Clinical Journal of Mycology [CJM]

January 2022 Volume 6 - ISSN 1646-6551

Mushroom Nutrition in Neurodegenerative Diseases

https://doi.org/10.54225/cjm.vol6.2010557

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Neuroinflammation is a specialized immune response that occurs in the central nervous system, mainly in older adulthood, and has been connected to chronic neurodegenerative disorders and characterized by a gradual loss of neurons from specific regions in the brain.

Brain inflammation has been linked to:

- Amyotrophic Lateral Sclerosis (ALS)
- Parkinson´s disease (PD)
- Dementia with Lewy bodies (DLB)
- Psychosis
- Ageing
- Multiple Sclerosis (MS)
- Alzheimer´s disease (AD)
- Depression and Stress
- Cognitive Functions

The effects of mushroom-preparations is an area of increasing interest associated with health benefits in a number of pathologies, mostly associated with oxidative stress and free-radical-induced cell damage[1]. Of particular note is the potential use of mushroom-preparation as a disease modifying therapy in neurodegenerative conditions.

The brain has a large potential oxidative capacity but a limited ability to counteract oxidative stress[2-4]. Within the cell, reactive oxygen species (ROS) are physiologically present at minimal concentration as by-products of aerobic metabolism as well as second messengers in many signal transduction pathways and, in normal conditions, there is a steady-state balance between pro-oxidants and antioxidants which is necessary to ensure optimal efficiency of antioxidant defenses[5-8]. However, when the rate of free radical generation exceeds the capacity of antioxidant defenses, oxidative stress ensues with consequential severe damage to biomolecules such as proteins, lipids, nucleic acids, and carbohydrates[9-11].

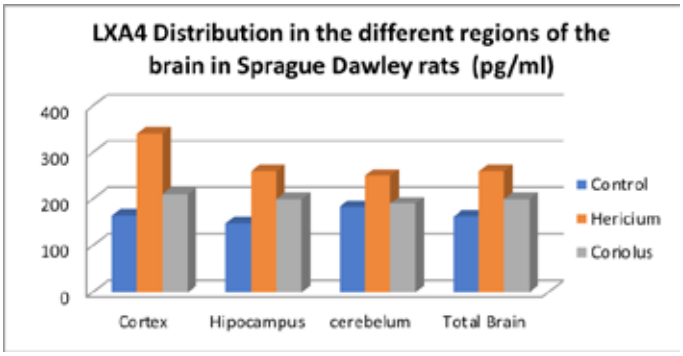
Increase Lipoxin A4

One approach to reduce neuroinflammation is to increase Lipoxin A4 (LXA4). This is an endogenously produced eicosanoid, that inhibits neutrophil recruitment and activation, reduces many cell responses evoked by pathogens and pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), blocks the generations of these pro-inflammatory proteins from Th1 cells, CD4+ cells, macrophages, and dendritic cells, and toxic compounds including ROS, thereby promoting resolution of inflammation, and acts as an endogenous "breaking signal" in the inflammatory process[12].

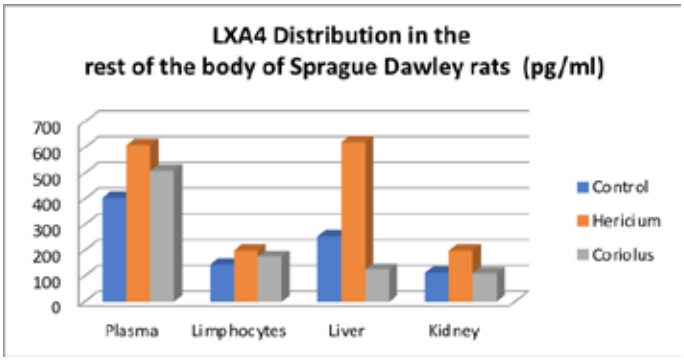
In 2015 and 2016 a team of researchers at the University of Catania, Italy, led by Professor Vittorio Calabrese demonstrated that mushroom-preparations, such as *Hericium erinaceus* and *Coriolus versicolor* can increase Lipoxin A4 in Sprague Dawley rats when compared to a control group in 90 and 30 days respectively[12-13]. The supplementation was an equivalent human dose of 3 g per day.

The following graphs A and B outline the LXA4 distribution in Sprague Dawley rats over 90 days with *Hericium erinaceus* biomass and over 30 days with *Coriolus versicolor* biomass in the brain and in the rest of the body.

GRAPH A



GRAPH B



Cite as: Calabrese V, Ontario M (2022). Mushroom Nutrition in Neurodegenerative Diseases. *Clinical Journal of Mycology*-CJM. Vol 6.3; https://doi.org/10.54225/cjm.vol6.3.71520

Increases in stress biomarkers

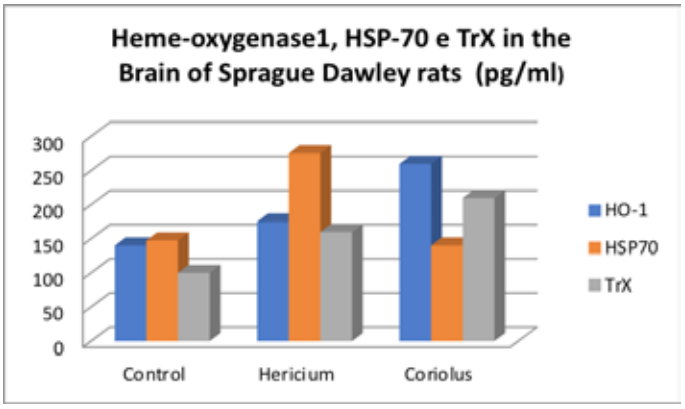
In addition to measuring LXA4, additional oxidative stress biomarkers were measured:

1) Heme-Oxygenase –1(HO-1) – an Nrf2-regulated gene that plays a critical role in the prevention of vascular inflammation, especially in atherogenesis.

