Neurological Activity of Lion's Mane (*Hericium erinaceus*)

Kevin Spelman, PhD, MCPP[a]
Elizabeth Sutherland, ND[b]
Aravind Bagade, MD[c]

DOI 10.14200/jrm.2017.6.0108

ABSTRACT

Hericium erinaceus, most commonly known as lion's mane, is an edible fungus, with a long history of use in Traditional Chinese Medicine. The mushroom is abundant in bioactive compounds including β-glucan polysaccharides; hericenones and erinacine terpenoids; isoindolinones; sterols; and myconutrients, which potentially have neuroprotective and neuroregenerative properties. Because of its anti-inflammatory properties and promotion of nerve growth factor gene expression and neurite (axon or dendrite) outgrowth, *H. erinaceus* mycelium shows great promise for the treatment of Alzheimer's and Parkinson's diseases. The fungus was well tolerated in two clinical studies, with few adverse events reported.

Keywords: Lion's mane; Neuroregeneration; Neurodegeneration; Neuroprotection; Neurotropins; Neurotrophic; Alzheimer's disease; Parkinson's disease; Multiple Sclerosis; Nerve growth factor

[a]Corresponding author: Health, Education & Research, POB 599, Ashland, OR 97520, USA,
Tel.: +1-541-708-3002; E-mail: phytochemks@gmail.com
[b]Adjunct faculty National University of Natural Medicine, Portland, OR, USA
[c]Executive Secretary and Researcher, Ayurveda Interdisciplinary Research Minds Association, Mysore, India

INTRODUCTION

Ancient, traditional, and modern cultures around the world have known about the nutritive and medicinal properties of mushrooms for centuries. As early as 450 BCE, the Greek physician Hippocrates identified mushrooms as potent anti-inflammatory agents, useful for cauterizing wounds. In the East, reverence for fungi is evident in the Chinese description of ling zhi (*Ganoderma lucidum*), as the "spirit plant," believed to provide longevity and spiritual potency.

Modern medicine has been slower to catch on to the immense potential of fungi. Despite Fleming's 1929 discovery of penicillin,[1] and the subsequent implementation of the fungi-chemical as a blockbuster pharmaceutical in the 1940s,[2] it is only in the last few decades that medical science has looked beyond the antimicrobial and cholesterol-lowering properties of fungi for other potential applications.

Clinicians now have greater access to mycelium extracts, which are used clinically for their cytotoxic, antineoplastic, cardiovascular, anti-inflammatory, and immune-modulating activities.[3–5] Functional studies and chemical assays also support their potential to act as analgesic, antibacterial, antioxidant, and neuroprotective agents. A number of mushrooms, including *Sarcodon scabrosus*, *Ganoderma lucidum*, *Grifola frondosa*, and *Hericium erinaceus* are reported to have activities related to nerve and brain health.[6] *Hericium erinaceus*, a member of the Herinaceae family, is a culinary and medicinal mushroom. Both the mycelium and fruiting bodies of *H. erinaceus* have been shown to have therapeutic potential for brain and nerve health.[7] The unique neurological activities of this fungus are the subject of this review.

TRADITIONAL USE OF LION'S MANE (*H. ERINACEUS*)

Hericium erinaceus (lion's mane, yamabushitake, or bearded tooth carpophore) grows on old or dead broadleaf trees, and is used as both food and medicine in parts of Asia. The fruiting body is called hóu tóu gū ("monkey head mushroom") in Chinese[8] and yamabushitake ("mountain monk mushroom") in Japanese. In Chinese and Japanese medical systems, it has traditionally been used to fortify the spleen, nourish the gut, and also as an anticancer drug.[9] Lion's mane is said to be nutritive to the five internal organs (liver, lung, spleen, heart, and kidney), and promotes good digestion, general vigor, and strength. It is also recommended for gastric and duodenal ulcers, as well as chronic gastritis (in prepared tablet form).[10] The mushroom is also known for its effects on the central nervous system, and is used for insomnia, vacuity (weakness), and hypodynamia, which are characteristic symptoms of Qi deficiency in Traditional Chinese medicine (TCM).

