Antiasthmatic effects of schizandrae fructus extract in mice with asthma

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Submitted: 25-04-2013 Revised: 01-05-2013 Published: 21-02-2014

ABSTRACT

Background: Schizandrae fructus (SF), the fruit of *Schisandra chinensis*, has been used for the treatment of cough, wheezing, dry mouth, hepatitis, cardiovascular disease, and as a tonic and astringent in China, Japan, and Korea. **Objective:** Investigation of the antiasthmatic effects of SF. **Materials and Methods:** We investigated the effects of SF on airway hyperresponsiveness (AHR) to methacholine, production levels of antigen-specific antibodies, and histopathological changes in the lung tissue in a mouse model (Balb/c) of asthma induced by repeated intranasal instillation of an antigen. **Results:** SF lowered AHR to methacholine ($P < 0.05$), antigen-specific immunoglobulin E (IgE) level ($P < 0.01$), and immune cell infiltration in mice with asthma. Prednisolone (PD) effectively decreased AHR ($P < 0.01$), total antibody ($P < 0.01$) and IgE ($P < 0.01$) levels, and immune cell infiltration. SF and PD did not affect the levels of antigen-specific IgG1 and IgG2a antibodies. **Conclusion:** Our data suggest that SF has possible application as an antiasthmatic drug. We also suggest that SF could be used as a complementary or alternative medicine to glucocorticoids.

Key words: Asthma, hyperresponsiveness, IgE, schizandrae fructus

Access this article online

Website: www.phcog.com

DOI: 10.4103/0973-1296.127348

Quick Response Code:

INTRODUCTION

The pathophysiology of asthma has three major features: Intermittent and reversible airway obstruction, bronchial smooth muscle cell hyperreactivity, also referred to as airway hyperresponsiveness (AHR), and chronic bronchial inflammation.[1] The chronic bronchial inflammation in asthmatic conditions is characterized by Th2 skewing reactions, including elevation of levels of interleukin-4 and immunoglobulin E (IgE) in bronchoalveolar lavage fluid and serum, and eosinophilic infiltration into airways.[2,3]

In asthmatic conditions, inhaled allergens cause an immediate asthmatic response (IAR), which reaches a peak level at 15-30 min after challenge. This response is considered to be mediated by newly generated inflammatory mediators released from the mast cells after IgE-dependent activation.[4] In many patients, IAR is followed by a late asthmatic response (LAR) and later LAR (LLAR). The LAR is characterized by eosinophil infiltration and AHR to allergens.[5,6]

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There are two major treatments for LAR: Anti-inflammatory therapy and bronchodilator therapy.[7] β2-adrenoceptor agonists are the most effective bronchodilators known and they inhibit the IAR, whereas corticosteroids inhibit both the LAR and the associated AHR.[8] Despite their effectiveness against asthma, there are some limitations to the use of β2-adrenoceptor agonists because of adverse effects. For example, the major adverse effect of β2-adrenoceptor agonists is sedation and corticosteroid therapy is strictly limited in use because of its well-known adverse effects, such as osteoporosis, cushingoid features, and weight gain.[6,9,10] For these reasons, there is a need for development of more effective and safe treatments for asthma. In that regard, herbal plants are attractive sources for the development of new treatments for asthma, probably because of their safety, efficacy, and relatively low cost.

Schizandrae fructus (SF) is the fruit of *Schisandra chinensis*. Donguibogam, a medical encyclopaedia which was added to UNESCO's Memory of the World Register in 2009, states that SF can be used for the treatment of cough, wheezing, dry mouth, hepatitis, and cardiovascular disease and is used as a tonic and astringent.[11-13] SF is also one of the components of So-Cheong-Ryong-Tang (SCRT, XQLT in China, SST in Japan), which is the most famous and well-researched remedy for asthma in East Asian countries.

