Neurological Activity of Lion’s Mane (*Hericium erinaceus*)

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ABSTRACT

*Hericium erinaceus*, most commonly known as lion’s mane, is an edible fungus, with a long history of use in Traditional Chinese Medicine. The mushroom is abundant in bioactive compounds including β-glucan polysaccharides; hericenones and erinacine terpenoids; isoindolinones; sterols; and myconutrients, which potentially have neuroprotective and neuroregenerative properties. Because of its anti-inflammatory properties and promotion of nerve growth factor gene expression and neurite (axon or dendrite) outgrowth, *H. erinaceus* mycelium shows great promise for the treatment of Alzheimer’s and Parkinson’s diseases. The fungus was well tolerated in two clinical studies, with few adverse events reported.

Keywords: Lion’s mane; Neuroregeneration; Neurodegeneration; Neuroprotection; Neurotropins; Neurotrophic; Alzheimer’s disease; Parkinson’s disease; Multiple Sclerosis; Nerve growth factor

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INTRODUCTION

Ancient, traditional, and modern cultures around the world have known about the nutritive and medicinal properties of mushrooms for centuries. As early as 450 BCE, the Greek physician Hippocrates identified mushrooms as potent anti-inflammatory agents, useful for cauterizing wounds. In the East, reverence for fungi is evident in the Chinese description of ling zhi (*Ganoderma lucidum*), as the “spirit plant,” believed to provide longevity and spiritual potency.

Modern medicine has been slower to catch on to the immense potential of fungi. Despite Fleming’s 1929 discovery of penicillin, and the subsequent implementation of the fungi-chemical as a blockbuster pharmaceutical in the 1940s, it is only in the last few decades that medical science has looked beyond the antimicrobial and cholesterol-lowering properties of fungi for other potential applications.

Clinicians now have greater access to mycelium extracts, which are used clinically for their cytotoxic, antineoplastic, cardiovascular, anti-inflammatory, and immune-modulating activities. Functional studies and chemical assays also support their potential to act as analgesic, antibacterial, antioxidant, and neuroprotective agents. A number of mushrooms, including *Sarcodon scabrosus*, *Ganoderma lucidum*, *Grifola frondosa*, and *Hericium erinaceus* are reported to have activities related to nerve and brain health.

Hericium erinaceus is called hóu tóu gū (“monkey head mushroom”) in Chinese and yamabushitake (“mountain monk mushroom”) in Japanese. In Chinese and Japanese medical systems, it has traditionally been used to fortify the spleen, nourish the gut, and also as an antitumor agent. Lion’s mane is said to be nutritive to the five internal organs (liver, lung, spleen, heart, and kidney), and promotes good digestion, general vigor, and strength. It is also recommended for gastric and duodenal ulcers, as well as chronic gastritis (in prepared tablet form). The mushroom is also known for its effects on the central nervous system, and is used for insomnia, vacuity (weakness), and hypodynamia, which are characteristic symptoms of Qi deficiency in Traditional Chinese medicine (TCM).

CHEMISTRY

The bioactive metabolites of *H. erinaceus* can be classified into high molecular weight compounds, such as polysaccharides, and low molecular weight compounds, such as polyketides and terpenoids.

POLYSACCHARIDES

Fungal polysaccharides are found mainly in cell walls, and are present in large quantities in both fruiting bodies and cultured mycelium. *Hericium erinaceus* fruiting bodies (HEFB) contain immunomodulatory β-glucan polysaccharides, as well as α-glucans and glucan-protein complexes. A total of more than 35 *H. erinaceus* polysaccharides (HEP) have been extracted to date from cultured, wild-growing, or fermentative mycelia and fresh/dried fruiting bodies. Of these β-glucans represent the main polysaccharides. HEP are composed of xylene (7.8%), ribose (2.7%), glucose (68.4%), arabinose (11.3%), galactose (2.5%), and mannose (5.2%). Four different polysaccharides isolated from the *H. erinaceus* sporocarp show antitumor activity: xylans, glucoxylans, heteroxylglucans, and galactoxyloglucans. Chemical analysis shows that the total content of HEP found in fruiting bodies is higher than that in mycelium. Table 1 lists the...
polysaccharides along with their source and chemical composition.

