Effects of *Prunella vulgaris* on Mast Cell–Mediated Allergic Reaction and Inflammatory Cytokine Production

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In this study, we investigated the effect of aqueous extract of *Prunella vulgaris* (Labiatae; PVAE) on the mast cell–mediated allergy model. We found that PVAE (0.001–0.1 g/kg) dose dependently inhibited compound 48/80–induced systemic anaphylaxis and serum histamine release in mice. PVAE decreased the IgE-mediated local allergic reaction, passive cutaneous anaphylaxis. In addition, PVAE attenuated phorbol 12-myristate 13-acetate (PMA) and calcium ionophore A23187-stimulated TNF-α, IL-6, and IL-8 secretion in human mast cells. The inhibitory effect of PVAE on proinflammatory cytokines was nuclear factor-κB (NF-κB) dependent. PVAE suppressed PMA and A23187-induced NF-κB/DNA binding activity and NF-κB–dependent gene reporter assay. Our findings provide evidence that PVAE inhibits mast cell–derived immediate-type allergic reactions and involvement of proinflammatory cytokines and NF-κB in these effects. Exp Biol Med 232:921–926, 2007

Key words: *Prunella vulgaris*; anaphylaxis; inflammatory cytokine; nuclear factor-κB; mast cells

Introduction

The *Prunella vulgaris* var. *lilacina* Nakai (Labiatae) is a perennial herb that is widely distributed throughout Korea, Japan, and China. The herb has been used as a traditional oriental medication for the treatment of scrofula, goiter, dermatosis, and skin allergy diseases in South Korea (1–3).

The primary effector cell in immediate-type allergic reactions is the mast cell. Mast cells are important mediators for inflammatory responses, such as allergy and anaphylaxis. Mast cell degranulation can be elicited by a number of positively charged substances collectively known as the basic secretagogues of mast cells (4). Compound 48/80 is best known as a potent inducer of degranulation and of the release from mast cells of histamine and other chemical mediators that are responsible for anaphylaxis (5).

The signaling pathway leading to the activation of mast cells has been extensively characterized (6–8). The activation of mast cells leads to the phosphorylation of tyrosine kinase and the mobilization of internal Ca^{2+}. This is followed by the activation of protein kinase C, nuclear factor-κB (NF-κB), and the release of inflammatory cytokines. Activated mast cells can produce a wide variety of inflammatory mediators, such as eicosanoids, proteoglycans, proteases, and several proinflammatory and chemotactic cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL-6), IL-8, IL-4, IL-13, and transforming growth factor-β (9–11). The transcriptional NF-κB is important as a mediator of cellular response to extracellular signals. NF-κB is thought to play an important role in the regulation of proinflammatory molecules of cellular responses, especially TNF-α, IL-6, and IL-8 (12).

Anal therapy is a drug delivery system through the anus. It is used in patients who have difficulty with oral

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administration. Absorbing a drug in the rectum avoids the first-pass effect in the liver and allows the drug to circulate directly in the whole body. The absorption rate in the rectum is faster than that in the gastrointestinal tract. The rate and total amount absorption through the rectum are not very different from those with venous administration (13). Thus, anal therapy is expected to have a better effect than oral therapy due to the increased absorption rate and the strong medical action. In this study we used anal therapy to enhance the effects of *P. vulgaris* (PVAE). The aim of this study was to evaluate the antiallergic effect of aqueous extract of PVAE and to understand the mechanism of its effects.

Materials and Methods

Animals. The original stock of male ICR mice, 6 wks of age and with an average body weight of 25 g, was purchased from the Dae-Han Experimental Animal Center (Daejeon, Korea). The animals were maintained in the College of Pharmacy of Woosuk University. The animals were housed 5–10 per cage in a laminar air flow room (conventional condition) and were maintained at a temperature of 22°C ± 2°C with a relative humidity of 55% ± 5% throughout the study. The care and treatment of the mice were in accordance with the guidelines established by the Public Health Service Policy on the Humane Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee.

Reagents and Cell Culture. Compound 48/80, antidinitrophenyl (DNP) IgE, DNP–human serum albumin (HSA), *o*-phthaldialdehyde, phorbol 12-myristate 13-acetate (PMA), and calcium ionophore A23187 were purchased from Sigma Chemical Co. (St. Louis, MO). Recombinant TNF-α, rIL-6, and rIL-8, and anti–TNF-α, anti–IL-6, and anti–IL-8 antibodies were purchased from R&D Systems Inc. (Minneapolis, MN). The human mast cell line (HMC-1) was grown in Iscove's media (Life Technologies, Grand Island, NY) supplemented with 10% fetal bovine serum and 2 m*M* glutamine at 37°C in 5% CO_2.

