



Effects of *Bambusae caulis* in Liquamen on the development of atopic dermatitis-like skin lesions in hairless mice

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ABSTRACT

Ethnopharmacological relevance: *Bambusae caulis* in Liquamen (BCL) is a nutritious liquid extracted from heat-treated fresh bamboo stems. It is an important traditional herbal medicine used to treat coughs and asthma in East Asia. In recent years, it has been studied for its anti-inflammatory, anti-allergenic, and immune-regulating properties.

Aim of the study: To examine whether BCL suppresses the development of 2,4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis (AD)-like skin lesions in hairless mice.

Materials and methods: The effects of BCL were analyzed by measuring transepidermal water loss (TEWL), melanin content, and erythema in the skin, leukocyte numbers and IgE levels in the serum, and mRNA expression of relevant cytokines in the spleen.

Results: The transdermal administration of BCL to hairless mice inhibited the development of DNCB-induced AD-like skin lesions by suppressing TEWL, melanin production and erythema of skin, the number of leukocytes and the level of IgE in serum, and the mRNA expression of IL-4, IL-13, and TNF- α in the spleen. However, BCL administration increased the expression of IFN- γ in the spleen.

Conclusions: These findings indicate that BCL suppresses the development of DNCB-induced AD-like skin lesions in hairless mice, suggesting that BCL may be a potential therapeutic agent for AD in a clinical setting.

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1. Introduction

Atopic dermatitis (AD) is a common chronic pruritic inflammatory skin disease that is characterized by peripheral blood eosinophilia and a high level of serum IgE (Soter, 1989; Uehara et al., 1990; Cooper, 1994; Rudikoff and Lebwohl, 1998). In recent years, the number of patients with AD in developed nations has increased (Leung and Bieber, 2003; Spengel and Paller, 2003). The causes of AD are multifactorial, and include immunological abnormalities and physiological and biochemical defects of the skin barrier structure (Leung, 1997; Akdis et al., 2000; Leung, 2000; Pastore et al., 2000; Romagnani, 2000). Previous studies have demonstrated that the ratio of IL-4 producing cells to IFN- γ producing cells is increased in acute AD lesions. Further, mononuclear cells from patients with

AD produce larger amounts of IL-4, IL-5, and IL-13 compared to those from healthy individuals (Poulsen et al., 1995; Leung, 2000). In contrast, chronic AD skin lesions have significantly fewer IL-4 and IL-13 mRNA-expressing cells but increased numbers of IL-5, IL-12, and IFN- γ mRNA-expressing cells compared to those in acute AD skin lesions. Moreover, AD tends to decrease skin hydration and thus increase transepidermal water loss (TEWL) (Lodén et al., 1992; Kim et al., 2006).

Despite the increase in the number of patients with AD in recent years, the pathogenesis of the disease has not yet been fully elucidated. Immunosuppressive drugs such as glucocorticoids are effective for atopic dermatitis however prolonged use of these drugs may cause adverse effects owing to its non-specific immune modulation (Kakinuma et al., 2001; Furukawa et al., 2004). Herbal medicines such as *Rumex japonicus* (Lee et al., 2006) and *Scutellaria baicalensis* (Lee et al., 2007) are used to treat atopic dermatitis in Eastern countries. *Bambusae caulis* in Liquamen (BCL), the nutritious liquid that is extracted from heat-treated fresh bamboo stems, is a traditional herbal medicine widely used in Eastern countries to treat coughs and asthma. Recent studies have shown

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that BCL exhibits anti-inflammatory, anti-allergenic, antioxidative, and immune-regulating effects (Jeon et al., 2003; Je et al., 2009). Furthermore, this liquid diluted with water is gaining widespread popularity in Eastern countries as a folk medicine for the treatment of skin diseases such as scabies, eczema, and atopic dermatitis (Kimura et al., 2002). However, the effect of BCL on AD-like skin lesions has not been evaluated.

In the present study, we demonstrate that BCL significantly suppresses the development of DNCB-induced AD-like skin lesions in hairless mice, a murine model of AD (Black et al., 1995).

