Original Article

Clinical Effects of Apple Polyphenols on Persistent Allergic Rhinitis: A Randomized Double-Blind Placebo-Controlled Parallel Arm Study

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Abstract. *Background*: We often encounter persistent allergic rhinitis due to house dust mites in the practice of otolaryngology, and its prevalence in Japan is high (18.7%). Persistent allergic rhinitis is usually treated with antihistamines and local steroids, but they often cause adverse effects such as sedation and drowsiness. Polyphenols derived from apples have been reported to suppress histamine release from rat cells, reduce auricular swelling in allergic mice, and alleviate skin inflammation in atopic patients. These effects suggest that apple polyphenols are effective for the treatment of various allergic disorders, but the results of their clinical use have not been reported.
Objective: To assess the effect of drinks containing apple polyphenols on clinical symptoms of persistent allergic rhinitis.
Methods: Thirty-three patients aged 15 to 65 years with moderate or severe persistent allergic rhinitis in whom the symptoms persisted for 3 years or longer were treated without apple polyphenols (control group), with a low dose of apple polyphenols, or with a high dose of apple polyphenols, and changes in the clinical symptoms were examined.
Results: Significant improvements were observed in sneezing attacks ($P < .05$) and nasal discharge ($P < .01$) in the high-dose group and in sneezing attacks ($P < .05$) in the low-dose group. Compared with the control group, an improvement was observed in sneezing attacks and nasal discharge in many patients of the polyphenol-treated groups. In terms of intranasal findings, a significant improvement was observed in swelling of the nasal turbinate in the low-dose group ($P < .05$). The percentage of patients who showed an improvement in swelling of the nasal turbinate was higher in the polyphenol-treated groups.
Conclusions: We conclude that apple polyphenols are effective in alleviating symptoms of persistent allergic rhinitis.

Key words: Apple polyphenols. Nasal allergy. Sneezing attack. Nasal discharge. Human clinical trial.

Resumen. *Antecedentes*: En las consultas de otolaringología, a menudo nos encontramos con rinitis alérgica persistente debida a ácaros de polvo doméstico. Su prevalencia en Japón es alta (del 18,7%). Normalmente la rinitis alérgica se trata con antihistamínicos y esteroides locales aunque éstos pueden conllevar efectos secundarios tales como sedación y somnolencia. Los polifenoles derivados de la manzana han demostrado suprimir la histamina liberada por células de ratas, reducir el edema en la zona auricular de ratones alérgicos y aliviar inflamaciones cutáneas en pacientes atópicos. Estos efectos sugieren que los polifenoles de la manzana son efectivos en el tratamiento de varios trastornos alérgicos, pero todavía no se han confirmado sus resultados en uso clínico.
Objetivo: Evaluar el efecto de bebidas que contienen polifenoles de manzana en síntomas clínicos de rinitis alérgica persistente.
Métodos: Se trataron 33 pacientes entre 15 y 65 años con rinitis alérgica persistente moderada o severa cuyos síntomas persistieron durante al menos 3 años sin polifenoles de manzana (grupo de control), con una dosis baja de polifenoles de manzana, o con una dosis elevada de polifenoles de manzana; finalmente se examinaron los cambios en los síntomas clínicos.
Resultados: Se observaron mejorías significativas en las salvas de estornudos ($P < 0,05$) y rinorrea ($P < 0,01$) en el

grupo de dosis alta así como en salvas de estornudos ($P < 0,05$) en el grupo de dosis baja. En comparación con el grupo de control, se observó mejoría en salvas de estornudos y rinorrea en muchos pacientes de los grupos tratados con polifenoles. En cuanto a los hallazgos intranasales, se observaron mejorías significativas en el edema de cornetes nasales en el grupo de dosis baja ($P < 0,05$). El porcentaje de pacientes con mejorías en el edema de cornetes nasales fue mayor en el grupo tratado con polifenoles.
Conclusiones: Concluimos que los polifenoles de manzana son efectivos para aliviar los síntomas de rinitis alérgica persistente.