According to phytochemical studies, the bioactive compounds isolated from SF are derivatives of lignan, such as deoxyschizandrin, gamma-schizandrin, and schizandrin.[14,15] Pharmacological studies have shown that some of the metabolites exhibit various properties, such as antihepatotoxic, antimicrobial, hypoglycaemic, antiallergic, anti-inflammatory, antioxidant, and anti-cancer effects.[16-20] Although schizandrin, the main constituent of SF, showed inhibitory activity on passive cutaneous anaphylaxis induced by the IgE-antigen complex, well-controlled clinical trials, or translational research on SF for asthma treatment are rare.[11]

As a preliminary study to develop safe and effective antiasthmatic drugs, the effects of SF on AHR to methacholine, production levels of antigen-specific antibodies in serum, and histopathological changes in the lung tissue were investigated using a mouse model of asthma induced by repeated intranasal instillation of an antigen.

MATERIALS AND METHODS

Reagents

Chicken egg ovalbumin (OVA) Grade V, methacholine, prednisolone, and goat antimouse polyvalent antibody were obtained from Sigma Chemical Co. (MO, USA). Aluminium hydroxide (Imject Alum Adjuvant) was obtained from Pierce Chemical Co. (IL, USA). Para-nitrophenyl phosphate (ρ-NPP) was obtained from Amresco (OH, USA). Goat antimouse IgG1 antibody, goat antimouse IgG2a antibody, and rat antimouse IgE antibody were obtained from Southern Biotech (AL, USA).

Animals

Eight-week-old male BALB/c (18~21 g) mice were purchased from Samtaco (Incheon, Korea). Animals were housed in a temperature-controlled room (24 ± 3°C) in our laboratory under a 12-h light/12-h dark cycle and provided with sterile food and water *ad libitum*. Animals were cared for and handled in accordance with the guidelines of the standard operating procedure of our institute and the study protocol was approved by our Institutional Animal Care Committee according to the international standards (PNU-2009-0029).

Preparation of herbal medicine

SF was purchased from Hwarim Pharmaceutical Co., Ltd. (Busan, Korea). A total of 50 g of SF was immersed in 1,000 mL of methanol and sonicated for 30 min, and then extracted for 24 h. The extract was filtered with Whatman filter paper No. 20 and evaporated under reduced pressure using vacuum evaporator (Eyela, Japan). The condensed extract was then lyophilized using a freeze dryer (Labconco, Kansas City, MO, USA). Finally, 15.9 g of lyophilized powder was obtained (yield, 31.8%). The extracts were stored at −20°C until use. The methanol extract of SF (Voucher No. MH2010-010) was deposited at the Division of Pharmacology, School of Korean Medicine, Pusan National University.

Induction of asthma and grouping of experimental animals

Allergic asthma was induced using the protocol previously described by Cho *et al.*, and Yoshida *et al.*[21,22] Briefly, mice were sensitized on days 1, 2, and 3 by intraperitoneal injection of 20 μg of OVA and 2 mg of aluminium hydroxide for 3 consecutive days. Five days later, mice were anesthetized with Zoletil (15 mg/kg) and Rompun (5 mg/kg) and received intranasal instillation of 10 μg of OVAOVA (day 8). After 8 days, intranasal instillation was conducted again on days 16, 17, 20 and 21. SF (600 $mg \cdot kg^{-1} \cdot day^{-1}$) was administered orally and prednisolone (PD) (5 $mg \cdot kg^{-1} \cdot day^{-1}$) was injected intraperitoneally for 6 consecutive days as shown in Figure 1. The daily dose of SF was 4 times higher than that for human adults. The dose was determined according to the basal metabolic rates and body weight.

The experimental groups are as follows: (1) Naive group ($n = 6$), neither sensitized nor challenged, fed with distilled water (D/W); (2) control group ($n = 6$), sensitized and challenged with ovalbumin (OVA), fed with D/W; (3) SF group ($n = 6$), sensitized and challenged with OVA, fed with SF; and (4) PD group ($n = 6$), sensitized and challenged with OVA, injected with PD.

