

Mushrooms as Functional Foods for Ménière's Disease

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Abstract: Food, not nutrients, is the fundamental unit in nutrition, and edible mushrooms are fungi that supply unique biological bioactive compounds, different from plant or animal origin, which significantly impact human health status. However, to date all these concepts are interpreted in different ways, with rapidly increasing knowledge on nutrition, medicine, molecular biology, and plant biotechnology changing the concepts of food, health, and agriculture. The bioactive elements conveyed by foodstuffs as nutrients or non-nutrients interfere with human metabolism and have influence on health, aging, and well-being. The influence of edible mushrooms on medicinal interventions has been known and studied for many years and their latest role in neurodegenerative disorders has been recently investigated, while their significance on many other diseases has been well demonstrated. Despite considerable research, the etiology and pathogenesis of Ménière's disease remains controversial and undefined, although usually associated with allergic, genetic, or trauma sources, and with viral infections and/or immune system-mediated mechanisms. With treatment still unknown, our attention is towards the eventual impact of complementary dietary interventions, synthesizing the recent knowledge of some edible mushrooms and preparations on Ménière's disease, which is a lifelong condition that can develop at any age, but most commonly emerges between 40 and 60 years of age. It is demonstrated that the oral administration of a biomass preparation, with 3 g/day of the mushroom *Coriolus versicolor* for 2 to 6 months, on some 40 human Ménière's disease patients reduced systemic oxidative stress and cellular stress response, decreased the number of crises and their duration, and the frequency of symptoms, improving the clinical grading of tinnitus severity.

Keywords: vertigo; tinnitus; functional foods; macrofungi; neuronal diseases



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1. Introduction

Foods are generally designated as functional if they encompass a bioactive element. These biologically active dietary elements are extrinsic non-nutritional substances that can regulate biochemical metabolic activities, leading to health promotion [1].

The term nutraceutical from nutrition and pharmaceutical was first coined in 1989 and next interchangeably used with the term pharmanutrient or functional food. However, functional foods are edibles that provide health benefits or disease risk reduction beyond their nutritional value, whereas nutraceuticals, different from functional foods, are commodities that may be considered a food or part of a food, but are supplied in different medicinal oral forms [2].

With treatment still unknown, our attention is towards the eventual impact of complementary dietary interventions, synthesizing the recent knowledge of some edible mushrooms and preparations on Ménière's disease. Mushrooms are edible fungi widely used as medicaments in Asia for ages. They are valuable macro-fungi that exist as an integral and vital component of the ecosystem as major decomposers. The unique composition of mushrooms, namely on specific enzymes, contributes to biodiversity, to traditional herbal medicines, and the supply of useful bioactive compounds [3]. Although some of these hold promising preventive and therapeutic opportunities, there is no universal definition

and harmonized regulatory framework among countries [4]. There are many thousands of mushroom species but just a handful are edible or defined as functional food, and there is as yet scarce clinical evidence for their efficacy, safety, and effectiveness [5].

We have recently reviewed how the enormous potential of the bioactive elements present in mushrooms complement the human diet, with various active molecules undetected or insufficient in common foodstuffs of plant and animal origin, being considered a functional food for health benefits or the prevention of several human diseases [6].

Edible mushrooms represent not only a huge storehouse of vitamins, minerals, and dietary fiber, but they are also an important source of bioactive components such as polysaccharides, terpenes, steroids, anthraquinone, phenolic acid, and benzoic acid, while primary metabolites contain proteins, oxalic acid, and peptides [7].

Without a complete understanding of the influence of mushroom bioactive constituents and their mode of action as nutraceuticals, it is challenging to effectively understand the role of mushrooms as dietary interventions in malfunctions and diseases [8]. The structural diversity of various mushroom bioactive secondary metabolites (e.g., terpenoids, acids, alkaloids, sesquiterpenes, polyphenolic compounds, lactones, sterols, nucleotide analogues, vitamins, and metal chelating agents), as well as their specific potency as a therapeutic prospect and/or antioxidants, have been widely investigated [9–11].

In general, mushrooms contain large amounts of chitin, mannans, galactans, xylans, glucans, krestin, lentinan, and hemicelluloses; therefore, they perform as potential candidates for prebiotics [12]. The prebiotic activity of mushrooms beneficially affects gut homeostasis performance and the balance of gut microbiota is enhanced [13].

