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Improving Effects of the Mushroom Yamabushitake (*Hericium erinaceus*) on Mild Cognitive Impairment: A Double-blind Placebo-controlled Clinical Trial

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A double-blind, parallel-group, placebo-controlled trial was performed on 50- to 80-year-old Japanese men and women diagnosed with mild cognitive impairment in order to examine the efficacy of oral administration of Yamabushitake (*Hericium erinaceus*), an edible mushroom, for improving cognitive impairment, using a cognitive function scale based on the Revised Hasegawa Dementia Scale (HDS-R). After 2 weeks of preliminary examination, 30 subjects were randomized into two 15-person groups, one of which was given Yamabushitake and the other given a placebo. The subjects of the Yamabushitake group took four 250 mg tablets containing 96% of Yamabushitake dry powder three times a day for 16 weeks. After termination of the intake, the subjects were observed for the next 4 weeks. At weeks 8, 12 and 16 of the trial, the Yamabushitake group showed significantly increased scores on the cognitive function scale compared with the placebo group. The Yamabushitake group's scores increased with the duration of intake, but at week 4 after the termination of the 16 weeks intake, the scores decreased significantly. Laboratory tests showed no adverse effect of Yamabushitake. The results obtained in this study suggest that Yamabushitake is effective in improving mild cognitive impairment.

Keywords: Yamabushitake; Hericium; HDS-R; dementia; Alzheimer's disease.

INTRODUCTION

Senile dementia is a serious social problem. In particular, Alzheimer's disease remains without effective therapeutic measures. Alzheimer patients have notable abnormalities in cholinergic neurons in the basal forebrain (Collerton, 1986). Among the neurotrophic factors promoting the differentiation and survival of neurons, nerve growth factor (NGF) especially acts on cholinergic neurons in the central nervous system, and therefore, is expected to be applied for the treatment of Alzheimer's disease (Takei *et al.*, 1989). However, NGF protein is unable to cross the blood–brain barrier, and its application to medicines is difficult. Alternatively, research is carried out on low-molecular weight compounds that promote NGF biosynthesis.

Yamabushitake (*Hericium erinaceus*) is a mushroom that grows on both living and dead broadleaf trees. Yamabushitake is used as food in Japan and China. Hericenones C–H (Kawagishi *et al.*, 1990, 1991, 1993) and erinacines A–I (Kawagishi *et al.*, 1994, 1996; Lee *et al.*, 2000), compounds capable of promoting NGF synthesis in cultured astrocytes, were isolated from the fruit body and mycelium of Yamabushitake, respectively. These results spotlighted the usefulness of Yamabushitake for the treatment and prevention of dementia.

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Regarding other mushrooms, *Sarcodon scabrosus* (Obara *et al.*, 1999) and *Dictyophora indusiata* (Kawagishi *et al.*, 1997) are reported to have components, scabronins and dictyophorines, which promote NGF synthesis. However, these mushrooms are difficult to put to practical use because cultivation techniques have not yet been established for them. In contrast, Yamabushitake can be cultivated in large quantities throughout the year in facilities. In short, Yamabushitake is an easily available, promising food.

However, there are few reports about the effects of oral intake of Yamabushitake on cognitive impairment, whether from human or animal experiments. Consequently, the efficacy of oral administration of Yamabushitake was examined in patients diagnosed with mild cognitive impairment, using a cognitive function scale based on the Revised Hasegawa Dementia Scale (HDS-R) as an indicator. Though Yamabushitake seemed to be safe because it has long been eaten with no report of harmful effects, laboratory tests were performed to confirm the absence of adverse effects of Yamabushitake.

