

Note

Clinical Efficacy of Apple Polyphenol for Treating Cedar Pollinosis

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A double-blind comparative study was conducted on cedar pollinosis patients in order to evaluate the treatment efficacy of apple polyphenol (Ap). Ap was administered (500 mg) once daily for 12 weeks, starting about 2 weeks prior to cedar pollen dispersion. Pollinosis symptoms during the study were evaluated according to the classification in the guidelines for allergic rhinitis diagnosis and treatment. The results show that the sneezing score was significantly lower for the Ap group than with the placebo group during the early period of pollen dispersion and during the main dispersion period. In addition, no adverse reactions were induced by Ap during the study. These results suggest that Ap may alleviate the symptoms of cedar pollinosis.

Key words: apple polyphenol; histamine; mast cells; cedar pollinosis

The changes in life style and environment in Japan have results in a sufficiently large increase in the number of patients with allergic diseases to constitute a social problem. Allergic rhinitis is a common disease, and the number of patients with cedar pollinosis, which is a subclass of allergic rhinitis, is estimated at between 18 and 23 million people.¹⁾ The main symptoms of cedar pollinosis are sneezing, rhinorrhea, nasal obstruction, and eye itching, with the disease disrupting daily life. The treatment guidelines for allergic rhinitis (including pollinosis) in Japan are focused on histamine receptor antagonists, leukotriene receptor antagonists, and steroids (nasal drops). However, such therapeutic drugs are associated with some adverse reactions, and other food-derived antiallergic ingredients are under investigation in many laboratories. Previous studies have reported that a red perilla extract²⁾ (luteolin being the main ingredient) and rubus suavissimus extract³⁾ (GOD ellagitannin being the main ingredient) alleviated the symptoms of cedar pollinosis through their antiallergic action,

although these studies were not of the double-blind type. Since the symptoms of cedar pollinosis greatly depend on the quantity of pollen dispersed, a double-blind study, using a placebo group as a control, is necessary to accurately evaluate the problem.

Polyphenols can be found in the fruits and vegetables of many natural plants, and have various physiological functions.^{4–11)} Apple polyphenol (Ap) can be extracted and refined from unripe apples. Its major component is apple condensed tannin (ACT) and it also contains such monomeric polyphenols as catechin, epicatechin, phlorizin, and chlorogenic acid. Studies on the antiallergic action of Ap have found that it suppressed the histamine release from mast cells and basophils (RBL-2H3) in rats,¹²⁾ inhibited hyaluronidase¹³⁾ and suppressed auricular swelling in mice.¹⁴⁾ It has been reported from a clinical study that Ap alleviated the itching in atopic dermatitis patients.¹⁵⁾ This phenomenon was attributed to the suppression of histamine release by ACT, the major component of Ap. We discovered that it inhibited 48-hour homologous passive cutaneous anaphylaxis (PCA) in rats and alleviated sneezing in a guinea pig allergic rhinitis model (unpublished results). However, the usefulness of Ap in treating allergic rhinitis has not previously been studied.

We therefore evaluated the efficacy of Ap given before and during the pollen dispersion period. A double-blind, randomized, parallel inter-group comparative study between a group treated with Ap and a group treated with a placebo was conducted in the Waseda Clinic between December 2001 and April 2002. This study was in accordance with the standard of the Declaration of Helsinki, and had the written approval of the Ethics Committee of the Waseda Clinic. Thirty-six healthy men aged from 20 to 64 years with cedar pollinosis who met the diagnostic criteria were enrolled as subjects. The diagnostic criteria included subjects who had the subjective symptoms of cedar pollinosis and who were in class 2 or higher for serum antigen-specific IgE anti-

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Abbreviations: Ap, apple polyphenol; ACT, apple condensed tannin; PCA, passive cutaneous anaphylaxis; 5-LO, 5-lipoxygenase

Table 1. Nasal and Ocular Symptoms (Okuda's classification)

