Inhibitory Effect of Gamisaenghyeolyunbueum on Mast Cell-Mediated Allergic Inflammatory Reactions

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Gamisaenghyeolyunbueum (GSYE) is a traditional Oriental herbal medicine prescription, which has been used for the treatment of various allergic disorders, atopic dermatitis, extravasated bleeding from skin, especially skin related disease. The author investigated the effects of GSYE on mast cell-mediated allergic inflammatory reactions. GSYE dose-dependently (0.01-1 g/kg) inhibited compound 48/80-induced systemic anaphylactic shock and ear swelling response. The inhibitory effect of GSYE on the histamine release from rat peritoneal mast cells induced by compound 48/80 reveals significantly ($P<0.05$) at concentrations ranging from 0.01 to 1 mg/ml in a dose-dependent manner. GSYE also inhibited the passive cutaneous anaphylaxis(PCA) by oral administration at 1 g/kg. In addition, GSYE dose-dependently (0.01-1 g/kg) inhibited the phorbol 12-myristate 13-acetate(PMA) and A23187-induced tumor necrosis factor-α secretion from human mast cell line HMC-1 cells. These results indicate that GSYE may be a beneficial applicability in the allergic-related diseases.

Key words : Gamisaenghyeolyunbueum(加味生血潤膚飮), mast cell, allergic inflammatory reactions, compound 48/80, anaphylaxis, tumor necrosis factor-α

Introduction

Allergic disease such as asthma, atopic dermatitis, allergic rhinitis and food allergy affect up to 20 % of human population in most countries and are believed to be increasing in prevalence[1]. Gamisaenghyeolyunbueum (GSYE) is a traditional Oriental herbal medicine prescription composed of fourteen oriental medicinal herbs, which has been used for the treatment of various allergic disorders, atopic dermatitis, extravasated bleeding from skin, especially skin related disease, widely including fever or diabetes. However, it is still unclear how GSYE prevents allergic diseases in experimental animal model.

In general, immediate-type allergic reactions that involves urticaria, allergic rhinitis and asthma is mediated by various chemical mediators released from mast cells[2]. Mast cells may play a crucial role in the development of many physiological changes during immediate allergic responses[3]. Histamine is one of the well characterized and potent vasoactive mediator implicated in the acute phase of immediate-type hypersensitivity reactions among the substances released on degranulation of mast cells[4,5]. Compound 48/80 is a inducer of degranulation and of the release of histamine from mast cell and induces ear swelling in skin anaphylactic reaction model which is a traditional predictive one of dermal sensitization in humans using mice[6,7]. The secretory responses of mast cells can be induced by aggregation of their cell surface-specific receptors for immunoglobulin E (IgE) by the corresponding antigen[8-10]. It has been established that the anti-IgE antibody induces passive cutaneous anaphylaxis (PCA) as a typical in vivo model for immediate-type hypersensitivity reactions[10]. Mast cells can produce a variety of inflammatory mediators and several proinflammatory and chemotaxic cytokines such as tumor necrosis factor-α (TNF-α), IL(interleukin)-1, IL-4, IL-6, IL-8 and IL-13[11-14]. It seems to be the useful therapeutic strategy for immune disease including allergic inflammatory disease to modulate various cytokines secretion from mast cells. Especially, TNF-α is known as a target cytokine in therapy of allergic disease, inflammatory and immune disease because the mast cell is the only known cell to prestore TNF-α and is able to release this mediator immediately upon activation[15,16].

In the present study, the author investigated whether

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GSYE inhibited the compound 48/80-induced systemic anaphylactic shock and ear swelling response, histamine release from rat peritoneal mast cells (RPMCs) and anti-dinitrophenyl (DNP) IgE antibody-induced PCA. The author also examined the effect of GSYE on cell viability of human mast cell line HMC-1 cells and phorbol 12-myristate 13-acetate (PMA) and A23187-induced TNF-α secretion from HMC-1 cells.

Materials and Methods

1. Materials

These plants materials were obtained from Kwangju Oriental Medical Center, Wonkwang University, South Korea (Table 1).

