The orally administration of the Hydrolysis Rice Bran prevents a common cold syndrome for the elderly people based on immunomodulatory function

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Abstract

The preventive effect of RIBEX against the common cold syndrome was examined on elderly people. RIBEX, containing arabinoxylan derivatives Hydrolysis Rice Bran (HRB), was prepared from the water soluble dietary fiber fraction from rice bran through partial processing by carbohydrate complex of *Lentinus Edodes mycelia* (shiitake). Using the non-chemical and non-biological treated water soluble fraction of Rice Bran (RB) as control, the examination was conducted by the cross-over double blind manner through the administration term of 6 weeks for each material. Fifty elderly people who stayed in a care institution under Japan's Long-term Care Insurance participated in this study. The results of thirty-six participants who showed comparative data in both terms were analyzed statistically. The most popular reason for withdrawal from the study was "leaving from the institution by a care contract". There was no withdrawal due to the side effects of test foods. We observed symptoms such as "cough", "fatigue", "fever", "sore throat", "sputum", "nasal signs", and "sore breast", and calculated them, based on the judgments of the medical staff. Although thirteen participants (36.1%) experienced at least one symptom in the both terms, the total scores were of significantly high value ($p<0.05$) in the term of R.B. The average duration in which the participants experienced symptoms was 2.6 days in the term of RB whereas 1.2 days in that of HRB, which was not statistically significant. While there are many reports that HRB increases NK cell activity, no significant data was observed in this study because the participants had enough NK cell activities from the start.

HRB shortened the duration of the symptoms, reduced the worse and the necessity of symptomatic therapy, and was useful for the reduction of physical burden of acute respiratory tract infection.

Key words hydrolysis rice bran, arabinoxylan, common cold syndrome, immunomodulatory function.

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Introduction

Carbohydrate, one of the main nutrients contained in food, consists of sugar, an energy source, and dietary fiber. The dietary fiber is barely digested or absorbed, but has a wide variety of physiological functions. Among them, the immunomodulatory function of the cell wall components of plants, microorganisms, and fungi have been reported by many researchers. β-1,3-Glucan from shiitake and suehirotake mushrooms has been used in clinical practice as an immunomodulatory agent.[1)] Approval has been received to display the beneficial effects of several kinds of dietary fibers on the labeles of foods containing them, e.g. inhibiting excessive increase in blood glucose after eating, lowering serum cholesterol, and regulation of intestinal function. This approval is based on the lebeling of foods for specified health uses in the system of foods with health claims, notified by the Pharmaceutical and Food Safety Bureau, MHLW, in 2001.

Rice bran, the residue left after polishing rice, contains a component that forms the cell wall skeleton for rice seed coats. Hydrolysis Rice Bran (hereafter called HRB) has been developed for use as a food product, and is closely related to the rice bran eaten by Japanese people from ancient times. The material for HRB, water-soluble dietary fiber extracted from rice bran, contains arabinoxylan as the main component. Different from β-1,3-glucan from mushrooms, arabinoxylan has a relatively low molecular weight even though it has a complex structure. RIBEX, produced by Daiwa Pharmaceutical Co., Ltd. is a granular food product containing HRB obtained by partially hydrolyzing the rice bran water-soluble fraction with many of the carbohydrases contained in shiitake mushrooms.

Many researchers have reported that HRB has an immunomodulatory effect on humans[2-7)]. Other effects reported include active-oxygen elimination[8)], sugar metabolism improvement[9)], and a reduction in the adverse effects of some chemicals [10)]that have been reported as functions of dietary fiber. These reports suggest that orally ingested HRB constantly exerts a positive effect. RIBEX, containing HRB and which boosts the human immune system, promises to help maintain and improve health.

The common cold syndrome is caused by viruses frequently encountered in daily life. There is no specific remedy and the only way is to wait for natural healing to occur[11)]. When an influenza epidemic is expected, however, it is important to give influenza vaccine to high risk populations such as children and the elderly to prevent influenza itself and secondary infection by bacteria[11)]. The risk of community-acquired pneumonia, which sometimes occurs secondarily when the common cold syndrome is exacerbated, is known to be high amongst individuals aged 75 or over[12)]. The risk of pneumonia is further increased in elderly patients with neurologic disorders, who are at higher risk of aspiration [13)]. It was reported that a decrease in activity of daily living (ADL) leads to decreased immunity in the elderly with low T-cell mediated cellular immunity[14)].

We studied the clinical usefulness of oral HRB based on its imunomodulatory effect in the prevention of common cold syndrome in the elderly who have low resistance due to decreased immune function. Although RIBEX is a food, this study was conducted in accordance with Good Clinical Practice.

Materials and Methods

(1) Subjects: Subjects were elderly people, without markedly impaired health, who stayed at a care facility for the elderly, Atreyu Uozaki, in Kobe City, Hyogo between January 2002 and March 2002 and who gave their consents to participate in this study. If at any time, subjects refused to take the study product or undergo the necessary tests, they were withdrawn from the study and the food product discontinued. When the attending physician judged that continuing the study might adversely affect the subject's health or was rendered impossible because the subject suffered an accident or fell ill or the subject left Atreyu Uozaki, the subject was withdrawn from the study and the food product discontinued.