2. Materials and methods

2.1. *Bambusae caulis in Liquamen (BCL)*

BCL was purchased from Nanumttel Co., Ltd. (Seoul, Korea). Fresh bamboo stems (*Phyllostachys bambusoides* Siebold et Zuccarini) were harvested from fields and mountains in the vicinity of Chuwol Mountain in Damyang (Chonnam, Korea). A voucher specimen (KNKA200506151038) was deposited in the herbarium of the Korea National Arboretum (Gyeonggi, Korea). Ten kilograms of fresh bamboo stems (30–50 cm segments) were heated indirectly at 200 °C for 12 h using a crock. About 2 l of liquid released directly from the bamboo stems were collected and then purified using an active carbon filtration device to remove impurities. The commercial BCL was further sterilized using a 0.2 µm filter (Toyo Roshi Kaisha Ltd., Tokyo, Japan), and stored at 4 °C until use.

2.2. Animals

Seven-week-old female hairless mice were purchased from Orient Bio (Sungnam, Korea). The animals were kept in a constant temperature (22 ± 2 °C) and humidity (55 ± 5%) environment, and provided with a standard diet and water throughout the experiments. This study was approved by the Yonsei University Animal Committee, and the animals were maintained in accordance with the guidelines for the care and use of laboratory animals of Wonju College of Medicine, Yonsei University.

2.3. Induction of AD-like skin lesions in hairless mice

DNCB (purchased from TCI, Japan) dissolved in acetone was used to induce dermatitis in hairless mice as described previously (Black et al., 1995; Matsumoto et al., 2004, 2005). Briefly, the dorsal skin of hairless mice in both the control (Con) group and experimental (Exp) groups were sensitized with 100 µl of 1% DNCB daily for 7 days. After the first challenge, 100 µl of 0.5% DNCB was repeatedly applied to the dorsal skin for a further 5 weeks at 2-day intervals. At the same time, 100 µl of BCL was applied daily to the entire dorsal skin of the hairless mice in the Exp group for 5 weeks and the application of BCL was separated by 7 h from that of DNCB. The normal (Nor) group was treated with distilled water instead of DNCB. No substances were applied to the skin surface on the last day of the experiment. The next day, measurements of skin barrier function including TEWL, melanin content, and erythema were carried out. The mice were then killed, and skin, spleen, and blood samples were collected for further analysis.

2.4. Transepidermal water loss (TEWL)

A cutometer MPA 580 (Courage & Khazaka, Cologne, Germany) was used to evaluate the skin surface of the hairless mice at the end of the experiment according to the manufacturer's instruction. TEWL was measured under standard conditions (a room tem-

perature of 20 ± 2 °C and a relative humidity of 45 ± 5%) using a Tewameter TM 210 probe (Courage & Khazaka, Cologne, Germany).

2.5. Melanin and erythema

Both melanin content and erythema of the dorsal skin were measured using a Mexameter MX 18 probe (Courage & Khazaka, Cologne, Germany) under the same conditions as described above in Section 2.4.

2.6. Scanning electron microscopy

For the scanning electron microscopy (SEM) observations, the skin tissues obtained from hairless mice after measurement of skin barrier function were fixed in 2.5% glutaraldehyde for 2 h at 4 °C, washed in 0.1 M phosphate buffer (pH 7.4), and then post-fixed in 1% osmium tetroxide in the same buffer for 90 min at 4 °C, dehydrated in a series of ethyl alcohol concentrations, and then critical point-dried. The specimens were coated with gold-palladium and then examined under a scanning electron microscope (TM-1000, HITACHI Co. Ltd., Japan) at 30 kV.

2.7. Serum leukocyte evaluation

After the experiment, blood samples were collected from the retro-orbital plexus of mice. A HEMAVET® 950 (DREW Scientific, USA) was used to evaluate the amount of leukocytes in the serum samples of hairless mice. We measured the number of white blood cells (WBC), neutrophils (NE), eosinocytes (EO), monocytes (MO), lymphocytes (LY), and basicytes (BA).

