

REVIEW ON LION'S MANE MUSHROOMS

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Abstract- Mane 's mushroom (*Heridium Erinaceus*) has been an essential in Traditional Chinese Medicine, with documented medicinal properties including potential benefits for neurological health, blood pressure reduction, cancer prevention, and hypolipidemia. This review explores the botanical description, Lionhabitat, and composition of Lion's Mane, describing active compounds such as erinacines and hericenones. Traditional uses across different cultures are highlighted, emphasizing its historical significance in Chinese and Japanese medicine. Current research underscores Lion's Mane's potential neuroprotective effects, promoting nerve growth factors and exhibiting antidepressant-like properties. The mushroom's anti-inflammatory, antioxidant, and immunomodulatory properties contribute to its diverse range of potential health benefits. Studies suggest positive outcomes in areas such as wound healing, gastric ulcers, and anti-tumor activities, supporting its traditional uses. Clinical studies and human trials further demonstrate Lion's Mane's efficacy in neuroprotection, cognitive improvement, anxiety reduction, and sleep enhancement. The mushroom's safety profile is generally favorable, with limited reported side effects. Toxicological studies confirm the absence of cytotoxicity in various cell types.

Keywords: Lion's Mane mushroom, *Heridium Erinaceus*, Traditional Chinese Medicine, medicinal properties, neurological health, blood pressure reduction, cancer prevention, hypolipidemia, erinacines, hericenones activities, neuroprotection effects, nerve growth factors, antidepressant-like properties, anti-inflammatory, antioxidant, immunomodulatory, gastric ulcers, anti-tumor activities, neuroprotection, cognitive improvement, anxiety reduction, sleep enhancement

INTRODUCTION

Traditional Chinese medicine has historically used this type of fungus, which can be found mainly in Eastern Asian nations. Many research have documented the possible medicinal properties or health-promoting properties associated with this mushroom, including its ability to prevent neurological disease, lower blood pressure, fight cancer, and hypolipidemia.(1) According to Jia (2004), it is a member of the family Hericiaceae, order Hericiales, and class Basidiomycetes. Recent research has revealed that the medicinal qualities of lion's mane (*Heridium Erinaceus*)(2) It has historically been employed in Chinese and Japanese medicine to strengthen the spleen, to nourishing the gastrointestinal tract, and as a treatment for cancer.(3) At present, most of the identified bioactive compounds that contribute to antidepressant-like effects are mostly associated with NGF-inducing activity Currently, the majority of the identified bioactive compounds that contribute to antidepressant-like effects are primarily associated with NGF-inducing activity(4) . The purpose of this review is to provide information about the natural habits and various nutritional and medicinal uses of lion's mane mushrooms. (5) This review aims to offer insights into the natural habits and diverse nutritional and medicinal applications of Lion's Mane mushrooms.

BOTANICAL DESCRIPTION AND COMPOSITION

- Physical characteristics and habitat of Lion's Mane mushroom.

FRUIT BODY DISCRIPTION:

The huge, irregularly bulbous, compact, snowy to creamy mass and width varies from 5 to 40 cm characterize the fruit body of the lion's mane (*Heridium Erinaceus*). Small, spore-producing rubbery spines that hang and are between 10 and 40 mm in size continuously govern it, along with a few distinct basal branches. Upon reaching maturity, the fruit's body turns from yellow to brown. (2) While the basidia are 25–40 x 5-7 μm , the spores have a snowy, warty, or roughened structure and range in size from 5-7 x 4-5.5 μm (Siwulski et al., 2010). (2)

(1)

NATURAL HABITAT:

Lion mane mushroom inhabits fallen broad leaves from trees like walnut, oak, and beech as well as the center dead wood of large trees and branches of living or dead trees. These are younger trees that have been harmed or injured. (2)



- Detailed composition including active compounds such as erinacines and hericenones.

