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Improvement of cognitive functions by oral intake of *Hericium erinaceus*

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ABSTRACT

Hericium erinaceus has been recognized as medical mushroom since ancient time, but its scientific evidence for human health has been still uncertain. In this study, we tested a randomized, double-blind, placebo-controlled parallel-group comparative study to evaluate the improvement of the cognitive functions by taking supplements containing fruiting body of *H. erinaceus* for 12 weeks. We performed three kinds of tests: Mini Mental State Examination (MMSE), Benton visual retention test, and Standard verbal paired-associate learning test (S-PA). MMSE alone showed that oral intake of *H. erinaceus* significantly improved cognitive functions and prevented from the deterioration. We speculate that various chemical compounds, including hericenones, in the mushroom have multiple effects to the brain neural networks and improve cognitive functions. Oral intake of *H. erinaceus* is safe and convenient method for dementia prevention so far.

Hericium erinaceus (also called lion's mane mushroom, HE) widely distributes in North America, Europe and Asia. The mushroom has been recognized as medical mushroom for long years, and especially popular in the traditional Chinese medicine (15, 27). Recently, we also found its anti-obesity effect during menopause (14) and intake of HE altered the behavioral rhythm (10) by experiments on mice. However, its scientific evidence for human health has been still uncertain. Previously, we showed that oral intake of the mushroom is significantly effective for the improvements of depression and anxiety (30). Numerous chemicals regulating biological functions of human have been found in the mushroom. Especially, hericenones, abundantly contained in the fruiting bodies of HE, seem to be important (17–19). Hericenones activate synthesis of nerve growth factor (NGF) in the astrocytes, which is necessary for the survival of neural cells in the brain (11–13). It has been widely passed down that taking supplements containing HE is also effective for the improvement of cognitive functions, but there has not been any scientific evidence yet. In this study, we tested a randomized, double-blind, placebo-controlled parallel-group comparative study to evaluate the improvement of the cognitive functions by taking the supplement containing HE for 12 weeks. We observed its significant effect for the improvement of cognitive functions.

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MATERIALS AND METHODS

We performed all our study in two institutes: collaboration II building of Kyusyu-university hospital and USL Health-up Salon, both locate in Fukuoka, Japan. All tests strictly followed the declaration of Helsinki, revised at Fortaleza in 2013, and Ethical Guidelines for Medical and Health Research Involving Human Subjects published by Japanese Government in 2014. We gave informed consent before the tests by explaining carefully the purpose and methods of the tests and confirmed that all subjects rec-

ognized them and participated in the study by their own wills.

Effects of HE were evaluated by performing a randomized, double-blind, placebo-controlled parallel-group comparative study (RCT). The method was basically followed by our previous test (30). In short, all participants were randomly divided into two groups: the *H. erinaceus* (HE) group taking four HE supplements in a day, and the placebo group taking four placebo supplements in a day that did not contain HE for 12 weeks. One HE supplement contained 0.8 g of the powdered fruiting body of HE and a placebo supplement did not contain any powder from HE. In our previous study, participants took cookies containing 2.0 g of HE for 4 weeks. However, in this study, we extended the duration to 12 weeks because we speculated that the improvement of cognitive functions needs longer time for remodeling nerve structure in brain.

We carefully sorted the participants by following rules: we selected the participants who are over 50 years old, healthy, and agreed with joining in the test by their own will, and excluded the following persons; who has regularly took any other functional foods, drags or supplements for the similar effects to our tests; who had changed or begun to take any health foods in past 4 weeks; who worked at the night time or by the day-and-night shift; who needed to have any medical treatments such as hormone replacement therapy, drag treatment, exercise therapy or food therapy and so on; who had previously had severe disorders of sugar metabolism, lipid metabolism, liver function, renal function, heart, circulatory organ, respiratory organs, endocrine system, immune system, or neurological diseases; who had a history of alcoholic or drag-addicted; who had risk of allergic reaction against the food; who were pregnant or lactating at the informed consent, or wanted to become pregnant during the test; who had participated in other experimentations of foods, medicines or quasi-pharmaceutical products or had a plan to participate in other human experiments during the test; or whom the study director considered not to be appropriate to participate in the study.

Improvement of the cognitive functions was evaluated by using following three methods. (i) Mini Mental State Examination (MMSE): an oral test for the recognition functions including disorientation, memory, calculation, language, and spatial abilities (16, 34, 38). (ii) Benton visual retention test: estimating abilities of visual recognition, memorization and construction (6, 7). (iii) Standard verbal paired-associate learning test (S-PA): a test for evaluation of short-term memories by counting the correct answers after listening and remembering 10 pairs of words (39, 40).

