한국버섯학회지 Journal of Mushrooms Review

A comprehensive review of the therapeutic effects of *Hericium erinaceus* in neurodegenerative disease

Young Ock Kim*, Sang Won Lee and Jin Seong Kim

Herbal Crop Utilization Research Team, Department of Medicinal Crop Research, National Institute of Horticultural & Herbal Science, Rural Development Administration, Eumseong 369-873, Republic of Korea

ABSTRACT: Mushrooms are considered not only as food but also for source of physiologically beneficial medicines. The culinary-medicinal mushrooms may important role in the prevention of age-associated neurological dysfunctions, including Alzheimer's and Parkinson's diseases. *Hericium erinaceus* (*H. erinaceus*), is edible mushrooms, is a parasitic fungus that grows hanging off of logs and trees and well established candidate for brain and nerve health. *H. erinaceus* contains high amounts of antioxidants, beta-glucan, polysaccharides and a potent catalyst for brain tissue regeneration and helps to improve memory and cognitive functions. Its fruiting bodies and the fungal mycelia exhibit various pharmacological activities, including the enhancement of the immune system, antitumor, hypoglycemic and anti-aging properties. *H. erinaceus* stimulates the synthesis of Nerve Growth Factor (NGF) which is the primary protein nutrient responsible for enhancing and repairing neurological disorders. Especially hericenones and erinacines isolated from its fruitin body stimulate NGF, synthesis. This fungus is also utilized to regulate blood levels of glucose, triglycerides and cholesterol. *H. erinaceus* can be considered as useful therapeutic agents in the management and/or treatment of neurodegeneration diseases. However, this review focuses on *in vitro, in vivo* and clinical trials for neurodegerative disease.

KEYWORDS: *Hericium erinaceus,* Nerve growth factor, Neurodegenerative disease, Blood-brain barrier

INTRODUCTION

There are over 100,000 species within the broad category of Fungi and within that there are 38,000 species of mushrooms. Recently, numerous studies used in traditional medicines, mushrooms are the manifestation of the common saying, "Medicines and foods have a common origin." and being investigated for their many ethnomycological claims of medicinal value. The mushrooms are being developed as nutraceuticals or nutriceuticals to garner the essence of mushrooms and to make consumption easy. Later scientific validation of traditional knowledge has positive effects of consuming mushrooms or processed on human health (Chang *et al.,* 2008).

H. erinaceus is an edible mushroom with medicinal values, which is also known as Lion's Mane Mushroom or Hedgehog Mushroom. The Latin name for lion's mane is Hericium erinaceus; both names mean "hedgehog" and is called "hóu tóu gû" and "yamabushitake," respectively (Yang *et al.,* 2003). *H. erinaceus* belongs to the class of Agaricomycetes under the phylum basidiomycota. *H. erinaceus* are increasingly sold by gourmet food chains which is roughly 20 percent protein, and one of the few that can taste like lobster or shrimp (Stamets, 2005). *H. erinaceus* is reported not only to have a hypoglycemic effect but also to reduce the elevation rates of serum triglyceride and total cholesterol levels when administered. Recently *H. erinaceus* given the attention of researchers for its famous nerve-regenerative properties.

H. erinaceus are studied for their neuroprotective effects by increasing. Two novel classes of NGFs - molecules stimulating the differentiation and re-myelination of neurons - have been discovered. These cyathane derivatives are termed "hericenones" and "erinacines". The levels of these compounds can differ substantially between strains,

J. Mushrooms 2014 June, 12(2):77-81
http://dx.doi.org/10.14480/JM.2014.12.2.77
Print ISSN 1738-0294, Online ISSN 2288-8853

*Corresponding author
E-mail : kyo9128@korea.kr
Tel : +82-43-871-5585, Fax : +82-43-871-5589
Received June 18, 2014
Revised June 20, 2014
Accepted June 25, 2014

based on the measurements has conducted.

Alzheimer-related deaths have blown up about 66 percent, while deaths from other primary diseases have generally declined. Our aging community is excessively seeking preventive measures to assure they are able to enjoy a better quality of life old age. AD is the most common cause of dementia among older people. Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities, to such an extent that it interferes with a person's daily life and activities. Dementia ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for basic activities of daily living. The current research settled NGF protein levels in the brains of patients with AD as compared with aged neurologically normal individuals. *H. erinaceus* can be regarded as a useful food for the prevention of dementia without any side effects (Mori *et al.,* 2009). This effect may be contributed to promotion of NGF by hericenones, but further studies are needed to clarify the mechanism.

