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ORIGINAL ARTICLE

An Evaluation of the Clinical Efficacy of Tomato Extract for Perennial Allergic Rhinitis

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ABSTRACT

Background: Recently, some common foods in daily life have been found to have anti-allergic effects. We have reported that tomato extract (TE) could possibly inhibit histamine release and mouse ear-swelling responses. Moreover, it is reported that TE could relieve the symptoms for Japanese cedar pollinosis.

Methods: To evaluate the anti-allergic effect of TE, we performed a randomized, double-blind, placebo-controlled study in 33 patients with perennial allergic rhinitis (PAR) using oral administration of TE (360 mg per day) or placebo for 8 weeks.

Results: We found that the sneezing score significantly decreased in the TE group at the end of the trial compared to the beginning ($P < 0.05$). There were decreasing tendencies of rhinorrhea and nasal obstruction in the TE group. The patients' quality of life was significantly improved in the TE group after 8 weeks of treatment ($P < 0.05$), but not in placebo group. A significant improvement in total symptom scores, combining sneezing, rhinorrhea and nasal obstruction, was observed after oral administration of TE for 8 weeks ($P < 0.01$). The safety of TE treatment was confirmed by laboratory tests and inspection of general conditions.

Conclusions: TE can be expected to safely improve the nasal symptoms of PAR.

KEY WORDS

clinical efficacy, eosinophils, histamine release, perennial allergic rhinitis, tomato extract

INTRODUCTION

Allergic diseases, such as allergic rhinitis, bronchial asthma and atopic dermatitis, have increased dramatically in the past decades. PAR is one of the representative allergic diseases. Its prevalence reached 18.7% in the Japanese population, which is higher than that of cedar pollinosis (16.2%).[1] The therapeutic strategy is usually focused on removal and evasion of antigens by environmental maintenance and pharmacotherapy. Inhibitors of chemical mediators, antihistamines, and topical steroids are used widely, but their potential side-effects are of concern with long-term application.

Recently, some common foods in daily life have been found to have anti-allergic effects. There is a growing interest especially in regard to the anti-allergic effects of plant polyphenols, some of which are also contained in tomatos. We have recently reported that tomato extract (TE), extracted from tomato skin with 60% aqueous ethyl alcohol, could inhibit histamine release from rat peritoneal mast cells stimulated by a 40/80 compound and mouse ear-swelling responses.[2] In addition, we have confirmed the anti-allergic activity of naringenin chalcone (Fig. 1), the main active component of TE, in our previous experimental study. Moreover, it is reported that TE can relieve the symptoms of Japanese cedar pollinosis.[3] These findings collectively indicate that TE may have therapeutic efficacy in allergic rhinitis.

In this study, we confirmed the anti-allergic activity of TE in a randomized, double-blind, placebo-controlled clinical trial in patients with PAR.

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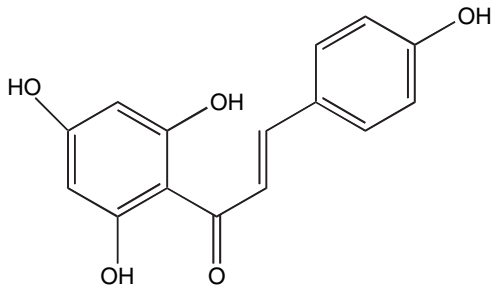

Fig. 1 Chemical Structure of Naringenin Chalcone, the Main Active Compound in Tomato Extract.

METHODS

SAMPLE PREPARATION OF TOMATO EXTRACT (TE)

Tomato (*Lycopersicon esculentum* Miller) extracts containing polyphenols were prepared from a mixture of its seeds and skin with 60% (v/v) ethyl alcohol at 60℃ for 2 hours with subsequent lyophilization. This extract contains 0.2% of naringenin chalcone.

SUBJECTS

Thirty-three adult PAR patients (14 men, 19 women, range 18–56 years of age) were enrolled in the clinical study. The inclusion criteria for PAR were that the positive results be confirmed in at least two of the following three tests according to the Guidelines for the Management of Allergic Rhinitis in Japan (2002)[1]: (a) the allergen skin test or serum allergen-specific IgE against house dust or mites; (b) the nasal provocation test; and (c) eosinophil count in nasal discharge. Each subject had a history of PAR for more than three years. Prior to participation in the present study, written informed consent was obtained from all patients. In addition, this study followed the tenets of the declaration of Helsinki.

