

The Efficacy of Early Treatment of Seasonal Allergic Rhinitis with Benifuuki Green Tea Containing O-methylated Catechin before Pollen Exposure: An Open Randomized Study

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ABSTRACT

Background: We previously reported that 'benifuuki' green tea containing O-methylated catechin significantly relieved the symptoms of perennial or seasonal rhinitis compared with a placebo green tea that did not contain O-methylated catechin in randomized double-blind clinical trials. In this study we assessed the effects of 'benifuuki' green tea on clinical symptoms of seasonal allergic rhinitis.

Methods: An open-label, single-dose, randomized, parallel-group study was performed on 38 subjects with Japanese cedar pollinosis. The subjects were randomly assigned to long-term (December 27, 2006 – April 8, 2007, 1.5 months before pollen exposure) or short-term (February 15, 2007: after cedar pollen dispersal – April 8, 2007) drinking of a 'benifuuki' tea drink containing 34 mg O-methylated catechin per day. Each subject recorded their daily symptom scores in a diary. The primary efficacy variable was the mean weekly nasal symptom medication score during the study period.

Results: The nasal symptom medication score in the long-term intake group was significantly lower than that of the short-term intake group at the peak of pollen dispersal. The symptom scores for throat pain, nose-blowing, tears, and hindrance to activities of daily living were significantly better in the long-term group than the short-term group. In particular, the differences in the symptom scores for throat pain and nose-blowing between the 2 groups were marked.

Conclusions: We conclude that drinking 'benifuuki' tea for 1.5 months prior to the cedar pollen season is effective in reducing symptom scores for Japanese cedar pollinosis.

KEY WORDS

'benifuuki' green tea, epigallocatechin-3-O- (3-O-methyl)-gallate (EGCG3"Me), Japanese cedar pollinosis, long-term pre-seasonal, O-methylated catechin

INTRODUCTION

Seasonal allergic rhinitis (SAR) is a very common disease in developed countries, and its occurrence has been increasing in recent years. The prevalence of

Japanese cedar pollinosis, the most common SAR in Japan, is estimated to be approximately 16.2% of the population.¹ Since medical costs for treating the disease are large and possible adverse effects of available medication are not negligible, there is a greater

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demand for the development of physiologically-functional foods for allergy prevention.

Tea (*Camellia sinensis* L.) is consumed globally and in large quantities in Japan and China, where it has been used not only as a daily beverage but also for medicinal purposes for thousands of years. Tea has been found to exhibit various bioregulatory activities,^{2,3} such as anti-carcinogenic, anti-metastatic, anti-oxidative, anti-hypertensive, anti-hypercholesterolemic, anti-dental caries, and anti-bacterial activities and to contribute to intestinal flora amelioration. Catechins, a group of polyphenolic compounds, have been shown to be largely responsible for these effects. Catechins play a significant role in anti-allergic responses. We have reported that *O*-methylated EGCGs (epigallocatechin-3-*O*-[3-*O*-methyl] gallate [EGCG3"Me; Fig. 1], epigallocatechin-3-*O*-[4-*O*-methyl] gallate [EGCG4"Me],⁴⁻⁷ and strictinin⁸ have anti-allergic functions and that the Japanese tea cultivar 'benifuuki' is rich in EGCG3"Me, which is not present in black tea.^{9,10} Oral administration of these methylated catechins, significantly and dose-dependently (5–50 mg/kg), inhibited type I allergic (anaphylactic) reactions in mice sensitized with ovalbumin and Freund's incomplete adjuvant.⁴ These catechins also strongly inhibit mast cell activation through the prevention of tyrosine phosphorylation (Lyn, Syk, and Btk) of cellular proteins, histamine and leukotriene release, and interleukin-2 secretion after Fc Epsilon RI cross-linking.⁷ Furthermore, we reported the *in vitro* and *in vivo* effects of 'benifuuki' green tea containing *O*-methylated catechin and a combination of food components that work synergistically with 'benifuuki' such as in inflammatory cytokine production from mast cells after antigen stimulation, symptom relief, and safety of subjects with Japanese cedar pollinosis (in a double-blinded clinical trial). We also reported on the blood levels of unconjugated EGCG and EGCG3"Me after giving 'benifuuki' green tea to humans.¹¹ In a previous paper, a double-blinded clinical study on subjects with Japanese cedar pollinosis was carried out to evaluate the effects and safety of 'benifuuki' green tea, containing EGCG3"Me, and a combination of 'benifuuki' green tea and ginger extract, compared with 'yabukita' green tea as a placebo. The 'benifuuki' and 'yabukita' green tea contained 44.7 mg and 0 mg of EGCG3"Me, 176.1 mg and 202.8 mg of EGCG, 71.4 mg and 84.6 mg of caffeine, and 432 mg and 425 mg of total catechin per 3 g, respectively. As the cedar pollen increased, the symptoms of pollinosis became exacerbated in the placebo group compared with the 'benifuuki' group. During the most severe cedar pollen period, 11 weeks after starting the treatment, the symptoms such as nose-blowing and itchy eyes, showed significant improvement in the 'benifuuki' group compared with the control group ($P < 0.05$). Among the groups, there were no clinically-relevant changes in the hematological examination,

