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ORIGINAL ARTICLE

# The Ethanol Extract of *Caragana sinica* Ameliorated Skin Lesions in Mice with Contact Dermatitis

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## ABSTRACT

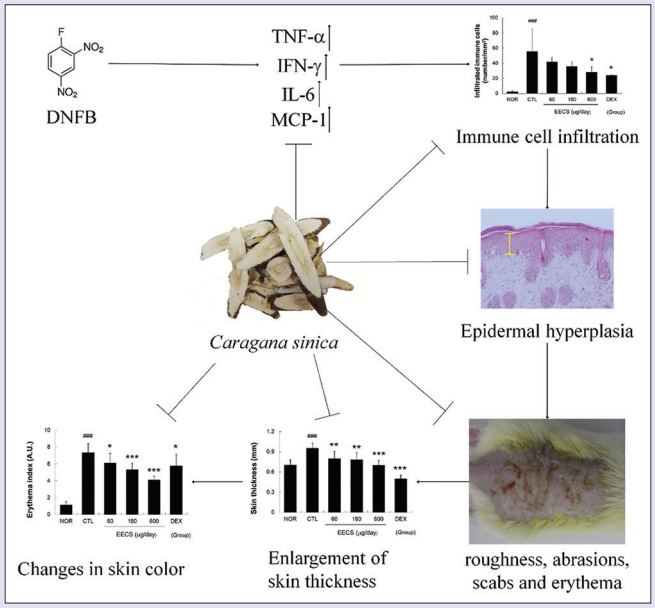
**Background:** *Caragana sinica* (Buc'hoz) Rehd, which belongs to the legume family, is used to treat a variety of diseases such as gout, high blood pressure, neuralgia, arthritis, and eczema. Morden studies reveal that *C. sinica* has anti-tumor, anti-viral, anti-hypertensive, immune-stimulatory, immune-suppressive and anti-inflammatory activities. **Aims:** This study aims to confirm its therapeutic efficacy on contact dermatitis (CD) induced by harmful chemical. **Materials and Methods:** The dried roots of *C. sinica* were extracted using 70% ethanol, then the extract was condensed and lyophilized (ethanol extract of *C. sinica,* [EECS]). We investigated the effects of EECS on skin lesion severities, erythema and melanin indices, skin weights and thicknesses, histopathological changes and cytokine levels in mice with CD induced by 1-fluoro-2,4-dinitrofluorobenzene. In addition, the effects on changes in body weight and spleen body weight ratios were also investigated. **Results:** EECS relieved skin lesions such as roughness, abrasions, scabs, erythema, and petechia, inhibited thickening of dorsal skin and lowered erythema and melanin indexes in the CD mice. Besides, EECS reduced epidermal hyperplasia and immune cell infiltration into inflamed tissues and reduced levels of Tumor necrosis factor-α, interferon-γ, interleukin-6, and monocyte chemotactic protein-1 (MCP-1) in inflamed tissues. Finally, body weight gains and spleen/weight ratios of CD mice were unaffected by EECS, unlike dexamethasone treatment. **Conclusion:** These results suggest that *C. sinica* has potential use as a therapeutic agent for CD and the therapeutic mechanism is different from that of corticosteroids.

**Key words:** *Caragana sinica,* contact dermatitis, herbal medicine, inflammation, skin

## SUMMARY

- Ethanolic extract of roots of *Caragana sinica* (EECS) relieved skin lesions and inhibited the thickening of dorsal skin
- EECS lowered erythema and melanin indexes in the contact dermatitis mice
- EECS reduced epidermal hyperplasia and immune cell infiltration in inflamed tissues
- EECS lowered levels of tumor necrosis factor -α, interferon -γ, interleukin -6 and MCP-1 in inflamed tissues.

