

Reduction of depression and anxiety by 4 weeks *Hericium erinaceus* intake

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ABSTRACT

Hericium erinaceus, a well known edible mushroom, has numerous biological activities. Especially hericenones and erinacines isolated from its fruiting body stimulate nerve growth factor (NGF) synthesis, which expects *H. erinaceus* to have some effects on brain functions and autonomic nervous system. Herein, we investigated the clinical effects of *H. erinaceus* on menopause, depression, sleep quality and indefinite complaints, using the Kupperman Menopausal Index (KMI), the Center for Epidemiologic Studies Depression Scale (CES-D), the Pittsburgh Sleep Quality Index (PSQI), and the Indefinite Complaints Index (ICI). Thirty females were randomly assigned to either the *H. erinaceus* (HE) group or the placebo group and took HE cookies or placebo cookies for 4 weeks. Each of the CES-D and the ICI score after the HE intake was significantly lower than that before. In two terms of the ICI, “insentive” and “palpitation”, each of the mean score of the HE group was significantly lower than the placebo group. “Concentration”, “irritating” and “anxious” tended to be lower than the placebo group. Our results show that HE intake has the possibility to reduce depression and anxiety and these results suggest a different mechanism from NGF-enhancing action of *H. erinaceus*.

H. erinaceus (Lion’s mane mushroom), a well-known edible mushroom, has been used as traditional medicine in several Asian countries to treat various human diseases. The compounds isolated from its fruiting bodies contain numerous biological activities, such as anti-tumor (18), hypolipidemic (26), hemagglutinating (17), cytotoxic (25), anti-microbial (27), endoplasmic reticulum (ER) stress-suppressive (20, 24), and antioxidant activities (3). Especially, it has been reported that hericenones (11, 12, 13) and erinacines (4, 15, 16) stimulate nerve growth factor (NGF) synthesis in cultured astrocytes. Erinacines were isolated from the cultured

mycelia of *H. erinaceus*, and identified as one of diterpenoids. Hericenones were isolated from the fruiting bodies of *H. erinaceus*, and determined its molecular formula as C₃₅H₅₄O₇. In addition, studies of the whole brain and cell cultures have shown that NGF affects the viability of cholinergic neurons and the level of activity of choline-acetyltransferase and acetylcholinesterase in the central nervous system (5, 8, 9). These reports have shown that some effects of *H. erinaceus* on cholinergic neurons could be expected. In fact, a clinical study has reported that *H. erinaceus* improved mild cognitive impairment in which the decrease of cholinergic neurons involved (20). However, despite the clinical importance of *H. erinaceus*, there have been few studies on elucidating other effects of it on the brain functions and autonomic nervous system.

Herein, we investigated the clinical effects of *H. erinaceus* on menopause, depression, sleep quality

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and indefinite complaints, using a variety of questionnaires; the Kupperman Menopausal Index (KMI) for menopause (2), the Center for Epidemiologic Studies Depression scale (CES-D) for depression (21), the Pittsburgh Sleep Quality Index (PSQI) for sleep quality (1), and the Indefinite Complaints Index (ICI) for indefinite complaints (6, 7).

MATERIALS AND METHODS

The trial was randomized, double-blind, placebo-controlled and was conducted over 4 consecutive weeks. Thirty females aged 41.3 ± 5.6 years with a variety of indefinite complaints and no specified diseases participated in it. The following exclusion criteria were applied: less than 75 percent intake of test samples ($n = 2$), epimenorrhea ($n = 1$), no report ($n = 1$). All participants were randomly assigned to either the *H. erinaceus* (HE) group or the placebo group. Each participant took either HE cookies or placebo cookies for 4 weeks. An HE cookie contained 0.5 g of the powdered fruiting body of *H. erinaceus* and a placebo cookie contained no powder. Each participant ate 4 cookies at any time of a day. Both HE and placebo cookies were supplied by Aso Biotech Inc (Kumamoto, Japan). Each participant completed her report forms every day, including her amount of intake per day, her physical condition and menorrhea, and was sent some questionnaires for psychometric measures before and after the trial.

Psychometric measures. The following 4 outcome measures were used: 1) the Japanese 17-item version (0–3 scale) of KMI, which was used to quantify the severity of perimenopausal somatic symptoms; 2) the Japanese 20-item version (0–3 scale) of CES-D, which was used to quantify the severity of depression; 3) the Japanese 19-item version (0–3 scale) of PSQI, which was used to quantify sleep quality and disturbances; and 4) the 40-item version (0–5 scale) of ICI, which used the accumulated scores to quantify the severity of indefinite complaints.