Edible mushrooms (e.g., *Lentinula edodes*, *Pleurotus* spp., *Agaricus* spp., and *Ganoderma* spp.) are valuable sources of protein for both food and medicine, containing more protein than vegetables, fruits, and grains. Mushrooms contain bioactive proteins and peptides known to have antihypertensive, immunomodulatory, antifungal, antibiotic, antibacterial activities, anticancer, antiviral, and antioxidant properties [14,15].

Bioactive components reported in different edible mushrooms include β -glucans, lentinan, peptidoglycan, ergosterol, cordycepin, tocopherols, quercetin, catechin, lovastatin, eritadenine, hericenones, erinacines, among many others [16]. Furthermore, mushroom bioactive elements include ribosome inactivating proteins, proteases, antifungal proteins, and lectins, present namely in *Ganoderma lucidum*, *Agaricus bisporus*, and *Boletus satanus* [17,18].

Protein from mushrooms contrasts from animal, vegetable, and microbial proteins, usually forming cytotoxic enzymes (efficient tools to combat cancer), and include fungal immunomodulatory proteins (FIPs), Ribosome Inactivating Proteins (RIPs), nucleases, ubiquitin-like proteins, and proteins possessing enzymatic activity such as ribonucleases and laccases [19–21].

Mushrooms contain ergothioneine, which humans are unable to synthesize, a unique sulfur-containing amino acid, an antioxidant, cytoprotective, and anti-inflammatory element with therapeutic potential, approved by world food agencies. The novel food, synthetic L-ergothioneine, has also been approved by the FDA and EFSA at a recommended dosage of 30 mg/day for adults [22–24].

Ergothioneine is a thiourea derivative of histidine synthesized by few bacteria and fungi and exclusively acquired by animals and plants from exogenous sources, representing a rich source of nutrients for microbiota in the host environment. Ergothioneine is a natural powerful antioxidant activity, derived from microorganisms, especially in edible mushrooms, and a close relationship with various oxidative stress-related diseases. Besides the antioxidant properties, it has a powerful cytoprotective role in some important cells and tissues [25,26]. Mushrooms have been proven to be the highest dietary source of ergothioneine, accounting for about 95% of dietary intake [27].

Ergothioneine has a protective role in chronic inflammatory disorders. The organic cation transporter OCTN1 has been presumed to carry organic cations across the plasma membrane, but the key substrate of this transporter is in fact ergothioneine [28]. The antioxidant activity of ergothioneine has many advantages over other antioxidants such as

glutathione and ascorbic acid due to its specific transportation of OCTN1. The molecular and genetic defects and the pathophysiology behind Ménière's disease, as well as the dysregulation of these ion transporters, can result in severe defects in hearing or even deafness, enhancing the dietary role of ergothioneine from mushrooms [29].

Ergothioneine is a chief amino acid but an under-recognized dietary nutrient known to avert several inflammatory and cardiovascular diseases, diabetes, and liver and neurodegenerative diseases and has been suggested as a “vitamin” and to have nutraceutical uses [26] (Figure 1). It is also considered that ergothioneine deficiency may be related to neuropathy and aging, which may increase the risk of aging-related oxidative stress diseases in the elderly. Ergothioneine ameliorates the deterioration of sleep quality caused by psychological stress, possibly through anti-inflammatory and antioxidant mechanisms in the central and peripheral nervous system (Figure 1) [30].

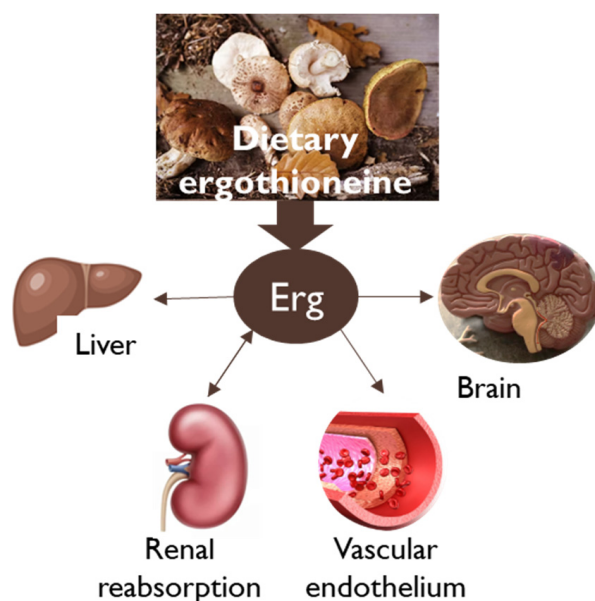


Figure 1. Ergothioneine, an antioxidant present in significant amounts in mushrooms, is an essential amino acid for humans, capable of clearing up hydroxyl radicals and maintaining bioenergetic homeostasis.

