Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : July 5, 2019
Accepted : July 29, 2019
Published online : September 30, 2019
doi:10.24659/gsr.6.3_151

Original article

Effects of Kuromoji (*Lindera umbellata* Thunb.) Extract-containing Candy on Cold Symptoms
– Reanalysis of 2017/2018 season randomized, double-blind, placebo-controlled, parallel-group study –

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Abstract

***Objectives*:** The objective of this study was to reanalyze the results of cold symptoms, which is a secondary outcome of the randomized, double-blind, placebo-controlled, parallel-group, comparative study conducted in the 2017/2018 season, during which the preventive effect of kuromoji (*Lindera umbellata* Thunb.) extract-containing candy on influenza infection was seen.
***Method*:** 135 subjects were divided into 2 groups, one group consumed kuromoji extract-containing candy while the other group consumed placebo candy, and the survey results of the cold symptoms after the completion of the study (after 90 days) and after 75 days when the dispersion count of cedar pollen increases was analyzed.
***Results*:** For the group that consumed kuromoji extract-containing candy, although there was no impact on the onset of cold symptoms up to 90 days, the duration of the symptoms was seen to reduce. The reduction of the duration of the symptoms was more pronounced in the survey conducted after 75 days.
***Conclusion*:** Consumption of kuromoji extract-containing candy has reduced the duration of cold symptoms. Furthermore, the reduction in the duration of the symptoms was more pronounced in the data of the period before being affected by pollinosis symptoms. The above results suggested that the consumption of kuromoji extract-containing candy has a mitigation effect on cold symptoms in addition to the prevention effect on influenza infection.

***KEY WORDS*:** kuromoji (*Lindera umbellata* Thunb.), cold symptoms, influenza vaccination, randomized controlled trial

Introduction

Kuromoji (*Lindera umbellata* Thunb.) of the Lauraceae family is an aromatic plant rich in volatile components such as linalool and geraniol [1,2]. Regarding non-volatile components, kuromoji is known to contain plenty of proanthocyanidin compounds which are polymers of flavan-3-ol such as procyanidin B1, procyanidin B2 and cinnamtannin D1 [3,4]. The branches of kuromoji are used as herbal medicine that is called "Usyou" [5] in medicinal liquors, and the kuromoji extract is reported to have a variety of pharmacological actions such as antioxidant, antiglycation, anti-ulcerative, immunity improvement and antiviral actions [4,6-9].

During the 2017/2018 season, a clinical trial was conducted with nursing staff who received flu shots at the Ehime University Hospital as subjects, and they were given kuromoji extract-containing candy, which significantly reduced the number of people infected with influenza

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indicating the possible effectiveness of kuromoji in preventing influenza. However, in the survey on cold symptoms, a secondary outcome of this trial, a difference was not observed in the number of people with the onset of cold [10, 11]. Cold, also known as "cold syndrome" or "common cold", which is a generic term for acute inflammation occurring from the nasal cavity and pharynx to the bronchioles and lungs and is an acute respiratory tract infection that mainly occurs in the upper respiratory tract [12]. Most colds are caused by viruses such as rhinovirus, coronavirus and adenovirus, while the rest are caused due to infection other than viruses such as bacteria, mycoplasma, and chlamydia [13]. Symptoms include systemic symptoms such as sneezing, nasal discharge, sore throat, cough, fever, headache and general malaise, which are sometimes accompanied by gastrointestinal symptoms such as nausea, vomiting and diarrhea. Although the initial symptoms of cold and influenza are similar, in the case of influenza, after a short incubation period following the infection with a virus, symptoms such as high fever above 38 °C, headache, myalgia, joint pain and general malaise, etc. suddenly appear, and symptoms of inflammation of the upper respiratory tract such as cough and nasal discharge continue. Influenza causes pneumonia *etc*. in the elderly, or patients with respiratory and heart diseases, *etc*. and in the worst case can lead to death and is distinguished from cold in terms of severity [13, 14]. On the other hand, as symptoms of cold are mild, even if onset is suspected, the symptoms may not be due to cold, and many times it becomes difficult to distinguish cold from other diseases. In particular, initial symptoms of pollinosis are similar to a cold such as sneezing, nasal discharge, sore throat, cough, *etc*., which are sometimes accompanied by fever and general malaise, and there are times when differentiation based only on the clinical symptoms is difficult. Therefore, careful differentiation from cold is necessary during the season when pollinosis spreads [15, 16].

