Hericium erinaceus in Neurological Conditions

Kevin Spelman, PhD, MCPP
Health, Education & Research
Ashland, OR
Conflicts of Interest

I am a Pharma and Natural Products Industry Consultant

Nothing to Declare
Mind Map of Lecture

- Alzheimer’s Disease
- Parkinson’s Disease
- Hericium erinaceus
- Neurotrophic Activity
- Peripheral Nerve injury
- Posology
- Thinking Globally
- Chemistry
- Adverse events
- Cognitive Function
A comment on animal models
**Hericium Traditional Use**

Fortify the spleen

Nourish the gut, promotes good digestion
gastric and duodenal ulcers, as well as chronic gastritis

Anti-cancer

Good for the 5 internal organs (liver, lung, spleen, heart, kidney)
general vigor, strength, and nutrition;

Known for its effects on the central nervous system -

Insomnia  Vacuity (weakness)  Hypodynamia

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Hobbs Christopher. Medicinal Mushrooms. Botanica Press, Santa Cruz, 3 edition (February 1, 1995)

H. erinaceus
Chemistry & Pharmacology
Chemistry

• High molecular weight compounds, such as polysaccharides
• low molecular weight compounds such as polyketides and terpenoids

Hericium erinaceus

- Polysaccharides
- Terpenoids; Sesterpenes & Diterpenoids
- Isoindolinones
- Sterols
- Myconutrients
Polysaccharides

In cells that were toxic from Aβ, *H. erinaceus* polysaccharides decreased the production of ROS from 80% to 58% in a dose-dependent manner and increased the efficacy of free radical scavenging.


Polysaccharides

*H. erinaceus* polysaccharides promoted cell viability under Aβ-induced toxic conditions and protected cells against Aβ-induced apoptosis


Polysaccharides

*H. erinaceus* polysaccharides possesses significant anti-fatigue activity by decreasing blood lactic acid, serum urea nitrogen, tissue glycogen and malondialdehyde.


Polysaccharides

A purified polysaccharide from the liquid culture broth of *H. erinaceus* mycelia was also found to provide neuroprotective activity through a dramatic delay of apoptosis (20 – 50% compared to control).

Polysaccharides

Mycelia more effective than control, NFG or BDNF alone in enhancing the growth of rat adrenal nerve cells and neurite extension.

Terpenoids

• Two classes of terpenoid compounds,
  • Hericenones
  • Erinacines

• Along with aromatic compounds have been found to stimulate nerve growth factor (NGF) synthesis

Hericenones and Erinacines

Both the mycelia (erinacines A-I) and the fruiting bodies (hericenone C-H) are compounds of interest in bioactive extracts

Easily cross the blood brain barrier

Hericenones and Erinacines

Neurotrophic activities

neurite outgrowth stimulation and induced NGF synthesis

Erinacines A, B, C, D, E, F, G, H, and I showed a stronger biological activity that stimulates NGF synthesis than epinephrine (positive control) on murine astroglial cells.

Erinacine A

Isolated from the cultured mycelia of *H. erinaceus* may act as an anti-inflammatory agent to bring about neuroprotection as well as contain potent nerve growth enhancing properties.

Erinacine A

Significantly increased the level of NGF in the locus coeruleus and hippocampus, but not in the cerebral cortex.

*H. erinaceus* mycelium has shown reduction of infarct volumes in global ischemic stroke by 22% at 50 mg/kg and 44% at concentrations of 300 mg/kg as compared to a control group.
Protection by Hericium Extract and Its Isolates Against Neuron and Nerve Impairment in Ischemia Reperfusion Injuries

Kam-Fai Lai, Chien-Chang Hsu, and Wen-Shih Hsiao

1. Department of Biomedical Science
2. Institute of Biomedicine
E-Mail: kamlai@gtu.edu.tw

Infarct area (%)

- SAM
- Hericium 50 mg/kg
- Hericium 300 mg/kg
- Erinacine A 1 mg/kg
- Erinacine A 5 mg/kg

Subcortex, Cortex, Total

* p < 0.05
# p < 0.01


International Journal of Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms
Hericium erinaceus mycelium

↓

iNOS

↓

p38 MAPK

↓

Inflammation factors

↓

CHOP

↓

Nitro-tyrosine

↓

ROS
Erinacine C

Strongest inducing effect on NGF synthesis, indicating a high potential to treat nervous diseases such as Alzheimer’s disease

Erinacine P, a cyathane-xyloside, and its biomimetic conversions into erinacine A and erinacine B was also found to induce NGF synthesis.