Preparation of PVAE. The plants of *P. vulgaris* were collected in Wanju, South Korea, on the July 19, 1999. The plant was identified by D.K. Kim (College of Pharmacy, Woosuk University), and the voucher specimen (WSP-99-36) was deposited at the Herbarium of the College of Pharmacy, Woosuk University. *P. vulgaris* was ground (400 *g*, 30 secs) at room temperature using a Micro Hammer-Cutter Mill (Culatti Co., Zurich, Switzerland). The particle size was 0.5–2 mm after grinding. The plant sample was extracted with distilled water at 70°C for 5 hrs (two times). The extract was filtered through Whatman No. 1 filter paper (Whatman, Florham Park, NJ) and the filtrate was lyophilized using a 0.45-μm syringe filter. The yield of dried extract from starting crude materials was about 10.1%. The dried extract was dissolved in saline for *in vitro* experiments and in Tyrode buffer for *in vivo* experiments before use.

Compound 48/80–Induced Systemic Anaphylactic Reaction. Compound 48/80–induced systemic reaction was carried out as previously described (14). Briefly, the mice were given an intraperitoneal injection of 0.008 g/kg body wt (BW) of the mast cell degranulator, compound 48/80. PVAE was administered anally using an 18-gauge feeding needle at doses of 0.001–0.1 g/kg BW 1 hr before the compound 48/80 injection ($n = 10$ per group). In the time-dependent experiment, PVAE (0.1 g/kg) was administered 5, 10, and 20 mins after compound 48/80 injection ($n = 10$ per group). Mortality was monitored for 1 hr after induction of anaphylactic shock.

Preparation of Serum and Histamine Determination. After 1 hr of compound 48/80 injection, blood was harvested and centrifuged at 400 *g* for 10 mins. The serum was withdrawn, and histamine content was measured by the *o*-phthaldialdehyde spectrofluorometric procedure (15). The fluorescence intensity was measured at emission 438 nm and excitation 353 nm using a spectrofluorometer (RF-5301 PC; Shimadzu, Kyoto, Japan).

Passive Cutaneous Anaphylaxis (PCA). The mice were injected intradermally with 0.5 μg anti-DNP IgE. After 48 hrs, each mouse received an injection of 1 μg DNP-HSA in phosphate-buffered saline containing 4% Evans blue (1:4) *via* tail vein. PVAE (0.001–0.1 g/kg BW) was administered anally 1 hr before the challenge. At 30 mins after the challenge, the mice were killed using CO_2 and the dorsal skin (diameter, 1 cm) was removed in order to measure the pigment area. The amount of dye was determined colorimetrically after extraction with 1 ml of 1 *M* KOH and 9 ml of a mixture of acetone and phosphoric acid (5:13). The intensity of the absorbent was measured at 620 nm in a spectrophotometer (UV-1201; Shimadzu).

Assay of TNF-α, IL-6, and IL-8 Secretion. Secretion of TNF-α, IL-6, and IL-8 was measured by modification of an enzyme-linked immunosorbent assay (ELISA). HMC-1 cells were sensitized with PMA (20 n*M*) and A23187 (1 μ*M*) for 8 hrs in the absence or presence of PVAE. The ELISA was performed by coating 96-well plates with 6.25 ng/well of monoclonal antibody with specificities for TNF-α, IL-6, and IL-8. For the standard curve, rTNF-α, rIL-6, and rIL-8 were added to the serum, which was previously determined to be negative to endogenous TNF-α, IL-6, and IL-8. After exposure to the medium, the assay plates were exposed sequentially to biotinylated anti-human TNF-α, IL-6, or IL-8 and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) tablet substrates. Optical density readings were made within 10 mins of the addition of the substrate with a 405-nm filter.

