

'Benifuuki' Green Tea Containing O-Methylated Catechin Reduces Symptoms of Japanese Cedar Pollinosis: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Methylated catechin, one of the active ingredients in green tea, has been reported to ameliorate allergic reactions. We evaluated the efficacy of 'Benifuuki' green tea, which contains O-methylated epigallocatechin-3-O-[3-O-methyl] gallate (O-methylated EGCG), in alleviating Japanese cedar pollinosis (JCP).

Methods: The study was a double-blind, randomized, placebo-controlled trial. The subjects with JCP were randomly assigned to drink 700 ml of 'Benifuuki' green tea containing O-methylated EGCG or 'Yabukita' green tea (not containing O-methylated EGCG) as a placebo every day from December 2007 through March 2008, which includes the pollen season. The primary outcome was the area under the curve (AUC) of symptom scores during the peak pollen season.

Results: Fifty-one adults with JCP participated in the study. Twenty-six subjects were assigned to 'Benifuuki' and 25 to 'Yabukita'. The AUC of symptom score during the peak pollen season in the 'Benifuuki' group was significantly smaller than in the 'Yabukita' group for each of runny nose, itchy eyes, tearing, total nasal symptom score, total ocular symptom score, nasal symptom-medication score and ocular symptom-medication score. The total QOL-related questionnaire score for one week in the peak pollen season was significantly better in the 'Benifuuki' group. Increase in the peripheral eosinophil count in response to pollen exposure was suppressed in the 'Benifuuki' group. No adverse events were reported in either group.

Conclusions: 'Benifuuki' green tea containing a large amount of O-methylated EGCG reduced the symptoms of JCP and has potential as a complementary/alternative medicine for treating seasonal allergic rhinitis.

KEY WORDS

allergic rhinitis, complementary and alternative medicine, efficacy, Japanese cedar pollinosis, treatment

ABBREVIATIONS

O-methylated EGCG, O-methylated epigallocatechin-3-O-[3-O-methyl] gallate; JCP, Japanese cedar pollinosis; CAMs, complementary and alternative medicines; QOL, quality of life; VAS, visual analogue scale.

INTRODUCTION

Japanese cedar pollen is released from February

through March in much of Japan and causes Japanese cedar pollinosis (JCP), the most prevalent pollinosis in Japan.¹ JCP causes not only symptoms of rhi-

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Conflict of interest: This study is supported by Asahi Soft Drinks. TF reports receiving grant support through his institution from GlaxoSmithKline and Kaketsuken, lecture fees from GlaxoSmithKline and Kyorin Pharmaceuticals. The rest of the authors

have no conflict of interest.

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Received 28 August 2013. Accepted for publication 11 November 2013.

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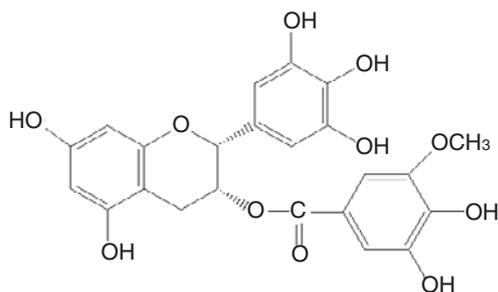


Fig. 1 Chemical structure of epigallocatechin-3-O-(3-O-methyl) gallate.

noconjunctivitis but also symptoms involving other organs, such as sore throat, cough, headache and general fatigue. JCP significantly lowers the quality of life (QOL) of patients.² The prevalence of JCP has increased drastically over time,³ and it now affects almost one fourth of the population.⁴⁻⁶ It is thus a significant burden on the nation. Current pharmacotherapy, including intranasal corticosteroids, non-sedating antihistamines and leukotriene receptor antagonists, can alleviate the symptoms,¹ but maintaining a good QOL remains difficult.

Green tea (*Camellia sinensis* (L)) is a traditional and popular drink in many Asian countries. Green tea has been reported to provide various health benefits,⁷⁻¹⁰ and several components have been identified as active ingredients responsible for those benefits.^{11,12} Among them, a methylated catechin derivative,¹³ *O*-methylated epigallocatechin-3-*O*-[3-*O*-methyl] gallate (*O*-methylated EGCG) (Fig. 1), was found to have anti-allergic properties, inhibiting type I and type IV hypersensitivity reactions.¹⁴⁻¹⁷ 'Benifuuki', a cultivar that was originally bred to produce black tea*, contains large amounts of *O*-methylated EGCG when it is processed as green tea, whereas the most-consumed green tea cultivars in Japan, such as Yabukita, do not contain it.¹¹ (*Black tea is also made from leaves of *Camellia sinensis*, but curing the leaves involves strong oxidation in order to give a strong flavor, and *O*-methylated EGCG is destroyed in the process.)