Table 1. Prescription of *Gamisaenghyeolyunbueum* (GSYE)

Herbal name	Herb Medicine name	Scientific name	Amount (g)
天門冬	Radix asparagi	*Asparagus cochinchinensis MERR.*	6
熟地黃	Rhizoma rehmanniae	*Rehmannia glutinosa LIBOSCH.*	4
生地黃	Rhizoma rehmanniae	*Rehmannia glutinosa LIBOSCH.*	4
麥門冬	Radix ophiopogonis	*Ophiopogon japonicus KER-GAWL.*	4
當歸	Radix angelicae gigantis	*Angelica sinensis DIELS.*	4
黃芪	Radix astragali	*Astragalus membranaceus BUNGE.*	4
黃芩	Radix Scutellariae	*Scutellaria baikalensis GORGY.*	2
瓜蔞仁	Semen trichosanthis	*Trichosanthes kirilowii MAX.*	2
桃仁	Semen persicae	*Prunus persica BATSCH.*	2
升麻	Rhizoma cimicifugae	*Cimicifuga heracleifolia KOM.*	0.8
紅花	Flos carthami	*Carthamus tinctorius L.*	0.4
榆白皮	Cortex ulmi pumilae	*Ulmus pumila L.*	4
枳實	Fructus poncini	*Poncirus trifoliata RAF.*	4
牛蒡子	Fructus arcutii	*Arctium lappa L.*	4
	Total amount		45.2

2. Methods

1) Chemicals

Compound 48/80, anti-DNP IgE, DNP-human serum albumin (HSA), metrizamide, PMA, A23187, o-phthaldialdehyde (OPA), 3-(4,5-dimethylthia-zol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Avidin-peroxidase, 2′-AZINO-bis (3-ethylbenzithiazoline-sullfonic acid) tablets substrate and evans blue were purchased from Sigma Chemical Co (St. Louis, MO, USA). The α-minimal essential medium was purchased from Flow Laboratories (Irvine, UK). Iscove's Modified Dulbecco's medium (IMDM), ampicillin, streptomycin and fetal bovine serum (FBS) were purchased from Gibco BRL (Grand Island, NY, USA). Recombinant human TNF-α, antihuman TNF-α antibody (Ab), biotinylated antihuman TNF-α Ab were purchased from R&D Systems (Minneapolis, MN, USA).

2) Animals

The original stock of male ICR mice and male Sprague-Dawley rats was purchased from the Dae-Han Experimental Animal Center (Daejon, Korea), and the animals were maintained at the College of Pharmacy, Wonkwang University. The rats were housed in a laminar air-flow room maintained at a temperature of 22±1℃ and relative humidity of 55±10 % throughout the study. No animal was used more than once. The research was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the US guidelines (NIH publication #85-23, revised in 1985).

3) Preparation of GSYE

The GSYE was obtained from kwangju Oriental Medical Center, Wonkwang University, South Korea and identified by Professor Won, Jin-Hee of College of Oriental Medicine, Wonkwang University. A voucher specimen (number 1-01-60) was deposited at the Herbarium of the Wonkwang University. An extract of GSYE was prepared by decocting the dried prescription of herbs with boiling distilled water. The duration of decoction was about 3 h. The decoction was filtered, lyophilized and kept at 4°C. The yield of dried extract from starting crude materials was about 24.1 %. The samples were dissolved in saline and then filtered through 0.45-μm syringe filter.

4) MTT assay

Cell aliquots (3×10^5) were seeded in microplate wells and incubated with 20 μl of an MTT solution (5 mg/ml) for 4 h at 37°C under 5 % CO_2 and 95 % air. Consecutively, 250 μl of DMSO was added to extract the MTT formazan and the absorbance of each well at 540 nm was read by an automatic microplate reader.

5) Compound 48/80-induced systemic anaphylactic reaction

Mice were given an intraperitoneal injection of the mast cell degranulator compound 48/80 (8 mg/kg). GSYE was dissolved in saline and administered orally 1 h before the injection of compound 48/80. Mortality was monitored for 30 min after induction of anaphylactic reaction.

6) Ear swelling response

Compound 48/80 was freshly dissolved in saline and injected intradermally into the dorsal aspect of a mouse ear using a microsyringe with a 28-gauge hypodermic needle. Ear thickness was measured with a digimatic micrometer (Mitutoyo, Japan) under mild anesthesia. Ear swelling response represented an increment in thickness above baseline control values. Ear swelling response was determined 40 min after compound 48/80 or vehicle injection. GSYE was administered orally 1 h before the compound 48/80-injection (100 μg/site). The values obtained would appear to represent the effect of compound 48/80 rather than the effect of the vehicle injection (physical swelling), since the ear swelling response evoked by physiologic

saline returned to almost baseline thickness within 40 min.

