Key Words: neuroinflammatory diseases, inflammation, neurogenesis, neuroprotection, nerve degeneration, antioxidants, oxidative stress, erinacine A

Theoretical Potential of Hericium Erinaceus Supplementation as an Add-On to Antipsychotics in Chronic and Treatment-Resistant Schizophrenia

By Joni F. Baker, Sharlene D. Newman

ABSTRACT *~ Schizophrenia is a serious mental illness that is a leading cause of disability worldwide. While antipsychotic agents are the most effective medications, up to one-third of patients experience treatment resistance, and approximately one-sixth of patients experience ultra-resistant illness. There is a growing body of evidence that inflammation, oxidative stress, and neurodegeneration may be contributing to pathophysiology and treatment response. Several agents with potential to improve inflammation and oxidative stress have been investigated, with some showing statistically significant benefits, though robust improvement in symptomatology has not been consistently demonstrated. Hericium erinaceus (HE) is an edible mushroom that has been used as a medicinal food for centuries. In pre-clinical studies, it has demonstrated anti-inflammatory, antioxidant, neuroprotective, and neurogenesis-promoting effects. The specific inflammatory markers that are impacted by HE align well with biomarkers shown to be altered in chronic and treatment resistant schizophrenia. Most clinical studies to date have assessed HE for the treatment of mild cognitive impairment, depression, and anxiety. In clinical studies, HE has been well tolerated, with the most common adverse effect of gastrointestinal disturbance. Given potential for HE to improve inflammation, reduce oxidative stress, and promote adult neurogenesis in the hippocampus, it is theorized that HE may have beneficial effects on symptomatology when used as an add-on to antipsychotic therapy in those with residual symptoms or treatment resistance. The goal of this review is to describe theoretical benefits and potential dosing strategies based on pre-clinical and clinical data.*
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Introduction

Schizophrenia is a complex, chronic, relapsing mental illness that affects approximately one percent of the population. It is frequently associated with significant functional impairment, premature mortality, and is a top 15 leading cause of disability worldwide.[1] Patients with schizophrenia may experience positive symptoms including hallucinations and delusions, negative symptoms such as avolition, social withdrawal, and diminished emotional expression, and cognitive dysfunction.[2] Antipsychotic drugs are the most effective agents for the treatment of schizophrenia, but approximately one-third of patients experience treatment resistance, commonly defined as an inadequate response to two or more antipsychotic trials at adequate dose and duration.[3] Clozapine is the only medication approved by the Food and Drug Administration for treatment resistant schizophrenia (TRS), with approximately 40% response rate. It has been estimated that 12–20% of people with schizophrenia will be ultra-resistant, and the best treatment strategy in those instances is not well defined.[4] Even with treatment response, typically defined as 20–30% improvement of Positive and Negative Syndrome Scale (PANSS) score, many patients continue to have residual positive, negative, and cognitive symptoms. The pathophysiology of schizophrenia is not completely understood, but dopaminergic and glutamatergic hypotheses have been well described. There is accumulating evidence that neuroinflammation, oxidative stress, and dysfunction in adult neurogenesis may be contributing factors to pathophysiology and treatment response. These pathophysiologic targets may be useful to identify additional novel treatment strategies.[5–8]

Hericium erinaceus (HE) is an edible mushroom that grows on hardwood trees and is native to North America, Europe, and Asia. It has a long history of being used as a medicinal food and in preclinical research has been shown to have anticancer, antidiabetic, antihyperlipidemic, anti-inflammatory, antioxidant, neuroprotective, and neurotrophic effects. Reported side effects with oral supplementation of HE include gastrointestinal (GI) disturbance, nausea, and skin rash.[9] Clinically, it has been studied in a variety of illnesses, most notably mild cognitive impairment (MCI), depression, and anxiety.[10–14] The most studied components of HE are mycelia and fruiting body, typically administered as a dry powder, aqueous extract, or ethanolic extract. The presence of compounds theorized to have benefit varies between mycelia and fruiting body, with fruiting body containing most hericenones, and mycelia containing most erinacines, including erinacine A.[15] Fifteen erinacines (A-K and P-S) and seven hericenones (A-H) have been identified and are believed to be hydrophobic compounds, with

