



Ethnopharmacological communication

Tanshinones isolated from the rhizome of *Salvia miltiorrhiza* inhibit passive cutaneous anaphylaxis reaction in miceHien Trung Trinh^a, Sun Ju Chae^a, Eun-Ha Joh^a, Kun Ho Son^b, Su Jin Jeon^b, Dong-Hyun Kim^{a,*}^a Department of Life and Pharmaceutical Sciences, Kyung Hee University, Dongdaemun-Ku, Seoul 130-701, Republic of Korea^b Department of Food Science and Nutrition, Andong National University, Andong, Gyung-sangbuk-do 760-749, Republic of Korea

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ABSTRACT

Ethnopharmacological relevance: The rhizome of *Salvia miltiorrhiza* Bunge (SM, family Labiatae), which contains tanshinones as main constituents, has been used as a cardiovascular and anti-inflammatory agent in Chinese medicine.

Aim of the study: This study aimed to elucidate anti-allergic effects of the root of *Salvia miltiorrhiza* Bunge (SM, family Labiatae) and its main constituents, tanshinones, against passive cutaneous anaphylaxis (PCA) reaction.

Materials and methods: PCA reaction was induced by IgE–antigen complex (IAC) in ICR mice. Protein expression of IL-4 and TNF- α in rat basophilic leukemia (RBL)-2H3 cells was performed by enzyme-linked immunosorbent assay and NF- κ B and c-jun (AP-1) activation assayed by immunoblot.

Results: Tanshinones inhibited the PCA reaction and reduced IL-4 and TNF- α production in mice as well as in IAC-stimulated RBL-2H3 cells. Tanshinones also inhibited NF- κ B and AP-1 activation in RBL-2H3 cells stimulated with IAC. Among tested tanshinones, tanshinone I exhibited the most potent inhibition, followed by 15,16-dihydrotanshinone I, tanshinone IIA and cryptotanshinone.

Conclusions: SM and tanshinones may ameliorate the PCA reaction by inhibiting the allergic cytokines IL-4 and TNF- α via NF- κ B and AP-1 pathways.

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1. Introduction

Allergic diseases such as asthma, allergic rhinitis, atopic dermatitis and food allergies represent a rapidly increasing chronic health problem in most countries (Geha, 2003). Allergic reactions occur in response to normally harmless environmental substances known as allergens. However, in some people, severe allergies to environmental or dietary allergens may result in life-threatening anaphylactic reactions. Anaphylaxis may be based on IgE-mediated pharmacological processes in a variety of cell populations, such as mast cells and basophils (Stevens and Austen, 1989; Wuthrich, 1989). Degranulation of mast cells and basophils, with antigen-crosslinked IgE, releases histamine, as well as cytokines, especially tumor necrosis factor (TNF)- α and interleukin (IL)-4 (Bruhns et al., 2005; Zhao et al., 2005). These cytokines have a critical biological role in the allergic reaction. 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 inhibition of the action

of TNF- α (Nickoloff, 1991). IL-4 induces IgE production in B cells and is associated with anaphylaxis (Mitre and Nutman, 2006). The inhibition of the expression of these cytokines from mast cells and basophils has been therefore used as a good target for reducing allergic symptoms.

The rhizome of *Salvia miltiorrhiza* Bunge (SM, family Labiatae), which contains tanshinones as main constituents, has been used as a cardiovascular and anti-inflammatory agent in Chinese medicine (Yagi and Takeo, 2003; Jang et al., 2006; Fang et al., 2008). SM and its main constituents, tanshinones, exert their anti-allergic activities by inhibiting both Fc ϵ RI-mediated tyrosine phosphorylation of ERK and phospholipase C γ 2 in mast cells and mast cell degranulation (Ryu et al., 1999; Choi and Kim, 2004). SM attenuates asthma by inhibiting the expression of IL-13 and eotaxin in rats, showing inhibitory effects synergistic with dexamethasone (Li et al., 2006). These results suggest that tanshinones may attenuate immediate hypersensitivity. Nevertheless, the anti-anaphylactic and anti-pruritic effects of tanshinones have not been studied thoroughly. Neither have the anti-allergic effects of SM nor tanshinones been studied thoroughly.