Hericenones (Kawagishi et al., 1991): an isolated fruiting body and the erinacines (Kawagishi et al., 1994; isolated from the mycelium)(6) Erinacines A, B, C, D, E, F, G, H, I, P, and Q were isolated from the mycelia of Lion mane (Kenmoku et al., 2002)(6) The cyathane skeleton of diterpenoids is made up of angularly compressed five-, six-, and seven-membered rings. Kawagishi et al. isolated erinacines A–F from Lion mane mushroom cultured mycelia. Shi et al (6) Aromatic compounds known as hericenones are isolated from the fruiting body of *Hericenaceus*. Eleven hericenones, or hericenones A through K, have been identified(7) The majority of erinacines have been isolated from *H. Erinaceus* mycelium; however, erinacines A and B are also present in the fruiting bodies. Erinacines are a type of diterpenoids called cyathin(7) From the fruiting body of HE, Wang et al. isolated a polysaccharide with two distinct structural moieties, called HPA and HPB, using boiling-water extraction, EtOH precipitation, and DEAE-Sephacel CL-6B column chromatography(8) A variety of low molecular weight components, including erinacines, hericenones, erinacerins, and the anti-ER stress-protective dilinoleoyl-phosphatidylethanolamine (DLPE), have been isolated from HE in addition to polysaccharides, as previously mentioned in the sections above. Moreover, ergosterols and ergosterol peroxide have been extracted from HE, along with isohericenone and geranylated isoindolinone(8) Many bioactive substances, such as polysaccharides, terpenes, alkaloids, flavonoids, and metal-chelating agents, are present in lion's mane mushrooms(9) A polysaccharide with a glucose molar ratio of 1.5: Lion's mane mushroom mycelium was isolated to yield galactose (1.7), xylose (1.2), mannose (0.6), and fructose (0.9)(10) Hericerins, erinacines, erinacerins-isoindolin-1-ones, erinaceolactones, glycoprotein, polysaccharides, and sterols Lion mane mushroom is known to contain various compounds including erinarols G-J, vitamin B12 lactone (c-lactone), and volatile compounds (2-methyl-3-furanthiol, 2-ethylpyrazine, and 2,6-diethylpyrazine)(11)

TRADITIONAL USES

- Exploration of historical and traditional medicinal uses of Lion's Mane across different cultures and regions.

In East Asia, the mushroom *Heridium Erinaceus*, also known as lion's mane or yamabushitake, has long been utilized as a food source and herbal remedy(12) For hundreds of years, lion's mane mushrooms have been prized in traditional Chinese and Japanese cuisine as well as herbal medicine(13) The lion mane mushroom has been utilized as an anticancer medication and as a means of nourishing the spleen and stomach in both Chinese and Japanese medical systems(14)

CURRENT RESEARCH ON MEDICINAL PROPERTIES

An fascinating study revealed that applying the aqueous extract from the fruiting bodies of the Lion Mane mushroom topically demonstrated encouraging wound healing properties(14) In a different study, the aqueous extract of the Lion mane mushroom was used as a pretreatment for rats with ethanol-induced gastric ulcers. This prevented leukocyte infiltration of the gastric wall and had a protective effect on the gastric mucosa(14) exceptional impact on prolonging cancer patients' lives(13) Hericium Erinaceus, commonly referred to as Lion's Mane mushroom, was ironically used as a preventative measure against cancer and to treat unrelated conditions like stomach aches (Kim et al., 2013)(15)

- Neuroprotective Effects

- Studies demonstrating its potential in promoting nerve growth factors, cognitive enhancement, and neuroprotective effects.