Studies of the polysaccharides found in *H. erinaceus* reveal a number of activities. For example, extracellular and intracellular polysaccharides showed a protective effect on oxidative hepatotoxicity in mice. Neuroprotective effects of HEPs were observed in an *in vitro* model of cells that were toxic from amyloid β plaque formation. In this model, HEPs decreased the production of reactive oxygen species from 80% to 58% in a dose-dependent manner, and increased the efficacy of free radical scavenging. HEPs also promoted cell viability and protected cells against apoptosis induced by amyloid β plaque formation. HEPs decreased blood lactic acid, serum urea nitrogen, tissue glycogen, and malondialdehyde, further supporting the beneficial role of HEPs on oxidative stress.

### TERPENOIDS: SESTERPENES, AND DITERPENOIDS

Terpenoids are a class of naturally occurring hydrocarbons that consist of terpenes attached to an oxygen containing group. Terpenoids make up over 60% of products in the natural world.

A variety of diterpenes and sesterpenes are found in the fruiting body and fermenting mycelium of *H. erinaceus*. Of particular pharmacological interest are two classes of terpenoid compounds thus far known to occur only in *Hericium* spp.: hericenones (C–H), a group of aromatic compounds isolated from the fruiting body; and erinacines (A–I), a group of cyathane-type diterpenoids found in the mycelium. Both groups of substances easily cross the blood-brain barrier, and have been found to have neurotrophic and in some cases neuroprotective effects. Erinacines (A–I) have demonstrated induction of nerve growth factor (NGF) synthesis. Table 2 lists the terpenoids, sesterpenes, and diterpenoids along with their source and chemical composition.

### STEROLS

Ten erinarols, described as erinarol A–J, five ergostane-type sterol fatty acid esters, and ten ergostane-type sterols have been identified in the fruiting body of *H. erinaceus*. Sterols, such as

<table>
<thead>
<tr>
<th>Polysaccharides</th>
<th>No.</th>
<th>Isolated from</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>(F10-a, F10-a-α, F10-a-β, F10-b, F11-1, F11-2b)</td>
<td>6</td>
<td>Fresh fruiting bodies of <em>H. erinaceus</em></td>
<td>Xylans, glucoxylans, heteroxylglucans, and galactoxylglucans</td>
</tr>
<tr>
<td>AF2S-2, BF2S-2</td>
<td>2</td>
<td>Fresh fruiting bodies</td>
<td>Backbone of β-(1→6)-linked D-glucopyranosyl residues, and had β-(1→3) and β-(1→6) glucosidic linkages</td>
</tr>
<tr>
<td>Heteropolysaccharides (HEPA1, HEPA4, HEPB2)</td>
<td>3</td>
<td>Mycelium</td>
<td>Glucose</td>
</tr>
<tr>
<td>Water extractable polysaccharides (HPA and HPB)</td>
<td>2</td>
<td>Aqueous extract</td>
<td>Glucose and galactose</td>
</tr>
<tr>
<td>Water soluble polysaccharide (HPI)</td>
<td>1</td>
<td><em>H. caput-medusae</em></td>
<td>Glucose and galactose</td>
</tr>
<tr>
<td>Neutral heteropolysaccharides (HEP-1 and HEP-4)</td>
<td>2</td>
<td>Fruiting bodies</td>
<td>Glucose</td>
</tr>
<tr>
<td>Glucans HEP-3 (β-glucan) and HEP-5 (α-glucan)</td>
<td>2</td>
<td>Fruiting bodies</td>
<td>Glucose</td>
</tr>
<tr>
<td>Acidic polysaccharide (HEP-2)</td>
<td>1</td>
<td>Fruiting bodies</td>
<td>Uronic acid</td>
</tr>
<tr>
<td>Heteropolysaccharide (HPB-3)</td>
<td>1</td>
<td>The maturating-stage IV, V, and VI fruiting body</td>
<td>F-fucose, d-galactose and d-glucose</td>
</tr>
<tr>
<td>Homopolysaccharides, a neutral glucan (HPP)</td>
<td>1</td>
<td>Fermentative mycelia</td>
<td>Glucose</td>
</tr>
</tbody>
</table>
ergosterol confer antioxidative properties.\textsuperscript{21,22} *Hericium erinaceus* has been found to be the most potent \textit{in vitro} inhibitor of both low-density lipoprotein (LDL) oxidation and HMG Co-A reductase activity, suggesting therapeutic potential for the prevention of oxidative stress-mediated vascular diseases.\textsuperscript{23}

