

The Inhibitory Effect of Bamboo Culm Extract on the Development of Pulmonary Inflammation in Pristane-Induced Lupus Mice

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Abstract – Pulmonary pathogenesis in lupus is characterized by interstitial inflammation and vasculitis in lungs. We investigated whether bamboo culm extract (BC) attenuates pulmonary inflammation and lung injury in pristane-induced lupus mice. The pristane-induced lupus mice and healthy mice were administrated with BC 0.5 ml/kg or PBS orally once a day for 14 days. Our results demonstrated that BC significantly attenuated levels of bronchoalveolar lavage (BAL) IL-6, IL-10, IFN- γ , PGE₂ and VEGF, and pulmonary vascular permeability in pristane-induced lupus mice. Therefore, these findings suggest that BC may inhibit development of pulmonary inflammation and lung injury in lupus.

Keywords – Bamboo culm, PGE₂, lupus, BAL proinflammatory cytokine, VEGF, pulmonary vascular permeability

Introduction

Systemic lupus erythematosus (SLE), a T cell-dependent autoimmune disease, is characterized by B cell hyperactivity, production of autoantibodies and inflammatory injuries of multiorgan including lungs (Hoffman, 2004; Nagy *et al.*, 2005). Multiorgan injuries in SLE are known to be most due to immunoregulatory abnormalities of T cells and hyperreactivity of B cells including overproduction of proinflammatory cytokines, leading to autoantibody production (Dean *et al.*, 2000; Nagy *et al.*, 2005; Chae and Shin, 2007). Th 1 cytokines, such as IL-6, IL-10, and IFN- γ , has been reported to contribute to autoantibody production, organ damage including lung, and high mortality in lupus (Llorente *et al.*, 1995; Theofilopoulos *et al.*, 2001; Ishihara and Hirano, 2002; Chun *et al.*, 2007).

Abnormal pulmonary function and nonspecific pulmonary injury are known to be found in SLE (Haupt *et al.*, 1981; Keane and Lynch, 2000). Pulmonary pathogenesis in lupus is characterized by interstitial inflammation and vasculitis in lungs (Groen *et al.*, 1992). Lupus patients with pulmonary involvement showed to have a stronger proinflammatory cytokine bias than those without pulmonary involvement (Al-Mutairi *et al.*, 2007). It demonstrated that BAL IL-6, IL-10, and IFN- γ contributed to development of lupus activity and might be associated with lupus

lung injury (Chae *et al.*, 2006; Chowdhary *et al.*, 2007). PGE₂ has been reported to mediate dysregulation of proinflammatory cytokine production and be associated with over-reactive B cells leading to production of autoantibody and organ injury in lupus (Herrera-Acosta *et al.*, 1987; Chae *et al.*, 2008). In addition, lupus is associated with collagen vascular disease and pulmonary dysfunction (Karim *et al.*, 2002). Pulmonary vascular permeability has been reported to be upregulated in pristane-induced lupus mice compared to those in healthy mice (Chae *et al.*, 2006).

Bamboo has been used as folk remedies traditionally for many centuries in the Orient. Bamboo has anti-fatigue activity, anti-oxidative capacity, anti-inflammatory effect, neuroprotective activity, and anti-tumor activity (Zhang *et al.*, 2006; Ito *et al.*, 2007; Lee *et al.*, 2008; Seki *et al.*, 2008). Bamboo culm extract has been reported to downregulate cell adhesion molecule expression and NF- κ B activity through suppression of the oxidative stress (Lee *et al.*, 2008). However, whether Bamboo culm extract (BC) attenuates development of pulmonary inflammation in lupus remains still unknown.

Our observation showed that BC inhibited production of BAL inflammatory mediators and pulmonary vascular permeability in pristane-induced lupus mice.

Experimental

Animals – Adult female BALB/c mice at 3 - 4 weeks

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of age were purchased from the Dae-Han Biolink (Chungbuk, Korea), and had been maintained in our animal facility on a regular 12-h light-dark cycle under a temperature of 22 ± 2 °C and relative humidity of $55 \pm 5\%$ with water and food available *ad libitum*. Mice were received *i.p.* a single injection of 0.5 ml of pristane (Sigma Chemical Co., St. Louis, MO, U.S.A.) or PBS (phosphate-buffered saline), and then, later 2 weeks, were used as a pristane-induced lupus model or healthy controls.