The purpose of this study is to reanalyze the results of cold symptoms, which is a secondary outcome of the randomized, double-blind, placebo-controlled, parallel-group comparative study [10, 11] conducted in the 2017/2018 season with the incidence of influenza as the primary outcome. Specifically, data were analyzed for the number of subjects who reported the symptoms of a cold in the questionnaire and for the duration of the symptoms, this analysis was not performed in the previous report [10, 11], and the group that consumed kuromoji extract-containing candy and group that consumed placebo candy were compared. Furthermore, dispersion information of cedar pollen in the same season was investigated, and the impact on the data was discussed.

Method

Subjects

The participants in the survey were 135 male and female nursing staff working at the Ehime University Hospital who received flu shots. The influenza vaccine was prepared using 4 strains, type A Singapore/GP1908/2015 (IVR-180) (H1N1) pdm09, type A Hong Kong/4801/2014 (X-263) (H3N2), type B Phuket/3073/2013 (Yamagata lineage) and type B Texas/2/2013 (Victoria lineage) selected based on the 2016/17 season Infectious Agents Surveillance Report [17].

Specimen

The trunks and branches of kuromoji (*Lindera umbellata* Thunb.) were crushed and added to water ten times its volume, and thermally extracted at 95°C for 60 minutes, the extract was filtered by centrifugation, then concentrated with a vacuum concentrator, sterilized by continuous sterilization and dried, and this was used as the kuromoji extract. Kuromoji extract-containing candy was prepared by blending sugar, starch syrup and flavor with 67 mg of kuromoji extract per tablet. The placebo candy was prepared by replacing kuromoji in the kuromoji extract-containing candy with caramel and coloring it with the same color as the kuromoji extract-containing candy (***Table 1***).

Table 1. Ingredient composition per one tablet (3.8 g).

	Kuromoji candy	Placebo
Energy (kcal)	14.9	15.0
Protein (g)	0	0
Fat (g)	0	0
Carbohydrate (g)	3.7	3.7
Water (g)	0	0
Na (mg)	0.1	0
Kuromoji extract (mg)	67.0	0

Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, comparative study. A person who was not involved in the study randomly allocated the subjects to 2 groups, the group that consumed kuromoji extract-containing candy and the group that consumed placebo candy. The allocation table was sealed and kept until unblinding. The subjects consumed 3 candies daily after each meal for 3 months from December 15, 2017, to March 15, 2018. Influenza infection was determined, which is the evaluation item for the primary outcome, based on a positive diagnosis with the influenza rapid diagnosis kit in a medical institution. For the secondary outcome, a survey was conducted for fever, throat and nasal symptoms, and duration of symptoms using a questionnaire.

Pollen dispersion situation

The data on the dispersion count of cedar pollen for the 2017/2018 season was obtained from the pollen observation data collection of the pollen observation system, "Hanakosan" (Ministry of the Environment), which uses the pollen automatic measuring device (KH-3000, Yamatronics Corporation, Yokosuka, Kanagawa, Japan) for measurements, from Ehime University's Faculty of Agriculture (Matsuyama, Ehime, Japan). The 24-hour pollen observation data [17] from February 1 to March 15, 2018 were tabulated, and daily dispersion count of pollen (grains/m^3/day) is shown on a graph.