To prove the anti-allergic properties of 'Benifuuki', we previously performed a double-blind, placebo-controlled study employing a small number of subjects with JCP and found that it alleviated the symptoms.¹⁸ We further found in an open-labeled study that starting drinking 'Benifuuki' regularly about 6 weeks before the start of the pollen dispersal season was more effective than starting after the season had already begun.¹⁹ Here, we present more comprehensive results from a randomized, double-blind, placebo-controlled trial of green tea for JCP that enrolled a larger number of subjects.

Table 1 Catechin and caffeine contents of the test drinks

	Content (mg/100 mL)	
	Benifuuki	Yabukita
<i>O</i> -methylated EGCG	5.83	0
EGCG	14.37	13.21
GCG	22.38	20.73
ECG	4.18	2.79
EGC	8.98	14.15
EC	3.73	4.19
Caffeine	20.99	15.85
Total catechin	89.27	94

O-methylated EGCG, *O*-methylated epigallocatechin-3-*O*-[3-*O*-methyl] gallate; EGCG, epigallocatechin-3-*O*-gallate; GCG, gallo-catechin-3-*O*-gallate; EGC, epigallocatechin; EC, epicatechin.

METHODS

SUBJECTS

The subjects were male and female volunteers with JCP who met the following inclusion criteria: (1) Japanese cedar pollen-specific IgE level \geq class 2 (Immune CAP), (2) a history of JCP for at least 2 seasons before the study, (3) 20-65 years of age and (4) ability to accurately maintain a diary. Patients were excluded if they (a) had concomitant sino-nasal disease (such as perennial allergic rhinitis, rhinosinusitis, nasal polyps, nasal septum deviation) that might confound accurate determination of the outcomes of the trial, (b) were undergoing cedar-pollen-specific immunotherapy, (c) had undergone sino-nasal surgery including laser vaporization, (d) had been administered anti-allergy drugs within 2 weeks of start of the study, (e) were being treated for severe systemic disease or (f) were pregnant or breastfeeding. All patients gave written informed consent prior to participation.

PREPARATION OF TEST DRINKS

A 'Benifuuki' tea drink was prepared as described previously.¹⁹ It contained *O*-methylated EGCG at 5.83 mg/100 ml. A 'Yabukita' tea drink of very similar color and taste as 'Benifuuki' tea, but containing no *O*-methylated EGCG, served as a placebo. Table 1 shows the contents of various catechins and caffeine in the test drinks.

STUDY DESIGN

This was a single-center, double-blind, randomized, placebo-controlled, parallel-group trial conducted at Mie National Hospital (Mie, Japan) from December 2007 through March 2008. The patients were randomized to drink a 350-ml bottle of either 'Benifuuki' or the placebo, 'Yabukita', green tea twice daily (total 700 ml/day) during the study period. That period ran

