Supplementation with *Hericium erinaceus* and *Coriolus versicolor* to Inhibit Progression of Alzheimer´s Disease

Professor Vittorio Calabrese,
Faculty of Medicine, University of Catania, Catania, Italy -
Tel:+39 3288310716 - calabres@unict.it

Maria Laura Ontario PhD.
University of Catania, Catania, Italy

Introduction

The World Health Organization reports that 47.5 million people are affected by dementia worldwide. With ageing populations and 7.7 million new cases each year, the burden of illness due to dementia approaches crisis proportions. Due to increased life expectancy, the prevalence of cognitive decline related to neurodegenerative diseases and to non-neurological conditions is increasing in western countries. Within this context, dementia is a syndrome associated with progressive declines in cognitive capacities and impairments that interfere with daily functioning. These conditions are the primary cause of dependency, disability and institutionalization among older populations.[1]

In 2014, one of the objectives of *Global Action Against Dementia* was to identify a cure or disease-modifying therapy for dementia by 2015. The objective of this paper is to propose a disease-modifying nutritional therapy for early stage dementia based on the use of mushroom nutrition .[2]..

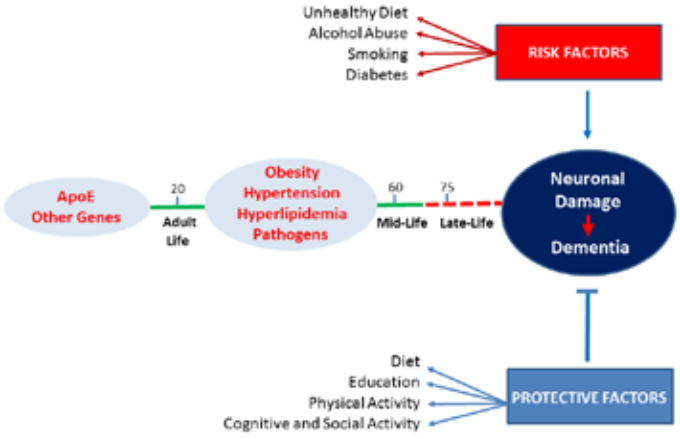

Figure 1: Risk Factors and Protective Factors

***Editors note:** This paper is drawn from the following two papers recently published in 2016 and published with the permission of the authors:

Redox modulation of cellular stress response and lipoxin A4 expression by *Coriolus versicolor* in rat brain: Relevance to Alzheimer´s disease pathogenesis.
Trovato A, Siracusa R, Di Paola R, Scuto M,Fronte V, Koverech C, Luca M, Serra A, Toscano M.A., Petralia A, Cuzzocrea S, Calabrese V. Neurotoxicology. 53:350-8. doi: 10.1016/j.neuro.2015.09.012. 2016.

Redox modulation of cellular stress response and lipoxin A4 expression by *Hericium Erinaceus* in rat brain: relevance to Alzheimer's disease pathogenesis
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What causes Dementia?

Dementia can be caused by:

1. Cerebrovascular diseases (Silent stroke, micro-infarcts, arteriosclerosis)
2. Traumatic Brain Injury (TBI)
3. Hypertension
4. Alzheimer´s disease (AD)

In all these conditions an increased burden of beta amyloid occurs and neuro-inflammations ensues. The most common cause of dementia is Alzheimer´s disease (AD).[3]

Dementia and AD are multifactorial disorders (Figure 1). Hypotheses regarding the cause of dementia have also changed over time. As recently as the 1960s, a vascular aetiology was the prevailing view, while now it is increasingly reported that mixed pathology dementias account for half or more of all dementia cases, with beta-amyloid and vascular disease constituting the most frequent combination of pathologies.

Atherosclerosis, arteriosclerosis, micro-infarcts, silent stroke, and diffuse white matter disease are all associated with increased risk of dementia. Recent evidence suggests an association between mid-life hypertension, a major risk factor for stroke and diffuse white matter disease, and mid-life obesity with future risk of dementia.