Data analysis

Age was expressed as mean ± standard deviation (SD) using the Mann-Whitney U test. The χ^2 test or Fisher exact test was used to compare between the 2 groups regarding gender, whether infected with influenza and influenza type. The observation period was set for 75 days from December 16, 2017 to February 28, 2018, and 90 days up to March 15, and from the questionnaire, the incidence was calculated by tabulation of those who responded with one or more of fever, throat or nasal symptoms other than influenza. Also, the prevalence rate was determined for the cases in each group based on the person-years method. The prevalence rate was expressed as the ratio of the total number of days with symptoms to the total number of observation days (person-days) for individual subjects in each group. The odds ratio and 95% confidence interval were determined for the incidence and prevalence, the cumulative prevalence was represented by the Kaplan-Meier curve, and the log-rank test was performed for the significant difference. Excel 2013 was used for statistical analysis, and the significance level was set to 5% or less for all the tests.

Ethical considerations

The study was conducted at the Ehime University Hospital, and the principal investigator supervised the work concerning the study by giving instructions and explanations to subjects, obtaining consent, interviewing the subjects, confirming and determining adverse events, preparing case reports and managing the trial implementation system. Before conducting the study, explanatory documents were issued to the subjects, and the principal investigator thoroughly explained the purpose and contents of the study, and the study was conducted only for those subjects from whom a written consent based on their free will was obtained. Adverse events were treated as needed. This study was conducted in compliance with the Helsinki Declaration (revised at the 2013 WMA General Assembly in Fortaleza) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology Ministry of Health, Labor and Welfare notification), and was carried out after review and approval by the Institutional Review Board, Ehime University Hospital (approval number: 1711022). This study was conducted after prior registration on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CT) (registration number: UMIN000030339).

Results

Subject background

Based on the randomized allocation of 135 subjects, 67 subjects (including 3 males) were allocated to the group that consumed kuromoji extract-containing candy, and 68 subjects (including 6 males) were allocated to the group that consumed placebo candy. However, 1 subject from the group that consumed placebo candy dropped out due to personal reasons and was excluded from the analysis. Also, though cold symptoms were mentioned in the questionnaire, 2 subjects from the group that consumed kuromoji extract-containing candy and 2 subjects from the group that consumed placebo candy were excluded from the survey as they did not fill in the onset date and duration of the symptoms. ***Table 2*** shows the subject background of the final 65 subjects from the group that consumed kuromoji extract-containing candy and 65 subjects from the group that consumed placebo candy. Differences in age and sex ratio between the 2 groups were not observed. Two (3.1%) subjects were infected with influenza in the group that consumed kuromoji extract-containing candy and 9 (13.8%) in the group that consumed placebo candy, showing a significant difference between the two groups ($p = 0.027$). Both the subjects from the group that consumed kuromoji extract-containing candy were infected with influenza type B, while in the group that consumed placebo candy, 6 subjects were infected with influenza type A while the remaining 3 were infected with influenza type B. Among the subjects infected with influenza, no one was infected more than once, and no one was infected in March.

Cedar pollen dispersion situation in 2018 season

Fig. 1 shows the dispersion count of cedar pollen from February 1 to March 15, 2018, which was the end date of the test period, measured at the Faculty of Agriculture, Ehime University (Matsuyama, Ehime). The dispersion count of pollen per hour showed an increasing trend from late February with a sudden increase in early March. The highest dispersion count of pollen was 5,647 grains/m^3/day on March 6. The mean dispersion count of pollen from February 1 to 28 was 293 grains/m^3/day, while the mean dispersion count of pollen from March 1 to 15 was 1,806 grains/m^3/day, which was 6-fold higher.

Table 2. Subject background.

	Kuromoji candy (n = 65)	Placebo (n = 65)	*p* values
Age (years)	37.8 ± 12.0	37.4 ± 10.4	0.920
Sex; male (n (%))	3 (4.6)	6 (9.2)	0.490
Influenza prevalence (n (%))	2 (3.1)	9 (13.8)	0.027
Type A (n (%))	0 (0)	6 (9.2)	0.028
Type B (n (%))	2 (3.1)	3 (4.6)	1.000