data demonstrating that some of these compounds cross the blood-brain barrier.[16–17] Stimulation of Nerve Growth Factor (NGF) and brain-derived neurotrophic factor (BDNF) has been attributed to erinacines A through I and hericenones C through H.[18–19] It is noted that products can vary greatly in the amount of erinacines and hericenones present. The aim of this review is to analyze theoretical benefit of HE as an add-on in the treatment of schizophrenia based on potential for anti-inflammatory, antioxidant, and neurogenesis promoting effects.

Neuroinflammation in Schizophrenia

Inflammation

It has been hypothesized that neuroinflammation and immune modulation may be contributing to the pathophysiology in at least a subset of patients with schizophrenia, and it has been proposed that TRS may be a possible indication for use of neuro-inflammation reducing and neuroprotective drugs.[20] It has been suggested that those with increased inflammatory markers may be less likely to respond to conventional treatments and more likely to experience negative symptoms and cognitive dysfunction.[6,21–25] When compared to treatment responsive patients, those with treatment resistant illness have been shown to have higher levels of inflammation, as evidenced by changes in neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, increased levels of C-reactive protein (CRP), and increased levels of numerous pro-inflammatory cytokines.[6–7,25–27] Several studies have researched inflammatory markers in different phases of schizophrenia, including first episode psychosis, acute exacerbation, chronic illness, and TRS. The most consistently altered inflammatory markers in all phases of schizophrenia are increased IL-6 and CRP.[6] Specific CRP levels have been associated with greater negative symptoms ($>$ 0.5 mg/dL) and resistance to conventional treatment ($>$ 3 mg/dL).[6,22] In assessing chronic illness and TRS compared with healthy controls, studies have shown an increase in IL-1β, IL-6, IL-8, IL-10, TNFα, CRP, IL-1RA, and sIL-2R.[6–7,25–26] Furthermore, when assessing treatment responsive versus treatment resistant patients, patients with TRS have been reported to have higher levels of IL-1β, IL-2, IL-6, IL-18, and TNFα.[7,25] Data describing the levels of anti-inflammatory cytokines (e.g., IL-10, IL-4) have been mixed in TRS, with some studies showing increase and some showing decrease.[7,25] The interaction between neuroinflammation and neurogenesis is complex, and dysregulation or overexpression of some pro-inflammatory cytokines, including IL-1β, TNFα, and IL-6, can interfere with adult neurogenesis.[5] Addressing

underlying inflammation may be one of the keys to improving treatment response in those with schizophrenia experiencing residual symptoms with conventional treatment.

Oxidative Stress

An imbalance between free radicals and antioxidants can cause alteration in lipid peroxidation, nucleic acids, and proteins.[28] Common antioxidant enzymes include superoxide dimustase (SOD), catalase (CAT), and glutathione peroxidases (GPx). SOD scavenges superoxide radicals and converts to hydrogen peroxide, CAT converts hydrogen peroxide to oxygen and water, and GPx catalyzes hydrogen peroxide and lipid peroxides to nontoxic alcohols.[28–29] Patients with schizophrenia have been reported to have reduced levels of antioxidants, CAT, and GPx, and increased production of reactive oxygen species.[7] It has been suggested that oxidative stress may have a negative effect on myelination, which has been demonstrated in post-mortem studies of schizophrenia patients.[30] Some studies assessing oxidative markers in schizophrenia have demonstrated significantly decreased GPx and SOD, and increased CAT versus healthy controls, and decreased levels of CAT and glutathione (GSH) in unmedicated patients.[29,31] Oxidative stress has potential to contribute to reduced neurogenesis and chronic inflammation.

