

## Effect of *Terminalia chebula* fruit on anaphylaxis by anal therapy

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### SUMMARY

The effect of aqueous extract of *Terminalia chebula* fruit (Combretaceae) (TCAE) by anal administration on mast cell-dependent immediate-type anaphylactic reactions was investigated. TCAE (0.005 to 1 g/kg) inhibited systemic anaphylaxis induced by compound 48/80 in mice. When TCAE was pretreated at the same concentrations with systemic anaphylaxis, the plasma histamine levels were reduced in a dose-dependent manner. TCAE (0.1 and 1 g/kg) also significantly inhibited local anaphylaxis activated by anti-DNP IgE. TCAE (0.001 to 1 mg/ml) dose-dependently inhibited the histamine release from rat peritoneal mast cells (RPMC) activated by compound 48/80 or anti-DNP IgE. Moreover, TCAE (0.01 and 0.1 mg/ml) had a significant inhibitory effect on anti-DNP IgE-mediated tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) production from RPMC. These results provide evidence that anal therapy of TCAE may be beneficial in the treatment of systemic and local mast cell-dependent anaphylaxis.

**Key words:** *Terminalia chebula*; Anal therapy; Anaphylaxis; Compound 48/80; Anti-DNP IgE; Histamine; Tumor necrosis factor- $\alpha$

### INTRODUCTION

The medicinal *Terminalia chebula* fruit is the dried ripe fruit of *Terminalia chebula* Retz. or *Terminalia chebula* Retz. var. *tomentella* Kurt (Combretaceae). It has been used in protracted diarrhea with hematochezia and prolapse of the rectum, chronic cough with sore throat and hoarseness of voice (Sung *et al.*, 1998; Zu, 1998).

It is now well established that the mast cell triggers anaphylaxis in response to allergens by releasing chemical mediators (Metcalf *et al.*, 1981; Kim and Lee, 1999). 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 (Petersen *et al.*, 1996). Mast cell degranulation can be elicited by a number of positively charged substances, collectively known as the basic secretagogues of mast cells (Lagunoff *et al.*, 1983). Compound 48/80 and polymers of basic amino acids, such as substance P, are some of the most potent secretagogues of mast cells (Ennis *et al.*, 1980). Compared with the natural process, a high concentration of compound 48/80 induces almost a 90% release of histamine from mast cells. Thus, an appropriate amount of compound 48/80 has been used as a direct and convenient reagent to study the mechanism of anaphylaxis (Allansmith *et al.*, 1989). The secretory response of mast cells can also be induced by aggregation of their cell surface-specific receptors for immunoglobulin E (IgE) by the corresponding antigen (Segal *et al.*, 1977; Metzger *et al.*, 1986; Alber *et al.*, 1991). It has been established that the anti-IgE antibody induces passive cutaneous anaphylaxis (PCA) reactions as a typical model for the immediate hypersensitivity. Given the recent

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evidence that upon antigen stimulation mast cells are a potential source of various cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), it is likely that they play a crucial role in allergic inflammation (Burd *et al.*, 1989; Plaut *et al.*, 1989; Wodnar-Filipowicz *et al.*, 1989; Galli *et al.*, 1991; Gurish *et al.*, 1991). Therefore, modulation of TNF- $\alpha$  production by mast cells should provide a useful therapeutic strategy for allergic disease.

Anal therapy is a kind of drug delivery system through the anus, which is utilized in the patients to whom oral administration is impossible. The drug absorbed in the rectum can avoid first-pass effect in the liver and circulate the whole-body directly. The absorption rate in the rectum is faster than that in the gastrointestinal tract. The absorption rate and total amount through the rectum have little difference with those of a venous administration. Thus, anal therapy can be expected to have good efficacy by the increased absorption rate and the strong medical action (Yi *et al.*, 2001; Won *et al.*, 2001). Medicine was administered to the experimental animal through the anus and investigated the inhibitory effect against allergic reaction.

The effect of the water soluble fraction of *Terminalia chebula* methanol extract on systemic and local anaphylaxis was reported (Shin *et al.*, 2001). The effect of *Terminalia chebula* water extract on immediate hypersensitivity reaction by intraperitoneally therapy was reported (Lee *et al.*, 2001).

This paper deals with an evaluation of the effect of TCAE on compound 48/80-induced systemic anaphylaxis and anti-dinitrophenyl (DNP) IgE antibody-induced PCA by anal therapy and histamine release from RPMC. Investigation of the influence of TCAE on TNF- $\alpha$  production was also carried out.

