentrations of SJ (0.01~1 mg/mL) for 1 h and subsequently stimulated with stimulated with TNF-α (10 ng/mL) plus IFN-γ (10 ng/mL) for 24 h. After then, MTT (50 μL) was subsequently added. After incubation for 4 h, the crystallized formazan was dissolved in DMSO and the absorbance was measured by a microplate reader (Molecular Devices, CA, USA).

Cytokine assay

Cytokine assays were performed using modified ELISA, as described previously (Kim et al., 2010). Briefly, micro plates were coated with monoclonal antibodies against IL-8, IL-6 or IgE Abs and incubated overnight at 4℃. After additional washes, the samples or IL-8, IL-6 or IgE standard solution was added and incubated. After additional washing, the plates were incubated to biotinylated Abs and incubated for 2 h. After washing the plates, AP and 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) substrates were sequentially added. The absorbance of the plates was measured at 405 nm.

Histamine assay

Histamine concentration derived from serum was evaluated using a histamine assay kit according to the manufacturer's protocol (Neogen, Lexington, USA).

Western blot analysis

Nuclear lysates of skin tissue were prepared by nuclear extraction reagent kit. The quantity of protein was determined using a BCA protein assay. The sample was mixed with 2x sample buffer, separated by gel electrophoresis and transferred to membrane. Membrane was blocked with 5% skimmed milk for 2 h and subsequently incubated with NF-κB p65 primary Abs. After washing, the membrane was reacted with secondary Abs. After washing with PBST, protein bands were visualized by ECL detection system.

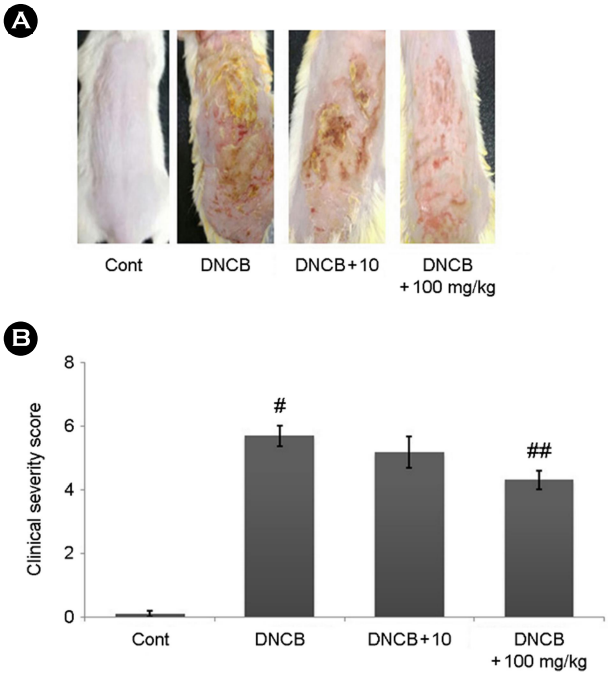

Fig. 1. Effect of SJ on DNCB-induced atopic dermatitis in mice (n=7/group). The mice were sensitized with DNCB in acetone-olive oil or vehicle applied to the dorsal skin for a total period of 3 weeks. SJ (10 or 100 mg/kg) was orally administered for 2 weeks before the end of the experiment. (A) Clinical feature of atopic dermatitis-like skin lesions in mice. (B) The scores of skin severity are presented. The results represent the mean ± S.D of three independent experiments ($^{\#}P < 0.05$ vs. control group, $^{\#\#}P < 0.05$ vs. DNCB-treated group).

Statistical analysis

The results are shown as the mean ± S.D. of independent experiment and statistical analyses were performed using a one-way ANOVA, offered by Tukey's multiple tests. A values of $P < 0.05$ were consideredsignificant.

RESULTS

The inhibitory effect of SJ on DNCB-induced atopic dermatitis-like dermatitis in mice

To measure the inhibitory effects of SJ on the clinical symptoms of atopic dermatitis, mice were treated with DNCB. When the mice received SJ extract (10 or 100 mg/kg) for 2 weeks, atopic dermatitis-like skin symptoms induced by DNCB, such as excoriation, erythema and skin thickening, were significantly alleviated (Fig. 1A). Additionally, we observed that the skin severity scores of mice treated with SJ (10 mg/kg or 100 mg/kg) were significantly lowered than those of DNCB-treated mice (Fig. 1B).