Neurodegeneration

Adult neurogenesis (AN) occurs in specific areas of the brain, including the subventricular zone of the lateral ventricle and the subgranular zone of the hippocampus. AN impacts learning and memory function, synaptic plasticity, and cognitive functioning.[5] It is estimated that this complex process takes approximately seven weeks.[32] It is well documented that patients with schizophrenia have reduced hippocampal volume compared with healthy controls. Neurodegeneration and disturbance in adult neurogenesis may be contributing to volume loss in the hippocampus, potentially contributing to the pathophysiology and symptomatology.[8] Microglial activation can lead to excessive synaptic pruning, decreased synaptic plasticity, neuron loss, and reduction in BDNF, which can result in neurodegeneration. It is known that increased BDNF expression can induce neuroplasticity, including adult neurogenesis, while low levels of BDNF can impair synaptic plasticity by reducing proliferation of synapses and causing excessive synaptic pruning.[8,23,33] Patients with TRS have been reported to have lower levels of BDNF compared to treatment responsive patients.[23] One study found those with TRS had larger lateral ventricles and significantly smaller

amygdala and hippocampus volume versus healthy controls. The same findings were noted when comparing TRS to non-TRS patients, though it did not meet statistical significance.[25] Given the role of the hippocampus in cognition, memory, and affective behaviors, promotion of adult neurogenesis in schizophrenia may be useful to improve symptoms and functional status.

Effect of Known Anti-Inflammatory Agents

Given interest in the neuroinflammatory hypothesis of schizophrenia, there have been numerous studies assessing the effect of anti-inflammatory agents for augmentation. Recent meta-analyses assessing the effectiveness of anti-inflammatory agents and antioxidants in schizophrenia have identified statistically significant effects for estrogen, N-acetylcysteine, and minocycline, with mixed results for HMG-CoA reductase inhibitors and thiazolidinediones. Aspirin demonstrated statistically significant results alone, but not when evaluated with other NSAIDs. When neurosteroids DHEA and pregnenelone were assessed as a group, there was statistically significant improvement in PANSS scores; however, when pregnenelone was assessed on its own, a significant change was not found.[34–35] Those with positive benefits have been noted to decrease IL-1β, IL-6, and TNFα, and downregulate nuclear factor kappa B (NFκB). Beneficial effects on positive symptoms, negative symptoms, and general pathology were demonstrated with add-on of anti-inflammatory agents overall.[35] There is some evidence that antipsychotics, particularly certain second-generation antipsychotics, may have anti-inflammatory effects by stimulating anti-inflammatory cytokines and diminishing pro-inflammatory cytokines. However, there have also been some pro-inflammatory effects associated with antipsychotic treatment, including increased CRP with haloperidol, increased CRP and TNFα with clozapine, and inconsistent upregulation of IL-6.[36] The effect of antipsychotic agents on promotion of adult neurogenesis has been investigated, with mixed effects from haloperidol, but a signal for promotion of neurogenesis from atypical antipsychotics including clozapine, olanzapine, paliperidone, and risperidone.[5]

Hericium Erinaceus

Anti-Inflammatory Effects

In pre-clinical studies, outlined in Table 1, HE has been shown to decrease inflammation though several proposed mechanisms. Several studies have demonstrated a reduction in inflammatory cytokines IL-1β,

TABLE 1

Pre-Clinical Studies

STUDY	HE FORMULATION	POPULATION, COMPARATORS	DOSE	PERTINENT FINDINGS
Fu 2024	HEM Erinacine A Erinacine S	Mice, cuprizone exposed 6 week cuprizone 12 week cuprizone Control	1 mg/kg 1 mg/kg 1 mg/kg Oropharyngeal route daily × 4 weeks	• HEM and Erinacine S: ◦ Restored APC+ oligodendrocytes ◦ Preserved myelin ◦ Suppressed microglia ◦ Attenuated astrogliosis ◦ Decreased IL-1β • HEM and Erinacine A: ◦ Decreased IL-6
Lee 2024	HEM ethanolic extract (low dose) HEM ethanolic extract (high dose) Erinacine C	Mice, mild traumatic brain injury Sham control mTBI group HEM Erinacine A Erinacine S	108.5 mg/kg PO 217 mg/kg PO 2 mg/kg IP Daily × 5 days	• Decreased time-to-right on beam walk test • Increased normal neurons in cerebral cortex and subcortex • Decreased number of activated microglial cells • Increased p-CREB expression, CAT, GSR, TrxR, SOD
Priori 2024	HEM and FB ethanolic extract	Mice, aging Control HEM and FB ethanolic extract	1 mg/day PO daily × 60 days	• Decreased shrunken cell density in hippocampus • Lower collagen fiber density • Decreased GFAP and IL-6
Hsu 2023	HEM powder	Mice, MPTP model of Parkinson's Disease	0.1 g/kg 0.3 g/kg 1 g/kg	• Reversed MPTP-induced neurodegeneration • Dose dependent reduction of MPTP-induced CAT, SOD, G6PDH, and GSR levels