Palabras clave: Polifenoles de manzana. Alergia nasal. Salvas de estornudos. Descarga nasal. Prueba clínica humana.

Introduction

The most frequent allergen in persistent allergic rhinitis is considered to be the house dust mite, and its primary pathogenic mechanism is reported to be type I allergic reaction triggered by an interaction between an allergen and specific IgE antibodies on mast cells. The prevalence of the disease in Japan is reported to be high at 18.7 % [1]. The disease is usually treated with antihistamines and local corticosteroids, but long-term administration is required and adverse effects of the drugs are often experienced.

There have been many reports of antiallergic activities displayed by polyphenols, including those of green tea, persimmon leaf, *ten-cha*, and perilla [2-5]. However, the active components have not been identified. Apple polyphenols have been registered among Japanese Standard Food Additives as antioxidants due to their strong antioxidant activity. Moreover, they have physiologic functions such as regulation of the metabolism of oxidized cholesterols in rats [6-8] and of cholesterols in humans [9]. They also display anticaries activities [10] and have been reported to be safe on long-term administration based on mutagenicity tests and a 90-day oral administration test [11]. Polyphenols have also been reported to inhibit histamine release from rat cells [12], suppress auricular swelling in allergic mice [13], and alleviate skin inflammation in atopic patients [14].

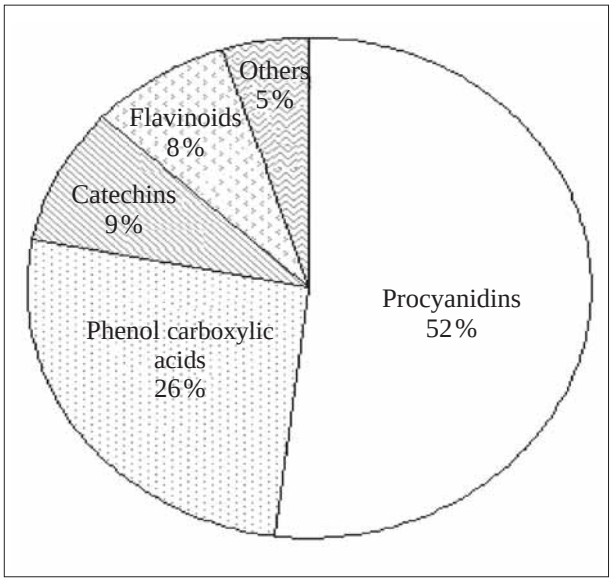

Figure 1. Composition of apple polyphenols.

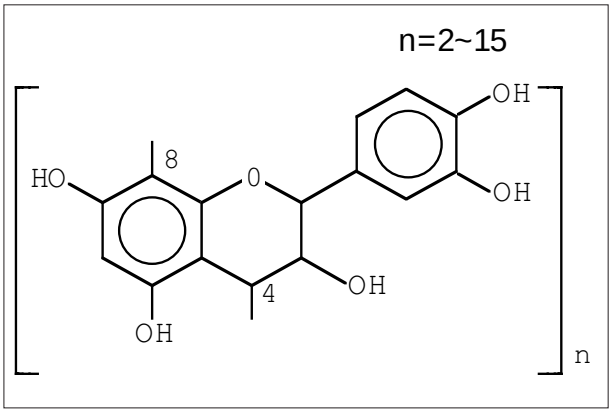

Figure 2. Chemical structure of procyanidins.

Apple polyphenols are extracted and purified from unripe apples and consist primarily of procyanidins (Figures 1 and 2), and a purified concentrated procyanidin fraction has been confirmed to have higher activity in tests using rat cells [12]. Stabilization of mast cells and basophils [12] and the control of immunotolerance [15] have been suggested as possible mechanisms underlying the action of polyphenols. These findings suggest that allergic symptoms may be alleviated by ingestion of apple polyphenols. However, as regular intake of an effective dose of apple polyphenols is difficult in an ordinary diet, they must be processed into forms that can be ingested readily, for example, by adding them to drinks. In this study, we prepared drinks containing apple polyphenols and evaluated their effects on clinical symptoms of persistent allergic rhinitis.