Diverse environmental factors, cerebrovascular dysfunction, and epigenetic phenomena, together with structural and functional genomic dysfunctions lead to amyloid deposition, neurofibrillary tangle formation and premature neuronal death, the major neuro-pathological hallmarks of AD.[4,5]

Two major hypotheses have been implicated in the pathogenesis of AD. namely the cholinergic hypothesis which ascribed the clinical features of dementia to the deficit cholinergic neurotransmission and the amyloid cascade hypothesis which emphasized on the deposition of insoluble peptides formed due to the faulty cleavage of the amyloid precursor protein. Current pharmacotherapy includes mainly the acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor agonist which offer symptomatic therapy and does not address the underlying cause of the disease.

The disease-modifying therapy has garnered a lot of research interest for the development of effective pharmacotherapy for AD. β and γ-Secretase constitute attractive targets that are focused in the disease-modifying approach. Potentiation of α-secretase also seems to be a promising approach towards the development of an effective anti-Alzheimer therapy. Additionally, the ameliorative agents that prevent aggregation of amyloid peptide and also the ones that modulate inflammation and oxidative damage associated with the disease are focused upon. On the other hand, development in the area of the vaccines is in progress to combat the characteristic hallmarks of the disease.[5]

The genetic, cellular, and molecular changes associated with Alzheimer disease provide evidence of immune and inflammatory processes involvement in its pathogenesis. These are supported by epidemiological studies, which show some benefit of long-term use of NSAID. The hypothesis that AD is in fact an immunologically mediated and even inflammatory pathological process may be in fact scientifically intriguing.

There are several obstacles that suggest the need for more complex view, in the process of targeting inflammation and immunity in AD. In 2000, researchers led by Dr Frank M LaFerla at the Department of Neurobiology and Behaviour at the University of California Irvine, Irvine, USA, demonstrated that a synthetic

protein that resembles the Herpes Simplex Virus (HSV-1) mimics the structure and function of a protein called β-amyloid, the toxic agent that accumulates in the brains of Alzheimer patients.[6] Moreover, genetic sequencing revealed that two-thirds of the viral protein is identical to the β-amyloid protein, and also, the viral protein generates abnormally twisted fibers similar to those found in AD brain brains (neurofibrillary tangles, formed of hyper-phosphorylated 'tau' protein) representing one of the hallmark of the disease.[7]
Several data indicate that neuronal infection with herpes simplex virus type 1 (HSV-1) causes biochemical alterations reminiscent of Alzheimer's disease (AD) phenotype. They include accumulation of amyloid-β (Aβ), which originates from the cleavage of amyloid precursor protein (APP), and hyper-phosphorylation of tau protein, which leads to neurofibrillary tangle deposition. HSV-1 infection triggers APP processing and drives the production of several fragments including APP intracellular domain (AICD) that exerts trans-activating pro-inflammatory properties. Although a recent study indicated unequivocally lack of evidence for a role of HHV-6 in the pathogenesis of Alzheimer's disease,[8] still there are evidence indicating that, for instance, HSV-1 infection might induce early upstream events in the cell that may eventually lead to Aβ deposition and tau hyper-phosphorylation and further suggest HSV-1 as a possible risk factor for AD.[9-14]

Increasing evidence indicates that aspirin-triggered Lipoxin A4 (LXA4) (15 μg/kg) s c, twice a day, reduced both NF-kB activation and levels of pro-inflammatory cytokines and chemokines, as well as increased levels of anti-inflammatory IL-10 and transforming growth factor B (beta). Basically, LXA4 seems to reduce brain inflammation.[15] Such changes in the cerebral milieu resulted in recruitments of microglia in an alternative phenotype as characterized by the up-regulation of Ym1 and arginase-1 and the down-regulation of inducible nitric oxide synthase expression.[16]

In effect, the researchers contend that activating LXA4 signalling may represent a novel therapeutic approach for AD. Given the potential gastrointestinal discomfort associated with aspirin intake, is there another manner to increase LXA4 in the brain as well as provide both anti-viral protection and anti-oxidant protection?