All participants were allocated into two groups (HE group and placebo group), without any statistic significant differences, by block randomization by the assignment director. All three tests (i to iii) were performed three times (designated as *ex-ante*, *interim*, and *ex-post* evaluations) with intervals of 6 weeks. Participants were required to note the intake of the supplements every day and report the progress in every four weeks.

Statistical analysis. Averages and standard deviations of all tests were calculated on each HE group and placebo group. Statistical analysis was performed as follows: (i) Results of MMSE, Benton visual retention test and S-PA obtained from each group were compared between the timings performed during the 12 weeks (designated as *ex-ante*, *interim*, and *ex-post* evaluations). We used paired *t*-test for the analysis and regulated the *P*-value by applying Bonferroni method in order to consider of the multiplicity. We judged their differences by the statistically significant of $P = 0.05$. In addition, when it was less than 0.10, we regarded that they have tendency to be significantly different. (ii) Next, results of these tests were compared between HE group and placebo group. By using unpaired *t*-test, we judged their differences by the statistically significant of $P = 0.05$ and 0.10 as mentioned.

RESULTS

We excluded the results of three persons from all 34 participants. Two subjects of them were excluded because we could not perform *ex-post* evaluation for them. The other one was omitted because the one had initially abnormal value in MMSE: the score was lower than 24. Therefore, we analyzed the data from 31 participants composed of 6 male and 10 female subjects for HE group, and 5 male and 10 female subjects for placebo group. All of them were over 50 years old. Possibility of suffering from cognitive functions is increased after the age of 60; it is crucial to regulate the average age of each group. The average ages of the two groups were 61.8 (HE group, SE = 1.7) and 60.8 (placebo group, SE = 2.2), respectively. Statistical analysis suggests there were no significant differences in age between the two groups with *P*-value of 0.732. Sixteen participants of the HE group took 99.6% of the total amount of the supplement during the test period, and 15 of the

Table 1 *Comparison of MMSE scores between HE and placebo groups*

	ex-ante			*interim*			*ex-post*		
	HE.	placebo	*P*-value	HE	*P*-value	*t*-test	HE	placebo	*P*-value
Orientation to place	5.00 (0.000)	5.00 (0.00)	ND	4.88 (0.085)	4.93 (0.07)	0.598	5.00 (0.000)	4.93 (0.07)	0.310
Orientation to time	4.63 (0.155)	4.67 (0.16)	0.853	4.88 (0.085)	4.80 (0.14)	0.654	5.00 (0.000)	4.73 (0.15)	0.0824‡
Immediate recall	2.94 (0.063)	3.00 (0.00)	0.341	3.00 (0.000)	3.00 (0.00)	ND	3.00 (0.000)	3.00 (0.00)	ND
Calculation	4.75 (0.250)	4.13 (0.40)	0.196	4.88 (0.125)	4.47 (0.32)	0.252*	5.00 (0.000)	4.93 (0.07)	0.310
Delayed recall	2.88 (0.085)	3.00 (0.00)	0.167	3.00 (0.000)	2.93 (0.07)	0.310	3.00 (0.000)	3.00 (0.00)	ND
Naming objects	2.00 (0.000)	2.00 (0.00)	ND	2.00 (0.000)	2.00 (0.00)	ND	2.00 (0.000)	2.00 (0.00)	ND
Repeat a sentence	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	0.93 (0.07)	0.310
Oral command	3.00 (0.000)	3.00 (0.00)	ND	3.00 (0.000)	3.00 (0.00)	ND	3.00 (0.000)	3.00 (0.00)	ND
Writing command	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND
Spontaneous writing of sentences	1.00 (0.000)	0.93 (0.07)	0.310	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND
Graphic drawing	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND
Total score	29.19 (0.430)	28.73 (0.43)	0.462	29.63 (0.180)	29.13 (0.43)	0.310*	30.00 (0.000)	29.53 (0.22)	0.0328†

ND: Not defined because two values were coincidence.
( ): Brackets denote Standard Errors.
†: The value suggests significant difference between HE and placebo groups.
‡: The value suggests tendency to be significantly different.
*: The value was calculated by Welch's *t*-test.

placebo group took 98.1% of that, indicating that the subjects in this study took almost all the supplements during the experiment.

At first, we compared the initial values of MMSE, Benton visual retention test and S-PA between HE group and placebo group. We did not find any significant differences between the two groups in all these tests. Therefore, we considered that these two groups had almost similar properties in these tests.

Mini mental state examination (MMSE)

MMSE is widely used for the dementia diagnosis and performed by an oral examination. Total scores of both groups increased by the time, but only the HE group showed the significant increase by comparing both *ex-ante*/*interim* tests and *ex-ante* / *ex-post* trials (Table 1).

Scores from HE group were always higher than those from placebo group. Total scores at *ex-post* trials were significantly different, and the values of "orientation to time" had tendency to be significantly different (Table 1). These results indicate that the intake of HE made better results in these tests.