(2) Food product ingested: The study food was RIBEX, whose principal constituent is the partially hydrolyzed water-soluble dietary fiber HRB. The control was a food the main component of which was a water-soluble extract of rice bran that is the raw material for HRB and is not hydrolyzed (hereafter called RB). Both foods were granular and sealed on three sides in an identical aluminum-foil film. They could not be identified. For both foods, the necessary amount for all subjects was prepared for every ingestion period. RB, a water-soluble extract, contained no chemically or biotechnologically treated water-soluble dietary fiber. The taste was the same for RB and HRB and both were rice bran derived foods. These are the reasons for choosing RB as the control. The ingestion dose of HRB was 500 mg/day because this is the dose expected to have an immunomodulatory effect based on our experience. The ingestion duration was 6 weeks, which was the shortest period necessary to ascertain any change in immune functions and common cold syndrome conditions. The study used a cross-over method, namely each subject ingested both foods for 2-week intervals. The subjects took the foods prepared by the facility personnel, who helped subjects to take the foods if necessary.

(3) Subject's living conditions: The daily environment and conditions of care for subjects were maintained in the same way as usual. The study was conducted in a double blind manner to eliminate observer bias. All subjects and facility staff members were blinded to the allocation of foods until the completion of the study.

(4) Examination and observation: Subject's background data were initials, date of birth, recent changes in body weight, complications during present treatment, history of respiratory disorders, height, and normal body temperature. To establish normal body temperature, each subject's temperature was measured over 2 weeks before the start of the study (if an abnormal temperature was noticed because of colds, etc., measurement was conducted in another period) and the median for the measurements was used.

Biomarkers, measured during the study, were common cold symptoms (onset and disappearance) and immune parameters such as NK cell activity. For fever, the highest temperature on each day was compared with the normal temperature and the difference was evaluated by 3 grades (No symptom, 1 Mild, 2 Moderate, and 3 Severe). "No symptom" meant a difference within 1°C between the highest and normal temperatures, "Mild" a difference of 1°C or more, "Moderate" a difference of 1°C or more and medical treatment given for the fever (such as cooling and antipyretics), and "Severe" where the highest body temperature exceeded 39°C. Common cold symptoms observed included typical general conditions (headache, malaise, myalgia, chills, and diaphoresis) and respiratory symptoms (cough, running/stuffy nose, sore throat, and chest pain)[15]. Each symptom was rated according to its worst manifestation on the day using 3 grades (No symptom, 1 Mild, 2 Moderate, and 3 Severe). "No symptom" meant the absence of symptoms, "Mild" the presence of mild symptoms but no need for symptomatic treatment, "Moderate" the presence of symptoms needing clinical observation and symptomatic treatment, and "Severe" indicated serious symptoms. Physicians and medical staff members at the facility, who were unaware of the food allocation, observed these items and recorded the results. For biomarkers other than cold symptoms, laboratory tests including hematology, blood biochemistry, and immunological tests, were conducted before and after each ingestion period. All laboratory tests were performed by S R L Co., Ltd.

(5) Evaluation: Background factors were age, sex, height, body weight, BMI, and normal body temperature, for which basic statistics were calculated. For common cold symptoms (fever, headache, malaise, chills, cough, sputum, running/stuffy nose, sore throat, and chest pain), if a subject had one or more symptom, the duration for which the symptom persisted (duration of symptoms) was recorded. In addition, the severity of each symptom was scored ("No symptom" = 0, 1 "Mild" = 1, 2 "Moderate" = 2, and 3 "Severe" = 3). All scores were summed for each subject and the total was divided by the number of days of ingestion to obtain the "cold symptom score." Changes in

cold symptoms, physical findings, and laboratory test values were analyzed by ingestion period and by study food. Abnormal findings were displayed in a summary table.

Results

1. Patient background

Subjects were 50 individuals staying at a care facility for the elderly, Atreyu Uozaki, in Higashinada, Kobe City in January 2002 and who gave their consent to participate in this study. Dropouts occurred due to the long study period and leaving the facility for reasons other than changes in health and physical condition. A total of 48 subjects took HRB in either period (HRB group) and 38 subjects took RB (RB group). No subjects withdrew from the study because of adverse reactions to the study food. Thirty-six subjects completed both ingestion periods, providing data that allowed comparison in the same subject to be made (comparison subjects).

No subjects drank alcohol habitually but 4 reported smoking.

Tables I and II show background factors. As correct heights could not be measured in many subjects because of spinal deformity, heights were taken as reference values in addition to BMI. The normal body temperature was between 36 and 37°C in almost all subjects with no wide variation. Statistical analysis (significant level: $p<0.1$) showed no significant difference in the age, height, body weight, or body temperature among all subjects and comparison subjects, suggesting no marked difference in backgrounds between both groups. The incidence of the most common complications was similar for both groups. These suggested that there was no change in background factors in subjects, although the number of subjects changed after enrollment.

2. Changes in cold symptoms

The actual to planned (42 days) ingestion periods, duration of cold symptoms, proportion of subjects with common cold symptoms, and cold symptom scores were expressed as the mean ± standard deviation. Table III shows results for subjects given HRB and RB respectively. The number of subjects given RB was smaller than that receiving HRB and the ingestion period shorter for the former group. The incidence of cough, malaise, body temperature, and sore throat were high in both the RB and HRB groups. The duration of common cold symptoms was shorter for the HRB group than for the RB group. The number of subjects with one or more symptoms was similar for both groups, being 21 (43.8%) for the RHB group and 15 (39.5%) for the RB group. The total score for common cold symptoms was higher for the RB group and the scores for frequent cough, malaise, and fever were also higher for the RB group, although the score for nasal symptoms was lower. These results showed the lower severity of common cold symptoms in the HRB group.

