SCIENCE

LION'S MANE MUSHROOM

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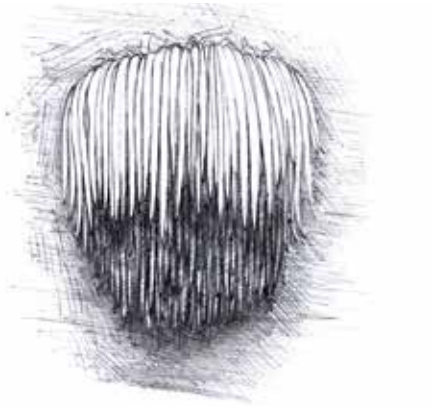
HERICIUM ERINACEUS



The lion´s mane fungus *Hericium erinaceus* is a well-known edible and medicinal mushroom found throughout eastern Asia. Its fruiting bodies and fungal mycelia exhibit various pharmacological activities, including enhancement of the immune system as well as anti-tumor, hypoglycemic, and anti-aging properties. Scientific analysis has shown that the aromatic compounds hericenones C–H and erinacines A–I isolated from the fruiting body and mycelium promote nerve growth factor (NGF) synthesis in cultured astrocytes. These results highlight the usefulness of *H. erinaceus* for the treatment and prevention of dementia. However, the biochemical mechanism responsible for this action is not yet totally understood. In Japan, the fungus is known colloquially as yamabushitake, while it is called the monkey's head mushroom in China and the lion's mane mushroom in the US. *Hericium erinaceus* colonizes both living and dead broadleaf trees and is distributed around the world. Some of the other better-known representatives of this genus are H. abietis, H. alpestre, H. americanum, H. coralloides, and H. laciniatum [1-4].

This summary will briefly explore some of the medically useful properties of *H. erinaceus*, including its effects on nerve growth factor and cognitive function. Also discussed are the anti-cancer, immune-enhancing, and hypoglycemic effects of the mushroom. Finally, the effects of *H. erinaceus* mushroom on platelet aggregation and its function as an antioxidant will be illuminated.

IMPROVEMENT OF COGNITION

To test the effects of orally administered *H. erinaceus* on cognitive function, a double-blind, parallel-group, placebo-controlled trial was performed on mildly cognitively impaired 50-80 year-old Japanese men and women aged. A cognitive function scale based on the Revised Hasegawa Dementia Scale (HDS-R) was used. In this study, 14 individuals received *H. erinaceus* while the remaining 15 individuals received placebo (5). The researchers observed that the *H. erinaceus* group increased their HDS-R score relative to controls depending on the time period when *H. erinaceus* was consumed. Specifically, significant differences in cognitive function appeared at weeks 8, 12, and 16 of the trial. During the 4 week follow-up period, however, the score of the *H. erinaceus* group decreased significantly compared with the week 16 score (figure 1). Thus, *H. erinaceus* is effective at reducing mild cognitive impairment but continuous intake may be necessary to maintain the beneficial effects of the fungus [5].

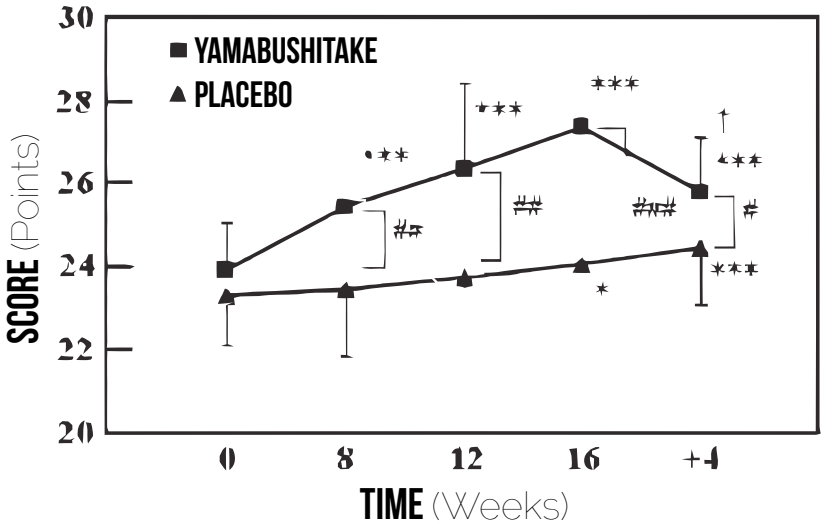


Figure 1.