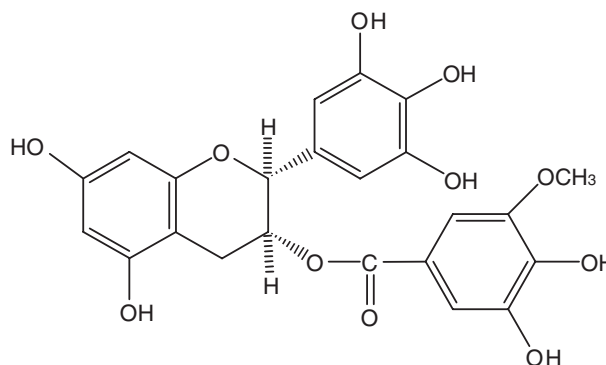


Fig. 1 The chemical structure of epigallocatechin-3-*O*-(3-*O*-methyl) gallate (an *O*-methylated catechin).

general biochemical examination, total IgG antibody titer, serum iron content, or interview results throughout the intake period. We also concluded that drinking 'benifuuki' green tea for over 1.5 months was useful in improving some Japanese cedar pollinosis symptoms while causing no effects in normal immune responses in subjects with seasonal rhinitis. However, it was not clear regarding when to initiate the drinking in order to optimize the beneficial effects of the tea. Therefore, in this study, we examined the efficacy of 'benifuuki' green tea in Japanese cedar pollinosis during the most prevalent season for allergic rhinitis in Japan, focusing on the effects of the drinking period on symptom improvement. We found that early initiation of drinking before the pollen season is significantly more effective than later initiation at the time of pollen exposure.

METHODS

PREPARATION OF THE 'BENIFUUKI' GREEN TEA DRINK

'Benifuuki' tea was extracted at 90°C for 6 minutes in a 30-fold dilution with distilled water (W/V). During the extraction, each infusion was stirred for 10 seconds every minute. After filtration, L-ascorbic acid and sodium bicarbonate were added to the tea infusions, and the concentration of polyphenol (tannin¹²) in the infusion was standardized. Thereafter, the tea infusion was pasteurized at 138°C for 30 seconds and poured into 350-ml plastic bottles (PET). The catechin and caffeine contents of the test drink were measured by high performance liquid chromatography (HPLC), as shown in Table 1.

SUBJECTS

We recruited 38 individuals with Japanese cedar pollinosis, aged between 25–60 years. All subjects had a history of seasonal rhinitis for at least the last 2 Japanese cedar pollen seasons and a positive Japanese cedar pollen-specific IgE value. We excluded subjects who had specific immunotherapy against Japanese cedar pollen disease in the past 2 years, or active or

Table 1 The catechin and caffeine contents of the test drink

Component	mg/100 mL
O-methylated EGCG	6.72
EGCG	15.64
GCG	25.59
ECG	4.64
EGC	9.56
EC	4.05
Caffeine	21.84