1) Kupperman Menopausal Index (KMI)

The KMI was based on Dr. Kupperman's experience in treating women with menopausal complaints and arose from his desire to provide a numerical score for complaints which could then be used to evaluate treatments (2). This is one of the most utilized assessments in clinical studies of menopause to assess menopausal symptoms, such as depressive moods, feelings of vertigo, headache, heart palpitation, hot flashes, joint pain, loss of concentration, nervous-

ness/irritability, profuse perspiration and sleep disturbances.

2) Center for Epidemiologic Studies Depression scale (CES-D)

The CES-D scale is a short self-report scale designed to measure depressive symptomatology in general population. The items of the scale are symptoms associated with depression which have been used in previously validated longer scales. The scale should be a useful tool for epidemiologic studies of depression (21).

3) Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-related questionnaire which assesses sleep quality and disturbance over a 1-month time interval. Nineteen individual items generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields 1 global score (1).

4) Indefinite Complaints Index (ICI)

The ICI was based on Keio Indefinite Complaints Index (KICI). KICI was composed of 40-items and based on Kupperman Menopausal Index, adding items associated with 8 symptoms, such as cognitive dysfunction, cutaneous, thinning of hair, bladder, vaginal, pharyngeal, ophthalmic, and gastroenterological, and another 5 items, such as lowback pain, back pain, irritation, anxiety, and apathy. It has been used and validated to evaluate the clinical effect of treatment for more than a decade in University Hospital of Keio (10). Some studies have showed that the ICI could quantify the severity of indefinite complaints and elucidated that some nutritional supplements reduced indefinite complaints (6, 7).

Statistics. Data were analysed with the SPSS statistical software. *t*-test and *chi*-squared test were used to determine statistical significance of participants' sample characteristics, including age, BMI, KMI, CES-D, PSQI, ICI, alcohol habit, cigarette smoking, stressful events and menorrhea. Wilcoxon signed rank test was used to determine statistical significance of KMI, CES-D, PSQI and ICI score between before and after the trial. Analysis of covariance (ANCOVA) was used for between-group comparisons, adjusting the mean of each population before the trial. Statistical significance was set at the $P = 0.05$ level.

RESULTS

Sample characteristics

Of 30 participants, 2 took cookies less than 75% of the total, 1 reported epimenorrhea (18 days menorrhoea/month) and 1 sent no report. To the exclusion of them, data on 26 participants (12 in the HE group and 14 in the placebo group) were analyzed. Characteristics of the HE and placebo groups were summarized in Table 1. There were no significant differences between the 2 groups with respect to physical characteristics (age and BMI), psychometric characteristics (KMI, CES-D, PSQI and ICI) or lifestyle habits (alcohol, cigarette smoking, stressful events and menorrhoea). These results showed that there was no significant variation in the data (Table 1).

*Effect of *H. erinaceus* on menopause index*

The mean KMI score after the trial was significantly

lower than the mean KMI score before the trial in the HE group ($P = 0.090$; Table 2). There was no significant difference of between the 2 groups with respect to a change before and after the trial (Fig. 1a).

*Effect of *H. erinaceus* on depression scale*

The mean CES-D score after the trial was significantly lower than the mean CES-D score before the trial in the HE group ($P = 0.033$; Table 2). There was no significant difference of between the 2 groups with respect to a change before and after the trial (Fig. 1b).

*Effect of *H. erinaceus* on sleep quality index*

There was no significant difference between the 2 groups before and after the trial (Fig. 1c).

*Effect of *H. erinaceus* on indefinite complaints index*

The mean ICI score after the trial was significantly

Table 1 Characteristics of subjects

| | HE group (n=12) | Placebo group (n=14) | <i>P</i> |
|-------------------|--------------------|-------------------------|----------|
| Age | 41.3 ± 5.6 | 38.4 ± 4.9 | n.s. |
| BMI | 20.9 ± 2.6 | 22.0 ± 3.7 | n.s. |
| KMI | 16.5 ± 10.2 | 17.1 ± 8.1 | n.s. |
| CES-D | 13.9 ± 7.8 | 15.1 ± 9.6 | n.s. |
| PSQI | 6.3 ± 2.3 | 6.2 ± 2.6 | n.s. |
| ICI | 46.1 ± 23.4 | 40.4 ± 17.5 | n.s. |
| Alcohol | 25% (n = 3) | 50% (n = 7) | n.s. |
| Cigarette smoking | 17% (n = 2) | 7% (n = 1) | n.s. |
| Stress events | 25% (n = 3) | 21% (n = 3) | n.s. |
| Menorrhoea | 17% (n = 2) | 21% (n = 3) | n.s. |

Age, BMI, KMI, CES-D, PSQI, and ICI are given as mean ± standard deviation.