Erinacine Q give rise to cyatha-3,12-dien-14-β-ol named erinacol and 11-O-acetylcyathin A3 are reported to have NGF-enhancing activities.

Thongbai, B., Rapior S., Hyde KD., Wittstein K., Stadler M. (2015), Hericium erinaceus, an amazing medicinal mushroom, Mycol Progress 14:91
Hericenone E was able to stimulate NGF secretion that was two-fold higher than that of the positive control (50 ng/mL of NGF)

3-Hydroxyhericenone F

Inhibits β-site Amyloid Precursor Protein-Cleaving Enzyme 1 (BACE1)
Thinking Globally
Several investigations have examined the effects of environmental exposures and epigenetic markers, and identified toxicants that modify epigenetic states. Available evidence supports the concept that epigenetics can predict health-related risks due to conditions of environmental exposure and individual susceptibility.
<table>
<thead>
<tr>
<th>Class</th>
<th>Exposure</th>
<th>Modification</th>
<th>Type</th>
<th>Tissue</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Disruptors</td>
<td>Methoxychlor</td>
<td>DNA methylation</td>
<td>Rat</td>
<td>Sperm, tail, liver, skeletal muscle, and ovaries</td>
<td>Struder and Pakowski-Giacobino (2011) and Zama and Urumcu (2009)</td>
</tr>
<tr>
<td>Endocrine disruptors</td>
<td>Vinpocetine</td>
<td>DNA methylation</td>
<td>Mouse embryo</td>
<td>Placenta, yolk sac, amnion, head, body, heart, liver, lung, stomach, and intestines</td>
<td>Kang et al. (2011)</td>
</tr>
<tr>
<td>Persistent organic pollutants (POPs)</td>
<td>Dichlorodiphenyltrichloroethane (DDT)</td>
<td>DNA methylation</td>
<td>Rat</td>
<td>Hypothalamus</td>
<td>Shutoh et al. (2005)</td>
</tr>
<tr>
<td>Persistent organic pollutants (POPs)</td>
<td>Organochlorine pesticides</td>
<td>DNA methylation</td>
<td>Human</td>
<td>Blood</td>
<td>Kim et al. (2010)</td>
</tr>
<tr>
<td>Persistent organic pollutants (POPs)</td>
<td>DDT, DDE, B-BC, oxchloroethane, ox-chloroethane, mires, PCBs</td>
<td>DNA methylation</td>
<td>Human</td>
<td>Blood</td>
<td>Rusiecki et al. (2008)</td>
</tr>
<tr>
<td>Metals</td>
<td>Arsenic</td>
<td>DNA methylation</td>
<td>In vitro</td>
<td>Rat liver epithelial cells</td>
<td>Zhao et al. (1997)</td>
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<tr>
<td>Metals</td>
<td>Arsenic</td>
<td>DNA methylation</td>
<td>In vitro</td>
<td>Mouse liver</td>
<td>Chen et al. (2004)</td>
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<tr>
<td>Metals</td>
<td>Arsenic</td>
<td>DNA methylation</td>
<td>Human</td>
<td>Blood</td>
<td>Chanda et al. (2006) and Pilner et al. (2006)</td>
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<tr>
<td>Herbicides</td>
<td>Paraquat</td>
<td>Histone modifications</td>
<td>In vitro</td>
<td>Human lymphoblastoid cells</td>
<td>Marsil et al. (2006)</td>
</tr>
<tr>
<td>Herbicides</td>
<td>Dieldrin</td>
<td>Histone modifications</td>
<td>In vitro</td>
<td>Immortalized rat mesencephalic dopaminergic cells (N97 cells)</td>
<td>Song et al. (2010)</td>
</tr>
<tr>
<td>Insecticides</td>
<td>Propoxur</td>
<td>Histone modifications</td>
<td>In vitro</td>
<td>Mouse kidney epithelial cells</td>
<td>Song et al. (2010)</td>
</tr>
<tr>
<td>Insecticides</td>
<td>Dichlorvos</td>
<td>microRNA expression</td>
<td>In vitro</td>
<td>Porcine kidney epithelial cells</td>
<td>Li et al. (2011)</td>
</tr>
<tr>
<td>Insecticides</td>
<td>Fipronil, triazophos</td>
<td>microRNA expression</td>
<td>Zebrafish</td>
<td>Whole body homogenate</td>
<td>Wang et al. (2010)</td>
</tr>
<tr>
<td>Fungicides</td>
<td>Triadimeton, propiconazole, myclobutanil</td>
<td>microRNA expression</td>
<td>Mouse</td>
<td>Liver</td>
<td>Ross et al. (2010)</td>
</tr>
</tbody>
</table>
Higher cumulative anticholinergic medication use is associated with an increased risk for dementia.
Mitochondrial Damaging Medications