METHODOLOGY

Patients. The subjects were 30 Japanese men and women from 50 to 80 years old who were diagnosed with mild cognitive impairment, scoring 22 to 25 out of 30 points on a cognitive function scale based on the Revised Hasegawa Dementia Scale in a preliminary examination. They were leading a clinically healthy life with no other disorder

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Table 1. Composition of the test foods

Component	Yamabushitake (%)	Placebo (%)
Yamabushitake powder	96.0	0.0
Cornstarch	0.0	20.0
Lactose	0.0	70.0
Caramel	0.0	2.0
Silicon dioxide	1.6	4.0
Fat	2.4	4.0

Table 2. Nutrient composition of the test foods

Component	Yamabushitake	Placebo
Energy (kcal/100 g)	253	388
Protein (g/100 g)	41.1	0.3
Carbohydrate (g/100 g)	38.0	93.1
Fat (g/100 g)	4.4	1.9
Sodium (mg/100 g)	0.9	34.8

seen as a problem in the examination. This experiment was conducted with the approval of the Institutional Review Board at Isogo Central and Neurosurgical Hospital, and with the written consent of the subjects in accordance with the Declaration of Helsinki (revised in 2004).

Test food. Yamabushitake used for the test food was cultured by Hokuto Corporation in its facilities (Nagano Japan). The fresh fruit bodies of Yamabusitake were air-dried at 60 °C overnight and powdered. The test food was 250 mg tablets containing 96% of Yamabushitake, prepared by adding silicon dioxide and fat to Yamabushitake powder, and tablets of the same shape containing cornstarch and lactose instead of Yamabushitake powder (Table 1). The nutrient composition of the test food is shown in Table 2. The subjects took four Yamabushitake-containing or placebo tablets three times a day for 16 weeks.

Design. The study consisted of a double-blind, parallel-group, placebo-controlled trial, performed by randomizing the 30 subjects into two 15-person groups, the Yamabushitake and placebo groups. There was no difference between the two groups, neither in scores on the cognitive function evaluation scale determined in the preliminary examination nor in the subjects' ages.

The total duration of the study was 22 weeks, consisting of 2 weeks of preliminary examination, 16 weeks of test food intake and 4 weeks of follow-up observation.

The use of donepezil hydrochloride which is the only drug that has received approval for use in Alzheimer's disease patients in Japan was restricted during the trial period. Drugs having possibilities of improvement of cognitive impairment by an increase of cerebral brood flow (ifenprodil tartrate, sermion, meclofenoxate, ibudilast, amantadine hydrochloride, tiapride hydrochloride, calcium hopantenate) were also restricted. In addition, the intake of foods reported to affect cognitive impairment, such as ginkgo leaf extract (Maurer *et al.*, 1997) or those containing a significant amount of DHA (Hashimoto *et al.*, 2005; Lim *et al.*, 2005), were restricted. The subjects were directed to record the intake of the test foods and subjective symptoms as well as changes in lifestyle in their diaries throughout the trial period.

Cognitive function scale. The degree of cognitive impairment was expressed as a score on a cognitive function scale developed by us, based on the Revised Hasegawa Dementia Scale (HDS-R) (Imai and Hasegawa, 1994). The Mini-Mental State Examination (MMSE) has been used most widely for screening cognitive impairment. However, since it was originally developed to evaluate elderly psychiatric patients rather than cognitive impairment patients, it is criticized for its level of sensitivity and specificity for cognitive impairment patients. The HDS-R, which has been used exclusively in East Asian countries, has reported to be more accurate than MMSE as a screening instrument for Alzheimer's disease (Kim *et al.*, 2005).

HDS-R is basically a verbal test, so a drawing test was added to evaluate visuospatial and constructional functions. On the drawing test, the subjects were requested to draw all numbers to make a clock on the pre-drawn 3 cm circle, and a score of 2 was given if the all numbers were present in the correct position. The HDS-R was reduced to a total score of 28 points from 30 points, and the drawing test was added as 2 points, making a total score of 30 points.

Laboratory tests. Any adverse effect of the test food was checked by laboratory tests: the body weight, body mass index (BMI), systolic/diastolic blood pressure, pulse rate, body temperature, blood tests (white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, platelet, total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), total cholesterol, HDL-cholesterol (HDL), triglyceride, LDL-cholesterol (LDL), uric acid, blood urea nitrogen (BUN), creatinine, glucose, sodium (Na), chlorine (Cl), potassium (K) and serum iron (Fe)) at weeks 0, 8 and 16 of the trial.