According to the study, the polysaccharide-rich aqueous extract of Lion's Mane mushroom may have therapeutic benefits in Alzheimer's disease by influencing cholinergic pathways, promoting neuroprotection, and modifying important neurotransmitter levels(16) Lion mane mushroom has been shown in a human clinical study to have beneficial effects on mental health, especially for lowering anxiety and depression. Additionally, a possible role in treating mild cognitive impairment is suggested by the improvement in cognitive scores. These results demonstrate the diverse range of benefits that the Lion's Mane mushroom may provide to improve mental health and overall wellbeing. Like any research, more investigation and clinical testing are required(16) Clinical studies have shown that the lion's mane mushroom is beneficial for dementia patients, improving their functionality and delaying the disease's progression. Furthermore, research indicates that substances present in lion's mane promote the development of myelin along axons. This characteristic is especially helpful in shielding the brain from the effects of aging and has great promise for treating patients suffering from diseases like multiple sclerosis, where a central feature is myelin damage(17) A number of studies suggest that lion's mane mushroom may have an effect by reducing the neuroinflammation linked to neurodegenerative diseases(18) The neuroprotective properties of the Lion's Mane mushroom, have been clearly demonstrated by the current study in both cells and a mouse model of Alzheimer's disease (AD). This is demonstrated by a notable improvement in cell viability, reduction of damage caused by neurotoxins, relief of nuclear and mitochondrial apoptotic changes, and improvement of abnormal behavior in mice. Together, these results highlight the potential therapeutic benefit of lion's mane mushroom in preventing neurodegenerative diseases and the behavioral abnormalities they cause(19) Numerous studies have identified a wide range of bioactive components, such as polysaccharides, erinacines, hericenones, alkaloids, steroids, and many more, and have reported significant neurotrophic effects. Friedman, 2015; Brandalise et al., 2017)(15) The stimulation of nerve growth factor (NGF) synthesis by hericenones from fruit bodies and erinacines from mycelium is the most promising action of lion mane mushrooms (Kawagishi et al., 2008). In vitro, an extract from fruit bodies demonstrated neurotrophic action and improved the process of myelination in mature fibers of neuronal cells (Moldavan et al., 2007)(20) Lion's mane mushroom's neuroprotective properties have been linked to cyathane diterpenoids, which are erinacines that can increase the synthesis of brain-derived neurotrophic factor(21) It was discovered that feeding wild-type mice dietary supplements containing lion mane mushroom enhanced their ability to recognize objects in the novel object recognition test and increased neurotransmission at the hippocampal mossy fiber-CA3 synapse(22) Numerous preclinical and clinical studies have clearly demonstrated the role of Lion mane mushroom in neuro health (Sabaratnam et al. 2013). A nerve growth factor synthesis is stimulated by bioactive compounds derived from Hericenones (A-H) and Erinacines (A-K and P-Q) isolated from Lion mane mushrooms (Phan et al. 2015; Sabaratnam et al. 2013)(23)

- Anti-Inflammatory Properties

β -glucan in Lion's Mane mushroom demonstrated potential in reversing inflammatory bowel disease (IBD)-induced changes in the colonic mucosa in a rat study. The enhancement in host immunity was attributed to the growth promotion of beneficial gut bacteria. A decrease in the activation of T cells, nuclear factor kappa B (NFkB), and myeloperoxidase (MPO) confirmed this effect(24) Erinacine C is known for having neuroprotective and anti-inflammatory properties. The mechanisms responsible for these functions are as follows: the upstream NF- κ B signal transduction transmit is involved in the regulation of inducible nitric oxide synthase (iNOS) protein expression; the Nrf2/HO-1 stress-protective pathway is activated; and I κ B and pI κ B α are inhibited (Wang et al., 2019a)(25) Lion's Mane mushroom's anti-inflammatory properties are essential for systemic outcome. Lion's mane contains bioactive compounds which enhance the synthesis of nerve growth factors, which helps to reduce systemic inflammation. Examples of these compounds are hericenones and erinacines(25) study showed that erinacine A could inhibit the expression of inflammatory cytokines, indicating that the neuroprotective properties of erinacine A might be caused by the brain tissue trauma effectors of nitro tyrosine (RNS) via iNOS/p38/MAPK/CHOP(26) In a study by Kim et al., it was discovered that extracts from the Lion's Mane mushroom prepared with hot water and microwaved 50% ethanol significantly decreased the growth and invasion of CT-26 colon cancer cells. Additionally, the extracts showed a

significant decline in CT-26 cell invasion and metastasis to the lungs, with decreases of 66% and 69%, respectively(27)