Mitochondrial toxicity testing is still not required by the US FDA for drug approval

Review

Medication-induced mitochondrial damage and disease

John Neustadt and Steve R. Pieczenik

Montana Integrative Medicine, Bozeman, MT, USA

Since the first mitochondrial dysfunction was described in the 1960s, the medicine has advanced in its understanding the role mitochondria play in health and disease. Damage to mitochondria is now understood to play a role in the pathogenesis of a wide range of seemingly unrelated disorders such as schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes, hepatitis C, and primary biliary cirrhosis. Medications have now emerged as a major cause of mitochondrial damage, which may explain many adverse effects. All classes of psychotropic drugs have been documented to damage mitochondria, as have stain medications, analgesics such as acetaminophen, and many others. While targeted nutrient therapies using antioxidants or their precursors (e.g., N-acetylcysteine) hold promise for improving mitochondrial function, there are large gaps in our knowledge. The most rational approach is to understand the mechanisms underlying mitochondrial damage for specific medications and attempt to counteract their deleterious effects with nutritional therapies.
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism medications</td>
<td>Disulfiram (Antabuse&lt;sup&gt;<em>&lt;/sup&gt;), acetalaminophen (Tylenol&lt;sup&gt;</em>&lt;/sup&gt;), diclofenac (Voltaren&lt;sup&gt;<em>&lt;/sup&gt;, Voltarol&lt;sup&gt;</em>&lt;/sup&gt;, Diclon&lt;sup&gt;<em>&lt;/sup&gt;, Dicloflex&lt;sup&gt;</em>&lt;/sup&gt;, Difen and Cataflam&lt;sup&gt;<em>&lt;/sup&gt;), fenoprofen (Nalfon&lt;sup&gt;</em>&lt;/sup&gt;), indomethacin (Indocin&lt;sup&gt;<em>&lt;/sup&gt;, Indocid&lt;sup&gt;</em>&lt;/sup&gt;, Indochron&lt;sup&gt;E-R&lt;/sup&gt;, Indocin-SR&lt;sup&gt;<em>&lt;/sup&gt;), Naproxen (Aleve&lt;sup&gt;</em>&lt;/sup&gt;, Naprosyn&lt;sup&gt;*&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Analgesic (for pain) and anti-inflammatory</td>
<td>Bupivacaine, lidocaine, propofol, Perhexiline, amiodarone (Cordarone&lt;sup&gt;<em>&lt;/sup&gt;), Diethylaminoethoxyhexestrol (DEAEH&lt;sup&gt;</em>&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Anesthetics</td>
<td></td>
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<tr>
<td>Angina medications</td>
<td>Amiodarone (Cordarone)</td>
</tr>
<tr>
<td>Antiarrhythmic (regulates heartbeat)</td>
<td>Tetracycline, antimycin A, Amitriptyline (Lentizol&lt;sup&gt;<em>&lt;/sup&gt;), amoxapine (Asendis&lt;sup&gt;</em>&lt;/sup&gt;), citalopram (Cipramil&lt;sup&gt;<em>&lt;/sup&gt;), fluoxetine (Prozac&lt;sup&gt;</em>&lt;/sup&gt;, Symbax&lt;sup&gt;<em>&lt;/sup&gt;, Sarafem&lt;sup&gt;</em>&lt;/sup&gt;, Fontex&lt;sup&gt;<em>&lt;/sup&gt;, Foxetin&lt;sup&gt;</em>&lt;/sup&gt;, Ladoxe&lt;sup&gt;<em>&lt;/sup&gt;, Flucin&lt;sup&gt;</em>&lt;/sup&gt;, Prodep&lt;sup&gt;<em>&lt;/sup&gt;, Fludac&lt;sup&gt;</em>&lt;/sup&gt;, Oxetin&lt;sup&gt;<em>&lt;/sup&gt;, Seronil&lt;sup&gt;</em>&lt;/sup&gt;, Lovan&lt;sup&gt;*&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
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<tr>
<td>Antidepressants</td>
<td>Chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine</td>