**Abbreviations used:** CD: Contact dermatitis; TNF: Tumor necrosis factor; IFN: Interferon; IP: Interferon gamma induced protein; IL: Interleukin; MCP: Monocyte chemotactic protein; DNFB: 2,4-dinitrofluorobenzene; EECS: Ethanol extract of *C. sinica*; NOR: Naïve controls; CTL: CD controls; DEX: Dexamethasone; iNOS: Inducible nitric oxide synthase; COX: Cyclooxygenase.

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## INTRODUCTION

*Caragana sinica* (Buc'hoz) Rehd. is a perennial deciduous and broad-leaved shrub plant that belongs to the legume family. *C. sinica* and similar species such as *C. koreana* and *C. microphylla* are mainly distributed in Northeast Asia in China and Korea.[1,2] In China, the name of the plant is Jinjier (锦鸡儿), and the name of the root, which is used for medical purposes, is Jinquegen (金雀根), whereas in Korea, the plant and its roots are called Goldamcho (骨擔草).[3] In traditional medicine, *C. sinica* is described as "a medicinal herb that is neutral in nature, and has a sweet and pungent flavor and is used to strengthen the spleen and promote blood circulation."[4] It has served as a treatment for various diseases such as gout, high blood pressure, neuralgia, arthritis, and eczema.[1,5]



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Modern studies on *C. sinica* have been shown that it has anti-tumor,[6] anti-viral,[7] anti-hypertensive,[2] immunostimulatory, immunosuppressive,[8] and anti-inflammatory activities,[5] and it has been well established that some active ingredients isolated from *C. sinica*, such as (+)-α-viniferin, resveratrol, kobophenol A, betulinic acid, and physcion have anti-inflammatory activities.[9]

In the United States, 5%–9% of men and 13%–15% of women have contact dermatitis (CD), which is an inflammatory skin disease characterized by itching, erythema, scab formation, and hyper-pigmentation caused by contact with external substances.[10] Histopathological analysis of CD typically reveals epidermal hyperplasia, immune cell infiltration, swollen capillaries in dermis, epithelial hyperkeratosis, spongiosis, spongiotic bubbles, and numerous neutrophils in epidermis.[11] Many cytokines and chemokines are involved in triggering these changes, and tumor necrosis factor (TNF)-α, interferon (IFN) gamma-induced protein – 10, IFN-γ, interleukin (IL)-1, IL-6, monocyte chemotactic protein (MCP)-1, and granulocyte-macrophage colony-stimulating factor are considered to play central roles in CD progression.[12]

Based on the above-mentioned background, we evaluated the anti-inflammatory effects of *C. sinica* in a mouse model of 2,4-dinitrofluorobenzene (DNFB) induced-CD by examining skin thicknesses and weights, skin lesions, skin color, and cytokine and chemokine histopathological changes in inflamed tissues.

## MATERIALS AND METHODS

### Preparation of *C. sinica* extract

Roots of *C. sinica* were obtained from Gwangmyeongdang (Ulsan, South Korea) and certified by Professor Jeong-Hoon Kim (Voucher no. MS2018-004). The ethanol extract of *C. sinica* (EECS) was produced as previously described.[13]

### Animals

Balb/c mice were used for all experiments (male, 6-week-old, Samtaco, Gyonggi, Republic of Korea). The study protocol was preapproved by our institution's Animal Care and Use Committee (PNU-2019-2269).

### Experimental design and induction of contact dermatitis

Experimental CD was produced using standardized methods as previously described.[14] The naïve controls (NOR) were administered vehicle topically for induction and treatment ($n = 7$). CD controls (CTL) were topically applied with DNFB and treated with vehicle ($n = 8$). EECS-treated animals were topically applied with DNFB and treated with EECS for 8 days ($n = 8$). Dexamethasone (DEX) applied topically at 150 μg/day for 8 days. The overall experimental process is summarized in Figure 1.

### Assessment of skin lesion severities

Skin lesion (roughness, excoriation, scabs, and erythema) severities were assessed on day 18 using a 4-point scale (0 = no, 1 = slight, 2 = mild, and 3 = severe symptoms), as previously described.[13]

### Assessment of erythema and melanin indices

Skin colors of shaved dorsal skin were evaluated on day 18 at three different points per mouse using a skin colorimeter (DSM II, Cortex Technology, Denmark).

