Erinacine and Hericinones from Hericium erinaceus: Health-Promoting Properties - A Review

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Abstract. *Hericium erinaceus* is traditionally consumed for its health-promoting properties and has become a well-known candidate for promoting beneficial activities related to brain and nerve health by inducing nerve growth factor from its bioactive components; this literature review will focus on the compounds erinacins and hericenones and their influence on neurodegenerative diseases. **Objective** This study aims to discuss the health-promoting properties of *Hericium erinaceus* and to understand how its components—erinacin A and hericinones C and D—work to help prevent or treat humans with neurological diseases. **Method** An integrative review was conduced in two academic databases (PubMed and Google Scholar). **Results** Two literature review studies and eight experimental research studies were selected and presented. **Conclusion** The compounds erinacin A and hericinones C and D from *Hericium erinaceus* have demonstrated significant potential in mitigating the impacts of neurodegenerative diseases, underscoring the imperative for more extensive and in-depth research to validate these findings and explore their therapeutic applications in clinical settings.

Keywords. *hericium erinaceus*, neurodegenerative diseases, neurite outgrowth activity, hericenone, erinacine A.

1. Introduction

Since ancient times, mushrooms have been used for their medicinal properties. They were widely used in the East, as discussed by the alchemist Tao Hongjing, who documented some medicinal mushrooms, including *Dendropolyporus umbellatus* (zhu ling) and *Ganoderma lucidum* (ling zhi), which were already used to treat infections. Due to the culture spread over millennia, *H. erinaceus* is traditionally used mainly for its gastrointestinal properties, as a preventive or curative supplement for chronic gastrointestinal diseases such as Crohn's disease in China. In Japan, the traditional use of the Lion's Mane mushroom is more related to its well-known neuroprotective properties for the central nervous system [1].

Notwithstanding this, the enigma of mushrooms is still present today because, despite their use in various cultures since ancient times, it is only recently that the modern medical field has begun to explore their potential. Mushrooms have evolved a wide range of chemical compounds as a means of survival against predators and nature itself, and these compounds show promise for the treatment of a variety of human conditions. [1].

As in the case of *Hericium erinaceus*, whose health-promoting properties have been reported in the body of the fruit, the mycelia, and bioactive compounds include antibiotics, anticarcinogens, cardioprotectors, nephroprotectors, and neuroprotectors, as well as the improvement of anxiety, cognitive function, and depression. It is also described as an immunostimulant, antioxidant, and anti-inflammatory [2].

Some compounds isolated from this mushroom that induce the expression of neurotrophic factors, such as nerve growth factors (NGF) synthesis in cultured astrocytes, have been intensively studied and reported. Hericenones were found specifically in the fruiting bodies, while erinacins were extracted from the mushroom's mycelia [3, 4, 5, 6, 7]. The erinacins were extracted from the cultivated mycelia of *H. erinaceus* and were determined to be one of the diterpenoids. Hericenones were isolated from the fruiting bodies of *H. erinaceus*, and their molecular formula was identified as C3H4O7 [8].

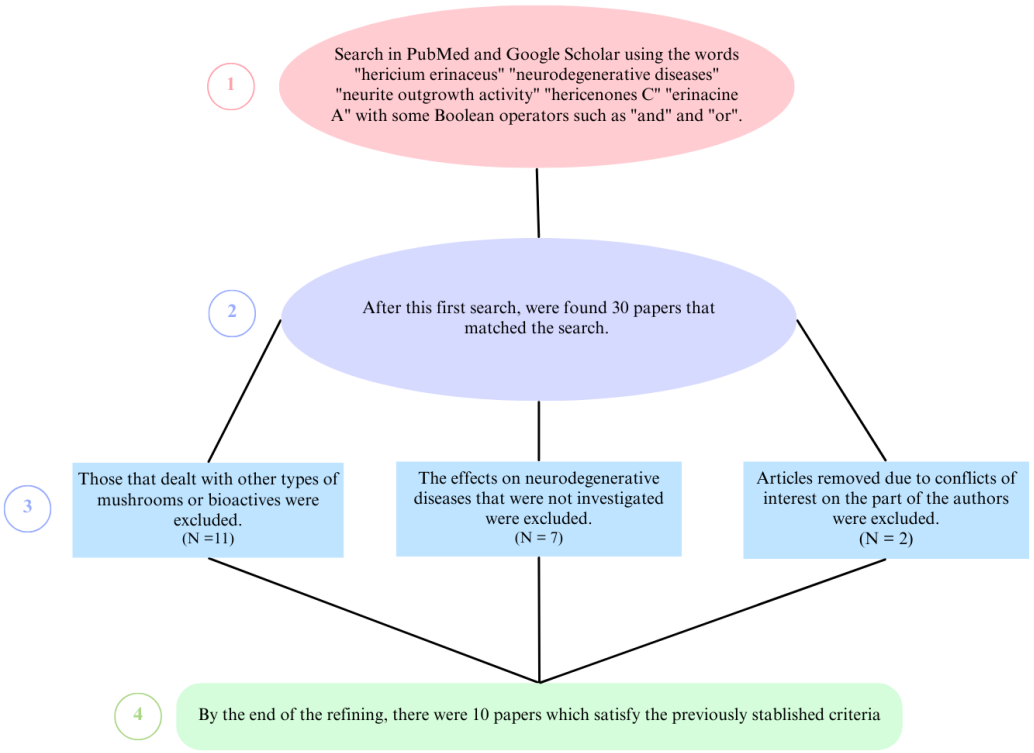
In addition, studies carried out on whole brain and cell cultures have shown that NGF affects the viability of cholinergic neurons and the level of activity of choline acetyltransferase and acetylcholinesterase in the central nervous system, thus suggesting that the effects of *H. erinaceus* could be analyzed in cholinergic neurons [9, 10, 11].