- Antioxidant Activity

The moderate antioxidant activities of *Hericium Erinaceus* (lion's mane) and *Tricholoma giganteum* (white matsutake) have been demonstrated (48.5% and 67.0% of lipid peroxidation, respectively; Lin, 1999)(28) The experiment on DPPH radical scavenging was slightly modified from Ahmed et al. (2012) to evaluate the antioxidant activity of extracts from Lion Mane Mushrooms(29) Shao et al. (2010) additionally observed that the antioxidant activity in the lipophilic fraction of Lion mane mushroom was mainly associated with ergosterol(29) According to the present study, a hot water extract of lion mane mushroom demonstrated strong antioxidant and free radical scavenging activity in a dose-dependent manner(30) According to Jang et al. (2010), lipopolysaccharide (LPS) that was isolated from mycelia demonstrated high antioxidant properties in mice by increasing hepatic glutathione levels. Antioxidant enzyme activities increased following the pre-administration of β -glucans(31) Research studies by Huang et al. (2008), Mujic et al. (2010), Mau et al. (2002), along with others have demonstrated the antioxidant activity of polyphenols in methanol extracts from dried fruiting bodies of the Lion mane mushroom. Zhang et al. (2012) have reported that endopolysaccharides that are extracted from ethanol extracts of mycelia demonstrate exceptionally high levels of antioxidant activity in vitro. Research studies by Ferreira et al. (2009), Abdullah et al. (2012), and Thongbai et al. (2015) investigated the highest total phenol content and ferric reducing antioxidant capacity (FRAP) in mycelial extracts, particularly in hot water extracts(31)

- Immunomodulatory Effects

The immunomodulatory effect of both organic and aqueous extracts of Lion mane mushroom has been reported in a number of studies; the mechanisms behind these activities seem to depend on the biochemical targets (Lee et al. 2010)(31) A low molecular weight fraction with a triple helix conformation of a b-1,3-branched-b-1,6-glucan was identified from the Lion Mane mushroom and among the different polysaccharide fractions. This fraction demonstrated immunostimulant activity, including the production of NO, the activation of macrophages, and the expression of IL-1b and TNF-a(32) According to study on the immunomodulatory potential of the Lion mane mushroom, polysaccharide fractions of the mushroom's ethanol extract and its derivatives can stimulate the activity of macrophages and TNF α production while also promoting dendritic cell maturation and dendritic cell-mediated cytokine production and T-cell proliferation. In vivo mouse studies have also shown stimulatory effects on the intestinal immune system, mainly characterized by increased surface IgA expression and natural killer cell activation, when the polysaccharide fraction of Lion mane mushroom was administered as a dietary supplement(33)

- Other Potential Benefits

Antihyperglycemic Activity

The anti-hyperglycemic effect of lion mane mushroom methanol extract was demonstrated by Wang et al. in streptozotocin-induced diabetes Wistar rats. Blood glucose, serum triglyceride, and total cholesterol levels decreased when 20–100 mg of extract from the lion mane mushroom was supplemented per kg of body weight(11) The in vitro antidiabetic properties of Lion Mane mushroom have been reported by Wu and Xu, who also discovered that the inhibition of α -glucosidase and aldose reductase activity occurred in a dose-dependent manner(11)

Anticancer Activity

J. S. Lee and Hong (2010) studied the anti-tumorigenic characteristics of the Lion's Mane mushroom in their study. The mushroom extract, according to the researchers, increases a cell's susceptibility to doxorubicin (Dox)-induced apoptosis. This is accomplished by increasing intracellular doxorubicin accumulation and stimulating JNK to decrease the expression of the c-FLIP protein(34) S. P. Kim et al. (2011) examined the effects of transplanting CT-26 colon cancer cells into Balb/c mice and extract from the Lion's Mane mushroom. When the extract was given every day for two weeks, the researchers saw a significant decrease in tumor weights (41% for microwaved hot water extract and 38% for boiled hot water extract). This indicates that, in a mouse model of colon cancer, the mushroom extract Lion's Mane may have anti-tumor properties(34) According to Kim et al. (2000) and Park et al. (2002), the fruit of the Lion mane mushroom or its broth from liquid cultivation exhibit antitumor activity(35)