CHEMISTRY

The bioactive metabolites of *H. erinaceus* can be classified into high molecular weight compounds, such as polysaccharides, and low molecular weight compounds, such as polyketides and terpenoids.[10,11]

POLYSACCHARIDES

Fungal polysaccharides are found mainly in cell walls, and are present in large quantities in both fruiting bodies and cultured mycelium. *Hericium erinaceus* fruiting bodies (HEFB) contain immunoactive β-glucan polysaccharides, as well as α-glucans and glucan-protein complexes.[12] A total of more than 35 *H. erinaceus* polysaccharides (HEP) have been extracted to date from cultured, wild-growing, or fermentative mycelia and fresh/dried fruiting bodies. Of these β-glucans represent the main polysaccharides. HEP are composed of xylose (7.8%), ribose (2.7%), glucose (68.4%), arabinose (11.3%), galactose (2.5%), and mannose (5.2%).[4] Four different polysaccharides isolated from the *H. erinaceus* sporocarp show antitumor activity: xylans, glucoxylans, heteroxyloglucans, and galactoxyloglucans.[5] Chemical analysis shows that the total content of HEP found in fruiting bodies is higher than that in mycelium. Table 1 lists the

Table 1: Polysaccharides: source and composition.

Polysaccharides	No.	Isolated from	Composition
(FI0-a, FI0-a-α, FI0-a-β, FI0-b, FII-1, FIII-2b)	6	Fresh fruiting bodies of *H. erinaceu*s	Xylans, glucoxylans, heteroxyloglucans, and galactoxyloglucans
AF2S-2, BF2S-2	2	Fresh fruiting bodies	Backbone of β-(1→6)-linked D-glucopyranosyl residues, and had β-(1→3) and β-(1→6) glucosidic linkages
Heteropolysaccharides (HEPA1, HEPA4, HEPB2)	3	Mycelium	Glucose
Water extractable polysaccharides (HPA and HPB)	2	Aqueous extract	Glucose and galactose
Water soluble polysaccharide (HPI)	1	*H. caput-medusae*	Glucose and galactose
Neutral heteropolysaccharides (HEP-1 and HEP-4)	2	Fruiting bodies	Glucose
Glucans HEP-3 (β-glucan) and HEP-5 (α glucan)	2	Fruiting bodies	Glucose
Acidic polysaccharide (HEP-2)	1	Fruiting bodies	Uronic acid
Heteropolysaccharide (HPB-3)	1	The maturating-stage IV, V, and VI fruiting body	I-fucose, d-galactose and d-glucose
Homopolysaccharides, a neutral glucan (HPP)	1	Fermentative mycelia	Glucose

polysaccharides along with their source and chemical composition.

Studies of the polysaccharides found in *H. erinaceus* reveal a number of activities. For example, extracellular and intracellular polysaccharides showed a protective effect on oxidative hepatotoxicity in mice.[11] Neuroprotective effects of HEPs were observed in an *in vitro* model of cells that were toxic from amyloid β plaque formation. In this model, HEPs decreased the production of reactive oxygen species from 80% to 58% in a dose-dependent manner, and increased the efficacy of free radical scavenging. HEPs also promoted cell viability and protected cells against apoptosis induced by amyloid β plaque formation.[13] HEPs decreased blood lactic acid, serum urea nitrogen, tissue glycogen, and malondialdehyde, further supporting the beneficial role of HEPs on oxidative stress.[14]

TERPENOIDS: SESTERPENES, AND DITERPENOIDS

Terpenoids are a class of naturally occurring hydrocarbons that consist of terpenes attached to an oxygen containing group. Terpenoids make up over 60% of products in the natural world.[15,16]