2.8. RT-PCR analysis

Total RNA from the spleen was isolated with Trizol (Molecular Research Center Inc., Cincinnati, USA) according to the manufacturer's instruction. cDNA was synthesized from total RNA (2 µg) using oligo (dT)₁₈ primers (0.5 µg) and the Prime RT Premix kit (GeNet Bio, Korea) according to the manufacturer's instruction. The primers used in this study were as follows: IL-4 (forward) 5'-AGT TGT CAT CCT GCT CTT CTT T-3', (reverse) 5'-GAC TGG GAC TCA TTC ATG GTG C-3'; IL-13 (forward) 5'-GCA ACG GCA GCA TGG TAT GGA G-3', (reverse) 5'-TGG TAT AGG GGA GGC TGG AGA C-3'; IFN-γ (forward) 5'-CTC AAG TGG CAT AGA TGT-3', (reverse) 5'-GAG ATA ATC TGG CTC TGC AGG ATT-3'; TNF-α (forward) 5'-CAC CAC GCT CTT CTG TCT ACT GAA C-3', (reverse) 5'-CCG GAC TCC GTG ATG TCT AAG TAC T-3'; and β-actin (forward) 5'-GCA CCA CAC CTT CTA CAA TGA G-3', (reverse) 5'-TTG GCA TAG AGG TCT TTA CGG A-3'. β-actin primers were used as an internal control. The PCR reaction was performed using the Prime Taq Premix kit (GeNet Bio, Korea) and a final reaction volume of 20 µl. All samples were pre-denatured for 5 min at 94 °C, followed by 32 thermal cycles (94 °C for 30 s, 55–62 °C for 30 s, and 72 °C for 1 min), and an additional extension at 72 °C for 7 min. Amplified cDNAs were subjected to electrophoresis on 2% agarose gels and visualized by staining with ethidium bromide.

2.9. Measurement of serum IgE

Blood samples were collected from the retro-orbital plexus of mice at the end of the experiment. Serum was obtained by centrifugation at 3000 × g for 10 min at 4 °C and stored at –70 °C until use. The serum IgE levels were measured using a mouse IgE enzyme-linked immunosorbent assay kit (Shibayagi Co., Ltd., Gunma, Japan) following the manufacturer's instruction.

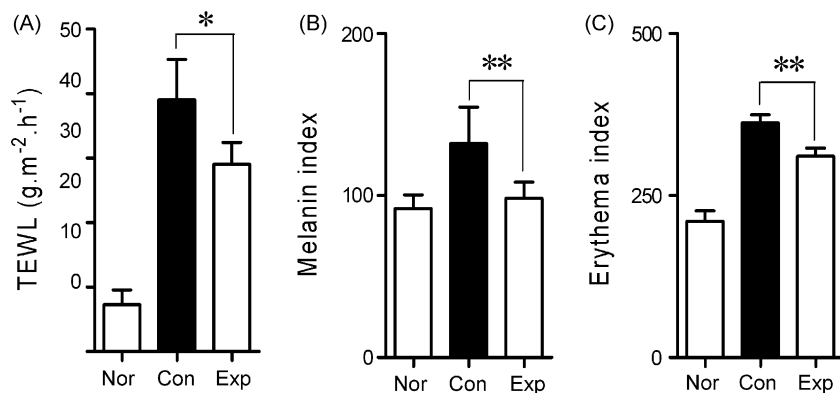


Fig. 1. Improvement in skin lesions in hairless mice treated with BCL. The amount of transepidermal water loss (TEWL) (A), melanin content (B) and erythema (C) in the dorsal skin of hairless mice was evaluated. 0.5% DNCB was applied to the dorsal skin of hairless mice in both the control (Con) and experimental (Exp) groups for 5 weeks in addition to the first week of challenge with 1% DNCB to elicit AD-like skin lesions. BCL was applied to Exp group from the 2nd week until the end of the experiment. Values are expressed as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$.