### Measurement of skin weights and thicknesses

Dorsal skins were removed and skin samples were obtained using a biopsy punch (diameter 5 mm). Skin thicknesses were measured using a Vernier caliper (Mitutoyo, Tokyo, Japan) and skin weights using a microbalance.

### Histopathological examination

Inflamed tissues were dissected, embedded in paraffin, stained with hematoxylin and eosin, and observed under an optical microscope (×100). Epidermal hyperplasia was evaluated as previously described.[13]

### Measurement of cytokine levels

Cytokine levels in skin samples were assessed using a cytometric bead array Mouse Inflammation kit (BD, San Jose, CA, USA).

### Calculation of spleen bodyweight ratios

Changes in body weights between day 1 and day 18 are expressed as percentage body weight increases. Spleens were weighed after sacrifice on day 18.

### Statistical analysis

After one-way ANOVA, Dunnett's multiple comparison test was used to determine the significances of differences between groups. The analysis was performed using Prism 5 (version 5.01) software. Results are expressed as means ± standard deviations (SDs), and statistical significance was accepted for $P < 0.05$.

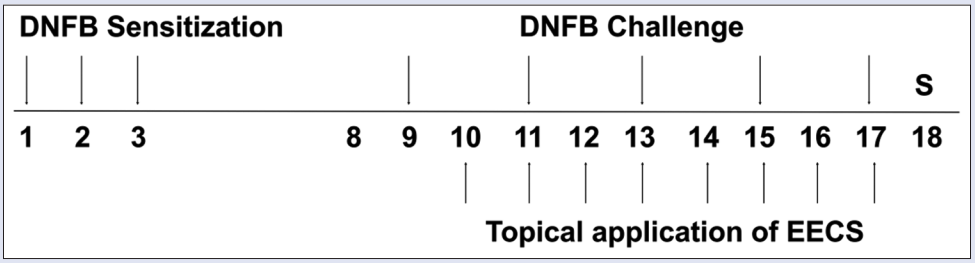


**Figure 1:** Experimental design. Balb/c mice with 2,4-dinitrofluorobenzene-induced Contact dermatitis were topically treated with an ethanol extract of *Caragana sinica* root (at 60, 180, and 600 μg/day) or dexamethasone (at 150 μg/day) for 8 days from day 10 to 17. Normal treatment- naïve controls were administered vehicle (acetone and olive oil, AOO, 4:1) topically for induction and treatment ($n = 7$). Contact dermatitis controls were sensitized and challenged with 2,4-dinitrofluorobenzene and treated topically with vehicle ($n = 8$). Ethanol extract of *Caragana sinica* -treated animals were sensitized and challenged with 2,4-dinitrofluorobenzene and treated with ethanol extract of *Caragana sinica* at 60, 180, or 600 μg/day topically for 8 days ($n = 8$). Dexamethasone applied topically at 150 μg/day for 8 days was used as the positive control. S means sacrifice. All animals were sacrificed on day 18

## RESULTS

### Ethanol extract of *Caragana sinica* alleviated skin lesions and inhibited thickening of dorsal skin

Topical application of 0.1% DNFB to dorsal skin induced CD symptoms such as roughness, abrasions, scabs, erythema, and petechia. Treatment with EECS suppressed these symptoms as compared with the CTL group [Figure 2a].

EECS treatment reduced skin lesion severity in a dose-dependent manner. Topical application of EECS also prevented the skin thickening induced by DNFB in the CTL group. Meanwhile, in the DEX-treated group, skin thickening was significantly reduced, but the severity of skin lesions was not significantly improved [Figure 2b and c].

### Ethanol extract of *Caragana sinica* lowered erythema and melanin indexes

In the CTL group, skin melanin and erythema indexes were significantly greater than in the NOR group. Topical application of EECS significantly reduced erythema and melanin indexes [Figure 3].