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<tr>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Anxiety medications</td>
<td>Alprazolam (Xanax&lt;sup&gt;*&lt;/sup&gt;), diazepam (valium, diastat)</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Amobarbital (Amytal&lt;sup&gt;<em>&lt;/sup&gt;), aprobarbital, butabarbital, butalbital (Fiorinal&lt;sup&gt;</em>&lt;/sup&gt;, hexobarbital (Sombulex&lt;sup&gt;<em>&lt;/sup&gt;), methylphenobarbital (Mebaral&lt;sup&gt;</em>&lt;/sup&gt;), pentobarbital (Nembutal&lt;sup&gt;<em>&lt;/sup&gt;), phenobarbital (Luminal&lt;sup&gt;</em>&lt;/sup&gt;), primidone, propofol, secobarbital (Seconal&lt;sup&gt;<em>&lt;/sup&gt;), Talbutal&lt;sup&gt;</em>&lt;/sup&gt;, thiobarbital</td>
</tr>
<tr>
<td>Cholesterol medications</td>
<td>Atorvastatin (Lipitor&lt;sup&gt;<em>&lt;/sup&gt;, Torvast&lt;sup&gt;</em>&lt;/sup&gt;), fluvastatin (Lescol&lt;sup&gt;<em>&lt;/sup&gt;), lovastatin (Mevacor&lt;sup&gt;</em>&lt;/sup&gt;, Altocor&lt;sup&gt;<em>&lt;/sup&gt;), pitavastatin (Livalo&lt;sup&gt;</em>&lt;/sup&gt;, Pitava&lt;sup&gt;<em>&lt;/sup&gt;), pravastatin (Pravachol&lt;sup&gt;</em>&lt;/sup&gt;, Selektine&lt;sup&gt;<em>&lt;/sup&gt;, Lipostat&lt;sup&gt;</em>&lt;/sup&gt;), rosuvastatin (Crestor&lt;sup&gt;<em>&lt;/sup&gt;), simvastatin (Zocor&lt;sup&gt;</em>&lt;/sup&gt;, Lipex&lt;sup&gt;<em>&lt;/sup&gt;) bile acids – cholestyramine (Questran&lt;sup&gt;</em>&lt;/sup&gt;), clofibrate (Atromid-S&lt;sup&gt;<em>&lt;/sup&gt;), ciprofibrate (Modalim&lt;sup&gt;</em>&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Cancer (chemotherapy) medications</td>
<td>Mitomycin C, profiromycin, adriamycin (also called doxorubicin and hydroxydaunorubicin and included in the following chemotherapeutic regimens – ABVD, CHOP, and FAC)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Tacrine (Cognex&lt;sup&gt;<em>&lt;/sup&gt;), Galantamine (Reminyl&lt;sup&gt;</em>&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td>Metformin (Fortamet&lt;sup&gt;<em>&lt;/sup&gt;, Glucophage&lt;sup&gt;</em>&lt;/sup&gt;, Glucophage XR, Riomet&lt;sup&gt;*&lt;/sup&gt;)</td>
</tr>
<tr>
<td>HIV/AIDS medications</td>
<td>Atripla&lt;sup&gt;®&lt;/sup&gt;, Combivir&lt;sup&gt;®&lt;/sup&gt;, Emtriva&lt;sup&gt;®&lt;/sup&gt;, Epivir&lt;sup&gt;®&lt;/sup&gt; (abacavir sulfate), Epzicom&lt;sup&gt;®&lt;/sup&gt;, Hivid&lt;sup&gt;(ddC, zalcitabine)&lt;/sup&gt;, Retrovir&lt;sup&gt;(AZT, ZDV, zidovudine)&lt;/sup&gt;, Trizivir&lt;sup&gt;®&lt;/sup&gt;, Truvada&lt;sup&gt;®&lt;/sup&gt;, Videx&lt;sup&gt;(ddI, didanosine)&lt;/sup&gt;, Videx&lt;sup&gt;®&lt;/sup&gt; EC, Viread&lt;sup&gt;®&lt;/sup&gt;, Zerit&lt;sup&gt;(d4T, stavudine)&lt;/sup&gt;, Ziagen&lt;sup&gt;®&lt;/sup&gt;, Racivir&lt;sup&gt;®&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Epilepsy/Seizure medications</td>
<td>Valproic acid (Depacon&lt;sup&gt;®&lt;/sup&gt;, Depakene&lt;sup&gt;®&lt;/sup&gt;, Depakene syrup, Depakote&lt;sup&gt;®&lt;/sup&gt;, depakote ER, depakote sprinkle, divalproex sodium)</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
</tr>
<tr>
<td>Parkinson's disease medications</td>
<td>Tolcapone (Tasmar&lt;sup&gt;®&lt;/sup&gt;, Entacapone (COMT&lt;sup&gt;®&lt;/sup&gt; Tan&lt;sup&gt;®&lt;/sup&gt;, also in the combination drug Staleve&lt;sup&gt;®&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>
Raised plasma nerve growth factor levels associated with early-stage romantic love