As a part of our studies on anti-allergic constituents from natural medicines, we isolated the main constituents, tanshinone I, tanshinone IIA, 15,16-dihydrotanshinone and cryptotanshinone (Fig. 1), from SM methanol extract, which potently inhibited the passive

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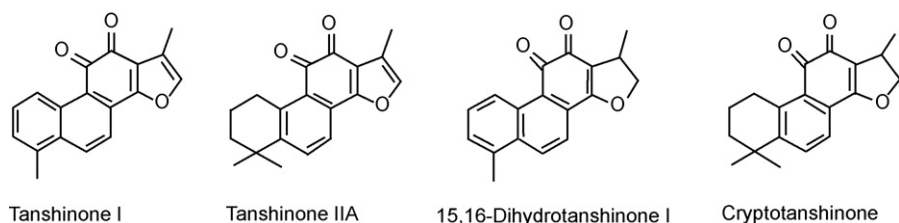


Fig. 1. Structure of tanshinone derivatives isolated from the roots of *Salvia miltiorrhiza*.

cutaneous anaphylaxis (PCA) reaction stimulated by IgE–antigen complex (IAC) in our preliminary experiment, and measured their inhibitory effects against PCA reaction in mice.

2. Materials and methods

2.1. Materials

Dulbecco's modified Eagles medium (DMEM), fetal bovine serum, dinitrophenol-human serum albumin (DNP-HSA), ovalbumin (OVA), and cremophor EL were purchased from Sigma Co. (St. Louis, MO, U.S.A.). Azelastine (purity, >98%) was from Enzo Life Sciences (Farmingdale, NY, U.S.A.). RNeasy® Antibodies for NF- κ B (p-p65 and p65), c-jun, p-c-jun, and β -actin were purchased from Cell Signaling Technology, Inc. (Danvers, MA, U.S.A.). ELISA kits for IL-4 and TNF- α were from Pierce Biotechnology (Rockford, IL, U.S.A.). The chemiluminescence detection kit was from Thermo Fisher Scientific Inc. (Rockford, IL, U.S.A.).

2.2. Isolation of main constituents, tanshinone derivatives from *Salvia miltiorrhiza*

The dried rhizome of *Salvia miltiorrhiza* (family Labiatae), which were purchased at Daegoo YangRyung Market, Taegoo, Korea (produced by China), were identified by one of the authors, K.H. Son. The voucher specimen (AU-200605) was deposited at the herbarium of Department of Food Science and Nutrition, Andong National University, Andong, Korea. The dried roots of SM (17.45 kg) were percolated with methanol three times and concentrated in vacuo (MeOH extract), and a residue (2.4 kg) was suspended in distilled water and partitioned successively with hexane, CH_2Cl_2 , EtOAc and butanol (BuOH), to give hexane (48.8 g), CH_2Cl_2 (27.9 g), EtOAc (212.2 g) and BuOH (149.1 g) soluble fractions, respectively. A portion of the hexane fraction and CH_2Cl_2 fraction (76.7 g) were chromatographed on silica gel (11.5 cm $\times$ 58 cm, 2.1 kg), using a graded series of n-hexane and CH_2Cl_2 (100:0, 95:5, 90:10, 85:15, 80:20, 70:30, 2.5 L for each gradient) as the elutant to yield eleven fractions (HC1–HC11) on their polarities. Fraction HC4 and HC5 were recrystallized with MeOH to give tanshinone IIA (0.9 g) and tanshinone I (1.2 g). Also fractions HC 8–10 (2 g) were rechromatographed on a silica gel column (3.8 cm $\times$ 62 cm, 300 g), eluted with hexane– CH_2Cl_2 (4:6–6:4, 1.5 L) to give six subfractions (HC8.1–HC8.6). HC8.3 and HC8.5 were recrystallized with MeOH enabled the isolation of pure cryptotanshinone (80 mg) and 15,16-dihydrotanshinone I (70 mg), respectively. The structure of tanshinone IIA, tanshinone I, cryptotanshinone, 15,16-dihydrotanshinone I were verified by comparison of the NMR data with those of the previously reported literatures (Kang et al., 1997; Ryu et al., 1997).