The exclusion criteria included the following: (a) a combination of other nasal diseases; (b) sensitization to other allergens which may influence the study; (c) complicated by systematic diseases; (d) attending another clinical trial simultaneously; (e) pregnancy or lactation; (f) poor condition when taking tomatos; and (g) inappropriate cases for the trial defined by physicians.

Detailed characteristics of recruited patients are described in Table 1. Among a total of 33 patients with PAR, 17 cases (51.5%) were diagnosed as mild, 13 cases (39.4%) were moderate, and 3 cases (9.1%) were severe according to the scores of three main nasal symptoms (sneezing, rhinorrhoea and nasal obstruction), on the basis of the guidelines.

STUDY DESIGN

A randomized, double-blind, placebo-controlled trial was performed at three institutions (Japanese Red Cross Society Wakayama Medical Centre, Dake ENT Clinic and Okuno ENT Clinic) in Wakayama and Osaka, Japan between October 2004 and January 2005, in order to avoid the influence of the Japanese cedar pollen season. This study was conducted at the TTC Co., Ltd. and was approved by the ethics committee of the Kaiyuu Clinic.

Table 1 Characteristics of patients enrolled in the study

	Tomato extract	Placebo
n	17	16
Age (mean)	34.7 ± 2.6	35.4 ± 3.1
Sex		
male	7	7
female	10	9
Severity		
Mild	8	9
Moderate	7	6
Severe	2	1
Symptom score		
Sneezing	1.18 ± 0.10	0.94 ± 0.17
Rhinorrhea	1.41 ± 0.19	1.25 ± 0.17
Nasal obstruction	1.29 ± 0.14	0.94 ± 0.19
QOL score	0.82 ± 0.13 *	0.44 ± 0.13

* $p < 0.05$ compared between two groups

METHODS

Subjects were randomly divided into two groups. One group of patients received an oral administration of tablets containing 360 mg of TE per day (TE group; $n = 17$) and another group received placebo (placebo group; $n = 16$). The placebo tablet contained dextrin in place of TE, with the same color and taste as the TE tablet. Each subject received two tablets *t.i.d.* per day for a course of 8 weeks. The clinical characteristics of patients in both groups are shown in Table 1. There were no significant differences among the patient characteristics.

The severity of nasal symptoms (sneezing, rhinorrhea and nasal obstruction) was scored using a patient diary, which was in accordance with the guidelines, written by patients themselves each day during the study. A questionnaire on quality of life (QOL) investigated issues in daily life, such as 'interference with work, study or housework', 'sleep disorder' and 'limitation on going out'. Responses were evaluated using five-grades based on the guidelines.

During the study period, each patient visited a doctor three times: at the beginning of the trial, week 4 during the trial, and at the end of the trial (week 8). The patient's diary was checked to score the degree of nasal symptoms, and the nasal signs (mucosal swelling, mucosal color, discharge volume and character) were evaluated on the basis of the guidelines.