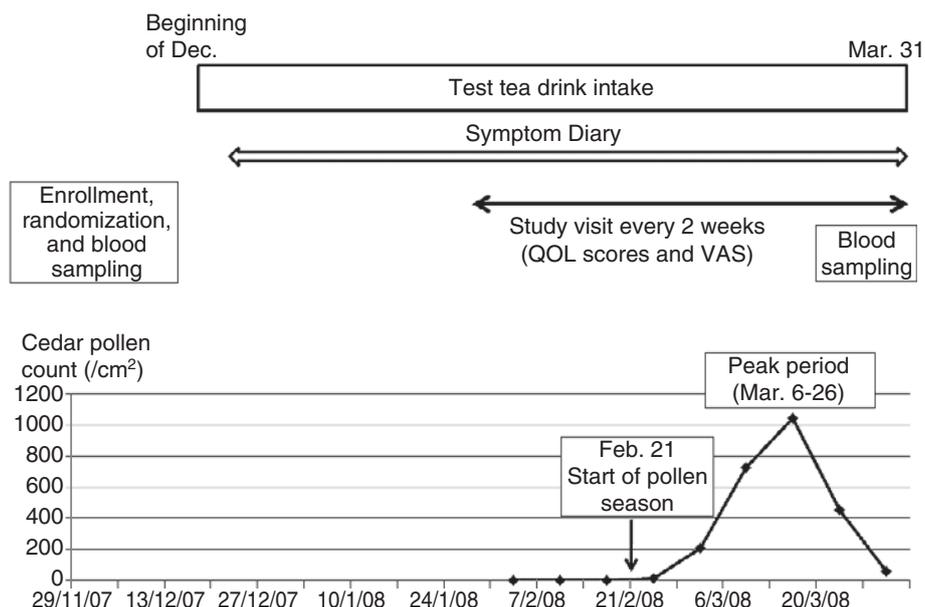


Fig. 2 Study design (top panel) and Japanese cedar pollen count in 2008 in Tsu City, Mie, Japan (bottom panel).

from the first week of December, approximately 10 weeks before start of the pollen season, until March 31, by which time pollen dispersal has usually ended. The dose of the test drink was determined based on the previous studies; In an initial preliminary study, daily intake of 34 mg *O*-methylated EGCG, not 17 mg, resulted in significant improvement in nasal symptoms of patients with perennial allergic rhinitis (published in Japanese). Then, in an open-label, single-dose, randomized, parallel-group study for JCP, we found that daily intake of 700 ml 'Benifuuki' green tea containing about 40 mg of *O*-methylated EGCG for 1.5 months prior to the cedar pollen season was effective in reducing symptom scores for JCP.¹⁹

They were allowed to take antihistamines and topical or systemic corticosteroids as rescue medication for no more than 2 consecutive days. The subjects recorded their nasal and other symptoms in a symptom diary every day. The QOL score and visual analog scale (VAS) were determined at visits every 2 weeks and blood sampling was performed at entry and at the end of the study (Fig. 2). The study protocol was approved by the Institutional Review Board of Mie National Hospital, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

POLLEN COUNT

The dispersed pollen count in Tsu City was determined by the Department of Otorhinolaryngology-Head and Neck Surgery, Mie University Graduate School of Medicine, by the gravity method using a Durham sampler and expressed as number/cm².

OUTCOME MEASURES

Participants recorded their nasal symptoms (sneezing, runny nose and nasal congestion), ocular symptoms (itchy eyes and tearing), sore throat and interference with daily life in the diary using a 5-point scale: nil, 0; mild, 1; moderate, 2; severe, 3; very severe, 4. The volume of tea consumed was also recorded in the diary. The medication score (MS) was rated as follows: antihistamine, 1; topical corticosteroids, 2; systemic corticosteroids, 3. The total nasal symptom score (TNSS) was the sum of sneezing, runny nose and nasal congestion, the total ocular symptom score (TOSS) was the sum of itchy eyes and tearing, and the nasal symptom medication score (NSMS) and the ocular symptom medication score (OSMS) were the sum of the MS and TNSS or TOSS, respectively.

Participants also filled out the Japanese Allergic Rhinitis QOL Standard Questionnaire No. 1 (JRQLQ No. 1)²⁰ and rated their nasal symptoms on a visual analog scale (VAS; a 10-cm scale from 0 points = no nasal symptoms to 10 points = most severe nasal symptoms) at each visit.

A complete blood count and blood chemistry tests were performed for each subject at entry and the end of the study to detect any adverse effect of the test drinks.

ENDPOINTS

The primary outcome was the area under the curve (AUC) of the plot of each symptom score during the peak pollen season. Secondary outcomes were the weekly symptoms, the total QOL-related questionnaire score, the VAS of nasal symptoms and the num-

Table 2 Demographics of the subjects

	'Benifuuki' group (n = 26)	'Yabukita' group (n = 25)	Statistics
Gender (n, male/female)	8/18	7/18	n.s.
Age (years)	39.6 ± 10.8	39.6 ± 9.3	n.s.
Duration of Japanese cedar pollinosis from the onset (years)	12.1 ± 7.6	13.2 ± 7.5	n.s.
Japanese cedar pollen-specific IgE (ImmunoCAP score)	3.8 ± 0.9	3.7 ± 1.0	n.s.
Total nasal symptom score at entry	2.9 ± 0.9	2.9 ± 0.8	n.s.

Data are expressed as the mean ± SD.

