J Am Holist Vet Med Assoc. 2023;70:15–20.
https://doi.org/10.56641/PSSJ9210

Lion's Mane (*Hericium erinaceus*): A Potential Treatment for Neurologic Disorders in Veterinary Medicine

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Abbreviations

DLPE	**Dilinoleoyl-phosphatidylethanolamine**
LM	**Lion's Mane**
NGF	**Nerve growth factor**

Abstract

The use of the culinary and medicinal mushroom Lion's Mane (LM) (*Hericium erinaceus*) has been extensively researched. Much of the recent research has been fueled by interest in using LM to prevent and treat neurological diseases such as cognitive decline, dementia, Parkinson's disease, and Alzheimer's disease and to stimulate peripheral nerve regeneration. This mushroom is rich in physiologically important components. The main bioactive phytochemicals extracted from LM's fruiting body and mycelia are hericenones, erinacines, polysaccharides, and dilinoleoyl-phosphatidylethanolamine (DLPE). β-glucan polysaccharides are immuno-active and responsible for LM's anti-cancer, immunomodulating, hypo-lipidemic, antioxidant, and neuroprotective actions. The hericenones and erinacines can cross the blood-brain barrier and stimulate nerve growth factor (NGF). Since NGF keeps the brain and nervous system regenerating and repairing itself, research has been focused on the effect of these compounds on brain and nervous system conditions. In veterinary medicine, supplementation of LM has potential in the treatment of many conditions, including peripheral nerve damage, dementia, cognitive decline, anxiety, and spinal cord trauma and degeneration.

Introduction

With our aging population and related diseases, interest has peaked in the potential for mushrooms as a treatment and prevention for these conditions. The use of the culinary and medicinal mushroom Lion's Mane (LM) (*Hericium erinaceus*) has been extensively researched. The fruiting body is the traditionally used part of most mushrooms; however, with the current medicinal use of LM, both the fruiting body and the mycelium are used, as the 2 parts of the fungus have different active constituents. Due to these specific phytochemicals and their ability to cross the blood-brain barrier, LM has been shown to improve many physical and mental neurologic conditions (1–3).

Traditional Uses

In China and East Asia, LM (also commonly called monkey's head, Hou Tou Gu in China, and Yamabushitake in Japan) has been in use for many centuries as a medicinal supplement, dried and powdered to be added to soups or made into a tea. Traditionally, the fresh mushroom has been cooked and eaten and is generally considered delicious (1, 2). Its flavor is considered to be umami. In TCM, LM has been used to strengthen the 5 major internal organs (Liver, Lungs, Heart, Kidneys, and Spleen), promote good digestion, improve vital energy (Qi) and stamina, treat gastritis and ulcers,and improve liver function (1, 2, 4–7). The mushroom has other beneficial properties including antioxidants; components to oppose cancer, infection, diabetes, hypertension, fatigue, and inflammation; and mechanisms to improve immune system modulation, fat and cholesterol metabolism, and wound healing (1, 2, 4–6). Buddhist monks have used LM to improve concentration powers before meditation. A sports drink called Houtou was used in the Eleventh Asian Sports Festival in 1990 and was considered influential in several victories (2, 8).

Phytopharmacology

Lion's Mane contains polysaccharides, proteins, 16 amino acids including 7 kinds of essential amino acids, vitamins (especially B12), minerals (magnesium, phosphorus, potassium, iron, copper, and zinc), a small number of lipids, unsaturated fatty acids (including linoleic acid), and sugars (glucose, galactose, mannose, and rhamnose). The mushroom is abundant in bioactive compounds, including β-glucan polysaccharides, diterpenes (hericenones and erinacines), isoindolinones, and sterols. Other phytochemicals include triterpenes, alkaloids, lactones, and glycoproteins (1–6, 9).

Of the primary bioactive phytochemicals in LM, the fruiting body contains the β-glucans, triterpenes, and hericenones. The mycelium contains the erinacines. Erinacines A and B are also present in the fruiting body. The hericenones and the erinacines have anti-cancer and neuroprotective actions and can cross the blood-brain barrier (2, 3, 5, 7, 10–14).

Hericenone B and lectin have hemagglutinating activity; hericenone B inhibits platelet aggregation by inhibiting arachidonic acid liberation, and lectin inhibits erythrocyte aggregation (3, 8, 14, 15).