Electrophoretic Mobility Shift Assays (EMSA). Nuclear protein (10 μg) was incubated for 20 mins at room temperature with 20 μg bovine serum albumin, 2 μg poly(dI-dC) from Pharmacia (Uppsala, Sweden), 2 μl buffer C (20 m*M* HEPES/KOH, 20% glycerol, 100 m*M* KCl, 0.5 m*M* phenylmethylsulfonyl fluoride, pH 7.9), 4 μl buffer F (20% ficoll-400, 100 m*M* HEPES/KOH, 300 m*M* KCl, 10

Table 1. Effect of PVAE on Compound 48/80–Induced Systemic Anaphylaxis[a]

PVAE treatment (g/kg BW)	Compound 48/80 (0.008 g/kg BW)	Mortality (%)
None (saline)	+	100
0.001	+	100
0.005	+	80
0.01	+	50
0.05	+	20
0.1	+	0
0.1	−	0

[a] Groups of mice ($n = 10$ per group) were anally pretreated with 200 μl PVAE at various doses 1 hr before the intraperitoneal injection of compound 48/80. Mortality (%) within 1 hr following compound 48/80 injection is represented as the number of dead mice × 100 / total number of experimental mice.

Table 2. Time-Dependent Effect of PVAE on Compound 48/80–Induced Systemic Anaphylaxis[a]

PVAE treatment (g/kg BW)	Compound 48/80 (0.008 g/kg BW)	Time (min)	Mortality (%)
None (saline)	+	—	100
0.1	+	0	0
0.1	+	5	0
0.1	+	10	50
0.1	+	20	100

[a] Mice ($n = 10$ per group) were anally pretreated with 200 μl PVAE. PVAE (0.1 g/kg) was given 5, 10, and 20 mins after the intraperitoneal injection of compound 48/80. Mortality (%) within 1 hr following compound 48/80 injection is represented as the number of dead mice × 100 / total number of experimental mice.

m*M* dithiothreitol, 0.5 m*M* phenylmethylsulfonyl fluoride, pH 7.9), and 20,000 cpm of a ^{32}P-labeled probe that encoded the κB consensus sequence (5′-CAG AGG GGA CTT TCC GAG AG-3′) in a final volume of 20 μl. DNA-protein complexes were resolved at 180 V for 4 hrs in a native 4% polyacrylamide gel, dried, and visualized (with autography using a Fuji x-ray film [Seoul, Korea]).

Transient Transfection and Luciferase Activity Assay. For transient transfections, HMC-1 cells were seeded at 2×10^6 in a six-well plate 1 day before transient transfection. The expression vector containing the NF-κB luciferase reporter construct (pNF-κB-LUC, plasmid containing NF-κB binding site; Stratagen, Grand Island, NY) or empty vector was transfected with serum- and antibiotic-free Iscove's medium containing 8 μl Lipofectamine 2000 reagent (Invitrogen, Carlsbad, CA). After 5 hrs of incubation, medium was replaced with Iscove's medium containing 10% fetal bovine serum and antibiotics. Cells were allowed to recover at 37°C for 20 hrs and were stimulated subsequently as indicated. Cell lysates were prepared and assay for luciferase activity using Luciferase Assay System (Promega, Madison, WI), according to the manufacturer's instructions.

Statistical Analysis. Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC). Treatment effects were analyzed using one-way ANOVA, followed by Duncan multiple range tests. $P < 0.05$ was used to indicate significance

Results

Effect of PVAE on Systemic and Local Anaphylactic Reaction. Initial experiments examined the effects of PVAE on compound 48/80–induced systemic anaphylactic reaction. Compound 48/80 (0.008 g/kg) was used as a model of induction for a systemic fatal allergic reaction. After the intraperitoneal injection of compound 48/80, the mice were monitored for 1 hr, after which the mortality rate was determined. When PVAE was anally pretreated at concentrations ranging from 0.001 to 0.1 g/kg for 1 hr, the mortality with compound 48/80 was dose dependently reduced (Table 1). PVAE completely inhibited anaphylactic reaction at a dose of 0.1 g/kg. In addition, the mortality of mice administered with PVAE (0.1 g/kg) at 5, 10, and 20 mins after compound 48/80 injection increased time dependently (Table 2). We evaluated the effect of PVAE treatment on compound 48/80–induced serum histamine release. PVAE dose dependently decreased the compound 48/80–induced serum histamine release (Fig. 1).