Tanshinone I. Brown needles (purity, >98%). $\text{C}_{18}\text{H}_{12}\text{O}_3$ (M.W. 276). mp 240–241 °C. IR ν_{max} cm^{-1} 3433–3257 (OH), 1671 (C=O). UV λ_{max} MeOH nm (log ϵ) 416 (3.82), 244 (4.71). EI-MS (m/z): 276 [M] $^+$.

Tanshinone IIA. Reddish orange needles (purity, >95%). $\text{C}_{19}\text{H}_{18}\text{O}_3$ (M.W. 294). mp 215–216 °C. IR ν_{max} cm^{-1} 3421–3257 (OH), 1671 (C=O), 1193 (C–O). UV λ_{max} MeOH nm (log ϵ) 457 (3.60), 352 (3.39), 268 (4.59), 222 (4.51). EI-MS (m/z): 194 [M] $^+$.

Cryptotanshinone. Orange needles (purity, >95%). $\text{C}_{19}\text{H}_{20}\text{O}_3$ (M.W. 296). mp: 191 °C. IR ν_{max} cm^{-1} 3431–3273 (OH), 1653 (C=O), 1624, 1558, 1507 (C=C), 1194 (C–O). UV λ_{max} MeOH nm (log ϵ) 445 (3.55), 356 (3.54), 262 (4.54), 217 (4.40). EI-MS (m/z): 296 [M] $^+$.

15,16-dihydrotanshinone I. Red needles (purity, >95%). $\text{C}_{18}\text{H}_{14}\text{O}_3$ (M.W. 278). mp 224–225 °C. IR ν_{max} cm^{-1} 3421–3256 (OH), 1684 (C=O), 1622, 1508 (C=C), 1192 (C–O). UV λ_{max} MeOH nm (log ϵ) 409 (3.72), 331 (3.61), 290 (4.31), 240 (4.50), 215 (4.42). EI-MS (m/z): 278 [M] $^+$.

2.3. Animals

The male ICR mice (5-week-old, 20–25 g) were supplied from Orient Experimental Animal Breeding Center (Seoul, Korea). All animals were housed in wire cages at 20–22 °C and $50 \pm 10\%$ humidity, fed standard laboratory chow (Orient Experimental Animal Breeding Center) and allowed water ad libitum. All experiments were performed in accordance with the NIH and Kyung Hee University guidelines for Laboratory Animal Care and Use and approved by the Committee for the Care and Use of Laboratory Animals in the College of Pharmacy, Kyung Hee University.

2.4. Assay of the PCA reaction

An IgE-dependent cutaneous reaction was measured according to the method of Choo et al. (2003). Male ICR mice were divided into groups of 6 mice [vehicle-treated (normal control), and IgE–antigen complex in the presence or absence of test agents (tanshinone I at doses of 10, 20 and 50 mg/kg; tanshinone IIA at doses of 20 mg and 50 mg/kg; 15,16-dihydrotanshinone at doses of 10, 20 and 50 mg/kg; or cryptotanshinone at doses of 20 and 50 mg/kg] and all groups were intradermally injected with 10 μg 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. Forty-eight hours later each mouse received an injection of 200 μL of 3% Evans blue in PBS, containing 200 μg of DNP-HSA, via the tail vein. The test agents were orally administered 1 h prior to the DNP-HSA injection. Thirty min after the DNP-HSA injection, the mice were sacrificed, their dorsal skins removed and the pigmented area measured. After extraction with 1 mL 1.0 M KOH and 4 mL of a mixture of acetone and 0.2 M phosphoric acid (13:5), the amount of dye was determined colorimetrically at 620 nm.