The β-glucan polysaccharides are pervasive in the fruiting bodies of all mushroom species. They are immunoactive and responsible for anti-neoplastic, immunomodulating, hypolipidemic, antioxidant, antimicrobial, and neuroprotective activities (1–3). The β-glucans also stimulate the following: interferon; interleukins; tumor necrosis factor; NK, B, and T lymphocytes; tumor-infiltrating lymphocytes; lymphokine-activated killer cells; macrophages; granulocytes; and the production of platelets in the bone marrow. The β-glucans attach to receptor sites on immune cells and activate them, thus enabling them to recognize cancer cells as foreign (2).

To date, 35 bioactive polysaccharides have been identified in LM, many of them β-glucans. Over the past decade, it has been demonstrated that LM's polysaccharides possess varous promising activities, including immunomodulation, neuroprotection and neuroregeneration, antioxidation, hepatoprotection, and actions against tumors, gastric ulcers, hyperlipemia, hyperglycemia, fatigue, and aging (1, 4–6, 16). Additionally, the polysaccharides induce dendritic cell activation; dendritic cells are mediators of immunity (both innate and adaptive) and secrete cytokines and chemokines that modulate T and B lymphocytes (6).

Neurologic Applications

Due to the complexity of this mushroom and the voluminous research on its properties and benefits, this review will focus on research in the areas of brain function and nerve regeneration. One field of great interest and study concerns the deterioration of the human brain during the "aging process" (oxidative stress), toxic chemical damage (chemotherapy, heavy metals, taxanes, etc.) to the brain, regeneration and repair of damaged brain cells, and the prevention of diseases such as dementia in humans. Oxidative stress and inflammation in the neuron-glia system are critical factors in the pathogenesis of neurodegenerative diseases. Research with LM is being focused on treatment for dementia, cognitive deterioration, Parkinson's disease, and Alzheimer's disease. There is great interest in the potential of using LM to improve brain function (3, 5, 11).

Lion's Mane has been shown to activate macrophages—key cells in the innate immune system and neuroregeneration, and a means by which LM improves cognitive function (11). Some of LM's antioxidant phytochemicals (hericenones and erinacines) can pass

ISSN 2474-1906

through the blood-brain barrier, reduce the toxic by-products that cause inflammation, and facilitate the repair of damaged brain cells (5,12,13,17). Hericenone B has also been shown to prevent thrombosis, which improves cognitive function by increasing cerebral blood flow (11). In Alzheimer's disease specifically, the mechanisms of action of LM include increased nerve growth factor (NGF) mRNA expression, lipoxin A4 in the brain, and acetylcholine and choline transferase concentrations, with decreased Aβ plaque burden, plaque-activated microglia and astrocytes, and Tau tangles (5, 15).

In one in vitro study, extracts of the fruiting body demonstrated potent neuroprotective activity by significantly increasing the viability of damaged neurons, accompanied by a significant reduction in free radicals (reactive oxygen species) and increased levels of glutathione and the antioxidant enzyme catalase. As a result, mitochondrial membrane potential was improved, increasing ATP levels while reducing mitochondrial toxicity. Additionally, there was decreased apoptosis. These findings demonstrated that LM is a potential neuroprotective and anti-inflammatory agent for brain cells (10).

