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Case Report

ALSUntangled #73: Lion's Mane

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Abstract

Lion's Mane (*Hericium erinaceus)* has historically been used as traditional medicine in Asia and Europe for its potential benefits in fighting infection and cancer. It has gained interest in the neurodegenerative disease field because of its mechanisms of action; these include anti-inflammation, neuroprotection, and promoting neurite growth demonstrated in various cell and animal models. A very small, double-blind, placebo-controlled trial in patients with mild cognitive impairment showed a temporary improvement in cognitive function; this finding has yet to be replicated. However, there have been no studies in ALS cell or animal models or in humans with ALS. Lion's Mane appears safe and inexpensive when consumed in powder or capsule, but one anaphylactic case was reported after a patient consumed fresh Lion's Mane mushroom. Currently, we do not have enough information to support the use of Lion's Mane for treating ALS. We support further research in ALS disease models and clinical trials to study its efficacy.

Keywords: *ALS, Lion's Mane, Hericium erinaceus*

ALSUntangled reviews alternative therapies on behalf of persons with ALS (PALS). Here we review the effectiveness of Lion's Mane mushroom in treating ALS. Lion's Mane is touted on multiple websites as an ALS treatment (https://www.forij.co/blogs/mushrooms/lions-mane-mushroom-als#lions_mane_for_als; https://www.medimushrooms.co.za/blog/go-beyond-the-ice-bucket-challenge-and-treat-als-naturally). We have received 919 requests to review this topic (https://www.alsuntangled.com/future-reviews).

Overview

Hericium erinaceus, also known as Lion's Mane or Yamabushitake, is an edible mushroom that has long been used in traditional Chinese medicine and in Europe for its potential antimicrobial, antineoplastic and lipid-lowering effects (1,2). Recently, it has gained interest for therapeutic development for neurodegenerative disorders because there is growing evidence suggesting it might have anti-inflammatory, antioxidant, neuroprotective, and neurotrophic properties (3,4). At least one website is currently advertising the potential benefits of Lion's Mane for ALS (https://www.naturesrise.com/blogs/brainfood/lions-mane-als).

Mechanisms

Neuroprotective effects against oxidative stress and inflammation demonstrated in cells and animal models

Excessive oxidative stress is implicated in the pathophysiology of neurodegenerative disorders, including ALS (5,6). Lion's Mane has potential

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Table 1. Table of evidence for Lion's Mane.

Category	Grade	Explanation
Mechanisms	B	Multiple plausible mechanisms demonstrated in non-ALS pre-clinical models
Pre-clinical models	U	No studies have been done in ALS cell or animal models.
Cases	F	Two patients reported no benefit and one reported only slight benefit on PatientsLikeMe.
Trials	U	No clinical trial in PALS to date
Risks	B	Less than 10% of exposed patients have experienced harms

antioxidant effects, as it contains a high-concentration of phenols (7,8). In a cultured cell model, polysaccharides derived from Lion's Mane decreased the reactive oxygen production and increased the free radical scavenging (9). A second study found that ethanol or hot water extracts from Lion's Mane could protect against oxidation and inflammation-caused cell damage. For example, Lion's Mane extract decreased lipopolysaccharide (LPS)-induced nitric oxide production in mouse microglia cells. It also increased the survival of hydrogen peroxide-treated mouse hippocampal neurons, suggesting a neuroprotective effect. These benefits were accompanied by a reduction of reactive oxygen species (ROS), upregulating antioxidant enzymes and mitochondrial ATP production and decreasing mitochondrial toxicity (10). Additional research found that a high dose of (400 mg/kg/day) sulfate-modified polysaccharides from Lion's Mane could mitigate hippocampal neuron degenerative changes in D-galactose-induced aging mouse model, and this benefit was also associated with reduced ROS and increased antioxidant enzyme activities (11).

Lion's Mane was also found to protect from neuronal death in the brain due to ischemic injury (i.e. stroke). The stroke animal models pretreated with either Lion's Mane mycelium extracts or its derivative, erinacine A, had smaller infarction sizes than controls (12). Further investigation revealed that an erinacine A derivative could reduce the serum levels of inflammatory cytokines, such as interleukin 1beta, interleukin 6, tumor necrosis factor-alpha, and ROS (12).

Neurotrophic effects demonstrated in cells and animal models

Neurotrophins are growth factors in the nervous system that are essential for neuronal development, survival, and function (13,14). Lion's Mane extract can induce nerve growth factor (NGF) synthesis in human astrocytoma cells; the mice fed with 5% Lion's Mane powder for 7 days had increased NGF mRNA expression in their hippocampus (15). The enhanced neurotrophin expression by Lion's Mane was also confirmed in studies using different glioma cell lines (16–18). Another study showed that when administered to mice that recently had a crush-injury to their hind limb, Lion's Mane accelerated the functional recovery of the limb. This most likely occurred by promoting peripheral nerve axon regeneration and reinnervation and activation of neurotrophic signaling at the ipsilateral dorsal root ganglia (19). Further, a new study found Lion's Mane extracts promoted hippocampal neuron neurite outgrowth by activating brain-derived neurotrophic factor (BDNF) pathway and improved short-term memory in mice (20). However, it is important to note that there is no current evidence suggesting Lion's Mane derivative or extract crosses blood brain barrier to promote NGF or BDNF synthesis in human.