Roda 2023	ERGO rich HE primordium ethanolic extract	Mice, aging	1 mg/day containing 1.3 ± 0.57 mg/gm ERGO PO daily × 8 months	• Decreased shrunken cell density in hippocampus • Decrease IL-6, TGFβ1, GFAP, Nrf2, SOD1, COX2 • Enhanced NMDAR1 and mGluR2 • Protective effect on recognition memory • Prevented cognitive deterioration
Ren 2023	HEM extract	Mice, colitis	50 mg/kg 100 mg/kg 200 mg/kg Gavage × 7 days	• Decreased IL-1β, IL-6, TNFα, iNOS, COX2, NLRP3 inflammasome expression • Inhibited NF-κB/Akt/MAPK signaling
Lee 2022	Erinacine A HEM	Rats, LPS-induced model of Parkinson's Disease	5 mg/kg 1 g/kg Oral gavage pre-treated daily × 7 days before LPS injection	• HEM and Erinacine A attenuated LPS-induced increases in TNFα, IL-1β, and iNOS • No direct effect on BDNF • HEM or Erinacine A attenuated condition medium-induced cell death and LPS-induced motor dysfunction
Roda 2021	HEM and sporophore ethanolic extract 0.58 mycelium 0.34 sporophore	Mice, aging	Erinacine A 150 mcg/g Hericenone C 500 mcg/g Hericenone D 20 mcg/g ERGO	• Increased cerebellar size • Decreased IL-6, GFAP, and immunoreactive astrocytes • Decreased SOD1, NOS2, and COX2 • Protective effect on locomotor and cognitive decline
Chong 2021	HE FB aqueous extract	Mice, depression	10 mg/kg injection 25 mg/kg injection 4 weeks	• In vitro increase in total antioxidant capacity, DPPH, and FRAP • Antidepressant and anxiolytic effect • Improved BDNF-TrkB-CREB signaling • Neurogenic effect in 10 mg/kg group

(Continued)

TABLE 1 *(Continued)*

Pre-Clinical Studies

STUDY	HE FORMULATION	POPULATION, COMPARATORS	DOSE	PERTINENT FINDINGS
Cordaro 2021	HEM + FB, PO	Rats, AlCl3-induced AD model	200 mg/kg PO daily × 6 weeks	• Decreased APP, p-Tau, and β-amyloid accumulation • Increased SOD, CAT, and GSH levels • Reduced nitrite, lipid peroxidation, and ROS in hippocampus • Reduced IL-1β, IL-18, iNOS, TNFα, IL-6 • Downregulation of NLRP3 and NFκB
Jang 2019	HE ethanolic extract –Crude extract	Mice, pilocarpine-induced seizures	60 mg/kg 120 mg/kg 300 mg/kg PO daily × 21 days	• Reduced neuronal death in hippocampus • Reduced COX-2 expression in glial cells • No effect on glial activation • No difference with 300 mg/kg
Kushairi 2019	HE FB ethanolic extract and aqueous extract	Mouse, hippocampal neurons		• NSD between aqueous and ethanolic extract in DPPH free radical scavenging • Both aqueous and ethanolic extract significantly decreased NO production, ethanolic extract more effective • Ethanolic extract protected against neurotoxicity and mitochondrial toxicity, decreased H2O2 induced apoptosis • Ethanolic extract increased CAT, GSH
Li 2019	Erinacine A-enriched mycelia, PO	Mice, life-prolonging	108 mg/kg 215 mg/kg 431 mg/kg	• Dose-dependent increase in life expectancy • Dose-dependent decrease in TBARS • Dose-dependent elevation of SOD, CAT, GPx
Ratto 2019	HEM and FB ethanolic extract	Mice, frailty during aging	1 mg/day Calc ~50 mg/kg/day based on 0.02 kg	• No change in locomotor parameters • Improved recognition memory • Increased PCNA in hippocampus and cerebellum

