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Oriental Pharmacy and Experimental Medicine 2004 **4(3)**, 125-136

Review

Oriental medicines with anti-anaphylactic effect

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SUMMARY

The pharmacological mechanisms of most Oriental medicines have not been clearly defined in spite of their effective use in treating many diseases throughout the world. Many Oriental medicines have been used against various allergic diseases for generations, and still occupy an important place in traditional medicine in far eastern countries including Korea. It is also still unclear how Oriental drugs prevent allergic disease in vivo or in vitro models.

Some Korean folk medicine inhibited the mast cell-mediated allergic reaction. This review summarizes the effective folk medicine in experimental effect on systemic or local anaphylaxis reaction. Potential anti-anaphylactic folk medicines include: *Poncirus trifoliata; Siegesbeckia glabrescence; Solanum lyratum; Aquilaria agallocha; Ulmi radicis; Polygonum tinctorium;* Hwanglyun-Haedok-Tang; *Rehmannia glutinosa;* Kum-Hwag-San; *Syzygium aromaticm; Spirulina platensis;* Sosiho-Tang; *Sinomenium acutum; Schizonepta tenuifolia;* Shini-San; *Magnoliae flos;* Sochungryong-Tang; *Oryza sativa; Cryptotympana atrata; Salviae radix; Rosa davurica; Asiasari radix;* Chung- Dae-San; *Cichorium intybus; Perilla frutescens; Vitex rotundifolia; Terminalia chebula;* Siberian Ginseng; *Solanum melongena;* Gahmi-Shini-San; *Alpinia oxyphylla; Acanthopanax senticosus* root; *Prunella vulgaris;* Allergina; *Ixeris dentate; Acanthopanax senticosus* stem; Tongkyutang; *Salvia plebeia; Rubus coreanus;* Sinpo-Tang; Dodutang; *Forsythia fructus; Xanthii fructus;* and Purple bamboo slat.

Ensuring the effects and understanding the mechanisms of action for these Oriental medicines can permit drug development and laying of the ground-work for evaluating potential synergistic effects by addition and subtraction of prescriptions.

Key words: Oriental medicine; Anti-anaphylactic; Mechanism

The mast cell is one of the major effector cells in allergic and inflammatory reactions and can be found in most tissues throughout the body (Nillson *et al.*, 1994). 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, IL-1, IL-4, IL-6, IL-8, IL-13 and TGF-1 (Plaut *et al.*, 1989; Wodnar-Filipowicz *et al.*, 1989; Bradding *et al.*, 1993). Histamine plays an important role in a wide variety of reactions, such as allergic reaction, inflammation, gastric acid secretion, neurotransmission in the central nervous system, and cell growth (Yatsunami *et al.*, 1994). Mast cell activation induces many of the acute changes observed in allergic disorders, including anaphylaxis, allergic asthma, rhinitis, and atopic dermatitis (Metcalf *et al.*, 1992; Galli, 1993).

Degranulation of mast cells can be triggered by various stimulators and at least three types of receptors: (1) Mast cell degranulation can be elicited by a number of positively charged

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substances, collectively known as the basic secretagogues of mast cells (Lagunoff *et al.*, 1983). Compared with the natural process, a high concentration of synthetic 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 allergic reaction (Allansmith *et al.*, 1989). (2) High affinity IgE receptor, FcεRI is found on the plasma membrane of mast cells and basophils (Steiner *et al.*, 2003). IgE stimulation on mast cells and basophils induces synthesis and secretion of cytokines including TNF-α, IL-6, granulocyte-macrophage-CSF, IL-8, IL-13 and leukemia-inhibitory factor with proinflammatory and immune regulatory properties via NF-κB activation (Bet *et al.*, 1993). (3) High affinity binding of SCF homodimer to the c-Kit receptor rapidly induces the mast cell degranulation and migration (Blueme-Jensen *et al.*, 1991). Stem cell factor (SCF) is a crucial growth factor in mast cell biology. It regulates such diverse cellular functions as proliferation, differentiation, survival, adhesion, and release of inflammatory mediators (Irani *et al.*, 1992). SCF acts as a mast cell chemotaxin (Nillson *et al.*, 1994). Furthermore, injection of SCF into the skin causes mast cell hyperplasia (Costar *et al.*, 1996), indicating the importance of SCF for the recruitment of mast cell *in vivo*. An accumulation of mast cells has been also described in several inflammatory conditions, e.g., allergic rhinitis (Enerback *et al.*, 1996), asthma (Laitinen *et al.*, 1993), and rheumatoid arthritis (Wasserman, 1984). SCF also induces the pro-inflammatory cytokines including TNF-α, IL-1, IL-6, IL-8, IL-16, and IL-18 from mast cells (12). Finally, (4) the G protein-coupled receptors (GPCRs) found predominantly on mast cells, basophils, neutrophils and macrophages (Steiner *et al.*, 2003).