Table 2 The characteristics of the participants enrolled in this study

	Long-term drinking	Short-term drinking
N	19	19
Age (mean)	41.0±9.8	40.9±10.5
Gender		
Male	13	12
Female	5	6
Nasal SS (starting point)	3.2±0.7	3.0±1.1

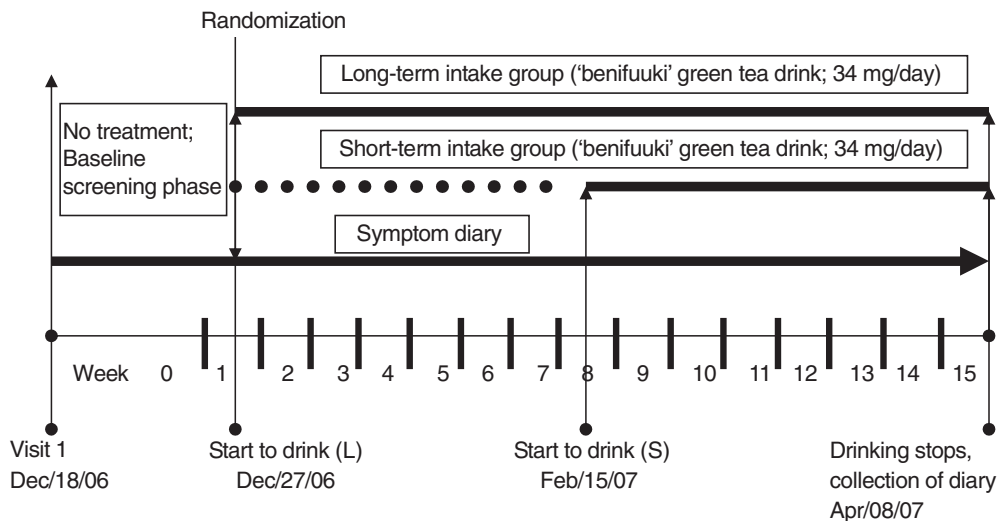


Fig. 2 Study schedule.

recent developments (within 3 months) of any other type of rhinitis, pregnant or nursing women, and patients with serious medical conditions. Table 2 shows the characteristics of the subjects in terms of age, gender, and the severity of nasal symptoms at the starting point.

STUDY DESIGN

An open-label, single-dose, randomized, parallel-group study was performed at National Institute of Vegetable and Tea Sciences (NIVTS) in Shizuoka and Mie, Japan, between December 2006 and April 2007. The study protocol was approved by the Institutional Review Board of the NIVTS for Human Research and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before participation.

During the study period, all subjects consumed 2 bottles of 'benifuuki' green tea (350-ml PET drink) each day. As shown in Figure 2, the test began on December 18, 2006, approximately 7 weeks before the cedar pollen season. The 38 subjects were randomly assigned to the long-term intake group or the short-term intake group. Tea intake began on December

27, 2006 for the long-term intake group and continued until April 8, 2007, and the short-term intake group began their intake from February 15, 2007 to April 8, 2007. All tests were completed on April 8, 2007.

SYMPTOM ASSESSMENT

During the test period, all subjects were required to record allergic symptoms in a diary, including the daily frequency of sneezing and nose-blowing, stuffy nose, itchy eyes, tears, throat pain, hindrance to activities of daily living (ADL), and the use of medication, in accordance with the method proposed by the Japanese Society of Allergology Allergic Rhinitis Committee. Symptoms were evaluated using a 5-point scale: 0, no symptoms; 1, mild; 2, moderate; 3, severe; 4, very severe symptoms present all day. The diaries were collected at the end of the study, and were used to first evaluate the Nasal Symptom Score (NSS) and Eye Symptom Score (ESS). The Nasal Medication Score was then calculated as the sum of the daily nasal rescue medication scores: use of a second-generation antihistamine or a histamine-release suppressor was scored as 1 point, use of a local corti-

costeroid as 2 points, nasal application of a vasoconstrictor or an anticholinergic drug as 1 point, and use of an oral corticosteroid mixed histamine-release suppressor as 3 points, based on the guidelines for allergic rhinitis management of the Japan Allergy Foundation.¹³ The rescue medications used by the subjects were Rizaben[®], Allelock[®], Allegra[®], Ebastel[®], Stac/nyscap[®], Rohto rhinitis soft capsule[®], Alguard[®], Hisporan[®], and Celestamine[®]. Finally, the Nasal Symptom Medication Score (Nasal SMS) was calculated as the sum of the daily NSS and the daily nasal medication score. The primary efficacy variable was the average weekly Nasal SMS during the examination period. Secondary efficacy variables included weekly symptoms.