Measurement of AHR

AHR to methacholine was measured using a whole-body plethysmograph (OCP 3000, Allmedicus, Korea) on day 22 of the experiment. Mice were exposed to four different doses (0, 12.5, 25, and 50 mg/mL) of methacholine with a nebulizer (HARVARD73-1963, Harvard Apparatus, MA) for 150 s at each concentration.[23] The indicated doses of methacholine dissolved in saline, at increasing concentrations from 0 to 50 mg/mL were administered for 150 s. Afterward, mice were immediately replaced

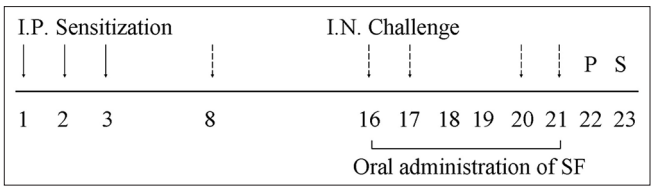

Figure 1: Experimental Schedule Control, prednisolone (PD), and schizandrae fructus (SF) groups were sensitized intraperitoneally on days 1, 2, and 3 and challenged intranasally on days 8, 16, 17, 20, and 21. The naive group was treated with vehicles in the same way. Animals were administrated orally with SF from days 16 to 21. Airway responsiveness was measured on day 22 (P). All animals were sacrificed on day 23 (S)

in chambers and measurements were obtained for 150 s after the completion of each nebulization. The enhanced pause (Penh) values measured during this period were averaged and expressed as absolute Penh values. A formula to calculate Penh values is as follows:[24]

Penh = [Te/(RT - 1)] × PEF/PIF

Te: expiration time (s)
RT: Relaxation time (s)
PEF: Peak expiratory flow rate (mL/s)
PIF: Peak inspiratory flow rate (mL/s)

OVA-specific antibody detection in serum

The levels of OVA-specific total antibodies IgE, IgG1, and IgG2a in serum were measured by enzyme-linked immunosorbent assay (ELISA). Blood samples were centrifuged at 220 g for 5 min to obtain sera. For ELISA, 96-well plates (Nunc) were coated with 50 μg/mL of OVA dissolved in a blocking solution [1% of skimmed milk and 0.05% of Tween 20 in phosphate buffered saline (PBS)] at room temperature for 3 h and incubated at 4°C overnight. After the plates were washed, the blocking solution was added and the plates were incubated at room temperature for 1 h. After washing, 100 μL of diluted serum (1: 20 in PBS) was added to each well and the plates were incubated at room temperature for 2 h. For detection of IgE, diluted serum (1:10) was used and incubated at 4°C overnight. After washing, alkaline phosphatase-conjugated antimouse Ig was added and the plates were incubated at room temperature for 1 h. After incubation, ρ-NPP was added. The optical density was measured at 405 nm by using a microplate spectrophotometer (ELX 808 multichannel microplate reader, BioTek, VT). The secondary antibodies used were goat antimouse polyvalent antibody (1:1000), goat antimouse IgG1 antibody (1:1000), goat antimouse IgG2a antibody (1:1000), and rat antimouse IgE antibody (1:500). OVA-specific serum obtained from another experiment was used as the standard serum, and all the titers were calculated as relative values to this serum.

Histopathological examination of lung tissue

Lung tissue specimens were removed and fixed overnight in 10% formaldehyde. The specimens were dehydrated, fixed, and embedded in paraffin wax and then cut to 4-μm-thick sections using a microtome (Leica, Wetzlar, Germany). These sections were stained with hematoxylin-eosin and examined using a photomicroscope (×200).

Statistical analysis

All statistical comparisons were made with the Student's *t*-test. The SigmaPlot version 11.0 (SYSTAT software) was used for statistical analysis. All data are represented as mean ± standard deviation. Differences with a value of $P < 0.05$ were considered significant.

RESULTS

Effects of SF on AHR

The effects of SF on AHR were evaluated by monitoring Penh for 150 s and the results are shown in Figure 2. AHR of the control group was significantly higher than that of the naive group. After exposure to 50 mg/mL of methacholine, the Penh value of the control group increased by 254% of that of the naive group (8.78 ± 3.01 vs. 3.46 ± 0.79). Compared with the control group, the SF group showed a lower Penh value by 43.9% (4.93 ± 1.41 vs. 8.78 ± 3.01). There were no significant differences in the Penh values between the PD and SF groups [Figure 2].