Table IV and Fig. 1 show changes in common cold symptoms in 36 comparison subjects who completed the HRB and RB ingestion periods. The ingestion period was almost the same for HRB and RB ingestions in the 36 comparison subjects. These subjects showed almost the same profile for common cold symptoms as the 50 subjects. The incidence of cough, malaise, fever, and sore throat were similar for both HRB and RB groups. The number of subjects with one or more symptoms was 13 (36.1%) for the HRB group and 13 for the RB group. However, the duration of symptoms was 1.2 days for the HRB group and 2.6 days for RB ingestion, although no significant difference was observed. The total symptom score was significantly higher for the RB group than for the HRB group ($p=0.0426$). For individual symptoms, the scores of frequent cough, malaise, and fever were higher for the RB group, but without a significant difference.

Table I Background of elderly subjects

Group		Total	HRB & RB	HRB	RB
n		50	36	48	38
gender	Male	15	9	15	9
	Female	35	27	33	29
	Ratio (M / F)	0.43	0.33	0.45	0.31
Age (years)	Min－Max	70 - 95	70 - 95	70 - 95	70 - 95
	Mean ± S.D.	84 ± 6.3	84 ± 7.2	84 ± 6.4	84 ± 7.1
Height (cm)	n	29	26	28	27
	Min－Max	132 - 165	132 - 165	132 - 165	132 - 165
	Mean ± S.D.	149 ± 8.0	149 ± 8.2	149 ± 8.2	148 ± 8.0
Weight (Kg)	n	43	36	41	38
	Min－Max	29 - 70	30 - 58	30 - 61	29 - 70
	Mean ± S.D.	43.8 ± 9.39	43.0 ± 7.76	43.6 ± 8.36	43.3 ± 9.05
BMI	n	29	26	28	27
	Min－Max	13.2 - 32.4	13.2 - 26.9	13.2 - 27.6	13.2 - 32.4
	Mean ± S.D.	20.1 ± 4.30	19.2 ± 3.31	19.6 ± 3.65	19.7 ± 4.12
BT (℃)	n	48	36	47	38
	Min－Max	36.2 - 37.1	36.2 - 36.9	36.2 - 37.1	36.2 - 36.9
	Mean ± S.D.	36.5 ± 0.21	36.5 ± 0.21	36.5 ± 0.21	36.5 ± 0.21

Total, all subjects participated in the clinical trial; HRB & RB, subjects administered both HRB and RB according to the plan; HRB, subjects administered HRB at least; RB, subjects administered RB at least.

Table II Background of elderly subjects - Major concomitant syndrome

Major concomitant syndrome	Total	HRB & RB	HRB	RB
Dementia	22 (44.0 %)	18 (50.0 %)	22 (45.8 %)	18 (47.4 %)
Sequela of Cerebral infarction	20 (40.0 %)	13 (36.1 %)	19 (39.6 %)	14 (36.8 %)
Subcapital fracture	12 (24.0 %)	12 (33.3 %)	12 (25.0 %)	12 (31.6 %)
Hypertension	10 (20.0 %)	4 (11.1 %)	9 (18.8 %)	5 (13.2 %)
Congestive Heart failure	8 (16.0 %)	4 (11.1 %)	7 (14.6 %)	5 (13.2 %)
Spondylitis deformans／Osteoporsis	6 (12.0 %)	5 (13.9 %)	6 (12.5 %)	5 (13.2 %)
Osteoarthritis	6 (12.0 %)	5 (13.9 %)	5 (10.4 %)	6 (15.8 %)
Gastriointestinal tract ulcer	5 (10.0 %)	3 (8.3 %)	5 (10.4 %)	3 (7.9 %)
Diabetes mellitus	5 (10.0 %)	3 (8.3 %)	4 (8.3 %)	4 (10.5 %)

Values are number of subjects observed concomitant syndrome(observed rate %). Total, all subjects participated in the clinical trial; HRB & RB, subjects administered both HRB and RB according to the plan; HRB, subjects administered HRB at least; RB, subjects administered RB at least.

Table Ⅲ Comparison of the common cold syndrome(CCS) conditions treated with HRB compared to RB in all subjects participated in the study

Group	HRB		RB	
n	48		38	
Duration of administration(days)	38.4±9.55		30.8±18.10	
Observation term of CCS (days)	1.8±3.86		2.4±5.80	
CCS symptom	n (%)[1)]	Score[2)]	n (%)[1)]	Score[2)]
Cough	12 (25.0 %)	0.0344±0.10578	12 (31.6 %)	0.0742±0.15143
Malaise	7 (14.6 %)	0.0234±0.10012	10 (26.3 %)	0.0649±0.17966
Fever	9 (18.8 %)	0.0202±0.09985	7 (18.4 %)	0.0548±0.17805
Sore throat	5 (10.4 %)	0.0089±0.02890	5 (13.6 %)	0.0207±0.06018
Sputum	3 (6.3 %)	0.0040±0.01653	3 (8.3 %)	0.0038±0.01301
Nasal discharge / Sneezeing	6 (12.5 %)	0.0094±0.03017	3 (8.3 %)	0.0028±0.01034
Chills	2 (4.2 %)	0.0010±0.00481	1 (2.6 %)	0.0006±0.00386
Sore breast	0		1 (2.6 %)	0.0006±0.00386
TOTAL	21 (43.8 %)	0.1013±0.32429	15 (39.5 %)	0.2225±0.48250