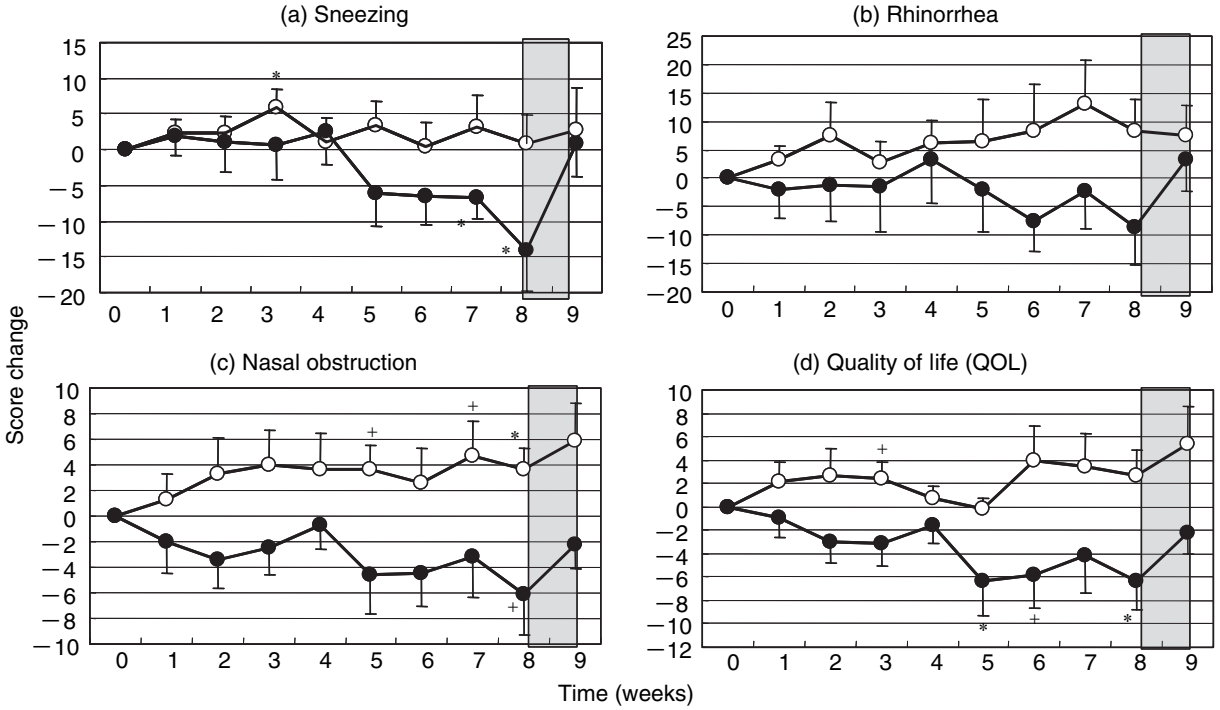

Fig. 2 Mean change rates from baseline of scores, evaluated using patient diaries in tomato extract (TE) (closed circle) and placebo (open circle) groups, (**a**) sneezing, (**b**) rhinorrhea, (**c**) nasal obstruction and (**d**) quality of life. The starting day of administration (baseline) is indicated on the graphs as 0 week. TE or placebo were administrated from 0 to 8 weeks, after the administration follow-up period was set up for one week (8 to 9 weeks). Each value is the mean +/− SE. + $P < 0.10$, * $P < 0.05$ compared with baseline in each group.

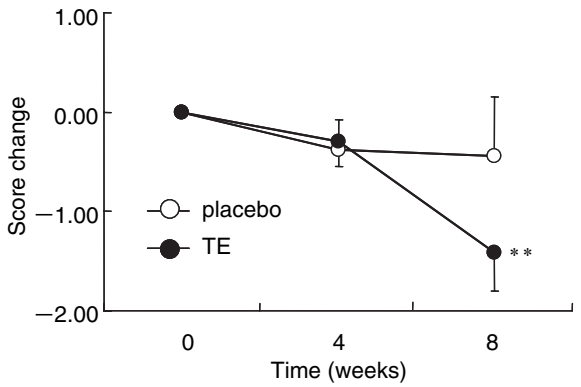

Fig. 3 Mean score change of total nasal symptom score, evaluated by a physician, from baseline in tomato extract (TE) (closed circle) and placebo (open circle) groups. The starting day of administration (baseline), 4 weeks after the start of administration and 8 weeks after administration (end-point) are indicated on the graph as 0, 4 and 8 weeks, respectively. Each value is the mean +/− SE. ** $P < 0.01$ compared with baseline in each group.