HE: *Hericum erinaceus*, BMI: Body-Mass Index, KMI: Kupperman Menopausal Index, CES-D: Center for Epidemiologic Studies Depression, PSQI: Pittsburgh Sleep Quality Index, ICI: Indefinite Complaints Index, n.s.: non-significant

Table 2 Comparison before and after the trial

| | before | | | | after | | | | In HE groups, before-and-after comparison | 2 groups comparison |
|----------|--------|------|---------|------|-------|------|---------|------|---|------------------------|
| | HE | | Placebo | | HE | | Placebo | | | |
| | mean | SD | mean | SD | mean | SD | mean | SD | | |
| KMI | 16.5 | 10.2 | 17.1 | 8.1 | 11.2 | 6.2 | 11.1 | 9.9 | $P = 0.090$ | n.s. |
| CES-D | 13.9 | 7.8 | 15.1 | 9.6 | 10.3 | 7.3 | 12.6 | 8.3 | $P = 0.033$ | n.s. |
| PSQI | 6.3 | 2.3 | 6.2 | 2.6 | 6.0 | 2.7 | 6.4 | 2.7 | n.s. | n.s. |
| ICI | 46.1 | 23.4 | 40.4 | 17.5 | 29.6 | 21.5 | 31.6 | 22.3 | $P = 0.004$ | n.s. |
| Total IC | 13.8 | 8.9 | 11.5 | 7.1 | 8.1 | 7.8 | 8.4 | 7.5 | $P = 0.004$ | n.s. |

HE: *Hericum erinaceus*, BMI: Body-Mass Index, KMI: Kupperman Menopausal Index, CES-D: Center for Epidemiologic Studies Depression, PSQI: Pittsburgh Sleep Quality Index, ICI: Indefinite Complaints Index, n.s.: non-significant