Chiu 2018	Erinacine A-enriched mycelium ethanolic extract	Mice, depression	100 mg/kg 200 mg/kg 400 mg/kg	• Improvement in restraint stress-induced reductions in DA (all doses), NE (high dose), and 5HT (medium and high dose) • Decrease IL-6 (medium and high dose) and TNFα (all doses) • Reverse stress-induced downregulation of BDNF, TrkB, and PI3K • Reduction of NFκB-induced inflammation
Ren 2018	HE mycelium dry powder polysaccharide, PO	Mice, colitis		• Decrease IL-6, IL-1β, TNFα and COX2 • Down-regulated NFκB, MAPK • Downregulated NO, MDA, total SOD, and MPO
Diling 2017	HE ethanol extract and polysaccharide, PO	Rats, inflammatory bowel disease	100 mg/kg/day PO daily × 2 weeks	• Decrease MPO activity • Downregulate NFκB • Decreased TNFα • Increased IL-10
Ryu 2017	HE ethanolic extract, PO	Mice	20 mg/kg 60 mg/kg	• Hippocampal neurogenesis
Chen 2016	Erinacine A Erinacine S	Mice	30 mg/kg	• Reduced amyloid plaque burden in cerebral cortex
Tsai-Teng 2016	Erinacine-A enriched mycelia	Mice, Alzheimer's disease	300 mg/kg PO daily × 30 days	• Reduced amyloid β plaque in cerebral cortex and hippocampus • Promoted hippocampal neurogenesis

(Continued)

TABLE 1 *(Continued)*

Pre-Clinical Studies

STUDY	HE FORMULATION	POPULATION, COMPARATORS	DOSE	PERTINENT FINDINGS
Yao 2015	Amycenone (HE fruiting body extract 0.5% hericenones and 6% amyloban)	Mice, LPS-induced inflammation	50 mg/kg 100 mg/kg 200 mg/kg PO	• Improved LPS-induced rise in TNFα • Increased serum IL-10 reduced by LPS
Lee 2014	HEM ethanol extract and erinacine A	Rats, brain ischemia	HEM: 50 mg/kg 300 mg/kg Erinacine A: 1 mg/kg 5 mg/kg 10 mg/kg	• Inhibition of iNOS, p38/ MAPK pathway • Decrease IL-1β, IL-6, TNFα, increase NGF
Shimbo 2005	Erinacine A	Rats	8 mg/kg	• Enhanced NGF synthesis • Increase noradrenaline and homovanillic acid in locus coeruleus

IL-18, TNFα, and IL-6.[37–47] Two studies demonstrated an increase in anti-inflammatory cytokine IL-10.[46,48] Downregulation of nuclear factor kappa B (NFκB), mitogen-activated protein kinase (MAPK), cyclooxygenase-2 (COX-2), and NLR family pyrin domain containing 3 (NLRP3) expression has also been shown in several studies.[43–49] The effect of HE on these specific anti-inflammatory markers correlates well with the inflammatory markers that are altered in TRS.

