

# Lion's Mane

## The Anti-Dementia Effect of Lion's Mane Mushroom (*Hericium erinaceum*) and Its Clinical Application

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### Introduction

Medicinal Mushrooms have become a hot item in the mass media in the last few years but the information being disseminated about them is not always scientifically accurate. Most of the studies on the efficacy of medicinal mushrooms that are available to the public are based on animal studies (usually in mice) or cultured cells. In these cases, the bioactivity of the mushroom extracts cannot always be correlated to their activity when ingested by humans – either orally or by injection.

Our research on components of Lion's Mane mushroom (*Hericium erinaceum*) and their biological activities in cell culture is a case where positive anti-

dementia results in the laboratory have been confirmed by analogous results in human use. In this article, we will introduce both the results from the laboratory and their clinical application.

### Conventional Treatments of Alzheimer's Disease

Alzheimer's disease is primarily a disorder of aging in which individuals become agitated and uncomprehending, with profound loss of cognitive function, ultimately requiring institutionalization. About 1 in 10 people over the age of 65 and as many as 5 out of 10 people over the age of 85 are affected. This disease is characterized biologically by the death of neurons in the forebrain, hippocampus, and cerebral cortex.

The most conventional approach to treatment of Alzheimer's disease currently in practice is to treat the symptoms caused by the death of cholinergic neurons. Four pharmaceutical products approved by the FDA that are presently on the market work by potentiating neurotransmission at cholinergic synapses. These drugs are: Aricept® by Pfizer, Exelon® by Novartis, Reminyl® by Janssen, and Cognex® by First Horizon. None of these products, however, reverses the damage done to cognitive functioning. They simply delay further deterioration. Recently, a new drug called memantine, produced by Forest Laboratories, was approved for use by the FDA. Memantine works by blocking the receptor for the glutamate

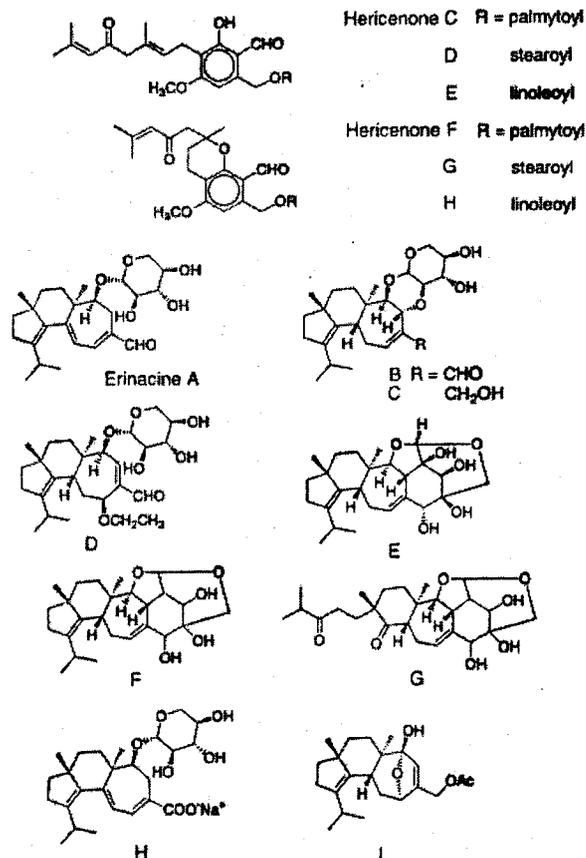
neurotransmitter whose overactivity may be responsible for the neurotoxicity of Alzheimer's disease. Likewise, its beneficial effect is only temporary.

### Inducers of Nerve Growth Factor Synthesis *in vitro*

One of the major new approaches to the study of treatments for Alzheimer's disease concerns the search for agents that stimulate Nerve Growth Factor (NGF) production in the brain. NGF is part of a family of proteins that play a role in the maintenance, survival and regeneration of neurons during adult life. Its absence in the adult brain of mice leads to a condition resembling Alzheimer's disease.

