

***Isodon japonicus* Inhibits Mast Cell-Mediated Immediate-Type Allergic Reactions**

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ABSTRACT

The effect of aqueous extract of *Isodon japonicus* Hara (Labiateae) (IJAE) on mast cell-mediated immediate-type allergic reactions was investigated. IJAE inhibited systemic allergic reaction induced by compound 48/80. When IJAE was pretreated at the same concentrations with systemic allergic reaction test, the plasma histamine levels were reduced in a dose-dependent manner. IJAE also inhibited local allergic reaction activated by anti-dinitrophenyl (DNP) IgE antibody. IJAE dose-dependently

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inhibited the histamine release from rat peritoneal mast cells (RPMC) activated by compound 48/80 or anti-DNP IgE. IJAE inhibited the secretion of tumor necrosis factor- α (TNF- α) and interleukin (IL)-6 in phorbol 12-myristate 13-acetate (PMA) plus calcium ionophore A23187-stimulated human mast cell line (HMC-1) cells. In addition, the expression of TNF- α mRNA in HMC-1 cells was inhibited by IJAE. These results indicate that IJAE may be beneficial in the regulation of immediate-type allergic reaction.

Key Words: *Isodon japonicus*; Allergic reaction; Compound 48/80; Anti-DNP IgE; TNF- α ; IL-6; Mast cells; TNF- α mRNA.

INTRODUCTION

The *Isodon japonicus* Hara (Labiateae), well known as 'Yeon-myeong-cho' in Korea, has been used for centuries as traditional medicine. This drug has the pharmacological functions of antibacterial effect, antitumor effect and anti-inflammatory effect.^[1-3]

Mast cells play an important role in a wide variety of biological responses. It is well established that they are critical effector cells in the development of many physiologic changes during allergic and anaphylactic responses.^[4] Mast cell activation both by IgE-dependent and IgE-independent stimuli, bring about the process of degranulation that results in the fusion of the cytoplasmic membranes with the plasma membrane. This is accompanied by both the fast external release of granule-associated stored mediators as well as by the generation and release of newly generated mediators, such as products of arachidonic acid metabolism and, at later times, by the production and release of an array of cytokines.^[5,6] Among the preformed and newly synthesized inflammatory substances released on degranulation of mast cells, histamine remains the best-characterized and most potent vasoactive mediator implicated in the acute phase of immediate hypersensitivity.^[7] Mast cell degranulation can be elicited by a number of positively charged substances, collectively known as the basic secretagogues of mast cells.^[8] The synthetic compound 48/80 is known to be one of the most potent secretagogues.^[9] An appropriate amount of compound 48/80 has been used as a direct and convenient reagent to study the mechanism of anaphylaxis.^[10] The secretory response of mast cells can be induced by aggregation of their cell surface-specific receptors for immunoglobulin E (Ig E) by the corresponding antigen.^[11-14] It has been established that the anti-IgE antibody induced passive cutaneous anaphylaxis (PCA) as a typical model for mast cell-dependent immediate type allergic reaction.^[15] Activated mast cells can produce histamine, as well as a wide variety of other inflammatory mediators such as eicosanoids, proteoglycans, proteases, and several proinflammatory and chemotactic cytokines such as TNF- α , interleukins (IL)-6, IL-4, IL-8, IL-13 and transforming growth factor (TGF)- β .^[16-21] Therefore, modulation of these cytokines secretion from mast cells can provide a useful therapeutic strategy for allergic inflammatory disease.

This paper deals with an evaluation of the effect of IJAE on the compound 48/80-induced systemic allergic reaction, anti-DNP IgE antibody-induced local allergic



reaction, and histamine release from RPMC. The effect of IJAE on phorbol 12-myristate 13-acetate (PMA) plus calcium ionophore A23187-induced TNF- α and IL-6 secretion in human mast cell line (HMC-1) cells was also investigated. TNF- α mRNA expression was studied in HMC-1 cells by reverse transcription-polymerase chain reaction (RT-PCR).