## MATERIALS AND METHODS

### Reagents

Compound 48/80, anti-DNP IgE, DNP-human serum albumin (HSA),  $\alpha$ -minimal essential medium ( $\alpha$ -MEM), o-phthalaldehyde and metrizamide were purchased from Sigma Chemical Co. (St Louis, MO). Murine TNF- $\alpha$  was obtained from R&D Systems Inc. (USA).

### Animals

The original stock of ICR mice and SD rats were

purchased from Dae-Han Biolink (Daejeon, Korea) and the animals were maintained in the College of Pharmacy, Woosuk University. The animals were housed five to ten per cage in a laminar air flow room maintained under a temperature of 22 $\pm$ 2°C and relative humidity of 55 $\pm$ 5% throughout the study.

### Preparation of TCAE

The fruits of *Terminalia chebula* were purchased from the oriental drug store, Bohwa Dang (Jeonju, Korea). A voucher specimen (number WSP-98-20) 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 (two times). The extract was filtered through Whatman No.1 filter paper, and the filtrate was lyophilized, and kept at -4°C. The yield of dried extract from starting crude materials was about 11.9%. The dried extract was dissolved in saline or Tyrode buffer A (10 mM HEPES, 130 mM NaCl, 5 mM KCl, 1.4 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 5.6 mM glucose, 0.1% bovine serum albumin) before use.

### Compound 48/80-induced systemic anaphylaxis

Compound 48/80-induced systemic anaphylactic reaction was examined as previously described (Yi *et al.*, 2001). Mice were given an intraperitoneal injection of 0.008 g/kg body weight (BW) of the mast cell degranulator, compound 48/80. The dried TCAE was dissolved in saline and administered anally ranging from 0.001 to 1 g/kg 1 h before the injection of compound 48/80 (n=10/group). In time dependent experiment, TCAE (1 g/kg BW) was administered anally at 0 min, 5 min, 10min, 20 min and 30 min after compound 48/80 injection (n=10/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.

### PCA reaction

An 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 tail vein. The anti-DNP IgE and DNP-HSA were diluted in PBS. The mice were injected intradermally with 0.5  $\mu$ g of anti-DNP IgE into each of two 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 mg of DNP-HSA in PBS containing 4% Evans blue (1:4) via the tail vein. TCAE (0.001 to 1 g/kg BW) was orally administered 1 h before the challenge. Then 30 min after the challenge, the mice were sacrificed 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 (13:5) based on the method of Katayama *et al.* (1978). The absorbent intensity of the extraction was measured at 620 nm in a spectrophotometer (Shimadzu, UV-1201, Japan) and the amount of dye was calculated with the Evans blue measuring-line.

#### **Preparation of plasma and histamine determination**

The blood was centrifuged at 400×g for 10 min. The plasma was withdrawn and histamine content was measured by the o-phthalaldehyde spectrofluorometric procedure of Shore *et al.* (1959). 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 (Kanemoto *et al.*, 1993). 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 NaHCO<sub>3</sub>, 2.7 mM KCl, 0.3 mM NaH<sub>2</sub>PO<sub>4</sub> and 0.1% gelatin) into the peritoneal cavity and the abdomen was gently massaged for about 90 seconds. 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×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.* (1977). 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×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<sup>5</sup> cells/ml) were preincubated for 10 min at 37°C before the addition of compound 48/80 (5 µg/ml). The cells were preincubated with the TCAE preparations, and then incubated (10 min) with the compound 48/80. RPMC suspensions (2×10<sup>5</sup> cells/ml) were also sensitized with anti-DNP IgE (10 µg/ml) for 6 h. The cells were preincubated with the TCAE at 37°C for 10 min prior to the challenge with DNP-HSA (1 µg/ml). The cells were separated from the released histamine by centrifugation at 400×g for 5 min at 4°C. Residual histamine in cells was released by disrupting the cells with perchloric acid and centrifugation at 400×g for 5 min at 4°C.