Why Mushroom Nutrition?

In the past ten years, the clinical development of mushroom nutrition has determined that *Coriolus versicolor* (biomass) has viral protective properties, while *Hericium erinaceus* (biomass) is extremely high in SOD content. Consistent with this notion *Coriolus versicolor* biomass has a clinically verified use in the reduction of viral load of EBV, CMV and HHV-6. These viruses are related to the onset of Chronic Fatigue Syndrome condition.[17,18] In addition, *Coriolus versicolor* has been used to increase the regression rate of LSIL lesions in HPV patients and to significantly reduce the viral load in HPV patients.[19]

Hericium erinaceus biomass has an extremely high super-oxide dismutase (SOD) content which in the presence of in vitro proteolytic enzymes (per 500 mg tablet) has a SOD content of 19.430 10^3 U.[20] This high SOD content is important given that with Herpes Simplex virus infection, apoE4 intensifies virus latency and is associated with the increased oxidative damage to the central nervous system. In addition there is some evidence that herpes simplex virus infection in combination with the apoE4 genotype may be associated with increased risk of Alzheimer´s disease (AD).[21]

Assessing the Capacity of *Coriolus versicolor* and *Hercium erinaceus* to Increase LXA4. LXA4, a metabolic product of arachidonic acid, is considered an endogenous 'stop signal' for inflammation and demonstrates strong anti-inflammatory properties in many inflammatory disorders, such as nephritis, periodontitis or arthritis.[22] Chronic brain inflammation sustains the progression of Alzheimer´s disease, so the objective is to find molecules that can reduce brain inflammation; thereby providing a disease-modifying therapy for dementia.

Research was conducted at Catania and Messina Universities to evaluate if the biomass form of *Coriolus versicolor* and *Hericium erinaceus* stimulates Lipoxin A4 (LXA4) activation in peripheral blood and in the CNS of male rats treated with an equivalent human dose of 3g per day given, orally. One group of rats were supplemented with ***Coriolus versicolor*** biomass and another group (Control) that was not supplemented over 30 days (N=10) [23]. This same protocol was conducted in a separate study with *Hericium erinaceus* biomass over 90 days.[24].

At the end of experimental period animals were sacrificed and the activity of LXA4 was determined in serum, lymphocytes and in different brain regions (cortex, striatum, substantia nigra, hippocampus and cerebellum) and compared with LXA4 of untreated animals, as control.[23,24]

The researchers focused on the impact of *Coriolus versicolor* and *Hericium erinaceus* supplementation on redox-dependent genes, called vitagenes, including heat shock proteins (Hsps), sirtuins, thioredoxin and lipoxin A4 (LXA4).

The differences in the up-regulation of the following vitagenes were measured:
a. Lipoxin A4 (LXA4)

b. Heme Oxygenase-1 (HO-1);

c. Heat Shock Protein 70 (Hsp 70).

d. Thioredoxin

Results: LXA4-Coriolus versicolor vs Control

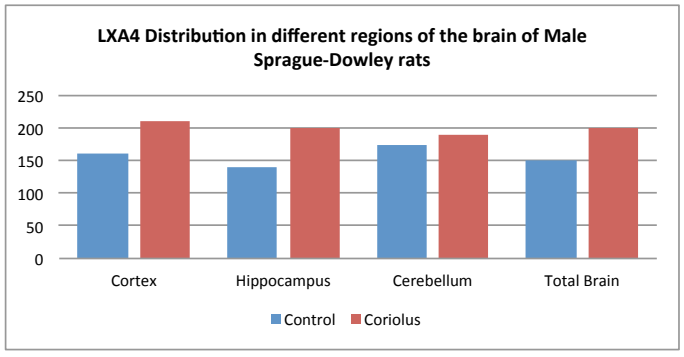

Figure 2

Densitometric Units	Control	Coriolus
Cortex	160	210
Hippocampus	140	200
Cerebellum	175	190
Total Brain	150	200

Table 1

As outlined in Figure 2 and Table I, regional distribution of Lipoxin A4 protein levels in different brain regions and in total brain of control or Coriolus-fed rats. Values are expressed as mean SEM of three independent analyses on 10 animals per group. CX: cortex; Hp: hippocampus; Cb: cerebellum; TB: total brain.