Preparation of plant extracts – Bamboo culm (*Phyllostachys bambusoides*; Gramineae, over 3 years old) was obtained from Damyang Jeonnam (Korea). The bamboo culm was washed and broken into about 5 cm fragments. The mineral material mixture that was composed of elvan (70 w/w %), germanium (20%), sericite (5%), jade (3%), and amethyst (2%) was heated at 250 - 300 °C to induce far-infrared radiation. The distilled bamboo culm fragments were exposed to the far-infrared radiation for 6 h and then distilled. The bamboo culm extract (BC) was used as a stock solution, which was yielded 4.8 ml (about 3%) from fresh bamboo culm 1.2 kg.

Administration of BC – The pristane-induced lupus mice and healthy mice were administrated with BC 0.5 ml/kg or PBS orally once a day for 14 days.

Preparation of bronchoalveolar lavage fluids – The lungs were removed under anesthetics from BC-treated lupus, lupus control, and healthy mice. Bronchoalveolar lavage (BAL) fluids were performed twice in a total volume of 1 ml of PBS through an intratracheal polyethylene tube attached to a 1 ml-syringe and centrifuged. The BAL fluids were collected and stored at ≤ -20 °C for cytokine, PGE₂ and VEGF assays.

Cytokine and VEGF assay – The concentrations of BAL TNF- α , IL-6, IL-10, IFN- γ , and VEGF in BC-treated lupus, lupus control, and healthy mice were determined by using monoclonal antibodies (BD Biosciences Pharmingen, U.S.A.). All measurements were carried out in duplicate. The results were measured in picograms per milliliter at 450 nm using an ELISA microplate reader (Molecular Devices Co., Ltd., U.S.A.). The lower limit of sensitivity for each of the ELISA was equal to or smaller than 5 pg/ml.

PGE₂ immunoassay – PGE₂ concentration in BAL fluids was determined by using a monoclonal antibody/enzyme immunoassay kit from Cayman Chemical, according to the manufacturer's instruction. Concentrations of PGE₂ were measured at 405 nm using ELISA.

Quantification of lung vascular permeability – Pulmonary vascular leak was studied by measuring the extravasation of Evans' blue, which, when given intrave-

nously, binds to plasma proteins, particularly albumin (Green *et al.*, 1988). BC-treated lupus, lupus control, and healthy mice were injected by tail vein with 160 mg/kg of Evans' blue (Sigma) in PBS 2 h prior to termination of the experiment and then the lungs were removed. Evans' blue was extracted from lungs by incubating samples in formamide at 60 °C for 14 - 18 h. The supernatant was separated by centrifugation at $5000 \times g$ for 30 min. The pulmonary vascular permeability was quantified at 650 nm.

Quantification of the relative weight of lung – The lungs were removed under anesthetics from BC-treated lupus, lupus control, and healthy mice. The ratios of lung weight to body weight (%) were measured.

Statistical analysis – All data were expressed as means \pm standard error (S.E.). Experiments were always run in duplicate and repeated at least twice. Analysis of variation and Student's *t*-test were used to determine statistical significance, and $p < 0.05$ was considered to be statistically significant.

Results and Discussion

BC attenuated levels of BAL proinflammatory cytokines in pristane-induced lupus mice – It has been reported that the pathogenesis via production of lupus-specific autoantibodies are started 1 - 2 mo after pristane treatment in pristane-primed female BALB/c mice and severe immune complex-mediated organ injuries including glomerulonephritis are developed 4 - 6 mo (Satoh and Reeves 1994; Satoh *et al.*, 1995). In the present study, mice were used 2 weeks after pristane treatment as a pristane-induced lupus model.

Lung injury is thought to result from intense inflammatory responses in the early stage directly or indirectly in lupus-like autoimmune diseases (Karim *et al.*, 2002). Lupus patients with pulmonary involvement exhibited a stronger proinflammatory cytokine bias than those without pulmonary involvement (Al-Mutairi *et al.*, 2007). Elevation of BAL IL-6, IL-10, and IFN- γ has been reported to be associated with pulmonary pathogenesis or lung injuries in lupus (Chae *et al.*, 2006; Al-Mutairi *et al.*, 2007). Elevated IL-6, a B cell differentiation factor, is correlated with induction of differentiation to autoantibody-forming cells in lupus (Liang *et al.*, 2006). IL-10 contributes to autoantibody production and high mortality in lupus and pulmonary overexpression of IL-10 is also associated with enhanced lung fibrosis and Th 2 responses (Llorente *et al.*, 1995; Barbarin *et al.*, 2005). IFN- γ has been reported to be required for lupus-like disease and lymphoaccumulation in MRL-*lpr* mice