As mentioned above, possibility of suffering from cognitive functions is closely related to age. To get the clearer relation, we performed an age amendment and compared the time change of the two groups by the repeated analysis of covariance (ANCOVA) (Fig. 1). The result showed significant interaction with *P*-value of 0.029 between the two groups by the time course of the test. Therefore, we got clear results that intake of the HE supplements improves cognitive functions of the people with normal MMSE value.

Benton visual retention test

This examination mainly checks the ability of visual cognitions. We analyzed the data from the same 31 participants. They did not show any significant changes during the trials in each group as shown in Table 2. They did not find any differences in the test between the two groups, either.

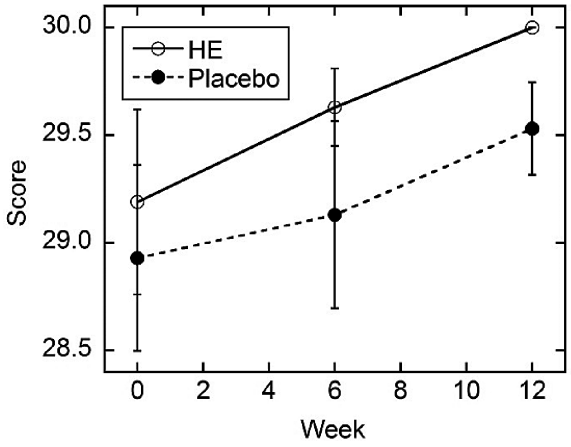

Fig. 1 Effect of HE intake to MMSE scores in 12 weeks. Change in the total score values of MMSE in HE and placebo groups. After an age amendment, repeated analysis of covariance (ANCOVA) was performed. Interaction between these groups and the time course was calculated to be $P = 0.029$, indicating significant difference between the groups.

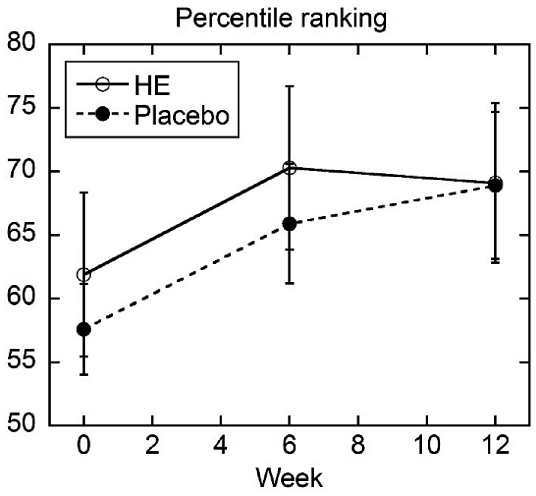

Fig. 2 Change in the percentile ranking of S-PA test of HE and placebo groups after the intake of HE for 12 weeks. There were no significant changes in the test period and no significant changes between the two groups either.

Table 2 *Comparison of Benton visual retention test between HE and placebo groups*

	ex-ante	*interim*	*ex-post*
HE ($n = 16$)	6.88 (0.531)	6.25 (0.382)	7.13 (0.473)
placebo ($n = 15$)	6.80 (0.55)	6.40 (0.48)	7.00 (0.45)
P-value (HE / placebo)	0.922	0.806	0.850

( ): Brackets denote Standard Errors.

Standard verbal paired-associate learning test (S-PA) S-PA, performed by listening, evaluates short term memory of words. Initial value in HE group was slightly higher than that of placebo group, and they got closer as experiment proceeded (Fig. 2). There were no statistically significant changes in both groups ($P < 0.100$), and no significant differences between the two groups, either (Table 3). Therefore, we did not find any clear effects of the HE intake from the test.

DISCUSSION

Chinese traditional medicines containing HE are regarded as drugs of various diseases, including cancers and autoimmune diseases (15). Here, we confirmed that longer intake of the HE supplements for 12 weeks is significantly effective for the improvement of the cognitive functions, especially in MMSE. It is notable that in our experiments there were only few participants who could not continue the experiment till the last evaluation. This suggests that our tests were performed appropriately and these results have high reliability.

In this study, we selected participants with normal cognitive functions. More studies are necessary to confirm if oral intake of HE was also effective for the patients with serious cognitive disorders. However, it is notable that not only did HE prevent from the deterioration of short-term memories, but also it improved the cognitive functions in MMSE. It indicates the possibility that HE helps regeneration of the neural networks in adult brain. Though it has been still under discussion if neurons are regenerated in the human adult brain (36), explant of neural stem cells in the brain is expected as a new treatment of dementia (42). Since ubiquitination of certain protein in synapse regulates synaptic communication (37, 41), it is also probable that HE might not help neural regeneration but it might facilitate the transmission between the existing synapses by regulating their responses through the ubiquitination. Further biochemical studies are desired and they should be a great clue for the development of new treatment for the regeneration of neurons.