Statistical analysis. The values obtained were expressed as mean ± standard deviation. The statistical processing was performed using Stat View 5.0 for Windows (SAS Institute, Inc.). Within-group variations between points in time were subjected to one-way repeated measures ANOVA, followed by multiple comparisons (Bonferroni/Dunn test). Between-group comparison at each point in time was analysed by unpaired Student's *t*-test. Also, a two-way repeated measures ANOVA was performed to assess the significant between-period differences and between-group differences as well as group-by-period interaction.

RESULTS

One subject was excluded from the statistical analysis. The subject voluntarily withdrew from the trial 4 weeks after its start, reporting stomach discomfort, although not severe enough to require withdrawal. Consequently, 29 subjects, 14 of the Yamabushitake group and 15 of the placebo group, were analysed statistically. None of these subjects interrupted test food intake or experienced

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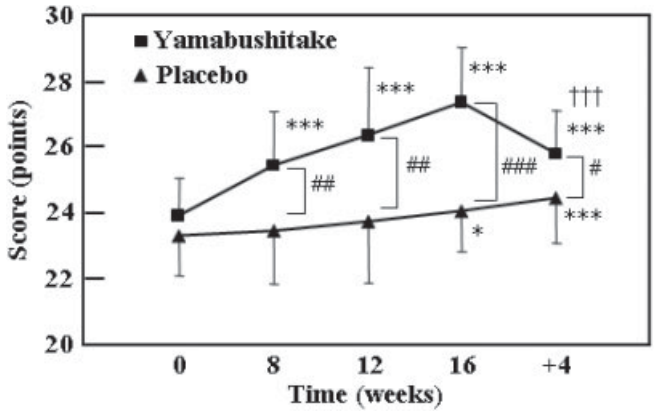

Figure 1. Score of the cognitive function scale. * $p < 0.05$, *** $p < 0.001$ vs week 0. ††† $p < 0.001$ vs week 16. #, ##, ### $p < 0.05$, 0.01, 0.001 Yamabushitake vs placebo at the same time.

changes in physical condition or lifestyle that could work against the trial.

The two-way repeated measures ANOVA showed significant between-group differences ($p < 0.001$) and between-period differences ($p < 0.001$) in scores on the cognitive function scale (Fig. 1) and also a group-by-period interaction ($p < 0.001$). At weeks 8, 12 and 16 of test food intake, and 4 weeks of follow-up, the Yamabushitake group showed significantly increased scores compared with the placebo group. The Yamabushitake group's scores increased with the duration of intake, but during the 4 weeks after the termination of the 16 week intake, the scores decreased significantly. The placebo group showed significantly increased scores at week 16. A comparison of both group's scores at week 16 with those at the start of intake (Fig. 2) revealed that 11 cases were judged 'notably improved' by a 3 and more point increase, 10 (71.4%) in the Yamabushitake group and 1 (6.7%) in the placebo group, and 4 cases were judged 'improved' by a 2 point increase, 3 (21.4%) in the Yamabushitake group and 1 (6.7%) in the placebo group. One case (7.1%) in the Yamabushitake group and 13 cases (86.7%) in the placebo group were judged 'unchanged' by a score shift of 1, 0 or –1. Neither of the groups had a case judged as worsened by a 2 or more point decrease.