The inhibitory effect of SJ on the serum histamine and IgE levels in DNCB-induced atopic dermatitis model

Increase of histamine and IgE levels is an important feature of atopic dermatitis pathology (Minami and Kamei, 2004). Thus, we investigated the effect of SJ on the serum histamine and IgE levels. We found that administration of SJ reduced the serum of the histamine and IgE levels induced by DNCB in a concentration-dependent manner (Fig. 2A and B). The inhibition rate of the histamine and IgE levels by SJ (100 mg/kg) was approximately 35.2% ($P < 0.05$) and 31.4% ($P < 0.05$), respectively.

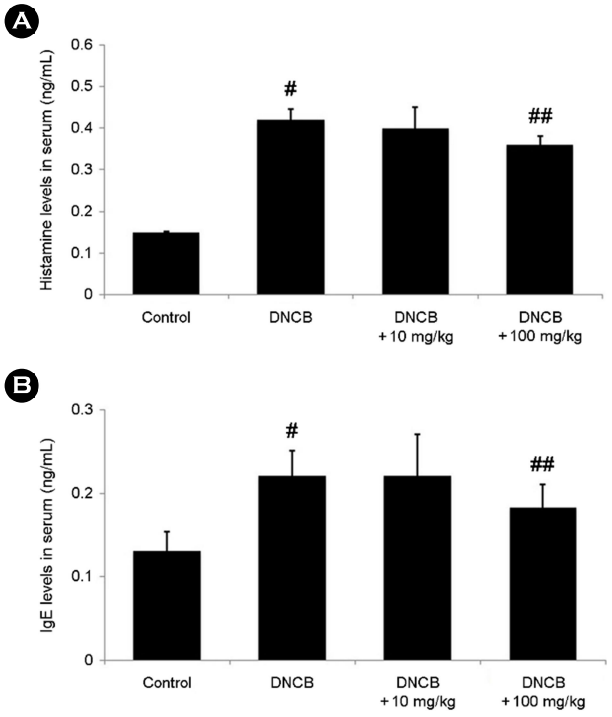

Fig. 2. Effect of SJ on the histamine and IgE levels in the DNCB-induced atopic dermatitis model. Blood were collected and the serum histamine (A) and IgE (B) levels in the indicated groups were determined using ELISA. The results presents the mean ± S.D of independent experiments ($^{\#}P < 0.05$ vs. control group, $^{\#\#}P < 0.05$. DNCB-treated group).