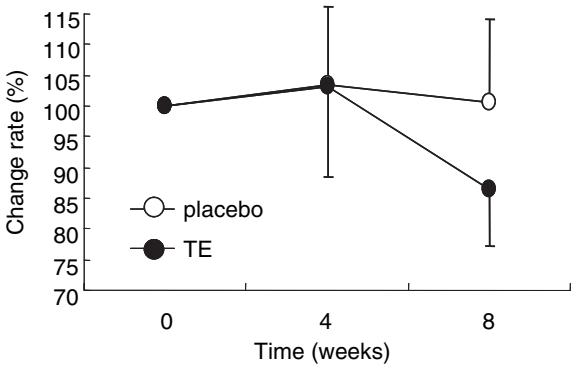

Fig. 4 Mean change rate of ECP in serum from baseline in tomato extract (TE) (closed circle) and placebo (open circle) groups. The starting day of administration (baseline), 4 weeks after start of administration and 8 weeks after administration (end-point), are indicated on the graph as 0, 4 and 8 weeks, respectively. Each value is the mean +/− SE.

The medication was recorded by drug character and using points according to the guideline as follows: second-generation antihistamines, mast cell stabilizers, vasoconstrictor or anti-cholinergic nasal drops, and mast cell stabilizer eye drops, 1 point, respectively; topical ocular and nasal steroids, 2 points, respectively. Any concurrent use of drugs that could influence the evaluation of efficacy was prohibited.

Peripheral blood and urine route examinations were performed three times when the patient visited the physician. Serum allergen-specific IgE (house

Table 2 Serum IgE titer

		0 weeks	4 weeks	8 weeks
Total IgE (IU/ml)	Tomato extract	1041.4 ± 691.2	876.7 ± 533.5	902.5 ± 551.9
	Placebo	378.4 ± 218.0	382.5 ± 224.1	305.5 ± 156.8
Mites Class	Tomato extract	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.4
	Placebo	2.8 ± 0.3	2.9 ± 0.3	2.8 ± 0.3
House dust Class	Tomato extract	3.5 ± 0.3	3.5 ± 0.4	3.6 ± 0.4
	Placebo	2.6 ± 0.3	2.7 ± 0.3	2.7 ± 0.3
Mugwort Class	Tomato extract	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.2
	Placebo	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.3
Cedar pollen Class	Tomato extract	2.2 ± 0.3	2.2 ± 0.3	2.4 ± 0.4
	Placebo	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4

Table 3 Eosinophil count in nasal discharge

		3 +	2 +	1 +	±	−
Tomato extract	0 weeks	0	7	8	0	2
	4 weeks	0	4	11	0	2
	8 weeks	1	7	7	0	2
Placebo	0 weeks	0	6	8	0	2
	4 weeks	0	8	6	0	2
	8 weeks	0	2	13	0	1

dust, *Dermatophagoides pteronyssinus*, Japanese cedar pollen and *Artemisia* pollen) and eosinophil cationic protein (ECP), and eosinophil count in nasal discharge were also measured.

STATISTICAL ANALYSIS

Data were expressed as the mean ± SE. Clinical study data was analyzed as follows; the ANOVA test was used to evaluate differences between the group's mean scores, and a non-parametric combination test was used to evaluate differences between groups. Statistically significant differences were considered when $P < 0.05$. The statistical analysis was performed using SPSS software.

RESULTS

NASAL SYMPTOMS AND SIGNS

The rate of change in patients' score of nasal symptoms and QOL during the study are shown in Figure 2. We found that the sneezing score of the TE group significantly decreased at the end of the trial (week 8) compared to the beginning of the trial ($P < 0.05$, Fig. 2a). However, the score returned to the baseline within one week after the trial (week 9, Fig. 2a). Interestingly, the patients' QOL was significantly improved in the TE group at week 5 and 8 ($P < 0.05$, Fig. 2d). Moreover there were decreasing tendencies of rhinorrhea and nasal obstruction in the TE group (Figs. 2b and c). In the placebo group, no significant change of nasal symptoms was found during the trial (Fig. 2).

A significant improvement of total nasal symptom scores, combined sneezing, rhinorrhea and nasal obstruction, was observed after oral administration of TE for 8 weeks ($P < 0.01$, Fig. 3).

Overall, the scores of nasal signs based on the physician examination showed no significant changes during the trial either in the TE group or the placebo group. After 8 weeks of treatment, the amount of nasal discharge showed a marginal decrease in the placebo group compared to the TE group.

ALLERGIC TESTS

As shown in Figure 4, there was no significant difference in the change of ECP concentration in the serum between the TE and placebo groups. However, a decreasing tendency of ECP concentration was observed at the end of the trial in the TE group compared with the beginning ($P = 0.147$, Fig. 4). Serum allergen-specific IgE levels and eosinophil count in nasal discharge showed no significant changes during the study period (Tables 2, 3).

