

Neuroprotective Effects of *Hericium erinaceus*: Evidence from Experimental and Clinical Studies—A Systematic Review and Limited Meta-Analysis

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Abstract: Neurodegenerative diseases, including Alzheimer’s disease and Parkinson’s disease, affect more than 55 million people worldwide and represent a growing public health challenge. *Hericium erinaceus* (Lion’s Mane mushroom) has attracted increasing attention due to its reported neuroprotective and antioxidant properties. This systematic review and limited meta-analysis evaluated current evidence regarding the effects of *Hericium erinaceus* on neurodegenerative disease-related outcomes. A systematic search of PubMed and Google Scholar was conducted following PRISMA guidelines for studies published between 2000 and 2026. From 1224 records identified, 23 studies met the inclusion criteria, comprising 12 animal studies, 8 in vitro studies and 3 human clinical trials. Study quality and risk of bias were assessed using SYRCLE and Cochrane tools. Across experimental models, *Hericium erinaceus* demonstrated consistent neuroprotective effects, which appeared to be mediated through multiple mechanisms, including enhancement of nerve growth factor and brain-derived neurotrophic factor signalling, activation of antioxidant defence pathways such as nuclear factor erythroid 2-related factor 2 (Nrf2) signalling, suppression of NLRP3 inflammasome activity, reduction of oxidative stress, and attenuation of neuronal apoptosis. Limited human studies suggested potential benefits for cognitive function and mood. Quantitative synthesis supported the neuroprotective potential of *Hericium erinaceus*, with improvements in oxidative stress-related biomarkers observed across experimental studies. However, substantial heterogeneity and limited clinical evidence precluded definitive conclusions. Overall, *Hericium erinaceus* shows promising preclinical neuroprotective through multiple interconnected mechanisms, including antioxidant, anti-inflammatory, neurotrophic and anti-apoptotic pathways. However, its clinical efficacy in neurodegenerative disease remains unconfirmed.

Keywords: *Hericium erinaceus*; Neuroprotection; Oxidative stress; Alzheimer’s disease; Parkinson’s disease; Nutraceuticals

1. Introduction

Neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD), are characterised by progressive neuronal loss and dysfunction within the central nervous system and represent one of the greatest health challenges associated with global population ageing. More than 55 million people worldwide are currently living with dementia, with prevalence expected to increase substantially over the coming decades. It



has been estimated that the number of individuals affected by Alzheimer's disease alone may reach 139 million by 2050, representing almost a threefold increase compared with current levels [1,2]. These disorders are associated with progressive cognitive and motor decline, loss of independence, and substantial healthcare and social care costs, resulting in a considerable burden on patients, caregivers, and healthcare systems [3].

At the pathological level, Alzheimer's disease is characterised by extracellular β -amyloid plaque accumulation and intracellular hyperphosphorylated tau aggregation, which disrupt synaptic function and contribute to progressive neuronal degeneration [1]. In contrast, Parkinson's disease is primarily characterised by the degeneration of dopaminergic neurones in the substantia nigra and the accumulation of α -synuclein-containing Lewy bodies, resulting in progressive motor dysfunction [3]. Although these diseases differ in their pathological features, increasing evidence suggests that oxidative stress, mitochondrial dysfunction, chronic neuroinflammation and impaired neuronal repair mechanisms contribute significantly to disease progression and severity [4,5]. Consequently, interventions capable of modulating these processes have attracted growing scientific interest.

Current pharmacological treatments for Alzheimer's disease, including cholinesterase inhibitors such as donepezil, and N-methyl-D-aspartate receptor antagonists such as memantine, and for Parkinson's disease, such as levodopa, are primarily designed to alleviate symptoms rather than may help delay or reduce risk of progression or halt disease progression [6]. While these therapies can improve quality of life and symptom management, their long-term effectiveness remains limited, and adverse effects may restrict their clinical utility in some patients [7]. Furthermore, many currently approved therapies do not directly target oxidative stress, neuroinflammation, or neuronal regeneration, which are increasingly recognised as important therapeutic targets [3]. As a result, there is growing interest in identifying complementary nutritional and nutraceutical approaches that may support neuroprotection and reduce oxidative damage [8].

Hericium erinaceus, commonly known as Lion's Mane mushroom, is an edible and medicinal mushroom traditionally used in East Asian countries and increasingly studied for its potential neurological benefits [4]. It grows naturally on hardwood trees in Asia, Europe and North America and contains a diverse range of bioactive compounds, including hericenones, erinacines, polysaccharides and phenolic compounds [4]. Hericenones, predominantly isolated from the fruiting body, have been associated with stimulation of nerve growth factor (NGF) synthesis, while erinacines, diterpenoids primarily found in the mycelium, have demonstrated the ability to cross the blood-brain barrier and promote neurotrophic activity [9,10]. In addition, *Hericium erinaceus* has been reported to activate nuclear factor erythroid 2-related factor 2 (Nrf2), an important regulator of antioxidant defence systems, suggesting potential roles in both neuroprotection and oxidative stress modulation [11].

The biological plausibility of *Hericium erinaceus* as a neuroprotective intervention is supported by several proposed mechanisms. NGF and brain-derived neurotrophic factor (BDNF) play essential roles in neuronal survival, differentiation and synaptic plasticity, and reductions in these neurotrophic factors have been implicated in neurodegenerative disease progression [1]. Furthermore, polysaccharides isolated from *Hericium erinaceus* have demonstrated immunomodulatory and antioxidant activities, while phenolic compounds contribute to free radical scavenging and oxidative stress reduction [12,13]. Collectively, these mechanisms suggest that *Hericium erinaceus* may influence multiple pathways relevant to neurodegeneration, including neurotrophic support, inflammation regulation and antioxidant defence.

A growing body of in vitro, animal and human studies has investigated the effects of *Hericium erinaceus* on neurological and oxidative stress-related outcomes [11]. Experimental evidence suggests that *Hericium erinaceus* may reduce oxidative stress markers such as malondialdehyde (MDA) and reactive oxygen species (ROS) while increasing antioxidant enzyme activities, including superoxide dismutase (SOD) and catalase [14,15]. Other studies have reported stimulation of NGF production, enhancement of neurite outgrowth, improved cognitive performance and reduced neuroinflammatory responses [16]. However, despite these encouraging findings, several important limitations remain.

First, much of the current evidence originates from in vitro and animal studies, whereas human clinical data remain limited. Existing human studies generally involve relatively small sample sizes and are frequently conducted in healthy individuals rather than patients diagnosed with neurodegenerative diseases [1]. Second, considerable heterogeneity exists regarding the form of *Hericium erinaceus* used, including fruiting body extracts, mycelial preparations, isolated erinacines, hericenones and polysaccharide-rich fractions. Differences in extraction methods, dosage regimens and intervention durations complicate comparisons between studies and limit the generalisability of findings [17]. Third, outcome measures vary substantially between studies, ranging from molecular biomarkers and cell viability assays to behavioural assessments and cognitive testing. Consequently, although the available literature is generally supportive of neuroprotective and antioxidant effects, the overall strength and translational relevance of the evidence remain uncertain.

Furthermore, while previous reviews have examined selected pharmacological properties or specific bioactive compounds derived from *Hericium erinaceus*, a comprehensive synthesis focusing simultaneously on both neuroprotective and antioxidant outcomes across experimental and clinical studies remains limited [11]. Given the growing interest in nutraceutical approaches for neurodegenerative diseases, a critical evaluation of the available evidence is warranted. Recent reviews have continued to highlight the therapeutic potential of *Hericium erinaceus*, including a 2025 narrative review by Contato and Conte-Junior [4] confirming its neuroprotective, antioxidant and anti-inflammatory properties, and a systematic review by Spagenberg et al. [11] specifically examining the role of erinacines in preclinical neuroprotection.

The aim of this systematic review and limited meta-analysis was therefore to evaluate and synthesise the current evidence regarding the neuroprotective and antioxidant effects of *Hericium erinaceus* across in vitro studies, animal models and human clinical trials. PRISMA reporting standards were followed to ensure methodological transparency, and study quality was assessed using Cochrane and SYRCLE risk-of-bias tools. This review seeks not only to summarise current findings but also to critically evaluate the quality, consistency and limitations of the available evidence, thereby identifying priorities for future mechanistic, translational and clinical research.

2. Methods

2.1. Study Design

This study was conducted as a systematic review with a limited meta-analysis, closely following PRISMA guidelines, and it examined the neuroprotective and antioxidant properties of *Hericium erinaceus*. The two databases used to identify relevant studies were PubMed and Google Scholar. The evidence gathered was thoroughly synthesised from in vitro, preclinical and clinical studies. The literature search was conducted throughout February and March 2026, including studies from 2000 to 2026, as well as specific foundational articles outside this date range that provided significant information relevant to the review.

2.2. Search Strategy

A Boolean search was used across both databases to gather relevant literature and clinical and experimental studies on the subject. The search string used to identify relevant records was (“*Hericium erinaceus*” OR “Lion’s Mane” OR “erinacine” OR “hericenone”) AND (neuroprotect* OR antioxidant OR “oxidative stress” OR “nerve growth factor” OR NGF). Although the review focused on studies from 2000 to 2026, certain articles were considered outside this date range due to the importance of their data and relevance to the topic. Additional studies were manually searched using keywords and the reference lists of primary and review articles. The PubMed search was conducted on 14 February 2026 using the following filters: English language and publication dates 2000–2026. The Google Scholar search was conducted on 21 February 2026 with no additional filter applied beyond the Boolean search string. No protocol registration was completed prior to the search, as this review was conducted as part of an undergraduate dissertation project. Manual searching of reference lists was carried out to identify additional relevant studies not captured by the database searches. No grey literature, conference proceedings, or unpublished studies were searched.

2.3. Inclusion and Exclusion Criteria

The eligibility criteria were developed using a modified PICO framework. The population (P) included in vitro neuronal cell models, animal models of neurodegenerative diseases or oxidative stress, and human participants. The intervention (I) consisted of *Hericium erinaceus* preparations, including fruiting body extracts, mycelial extracts, powders, and isolated bioactive compounds such as erinacines and hericenones. Comparators (C) included untreated controls, placebo groups, vehicle controls, or standard treatments where applicable. Outcomes (O) included neuroprotective and antioxidant measures, such as nerve growth factor, brain-derived neurotrophic factor, neuronal viability, cognitive performance, reactive oxygen species, malondialdehyde, catalase, superoxide dismutase, and related biomarkers of oxidative stress and neuronal function.