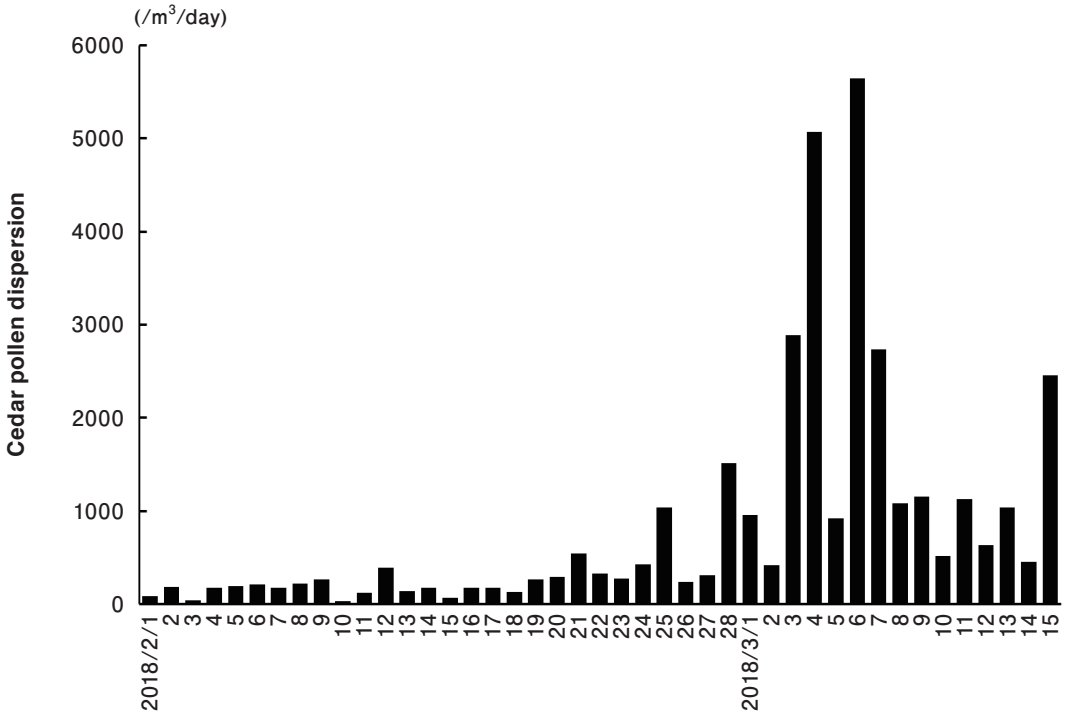

Fig. 1. **Cedar pollen counts in Matsuyama, Ehime from February 1 to March 15 in 2018.**

Table 3. Number of onset of cold symptoms.

Items	Observation period	Group	Number (n)	Prevalence (%)	Odds ratio	95% CI		*p* values
						Lower limit	Upper limit	
Cold symptoms (one of fever, throat discomfort or nasal symptoms)	75 days (until February 28, 2018)	Test	10	15.4	0.66	0.27	1.62	0.38
		Placebo	14	21.5	1.00			
	90 days (until March 15, 2018)	Test	10	21.5	1.00	0.43	2.31	0.94
		Placebo	14	21.5	1.00			

Number of subjects with the onset of cold symptoms

Table 3 shows the data collected after 75 days up to February 28, 2018, and after 90 days up to March 15, 2018 for the number of subjects with the onset of cold, who had at least one or more of fever, throat and nasal symptoms. A significant difference was not observed in the incidence of cold between the 2 groups from the data of 75 and 90 days.

Duration of the cold symptoms

Table 4 shows the data collected for 75 days and 90 days regarding the number of days with cold symptoms. ***Fig. 2*** shows the cumulative prevalence of common cold symptoms for 75 days. ***Fig. 3*** shows the cumulative prevalence of common cold symptoms for 90 days. The prevalence odds ratio for cold symptoms at 75 days after the start of the study was 0.49 for cold symptoms in the group that consumed kuromoji extract-containing candy, which was significantly lower than that of the group that consumed placebo candy ($p < 0.001$). Even after 90 days, the prevalence odds ratio for cold symptoms in the group that consumed kuromoji extract-containing candy was 0.76 ($p = 0.026$), a significantly lower value. Regarding the prevalence odds ratio of each symptom for 75 days, there was no difference only in the case of fever, while the odds ratio was 0.52 ($p < 0.001$) for throat symptoms and 0.37 ($p < 0.001$) for nasal symptoms, which was significantly less. After 90 days, the odds ratio only for the nasal symptoms was 0.61 ($p = 0.001$), which was considerably less.