MATERIALS AND METHODS

Reagents

Compound 48/80, anti-DNP IgE, DNP-human serum albumin (HSA), α -minimal essential medium (α -MEM), *o*-phthaldialdehyde, evans blue, phorbol 12-myristate 13-acetate (PMA), calcium ionophore A23187 and metrizamide were purchased from Sigma Chemical Co. (St Louis, MO). The rTNF- α and rIL-6 were purchased from R&D Systems Inc. (Minneapolis, MN, USA).

Animals

The original stock of male ICR mice and male Sprague-Dawley rats were purchased from Biolink Co. (Daejeon, Korea). The animals were housed five to ten per cage in a laminar air flow room maintained under a temperature of $22 \pm 2^\circ\text{C}$ and relative humidity of $55 \pm 5\%$ throughout the study.

Preparation of IJAE

The plants of *Isodon japonicus* were collected in Soonchang, Jeonbuk, Korea, on the 13th of August, 2000. A voucher specimen (number WSP-00-35) was deposited at the Herbarium of the College of Pharmacy, Woosuk University. The plant sample was extracted with purified water at 70°C for 5 h. The extract was filtered through Whatman No. 1 filter paper, and the filtrate was lyophilized. The yield of dried extract from starting crude materials was about 10.1%. The dried extract was dissolved in saline or Tyrode buffer A (10 mM HEPES, 130 mM NaCl, 5 mM KCl, 1.4 mM CaCl_2 , 1 mM MgCl_2 , 5.6 mM glucose, 0.1% bovine serum albumin) before use.

Compound 48/80-Induced Systemic Allergic Reaction

Compound 48/80-induced systemic allergic reaction was examined as previously described.^[22] Mice were given an intraperitoneal injection of 0.008 g/kg body weight (BW) of the mast cell degranulator, compound 48/80. IJAE was dissolved in saline and administered intraperitoneally ranging from 0.0001 to 1 g/kg BW 1 h before the injection of compound 48/80 ($n = 10/\text{group}$). In time dependent experiment, IJAE (1 g/kg BW) was administered intraperitoneally at 5 min, 10 min, 20 min and 30 min after compound 48/80 injection ($n = 10/\text{group}$). Mortality was monitored for 1 h after induction of anaphylactic shock. After the mortality test, blood was obtained from the heart of each mouse. The blood was centrifuged at $400 \times g$ for 10 min.



PCA Reaction

An IgE-dependent cutaneous reaction was generated by sensitizing skin with an intradermal injection of anti-DNP IgE followed 48 h later with an injection of DNP-HSA into the mouse tail vein. The anti-DNP IgE antibody and DNP-HSA were diluted in PBS. The mice were injected intradermally with 0.5 μ g of anti-DNP IgE into each of 2 dorsal skin sites that had been shaved 48 h earlier. The sites were outlined with a water-insoluble red marker. Each mouse, 48 h later, received an injection of 1 μ g of DNP-HSA in PBS containing 4% Evans blue (1:4) via tail vein. IJAE (0.001 to 1 g/kg BW) was intraperitoneally administered 1 h before the challenge. Then thirty min after the challenge, the mice were killed and the dorsal skin was removed for measurement of pigment area. The amount of dye was then determined colorimetrically after extraction with 1 mL of 1 M KOH and 9 mL of mixture of acetone and phosphoric acid (5:13) based on the method of Katayama et al.^[23] The absorbent intensity of the extraction was measured at 620 nm in a spectrophotometer (Shimadzu, UV-1201, Japan).

Assay of Histamine

The histamine content was measured by the *o*-phthaldialdehyde spectrofluorometric procedure of Shore et al.^[24] The fluorescent intensity was measured at 438 nm (excitation at 353 nm) in a spectrofluorometer (Shimadzu, RF-5301 PC, Japan).