Studies that met the eligibility criteria were considered for inclusion if they specifically investigated *Hericium erinaceus*, including powder, extracts, or isolated bioactive compounds. Additionally, studies were included if they focused on neuroprotective and antioxidant outcomes, as well as studies that included a control or placebo group. Lastly, the articles had to be written in English across all study types, including in vitro, animal, and human trials.

Studies that did not meet the criteria above were excluded, such as those that focused on anything besides *Hericium erinaceus* as the primary topic, including studies mainly investigating other mushrooms or unrelated mechanisms. Studies were also excluded if they did not assess neuroprotective or antioxidant outcomes, as well as

studies that focused solely on non-neurological issues, such as gut health or cancer. Lastly, studies that were not in English and were not peer-reviewed were also not included. Any duplicate articles identified from both databases were also removed before screening took place.

2.4. Screening and Data Collection

Across the two databases, 1224 records were identified, including 144 from PubMed and 1080 from Google Scholar, following use of the Boolean search string. A total of 35 duplicates were removed, leaving 1189 records for screening. These results were then screened by title and abstract to assess their relevance to the topic according to the inclusion and exclusion criteria, with most records excluded because they were not relevant to the review topic. The remaining full-text articles were fully examined and assessed for eligibility. Following article screening, 42 studies were included in the final review, of which 23 were primary studies. The entire screening process is shown in the Results section using the PRISMA flow diagram (Figure 1). Of these, 23 were identified as primary studies meeting the systematic review inclusion criteria, while the remaining 19 were secondary reviews used for contextualisation only.

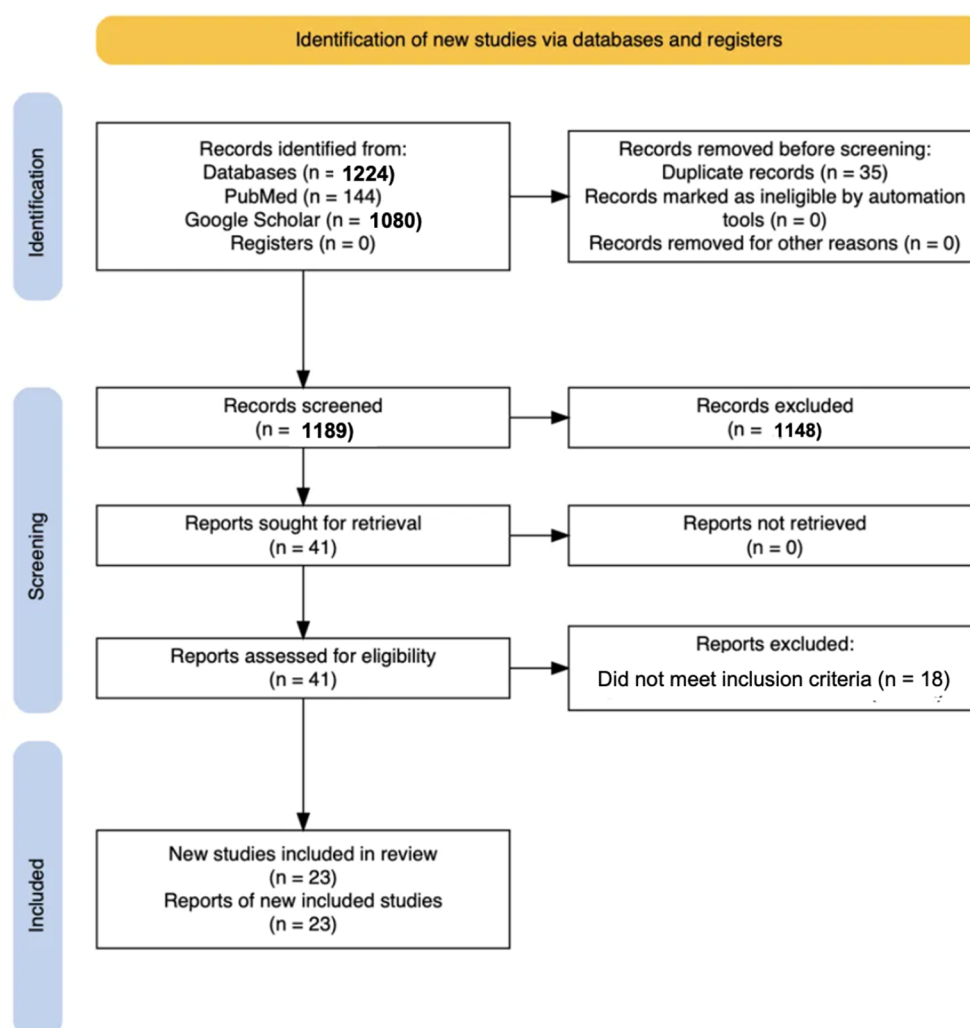


Figure 1. PRISMA 2020 flow diagram illustrating the study selection process. Records were identified through PubMed (n = 144) and Google Scholar (n = 1080), resulting in a total of 1224 records. Following the removal of duplicate articles (n = 35), screening of titles and abstracts, and assessment of full-text eligibility, 23 primary studies were included in the final systematic review.

2.5. Data Extraction

Data were extracted from each study systematically using predefined key information, including the author, year of publication, and the type and duration of the study, such as whether it was an animal, in vitro, or human

study. The samples used, the form and quantity of *Hericium erinaceus*, the study outcomes, and the final conclusions drawn from the results were also extracted from each of the 42 studies. Of the 42 studies included, 23 were identified as primary articles and were included in the study characteristics table, while the remaining 19 were secondary reviews or systematic reviews, which aided the contextualisation of the searched information. The outcomes and results relevant to this review were neuroprotective and antioxidant markers, such as nerve growth factor and neuronal cell viability, as well as catalase, MDA, ROS, and SOD, respectively. The data gathered were organised in a table to facilitate comparison across all studies, which is presented in the Results section.

2.6. Risk of Bias

Before accepting the findings of the included studies, a risk of bias assessment was conducted to evaluate whether the study design, methodology, and reporting were sufficiently rigorous and unbiased. This assessment considered whether experiments were conducted fairly and appropriately randomised and whether all relevant outcomes were reported rather than selectively presenting positive findings. Assessing the risk of bias helps ensure that the evidence included in this review is reliable and of appropriate methodological quality.

The two assessment tools used were the SYRCLE Risk of Bias tool for animal studies and the Cochrane Risk of Bias tool for clinical trials, respectively. These tools evaluate key domains, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias.

Due to the lack of a universally accepted risk of bias assessment tool for in vitro studies, these studies were evaluated based on the validity of the experimental design, suitability of the cell models used, appropriateness of the intervention and outcome measures, and the inclusion of relevant control groups.

For animal studies assessed using SYRCLE, key domains evaluated included sequence generation, baseline characteristics, allocation concealment, random housing, blinding of carers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. For human clinical trials assessed using the Cochrane tools, domains evaluated included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Across the animal studies, the majority were judged to be at unclear risk of bias for several domains due to insufficient reporting of randomisation and blinding procedures. The three human clinical trials were generally at low to unclear risk of bias, with the two double-blind placebo-controlled trials demonstrating stronger methodological rigour. Overall, the risk of bias assessment suggests that while most studies demonstrated adequate experimental design, incomplete reporting limited the confidence of bias judgements across several domains.

2.7. Narrative Synthesis

For studies that could not be quantitatively pooled, their key findings, study characteristics, and conclusions were described and compared narratively. Studies were grouped according to study type, including animal, in vitro, and human trials, to allow clearer comparison across the available evidence. This approach enabled findings from heterogeneous studies to be synthesised while acknowledging differences in study design, intervention form, dose, duration, and outcome measures.

2.8. Statistical Analysis

Where sufficient quantitative data were available, a limited meta-analysis was performed. Due to substantial methodological heterogeneity among studies, including differences in experimental models, intervention forms, dosages, outcome measures and reporting methods, most studies were synthesised narratively rather than quantitatively pooled. The standardised mean difference (SMD) was used as the common effect size, calculated as Hedges' g , in order to compare studies despite differences in measurement scales. A random-effects model was applied to account for variation in study design, laboratory conditions, doses, intervention forms, and experimental settings. Heterogeneity, defined as variability in effect estimates between studies, was assessed using I^2 , which is expressed as a percentage from 0 to 100. Lower I^2 values indicate greater consistency between studies, whereas higher values indicate greater variability.

For papers that did not present sufficient quantitative data for comparison, a narrative synthesis was conducted, describing the relevant findings that could not be pooled statistically. Where sufficient numerical data were available, a limited meta-analysis was conducted using Meta-Essentials software, as RevMan 5 is no longer supported by Cochrane [18]. However, due to substantial methodological heterogeneity across the primary studies, including differences in model design, dose, form of *Hericium erinaceus*, and outcome measures, quantitative pooling was not possible for most studies. Therefore, a narrative synthesis was completed for the remaining outcomes.

Assessment of publication bias using funnel plots or statistical tests was not performed because the number of studies included in the quantitative synthesis was insufficient to provide a reliable evaluation. However, publication bias remains an important consideration in this review. The nutraceutical literature is particularly susceptible to positive publication bias, whereby studies reporting significant or beneficial effects of *Hericium erinaceus* are more likely to be published than those reporting null or negative findings. This may have resulted in an overestimation of the beneficial effects observed across the included studies. Furthermore, the restriction of the search to English-language publications may have excluded relevant studies published in other languages, particularly given the significant body of research on *Hericium erinaceus* originating from East Asian countries. These factors should be considered when interpreting the overall findings of this review.

3. Results

3.1. Study Characteristics

A total of 23 primary research studies were included in this review, with 12 animal studies, 8 in vitro studies, and 3 human clinical trials. The studies were published between 2010 and 2024, with the majority published within the last decade, which reflects the increasing interest in the possible benefits of *Hericium erinaceus*. Each study administered *Hericium erinaceus* in a variety of forms, such as aqueous, ethanolic and methanolic extracts, mycelial and fruiting body preparations, as well as isolated bioactive compounds found in the mushroom, such as erinacine A and C. The most common outcomes reported in each study included neuroprotective markers such as NGF, BDNF, and cognitive function, together with antioxidant markers including catalase, ROS, SOD, and MDA. The full list of descriptive details included for each study is presented in Table 1 below, displaying the models used, doses and forms of *Hericium erinaceus*, outcomes measured, and the key findings. Due to differences in study design, intervention form, dose, and outcome measures, substantial methodological heterogeneity was observed across the included studies.