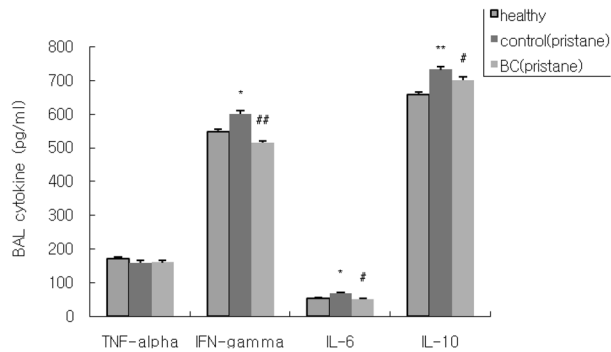


Fig. 1. BC attenuated levels of BAL proinflammatory cytokines in pristane-induced lupus mice.

Bamboo culm extract (BC) or PBS was administered orally once a day for 14 days in the pristane-induced lupus mice and healthy mice. The lungs were removed under anesthetics from BC-treated lupus, lupus control, and healthy mice. BAL fluids were performed twice in a total volume of 1 ml of PBS through an intratracheal polyethylene tube attached to a 1 ml-syringe and centrifuged. The BAL fluids were collected and the concentrations of BAL cytokines were measured at 450 nm using ELISA. All measurements were carried out in duplicate. Each value represents the mean \pm S.E. * ($p < 0.05$) and ** ($p < 0.01$): Significantly different from the value in healthy control. # ($p < 0.05$) and ## ($p < 0.01$): Significantly different from the value in pristane-induced lupus controls.

(Balomenos *et al.*, 1998) and to be associated with autoantibody production and immune complex-mediated organ injuries in lupus (Haas *et al.*, 1998).

Our previous results demonstrated that BC significantly decreased levels of serum and BAL IL-6 in the late stage in pristane-induced lupus mice (Chae and Park, 2009). In the present study, our results demonstrated that levels of early BAL IL-6, IL-10, and IFN- γ were enhanced in pristane-induced lupus mice compared to those in healthy mice. Early BAL IL-6, IL-10, IFN- γ but not TNF- α levels were remarkably downregulated by BC in pristane-induced lupus mice (Fig. 1). Our previous study showed that BC remarkably downregulated serum TNF- α , IL-6, IL-10, and IFN- γ levels in the early stage in pristane-induced lupus mice (Chae, 2010). Therefore, our findings indicate that BC may attenuate pulmonary inflammation and autoantibody production via downregulation of overproduction of BAL IL-6, IL-10, and IFN- γ in the early stage in pristane-induced lupus mice. However, we observed here that production of BAL TNF- α was not affected in pristane-induced lupus mice compared to those in healthy mice and that levels of BAL TNF- α were not affected by BC in pristane-induced lupus mice. It has been reported that TNF- α apparently plays a significant role in the inflammatory process in lupus (Aringer and Smolen, 2003) and, at the same time, TNF- α is associated

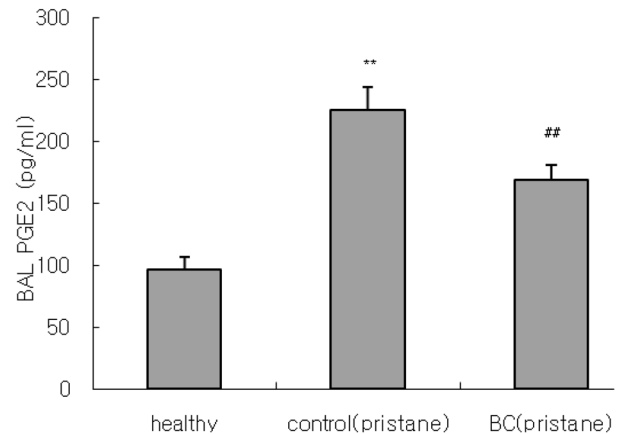


Fig. 2. BC reduced levels of BAL PGE₂ in pristane-induced lupus mice.

The concentrations of PGE₂ in BAL fluids collected from BC-treated lupus, lupus control, and healthy mice were measured at 405 nm using ELISA. All measurements were carried out in duplicate. Each value represents the mean \pm S.E. Other legends and methods are the same as in Fig. 1. ** ($p < 0.01$): Significantly different from the value in healthy control. ## ($p < 0.01$): Significantly different from the value in pristane-induced lupus controls.

with induction of apoptosis of T cells in autoimmune disease that can normally eliminate autoreactive T cells in lupus (Ucker, *et al.*, 1989; Theofilopoulos and Lawson, 1999). Further studies need to determine the exact mechanism by which production of BAL TNF- α was not affected in pristane-induced lupus mice compared to those in healthy mice.