### Ethanol extract of *Caragana sinica* prevented epidermal hyperplasia and immune cell infiltration into inflamed tissues

Marked epidermal hyperplasia, immune cell infiltration, papillary dermal edema, vasodilation, and hyperkeratosis were appeared in the CTL group, but these abnormalities were suppressed by the topical application of EECS [Figure 4a]. Treatment with more than 180 μg/day of EECS reduced epidermal hyperplasia significantly in inflamed tissues, and treatment at 600 μg/day markedly reduced immune cell infiltration [Figure 4b and c].

### Ethanol extract of *Caragana sinica* reduced levels of tumor necrosis factor-α, Interferon -γ, interleukin-6 and MCP-1 in inflamed tissues

Significant increases in the levels of TNF-α, IFN-γ, IL-6, and MCP-1 were observed in the skin tissues of mice in the CTL group, but these increases were significantly suppressed by EECS. Skin TNF-α levels was reduced by all concentrations of EECS, and levels of IFN-γ, IL-6, and MCP-1 were reduced in a dose-dependent manner [Figure 5].

### Ethanol extract of *Caragana sinica* did not affect spleen/body weight ratios in contact dermatitis mice

Bodyweight gains and spleen/weight ratios of CD mice were unaffected by EECS. On the other hand, DEX treatment inhibited gaining weight and significantly reduced spleen/weight ratios [Figure 6].

## DISCUSSION

There are arguments in Korea and China about the efficacy and flavor of *C. sinica*. According to Korean literature, it is sweet and pungent, so it invigorates lungs. However, in Chinese literature, it is bitter, and thus, expels lung heat. Contrary to what has been described in Korean textbooks, *C. sinica* is customarily used as an analgesic and anti-inflammatory agent in Korea. This situation seems to have arisen because of differences between Chinese and Korean literature as herbal