Another way to test allergic reaction is to induce passive cutaneous anaphylaxis (PCA). A local extravasation was induced by a local injection of IgE followed by an antigenic challenge. When PVAE (0.001–0.1 g/kg) was

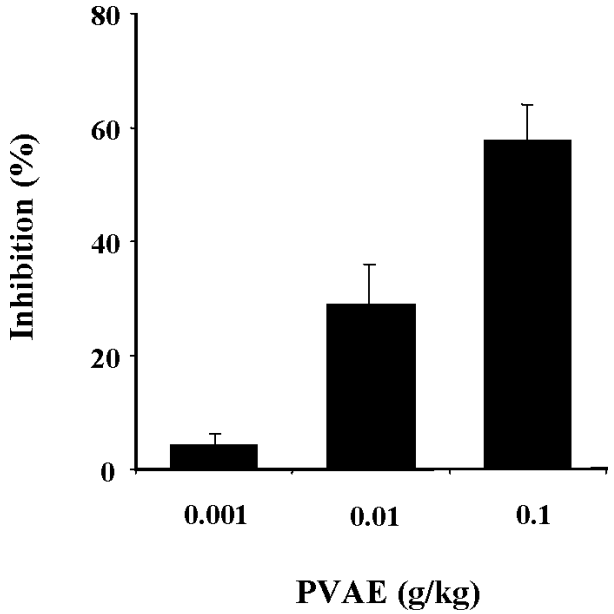

Figure 1. Effect of PVAE on compound 48/80–induced serum histamine release. Groups of mice ($n = 10$ per group) were anally pretreated with 200 μl PVAE. PVAE was given at various doses 1 hr before the injection of compound 48/80. The compound 48/80 solution was given intraperitoneally to the group of mice. Each bar represents the mean ± SEM of two independent experiments.

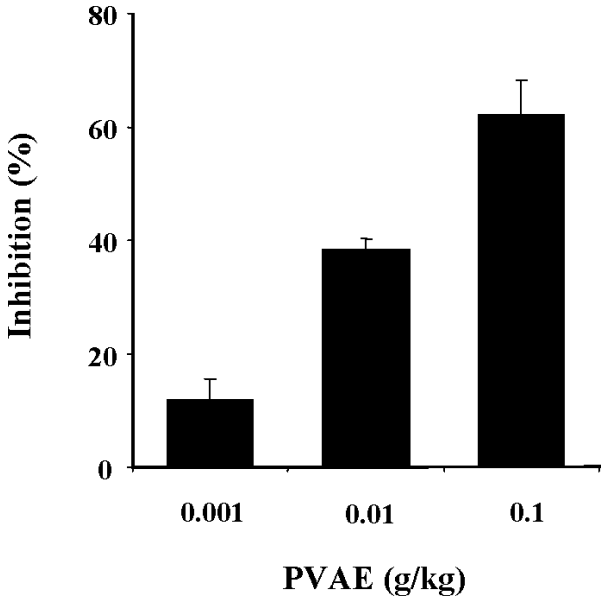

Figure 2. Effect of PVAE on the 48 hrs of PCA. PVAE was anally administered 1 hr prior to the challenge with antigen. Each bar represents the mean ± SEM of three independent experiments.

given anally to mice, PVAE dose dependently inhibited PCA (Fig. 2).

Effect of PVAE on Secretion of TNF-α, IL-6, and IL-8 from HMC-1 Cells. TNF-α, IL-6, and IL-8 are important inflammatory cytokines released from mast cells. The HMC-1 cell line is a useful cell for studying the cytokine activation pathway (16). Therefore, we tested the effects of PVAE on the secretion of TNF-α, IL-6, and IL-8 from HMC-1 cells. Culture supernatants were assayed for each cytokine level by ELISA. As shown in Table 3, PVAE inhibited the secretion of TNF-α, IL-6, and IL-8 in PMA and A23187 (PMACI)–stimulated HMC-1 cells. No significant cytotoxicity of PVAE on the culture was observed in the concentrations used in the experiments, as assessed by Trypan blue exclusion.