However, despite the clinical importance of *H. erinaceus*, there are few studies elucidating the plant's other effects on brain function and the autonomic nervous system. This study investigated the clinical effects of erinacin A and hericenones C and D from *H. erinaceus* on neurodegenerative diseases.

2. Methodology

To conduct this literature review, Google Scholar and PubMed search tools were utilized to select peer-reviewed studies. Included in the review were studies that address the potential therapeutic benefits and medicinal properties of *Hericium erinaceus*, focus on its bioactive compounds, hericenones C and D, and erinacin A, discuss their implications in neurodegenerative diseases, were published after the year 2014 (Table 1).

The choice of paper is illustrated in the following flowchart.



3. Results

Table 1 – Results from the bibliography survey

Title	Author (s)	Year of publishing	Purpose	Conclusion
Neurohealth Properties of *Hericium erinaceus* Mycelia Enriched with Erinacines. [12]	Li IC, Lee LY, Tzeng TT, Chen WP, Chen YP, Shiao YJ, Chen CC	2018	The main objective is to discuss and review the Neuroprotective properties of *H. erinaceus* mycelia enriched with erinacines, as well as their safety and therapeutic potential in various neurological conditions.	Although it is challenging to extrapolate in vivo studies to clinical situations, pre-clinical studies have shown that there might be improvements in conditions such as stroke, Parkinson's disease, Alzheimer's disease, and depression if *H. erinaceus* mycelia enriched with erinacines are included in daily meals.

Neuroprotective Metabolites of *Hericium erinaceus* Promote Neuro-Healthy Aging [13]	Roda E, Priori EC, Ratto D, De Luca F, Di Iorio C, Angelone P, Locatelli CA, Desiderio A, Goppa L, Savino E, Bottone MG, Rossi P.	2021	The study investigated the effects of oral supplementation with standardized extracts of *Hericium erinaceus* in frail elderly rats, focusing on its ability to reverse locomotor frailty and aging-associated cerebellar alterations.	*Hericium erinaceus* demonstrated neuroprotective properties, aiding in the partial recovery of age-related decline in locomotor performances and improving cerebellar alterations. It also reduced inflammation and oxidative stress in frail rats, enhancing longevity and neuroprotection. Thus, it emerges as a promising supplementary therapy alongside conventional geriatric treatments.
Erinacine A enriched *Hericium erinaceus* mycelium ameliorates Alzheimer's diseaserelated pathologies in APPswe/PS1dE9 transgenic mice. [15]	Tsai-Teng T, Chin-Chu C, Li-Ya L, Wan-Ping C, Chung-Kuang L, Chien-Chang S, Chi-Ying HF, Chien-Chih C, Shiao YJ.	2016	To study the effects of *Hericium erinaceus* mycelia enriched with erinacin A (HE-My) and its ethanol extracts (HE-Et) on pathological changes in the APPswe/PS1dE9 transgenic mouse model of Alzheimer's disease.	The findings obtained in this in vivo experimental study suggest a therapeutic potential of HE-My and HE-Et on Alzheimer's disease, indicating the possibility for the future development of therapeutic drugs based on the effective components of HE-My and HE-Et to treat Alzheimer's disease.
Erinacine A-Enriched *Hericium erinaceus* Mycelium Produces Antidepressant-Like Effects through Modulating BDNF/PI3K/Akt/GSK-3β Signaling in Mice. [14]	Chiu CH, Chyau CC, Chen CC, Lee , Chen WP, Liu JL, Lin WH, Mong MC.	2018	The aim of study was to analise the antidepressant-like effects of ethanolic extract of *Hericium erinaceus* (HE) mycelium enriched in erinacine A on depressive mice with repeated restraint stress (RS).	HE supplementation has been shown to attenuate stress-induced behavioral changes, exhibiting antidepressant effects. This is attributed to the restoration of neurotransmitters, the reduction of inflammation and the modulation of key neurological pathways (the PI3K/Akt/GSK3β pathway), leading to an increase in BDNF expression, suggesting that HE is a potent alternative therapy for depression.