Values are mean ± S.D. HRB, subjects administered HRB at least; RB, subjects administered RB at least.
The study was planned as a crossover method in which subjects take both foods in turn for a term of six weeks. Above are the groups with the observations for each and their evaluations.
1) : Number of subjects observed CCS symptom(observed rate %)
2) : The score was calculated by the following methods. The medical stuff recorded the worst condition of each CCS symptom once a day. Zero point CCS symptoms was not observed. When any condition was observed, one point was considered as slightly worse, two points required symptomatic therapy, and three points was considered as a serious phenomenon. However, a serious event was not seen in the study. These were integrated according to the observed term and it was divided by the duration days individually.

Table Ⅳ Comparison of the common cold syndrome (CCS) conditions of 36 subjects treated with HRB compared to RB in both HRB and RB administration according to the plan

Group	HRB		RB		HRB vs RB[3)]
Duration of administration (days)	41.6±1.78		41.1±4.08		–
Observation term of CCS (days)	1.2±2.20		2.6±5.94		p = 0.2721
CCS symptom	n (%)[1)]	Score[2)]	n (%)[1)]	Score[2)]	HRB vs RB
Cough	7 (19.4 %)	0.0180±0.04778	10 (27.8 %)	0.0501±0.11160	p = 0.0626
Malaise	2 (5.6 %)	0.0079±0.03367	8 (22.2 %)	0.0423±0.15070	p = 0.0506
Fever	5 (13.9 %)	0.0040±0.01065	5 (13.9 %)	0.0377±0.15382	p = 0.0702
Sore throat	3 (8.3 %)	0.0053±0.01897	4 (11.1 %)	0.0185±0.05945	p = 0.1003
Sputum	1 (2.8 %)	0.0013±0.00794	2 (5.6 %)	0.0026±0.01106	p = 0.1116
Nasal discharge / Sneezeing	5 (13.9 %)	0.0119±0.03439	2 (5.6 %)	0.0015±0.00633	p = 0.2855
Chills	1 (2.8 %)	0.0007±0.00397	1 (2.8 %)	0.0007±0.00397	p = 0.9680
Sore breast	0		0		–
TOTAL	13 (36.1 %)	0.0491±0.09083	13 (36.1 %)	0.1535±0.38591	p = 0.0426*

Values are mean ± S.D. HRB, observations in term of administered HRB; RB, observations in term of administered RB.
The study was planned as a crossover method in which subjects take both foods in turn for a term of six weeks. Above are the observations of 36 subjects for which both terms can be evaluated.
1) : Number of subjects observed CCS symptom(observed rate %)
2) : The score was calculated by the following method. The medical stuff recorded the worst condition of each CCS symptom once a day. Zero point CCS symptoms was not observed. When any condition was observed, one point was considered as slightly worse, two points required symptomatic therapy, and three points was considered as a serious phenomenon. However, a serious event was not seen in the study. These were integrated according to the observed term and it was divided by the duration days individually.
3) : It evaluated by paired t test. * $p < 0.05$