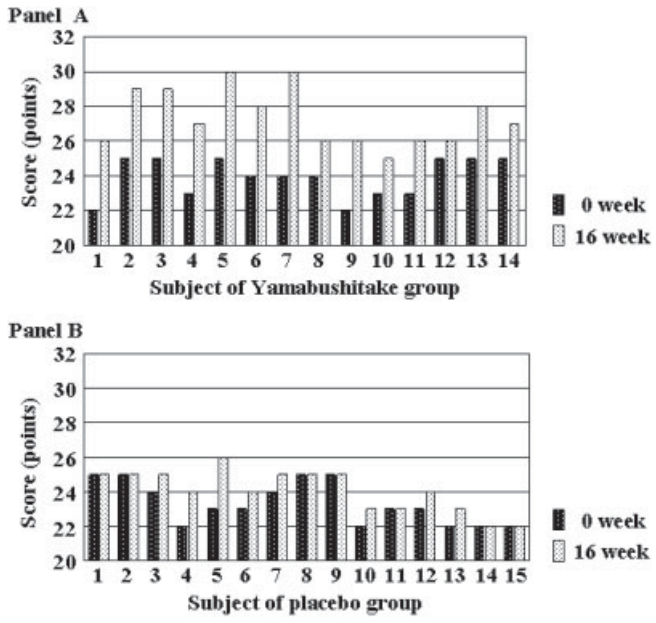

Figure 2. Individual cognitive function scale score of Yamabushitake group (A), and placebo group (B) at weeks 0 and 16.

Meanwhile, in the laboratory tests (Table 3), the placebo group showed significant within-group variations in systolic blood pressure, AST (GOT), LDH, HDL-cholesterol and Cl, and the Yamabushitake group showed significant within-group variations in creatinine (CRE), Na and K, but all these variations were within the normal range. Also, the two groups showed significant between-group differences in total cholesterol at the start of trial, and in uric acid (UA) at week 16, and in creatinine at the start and week 16, but all within the normal range. While seven subjects of the Yamabushitake group and six subjects of the placebo group reported poor physical condition, all these cases were mild stomach discomfort and diarrhea, requiring no treatment.

DISCUSSION

On the cognitive function scale, Yamabushitake group increased the score dependent on the intake period of Yamabushitake, showing significant differences compared with the placebo group at weeks 8, 12 and 16 of the trial. But the Yamabushitake group score decreased significantly after 4 weeks of follow-up observation compared with the score at week 16. Thus, Yamabushitake is effective in improving the mild cognitive impairment reversibly, and its continuous intake is necessary to maintain the effect. The scores of the placebo group also showed significant increases at weeks 8 and 16 compared with the start of the trial. Possible causes of such an increase in the placebo group might be the placebo effect or due to the habituation of the subjects with the cognitive function scale.

There are reports about hericenones C-H, capable of promoting NGF synthesis, isolated from the fruit body of Yamabushitake (Kawagishi *et al.*, 1991, 1993). However, many of these reports come from studies using cultured astrocytes from rodents, and it is still unknown whether hericenones show an analogous effect on human cells or whether they are able to pass through the brain–blood barrier into the brain to promote NGF synthesis *in vivo*. The improvement of cognitive impairment observed in our trial may be attributed to the effects of hericenones, but further studies are needed to determine the active ingredients and the mechanism of action.

The laboratory tests showed statistically significant within-group variations or between-group differences, but those were small variations within the standard value range or the imbalance that is incidentally generated by the random grouping, indicating that the differences were not clinically meaningful. Although seven subjects of the Yamabushitake group and six subjects of the placebo group reported stomach discomfort or diarrhea, all these cases were mild requiring no treatment, and there was no difference in the incidence between the groups. These results suggest that the intake of Yamabushitake is effective for improving mild cognitive impairment without serious adverse effects.

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Table 3. Result of laboratory tests