POLLEN COUNTS

The Japanese cedar pollen counts in the Shizuoka and Mie area that were announced during the study by Kissei Pharmaceutical Co., Ltd (Nagano, Japan) were used. Data were expressed as the means per week.

The Japanese cedar pollen dispersion period started at the beginning of February and ended at the end of April. The long-term intake group began the first consumption of tea at least 1 month prior to the estimated starting date of the Japanese cedar pollen dispersion period, and the drinking period for the short-term intake group began at the start of the period.

CALCULATION OF AREA UNDER THE CURVE (AUC) VALUES

To evaluate the differences between symptom scores, the AUC values at the first peak of the pollen season (February 4 – March 25) were calculated. The average AUC values of each symptom score for each group were calculated daily to give the sum of the scores for each subject during the period.

STATISTICAL ANALYSIS

Data were expressed as the mean per week or AUC \pm SD. Differences in individual symptom scores, total symptom scores for each week, and each AUC value at the first peak of the pollen season were evaluated between the 2 groups using the Mann-Whitney U test, assuming a significance level of 5% or 1% using Statcel software (ver. 2).

RESULTS

SUBJECT CHARACTERISTICS

Of the 38 subjects, 1 subject in the long-term intake group and 1 subject in the short-term intake group dropped out from the study because of personal reasons. The remaining 36 subjects were enrolled in the study (18 in the long-term group and 18 in the short-term group). No significant differences were found between the long-term and short-term intake group

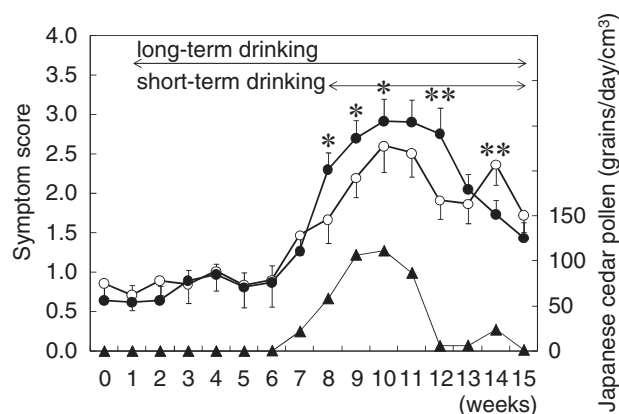


Fig. 3 The mean 1-week Nasal SMS of changes found in subjects given 'benifuuki' green tea in the long-term and short-term intake groups. Circles represent the long-term intake group; solid dots represent the short-term intake group. Solid triangles represent the scattering number of Japanese cedar pollen. The mean 1-week Nasal Symptom Medication Score of changes found in subjects given 'benifuuki' green tea. A comparison between the long-term intake group and the short-term intake group was performed using the Mann-Whitney U-test. * $P < 0.05$ vs. another group.

with respect to patient characteristics (Table 2). A high overall compliance rate (more than 95%) was obtained. There were no significant differences in the baseline symptom scores for sneezing, nose-blowing, stuffy nose, itchy eye, tears, or throat pain between the groups (Fig. 3, 4), but the baseline symptom scores for hindrance to ADL in the long-term intake group were significantly higher than those of the short-term intake group ($P < 0.01$).

EFFICACY

The effects of long-term 'benifuuki' green tea intake, beginning before pollen dispersion, on allergic symptoms were examined by comparing the time-course changes in 3 nasal or 4 non-nasal symptom scores in the long-term intake group with those of the short-term intake group, which began tea intake after pollen scattering began. (Fig. 3, 4). All symptom scores increased as the pollen count increased.