Ergothioneine extracted from *Pleurotus ostreatus*, the second most cultivated edible mushroom worldwide, was shown to exhibit strong antioxidant activity; hence, it could be a functional food for the prevention and treatment of ulcerative colitis [31].

The *Pleurotus ostreatus* (oyster) and *Ganoderma lucidum* (reishi) bioactive compounds have antimicrobial and prebiotic properties which are distributed in the mushroom mycelium and fruiting body. These mushrooms are rich in non-digestible carbohydrates (e.g., chitin and glucan) and secondary metabolites (phenolic compounds, terpenoids, and lectins), which act as prebiotics and support the growth and activity of beneficial gut microbiota, thereby maintaining a healthy balance in the gut microbiome and reducing the risk of antibiotic resistance [32].

Approved for many years in Asian countries, *Ganoderma lucidum* food components or supplements were recently given the Generally Recognized as Safe (GRAS) status and approved by the Food and Drug Administration (FDA) [33].

It is well-documented that the microbiota in the gastrointestinal tract is continuously reshaped by multiple environmental factors, especially diet, and it is decisive in human health and its balance is immunomodulated by mushroom bioactive components [34]. Nevertheless, and surprisingly, mushrooms are rarely included in most food guidelines [6].

Indeed, indigestible (by human enzymes) mushroom polysaccharides provide exceptional origin of prebiotics and curtail the reproduction of opportunistic pathogens,

promoting the growth of beneficial probiotic bacteria and restoring the bacterial imbalance in the gastrointestinal tract [35,36]. Mushrooms polysaccharides have also been shown to enhance the antioxidant status, exercising anti-diabetic activity by lowering glycaemia and improving insulin resistance, bearing anti-intestinal inflammation and antineoplastic effects by regulating gut microbiota through improving microbiome diversity in the gut [37].

Nutrition for the increasingly susceptible aging brain has been vastly studied, and it is now well established that many dietary components play an important role in early prevention against neurodegenerative diseases. In the growing elderly population, the progressive loss of structure or function of brain neurons negatively influences the beginning, seriousness, and span of neurodegenerative diseases.

Several studies on neurological impact and contributions to the growth of nerves and brain cells indicated that the presence of polyphenols in edible mushrooms demonstrated protective effects against neurodegenerative disorders and aging [38].

Very recently, mushroom components, through multiple mechanisms, were shown to have a protective role in redox homeostasis and modulated effects by hormetic nutrients in complex neurodevelopment disorders such as autism spectrum disorders [39].

Presently, the medicinal role of mushrooms in nutrient balancing, in strengthening the human immune system, in enhancing natural body resistance, and in lowering proneness to disease is well established [40].

Coriolus versicolor is a type of white rot fungus found primarily on dead logs and the fungal mycelium secretes a variety of compounds into its substrate, altering its chemical composition [41]. Some mushroom bioactive elements, enzymes, and secondary metabolites have been identified and used for medicinal purposes in a purified form (Table 1) [42].

Table 1. Bioactive compounds of some edible mushrooms and their health benefits [5,6,40,42].

Edible Mushrooms	Bioactive Compounds	Health Benefits
		Anti-diabetic
		Anti-inflammatory
		Anti-carcinogenic
		Anti-microbial
		Anti-oxidative
		Anti-proliferative
		Cholesterol-lowering
		Anti-viral
		Immuno-modulatory
		Osteoporosis
		Pre-biotic
		Anti-hypertensive
		Obesity
		Anti-cataractogenic
		Anti-viral
		Anti-ageing
		Gastrointestinal health
<i>Agaricus bisporus</i>	Polyphenols	
<i>Pleurotus ostreatus</i>	Dietary fibres	
<i>Coriolus versicolor</i>	Lectins	
<i>Lentinula edodes</i>	Terpenoids	
<i>Flammulina velutipes</i>	Antioxidants	
<i>Ganoderma lucidum</i>	Flavonoids	
<i>Cordyceps sinensis</i>	Peptidoglycans	
<i>Auricularia auricular</i>	B-glucan	
<i>Pleurotus sajor-caju</i>	Phytosterols	
<i>Hericium erinaceus</i>	Functional proteins	
<i>Grifola frondosa</i>		

These enzymes from *Coriolus versicolor* prevent oxidative stress (i.e., superoxide dismutase-SOD; catalase; glutathione-GSH peroxidase), inhibit cell growth (i.e., protease, glucose-2-oxidase), and play a role in detoxification (i.e., peroxidases, cytochrome P450) (Table 2).