Preparation of RPMC

RPMC were isolated as previously described.^[25] In brief, rats were anesthetized by ether and injected with 20 mL of Tyrode buffer B (137 mM NaCl, 5.6 mM glucose, 12 mM NaHCO₃, 2.7 mM KCl, 0.3 mM NaH₂PO₄ and 0.1% gelatin), into the peritoneal cavity and the abdomen was gently massaged for about 90 s. The peritoneal cavity was carefully opened and the fluid containing peritoneal cells was aspirated by a Pasteur pipette. Thereafter, the peritoneal cells were sedimented at 150 $\times$ g for 10 min at room temperature and resuspended in Tyrode buffer B. Mast cells were separated from the major components of rat peritoneal cells, i.e. macrophages and small lymphocytes, according to the method described by Yurt et al.^[26] In brief, peritoneal cells suspended in 1 mL of Tyrode buffer B were layered on 2 mL of metrizamide (22.5 w/v%) and centrifuged at room temperature for 15 min at 400 $\times$ g. The cells remaining at the buffer-metrizamide interface were aspirated and discarded; the cells in the pellet were washed and resuspended in 1 mL Tyrode buffer A.

Inhibition of Histamine Release

Purified RPMC were resuspended in Tyrode buffer A for the treatment of compound 48/80. RPMC suspensions (2×10^5 cells/mL) were preincubated for 10 min at 37°C before the addition of compound 48/80 (5 μ g/mL). The cells were preincubated with the IJAE (0.001 to 1 mg/mL) preparations, and then incubated (10 min) with the compound 48/80. RPMC suspensions (2×10^5 cells/mL) were also sensitized with anti-DNP IgE (10 μ g/mL) for 16 h. The cells were preincubated with the IJAE (0.001 to 1 mg/mL) at 37°C for 10 min prior to the challenge with DNP-HSA (1 μ g/mL). The cells were separated from the released histamine by centrifugation at 400 $\times$ g for 5 min.



Table 1. Effect of IJAE on compound 48/80-induced systemic allergic reaction.

IJAE treatment (g/kg BW)	Compound 48/80 (0.008 g/kg BW)	Mortality (%)
None (saline)	+	100
0.0001	+	100
0.001	+	60
0.01	+	20
0.1	+	0
1	+	0
1	—	0

Groups of mice ($n = 10/\text{group}$) were intraperitoneally pretreated with 200 μL saline or IJAE. IJAE was given at various doses 1 h before the compound 48/80 injection. The compound 48/80 solution was intraperitoneally given to the group of mice. Mortality (%) within 1 h following compound 48/80 injection was represented as the number of dead mice $\times 100/\text{total number of experimental mice}$.

at 4°C. Residual histamine in cells was released by disrupting the cells with perchloric acid and centrifugation at $400 \times g$ for 5 min at 4 °C.

Assay of TNF- α and IL-6 Secretion

TNF- α and IL-6 secretion was measured by modification of an enzyme-linked immunosorbent assay (ELISA) as described previously.^[27] HMC-1 cells (3×10^5) were cultured with α -MEM plus 10% FBS and resuspended in Tyrode buffer A. The cells were sensitized with PMA (20 nM) plus A23187 (1 μM) for 6 h in the absence or presence of IJAE. The ELISA was sensitive to TNF- α and IL-6 concentrations in the medium above 0.01 ng/mL. The ELISA was performed by coating 96-well plates with 6.25 ng/well of murine monoclonal antibody with specificity for murine TNF- α and IL-6 respectively. Before use and between subsequent steps in the assay, the coated plates were washed twice with PBS containing 0.05% Tween-20 and twice with PBS alone. All reagents used in this assay and the coated wells were incubated for 1 h at room temperature. For the standard curve, rTNF- α and rIL-6 were added to serum previously determined to be negative to endogenous TNF- α and IL-6. After exposure to the medium, the assay plates were exposed sequentially to biotinylated anti-human TNF- α and IL-6, 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) tablets substrates. Optical density readings were made within 10 min of the addition of the substrate on a Titertek Multiscan (Flow Laboratories) with a 405 nm filter.