Ca^{2+} acts as a second messenger during cell activation (Rasmman and Goodman, 1977). An increase in the intracellular Ca^{2+} has been proposed as an essential trigger for mast cell activation (White *et al.*, 1985). Stimulation of mast cells with compound 48/80 initiates the activation of a signal transduction pathway. The action of compound 48/80 on isolated rat mast cells has been shown to be non-lytic. Compound 48/80 also increases the calcium levels in ear swelling response. Calcium increase may be an essential trigger for the release of the mediator by compound 48/80 from the mast cells in ear swelling reaction (Pearce *et al.*, 1989). The immunological stimulation of mast cells leading to their secretory response is initiated by clustering of IgE receptor. This system is widely employed as a paradigm for the cascades which couple immunological cell stimulation to their respective affected functions (Ishizaka *et al.*, 1984; Gericke *et al.*, 1995). One process that was found to be common to most coupling cascades is a rise in the concentration of free cytosolic Ca^{2+} ions, Ca^{2+}_i (Mohr and Fewtrell, 1987a; Mohr and Fewtrell, 1987b; Mohr and Fewtrell, 1987c; Dar and Pecht, 1992). This Ca^{2+}_i response is biphasic, composed of an initial spike due to Ca^{2+}-release by inositol-1, 4, 5-triphosphate from intracellular stores followed by a sustained Ca^{2+}_i elevation assigned to the opening of a Ca^{2+}-influx pathway via the plasma membrane (Neher, 1991; Berridge, 1993). An increase in the intracellular Ca^{2+} level results in degranulation of mast cells. It has been reported that release of intracellular Ca^{2+} from internal stores is required for phospholipase D (PLD) and IB kinase (IKK) activation (Nakamura *et al.*, 1996; Todisco *et al.*, 1999). Especially, IKK is a recently discovered kinase complex composed of the kinase IKK and IKK. Phophorylation of IB by the IKK complex is a critical step leading to IB degradation and activation of transcription factor NF-κB (Tojima *etal.*, 2000). Recent studies have indicated that

IKK is essential for the activation of NF-κB in re- sponse to proinflammatory stimuli (Delhase *et al.*, 1999; Hu *et al.*, 1999; Li *et al.*, 1999; Takeda *et al.*, 1999). Transcription factor NF-κB is a candidate for regulation of TNF-α and IL-6 gene because consensus-binding sites for the transcription factor are present in the TNF-α and IL-6 gene (Collart *et al.*, 1990; Scherer *et al.*, 1995). TNF-α has been suggested to induce neuronal damage following tissue damage and it is also considered a major initiator of inflammation (Kim *et al.*, 1999). IL-6 plays an important role in the growth of myeloma cells and plasmacyomagenesis. These two cytokines can be generated in the mast cell and potentiate inflammatory immune responses through the subsequent induction of other inflammatory mediators. Therefore, modulation of signal transduction pathways on inflammatory cytokines production by mast cells should provide us with a useful therapeutic strategy for allergic and inflammatory diseases.

For treatment of various diseases with herbal medicine, knowledge of the condition of "Yin-Yang" excess-deficiency, and "cold-hot" is considered important. The "excess-deficiency" condition is a physically and psychologically strong or weak condition. The "cold-hot" condition is exacerbation of various clinical signs by exposure to cold or hot temperatures (Shin, 1994). We have tried to select prescriptions that have been known to be effective based on this classical theory of Oriental medicine as an object of our studies.

After the ip injection of compound 48/80, the animals were monitored for 1 h, after which the mortality rate was determined. Injection of compound 48/80 plus saline as a control induced fatal shock in 100% of each group. When the Oriental medicines were pretreated for 1 h, the mortality with compound 48/80 was reduced respectively (Table 1).

A way to test local allergic reaction is to induce passive cutaneous anaphylaxis (PCA) reaction. As described in the previous experimental procedures, local extravasation is induced by a local injection of anti-DNP IgE followed by an intravenous antigenic challenge (Kim *et al.*, 1998 c). Administration of Oriental medicines showed a marked inhibition rate in PCA reaction (Table 2).

While plasma levels of histamine were markedly elevated after the compound 48/80 injection in all groups of mice, the mice injected with the indicated Oriental medicines showed a reduction.

Anti-DNP IgE stimulation of mast cells resulted in *de novo* synthesis of TNF-α that was detectable in the medium by 1 h. TNF-α continued to accumulate in the medium to reach maximal levels by 6 h but the levels of TNF-α declined after that. Oriental medicines (*Ulmi radicis*; Hwanglyun-Haedok-Tang; *Rehmannia glutinosa*; *Spirulina platensis*; *Sinomenium acutum*; *Rosa davurica*, *Xanthii fructus*, *Salvia plebeia*, *Acanthopanax senticosus* stem, *Solanum melongena*, Siberian Ginseng) inhibited IgE-mediated TNF-α production from mast cells. No significant cytotoxicity of Oriental medicines was observed in the concentration used in the experiments as assessed by trypan blue uptake.