Table 2. *Coriolus versicolor* (CV) in vitro enzyme activity (analyzed per tablet of 500 mg CV plus 225 mg excipient). The presence of pepsin or trypsin was performed to evaluate eventual gastric degradation [43].

	In the Absence of Proteolytic Enzymes	In the Presence of	
		Pepsin	Trypsin
Cytochrome P-450	0.51 nmoles	0.49 nmoles	0.52 nmoles
Cytochrome P-450 reductase	11.9 mU	9.52 mU	11.1 mU
Glucoamylase/Beta-glucanase activity	6.9 U	ND	ND
Glucose 2-oxidase activity	49.5 mU	ND	ND
Laccase activity	521.5 mU	522.6 mU	ND
Peroxidase activity	67.2 mU	60.4 mU	52.6 mU
Protease activity	5.9 U	5.0 U	5.7 U
Protein content	17.3 mg	15.7 mg	16.6 mg
Protein-bound polysaccharide	91.5 mg	80.5 mg	78.1 mg
Reducing sugars	14.8 mg	14.5 mg	261 mg *
Secondary metabolites (Thrombin inhibitors)	59%	54.20%	52%
Superoxide dismutase (SOD) activity	77.1 mU	61.2 U	68.5 U

* The presence of reducing sugars is due to the use of maltodextrin in the manufacturing process. ND—non-determined.

2. Ménière's Disease

Ménière's disease (MD) was first described by Prosper Ménière in 1861 when investigating migraine headaches [44]. MD represents a non-communicable disorder of the inner ear with a high clinical heterogeneity but characterized by episodes of spontaneous vertigo, tinnitus, fluctuating sensorineural hearing loss, and a sensation of the ear being full that affects one or both ears [45]. Hearing loss is the most common sensory defect and affects 450 million people worldwide in a disabling form.

Thus far, the etiology of MD remains largely unknown, mainly caused by a buildup of fluid in the chambers in the inner ear. There is growing evidence implying that oxidative stress and neuroinflammation, involving proinflammatory cytokines, may be fundamental to the occurrence of abnormal fluctuations of primary endolymphatic hydrops in the inner ear's labyrinth [46] (Figure 2).

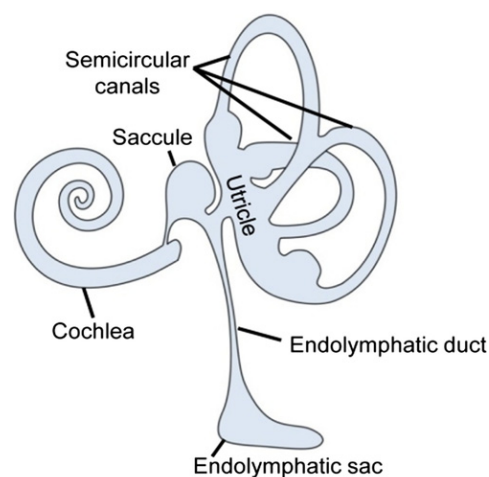


Figure 2. Diagram of the inner ear anatomy [47] showing the endolymphatic sac where the hydrostatic pressure and endolymph homeostasis is maintained.

Symptoms of Meniere's disease include: (a) Tinnitus: ringing, buzzing, roaring, whistling, or hissing sound in the ear. (b) Vertigo: regular dizzy bouts, spinning feeling starting and stopping unexpectedly, without warning. It usually lasts 20 min to 12 h, but not more than 24 h; serious vertigo can cause nausea. (c) Hearing disorder. Hearing

loss may come and go, especially early on. Over time, hearing loss can be long-lasting and eventually can be permanent. (d) Aural fullness: feeling of fullness in the ear, feeling pressure in the ear.

Complaints can range from mild to severe dizziness and nausea and vomiting. Symptoms can last for days, weeks, months, and may recur even after years [48]. Due to aging, otolithic degeneration and displacement in the reuniting duct and stockpile of debris in the semicircular canals may cause an otolithic crisis [49].

Although the evidence of a causal association between allergy and MD is inconclusive, the inclusion of allergy control as part of the treatment plan for MD is low risk and has been suggested by multiple authors [50,51].

Several researchers using different methodologies have been investigating candidate genes related to MD and the prevalence of autoimmune diseases diagnosed along with MD among different populations [52–55].