	Score (point)				
	4	3	2	1	0
Sneezing*	>21	20–11	10–6	5–1	0
Rhinorrhea**	>21	20–11	10–6	5–1	0
Nasal obstruction	Complete nasal obstruction all day	Severe nasal obstruction and breathing through the mouth performed for a considerable time	Marked nasal obstruction marked and breathing through the mouth performed several times a day	No breathing through the mouth, but nasal obstruction present	No nasal obstruction
Eye itching	>3 point	Eye rubbed frequently	Eye sometimes rubbed	No eye rubbing	No eye itching

* Number of sneezes

** Number of rhinorrhea attacks

bodies (RAST). Subjects whose symptoms in the previous year had been ranked medium or lower were also included (based on the guidelines for diagnosis and treatment of allergic rhinitis, 1999¹⁾). Any subjects with such concomitant nasal diseases as perennial allergic rhinitis, acute/chronic rhinitis, and sinusitis, those who had taken drugs that could have an effect on the evaluation, those who had any symptoms before the annual dispersion period of cedar pollen, those who were class 2 or higher for serum house dust- or mite-specific IgE, and those considered by the chief investigator as unsuitable were all excluded. The subjects were randomly allocated to the Ap (500 mg) group or placebo group, and monitored from about 2 weeks before pollen dispersion for 12 weeks (January 9 to March 31). An allergy diary was used to score the severity of such pollinosis symptoms as sneezing, rhinorrhea, eye itching, and nasal obstruction in the subjects each day during the study period in accordance with Okuda's classification in the guidelines for allergic rhinitis diagnosis and treatment (Table 1). Safety was assessed by physiological checks and laboratory tests for hematology, blood biochemistry and serum biochemistry.

The scores for each symptom at each time point were compared between the two groups. A statistical analysis was performed by using the Wilcoxon test.

The pollen dispersion in the Kanto Region was greater this year than last year. This dispersion started on January 29th in some places, and pollen of 20 units/cm² or greater was observed around February 7th. Figure 1 shows the pollen dispersion in five places in the Tokyo region (Chiyoda, Katsushika, Suginami, Hachioji, and Chofu public health centers). There was no difference between the Ap group and placebo group with regard to age, body height, body weight, place of residence, work place, severity of nasal symptoms and ocular symptoms (last year), specific IgE (cedar, mite, and house dust), duration of rhinitis, development time of onset, and the presence of nose complications.

During the study period, all the symptoms got worse when the pollen dispersion increased. The sneezing score was significantly lower with the Ap group than with the placebo group in weeks 1, 2, 3 and 4, which were in the early period of pollen dispersion, and in weeks 9, 10 and 11 which were in the main dispersion period. The rhinorrhea score, which like sneezing is considered to be a histamine-dependent symptom, was significantly lower with the Ap group than with the placebo group in weeks 3 and 4 which were in the early period of pollen dispersion. During the main dispersion period, the rhinorrhea score with the Ap group was lower than with the placebo group, although not significantly. Moreover, no definite action was found toward eye itching or nasal obstruction (Fig. 2).

In respect of safety, no changes were apparent during the study in the subjective symptoms of the subjects or in any of the hematological and serum biochemical tests.

The mechanisms for the action of Ap, a red perilla extract and a rubus suavissimus extract were compared. The major components of the red perilla extract were luteolin, rosmarinic acid, and caffeoyl quinic acid which respectively inhibited 5-lipoxygenase (5-LO), suppressed TNF- α production and suppressed IgE production. A study on cedar pollinosis patients found that a red perilla extract improved nasal obstruction which contributed to the 5-LO inhibition activity.²⁾ The rubus suavissimus extract inhibited cyclooxygenase, suppressed the histamine release from mast cells, and suppressed the TNF- α production from macrophages. Moreover, in a study on cedar pollinosis patients, the rubus suavissimus extract improved all the nasal symptoms which contributed to the suppression of chemical mediator release by GOD-type ellagitannin.³⁾ Ap has been reported to suppress the histamine release from peritoneal mast cells in rats induced by compound 48/80 stimulation, and to suppress the histamine release from basophilic leukemia cells (RBL-2H3) in rats induced by an antigen antibody reaction.¹²⁾ It has also been found that the mechanism