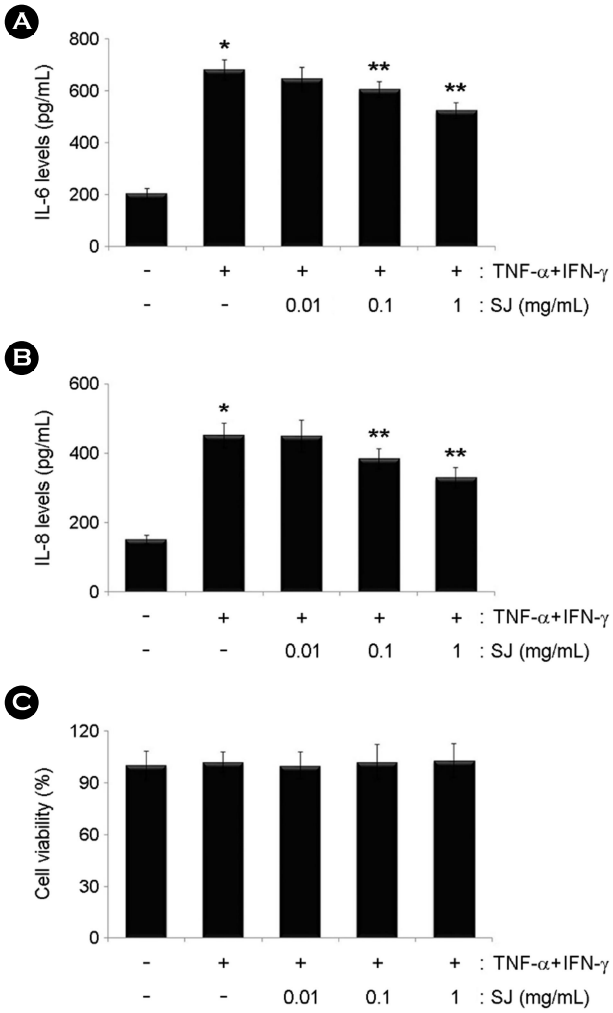

Fig. 3. The effect of SJ on the IL-6 and IL-8 levels in HaCa T cells. Cells (3×10^5 cell/well) were treated with various concentrations of SJ (0.01~1 mg/mL) for 1 h and subsequently stimulated with TNF-α (10 ng/mL) plus IFN-γ (10 ng/mL) for 24 h. (A) The IL-6 and IL-8 concentration was measured in cell supernatants using ELISA. (B) Cell viability was evaluated by an MTT assay. The results are the mean ± S.D of determinations from three separate experiments ($^{*}P < 0.05$ vs. un-treated cell, $^{**}P < 0.05$ vs. TNF-α + IFN-γ alone).

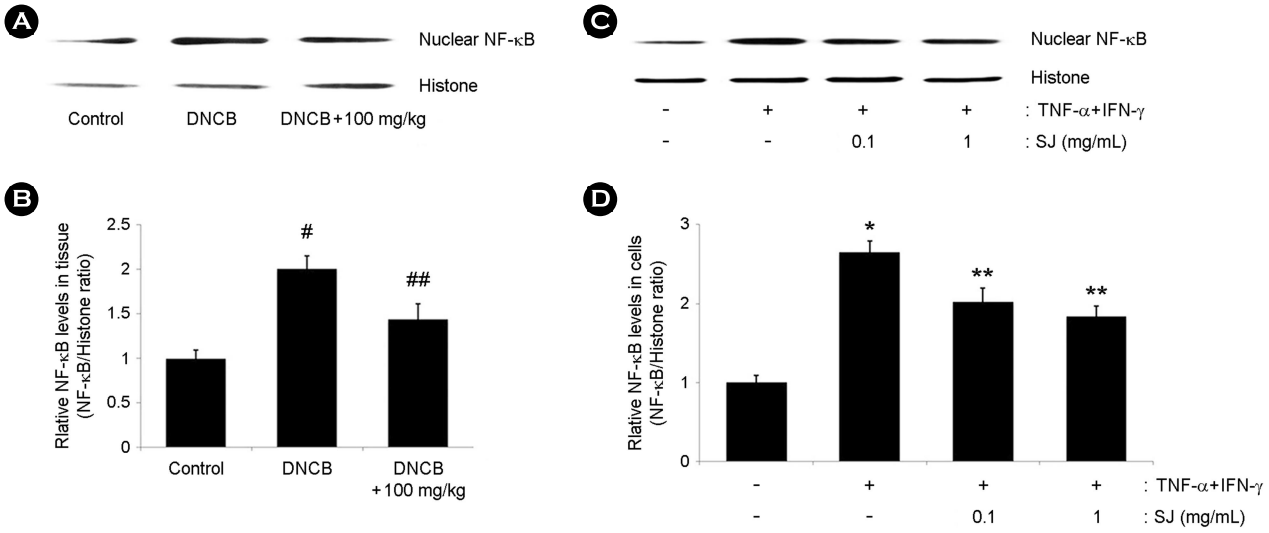

Fig. 4. Effect of SJ on NF-κB activation in atopic dermatitis-like skin lesion and HaCaT cells. (A) The skin tissues were cut out and homogenized. Nuclear lysates were prepared by nuclear extraction kit and he level of nuclear NF-κB p65 in atopic dermatitis-like skin lesion was measured using Western blot analysis. (B) The relative ratio of nuclear NF-κB p65 in skin tissue was determined by densitometry. (C) Cells (5×10^6 cell/well) were treated with SJ (0.1~1 mg/mL) and then stimulated with TNF-α (10 ng/mL) plus IFN-γ (10 ng/mL) for 2 h. The nuclear NF-κB p65 level in cell was measured. (D) The relative ratio of nuclear NF-κB p65 were determined by densitometry. All results were presented in the mean ± S.D of determinations from separate experiments ($^{\#}P < 0.05$ vs. control, $^{\#\#}P < 0.05$ vs. DNCB-treated group, $^{*}P < 0.05$ vs. un-treated cell, $^{**}P < 0.05$ vs. TNF-α + IFN-γ alone).