BC attenuated levels of BAL PGE₂ in pristane-induced lupus mice – PGE₂ is known to play an important role in development of inflammatory responses and tissue injuries. PGE₂ has been a novel therapeutic target in the lupus inflammation and organ injuries (Herrera-Acosta *et al.*, 1987; Tsai *et al.* 1994; Akaogi *et al.*, 2006). Recently, it has been reported that levels of serum and BAL PGE₂ was remarkably enhanced in pristane-induced lupus mice compared to those in healthy controls (Chae *et al.*, 2008). Also, BC greatly has been reported to attenuate levels of serum PGE₂, and production of PGE₂ and expression of COX-2 mRNA by macrophages with/without LPS stimulation in pristane-induced lupus mice (Chae, 2010). Here, as shown in Fig. 2, our results demonstrated that BC remarkably reduced levels of BAL PGE₂ in pristane-induced lupus mice. Some evidences demonstrated that PGE₂ attenuates the activation and capability of T cells to produce Th 1 cytokines with a shift toward Th 2 cytokine responses (Betz and Fox, 1991). Endogenous PGE₂ showed to mediate overproduction of IL-6 and IL-10 in pristane-induced lupus mice

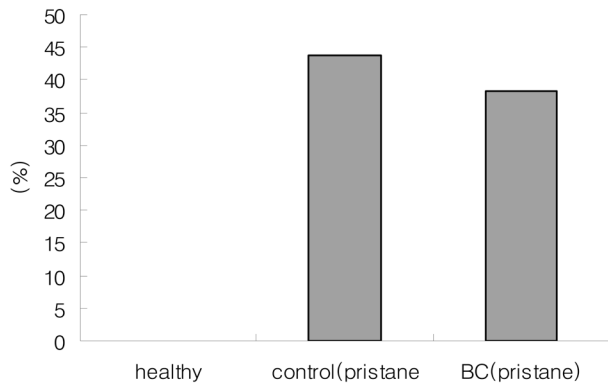


Fig. 3. Effect of BC on the relative weight of lung in pristane-induced lupus mice.

Lungs were removed under anesthetics in BC-treated lupus, lupus control, and healthy mice. Increase (%) in the relative weight of lung to body weight (BW) follows as:

$$\frac{(\text{lung weight/BW in each group} - \text{lung weight/BW in healthy mice})}{\text{lung weight/BW in healthy mice}} \times 100$$

All measurements were carried out in duplicate. Each value represents the mean \pm S.E (n = 5 mice). Other legends and methods are the same as in Fig. 1.

(Chae *et al.*, 2008). PGE₂ also exhibited to play a role in induction of IL-6 in a murine model of inflammation (Hinson *et al.*, 1996). Therefore, these findings suggest that BC may have protective effect from development of lung inflammation and lung injuries in lupus through downregulation of elevated PGE₂.

Quantification of the ratio of lung weight to body weight (%) – The ratios of lung weight to body weight (%) in BC-treated lupus, lupus control, and healthy mice were measured. Edema of lungs is thought to be associated with lung inflammation in lupus models. Increase (%) in the ratios of lung weight to body weight was measured as difference from the value in healthy mice. Here, it demonstrated that the relative weights of lung to body weight were increased by about 43.62% in lupus control and 38.28% in BC-treated lupus mice compared to those in healthy mice, respectively (Fig. 3). Also, the relative weights of lung were decreased by about 3.72% in BC-treated lupus mice compared to those in lupus control, suggesting that BC may inhibit lung inflammation in pristane-induced lupus mice.

BC downregulated pulmonary vascular permeability in pristane-induced lupus mice – Systemic inflammation promotes multiple organ failure through the induction of diffuse microvascular leak (Anderson and Harken, 1990). Altered pulmonary vascular permeability is induced

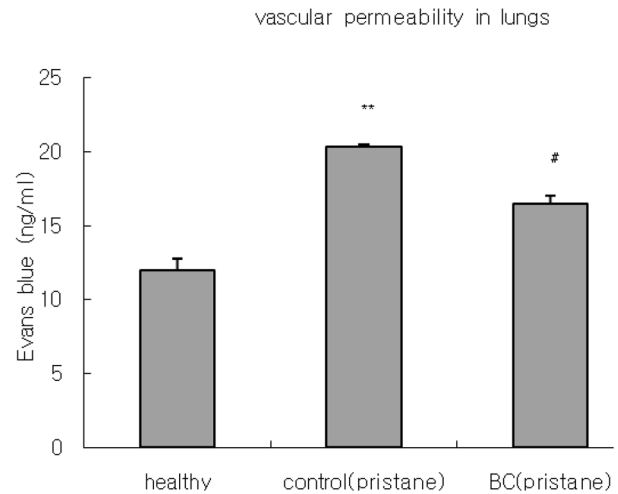


Fig. 4. BC downregulated pulmonary vascular permeability in pristane-induced lupus mice.