7) Preparation of RPMCs

RPMCs were isolated as previously described[17]. In brief, rats were anesthetized by ether, and injected with 20 ml of Tyrode buffer B (NaCl, glucose, $NaHCO_3$, KCL, NaH_2PO_4) containing 0.1 % gelatin (Sigma) into the peritoneal cavity; the abdomen was gently massaged for about 90 sec. The peritoneal cavity was carefully opened, and the fluid containing peritoneal cells was aspirated by Pasteur pipette. Then the peritoneal cells were sedimented at 150 × 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[18]. In brief, peritoneal cells suspended in 1 ml of Tyrode buffer B were layered onto 2 ml of 0.225 g/ml metrizamide (density 1.120 g/ml; Sigma) and centrifuged at room temperature for 15 min at 400 × 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 of 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) containing calcium. Mast cell preparations were about 95 % pure as assessed by toluidine blue staining. More than 97 % of the cells were viable as judged by trypan blue uptake.

8) Histamine assay

Purified RPMCs were resuspended in Tyrode buffer A containing calcium for the treatment with compound 48/80. RPMCs suspensions (2×10^5 cells/ml) were preincubated for 10 min at 37℃ before the addition of compound 48/80 for stabilization. The cells were preincubated with the EA for 20 min, and then incubated for 15 min with compound 48/80 (6 g/ml). The reaction was stopped by cooling the tubes in ice. The cells were separated from the released histamine by centrifugation at 400 × g for 5 min at 4℃. Residual histamine in the cells was released by disrupting the cells with perchloric acid and centrifugation at 400 × g for 5 min at 4℃. The histamine content was measured by the o-phthalaldehyde spectrofluorometric procedure of Shore et al[19]. The fluorescent intensity was measured at 440 nm (excitation at 360 nm) in spectrofluorometer.

The inhibition percentage of histamine release was calculated using the following equation:

% inhibition = (A - B) 100 / A

where A is histamine release without GSYE and B is histamine release with GSYE.

9) Alcian blue-nuclear fast red (NFR) staining

In order to compare the status of mast cells before or after the addition of GSYE would make it clear whether GSYE affects the degranulation process or not, alcian blue-NFR staining was performed. Mast cells were centrifuged with 1 % alcian blue and NFR solution. They were then rinsed in distilled water and gradually dehydrated in a series of 80 %. 90 %, 95 % and 100 % alcohol. The slides were cleared in xylene and mounted with mounting medium.

10) PCA reaction

IgE-dependent cutaneous reaction was generated by sensitizing the skin with an intradermal injection of anti-DNP IgE followed 48 h later with an injection of DNP-HSA into the mice tail vein. The DNP-HSA was diluted in phosphate-buffered saline (PBS). The mice were injected intradermally with 100 ng of anti-DNP IgE into each of three dorsal skin sites that had been shaved 48 h earlier. The sites were outlined with a water-insoluble red marker. Forty-eight hours later, each mouse received an injection of 200 μl of the 1:1 mixture of 1 mg/ml DNP-HSA in PBS and 4 % Evans blue via the tail vein. One hour before this injection, GSYE was administered orally. The mice were sacrificed 40 min after the intravenous challenge. The dorsal skin of the mouse was removed for measurement of the pigment area. The amount of dye was then determined colorimetrically after extraction with 0.5 ml of 1.0 mol/l KOH and 4.5 ml of a mixture of acetone and phosphoric acid (with the ratio of 5:13), based on the method of Katayama et al.[20]. The absorbent intensity of the extraction was measured at 620 nm in a spectrofluorometer, and the amount of dye was calculated with the Evans blue measuring-line.