SAFETY

No adverse effects were observed throughout the study. Cold and diarrhea were reported by some patients but the degree was slight and disappeared during the study, which may have had no relationship with the trial. There was no significant change in the results of the urinalysis, blood or biochemistry in-

spection during the study period in the two groups.

DISCUSSION

In Japan, cedar pollinosis remains a public health problem. However, the prevalence of PAR, mainly caused by house dust and mites, is higher than that of Japanese cedar pollinosis.[1] PAR attacks in all seasons and also dominates in younger children, which makes it harder to be cured. Now, many kinds of medicine have been developed and applied clinically. Patients typically need to use these drugs for an entire year with consideration of their side-effects. Additionally, there are only a few kinds of medicine that are appropriate for younger children.

With this background, it is interesting to find food with anti-allergic effects, which could be expected to reduce the dependence on drugs to some extent. Recently, many experimental and clinical studies have been carried out for this purpose in Japan, but reports on anti-allergic foods were mainly against cedar pollinosis, such as lactic acid bacterium,[4-9] and plant extract such as sweet tea,[10,11] perilla leaf and seed[12,13] and persimmon leaf,[14] suggesting an anti-allergic activity of plants with polyphenols.

We have searched for anti-allergic components in various kinds of fruits and vegetables, and found that TE has activity in inhibiting histamine release from mast cells stimulated by a 40/80 compound.[2] The main active component of TE is naringenin chalcone, which is one kind of polyphenol and exists in the skin of red tomatos, but not in pink tomatos.[15]

TE could be used as a new preventive and therapeutic modality if the materials from such foods can be shown to prevent allergic diseases and relieve allergic symptoms. Ryu *et al*. have reported that 360 mg of TE per day significantly improved 8 of 11 subjective allergic symptoms, and 1 of 5 contents of QOL in 24 volunteer patients with Japanese cedar pollinosis during the peak of pollen scattering.[3] This fact indicates that TE may improve allergic symptoms of pollinosis. This suggested that TE might improve allergic symptoms not only in cedar pollinosis but also in PAR.

In the present study, we evaluated the clinical effects and safety of TE for PAR treatment. Patients in the TE group did not show serious adverse events throughout the study period, suggesting that TE is a safe food. Considering TE is at first a type of food, we performed this study on mild-to-moderate, but not severe patients. In addition, this study is designed as a randomized, double-blind, placebo-controlled trial, and a relatively long test period of 8 weeks was set. Although there was no significant change in nasal signs by physician examination, patient QOL and nasal symptoms, especially sneezing, improved with the intake of TE. This result suggested that TE is useful in controlling PAR; however, it likely does not act so quickly in the case of cedar pollinosis.[3] It is known that type I allergy has two phases of allergic response, *i.e.* an early phase and late phase. The early phase response is caused by chemical mediators, such as histamine, thromboxanes and leukotrienes released from mast cells after stimulation of antigen, and is the main mechanism in the onset of cedar pollinosis. The late phase response is caused by chemical mediators, such as LTs and ECP, and causes PAR generally.[16] The anti-allergic function of TE is attributed more to inhibition of histamine release from mast cells than an anti-histamine effect. Therefore, TE acts more quickly in the case of cedar pollinosis than in PAR.

This clinical study showed a decreasing tendency of ECP concentration. ECP is one of the chemical mediators released from eosinophils and its quantity is controlled by the activity and quantity of eosinophils.[17,18] TE inhibited release of some chemical mediators in the animal inflammation model.[2] TE might inhibit release of chemical mediators, such as ECP, by decreasing eosinophils and, as a result, might inhibit allergic reactions. However, the mechanism remains unknown. The detailed pharmacological mechanisms and clinical outcomes of TE need to be investigated further.

In conclusion, the oral administration of TE can be expected to safely improve the nasal symptoms of PAR. The TE dosage and administrative period were fixed in the present trial. Further studies are needed to discuss the most appropriate dosage and intake period in a large sample of patients with allergic rhinitis.

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