A variety of diterpenes and sesterpenes are found in the fruiting body and fermenting mycelium of *H. erinaceus*.[17] Of particular pharmacological interest are two classes of terpenoid compounds thus far known to occur only in *Hericium* spp.: hericenones (C–H), a group of aromatic compounds isolated from the fruiting body; and erinacines (A–I), a group of cyathane-type diterpenoids found in the mycelium.[18] Both groups of substances easily cross the blood-brain barrier, and have been found to have neurotrophic and in some cases neuroprotective effects.[19] Erinacines (A–I) have demonstrated induction of nerve growth factor (NGF) synthesis.[20] Table 2 lists the terpenoids, sesterpenes, and diterpenoids along with their source and chemical composition.

STEROLS

Ten erinarols, described as erinarol A–J, five ergostane-type sterol fatty acid esters, and ten ergostane-type sterols have been identified in the fruiting body of *H. erinaceus*.[21] Sterols, such as

Table 2: Sesterpenes and diterpenoids: source and composition.

Terpenoids	Isolated from	Composition
Hericenones Erinacines	Fresh fruiting bodies of *H. erinaceu*s Mycelia	Erinacerins C–L together with (E)-5- (3,7- methylocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one
Diterpenoids	Fresh fruiting bodies of *H. erinaceu*s	Erinacines A–I
Isoindolinones	Fresh fruiting bodies of *H. erinaceu*s	Erinaceolactams A–E, hericenone A, hericenone J, *N*-De phenylethylisohericerin, erinacerin A, and hericerin

ergosterol confer antioxidative properties.[21,22] *Hericium erinaceus* has been found to be the most potent *in vitro* inhibitor of both low-density lipoprotein (LDL) oxidation and HMG Co-A reductase activity, suggesting therapeutic potential for the prevention of oxidative stress-mediated vascular diseases.[23]

NEUROLOGICAL ACTIVITY

NEUROPROTECTION

Hericenones and erinacines isolated from *H. erinaceus* have demonstrated neuroprotective properties.[24] *Hericium erinaceus* mycelia (HEM), and its isolated diterpenoid derivative, erinacine A, reduced infarction by 22% at 50 mg/kg and 44% at 300 mg/kg in an animal model of global ischemic stroke. This effect was thought to be partially mediated by its ability to reduce cytokine levels.[25]

A purified polysaccharide from the liquid culture broth of HEM was also found to possess neuroprotective activity in an *in vitro* model through a dramatic delay of apoptosis, which was 20%–50% greater than that seen in the control sample. The same study showed HEM to be more effective than control, NGF, or brain-derived neurotrophic factor (BDNF) alone in enhancing the growth of rat adrenal nerve cells and neurite (axon or dendrite) extension.[26] However, in a model of NG108-15 neuroblastoma cells subjected to H_2O_2 oxidative stress in pre-treatment and co-treatment, the aqueous extract of *H. erinaceus* (as opposed to a purified polysaccharide), failed to show a protective effect.[27] Although it is challenging to draw clinically relevant conclusions from *in vitro* studies, this suggests that water extracts would not have a neuroprotective effect without one particular polysaccharide being highly concentrated.

NEUROTROPHIC ACTIVITY AND MYELINATION

The addition of an ethanol extract of HEFB resulted in NGF gene expression in human astrocytoma cells, in a concentration-dependent manner. Neurite outgrowth was also improved. The same investigators also observed that mice fed 5% HEFB dry powder for 7 days, showed an increase in the level of NGF mRNA expression in the hippocampus.[28] Another study showed that an aqueous extract of HEFB increased secretion of extracellular NGF and neurite outgrowth activity. These researchers also observed a synergistic interaction between *H. erinaceus* aqueous extract and exogenous NGF on neurite outgrowth stimulation of neuroblastoma-glioma cells at physiologically relevant concentrations (1 μg/mL HEFB extract +10 ng/mL NGF).[21] Myelin sheath formation in the presence of *H. erinaceus* extract proceeded at a higher rate and was completed by day 26, as compared to day 31 in controls. No toxic effects of the extracts were observed in this model.[30]