Enzo Emanuele, Pierluigi Politi, Marika Bianchi, Piercarlo Minoretti, Marco Bertona, Diego Geroldi

\textsuperscript{a}Interdepartmental Center for Research in Molecular Medicine (CIRMC), University of Pavia, Viale Taramelli 24, I-27100 Pavia, Italy
\textsuperscript{b}Department of Health Sciences, Section of Psychiatry, University of Pavia, Pavia, Italy

Received 5 August 2005; received in revised form 12 September 2005; accepted 15 September 2005
Neurotrophic Activity and Myelination
An ethanol extract of *H. erinaceus* fruiting body demonstrated NGF gene expression in astrocytoma cells in a concentration dependent manner. Secretion of NGF was also enhanced by *Hericium* extracts, and the neurite outgrowth was improved.
In vivo 5% *H. erinaceus* fruiting body dry powder for 7 days showed an increase in the level of NGF mRNA expression in the hippocampus by activation of the JNK pathway.
Nerve Growth Factor-Inducing Activity of *Hericium erinaceus* in 1321N1 Human Astrocytoma Cells

Koichiro Mori, a,c Yutaro Obara, a,b Mitsuru Hirot, d Yosh Satoshi Inatomi, e and Norimichi Nakahata*, a,b

a Department of Cellular Signaling, Graduate School of Pharmaceutical Program “CRESCENDO”, Graduate School of Pharmaceutical Sciences, Sendai 980-8578, Japan. c Mushroom Laboratory, Hokuto Corp Japan; and d Department of Bioscience and Biotechnology, Faculty minowa, Kami-in, Nagano 399-4598, Japan.