Some Oriental medicines pretreatment profoundly affected compound 48/80-induced systemic allergic reaction and anti-DNP IgE-induced local allergic reaction. These results indicate that mast cell-mediated immediate-type allergic reactions are inhibited by the Oriental medicines. Some recent studies have shown that compound 48/80 and other polybasic compounds are able, apparently direct, to activate G-proteins (Mousli *et al.*, 1990 a; Mousli *et al.*, 1990 b). 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 membrane permeability increase may be an essential trigger for the

Table 1. Effect of some Oriental medicine on compound 48/80-induced systemic anaphylactic reaction

Treatment	Dose (g/kg)	Compound 48/80	Mortality (%)	Reference
None		+	100	
Poncirus trifoliata	0.4-0.6 (ip)	+	0	Lee et al., 1996
Siegesbeckia glabrescence	1, 10 (ip)	+	0	Kang et al., 1997 b
Solanum lyratum	1 (ip)	+	0	Kang et al., 1997 a
Aquilaria agallocha	0.5 (ip)	+	0	Kim et al., 1997
Ulmi radicis	1 (ip)	+	0	Kim et al., 1998h
Polygonum tinctorium	0.1-1 (ip)	+	0	Kim et al., 1998a
Rehmannia glutinosa	0.01 (ip)	+	53	Kim et al., 1998e
Syzygium aromaticm	0.03 (ip)	+	50	Kim et al., 1997a
Spirulina platensis	0.5-1 (ip)	+	0	Yang et al., 1997
Sosiho-Tang	1 (po)	+	0	Kim et al., 1998b
Sinomenium acutum	1 (ip)	+	50	Kim et al., 1999f
Schizonepta tenuifolia	0.5, 1 (ip)	+	0	Shin et al., 1999a
Shini-San	1 (po)	+	60	Kim et al., 1999a
Magnoliae flos	1 (ip)	+	0	Kim et al., 1999h
Sochungryoung-Tang	0.1 (po)	+	0	Kim et al., 2000a
Oryza sativa	1 (ip)	+	40	Kim et al., 1999g
Cryptotympana atrata	0.5, 1 (ip)	+	0	Shin et al., 1999b
Salviae radix	1 (po)	+	90	Kim et al., 1999c
Rosa davurica	1 (po)	+	0	Kim et al., 1999d
Chung-Dae-San	1 (ip)	+	0	Kim et al., 1999b
Cichorium intybus	1 (ip)	+	0	Kim et al., 1999a
Perilla frutescens	1 (ip)	+	0	Shin et al., 2000a
Vitex rotundifolia	1 (po)	+	0	Shin et al., 2000b
Terminalia chebula	1 (po)	+	0	Shin et al., 2001a
Siberian Ginseng	1 (po)	+	0	Jeong et al., 2001a
Solanum melongena	0.1 (po)	+	0	Lee et al., 2001
Alpinia oxyphylla	1 (ip)	+	0	Shin et al., 2001b
Acantohpanax senticosus root	1 (po)	+	50	Yi et al., 2001
Prunella vulgaris	1 (ip)	+	0	Shin et al., 2001c
Allergina	5 (ip)	+	0	Jeong et al., 2001b
Ixeris dentate	0.1 (po)	+	25	Yi et al., 2002a
Acantohpanax senticosus stem	1 (po)	+	50	Yi et al., 2002b
Salvia plebeia	1 (ip)	+	0	Shin et al., 2002a
Rubus coreanus	1 (ip)	+	0	Shin et al., 2002b
Xanthii fructus	1 (po)	+	0	Hong et al., 2003
Yunbutang	1 (po)	+	33.3	Na et al., 2004
Isodon japonicus	1 (ip)	+	0	Shin et al., 2004 b
Rubus croceacanthus	1 (po)	+	0	Moon et al., 2004