COGNITIVE FUNCTION

In a behavior test on wild-type mice, oral supplementation with *H. erinaceus* induced a

statistically significant improvement in spatial short-term and visual recognition memory.[31] In a double-blind placebo-controlled clinical trial of 50–80-year-old Japanese adults (*n*=30) diagnosed with mild cognitive impairment, oral intake of *H. erinaceus* 250 mg tablets (96% dry powder) three times a day for 16 weeks was associated with marked improvement in the revised Hasegawa Dementia Scale (HDS-R) as compared to controls. Scores on the HDS-R decreased, however, by 4 weeks after cessation of the intervention.[28]

ALZHEIMER'S DISEASE

In a mouse model of Alzheimer's disease, oral administration of HEFB increased expression of NGF mRNA in the hippocampus, and prevented impairments of spatial, short-term, and visual recognition memory induced by amyloid β plaque that were observed in non-treated mice.[28] In another study using an Alzheimer's model of mice that develop amyloid plaque deposits by 6 months of age, a 30-day oral administration of HEM resulted in fewer plaque deposits in microglia and astrocytes in the cerebral cortex and hippocampus.[32] In an aluminum chloride induced animal model of Alzheimer's disease, HEM increased serum and hypothalamic concentrations of acetylcholine and choline acetyltransferase in a dose-dependent manner.[29] Figure 1 illustrates the apparent mechanisms of action for the effects that *H. erinaceus* may have in Alzheimer's disease.

PARKINSON'S DISEASE

Oral administration of low-dose HEM (10.76 or 21.52 mg/day) used in an animal model of Parkinson's disease led to significant improvement in oxidative stress and dopaminergic lesions in the striatum and substantia nigra after 25 days.[33]

PERIPHERAL NERVE INJURY

An aqueous extract of HEFB that was administered to animals at a dose of 10 mL/kg for 14 days following crush injury improved nerve regeneration and increased the rate of motor functional recovery. The animals treated with HEFB recovered 4–7 days earlier than animals in the control group, as assessed by walking track analysis. Normal toe spreading, a measure of reinnervation, was achieved 5–10 days earlier in the aqueous extract group than in the control group. Based on functional evaluation and the morphological examination of regenerated nerves, ipsilateral dorsal root ganglia, and target extensor digitorum longus muscles, researchers concluded that HEFB aqueous extract promoted peripheral

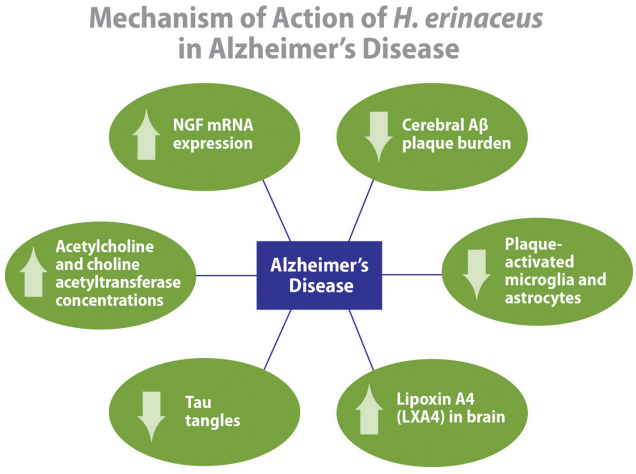

Figure 1: Mechanism of action of *Hericium erinaceus* in Alzheimer's disease.

Table 3: Outcomes of clinical trials of *H. erinaceus*.