Nerve Growth Factor itself cannot be used as an orally administered drug to regenerate brain tissue because it does not cross the blood-brain barrier. If bioactive substances with low molecular weight can be found that penetrate the barrier and induce the synthesis of NGF inside the brain, such substances may be applied as oral agents to prevent this disease. Even if these substances cannot go through the barrier, the enhancement of NGF production would be beneficial for disorders of the peripheral nervous system since NGF has a similar effect on neurons in the periphery.

We have been engaged in a study to search for NGF synthesis-promoting agents in medicinal mushrooms since 1991. We discovered a class of benzyl alcohol and chroman derivatives in the fruit body of Lion's Mane mushroom called the hericenones C-H that stimulate NGF production from mouse astroglial cells in culture.<sup>1-18</sup> Subsequently, we discovered another group of cyathane derivative compounds from the mycelium of the same mushroom called the erinacines A-I that also induce NGF production.<sup>4-22</sup> (Figure 1)



**Figure 1 – Structures of Hericenones and Erinacines from Lion's Mane Mushroom**

### Hericenones Isolated from the Fruit Body of Lion's Mane

The hericenones were derived from Lion's Mane as follows. The fruit body of the mushroom was crushed in acetone by a blender and left for 1-2 days to allow extraction of nonpolar substances. The liquid extract was processed with vacuum filtration and the mushroom fruit body was further extracted twice by acetone. The extract was concentrated using an evaporator until 2 liters of volume was obtained, and then this was fractionated with chloroform. Ethyl acetate was added to the aqueous phase for an additional extraction.

The fractionation of the extract is an essential step for applying the compounds to the NGF assay, because there is an optimum concentration for the activation of NGF synthesis, and also most of the fractions at this stage exhibit cytotoxic activity. For separation purposes, silica gel chromatography and preparative thin layer chromatography (TLC) were employed, and two types of fractions were obtained: one with hericenones C-E and the other with hericenones F-H. Both fractions were spotted at almost the same distance on the silica gel TLC and thus separation was only possible by high performance liquid chromatography (HPLC), using an ODS column.

These compounds were the first active substances found in natural products that are as effective as epinephrine in inducing NGF synthesis *in vitro*. Each group of hericenones, C-E and F-H, contains a characteristic alcohol site, and each hericenone contains one of three simple fatty acids. Hericenone D demonstrated the strongest stimulating activity in synthesis of NGF from astroglial cells. The activity level of these compounds varies according to the structure of its fatty acid constituent.

### Erinacines Isolated from the Mycelium of Lion's Mane

The erinacines were obtained from Lion's Mane as follows. Following 4 weeks in culture, the mycelium was extracted with 85% ethanol. The ethanol extract was concentrated, and then fractionated with ethyl acetate and water. Erinacines A-I were isolated by silica gel column chromatography on HPLC and preparative TLC.

Erinacines A-I are a series of diterpenoids, with different chemical structures from those of the hericenones, that have powerful activities in stimulating NGF synthesis. The activities of erinacines A-G *in vitro* are

shown in Figure 2. As can be seen, all of these compounds are more potent inducers of NGF synthesis than epinephrine. The newly-discovered erinacine H stimulated 31.5 +/- 1.7 pg/ml of NGF secretion into the medium at 33.3 µg/ml concentration, which was five times greater than NGF secretion in the absence of the compound. The erinacines are the most powerful inducers of NGF synthesis among all currently identified natural compounds.

### Clinical Study of Lion's Mane Mushroom on Dementia Patients

Lion's Mane mushroom, therefore, contains at least two types of compounds – the hericenones and erinacines – that strongly stimulate NGF synthesis *in vitro*. Both of these types of substances, potentially, can cross the blood-brain barrier. The question is, do these substances work when given orally to human patients?