Parameter	Time	Yamabushitake	Placebo
Body weight (kg)	W0	54.49 ± 11.40	61.15 ± 13.74
	W8	54.37 ± 11.31	61.65 ± 13.90
	W16	54.20 ± 11.42	61.48 ± 13.70
BMI (kg/m^2)	W0	22.65 ± 3.58	23.60 ± 3.67
	W8	22.60 ± 3.53	23.59 ± 3.70
	W16	22.53 ± 3.59	23.53 ± 3.63
Systolic blood pressure (mmHg)	W0	123.0 ± 17.0	128.5 ± 15.3
	W8	128.1 ± 20.0	129.1 ± 14.6
	W16	120.8 ± 21.7	125.5 ± 14.5[d]
Diastolic blood pressure (mmHg)	W0	73.9 ± 16.1	79.9 ± 10.5
	W8	75.2 ± 14.9	80.5 ± 10.9
	W16	74.7 ± 17.6	76.8 ± 10.0
Pulse rate (beats/min)	W0	72.5 ± 11.2	78.1 ± 13.2
	W8	70.7 ± 7.8	76.1 ± 9.9
	W16	72.0 ± 12.1	74.1 ± 10.7
Body temperature (°C)	W0	36.16 ± 0.54	35.99 ± 0.43
	W8	36.08 ± 0.38	35.91 ± 0.37
	W16	36.07 ± 0.32	35.99 ± 0.36
WBC ($\times 10^3$/mL)	W0	5.57 ± 1.33	6.51 ± 1.56
	W8	5.41 ± 1.33	6.01 ± 1.32
	W16	5.25 ± 1.29	6.09 ± 0.97
RBC ($\times 10^4$/mL)	W0	431.4 ± 38.3	449.8 ± 45.4
	W8	436.4 ± 40.5	446.1 ± 49.3
	W16	438.4 ± 29.8	454.9 ± 41.5
Hemoglobin (g/dL)	W0	13.18 ± 1.09	13.83 ± 1.60
	W8	13.36 ± 1.29	13.70 ± 1.65
	W16	13.49 ± 1.02	13.85 ± 1.55
Hematocrit (%)	W0	39.61 ± 3.11	41.28 ± 4.04
	W8	40.28 ± 3.89	40.82 ± 4.26
	W16	40.74 ± 3.23	41.39 ± 3.45
Platelet ($\times 10^4$/mL)	W0	25.49 ± 6.27	23.98 ± 6.32
	W8	24.98 ± 6.50	24.30 ± 6.64
	W16	24.10 ± 6.15	23.86 ± 5.12
Total protein (g/dL)	W0	7.25 ± 0.46	7.25 ± 0.43
	W8	7.19 ± 0.33	7.13 ± 0.37
	W16	7.25 ± 0.25	7.19 ± 0.37
Albumin (g/dL)	W0	4.43 ± 0.24	4.37 ± 0.23
	W8	4.34 ± 0.22	4.27 ± 0.29
	W16	4.46 ± 0.17	4.36 ± 0.27
Total bilirubin (mg/dL)	W0	0.61 ± 0.20	0.59 ± 0.18
	W8	0.52 ± 0.16	0.65 ± 0.21
	W16	0.64 ± 0.12	0.70 ± 0.30
AST (U/L)	W0	27.9 ± 8.5	24.5 ± 7.2
	W8	25.2 ± 13.2	22.5 ± 6.36[d]
	W16	25.1 ± 8.1	20.9 ± 5.1[f]
ALT (U/L)	W0	26.8 ± 14.8	22.7 ± 16.6
	W8	21.8 ± 15.6	21.7 ± 13.6
	W16	23.2 ± 10.6	20.3 ± 12.2
ALP (U/L)	W0	219.8 ± 80.7	252.6 ± 55.4
	W8	227.9 ± 84.5	239.5 ± 49.6
	W16	210.8 ± 69.3	244.6 ± 44.7
LDH (U/L)	W0	221.8 ± 36.1	215.9 ± 59.3
	W8	211.1 ± 31.8	199.6 ± 40.1[d]
	W16	213.9 ± 35.0	202.5 ± 36.1[d]
γ-GTP (U/L)	W0	27.9 ± 16.6	28.2 ± 12.3
	W8	28.9 ± 19.9	28.4 ± 12.4
	W16	29.3 ± 17.4	28.7 ± 13.3
Total cholesterol (mg/dL)	W0	236.7 ± 33.2[a]	210.9 ± 33.8
	W8	227.3 ± 30.7	210.5 ± 36.5
	W16	283.9 ± 41.0	213.7 ± 36.0
HDL (mg/dL)	W0	71.8 ± 21.0	61.3 ± 12.5
	W8	68.1 ± 24.4	57.5 ± 12.1[d]
	W16	73.6 ± 20.2	61.2 ± 13.2
Triglyceride (mg/dL)	W0	121.9 ± 103.4	126.5 ± 80.3
	W8	116.0 ± 76.6	140.3 ± 104.9
	W16	90.6 ± 41.2	110.1 ± 61.7