Erinacine A attenuates glutamate transporter 1 downregulation and protects against ischemic brain injury. [18]	Hsu PC, Lan YJ, Chen CC, Lee LY, Chen WP, Wang YC, Lee YH.	2022	The study aimed to investigate the neuroprotective effect of erinacine A (EA), an active component of *Hericium erinaceus* (HE), with a specific focus on the function of the glutamate transporter 1 (GLT-1) in both in vitro and in vivo cerebral ischemia mouse models.	Erinacine A effectively preserved the GLT-1 and glutamate clearance machinery, offering protection against excitotoxicity following ischemic brain injury. The study suggests that Erinacine A is beneficial in maintaining glutamate homeostasis, which is crucial for neuronal survival, especially after brain injury.

Hericium erinaceus Improves Recognition Memory and Induces Hippocampal and Cerebellar Neurogenesis in Frail Mice during Aging. [17]	Ratto D, Corana F, Mannucci B, Priori EC, Cobelli F, Roda E, Ferrari B, Occhinegro A, Di Iorio C, De Luca F, Cesaroni V, Girometta C, Bottone MG, Savino E, Kawagishi H, Rossi P.	2019	The objective of the study was to investigate the potential benefits of *Hericium erinaceus* supplementation in improving recognition memory and inducing neurogenesis in frail mice during aging, focusing on its standardized amounts of erinacine A and hericenones C and D.	The study concluded that two-month oral supplementation with *H. erinaceus* reversed the age-related decline of recognition memory in mice. It supported a positive effect of *H. erinaceus* on neurogenesis in frail mice, as evidenced by proliferating cell nuclear antigen (PCNA) and doublecortin (DCX) immunohistochemistry in the hippocampus and cerebellum. The results suggest that *H. erinaceus* could potentially serve as a therapeutic agent for age-related cognitive decline and neurodegenerative diseases.
Post-Treatment with Erinacine A, a Derived Diterpenoid of *H. erinaceus* , Attenuates Neurotoxicity in MPTP Model of Parkinson's Disease. [16]	Lee KF, Tung SY, Teng CC, Shen CH, Hsieh MC, Huang CY, Lee KC, Lee LY, Chen WP, Chen CC, Huang WS, Kuo HC.	2020	It was investigated whether post-treatment with Erinacin A would be able to attenuate the neurotoxicity induced by 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP), exploring the underlying molecular mechanisms and evaluating the potential cell signaling pathways involved in neuroprotection.	Erinacine A was found to attenuate cytotoxicity in neuronal cells and ROS production both in vitro and in vivo. The compound acted by upregulating neuronal survival pathways and reducing the expression of molecules associated with cell death. The results suggest that Erinacine A may offer protection against neurotoxicity through the modulation of cellular signaling pathways related to neuronal survival and death, representing a potential therapeutic agent for neurodegenerative diseases such as Parkinson's disease.
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. [19]	Lee KF, Chen JH, Teng CC, Shen CH, Hsieh MC, Lu CC, Lee KC, Lee LY, Chen WP, Chen CC, Huang WS, Kuo HC.	2014	To investigate the antiinflammatory and neuroprotective effects of *H. erinaceus* mycelium and erinacine A in a model of global ischemic stroke.	*H. erinaceus* mycelium and its isolated compound, erinacine A, exhibited significant neuroprotective effects against ischemiareperfusion brain injuries, reducing inflammation and infarcted volumes in the brain. Erinacine A modulated the expression of proteins involved in inflammation and ischemia injury, suggesting its potential as a therapeutic agent for ischemic stroke.