Antioxidant Effects

The antioxidant effects of HE have been demonstrated in several pre-clinical studies. They have been shown to induce endogenous antioxidant enzymes such as heme oxygenase-1 (HO-1), γglutamylcysteine (γ-GCLC), SOD, CAT, COX2, and GSH.[18,38,42–43,45,49–55] HE was found to reduce levels of nitrite, lipid peroxidation, and reactive oxygen species (ROS) in the hippocampus of the rat brain.[43] One study found hot water and ethanolic extracts of HE to have similar 2,2-Diphenyl-1-picrylhydrazyl (DPPH) scavenging abilities.[55] Interestingly, while hot water and ethanolic extracts both significantly decreased nitric oxide (NO) production induced by lipopolysaccharide (LPS), the ethanolic extract was more effective. The ethanolic extract was found to provide neuroprotection for hydrogen peroxide induced neurotoxicity, mitochondrial toxicity, and apoptosis in a dose-dependent manner.[55] The antioxidant effects of HE may be useful to reduce oxidative stress in those with schizophrenia.

Effect on Neurogenesis

In mouse models, HE has been shown to reduce hippocampal neuron loss in Alzheimer's dementia, decrease hippocampal cell death after pilocarpine-induced status epilepticus, protect from brain-ischemia induced neuronal cell death, and promote longevity.[43,49–50,54] It has demonstrated induction of hippocampal and cerebellar neurogenesis, prevention of neurodegeneration, and prevention of neuroinflammation-induced neuronal cell death.[18,33,38,40,42,49,56–57] It has been shown to decrease glial fibrillary acidic protein (GFAP) immunopositive fibers, suppress microglial activation, and preserve myelin.[37–39,42,51] HE administration may enhance expression of genes and proteins related to neuroplasticity, including BDNF, tropomyosin receptor kinase B (TrkB), and cAMP response element binding protein (CREB).[33] The effect appears to be dose dependent, with lower doses of fruiting body having higher efficacy for adult neurogenesis and neuroprotective effect

to diminish neuronal cell death.[33,49] Certain hericenones (D, E, H) and erinacines (A, B, C, D, E, F, G, H, I) found in HE have been found to induce NGF synthesis. Based on pre-clinical studies, it is hypothesized that chronic administration of HE could promote the proliferation of hippocampal neural stem or progenitor cells and increase the number of mature hippocampal neurons.[33] Theoretically, HE promotion of neurogenesis in schizophrenia could result in improved symptomatology, particularly with memory and learning, but potentially other symptoms as well.

Clinical Studies

Clinical studies of HE, outlined in Table 2, have primarily focused on cognition, depression, and anxiety with sample sizes ranging from one to 77. Some studies targeted specific diagnoses, while others studied the effects of supplementation on healthy populations. Type of HE supplementation and dose of supplementation have varied throughout the studies. Most studies thus far have utilized fruiting body, with two studies using a combination of mycelia and fruiting body, and one study using erinacine A-enriched mycelia, with doses ranging from 1050 mg to 11700 mg. The duration of studies ranged from 4 weeks to 49 weeks. Statistically significant improvement in dementia rating scales, including Mini Mental State Exam (MMSE) and Revised Hasegawa Dementia Scale (R-HDS), has been demonstrated in studies of MCI, but these did not always separate from placebo.[11,58–59] Some studies have reported decreased depression, anxiety, and subjective stress levels.[12–14,60] Overall, studies for depression and anxiety have shown some positive signals during 4 week trials, but it seems longer duration is needed when assessing cognition, which is rational considering adult neurogenesis is estimated to take approximately 7 weeks. In clinical trials it has demonstrated good safety and tolerability, with GI disturbance being the most commonly reported effect.

Hericium Erinaceus in Schizophrenia

No pre-clinical studies were found assessing the impact of HE supplementation on a mouse model of schizophrenia, and only one case report has been identified assessing the clinical effect of HE supplementation in a patient with schizophrenia.[61] This case report described marked improvement with greater than 50% reduction in

PANSS and State-Trait Anxiety Inventory with supplementation of Amyloban3399 at a dose of six 1950 mg tablets per day.[61]