Effects of SF on levels of OVA-specific Igs

The effects of SF on the production of OVA-specific antibodies in serum were also characterized. Prominent increases in the levels of OVA-specific total Igs, IgE, IgG1, and IgG2a were observed in the control group. Treatment with SF decreased the serum level of OVA-specific IgE by 40.1% compared to that in the control condition. Oral administration of SF did not affect the levels of total antibodies, IgG1 and IgG2a. Treatment with PD decreased the levels of OVA-specific total antibodies and IgE [Figure 3].

Effects of SF on histopathological changes in the lung tissue

In the control group, inflammatory cells were seen to infiltrate the connective tissue around the small vessels and airways (indicated by solid arrows) [Figure 4b]. SF and PD groups showed moderate cellular infiltration around the small vessels [Figures 4c and 4d]. Cellular

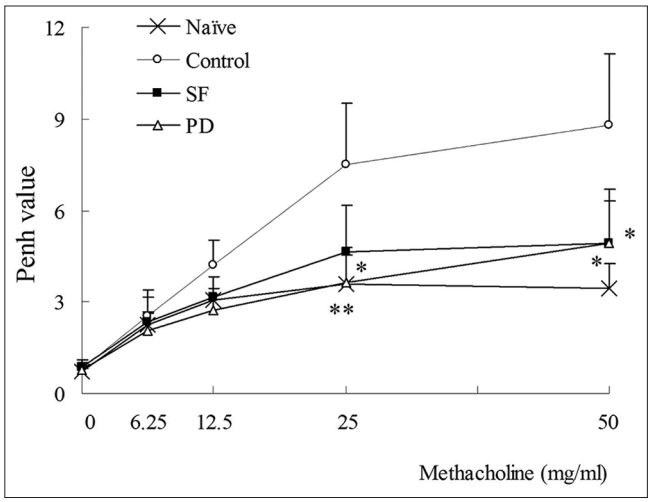

Figure 2: Effects of schizandrae fructus (SF) on airway hyperresponsiveness (AHR). Airway hyperresponsiveness was measured by measuring Penh on day 22. SF, 600 mg•kg-1•day-1 for SF group; prednisolone (PD), 5 mg•kg-1•day-1 for PD group. Results were represented as mean ± standard deviation. *$P < 0.05$, **$P < 0.01$ as compared with the control group ($n = 6$)