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Neurotrophic factors are essential to maintain and develop nerve-like substances or their inducers are expected to be effective for diseases such as Alzheimer’s disease. In the present study, we first investigated the neurotrophic activity of *Hericium erinaceus* (Yamabushitake), *Pleurotus* *Agaricus blazei* (Himematsutake), on nerve growth factor synthesis in 1321N1 cells. Among the four mushroom extracts, only *H. erinaceus* extracts showed concentration-dependent manner. In addition, secretion of *H. erinaceus* extracts, and the conditioned medium of 1321N1 neurite outgrowth of PC12 cells. However, hericenones promote NGF gene expression in 1321N1 cells. The enhancement was inhibited by the c-jun N-terminal kinase (JNK) induced phosphorylation of JNK and its downstream substrates. *H. erinaceus* promotes NGF gene expression via JNK signaling. Furthermore we examined the efficacy of *H. erinaceus* in vivo. ddY mice given feed containing 5% *H. erinaceus* dry powder for 7 d showed an increase in...
Aqueous extract of *H. erinaceus* fruiting body has demonstrated an increase in the secretion of extracellular NGF in neurons and neurite outgrowth activity.

A synergistic interaction between *H. erinaceus* aqueous extract and exogenous NGF on the neurite outgrowth stimulation of neurons at physiological relevant concentrations was observed in pre-treatment and co-treatment modes. In conclusion, the aqueous extract of *H. erinaceus* contained neuroactive.
The process of the myelin sheath formation in the presence of *H. erinaceus* extract proceeded at a higher rate and was completed by day 26 as compared to controls.
50-80 year old Japanese adults diagnosed with mild cognitive impairment, 250 mg tablets of dry *H. erinaceus* powder (TID x 4 wk) showed marked improvement in revised Hasegawa Dementia Scale (HDS-R) as compared to the placebo group.
In wild-type mice, the oral supplementation of *H. erinaceus* induced a significant improvement in recognition memory.

In hippocampal slices, an increase in spontaneous and evoked excitatory synaptic current in mossy fiber-CA3 synapse shown in a behaviour test.
Dietary Supplementation of *Hericium erinaceus* Increases Mossy Fiber-CA3 Hippocampal Neurotransmission and Recognition Memory in Wild-Type Mice

Federico Brandalise,1 Valentina Cesaroni,2 Andrej Gregori,3 Margherita Repetti,2 Chiara Romano,2 Germano Orrù,3 Laura Botti,2 Carolina Girometta,5 Maria Lidia Guglielminetti,5,6 Elena Savino,5,6 and Paola Rossi2,6

*H. erinaceus* prevents the impairment of spatial short-term and visual recognition memory.
Effect of Hericium erinaceus on nerve cell growth

Young Shik Seo, Hyeon Yong Lee

1School of Biotechnology, Hanyang University, Ansan 200-701, S. Korea; 2Department of Animal Science, Sunchon National University, Sunchon 540-742, S. Korea; *Author

Received 14 November 2002.

Key words: BDNF, NGF, PC12 cell

Abstract

It was found that the ratio of glucose:galactose of Hericium erinaceus mycelia broth was 1.5:1.7:1.2:0.6:0.9, and the culture broth of Hericium erinaceus improved the extension of nerve growth factors such as BDNF and NGF. The use of two standards has not been
Alzheimer’s Disease

A living body and an absent mind... the great fear
With the increased lifespan of the world’s population, it is estimated that about 80 million people will suffer from dementia by 2040 whereby AD will account for almost 60% of dementia cases.

“A genuinely new Alzheimer’s drug has not been approved since 2003, and the currently approved Alzheimer’s medications are ineffective in stopping or slowing the course of the disease.”

Alzheimer’s Association

243 of 244 drug failures from 2000 – 2010

FDA
Sister Mary, the gold standard for the Nun Study, was a remarkable woman who had high cognitive test scores before her death at 101 years of age. What is more remarkable is that she maintained this high status despite having abundant neurofibrillary tangles and senile plaques, the classic lesions of Alzheimer’s disease. Findings from Sister Mary and all 678 participants in the Nun Study may provide unique clues about the etiology of aging and Alzheimer’s disease, exemplify what is possible in old age, and show how the clinical expression of some diseases may be averted.

Key Words: Neuropathology, Alzheimer’s disease, Dementia, Cognition

Aging and Alzheimer’s Disease: Lessons From the Nun Study

David A. Snowdon, PhD

And what was the secret to her longevity? I remember her telling me that one day she had wondered out loud to her doctor if perhaps he was giving her medicine to keep her alive, and after all, her desire was to be with Jesus. Her doctor replied, “Sister, it’s not my medicine that’s keeping you alive. It’s your attitude!” And it was that wonderful attitude that we all loved. It was Catholics, had grade school educations, and were members of the working class.