2.5. Enzyme-linked immunosorbent assay (ELISA) and immunoblot

Prior to the enzyme-linked immunoassay (ELISA) for IL-4 and TNF- α in IgE-injected mouse dorsal skin, Evans blue dye was not added to the PCA reaction assay, and IgE-injected dorsal skin was removed and homogenized. The supernatant was transferred into

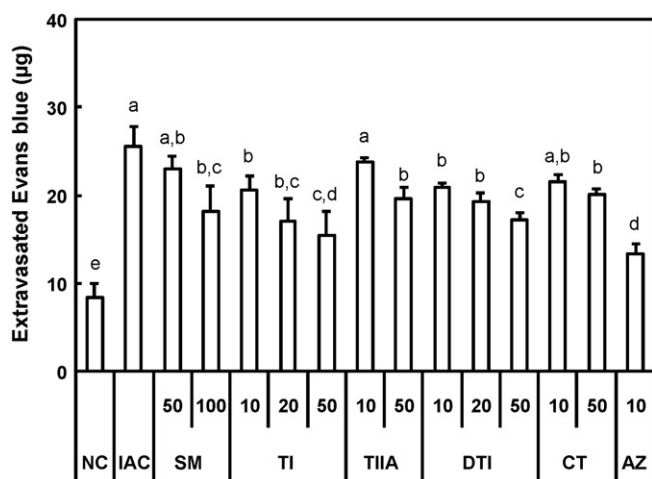


Fig. 2. Effect of *Salvia miltiorrhiza* (SM) and its constituents, tanshinones, on the passive cutaneous anaphylaxis (PCA) reaction induced by IgE–antigen complex in ICR mice. The amounts of extravasated Evan blue from the dorsal skin (1 cm × 1 cm) of IgE–antigen complex-treated (IAC) and vehicle-treated normal (NC) groups were 25 ± 4 and 8 ± 3 µg, respectively. Each test agents (IAC, vehicle alone; SM, 50 mg/kg (50) and 100 mg/kg (100) of SM extract; TI, 10 mg/kg (10), 20 mg/kg (20) and 50 mg/kg (50) tanshinone I; TIIA, 10 and 50 mg/kg tanshinone IIA; DTI, 10, 20 and 50 mg/kg 15,16-dihydrotanshinone I; CT, 10 and 50 mg/kg cryptotanshinone; AZ, 10 mg/kg azelastine) in 5% cremophor or vehicle alone were orally administered to mice 1 h before IAC treatment. Inhibition values indicate the mean $\pm$ S.D. ($n = 6$). a,b,c,d,e Those with the same letter are not different at $P < 0.05$.

96-well (ELISA) plates, and IL-4 and TNF- α concentrations were determined using commercial ELISA kits.

The enzyme-linked immunoassays for IL-4 and TNF- α in RBL-2H3 cells were performed by the method of Choo et al. (2003). Briefly, the previously cultured RBL-2H3 cells (5×10^5 cells) were treated with 0.5 µg/mL of mouse monoclonal IgE for sensitization of cells. The cells (1.8 mL) were exposed to 0.2 mL of test agents for 1 h (for immunoblot) or 4 h (for ELISA), followed by the treatment with 0.2 mL of DNP-HSA (1 µg/mL) for 40 min at 37 °C. The supernatant (50 µL) was transferred into 96-well (ELISA) plates and then IL-4 and TNF- α concentrations were determined using commercial ELISA Kits. The immunoblot analysis for NF- κ B [phospho-p65 (p-p65) and p65], c-jun, p-c-jun and β -actin was performed according to the method of Lee et al. (2008). Briefly, the protein fractions were subjected to electrophoresis on 10% sodium dodecyl sulfate-polyacrylamide gel and then transferred to a nitrocellulose membrane. NF- κ B (p-p5 and p65), phospho-c-jun (p-c-jun), and c-jun were assayed using their corresponding antibodies. Immunodetection was carried out using an enhanced chemiluminescence detection kit. Their intensities were quantified by scanning densitometry.

The cytotoxicity of tanshinones against RBL-2H3 cells was assayed by SRB method (Gu and DeAngelis, 2005).

2.6. Statistical analysis

All the data were expressed as the mean $\pm$ standard deviation, and statistical significance was analyzed by one-way ANOVA followed by Student–Newman–Keuls test.