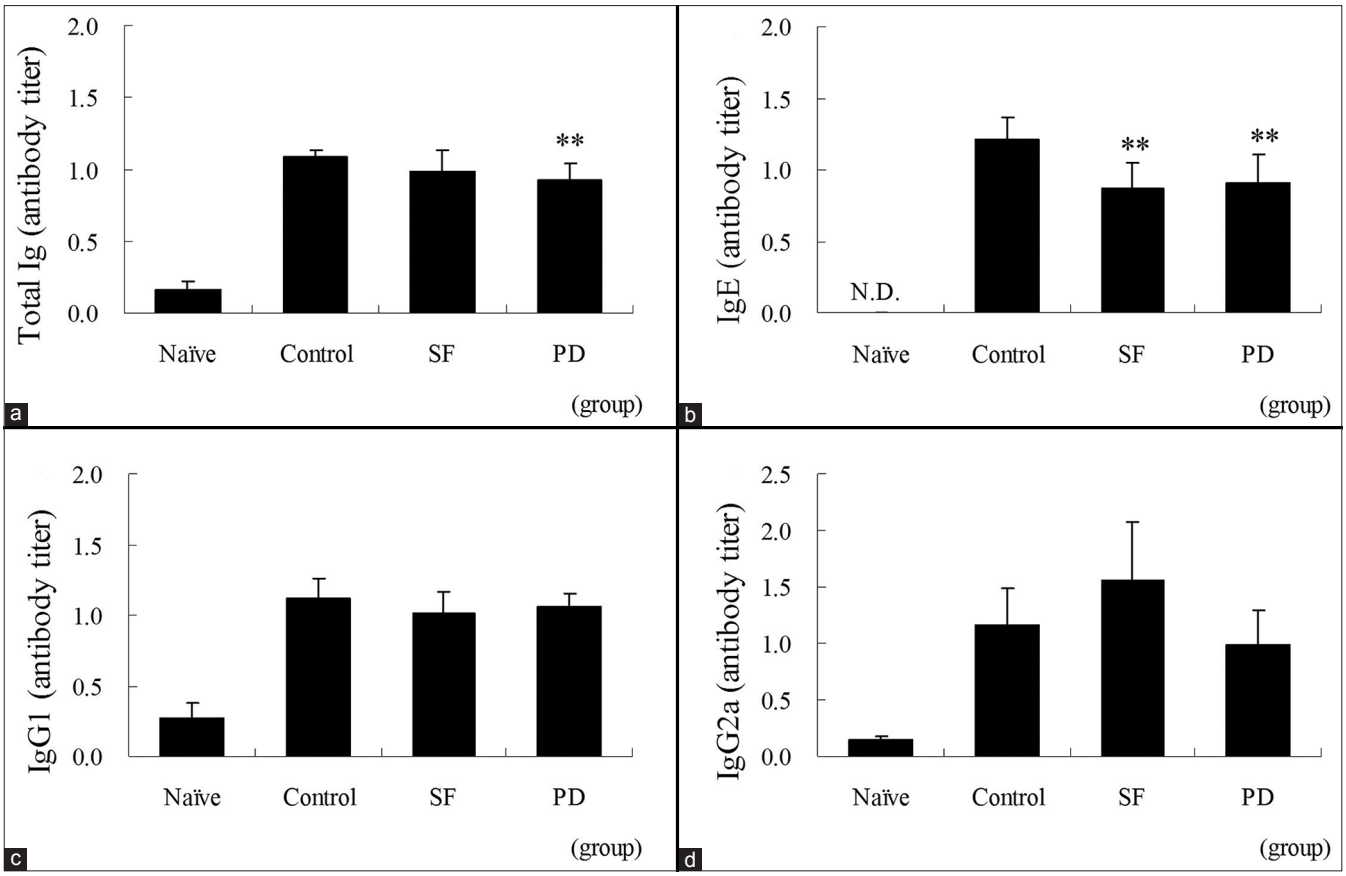

Figure 3: Effects of schizandrae fructus (SF) on ovalbumin (OVA)-specific antibody levels in serum Naïve mice with asthma; Control, mice with asthma; SF, 600 mg•kg-1•day-1 of SF administered to mice with asthma; prednisolone, 5 mg•kg-1•day-1 of prednisolone injected in mice with asthma. N.D. means not detectable. (a) OVA-specific total antibodies, (b) OVA-specific immunoglobulin (Ig) E, (c) OVA-specific IgG1, and (d) OVA-specific IgG2a. $^{**}P < 0.01$ as compared with the control group ($n = 6$)

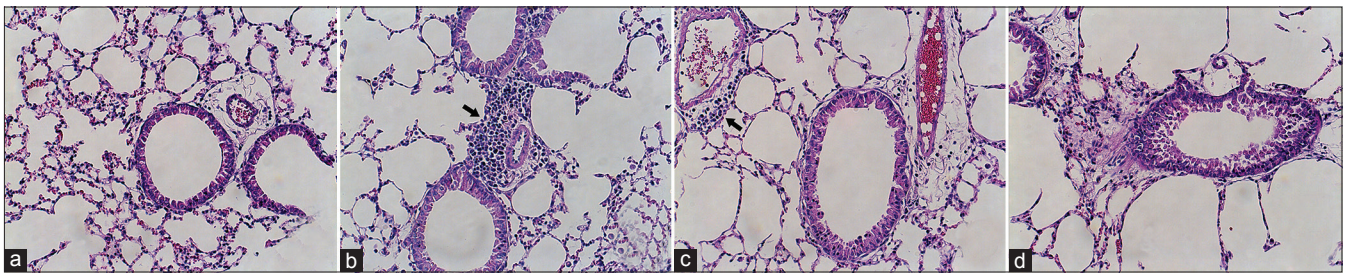

Figure 4: Effects of Schizandrae Fructus (SF) on histopathological changes in the lung tissue. The lung tissue sections were stained with hematoxylin and eosin and examined using a photomicroscope (×200). a, naïve group; b, control group; c, SF group; d, prednisolone group. Solid arrows indicate infiltration of inflammatory cells into the connective tissue around small vessels

infiltration in the PD group was less than that in the SF group [Figure 4d].