Materials and Methods

Subjects

The study involved 33 patients with persistent allergic rhinitis due to house dust mite allergy in whom moderate or severe allergic symptoms had been present for at least 3 years. Patients were recruited on the basis of a clinical history of allergic rhinitis and at least 2 of the following criteria: positive skin tests or demonstration of IgE to

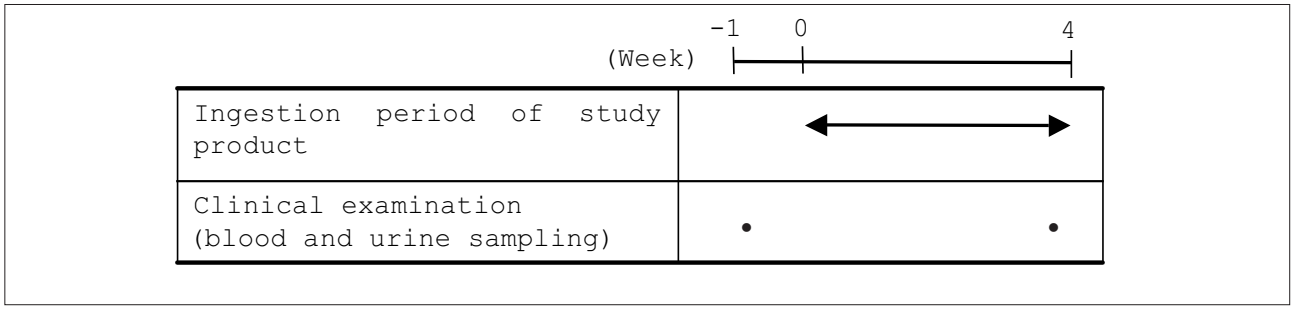

Figure 3. Test schedule.

house dust mites, eosinophils in nasal discharge, and positive reaction on nasal challenge. Those individuals who had undergone specific immunotherapy in the 4 weeks prior to recruitment were excluded from the study. The other exclusion criteria were the presence of other nasal complications, the use of drugs that might affect the efficacy evaluation (antihistamines, antiallergic drugs, corticosteroids, etc), multiple sensitization that might affect the study, and pregnancy or lactation in women. If the use of drugs was unavoidable during the study, second-generation antihistamines were used and the drug names, periods of use, and doses were recorded in the nasal allergy diaries.

All subjects were enrolled after giving informed consent to participate in the study according to the process approved by the Ethics Committee, Seikokai Clinic, Tokyo.

Administration of Apple Polyphenols

The study followed a randomized, double-blind, placebo-controlled, parallel arm design with control, low-dose, and high-dose groups to examine time of onset and dose-dependence of the effect of apple polyphenols. Applephenon (Asahi Food and Healthcare Ltd, Tokyo, Japan) was used to prepare drinks with a polyphenol content of 50 mg per bottle for the low-dose group and 200 mg per bottle for the high-dose group. A sham drink that did not contain apple polyphenols was prepared for the control group. The 3 drinks were made indistinguishable in taste or appearance, bottled, and sealed with caps on which only code numbers were printed. The study was performed according to the schedule shown in Figure 3, and the test drinks were taken by the subjects at a dose of 1 bottle per day for 4 weeks. Table 1 shows characteristics of the subjects in terms of sex, age, severity of symptoms, presence or absence of multiple sensitization, and presence or absence of complications. Since the multiple sensitizations shown by 7 subjects in each group were mild, the subjects were enrolled in the study. No significant difference was observed between the groups. The nutritional contents of the test drinks per 100 g were as follows: energy, 70 kcal; protein, 0 g; lipid, 0 g; and carbohydrates, 17 g.

Table 1. Subject Characteristics*

	Group			
	Placebo	Low	High	*P*
Number of subjects	11	11	11	
Sex, male/female	2/9	6/5	1/10	<.05
Age, years	34.5±3.73	32.5±3.41	38.5±2.77	
Eosinophils in nasal discharge, positive	11	11	11	
Ratio of positive subjects on nasal challenge	3/3	3/3	4/4	
Severity of rhinitis Mild Moderate Severe	 0 11 0	 0 8 3	 0 11 0	<.05
Multiple sensitization	7	7	7	
Other allergic disorders	0	1	4	

*Data are shown as number or mean ± SEM.

