Available online at www.sciencedirect.com
ScienceDirect
Toxicology and Applied Pharmacology 220 (2007) 227–234
Toxicology and Applied Pharmacology
www.elsevier.com/locate/ytaap

Meliae cortex extract exhibits anti-allergic activity through the inhibition of Syk kinase in mast cells

Jun Ho Lee [a], Na Young Ko [a], Nam Wook Kim [a], Se Hwan Mun [a], Jie Wan Kim [a], Erk Her [a], Bo Kyung Kim [a], Dong Wan Seo [b], Hyun Wook Chang [c], Tae Chul Moon [c], Jeung Whan Han [d], Young Mi Kim [e], Wahn Soo Choi [a,*]

[a] *College of Medicine, Konkuk University, Chungju 380-701, South Korea*
[b] *School of Bioscience and Biotechnology, Kangwon National University, Gangwon-do 200-701, South Korea*
[c] *College of Pharmacy, Yeungnam University, Gyongsan 712-749, South Korea*
[d] *College of Pharamacy, Sungkyunkwan University, Suwon 440-746, South Korea*
[e] *College of Pharmacy, Duksung Women's University, Seoul 132-714, South Korea*

Received 8 August 2006; revised 19 October 2006; accepted 20 October 2006
Available online 15 February 2007

Abstract

The anti-allergic action of various Oriental medicinal herbs was investigated using in vitro and in vivo experimental models. Of these extracts, the ethanol extract of *Meliae cortex* (MC) exhibited the most potent activity in mast cells; its IC_{50} values were 29±1.5 μg/ml for antigen stimulation and 57±3.4 μg/ml for thapsigargin stimulation. It inhibited compound-48/80-induced systemic anaphylaxis by 52.9% at a dose of 300 mg/kg in mice; it also inhibited the expression of the proinflammatory mediator TNF-α. With regard to its mechanism of action, MC suppressed the activating phosphorylation of Syk, a key enzyme in mast-cell signaling processes and that of Akt in a dose-dependent manner. It also inhibited the MAP kinase ERK1/2, which is critical for the production of inflammatory cytokines in mast cells, as indicated by the suppression of the activating phosphorylation of ERK1/2. Taken together, these results suggest that the anti-allergic activity of MC may be due to the inhibition of histamine secretion and cytokine expression through the Syk inhibition in mast cells.

Keywords: *Meliae cortex*; Allergic reaction; Mast cells; Syk kinase; MAP kinase

Introduction

Allergic rhinitis, asthma, atopic dermatitis, and atopic eczema are among the common causes of chronic ill health. It is well known that IgE-dependent mast cell activation is associated with the allergic diseases. Upon IgE-dependent activation, mast cells rapidly secrete the preformed and de novo synthesized allergic mediators such as histamine, cytokines, proteases, and arachidonic derivatives. Consequently, various acute and chronic allergic responses are induced by these mediators (Church and Levi-Schaffer, 1997; Metcalfe et al., 1981). Although there are many approaches to the treatment of these diseases, such as allergen-specific immunotherapy, DNA vaccination, monoclonal anti-IgE antibody administration, soluble IL-4 receptor treatment, and treatment with antagonists to leukotriene and histamine receptors, certain difficulties and side effects are encountered while employing these therapies (Kay, 2001a, 2001b). Hence, various approaches are being explored to develop new therapies. Among them, complementary and alternative medicine is one such promising field.

In Asian countries, many herb extracts have been used as traditional folk remedies for treating various diseases. However, the active components and mechanisms of action of most herbs are largely unknown, and few herbs have been screened for their in vitro and in vivo pharmacological activity. Therefore, a systematic study of these herbal remedies must be conducted. Recently, various medicinal herbs have been reported to exhibit in vitro and in vivo anti-allergic activities (Lee et al., 2006; Nagai et al., 2004; Makino et al., 2003; Kim et al., 2003; Lee

* Corresponding author. Fax: +82 43 851 9329.
E-mail address: wahnchoi@kku.ac.kr (W.S. Choi).

0041-008X/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.taap.2006.10.034

Table 1
Effects of medicinal herb extracts on the antigen-induced degranulation in mast cells