Table 3 The area under the curve (AUC) of each symptom score and VAS during the peak pollen season (Mar. 6-26)

Outcome measure	'Benifuuki' group (n = 26)	'Yabukita' group (n = 25)
Sneezing	30.8 ± 18.0	32.0 ± 17.6
Runny nose	33.8 ± 20.8*	36.9 ± 19.2
Nasal congestion	22.8 ± 20.8	24.7 ± 17.2
Itchy eyes	30.7 ± 20.9**	37.4 ± 19.5
Tearing	17.7 ± 19.9**	21.4 ± 18.9
Sore throat	21.8 ± 19.8	23.6 ± 19.8
Total Nasal Symptom Score	38.0 ± 19.2**	43.0 ± 18.1
Total Ocular Symptom Score	31.5 ± 20.5**	38.2 ± 19.9
Nasal Symptom Medication Score	41.0 ± 22.1**	44.4 ± 19.3
Ocular Symptom Medication Score	35.2 ± 25.0**	39.8 ± 20.0
Interference with daily life	16.5 ± 17.6**	19.0 ± 14.5
Visual Analog Scale	4.23 ± 2.56	4.46 ± 2.62

Data are expressed as the mean ± SD.

** $p < 0.01$, * $p < 0.05$; 'benifuuki' group vs. 'yabukita' group in Mann-Whitney U test.

ber of eosinophils in the peripheral blood.

STATISTICAL ANALYSIS

The background data of the participants, symptom scores, total QOL-related questionnaire score, AUC of the symptom scores and VAS during the peak pollen season were compared between the 'Benifuuki' and 'Yabukita' groups using the Mann-Whitney U test.

RESULTS

Seventy-six subjects were screened, and 51 (15 males and 36 females, mean age 39.6 years) were eligible for the study. Twenty six subjects were assigned to 'Benifuuki' tea and 25 to 'Yabukita' tea. There were no significant differences in the demographics between the two groups (Table 2). Adherence to consuming the test drink was more than 90% for all participants throughout the study period. All participants completed the protocol.

The pollen season started on February 21, and the peak period of pollen dispersal continued from March 6 to 26. Figure 2 shows the weekly pollen counts.

Table 3 shows the AUC data for the symptom scores during the peak pollen season. The AUC values were significantly smaller in the 'Benifuuki' group than in the 'Yabukita' group for the following

nasal and ocular symptoms: runny nose ($p < 0.05$), itchy eyes ($p < 0.01$) and tearing ($p < 0.01$). Similarly, the AUC data for TNSS, TOSS, NSMS and OSMS were significantly smaller in the 'Benifuuki' group than in the 'Yabukita' group ($p < 0.01$).

Figure 3A plots the TNSS for every week during the examination period, including the pollen season. Overall, the TNSS appears to be lower in the 'Benifuuki' group compared with the 'Yabukita' group. The score in the week of March 17 was significantly lower in the 'Benifuuki' group ($p < 0.01$). Similarly, in Figure 3B, the TOSS in every week appears to be lower in the 'Benifuuki' group than in the 'Yabukita' group. The scores for three weeks beginning from March 3 were significantly lower in the 'Benifuuki' group ($p < 0.05$ in the first and second weeks, $p < 0.01$ in the third week).

As shown in Table 3, the AUC of interference with daily life was significantly smaller in the 'Benifuuki' group than in the 'Yabukita' group ($p < 0.01$). The weekly total QOL-related questionnaire score for the week of March 10 was significantly higher in the 'Benifuuki' group (data not shown), i.e., the QOL of the subjects taking 'Benifuuki' tea was better than with 'Yabukita'.