To answer this question, a study was done in a rehabilitative hospital in the Gunma prefecture in Japan, with 50 patients in an experimental group and 50 patients used as a control.<sup>23</sup> All patients were elderly and suffered from cerebrovascular disease, degenerative orthopedic disease, Parkinson's disease, spinocerebellar degeneration, diabetic neuropathy, spinal cord injury, or disuse syndrome. Seven of the patients in the experimental group suffered from different types of dementia. The patients in this group received 5 g of dried Lion's Mane mushroom per day in their soup for a 6-month period. All patients were evaluated before and after the treatment

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period for their Functional Independence Measure (FIM),<sup>24,25</sup> which is a measure of independence in physical capabilities (eating, dressing, walking, etc.) and in perceptual capacities (understanding, communication, memory, etc.).

The results of this preliminary study show that after six months of taking Lion's Mane mushroom, six out of seven dementia patients demonstrated improvements in their perceptual capacities, and all seven had improvements in their overall FIM score (see Figures 3 and 4). A more extensive clinical study is currently underway to further investigate the findings from this small sample.

The focus of research on medicinal mushrooms until now has been primarily on their anticancer and immune-enhancing properties. The preliminary findings from the studies described above on Lion's Mane mushroom suggest that this mushroom may be a potent inducer of brain tissue regeneration. More research on this subject is clearly needed.

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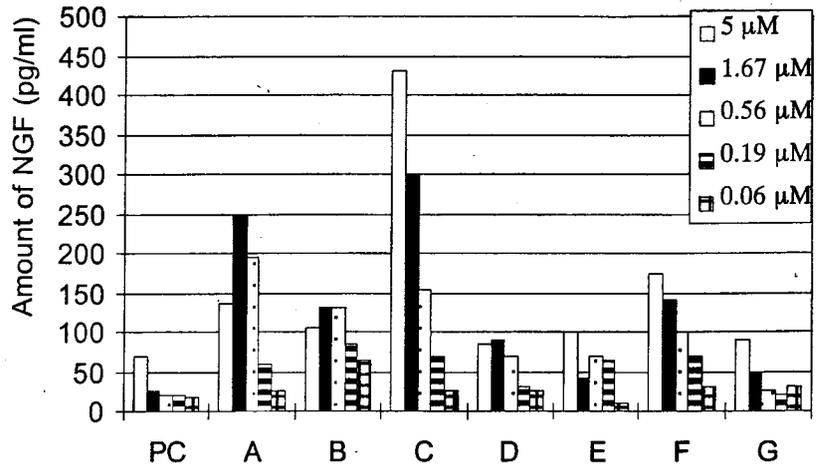
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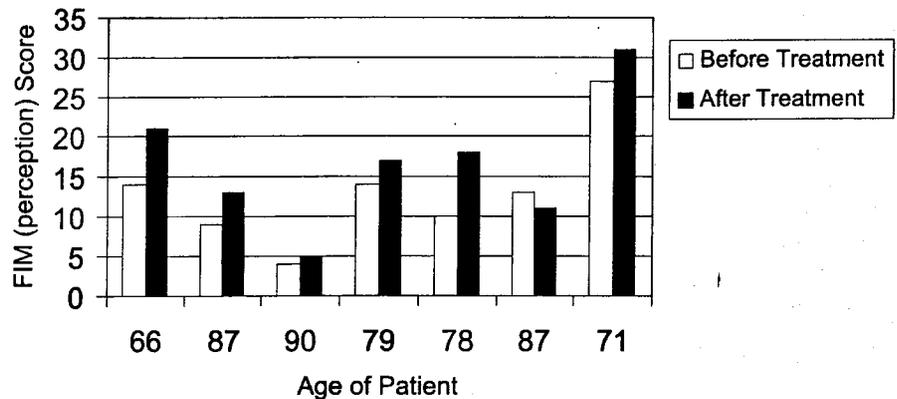
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**Figure 2**  
Activity of NGF Synthesis with Erinacines A-G  
PC: Epinephrine as positive control



**Figure 3**  
The effect of Lion' Mane Treatment on the perception part of the Functional Independence Measure score



**Figure 4**  
The effect of Lion's Mane Treatment on the total Functional Independence Measure score