Areas of research

Nerve Growth Stimulant

In 1987, a neutrophic factor called NGF was discovered. NGF acts on cholinergic neurons in the central nervous system, such as the induction of neuronal differentiation, the promotion of neuronal survival, and regeneration (Obara Y and Nakahata 2002) and ameliorates neurodegeneration and cognitive deficits (Capsoni *et al.,* 2002). Low levels NGF are shown to be linked to early stages of both AD and dementia and also to cardiovascular diseases and diabetes. NGF is also known to stimulate and develop "growth of new neuron" in the central and peripheral nerves systems. When many kinds of neurological disorders happen, the brain is unable to make its own internal source of NGF. To make matters worse, the semi-permeable membrane, called the myelin sheath or blood-brain barrier, inhibits the body from delivering external sources of NGF and deterioration of brain neurons begins to slowly happen over time. The current research analyzed NGF protein levels in the brains of patients and animal with AD as compared with aged neurologically normal individuals.

Two major groups of ingredients in *H. erinaceus* act as a important role in supporting nervous system. Hericenones

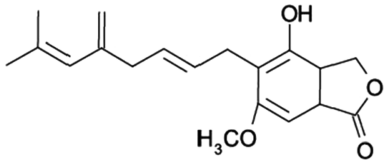

Fig. 1. Hericione

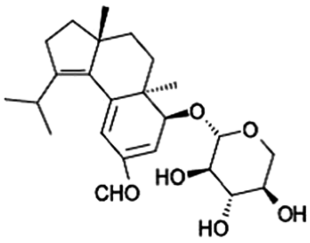

Fig. 2. Erinacine

(isolated from the fruiting body, Kawagishi *et al.,* 1991) and the erinacines (isolated from the mycelium, Kawagishi *et al.,* 1994) are small molecules that pass through the blood-brain barrier. Amazingly, these naturally occurring mushroom molecules are bioavailable to the human body and brain through dietary medical mushrooms. But NGF cannot pass blood-brain barrier. So, these ingredients stimulate the production of NGF within the brain and they also increase myelination. This is one of the most significant discoveries and is why the Novel Prize was awarded for its discovery. As the erinacines actually promote NGF production *throughout* the body, erinacines protect our whole nervous system against degeneration. Also help to alleviate symptoms of peripheral neurological dysfunction. The medicinal value of *H. erinaceus* has been the find out and exploration of erinacines that have shown the ability to stimulate the production of NGF in animal trials and therapeutic agents in the treatment of AD and other neurodegenerative diseases (Yamada *et al.,* 1997).

Treating AD patients with NGF may improve cholinergic function and memory. Since AChesterase inhibitors (the most common group of pharmacological compounds used for treatment of AD are not likely restoring dying or degenerating neurons, NGF makes as a therapeutic agent, with the hope that it will not only extinguish further death of cholinergic neurons, but also restore function of degenerating cells (Tuszynski *et al.,* 1990).

***In vitro* model**

Park *et al.* did a study where the effects of an exo-

polysaccharide isolated from *H. erinaces* on the growth of rat pheochromocytoma cells (PC12) are investigated It was found that an exo-biopolymer purified from the liquid culture both of *H. erinaceus* mycelium enhanced the growth of rat adrenal nerve cells (Park *et al.,* 2002). The polymer also improved the extension of the neurites of PC12 cell. The ethanol extract of *H. erinaceus* promoted NGF mRNA expression in a concentration-dependent manner via the activation of the JNK pathway (Mori *et al*., 2008).

In a study by Wong et al*.,* the extracts of *H. erinaceus* fruiting body and mycelium induced neurite outgrowth of neuronal cells NG108-15 *in vitro.* Also, ethanol extract of *H. erinaceus* promoted the neurite outgrowth of PC12 cells, enhanced NGF mRNA expression, and the secretion of NGF from 1321N1 human astrocytoma cells (Wong *et al.,* 2007). In a astrocytoma cells (Mori *et al.,* 2008), it was determined that while a methanol extract of *H. erinaceus* stimulated an increase in NGF as evidenced in the assay of RNA associated with NGF production.

***In vivo* model**

Mice hyppocampal sagittal slices 200-300 mm of depth were prepared by 40-50 days old mice after placebo or after *H. erinaceus* treatment. Spontaneous and awake activity at the synapse between mossy fiber-CA3 neurons shows a statistically significant increases, probably due to an increase in neurotransmitter release from mossy fiber terminal. *H. erinaceus* treated mice in PCR experiments shows a significant increase in mRNA NGF expression in hippocampus. In vivo exploration behavior and space-memory were tested. In conclusion 3 months *H. erinaceus* supply in wild type mice increases neurotransmitter release and the level of NGF-mRNA in hippocampus and increases exploratory recognition memory in learning and memory test *in vivo* (Mori *et al.,* 2008).