As our understanding concerning the etiology and medical intervention of the disease expands, the argument encircling the pathogenesis of MD deepens. Our aim here is not to describe this disorder or treatment but to outline the impact of diet and mushroom nutrition on MD, as already demonstrated in other neurodegenerative diseases.

Further to the ongoing genetic research, multiple studies have concentrated on the pharmacology and usefulness of bioactive elements and metabolites, as well as gut microbiome mediation, as a novel relevant procedure to address a number of human diseases, but mainly those related to neurological degeneration [56].

Treatment of Ménière's Disease

Ménière's disease does not have a cure yet, but there are some recommendations to help in coping with the condition and lifestyle modifications and the following treatments can help affected people cope with the symptoms [57].

However, none are considered effective by the scientific community. They include:

Medications. The most debilitating symptom of an outbreak of MD is dizziness. Prescription drugs such as anxiolytic diazepam (e.g., valium®), anticholinergic glycopyrrolate (e.g., robinul®), antihistamine meclizine (e.g., verticalm®) to control nausea, vomiting, and dizziness, and sedative lorazepam (e.g., ativan®) can help relieve dizziness and shorten the onset [58].

Holistic medicine. Some alternative treatments are occasionally used for MD but nothing indicates the advantages of therapies such as acupuncture or acupressure, martial arts, or herbal remedies such as ginkgo biloba, B3 niacin, or ginger rhizome.

Restriction of salt and use of diuretics. Low-salt or a salt-free diet and taking diuretics (e.g., diamox®-acetazolamide) may help some control dizziness by reducing the fluid retention in the body and lowering fluid volume and pressure in the inner ear.

Cognitive Processing Therapy. A type of psychotherapy talk may help people focus on how they interpret and react to life experiences, reducing symptoms of various mental health conditions, primarily depression and anxiety [59].

Infusions. Injecting antibiotics (e.g., intratympanic gentamycin) into the middle ear or a corticosteroid often helps reduce dizziness and has no risk of hearing loss [60].

Positive pressure therapy. The U.S. Food and Drug Administration (FDA) approved a portable minimally invasive but costly device (Meniett) for Ménière's disease that delivers intermittent air pressure pulses to the middle ear and fits into the outer ear. The air pressure pulses appear to act on endolymph fluid to prevent dizziness [61]. However, this treatment has been recently claimed to be very uncertain [62].

Surgical procedures. Surgery may be recommended when all other treatments have failed to relieve dizziness. A number of surgical modalities, of varying levels of invasiveness, have been developed on the endolymphatic sac to decompress it. Another possible surgery is to cut the vestibular nerve or labyrinthectomy, although this occurs less frequently [63].

Dietary control and attitude shifts. Eliminating caffeine, chocolate, and alcohol may reduce symptoms; hence, the need to avoid or limit them in their diet. Not smoking and reducing stress also may help lessen the symptoms [64]. SPC (special processed cereals, in flakes) show a significant reduction in vertigo spells and a positive effect on tinnitus severity [65].

Triple semicircular canal plugging (TSCP). A study with a total of 116 MD patients revealed that this technique was comparable to labyrinthectomy for the control of vertigo in intractable MD, representing an effective therapy [66].

3. Ménière's Disease and Brain Function

Understandably, available research on cognitive function in Ménière's disease (MD) human patients is quite limited. Cognitive function, hearing thresholds, emotional stress, and speech discrimination scores were recently studied in patients using detailed neuropsychological tests to measure how well a person's brain is working [67].

No gold standard diagnostic test for Ménière's disease exists. MD is distinguished by discontinuous events of vertigo, fluctuating sensorineural hearing loss, tinnitus, and the feeling of fullness and stuffiness in the ear (aural pressure), while some consider that it could be a migraine-related phenomenon [68].

Vestibular dysfunction is considered a likely adjustable risk factor for cognitive decline [69] on occasions combined with "brain fog" in the form of dullness, difficulty concentrating, poor memory, or confusion [70]. In MD patients, anxiety, depression, panic, and dyssomnia may arbitrate the link between vestibule dysfunction and cognition [71].

This is observed namely in Ménière's Disease chronic vestibular syndromes and migraine-associated dizziness, when compared to acute spinning vertigo such as benign paroxysmal positional vertigo (BPPV) [72]. The same vulnerability to derangements in homeostasis may also explain the common triggering factors of both MD attacks and migraine headaches, including stress, weather, and diet. Therefore, different foods and nutrients may assist in maintaining a metabolic balance, which is essential to both maintain energy homeostasis and prevent MD and neurological disorders [73]. The outlook was further complicated when hearing loss was recognized as a risk factor for dementia, widening the spectrum of negative consequences [74].