Trial	Parameter assessed/Scale	Results	Adverse events	Dose	Citation
Double-blind, parallel-group, placebo-controlled trial	Mild cognitive impairment/Revised Hasegawa Dementia Scale (HDS-R)	Significant improvement in cognitive function scale	None	250 mg tid×16 weeks	Mori *et al.,* 2009[28]
Randomized placebo-controlled trial	Anxiety and depression/Center for Epidemiologic Studies Depression Scale (CES-D) and Indefinite Complaints Index (ICI)	Significant improvement in some anxiety and depression scores	None	2 g/day×4 weeks	Nagano *et al.,* 2010[29]

nerve regeneration with significant functional recovery.[33]

CLINICAL TRIALS

As previously described under Cognitive Function, a double-blind placebo-controlled study of 50–80-year-old Japanese men and women (*n*=30) diagnosed with mild cognitive impairment showed marked improvement in cognitive function, as measured by the revised Hasegawa Dementia Scale (HDS-R), when compared to controls, following oral intake of *H. erinaceus* 250 mg tablets (96% dry powder) three times a day for 16 weeks. Scores on the HDS-R decreased, however, by 4 weeks after cessation of the intervention.[28]

In another clinical trial, administration of HEFB at 2.0 g/day (in cookies) over 4 weeks showed a reduction in some symptoms of anxiety and depression in menopausal women (*n*=30). The Indefinite Complaints Index categories for Palpitation and Incentive showed a statistically significant improvement in women taking HEFB compared to those taking placebo. The categories of Irritating, Anxious, and Concentration indicated a trend in the direction of improvement with HEFB as compared to placebo.[29] Table 3 summarizes the two clinical trials reported on in this paper.

POSOLOGY

COGNITION AND NGF PRODUCTION

The recommended dose of *H. erinaceus* dried fruiting body for increasing NGF production is 3–5 g per day.[34] *Hericium erinaceus* dosed at 250 mg tablets (96% dry powder) three times a day for 16 weeks was associated with significant improvement on a dementia rating scale in subjects with mild cognitive impairment.[28] The dose utilized in the study of menopausal women that showed reduction in symptoms of depression and anxiety was 2.0 g/day of HEFB (in cookies) for 4 weeks.[29]

TOXICOLOGY

In an *in vitro* model, HEFB aqueous extract demonstrated a remarkable lack of cytotoxicity.[31] Toxicology studies of *H. erinaceus* in rats suggest that mycelia enriched with 5 mg/g erinacine A at doses of up to 5 g/kg bodyweight/day are safe. No toxicity was found in the two clinical trials reported on here.[28,29]

REPORTED ADVERSE EVENTS

No adverse clinical or biochemical events were reported in the clinical trial of subjects with mild cognitive impairment.[28] In the study of

menopausal women, one subject reported epimenorrhea (18 days menorrhea/month). However, whether or not supplementation with *H. erinaceus* was the cause of the epimenorrhea is inconclusive.[29]

Allergies and sensitivities to mushrooms are not unusual. One case report describes a 63-year-old male who suffered acute respiratory failure and lymphocytosis in his lungs. The report suggests he had used an extract of dry *H. erinaceus* (with no further description given) daily for 4 months in commonly available doses, and the connection between the two was considered to be probable. In another case report, a 53-year-old male exposed to HEFB occupationally, developed chronic dermatitis on his hands, with painful fissures within 1 month of exposure. The dermatitis spread to his forearms, face, and legs, at which point he ceased exposure to the HEFB and his symptoms resolved. His patch tests were negative for the European standard series, and positive for HEFB. Sensitization was confirmed by a highly positive repeated open application test (ROAT) with an aqueous emulsion of HEFB. Interestingly, patch and prick tests were negative for other culinary mushrooms suggesting a lack of cross-sensitivity.

CONCLUSION

To the best of this author's knowledge, no toxicity was established for *H. erinaceus* in the experimental, animal, or two clinical trials reported here. The adverse event (epimenorrhea) reported in one of the clinical trials could not be conclusively attributed to the intervention. The substantial historical record for the traditional use of lion's mane for chronic ailments, together with the results of studies so far, suggest *H. erinaceus* is safe and has important potential as a neuroprotective and neurotrophic therapeutic agent in neurological conditions.[35] Its rich myconutrient composition suggest that using the whole fungus may be most advantageous clinically. More clinical studies are needed to corroborate these conclusions.