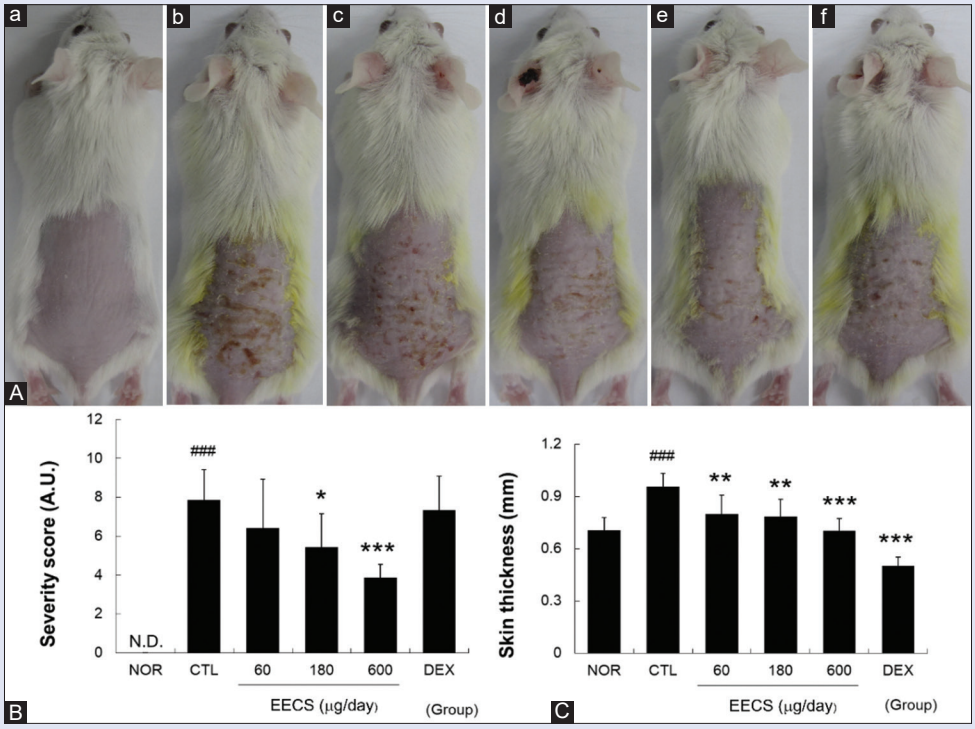


**Figure 2:** The effects of ethanol extract of *Caragana sinica* on skin lesions and thicknesses in Contact dermatitis mice. Skin surfaces were photographed using a digital camera on experimental day 18. a, Naïve controls; b, contact dermatitis controls; c, 60 μg/day of ethanol extract of *Caragana sinica*; d, 180 μg/day of ethanol extract of *Caragana sinica*; e, 600 μg/day of ethanol extract of *Caragana sinica*; f, 150 μg/day of dexamethasone (A). Lesion severity scores were determined using a semi-quantitative method (0–3 point scale) (B). Skin thicknesses were measured using a vernier calliper on day18 (C). Naïve controls, nontreated normal mice; contact dermatitis controls, nontreated contact dermatitis mice; (ethanol extract of *Caragana sinica*) treated contact dermatitis mice; dexamethasone treated contact dermatitis mice. All values are expressed as the means ± SD. $^{###}P < 0.001$ versus naïve controls; $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus contact dermatitis controls

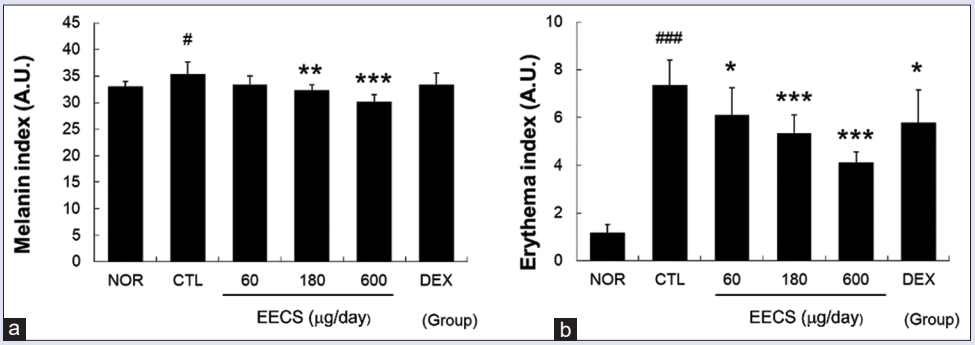


**Figure 3:** The effects of Ethanol extract of *Caragana sinica* on melanin and erythema indexes of dorsal skin surfaces. Melanin indices (a) and erythema indices (b) were measured using a dermo-spectrophotometer on day 18. Abbreviations are the same as those used in Figure 2. All values are expressed as means ± standard deviations. $^{\#}P < 0.05$ and $^{\#\#\#}P < 0.001$ versus Naïve controls; $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus contact dermatitis controls