3. Results

As a part of our studies on anti-allergic constituents from natural medicines, we isolated the main constituents from SM methanol extract and measured their inhibitory effect against PCA reaction in mice (Fig. 2). Tanshinones potently inhibited the IAC-stimulated PCA reaction. Tanshinone I at a dose of 50 mg/kg showed the most

potent inhibition (59%), followed by 15,16-dihydrotanshinone I (49%), tanshinone IIA (35%) and cryptotanshinone (32%). These tanshinones also inhibited IL-4 and TNF- α expression, although the effect of 15,16-dihydrotanshinone I could not be measured due to its shortage (Fig. 3). Among these tanshinones, tanshinone I inhibited the expression most potently, followed by tanshinone IIA and cryptotanshinone. Tanshinone I (50 mg/kg) inhibited IL-4 and TNF- α expression by 89% and 71%, respectively.

When their inhibitory effects against IL-4 and TNF- α in IAC-stimulated rat basophilic leukemia (RBL)-2H3 cells were investigated using an ELISA (Fig. 4), tanshinone I and 15,16-dihydrotanshinone I potently inhibited IL-4 expression, followed by and tanshinone IIA. Tanshinone I and 15,16-dihydrotanshinone I (50 µM) inhibited IL-4 by 65% and 63% and TNF- α expression by 42% and 41%, respectively. These tanshinones also inhibited the activation of transcription factor NF- κ B and c-jun in IAC-stimulated RBL-2H3 cells. Among tested tanshinones, tanshinone I and 15,16-dihydrotanshinone I potently inhibited the activation of transcription factors NF- κ B and c-jun. However, at 50 µM, these tanshinones did not show cytotoxicity against RBL-2H3 cells.

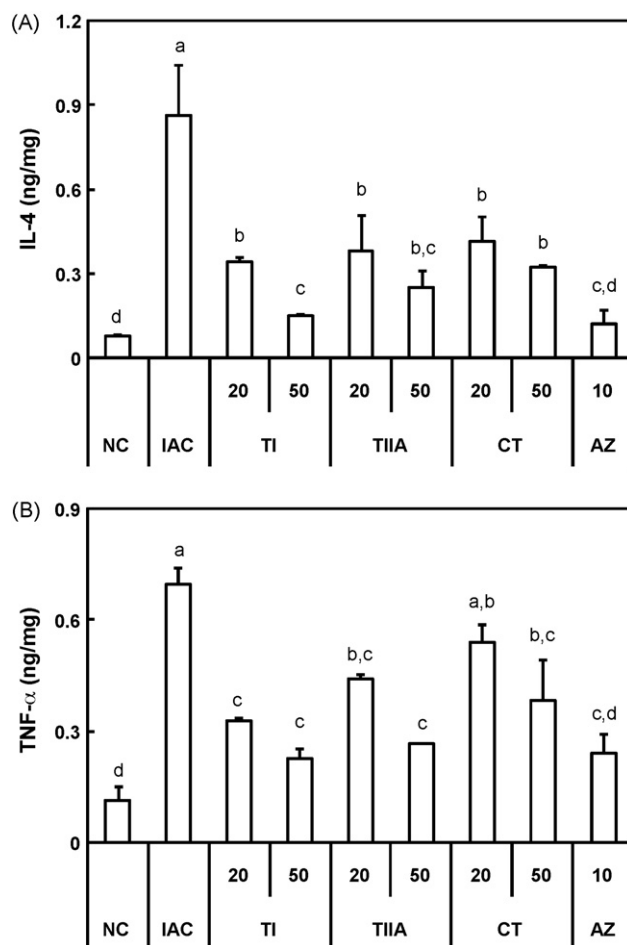


Fig. 3. Effect of tanshinones on IL-4 (A) and TNF- α expression (B) in IgE–antigen complex-treated mice. The amounts of IL-4 and TNF- α in the dorsal skin (1 cm × 1 cm) of the control group stimulated with IgE–antigen complex (IAC) in the presence or absence of test agents and vehicle-treated normal (NC) groups were determined by ELISA. Each test agent (IAC, vehicle alone; TI, 20 mg/kg (20) and 50 mg/kg (50) tanshinone I; TIIA, 20 and 50 mg/kg tanshinone IIA; CT, 20 and 50 mg/kg cryptotanshinone; AZ, 10 mg/kg (10) azelastine) in 5% cremophor or vehicle was orally administered to mice 1 h before IAC treatment. Inhibition values indicate the mean $\pm$ S.D. ($n = 6$). a,b,c,d Those with the same letter are not different at $P < 0.05$.