Administration of *Coriolus versicolor* for 30 days at the oral daily dose of 200 mg/kg induced an increase in the protein levels of LXA4 in all brain regions examined. This effect was significant (P<0.05) in the cortex, hippocampus and in the total brain compared to control group, but not in the cerebellum[23].

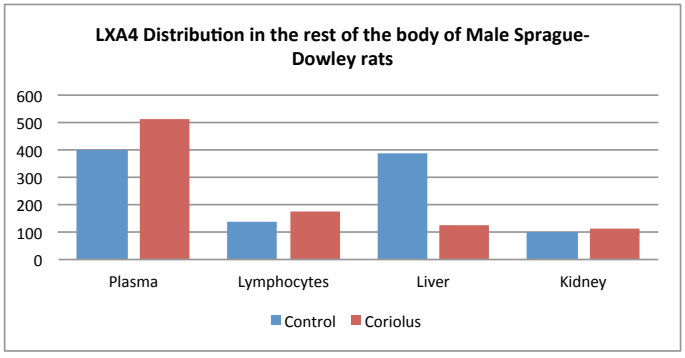

Figure 3

Densitometric Units	Control	Coriolus
Plasma	400	510
Lymphocytes	140	175
Liver	387	125
Kidney	100	110

Table II

In Figure 3 and Table II, demonstrates the distribution of LXA4 levels in plasma from rats fed Coriolus biomass preparation as compared to the control group. Data are expressed as mean SEM of 10 animals per group. *P < 0.05 vs controls; LXA4 levels in liver, kidney and in lymphocytes from rats fed Coriolus biomass preparation as compared to control group. Data are expressed as mean SEM of 10 animals per group. *P < 0.05 vs controls.

As outlined in Table II, animals receiving chronic administration of Coriolus compared to untreated controls, brain changes in LXA4 protein were associated with a significant (P<0.05) increase in plasma (Figure 4 A), lymphocytes and peripheral organs, such as liver and kidney [23].

Heme Oxygenase-1/ Hsp-70 /TrX -*Coriolus versicolor* vs Control

In both Figure 4 and Table III, the Heme oxygenase-1 (HO-1) protein levels in the brain of rats fed Coriolus biomass preparation are compared to the control group. Total brain homogenates from control and mushroom-supplemented rats were assayed for HO-1 expression by Western blot.

As demonstrated in Table III, Coriolus supplementation resulted in up-regulation of brain cellular stress response protein heme oxygenase-1 (HO-1).

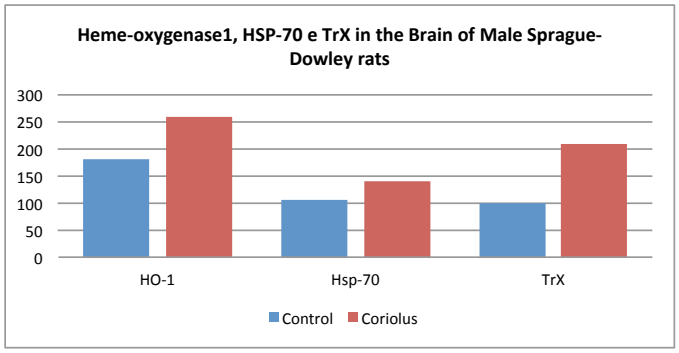

Figure 4

Densitometric Units	Control	Coriolus
HO-1	180	260
Hsp-70	105	140
TrX	100	210

Table III

Inducible Heat shock protein (Hsp-70) protein levels in the brain of rats fed Coriolus biomass preparation are compared to control group. Total brain homogenates from control and mushroom supplemented rats were assayed for Hsp70 expression by Western blot.

