



*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

## Lion's Mane (also known as *Hericium erinaceus*)

### Evidence Summary

Although there are some interesting preclinical results, most studies use different preparations of Lion's mane which may not have the same effects as the Lion's mane supplements available in the store.

**Neuroprotective Benefit:** Although there are some effects in preclinical models, clinical trials in patients were small and had inconsistent results.

**Aging and related health concerns:** Lion's mane provides some age-related health benefits, but most studies use specific extracts which may not be equivalent to the types of Lion's mane available in the store.

**Safety:** There is little clinical data on the safety of Lion's mane, though it is a common supplement.

<b>Availability:</b> Available OTC	<b>Dose:</b> Clinical trials have used ~3g/day of powdered fruiting bodies	<b>Molecular formula:</b> N/A <b>Molecular weight:</b> N/A
<b>Half-life:</b> N/A – different constituents may have different half-lives	<b>BBB:</b> Possibly penetrant	
<b>Clinical trials:</b> One in MCI patients and one in healthy individuals	<b>Observational studies:</b> None	

### What is it?

Lion's mane (also known as *Hericium erinaceus*, and yamabushitake) is a medicinal, edible mushroom native to North America, Europe, and Asia. Consumption or supplementation of Lion's mane is reported to increase nerve growth factor (NGF). Lion's mane contains hericenones (derived from the fruiting body of the mushroom) and erinacines (derived from the mycelia of the mushroom). Erinacines are cyathin diterpenoids, of which 15 (erinacine A-K and P-S) have been identified to date in Lion's mane. Erinacines are reported to have the greatest biological activity, especially erinacine A ([Li et al, 2018](#); [Khan et al, 2013](#)).

Lion's mane is reported to have neuroprotective, anti-cancer, and anti-inflammatory properties. However, there is no standardized treatment of Lion's mane. Some studies use powdered fruiting bodies or mycelia, while other studies use extracts from these different components. Similarly, Lion's mane available in stores come in different formulations.



**Neuroprotective benefit:** Although there are some effects in preclinical models, clinical trials in patients were small and had inconsistent.

Types of evidence:

- Three RCTs, one in each AD, MCI, and in healthy subjects
- Five preclinical studies in Alzheimer's animal models
- Two preclinical studies in healthy mice
- Three preclinical studies in other neurodegenerative diseases (stroke, Parkinson's)
- Four *in vitro* studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

[Mori et al \(2009\)](#) reported that in 30 patients with mild cognitive impairment (MCI) 16-week treatment with 3000mg (four 250mg tablets three times per day) of 96% Lion's mane supplement, derived from the fruiting body, improved cognition on the Revised Hasegawa Dementia Scale (HDS-R – a dementia scale used in Japan). Cognitive performance began to drop after a four-week washout period. Cognition in the placebo group also increased slightly over time, even through the washout period, though not as much as the treatment group. Side effects were balanced between the groups (gastrointestinal in nature), and laboratory measures suggest a slight drop in uric acid in the treatment group that was still within the normal range.

In an RCT of 31 cognitively healthy participants who were aged 50 or older, 12-week treatment with Lion's Mane (3.2g per day) improved cognition on the Mini Mental State Examination (MMSE) compared to placebo but not on the Benton visual retention test or standard verbal paired-association test ([Saitsu et al, 2019](#)). This result is surprising given that the MMSE is a test for dementia, and the patients were cognitively healthy.

Human research to suggest benefits to patients with dementia:

One small RCT in patients with Alzheimer's disease suggested that Lion's mane improved scores on the activities of daily living (e.g., personal hygiene, dressing, preparing food, etc.) over 49 weeks. However, there were no significant improvements in cognition compared to the placebo group, possibly due to the low number of patients in the study ([Li et al, 2020](#)).