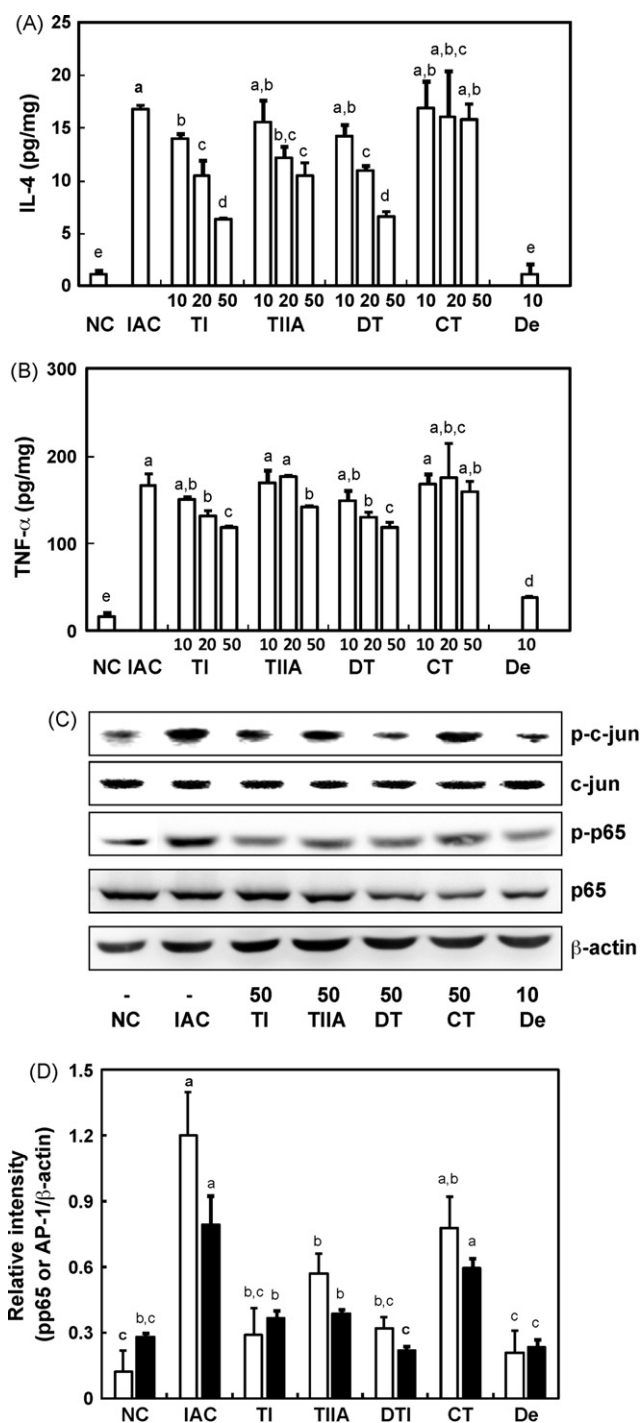


Fig. 4. Effect of tanshinones on the protein expression of IL-4 and TNF- α and activation of NF- κ B AP-1 in RBL-2H3 cells induced by IgE-antigen complex. RBL-2H3 cells (5×10^5 cells) were treated with 0.5 μ g/mL of mouse monoclonal IgE, and exposed to 0.2 mL of each test agent (IAC, vehicle alone; TI, 10 μ M (10), 20 μ M (20) and 50 μ M (50) tanshinone I; TIIA, 10, 20 and 50 μ M tanshinone IIA; DT, 10, 20 and 50 μ M 15,16-dihydrotanshinone I; CT, 10, 20 and 50 μ M cryptotanshinone; De, 10 μ M dexamethasone) in 0.5% DMSO or vehicle alone for 1 h (for immunoblot) or 4 h [for enzyme-linked immunoassay (ELISA)], followed by the treatment with 0.2 mL of dinitrophenol-human serum albumin (1 μ g/mL) for 4 h (protein expression) at 37 $^{\circ}$ C. Normal group (NC) was treated with vehicle alone instead of agent and IgE-antigen complex. (A) Effect in IL-4 expression. (B) Effect in TNF- α expression. These cytokines were determined by ELISA. (C) Effect in NF- κ B and c-jun (AP-1) activation. These transcription factors, NF- κ B (p-p65 and p65), p-c-jun and c-jun, were assayed by immunoblot analysis. (D) Relative intensities of activated NF- κ B (open column) and AP-1 (closed column) for β -actin. These intensities were quantified by scanning densitometry. Values represent the mean $\pm$ S.D. for triplicate experiments. a,b,c,d,e Those with the same letter are not different at $P < 0.05$.