2) Heat Shock Protein 70 (Hsp-70 – a cell protector from thermal or oxidative stress; such stresses cause proteins to "unfold" and possible aggregation; Hsp-70 binds to unfolded proteins thereby suppressing possible aggregation. Hsp-70 directly inhibits apoptosis.

3) Thioredoxin – a stress-inducible antioxidant protein playing a cytoprotective role and being central metabolic regulators.

GRAPH C



The University of Catania researchers noted that there was a significant increase in Heme-Oxygenase-1 (HO-1), Heat Shock Protein (Hsp 70) and Thioredoxin in the total brain of Sprague Dawley rats supplemented with *Coriolus versicolor* and *Hericium erinaceus* when compared to control groups. The supplementation was an equivalent human dose of 3g per day[12-13].

***Coriolus versicolor* Supplementation in Meniere´s Disease**

Meniere's disease (MD) is a clinical syndrome affecting approximately 12 in every 1000 people world-wide[14]. It is characterised by episodes of spontaneous vertigo associated with fluctuating, low-to-medium frequencies sensorineural hearing loss (SNHL), tinnitus and aural fullness in one or both ears[15].

To date, the cause of MD remains largely unknown, although increasing evidence suggests that, as an oxidant disorder, oxidative stress, immunomodulation and neuroinflammation may be central to its pathogenesis[16]. At present, there is no cure for this distressing neurodegenerative condition.

In 2018 and 2019, researchers in the University of Catania enrolled 40 patients with Meniere's disease of which 22 were supplemented with *Coriolus versicolor* biomass (3 g/day-6 tablets per day-3 tablets in morning and 3 tablets in evening) over two months and 18 participants were part of the control group [17].

By supplementing Meniere´s Disease (MD) patients with *Coriolus versicolor* biomass (3g/day) for two months one can test the possibility that mushroom supplementation, in a clinical setting, can reverse oxidative damage, and conceivably affect beneficially the clinical course of Meniere's disease.

The researchers lead by Professors Luigi Maiolino and Vittorio Calabrese at the University of Catania tested the hypothesis that neurotoxic insult represents a critical primary mediator operating in Meniere´s Disease pathogenesis, reflected by quantitative increases of markers of oxidative stress and cellular stress response in the peripheral blood of human patients. (see Table 1)

Changes in systemic oxidative stress		Changes in cellular stress response
Carbonyl groups		Heat shock protein (Hsp70)
4-Hydroxynonenal (HNE)		Heme oxygenase-1 (OH-1)
Lipoxin A4		Thioredoxin levels
Isoprostane PF2		Sirtuin-1
Isoprostane PGF2		GSH and γ-GC ligase
11-dhydro TXB2		

1. Changes in systemic oxidative stress status

The effect of *Coriolus versicolor* supplementation on systemic oxidative status in MD was assessed by measuring differences in levels of oxidative stress biomarkers, anti-inflammatory and pro-inflammatory eicosanoids in Coriolus-treated and untreated patients.

Biomarkers of oxidative stress

Oxidative stress in tissue leads to the formation of carbonyl groups in amino acid residues of proteins, and to peroxidation of lipids, which produces 4-hydroxynoneneal (HNE) from arachidonic acid or other unsaturated fatty acids[18].

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Carbonyl Groups and 4-hydroxynoneneal (HNE)

Protein carbonylation is generally irreversible, and leads to production of potentially harmful protein aggregates, causing cellular dysfunction and loss of viability. HNE formation is associated with various toxic effects, primarily apoptosis. The levels of both these markers can be used as a measure of oxidative stress. Additionally, it is possible to indirectly estimate the presence of reactive oxygen species (ROS) by measuring enhanced intensity of the normal ultraweak luminescence (UWL) emitted by all living cells [18].

The effect of Coriolus on systemic oxidative status was assessed by measuring plasma carbonyl groups and HNE, and plasma and lymphocyte UWL in both patient groups at the end of the 2-month trial. Each of these markers of oxidative stress was significantly lower in the Coriolus-treated vs untreated patients. In fact, UWL in treated patients was similar to control samples taken from healthy volunteers (Fig. 1).