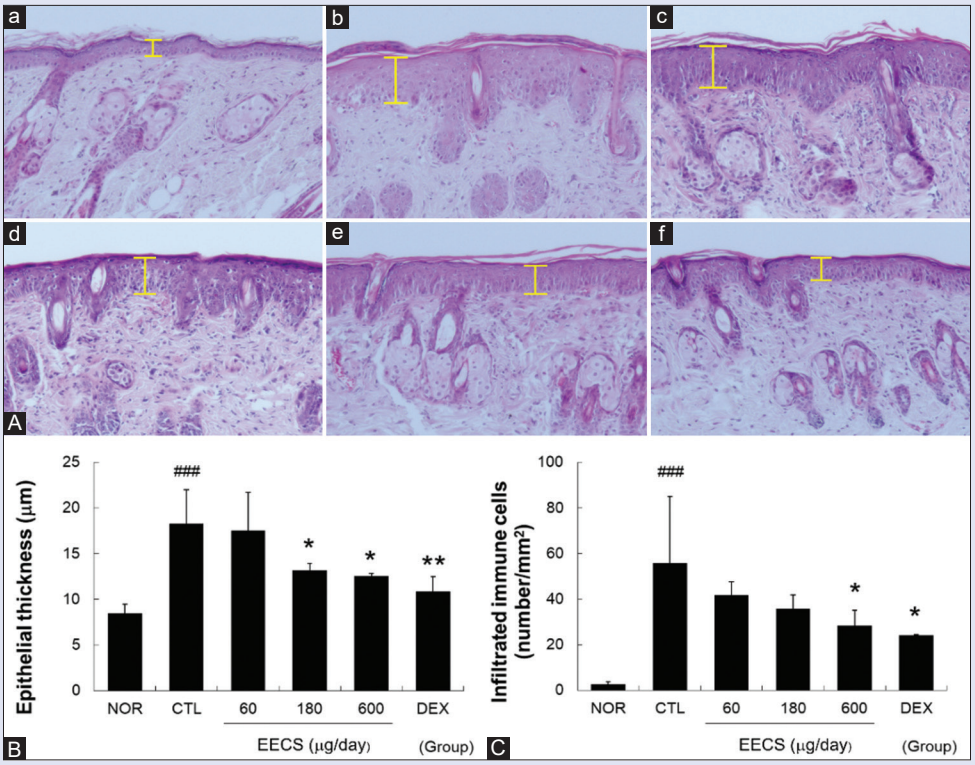


**Figure 4:** The effects of Ethanol extract of *Caragana sinica* on contact dermatitis -induced histopathologic changes. Skin tissues were H and E stained and observed under a light microscope. All observations were made at a magnification of ×200. The yellow bars indicate epidermal depths (A). Epidermal thicknesses (B) and the numbers of infiltrated immune cells in the visible grids (C) were also evaluated. Abbreviations are the same as those used in Figure 2. All values are expressed as means ± standard deviations. $^{\#\#\#}P < 0.001$ versus naïve controls; $^{*}P < 0.05$ and $^{**}P < 0.01$ versus contact dermatitis controls

medicines with a bitter flavor, which can remove heat in traditional medicine, frequently have anti-inflammatory effects in western medicine.[3,4] It means that Korean people perceive *C. sinica* has a bitter flavor, as described in Chinese literature.

Considering previous studies regarding the anti-inflammatory and immunomodulatory effects of *C. sinica*, this study was conducted based on the hypothesis that CD symptoms are alleviated by the topical application of EECS. In our animal model, repeated application of DNFB caused skin color changes and skin lesions such as roughness, abrasions, scabs, rashes, and skin swelling due to repeated scratching of dorsal skin. Given these symptoms, we believe that our animal model well-mimicked human CD.

Topical application of DNFB can increase skin thickness in mice,[15] and CD is frequently accompanied by various skin lesions which are indicators of CD aggravation.[16] Topical application of EECS alleviated these surface symptoms and inhibited skin thickening. These results imply that *C. sinica* can be used as a therapeutic agent for CD.

In the inflamed tissues of CD, epidermal hyperplasia and hyperkeratosis are induced by various inflammatory mediators that can activate keratinocytes, which when activated play a key role in inflammation.[17] In addition, immune responses initiated by resident cells result in inflammatory responses such as papillary dermal edema, vasodilation, and perivascular immune cell infiltration,[18] and topical EECS inhibited these histopathological abnormalities [Figure 4a]. These