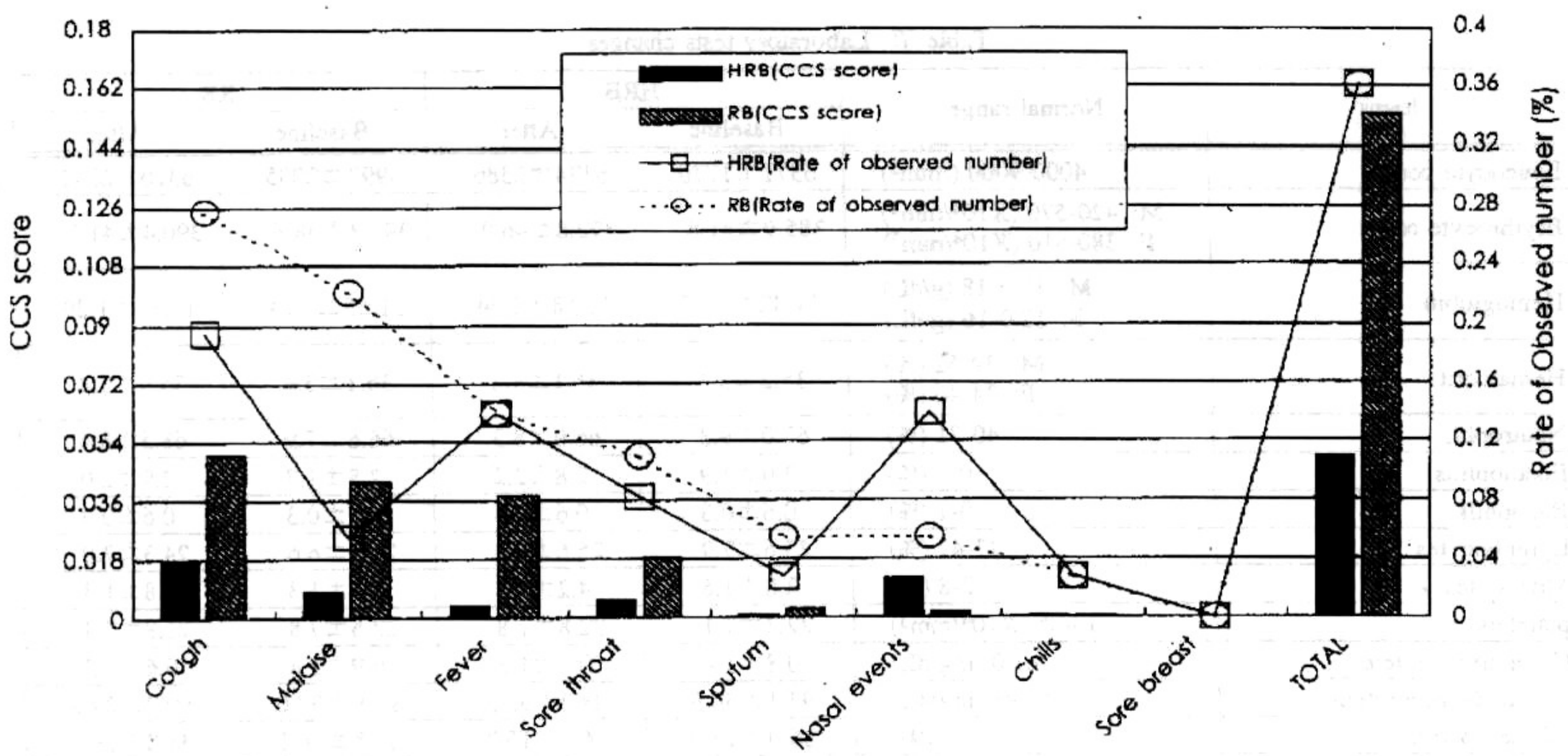

Fig. 1 Comparison of the common cold syndrome (CCS) conditions of 36 subjects treated with HRB compared to RB in both HRB and RB administered according to the plan

Table V Laboratory tests changes

Items	Normal range	HRB		RB	
		Baseline	After	Baseline	After
Total serum protein	6.6-8.4 (g/dL)	6.7±0.51	6.85±0.37	6.85±0.43	6.81±0.38
Serum albumin	3.5-5.2 (g/dL)	3.75±0.30	3.80±0.33	3.84±0.32	3.79±0.31
A/G rate	1.1-2.0	1.31±0.23	1.27±0.24	1.31±0.24	1.29±0.25
Blood urea nitrogen	8-20 (mg/dL)	22.44±6.2	22.15±5.9	22.23±6.5	21.56±5.9
Serum creatinine	0.7-1.5 (mg/dL)	0.95±0.19	0.95±0.18	0.96±0.20	0.93±0.21
Serum total choresterol	130-219 (mg/dL)	196±34	200±33	196±30	200±34
Serum HDL-choresterol	M: 38-72 (mg/dL) F: 43-77 (mg/dL)	49.13±11.62	49.23±11.89	51.87±13.06	49.71±12.33
Serum trigliseride	50-150 (mg/dL)	141±55	164±84	126±56	140±62
Alkaline phosphatase	100-350 (IU/L)	295±76	316±94	298±77	318±89
Cholinesterase	100-240 (IU/L)	125±29	129±31	126±28	128±31
Asparate aminotransferase (AST)	8-40 (IU/L)	18.4±5.3	19.9±8.0	18.4±6.6	18.5±6.4
Alanine aminotransferase (ALT)	5-43 (IU/L)	12.6±6.9	14.8±10.9	12.8±9.0	12.9±9.4
Lactate dehyrogenase	210-470 (IU/L)	338±57	351±100	336±56	357±145
γ-Glutamil transpeptidase	M: <70 (IU/L) F: <35 (IU/L)	16.5±7.3	17.8±7.6	17.3±7.5	16.8±6.4
Leukocyte alkaline phosphatase	30-80 (IU/L)	45±8.5	44.8±8.6	45.4±8.8	44.1±9.0
Vitamin A	431-1,041 (ng/mL)	428±102	451±96	411±121	445±99
Vitamin E	0.75-1.41 (mg/dL)	1.106±0.304	1.104±0.285	1.153±0.315	1.155±0.291
Vitamin B12	233-914 (Pg/mL)	451.4±254.1	443.4±349.6	468.1±323.5	414.7±241.4
Folic acid	2.4-9.8 (ng/mL)	8.46±3.69	9.00±4.77	8.17±4.24	8.87±3.43
Serum Zn	64-111 (μg/dL)	60±10	63±11	62±9	60±9
Serum Cu	70-132 (μg/dL)	118±19	117±23	123±22	120±17
Serum Mg	1.9-2.5 (mg/dL)	2.43±0.32	2.38±0.31	2.37±0.23	2.44±0.28
Serum Fe	M: 80-180 (μg/dL) F: 70-160 (μg/dL)	58.45±20.0	60.58±20.4	62.06±26.0	60.06±21.1
Transferrin	190-320 (mg/dL)	212±43	218±42	207±41	211±37

Values are mean ± S.D. HRB, subjects administered HRB at least; RB, subjects administered RB at least. Difference from baseline was evaluated by paired t test. * $p< 0.05$