Myelin sheaths wrap neuronal axons and provide support, protection, feeding and isolation of the neurons, and an injury of myelin structure leads to the impairment and severe illness of the nerve system. *H. erinaceus* prevented the impairments of spatial short-term and visual recognition memory induced by amyloid â (25–35) peptide in mice (Nagano *et al.,* 2010). Once digested, they are small enough to safely pass through the blood-brain barrier and stimulate the production of NGF in the brain. This allows them to stimulate and repair nerve cells in the brain itself, increasing cognitive function. Myelin sheaths wrap neuronal axons and provide support, protection, feeding and isolation of the neurons, and an injury of myelin structure leads to the impairment and severe illness of the nerve system. Before the discovery of this significant nutritional value found in *H. erinaceus*, most modern medical practitioners believed that it was not possible to stimulate the production of new neurons through the ingestion of foodstuffs.

Erinacines are known to have a potent stimulating activity for NGF and have been proposed as medicines for degenerative neuronal disorder such as Alzheimer's disease and peripheral nerve regeneration (Watanabe *et al.,* 2007). Erinacines A, B, C, D, E, F, G, H, I, P, and Q were isolated from the mycelia of *H. erinaceus* (Kenmoku *et al.,* 2002). All of these diterpenoids has a cyathane skeleton consisting of angularly condensed five-, six-, and seven-membered rings. Erinacines A–F were isolated from the cultured mycelia of *H. erinaceus* by Kawagishi et al. These cyathane xylosides are able to stimulate NGF secretion in mouse astroglial cells, albeit at rather high concentrations (1–5 mM). The *in vivo* effect of erinacine A was also studied. Specifically, rats treated with showed an increase in the levels of both noradrenaline and homovanillic acid, and displayed enhanced NGF secretions in both the locus coeruleus and hippocampus. Erinacine E is a selective agonist of κ-opioid receptors (Saito *et al.,* 1998) which is present on the peripheral terminals of primary afferent neurons. It has been reported that activation of these receptors reduces hyperalgesia in a rat model of inflammation (Stein *et al.,* 1989). The κ-opioid receptors effects include altering the perception of pain, consciousness, motor control, and mood.

Brain Function

The influence of *H. erinaceus* on neurological functions is specific feature in clinical research. The subjects of the *H. erinaceus* group took four 250 mg tablets containing 96 percent of *H. erinaceus* dry powder three times a day for 16 weeks. After termination of the intake, the subjects were observed for the next four weeks. At weeks 8, 12 and 16 of the trial, the *H. erinaceus* group showed significantly increased scores on the cognitive function scale compared with the placebo group. The test subjects were given 1 gram of dry powder 3 times per day. The *H. erinaceus* group's scores increased with the duration of

intake (Mori *et al.,* 2009). The *H. erinaceus* extract not only crossed the blood-brain barrier quickly, it arrested the accumulation of beta-amyloid plaques. These results suggest that the intake of *H. erinaceusis* is effective for improving mild cognitive impairment without serious adverse effects.

Depression

The aging population which is projected to be more than 80-90 million of people age 65 and above in 2050 who may be affected by age-related neurodegenerative disorders. Giving *H. erinaceus* to 30 older adults with mild cognitive impairment Japanese patients resulted in significant benefits for as long as they consumed the mushrooms. The results that members of the *H. erinaceus* group were less irritable, depressed and anxious and had less difficulty concentrating than members of the placebo group. Post-menopausal women who consumed *H. erinaceus* baked into cookies vs. those without showed less anxiety and depression. *H. erinaceus* intake has the possibility to reduce depression and anxiety. And it is still relevant to frustration and palpitation (Nagano *et al.,* 2010). Scientific validation is needed if these mushrooms are to be considered and this can be achieved by understanding the molecular and biochemical mechanisms involved in the stimulation of neurite outgrowth.

Taken as a whole, *H. erinaceus* has shown neurological properties such as neuronal survival and neurite outgrowth activities, including improvement in recovery and function in both *in vivo* and clinical research. Therefore, based on the studies discussed in this review, we propose *H. erinaceus* may have therapeutic values to treat human neurological diseases. However, involving human models, must be carried out with great care and caution as the pharmacological and negative effects of *H. erinaceus* are not well established even though many of *H. erinaceus* is edible. We expect this review will accelerate interest on *H. erinaceus* study in the experimental clinical neurology area with a long-term objective of developing effective therapies for neurological diseases. More basic clinical studies are recommended as further study to set up its therapeutic potential against life threatening human disorders.

Acknowledgements

This study was financially supported by th Medicinal Crops Division, Ginseng and Medicinal Plants Research Institute Rural Development Administration(PJ009385).