**NEUROLOGICAL ACTIVITY**

**NEUROPROTECTION**

Hericenones and erinacines isolated from *H. erinaceus* have demonstrated neuroprotective properties.\textsuperscript{24} *Hericium erinaceus* mycelia (HEM), and its isolated diterpenoid derivative, erinacine A, reduced infarction by 22\% at 50 mg/kg and 44\% at 300 mg/kg in an animal model of global ischemic stroke. This effect was thought to be partially mediated by its ability to reduce cytokine levels.\textsuperscript{25}

A purified polysaccharide from the liquid culture broth of HEM was also found to possess neuroprotective activity in an \textit{in vitro} model through a dramatic delay of apoptosis, which was 20\%–50\% greater than that seen in the control sample. The same study showed HEM to be more effective than control, NGF, or brain-derived neurotrophic factor (BDNF) alone in enhancing the growth of rat adrenal nerve cells and neurite (axon or dendrite) extension.\textsuperscript{26} However, in a model of NG108-15 neuroblastoma cells subjected to H\textsubscript{2}O\textsubscript{2} oxidative stress in pre-treatment and co-treatment, the aqueous extract of *H. erinaceus* (as opposed to a purified polysaccharide), failed to show a protective effect.\textsuperscript{27} Although it is challenging to draw clinically relevant conclusions from \textit{in vitro} studies, this suggests that water extracts would not have a neuroprotective effect without one particular polysaccharide being highly concentrated.

**NEUROTROPHIC ACTIVITY AND MYELINATION**

The addition of an ethanol extract of HEFB resulted in NGF gene expression in human astrocytoma cells, in a concentration-dependent manner. Neurite outgrowth was also improved. The same investigators also observed that mice fed 5\% HEFB dry powder for 7 days, showed an increase in the level of NGF mRNA expression in the hippocampus.\textsuperscript{28} Another study showed that an aqueous extract of HEFB increased secretion of extracellular NGF and neurite outgrowth activity. These researchers also observed a synergistic interaction between *H. erinaceus* aqueous extract and exogenous NGF on neurite outgrowth stimulation of neuroblastoma-glioma cells at physiologically relevant concentrations (1 μg/mL HEFB extract +10 ng/mL NGF).\textsuperscript{21} Myelin sheath formation in the presence of *H. erinaceus* extract proceeded at a higher rate and was completed by day 26, as compared to day 31 in controls. No toxic effects of the extracts were observed in this model.\textsuperscript{30}

**COGNITIVE FUNCTION**

In a behavior test on wild-type mice, oral supplementation with *H. erinaceus* induced a

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**Table 2: Sesterpenes and diterpenoids: source and composition.**