#### **Assay of TNF-α production**

TNF-α production was measured with the quantitative sandwich enzyme immunoassay technique, using a commercial kit (R&D Systems, U.S.A.). RPMC (3×10<sup>5</sup> cells/ml) were sensitized with anti-DNP IgE (1 µg/ml) and incubated for 18 h in the absence or presence of TCAE (0.001 to 0.1 mg/ml) before the challenge DNP-HSA (0.1 µg/ml). TNF-α production was measured by ELISA. The ELISA was performed by coating 4-well plates with murine polyclonal antibody with specificity for murine TNF-α Standard, controls, and samples are pipetted into the wells and any mouse TNF-α present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for mouse TNF-α is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution (100 µl) was added to the wells. The enzyme reaction yielded a blue product that turns yellow when the Stop solution (100 µl) was added. The intensity of the color measured is in proportion to the amount of mouse TNF-α bound in the initial step. Optical density readings were made on a Titertek Multiscan (Flow Laboratories) with a 405 nm filter. The sample values are then read off the standard curves.

#### **Statistical analysis**

The results obtained were expressed as mean± 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.

## RESULTS

### Effect of TCAE on compound 48/80-induced systemic anaphylaxis

To determine the effect of TCAE by anal therapy in systemic anaphylaxis, Compound 48/80 (0.008 g/kg) as a fatal anaphylaxis inducer was used. After the intraperitoneal injection of compound 48/80, the mice were monitored for 1 h, after which the mortality rate was determined. As shown in Table 1, an anal administration of 200  $\mu$ l saline as a control induced a fatal shock in 100% of mice. When the TCAE was anally administered at a concentrations ranging from 0.005 to 1 g/kg BW for 1 h, the mortality

**Table 1.** Effect of TCAE on compound 48/80-induced systemic anaphylaxis

TCAE treatment (g/kg BW)	Compound 48/80 (0.008 g/kg)	Mortality (%)
None(saline)	+	100
0.001	+	100
0.005	+	70 $\pm$ 20
0.01	+	40 $\pm$ 10
0.05	+	10 $\pm$ 10
0.1	+	0
0.5	+	0
1	+	0
1	-	0

Groups of mice ( $n=10$ /group) were anally pretreated with 200  $\mu$ l saline or TCAE. TCAE 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/total number of experimental mice.

with compound 48/80 was reduced dose-dependently. In addition, the mortality of mice administered anally with TCAE (1 g/kg) 0 min, 5 min, 10 min, 20 min and 30 min after compound 48/80 injection increased time-dependently (Table 2).

### Effect of TCAE on compound 48/80-induced plasma histamine release

The ability of TCAE on compound 48/80-induced plasma histamine release was investigated. TCAE was given from 0.005 to 1 g/kg BW 1 h before ( $n=10$ /group) compound 48/80 injection. The correlative results with those of the mortality test were shown when their plasma histamine contents were measured (Table 3). The inhibition rate of histamine by TCAE was significant at doses of 0.05 to 1 g/kg.

### Effect of TCAE on anti-DNP IgE-induced PCA

Local extravasation is induced by a local injection of anti-DNP IgE followed by an intravenous antigenic challenge. Anti-DNP IgE was injected into the right dorsal skin sites. As a control, the left dorsal skin site of these mice was injected with saline alone. After 48 h, all animals were injected intravenously with DNP-HSA plus Evans blue dye. TCAE was administered anally 1 h prior to the challenge with antigen. As shown in Table 4, TCAE (0.1 and 1 g/kg) showed a marked inhibition in PCA reaction.

### Effect of TCAE on compound 48/80-induced or anti-DNP IgE-mediated histamine release from RPMC

The inhibitory effect of TCAE on compound 48/80-induced or anti-DNP IgE-mediated histamine

**Table 2.** Time-dependent effect of TCAE on compound 48/80-induced systemic anaphylaxis

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

Groups of mice ( $n=10$ /group) were anally pretreated with 200  $\mu$ l saline or TCAE. TCAE (1 g/kg) was given at 0 min, 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/total number of experimental mice.

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

TCAE treatment (g/kg BW)	Compound 48/80 (0.008 g/kg)	Amount of histamine (ng/ml)
None(saline)	+	80±9
0.005	+	76±7
0.01	+	48±6
0.05	+	39±5*
0.1	+	31±4*
0.5	+	26±4*
1	+	19±2*

Groups of mice ( $n=10$ /group) were orally pretreated with 200  $\mu$ l saline or TCAE. TCAE was given at various doses 1 h before the compound 48/80 injection. Each datum represents the mean±SEM of three independent experiments. \* $p<0.05$ ; Significantly different from the saline value.

