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Overview on therapeutic application of lion's mane – (Hericium erinaceus) dealing with neuroprotection, neurogenerationand in other clinical settings.

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ABSTRACT
Hericium erinaceus, colloquially known as lion's mane, represents a fungal species deeply entrenched in the annals of Traditional Chinese Medicine and other ancient medical traditions of Asia. Renowned for its therapeutic properties, this mushroom harbors a complex profile of bioactive compounds, including β-glucan polysaccharides, hericenones, erinacine terpenoids, isoindolinones, sterols, and myconutrients. These constituents exhibit significant promise in fostering neuroprotective and neuroregenerative effects, marking lion's mane as a potent agent in neurological health. Owing to its capacity to modulate inflammatory responses and enhance the expression of nerve growth factor (NGF) genes while facilitating neurite outgrowth (comprising axons or dendrites), the mycelium of H. erinaceus emerges as a promising candidate for addressing conditions like Alzheimer's and Parkinson's diseases. Notably, in two clinical investigations, the administration of this fungus exhibited favorable tolerability profiles, with minimal occurrence of adverse events documented.
Keywords: Lion's mane; Neuroregeneration; Neurodegeneration; Neuroprotection; Neurotropins; Neurotrophic; Alzheimer's disease; Parkinson's disease; Nerve growth factor; immune-modulatory; anti-cancer; anti-dementia; Multiple Sclerosis (MS), Anxiety; Depression; Neuropathy; Menopausal Syndrome; MSRA(Methicillin-resistant Staphylococcus aureus) and Gastric Ulcers.

I. INTRODUCTION:

Anthropological observations provide compelling evidence of mushrooms being utilized as both sustenance and medicinal resources by early hunter-gatherer societies. Dating back approximately 4600 years, mushrooms earned the epithet "the plant of immortality" among ancient Egyptians, esteemed for their delectable qualities and favored even by royalty. The earliest documented account of mushrooms as a delicacy fit for royalty can be traced to the writings of the Greek philosopher Theophrastus, dating between 372 and 287 BC. Across diverse cultures spanning ancient Greece, Russia, China, Mexico, and Latin America, mushrooms have enjoyed widespread acceptance as a palatable and nutritious food source since antiquity. India's introduction to mushrooms occurred via the northwest route, traversing through Afghanistan, and making an entrance into the revered Indus Valley civilization.[1]

Throughout history, various cultures across the globe have recognized the nutritional and therapeutic benefits of mushrooms. Dating back to 450 BCE, the Greek physician Hippocrates acknowledged mushrooms for their anti-inflammatory properties and their efficacy in wound cauterization. In Eastern traditions, such as Chinese culture, mushrooms hold a special reverence. For instance, Ganoderma lucidum, known as ling zhi in Chinese, is referred to as the "spirit plant." It is believed to bestow longevity and enhance spiritual potency. These ancient beliefs and practices reflect the enduring significance of mushrooms in traditional medicine and cultural heritage worldwide.

Contemporary medicine has been comparatively sluggish in recognizing the vast potential of fungi. Notwithstanding Fleming's 1929 revelation of penicillin,[2]and the subsequent utilization of the fungal-derived compound as a blockbuster pharmaceutical in the 1940s,[3]In recent decades, the field of medical science has extended

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its focus beyond the antimicrobial and hypocholesterolemic attributes of fungi to explore additional prospective applications.

Healthcare practitioners now have expanded availability of mycelial extracts, prized for their cytotoxic, antineoplastic, cardiovascular, anti-inflammatory, and immune-modulating properties, which are applied in clinical settings.[4–6]Functional investigations and chemical analyses additionally substantiate their capacity to function as analgesic, antibacterial, antioxidative, and neuroprotective agents. Several fungal species, such as Sarcodon scabrosus, Ganoderma lucidum, Grifola frondosa, and Hericium erinaceus, have been documented to exhibit properties relevant to neural and cerebral (mental health) well-being.[7]Hericium erinaceus, belonging to the Herinaceae family, is a fungus renowned for its culinary and medicinal properties. Research indicates that both the mycelium and fruiting bodies of H. erinaceus harbor promising therapeutic attributes, particularly in promoting brain and nerve health.[8] The unique neurological activities of this fungus are the subject of this review.The term "mushroom" originated from the cultivation of the Agaricus bisporus, commonly known as the button mushroom. This species typically features a stipe (stem), a pileus (cap) with an umbrella-like shape, and lamellae (gills) located beneath the cap. The term "macrofungi" was initially introduced to describe Basidiomycota and Agaricomycota species characterized by distinct fruiting bodies, which may emerge either aboveground (epigeous) or belowground (hypogeous) and are readily observable without magnification.[9]

TRADITIONAL USE OF LION'S MANE (HERICIUM ERINACEUS).