Effect of PVAE on NF-κB Activation. To evaluate the mechanisms of effect of PVAE on cytokine secretion, we examined the effect of PVAE on NF-κB activation. Expression of proinflammatory cytokines, such as TNF-α, IL-6, and IL-8, is regulated by a transcription factor, NF-κB. We previously showed that NF-κB regulates PMACI-induced secretion of TNF-α, IL-6, and IL-8 in HMC-1 cells (17, 18). We used PDTC, a potent inhibitor of NF-κB, as a positive control. Cells pretreated with either PVAE or PDTC (10 μ*M*) were subsequently stimulated with PMACI, and the effect of PVAE and PDTC on binding activity of NF-κB was examined. Treatment of PMACI caused a significant increase in the DNA binding activity of NF-κB within 4 hrs (Fig. 3A). PVAE markedly suppressed PMACI-induced NF-κB/DNA binding activity. To confirm the inhibitory effect of PVAE on NF-κB activation, we examined the effect of PVAE on the NF-κB–dependent gene reporter assay. HMC-1 cells were transiently transfected with NF-κB–luciferase reporter construct or empty vector. Exposure of cells to PMACI increased the luciferase activity in the cells transfected with the NF-κB–luciferase reporter construct (Fig. 3B). PVAE significantly reduced PMACI-induced luciferase activity.

Discussion

The results of this study showed that PVAE has some antiallergic properties. PVAE inhibited compound 48/80–induced systemic allergic reaction and serum histamine release in mice. These results indicate that mast cell-mediated immediate-type allergic reactions are inhibited by PVAE. In addition, the PVAE-administered mice were protected from IgE-mediated PCA, which is one of the most important *in vivo* models of anaphylaxis in a local allergic reaction. This finding suggests that PVAE might be useful in the treatment of allergic skin reactions.

Numerous reports have established that stimulation of mast cells with compound 48/80 or IgE initiates the activation of signal transduction pathway, which leads to histamine release. Several recent studies have shown that compound 48/80 and other polybasic compounds are able (apparently directly) to activate G proteins (19). Compound 48/80 increases the permeability of the lipid bilayer membrane by causing a perturbation in the membrane. This result indicates that the increase in membrane permeability may be an essential trigger for the release of the mediator from mast cells. In this sense, antiallergic agents having a membrane-stabilizing action may be desirable. PVAE might

Table 3. Effect of PVAE on the Secretion of Proinflammatory Cytokines[a]

Treatment	TNF-α (ng/ml)	IL-6 (ng/ml)	IL-8 (ng/ml)
None (saline)	0.618 ± 0.16	0.15 ± 0.03	2.37 ± 0.49
PMA + A23187	2.116 ± 0.41	0.70 ± 0.07	7.21 ± 2.63
PMA + A23187 + PVAE, 0.01 mg/ml	1.860 ± 0.55 (17.0%)	0.56 ± 0.03 (26.9%)*	6.81 ± 2.12 (8.2%)
PMA + A23187 + PVAE, 0.1 mg/ml	1.495 ± 0.69 (41.4%)*	0.48 ± 0.05 (41.2%)*	5.62 ± 1.64 (32.8%)*
PMA + A23187 + PVAE, 1 mg/ml	0.904 ± 0.22 (80.9%)*	0.20 ± 0.08 (91.5%)*	3.98 ± 0.77 (66.5%)*

[a] PMA (20 n*M*) and A23187 (1 μ*M*)–stimulated HMC-1 cells were incubated for 8 hrs in the absence or presence of PVAE. TNF-α, IL-6, and IL-8 secreted into the medium are presented as the mean ± SEM of the three independent experiments. Percentages in parentheses indicate the percent change from the PMA + A23187 value.
* Statistically significant from the PMA and A23187 value at $P < 0.05$.