**Table 4.** Effect of TCAE on the 48h PCA

TCAE treatment (g/kg BW)	Anti-DNP IgE plus DNP-HSA	Amount of dye ( $\mu$ g/site)
None(saline)	+	7.04±0.77
0.001	+	6.69±0.75
0.01	+	5.63±0.50
0.1	+	3.87±0.43*
1	+	2.46±0.22*

TCAE was administered orally 1 h prior to the challenge with antigen. Each datum represents the mean±SEM of three independent experiments. \* $p<0.05$ ; Significantly different from the saline value.

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

TCAE treatment (mg/ml)	Compound 48/80 (5 $\mu$ g/ml)	Amount of histamine (ng/ml)
None(saline)	+	319±33
0.001	+	257±27
0.01	+	241±23
0.1	+	93±10*
1	+	48±5*

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

**Table 6.** Effect of TCAE on IgE-mediated histamine release from RPMC

TCAE treatment (mg/ml)	Anti-DNP IgE plus DNP-HSA	Amount of histamine (ng/ml)
None(saline)	+	145±17
0.001	+	138±12
0.01	+	102±9
0.1	+	70±8*
1	+	51±4*

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

release from RPMC are shown in Table 5 and Table 6. TCAE dose-dependently inhibited compound 48/80-induced or anti-DNP IgE-mediated histamine release at concentrations of

0.001 to 1 mg/ml. Especially, TCAE significantly inhibited the compound 48/80-induced or IgE-mediated histamine release at the concentrations of 0.1 and 1 mg/ml.

**Table 7.** Effect of TCAE on anti-DNP IgE-mediated TNF- $\alpha$  production in RPMC

TCAE treatment (mg/ml)	Anti-DNP IgE plus DNP-HSA	TNF- $\alpha$ production (pg/ml)
None(saline)	-	69.5 $\pm$ 5.8
None(saline)	+	209.1 $\pm$ 18.7
0.001	+	197.0 $\pm$ 20.3
0.01	+	88.6 $\pm$ 9.9*
0.1	+	89.7 $\pm$ 8.6*

The cells ( $3 \times 10^5$  cells/ml) were sensitized with anti-DNP IgE (1  $\mu$ g/ml) and incubated for 18 h in the absence or presence of TCAE before the challenge with DNP-HSA (0.1  $\mu$ g/ml). Each datum represents the mean $\pm$ SEM of three independent experiments. \* $p < 0.05$ ; Significantly different from the saline value.

### Effect of TCAE on anti-DNP IgE-mediated TNF- $\alpha$ production from RPMC

Whether TCAE could also regulate TNF- $\alpha$  production by RPMC was examined. TCAE significantly inhibited TNF- $\alpha$  production at concentrations of 0.01 and 0.1 mg/ml (Table 7). No significant cytotoxicity of TCAE on the culture was observed in the concentrations used in the experiments, as assessed by trypan blue uptake.

## DISCUSSION

The present study showed that TCAE pretreatment profoundly affected compound 48/80-induced and anti-DNP IgE mediated anaphylactic reaction *in vivo* and *in vitro*. TCAE (0.01 to 1 g/kg) orally administered 1 h before the compound 48/80 injection has a preventive effect, a remedial significance (Table 1, Table 2, Table 3). In addition, compound 48/80 or anti-DNP IgE-induced histamine release from RPMC was significantly inhibited by TCAE at the concentrations of 0.1 and 1 mg/ml (Table 5, Table 6). There is no doubt 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 (Mousli *et al.*, 1990a; Mousli *et al.*, 1990b). The evidence indicates that the protein is G inhibitory-like and that the activation is inhibited by benzalkonium chloride (Bueb *et al.*, 1990). Tasaka *et al.* (1986) reported that compound 48/80 increased the permeability of the lipid bilayer membrane by causing a perturbation of the membrane. This result indicates that the permeability increase of

the cell membrane 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. TCAE might act on the lipid bilayer membrane affecting the prevention of the perturbation being induced by compound 48/80. The TCAE (0.1 and 1 g/kg) orally administered mouse is protected from local anaphylaxis, which suggests that TCAE might be useful in the treatment of allergic skin reactions (Table 4). The data also demonstrated that TCAE (0.01-1 mg/ml) inhibited anti-DNP IgE-mediated TNF- $\alpha$  production from mast cells (Table 7). The effect of TCAE on mast cell cytokine production *in vivo* and the relative importance of mast cells as a source of TNF- $\alpha$  during inflammatory and immune responses are important areas for future studies.

In conclusion, these results provide evidence that anal therapy of TCAE may be beneficial in the treatment of allergic diseases.

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