Hericium erinaceus, commonly known as lion's mane, yamabushi take, or bearded tooth carpophore, is a fungus that typically thrives on decaying or aged broadleaf trees. It holds significance in various Asian cultures, where it serves dual purposes as a culinary delicacy and a traditional medicinal remedy. The fruiting body is called hóu tóu gū ("monkey head mushroom") in Chinese[10] and yamabushitake ("mountain monk mushroom") in Japanese. In traditional Chinese and Japanese medicine, Lion's Mane has long been prescribed for its purported efficacy in augmenting spleen function, enhancing gastrointestinal health, and exhibiting anticancer properties. Additionally, Lion's Mane is believed to possess nutritive attributes beneficial to the five major internal organs (liver, lung, spleen, heart, and kidney), fostering optimal digestive function, overall vitality, and physical robustness.

It is also recommended for gastric and duodenal ulcers, as well as chronic gastritis (in prepared tablet form).[12] The mushroom is also known for its effects on the central nervous system, and is used for insomnia, vacuity (weak ness), and hypodynamia, which are characteristic symptoms of Qi deficiency in Traditional Chinese medicine (TCM).

CHEMICAL COMPOSITION:

The bioactive metabolites derived from H. erinaceus encompass a spectrum of molecular entities, segregating into categories of both high and low molecular weight. Among these, high molecular weight compounds include polysaccharides, while low molecular weight compounds comprise polyketides and terpenoids.[13,14]

POLYSACCPOLYSACCHARIDES

Fungal polysaccharides are predominantly situated within the cellular matrices of fungal cell walls, exhibiting substantial abundance across both fruiting bodies and cultivated mycelial structures. Hericium erinaceus fruiting bodies (HEFB) contain immune-active β-glucan polysaccharides, as well as α-glucans and glucan-protein complexes.[15] A total of more than 35 H. erinaceus polysaccharides (HEP)consists various compounds have been isolated and extracted from cultivation, naturally occurring, or fermentatively grown mycelium, as well as from fresh or desiccated fruiting bodies. Of these β-glucans represent the main polysaccharides. HEP are composed of xylose (7.8%), ribose (2.7%), glucose (68.4%), arabinose (11.3%), galactose (2.5%), and mannose (5.2%).[4] Four different polysaccharides isolated from the H. erinaceus sporocarp show antitumor activity: xylans, glucoxylans, heteroxyloglucans, and galactoxyloglucans.[5] Chemical analysis shows that the total content of HEP found in fruiting bodies is higher than that in mycelium. Table 1 lists the polysaccharides along with their source and chemical composition.

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Table 1: Polysaccharides: source and composition.

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

Table 2: Sesterpenes and diterpenoids: source and composition.

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

Research on the polysaccharides extracted from H. erinaceus has unveiled various biological activities. Specifically, both extracellular and intracellular polysaccharides demonstrated hepatoprotective effects against oxidative damage in murine models. [14]The neuroprotective efficacy of HEPs was demonstrated in an in vitro cellular model characterized by toxicity induced by amyloid β plaque formation. In this model, HEPs exhibited a dose-dependent reduction in reactive oxygen species (ROS) production, decreasing it from 80% to 58%. Additionally, HEPs enhanced the capacity for free radical scavenging. Moreover, HEPs bolstered cell viability and conferred protection against apoptosis triggered by amyloid β plaque formation.[16]HEPs attenuated the levels of blood lactic acid, serum urea nitrogen, tissue glycogen, and malondialdehyde, providing additional evidence for the favorable impact of HEPs on oxidative stress.[17]

TERPENOIDS: SESTERPENES, AND DITERPENOIDS.