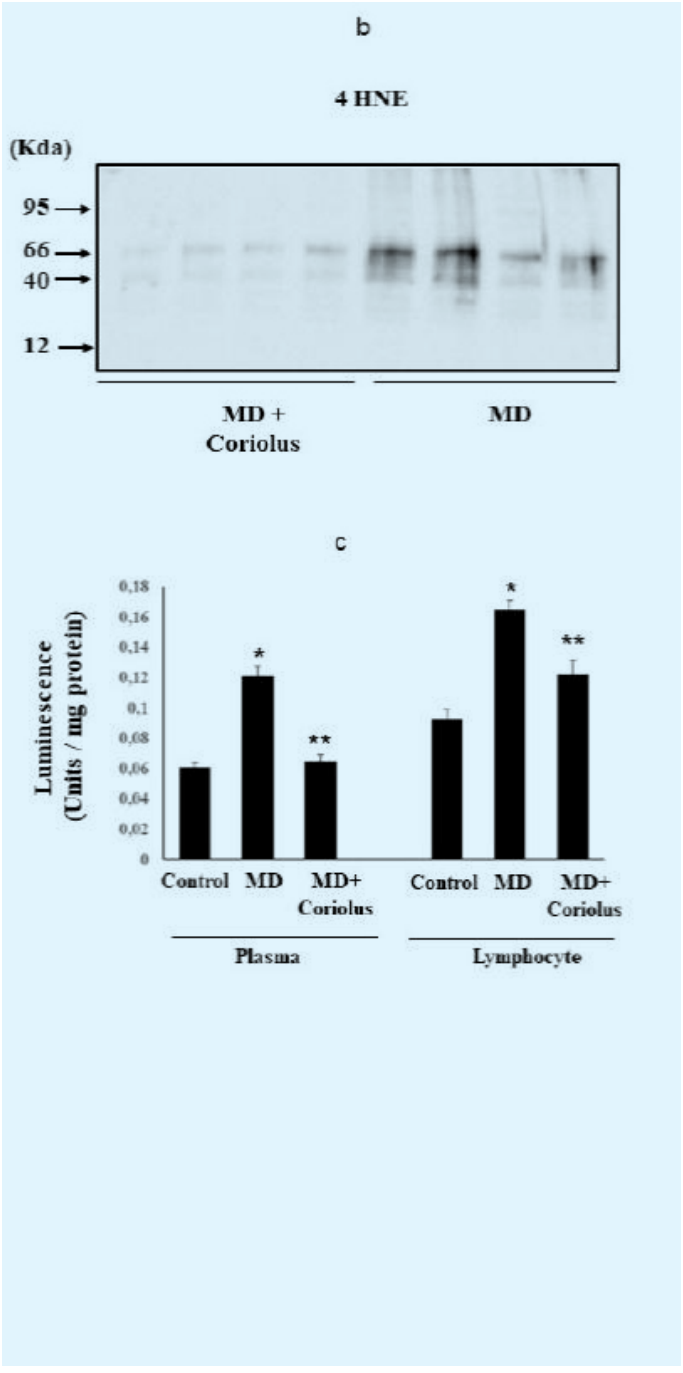
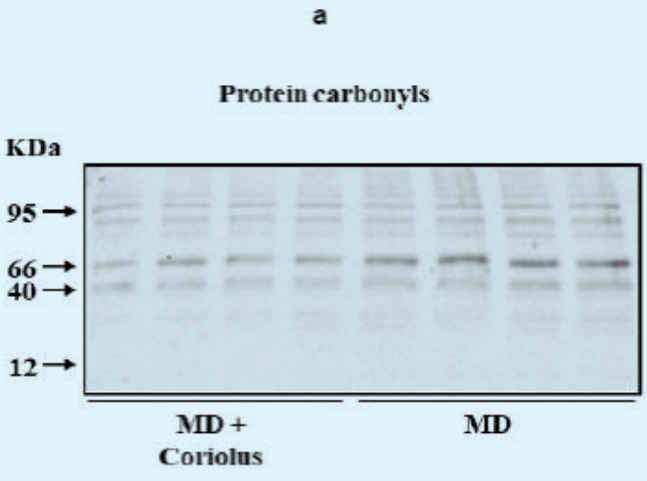


Fig. 1: Western blots (subsequently quantified by immunoassay – (data not shown) of plasma protein carbonyls (a) and HNE (b), and plasma and lymphocyte UWL (c) in Coriolus-treated and un-treated MD patients (healthy volunteer control samples were included for UWL analysis). *p < 0.05 vs control; **p < 0.05 vs untreated MD.