Table 4. Number of days with cold symptoms.

Items	Observation days	Group	Observation period (person-days)	Number of days with symptoms (days)	Symptom prevalence (%)	Odds ratio	95% CI		*p* values
							Lower limit	Upper limit	
Cold symptoms (one of fever, throat or nasal symptoms)	75 days (until February 28, 2018)	Test	4,875	73	1.5	0.49	0.37	0.64	<0.001**
		Placebo		148	3.0	1.00			
	90 days (until March 15, 2018)	Test	5,850	118	2.0	0.76	0.60	0.97	0.026*
		Placebo		154	2.6	1.00			
Fever	75 days	Test	4,875	25	0.5	0.83	0.49	1.42	0.500
		Placebo		30	0.6	1.00			
	90 days	Test	5,850	35	0.6	1.17	0.72	1.90	0.540
		Placebo		30	0.5	1.00			
Throat symptoms	75 days	Test	4,875	63	1.3	0.52	0.38	0.71	<0.001**
		Placebo		119	2.4	1.00			
	90 days	Test	5,850	98	1.7	0.78	0.60	1.02	0.067
		Placebo		125	2.1	1.00			
Nasal symptoms	75 days	Test	4,875	40	0.8	0.37	0.26	0.54	<0.001**
		Placebo		106	2.2	1.00			
	90 days	Test	5,850	67	1.1	0.61	0.45	0.83	0.001**
		Placebo		109	1.9	1.00			

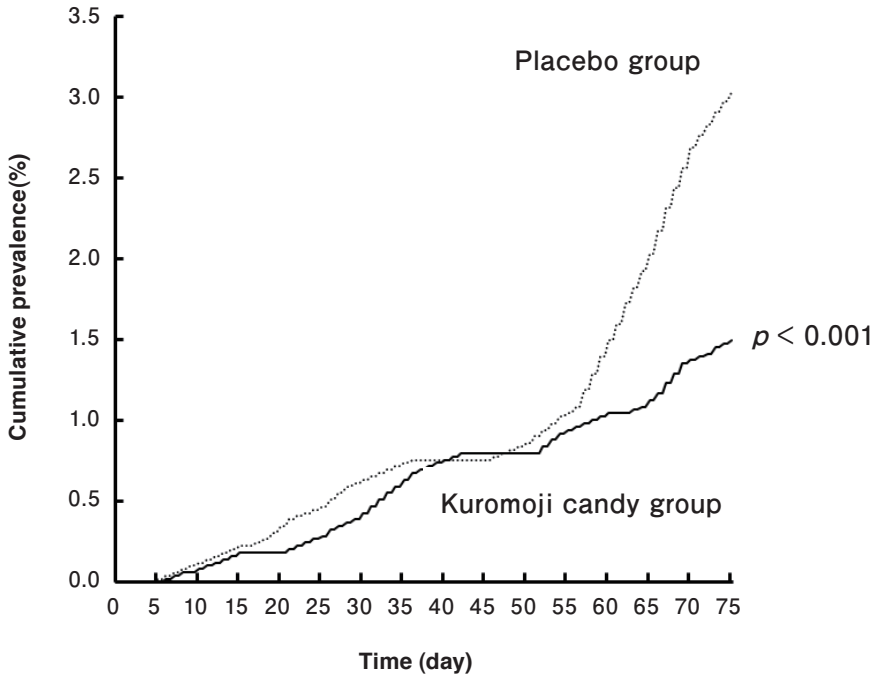

Fig. 2. **The cumulative incidence of common cold symptoms during 75 days from December 16, 2017 to February 28, 2018.**