Table 1. Characteristics of primary studies included in the systematic review.

Author & Year	Model	HE Form & Dose	Outcomes Measured	Key Findings
Animal Studies				
D’Amico et al. (2021) [19]	Mice—traumatic brain injury model	HE and <i>Coriolus versicolor</i> oral treatment daily	Neuroinflammation, oxidative stress, dopamine	HE prevented oxidative damage and restored proper behaviour
Hsu et al. (2023) [15]	Mice—Parkinson’s model	Micronized HE mycelium given orally	Catalase, MDA, SOD, dopamine	Reduced MDA and protein carbonyl levels, as well as the recovery of dopamine from 1535 to 4527 ng/g using the highest dose. Elevation of SOD, G6PDH, glutathione reductase, and catalase was reported, as well as an increase of TH-positive cells from 4% to 10%
Shirvani et al. (2024) [14]	Male Wistar rats—Alzheimer’s model	300 mg/kg of HE extracts daily for 2 weeks	Catalase, TAC, LPO, BDNF, neuroprotection	Improved BDNF levels and function of memory
Cordaro et al. (2021) [20]	Rats—Alzheimer’s model	HE oral gavage daily	Tau, beta-amyloid, oxidative stress, NLRP3 inflammasome	Inhibited the activation of inflammasomes and reduced oxidative stress
Lee et al. (2024) [21]	Rats—brain injury model	Oral treatment of HE mycelium and erinacine C	Catalase, SOD, Nrf2 antioxidant pathway, oxidative stress	Reduced inflammation of the brain, and activated Nrf2
Lee et al. (2021) [22]	Mice—cellular aging model	108, 215, and 431 mg/kg doses of erinacine A-enriched <i>Hericium erinaceus</i> mycelium (EAHEM) for 12 weeks	Cognitive function, oxidative stress, TBARS, iNOS	Reduced oxidative stress and enhanced memory
Roda et al. (2021) [23]	Aged mice	HE extracts for 2 months	Oxidative stress, inflammation, locomotor function	Reduced inflammation and stress, as well as improving locomotion
Roda et al. (2023) [24]	Aged mice	Ergothioneine-rich HE extracts	Oxidative stress, SOD1, Nrf2	Reduced oxidative stress in the hippocampus, and improved recognition
Tsai et al. (2019) [25]	Mice—high-fat diet model	HE mycelium and erinacine A for 18 weeks	NGF, neuroinflammation, TNF- α	Promoted production of NGF, reduced inflammation in the brain, and memory
Tsai et al. (2021) [26]	Sprague-Dawley rats	50 mg/kg of erinacine A orally	Bioavailability, blood-brain-barrier penetration	Erinacine A found in the brain tissue after an hour, indicating success with crossing of the BBB
Chen et al. (2024) [27]	Landrace pig	5 mg/kg of erinacine A, administered intravenously	Pharmacokinetics, cerebrospinal fluid penetration	Erinacine A found in CSF within 15 min of treatment, exhibiting evidence of BBB penetration
Martínez-Mármol et al. (2023) [16]	Hippocampal neurons and mice	Hericenone A and N-de phenylethyl isohericerin (NDPIH) extracted from HE	ERK1/2, neurite outgrowth, memory	Compounds encouraged neurite growth and enhanced memory
In vitro Studies				
Lew et al. (2020) [28]	PC-12 cells—oxidative stress (depression-mimicked) model	Aqueous extract from HE (0.25 to 1 mg/mL)	Cell viability, antioxidant enzyme activity, ROS levels, MMP	Increased cell viability, repaired MMP, enhanced antioxidant activities, reduction of ROS
Zhang et al. (2015) [29]	PC-12 cells	Fruiting body compounds combined with NGF	NGF-mediated neurite outgrowth	A new meroterpenoid (hericenone K) showed a significant increase in neurite-bearing cells
Tamrakar et al. (2023) [30]	Human astrocytoma cells	Hericenone C and deacylhericenone	BDNF, oxidative stress	Showed the strongest bioactive form for hericenone C is deacyl hericenone as a result of protection from oxidation, and expression of BDNF was higher
Lin et al. (2023) [31]	Peripheral and central nervous system cells	Erinacine S-derived from HE	Neurotrophic growth, regeneration of axons	Revealing an unknown effect of Erinacine S, which enhanced neurite growth, as it raised levels of neurosteroid
Wu et al. (2024) [32]	Neuronal cells and <i>drosophila</i>	5 mg/g of erinacine-A enhanced HE mycelium	Nrf2, autophagy, antioxidant activity	Nrf2 activation, reduced protein aggregation, increased antioxidant activity
Ghosh et al. (2021) [33]	Fruiting body from HE extracts	Methanolic and ethanolic extracts of HE	DPPH, ABTS free radical	76% of DPPH and 81% of ABTS showed scavenging activity, with ethanolic showing highest antioxidant activity and methanolic showing moderate antioxidant activity
Qiao et al. 2024 [34]	HE glucan fraction	Alkaline-extracted β -glucan purified bodies from HE	DPPH, ABTS free radical, hydroxyl radicals scavenging assays	Exhibited strong antioxidant levels across the three assays used
Amara et al. (2020) [35]	PC-12 cells in a DEHP-induced oxidative stress model	HE extracts at 0.5, 1, 1.5, and 2 mg/mL for 24 h	MMP, ROS, cell viability, oxidative stress, apoptosis, Nrf2 activation	HE reduced ROS levels, stabilised MMP, and shows evidence of emerging nutritional strategy protecting against DEHP-induced apoptosis based on the dose given

Table 1. Cont.

Author & Year	Model	HE Form & Dose	Outcomes Measured	Key Findings
Human Studies				
Saitsu et al. (2019) [36]	30 middle-aged adults in a randomised double-blind placebo-controlled comparative setting	Fruiting body of 0.8 g HE supplements 4x/day for 12 weeks	Cognitive results and MMSE	Showned significant improvement in cognitive function tests compared to the placebo group and is deemed safe for dementia prevention
Docherty et al. (2023) [17]	41 adults in a double-blind setting	1.8 g of HE for 28 days	Stress and mood, as well as cognitive function	Cognitive function improved speedily and showed decreased stress after treatment for 28 days
Nagano et al. (2010) [37]	30 women in a double-blind placebo-controlled setting	Cookies made with 0.5 g HE for 4 weeks	Depression and anxiety	Showned a significant decrease in depression and anxiety compared to those in the placebo group

Note. HE, *Hericium erinaceus*; MMSE, Mini-Mental State Examination; DEHP, Di-(2-ethylhexyl) phthalate; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde. G6PDH, glucose-6-phosphate dehydrogenase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Nrf2, nuclear factor erythroid 2-related factor 2; BBB, blood-brain barrier; TBI, traumatic brain injury; TAC, total antioxidant capacity; LPO, lipid peroxidation; MMP, mitochondrial membrane potential; TBARS, thiobarbituric acid reactive substances; iNOS, inducible nitric oxide synthase; ERK1/2, extracellular signal-regulated kinases 1/2; CSF, cerebrospinal fluid.

3.2. Neuroprotective Effects

Hericium erinaceus was demonstrated to have neuroprotective effects across the in vitro, animal, and human studies, with most evidence being present in preclinical trials. Neuroprotective properties were repeatedly demonstrated in in vitro studies. Lew et al. [28] investigated *Hericium erinaceus* in an aqueous form at concentrations of 0.25 to 1 mg/mL in PC-12 cells subjected to damage by corticosterone at 400 μ M to represent a depression-mimicked model. Pre-treatment with *Hericium erinaceus* was applied to these cells at 0.25 to 1 mg/mL for 48 h before exposure to corticosterone, which resulted in the restoration of cell viability from 59.85% to 75.66%, representing improved cellular activity. Amara et al. [35] focused on DEHP as a stressor due to its toxicity to neuronal cells. PC-12 cells were pre-treated with *Hericium erinaceus* at concentrations of 0.5 to 2 mg/mL for 24 h before being exposed to 85 μ M of DEHP, showing an increase in cell viability from 51.16% to 78.73%. Additionally, Nrf2 was activated, which may prevent apoptosis and mitochondrial dysfunction. Zhang et al. [29] isolated compounds from the fruiting body of *Hericium erinaceus*, including a meroterpenoid called ‘hericenone K’, which is a bioactive compound that had not yet been identified in previous literature. They were tested on PC-12 cells, using NGF at the same time at 20 ng/mL, showing increased neurite development after treatment, suggesting the mushroom’s support of neuronal growth as well as cell survival. Tamrakar et al. [30] compared the efficacy of hericenone C with another lipase-treated isolated compound called deacylhericenone. The results showed that the modified version performed significantly better than the original hericenone due to the increase in BDNF mRNA expression in human astrocytoma cells, indicating the potential beneficial role of *Hericium erinaceus* in neurotrophic factor production. Lin et al. [31] discovered that erinacine S, which is found in the mycelium of *Hericium erinaceus*, promotes the growth of neurites and axon regeneration in the peripheral and central nervous systems through neurosteroid accumulation. Wu et al. [32] tested a *Hericium erinaceus* extract from mycelium enriched in erinacine A at 5 mg/g on SK-N-SH neuroblastoma cells and a *Drosophila* spinocerebellar ataxia model. Findings from this study showed the activation of Nrf2 and the reduction of protein aggregation, as well as improved locomotor activity, supporting its potential as a neuroprotective intervention. The identification of Nrf2 activation in this study as well as Lee et al. [21] reported Nrf2 activation, which is significant due to their similar neuroprotective outcomes across different models. Lastly, Martínez-Mármol et al. [16], in both an animal and an in vitro study, discovered that hericenone A and N-de phenylethyl isohericerin (NDPIH) promote axon and neurite outgrowth in hippocampal neurones through the ERK1/2 pathway, improving memory and cognition. Ghosh et al. [33] and Qiao et al. [34], the two remaining in vitro studies, focus on antioxidant activity and are discussed in Section 3.3.