4. Discussion

Mast cells and basophils are critical participants in allergic diseases (Stevens and Austen, 1989). These cells express surface membrane receptors with high affinity and specificity for IgE, which is induced by IL-4 (Mitre and Nutman, 2006). The interaction of antigen-bound IgE with surface membrane receptors causes the release of histamine, prostaglandins, leukotrienes, and cytokines. These cytokine-induced reactions then cause tissue inflammation, anaphylaxis, and scratching behavior. TNF- α , which is released from mast cells, is an important cytokine involved in systemic inflammation, and dysregulation of TNF- α production has been implicated in a variety of human diseases. The biosynthesis of these cytokines is regulated by the transcription factor NF- κ B (Nickoloff, 1991; Zhao et al., 2005). Anti-allergic agents, such as anti-histamines, steroids and immunosuppressants, have been used to treat allergic diseases, including atopic dermatitis, asthma, itching and food allergies (Simons, 1992; Schafer-Korting et al., 1996; Sakuma et al., 2001), but improving these diseases is very difficult. And these drugs have side effects, such as osteoporosis and kidney dysfunction. Therefore, herbal medicines have been advanced for allergic diseases, and their effectiveness has received increasing attention (Yang et al., 2001). In the present study, SM methanol extract and its main constituents, tanshinones, inhibited the PCA reaction as well as IL-4 and TNF- α expression in IAC-treated mice. These tanshinones also inhibited the protein expression of the proinflammatory cytokine TNF- α and IgE-switching cytokine IL-4, as well as NF- κ B and c-jun (AP-1) activation, in IAC-stimulated RBL-2H3 cells. These transcription factors NF- κ B and AP-1 regulate TNF- α and IL-4 expression, respectively (Zhao et al., 2005; Hirano et al., 2006). These results were supported by the previous report that SM exhibits anti-inflammatory effects by attenuating cyclooxygenase-2 via the inhibition of NF- κ B activation in intestinal epithelial cells as well as cyclooxygenases in bone marrow-derived mast cells (Kim et al., 2002, 2005). Its main constituent tanshinone IIA also exhibit anti-inflammatory effect by inhibiting NF- κ B activation (Jang et al., 2006). Among tested tanshinones, tanshinone I and 15,16-dihydrotanshinone I showed the potent inhibition against PCA reaction. Tanshinone IIA, which is 4-methyl-1,2,3,4-tetrahydro-tanshinone I, weakly inhibited PCA reaction and allergic cytokines, IL-4 and TNF- α , expression. However, cryptotanshinone, which is 4-methyl-1,2,3,4,15,16-hexahydro-tanshinone I, did not inhibit PCA reaction and showed the weak inhibition in allergic cytokines, IL-4 and TNF- α , expression. Thus, the hydrogenation at 1, 2, 3, 4, 15 and 16 positions and methylation at 4 position in tanshinone I attenuated the anti-PCA reaction effect. The hydrogenation at 1, 2, 3 and 4 positions and methylation at 4 position in tanshinone I significantly attenuated the anti-allergic effects rather than the hydrogenation at 15 and 16 positions. These results suggest that the 1, 2, 3 and 4 positions of tanshinone I may be the active site for the PCA reaction-inhibitory effect.

Based on these findings, SM, particularly tanshinone I, may improve allergic reactions such as anaphylaxis by inhibiting the expression of the IgE-switching cytokine IL-4 and the proinflammatory cytokine TNF- α via the NF- κ B and AP-1 pathways.

Acknowledgements

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