As demonstrated in Table III, levels of Hsp 70 were significantly increased.

Thioredoxin (TrX) protein levels in the brain of rats fed Coriolus biomass preparation are compared to the control group. Total brain homogenates from control and mushroom-supplemented rats were assayed for thioredoxin (Trx) by Western blot.

As outlined in Table III, there was a significant increased expression of redox-sensitive thioredoxin in total brain homogenate of Coriolus fed rats when compared to the Control group of rats [23] .

Results II: LXA4 - *Hericium erinaceus* vs Control

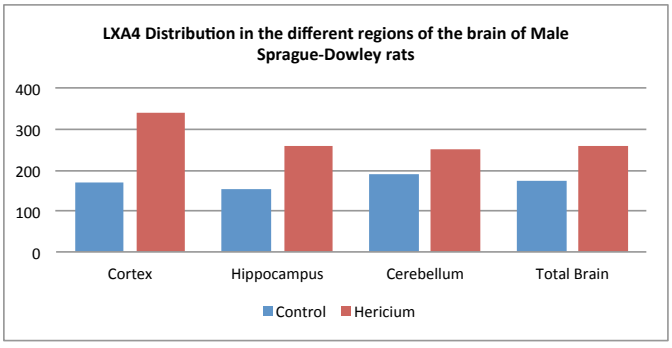

Figure 5

Densitometric Units	Control	Hericium
Cortex	170	340
Hippocampus	155	260
Cerebellum	190	250
Total Brain	175	260

Table IV

As outlined in Figure 5 and Table IV, the regional distribution of Lipoxin A4 protein levels in different brain regions and in total brain of control vs Hericium-fed rats. Values are expressed as mean SEM of three independent analyses on 10 animals per group. CX: cortex; Hp: hippocampus; Cb: cerebellum; TB: total brain. Hericium, was given orally at the dose of 200 mg/kg for 90 days.

Administration of *Hericium erinaceus* for 90 days at the oral daily dose of 200 mg/kg induced an increase in the protein levels of LXA4 in all brain regions examined. This effect was significant (P<0.05) in the cortex, hippocampus, cerebellum and in the total brain compared to control group [24].

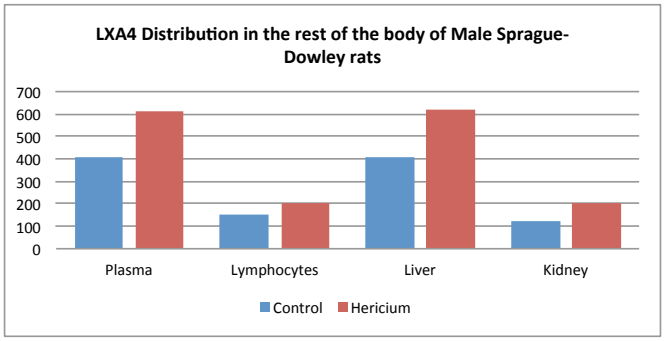

Figure 6

Densitometric Units	Control	Hericium
Plasma	410	610
Lymphocytes	150	200
Liver	410	620
Kidney	125	200

Table V

Outlined in Figure 6 and Table V, provides a comparision of the LXA4 levels in plasma from rats fed Hericium biomass preparation to the control group after 90 days. Data are expressed as mean SEM of 10 animals per group. *P < 0.05 vs controls; LXA4 levels in liver, kidney and in lymphocytes from rats fed Hericium biomass preparation as compared to control group. Data are expressed as mean SEM of 10 animals per group. *P < 0.05 vs controls.

As outlined in Table V, animals receiving chronic administration of Hericium compared to untreated controls, brain changes in LXA4 protein were associated with a significant (P<0.05) increase in plasma , lymphocytes and peripheral organs, such as liver and kidney [24].