### Mechanisms of action for neuroprotection identified from laboratory and clinical research

Treatment of 5-month-old Alzheimer's mice for 30 days with either Lion's mane mycelium or its ethanol extract reduced the number of amyloid plaques (the non-compact part and not the plaque core). The ethanol extract reduced soluble A $\beta$ 42, but there were no other effects on soluble A $\beta$ 40 or insoluble A $\beta$ 40/42. Both compounds also improved behavior, increased expression of insulin degrading enzyme (IDE), increased neurogenesis, reduced astro- and microgliosis, and increased the NGF/pro-NGF ratio ([Tsai-Teng et al, 2016](#)). Treatment of 5-month-old Alzheimer's mice with erinacine A or S also reduced amyloid plaques, astro- and microgliosis, increased levels of IDE (but not NGF), increased neurogenesis, and improved cognition ([Chen et al, 2016](#); [Tzeng et al, 2018](#)). The mycelium polysaccharide-enriched aqueous extract of Lion's mane also improved cognition and increased the levels of acetylcholine and choline acetyltransferase (ChAT) in a D-galactose-induced model of Alzheimer's disease ([Zhang et al, 2016](#)). Finally, feeding mice a diet of Lion's mane improved cognition in a model of intracerebroventricular (ICV) injection of A $\beta$  ([Mori et al, 2010](#)).

Lion's mane treatment in healthy mice increased the mRNA of NGF in the hippocampus ([Mori et al, 2008](#)). In young, healthy mice, Lion's mane treatment also improved cognition and improved neurotransmission in hippocampal slices from healthy mice ([Brandalise et al, 2017](#)).

*In vitro*, Lion's mane, and some of its constituents, was reported to increase the expression of NGF in several cell lines ([Mori et al, 2008](#); [Li et al, 2018](#)). Several constituents from Lion's mane mycelia were able to stimulate neurite length in the presence of NGF, an effect that was mediated through TrkA and Erk1/2, and reduced cell death of neuronally-differentiated PC12 cells after NGF removal. They also increased neurite outgrowth of primary rat cortical neurons ([Zhang et al, 2017](#)). More than a dozen studies have examined whether components of Lion's mane increase the expression of NGF or increase neurite outgrowth *in vitro*. Most show beneficial effects on these outcomes, some show no effect, whereas one showed a reduction of NGF-stimulated neurite outgrowth in PC12 cells (scabronine M) ([Bailly and Gao, 2020](#)).

### *Other neurodegenerative diseases*

One study reported that Lion's mane-enriched erinacine A extract reduced ischemic stroke infarct size by up to 44% and reduced the levels of several inflammatory cytokines (IL-1 $\beta$ , IL-6, TNF $\alpha$ ) ([Lee et al, 2014](#)).

In Parkinson's models, Lion's mane mycelium-enriched erinacine A reduced dopaminergic cell loss, the production of reactive oxygen species, and improved motor deficits ([Kuo et al, 2016](#); [Lee et al, 2020](#)).



APOE4 Interactions:

None reported

**Aging and related health concerns:** Lion's mane provides some age-related health benefits, but most studies use specific extracts which may not be equivalent to the types of Lion's mane available in the store.

Types of evidence:

- Three lifespan/aged animal studies
- Five preclinical studies in neuropathy
- Three preclinical metabolic studies
- Three preclinical cancer studies

*Lifespan*

[Ratto et al \(2019\)](#) developed a frailty index in old mice based on locomotion and cognition. Two-month treatment with a Lion's mane extract improved scores on the frailty index. This was driven by an improvement in cognitive performance. In addition, hippocampal neurogenesis was increased after supplementation.

In aged mice fed a high fat/high sucrose diet, treatment with Lion's mane or erinacine A improved cognition and reduced mRNA of inflammatory genes (TNF $\alpha$ , IL- $\beta$ ) in the hippocampus. In addition, Lion's mane, but not erinacine A, increased mRNA expression of NGF and NeuN in the hippocampus. Lion's mane and erinacine A also improved several metabolic parameters such as adipose tissue weight, plasma glucose, total cholesterol, and liver triacylglycerol and cholesterol ([Tsai et al, 2019](#)).

Erinacine A-enriched Lion's mane mycelia also increased maximum lifespan of *Drosophila* and in 6-month-old SAMP8 mice by 32% and 23%, respectively. Life extension for SAMP8 mice was most effective at the highest dose (431mg/kg BW/day) ([Li et al, 2018](#)).

*Neuropathy*

[Yang et al \(2020\)](#) reported that Lion's mane mycelium extract and erinacine S (but not erinacine A) could counteract the cytotoxic effects of purinoreceptor (P2R – thought to be involved with pain signaling) in human osteosarcoma HOS cells and human neuroblastoma cells. Both Lion's mane extract and erinacine



S reduced neuropathic pain (measured by paw withdrawal pressure) in mouse models of spinal nerve ligation. Both also reduced inflammation (IL-6, GFAP, Iba1) in the ligation site (see also [Liu et al, 2017](#)). Lion's mane fruiting bodies were also reported to improve functional activity and nerve regeneration following a peroneal nerve crush injury ([Wong et al, 2012](#); [Wong et al, 2010](#)). In a rat model of alloxan induced diabetic neuropathic pain, Lion's mane treatment increased pain threshold and increased the total antioxidant status in the plasma ([Yi et al, 2015](#)).