The fruiting bodies and mycelium positively affect the brain and peripheral nerve regeneration due to various compounds. The mushroom shows great promise for treating Alzheimer's disease and Parkinson's disease as well as general cognitive decline because of its anti-inflammatory properties, stimulation of NGF gene expression, and axon or dendrite activation (7, 11, 14, 18, 19). Improved cognition has been linked to the ability of LM to decrease cholinergic neurons (14). After ischemic stroke, erinacine A-enriched LM mycelia were shown to decrease neuronal apoptosis and reduce stroke cavity size (20). In Parkinson's disease, erinacine A-enriched LM mycelia improved dopaminergic lesions and oxidative stress in the brain and reversed some motor deficits (20). In Alzheimer's disease, LM mycelia enhanced the proliferation of neuron progenitors and the number of neurons in the dentate gyrus region of the brain, increased the ratio of NGF to NGF-precursor, promoted the expression of insulin-degrading enzyme, attenuated cerebral β-amyloid plaque burden, and prevented the recruitment and activation of plaque-associated microglia and astrocytes (20). To date, 15 erinacines (erinacines A–K, P–S) have been identified, and further investigations have demonstrated that 8 of them have various neuroprotective properties, including enhancing NGF release, reducing amyloid-β deposition, increasing insulin-degrading enzyme expression, and managing neuropathic pain (18, 20). It has been challenging to extrapolate the in vivo studies to clinical situations, but preclinical studies have shown that there can be improvements in ischemic stroke, Parkinson's disease, Alzheimer's disease, and depression if LM mycelia enriched with erinacines are included in daily meals. Further, when the mushroom is discontinued, the improvements abate, so LM must be ingested daily on an ongoing basis (19). While more clinical research is needed to fully understand the potential applications of erinacine-enriched LM mycelium, most preclinical data strongly suggest that this LM component is safe and offers much-needed neuroprotective applications.

Clinical trials demonstrated that Lion's Mane was effective in patients with dementia by improving their functionality and retarding the progression of the disease (11, 17, 20). Studies show that the compounds in LM help to stimulate myelin growth along axons, which is particularly useful in protecting the brain from the impacts of aging and has substantial potential in treating patients with multiple sclerosis. The proposed mechanisms of action include direct neurotrophic factors-like activity, promotion of the effects of nerve-derived neurotrophic factor, effects on the adherence of platelets and macrophages, and the release of cytokines, leading to a decrease in permeability and edema and an increase in capillary perfusion (5, 21–23).

The protein NGF is involved in the ongoing regeneration and repair of the brain and the nervous system. It has been shown that NGF can prolong the longevity of neuronal axons, maintain the survival of neurons, regulate the formation of neurons, and promote their regeneration in declining animals and humans (3, 5). It has also been demonstrated that NGF is very important in preventing and treating Alzheimer's disease, as levels are decreased in the brains of patients with Alzheimer's. Additionally, NGF has been shown to reverse neurodegeneration and cholinergic cell body atrophy, reduce the number of amyloid plaques, and improve spatial memory retention (12, 17).

There are 2 primary classes of phytochemicals from LM that induce NGF: hericenones and erinacines, with erinacines being stronger than hericenones (10,13,17).

Erinacine A specifically has been shown to increase catecholamines and NGF in the CNS, thereby increasing the levels of noradrenaline and other brain chemicals (8). Other phytochemicals from LM that induce NGF include hericipins, polysaccharides, and dilinoleoyl-phosphatidylethanolamine (DLPE) (15). These compounds significantly induced the synthesis of NGF in vitro and in vivo (4, 5, 8, 12, 13, 15, 17). Additionally, DLPE was isolated from the mushroom and found to protect against neuronal cell death caused by β-amyloid peptide toxicity, endoplasmic reticulum stress, and oxidative stress (8, 20, 24).

The mushroom has been shown to have anti-anxiety and anti-depression actions on the brain (3, 5, 7). A clinical trial on menopausal women showed marked improvement in anxiety and depression scores after 4 weeks of twice-a-day treatment. The mechanism of action of this improvement was postulated to be due to the effect of NGF stimulation on neurogenesis (14). Other studies using LM to treat depression and anxiety showed relief of inflammation-associated depression due to neuroprotection and improvement in depressive symptoms such as binge eating and insomnia (7). Levels of NGF are lower in patients with depression; raising the levels of NGF is therapeutic (20). Additionally, LM mycelium was shown to normalize decreased levels of norepinephrine, dopamine, and serotonin and increase levels of IL6 and TNF-α (20). The overall mechanism of action of LM in alleviating depression and anxiety was suggested to be through the modulation of pro-inflammatory cytokines and monoamine neurotransmitters and the activation of brain-derived neurotropic factor pathways (7, 20).