Pulmonary vascular leak was studied by measuring the extravasation of Evans' blue, which, when given intravenously, binds to plasma proteins, particularly albumin. BC-treated lupus, lupus control, and healthy mice were injected by tail vein with 160 mg/kg of Evans' blue in PBS 2 h prior to termination of the experiment and then the lungs were removed. Evans' blue was extracted from lungs by incubating samples in formamide at 60 °C for 14 - 18 h. The concentration of Evans' blue in lung supernatants was measured by a dual wavelength spectrophotometric method at absorptions of 650 nm for the vascular leak syndrome. Each mouse was individually analyzed for vascular leak, and data from five mice were expressed as mean \pm S.E. Other legends and methods are the same as in Fig. 1. Each value represents the mean \pm S.E (n = 5 mice). ** (p < 0.01): Significantly different from the value in healthy control. # (p < 0.05): Significantly different from the value in pristane-induced lupus controls.

by stimulated neutrophils and results in lung damage (Tanita *et al.*, 1999). Lupus is associated with collagen vascular disease and pulmonary dysfunction (Karim *et al.*, 2002). Pulmonary vascular permeability has been reported to be upregulated in pristane-induced lupus mice compared to those in healthy mice (Chae *et al.*, 2006). In this study (Fig. 4), pulmonary vascular permeability was strongly upregulated in pristane-induced lupus mice compared to healthy controls, whereas BC remarkably down-regulated pulmonary vascular permeability in pristane-induced lupus mice, indicating that BC may protect from pulmonary vascular inflammation and lung injury in pristane-induced lupus mice.

BC reduced levels of BAL VEGF in pristane-induced lupus mice – Lupus-like rheumatoid inflammation and SLE were associated with collagen vascular disease and elevated vascular endothelial growth factor (VEGF) (Ballara *et al.*, 2001; Ciprandi *et al.*, 2008). In our previous study, BC has been reported to significantly downregulate levels of serum VEGF in pristane-induced

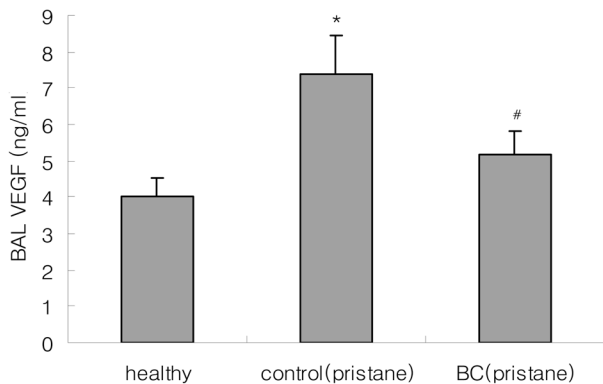


Fig. 5. BC attenuated levels of BAL VEGF in pristane-induced lupus mice.

The concentration of BAL VEGF in BC-treated lupus, lupus control, and healthy mice was determined at 450 nm using ELISA reader. Each value represents the mean \pm S.E. Other legends and methods are the same as in Fig. 1. * ($p < 0.05$): Significantly different from the value in healthy control. # ($p < 0.05$): Significantly different from the value in pristane-induced lupus controls.

lupus mice (Chae, 2010). In the present study, we investigated whether BC attenuates levels of BAL VEGF characterized by pulmonary vascular permeability and inflammation in the lupus animal model. Here, we observed that levels of BAL VEGF were remarkably enhanced in pristane-induced lupus mice compared to those in healthy mice, indicating that BAL VEGF can be a target for pulmonary vascular inflammation therapy in lupus. As shown in Fig. 5, these data also demonstrated that BC significantly attenuated elevated BAL VEGF in pristane-induced lupus mice. Nakahara *et al.* (2003) reported that anti-IL-6 receptor antibody therapy reduced VEGF production in rheumatoid arthritis. Therefore, our findings indicate that BC may attenuate pulmonary vascular permeability and inflammation through inhibition of BAL VEGF in pristane-induced lupus mice.

In conclusion, our findings indicate that BC may attenuate development of lupus autoimmunity and lung injury via inhibition of inflammatory mediators and amelioration of abnormal costimulation between T cells and B cells.

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