HE contains many chemicals stimulating human health (26). Hericenones are reported to activate synthesis of NGF in the astrocytes (17–19). NGF emitted from the astrocytes is transmitted into the nerve cells, and is necessary for the survival of neu-

Table 3 *Comparison of S-PA scores between HE and placebo groups*

		ex-ante			*interim*			*ex-post*		
		HE	placebo	*P*-value	HE	placebo	*P*-value	HE	placebo	*P*-value
Related words	1st trial	9.43 (0.157)	8.80 (0.416)	0.169*	9.31 (0.237)	8.73 (0.452)	0.269*	8.50 (0.465)	8.27 (0.371)	0.700
	2nd trial	10.0 (0)	9.80 (0.145)	0.164	9.94 (0.063)	9.47 (0.350)	0.205*	9.63 (0.155)	9.87 (0.091)	0.191*
	3rd trial	10.0 (0)	9.93 (0.067)	0.310	10.0 (0)	9.67 (0.270)	0.212	9.94 (0.063)	9.93 (0.067)	0.964
Unrelated words	1st trial	3.81 (0.678)	2.80 (0.460)	0.233	3.50 (0.677)	2.47 (0.401)	0.201*	3.19 (0.672)	3.00 (0.543)	0.831
	2nd trial	5.13 (0.795)	4.53 (0.424)	0.518*	5.75 (0.819)	5.00 (0.498)	0.448	5.56 (0.846)	5.533 (0.792)	0.980
	3rd trial	5.75 (0.854)	5.60 (0.567)	0.886	6.81 (0.754)	6.00 (0.569)	0.401	6.75 (0.783)	6.67 (0.637)	0.935
Overall judgment		0.188 (0.101)	0.00 (0)	0.082	0.0625 (0.063)	0.133 (0.091)	0.521	0.0625 (0.063)	0.00 (0)	0.341
Score of related words		29.4 (0.157)	28.5 (0.496)	0.101*	29.3 (0.266)	27.9 (1.01)	0.204*	28.1 (0.616)	29.1 (1.02)	0.400
Score of unrelated words		14.7 (2.22)	12.9 (1.18)	0.493*	16.1 (2.17)	13.5 (1.15)	0.301*	15.5 (2.15)	15.2 (1.84)	0.917
Percentile ranking		61.9 (6.46)	57.6 (3.57)	0.562*	70.3 (6.44)	65.9 (4.70)	0.591	69.1 (6.28)	68.9 (5.78)	0.982

( ): Brackets denote Standard Errors.
*: The value was calculated by Welch's *t*-test.

ral cells in brain (11–13). This is supported by some reports, showing that astrocytes have ability to help neuroregeneration in CNS (2). NGF is a neuropeptide, unable to cross the blood-brain barrier and also easily digested by peptidases. Recently, injection of NGF in brain is expected to be effective for the Parkinson disease (1, 3–5). However, the direct injection of NGF to the human brain carries a certain degree of risk. Therefore, activation of the NGF synthesis of astrocytes by the oral intake of HE is safe and convenient therapy for dementia prevention so far.

There are different types of hericenones. While most of all hericenones show stimulating activity for the biosynthesis of NGF in astrocytes, hericenone B has been reported to prevent thrombosis, and considered to be effective for the protection from cerebrovascular disturbance (29). This function might also contribute to the improvement of the cognitive functions because cerebral blood flow is regarded as an important factor to dementia.

Other potent chemicals of HE for the improvement of cognitive functions are erinacines, that also stimulate NGF synthesis *in vitro* and in CNS (9, 20, 23–25, 35). Total chemical synthesis of both hericenones and erinacines has been studied (22), then we could obtain a few kinds of these chemicals, hericenone A, B, I and so on, by the total chemical synthesis without purification from the mushroom. While hericenones are abundant in fruiting body of the mushroom, erinacines are mainly contained in mycelia. Therefore, we consider that the improvement in our study was mainly likely due to hericenones, because HE supplements in our study were made from the fruiting body. However, Mori *et al.* argued the existence of other chemicals soluble in oil, stimulating NGF production (28). β-Glucan is also abundantly contained in the mushroom (8). Its cholesterol-lowering effect lowers the risk of the heart diseases. Furthermore, it has an antitumor effect by activation of innate immune cells, such as macrophages and dendritic cells, via binding to β-glucan receptors, for example dectin-1 and CR3 (31). It matches with the report that the extract from HE activates macrophages resulting in antitumor effect (21). Macrophages play an important role not only in the innate immune system but also in neuroregeneration process (32, 33). Therefore, the immune activation might also participate in the improvement of cognitive functions. We speculate these various compounds contained in HE have multiple effects to the brain neural networks and improve the cognitive functions.

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