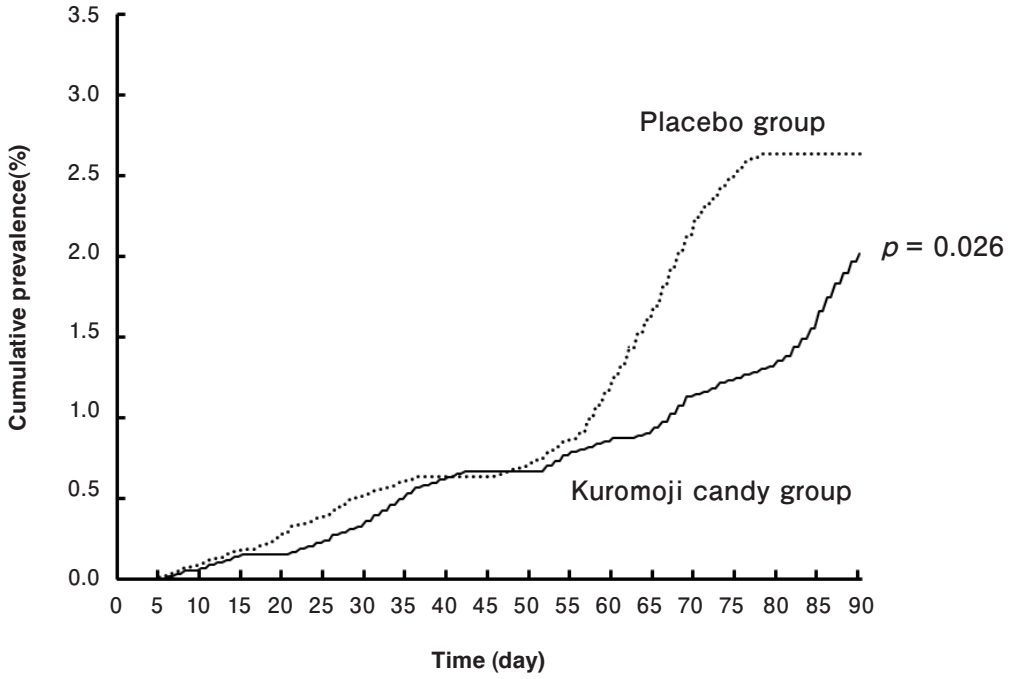

Fig. 3. **The cumulative incidence of common cold symptoms during 90 days from December 16, 2017 to March 15, 2018.**

Discussion

We carried out a reanalysis of cold symptoms, which was the secondary outcome of the randomized, double-blind, placebo-controlled, parallel-group, comparative study conducted in the 2017/2018 season. As a result, although there was no difference observed in the number of cases of onset as in the previous report [10, 11], the duration of cold symptoms presenting at least one or a combination of fever, throat symptoms and nasal symptoms was significantly reduced in the group that consumed kuromoji extract-containing candy. Furthermore, the reduction in the prevalence of cold symptoms was more pronounced in the data collected for 75 days, when compared to the results for 90 days.

Since initial symptoms of pollinosis are similar to a cold, such as sneezing, nasal discharge, sore throat, cough, *etc*. which are sometimes accompanied by fever and general malaise, in the season when pollinosis spreads, careful differentiation from cold is necessary [15, 16]. According to the observational records [18] of the monthly dispersion count of cedar pollen over a period of 5 years from 2014 to 2018 in Matsuyama located in the vicinity of Toon, Ehime (Ehime University Hospital) where the clinical study was implemented, the dispersion count of pollen reached a peak in March or April during all the years, and the year with the lowest dispersion count of pollen in March was 475 grains/m^3/day recorded in 2016, while the highest dispersion count of pollen was 2,424 grains/m^3/day in 2018, the year when this study was conducted. Also, the mean value during the actual study period from March 1 to 15, 2018 was 1806 grains/m^3/day.