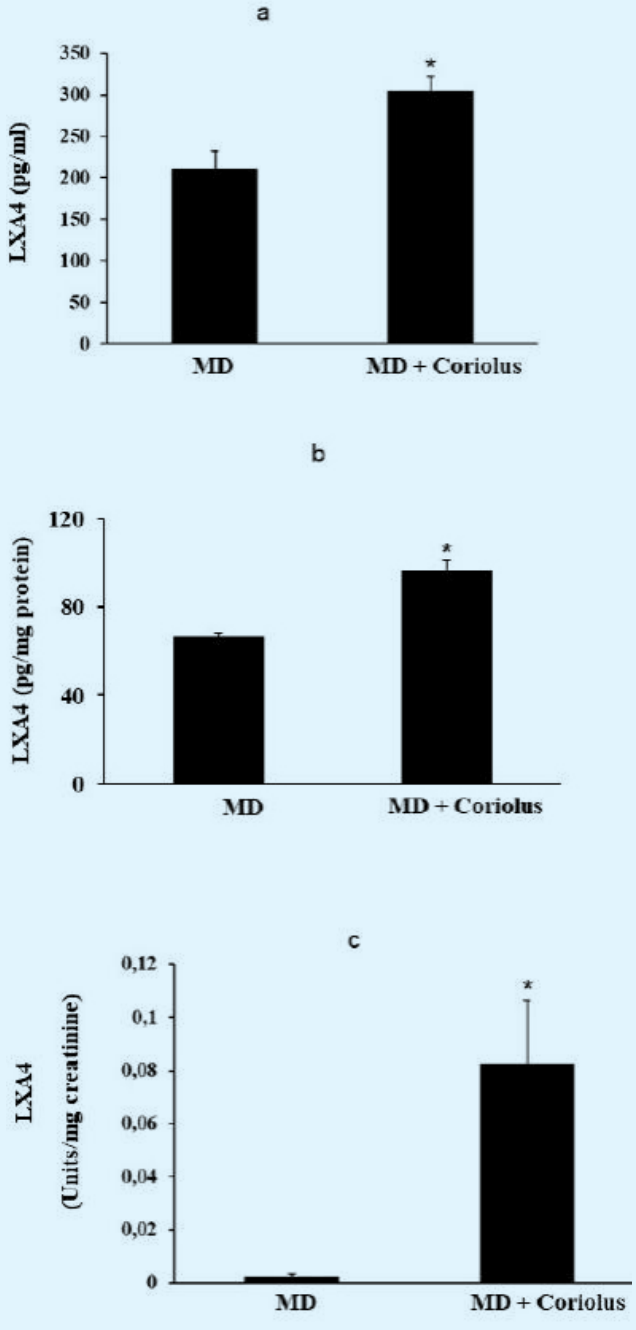


Endogenous anti-inflammatory eicosanoids: Lipoxin A4

Lipoxin A4 (LXA4) is an endogenously produced eicosanoid. It inhibits neutrophil recruitment and activation, reduces many cell responses evoked by pathogens and pro-inflammatory cytokines, and blocks the generation of pro-inflammatory cytokines and toxic compounds, including ROS. LX4A thereby promotes resolution of inflammation, acting as an endogenous 'braking signal' in the inflammatory process [12].

At the end of the 2-month trial, levels of LXA4 in plasma, lymphocytes and urine was significantly higher in patients treated with Coriolus. (Fig 2)

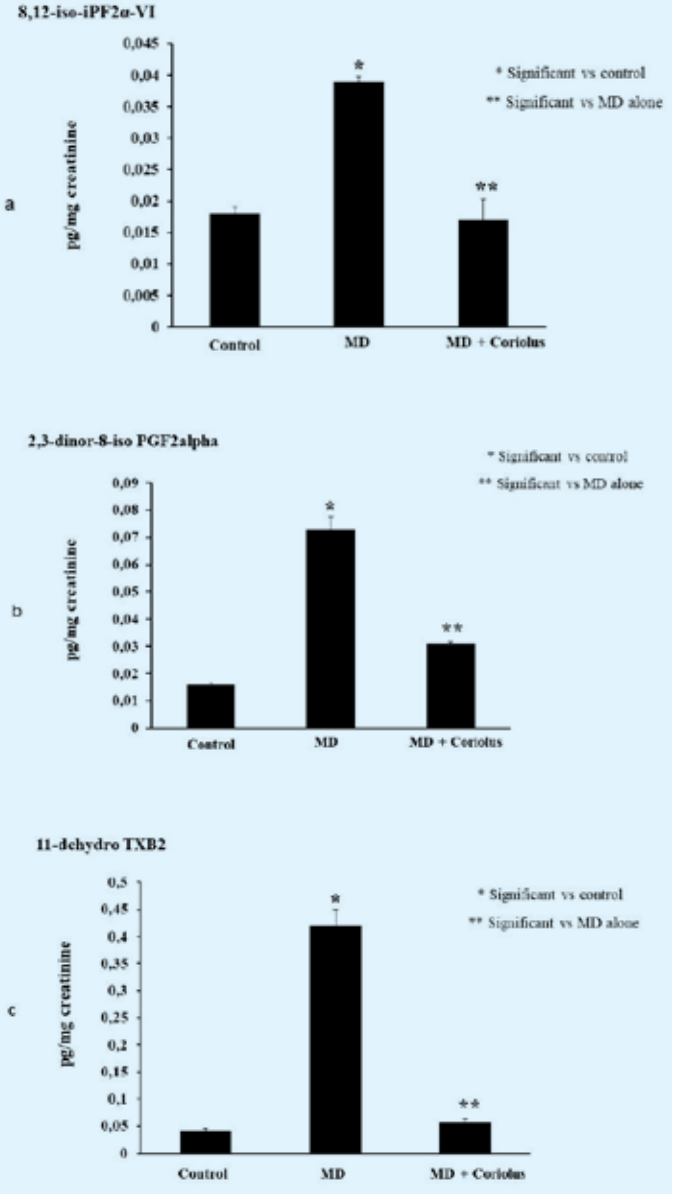
Fig. 2: Levels of LXA4 in the plasma (a), lymphocytes (b) and urine (c) of treated and untreated MD patients (estimated by HPLC + mass spectrometry). *p < 0.05 vs untreated MD.



Endogenous pro-inflammatory eicosanoids

At the end of the study period, urinary levels of pro-inflammatory eicosanoids – isoprostane PGF2 alpha-VI; 2,3 isoprostane PGF2 alpha; and 11-dehydro TXB2 – were significantly lower in the Coriolus-treated patients.

Fig.3: Levels of pro-inflammatory eicosanoids in urine: isoprostane PGF2 alpha-VI (a), 2,3 isoprostane PGF2 alpha (b) and 11-dehydro TXB2 (c) (estimated by HPLC + mass spectrometry). *Significant vs control; **significant vs untreated MD.