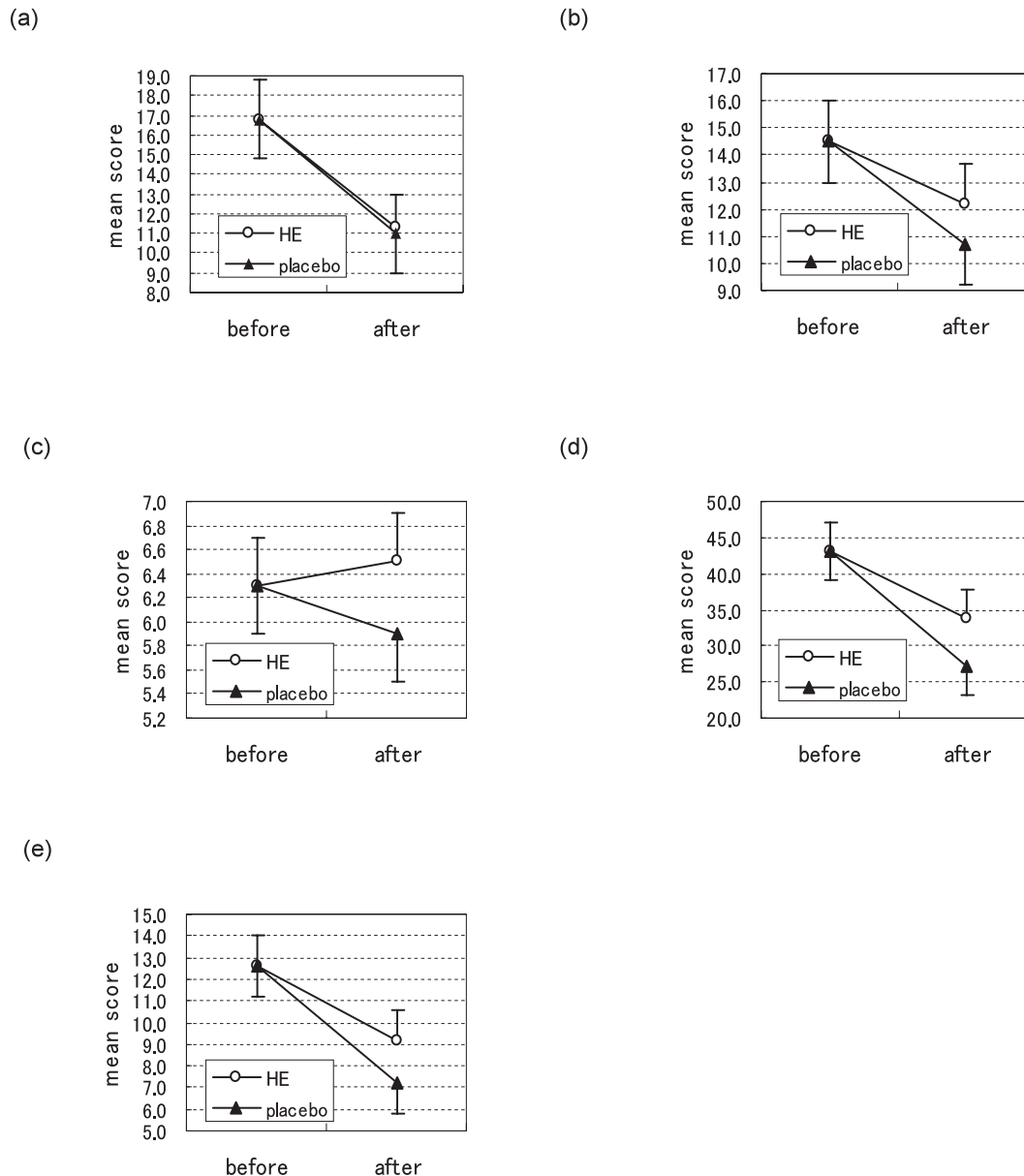


Fig. 1 Comparison before and after the trial: (a) The mean Kupperman Menopausal Index (KMI) score after the trial was significantly lower than that before in the *Hericium erinaceus* (HE) group ($P = 0.090$). (b) The mean Center for Epidemiologic Studies Depression Scale (CES-D) score after the trial was significantly lower than that before in the HE group ($P = 0.033$). (c) The mean Pittsburgh Sleep Quality Index (PSQI) score has no significant difference between the 2 groups before and after the trial. (d) The mean Indefinite Complaints Index (ICI) score after the trial was significantly lower than that before in the HE group ($P = 0.004$).

lower than the mean ICI score before the trial in the HE group ($P = 0.004$; Fig. 1d, e). Then, statistical significance of each subscale was determined. In two terms, “palpitation” ($P = 0.032$; Fig. 2c) and “insentive” ($P = 0.047$; Fig. 2d), each of the mean score of the HE group was significantly lower than the placebo group. In three terms, “irritating” ($P = 0.076$; Fig. 2a), “anxious” ($P = 0.067$; Fig. 2b),

and “concentration” ($P = 0.090$; Fig. 2e), each of the mean score of the HE group tended to be lower than the placebo group.

DISCUSSION

The present study investigated the clinical effects on menopause, depression, sleep quality, and indefinite