Table 3. (*Continued*)

Parameter	Time	Yamabushitake	Placebo
LDL (mg/dL)	W0	123.3 ± 36.5	120.0 ± 31.6
	W8	130.1 ± 28.5	124.5 ± 30.7
	W16	137.2 ± 36.6	124.7 ± 30.4
Uric acid (mg/dL)	W0	4.59 ± 0.98	5.35 ± 1.30
	W8	4.62 ± 0.73	5.43 ± 1.43
	W16	4.22 ± 0.55[c]	5.57 ± 1.16
BUN (mg/dL)	W0	14.01 ± 3.53	15.12 ± 5.95
	W8	13.56 ± 3.83	15.17 ± 4.79
	W16	13.92 ± 3.52	15.98 ± 5.92
Creatinine (mg/dL)	W0	0.634 ± 0.110[a]	0.786 ± 0.207
	W8	0.647 ± 0.112	0.757 ± 0.196
	W16	0.591 ± 0.104[b,d]	0.758 ± 0.202
Blood glucose (mg/dL)	W0	100.6 ± 17.6	105.8 ± 24.0
	W8	98.6 ± 39.6	107.9 ± 24.4
	W16	105.2 ± 30.8	108.3 ± 36.1
Na (mEq/L)	W0	144.2 ± 1.5	143.7 ± 1.4
	W8	144.2 ± 1.2	143.3 ± 2.0
	W16	143.0 ± 1.9[d]	143.5 ± 2.13
Cl (mEq/L)	W0	104.4 ± 2.9	104.8 ± 2.6
	W8	104.3 ± 2.6	103.4 ± 2.5[e]
	W16	103.4 ± 1.9	104.0 ± 2.2
K (mEq/L)	W0	4.10 ± 0.25	4.22 ± 0.55
	W8	4.16 ± 0.40	4.21 ± 0.42
	W16	4.29 ± 0.25[d]	4.28 ± 0.37
Fe (mg/dL)	W0	98.7 ± 36.0	97.7 ± 32.0
	W8	83.6 ± 26.1	98.1 ± 33.4
	W16	95.9 ± 28.9	103.7 ± 28.6

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ vs placebo. [d] $p < 0.05$, [e] $p < 0.01$, [f] $p < 0.001$ vs week 0.

At present, acetylcholinesterase inhibitors such as donepezil hydrochloride are favored as therapeutic agents for Alzheimer's disease (Rogers *et al.*, 1998). They can alleviate the symptoms and delay the progression of Alzheimer's disease. However, complete prevention or treatment of Alzheimer's disease has not yet been achieved by any method. According to available reports, the etiology of Alzheimer's disease includes many factors: genetic such as mutations in the amyloid precursor protein, presenilin-1 and presenilin-2 genes, and environmental such as depression, traumatic brain injury, cardiovascular disease, smoking, and diet including calorie intake, vitamins, fat and alcohol (Luchsinger and Mayeux, 2004; Mattson, 2003). Although the way to complete prevention of Alzheimer's disease is also unknown, the data obtained in this study suggest that continuous intake of foods which promote NGF synthesis may be one of the effective ways to prevent or alleviate Alzheimer's disease. Yamabushitake is a rare food which contains components promoting NGF synthesis. Furthermore, among various foods, mushrooms are known to be low in calories and rich in fiber, and they are safe for patients with diabetes, hyperlipemia and arteriosclerosis, mostly elderly people.

Consequently, Yamabushitake can be regarded as a useful food for the prevention of dementia without any adverse effects. This effect may be attributed to promoting NGF by hericenones, but further studies are needed to clarify the mechanism.

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