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Inhibitory effects of *Chelidonium majus* extract on atopic dermatitis-like skin lesions in NC/Nga mice

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ABSTRACT

Aim of the study: Chelidonium majus (CM) has traditionally been used for treatment of various inflammatory diseases including atopic dermatitis (AD). However its action on atopic dermatitis (AD) is unclear. Therefore, we investigated the effect of CM on AD using NC/Nga mice as an AD model.
Materials and methods: The effect of CM on 1-chloro-2,4-dinitrobenzene (DNCB) induced NC/Nga mice was evaluated by examining skin symptom severity, itching behavior, ear thickness, levels of serum immunoglobulin E (IgE), tumor necrosis factor-α (TNF-α), and interlukin-4 (IL-4), skin histology.
Results: The CM significantly reduced the total clinical severity score, itching behavior, ear thickness and the level of serum IgE in AD mouse model. CM not only decreased TNF-α but also IL-4.
Conclusion: These results suggest that CM may be a potential therapeutic modality for AD.

1. Introduction

Atopic dermatitis (AD) is a common disease affecting both children and adults. AD develops from a complex interplay between environmental, genetic, immunologic and biochemical factors (Pugliarello et al., 2010). Chronic inflammation in AD is associated with elevated levels of serum immunoglobulin E (IgE) and eosinophilia in the tissues and peripheral blood, and frequently occurs in response to environmental allergens such as house-dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* (Leung, 2000; Matsuoka et al., 2003).

The NC/Nga mouse is the most extensively studied animal model of AD. The NC/Nga strain originated from Japanese fancy mice and was established as an inbred strain by Kondo et al. in 1957. These mice spontaneously develop AD-like eczematous skin lesions when kept under conventional conditions, but not when maintained under specific pathogen-free (SPF) conditions (Shiohara et al., 2004). Clinical symptoms begin with itching, erythema, hemorrhage, scaling, dryness, and alopecia at the age of 8 weeks. These eczematous skin lesions are typically observed on the face, nose, ears, neck and back, suggesting that they are caused by hind limb scratching. The clinical severity of the dermatitis, as determined by a scoring system which has been established for human AD, increases with age and reaches a maximum at around 17 weeks of age (Matsuda et al., 1997).

Chelidonium majus L. is a plant which grows in the wild in Southern and Central Europe, part of Asia, North America and in the Azores archipelago (Tin-Wa et al., 1972; Colombo and Bosisio, 1996). *Chelidonium majus* L. (family Papaveraceae), or greater celandine, is an important plant in western phytotherapy and in traditional Chinese medicine. *Chelidonium majus* L. has multiple applications in folk medicine because of its antitumoral, cytotoxic, anti-inflammatory and anti-microbial activities (Kim et al., 1969; Saglam and Arar, 2003). Crude extracts of *Chelidonium majus* as well as purified compounds derived from it exhibit a broad spectrum of biological activities (antiinflammatory, antimicrobial, antitumoral, analgesic, hepatoprotective) that support some of the traditional uses of *Chelidonium majus* (Gilca et al., 2010). The plant contains, as major secondary metabolites, isoquinoline alkaloids, such as sanguinarine, chelidonine, chelerythrine, berberine and coptisine. Isoquinoline alkaloids have anti-inflammatory activity (Kupeli et al., 2002). Sanguinarine, chelerythrine and quaternary benzophenanthridine fraction were screened for their anti-inflammatory activity in assays involving carrageenan-induced rat paw edema. Sanguinarine showed a higher anti-inflammatory activity than chelerythrine, which could be explained with the different oxygen electrodonating substituents (Lenfeld et al., 1981). In spite of the traditional usage

Abbreviations: AD, atopic dermatitis; CM, *Chelidonium majus*; IL-4, interleukin-4; IgE, immunoglobulin E; TNF-α, tumor necrosis factor-α; DNCB, 1-chloro-2,4-dinitrobenzene; NOR, normal group; CON, control group; CMP 1, *Chelidonium majus* Methanol Extract 100 mg/kg, p.o. group; CMP 4, *Chelidonium majus* Methanol Extract 400 mg/kg, p.o. group; CMS 1, *Chelidonium majus* Methanol Extract 1% (200 μl) smear group; CMS 2, *Chelidonium majus* Methanol Extract 2% (200 μl) smear group.