Terpenoids encompass a class of biologically derived hydrocarbons characterized by the presence of terpenes conjugated with an oxygen-functionalized moiety. Terpenoids constitute more than 60% of the compounds found in nature.[18,19]

A plethora of diterpenes and sesterterpenes are present in both the basidiocarp and fermenting mycelium of Hericium erinaceus.[20]Of particular pharmacological interest are two classes of terpenoid compounds thus far known to occur only in Hericium spp.: hericenones (C–H), a group of aromatic compounds separated from the fruiting body; and erinacines (A–I), a

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group of cyathane-type diterpenoids found in the mycelium.[21]Both groups of substances readily penetrate the blood-brain barrier, exhibiting neurotrophic properties and, in certain instances, demonstrating neuroprotective effects.[22]Erinacines (A–I) have demonstrated induction of nerve growth factor (NGF) synthesis.[23]Table -2 lists the terpenoids, sesterpenes, and diterpenoids along with their source and chemical composition.

STEROLS.

Ten erinarols, designated as erinarol A–J, five ergostane-type sterol fatty acid esters, and ten ergostane-type sterols have been characterized in the carpophore of H. erinaceus.[24]Sterols, such as ergosterol constitutes antioxidative properties.[24-25]Hericium erinaceus exhibits remarkable efficacy as an in vitro inhibitor of both low-density lipoprotein (LDL) oxidation and HMG Co-A reductase activity, indicating promising therapeutic prospects for mitigating oxidative stress-mediated vascular pathologies.[26]

NEUROLOGICAL ACTIVITY – a. NEUROPROTECTION.

Hericenones and erinacines derived from Hericium erinaceus have exhibited neuroprotective characteristics.[27]The mycelium of Hericium erinaceus (HEM), along with its isolated diterpenoid derivative, erinacine A, exhibited a reduction in infarction by 22% at 50 mg/kg and 44% at 300 mg/kg in an animal model of global ischemic stroke. This effect was postulated to be partly mediated by its capacity to diminish cytokine levels.[28]A purified polysaccharide extracted from the liquid culture broth of H. erinaceus mycelium (HEM) was discovered to exhibit neuroprotective properties in an in vitro model by significantly delaying apoptosis, with a potency 20%–50% greater than the control sample.

Furthermore, HEM demonstrated superior efficacy compared to control, nerve growth factor (NGF), or brain-derived neurotrophic factor (BDNF) alone in promoting the growth of rat adrenal nerve cells and facilitating neurite extension (axon or dendrite)[29]. Conversely, when tested in a model involving NG108-15 neuroblastoma cells exposed to oxidative stress induced by H_2 O_2, the aqueous extract of H. erinaceus showed no protective effect, unlike its purified polysaccharide counterpart[30]. While translating findings from in vitro studies to clinical relevance poses challenges, these results suggest that the neuroprotective effects may be contingent on a high concentration of a specific polysaccharide present in water extracts.

NEUROTROPHIC ACTIVITY AND MYELINATION.

An incorporation of an ethanol extract of HEFB resulted in NGF gene expression in human astrocytoma cells, in a concentration-dependent manner. Neurite outgrowth was also improved. The same investigators also observed that mice fed 5% HEFB dry powder for 7 days, showed an increase in the level of NGF mRNA expression in the hippocampus.[31]Another investigation demonstrated that an aqueous extract of Hericium erinaceus fruiting bodies (HEFB) augmented the secretion of extracellular nerve growth factor (NGF) and enhanced neurite outgrowth activity. Additionally, these scientists noted a synergistic interplay between the H. erinaceus aqueous extract and exogenous NGF, leading to the stimulation of neurite outgrowth in neuroblastoma-glioma cells at concentrations relevant to physiological conditions (1 μg/mL HEFB extract + 10 ng/mL NGF).[24]Formation of the myelin sheath in the presence of H. erinaceus extract exhibited accelerated progression, reaching completion by day 26, contrasting with day 31 in the control group. No adverse effects were noted from the administration of the extracts in this model. [32]

COGNITIVE PROCESSES.