The inhibitory effects of SJ on the secretion of inflammatory cytokines in HaCaT cells

Keratinocyte-derived cytokines and chemokines are involved in the inflammatory responses of atopic dermatitis (Liu et al., 2019). To identify the anti-atopic effect of SJ, we evaluated whether SJ could regulate IL-6 and IL-8 production in TNF-α plus IFN-γ-stimulated HaCaT cells using ELISA. As shown in Fig. 3A, IL-6 and IL-8 production was increased by stimulation with TNF-α plus IFN-γ, and these increases were inhibited in a concentration-dependent manner by SJ treatment. In particular, the inhibition rate of IL-6 and IL-8 by SJ (1 mg/mL) was approximately 39.76% ($P < 0.05$) and 31.75% ($P < 0.05$), respectively. The effect of SJ on the cell viability was examined using an MTT assay. We also observed that SJ treatment with 0.01~1 mg/mL was not cytotoxic to HaCaT cells (Fig. 3B).

Effect of SJ on NF-κB activation in atopic dermatitis-like skin lesion and HaCaT cells

As the attenuation of NF-κB activation has been linked to anti-inflammatory reaction (DiDonato et al., 2012), we predicted that the pharmacological mechanism of SJ may be mediated via the regulation of NF-κB pathway. Because activation of NF-κB requires the translocation of NF-κB p65 (subunit) into the nucleus, we investigated the mechanism by which SJ affects the nuclear pool of NF-κB in atopic dermatitis-like skin lesions. The results showed that the levels of nuclear NF-κB p65 increased in DNCB-induced atopic dermatitis-like skin lesion, whereas treatment with SJ reduced the increase in the nuclear NF-κB p65 levels (Fig. 4A). The relative rations of NF-κB p65 in skin tissue are shown in Fig. 4B. We also evaluated the effect of SJ on NF-κB activation in HaCaT cells. As shown in Fig. 4C, TNF-α plus IFN-γ considerably increased the nuclear NF-κB p65 protein level, indicating the nuclear translocation of NF-κB p65. Treatment with SJ inhibited the increase in the nuclear NF-κB p65 levels in HaCaT cells. The relative rations of NF-κB p65 are shown in Fig. 4D.

DISCUSSION

Natural products have been a subject of growing interest because of their potential for the treatment of atopic derma-

titis. SJ, an edible brown algae, is known to exhibit beneficial effects on human health, such as anti-oxidative, immune-modulating, and anti-cancer properties. However, the regulatory mechanisms of SJ in atopic dermatitis-like dermatitis are not completely understood. The findings of this study showed that SJ alleviated DNCB-induced atopic dermatitis-like skin symptoms in mice. Furthermore, we showed that the anti-atopic mechanism of SJ was mediated by the suppression of NF-κB activation in atopic dermatitis-like skin lesions and stimulated HaCaT cells.

Atopic dermatitis is a common chronic inflammatory skin disease and a feature of atopic dermatitis is dry skin and long lasting itching (Berke et al., 2012). The pathogenesis and progression of atopic dermatitis are influenced by genetic, environmental, and immunological factor (Saeki et al., 2009; Sugimoto et al., 2006). Steroid therapy is crucial for the treatment of atopic dermatitis. However, steroids cannot be administered for long time because of their deleterious side effects such as skin thinning, atrophy and hypopigmentation (Das and Panda, 2017; Berke et al., 2012). Therefore, natural materials with high effectiveness and lower toxicity are being investigated as potential anti-atopic dermatitis agents. Immunologic dysregulation is a crucial factor in atopic dermatitis pathogenesis. Especially, atopic dermatitis is associated the increase of histamine and IgE levels (Minami and Kamei, 2004). Several studies have shown that the IgE and histamine levels are generally elevated in patients with atopic dermatitis (Brenninkmeijer et al., 2008; Moon et al., 2021). IgE binds to the FcεRI of mast cells, triggering an inflammatory cascade through the release of inflammatory mediators, including histamine and constitute an immediate hypersensitivity reaction in atopic dermatitis (Gilfillan and Beaven, 2011). Based on these findings, we evaluated the effects of SJ on IgE and histamine levels in the DNCB-induced atopic dermatitis model. The findings revealed that SJ significantly relieved the DNCB-induced the symptoms of atopic dermatitis, such as excoriation, erythema and skin thickening in atopic dermatitis-like skin lesion. Additionally, our study showed that SJ (10 or 100 mg/kg) suppressed the increase in the serum IgE and histamine levels induced by DNCB. From this, SJ is a therapeutic agents that could attenuate the clinical symptom of atopic dermatitis.