Table VI Laboratory tests changes

Items	Normal range	HRB		RB	
		Baseline	After	Baseline	After
Leucocyte count	4000-9000 (/mm³)	6371±1770	6374±2386	5997±2035	6310±2042
Erythrocyte count	M: 420-570 (X10⁴/mm³) F: 380-510 (X10⁴/mm³)	385.9±41.8	392.8±46.0	392.3±38.6	390.4±41.7
Hemoglobin	M: 13.5-18 (g/dL) F: 12.0-16 (g/dL)	11.42±1.17	11.58±1.54	11.65±1.24	11.55±1.29
Hematocrit	M: 39-52 (%) F: 34-46 (%)	35.2±3.1	36.1±4.2	36.1±3.4	35.9±3.4
Neutrophil	40-71 (%)	67.0±9.3	66.9±8.3	66.6±7.9	68.5±8.4
Eosinophils	0-7 (%)	3.0±1.9	2.8±2.2	2.8±1.7	2.9±2.0
Basophils	0-1 (%)	0.6±0.3	0.6±0.3	0.7±0.3	0.6±0.3
Lymphocytes	27-47 (%)	25.6±7.9	25.6±6.4	25.9±6.6	24.3±7.0
Monocytes	2-8 (%)	3.8±1.6	4.2±1.5	4.1±1.3	3.8±1.3
platelets	13-35 (X10⁴/mm³)	22.3±7.1	22.8±7.8	22.5±7.8	21.8±7.4
C-reactive protein	<1.0 (mg/dL)	0.8±1.4	0.7±1.2	0.9±1.8	0.6±1.3
α 1-acidglycoprotein	42-93 (mg/dL)	93.1±30.9	88.3±32.3	95.9±39.0	90.2±29.8
NK cell activity	(%)	36.9±17.0	36.4±15.7	38.8±16.1	38.8±18.7
neutrophil phagocytosis function	70-87 (%)	79.6±8.4	80.2±8.4	76.5±10.2	79.5±9.5
lymphocyte blastgenesis, mitogensPHA	41000-79900 (cpm)	54605±17372	50487±15897*	47470±20582	37146±20506*
lymphocyte blastgenesis (control)	180-660 (cpm)	298±189	367±221	337±205	400±142

Values are mean ± S.D. HRB, subjects administered HRB at least; RB, subjects administered RB at least. Difference from baseline was evaluated by paired t test. * $p< 0.05$

3. Safety

No subjects given HRB and/or RB showed changes in symptoms or laboratory test values. Among the 36 comparison subjects, 31 underwent planned laboratory tests. Tables V and VI show changes in laboratory test values (mean ± standard deviation) in these subjects. A significant decrease before and after ingestion was observed in PHA stimulated lymphocyte blastogenesis ($p<0.05$). All other changes in laboratory test items were minor and showed no consistent trend.

The test values for PHA stimulated lymphocyte blastogenesis decreased for the ingestion of both foods but the degree of decrease was greater for RB than for HRB, and the difference was statistically significant. There was no difference in NK cell activity before and after either HRB or RB ingestion.

Discussion

The common cold syndrome is caused by viruses frequently encountered in our daily life. There is no specific remedy and the only rational approach is to treat symptoms, observe the clinical course, and wait for host's own immune system to effect healing naturally[11]. Some causal viruses are transmitted via air or in droplet spray from the infection source and thus isolation and protection are difficult. To prevent an epidemic and to stop infected patients from getting worse, it is important to improve immunity by various methods including vaccination, and medical agencies should take adequate measures to see that these measures are implemented. Vaccination priority is given to populations with low immunity, including immunologically naïve children and elderly people with decreased immunity[12,13]. Cellular immunity, mainly mediated by T cells, is low in the elderly and it is reported that decreased activity of daily living (ADL) leads to decreased immunity in the elderly[14]. For the elderly at high risk of common cold syndrome and its more serious sequelae, it is important to prevent common cold syndrome by increasing resistance.

The clinical usefulness of RIBEX containing HRB was examined in infection with common cold syndrome. A series of symptoms that starts

with viral infection are caused by the immune response reactions and respiratory clearing mechanism and thus it is appropriate to use observations of these symptoms as indicators of the immunomodulatory effect of HRB[15]. Immunity tests were also included, based on previous studies of HRB.

RIBEX, a food product containing HRB, is produced by Daiwa Pharmaceutical Co., Ltd. It is a medicinally effective way of utilizing rice, which has long been the staple food of the Japanese people. HRB is a water-soluble dietary fiber derived from rice bran and contains partially hydrolyzed arabinoxylan. It has been reported to modulate immunity[2-7], scavenge active oxygen[8], improve sugar metabolism[9], and to reduce the adverse effects of some chemicals[10]. This study was conducted to evaluate the usefulness of HRB (that has an immunomodulatory function) in preventing common cold syndrome in elderly people with decreased immunity and resistance.

RB is a water-soluble extract from rice bran, containing a lot of dietary fiber and nutrients. Thus, it cannot be said to be a perfect placebo but we chose RB as the control food because the taste of HRB and RB are the same and both are rice bran derived foods.

Subjects were 50 elderly people, who were residents at Atreyu Uozaki, a care facility for the elderly and who gave their consent to participate in this study. Among them, 36 completed the necessary observations and tests for both periods of HRB and RB administration. The main reason for subjects discontinuing the study was leaving the facility. No subjects withdrew from the study due to adverse reactions to the study food. As there was no difference in background factors between all 50 subjects and the 36 comparison subjects, results for the 36 comparison subjects were compared and statistically analyzed.