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Summary

In Coriolus-treated patients (compared with untreated):

- Oxidative stress biomarkers were lower
- Anti-inflammatory LXA4 levels were higher
- Pro-inflammatory eicosanoid levels were lower

2. Heightened cellular stress responses

Vitagenes are genes that encode proteins whose function is to preserve cell survival under conditions of stress. Vitagenes encompass: vital heat shock proteins (Hsp70 and heme oxygenase-1 [HO-1]); sirtuin-1 (SIRT1); thioredoxin; and γ-glutamylcysteine ligase (γ-GC ligase)[12][19]. The effect of Coriolus supplementation on cellular stress response in MD patients over 2 months was assessed by comparing the levels of each of these biomarkers in both treated and untreated groups at the end of the study.

Heat shock proteins

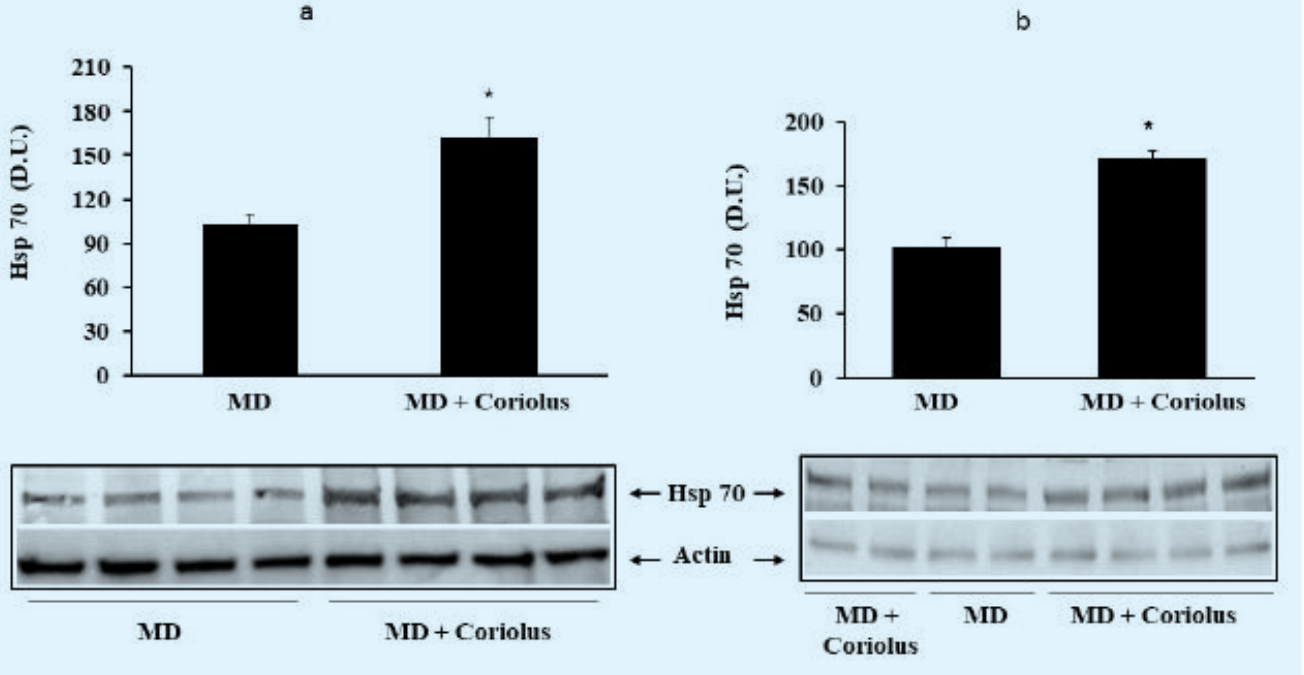
Evolutionarily, heat shock proteins (HSPs) are a highly conserved family of proteins that play a critical role in guiding both the initial folding of nascent proteins and the subsequent refolding of partially denatured structures, thus conferring protection to cells against stressful environments[20]. HSPs are produced in response to thermal or oxidative stress. They include Hsp70 and HO-1, both of which can act as markers of response to thermal and/or oxidative stress.

Hsp70: Thermal and oxidative stresses can cause proteins to 'unfold', which can eventually lead to them clumping together as protein aggregates. Hsp70 binds to unfolded proteins and, in doing so, reduces the potential for aggregation.

HO-1: This is a transcription product of an Nrf2*-regulated gene that plays a critical role in the prevention of vascular inflammation, especially in atherogenesis[21].