At weeks 8, 9, 10, and 12, the mean Nasal SMS, which was the primary efficacy variable, of the long-term intake group was significantly lower than that of the short-term intake group ($P < 0.01$ or 0.05) (Fig. 3).

The long-term intake group had a significantly lower incidence of nose-blowing at weeks 8, 9, 10, and 12 (Fig. 4b); itchy eyes at week 12 (Fig. 4d); tears at weeks 8, 10, 11, and 12 (Fig. 4e); throat pain at weeks 8, 9, 10, 11, and 12 (Fig. 4f); hindrance to ADL at weeks 8 and 11 (Fig. 4g); and NSS at weeks 8 and 12 (Fig. 4h) compared with the short-term intake

The Efficacy of Benifuuki Tea against Pollinosis

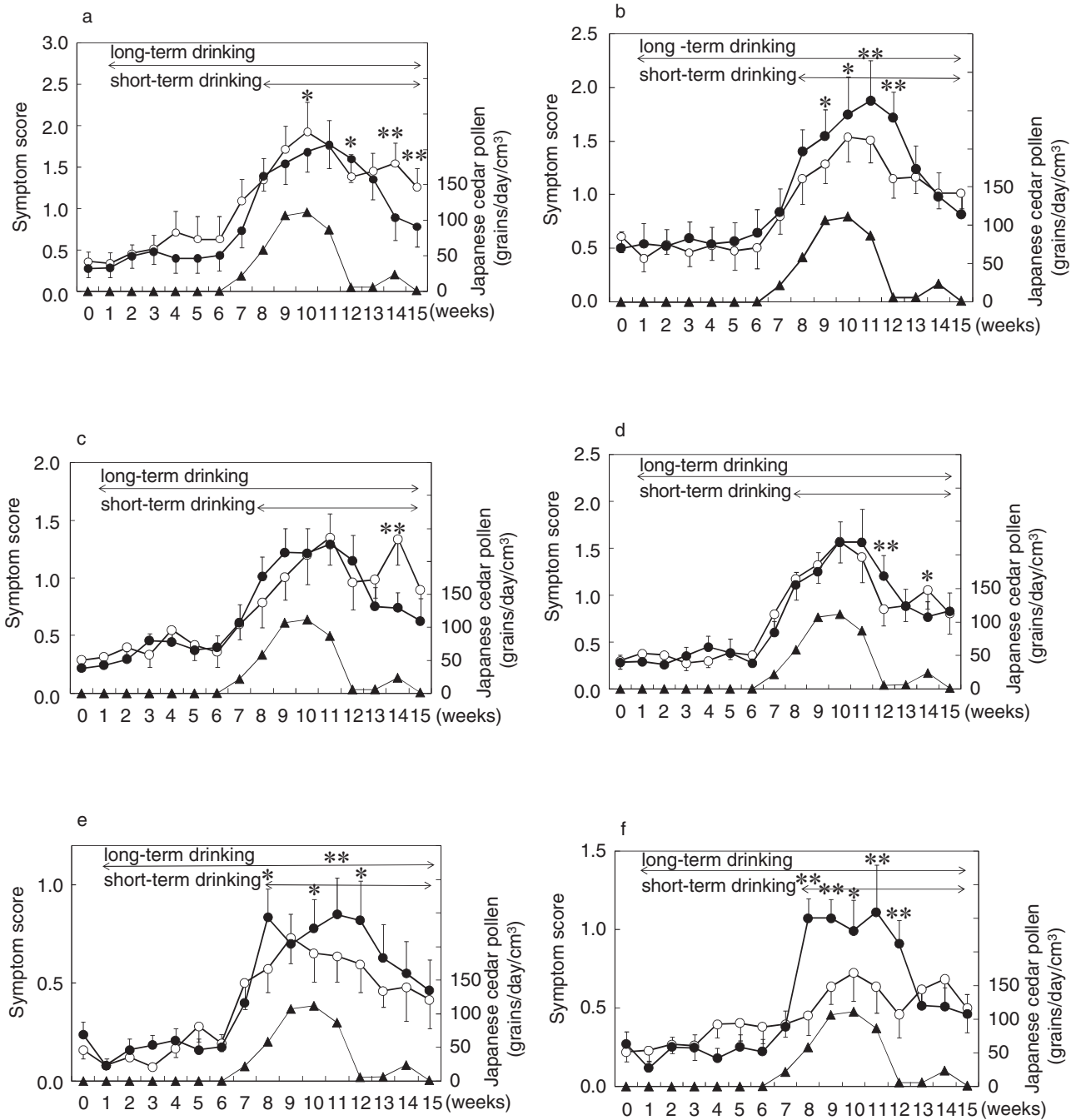


Fig. 4-1 Mean nasal and eye symptom scores, throat pain, and hindrance to activities of daily living of the changes in 1-week symptoms of subjects given 'benifuuki' green tea in the long-term and short-term intake groups. Circles represent the long-term intake group; solid dots represent the short-term intake group. Solid triangles represent the scattering number of Japanese cedar pollen. **a:** sneezing, **b:** nose-blowing, **c:** stuffy nose, **d:** itchy eye, **e:** tears, **f:** throat pain. A comparison between the long-term intake group and the short-term intake group was performed using the Mann-Whitney U test. ** $P < 0.01$, * $P < 0.05$ vs. another group.

group. The differences in throat pain and nose-blowing symptom scores between the 2 groups were marked.

As shown in Table 3, the AUC of Nasal SMS, nose-blowing, tears, throat pain, and hindrance to ADL in

the long-term intake group were significantly lower than that of the short-term intake group at the first peak of the pollen season ($P < 0.01$; Nasal SS, nose-blowing, tears, throat pain, $P < 0.05$; hindrance to ADL). On the contrary, sneezing in the long-term in-