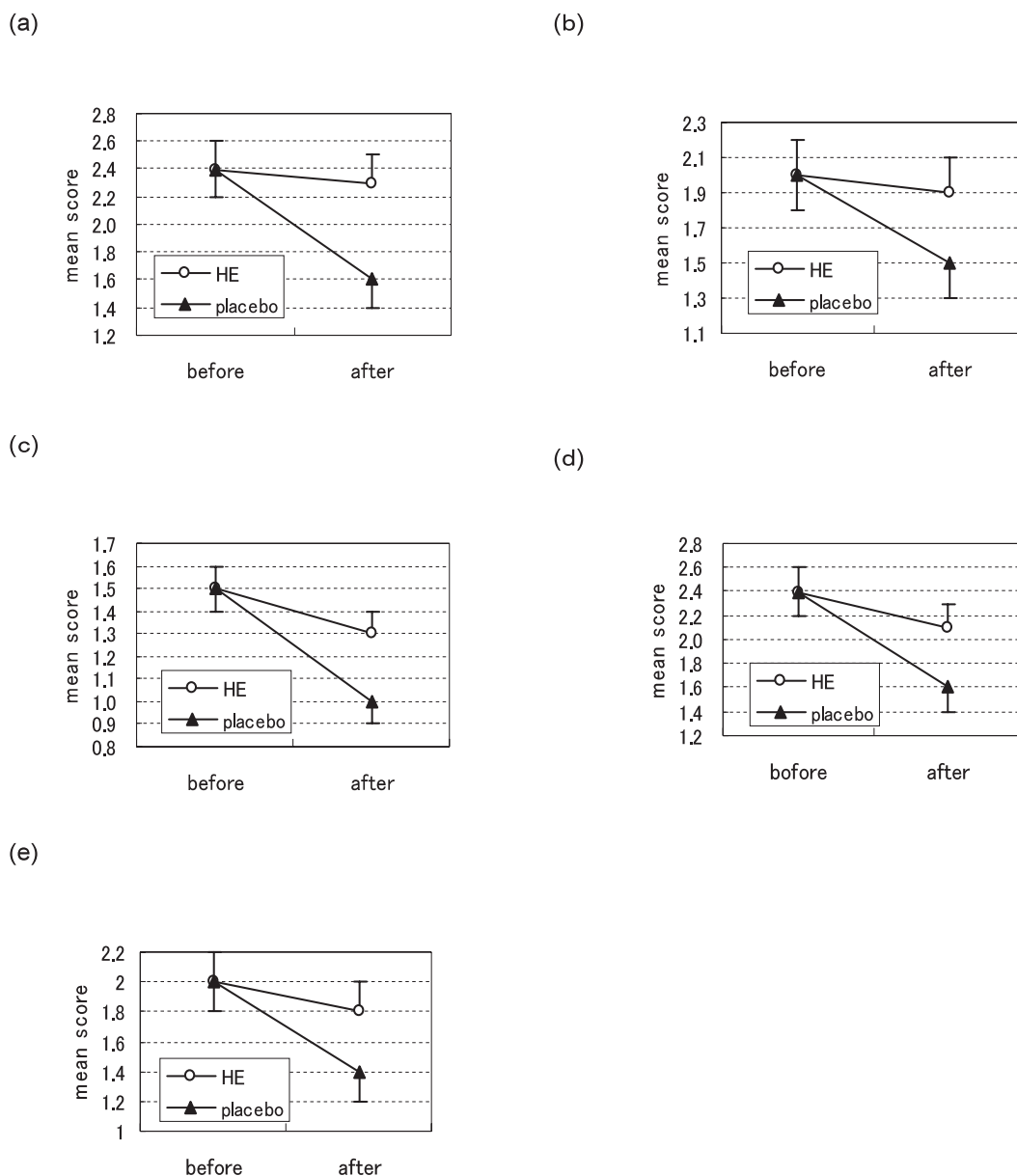


Fig. 2 The mean Indefinite Complaints Index (ICI) score of *Hericum erinaceus* (HE) and placebo group: (a) In the term, “irritating”, the mean ICI score of the *Hericum erinaceus* tended to be lower than the placebo group ($P=0.076$). (b) In “anxious”, the mean ICI score of the HE group tended to be lower than the placebo group ($P=0.067$). (c) In “pulpitation”, the mean ICI score of the HE group was significantly lower than the placebo group ($P=0.032$). (d) In “incentive”, the mean ICI score of the HE group was significantly lower than the placebo group ($P=0.047$). (e) In “concentration”, the mean ICI score of the HE group was tended to be lower than the placebo group ($P=0.090$).

complaints caused by 4-weeks intake of *H. erinaceus*. With regard to some sort of indefinite complains, the ICI scores in HE group were significantly lower than in placebo group. The CES-D and the ICI scores were lower than after the HE-intake. Then, the terms of the ICI, “incentive” and “concentration” were relevant to depression and the term, “anxious” was relevant to anxiety. These results

suggest the possibility that *H. erinaceus* reduces depression and anxiety.

Hericenones and erinacines have been shown to stimulate NGF synthesis in cultured astrocytes. Erinacines were isolated from the cultured mycelia of *H. erinaceus*, and hericenones were isolated from the fruiting bodies of *H. erinaceus*. Prior studies have reported that NGF enhanced their neurochemi-

cal differentiation following intraventricular injection, and these neurogenesis-inducing effects have led to antidepressant activity (22) and antianxiety activity (23). These reports support our suggestion that NGF-enhancing action of *H. erinaceus* reduces depression and anxiety. Hericenones and erinacines are potential substances which involved in this action, but further clinical research is needed to identify. Furthermore, it is still unknown whether hericenones and erinacines are able to pass through the brain-blood barrier into the brain to promote NGF synthesis *in vivo*, and further studies are needed to determine the active ingredients and the mechanism of action.

As seen above, our results show that *H. erinaceus* intake has the possibility to reduce depression and anxiety. And it is still relevant to frustration and palpitation because *H. erinaceus* intake lowers each score of the terms, “frustrating” and “palpitation”. These results suggest a different mechanism from NGF-enhancing action of *H. erinaceus*. To understand the mechanism, additional researches in connection with other physiological markers such as autonomic nerve activities and hormones is needed.

Our previous research has reported that a questionnaire investigation could elucidate a reducing effect of pain and indefinite complains by some functional food (6, 7). Also, this research demonstrates the effectiveness of *H. erinaceus* by means of the questionnaire investigation and detects a between-group difference, which shows that the investigation can be a valid and objective evaluating method to determine the effect of food on indefinite complains. This method could be a prospective way to screen a variety of food ingredients to demonstrate their effectiveness.

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