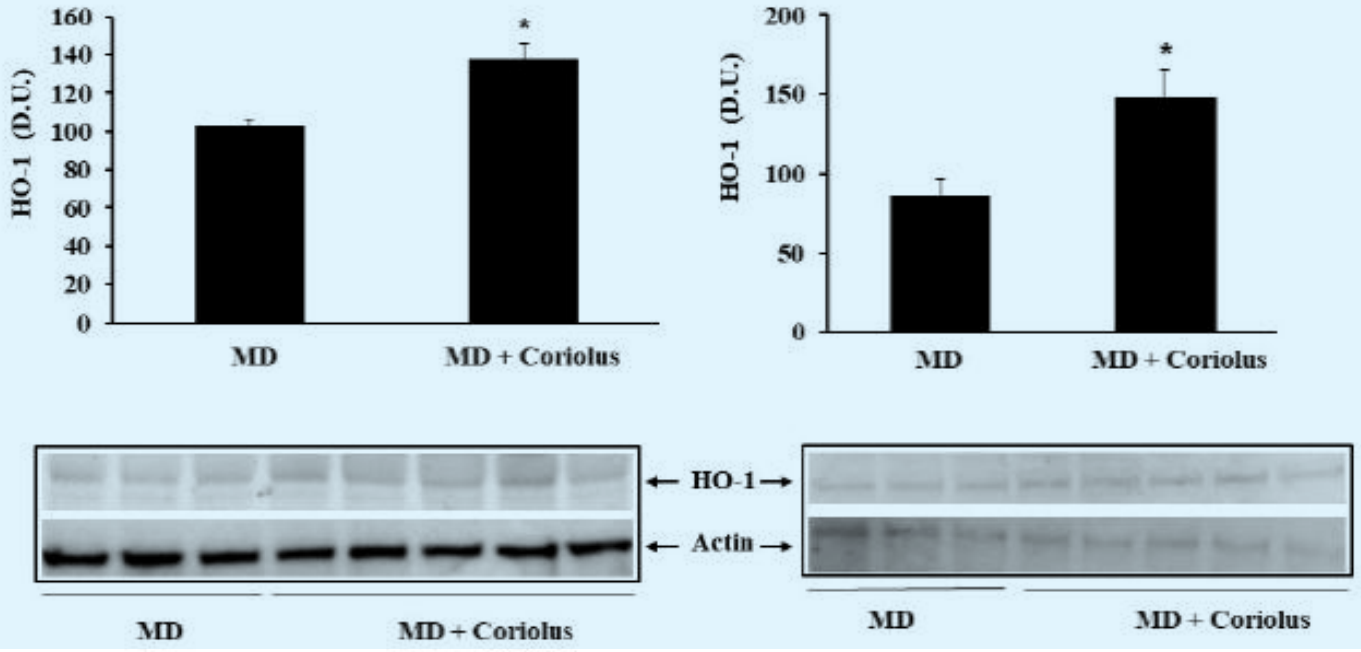
The extent to which Coriolus-treated and untreated patients were able to respond to oxidative stress was assessed by measuring differences between the two groups in up-regulation of the inducible isoform of Hsp70 and HO-1 in lymphocytes and plasma. The levels of both of these HSPs were greater in treated patients, indicating that they were responding more effectively than untreated patients (Fig. 4 and 5).

Fig. 4: Levels of oxidative stress measured as up-regulation of the inducible isoform of Hsp 70 in lymphocytes (a) and plasma (b) (estimated by Western blot + immunoassay). *p < 0.05 vs untreated MD.



*Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that coordinates the basal and stress-inducible activation of a vast array of cytoprotective genes. *p < 0.05 vs untreated MD.

Fig. 5: Levels of anti-inflammatory response measured as up-regulation of the inducible isoform of HO-1

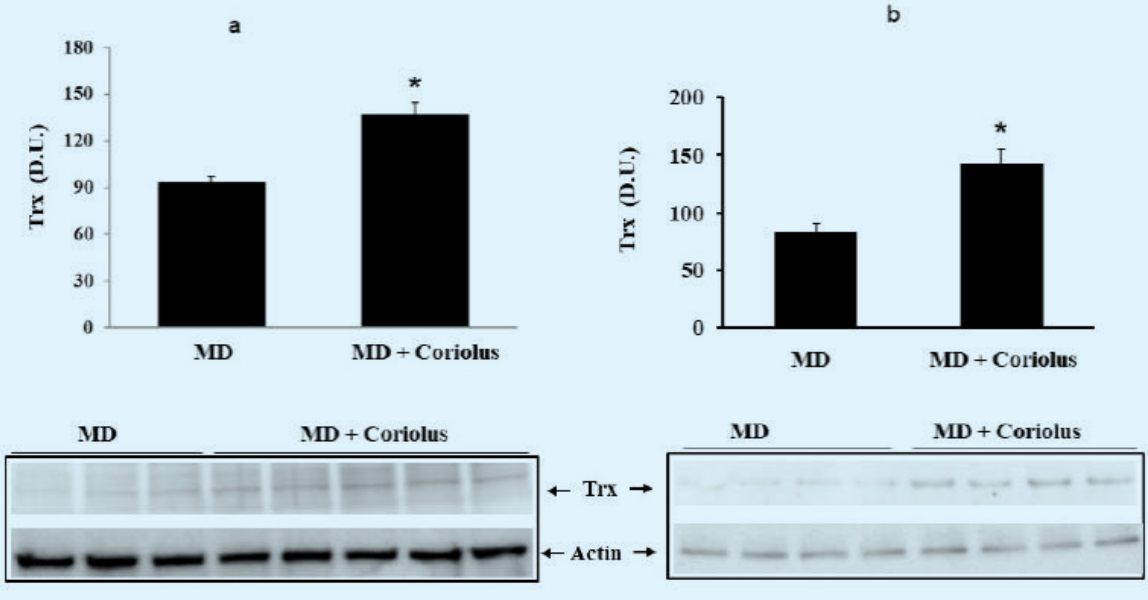


Thioredoxin

Thioredoxin is a class of small redox proteins that act as biological antioxidant by facilitating the reduction of other proteins, thus maintaining proper, functional, redox state[22].