RT-PCR Analysis

Total RNA was isolated from HMC-1 cells with Easy-blue according to the manufacturer's instruction, PCR was performed with following primers for TNF- α (5'CGG GAC GTG GAG CTG GCC GAG GAG3'; 5'CAC CAG CTG GTT ATC TCT CAG CTC 3'). The actin (5'GTG GGG CGC CCC AGG CAC CA3'; 5'GTC CTT AAT GTC ACG CAC GAT TTC3') was used to verify that equal amounts of RNA were used for reverse transcription and PCR amplification from different experimental



Table 2. Time-dependent effect of IJAE on compound 48/80-induced systemic allergic reaction.

IJAE treatment (g/kg BW)	Time (min)	Compound 48/80 (0.008 g/kg BW)	Mortality (%)
None (saline)		+	100
1	5	+	0
	10	+	20
	20	+	70
	30	+	100

Groups of mice ($n = 10/\text{group}$) were intraperitoneally pretreated with 200 μL saline or IJAE. IJAE (1 g/kg) was given at 5 min, 10 min, 20 min and 30 min after the compound 48/80 injection. The compound 48/80 solution was intraperitoneally given to the group of mice. Mortality (%) within 1 h following compound 48/80 injection was represented as the number of dead mice $\times 100/\text{total}$ number of experimental mice.

conditions. The annealing temperature was 60 °C for TNF- α and actin. Amplified fragment sizes for TNF- α and actin were 355 bp, 661 bp, respectively. Products were electrophoresed on a 1.5% agarose gel and visualized by staining with ethidium bromide.

Statistical Analysis

The results obtained were expressed as mean $\pm$ SEM. The Student's t -test was used to make a statistical comparison between the groups. Results with $p < 0.05$ were considered statistically significant.

RESULT

IJAE Inhibits Compound 48/80-Induced Systemic Allergic Reaction

To determine the effect of IJAE in allergic reaction, an in vivo model of systemic allergic reaction was used. After the intraperitoneal injection of compound 48/80, the

Table 3. Effect of IJAE on compound 48/80-induced plasma histamine release.

IJAE treatment (g/kg BW)	Compound 48/80 (0.008 g/kg BW)	Amount of histamine ($\mu\text{g/mL}$)
None (saline)	+	0.111 ± 0.018
0.001	+	0.095 ± 0.010
0.01	+	$0.053 \pm 0.006^*$
0.1	+	$0.035 \pm 0.003^*$
1	+	$0.018 \pm 0.003^*$

Groups of mice ($n = 10/\text{group}$) were intraperitoneally pretreated with 200 μL saline or IJAE. IJAE was given at various doses 1 h before the compound 48/80 injection. The compound 48/80 solution was intraperitoneally given to the group of mice. Each datum represents the mean $\pm$ SEM of three independent experiments. $^*p < 0.05$; significantly different from the saline value.



Table 4. Effect of IJAE on the 48 h PCA.

IJAE treatment (g/kg BW)	Anti-DNP IgE plus DNP-HSA	Amount of dye ($\mu\text{g}/\text{site}$)
None (saline)	+	4.951 ± 0.536
0.001	+	4.753 ± 0.504
0.01	+	3.961 ± 0.362
0.1	+	$2.575 \pm 0.283^*$
1	+	$1.337 \pm 0.179^*$

IJAE was administered intraperitoneally 1 h prior to the challenge with antigen. Each datum represents the mean $\pm$ SEM of three independent experiments. $^*p < 0.05$; significantly different from the saline value.

mice were monitored for 1 h, after which the mortality rate was determined. As shown in Table 1, an intraperitoneal injection of 200 μL saline as control induced a fatal shock in 100% of each group. When the IJAE was intraperitoneally administered at concentrations ranging from 0.0001 to 1 g/kg BW for 1 h, the mortality with compound 48/80 was reduced dose-dependently. In addition, the mortality of mice administered intraperitoneally with IJAE (1 g/kg) 5 min, 10 min, 20 min and 30 min after compound 48/80 injection increased time-dependently (Table 2).

