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Antiallergy drugs from Oriental medicines

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SUMMARY

Although Oriental medicines have long been used effectively in treating many diseases throughout the world, the pharmacological mechanisms of most Oriental medicines used have not been defined. As part of our continuing search for biologically active antiallergic drugs from natural sources, Oriental medicines were analyzed. Some Oriental medicines have been used against various allergic diseases for generations, and still occupies an important place in traditional medicine in Korea. It is also still unclear how Oriental medicine prevents allergic disease in experimental animal models. Some Korean folk medicines inhibited the mast cell-mediated allergic reaction. This review summarizes the effective folk medicine in experimental effect of allergic reaction. Potential antiallergic 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*; Sochungryoung-Tang; *Oryza sativa*; *Cryptotympana atrata*; *Salviae radix*; *Rosa davurica*; *Asiasari radix*; Chung-Dae-San; and *Cichorium intybus*. 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 medicines; Antiallergic drugs; Mast cell mediated allergic reaction; Drug development

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Mast cells are widely distributed throughout vascularized tissues and certain epithelia. Mast cells were traditionally thought to be associated with allergic reactions resulting from release of chemical mediators such as histamine from secretory granules. 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). 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). The multivalent binding of antigen to receptor bound IgE and the subsequent aggregation of the high-affinity FcεRI provide the trigger for activation of mast cells. Mast cell activation induces many of the acute changes observed in IgE-dependent allergic disorders, including anaphylaxis, allergic asthma, rhinitis, and atopic dermatitis (Galli, 1993; Metcalf *et al.*, 1992). Given the recent evidence that upon antigen stimulation mast cells are also a potential source of various cytokines, including tumor necrosis factor-α (TNF-α, Gordon and Galli, 1990), it is likely that they play a crucial role in initiating allergic inflammation. Therefore, modulation of TNF-α production by mast cells should provide us with a useful therapeutic strategy for allergic 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). The author has tried to select prescriptions which 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 which 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*) 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 IgEinduced 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 directly, 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 release of the mediator from mast cells.

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

Treatment	Dose (g/kg)	Compound 48/80	Mortality (%)	References
None		+	100	
Poncirus trifoliata	0.4-1.6 (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.*, 1998 h
Polygonum tinctorium	0.1-1 (ip)	+	0	Kim *et al.*, 1998 a
Rehmannia glutinosa	0.01 (ip)	+	53	Kim *et al.*, 1998 e
Syzygium aromaticm	0.03 (ip)	+	50	Kim *et al.*, 1997 a
Spirulina platensis	0.5, 1 (ip)	+	0	Yang *et al.*, 1997
Sosiho-Tang	1 (po)	+	0	Kim *et al.*, 1998 b
Sinomenium acutum	1 (ip)	+	50	Kim *et al.*, 1999 f
Schizonepta tenuifolia	0.5, 1 (ip)	+	0	Shin *et al.*, 1999 a
Shini-San	1 (po)	+	60	Kim *et al.*, 1999 a
Magnoliae flos	1 (ip)	+	0	Kim *et al.*, 1999 h
Sochungryoung-Tang	0.1 (po)	+	0	Kim *et al.*, in press
Oryza sativa	1 (ip)	+	40	Kim *et al.*, 1999 g
Cryptotympana atrata	0.5,1 (ip)	+	0	Shin *et al.*, 1999 b
Salviae radix	1 (po)	+	90	Kim *et al.*, 1999 c
Rosa davurica	1 (po)	+	0	Kim *et al.*, 1999 d
Chung-Dae-San	1 (ip)	+	0	Kim *et al.*, 1999 b
Cichorium intybus	1 (ip)	+	0	Kim *et al.*, 1999 a

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

Treatment	Dose (g/kg)	Inhibition (%)	References
Poncirus trifoliata	200 (po)	72.2	Lee *et al.*, 1997
Siegesbeckia glabrescence	0.1 (po)	58.6	Kang *et al.*, 1997 b
Solanum lyratum	0.05 (po)	69.3	Kang *et al.*, 1997 a
Aquilaria agallocha	0.5 (po)	96.6	Kim *et al.*, 1997
Ulmi radicis	1 (po)	68.4	Kim *et al.*, 1998 h
	1 (io)	79.1	
Polygonum tinctorium	1 (po)	92.5	Kim *et al.*, 1998 a
	1 (ip)	91	
	1 (id)	90.2	
	1 (iv)	8.6	
Hwanglyun-Haedok-Tang	1 (po)	78.5	Kim *et al.*, 1998 f
	1 (ip)	69.1	
	1 (id)	61.3	
	1 (iv)	39.8	
Rehmannia glutinosa	1 (po)	78.5	Kim *et al.*, 1998 e
Kum-Hwang-San	0.19 g/skin (id)	56.8	Kim *et al.*, 1998 g
Syzygium aromaticm	0.02 (po)	50	Kim *et al.*, 1997 a
	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.*, 1998 b
Sinomenium acutum	1 (ip)	45	Kim *et al.*, 1999 f
Magnoliae flos	1 (id)	77.6	Kim *et al.*, 1999 h
Oryza sativa	1 (po)	45.8	Kim *et al.*, 1999 g
Salviae radix	1 (po)	63.9	Kim *et al.*, 1999 c
Rosa davurica	1 (po)	61	Kim *et al.*, 1999 d
Chung-Dae-San	1 (po)	88	Kim *et al.*, 1999 b
	1 (ip)	73.5	
	1 (id)	82	
	1 (iv)	7.9	
	1 (tp)	62	
Cichorium intybus	1 (ip)	60	Kim *et al.*, 1999 a

The Oriental medicines might act on the lipid bilayer membrane and prevent 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 of TNF-α production in mast cells. Many signals for allergic reaction, including protein kinase C and Ca^{2+}, are also involved in production of TNFα (Ozawa *et al.*, 1993; Hide and Beaven, 1991) but there may be an intrinsic regulatory mechanism for cytokine production in mast cells distinct from that for degranulation. Further work should address the possibility that Oriental medicines may also be active in the inhibition of human mast cell degranulation and, therefore, 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 cellderived TNF-α has been implicated.

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