Additionally, animal studies have also reported promising neuroprotective outcomes across a variety of models and experiments. Shirvani et al. [14] gave *Hericium erinaceus* at a dose of 300 mg/kg daily for 2 weeks to male Wistar rats in an Alzheimer’s model, noting evidence of an increase in BDNF levels as well as improved performance in the water maze compared to the controls used in the experiment. Cordaro et al. [20] also used *Hericium erinaceus* on rats in an Alzheimer’s model, showing a significant reduction in neuronal degeneration in the hippocampus, as well as decreasing beta-amyloid accumulation and phosphorylated tau levels. A noteworthy finding also included the suppression of NLRP3 inflammasome activation, which is a key contributor to neuroinflammation in Alzheimer’s disease. Two studies from Lee et al. observed neuroprotective effects across two models, reflecting the development of this research area over time. Lee et al. [22] administered erinacine A-enriched *Hericium erinaceus* mycelium (EAHEM) to ageing mice in increasing doses of 108, 215, and 431 mg/kg for 12 weeks. Results from all three doses showed significant improvement in memory in avoidance tests. Lee et al. [21] studied Sprague-Dawley rats treated in a traumatic brain injury model with *Hericium erinaceus* and erinacine C, resulting in the activation of Nrf2, an increase in BDNF, and a reduction in microglial activation, which may explain the beneficial effects of erinacine C. Tsai et al. [25] treated ageing mice that were on a high-fat diet with *Hericium erinaceus* and erinacine A for 18 weeks, showing a rise in NGF and NeuN expression in the hippocampus and an improvement in spatial learning in the water maze and Y-maze. Roda et al. also published two studies that suggested *Hericium erinaceus* supports the cognitive functions and physical aspects of the ageing brain and neurological health. They discovered that two months of *Hericium erinaceus* supplementation in aged mice supported locomotor function and reduced cerebellar neurodegeneration [23]. They also reported that a *Hericium erinaceus* extract enriched in ergothioneine improved recognition memory and reduced inflammation in the hippocampus, as well as lowering oxidative markers [24]. D’Amico et al. [19] used mice in a TBI model, in which the animals were administered *Hericium erinaceus* and *Coriolus versicolor* treatment daily, and reported prevention of the loss of tyrosine hydroxylase as well as preservation of dopamine transporter expression in the substantia nigra, indicating an improvement in behavioural performance. Hsu et al. [15] treated mice in an MPTP-induced Parkinson’s model with orally given micronised *Hericium erinaceus* at doses of 0.1, 0.3, and 1 g/kg for 30 days. Dopamine was

recovered in the striatum from 1535 ng/g to 4527 ng/g after treatment with the highest dose. Furthermore, there was an increase from 4% to 10% of TH-positive cells, implying neuronal survival following the treatment. The approximate threefold recovery at the dose of 1 g/kg represents a significant neuroprotective outcome with the treatment of *Hericium erinaceus*. Tsai et al. [26] tested Sprague-Dawley rats, administering *Hericium erinaceus* mycelial extract orally at 2.381 g/kg body weight (equivalent to 50 mg/kg body weight of erinacine A) confirming that erinacine A crossed the blood-brain barrier and detecting the compound in the brain tissue within 1 h, as well as an absolute bioavailability of 24.39%. A similar study from Chen et al. [27] further confirmed penetration through the BBB using a Landrace pig model, detecting erinacine A in CSF within 15 min of treatment using a dose of 5 mg/kg, resulting in a brain tissue concentration of 77.45 µg/L. These two pharmacokinetic studies provide evidence confirming erinacine A crossing the BBB, suggesting its potential relevance to neuroprotective outcomes. Martínez-Mármol et al. [16], a study mentioned previously in the in vitro findings, also provided animal evidence with mice fed with hericenone A and NDPIH extracted from *Hericium erinaceus*, demonstrating enhanced hippocampal memory and significant neurite outgrowth.

Three human trials were included in this review, providing preliminary evidence of cognitive and psychological benefits in healthy adults following supplementation with *Hericium erinaceus*; however, the clinical evidence remains limited compared with the extensive preclinical and in vitro findings. Saitsu et al. [36] conducted double-blind placebo-controlled trials with 30 adults for 12 weeks, supplementing them with a dose of 0.8 g of *Hericium erinaceus* fruiting body 4 times a day. The results from this trial showed improvement in MMSE cognitive scores compared with the placebo group. Docherty et al. (2023) administered 41 healthy adults, aged from 18 to 45, a dose of 1.8 g of *Hericium erinaceus* in a double-blind design daily for 28 days, with both acute effects assessed after the first dose and chronic effects assessed after 28 days. With just this single dose, the mushroom was able to improve speed on the Stroop task in 60 min, as well as showing a decrease in stress after 28 days of treatment. Lastly, Nagano et al. [37] conducted a trial with 30 women who were administered cookies containing *Hericium erinaceus* or a placebo for 4 weeks, reporting decreased depression and anxiety scores in the participants who received *Hericium erinaceus* rather than the placebo. However, there are limitations within the three human trials, as they were conducted in healthy populations rather than individuals with an existing neurodegenerative disease, which complicates the study and raises questions as to whether *Hericium erinaceus* would provide similar benefits in patients living with these conditions.

In the field of veterinary medicine, Çevik et al. [38] conducted a multimodal assessment of *Hericium erinaceus* and *Valeriana officinalis* in dogs exhibiting clinically relevant anxiety, administering 1000 mg per 10 kg body weight daily for four weeks. Using EEG recordings, neurochemical analysis and behavioural surveys, the study reported anxiolytic effects, providing novel evidence of the neurological effects of *Hericium erinaceus* in a non-rodent animal model. A subsequent study by Çevik et al. [39] further investigated the chronic metabolic consequences of anxiety in dogs following *Hericium erinaceus* supplementation, analysing hair trace element profiles in anxious dogs, with behavioural recovery following *Hericium erinaceus* administration is not fully reflected in hair mineral changes, suggesting complex neuro-endocrine interactions that warrant further investigation.

Antioxidant and Oxidative Stress Outcomes

Antioxidant defence represents one of the key mechanisms underlying the neuroprotective effects of *Hericium erinaceus*, with several studies providing quantifiable evidence of its ability to reduce oxidative stress markers and upregulate antioxidant enzyme activity. Ghosh et al. [33] tested ethanolic and methanolic extracts from the fruiting body of *Hericium erinaceus* using free radical scavenging assays. The ethanolic extract showed greater activity than the methanolic extract, with 76% DPPH and 81% ABTS radical scavenging activity. Qiao et al. [34] extracted an alkaline beta-glucan fraction from *Hericium erinaceus* fruiting body, which showed strong antioxidant activity across DPPH, ABTS, and hydroxyl radical scavenging assays, indicating the potential antioxidant benefits of polysaccharides derived from *Hericium erinaceus*. Lew et al. [28] subjected PC-12 cells to corticosterone-induced damage, mimicking a depression model using pretreatment with *Hericium erinaceus* at concentrations ranging from 0.25 mg/mL to 1 mg/mL, reporting a reduction in intracellular ROS from 128.52% to 91.07%, as well as restoring SOD activity to 99.97% in PC-12 cells that were previously damaged with corticosterone. Amara et al. [35] discovered that *Hericium erinaceus* at concentrations of 0.5 to 2 mg/mL helped to reduce ROS generation in PC-12 cells exposed to DEHP as well as stabilising mitochondrial membrane potential (MMP), protecting the cells from oxidative damage. Wu et al. [32] showed that erinacine A-enriched *Hericium erinaceus* reduced oxidative toxicity in SK-N-SH cells, as well as enhancing antioxidant capacity, confirming Nrf2 activation as an antioxidant mechanism.

Animal studies have consistently reported significant evidence of *Hericium erinaceus*' ability to provide antioxidant effects using a range of models, resulting in reduced oxidative stress markers and improvements in antioxidant enzyme activity. Hsu et al. [15] used *Hericium erinaceus* from the mycelium in a micronised form at a dose of 1 g/kg, resulting in a significant reduction in MDA and protein carbonyl levels in the brains of mice treated with MPTP, which is a neurotoxin that induces Parkinsonian-like neurodegeneration. Additional outcomes included the elevation of a range of antioxidant enzymes such as SOD, catalase, glutathione reductase, and G6PDH in a dose-dependent manner. Shirvani et al. [14] confirmed that a 300 mg/kg dose of *Hericium erinaceus* improved antioxidant capacity, as well as reduced lipid peroxidation. Lee et al. [22] observed that erinacine A-enriched *Hericium erinaceus* reduced thiobarbituric acid reactive substances (TBARS) depending on the dose administered, reducing oxidative stress mediated by nitric oxide. Another study from Lee et al. [21] reported that the use of erinacine C was capable of activating Nrf2 in rats in a traumatic brain injury model, as well as increasing SOD, catalase, and thioredoxin reductase. Roda et al. [23] supplemented aged mice with *Hericium erinaceus* and observed reduced oxidative stress markers, similarly to Roda et al. [24], which provided results of reduced oxidative and inflammatory stress, as well as a decrease in SOD1, Nrf2, and NOS2 levels in the hippocampus. Cordaro et al. [20] demonstrated that the administration of *Hericium erinaceus* to rats in an Alzheimer's model decreased oxidative stress, as well as preventing NLRP3 inflammasome activation. D'Amico et al. [19] revealed a reduction of neuroinflammation following the supplementation of *Hericium erinaceus* in mice with TBI, as well as decreased oxidative stress markers and restored dopaminergic function.

Whilst there were a few human trials that measured neuroprotective effects from *Hericium erinaceus*, none directly measured antioxidant biomarkers, such as SOD, MDA, or ROS. Nevertheless, the consistent improvements in cognitive function and memory across Docherty et al. [17], Nagano et al. [37], and Saitsu et al. [36] suggest that oxidative stress and additional antioxidant mechanisms may be indirectly involved in the clinical benefits listed in each study. Direct assessment of human studies, especially with respect to antioxidant markers, represents a significant gap in current literature and should be further investigated in future trials.

Table 2 and Figure 2 illustrate the antioxidant outcomes across the in vitro and animal studies included in this study. A 29% reduction in intracellular ROS levels was reported from 128.52% to 91.07% following the administration of *Hericium erinaceus* in PC-12 cells damaged with corticosterone, as well as the simultaneous restoration of SOD activity to 99.97% [28]. MDA levels and lipid peroxidation also showed decreases, while antioxidant enzyme activity showed dose-dependent increases, providing evidence for *Hericium erinaceus*' potential antioxidant effects in preclinical settings.