IJAE Inhibits Compound 48/80-Induced Plasma Histamine Release

The ability of IJAE on compound 48/80-induced plasma histamine release was investigated. IJAE was given at concentrations ranging from 0.001 to 1 g/kg BW 1 h before ($n = 10/\text{group}$) compound 48/80 injection. The correlation results with those of the mortality test were shown when their plasma histamine contents were measured (Table 3).

IJAE Inhibits PCA Reaction

PCA is one of the most important in vivo models of anaphylaxis in local allergic reactions.^[28] As described in experimental procedures, local extravasation is induced by a local injection of anti-DNP IgE followed by an intravenous antigenic challenge. IJAE (0.001-1 g/kg) dose-dependently inhibited PCA reaction (Table 4).

Table 5. Effect of IJAE on compound 48/80-induced histamine release from RPMC.

IJAE treatment (mg/mL)	Compound 48/80 (5 $\mu\text{g}/\text{mL}$)	Amount of histamine ($\mu\text{g}/\text{mL}$)
None (saline)	+	0.179 ± 0.024
0.001	+	0.156 ± 0.017
0.01	+	0.090 ± 0.015
0.1	+	$0.032 \pm 0.004^*$
1	+	$0.006 \pm 0.001^*$

The cells (2×10^5 cells/mL) were preincubated with IJAE at 37°C for 10 min prior to incubation with compound 48/80. Each datum represents the mean $\pm$ SEM of three independent experiments. $^*p < 0.05$; significantly different from the saline value.



Table 6. Effect of IJAE on Anti-DNP IgE-mediated histamine release from RPMC.

IJAE treatment (mg/mL)	Anti-DNP IgE plus DNP-HSA	Amount of histamine ($\mu\text{g/mL}$)
None (saline)	+	0.152 ± 0.016
0.001	+	0.132 ± 0.011
0.01	+	0.115 ± 0.019
0.1	+	$0.063 \pm 0.007^*$
1	+	$0.042 \pm 0.005^*$

The cells (2×10^5 cells/mL) were preincubated with IJAE at 37°C for 10 min prior to challenge with DNP-HSA. Each datum represents the mean $\pm$ SEM of three independent experiments. * $p < 0.05$; significantly different from the saline value.

IJAE Inhibits Compound 48/80-Induced or Anti-DNP IgE-Mediated Histamine Release from RPMC

The inhibitory effect of IJAE on compound 48/80-induced or anti-DNP IgE-mediated histamine release from RPMC are shown in Table 5 and Table 6. IJAE dose-dependently inhibited compound 48/80-induced or anti-DNP IgE-mediated histamine release at concentrations of 0.001 to 1 mg/mL. The inhibitory effect of IJAE on histamine release was more significant in the case of compound 48/80 treatment.

IJAE Inhibits TNF- α and IL-6 Secretion from HMC-1 Cells

The next test examined whether IJAE could also regulate TNF- α and IL-6 secretion by HMC-1 cells. Culture supernatants were assayed for TNF- α and IL-6 levels by ELISA methods. IJAE inhibited the secretion of TNF- α and IL-6 in PMA plus A23187-stimulated HMC-1 cells (Table 7).

IJAE Inhibits the Expression of TNF- α mRNA in HMC-1 Cells

The inhibitory effect of IJAE on expression of TNF- α mRNA in HMC-1 cells stimulated with PMA plus A23187 through RT-PCR are shown in Fig. 1. PMA

Table 7. Effect of IJAE on PMA plus A23187-stimulated TNF- α and IL-6 secretion from HMC-1 cells.