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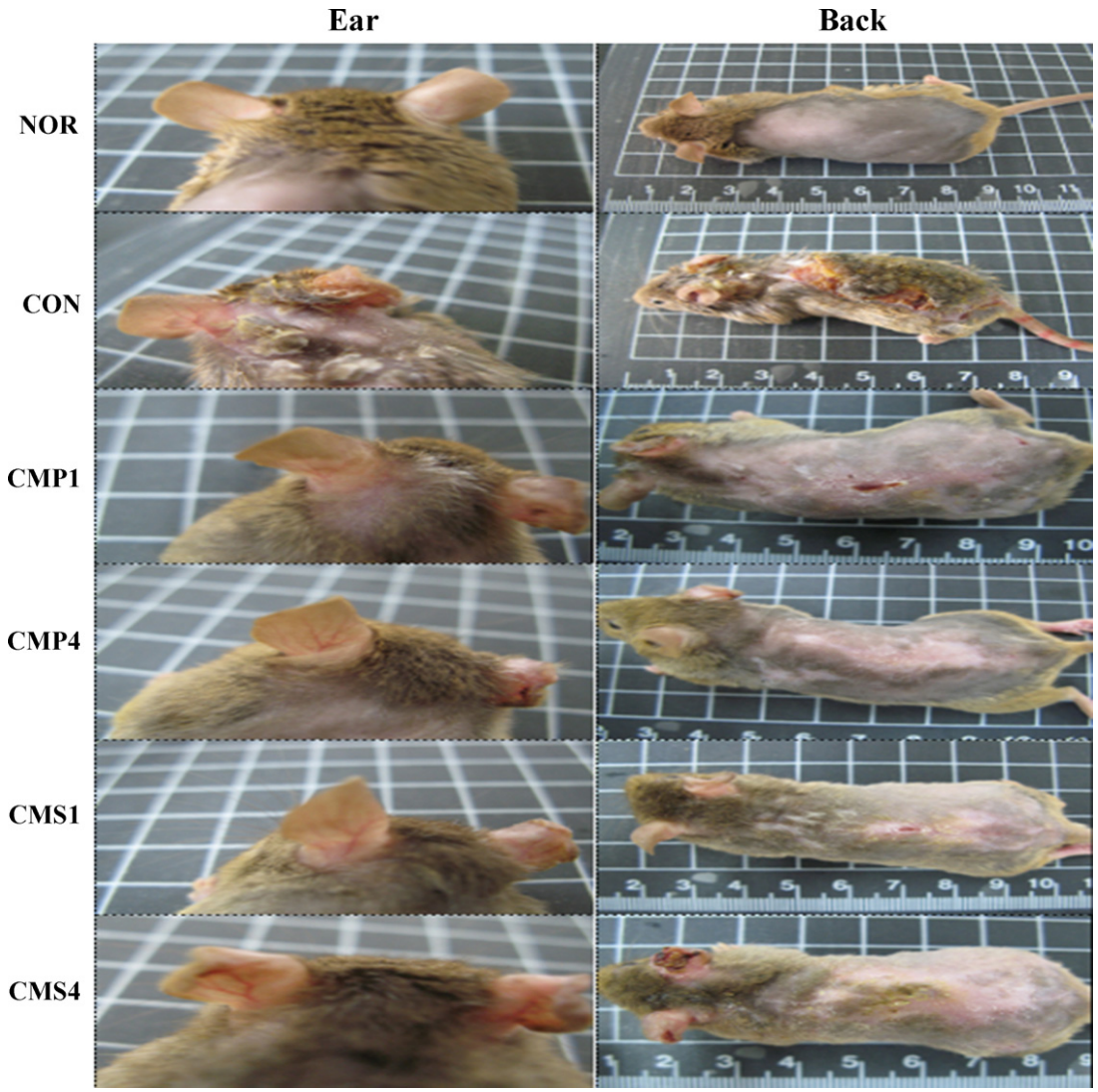

Fig. 1. Clinical features of NC/Nga mice. The photograph was taken on the 6 weeks after sensitization.

of *Chelidonium majus* to treat allergic disease, its mechanism has not been fully verified using scientific tools. Under the circumstances, we investigated the anti-allergic effects of *Chelidonium majus* extract on NC/Nga mice as a model of DNCB-induced atopic dermatitis.

2. Materials and methods

2.1. Preparation of CM extract

Chelidonium majus as a dried herb was collected from Gunwi, Kyungpook Province, South Korea and authenticated by H.-Y. Choi, College of Oriental Medicine, Kyung Hee University. A voucher specimen was deposited at the Herbarium of the College of Oriental Medicine, Kyung Hee University. The dried aerial part of *Chelidonium majus* (5 kg) was extracted twice with 70% ethanol (with 2 h reflux), and extract was then concentrated under reduced pressure. The decoction was filtered, lyophilized, and serially stored at 4 °C. The yield of dried extract from starting crude materials was about 6.64% (w/w). The extract was dissolved in saline or phosphate-buffered saline (PBS) and then filtered through a 0.22-μm syringe filter for experiments.

2.2. Experimental animals

Female 5-week-old NC/Nga mice were purchased from SLC, Inc. (Hamamatsu, Japan) and were maintained for 1 week prior to experiments. They were housed in an air-conditioned animal room with a 12-h light/12-h dark cycle at a temperature of 22 ± 1 °C and humidity of 50 ± 10%. Mice were provided with a laboratory diet and water *ad libitum*. All experimental protocols for animal care involving the use of animals were conducted in accordance with National Institutes of Health (NIH) Guidelines and approved by the Committee on Animal Care of our institute.

2.3. Induction of dermatitis

1-Chloro-2,4-dinitrobenzene (DNCB; Sigma–Aldrich, St Louis, MO, USA) was used to induce dermatitis in all three groups of NC/Nga mice through repeated cutaneous application as previously described. Allergic dermatitis on NC/Nga mice was induced according to the protocol reported by Gao et al. (2005) with a slight modification. Briefly, DNCB in an acetone/olive oil mixture (1:3) was used. Dorsal skin regions were shaved with an electric razor and these and the glabrous ears were sensitized epicutaneously with 200 μl of a 1% DNCB solution. Controlled dermatitis