In anassessment of behavioural patterns in wild-type mice, oral supplementation with H. erinaceus induced a statistically significant improvement in spatial short-term and visual recognition memory.[33] In a double-blind placebo-controlled clinical trial of 50–80-year-old Japanese adults (n=30) diagnosed with mild cognitive impairment, oral intake of H. erinaceus 250 mg tablets (96% dry powder) three times a day for 16 weeks was associated with marked improvement in the revised Hasegawa Dementia Scale (HDS-R) as compared to controls. Scores on the HDS-R decreased, however, by 4 weeks after cessation of the intervention.[31]

In a murine model of Alzheimer's disease, oral ingestion of HEFB augmented the expression of NGF mRNA in the hippocampus, mitigating deficits in spatial, short-term, and visual recognition memory induced by amyloid β plaques evident in untreated mice.[31]In a separate investigation employing a murine model of Alzheimer's disease characterized by the emergence of amyloid plaque deposits by the age

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of 6 months, a 30-day regimen of oral administration of HEM led to reduced plaque deposition within microglia and astrocytes located in the cerebral cortex and hippocampus.[34]In an animal model of Alzheimer's disease induced by aluminum chloride, HEM augmented serum and hypothalamic levels of acetylcholine and choline acetyltransferase in a manner contingent upon dosage.[35] Figure 1 illustrates the apparent mechanisms of action for the effects that H. erinaceus may have in Alzheimer's disease.

PARKINSON'S DISEASE.

The oral administration of low-dose (HEM) at doses of 10.76 or 21.52 mg/day, employed in an animal model of Parkinson's disease, resulted in notable amelioration of oxidative stress and dopaminergic lesions within the striatum and substantia nigra following a 25-day treatment regimen.[36]

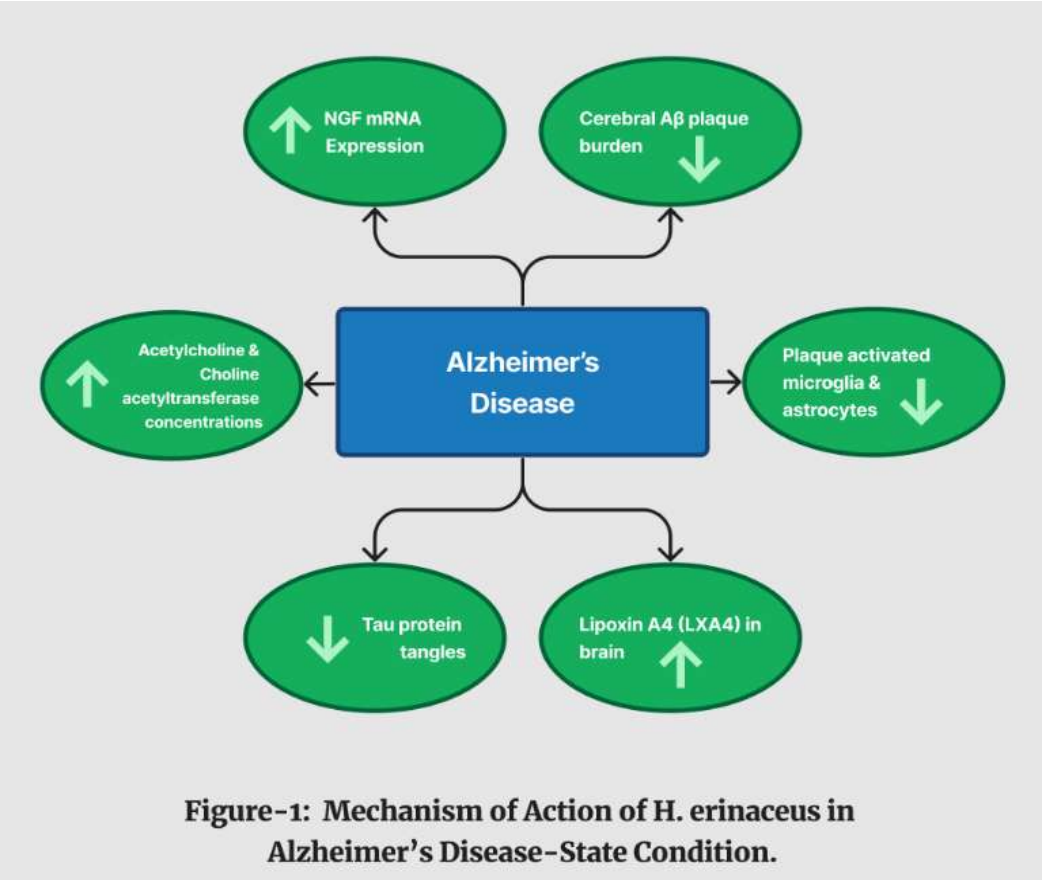

Figure-1: Mechanism of Action of H. erinaceus in Alzheimer's Disease-State Condition.