<table>
<thead>
<tr>
<th>Terpenoids</th>
<th>Isolated from</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hericenones</td>
<td>Fresh fruiting bodies of <em>H. erinaceus</em></td>
<td>Erinacines C–L together with (E)-5- (3,7- methylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one</td>
</tr>
<tr>
<td>Erinacines</td>
<td>Mycelia</td>
<td>Erinacines A–I</td>
</tr>
<tr>
<td>Diterpenoids</td>
<td>Fresh fruiting bodies of <em>H. erinaceus</em></td>
<td>Erinaceolactams A–E, hericenone A, hericenone N-De</td>
</tr>
<tr>
<td>Isoindolinones</td>
<td>Fresh fruiting bodies of <em>H. erinaceus</em></td>
<td>phenylethylisohericerin, erinacerin A, and hericenone</td>
</tr>
</tbody>
</table>
statistically significant improvement in spatial short-term and visual recognition memory. In a double-blind placebo-controlled clinical trial of 50–80-year-old Japanese adults (n=30) diagnosed with mild cognitive impairment, oral intake of H. erinaceus 250 mg tablets (96% dry powder) three times a day for 16 weeks was associated with marked improvement in the revised Hasegawa Dementia Scale (HDS-R) as compared to controls. Scores on the HDS-R decreased, however, by 4 weeks after cessation of the intervention.

ALZHEIMER’S DISEASE

In a mouse model of Alzheimer’s disease, oral administration of HEFB increased expression of NGF mRNA in the hippocampus, and prevented impairments of spatial, short-term, and visual recognition memory induced by amyloid β plaque that were observed in non-treated mice. In another study using an Alzheimer’s model of mice that develop amyloid plaque deposits by 6 months of age, a 30-day oral administration of HEM resulted in fewer plaque deposits in microglia and astrocytes in the cerebral cortex and hippocampus. In an aluminum chloride induced animal model of Alzheimer’s disease, HEM increased serum and hypothalamic concentrations of acetylcholine and choline acetyltransferase in a dose-dependent manner. Figure 1 illustrates the apparent mechanisms of action for the effects that H. erinaceus may have in Alzheimer’s disease.

PARKINSON’S DISEASE

Oral administration of low-dose HEM (10.76 or 21.52 mg/day) used in an animal model of Parkinson’s disease led to significant improvement in oxidative stress and dopaminergic lesions in the striatum and substantia nigra after 25 days.

PERIPHERAL NERVE INJURY

An aqueous extract of HEFB that was administered to animals at a dose of 10 mL/kg for 14 days following crush injury improved nerve regeneration and increased the rate of motor functional recovery. The animals treated with HEFB recovered 4–7 days earlier than animals in the control group, as assessed by walking track analysis. Normal toe spreading, a measure of reinnervation, was achieved 5–10 days earlier in the aqueous extract group than in the control group. Based on functional evaluation and the morphological examination of regenerated nerves, ipsilateral dorsal root ganglia, and target extensor digitorum longus muscles, researchers concluded that HEFB aqueous extract promoted peripheral

Figure 1: Mechanism of action of Hericium erinaceus in Alzheimer’s disease.
nerve regeneration with significant functional recovery.33

CLINICAL TRIALS

As previously described under Cognitive Function, a double-blind placebo-controlled study of 50–80-year-old Japanese men and women (n=30) diagnosed with mild cognitive impairment showed marked improvement in cognitive function, as measured by the revised Hasegawa Dementia Scale (HDS-R), when compared to controls, following oral intake of \textit{H. erinaceus} 250 mg tablets (96% dry powder) three times a day for 16 weeks. Scores on the HDS-R decreased, however, by 4 weeks after cessation of the intervention.28

In another clinical trial, administration of HEFB at 2.0 g/day (in cookies) over 4 weeks showed a reduction in some symptoms of anxiety and depression in menopausal women (n=30). The Indefinite Complaints Index categories for Palpitation and Incentive showed a statistically significant improvement in women taking HEFB compared to those taking placebo. The categories of Irritating, Anxious, and Concentration indicated a trend in the direction of improvement with HEFB as compared to placebo.29 Table 3 summarizes the two clinical trials reported on in this paper.