Anti-Ulcer Activity

Many substances, including polysaccharides, alkaloids, amino acids, and phenolics, are present in lion's mane mushrooms; however, little is known about the active component that promotes the anti-ulcer activity(36) According to Garg et al., rats with ethanol-induced ulcer model stomachs were used to test the gastroprotective properties of an aqueous extract of Lion mane mushroom(37) Tsukimi et al. demonstrated that inhibiting neutrophil infiltration during an inflammatory response could improve the healing of gastric ulcers. By inhibiting neutrophil infiltration, the aqueous extract of the Lion Mane Mushroom may protect the stomach mucosa(37) The aqueous extract of Lion Mane Mushroom

prevented ethanol-induced damage to the stomach mucosa. The application of Lion mane mushroom aqueous extract significantly ($p < 0.05$) reduced lipid peroxidation and increased SOD and CAT activities, demonstrating its effectiveness in avoiding damage from free radicals damage in the stomach tissue caused by suppressing free radicals. The rats that were given ethanol showed signs of gastroprotective activity(37)

Anti-osteoporotic Activity

A few studies that investigated how the lion mane mushroom affects bone metabolism. The constituents of the lion mane mushroom are polysaccharides, fatty acids, aromatic compounds, and sterols(38) In a D-galactose-induced osteoporosis model, Luo and Chen gave rats selenium-enriched polysaccharides extracted from the Lion mane mushroom. They demonstrated that this kind of treatment prevented the femur's mechanical characteristics and the skull's BMD (bone mineral density) from decreasing(38)

Anxiolytic effect

In their study, the effects of this medicinal mushroom on behavior were examined using mice that were given either a regular rodent diet or one that included Lion mane mushroom for 4.5 months. In contrast, the tau mice that were fed Lion mane mushroom had significantly shorter latencies to reach the center of the open field (OF) ($p < 0.05$) and spent significantly more time ($p < 0.001$) in the open arms of the elevated zero maze (EZM). Mice treated with Lion mane mushroom showed a significant increase ($p < 0.05$) in the amount of time they spent in the open arms and nose dips in the elevated zero maze (EZM). The anxiolytic effects of Lion mane mushroom did not result in an improvement in daily living activities or spatial memory (39).