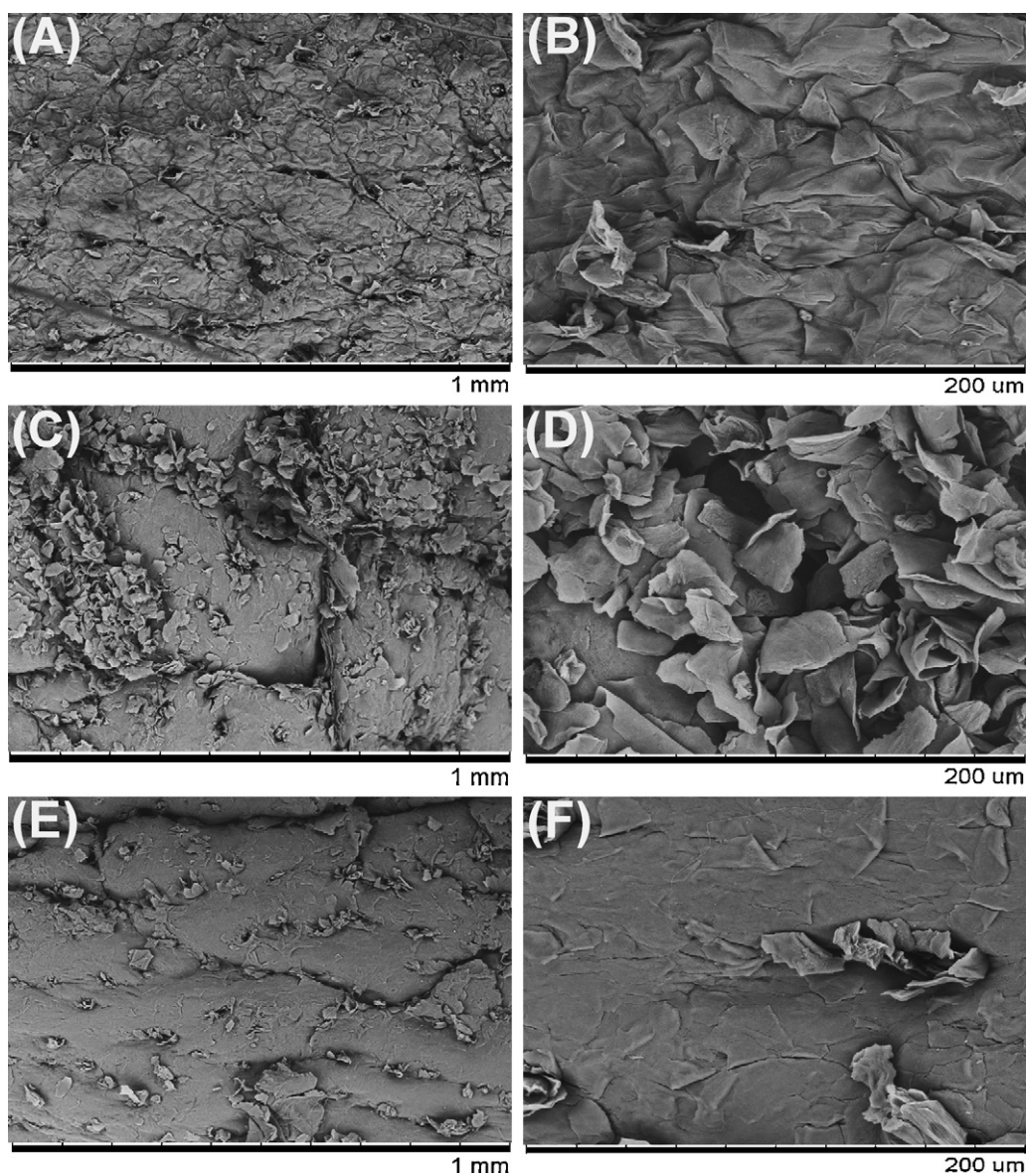


Fig. 2. Scanning electron micrographs of skin lesions in hairless mice. Skin tissue was obtained from hairless mice at the end of the experiment. The Nor group was treated with distilled water (A, B), while the Con group received DNCB alone (C, D), and the Exp group was treated with DNCB and BCL (E, F) (magnification = 100 $\times$ and 500 $\times$).