Assessment of Nasal Scores

Nasal symptoms (sneezing attacks, nasal discharge, and nasal obstruction) and signs (swelling of the nasal turbinate, color of inferior turbinate, watery secretion, and character of nasal discharge) were scored independently before and after treatment using a 4-point scale (for most variables, 0 indicates no symptom or sign; 1, mild; 2, moderate; 3, severe; but in the case of the color of the inferior turbinate, 0 corresponds to normal, 1 to slight redness, 2 to red, and 3 to pale) based on the method described by Okuda et al [16]. A medications score was used based on the guidelines of the Japanese Society of Allergology [1]: use of a second-generation antihistamine or a histamine-release suppressor was scored as 1, use of a local corticosteroid as 2, nasal application of a vasoconstrictor or an anticholinergic drug as 1, and use of an oral corticosteroid as 4.

Statistical Analysis

The Statview computer package (Abacus Concepts, NJ, USA) was used for all analyses. Data are expressed as mean ± SEM. Changes in the values of each parameter from the beginning (week 0) to the end (week 4) of administration were analyzed by Wilcoxon signed rank test or paired *t* test. Comparisons between groups were performed by analysis of variance (Dunnett's test or Kruskall-Wallis test) or Wilcoxon test. Statistical significance was established at $P < .05$ or $P < .01$.

Results

Intake of Test Drinks

The control group, low-dose group, and high-dose group each comprised 11 subjects. Table 2 shows the frequency of intake of the test drinks in the 33 subjects. One subject in the high-dose group developed a rash on the forehead 2 days after beginning intake of the test drink, and the symptom deteriorated with continued intake. However, as the compliance of this subject was 78.5%, the subject was included in the analyses. There was no problem in the compliance of the other subjects with the test regimen that might affect the analyses. Comparison of the values in the high-dose and low-dose groups with those in the control group using Dunnett's test revealed no significant differences (Table 2).

Use of Other Medications

Other medications were used by 8 subjects in the control group, 6 subjects in the low-dose group, and 5 subjects in the high-dose group. The periods over which those medications were used were short in all subjects. The use of medications was quantified using the medication score and compared between the groups. Comparison of the values in the high-dose and low-dose groups with those in the control group by Kruskal-Wallis test revealed no significant differences (Table 2).

Changes in Clinical Symptoms

The occurrence of sneezing attacks, nasal discharge, and nasal obstruction was scored according to Okuda et al [16] on the basis of the subject's entries in the allergy diaries, and the scores before and 4 weeks after the beginning of the intake were compared by Wilcoxon test (Table 3). Significant improvements were observed in sneezing attacks ($P < .05$) and nasal discharge ($P < .01$) in the high-dose group and in sneezing attacks ($P < .05$) in the low-dose group. However, there were no significant differences between the high-dose or low-dose group and the control group. Among the symptoms, improvements in sneezing attacks and nasal discharge were greater in the apple polyphenol-treated groups than in the control group. When intranasal findings were assessed, a significant improvement ($P < .05$) was observed in swelling of the nasal turbinate in the low-dose group. Consumption of apple polyphenols led to greater improvements in sneezing attack, nasal discharge, and swelling of inferior turbinate compared with placebo.

Table 2. Compliance and Medication Score*

	Group			
	Placebo	Low	High	*P*
Number of subjects	11	11	11	
Compliance, %	99.7 ± 0.32	97.1 ± 1.58	96.8 ± 2.23	NS
Medication score	2.00 ± 1.62	0.55 ± 0.37	0.91 ± 0.48	NS

* Data are shown as number or mean ± SEM.
NS indicates not significant.