11) TNF-α assay

Human mast cell line HMC-1 cells were grown in IMDM (Gibco BRL, USA) with 10 % FBS (JRH Bioscience, USA) at 37℃ in 5 % CO_2 and 95 % humidity. HMC-1 cells were pretreated with various concentration of GSYE for 30 min prior to PMA (50 nM) and A23187 (1 μM) stimulation. Culture supernatants were assayed for TNF-α protein levels by enzyme-linked immunosorbent assay (ELISA) method. Cytokines were measured by a modified ELISA as described[21]. The ELISA for TNF-α was carried out in duplicate in 96-well ELISA plates (Nunc, Denmark) coated with each of 100 μl aliquots of mouse anti-human TNF-α monoclonal antibodies (R&D, Minneapolis, MN, USA) and was incubated overnight at 4℃. The plates were washed in PBS containing 0.05 % Tween-20 (Sigma, St. Lousis, MO, USA) and blocked with PBS containing 1 % BSA, 5 % sucrose and 0.05 % NaN3 for 1 h. After additional washes, sample or recombinant TNF-α standards were added and incubated at 37℃ for 2 h. After 2 h of incubation at 37℃, the wells were washed and then each

of 0.2 μg/ml of biotinylated anti-human TNF-α were added and again incubated at 37℃ for 1 h. After washing the wells, avidin-peroxidase was added and plates were incubated for 30 min at 37℃. Wells were again washed and ABTS substrate (Sigma) was added. Color development was measured at 405 nm using an automated microplate ELISA reader. A standard curve was run on each assay plate using recombinant human TNF-α in serial dilutions.

12) Statistical analysis

The results were expressed as mean ± S.E.M. for the number of experiments. Statistical significance was compared between each treated group and control by the Student's t-test. Results with $P < 0.05$ were considered statistically significant.

Results

1. Effect of GSYE on compound 48/80-induced systemic anaphylaxis

To assess the contribution of GSYE in anaphylactic reactions, the author first used the in vivo model of systemic anaphylaxis. As a non-immunologic stimulator, compound 48/80 (8 mg/kg) was used. After the injection of compound 48/80, the mice were monitored for 30 min, after which the mortality rate was determined. As shown in Table 1, an oral administration of saline as a control induced a fatal reaction in 100 % of each group. When the GSYE was orally administered at concentrations of 0.01, 0.1, 1 g/kg 1 h before compound 48/80 injection, the mortality was dose-dependently reduced (Table 2).

Table 2. Effect of GSYE on compound 48/80-induced systemic anaphylactic reaction

GSYE dose (g/kg)[a]	Compound 48/80 (8 mg/kg)[b]	Mortality (%)[c]
None (saline)	+	100.0
0.01	+	66.7
0.1	+	50.0
1	+	33.3
1	-	0.0

a : The groups of mice were orally pretreated with 200 μl of saline or GSYE was given at various doses 1 h before the compound 48/80 injection. b : The compound 48/80 solution was intra-peritoneally given to the groups of mice. c : Mortality (%) is presented as the No. of dead mice 100/ Total no. of experimental mice.

2. Effect of GSYE on ear swelling response

The fact that intradermal application of compound 48/80 at the concentration of 50-200 μg/site can induce an ear swelling response in normal mice has been confirmed in the previous experiment[22]. The author chose a concentration of 100 g/site for compound 48/80-induced optimal ear-swelling response in this experiment. As shown in Table 2, when mice were pre-treated with GSYE for 1 h, the ear swelling responses derived from compound 48/80 were significantly reduced at concentration of 1 g/kg (Table 3).

Table 3. Effect of GSYE on compound 48/80-induced ear-swelling response in mice[a]

GSYE dose (g/kg)[b]	Thickness (mm)[c]	Inhibition (%)
None	0.216±0.033	-
0.01	0.160±0.021	25.93
0.1	0.136±0.015	37.04
1	0.107±0.009*	50.46

a : Twenty μl of compound 48/80 (100 μg/site) were applied intradermally. b : The mice were orally administered with the indicated concentration of GSYE for 1 h prior to the compound 48/80 application. c : Each datum represents the mean ± S.E.M. *P<0.05: significantly different from the saline value.

3. Effect of GSYE on histamine release from RPMCs

The inhibitory effect of GSYE on compound 48/80-induced histamine release from RPMCs is shown in Fig. 1. GSYE dose-dependently inhibited compound 48/80-induced histamine release at concentrations of 0.01-1 mg/ml (Fig. 1).