Table 2. Effect of some Oriental medicines on anti-IgE-induced PCA reaction

Treatment	Dose (g/kg)	Inhibition (%)	Reference
Poncirus trifoliata	200 (po)	72.2	Lee et al., 1996
Siegesbeckia glabrescence	0.1 (po)	58.6	Kang et al., 1997b
Solanum lyratum	0.05 (po)	69.3	Kang et al., 1997a
Aquilaria agallocha	0.5 (po)	96.6	Kim et al., 1997
Ulmi radicis	1 (po)	68.4	Kim et al., 1998h
	1 (io)	79.1	
Polygonum tinctorium	1 (po)	92.5	Kim et al., 1998a
	1 (ip)	91	
	1 (id)	90.2	
	1 (iv)	8.6	
Hwanglyun-Haedok-Tang	1 (po)	78.5	Kim et al., 1998f
	1 (ip)	69.1	
	1 (id)	61.3	
	1 (iv)	39.8	
Rehmannia glutinosa	1(po)	78.5	Kim et al., 1998e
Kum-Hwag-San	0.19 g/skin(id)	56.8	Kim et al., 1998g
Syzygium aromaticm	0.02 (po)	50	Kim et al., 1997a
	0.02 (iv)	50	
Spirulina platensis	0.5 (po)	68.7	Yang et al., 1997
Sosiho-Tang	0.1 (po)	48.6	Kim et al., 1998b
Sinomenium acutum	1 (ip)	45	Kim et al., 1999f
Magnoliae flos	1 (id)	77.6	Kim et al., 1999h
Oryza sativa	1 (po)	45.8	Kim et al., 1999g
Salviae radix	1 (po)	63.9	Kim et al., 1999c
Rosa davurica	1 (po)	61	Kim et al., 1999d
Chung-Dae-San	1 (po)	88	Kim et al., 1999b
	1 (ip)	73.5	
	1 (id)	82	
	1 (iv)	7.9	
	1 (tp)	62	
Cichorium intybus	1 (ip)	60	Kim et al., 1999a
Vitex rotundifolia	1 (po)	55.9	Kim et al., 2000c
Terminalia chebula	1 (po)	63.5	Shin et al., 2001a
Siberian Ginseng	1 (po)	51	Jeong et al., 2001a
Solanum melongena	1 (po)	83.1	Kim et al., 2001a
Gahmi-Shini-San	1 (po)	37	Hong et al., 2001
Acantohpanax senticosus root	2 (po)	53.2	Yi et al., 2001
Prunella vulgaris	1 (ip)	about 70	Shin et al., 2001c
Allergina	1 (ip)	84	Jeong et al., 2001b
Ixeris dentata	0.1 (po)	81.4	Yi et al., 2002a
Acantohpanax senticosus stem	1 (po)	36.7	Yi et al., 2002b
Tongkyungtang	1 (po)	49.5	Na et al., 2002

Table 2. Continued

Treatment	Dose (g/kg)	Inhibition (%)	Reference
Salvia plebeia	1 (ip)	about 50	Shin et al., 2002a
	1 (iv)	about 75	
	1 (po)	about 79	
Rubus coreanus	1 (ip)	about 58	Shin et al., 2002b
Sinpo-tang	0.1 (rectal)	68	Jeong et al., 2002
Dodutang	5 (po)	78.9	Shin et al., 2002c
Xanthii fructus	1 (po)	53.7	Hong et al., 2003
Purple bamboo salt	1 (po)	51.9	Shin et al., 2004 a
Isodon japonicus	1 (ip)	72.2	Shin et al., 2004 b
Rubus croceacanthus	1 (po)	about 45	Moon et al., 2004

release of the mediator from mast cells. The Oriental medicines might act on the lipid bilayer membrane preventing the perturbation induced by compound 48/80. This is supported by a previous report that benzalkonium chloride and another selective antagonists inhibit the histamine release induced by compound 48/80 (Piotrowski *et al.*, 1984).

The Oriental medicines-administered rats were protected from PCA reaction. The results obtained proved that they inhibited the IgE-mediated allergic reaction *in vivo* in a murine model. It is believed that cytokines, including TNF-α, play a major role in triggering and sustaining the allergic inflammatory response. The Oriental medicines were a potent inhibitor of TNF-α production by mast cells. Moreover, the Oriental medicines inhibited TNF-α production at lower concentrations than needed for the inhibition of allergic reaction, suggesting the differential regulation of the allergic reaction process and TNF-α production in mast cells. Many signals for allergic reaction, including protein kinase C and Ca^{2+}, are also involved in production of TNF-α (Hide and Beaven, 1991; Ozawa *et al.*, 1993) but there may be an intrinsic regulatory mechanism for cytokine production in mast cells distinct from that for degranulation. Some Oriental medicines were revealed to have inhibitory effect against TNF-α secretion in HMC -1, a human mast cell line (*Isodon japonicus*; Madimadi; *Forsythia fructus*; Daeganghwal-tang; Cool-Cool).

Further work should address the possibility that Oriental medicines may also be active in the treatment of human allergic disorders. In addition, it is interesting that Oriental medicines exerts its inhibitory actions on TNF-α production in concentrations close to clinical doses, and this effect may explain additional mechanisms for the therapeutic action of Oriental medicines, particularly in chronic inflammation, in which mast cell-derived TNF-α has been implicated.

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