The AUC of the VAS for nasal symptoms in the

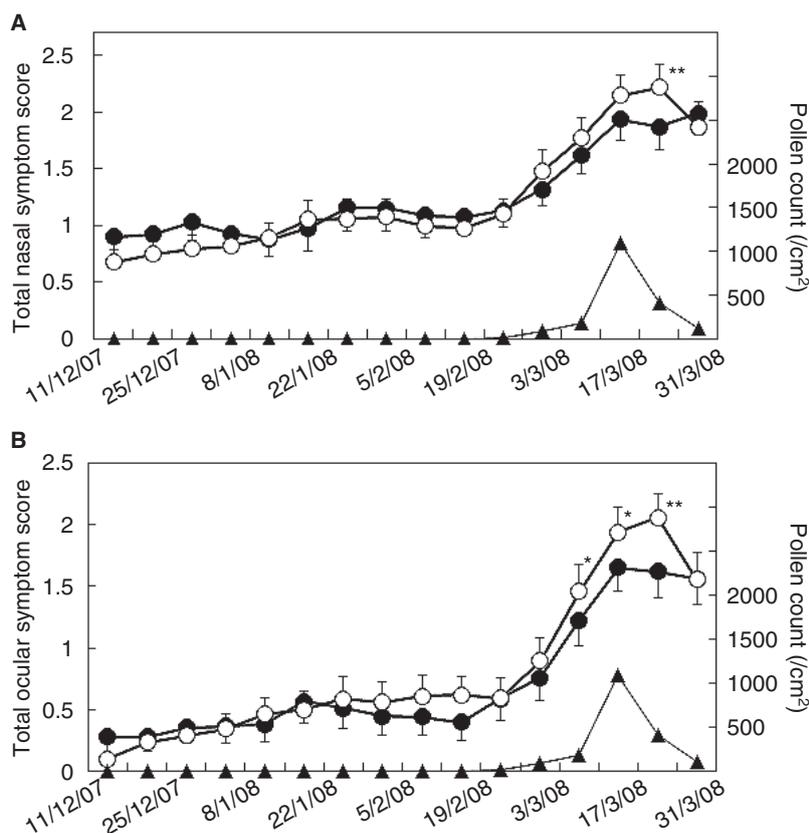


Fig. 3 Changes in weekly total nasal symptom score (TNSS; **A**) and ocular symptom score (TOSS; **B**) during the examination period. The TNSS for the week of Mar. 17 (** $p < 0.01$) and the TOSS for each of three consecutive weeks beginning from Mar. 3 (* $p < 0.05$ in the first and second weeks; ** $p < 0.01$ in the third week) were significantly lower in the 'Benifuuki' group. Open circles show the 'Yabukita' group, closed circles show the 'Benifuuki' group, and triangles show the pollen count.

peak pollen season did not differ significantly between the 'Benifuuki' and 'Yabukita' tea groups (Table 3). The weekly VAS also did not differ between the two groups during the examination period.

Table 4 compiles the blood chemistry and hematology results before and after drinking the test teas. In the 'Yabukita' group, the number of peripheral eosinophils was significantly ($p < 0.05$) increased at the end of the study. In contrast, the increase in peripheral eosinophils in the 'Benifuuki' group was not observed.

In the 'Benifuuki' group, total protein and total cholesterol were significantly decreased at the end of the study compared with at the start. In the 'Yabukita' group, total protein, total cholesterol, aspartate amino transferase (AST), alanine transaminase (ALT) and the red blood cell count were significantly decreased. However, all the changes in both groups were within the normal ranges.

No adverse events were reported throughout the study period, and no significant abnormalities were

found in the physical examinations in either group.

DISCUSSION

In this randomized double-blind, placebo-controlled trial, we found that drinking 'Benifuuki' tea significantly reduced the symptoms of Japanese cedar pollinosis, improved the QOL and suppressed the increase in peripheral eosinophils that is often seen during the pollen season.

Tea is consumed globally and in especially 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 falls in the category of complementary and alternative medicines (CAMs). CAMs, which include homeopathy, acupuncture, herbal medicines and yoga, are very popular for alleviation of symptoms of allergic rhinitis and asthma, but evidence-based recommendations are lacking.²¹ The use of CAMs in the United States has been increasing at a substantial rate and the spending for CAMs exceeds expenditure for all other physician

Table 4 Blood chemistry and hematology results before and after drinking the test teas