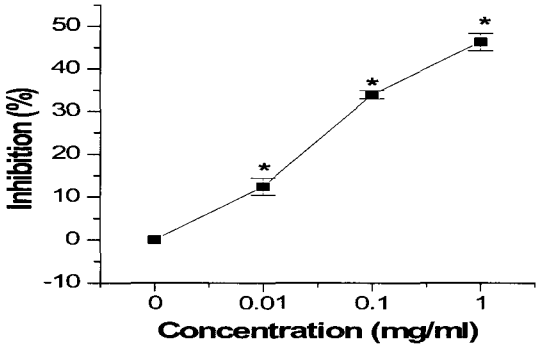

Fig. 1. Effect of GSYE on compound 48/80-induced histamine release from RPMCs. RPMCs (2×10^5 cells) were preincubated with various concentrations of GSYE at 37℃ for 10 min prior to incubation with compound 48/80. *P<0.05: significantly different from the saline value.

4. Effect of GSYE on degranulation of mast cells

Fig. 2 showed photographs of alcian blue-NFR stained-RPMCs. Compound 48/80-stimulated RPMC was extensively degranulated compared with GSYE-treated cell, which is correlated with an inhibition of histamine release. This explains that GSYE inhibits the compound 48/80-induced degranulation from mast cells (Fig. 2).

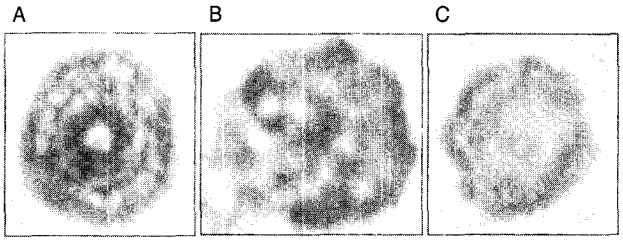

Fig. 2. The photographs of alcian blue-NFR staines mast cells. Isolated RPMC was preincubated at 37℃ for 10 min (A). Compound 48/80-stimulated RPMC was incubated for 10 min in the absence (B) or in the presence (C) of GSYE (1 mg/ml). Magnifications were × 400.

5. Effect of GSYE on PCA

PCA is one of the most important in vivo models of anaphylaxis in local allergic reactions[23]. Local injection of anti-DNP IgE followed by an intravenous antigenic challenge

was performed. Anti-DNP IgE was injected into dorsal skin sites. After 48 h, all animals were injected intravenously with DNP-HSA containing Evans blue dye. The passive cutaneous anaphylactic (PCA) reaction was best visualized by the extravasation of dye. When GSYE was orally administered to the mouse, the PCA reaction was inhibited at concentration of 0.01, 1 g/kg (Table 4).

Table 4. Effect of GSYE on 24 h PCA in mice[a]

GSYE dose (g/kg)	Amount of dye (㎍ site)[b]	Inhibition (%)
None	0.501±0.312	-
0.01	0.265±0.008*	47.11
0.1	0.458±0.021	8.58
1	0.135±0.014*	73.05

a : GSYE was administered orally 1 h prior to the challenge with antigen (DNP-HSA). b : Each datum represents the mean ± S.E.M. *P(0.05: significantly different from the saline value.

6. Effect of GSYE on TNF-α secretion from HMC-1 cells

Human mast cell line HMC-1 cells were stimulated with PMA (50 nM) and calcium ionophore A23187 (1 μM). To assess the effect of GSYE in PMA and A23187-induced TNF-α secretion, the cells were pretreated with various concentrations of GSYE for 30 min prior to stimulators. The results showed that pretreatment of the cells with GSYE resulted in inhibition of TNF-α secretion. The effect of GSYE on the TNF-α secretion from HMC-1 was significantly inhibited ($P<0.05$) in a dose dependent manner (Table 5).

Table 5. Effect of GSYE on PMA and A23187-induced TNF-α secretion from HMC-1 cells

GSYE addition (mg/ml)	TNF-α secretion[a,b] (ng/ml)
None (saline)	3.65±0.04
0.01	2.93±0.19*
0.1	2.40±0.08*
1	2.20±0.17*

a : TNF-α levels in supernatant were measured using ELISA method. b : Each datum represents the mean ± S.E.M. *P(0.05: significantly different from the saline value.

7. Effect of GSYE on cell viability of HMC-1 cells

To assess the effect of GSYE on the cell viability of mast cell, the author performed MTT assay.