COMPETING INTERESTS

The authors declare they have no competing interests.

REFERENCES

1. Hobbs C. *Medicinal Mushrooms,* 3rd edn. Santa Cruz: Botanica Press; 1995.
2. Zhou J, Xie G, Yan X. *Encyclopedia of Molecular Structures, Pharmacological Activities, Natural Sources and Applications Traditional Chinese Medicines Vol. 5: Isolated Compounds T–Z.* Berlin Heidelberg: Springer-Verlag; 2011.
3. Kwagishi H, Shimada A, Shirai R, *et al.* Erinacines A, B and C strong stimulators of nerve growth factor (NGF)-synthesis from the mycelia of Hericium erinaceum. *Tetrahedron Lett.* 1994;35:1569–72.
4. Shen JW, Yu HY, Ruan Y, *et al.* Hericenones and erinacines: stimulators of nerve growth factor (NGF) biosynthesis in Hericium erinaceus. *Mycol Int J Fungal Biol.* 210;1:92–8.
5. Mizuno T, Wasa T, Ito H, *et al.* Antitumor-active polysaccharides isolated from the fruiting body of Hericium erinaceum, an edible and medicinal mushroom called Yamabushitake or Houtou. *Biosci Biotechnol Biochem.* 1992;56:347–8.
6. He X, Wang X, Fang J, *et al.* Structures, biological activities, and industrial applications of the polysaccharides from Hericium erinaceus (Lion's Mane) mushroom: a review. *Int J Biol Macromol.* 2017;97:228–37.
7. Cheng JH, Tsai CL, Lien YY, *et al.* High molecular weight of polysaccharides from Hericium erinaceus against amyloid beta-induced neurotoxicity. *BMC Complement Altern Med.* 2016;16:170.
8. Cui F, Gao X, Zhang J, *et al.* Protective effects of extracellular and intracellular polysaccharides on hepatotoxicity by Hericium erinaceus SG-02. *Curr Microbiol.* 2016;73(3):379–85.
9. Liu J, Du C, Wang Y, Yu Z. Anti-fatigue activities of polysaccharides extracted from Hericium erinaceus. *Exp Ther Med.* 2015;9(2):483–7.
10. Thongbai B, Rapior S, Hyde KD, *et al.* Hericium erinaceus, an amazing medicinal mushroom. *Mycol Progress.* 2015;14:91.
11. Wang K, Bao L, Qi Q, *et al.* Erinacerins C-L, isoindolin-1-ones with alpha-glucosidase inhibitory activity from cultures of the medicinal mushroom Hericium erinaceus. *J Nat Prod.* 2015;78(1);146–54.
12. Moldavan MG, Gryganski AP, Kolotushkina OV, *et al.* Neurotropic and trophic action of lion's mane mushroom Hericium erinaceus (Bull.: Fr.) Pers. (Aphyllophoromycetideae) extracts on nerve cells *in vitro*. *Int J Med Mushrooms.* 2007;9:15–28.

13. Li JL, Lu L, Dai CC, *et al.* A comparative study on sterols of ethanol extract and water extract from Hericium erinaceus. *Zhongguo Zhong Yao Za Zhi.* 2001;26:831–4.

14. Abdullah N, Ismail SM, Aminudin N, *et al.* Evaluation of selected culinary-medicinal mushrooms for antioxidant and ACE inhibitory activities. *Evid Based Complement Alternat Med*. 2012 (2012), Article ID 464238, 12 pages. http://dx.doi.org/10.1155/2012/464238.

15. Gershenzon J, Dudareva N. The function of terpene natural products in the natural world. *Nat Chem Biol.* 2007;3(7):408–14.

16. Chappell J. The genetics and molecular genetics of terpene and sterol origami. *Curr Opin Plant Biol.* 2002;5(2):151–7.