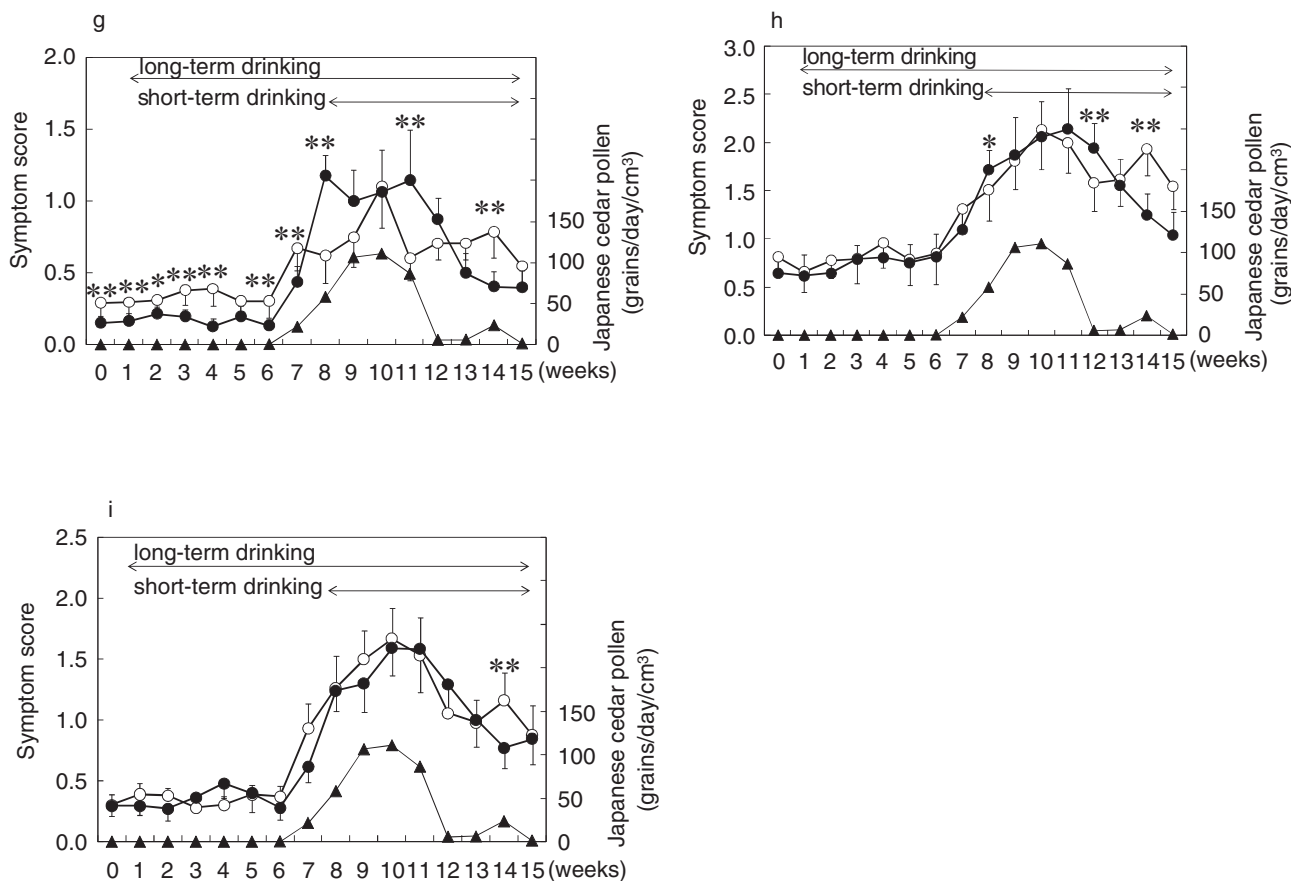


Fig. 4-2 g: hindrance to activities of daily living, h: nasal symptom score, i: eye symptom score.

Table 3 The area under the curve (AUC) of symptom scores during the first peak of the pollen season

Symptoms/AUC (Feb. 4–Mar. 25)	AUC in long-term intake	AUC in short-term intake	Z (Mann-Whitney U test)	P (Mann-Whitney U test)
Sneezing	75.2±28.2	71.1±29.9	2.128	0.033
Nose-blowing	61.3±36.1	73.7±36.2	5.769	7.95E-09
Stuffy nose	48.5±25.0	51.3±29.0	0.927	0.355
Itchy eyes	56.6±32.6	57.6±32.5	0.341	0.732
Tear	29.3±39.6	35.3±32.2	4.273	1.92E-05
Throat pain	27.9±26.9	42.6±33.5	6.504	7.79E-11
Hindrance to activities of daily living	37.7±26.5	43.5±26.6	2.328	0.0199
Nasal symptom score	84.7±23.7	88.3±28.6	1.422	0.155
Eye symptom score	62.9±35.6	60.4±31.9	0.994	0.320
Nasal symptom medication score	91.7±28.3	103.4±37.8	3.468	5.23E-04

Data are expressed as the mean of the AUC for each subject during the first peak of the pollen season (Feb. 4 to Mar. 25)±SD.

A comparison between the long-term intake group and the short-term intake group was performed using the Mann-Whitney U test.

take group was significantly higher than that of the short-term intake group ($P < 0.05$).

During the study period, no adverse events were observed. Some physical disorders such as cold symptoms (6 subjects), nausea (1 subject), and stom-

achache (2 subjects) were reported. There were no differences in the number of disorders between the 2 groups. None of the conditions were related to the intake of the test drink except the stomachache. The subjects that complained of stomachache were in-

structed not to consume the test beverage when fasting, because of its rich polyphenol content.

DISCUSSION

Previous randomized, double-blind, and placebo-controlled clinical studies of 'benifuuki' green tea as a treatment for seasonal allergic rhinitis¹¹ and perennial allergic rhinitis^{14,15} have demonstrated that drinking the tea, corresponding to an intake of 34 mg/day of *O*-methylated catechin, markedly improves the symptoms of allergic rhinitis. However, the optimal starting period for drinking 'benifuuki' green tea was not elucidated. The present randomized, open-label, parallel-group study provided clinical evidence that the drinking tea 1.5 months prior to the Japanese cedar pollen dispersion period is effective in improving symptoms against SAR.