Shortly before the close of the nineteenth century, Sister Mary began attending St. Boniface Grade School in Philadelphia. A few months shy of her 13th birthday, she received her First Holy Communion. Later that year, her mother died giving birth to Sister Mary’s tenth sibling.
Reversal of cognitive decline: A novel therapeutic program

Dale E. Bredesen

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Key words: Alzheimer’s, dementia, mild cognitive impairment, neurobehavioral disorders, neuroinflammation, neurodegeneration, systems biology

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Correspondence to: Dale E. Bredesen, MD; E-mail: dbredesen@mednet.ucla.edu; dbredesen@buckinstitute.org

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Abstract: This report describes a novel, comprehensive, and personalized therapeutic program that is based on the underlying pathogenesis of Alzheimer’s disease, and which involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilized this program include patients with memory loss associated with Alzheimer’s disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI). Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months,
Physiological Nudges

- Synaptoblastic Inputs
- Lipoxins
- Neurotrophic Factors
  - NGF
  - BDNF
- Glutamate Inhibition
- Antioxidants
  - Endogenous
  - Exogenous
    - Hormesis
In an Alzheimer’s model a 30 day oral administration of *H. erinaceus* mycelium and its ethanol extracts attenuated cerebral Aβ plaque burden.

The results showed diminished number of plaque-activated microglia and astrocytes in cerebral cortex and hippocampus, increased ratio of nerve growth factor (NGF) to NGF precursor (proNGF), in turn promoting hippocampal neurogenesis after the *H. erinaceus* mycelia administrations.
Initiation of Tau capture by neuronal waste products

Autocatalytic propagation by Tau aggregation

Tau Fibrils

Ghost Tangle

Mutations

Nucleation Event

Healthy Neuron

Tau proteins begin to aggregate

Tau proteins form Paired Helical Filaments

Neuritic plaque

Bundles of PHF’s accumulate as Neurofibrillary Tangle (NFT)

Extracellular NFT

Mature neuritic plaque with tau protein fragments

AGGREGATION INHIBITOR TARGET

Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction

As aggregation continues, short, thin fibrils, known as paired helical filaments (PHFs) form and accumulate into neurofibrillary tangles

Tau aggregates form inside neurons until the neuronal membrane bursts and ultimately kill the neuron. The only remnants being the extracellular “ghost” neurofibrillary tangles

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Molecular docking studies demonstrated 3-Hydroxyhericenone F, Hericenone G, Hericenone F, Hericerin, and Hericene B, respectively with potential activity against BACE1 inhibition.

Administration with *H. erinaceus* decreased the serum cytokine levels (IFN-γ, IL-1β, IL-17α, and TNF-α) and further decreased the production of ROS.
3HF can ameliorate neuronal damage by reversing the decreased levels of \([\text{Ca}^{2+}]_i\) and ROS and improve mitochondrial function, via the increase in mitochondrial membrane potential and ATP levels of the mitochondrial respiratory chain complexes.

Decreased expression levels of the AD intracellular markers BACE1, p-Tau, and Aβ42.
In a model of AD, oral administration of a mixture of *H. erinaceus* fruiting body and mycelium, was given for three months and demonstrated up-regulation of lipoxin A4 (LXA4) in the cortex > hippocampus > substantia nigra > striatum and cerebellum.
Lipoxin A4
Regional distribution of Lipoxin A4

<table>
<thead>
<tr>
<th>Region</th>
<th>Distribution (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td></td>
</tr>
<tr>
<td>S. Nigra</td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td></td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
</tr>
<tr>
<td>Total brain</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes significant difference from baseline.
Lipoxin in Tissues after *H. erinaceus* Feeding
In an animal model of AD, *H. erinaceus* successfully enhanced the acetylcholine and choline acetyltransferase concentrations in both the serum and the hypothalamus in a dose dependent manner.
Attenuation of cerebral Aβ plaque burden