Table 3. Effects of 4 Weeks Daily Intake of Apple Polyphenol Drinks *

Nasal Symptom or Sign	Group		Score				n	*P*†
			3	2	1	0		
Sneezing attack	Placebo	Baseline	1	2	7	1	11	
		4 Weeks	0	1	7	3	11	
	Low	Baseline	2	5	3	1	11	<.05
		4 Weeks	0	2	6	3	11	
	High	Baseline	0	6	5	0	11	<.05
		4 Weeks	0	1	7	3	11	
Nasal discharge	Placebo	Baseline	0	5	6	0	11	
		4 Weeks	0	0	9	2	11	
	Low	Baseline	2	5	3	1	11	
		4 Weeks	0	3	6	2	11	
	High	Baseline	0	8	3	0	11	<0.1
		4 Weeks	0	0	7	4	11	
Nasal obstruction	Placebo	Baseline	0	5	4	2	11	
		4 Weeks	0	3	3	5	11	
	Low	Baseline	1	5	4	1	11	
		4 Weeks	1	2	6	2	11	
	High	Baseline	1	1	6	3	11	
		4 Weeks	0	1	6	4	11	
Swelling of inferior turbinate	Placebo	Baseline	1	8	2	0	11	
		4 Weeks	2	6	2	1	11	
	Low	Baseline	2	7	2	0	11	<.05
		4 Weeks	0	4	7	0	11	
	High	Baseline	2	5	4	0	11	
		4 Weeks	1	6	4	0	11	
Color of inferiorturbinate	Placebo	Baseline	4	2	5	0	11	
		4 Weeks	4	1	5	1	11	
	Low	Baseline	5	0	6	0	11	
		4 Weeks	4	0	7	0	11	
	High	Baseline	4	2	5	0	11	
		4 Weeks	3	2	6	0	11	
Quantity of watery discharge	Placebo	Baseline	0	3	6	2	11	
		4 Weeks	0	0	7	4	11	
	Low	Baseline	0	5	5	1	11	
		4 Weeks	0	1	7	3	11	
	High	Baseline	0	4	5	2	11	
		4 Weeks	0	2	5	4	11	
Character of nasal discharge	Placebo	Baseline	7	0	2	2	11	
		4 Weeks	6	0	1	4	11	
	Low	Baseline	9	0	1	1	11	
		4 Weeks	6	0	2	3	11	
	High	Baseline	7	0	2	2	11	
		4 Weeks	6	0	1	4	11	

*Data are shown as number of subjects. Nasal symptoms and signs scored according to the method described by Okuda et al [16].

† Comparisons between baseline and 4 weeks by Wilcoxon test.

Overall Safety

Hematologic and serologic tests revealed significant changes in hematocrit (increased by 0.9%) in the low-dose group and platelet count (increased by 1.8×10^4 cells/μL) in the high-dose group. Biochemical tests showed that uric acid concentration was significantly increased to 0.42 mg/dL in the high-dose group, while urinalysis showed that the pH was increased by 0.64 in the low-dose group. All these changes were slight when considered within the standard ranges and none posed clinical problems.

In terms of adverse effects observed during the test-drink intake period, 1 subject developed a rash on the forehead, as mentioned. Other physical disorders included soft stool (1 subject), diarrhea (2), constipation (2), headache (1), cold symptoms (5), lower back pain (1), and mild dizziness (1). However, none of the conditions were related to the intake of the test drink.

Discussion

Persistent allergic rhinitis is a common disease in developed countries and its prevalence, which has been increasing in recent years, is reported to be high (18.7%) in Japan [1]. The disease is primarily caused by house dust mites and is considered to occur via a type I allergic reaction triggered by an interaction between the allergen and specific IgE antibodies on mast cells. The disease is mainly treated with antihistamines and local corticosteroids, and long-term treatment is usually required. During treatment with antihistamines, adverse effects such as drowsiness due to suppression of the central nervous system and thirst due to anticholinergic effects must not be overlooked. In particular, drowsiness reduces quality of life and work efficiency, and may therefore lead to associated economic losses. The use of corticosteroids, which have diverse pharmacological effects, must take into consideration the adverse reactions that may appear with prolonged use [17]. In these circumstances, screening familiar food items for antiallergic activities, developing them as functional foods, and using them to alleviate allergic symptoms may be a therapeutic strategy worthy of consideration.