Figure 1. Cognitive function score in the Hericium erinaceus (Yamabushitake) group versus the placebo group [5].

EFFECTS ON NERVE GROWTH FACTOR

Mori et al. [6] demonstrated that ethanol extract of *H. erinaceus* promotes synthesis of nerve growth factor (NGF) in 1321N1 human astrocytoma cells. An amount of 100 mg/ml of *H. erinaceus* ethanol extract significantly increased NGF mRNA expression but did not affect NGF protein synthesis. Thus, concentrations of *H. erinaceus* ethanol extract that induce NGF protein synthesis and secretion differs from that required to induce NGF mRNA expression, possibly because protein synthesis/secretion is regulated by several different factors. Moreover, the enhancement of NGF gene expression by *H. erinaceus* was inhibited by the c-jun N-terminal kinase (JNK) inhibitor SP600125 that was phosphorylated by ethanol extract of *H. erinaceus*. These results suggest that JNK is involved in the enhancement of

NGF gene expression induced by *H. erinaceus*.

A previous study reported that the active components of *H. erinaceus*, hericenones C–H, stimulate NGF protein synthesis in mouse and rat astrocytes [5]. However, hericenones C, D, and E did not exhibit NGF-promoting activity at all using 1321N1 human astrocytoma cells. These results thus raise the possibility that *H. erinaceus* has active but, as of yet, uncharacterized lipid-soluble compounds that promote NGF expression.

Furthermore, oral administration of *H. erinaceus* increased NGF mRNA expression in mouse hippocampus. This result suggests the possibility that the hypothetical compound could be absorbed into blood and delivered to the central nervous system through the blood–brain barrier. However, the mycelia of *H. erinaceus* are known to contain erinacines that also stimulate NGF synthesis. It has been reported that oral administration of erinacine A significantly increases the level of NGF in the rat locus coeruleus and hippocampus, but not in the cerebral cortex. However, it is not yet known if the fruiting body of *H. erinaceus* contains erinacines. In conclusion, *H. erinaceus* contains active yet poorly understood compounds that stimulate NGF synthesis via activation of the JNK pathway. These compounds are not likely to be hericenones. [6]

Park et al. [7] investigated the effects of an exo-polysaccharide from *H. erinaceus* on growth of pheochromocytoma cells (PC12) in an in vitro rat model. It was found that an exo-biopolymer purified from a liquid culture broth of *H. erinaceus* mycelium enhanced growth of rat adrenal nerve cells. The polymer also boosted extension of PC12 neurites. Its efficacy was found to be higher than those from known nerve growth factors such as NGF and brain-derived nerve factor (BDNF). Although the polymer improved both cell growth and neurite extension, NGF and BDNF did more than influence growth of neurites. It was also confirmed that the polymer reacted with nerve cells within 30 min after adding the sample, compared to 80 min when adding two other growth factors. Number of neurite-bearing cells remained relatively steady after adding the polymer even though cell growth had begun to decrease. It was interesting that the polymer effectively delayed apoptosis of PC12 cells by dramatically reducing the ratio of apoptotic cells in the treatment relative to control from 50% to 20%.