Name of the herbal drug	Plant name and authority	Voucher specimen number	Family	Percent inhibition of hexosaminidase [a]
Achyranthis bidentatae radix	*Achyranthes bidentata*	NP20-146	Amaranthaceae	26.5
Adenophorae radix	*Adenophora triphylla* var. *japonica*	NP20-179	Campanulaceae	18.8
Agrimoniae herba	*Agrimonia pilosa*	NP20-125	Rosaceae	8.3
Akebiae caulis	*Akebia quinata*	NP20-099	Lardizabalaceae	0.0
Albiziae cortex	*Albizia julibrissin*	NP20-170	Leguminosae	19.6
Alismatis rhizome	*Alisma plantago–aquatica* var. *orientale*	NP20-092	Alismataceae	9.5
Aloe	*Aloe vera*	NP20-070	Liliaceae	3.7
Ampelopsis radix	*Ampelopsis japonica*	NP20-056	Vitaceae	3.8
Belamcandae rhizome	*Belamcanda chinensis*	NP20-048	Iridaceae	71.7
Bitae cacumen	*Biota orientalis*	NP20-133	Cupressaceae	27.0
Bletillae rhizome	*Bletilla striata*	NP20-126	Orchidaceae	10.1
Sappan lignum	*Caesalpinia sappan*	NP20-149	Leguminosae	47.6
Carpesii fructus	*Carpesium abrotanoides*	NP20-122	Compositae	1.0
Cassiae semen	*Cassia tora*	NP20-174	Leguminosae	0.0
Celosiae semen	*Celosia argentea*	NP20-023	Amaranthaceae	8.9
Chrysanthemi flos	*Chrysanthemum morifolium*	NP20-005	Compositae	11.6
Cimicifugae rhizome	*Cimicifuga heracleifolia*	NP20-008	Ranunculaceae	18.9
Cirsii japonici herba	*Cirsium japonicum* var. *ussuriense*	NP20-129	Compositae	30.8
Aurantii immaturus fructus	*Citrus aurantium*	NP20-111	Rutaceae	3.7
Aurantii fructus	*Citrus aurantium*	NP20-112	Rutaceae	0.0
Clerodendri trichotomi folium	*Clerodendron trichotomum*	NP20-087	Verbenaceae	3.2
Daphnis genkwa flos	*Daphne genkwa*	NP20-075	Thymelaeaceae	82.6
Dendrobii herba	*Dendrobium nobile*	NP20-182	Orchidaceae	0.0
Dianthi herba	*Dianthus superbus*	NP20-106	Caryophyllaceae	0.4
Ecliptae herba	*Eclipta prostrata*	NP20-188	Compositae	12.8
Equiseti hiemalis herba	*Equisetum hiemale*	NP20-012	Equisetaceae	6.3
Eriobotryae folium	*Eriobotrya japonica*	NP20-162	Malaceae	1.5
Forsythiae fructus	*Forsythia koreana*	NP20-038	Oleaceae	4.4
Fraxini cortex	*Fraxinus rhynchophylla*	NP20-052	Oleaceae	1.5
Gentianae radix	*Gentiana scabra* var. *buergeri*	NP20-028	Gentianaceae	8.8
Ginkgo semen	*Ginkgo biloba*	NP20-167	Ginkgoaceae	10.9
Glycyrrhizae radix	*Glycyrrhiza uralensis*	NP20-177	Leguminosae	86.8
Hordei fructus	*Hordeum vulgare* var. *hexastichon*	NP20-117	Graminae	0.0
Imperatae rhizome	*Imperata cylindrica* var. *koenigii*	NP20-135	Gramineae	4.5
Laminariae thallus	*Laminaria japonica*	NP20-160	Laminariaceae	5.4
Leonuri herba	*Leonurus sibiricus*	NP20-144	Labiatae	2.0
Leonuri semen	*Leonurus sibiricus*	NP20-151	Labiatae	38.2
Lepidii semen	*Lepidium apetalum*	NP20-165	Cruciferae	1.3
Ligustri lucidi fructus	*Ligustrum lucidum*	NP20-189	Oleaceae	18.7
Lilii bulbus	*Lilium lancifolium*	NP20-185	Liliaceae	21.4
Malvae semen	*Malva verticillata*	NP20-107	Caryophyllaceae	0.5
Meliae cortex	*Melia azedarach L.* var. *japonica*	NP20-120	Meliaceae	85.1
Toosendan fructus	*Melia toosendan*	NP20-114	Meliaceae	0.0
Menthae herba	*Mentha arvensis* var. *piprerascens*	NP20-002	Labiatae	8.3
Oldenlandiae diffusae herba	*Oldenlandia diffusa*	NP20-054	Rubiaceae	5.0
Paeoniae radix rubra	*Paeonia lactiflora*	NP20-035	Paeoniaceae	17.2
Paeoniae radix alba	*Paeonia lactiflora*	NP20-178	Paeoniaceae	17.2
Moutan cortex	*Paeonia suffruticosa*	NP20-034	Paeoniaceae	0.0
Paridis rhizome	*Paris verticillata*	NP20-044	Liliaceae	3.6
Patriniae radix	*Patrinia villosa*	NP20-054	Valerianaceae	2.2
Peucedani radix	*Peucedanum decursivum*	NP20-153	Umbelliferae	0.0
Pharbitidis semen	*Pharbitis nil*	NP20-076	Convolvulaceae	4.7
Phaseoli semen	*Phaseolus calcaratus*	NP20-095	Leguminosae	8.2
Phaseoli radiate semen	*Phaseolus radiatus*	NP20-059	Leguminosae	5.9
Phellodendri cortex	*Phellodendron amurense*	NP20-027	Rutaceae	14.5
Phragmitis rhizoma	*Phragmites communis*	NP20-014	Graminae	2.3
Phyllostachys folium	*Phyllostachys nigra M.* var. *henonis*	NP20-016	Bambusaceae	14.3
Phyllostachys folium	*Phyllostachys nigra M.* var. *henonis*	NP20-016	Bambusaceae	0.0
Phytolaccae radix	*Phytolacca esculenta*	NP20-077	Phytolaccaceae	2.0
Picrorrhizae rhizoma	*Picrorrhiza scrophulariaeflora*	NP20-068	Scrophulariaceae	2.1
Plataginis semen	*Plantago asiatica*	NP20-098	Plantaginaceae	0.0
Rhei radix et rhizoma	*Rheum palmatum*	NP20-069	Polygonaceae	82.4
Rumexcis radix	*Rumex japonicus*	NP20-136	Polygonaceae	16.7
Scutellariae radix	*Scutellaria baicalensis*	NP20-025	Labiatae	80.5