In Coriolus-treated patients, there was significantly greater up-regulation of thioredoxin in lymphocytes and plasma compared with untreated patients (Fig. 6).

Fig. 6: Levels of thioredoxin proteins in lymphocytes (a) and plasma (b) (estimated by Western blot + immunoassay). *p < 0.05 vs untreated MD.



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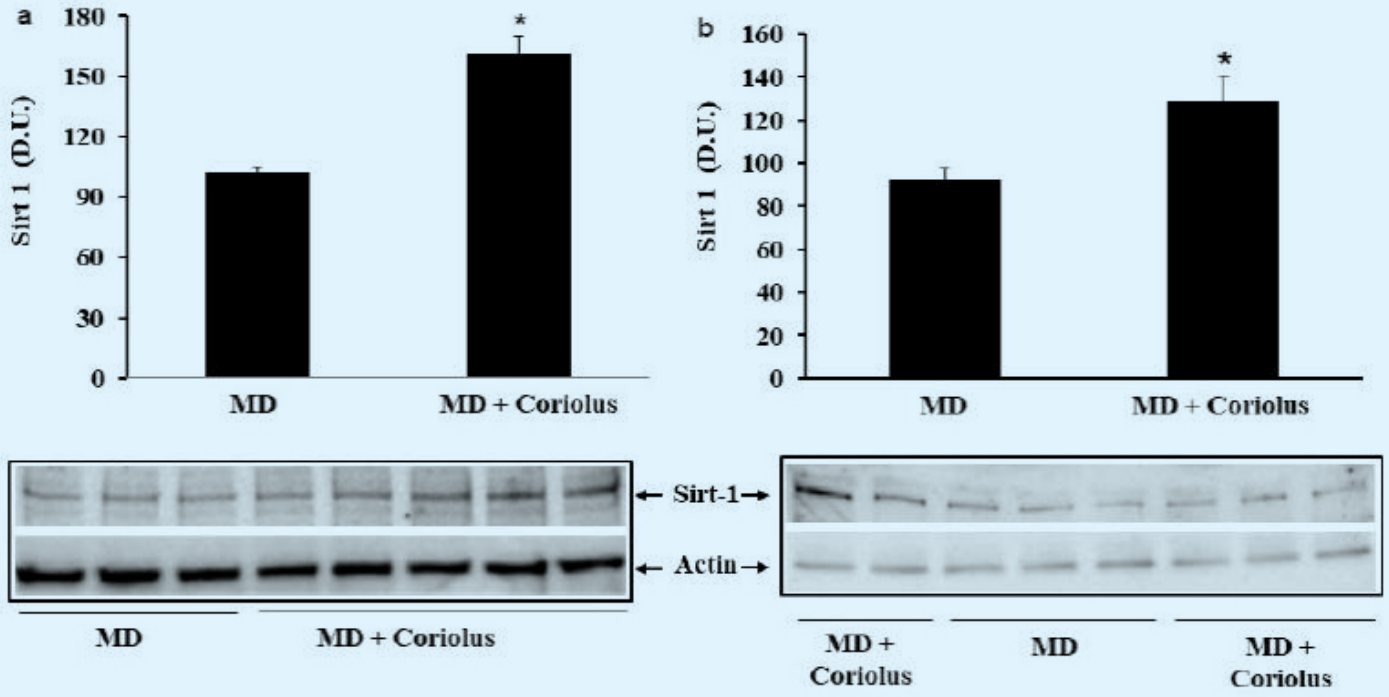
Sirtuin-1

SIRT1 is an enzyme that deacetylates proteins involved in cellular regulation. Activation of SIRT1 suppresses oxidative stress and confers protection against physiological and cognitive disturbance in old age[23]. In Coriolus-treated patients, there was significantly greater up-regulation of SIRT1 in lymphocytes and plasma compared with untreated patients (Fig. 7).

Fig. 7: Levels of Sirtuin-1 proteins in lymphocytes (a) and plasma (b) (estimated by Western blot + immunoassay). *p < 0.05 vs untreated MD.

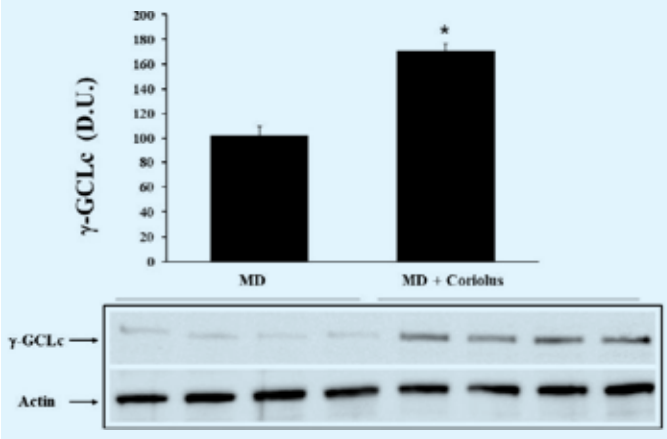


Glutathione (GSH) and Glutamate-cysteine ligase (GCL/γ-GC ligaseGlutathione is an antioxidant that can prevent damage to important cellular components caused by ROS.