Prevention of Early Alzheimer's Disease by Erinacine A-Enriched *Hericium erinaceus* Mycelia Pilot Double-Blind Placebo-Controlled Study. [20]	Li IC, Chang HH, Lin CH, Chen WP, Lu TH, Lee LY, Chen YW, Chen YP, Chen CC, Lin DP.	2020	The objective of this study was to investigate the efficacy and safety of three *H. erinaceus* mycelia (EAHE) capsules (each containing 5 mg/g erinacine A active ingredient) per day in treating patients with mild Alzheimer's Disease (AD).	After 49 weeks of intervention with EAHE, subjects with mild Alzheimer's Disease exhibited notable improvements in cognitive functions and contrast sensitivity. Significant enhancements were observed in the Mini-Mental State Examination score and Instrumental Activities of Daily Living score in the EAHE group compared to the placebo group. The findings endorse EAHE's potential in alleviating neurodegenerative disorders, especially Alzheimer's Disease.
Erinacine A Prevents LipopolysaccharideMediated Glial Cell Activation to Protect Dopaminergic Neurons against Inflammatory Factor-Induced Cell Death In Vitro and In Vivo. [21]	Lee SL, Hsu JY, Chen TC, Huang CC, Wu TY, Chin TY.	2022	The study aimed to explore the anti--neuroinflammatory and neuroprotective effects of Erinacine A (EA) from *Hericium erinaceus* (HE) on LPS-induced glial cell activation and neural damage, focusing on its potential implications in neurodegenerative diseases like Parkinson's disease (PD).	Erinacine A (EA) exhibited notable antineuroinflammatory and neuroprotective properties. In vitro, EA mitigated LPS-induced inflammatory expressions and productions in cells. In vivo, EA and HEM improved motor dysfunction and decreased proinflammatory mediators in rats. These findings suggest EA's potential benefits in neurodegenerative diseases like Parkinson's due to its ability to ameliorate neuroinflammation.

4. Discussion

The exploration of Erinacine A and Hericinones C and D from *Hericium erinaceus* in the context of neurodegenerative diseases has unveiled a plethora of potential therapeutic applications. This literature review has synthesized the existing knowledge, emphasizing the multifaceted roles of these compounds in promoting neurohealth.

4.1 Neuroprotective Properties:

The studies included in this review consistently highlighted the neuroprotective properties of Erinacine A and Hericinones C and D. These compounds have demonstrated significant potential in attenuating neurotoxicity, reducing inflammation, and modulating cellular signaling pathways related to neuronal survival and death. The neuroprotective role of these compounds is crucial in the context of neurodegenerative diseases, where neuronal damage is a predominant feature.

4.2 Impact on Neurodegenerative Diseases:

The potential of these compounds in mitigating the progression of various neurodegenerative diseases such as Alzheimer's and Parkinson's disease is noteworthy. The studies reviewed have shown promising results in improving cognitive functions, reducing the burden of amyloid-beta plaques, and promoting neurogenesis, which are pivotal in combating neurodegenerative diseases.

4.3 Mechanism of Action:

The mechanism through which these compounds exert their effects is multifaceted, involving the modulation of neuroinflammatory responses, enhancement of neurotrophic factors, and regulation of oxidative stress. Understanding the intricate mechanisms of action is paramount for optimizing the therapeutic application of these compounds.

4.4 Clinical Implications:

The clinical implications of the findings from the reviewed studies are substantial. The potential of Erinacine A and Hericinones C and D to serve as adjuvant therapies in conjunction with conventional treatments could revolutionize the management of neurodegenerative diseases. However, the translation of these findings to clinical practice necessitates further research, including well-designed clinical trials to validate the efficacy and safety of these compounds in humans.

4.5 Limitations and Future Directions:

While the reviewed studies provide valuable insights, it is crucial to acknowledge the limitations inherent in the existing literature, such as the variability in study designs, sample sizes, and methodologies. Future research should aim to address these limitations by conducting rigorous and standardized studies to corroborate the findings. Additionally, exploring the synergistic effects of these compounds with other bioactive components and their bioavailability will be instrumental in maximizing their therapeutic potential.

5. Conclusion

In conclusion, Erinacine A and Hericinones C and D from *Hericium erinaceus* have emerged as promising candidates for the development of novel therapeutic strategies for neurodegenerative diseases. The evidence synthesized in this review underscores their potential in neuroprotection, modulation of neuroinflammatory responses, and enhancement of cognitive functions. However, the realization of their therapeutic potential necessitates further research to elucidate the underlying mechanisms, optimize the delivery methods, and validate their efficacy in clinical settings. The advancements in this field hold the promise of paving the way for innovative interventions to alleviate the burden of neurodegenerative diseases.

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