Table 2. Summary of the key antioxidant outcomes across the primary studies after the administration of *Hericium erinaceus*.

Study	Study Type	Outcomes	HE Results	Control Results
[33]	In vitro	DPPH radical scavenging activity	76%	N/A, no control group
[33]	In vitro	ABTS radical scavenging activity	81%	N/A, no control group
[28]	In vitro	Intracellular ROS	91.07%	128.52%
[28]	In vitro	SOD activity	99.97%	Significant reduction
[15]	Animal	MDA and protein carbonyl levels	Significant reduction	Elevation due to MPTP damage
[15]	Animal	SOD, catalase, G6PDH, glutathione reductase	Elevated based on dose given	Reduction due to MPTP damage
[14]	Animal	Lipid peroxidation	Reduced	Elevation
[21]	Animal	SOD and catalase through activation of Nrf2	Elevated	No significant elevation observed

HE—*Hericium erinaceus*; SOD—superoxide dismutase; MDA—malondialdehyde; G6PDH—glucose-6-phosphate dehydrogenase; ROS—reactive oxygen species; MPTP—1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DPPH—2,2-diphenyl-1-picrylhydrazyl; ABTS—2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); Nrf2—nuclear factor erythroid 2-related factor 2; N/A—not applicable (no control group used); percentage values for Ghosh et al. [33] represent radical scavenging activity measured directly, not relative to a control group.

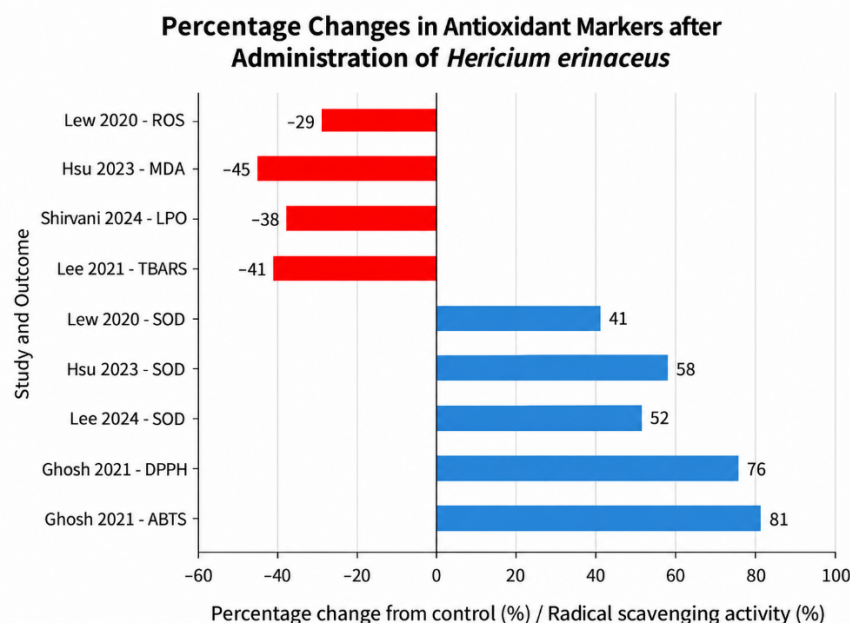


Figure 2. Bar chart illustrating percentage changes in antioxidant markers following the administration of *Hericum erinaceus*. The negative values indicate reductions in oxidative stress markers, and the positive values indicate increases in antioxidant enzyme capacity or radical scavenging activity. Values for Ghosh et al. [33] (DPPH: 76%; ABTS: 81%) represent direct radical scavenging activity rather than percentage change from control, no control group was used.

3.3. Exploratory Quantitative Synthesis and Narrative Synthesis

An exploratory quantitative synthesis was conducted using numerical data from Lew et al. [28] as an illustrative analysis only and should not be interpreted as a formal meta-analysis. The two outcomes examined were apoptosis in PC-12 cells and intracellular ROS levels under corticosterone-induced oxidative stress, as illustrated in Figure 3 and summarised in Table 3.

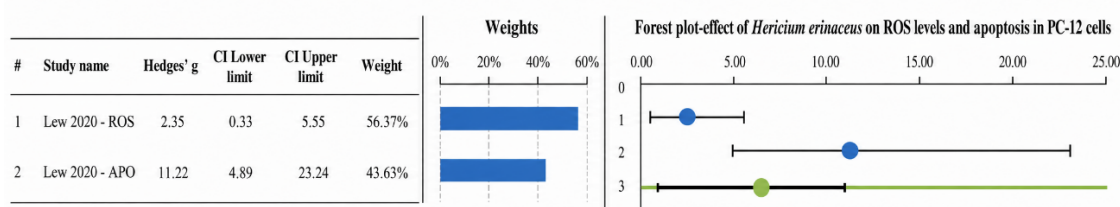


Figure 3. Forest plot showing the effect of *Hericum erinaceus* treatment on apoptosis and intracellular ROS levels in PC-12 cells exposed to corticosterone-induced oxidative stress, using a random-effects model with Hedges' g as the effect size measure [28].

A random-effects model was used with Hedges' g as the effect size measure, as illustrated in Figure 3. The Hedges' g for ROS levels under oxidative stress was 2.35 (95% CI: 0.33–5.55), contributing 56.37% of the weight to the pooled estimate, indicating a reduction in oxidative damage after treatment with *Hericum erinaceus*. However, this result should be interpreted cautiously due to the small sample size. Apoptosis demonstrated a larger effect size, with a Hedges' g of 11.22 (95% CI: 4.89–23.24), and contributed 43.63% of the weight to the pooled estimate, together with the results from ROS levels, reflecting a substantial decrease in cell death. The total pooled Hedges' g was 6.22, suggesting a large protective effect of *Hericum erinaceus*, although it did not reach statistical significance ($p = 0.158$), most likely due to the sample size of $N = 3$ per group and the high heterogeneity between the two outcomes ($I^2 = 85.02\%$). Despite the lack of statistical significance and small sample size, the effect sizes of each outcome suggest potential protective effects of *Hericum erinaceus* against oxidative stress and damage.

Conducting a full meta-analysis across all 23 primary studies was not feasible due to significant methodological heterogeneity. The study designs varied across in vitro models, animal models of Alzheimer's disease, TBI, and Parkinson's disease, as well as human trials. The forms and doses of *Hericium erinaceus* also varied, with some studies using aqueous extracts, recently discovered isolated bioactive compounds, micronised powders, and food-based items and supplements containing *Hericium erinaceus*. Additionally, the numerical outcome data in most studies were presented graphically rather than as extractable mean and standard deviation values. Despite this heterogeneity and limited quantitative synthesis, the findings across the included studies were generally consistent, showing *Hericium erinaceus* to demonstrate neuroprotective and antioxidant effects across models of oxidative stress and neurodegeneration. Future research should use standardised *Hericium erinaceus* preparations and doses, as well as report numerical outcome data in an extractable format to facilitate quantitative synthesis and address current gaps in the literature.

Table 3. Summary of the combined effect size and heterogeneity statistics derived from the numerical data reported by Lew et al. [28], which were used to generate the forest plot shown in Figure 3. $I^2 = 85.02\%$, pooled Hedges' $g = 6.22$, and $p = 0.158$.

Meta-Analysis Model	
Model	Random Effects Model
Effect Size Measure	Hedges' g
Confidence level	95%
Presentation	
Sort By	Entry
Order	Ascending
Combined Effect Size	
Hedges' g	6.22
Standard error	4.40
CI Lower limit	-49.72
CI Upper limit	62.16
PI Lower limit	-86.18
PI Upper limit	98.62
Z-value	1.41
One-tailed p -value	0.079
Two-tailed p -value	0.158
Number of incl. subjects	12
Number of incl. outcomes	2
Heterogeneity	
Q	6.67
p_Q	0.010
I^2	85.02%
T^2	33.50
T	5.79

3.4. Safety Profile

As gathered from all three human trials in this review, *Hericium erinaceus* was consistently shown to be safe for administration and well-tolerated by the participants studied. Following 12 weeks, 28 days, and 4 weeks of *Hericium erinaceus* supplementation, respectively, Saitsu et al. [36], Docherty et al. [17], and Nagano et al. [37] each reported no adverse effects, suggesting the mushroom's safe use. An additional study from Muhanna et al. [40] notes that *Hericium erinaceus* seems to be safe for consumption in humans but reported a case of anaphylaxis after the mushroom was taken in its fresh form, suggesting that processed preparations should be used for future research as well as for long-term use. The absence of serious side effects across these primary clinical trials is consistent with a favourable short-term safety profile of *Hericium erinaceus* but still calls for supplementary and longer-term data to fully establish its safety in patients with diagnosed neurodegenerative diseases.

In addition to the absence of adverse effects reported in the clinical trials, several safety considerations warrant attention. Allergic reactions to *Hericium erinaceus* have been documented, including a case of anaphylaxis following consumption of the fresh mushroom, suggesting that processed or standardised preparations may be safer for clinical use [40]. Potential drug interactions have not been systematically investigated, and caution is advised in individuals taking anticoagulant, antidiabetic, or immunosuppressant medications, given the immunomodulatory and bioactive properties of *Hericium erinaceus*. Furthermore, considerable variability exists in the composition and quality of commercially available *Hericium erinaceus* supplements, with differences in preparation method, bioactive compound concentration, and standardisation potentially affecting both efficacy and

safety. Consumers and clinicians should therefore exercise caution when selecting commercial preparations until standardised formulations with established safety profiles become available.

4. Discussion

4.1. Summary of Findings

This systematic review gathered evidence and numerical data from 23 primary studies, of which 12 were animal studies, 8 in vitro studies, and 3 human clinical trials published between 2010 and 2024. The overall findings consistently support the hypothesis that *Hericium erinaceus* possesses neuroprotective and antioxidant properties. The strongest evidence was derived from preclinical studies, whereas clinical evidence remains limited.