PERIPHERAL NERVE INJURY.

An aqueous extract of Hericium erinaceus fruiting bodies (HEFB), administered to animals at a dosage of 10 mL/kg for 14 days post-crush injury, demonstrated enhanced nerve regeneration and accelerated motor functional recovery. Compared to the control group, animals treated with HEFB exhibited recovery 4–7 days earlier, as evidenced by walking track analysis. Normal toe spreading, indicative of reinnervation, occurred 5–10 days sooner in the aqueous extract group. Through functional assessment and morphological analysis of regenerated nerves, ipsilateral dorsal root ganglia, and target extensor digitorum longus muscles, it was concluded that HEFB aqueous extract effectively facilitated peripheral nerve regeneration, leading to significant functional improvement. [36]

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Trial	Parameter Scale	Results	ADR	Dose	Citation
Double blind, Parallel-grp, placebo-controlled trial.	Mild Cognitive impairment/Revised Hasegawa Dementia Scale(HDS-R)	Significant improvement in cognitive function scale.	None	250 mg tid × 16 weeks	Mori et al., 2009 [31]
Randomized placebo - controlled trial	Anxiety & Depression/ Center for Epidemiologic Studies Depression Scale (CES-D) & Indefinite Complaints Index (ICI).	Significant Improvement in some anxiety and depression cases.	None	2 g/day × 4 weeks	Nagano et al., 2010 [35]

Table 3: Outcomes of clinical trials of Hericium erinaceus.

CLINICAL TRIALS.

As outlined in the section on Cognitive Function, a double-blind, placebo-controlled trial was conducted with a cohort of 50–80-year-old Japanese individuals (n=30) diagnosed with mild cognitive impairment. The study demonstrated significant enhancements in cognitive function, as assessed using the revised Hasegawa Dementia Scale (HDS-R), compared to the control group, subsequent to the administration of H. erinaceus 250 mg tablets (96% dry powder) orally thrice daily over a span of 16 weeks. Notably, HDS-R scores declined four weeks post-intervention cessation.[31]

In a separate clinical trial, the ingestion of 2.0 g/day of HericiumerinaceusFruiting Body(HEFB), incorporated into food recipes like cookies, for a duration of 4 weeks exhibited ameliorative effects on select symptoms of anxiety and depression among menopausal women (n=30). Notably, individuals consuming HEFB demonstrated statistically significant enhancements in the Indefinite Complaints Index categories related to Palpitation and Incentive compared to those receiving a placebo. Moreover, there was a discernible tendency towards improvement in the categories of Irritation, Anxiety, and Concentration among participants receiving HEFB relative to the placebo group. [35] Table 3 summarizes the two clinical trials reported on in this paper.

DRUG DOSING. COGNITION AND NGF (Nerve Growth Factor) PRODUCTION.

The optimal dosage of dried fruiting body from H. erinaceus to enhance NGF production ranges from 3 to 5 grams daily. [37]Subjects with mild cognitive impairment exhibited significant improvement on a dementia rating scale after being administered 250 mg tablets of Hericium erinaceus (comprising 96% dry powder) three times daily for a duration of 16 weeks. [31]The dosage administered in the clinical trial involving menopausal women, which demonstrated a decrease in depressive and anxious symptoms, was 2.0 grams per day of Hericiumerinaceusfruiting body extract (HEFB) incorporated into food (cookies) over a span of 4 weeks. [35]

TOXICOLOGICAL STUDIES.

In an in vitro model, the aqueous extract of HEFB exhibited significant non-cytotoxic properties[33]. Toxicological investigations on H. erinaceus in rodent models indicate that mycelia containing 5 mg/g of erinacine A, administered at doses of up to 5 g/kg body weight per day, demonstrate safety. No adverse events were observed in the two clinical trials referenced herein. [31,35]

REPORTED ADVERSE EVENTS.