GLC enzymatic function and activity is known to be involved in the vast majority of human diseases such as diabetes, Parkinson´s disease, Alzheimer´s disease and cancer. When GLC is impaired, this leads to decreased GSH biosynthesis, reduced cellular antioxidant capacity and the induction of oxidative stress. GSH concentration and γ-GC ligase activity in the central nervous system decline with age in association with increased oxidative stress[24].

In Coriolus-treated patients, lymphocyte levels of γ-GC ligase were significantly higher than in untreated patients (Fig. 8), reflecting the expression of γ-GC ligase in lymphocytes, plasma levels of GSH were significantly higher in Coriolus-treated patients. This corresponded to significantly lower oxidised glutathione (GSSG) levels and resulted in a significantly higher plasma GSH/GSSG ratio. (see Table 2 on next page)

Fig. 8: Levels of γ-GC ligase in lymphocytes (estimated by Western blot + immunoassay). *p < 0.05 vs untreated MD. *p < 0.05 vs untreated MD



Summary

Coriolus-treated subjects had a more pronounced biological response to oxidative stress than untreated patients

Table 2: Levels of GSH and GSSG, and GSH/GSSG ratio in lymphocytes (measured by NADPH-dependent] GSSG reductase assay) of Coriolus-treated and untreated MD patients, and healthy volunteers (control).
*p < 0.05 vs control; **p < 0.05 vs untreated MD.

	Plasma (nmol/mL)			Lymphocyte (nmol/mg. Protein)		
	Control	MD	MD+Coriolus	Control	MD	MD+Coriolus
Total GSH	16.7 ± 2.1	8.33 ± 3.0*	14.23 ± 2.4**	9.81 ± 0.8	5.3 ± 0.7*	7.3± 0.5**
GSH	15.62 ± 2.0	8.44 ± 1.7*	13.44 ±1.7**	9.58 ± 0.6	4.27 ± 0.4*	7.20 ± 0.5**
GSSG	0.138 ± 0.01	0.169 ± 0.01*	0.146 ± 0.01**	0.093 ± 0.01	0.118 ± 0.01**	0.096 ± 0.006**
Ratio GSH/GSSG	113.2 ± 11	56.9 ± 15*	92.05 ± 13**	96.5 ± 10	42.6 ± 7.9	75.0 ± 9.6**
* Significantly different from control (p<0.05). **Significant different from MD alone (p<0.05)						

Study findings

Improved symptom scores At the onset and end of the 2-month study, the researchers measured MD symptoms in both groups.

The psycho-emotional status of all patients was assessed using a Profile of Mood States (POMS) questionnaire.

Total mood disturbance was improved in patients treated with *Coriolus versicolor* biomass (3g/day) but remained unchanged in the untreated patients (Table 1). Improvement was seen in five of the six mood parameters measured: anger, confusion, depression, fatigue, and tension; only vigour was unchanged. All the parameters in the untreated patients remained unchanged [24].

Table 3: Profile of mood status in Coriolus-treated (A) and untreated (B) MD patients.
*Significant vs Group A pre-therapy scores.

	Pre-Therapy (T0)		Post-Therapy (T1)	
	Score		Score	
Group	**A**	**B**	**A**	**B**
Anger (0-48)	28	29	22	29
Confusion (0-28)	17	17	10	16
Depression (0-28)	41	39	25	37
Fatigue (0-28)	16	19	10	19
Tension (0-36)	31	29	13	28
Vigour (0-32)	19	17	19	16
Total Mood Disturbance (-32 to 200)	114 ± 9.8	116 ± 8.6	61 ± 6.11	113 ± 8.1

All patients completed a Tinnitus Handicap Inventory (THI) questionnaire to define the clinical grading of tinnitus. This measures changes in frequency range, average hearing loss in decibels, and verbal discrimination. Tinnitus in treated group showed significant improvement at the end of 2 months but was unchanged in the untreated group (Table 3).

Table 4: Tinnitus handicap inventory in Coriolus-MRL-treated (A) and untreated (B) MD patients. p <0.05 vs untreated MD

Tinnitus Handicap		Inventory	
Pre-Therapy Score		(T0) Post-Therapy Score	(T1)
Group A	Group B	Group A	Group B
74 ± 2.46	78±2.73	52 ±1.73*	74 ± 2.65
*significantly different vs. control untreated MD patients ($p<0.05$)			

Summary

Mood and tinnitus improved
in patients treated with Coriolus supplementation

CONCLUSION: Present results strongly indicate MD as an oxidant disorder, with the underlying pathology involving systemic oxidative stress and demonstrate that *Coriolus versicolor* biomass supplementation (3g/day) for at least two to six months may provide a useful means to amplify the body's response to oxidative challenge and cellular stress in Meniere's disease.

This improved stress response appears to translate into measurable symptom relief (reduction in tinnitus and improved mood). The finding offers the exciting possibility that nutritional supplementation with *Coriolus versicolor* biomass supplementation has potential as a modulator of the MD pathological process with significant reduction in symptom severity in affected patients. (Further studies are in process to further support these conclusions.)

Another conclusion, confirming other previous studies, reveals a proof of concept that mushroom-preparations do reduce oxidative stress and free-radical-induced cell damage; thereby reinforcing further research on the use of mushroom-preparation as a disease modifying therapy in other neurodegenerative conditions.

Acknowledgement:

I would like to thank Ms. Diane Lace for the initial editing of the manuscript

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

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ISSN 1646-6551