The study was performed using the cross over method, where HRB and RB were given to the same subjects for 6 weeks each. The mean ingestion period for subjects including cases of discontinuation was 38.4 days for the HRB group (48 subjects) and 30.8 days for the RB group (38 subjects). In the 36 comparison subjects, the mean ingestion period exceeded 41 days. Subjects remained at the facility under ideal conditions that allowed the usefulness of the food to be properly evaluated. There was little variation in room humidity and temperature, the amount of exercise, and meals and the study period for both groups were roughly equal.

When the study was conducted, there was no epidemic of influenza in the district where the care facility was according to MHLW's infection trend survey. Influenza causes a severe fever and symptoms easily worsen and thus HRB may not have the same effect on influenza as seen in this study. Although the causal viruses of common cold syndrome were not specified in this study, the types of causal viruses may not have been numerous because the study was conducted within the same closed facility. In this study, common cold syndrome may have been caused by common cold viruses such as adenovirus and Coxsackievirus that cause pharyngitis, coronavirus and rhinovirus that cause rhinitis and febrile inflammation, and parainfluenza virus and respiratory syncytial virus. All infections caused by these viruses have a similar clinical profile and it can be expected that HRB would produce the same effect as shown in this study.

If a multicenter study were to be conducted, planning and analysis would face a significant difficulty because the difference between facilities in terms of background factors such as living conditions and the mode of infection spread have a considerable influence on clinical efficacy. Among common cold symptoms, cough, malaise, fever, and sore throat were more frequent in both food ingestion periods, reflecting acute immune reactions. These were followed by sputum and nasal symptoms. Almost no subjects complained of chest pain and there was no case of pneumonia secondary to worsened common cold syndrome. Symptoms were scored using 3 grades based on the results of evaluation by the physicians and medical staff at the facility. "Mild" (1 point) and "Moderate" (2 points) were differentiated according to the presence or absence of symptomatic therapy. "Severe" (3 points) indicated serious symptoms but no subjects had symptoms falling into this category.

The duration of symptoms and symptom scores changed in a similar way in all 50 subjects and the 36 comparison subjects. In the 36 comparison subjects, the number of subjects with one or more symptoms was 13 (36.1%) in both ingestion periods but the total score for symptoms was significantly higher in the RB ingestion period ($p<0.05$). As the study food was given preventively, the number of subjects with symptoms should theoretically have been different between HRB and RB ingestions if the study food had a preventive effect on primary infection of the nasal membrane. However, no difference was observed between HRB and RB but the total score for symptoms was different, suggesting that HRB acts on the expression and progression of symptoms after primary infection.

For individual symptoms, although the score for nasal symptoms was lower, those for cough, malaise, fever, and sore throat were higher in RB ingestion, but without a statistically significant difference. The duration of symptoms was 1.2 days for HRB ingestion and 2.6 days for RB ingestion. The difference in the symptom scores was more significant than the difference in the duration of symptoms between HRB and RB ingestions. The duration of the general symptoms of malaise and fever and the upper airway inflammatory symptoms, cough and sore throat, shortened in the HRB ingestion period. These results may have been obtained because HRB exerted an immunomodulatory effect and suppressed excessive inflammation. On the other hand, the score for nasal symptoms was higher for HRB ingestion. One possible explanation for this was that the subjects recovered the ability to discharge secretions from the upper airway and nasal membranes, which is associated with immune response and which is usually decreased in the elderly. In a clinical study on respiratory infection artificially induced by cold viruses, nasal symptoms were prominent, suggesting that cold viruses entered the body mainly through the nasal cavity. It was considered that HRB did not prevent primary infection itself but relieved cold symptoms by shortening the duration of symptoms and by decreasing the need for symptomatic therapy. HRB may have contributed to a reduction in the degree of physical stress during the acute phase of infection and prevented any worsening of the condition through a mechanism different from anti-inflammatory action.

In laboratory tests to monitor safety and changes in immune parameters, there was no clinically significant change before and after ingestion in any parameter, with the exception that PHA stimulated lymphocyte blastogenesis. No adverse reaction was observed. Thus, it was considered that HRB was safe. The PHA stimulated lymphocyte blastogenesis test is to induce the blastogenesis of T cells responsible for cellular immunity in the blood by the selective stimulator phytohemagglutinin (PHA) and to determine the degree of blastogenesis using DNA synthesis. Although elderly people have decreased cellular immunity, the degree of decrease was lower in the HRB ingestion phase during the study, suggesting the possibility that the T cell function might be normalized through the immunomodulatory effect of HRB.

There are many studies reporting that NK cell activity is increased by HRB ingestion[2,4,6]. However, no significant change was observed before and after ingestion in the present study. One possible reason for this is that the NK cell activity was relatively high in our subjects: the mean value exceeded 30%. This may be because the subjects were adequately cared for under good nutritional, daily-environmental, and sanitary conditions. The NK cell activity decreased to under 20% in 6 subjects given HRB and 7 given RB, 3 of whom had a low value less than 10%. As mentioned above, however, an immunomodulatory effect was noticed. A further study is needed to elucidate the relationship with these immune parameters.

It has been reported that oral HRB has an immunomodulatory effect[2-7]. In the present study, HRB reduced common cold symptoms in subjects with adequate NK cell activity. This suggests that the effect of HRB may consist of not only enhancement of NK cell activity, as previously reported, but also stimulation of the entire immune system including humoral immunity or control of excessive expression of

local and systemic physiological responses such as fluid secretion and fever.