There are still no studies aimed at matching cognitive performance and multiple clinical features of these MD patients, or on whether mental personality changes could be protected or improved after successful treatment [75]. Recent studies with some 500 patients confirm a possible link between late-onset MD and an increased incidence of all-cause dementia, where the loss of hearing and vestibular function emerged as an important risk factor for senile mental illness [76].

Despite few claims [76], to date, the relationship between MD and dementia, including Alzheimer's disease and vascular dementia, has not yet been clarified. The absence of research and data in this field is justified by the lack of neurotologist experts and work being performed by general neurologists [77].

The clinical grading of tinnitus severity (ringing, rustling, or buzzing sound) has brought renewed hope to the treatment or prevention of auditory neurodegeneration. However, a correct diagnosis of the underlying vestibular disorder is necessary and new techniques to diagnose these disorders have been developed, where machine learning methods have the potential to perform better than clinical scores [78,79].

The goal of this review is to provide clues about how mushroom nutritional studies may help to better understand the tight relationship between food, metabolic balance, MD, brain activity, and aging.

4. Five Way Interactions and Ménière's Disease

The five way event interactions between Environment–Host–Drug–Microbiota–Nutrient reflect the importance of gut metabolites in energy metabolism, cell communication, and host immunity, and on the mediation of several physiological activities [80] (Figure 3).

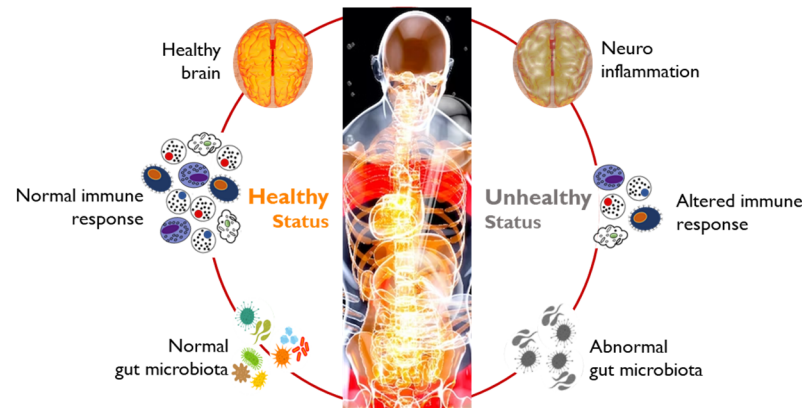


Figure 3. The multiple role of gut microbiome in neuroinflammation. Adapted from [81].

The correlation between gut microbiota neurotransmitters (e.g., dopamine, serotonin, norepinephrine, and δ -amino butyric acids-GABA) and brain functions has been well described under the designation of the “gut-brain axis” [82,83].

Numerous studies have enhanced the existing interaction between the microbiota and human health and disease [84]. Although the composition of gut microbiota remains quite stable since birth and in eubiosis, possible changes may induce dysbiosis and damages to the intestinal cell wall villi which may induce inflammatory reactions [85].

Considering that 99% of the genetic information in the human body is from the oral and gut microbiome, since microbiota (e.g., Firmicutes and Bacteroidetes) have an estimated 3.3 million genes compared to a human’s 23,000 [86], this is extremely critical for regulating gut metabolism, which is also important for the human immune system [87].

The multidirectional communication between loose nutrients in the lumen, gut microbiota, and the brain and other tissues is related to several neurological disorders [88], but specific crosstalk between the microbiome, gut, and host has not been clearly elucidated in relation to diet [39,89].

5. Nutrition in Idiopathic Endolymphatic Hydrops

Diet is a key element in healthy living and adequate nutrition impacts metabolic balance as a key component of healthy aging; however, little is known about the mechanisms involved in the beneficial effects of diets on cognitive function and general health [90].

It is important to remember that studies on healthy populations are infrequent and there has been a limited number of epidemiological studies on Ménière’s disease, characterized by spontaneous vertigo attacks (each lasting 20 min to 12 h). The disease is presumed to have a frequency of some 0.2% in western countries, with 50,000 people diagnosed annually [40], namely in people aged >65 years [91].