17. Guillamón E, García-Lafuente A, Lozano M, *et al.* Edible mushrooms: role in the prevention of cardiovascular diseases. *Fitoterapia*. 2010;81(7):715–23.

18. Rahman MA, Abdullah N, Aminudin N. Inhibitory effect on *in vitro* LDL oxidation and HMG Co-A reductase activity of the liquid-liquid partitioned fractions of *Hericium erinaceus* (Bull.) Persoon (lion's mane mushroom). *BioMed Res Int*. 2014;2014:828149. doi:10.1155/2014/828149.

19. Lee KF, Chen JH, Teng 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(9):15073–89.

20. Yaoita Y, Kakuda R, Machida K, *et al.* Ceramide constituents from five mushrooms. *Chem Pharmaceut Bull*. 2002;50(5):551–3.

21. Mori K, Obara Y, Hirota M, *et al.* Nerve growth factor-inducing activity of Hericium erinaceus in 1321N1 human astrocytoma cells. *Biol Pharm Bull*. 2008;31:1727–32.

22. Mori K, Obara Y, Moriya T, *et al.* Effects of Hericium erinaceus on amyloid beta(25–35) peptide-induced learning and memory deficits in mice. *Biomed Res.* 2011;32(1):67–72.

23. Tzeng TT, Chen CC, Lee LY, *et al.* Erinacine A-enriched *Hericium erinaceus* mycelium ameliorates Alzheimer's disease-related pathologies in APPswe/PS1dE9 transgenic mice. *J Biomed Sci.* 2016;23:49.

24. Trovato A, Siracusa R, Di Paola R, *et al.* Redox modulation of cellular stress response and lipoxin A4 expression by *Hericium erinaceus* in rat brain: relevance to Alzheimer's disease pathogenesis. *Immun Ageing*. 2016;13:23.

25. Zhang J, An S, Hu W, *et al.* The neuroprotective properties of *Hericium erinaceus* in glutamate-damaged differentiated PC12 cells and an Alzheimer's disease mouse model. *Int J Mol Sci.* 2016;17(11);1810.

26. Kuo HC, Lu CC, Shen CH, *et al*. *Hericium erinaceus* mycelium and its isolated erinacine A protection from MPTP-induced neurotoxicity through the ER stress, triggering an apoptosis cascade. *J Translat Med.* 2016;14:78.

27. Wong KH, Naidu M, David RP, *et al.* 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(5):427–46.

28. Mori K, Inatomi S, Ouchi K, *et al.* 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.

29. Nagano M, Shimizu K, Kondo R, *et al.* Reduction of depression and anxiety by 4 weeks Hericium erinaceus intake. *Biomed Res.* 2010;31:231–7.

30. *Operational guidance: Information needed to support clinical trials of herbal products.* http://www.who.int/tdr/publications/documents/operational-guidance-eng.pdf.

31. Lai PL, Naidu M, Sabaratnam V, *et al.* Neurotrophic properties of the Lion's mane medicinal mushroom, Hericium erinaceus (Higher Basidiomycetes) from Malaysia. *Int J Med Mushrooms.* 2013;15(6);539–54.

32. *Chinese pharmacopoeia*. Beijing: Chinese Medicine Science and Technology Publishing House; 2010.

33. Wong KH, Naidu M, David P, *et al.* Peripheral nerve regeneration following crush injury to rat peroneal nerve by aqueous extract of medicinal mushroom Hericium erinaceus (Bull.: Fr) Pers. (Aphyllophoromycetideae). *Evid Based Complement Alternat Med*. 2011;2011:580752.

34. Tanaka A, Matsuda H. Expression of nerve growth factor in itchy skins of atopic NC/NgaTnd mice. *J Vet Med Sci*. 2005;67:915–9.

35. Nakatsugawa M, Takahashi H, Takezawa C, *et al.* Hericium erinaceum (yamabushitake) extract-induced acute respiratory distress syndrome monitored by serum surfactant proteins. *Intern Med*. 2003;42:1219–22.