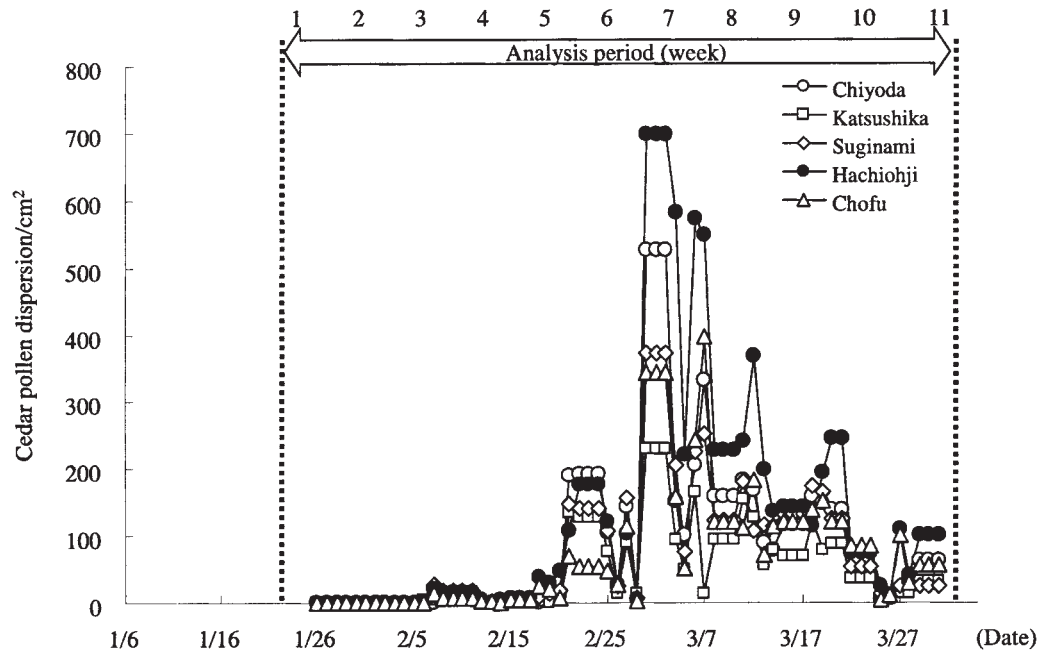


Fig. 1. Cedar Pollen Dispersion (Bureau of Public Health, Tokyo Metropolitan Government).

Shown in the cedar pollen dispersion at 5 locations in the Tokyo region (Chiyoda, Katsushika, Sugunami, Hachioji, and Chofu public health centers).