Reference

Capsoni S, Giannotta S, Cattaneo A. 2002. Nerve growth factor and galatamine ameliorate early signs of neurodegeneration in anti-nerve growth factor mice. *Proc Natl Acad Sci USA*. 99:12423-12437.

Chang ST, Buswell JA. 2008. Development of the world mushroom industry: Applied mushroom biology and international mushroom organizations. *Int J Med Mushrooms.* 10:195-208.

Kawagishi H, Ando M, Mizuno T. 1990. Hericenone A and B as cytotoxic principles from the mushroom Hericium erinaceum. *Tetrahedron Lett*. 31:373-376.

Kawagishi H, Ando M, Sakamoto H. 1991. Hericenone C, D and E, stimulators of nerve growth factor (NGF) synthesis, from the mushroom Hericium erinaceum. *Tetrahedron Lett*. 32:4561-4564.

Kawagishi H, Ando M, Shinba K. 1993. Chromans, hericenone F, G and H from the mushroom Hericium erinaceum. *Phytochemistry.* 32:175-178.

Kawagishi H, Shimada A, Shirai R. 1994. Erinacines A, B and C, strong stimulators of nerve growth factor (NGF)-synthesis, from the mycelia of Hericium erinaceum. *Tetrahedron Lett*. 35:1569-1572.

Kenmoku H, Shimai T, Toyomasu T, Kato N, Sassa T, Erinacine Q. 2002. A new erinacine from Hericium erinaceum, and its biosynthetic route to erinacine C in the basidiomycete. *Biosci Biotechnol Biochem*. 66:571-575.

Mattson MP. 1997. Neuroprotective signal transduction: relevance to stroke. *Neurosci Biobehav Rev.* 21:193-206.

Mori K, Obara Y, Hirota M, Azumi Y, Kinugasa S, Inatomi S, Nakahata N. 2008. Nerve growth factor-inducing activity of Hericium erinaceus in 1321N1 human astrocytoma cells. *Biol Pharm Bull.* 31:1727-1732.

Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. 2009. Improving effects of the mushroom Yamabushitake (Hericium erinaceus) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. *Phytother Res*. 23:367-372.

Nagano M, Shimizu K, Kondo R, Hayashi C, Sato D, Kitagawa K, Ohnuki K. 2010. Reduction of depression and anxiety by 4 weeks Hericium erinaceus intake. *Biomed Res.* 31:231-237.

Obara Y, Nakahata N. 2002. The signaling pathway of neurotropic factor. *Drug News and Perspect*. 15:290-298.

Park YS, Lee HS, Won MH, Lee JH, Lee SY, Lee HY. 2002. Effect of an exo-polysaccharide from the culture broth of hericium erinaceus on enhancement of growth and differentiation of rat adrenal nerve cells. *Cytotechnology.* 39:155-162.

Saito T, Aoki F, Hirai H, Inagaki T, Matsunaga Y, Sakakibara T, Sakemi S, Suzuki Y, Watanabe S, Suga O, Sujaku T, Smogowicz AA, Truesdell SJ, Wong JW, Nagahisa A, Kojima Y, Kojima N. 1998. Erinacine E as a kappa opioid receptor agonist and its new analogs from a basidiomycete, Hericium ramosum. *J Antibiot (Tokyo)*. 51:983-990.

Stamets P. 2005. Notes on nutritional properties of culinary-

medicinal mushrooms. *Int J Med Mushrooms*. 7:109-116.

Stein C, Millan M J, Shippenberg T S, Peter K, Herz A. 1989. Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta and kappa receptors. *Pharmacol Exp Ther.* 248:1269-1275.

Tuszynski MH, U HS, Amaral DG, Gage FH. 1990. Nerve growth factor infusion in the primate brain reduces lesion-induced cholinergic neuronal degeneration. *J Neurosci.* 10:3604-36014.

Watanabe H, Takano M, Umino A, Ito T, Ishikawa H, and Nakada M. 2007. Enantioselective total synthesis of (-)-erinacine B. *Org Lett.* 18:359-362.

Wong KH, Sabaratnam V, and Abdullah N. 2007. Activity of aqueous extracts of Lion's Mane Mushroom *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae) on the neural cell line NG108-15. *Int J Med Mushrooms*. 9:57–65.

Yamada K, Nitta A, Hasegawa T, Fuji K, Hiramatsu M, Kameyama T, Furukawa Y, Hayashi K, Nabeshima T. 1997. Orally active NGF synthesis stimulators: potential therapeutic agents in Alzheimer's disease. *Behav Brain Res.* 83:117-122.

Yang BK, Park JB, Song CH. 2003. Hypolipidemic effect of an Exo-biopolymer produced from a submerged mycelial culture of Hericium erinaceus. *Biosci Biotechnol Biochem*. 67:1292–1298.