It is important to note that the evidence included in this review represents fundamentally different levels of scientific evidence. In vitro studies provide mechanistic insight into how *Hericium erinaceus* interacts with neuronal cells at a molecular level but cannot account for the complexity of the human brain or systemic factors. Animal studies provide proof-of-concept evidence in living organisms but are subject to significant translational limitations when extrapolating findings to humans, particularly given the pharmacological models used to induce disease states. Human clinical trials represent the highest level of evidence for clinical applicability; however, the three trials included in this review were conducted exclusively in healthy adults, limiting their direct relevance to patients with neurodegenerative diseases. These distinctions should be kept in mind when interpreting the findings presented in this review.

The limited meta-analysis identified large effect sizes for both oxidative stress and apoptosis-related outcomes, with Hedges' *g* values of 2.35 for intracellular ROS and 11.22 for apoptosis. The pooled Hedges' *g* was 6.22, suggesting a potentially substantial biological effect. However, the pooled estimate did not reach statistical significance ($p = 0.158$) and should be interpreted cautiously because it was derived from a single study with a very small sample size ($n = 3$ per group) and substantial heterogeneity ($I^2 = 85.02\%$).

Despite significant methodological heterogeneity across the included studies, the direction of findings was remarkably consistent, supporting the potential of *Hericium erinaceus* as a promising candidate for neuroprotection and oxidative stress reduction. Nevertheless, the limited number of human studies, the absence of trials in patients with neurodegenerative diseases, and the lack of standardisation in mushroom preparations and outcome measures currently prevent definitive clinical conclusions from being drawn. Future research should prioritise well-designed randomised controlled trials using standardised *Hericium erinaceus* preparations and clinically relevant neurological populations.

4.2. Neuroprotective Mechanisms

4.2.1. Neurotrophic Mechanisms: NGF, BDNF and Neurite Outgrowth

One of the most consistently reported neuroprotective mechanisms of *Hericium erinaceus* was its ability to modulate neurotrophic signalling pathways, particularly those involving nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurite outgrowth. These neurotrophic factors are essential for neuronal survival, differentiation, synaptic plasticity and repair, all of which are impaired during the progression of neurodegenerative diseases.

Across the included studies, several bioactive compounds, particularly hericenones from the fruiting body and erinacines from the mycelium, were associated with increased NGF and BDNF activity. This distinction is of considerable importance because the two preparations may exert their effects through different biological pathways. Hericenones have been reported to stimulate NGF synthesis, whereas erinacines appear capable of crossing the blood–brain barrier and influencing neurotrophic signalling directly within the central nervous system. Despite this potentially important difference, few studies clearly distinguished between fruiting body and mycelial preparations, highlighting a major limitation of the current evidence base and the need for greater standardisation in future studies.

Several in vitro studies support the neurotrophic potential of *Hericium erinaceus*. Zhang et al. [29] isolated hericenone K from the fruiting body and demonstrated enhanced neurite outgrowth alongside NGF stimulation in PC-12 cells. Supporting evidence from Lai et al. [41] further confirmed that aqueous extracts of *Hericium erinaceus* stimulated NGF release in NG108-15 cells. Tamrakar et al. [30] additionally indicated that deacylhericenone, a lipase-treated derivative of hericenone C, produced greater BDNF mRNA expression than the parent compound in human astrocytoma cells, suggesting that structural modification of mushroom-derived compounds may further enhance neurotrophic activity.

Animal studies provided additional support for these findings. Tsai et al. [26] reported increased hippocampal NGF expression and improved cognitive performance in ageing mice following supplementation with erinacine A-enriched *Hericium erinaceus*. Martínez-Mármol et al. [16] further identified hericenone A and NDPIH as novel compounds capable of promoting neurite outgrowth and improving memory performance. Interestingly, these compounds appeared to act through the ERK1/2 pathway rather than the classical TrkB pathway, suggesting that *Hericium erinaceus* may promote neuronal repair through multiple signalling mechanisms. This observation may be particularly relevant in neurodegenerative conditions where conventional neurotrophic signalling pathways become impaired.

A further important mechanism identified across several studies was activation of the Nrf2 pathway. Lee et al. [21] and Wu et al. [32] demonstrated Nrf2 activation in traumatic brain injury, neuroblastoma cell and *Drosophila* models, respectively. Importantly, Wu et al. [32] showed that silencing Nrf2 abolished the neuroprotective effects of *Hericium erinaceus*, providing stronger mechanistic evidence than simple association studies. Similarly, Alsoufi et al. [42] reported that polysaccharide-mediated neuroprotection was highly dependent upon Nrf2 activation. These findings suggest that Nrf2 may represent a central regulatory pathway linking neuroprotection and antioxidant defence, thereby providing a common biological explanation for many of the observed benefits of *Hericium erinaceus*. However, the specific compounds responsible for Nrf2 activation varied across studies, with erinacine-enriched preparations most frequently implicated in animal models and polysaccharide-rich extracts appearing more relevant in cell-based studies. Further research is therefore required to determine whether different bioactive components converge on the same signalling pathway or exert distinct biological effects.

Despite the consistency of the preclinical findings, translation to human populations remains uncertain. The three clinical trials included in this review reported improvements in cognition, mood and psychological well-being; however, none directly measured NGF, BDNF, neurite-related biomarkers or Nrf2 activity. Consequently, although the neurotrophic and neuroprotective effects of *Hericium erinaceus* are biologically plausible and strongly supported by experimental evidence, direct confirmation of these mechanisms in humans is currently lacking. Future clinical studies should therefore incorporate validated neurotrophic and molecular biomarkers to establish whether the mechanistic findings observed in experimental models translate into clinically meaningful outcomes (Figure 4).

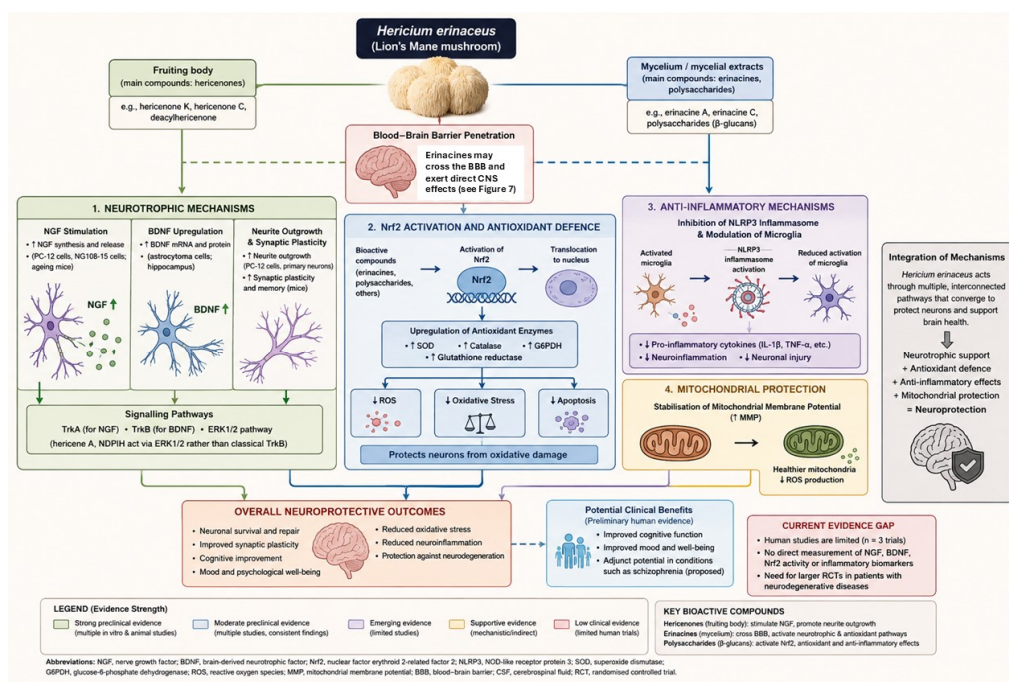


Figure 4. Integrated neuroprotective mechanisms of *Heridium erinaceus*.

Heridium erinaceus may support brain health through several linked mechanisms. Hericenones from the fruiting body may stimulate NGF production and neurite outgrowth, while erinacines from the mycelium may cross the blood–brain barrier and enhance neurotrophic signalling. Polysaccharides and other bioactive compounds may activate Nrf2, increase antioxidant enzymes, reduce ROS and oxidative stress, suppress NLRP3-related inflammation, and protect mitochondrial function. Together, these pathways may promote neuronal survival, synaptic plasticity and cognitive function. Evidence is mainly from in vitro and animal studies, with limited human

confirmation. Abbreviations: NGF—nerve growth factor; BDNF—brain-derived neurotrophic factor; Nrf2—nuclear factor erythroid 2-related factor 2; NLRP3—NOD-like receptor protein 3 inflammasome; ROS—reactive oxygen species; SOD—superoxide dismutase; G6PDH—glucose-6-phosphate dehydrogenase; BBB—blood–brain barrier; MMP—mitochondrial membrane potential; CNS—central nervous system. Note: This figure represents a proposed mechanistic pathway synthesised from current preclinical evidence and should not be interpreted as an experimentally validated integrated pathway.

4.2.2. Anti-Inflammatory Mechanisms: NLRP3 and Microglial Activation

The anti-inflammatory effects of *Hericium erinaceus* may represent another important mechanism contributing to its neuroprotective potential. Neuroinflammation is increasingly recognised as a central contributor to the progression of neurodegenerative diseases, particularly through activation of microglia and inflammatory signalling pathways such as the NLRP3 inflammasome. Persistent microglial activation promotes the release of pro-inflammatory mediators, oxidative stress and neuronal injury, thereby accelerating neurodegeneration.

Several studies included in this review reported that *Hericium erinaceus* attenuated inflammatory responses in experimental models. Cordaro et al. [20] demonstrated suppression of NLRP3 inflammasome activation in an Alzheimer's disease model, alongside reductions in beta-amyloid accumulation, phosphorylated tau and oxidative stress. This finding is particularly important because NLRP3 activation is increasingly recognised as a key driver of neuroinflammation and disease progression in Alzheimer's disease. Similarly, Lee et al. [21] reported reduced microglial activation in a traumatic brain injury model following treatment with *Hericium erinaceus* and erinacine C, while Roda et al. [24] observed reduced hippocampal inflammation in aged mice treated with an ergothioneine-rich extract. D'Amico et al. [19] further reported reduced neuroinflammation and improved neurological outcomes following supplementation in a traumatic brain injury model.