Treatment	Concentration (mg/mL)	Content (ng/mL)	
		TNF- α	IL-6
None (saline)	—	0.588 ± 0.110	0.039 ± 0.008
PMA + A23187	—	2.553 ± 0.329	1.081 ± 0.036
PMA + A23187 + IJAE	0.1	2.372 ± 0.073	$0.571 \pm 0.029^*$
	1	$1.157 \pm 0.329^*$	$0.376 \pm 0.009^*$

PMA plus A23187-stimulated HMC-1 cells (3×10^5) were incubated for 6 h in the absence or presence of IJAE. TNF- α and IL-6 secreted into the medium are presented as the mean $\pm$ SEM of three independent experiments. * $p < 0.05$; significantly different from the saline value.



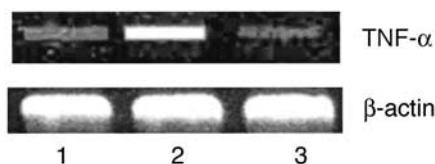


Figure 1. Inhibitory effect of IJAE on the expression of TNF- α mRNA in HMC-1 cells by RT-PCR. Total RNA was isolated from HMC-1 cells. HMC-1 cells were pretreated with IJAE (1 mg/mL) for 30 min prior to PMA plus A23187 stimulation. Lane 1, Saline; Lane 2, Control (PMA plus A23187); Lane 3, PMA plus A23187 plus IJAE (1 mg/mL).

plus A23187-stimulated HMC-1 cells increased TNF- α mRNA expression while unstimulated HMC-1 cells expressed very little TNF- α mRNA. IJAE (1 mg/mL) inhibited the increased TNF- α mRNA expression by PMA plus A23187. β -actin was used as a control for RNA integrity and equal loading.

DISCUSSION

The results of this study demonstrated that IJAE pretreatment profoundly inhibited compound 48/80-induced systemic allergic reaction and anti-DNP IgE-mediated local allergic reaction. IJAE also inhibited compound 48/80-induced or anti-DNP IgE-mediated histamine release from RPMC. These results indicate that mast cell-mediated immediate-type allergic reactions are inhibited by IJAE. It is believed that stimulation of mast cells with compound 48/80 or anti-DNP IgE initiates the activation of signal-transduction pathway, which leads to histamine release. Some recent studies have shown that compound 48/80 and other polybasic compounds are able, apparently directly, to activate G-proteins.^[29,30] The evidence indicates that the protein is Gi-like and that the activation is inhibited by benzalkonium chloride.^[31] Tasaka et al.^[32] reported that compound 48/80 increases the permeability of the lipid bilayer membrane by causing a perturbation of the membrane. This result indicates that the membrane permeability increase may be an essential trigger for the release of the mediator from mast cells. In this sense, anti-allergic agents having a membrane-stabilizing action may be desirable. IJAE might act on the lipid bilayer membrane affecting the prevention of the perturbation being induced by compound 48/80. More recently, studies have suggested the importance of chloride channels that provide the driving force for calcium influx during mast cell activation. Nedocromil sodium was shown to block intermediate conductance chloride channels in cultured mucosal-like mast cells and chloride channels may play a functional role in compound 48/80-induced histamine release from mast cells.^[33,34] IJAE might inhibit compound 48/80-induced histamine release from mast cells by blocking chloride channel. PCA is one of the most important *in vivo* models of anaphylaxis in local allergic reaction. The IJAE administered mice are protected from IgE-mediated PCA. This finding suggests that IJAE might be useful in the treatment of allergic skin reactions. HMC-1 cell line was a useful cell for studying cytokine activation pathways.^[35] IJAE inhibited the secretion of TNF- α and IL-6 in PMA plus A23187-stimulated HMC-1 cells. IJAE also inhibited the main inflammatory cytokine TNF- α mRNA expression in HMC-1 cells. The effect of IJAE



on mast cell cytokine secretion in vivo and the relative importance of mast cells as a source of TNF- α and IL-6 during inflammatory and immune responses are important areas for future studies. In conclusion, the results obtained in the present study provide evidence that IJAE importantly contributes to the prevention or treatment of mast cell-mediated allergic diseases.

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