	'Benifuuki' group (n = 26)		'Yabukita' group (n = 25)	
	Pre	Post	Pre	Post
Total protein (g/dl)	7.51 ± 0.40	7.36 ± 0.36*	7.45 ± 0.38	7.18 ± 0.48**
Glucose (mg/dl)	109.2 ± 34.2	105.3 ± 35.0	105.5 ± 14.7	106.6 ± 28.8
Triglyceride (mg/dl)	129.6 ± 88.1	118.9 ± 85.3	104.4 ± 57.2	116.9 ± 68.8
Total cholesterol (mg/dl)	203.8 ± 29.3	196.3 ± 31.9*	198.8 ± 35.9	189.8 ± 33.5*
Blood urea nitrogen (mg/dl)	11.73 ± 2.63	12.61 ± 5.27	12.35 ± 2.78	12.95 ± 2.82
Creatinine (mg/dl)	0.62 ± 0.17	0.63 ± 0.17	0.62 ± 0.15	0.63 ± 0.14
Serum iron (μg/ml)	83.3 ± 41.6	85.1 ± 35.7	71.9 ± 35.6	77.6 ± 40.3
Aspartate amino transferase (IU/l)	21.0 ± 9.27	19.8 ± 10.7	18.8 ± 4.27	17.6 ± 4.40*
Alanine transaminase (IU/l)	22.5 ± 22.9	19.2 ± 23.9	15.4 ± 8.65	13.2 ± 6.22*
White blood cells (×1/μl)	6065 ± 1263	5823 ± 1421	6280 ± 1256	5992 ± 1716
Red blood cells (×10000/μl)	456.7 ± 42.0	454.9 ± 39.7	450.9 ± 35.5	442.8 ± 32.7*
Hemoglobin (g/dl)	13.30 ± 1.60	13.2 ± 1.49	13.34 ± 1.73	13.0 ± 1.56
Platelets (×10000/μl)	28.5 ± 6.52	28.3 ± 5.77	27.1 ± 5.56	26.2 ± 5.10
Eosinophils (×1/μl)	3.11 ± 2.21	3.73 ± 2.93	3.80 ± 3.34	5.64 ± 4.28*

*Mann-Whitney U test $P < 0.05$, comparison between pre- and post-data.

**Mann-Whitney U test $P < 0.01$, comparison between pre- and post-data.

services.²² Some of the reasons for using CAMs include distrust of conventional science-based medicine, absence of a satisfactory physician-patient relationship and the belief that CAMs are safe (devoid of side effects) products/procedures.²¹ Recommendations for the use of CAMs should be based only on rigorous proof of efficacy derived from high-quality studies, because of the considerable cost (to patients and health care systems) and potential risks (such as malpractice, incorrect prescription and drug interactions) associated with their use in a non-evidenced-based approach.²² It is necessary to clarify the effects and risks *in vitro* at the molecular level and *in vivo* at the clinical level by means of well-designed randomized, double-blind, placebo-controlled trials.

Mechanism by which 'Benifuuki' green tea ameliorated the symptoms of pollinosis in this study may be attributed to the inhibitory effects of its active ingredient, *O*-methylated EGCG, on IgE-mediated mast cell activation, such as histamine and leukotriene release, and cytokine production and release.¹⁷ *O*-methylated EGCG, more potently than the non-methylated form of EGCG, inhibits multiple protein kinases downstream of FcεR I on mast cells.¹⁷ EGCG was also reported to inhibit proliferation and differentiation of an eosinophilic cell line, EOL-1.²³ The present finding that the eosinophilia usually seen in allergen-exposed patients did not occur in those who took 'Benifuuki' can be attributed to the anti-eosinophilic effect of *O*-methylated EGCG.

In this study, we found that drinking either 'Benifuuki' or 'Yabukita' for about four months reduced the serum total cholesterol level, although the mean pre- and post-trial levels were within the normal range. Catechins were reported to reduce serum cho-

lesterol,^{24,25} and our present results appear to confirm those earlier findings.

Although the efficacy of 'Benifuuki' in this study was statistically significant, its overall effects were not potent enough to be a new 'controller' for pollinosis. In addition, the number of the scattered pollen in the year when the study was performed was relatively small and the efficacy was not tested in years of massive scattering of the pollen. We do not suggest that 'Benifuuki' is an alternative to guideline-based pharmacologic treatments, such as antihistamines and topical corticosteroids, but we suspect that the QOL of patients with seasonal allergic rhinitis can be improved by choosing a "better" tea for daily consumption, one which reduces the symptoms. Moreover, regular drinking of 'Benifuuki' may decrease the use of medicines, anxiety regarding possible side effects of medications, the troublesomeness of visiting a hospital and the economic burden on patients.

In conclusion, we demonstrated that 'Benifuuki' green tea reduced the symptoms of Japanese cedar pollinosis and may be beneficial in control of allergic rhinitis.

ACKNOWLEDGEMENTS

We thank Dr. Hiroshi Yasueda, of the Clinical Research Center, National Sagamihara Hospital, for his kind gift of reagents, and Ms. Kumiko Ota and Ms. Manami Negoro for their excellent technical assistance.

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