ALSUntangled assigns a TOE 'Mechanism' grade of B (Table 1).

Pre-Clinical

We did not find studies of Lion's Mane in ALS related cell or animal models. In a peripheral nerve injury mouse model, Lion's Mane accelerated the functional recovery of the injured limb (19). Because there were no ALS pre-clinical studies, ALSUntangled assigns a TOE 'Pre-Clinical Model' grade of U.

Cases

Eleven PALS have reported using Lion's Mane in the online community PatientsLikeMe, four of whom provided evaluations of their experience and perceived effectiveness of the mushroom in relieving their ALS symptoms. One patient (who reported always being compliant) reported that it was slightly effective without further description of the effects, while the other three (two reported always being compliant, and one reported sometimes being compliant) reported no effect. We were not able to verify their ALS diagnoses or compliance with the regimen. Therefore, we assign a TOE 'Cases' grade of D.

Trials

We found no past or ongoing clinical trials of Lion's Mane in PALS. Therefore, we assign a TOE 'Trials' grade of U.

Of potential interest, a clinical trial was conducted in people with mild cognitive impairment (MCI), a neurodegenerative disease with some shared pathophysiology with ALS (21). The double-blind, placebo-controlled trial in 30 Japanese MCI patients from 50 to 80 years old showed that

Lion's Mane improved early cognitive deficit. Fifteen participants were enrolled in the Lion's Mane group and fourteen of them took 1000mg three times a day for 16 weeks; one patient withdrew from the trial at 4 weeks due to stomach discomfort and was excluded from statistical analysis. At 4, 8, and 16 weeks, these patients' performance on the Revised Hasegawa Dementia Scale (HDS-R, total score of 30) improved compared to their baseline and the placebo group. By week 16, 10 patients taking Lion's Mane had an increased score $\geq$3 points and 3 patients had a 2 point increase from the baseline average score of 24. Only two participants on placebo had 2 and 3 points increases respectively. Notably, participants in Lion's Mane group had a cognitive decline at 4 weeks of follow up after the cessation of the medication, indicating its continued intake is required to sustain the benefit. The benefits seen in this very small trial has yet to be replicated.

Risks, dosing, and costs

Lion's Mane is taken orally, either in the form of an edible mushroom, powder, or capsule. There has been no dosing regimen studied in PALS. The dosing in the MCI clinical trial was 1000 mg of Lion's Mane extract powder three times daily. The cost is about $25-50 a month.

We found one case report of anaphylactic reaction after Lion's Mane mushroom consumption (22). The patient developed hives, abdominal pain and diarrhea within minutes after consuming the mushroom; no respiratory compromise or hypotension were reported and the symptoms resolved within 24 hours after taking Benadryl. Skin testing using fresh Lion's Mane mushroom was positive, but testing using mushroom extract was negative. In the MCI clinical trial, no adverse effects were reported (21). Of the four evaluations that PALS reported on PatientsLikeMe, three reported "none" for side effects, and one listed "mild" side effects, although he did not specify the side effects. Three other patients on PatientsLikeMe have reported taking Lion's Mane for Multiple Sclerosis, Primary Lateral Sclerosis, and myalgic-encephalomyelitis-associated brain fog. All three of these patients reported "none" regarding side effects. In addition, a rodent study showed that after 13 weeks of daily oral administration of various doses (0, 875, 1750, and 2625 mg/kg), there were no differences in weight or appetite, no discernable toxic effects, no significant hematological, biochemical, or histological differences, and no deaths in any of the rats (23).

Due to one case report of anaphylaxis to Lion's Mane mushroom, we assign a TOE 'Risks' grade of B.

Conclusion

While Lion's Mane may have neuroprotective, neurotrophic, antioxidant, and anti-inflammatory properties that could, at least in theory, potentially help ALS, there are still no studies in ALS-relevant cell or animal models, nor in humans with ALS. Therefore, we do not have enough information to support the current use of Lion's Mane for treating ALS. We hope to see the validation of its neuroprotective and anti-inflammatory benefits in ALS disease models, which may ultimately lead to clinical trials in PALS.

Declaration of interest

Richard Bedlack has research support from ALSA, Orion, MediciNova, and the Healey Center, and consulting support from AB Science, Alexion, ALSA, Amylyx, Biogen, Black Swan, Brainstorm Cell, Cytokinetics, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, PTC Therapeutics, Projects in Knowledge, Shinkei and Woolsey Pharma. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Reference