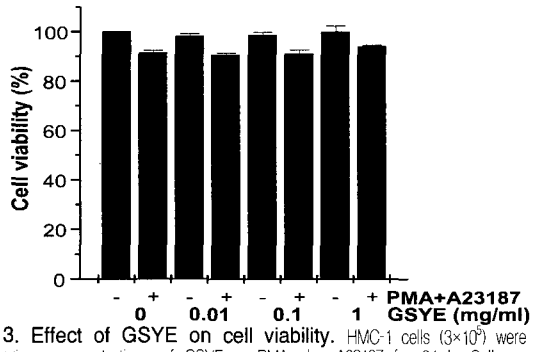

Fig. 3. Effect of GSYE on cell viability. HMC-1 cells (3×10^5) were treated with various concentrations of GSYE or PMA plus A23187 for 24 h. Cells were then collected and assessed for viability using MTT. Values are the mean±S.E.M. of duplicate determinations from three separate experiments.

As shown in Fig. 3, they did not affect cell viability in the GSYE (0.01, 0.1, 1 mg/ml) with PMA (50 nM) plus A23187 (1 μM)-treated cells compared to PMA plus A23187-treated cells without GSYE treatment (Fig. 3).

Discussion

The Present study showed that GSYE pretreatment profoundly affected compound 48/80-induced systemic anaphylaxic reaction and ear swelling response in mice. GSYE inhibited the compound 48/80 induced histamine release from RPMC and anti-DNP IgE-induced PCA reaction in a murine model. The inhibitory effects of GSYE on anaphylactic reactions in mice appears to be attributable to derive from inhibition of mediator release from the mast cells. Previous study showed that the topical application of compound 48/80 did not induce a swelling response in ear of WBB6F1-W/WV mice-locally and selectively repaired of mast cell deficiency[24]. Therefore, the inhibitory effects of GSYE on ear swelling indicate that mast cell-mediated immediate type allergic reactions are reduced by GSYE. Stimulation of mast cells with compound 48/80 is believed to initiate the activation of a signal transduction pathway which leads to histamine release[25]. Some reports have shown that compound 48/80 is able to activate G proteins[26-28]. Chadi et al. announced that compound 48/80 activates mast cell phospholipase D via heterotrimeric GTP-binding proteins[29]. Murine mast cells are a good experimental model for the study on compound 48/80-induced histamine release[30]. There are some studies that the permeability of the lipid bilayer membrane via perturbation of the membrane is increased by compound 48/80[31]. Because the membrane permeability increase may be an essential trigger for the release of mediators from mast cells, GSYE might act on the lipid bilayer membrane affecting the prevention of the perturbation induced by compound 48/80. The effects of GSYE on PCA show that mouse GSYE-administered are protected from IgE-mediated local allergic reaction. The mechanism of the protection against anti-DNP IgE may be suggested only in some particular conditions. It is conceivable that GSYE inhibits the initial phase of immediate type allergic reactions, probably through interference with the degranulation system.

The author have demonstrated that GSYE treatment induced the inhibitory effect on the TNF-α release in PMA and A23187-stimulated HMC-1 cell line in the dose dependent manner. This results indicates that GSYE has the effective anti-inflammatory because TNF-α plays a crucial role in allergic inflammation by releasing mediator immediately, TNF-

α, upon mast cell activation[16]. However, future study should be followed to clarify the mechanism how GSYE inhibits TNF-α release on the mast cells.

Conclusively, the present results provide evidence that GSYE inhibited the mast cell-dependent immediate-type allergic reactions and inflammatory cytokines, TNF-α secretion from mast cells in vivo and in vitro. The author expect that administration of GSYE may be a beneficial applicability in the allergic-related diseases.

Conclusion

In this study, the ability of Korean medicine prescription, GSYE's (Gamisaenghyeolyunbueum) inhibitory effects was investigated on mast cell-mediated allergic inflammatory reactions.

GSYE dose-dependently (0.01-1 g/kg) inhibited compound 48/80-induced systemic anaphylactic shock and ear swelling response derived from compound 48/80. GSYE inhibited the compound 48/80-induced histamine release from RPMCs and the compound 48/80-induced degranulation from mast cells. GSYE also inhibited the passive cutaneous anaphylaxis(PCA) reaction by oral administration at 0.01 and 1 g/kg. In addition, GSYE dose-dependently (0.01-1 g/kg) inhibited the phorbol 12-myristate 13-acetate(PMA) and A23187-induced tumor necrosis factor-α secretion from human mast cell line HMC-1 cells.

Thus, the author expected that GSYE may be a beneficial applicability in the allergic-related diseases.

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