ANTI-CANCER EFFECT

It has been demonstrated that *H. erinaceus*, which primarily consists of polysaccharides, has tumor-fighting properties. However, the mechanisms by which *H. erinaceus* inhibits growth of human hepatocellular carcinoma (HCC) is largely unknown. However, two studies performed by Lee et al. [8, 9] demonstrate that *H. erinaceus* acts as an enhancer to sensitize apoptotic signaling mediated by doxorubicin (Dox). Moreover, sensitization can be achieved by reducing the inhibitory protein c-FLIP expression via c-Jun NH2-terminal kinase (JNK) activation and enhancing intracellular Dox accumulation via inhibition of NF-κB activity (note that Dox is an effective chemotherapeutic drug to treat patients with HCCs). These

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findings suggest that *H. erinaceus* in combination with Dox serves as an effective tool for treating drug-resistant human hepatocellular carcinoma.

IMMUNE-ENHANCING PROPERTIES

Polysaccharides are the best known and most potent mushroom-derived substances that display immuno-pharmacological properties. In a trial done by Lee et al. [9], the water soluble crude polysaccharide HEB-P, which was obtained from the liquid culture broth of *H. erinaceus* by ethanol precipitation, were fractionated by DEAE cellulose and Sepharose CL-6B column chromatography. This fractionation process resulted in two polysaccharide fractions that were termed HEB-NP Fr I and HEB-AP Fr I. Only HEB-AP Fr I upregulated the functional events mediated by activated macrophages, such as production of nitric oxide (NO) and expression of cytokines (IL-1β and TNF-α). HEB-AP Fr I, which was found to act as an immunostimulant through the activation of macrophages, was shown to be a β-mannan with a laminarin-like triple helix conformation with a low molecular mass. It has been shown that a triple-helical tertiary conformation of medicinal mushroom-derived polysaccharide was important for immune-stimulating activity indicating that polysaccharide-mediated immuno-pharmacological activities were dependent on the helical conformation [9].

HYPOGLYCEMIC EFFECT

A study by Wang et al. [10] evaluated the effect of extract of *H. erinaceus* fruiting body on blood glucose levels in a diabetic rat model. The major components of the extract were D-threitol, D-arabinitol and well-known polyhydroxy alcohols identified by their chromatographic profiles and spectroscopic characteristics. Some polyols, such as erythritol, threitol, ribitol, arabitol and galactitol are found in mammalian tissue, and these compounds may influence the blood glucose regulation mechanism. The methanol extract of *H. erinaceus* (HEM) was concentrated to remove solvent yielding a residue which was added to the diet. The hypoglycemic effects of feeding HEM to rats with streptozotocin-induced (STZ) diabetes were studied. Polydipsia was stronger in diabetes-induced rats not fed HEM than in those receiving HEM. Rats fed with HEM had significantly lower elevation rates of blood glucose level than those not fed with HEM. The HEM-fed group had a significantly lower increase in serum total cholesterol levels than the non-HEM-fed group and when the dosage of HEM was increased, the difference in serum total cholesterol levels became more significant. Even the effects on blood glucose levels were more significant in the rats fed daily with HEM at doses of 100 mg/kg body weight (bw) rather than 20 mg/kg bw. In summary, Wang and colleagues showed that extracts of *H. erinaceus* not only have a hypoglycemic effect but also reduce rates of increase of serum triglyceride and reduce total cholesterol levels when administered to rats with STZ-induced diabetes [10].

INHIBITION OF PLATELET AGGREGATION

Platelet aggregation in blood vessels causes thrombosis. Therefore, inhibitors of platelet aggregation promise to be preventative or therapeutic agents of various vascular diseases. Mori et al. [2] fractioned ethanol extracts of *H. erinaceus* to isolate and identify compounds that inhibit platelet aggregation; hericenone B–E were found to have such effects. The anti-platelet activity of each fraction was determined using washed rabbit platelets. Hericenone B inhibited