Proposed Formulation and Dosing

Based on pre-clinical and clinical studies reviewed, it is theorized that an ethanolic extract of fruiting body combined with erinacine A-enriched mycelia would be the most logical selection for a study in schizophrenia. Since erinacines and hericenones are hydrophobic, an ethanolic extract would be expected to yield more useful compounds compared to an aqueous extract, and pre-clinical studies have shown greater antioxidant effects of ethanolic extract. Since erinacines are primarily found in mycelia and hericenones are primarily found in fruiting body, and both compounds have been shown to have beneficial effects on a variety of parameters as outlined above, a supplement of fruiting body and mycelia would be expected to give the most substantial benefit. In defining the most appropriate dose, pre-clinical and clinical studies can give some guidance. In pre-clinical mouse studies, doses of fruiting body ethanolic extract have ranged from 10–300 mg/kg/day, combination product of mycelia and fruiting body have ranged from 50–200 mg/kg/day, and erinacine A-enriched mycelia ranged from 30–431 mg/kg/day. In studies of fruiting body extracts (ethanolic and aqueous), neuroprotective and neurotrophic effects have been dose-dependent, with doses of 60–120 mg/kg oral ethanolic extract or 10 mg/kg aqueous injection having a more profound effect than higher doses of 300 mg/kg oral ethanolic extract or 25 mg/kg aqueous injection.[33,49] Some studies of erinacine A-enriched mycelia have found dose-dependent effects with more robust benefits at higher doses.[44,54] For estimating human equivalent dose calculation based on body surface area, this would calculate to approximately 4.86–16.2 mg/kg/day for ethanolic extract of fruiting body and 8.1–34.9 mg/kg/day of erinacine A-enriched mycelia.[62] Studies assessing erinacine A specifically have used doses ranging from 1–10 mg/kg/day in rats, which would equate to approximately 0.16–1.6 mg/kg/day in humans. Based on review of the pre-clinical data, author proposes an ideal mouse dose of 100 mg/kg/day ethanolic extract of fruiting body in combination with 400 mg/kg/day erinacine A-enriched mycelia, which would equate to approximately 567 mg/2268 mg daily for a human with weight of 70 kg, with proposed simplified dosing of 600 mg/2400 mg daily for study protocol.

TABLE 2

Clinical Studies

STUDY	DESIGN	POPULATION	INTERVENTION	OUTCOMES
Docherty 2023	R, DB, PC, parallel group	18–45 yo Healthy adults N = 43	Sempera organics HE mushroom complex (mycelium + fruiting body 1.8 g/day vs. placebo × 28 days	• Decrease subjective stress • Recalled significantly less words than placebo
Grozier 2022	PC, SB, parallel group	College age Healthy N = 24	Nammex organic mushroom hot water extract from fruiting bodies 10 g/day, 5 g BID HE vs. placebo × 4 weeks	• NSD in cognition
Li 2020	R, DB, parallel group	> 50 yo Mild AD N = 41	Erinacine A enriched HEM – 350 mg HE, 5 mg/g erinacine A 3 capsules/day (n = 20) vs. placebo (n = 21) × 49 weeks	• Significantly increased MMSE scores in HE group, NSD in placebo, though NSD between HE and placebo
Saitsu 2019	R, DB, PC, parallel group	> 50 yo Healthy N = 31	Powdered fruiting body 3.2 g/day (n = 16) vs. placebo (n = 15) × 12 weeks	• MMSE: SS difference • Benton visual retention test: NSD • Standard verbal paired-associate learning test: NSD
Vigna 2019	R, parallel group	Adults Overweight or obese with mood or sleep disorder N = 77	80% HEM and 20% FB extract Low calorie diet + 1500 mg/day (n = 40) vs. low calorie diet (n = 37) × 8 weeks	• Zung-anxiety and Zung-depression sig decreased in HE group • Symptom Checklist-90 depression and anxiety sig decreased in HE group • Increased pro-BDNF with HE