Heme Oxygenase-1/ Hsp-70 /TrX –*Hericium erinaceus* vs Control

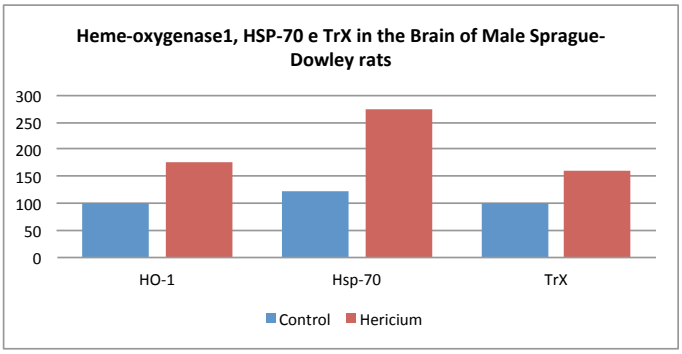

Figure 7

Densitometric Units	Control	Hericium
HO-1	100	175
Hsp-70	124	275
TrX	100	160

Table VI

Outlined in Figure 7 and Table VI are the Heme oxygenase-1 (HO-1), the Inducible Heat Shock (Hsp-70) and Thiorexdoxin (TrX) protein levels in the brain of rats fed Hericium biomass preparation as compared to the control group after 90 days. Total brain homogenates from control and mushroom-supplemented rats were assayed for HO-1 expression by Western blot.
As demonstrated in Table VI, Hericium supplementation resulted in up-regulation of brain cellular stress response protein heme oxygenase-1 (HO-1).

As demonstrated in Table VI, levels of Hsp 70 were significantly increased.
As outlined in Table VI, there was a significant increased expression of redox-sensitive thioredoxin in total brain homogenate of Hericium fed rats when compared to the Control group of rats [24].

Conclusion

Coriolus versicolor biomass and *Hericium erinaceus* biomass supplementation has been shown to significantly up-regulate LXA4 in the brain in rats (in 30 days and 90 days respectively) when compared to separate control groups. In addition, there was a significant increase in heme oxygenase-1, Hsp 70 and thioredoxin in the total brain of both Coriolus-fed rats and Hericium-fed rates when compared to their respective control groups.[23,24]

These results could have implications for the development of a mushroom nutrition based, disease-modifying therapy, for the treatment of patients with Mild Cognitive Impairment (MCI) or pre-Alzheimer´s disease. In such a patient group, the objective is to reduce the first signs of brain inflammation while testing for both viral infections (HSV1, HSV2 or CMV) and genetic susceptibility to AD [24].
This finding has been further refined and consolidated in a subsequent study indicating the powerful therapeutic potential of a supplementation with mushroom nutrition in the control of neuroinflammatory alterations sustaining the pathogenesis of MCI or pre-Alzheimer's disease with potential impact on the course and the progression of the disease.[23,24]
This nutritional approach is not a cure, but a stop-gap approach until a pharmaceutical alternative can be discovered and confirmed.
The next step is to construct a clinical trial that provides a 'proof of concept' in patients.

Supplementation with *Hericium erinaceus* and *Coriolus versicolor* to Inhibit Progression of Alzheimer´s Disease *continued…*

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Note: The *Coriolus versicolor* and *Hericium erinaceus* biomass was supplied by Mycology Research Laboratories Ltd.-United Kingdom. (www.mycologyresearch.com)

Editors Note:
For more information, we recommend that readers review the article entitled "*Link Between Herpes simplex Virus and Alzheimer´s Disease: Potential Role of Mushroom Nutrition Supplementation in Prevention.*" Fernandes, T, Calabrese, V. Clinical Journal of Mycology Vol IV, (Nov 2013).
http://www.mycologyresearch.com/pdf/newsletter/CJourVol4-web3.pdf

Clinical Journal of Mycology
is published by Aneid Press, a division of Aneid Lda
Editor:
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