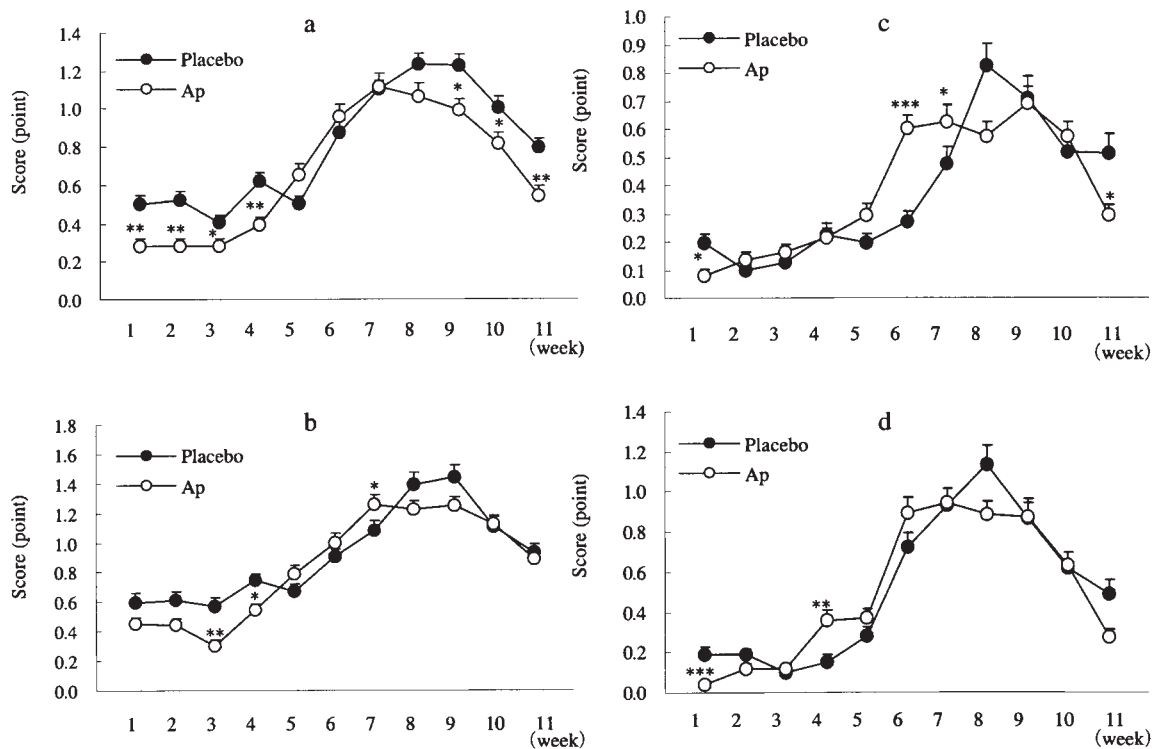


Fig. 2. Effect of Nasal Symptoms (a, sneezing; b, rhinorrhea; c, nasal obstruction) and Ocular Symptoms (d, eye itching) for Each Treatment Group. Each data value is the mean $\pm$ SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with the placebo group.

for this suppression was the decrease in intracellular calcium concentration of mast cells that followed the antigen antibody reaction.¹²⁾ Moreover, in an open study conducted on patients with atopic dermatitis, Ap

reportedly alleviated the pruritus symptoms, starting from the second week of treatment, and caused a decrease in the peripheral eosinophil count in the eighth week of treatment. It is considered that these phenomena

were induced by a suppression of the histamine release by ACT, the major component of Ap.¹⁵⁾ We examined the usefulness of Ap in a guinea pig allergic rhinitis model, and found that while a single administration of Ap before antigen challenge had no effect, a 17-day continuous administration of Ap before and during antigen sensitization alleviated sneezing. It is considered that a histamine release inhibitor is more effective during continuous administration, so we speculate that Ap acted in a similar manner to that of a chemical mediator release inhibitor such as sodium cromoglycate. In this present study, alleviation of the nasal symptoms by Ap is thought to have contributed to the suppression of histamine release by ACT. Moreover, Ap contained epicatechin which has inhibitory activity toward 5-LO. 5-LO is the initial enzyme in leukotriene production and is considered to play an important role in nasal obstruction.¹⁶⁾ We therefore expect that Ap would improve nasal obstruction by a high-dose intake.

The results of our study demonstrate that Ap may be especially useful against sneezing, one of the pollinosis symptoms. Taking Ap prior to pollen dispersion can be expected to reduce the dose of a therapeutic drug or its administration rate. However, since the evaluation of the efficacy in this study was based on the subjective symptoms of the subjects alone, we intend to conduct a further study by adding an objective evaluation by rhinoscopy and the number of eosinophils in the nasal lavage, and to confirm the usefulness of Ap in cedar pollinosis treatment.

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