Keratinocytes are epidermal cells that play a critical role in atopic dermatitis (Vestergaard et al., 2000). Keratinocyte produces inflammatory cytokine and chemokine through various stimulations (Liu et al., 2019). These mediators contribute to the infiltration of inflammatory cells into sites of inflammation in the skin (Homey et al., 2006; Wong et al., 2001). Recent studies have reported that inflammatory cytokines are highly expressed in keratinocytes of human atopic dermatitis patients. Based on these observations, the suppression of inflammatory mediators may be an effective therapeutic strategy for preventing atopic dermatitis. In this study, our results revealed that SJ suppressed the levels of IL-6 and IL-8 in TNF-α plus IFN-γ-stimulated HaCaT cells. In particular, the inhibition rate of IL-6 and IL-8 release by SJ (1 mg/mL) was approximately 42.76% and 33.75%, respectively. Our finding suggested that SJ exerts anti-atopic effects by suppressing the production of inflammatory cytokines.

NF-κB signaling is associated with atopic dermatitis through the overproduction of inflammatory mediators (DiDonato et al., 2012). In skin inflammatory process, the IκB kinase complex phosphorylates and degrades the IκB proteins and NF-κB is translocate into the nucleus, where it combines to the promoter and activate inflammatory mediators including histamine, IgE and cytokines (Chung et al., 2014). Based on this phenomenon, the suppression of NF-κB activation has been identified as an anti-inflammatory strategy. Previous other study reported that SJ has anti-inflammatory activity via blocking NF-κB, MAPK and STAT pathways in macrophages (Ye et al., 2020). To identify the anti-inflammatory mechanism of SJ in atopic dermatitis-like skin lesion, we evaluated whether SJ could suppress the activation of nuclear NF-κB p65. Our results showed that the levels of nuclear NF-κB p65 were increased in DNCB-induced atopic dermatitis-like skin lesions, whereas treatment with SJ reduced the increase in the nuclear NF-κB p65 levels. It is known that the activation of NF-κB in keratinocytes is associated with atopic dermatitis, and keratinocyte stimulated with TNF-α plus IFN-γ is widely used for verification of the *in vitro* efficacy of anti-atopic dermatitis. It was reported that neferine exerts anti-inflammatory effects by inhibiting the expression of inflammatory cytokines and the

MAPK activation induced by TNF-α plus IFN-γ in keratinocyte (Yang et al., 2021). In this study, we confirmed that the enhanced nuclear NF-κB p65 levels in TNF-α plus IFN-γ-stimulated HaCaT cells were downregulated by treatment with SJ in a dose-dependent manner. Thus, we indicated that SJ exerts its anti-atopic mechanism through the regulation of nuclear NF-κB activation. Although SJ attenuated NF-κB activation, the effect of SJ on another pathway including MAPK or STAT signaling was not elucidated. Thus, further study is necessary to clarify the precise mechanism of SJ in the progression of atopic dermatitis.

In conclusion, this study suggests that SJ regulates allergic inflammatory responses *in vivo* by alleviating DNCB-induced clinical symptoms of atopic dermatitis and serum IgE and histamine levels in mice. Furthermore, we indicated that the anti-atopic mechanism of SJ may be attributed to the inhibition of nuclear NF-κB p65 activation in atopic dermatitis-like skin lesions and TNF-α plus IFN-γ-stimulated HaCaT cells. Therefore, our findings demonstrated that SJ could potentially be developed as a novel therapeutic agent for treatment of atopic dermatitis.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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