DISCUSSION

SF, the fruit of the medicinal plant *Schisandra chinensis*, has been used as food and medicine for a long time in China, Japan, and Korea. In the present time, SF is not only used for medical purposes, such as a tonic or an astringent, but also as a raw material in food and natural dyes.

SF can be used to treat patients with respiratory diseases in traditional therapy. A total of 34% of the medications containing SF are used in patients with cough in Donguibogam, which is famous book on traditional medicine in Korea (Memory of the World).[25]

Recently, SF and its constituents have been shown to have antiallergic activities. For these reasons, we hypothesized that SF could lower AHR and the level of IgE and prevent infiltration of immune cells into the airway.

In this experiment, repeated intranasal instillation of OVA caused AHR, infiltration of inflammatory cells into the lung tissue, elevation of OVA-specific Ig isotypes including IgE and IgG1 in serum. These aspects were thought to mimic the asthmatic condition well.

In the present study, SF lowered AHR effectively [Figure 2] Immediate bronchoconstriction (IAR) is mediated by mast cells after IgE-dependent activation.[4] In a recent study, schizandrin, the major component of SF, was found to improve IgE-induced anaphylaxis and scratching behaviors.[11] In addition, schizandrin inhibited degranulation of compound 48/80-induced rat peritoneal mast cells and IgE-induced RBL 2H3 cells *in vitro*.[11] For these reasons, the antihyperresponsive reaction of SF might be involved in the activity against degranulation of mediators by mast cells.

It has been reported that AHR can be induced by IgE- and mast cell-dependent mechanisms,[26-28] and that AHR and eosinophil infiltration can be elicited in mouse models in the absence of IgE.[6] In addition, IgE has long been considered the main target for asthma therapy. In our study, SF decreased serum IgE levels significantly [Figure 3b]. In a previous study, SF also decreased the serum IgE levels in mice with asthma induced by intraperitoneal injection of OVA.[11] Therefore, the lowering of IgE levels by SF might be involved in the suppressive mechanism related to hyperresponsiveness and eosinophil infiltration.

Histopathological analysis of the SF group showed less cellular infiltration around the small vessels compared with control group [Figure 4]. Most infiltrated immune cells were confirmed to be eosinophils upon photomicroscopic observation (data not shown). It is known that an increase in the number of eosinophils is important since it correlates in time with an increase in bronchial hyperresponsiveness.[29] Eosinophils can infiltrate the airways in response to chemokine recruitment.[30] Eotaxin, an eosinophil-specific chemokine released in the respiratory epithelium following allergic stimulation, plays a central role in eosinophil migration.[29] In a previous study, both SF and schizandrin lowered the levels of eotaxin.[31] In addition, SF decreased messenger ribonucleic acid expression levels in the A549 cells. In particular, eosinophil recruitment to lung epithelial cells was also reduced by SF *in vitro*.[31] For these reasons, the suppressive effect of SF on eosinophil infiltration might be one of the possible mechanisms involved in antihyperresponsive action of SF.

In the present experiment, PD significantly decreased AHR and the levels of antigen-specific total antibodies and IgE. In addition, PD also decreased immune cell infiltration into the lung tissue. The mechanisms of action of SF and PD seemed almost similar; however, PD affected the level of total antibodies, whereas SF did not. This may be the clue to distinguish the actions of PD and SF. Regarding general suppression of PD, SF is thought to have more specific effects on asthma.

Briefly, SF lowered AHR, IgE level, and immune cell infiltration in mice with asthma. These results suggest that SF might have possible uses as an antiasthmatic drug. We also suggest that SF might be used as a complementary or alternative medicine to glucocorticoids. Further clinical trials are needed to examine these possibilities.

ACKNOWLDGMENT

("This work was supported by a grant from the New Growth Engine Industry Division, Busan Metropolitan City, Korea") into Source of Support after" National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012011676).

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Cite this article as: Kim H, Ahn Y, Kim YS, Cho SI, An WG. Antiasthmatic effects of schizandrae fructus extract in mice with asthma. Phcog Mag 2014;10:S80-5.

Source of Support: National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012011676),
Conflict of Interest: None declared.