1. Zhang Z, Liu R-N, Tang Q-J, Zhang J-S, Yang Y, Shang X-D. A new diterpene from the fungal mycelia of Hericium erinaceus. Phytochem Lett. 2015;11:151–6.
2. Liang B, Guo Z, Xie F, Zhao A. Antihyperglycemic and antihyperlipidemic activities of aqueous extract of *Hericium erinaceus* in experimental diabetic rats. BMC Complement Altern Med. 2013;13:253.
3. Lewis JE, Poles J, Shaw DP, Karhu E, Khan SA, Lyons AE, et al. The effects of twenty-one nutrients and phytonutrients on cognitive function: a narrative review. J Clin Transl Res 2021;7:575–620.
4. Friedman M. Chemistry, nutrition, and health-promoting properties of *Hericium erinaceus* (Lion's Mane) mushroom fruiting bodies and mycelia and their bioactive compounds. J Agric Food Chem. 2015; 63:7108–23.
5. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. Molecules 2019;24:1583.
6. Obrador E, Salvador-Palmer R, López-Blanch R, Jihad-Jebbar A, Vallés SL, Estrela JM. The link between oxidative stress, redox status, bioenergetics and mitochondria in the pathophysiology of ALS. Int J Mol Sci 2021;22:6352.

7. Ghosh S, Nandi S, Banerjee A, Sarkar S, Chakraborty N, Acharya K. Prospecting medicinal properties of Lion's Mane mushroom. J Food Biochem. 2021;45:13833.
8. Ghosh S, Chakraborty N, Banerjee A, Chatterjee T, Acharya K. Mycochemical profiling and antioxidant activity of two different tea preparations from Lion's Mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes). Int J Med Mushrooms. 2021;23:59–70.
9. Yao F, Gao H, Yin CM, Shi DF, Lu Q, Fan XZ. Evaluation of in vitro antioxidant and antihyperglycemic activities of extracts from the Lion's Mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes). Int J Med Mushrooms. 2021;23:55–66.
10. Kushairi N, Phan CW, Sabaratnam V, David P, Naidu M. Lion's Mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. Suppresses H_2O_2-induced oxidative damage and LPS-induced inflammation in HT22 hippocampal neurons and BV2 microglia. Antioxidants 2019;8:261.
11. Li H, Zhao H, Liu W, Feng Y, Zhang Y, Yuan F, et al. Liver and brain protective effect of sulfated polysaccharides from residue of Lion's Mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes), on D-galactose-induced aging mice. Int J Med Mushrooms. 2021;23:55–65.
12. Lee KF, Chen JH, Teng CC, Shen CH, Hsieh MC, Lu CC, et al. Protective effects of Hericium erinaceus mycelium and its isolated erinacine A against ischemia-injury-induced neuronal cell death via the inhibition of iNOS/p38 MAPK and nitrotyrosine. Int J Mol Sci. 2014; 15:15073–89.
13. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci. 2001;24: 677–736.
14. Pöyhönen S, Er S, Domanskyi A, Airavaara M. Effects of Neurotrophic factors in glial cells in the central nervous system: expression and properties in neurodegeneration and injury. Front Physiol. 2019;10:486.
15. Mori K, Obara Y, Hirota M, Azumi Y, Kinugasa S, Inatomi S, et al. Nerve growth factor-inducing activity of *Hericium erinaceus* in 1321N1 human astrocytoma cells. Biol Pharm Bull. 2008;31:1727–32.
16. Ryu SH, Hong SM, Khan Z, Lee SK, Vishwanath M, Turk A, et al. Neurotrophic isoindolinones from the fruiting bodies of *Hericium erinaceus*. Bioorg Med Chem Lett. 2021;31:127714.
17. Samberkar S, Gandhi S, Naidu M, Wong KH, Raman J, Sabaratnam V. Lion's Mane, *Hericium erinaceus* and tiger milk, lignosus rhinocerotis (higher basidiomycetes) medicinal mushrooms stimulate neurite outgrowth in dissociated cells of brain, spinal cord, and retina: an in vitro study. Int J Med Mushrooms. 2015;17:1047–54.
18. Lai PL, Naidu M, Sabaratnam V, Wong KH, David RP, Kuppusamy UR, et al. Neurotrophic properties of the Lion's Mane medicinal mushroom, *Hericium erinaceus* (higher basidiomycetes) from Malaysia. Int J Med Mushrooms. 2013;15:539–54.
19. Wong KH, Naidu M, David RP, Bakar R, Sabaratnam V. Neuroregenerative potential of Lion's Mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (higher Basidiomycetes), in the treatment of peripheral nerve injury (review). Int J Med Mushrooms. 2012;14:427–46.
20. Martínez-Mármol R, Chai Y, Conroy JN, Khan Z, Hong SM, Kim SB, et al. Hericerin derivatives activates a pan-neurotrophic pathway in central hippocampal neurons converging to ERK1/2 signaling enhancing spatial memory. J Neurochem. 2023;165:791–808.
21. Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Phytother Res. 2009;23:367–72.
22. Watson C, Kobernick A. Dangers at the dinner table – A report of anaphylaxis to Lion's Mane mushroom. Ann Allergy Asthma Immunol. 2022;129:S147.
23. Lee LY, Li IC, Chen WP, Tsai YT, Chen CC, Tung KC. Thirteen-week oral toxicity evaluation of Erinacine A enriched Lion's Mane medicinal mushroom, *Hericium erinaceus* (Agaricomycetes), mycelia in Sprague-Dawley rats. Int J Med Mushrooms. 2019;21:401–11.