An array of potential etiopathologies have been pinpointed during the course of MD. Perhaps the most entrenched is the finding of endolymphatic hydrops (ELH). These are considered the main etiology of Ménière’s disease; however, it seems that supplementary intermediate cofactors (e.g., allergies, viral infections) are necessary to develop the usual symptoms [92]. The role of the endolymphatic sac as an immune mediator for the middle ear and hormonal mechanisms presents other modes by which MD could be provoked, with endolymph in excess [93].

To prevent permanent effects of the symptoms on the hearing and balance system, changes in lifestyle are promoted. Dietary recommendations for the control of MD include abundant water intake, a low salt diet, moderate alcohol and caffeine consumption, and a

gluten-free diet [94], together with diuretics, vasodilator corticosteroids, and intra-tympanic steroids [95]. Taking extra vitamin D plus calcium is considered to cut the odds of getting a debilitating form of benign paroxysmal positional vertigo [96]. However, the daily requirement of vitamin D has been recently under debate as most guidelines state 600–800 IU daily when other authors claim that these levels are low and should be around 8000 IU for young adults and thereafter, or even 20,000 IU once every two weeks [97,98].

However, although some research has revealed an improvement with these first line dietary mediations, namely in the control of relapsing, presently there is no constant agreement on their effectiveness [99].

6. Mushroom Nutrition in Neurodegenerative Diseases

Ménière's disease has a degenerative course that often results in permanent sensorineural hearing loss with different "clinical phenotypes", but its etiology remains elusive [100]. The pivotal role of mitochondria in redox regulation and oxidative stress has a critical performance in the development of several age-related conditions and several chronic diseases, but it can also be considered as a healing perspective to certain clinical conditions [101].

The brain and nervous tissues have a large potential oxidative capacity but a limited ability to counteract oxidative stress [102]. The administration of mushroom nutritional supplements has been the subject of research in several diseases, mostly associated with enhancement of antioxidant factors against oxidative stress and free-radical-induced cell damage [103].

Mushroom supplementation represents a valid support in health-promoting strategies and has shown effective prophylactic and therapeutic antioxidant intervention to maintain the wholeness and persistence of neurons and to oppose age-related neurodegenerative pathologies [104,105].

The possible mechanisms of action of edible mushrooms on preventing several age-based neuronal diseases are still undisclosed, but it is advocated that they could contribute through a reduction in oxidative stress, neuroinflammation, and on the modulation of acetylcholinesterase activity, protecting neurons or stimulation, and regulating neurotrophins synthesis, on the rough endoplasmic reticulum [106,107].

The tripeptide glutathione, commonplace in every cell, is a reliable biomarker for the redox balance, being reduced in neurodegenerative disorders such as stroke, and Alzheimer's, Huntington's, and Parkinson's disease. Many edible mushroom species (e.g., *Hericium erinaceus*, *Ganoderma lucidum*, *Agaricus bisporus*, *Grifola frondosa*, *Pleurotus ostreatus*, *Lentinula edodes*) are reliable sources of glutathione and thus are good nutritional supporters of the regulation of homeostasis and metabolism in the nervous system [108].

Vitagenes are genes implicated in cellular homeostasis by perceiving the intracellular nutrient and energy status, the functional state of mitochondria, and the concentration of ROS produced in mitochondria [109].

These vitagenes encode for heat shock proteins, the small ubiquitous redox proteins, and the sirtuin family of signaling protein systems, which are significant in longevity processes [110]. Dietary antioxidants from exogenous nutritional approaches, such as mushrooms, have recently been demonstrated to be neuroprotective through the activation of hormetic pathways, including vitagenes [111].

Brain neuroinflammation has been linked to chronic neurodegenerative disorders, including: Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), Dementia with Lewy bodies (DLB), depression and stress, psychosis, cognitive functions, and aging [110].

Heat shock proteins (HSPs) are one of the major groups of proteins which help respond to and mitigate stresses. To cope with stress, organisms, including mushrooms, express Hsps or chaperons to stabilize client proteins involved in various cell functions in fungi [112]. The HSP mushroom-derived lipoxin A4 (LXA4) is a short-lived endogenous bioactive lipid eicosanoid (oxidized derivatives of arachidonic acid) able to promote the

resolution of inflammation, acting as an endogenous “braking signal” in the inflammatory process [113,114].

Lipoxin A4 may serve as biomarker and play a significant role in several auto-immune diseases [115]. *Hericium erinaceus* and *Coriolus versicolor* mushrooms administered to mice were found to be neuroprotectors through their ability to increase levels of the anti-inflammatory mediator lipoxin A4 [114,116].