Collectively, these findings suggest that *Hericium erinaceus* may attenuate neuroinflammation through modulation of both NLRP3 inflammasome activity and microglial responses. A review by Friedman [13] similarly highlighted the anti-inflammatory properties of *Hericium erinaceus* bioactive compounds, suggesting that their multi-target activity may offer advantages over conventional pharmaceutical approaches that typically focus on a single pathway. However, several important limitations remain. Evidence for NLRP3 suppression was derived primarily from a single study, and the specific bioactive compounds responsible for this effect were not isolated or identified. Furthermore, the available evidence is almost exclusively derived from animal models, while none of the human studies directly assessed inflammatory biomarkers.

Consequently, although the anti-inflammatory properties of *Hericium erinaceus* appear biologically plausible and potentially important for neuroprotection, further mechanistic studies are required before definitive conclusions regarding therapeutic relevance can be drawn. Future clinical studies should incorporate inflammatory biomarkers such as NLRP3, interleukin-1 beta, tumour necrosis factor alpha, and microglial-related neuroimaging outcomes to determine whether these mechanisms translate to human populations.

4.2.3. Blood–Brain Barrier Penetration

Blood–brain barrier (BBB) penetration is an important consideration when evaluating the neuroprotective potential of *Hericium erinaceus*, as bioactive compounds must reach the central nervous system to exert direct neuronal effects. Among the included studies, Tsai et al. [26] reported that erinacine A was detected in rat brain tissue within one hour following oral administration, with an absolute bioavailability of 24.39%. Chen et al. [27] further supported these findings in a Landrace pig model, where erinacine A was detected in cerebrospinal fluid within 15 min of administration.

These pharmacokinetic findings provide important biological support for the neuroprotective potential of erinacine-enriched mycelial preparations. Unlike many natural products that demonstrate beneficial effects in vitro but fail to reach the brain in vivo, the detection of erinacine A in brain tissue and cerebrospinal fluid suggests that at least some *Hericium erinaceus*-derived compounds can access the central nervous system directly. This may partly explain the cognitive, neurotrophic and neuroprotective effects reported across multiple experimental models.

Additional support for direct neuronal actions comes from Martínez-Mármol et al. [16], who identified two novel compounds, hericine A and NDPIH, capable of promoting neurite outgrowth and improving memory performance. Interestingly, these compounds appeared to act through the ERK1/2 signalling pathway rather than the classical TrkB pathway, suggesting alternative routes through which neuronal repair and regeneration may occur. Such findings may be particularly relevant in neurodegenerative diseases where conventional neurotrophic signalling pathways become impaired.

Despite these promising findings, several limitations should be acknowledged. Evidence for BBB penetration currently remains restricted to erinacine A and a limited number of experimental models. It remains unclear whether other important bioactive compounds, including hericenones, polysaccharides and phenolic compounds, are capable of crossing the BBB or whether they exert their effects indirectly through gut–brain, immune or metabolic pathways. Furthermore, pharmacokinetic findings obtained from rodents and pigs cannot be directly extrapolated to humans. To date, no studies have provided evidence suggesting BBB penetration of erinacine A or other *Hericium erinaceus* compounds in human subjects, representing a significant gap in current knowledge. Future clinical studies should therefore investigate the pharmacokinetics, bioavailability and brain distribution of major *Hericium erinaceus* bioactive compounds in humans. The proposed BBB penetration and anti-inflammatory mechanisms are illustrated in Figure 5.

4.2.4. Antioxidant Defence Mechanisms

Despite the strong and consistent antioxidant evidence observed in preclinical studies, important limitations remain. None of the human trials included in this review directly measured antioxidant biomarkers such as ROS, MDA, SOD, catalase or glutathione-related enzymes. Consequently, it remains unclear whether the antioxidant mechanisms observed in experimental models translate directly to humans. Although improvements in cognition, mood and psychological well-being reported in clinical studies may partly reflect reduced oxidative stress, these outcomes were not accompanied by biochemical measurements capable of confirming this relationship. Baker and Newman [43] similarly noted the close association between the neurological and antioxidant properties of *Hericium erinaceus*. Therefore, future clinical trials should incorporate validated oxidative stress biomarkers alongside cognitive and neurological outcomes to establish whether antioxidant mechanisms contribute directly to the clinical benefits observed in humans.

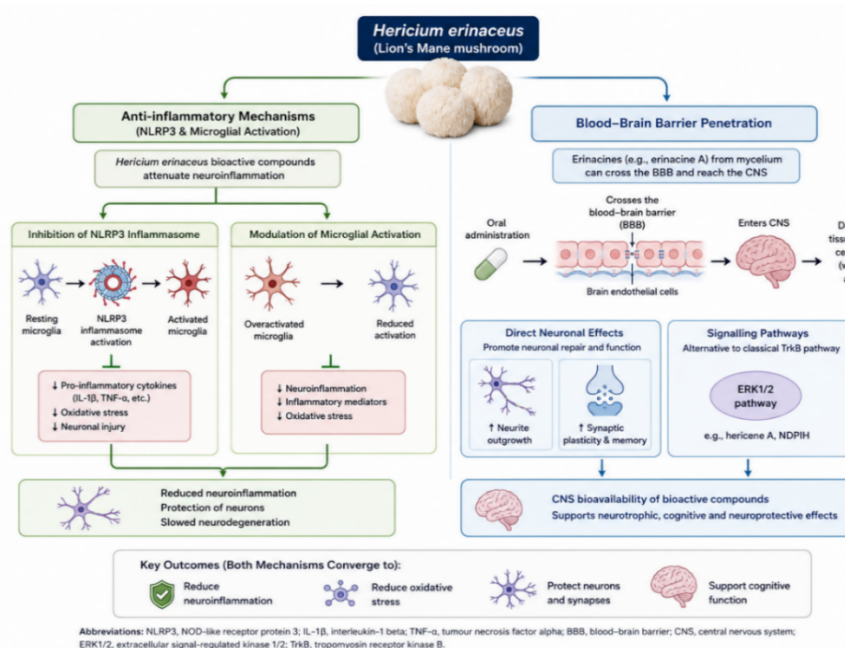


Figure 5. Blood–brain barrier penetration and anti-inflammatory mechanisms of *Hericium erinaceus*. *Hericium erinaceus* bioactive compounds, particularly erinacines, hericenones and polysaccharides, may exert neuroprotective effects through suppression of neuroinflammation and direct actions within the central nervous system. Anti-inflammatory mechanisms include inhibition of NLRP3 inflammasome activation, modulation of microglial activity, and reduction of pro-inflammatory cytokines and oxidative stress. Erinacine A has been shown to cross the blood–brain barrier in animal models, allowing direct interaction with neuronal signalling pathways. These mechanisms collectively contribute to reduced neuroinflammation, enhanced neuronal survival, neurite outgrowth, synaptic plasticity and cognitive function. Abbreviations: NLRP3, NOD-like receptor protein 3; IL-1β, interleukin-1 beta; TNF-α, tumour necrosis factor alpha; BBB, blood–brain barrier; CNS, central nervous system; ERK1/2, extracellular signal-regulated kinase 1/2; TrkB, tropomyosin receptor kinase B; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor. Note: This figure represents a proposed mechanistic pathway synthesised from current preclinical evidence and should not be interpreted as an experimentally validated integrated pathway.

4.3. Limitations

Despite the consistency across the included studies, there are several methodological limitations that must be mentioned when studying the evidence. The considerable methodological heterogeneity across the 23 primary studies includes a wide difference in models, doses and forms, as well as outcome measures. A majority of the animal studies used models induced with a variety of pharmacological agents, such as MPTP for Parkinson's and scopolamine for Alzheimer's, and whilst results were deemed to be beneficial, they are not comparable, nor do they replicate the disease in humans. Additionally, animal studies primarily used male rodents, limiting the applicability of the findings to female populations. In vitro studies used cells grown in a controlled lab environment, such as PC-12 cells, which do not reflect the intricacy of the human brain. There was also a wide variation in the way *Hericium erinaceus* was prepared for each experiment, including aqueous, mycelium and fruiting body-isolated compounds and ethanolic extracts, causing difficulty when attempting to directly compare the doses. This lack of standardisation also makes it difficult to attribute specific mechanisms, such as Nrf2 activation of NGF stimulation, to particular bioactive compounds, as discussed in the preceding sections. Notably, Lai et al. [41] reported that *Hericium erinaceus* was not able to protect NG108-15 cells against oxidative stress, suggesting that the antioxidant effects may depend on the way the preparation is made rather than the mushroom itself. The numerical data were also only presented in graphs, which limited the meta-analysis to one study and a completion of a narrative synthesis for the additional outcomes. Furthermore, the animal studies were all held for short durations from 2 to 18 weeks, which do not reflect the long-term effects of *Hericium erinaceus*. Lastly, a majority of studies when researching on databases focus on Alzheimer's and Parkinson's models, neglecting other neurodegenerative diseases, such as ALS, which have no animal, in vitro, or human trials in the current literature to date (3).

Furthermore, the clinical evidence of *Hericium erinaceus* remains limited due to the inclusion of only three human trials in this review. Each of these trials used participants from healthy populations, complicating the results as none of the participants had a pre-existing neurodegenerative disease. The sample sizes of these trials were notably small, recruiting about 30 to 41 individuals, as well as being held in short durations of 4 weeks to 12 weeks, limiting the statistical significance and preventing an assessment of *Hericium erinaceus*' long-term effects. Whilst the trials reported significant neuroprotective properties from their experiments, none of them measured any antioxidant enzyme biomarkers. It is also important to consider the possibility of publication bias, in which articles that provide positive results are more likely to get published. Finally, the meta-analysis was limited to one study by Lew et al. [28] due to a majority of articles presenting their data graphically, rather than in extractable numerical forms. Furthermore, the literature search was restricted to PubMed and Google Scholar. Major biomedical databases including Scopus, Web of Science, and Embase were not searched, which may have resulted in the omission of relevant studies. This represents a significant methodological limitation, as a more comprehensive search strategy across multiple databases would be expected in a full systematic review intended for publication. The findings should therefore be interpreted with this limitation in mind.