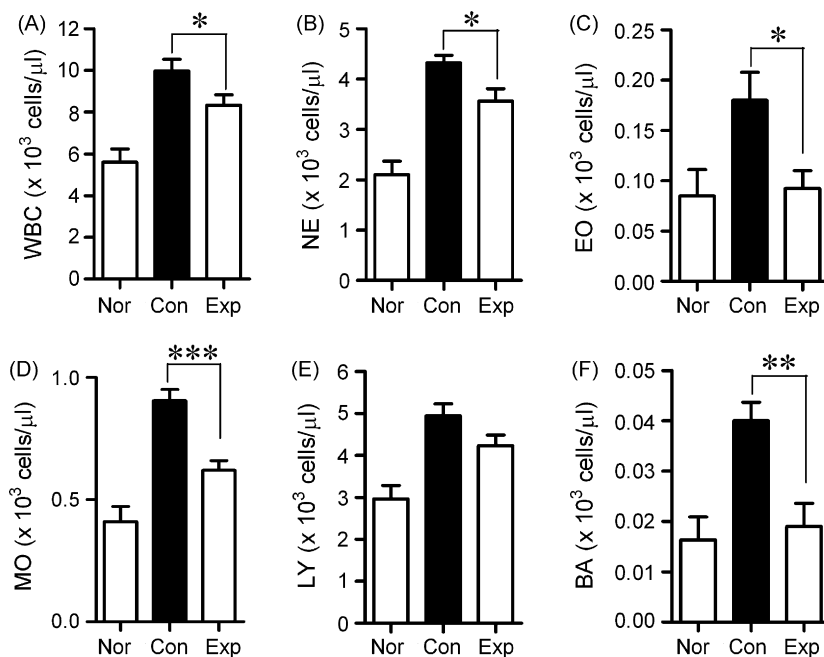


Fig. 3. Effects of BCL on the production of serum leukocytes in DNCB-induced hairless mice. Amount of (A) white blood cells (WBC), (B) neutrophils (NE), (C) eosinocytes (EO), (D) monocytes (MO), (E) lymphocytes (LY) and (F) basicytes (BA) in the serum of hairless mice from different groups was evaluated at the end of experiment. Values are expressed as means $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

2.10. Statistical analysis

The statistical differences between two groups were analyzed with Student's *t*-test. A *p*-value < 0.05 was considered to be statistically significant. All data are shown as mean $\pm$ SEM ($n = 8$).

3. Results

3.1. Improvement of skin lesions in BCL-treated hairless mice

The barrier function of the skin at lesional sites in AD patients is deficient (Imokawa et al., 1991). We thus examined the effect of BCL on DNCB-induced skin lesions in hairless mice. TEWL was measured as a marker of barrier function. DNCB greatly increased TEWL to $39.06 \pm 6.24 \text{ g m}^{-2} \text{ h}^{-1}$, whereas it was significantly reduced to $29.08 \pm 3.34 \text{ g m}^{-2} \text{ h}^{-1}$ by the transdermal administration of BCL ($p < 0.05$) (Fig. 1A). Furthermore, the melanin content and erythema of AD-like skin lesions in the Exp group decreased significantly in comparison with non-BCL-treated hairless mice in the Con group (both $p < 0.01$; Fig. 1B and C).

3.2. Observation of the skin surface using electron microscopy

Changes in epidermal skin lesions in the hairless mice were also examined using a scanning electron microscopy (SEM). The skin surface appeared to be smooth in the Nor group (Fig. 2A and B). However, the skin surface was remarkably rough and rugged in mice with DNCB-induced skin lesions (Con and Exp groups, Fig. 2C–F). The roughness of the skin surface was markedly suppressed by BCL in the Exp group (Fig. 2E and F).

3.3. Effect of BCL on the production of serum leukocytes in hairless mice

Leukocytes play an important role in inflammation (Soter, 1989; Uehara et al., 1990; Jenerowicz et al., 2007). We therefore measured the amount of various serum leukocyte species (WBC, NE, EO, MO, LY, and BA) in DNCB-treated hairless mice, and found

that DNCB application increased the amount of leukocytes. In contrast, BCL significantly decreased the numbers of all DNCB-induced leukocyte species, with the exception of LY (WBC, NE and EO, $p < 0.05$; BA, $p < 0.01$; MO, $p < 0.001$) (Fig. 3A–D, F). The amount of LY in BCL-treated hairless mice was slightly lower than that in the DNCB-treated Con group, though this difference was not significant (Fig. 3E).

3.4. Effect of BCL on serum IgE levels in DNCB-treated mice

To examine whether BCL decreases the increase in IgE induced by DNCB in hairless mice, serum IgE levels were measured by ELISA analysis. As shown in Fig. 4, serum IgE levels ($38.26 \pm 5.51 \text{ } \mu\text{g/ml}$) were elevated in the DNCB-induced group (Con) compared with the normal (Nor) group ($p < 0.001$), whereas BCL remarkably reduced these IgE levels to $14.34 \pm 6.31 \text{ } \mu\text{g/ml}$ in the Exp group ($p < 0.05$).