The hydrolysis rice bran given orally, based on its immunomodulatory effect, shortened the duration of common cold symptoms and reduced the severity of symptoms and the need for symptomatic therapy in elderly subjects in this study. The hydrolysis rice bran was shown to be useful in the reduction of physical stress at the early stage of respiratory infection.

Conclusion

The preventive effect of RIBEX on common cold syndrome was studied in elderly people. RIBEX contains HRB, consisting of arabinoxylan derivatives produced by processing the water soluble dietary fiber extracted from rice bran with carbohydrases contained in shiitake mushrooms. The control food was an extract from rice bran without chemical or biotechnological treatment. These foods were given for 6 weeks each in a double-blind cross-over manner. Subjects were 50 elderly people at a care facility for the elderly. A total of 36 subjects completed both ingestion periods and allowed comparison between HRB and RB in the same subject. The main reason for discontinuation was leaving the facility and there was no withdrawal because of adverse reactions. The symptoms of cough, malaise, fever, sore throat, sputum, nasal symptoms, and chest pain were observed by the medical staff in the facility and scored based on the medical staff's judgment. The number of subjects with one or more symptoms was 13 (36.1%) for both groups but the total symptom score was significantly higher for RB ingestion ($p<0.05$). The duration of symptoms was 1.2 days for HRB ingestion and 2.6 days for RB ingestion but no significant difference was observed. Although many researchers reported that HRB increased NK cell activity, no significant change was observed in this study possibly because our subjects had high NK activity before ingestion.

In conclusion, HRB shortened the duration of common cold symptoms and reduced the severity of symptoms and the need for symptomatic therapy, demonstrating its usefulness in reducing physical stress at the acute stage of respiratory infection.

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References

1) Fujimoto, S., Okui, S.: Gan to menneki (Cancer and immunity). pp. 88-95, K.K. Medical Review, Tokyo, Japan, 1988 (in Japanese).

2) Ghoneum, M.: Enhancement of Natural Killer cell activity by modified Arabinoxylan from Rice Bran (MGN-3). *Int. Immunotherapy* 14, 89-99, 1998.

3) Ghoneum, M.:Anti-HIV activity in vitro of MGN-3, an activated Arabinoxylan from Rice Bran. *Biochem Biophys Res Commun* 243, 25-29, 1998.

4) Ghoneum, M., Brown, J.: NK immunorestoration of cancer patients by MGN-3, a modified Arabinoxylan from Rice Bran (Study of 32 patients followed for up to four years). *Anti-Aging Medical Therapeutics* 3, 217-226, 1999.

5) Ghoneum, M., Jewett, A.: Production of Tumor Necrosis Factor alpha and Interferon-gamma form human peripheral blood lymphocytes by MGN-3, a modified Arabinoxylan from Rice Bran, and its synergy with Interleukin-2 in vitro. *Cancer Detect Prev*. 24, 314-324, 2000.

6) Maeda, H.: Immunostimulation effects of Rice Bran Arabinoxylan. *Food Style* 21 31, 56-58, 1999 (in Japanese).

7) Kubo, C., Sudo, N., XN Yu, Oyama, N., Nukina, H., Hirayama, K.: Biophlatic enhancement effects of MGN-3. *Clinical and Research*, 78, 193-196, 2001 (in Japanese).

8) Tazawa, K., Namikawa, H., Oida, N., Itch, K., Yatsuzuka, M., Koike, J., Masada, M., Maeda, H.: Scavenging activity of MGN3 (Arabinoxylan from Rice Bran) with Natural

Killer cell activity on free radicals. *Biotherapy* 14, 493-495, 2000 (in Japanese with English abstract).

9) Ohara, L, Tabuchi, R., Onai, K.: Effects of modified Rice Bran on serum lipid and taste preference in Streptozotocin-induced diabetes rats. *Nutritution Res*. 20, 59-68, 2000.

10) Jacoby, H., Wnorowski, G., Sakata, K. and Maeda, H.: The effect of MGN-3 on Cisplatin and Adriamycin induced toxicity in the rat. *Gastroenteology* 118, 4962, 2000.

11) Nagatake, T., Yamashita, H., Degawa, S.:Kaze Shoukougun no chiryou (Treatment of common cold syndrome). *J. Jpn. Soc. Intern*. Med. 87, 79-85, 1998 (in Japanese).

12) Kobashi, Y., Ohba, H., Yoneyama, H., Okimoto, N., Matsushima, T., Soejima, R.: Clinical analysis of patients with community-acquired pneumonia requiring hospitalization classified by age group. *J. Infect. Chemother*. 75, 193-200, 2001 (in Japanese with English abstract).

13) Kaji, M., Tsuru, T., Oizumi, K.: Efficacy and safety of influenza vaccination to elderly patients with neurological disease. *J. Infect. Chemother*. 75, 411-415, 2001 (in Japanese with English abstract).

14) Moriguchi, S., Muraga, M., Shimizu, E.: Effect of nutrition and exercise on decrease cellular immunity in the aged. *J. Jpn. Soc. Nutr. Food Sci*. 53, 23-27, 2000 (in Japanese).

15) George Gee Jakson, Harry F. Dowling, Irwin G. Spiesman, Arthur V. Boand: Transmission of common cold to volunteers under control conditions. *Arch. Intern. Med.* 101, 267-278, 1958.