POSOLOGY

COGNITION AND NGF PRODUCTION

The recommended dose of \textit{H. erinaceus} dried fruiting body for increasing NGF production is 3–5 g per day.34 \textit{Hericium erinaceus} dosed at 250 mg tablets (96% dry powder) three times a day for 16 weeks was associated with significant improvement on a dementia rating scale in subjects with mild cognitive impairment.28 The dose utilized in the study of menopausal women that showed reduction in symptoms of depression and anxiety was 2.0 g/day of HEFB (in cookies) for 4 weeks.29

TOXICOLOGY

In an \textit{in vitro} model, HEFB aqueous extract demonstrated a remarkable lack of cytotoxicity.31 Toxicology studies of \textit{H. erinaceus} in rats suggest that mycelia enriched with 5 mg/g erinacine A at doses of up to 5 g/kg bodyweight/day are safe. No toxicity was found in the two clinical trials reported on here.28,29

REPORTED ADVERSE EVENTS

No adverse clinical or biochemical events were reported in the clinical trial of subjects with mild cognitive impairment.28 In the study of

<table>
<thead>
<tr>
<th>Trial</th>
<th>Parameter assessed/Scale</th>
<th>Results</th>
<th>Adverse events</th>
<th>Dose</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind, parallel-group, placebo-controlled trial</td>
<td>Mild cognitive impairment/Revised Hasegawa Dementia Scale (HDS-R)</td>
<td>Significant improvement in cognitive function scale</td>
<td>None</td>
<td>250 mg tid x16 weeks</td>
<td>Mori et al., 200928</td>
</tr>
<tr>
<td>Randomized placebo-controlled trial</td>
<td>Anxiety and depression/Center for Epidemiologic Studies Depression Scale (CES-D) and Indefinite Complaints Index (ICI)</td>
<td>Significant improvement in some anxiety and depression scores</td>
<td>None</td>
<td>2 g/day x4 weeks</td>
<td>Nagano et al., 201029</td>
</tr>
</tbody>
</table>
menopausal women, one subject reported epi-
menorrhea (18 days menorrhea/month). However,
whether or not supplementation with *H. eri-
naceus* was the cause of the epimenorrhea is
inconclusive.²⁹

Allergies and sensitivities to mushrooms are not
unusual. One case report describes a 63-year-old
male who suffered acute respiratory failure and
lymphocytosis in his lungs. The report suggests
he had used an extract of dry *H. erinaceus* (with
no further description given) daily for 4 months
in commonly available doses, and the connection
between the two was considered to be probable. In
another case report, a 53-year-old male exposed to
HEFB occupationally, developed chronic dermatitis
on his hands, with painful fissures within 1 month
of exposure. The dermatitis spread to his forearms,
face, and legs, at which point he ceased exposure
to the HEB and his symptoms resolved. His
patch tests were negative for the European stan-
dard series, and positive for HEB. Sensitization
was confirmed by a highly positive repeated open
application test (ROAT) with an aqueous emulsion
of HEB. Interestingly, patch and prick tests were
negative for other culinary mushrooms suggesting a
lack of cross-sensitivity.

**CONCLUSION**

To the best of this author’s knowledge, no toxicity
was established for *H. erinaceus* in the experimen-
tal, animal, or two clinical trials reported here. The
adverse event (epimenorrhea) reported in one of the
clinical trials could not be conclusively attributed to
the intervention. The substantial historical record for
the traditional use of lion’s mane for chronic ailments,
together with the results of studies so far, suggest
*H. erinaceus* is safe and has important potential as a
neuroprotective and neurotrophic therapeutic agent
in neurological conditions.³⁵ Its rich myconutrient
composition suggest that using the whole fungus may
be most advantageous clinically. More clinical studies
are needed to corroborate these conclusions.

**COMPETING INTERESTS**

The authors declare they have no competing interests.