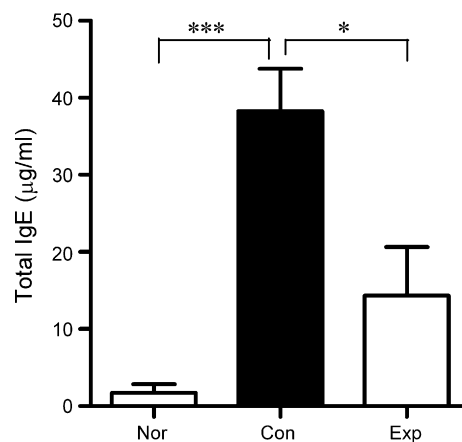


Fig. 4. Effects of BCL on serum IgE levels in DNCB-induced hairless mice. The serum IgE levels in hairless mice were measured at the end of the experiment using an ELISA kit. Transdermal administration of BCL significantly decreased serum IgE levels in DNCB-induced hairless mice. Values are means $\pm$ SEM. * $p < 0.05$, *** $p < 0.001$.

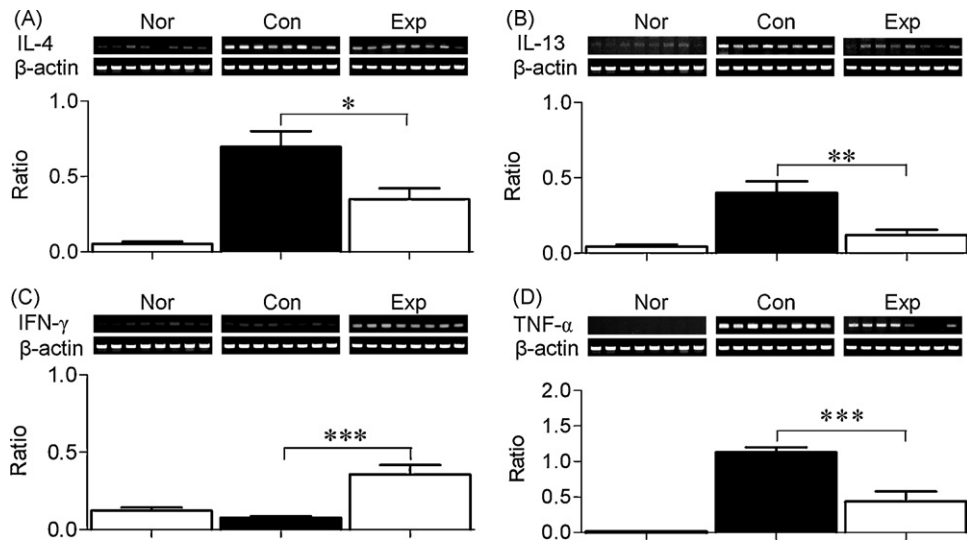


Fig. 5. Cytokine mRNA expression in the spleen of hairless mice from the normal group (Nor), control group (Con), and experimental group (Exp). The lower panel showed the mean ratio of cytokine to β -actin mRNA expression in the three groups. All values are means $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (A) IL-4, (B) IL-13, (C) IFN- γ , and (D) TNF- α .

3.5. Cytokine mRNA expression in BCL-treated hairless mice

An imbalance between Th1 and Th2 responses is thought to underlie immune system diseases such as AD and asthma, which are characterized by Th2-dominated allergic inflammation (Grewe et al., 1998; Spengel et al., 1999; Vestergaard et al., 1999). We therefore examined changes in the mRNA expression of Th1- and Th2-type cytokines in the spleen at the end of the experiment. Fig. 5 shows that BCL markedly suppressed the DNCB-induced mRNA expression of IL-4, IL-13, and TNF- α . Conversely, IFN- γ mRNA expression was increased in the Exp group compared to the Con group. These findings suggest that transdermal administration of BCL may modulate the DNCB-induced immune response in the skin of hairless mice.