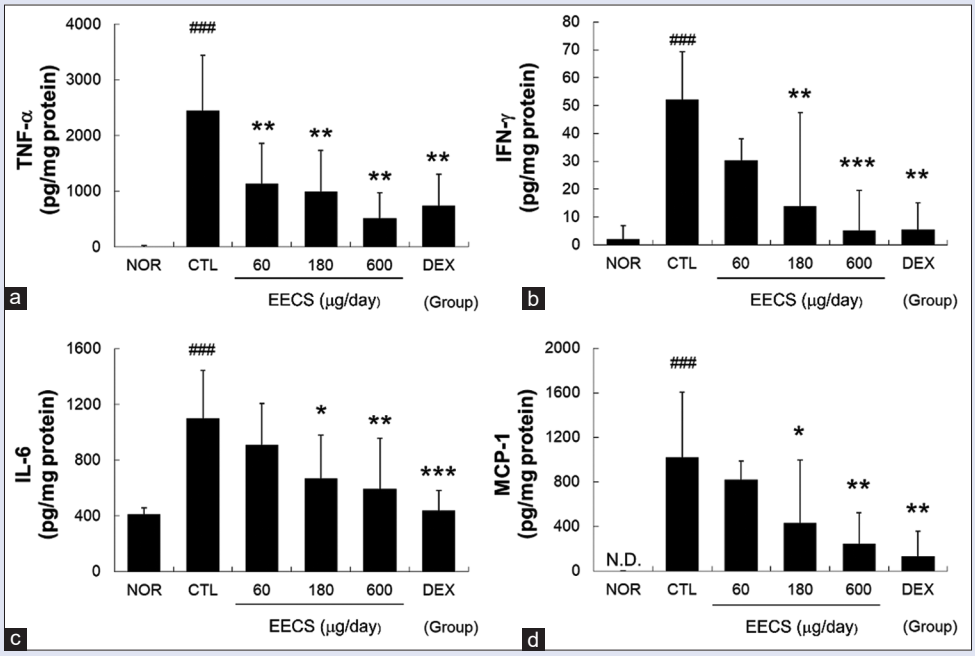


**Figure 5:** The effects of ethanol extract of *Caragana sinica* on cytokine and chemokine production in inflamed tissues. Tumor necrosis factor -α, interferon-γ, interleukin -6, and MCP-1 levels in skin tissues were measured using the cytometric bead array method. (a) Tumor necrosis factor-α; (b) interferon -γ; (c) interleukin -6; (d) MCP-1. Abbreviations are the same as those used in Figure 2. All values are expressed as means ± standard deviations. $^{###}P < 0.001$ versus Naïve controls; $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus contact dermatitis controls

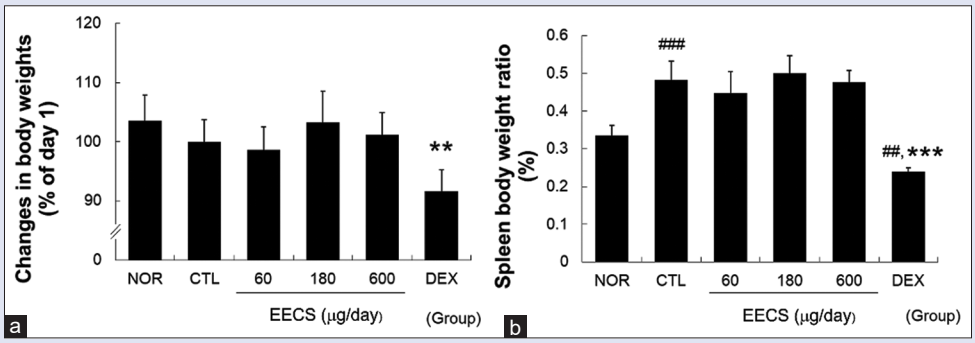


**Figure 6:** The effects of Ethanol extract of *Caragana sinica* on contact dermatitis -induced changes in body weights and spleen/body weight ratios. Body and spleen weights were measured on day 18 and changes in body weights (a) and spleen/body weight ratios (b) were calculated. Abbreviations are the same as those used in Figure 2. All values are expressed as means ± standard deviations. $^{#}P < 0.05$ and $^{###}P < 0.001$ versus Naïve controls; $^{**}P < 0.01$ and $^{***}P < 0.001$ versus contact dermatitis controls

results mean that *C. sinica* can alleviate skin lesions by suppressing histopathological abnormalities such as epidermal hyperplasia, papillary dermal edema, vasodilation, and perivascular immune cell infiltration in inflamed tissues.