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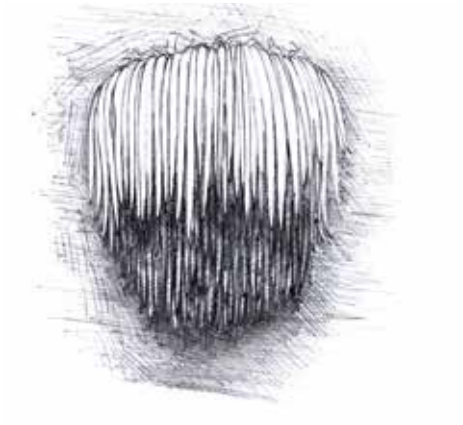
collagen-induced (3 μg/ml) platelet shape change and aggregation in a concentration-dependent manner. Complete inhibition was obtained at 30 μM. However, hericenone C, D, and E (100 μM) did not show any inhibitory activity on the aggregation. Thus, Mori and colleagues concluded that hericenones contain a fatty acid chain that may inhibit platelet aggregation, and that the inhibitory activity of platelet aggregation is associated with hericenone B. However, hericenone B did not suppress the aggregation induced by U46619 (TXA4 analogue), ADP, thrombin, or adrenaline, nor did hericenone B inhibit platelet aggregation induced by either arachidonic acid or convulxin. These results suggest that the site of hericenone B may be upstream of arachidonic acid liberation and GPVI is not involved in the inhibitory effect of hericenone B on collagen-induced aggregation. Hericenone B is thus hypothesized to block collagen signaling from integrin α2/β1 to arachidonic acid release.

Moreover, hericenone B inhibited collagen-induced aggregation in human platelets in a concentration-dependent manner with an IC 50 value of about 3 μM. The effective concentration was approximately equal to that observed in rabbit platelet aggregation. Therefore, hericenone B may be used to prevent thrombosis in human [(2)].

ANTIOXIDANT ACTIVITY

In a study performed by Zhang et al. [(1)], three fractions of intracellular polysaccharides were obtained by fractional precipitation of *H. erinaceus* mycelium with gradient concentrations of ethanol at 40, 60, and 80%. The chemical and physical characteristics of the three crude polysaccharides were investigated with a combination of chemical and instrumental analysis methods. The in vitro studies to evaluate the antioxidant potential of these polysaccharides and their hepatoprotective effects showed that the three fractions had different activities in different systems of evaluation. HEP80 showed strong antioxidant activity in vitro and potent hepatoprotective effect in vivo. The hepatoprotective effect may be due to its potent antioxidant capacity. Thus, *H. erinaceus* polysaccharide could be exploited as an antioxidant product and a supplement to aid prevention of hepatic diseases.



CONCLUSIONS

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Hericium erinaceus is a well-known edible and medicinal mushroom. Its fruiting bodies and the fungal mycelia exhibit various pharmacological properties, including factors that enhance the immune system, fight cancer, lower blood glucose, and promote nerve growth. This summary reviewed evidence showing that H. erinaceus reduces mild cognitive impairment, although continuous intake of the fungus may be necessary to maintain the beneficial effects. It has also been discovered that some hericenone compounds improve NGF. A study by Mori et al. [6] reports that H. erinaceus contains active compounds that are not hericenones but nevertheless stimulate NGF synthesis. Even growth of adrenal nerve cells and extension of neurites were shown to be enhanced by fungus exo-biopolymers.

Hericium erinaceus in combination with Dox serves as an effective tool for treating drug-resistant human hepatocellular carcinoma. Moreover, fractions from H. erinaceus upregulate the functional events mediated by activated macrophages. The fungus also has hypoglycemic effects and reduces rates of increase of serum triglyceride and reduces total cholesterol levels in STZ-diabetic rats. Finally, hericenone B inhibits collagen-induced platelet shape change and aggregation in a concentration-dependent manner, and polysaccharides from the fungus work as antioxidants and supplements to aid the prevention of hepatic diseases.

DISCLAIMER

Statements throughout this publication have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease process.

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