The determination criteria for the pollen dispersion count, which is generally reported in the media *etc*., are based on data measured by a Durham sampler [19], which differs from an automatic measuring device, where dispersion count of pollen fewer than 10 grains/cm^2/day is expressed as "Low", 10 or more to less than 30 grains/cm^2/day as "Slightly High", 30 or more to less than 50 grains/cm^2/day as "High" and 50 or more grains/cm^2/day as "Extremely High". Since the principle of measurement and units of the measured value of an automatic measuring device and Durham sampler also differ, K/D ratio (KH-3000/Durham) ratio, which is expressed by, automatic measuring device (grains/m^3/day)/Durham sampler (grains/cm^2/day), is often used for comparison between the two. In the report that compared the K/D ratio of the dispersion count of cedar pollen over a period of 9 years from 2008 to 2016 [20], a wide variation from 8.4 to 39.6 was observed, however, when divided by the mean value of 21.1, the mean for February 2018 was 14 grains/cm^2/day, whereas the mean for the study period in March was estimated to be 86 grains/cm^2/day, which is about 6 times that of February. When the determination criteria are applied, it is expressed as "Slightly High" for February as the dispersion count of pollen is between the range 10 to less than 30 grains/cm^2/day, and as "Extremely High" for March since the value is 50 or more grains/cm^2/day.

In recent years, the number of pollinosis patients in Japan has been increasing rapidly, and according to the fact-finding survey on pollinosis patients in Tokyo [21], the prevalence of cedar pollinosis determined based on the positive result for cedar specific IgE antibodies in the serum, was reported to be 28.2% in 2006. Also, the prevalence

reported in the survey of 2016 is 48.8% indicating an increase of approximately 1.7 times in 10 years, and it is estimated that 1 in 2 people have pollinosis.

In the 2018 season, there was a sudden increase in the dispersion count of pollen in March, and it is considered that a substantial amount of cedar pollen was dispersed, which is unusual. At the same time, the number of pollinosis patients, too, is presumed to have increased suddenly in March, and there could also be a possibility that the symptoms of pollinosis had an impact on the evaluation of cold symptoms reported by the subjects. According to the information on detection of viruses and other infectious agents causing upper respiratory tract inflammation throughout Japan in 2018, by the National Institute of Infectious Diseases, the number of reports on the upper respiratory tract inflammation caused due to viruses tended to be maximum from mid-January to mid-February, 2018 [22]. Although the number of viruses detected in the vicinity of the study site is not known, it is considered to have a correlation with the above information, since there was a sudden increase in the onset of cold symptoms during the study period, and it was the highest in February, which is nearly consistent with the information.

From this, data collected for 75 days before the increase in the dispersion count of pollen reflects the actual conditions of the cold more accurately, and the effect on the cold symptoms in the group that consumed kuromoji extract-containing candy is considered to be quite noticeable.

Kuromoji consists of a large number of proanthocyanidin compounds, which contain flavan-3-ol polymers [3, 4]. The fractions of proanthocyanidins from kuromoji have vigorous inhibition activity on viral growth, which is reported to be a nonspecific activity [9]. In the present analysis, though a clear difference was not seen in the number of cases with onset of cold symptoms in the group that consumed kuromoji extract-containing candy, a reduction in the duration of the symptoms was observed. It can be considered that even if in the case of a viral infection, with the consumption of kuromoji extract-containing candy, the prognosis is improved and duration of symptoms is reduced because the growth of the virus is suppressed.

Cold is the most common disease, and its prolongation causes many harmful effects. For example, it leads to harmful social effects such as increased medical expenses, decreased productivity at the workplace, and loss of working days. In the United States, it is reported that children are infected 6 to 8 times and adults 2 to 4 times a year, and children are absent from school for a total of 22 million days while adults take 20 million days off from work due to cold [23]. Also, according to an attitude survey conducted for private companies targeting businesspersons of Japan in their 20s and 30s, the results indicate that the average productivity loss is 44,270 yen every time there is an onset of cold symptoms and the economic loss is immeasurable [24]. Therefore, the prevention of cold and to have a good prognosis after the infection is of great importance.

According to the current reanalysis, the consumption of kuromoji extract-containing candy reduced the duration of various cold symptoms. From the above, it suggested that in addition to the influenza prevention effect reported until now, the consumption of kuromoji extract-containing candy has a mitigating effect on cold symptoms.

Conflict of interest statement

The present study was supported by a SIP cooperative company, Yomeishu Seizo Co. Ltd.

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