We have previously demonstrated that *O*-methylated catechin and 'benifuuki' green tea have strong anti-allergic effects *in vitro*. *O*-methylated EGCG strongly inhibits the activation and degranulation of murine bone marrow derived mast cells and human basophilic KU812 cells through the inhibition of tyrosine phosphorylation (Lyn, Syk, and Btk) of cellular proteins,⁷ myosin light chain phosphorylation,¹⁶ and the expression of FcεRI.⁶ Therefore, we speculated that the potent anti-allergic activities of *O*-methylated EGCG might explain the clinical effects of 'benifuuki' green tea, which contains high amounts of *O*-methylated EGCG, on allergic rhinitis.

Our previous clinical study on cedar pollinosis demonstrated that drinking 'benifuuki' green tea containing 34 mg/day of *O*-methylated catechin over 1.5 months before pollen dispersion significantly relieved nose-blowing and itchy eyes compared with drinking a placebo green tea containing no *O*-methylated catechin during the most severe cedar pollen dispersion period.¹¹ Another of our previous studies on mild perennial allergic rhinitis showed that the scores for nasal and eye symptoms of the 'benifuuki' green tea (34 mg/day of *O*-methylated catechin) intake group were significantly lower than that of a group that drank 'yabukita' at weeks 7–12 for nasal symptom scores, and at weeks 4–12 for eye symptom scores.¹⁵

This study showed that the Nasal SMS, NSS, nose-blowing, itchy eyes, tears, throat pain, and hindrance to ADL scores after 1.5 months of consecutive intake of 'benifuuki' green tea before pollen dispersion (long-term intake group) were significantly lower than that of the short-term intake subjects who began their intake after pollen scattering during the most severe cedar pollen scattering period. Furthermore, the AUCs of the Nasal SMS, nose-blowing, tears, throat pain, and hindrance to ADL in the long-term intake group were significantly lower than those of the short-term intake group at the first peak of the pollen season. These results suggest that a 1.5-month consecutive intake of 'benifuuki' green tea prior to pollen

exposure is necessary to produce the desired efficacy.

The score of hindrance to ADL from weeks 0 to 6 in the long-term intake group was significantly higher than that of the short-term intake group. We surmise that this difference is only owing to the difference of baseline.

Inhibitory effects were clearly identified in short-term *in vitro* experiments, but this was not the case in clinical tests. Several reasons may account for this discrepancy. First, pollinosis symptoms are not only caused by mast cells but also by other inflammatory cells of the immune system. Although mast cells play a critical role as initiators of IgE-dependent immediate hypersensitivity¹⁷ and the suppression of mast cell activation eventually leads to suppression of the entire inflammatory response, this process may take time. Secondly, the mast cells may have already been primed before the pollen season because the immunological microenvironment of patients with seasonal allergic rhinitis shifts to Th2-mediated responses.¹⁸ Thus, at allergen exposure the 'primed' mast cells would induce an enhanced allergic inflammatory cascade. Therefore, we concluded that *O*-methylated EGCG is more effective at restraining the primed mast cell activation that occurs prior to antigen exposure and thereby suppresses the symptoms of pollinosis during the cedar pollen season. It has been reported that early treatment with antihistamine or anti-leukotriene drugs before cedar pollen dispersal is very effective.¹⁹ The present clinical effects of long-term intake of *O*-methylated catechins are in agreement with these studies. We suspect that the crucial step for its efficacy may be effective inhibition of primed mast cells before the appearance of an inflammatory cascade.

The main pillar in the management of seasonal allergic rhinitis is drug treatment such as antihistamines and topical corticosteroids²⁰; however, it is more desirable to relieve the symptoms by modifying lifestyles, for example, by choosing a "better" tea that is consumed every day. The amount of 'benifuuki' taken daily in this study is not an excessive amount. Therefore, a patient with seasonal allergic rhinitis may be able to manage his/her symptoms by drinking 'benifuuki' green tea regularly. We conclude that drinking 'benifuuki' green tea for 1.5 months prior to cedar pollen season is effective in reducing the symptom scores for Japanese cedar pollinosis compared with a short-term intake group which began tea intake after pollen scattering began.

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