Assessment of publication bias using funnel plots or statistical tests was not performed because the number of studies included in the quantitative synthesis was insufficient to provide a reliable evaluation. However, publication bias remains an important consideration in this review. The nutraceutical literature is particularly susceptible to positive publication bias, whereby studies reporting significant or beneficial effects of *Hericium erinaceus* are more likely to be published than those reporting null or negative findings. This may have resulted in an overestimation of the beneficial effects observed across the included studies. Furthermore, the restriction of the search to English-language publications may have excluded relevant studies published in other languages, particularly given the significant body of research on *Hericium erinaceus* originating from East Asian countries. These factors should be considered when interpreting the overall findings of this review.

A further important limitation is the substantial variability in *Hericium erinaceus* preparations used across the included studies. The interventions ranged from whole fruiting body extracts, mycelial preparations, aqueous and ethanolic extracts, and micronised powders to isolated bioactive compounds such as erinacine A, erinacine C, erinacine S, hericenone C, hericenone A, and beta-glucan fractions. These preparations are unlikely to be biologically equivalent, as their bioactive compound profiles, concentrations, and bioavailability may differ substantially. Table 4 summarises the preparation types used across the included primary studies.

A further translational limitation concerns the wide range of doses used across the animal studies included in this review, which ranged from 50 mg/kg to 1000 mg/kg. No attempt was made within the included studies to calculate or discuss human equivalent doses (HED) based on body surface area conversion, which is the standard method recommended for translating animal doses to human clinical contexts. Without this conversion, it is difficult to assess whether the doses used in animal studies are clinically achievable or relevant in humans. Future

studies should report human equivalent doses to improve the translational relevance of their findings and to support the design of appropriate human clinical trials.

Table 4. Classification of primary studies according to *Hericium erinaceus* preparation type.

Preparation Type	Studies
Aqueous extract	Lew et al. [28], Amara et al. [35]
Ethanol/methanol extract	Ghosh et al. [33], Shirvani et al. [14]
Mycelial preparation	Hsu et al. [15], Lee et al. [22], Lee et al. [21], Tsai et al. [26]
Micronised powder	Hsu et al. [15]
Isolated erinacines	Tsai et al. [26], Chen et al. [27], Lin et al. [31], Wu et al. [32]
Isolated hericenones	Zhang et al. [29], Tamrakar et al. [30], Martínez-Mármol et al. [16]
Beta-glucan fraction	Qiao et al. [34]
Food-based supplement	Saito et al. [36], Docherty et al. [17], Nagano et al. [37]
HE with standard diet/model (no active co-treatment)	D'Amico et al. [19], Cordaro et al. [20], Roda et al. [23], Roda et al. [24]

4.4. Clinical Implications and Future Research

Despite the limitations discussed above, the preclinical evidence gathered in this review suggests that *Hericium erinaceus* shows promising but as yet unconfirmed potential as a neuroprotective and antioxidant intervention, and clinical efficacy in patients with neurodegenerative diseases remains to be established. The proposed mechanistic pathways linking *Hericium erinaceus* bioactive compounds to neuroprotective outcomes are summarised in Figure 6.

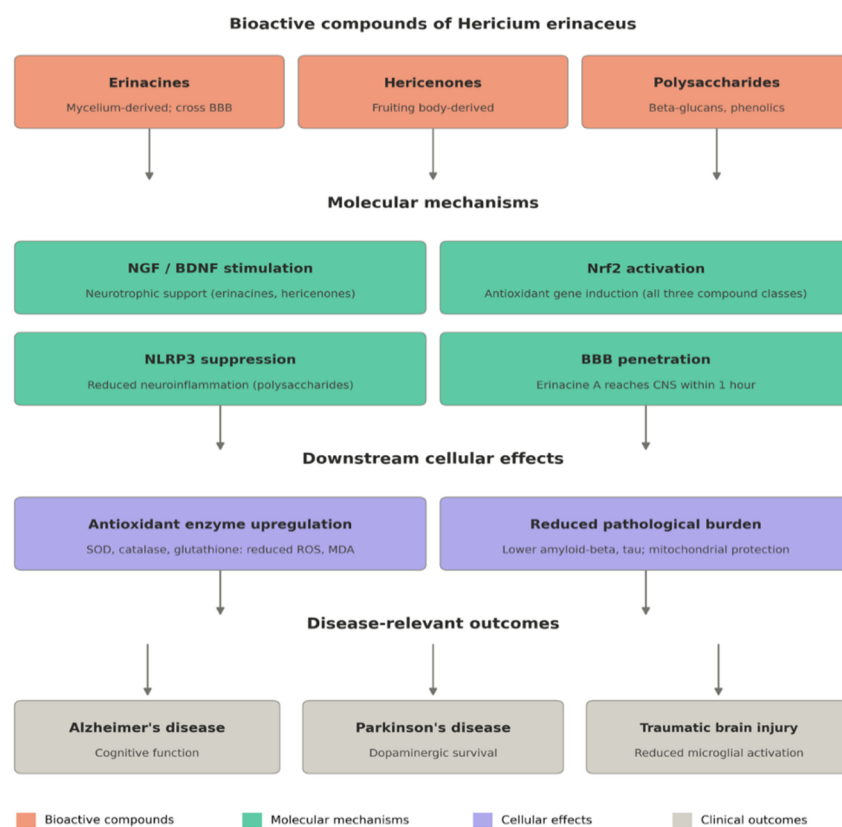


Figure 6. Proposed mechanistic pathways linking *Hericium erinaceus* bioactive compounds to neuroprotective and antioxidant outcomes. Erinacines (mycelium-derived) cross the blood-brain barrier and contribute to NGF/BDNF stimulation and BBB penetration, whilst hericenones (fruiting body-derived) also support NGF/BDNF stimulation, and polysaccharides (beta-glucans, phenolics) contribute to Nrf2 activation and NLRP3 suppression. These mechanisms converge on antioxidant enzyme upregulation and reduce pathological burden, with relevance to Alzheimer's disease, Parkinson's disease, and traumatic brain injury. Clinical outcomes reflect preclinical evidence and have not yet been confirmed in human trials. Note: This figure represents a proposed mechanistic pathway synthesised from current preclinical evidence and should not be interpreted as an experimentally validated integrated pathway.

The consistency of findings across in vitro and animal studies supports its biological plausibility as a candidate for the prevention or management of neurodegenerative disorders. Across the included human studies, *Hericium erinaceus* was generally well tolerated, with no serious adverse effects reported, supporting a favourable short-term safety profile. Baker and Newman [43] have also proposed *Hericium erinaceus* as a potential adjunct to antipsychotic therapy in patients with schizophrenia due to its neuroprotective and antioxidant properties. Furthermore, Muhanna et al. [40] highlighted the need to investigate additional neurological disorders, including amyotrophic lateral sclerosis (ALS), where evidence remains limited despite plausible mechanistic benefits.

When conducting future research, larger-scale randomised controlled trials should be prioritised, particularly in individuals diagnosed with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and other conditions associated with oxidative stress and neuroinflammation. Future studies should also adopt standardised *Hericium erinaceus* preparations, clearly distinguish between fruiting body and mycelial extracts, and establish consistent dosing regimens to improve comparability across studies. In addition, trial duration should be sufficient to evaluate both efficacy and long-term safety outcomes.

A further priority is the incorporation of mechanistic biomarkers into clinical research. Direct assessment of oxidative stress biomarkers, including ROS, MDA, SOD, catalase and glutathione-related enzymes, would provide important evidence regarding whether the antioxidant effects observed in experimental models translate to humans. Similarly, biomarkers associated with neurotrophic signalling, neuroinflammation and neuronal injury should be incorporated where possible. Brandalise et al. [44] further emphasised the urgent need for high-quality clinical studies to bridge the gap between preclinical and human evidence. Only through well-designed clinical trials will it be possible to determine whether the promising neuroprotective and antioxidant effects of *Hericium erinaceus* observed in experimental studies can be translated into clinically meaningful benefits for patients.

It is also useful to contextualise the neuroprotective potential of *Hericium erinaceus* relative to other well-studied nutraceuticals. Curcumin, the active compound in turmeric, has suggested anti-inflammatory and antioxidant properties in preclinical models of Alzheimer's disease, though its poor bioavailability remains a significant limitation [45]. Resveratrol, found in red grapes, has shown neuroprotective effects through SIRT1 activation and reduction of amyloid-beta accumulation, but clinical evidence remains inconsistent [45]. Omega-3 fatty acids, particularly DHA, have demonstrated benefits for cognitive function and neuroinflammation reduction, with stronger clinical evidence than many other nutraceuticals [45]. Ginkgo biloba has been investigated for cognitive decline and dementia prevention, with some positive clinical trial data, though effect sizes have been modest [45]. Compared with these nutraceuticals, *Hericium erinaceus* offers a distinctive mechanistic profile through NGF and BDNF stimulation and confirmed blood-brain barrier penetration, which may represent a complementary or additive approach to neuroprotection. However, direct comparative clinical trials between *Hericium erinaceus* and these nutraceuticals are currently lacking and represent an important direction for future research.

5. Conclusions

This systematic review and limited meta-analysis evaluated 23 primary studies published between 2010 and 2024. Overall, *Hericium erinaceus* showed promising neuroprotective effects, predominantly in in vitro and animal studies, with current evidence insufficient to provide evidence suggesting clinical efficacy in patients with neurodegenerative diseases. Key mechanisms included activation of Nrf2 signalling, stimulation of NGF and BDNF, inhibition of NLRP3 inflammasome activity, mitochondrial protection, reduction of oxidative stress, and attenuation of neuronal apoptosis.

It should be explicitly acknowledged that the evidence base underpinning these conclusions is predominantly preclinical, derived from in vitro and animal studies, and that clinical evidence in patients with neurodegenerative diseases remains absent. The findings of this review should therefore be interpreted as hypothesis-generating rather than as definitive evidence of clinical efficacy.

However, human evidence remains limited to three small trials in healthy adults; therefore, clinical efficacy in patients with neurodegenerative diseases cannot yet be confirmed. Future studies should use standardised *Hericium erinaceus* preparations, clinically diagnosed populations, validated cognitive outcomes, and measurable biomarkers of oxidative stress, neuroinflammation, and neurotrophic signalling.

Author Contributions

M.G.N. conceived the review, performed the literature search, study screening, data extraction, and meta-analysis, and drafted the initial manuscript. S.Z. supervised the study, contributed to the study design and interpretation of the findings, and together with G.Z. reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest. Given the role as Editor, Guoqiang Zhang had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used Claude (Anthropic) to assist with manuscript editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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