In the inflammatory tissues of CD patients, serum levels of TNF-α and IFN-γ, which both play a major role in the pathogenesis of CD, are up-regulated.[19] These pro-inflammatory cytokines synergistically up-regulate inflammatory cascades and can activate keratinocytes,[12,20] which in turn, can cause epidermal hyperplasia and hyperkeratosis, and contribute to immune cell infiltration by inducing the over-expression of intercellular adhesion molecule-1 and inflammatory mediator release.[15]

TNF-α is a primary cytokine that causes the release of secondary cytokines and chemokines such as IL-6 and MCP-1. IL-6, which is regulated by keratinocytes, induces lymphocyte and monocyte infiltration and thus sustains skin inflammation.[12] MCP-1, also known as C-C motif chemokine ligand 2, acts as a chemotactic that promotes the infiltrations of immune cells such as monocytes, T cells, and dendritic cells.[12,21]

According to our results, EECS significantly lowered the levels of TNF-α, IFN-γ, IL-6, and MCP-1 in the skin tissues of CD mice, which suggest that *C. sinica* has anti-inflammatory effects that can prevent histopathological abnormalities such as epidermal hyperplasia and immune cell infiltration and that these effects are due to the down-regulation of cytokine and chemokine production.

Kobophenol A and (+)-α viniferin are oligo stilbenes with anti-inflammatory activities,[5,9] and are also major components of *C. sinica*. Kobophenol A can inhibit the expressions of IL-6, nitric oxide, and inducible nitric oxide synthase by inhibiting the nuclear translocation of nuclear factor-κ*B* in macrophages,[12] and (+)-α-Viniferin has been shown to suppress prostaglandin H2 synthase by inhibiting cyclooxygenase activity in purified sheep seminal vesicles.[9] In view of

these reports, it seems likely that kobophenol A and (+)-α viniferin are major contributors to the therapeutic properties of *C. sinica*.

Antihistamines and corticosteroids are commonly used to treat patients with CD. However, antihistamines have only temporary ameliorative effects and systemic corticosteroids are known to have many adverse effects. Even when corticosteroids are used topically, long-term application is not only less effective but also induces skin atrophy and has a "rebound effect" caused by lowering the thresholds of external triggers.[22,23]

As shown in Figure 2, DEX prevented skin thickening in our CD model but was less effective at alleviating skin symptoms, which suggests despite its inhibitory effect on skin thickening, DEX is not an adequate treatment for dermatitis. We suggest that the anti-inflammatory effect of DEX (a main effect of DEX) combined with skin atrophy (an adverse effect of DEX) caused the observed skin thickness reduction.

Systemic corticosteroid administration can have extensive immunosuppressive effects.[22,24] In the present study, spleen/body weight ratios were significantly lower in the DEX group than in the NOR and CTL groups. On the other hand, EECS did not affect spleen/weight ratios of CD mice. These results imply that the action mechanisms of EECS and DEX differ, and notably, EECS did not have the general immunosuppressive effect of corticosteroids.

Taken together, these results suggest that *C. sinica* has potential functions as a therapeutic agent for CD. Furthermore, although its effects are similar to those of corticosteroids, we believe that it is likely to be safer because it is a natural product with a different action mechanism.

## CONCLUSION

This study confirms that ethanol extracts of *C. sinica* roots can prevent epidermal hyperplasia, papillary dermal edema, vasodilation, and immune cell infiltration by inhibiting the productions of cytokines and chemokines such as TNF-α, IFN-γ, IL-6, and MCP-1, and these successive anti-inflammatory effects of EECS alleviated skin lesions in our mouse model. Furthermore, the efficacy of the EECS was similar to that of DEX, but its action mechanism appeared to differ. These results suggest that *C. sinica* has potential use as a therapeutic agent for CD.

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## Conflicts of interest

There are no conflicts of interest.

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