Polyphenols derived from unripe apples have been reported to have antiallergic activities. In human atopic dermatitis, itching, sleep disturbance, and peripheral eosinophil count have been reported to be significantly reduced in a group receiving oral apple polyphenols at 10 mg/kg for 8 weeks compared with a placebo-treated control group [14]. In animal experiments, swelling of the auricle was reported to be prevented by oral administration of apple polyphenols in a murine model of type I allergy in which the auricle is thickened by the administration of anti-TNP IgE antibody-producing cells followed by the application of picryl chloride, a hapten antigen, to the auricle [13]. In that study, when the interval between the administration and antigenic stimulation was changed in the same model animals, the percentage inhibition of auricular swelling was highest when the interval was 2 to 4 hours but was very low when the interval was 24 hours. These findings are consistent with a report showing that the blood concentration of procyanidin in rats increased 1 to 4 hours after oral administration of the procyanidin fraction of apple polyphenols but decreased after 24 hours [18].

Insight into the mechanism through which apple polyphenols inhibit allergic reactions is provided by the observation that apple polyphenols and the procyanidin fraction prevent degranulation and histamine release by inhibiting the increase in calcium concentration in antigen-stimulated rat basophils (RBL-2H3 cells) [12]. Apple polyphenols are suggested to prevent degranulation by promoting the stability of granulocytes and inhibiting histamine release. In addition, apple polyphenols and their procyanidin fraction may also suppress inflammation, since they have been reported to have a dose-dependent inhibitory effect on the activity of hyaluronidase, an enzyme which is associated with inflammation and is released by degranulation [12].

Apple polyphenols are made up of 50% to 60% procyanidins, which are oligomers and polymers of catechins, along with low-molecular-weight polyphenols such as chlorogenic acid and catechins. However, macromolecular procyanidins are not absorbed and are considered to be mostly excreted [19]. The percentage of γδ T cells in intestinal epithelial cells—an index of food allergy—was shown to decrease in a mouse model generated by continuous oral ingestion of ovalbumin, but this decrease was prevented by administration of the procyanidin fraction derived from apples [15]. In contrast, the decrease was not inhibited when catechins alone were administered. These results suggest that the apple-derived procyanidin fraction may induce oral immunotolerance.

All of those findings strongly suggest that apple polyphenols are effective for the treatment of persistent allergic rhinitis, which is a typical allergic disease. This study was therefore performed to examine the effectiveness of apple polyphenols for the treatment of persistent allergic rhinitis. Apple polyphenols were prepared as drinks to facilitate their regular daily intake in an effective dose. As a result, a compliance of 79% or higher could be achieved in each group. In terms of clinical symptoms, sneezing attacks and nasal discharge showed significant improvements ($P < .05$ and $P < .01$, respectively) after the treatment compared with the levels before the treatment in the high-dose group, and sneezing attacks also showed a significant improvement in the low-dose group ($P < .05$). Moreover, improvements in sneezing attacks and nasal discharge were observed more frequently in the polyphenol-treated groups than in the control group. Assessment of intranasal findings showed that swelling of the nasal turbinate was significantly alleviated in the low-dose group ($P < .05$), and improvements in swelling of the nasal turbinate were observed in many subjects of the polyphenol-treated groups. The safety of administering apple polyphenols was confirmed by various

tests prior to the study [11], and adverse effects or abnormal results on hematologic tests, serologic tests, or urinalysis were few and mild in this study. Therefore, the results of this pilot study suggest that apple polyphenols could be an excellent food component that contributes to the alleviation of clinical symptoms of persistent allergic rhinitis and the burdens of drug therapy. We will perform a clinical trial in a larger group to confirm the efficacy of apple polyphenols for the treatment of rhinitis. In this study, we prepared apple polyphenols as drinks and achieved a high compliance. Although a drink is a suitable dosage form to ensure continuous intake of an effective dose of apple polyphenols, other dosage forms that further improve the ease of intake may be developed by including them in other processed foods.

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