4. Discussion

Bambusae caulis in Liguamen (BCL) is a liquid extracted from heat-treated fresh bamboo stems. It has been used as a traditional herbal medicine for many years in East Asia to relieve coughs and asthma, and to remove phlegm. Several studies in recent years have demonstrated that BCL has anti-inflammatory, anti-allergic, immune-regulating, antioxidative, and anti-carcinogenic properties (Jeon et al., 2003; Je et al., 2009). In the present study, we showed that BCL suppresses the development of DNCB-induced AD-like skin lesions in hairless mice.

The skin of patients with AD is often dry and characterized by heightened transepidermal water loss (TEWL), increased roughness, and erythema (Takahashi et al., 2008). Therefore, we first examined the effects of BCL on TEWL, melanin content, and erythema in DNCB-treated hairless mice. We found that transdermal administration of BCL greatly suppressed TEWL, melanin content, and erythema in DNCB-treated hairless mice. SEM analysis of the skin confirmed that BCL improved AD-like skin symptoms (Fig. 2). It has been found that the lack of some minerals plays an important role in the development of AD. For example, zinc deficiency exacerbates atopic dermatitis, which influences the skin barrier system and immune system (Takahashi et al., 2008). Furthermore, magnesium ions can improve skin barrier function, enhance skin hydration, and reduce inflammation in atopic dry skin (Schempp et al., 2000; Proksch et al., 2005). BCL is the liquid isolated from fresh bamboo stems which contains various minerals, including magne-

sium, zinc, calcium, and potassium (Li et al., 1997a,b; Nirmala et al., 2007). Thus, BCL may have improved the skin barrier function in the hairless mice owing at least in part to its mineral content. This idea is supported by previous studies that have shown that minerals such as magnesium and zinc improve skin barrier function in atopic dry skin (Schempp et al., 2000; Proksch et al., 2005; Takahashi et al., 2008).

Several studies have demonstrated that serum IgE levels are elevated in patients with AD. Leung (1993) demonstrated a correlation between the degree of serum IgE elevation and the extent of skin involvement. Further, serum IgE levels have been shown to be elevated in NC/Nga mice with AD-like skin lesions (Matsuda et al., 1997; Kotani et al., 2000; Ohmura et al., 2004; Shiohara et al., 2004). In this study, the serum levels of leukocytes and IgE were measured to assess the effects of BCL on immune response. BCL greatly decreased the amount of leukocytes (Fig. 3) and the serum level of IgE (Fig. 4) in DNCB-treated hairless mice. IgE synthesis by B cells is regulated primarily by cytokines. Th2 cytokines such as IL-4 and IL-13 play a key role in the hyperproduction of IgE, whereas Th1 cytokines, especially IFN- γ , are strong inhibitors of IgE synthesis, Th2 cell proliferation, and IL-4 receptor expression on T-cells (Leung and Bieber, 2003). Several studies have reported that natural substances from plants and herbs can inhibit the development of AD-like skin lesions in NC/Nga mice by modulating the Th1 and/or Th2 cell response (Kotani et al., 2000; Gao et al., 2005). We thus examined the mRNA expression of IL-4, IL-13, IFN- γ , and TNF- α in the spleen of hairless mice after BCL treatment. We found that transdermal administration of BCL remarkably reduced mRNA expression of IL-4, IL-13 and TNF- α , but increased mRNA expression of IFN- γ (Fig. 5). These results imply that BCL treatment reduces the serum levels of total IgE by suppressing the Th2 response and modulating the Th1 response. Certain bamboo extracts have been shown to inhibit IL-12 in mouse macrophages via suppression of the nuclear factor-kappa B (NF- κ B) inflammatory signaling pathway (Kim et al., 2007). In addition, BCL has been reported to mediate the expression of different CD (cluster of differentiation) genes in human mast cells (Jeon et al., 2003). Together, these results indicate that bamboo extracts have immune-regulating effects as shown in the results of this study.

In summary, we demonstrated that BCL suppresses the development of DNCB-induced AD-like skin lesions in hairless mice by improving skin barrier function, suppressing the overproduction of

serum IgE and leukocytes, and balancing the expression of Th1/Th2 cytokines in the spleen. These results indicate that BCL might be a clinically relevant therapeutic agent for AD. Additional studies are required to identify the major components of BCL that are responsible for the inhibition of the development of AD-like skin lesions in hairless mice.

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