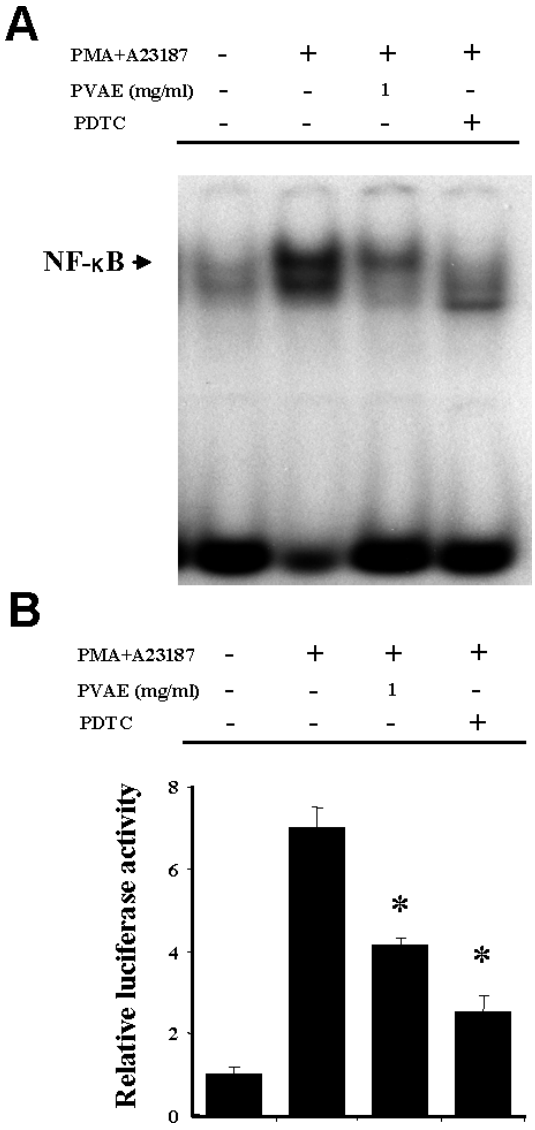

Figure 3. Effect of PVAE on the activation of NF-κB. HMC-1 cells were pretreated with PVAE or PDTC (10 μ*M*) for 30 mins prior to PMA (20 n*M*) and A23187 (1 μ*M*) stimulation. (A) Nuclear extracts prepared and incubated with ^{32}P-labeled oligonucleotides corresponding to NF-κB were analyzed by EMSA. (B) Cells were transiently transfected with NF-κB–luciferase reporter construct or empty vector. Then, the cells were incubated with PMA and A23187 with or without PVAE. NF-κB–dependent transcriptional activity was determined by luciferase activity assay. *Statistically significant from the PMA and A23187 value at $P < 0.05$.

stabilize the lipid bilayer membrane, thus preventing the perturbation being induced by compound 48/80.

The HMC-1 cell line is a useful cell for studying cytokine activation pathways (16). The spectrum of cytokines produced by HMC-1 cells with PMACI stimulation supports the well-recognized role of mast cells in immediate-type hypersensitivity. Proinflammatory cytokines, including TNF-α, IL-6, and IL-8, play a major role in triggering and sustaining the allergic inflammatory response in mast cells (20–22). Mast cells are a principal source of TNF-α in human dermis, and degradation of mast cells in the dermal endothelium is abrogated by the anti–TNF-α antibody (21). IL-6 also is produced from mast cells, and its local accumulation is associated with PCA reaction (20). IL-8 from mast cells acts on surrounding cells, such as neutrophils, T lymphocytes, and eosinophils, and plays a role in activation of inflammatory effector cells (23). These reports indicate that the reduction of proinflammatory cytokines from mast cells is one of the key indicators of reduced allergic symptom. In our present study, PVAE inhibited the secretion of TNF-α, IL-6, and IL-8 in PMACI-stimulated HMC-1 cells. This result suggests that the antiallergic effect of PVAE results from its reduction of TNF-α, IL-6, and IL-8 generation from mast cells. Expression of TNF-α, IL-6, and IL-8 genes is dependent on the activation of transcription factor NF-κB (24). In PMACI-stimulated mast cells, PVAE inhibited DNA binding of NF-κB and NF-κB–dependent gene expression. These data demonstrate that PVAE attenuates activation of NF-κB and downstream TNF-α, IL-6, and IL-8 production.

Because we used a whole-water extract of *P. vulgaris* and not a purified component, the active components that are responsible for the biologic effect are not clear at this time. The effort to identify active components from *P. vulgaris* in the immediate-type allergic reaction is ongoing in our laboratory. Recently, the antioxidative, antimicrobial, and antiviral effects of extracts of *P. vulgaris* have been reported (25–27). Ryu *et al.* (28) reported that dihyroxyursolic acid, a triterpene from *P. vulgaris*, inhibited the release of beta-hexosaminidase, one of the indicators of mast cell degranulation, from RBL-2H3 mast cells. In addition, rosmarinic acid, a phenolic acid component from *P. vulgaris*, decreased UV-induced reactive oxygen species production and lipid peroxidation in human keratinocytes (25). In the present report we provided evidence that PVAE inhibits a model of mast cell–mediated allergic reactions and their possible mechanisms, such as NF-κB and downstream proinflammatory cytokines. The results obtained in the present study show that PVAE contributes to the prevention or treatment of mast cell–mediated allergic diseases.

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