#### *Metabolic*

[Zhang et al \(2017\)](#) treated streptozotocin (STZ)-induced diabetic mice with two intracellular polysaccharide (HIPS) purified fractions (HIPS1 and HIPS2) from Lion's mane with the idea that they could prevent the absorption of glucose by inhibiting carbohydrate-hydrolyzing enzymes. Both inhibited  $\alpha$ -amylase and  $\alpha$ -glucosidase, with HIPS1 being more effective. Two-week treatment reduced plasma glucose levels, and suppressed abnormal elevations of liver enzymes, urea nitrogen, and creatine in the plasma. They also increased levels of antioxidant enzymes and attenuated pathology in the liver and kidney.

Additionally, 28-day treatment with an aqueous extract of Lion's mane in a diabetic rat model reduced serum glucose levels, increased serum insulin levels, improved lipid levels (triglycerides, cholesterol, LDL, HDL), increased the activity of several antioxidant enzymes, and reduced malondialdehyde (a marker of oxidative stress) in the liver ([Liang et al, 2013](#)). Another study also showed metabolic improvements in a mouse model fed a high-fat diet after 28-day treatment with a hot-water or ethanol extract of Lion's mane ([Hiwatashi et al, 2010](#)).

#### *Cancer*

In a mouse model with transplanted colon cancer cells on the back, two-week treatment with hot water or ethanol Lion's mane extracts reduced tumor weight by 38% and 41%, respectively. There was an increase in the cytolytic activity of splenic natural killer cells, an increase in the phagocytic activity of macrophages, an increase in pro-inflammatory cytokines from macrophages, and a ~60% reduction of blood vessel infiltration in the tumors ([Kim et al, 2011](#)). Another mouse model suggested that these two extracts could inhibit infiltration of colon carcinoma cells into the lung by ~66% and prevented the increase in lung weight due to tumor nodules ([Kim et al, 2013](#)).

*In vitro* studies suggest that Lion's mane may have anti-proliferation and pro-apoptotic effects in different cancer cell lines ([Wang et al, 2018](#)).

**Safety:** There is little clinical data on the safety of Lion's mane, though it is a common supplement.

Types of evidence:

- Two clinical trials
- Preclinical animal studies

Little information is available on the safety of Lion's mane. In rats, its LD<sub>50</sub> was reported to be higher than 5g/kg ([Li et al, 2018](#)). One clinical study of Lion's mane did not report safety outcomes ([Saitsu et al, 2019](#)) while another only reported mild gastrointestinal symptoms which were balanced between the treatment group and placebo ([Mori et al, 2009](#)). [Drugs.com](#) reports there is limited clinical data on safety. However, Lion's mane is a relatively common supplement. Long-term studies with standardized treatments are needed to fully understand the safety of Lion's mane supplementation.

**Drug interactions:**

Not known

**Sources and dosing:**

Lion's mane mushroom is available as a supplement. In vitamin stores they come in different varieties (e.g. fermented Lion's mane, powdered Lion's mane mycelium, etc.). Dosing is not fully known. One study used 1g three times per day of powdered Lion's mane fruiting bodies ([Mori et al, 2009](#)). Another used 3.2g of powdered Lion's mane fruiting bodies per day ([Saitsu et al, 2019](#)). Preclinical studies used various extracts of Lion's mane.

**Research underway:**

One study is testing the effect of Lion's mane for non-motor symptoms of Parkinson's disease ([NCT04428983](#)).

**Search terms:**

- Hericium erinaceus + Alzheimer, neuropathy, diabetes, cardiovascular, cancer
- Lion's mane + neuropathy, diabetes, cardiovascular
- hericenone + neuropathy, diabetes, cardiovascular
- erinacine + neuropathy, diabetes, cardiovascular



**Websites visited:**

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [Pubmed](https://pubmed.ncbi.nlm.nih.gov/)
- [Drugs.com](https://www.drugs.com/)

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