Okamura 2015	Open label pilot	Female Healthy N = 8	Amycenone HE fruiting body extract (0.5% hericenones and 6% amyloban) 6 1950 mg tablets divided BID-TID × 4 weeks	• Decreased GHQ-28 scores ◦ Somatic: decreased, NSD ◦ Anxiety and insomnia: decreased, $p < 0.1$ ◦ Depression: decreased, NSD
Inanaga 2014	Case report	Male patient N = 1	Amycenone HE fruiting body extract (0.5% hericenones and 6% amyloban) 6 1950 mg tablets divided BID-TID × 6 months	• PANSS score decreased from 62 to 30 • STAI State decreased from 80 to 35 • STAI Trait decreased from 80 to 29
Nagano 2010	R, DB, PC	41.3 ± 5.6 yo Females N = 26	Powdered fruiting body in 0.5 g cookies 2 g/day (n = 12) vs. placebo (n = 14) × 4 weeks	• Perimenopausal sx: sig decrease over time with HE, NSD vs. placebo • CES-D, depression: sig decrease over time with HE, NSD vs. placebo • PSQI, sleep: NSD • Indefinite complaints index: sig decrease over time with HE, NSD vs. placebo
Mori 2009	R, DB, PC, parallel group	50-80 yo Mild cognitive impairment N = 29	Powdered fruiting body 1 g TID – 3 g/day (n = 14) vs. placebo (n = 15) × 16 weeks	• R-HDS dementia scale • 10 improved > 3 points in HE, vs. 1 in placebo • 3 improved > 2 points in HE, vs. 1 in placebo • 1 unchanged in HE, 13 unchanged in placebo

Key: 5HT: serotonin; APC+: adenomatous polyposis coli; APP: amyloid precursor protein; BDNF: brain derived neurotrophic factor; CAT: catalase; CES-D: center for epidemiologic studies depression scale; COX: cyclooxygenase; DA: dopamine; DB: double-blind; DPPH: 2,2-diphenyl-1-picrylhydrazl; ERGO: ergothionene; FB: fruiting body; FRAP: ferric reducing antioxidant power; GFAP: glial fibrillary acidic protein; GPx: glutathione peroxidase; GHS: glutathione; GSR: glutathione reductase; G6PDH: glucose-6-phosphate dehydrogenase; HE: hericium erinaceus; HEM: Hericium erinaceus mycelium; IL: interleukin; iNOS: inducible nitric oxide synthase; IP: intraperitoneally; MAPK: mitogen-activated protein kinases; mGluR2: metabotropic glutamate receptor 2; MDA: malondialdehyde; MMSE: mini mental status exam; MPO: myeloperoxidase; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NE: norepinephrine; NFκB Nfr2: nuclear factor erythoid 2-related factor; NGF: nerve growth factor; NLRP3: NLR family pyrin domain containing 3; NMDAR: N-methyl-D-aspartate receptor; NOS: nitric oxide synthase; NSD: no significant difference; PANSS: positive and negative syndrome scale; PC: placebo-controlled; PCNA: proliferating cell nuclear antigen; p-CREB: phosphor-CAMP-response element-binding; PI3K: phosphoinositide 3-kinase; R: randomized; PSQI: Pittsburg sleep quality index; R-HDS: Revised Hasegawa dementia scale; SOD: superoxide dismutase; SS: statistically significant; STAI: State trait anxiety inventory; TBARS: thiobarbituric acid reactive substances; TGF: transforming growth factor; TNF: tumor necrosis factor; TrkB: tropomysin receptor kinase B; TrxR: thioredoxin reductase.

Conclusions

The anti-inflammatory, antioxidant, and neurogenesis promoting effects of HE demonstrated in pre-clinical and clinical studies align well with alterations noted in the neuroinflammatory hypothesis of schizophrenia. This, combined with good tolerability and minimal adverse effects noted in studies, indicates a theoretical role of HE as an add-on or augmentation agent to standard antipsychotic therapy in those with residual symptoms on recommended treatment. As only one case report has been identified assessing HE in the treatment of schizophrenia, benefits are all theoretical at this point. A study assessing the potential benefit of HE as add-on therapy to antipsychotics in those with chronic or TRS may be useful to assess if these theoretical benefits may be realized. ✤

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