No adverse clinical or biochemical events were reported in the clinical trial of subjects with mild cognitive impairment.(31) In the study of menopausal women, one subject reported epi menorrhea (18 days menorrhea/month). However, whether or not supplementation with H. erinaceus was the cause of the epimenorrhea is undetermined.[35]Allergic reactions and hypersensitivities to mushrooms are not uncommon. In one case study, a 63-year-old male experienced acute respiratory failure and lymphocytosis in his lungs. The individual had been regularly consuming an extract of dried H. erinaceus at standard doses for four months, leading researchers to consider a probable connection between the two events. In another case report, a 53-year-old male exposed to H. erinaceus fruiting bodies occupationally developed chronic

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dermatitis on his hands, characterized by painful fissures within one month of exposure. The dermatitis later spread to his forearms, face, and legs. Upon discontinuation of exposure to H. erinaceus fruiting bodies, the symptoms resolved. Patch tests using the European standard series yielded negative results, while testing positive for H. erinaceus fruiting bodies. Sensitization was confirmed through a highly positive repeated open application test (ROAT) using an aqueous emulsion of H. erinaceus fruiting bodies. Notably, patch and prick tests for other common culinary mushrooms were negative, proposing a lack of cross-sensitivity.

Therapeutic applications in other specific disease-state conditions. Hericium erinaceus:

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Japanese Name: Yamabushitake
Chinese Name: Hou Tou Gu (Monkey Head Mushroom)
English Name: Lion's Mane Mushroom/Hedgehog Mushroom.

This delicious mushroom has been referred to as 'Nature's Nutrient for the Neurons' on account of its ability to stimulate the production of nerve growth factor (NGF).[38,39]

NGF (Nerve Growth Factor) exerts pivotal influence on the differentiation and viability of various cell cohorts within the central and peripheral nervous systems. Suboptimal concentrations of NGF have been associated with the initial phases of Alzheimer's disease and dementia. [40,41]

Although therapeutic interest has largely focussed on its importance for neurological function, NGF plays a much wider role in maintaining homoeostasis in the body.[42,43] It is known to have insulinotropic, angiogenic, and antioxidant properties and reduced plasma levels of NGF have been associated with cardiovascular diseases and metabolic syndromes, including type 2 diabetes.[44,45] It has been shown to accelerate wound healing and there is evidence that it could be useful in the treatment of skin and corneal ulcers.[46] Animal studies have shown NGF to have a profound effect on airway inflammation and asthma-related symptoms with increased NGF levels observed in bronchoalveolar lavage fluid and serum from patients with asthma.[47]

NGF also has a dynamic relationship with the immune system. Generation of NGF is increased after brain injury, in part due to cytokines produced by immune cells. At the same time immune cells express receptors for NGF, which is involved in immune modulation.[48]Two classes of compounds derived from H. erinaceus have been discerned for their efficacy in inducing NGF production: the aromatic hericenones (extracted from the fruiting body) and the diterpenoid erinacines (extracted from the mycelium). Notably, these bioactive molecules possess molecular dimensions conducive to permeating the blood-brain barrier. There is also evidence that they can increase myelination.[38,49-50]

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In China the mycelium is used to make H. erinaceus pills to treat gastric and duodenal ulcers, chronic gastritis, gastric and oesophageal cancer.

Therapeutic Applications.

1. DEMENTIA -

In controlled studies H. erinaceus supplementation resultedtherapeutic effects in patients with mild dementia. In one study six out of seven patients showed improvement in functional capacity (understanding, communication, memory etc.) while all seven showed improved Functional Independence Scores (eating, dressing, walking etc.), after consuming 5g H. erinaceus fruiting body daily in soup for six months.[38] In another study, 30 patients aged 50-80 with mild dementia were randomized into treatment and control groups. H. erinaceus was given as tablets at 3g/day for 16 weeks and induced significant improvement in cognitive function in the treatment group. However, four weeks after the conclusion of the trial, cognitive function scores decreased indicating a need for continued supplementation.[51]

2. MULTIPLE SCLEROSIS (M.S) –

H. erinaceus fruiting body extract has been shown to improve the myelination process in mature myelinating fibres with potential therapeutic advantages for MS patients.[50,52] NGF has also been shown to have a protective effect on axons and myelin by suppressing the immune mediated inflammatory processes responsible for chronic brain destruction in neurodegenerative disorders such as MS by switching the immune response to an anti-inflammatory, suppressive mode in a brain-specific environment.[46]