Increased NGF mRNA expression

Diminished plaque-activated microglia and astrocytes

Up-regulation of liopxin A4 (LXA4) in brain

Nutrient Deficiencies

Increased Acetylcholine (Ach) and choline acetyltransferase (ChAT) concentrations

Down regulation of Tau tangles

MOA of *H. erinaceus* in Alzheimer’s disease

Alzheimer’s Disease
Nutrients associated with Dementia

Serum zinc in the normal range may be associated with low senile plaque counts in the elderly

Serum zinc levels significantly lower in dementia pts than controls who were not demented

Same results for a younger group just starting to show dementia signs


In vivo data showed oxidative stress and dopaminergic lesions in the striatum and substantia nigra significantly improved after 25 days of oral treatment with *H. erinaceus* mycelia at low doses (10.76 or 21.52 mg/d).

Consistent with cell culture results, MPTP protection by HEM and erinacine A treatment appeared to be due to a significant reduction of Fas expression in the mouse model.
Peripheral Nerve Injury

Aqueous extract of HEFB (pretreatment of 10 mL/kg 1:1 aqueous extract x 14 days) improved nerve regeneration and increased the rate of motor functional recovery after crush injury. The HEFB animals recovered to pre-surgery values 4 to 7 days earlier than animals in the control group as assessed by walking track analysis.

Normal toe spreading, was achieved 5 to 10 days earlier in the aqueous extract group than in the control group. HEFB aqueous extract promoted peripheral nerve regeneration with significant functional recovery.
Clinical Trials
50-80 year old Japanese adults diagnosed with mild cognitive impairment, 250 mg tablets of dry *H. erinaceus* powder (TID x 4 wk) showed marked improvement in revised Hasegawa Dementia Scale (HDS-R) as compared to the placebo group.
In a study of questionable quality, HEFB (2.0 g/d in cookies over 4 weeks) showed a reduction in some symptoms of anxiety and depression in menopausal women (n = 30).

Using the Indefinite Complaints Index categories for palpitation and incentive showed a statistically significant improvement compared to placebo. For the categories of irritating (p=0.076), anxious (p=0.067) and concentration (0.090) there were trends of improvement as compared to placebo.
Posology
Cognition & NGF production

*H. erinaceus* at doses 3 g (98% *H. erinaceus* powder) showed significant improvement in dementia rating scale in general cognitive decline subjects in a clinical trial.

Cognition & NGF production

3–5 g/day is the recommended daily dosage of dried fruiting body of *H. erinaceus* for increasing NGF production

In a study on anxiety and depression, 2.0 g/d of *Hericium* fruiting body (in cookies) was the dose utilized.

Safety
In an *in vitro* model, HEFB aqueous extract on MRC-5 and NG108-15 cell lines showed a remarkable lack of cytotoxicity. The IC$_{50}$ value for MRC cells was $34.095 \pm 1.200$ mg/mL and for NG108-15 cells it was $17.446 \pm 1.548$ mg/mL.
In an animal model, toxicology studies on *H. erinaceus* suggest that *H. erinaceus* mycelia, enriched with 5 mg/g erinacine A at doses up to 5 g/kg bodyweight are safe.

Toxicology

In clinical trials no toxicity has been reported


Reported Adverse Events

In a double-blind, placebo controlled trial on 50-80 year old Japanese with *H. erinaceus* mycelia (250 mg tablets of 96% dry powder) for 16 weeks, there was no adverse events reported clinically or biochemically in all the study subjects.

Reported Adverse Events

One study subject in a clinical trial on menopausal depression, reported epimenorrhea and discontinued intake of *H. erinaceus* fruiting body cookies.

The possibility of *H. erinaceus* resulting in epimenorrhea in this trial could not be conclusive.

Sensitivities and Allergies

Case report of a 53 y/o male occupationally exposed to *H. erinaceus* fruiting body, after 1 mo developed chronic dermatitis on his finger pulp and dorsa of hands, with painful fissures. The dermatitis spread to his forearms, face and legs at which point exposure discontinued and symptoms resolved.

Thank You