Many studies have been performed in vitro and in vivo on peripheral nerve regeneration following crush injuries in rats and mice (5, 8, 9, 16, 22, 23). In one study, the peroneal functional index (an index used to monitor motor nerve function) was determined before the nerve procedure and after as rats showed signs of recovery. Histological examinations were performed on the peroneal nerve by immunofluorescence staining and neuromuscular junction by combined silver-cholinesterase staining. Upregulation of signaling pathways and axonal protein synthesis and degradation were consistent with the beginning of motor-functional recovery of an injured nerve within a limb (5). Other studies utilized a hot water

ISSN 2474-1906

extract of the fruiting body and the mycelia to yield hericenones and erinacines which stimulate NGF release and facilitate regeneration (8, 16, 22, 23). The data in many studies suggest that daily oral administration of aqueous extract of LM fresh fruiting bodies could promote the regeneration of injured rat peroneal nerve and increase the rate of motor function return in the early stage of recovery (5).

Immunofluorescence studies also showed that dorsal root ganglia neurons ipsilateral to the crush injury in rats of LM-treated groups expressed higher immunoreactivities for protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) signaling pathways as well as c-Jun and c-Fos genes compared to the control group, suggesting effects of LM on neurotrophin-promoted cell survival and neurite outgrowth (8, 16). Sensory nerve responses were noted by some researchers by tracking the animals' sensitivity to heat (20). Peripheral nerve injury leads to changes at the axonal site of injury and remotely in the dorsal root ganglion, which contains the cell bodies of sensory afferent neurons. Sensory recovery may extend for a longer time than motor recovery, as the axons of sensory neurons provide cutaneous sensation to a larger area than before the injury. Even when motor recovery occurs, sensory deficits may impair the functional outcome, particularly in proprioception. The LM extract accelerates the return of sensory functions after the nerve crush injury by activating protein kinase signaling pathways and restoring the blood-nerve barrier (4, 23). Moreover, results have indicated that administering LM mycelia enriched with its active compounds alone can promote functional recovery and enhance nerve regeneration in rats with neuropathic pain (8, 16, 20, 22, 23). Additionally, there is a neuroregenerative role of polysaccharides from LM fresh fruiting bodies, promoting a more rapid return of sensory function of injured peripheral nerves and facilitating recovery in rats with traumatic nerve injury (20).

Potential Applications in Veterinary Medicine

LM has potential for treating certain neurologic problems in animals. This mushroom could be considered in the support of nerve regeneration in dogs and cats with injuries, including radial and spinal nerve paralysis. There is also the potential to use LM with patients experiencing loss of proprioception, declining cognition, dementia, brain tumors, and seizures, as well as for geriatric pet care and preventive therapy. Other potential uses of LM in veterinary medicine include stomach ulcers in anxiety-prone horses; inflammatory bowel disease and colitis; gastric and esophageal carcinoma; separation anxiety; fear of loud noises including thunderstorms; spinal cord conditions such as degenerative myelopathy, trauma, and intervertebral disc disease; peripheral nerve damage (radial nerve); nerve pain or sensory nerve analgesia; cognitive decline and dementia in geriatric animals; brain tumors; and seizures due to exposure to toxins (25).

One suggested dosage of hot water-extracted and then dehydrated LM powder is ¼ to ½ teaspoon per 4.5 kg body weight twice daily. Other potential dosages include dried raw powder administered at 70-750 mg/kg/day and double decoction 0.1 mL-0.2 mL/kg/day divided BID. A double decoction is a preparation in which the mushroom is extracted in both water and alcohol to maximize constituent extraction. Simply feeding fresh LM is another option. For humans, Spelman lists dosages according to the condition: for NGF production, 3-5 g/day of the dried fruiting body; for dementia or cognitive impairment, 250 mg tablets TID for a minimum of 16 weeks; for depression or anxiety, 2 g/day of fruiting bodies in food for a minimum of 4 weeks (5).

It is important to note that the potency of a commercial LM product might differ from product to product due to how it is grown (medium), harvested, processed, and stored. Different methods used to extract and process the compounds produce slightly different compounds and molecular structures, as well as the percentages of the constituents (1, 26). Additionally, the mycelium and the fruiting body differ in phytochemical content and potency. Post-harvesting processing such as oven-drying (to increase shelf life) can affect the potency of the mushroom. The extracts of fruiting bodies dried in the oven were demonstrated to have lost their ability to stimulate neurite growth (26).

No adverse effects or toxicity have been reported. However, all mushrooms can cause sensitivity or allergic reactions in certain individuals (5, 19, 20).

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ISSN 2474-1906