3. NEUROPATHY –

NGF plays a role in pain sensitivity and low NGF levels have been linked to sensory neuropathy in both in vivo and in vitro studies.(43) Enhanced NGF production has been shown to protect sensory function in diabetic rats and NGF reduction has been shown to cause cardiac sensory neuropathy.[53,54]

Clinical studies with recombinant human NGF indicate benefit in patients with diabetic polyneuropathy(55) and NGF has also been reported to reduce pain in patients with HIV associated sensory neuropathy. [56,57] .However, ability to promote regeneration of sensory neurons has yet to be demonstrated.[58,59]

4. ANXIETY / DEPRESSION –

A study indicates a decrease in anxiety and depression symptoms following the ingestion of 2g/day (administered via cookies), with patients frequently noting heightened sensations of well-being upon consuming H. erinaceus. This effect is purportedly attributed to the kappa opioid receptor agonist activity exhibited by the erinacines. [64,65]

5. MENOPAUSAL SYNDROME –

Several patients have reported a decrease in symptoms associated with menopause and perimenopause, such as sleep disruption, anxiety, and hot flashes, following the consumption of H. erinaceus at a dosage of 3-5g/day d.w. However, this assertion lacks empirical support from clinical investigations. [64]

6. MRSA (Methicillin-resistant Staphylococcus aureus) -

Fruit body and mycelium extracts demonstrate anti-MRSA efficacy, with erinacines identified as the active constituents. Clinical trials conducted in Japan have reported the eradication of MRSA in several patients following dietary supplementation with H. erinaceus. [66]

7. GASTRIC ULCERS –

One of the therapeutic applications of H. erinaceus involves its potential antibacterial properties attributed to the erinacines and hericenones. This suggests that these bioactive compounds may play a role in its therapeutic efficacy, particularly considering recent findings identifying Helicobacter pylori as a significant contributor to gastric ulcers and chronic gastritis. [67-69]

A rat study on the effects of H. erinaceus aqueous extract on alcohol-induced ulcers showed a considerable reduction of the ulcer area, as well as fortification against gastric mucosa injury, while an in vitro study found that H. erinaceus extract was active against nine clinical strains of H. pylori with a 0.02% concentration having a 50% bactericidal activity.[70,71]

CLINICAL SUMMARY –

Therapeutic Application - Dementia, Alzheimer's disease, MS (Multiple Sclerosis), nerve damage, menopausal syndrome.

Key Component - Hericenones and erinacines.

Dose–Since , Clinical investigations support the use of dried fruiting body at a dose of 3 - 5g/day

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for increasing NGF production while animal studies on the use of H. erinaceus for gastric ulcers produced the best results with a daily intake of 500mg/kg, which equates to the dosage prescribed in the Chinese Phamacopoeia of 25-50g/day.[34] It is likely that similar doses would be required in cases of MRSA.

High in vitro NGF promoting activity of mycelial extracts and the fermentation broth also indicates potential for the use of mycelial biomass products.[72,73]

Caution - Asthma and other allergic conditions. Erinacine E (in Hericium ramosum (Comb's Tooth Fungus which is identical to H. erinaceus possesses neuroprotective properties but differ in growth characteristics) is a potent agonist of the kappa opioid receptor with potential hallucinogenic properties. [74]

II. CONCLUSION.

To the best of the author's understanding, no evidence of toxicity associated with H. erinaceus has been identified in the experimental, animal, or two clinical trials discussed herein. The adverse event (epimenorrhea) documented in one of the clinical trials could not definitively be linked to the intervention. The extensive historical documentation of lion's mane's traditional application in treating chronic ailments, coupled with the findings of the studies conducted thus far, indicate that H. erinaceus is safe and holds significant promise as a neuroprotective and neurotrophic therapeutic agent for neurological disorders. [35]The abundance of myconutrients within the composition indicates that employing the entire fungus could potentially offer optimal clinical benefits. Further clinical investigations are warranted to validate these findings.

COMPETING INTERESTS.: The authors declare they have no competing or conflict of interests.

III. FUNDING.

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