CLINICAL STUDIES AND HUMAN TRIALS

Recent preclinical and clinical studies have demonstrated that lion mane mushroom not only provides neuroprotection and improves cognitive function, but it also reduces anxiety, depression, and sleep disturbances(40) Sleep disturbances were found to be positively affected by consuming Lion's Mane mushroom extract for four weeks, according to a pilot study done on female undergraduate students. Subjective measures, including well-being and sleep quality questionnaires (PSQI - Pittsburgh Sleep Quality Index and GHQ-28), served as the basis for the assessment. Additionally, salivary levels of free 3-methoxy-4-hydroxyphenylglycol were measured. This compound is linked to sympathetic nervous system activity and is an index of chronic stress and depressive symptoms. Significant improvements in subjective sleep quality and well-being were discovered, along with a decrease in depressive symptoms and chronic stress. However, it was discovered that after rising up, salivary levels of the stress marker increased, indicating that consuming Lion's Mane mushroom extract had a beneficial impact on anxiety and sleep quality(40) According to Mori et al., research subjects' cognitive scores significantly improved, demonstrating the fruiting bodies of Lion's mane efficacy in treating mild cognitive impairment [12] as follows: The study lasted 16 weeks, and the subjects were given 1g tablets containing 96% Lion's mane (dry powder) three times a day. After that, the participants were assessed using the Revised Hasegawa Dementia Scale and contrasted with a group that received a placebo. Research on cells, rodents, and humans suggested that Lion mane mushrooms may be used to treat neurological conditions like depression, Parkinson's disease, and Alzheimer's. These findings should only be interpreted cautiously, though, if future research—especially clinical trials involving human subjects—can confirm similar results(16) Kim et al. identified that intraperitoneal injections of aqueous and aqueous/ethanol extracts of lion mane caused the tumors to shrink. Serum pro-inflammatory cytokines and intraperitoneal M Φ levels increased in response to this effect. Moreover, it was observed that the genes encoding cyclooxygenase 2 (Cox 2), 5-lipoxygenase (5-LOX), and vascular endothelial growth factor (VEGF) were expressed more frequently. It was demonstrated that administering these extracts prevented the cancer cells from migrating to the lungs by 66% and 69%, respectively. The cancer cells in these animals exhibited decreased expression of matrix metalloproteinases MMP-2 and MMP-9, which may have inhibited migration and invasion. Using xenografted human gastric, colon, and liver cancer cells in a different murine model(24) The current pilot study investigated how young, healthy adults' moods and cognitive performance were affected by lion mane mushroom. This trial evaluated the effects of a single 1.8 g dose of Lion mane mushroom and again after 28 days of supplementation, developing on the limited research that has been performed to date(41) A significant decrease in serum glucose and serum lipid profiles, as well as a significant increase in insulin, was observed in diabetic rats given 100 and 200 mg/kg body weight of Lion mane mushroom aqueous extract over a four-week period (He et al., 2017b)(42) The effects of HE-A on learning, memory, and brain aging were studied previously by Lee et al. (2021). They discovered that HE-A preparation significantly reduced aging-related cognitive impairment and enhanced cognitive function in both active and passive avoidance behavioral tests(43) Polysaccharides from lion mane mushrooms improve lipid metabolism, lower fasting blood sugar, improve glucose tolerance, and prevent lipid peroxidation. According to Cai et al. (2020), they also initiate the PI3K/Akt signaling pathway(44) Research specifically on the Lion mane mushroom demonstrated significant improvements in cognitive function throughout various clinical trials involving mushrooms. The experimental group in a 16-week Japanese study demonstrated a significant improvement in cognitive function

compared to the control group. The experimental group continued to take a tablet containing 250 mg of Lion mane mushroom extract three times a day(45) In a study published in 2014, Phan et al. investigated neurite growth activity and signaling pathways related to neurogenesis following induction of Lion mane mushrooms in PC12 cells. It has been found that these cells show neurotrophic effects of hericenone E. This action is related to the stimulation of nerve growth factor (NGF) synthesis and the subsequent increase of NGF-induced TrkA receptor phosphorylation, which stimulates the ERK and Akt signaling pathways(46) A prior human pilot study investigated the effectiveness of oral administration of Lion mane mushroom in Japanese men and women aged 50 to 80 who had been diagnosed with mild cognitive impairment. For 16 weeks, the participants in the group supplemented with four pills of Lion mane mushroom three times a day, and their cognitive abilities improved (Mori et al., 2009)(47)

SAFETY AND TOXICOLOGY

Safety

When used consistently, a lion's mane is comparatively safe. Similar to other herbal extracts, it may occasionally result in allergies or gastrointestinal problems(48) The safety and effectiveness of Lion's Mane supplements remain unclear due to the fact that dietary supplements lack the same level of regulation as food and drug products(49)

TOXICOLOGY

Lion's mane fruiting body aqueous extract demonstrated an incredible lack of cytotoxicity in an in vitro model. According to rat toxicology research, mycelia enriched with 5 mg/g erinacine A at dosages as high as 5 g/kg bodyweight/day are safe(3) According to toxicological research, the mushroom is safe to use for a long period of time and does not have any serious side effects. Still, additional research is required to determine its safety(48)Extracts from Lion's Mane and Reishi mushrooms were found to exhibit no toxic effects on keratinocytes (HaCaT) and fibroblasts (BJ cells)(50)

CONCLUSION

In essence, the comprehensive investigation points out the lion's mane mushroom as a versatile and promising medicinal ingredient with a long history and current use. More investigation is necessary to completely realize its potential and determine its role in modern medical treatments, particularly through complex clinical trials.

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