7. Targeting Neurogenesis with Mushroom Nutraceuticals

Neurogenesis, or formation of neurons de novo, is the process by which new neurons are formed in the brain even late throughout one’s lifespan. The mature brain has many specialized areas of function and neurons that differ in structure and connections. The hippocampus alone, which is a brain region that plays an important role in memory function and spatial navigation, has at least 122 different types of neurons [117,118].

We have previously reviewed this subject showing that ongoing neurogenesis does decline with age, which is possibly linked to compromised neurocognitive-psychological human resilience. Hippocampal neurogenesis drops sharply during the early stages of Alzheimer’s disease, while older individuals have less angiogenesis and neuroplasticity and a smaller quiescent neural stem cell pool [119,120].

Ménière’s disease patients, exposed to chronic stress, also have significantly decreased hippocampal volume, interrelated with memory and key clinical, vascular, and genetic risk factors, which is consistent with severity hyperacusis and vestibular balance disorders of the affected side [121,122].

We have previously evaluated in mice the safety and toxicity of *Coriolus versicolor* based on EU guidelines [123]. Other in vivo trials with mice fed an edible mushroom, *Coriolus versicolor*, revealed no change in the dentate gyrus volume or proliferation in newly generated neurons. It was found that mice treated with this mushroom biomass supplementation had a significant increase in the complexity of the long and short immature neurons (increase in dendritic complexity) [118].

This indicated that *Coriolus versicolor* biomass promoted hippocampal neurogenic reserve in mice by increasing levels of β -catenin in the nucleus and cytoplasm of newly developed neurons, which may translate into enhanced cognitive reserves which are essential for learning and memory [124].

Although mushroom bioactive compounds elicit beneficial health outcomes, exercised via numerous approaches [125], little consideration is given to how their elements may generate internal mechanisms of safeguarding immunity by modulating cellular signaling, processes such as key transcription factors, regulating the pathways and cellular responses against reactive electrophilic and oxygen species stresses [126].

8. Mushroom Nutrition in Ménière’s Disease

Dizzy spells and vertigo may be caused by different factors and may cause nausea and vomiting. Diet and dehydration can also cause blood pressure to drop, which can lead to dizzy spells. Prolonged episodes of whirling vertigo along with hearing problems in one ear could be Ménière’s, while frequent bouts of dizziness and vertigo can also indicate B12 deficiency [127].

Immune system dysregulation is increasingly being attributed to the development of a multitude of neurodegenerative diseases [128]. It is admissible that MD, as a systemic oxidant disorder involved in its pathogenesis and by the neurodegenerative nature of the inner ear cochlear spiral ganglion neurons, can be considered a neurodegenerative disorder [129].

Many studies have reported that *Coriolus versicolor* has several well researched effects, namely antioxidant, hypoglycemic, and immune-enhancing outcomes (Figure 4).

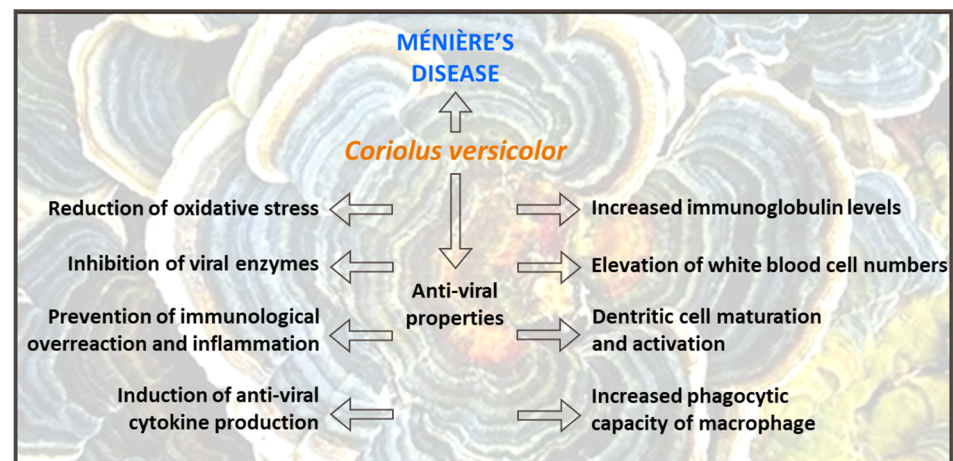


Figure 4. Some of the multiple roles of *Coriolus versicolor*.

One emerging and complementary strategy in tackling MD is the nutritional supplementation with mushrooms. In a specific and pioneer human trial, conducted by the Italian team of Professor V. Calabrese on 40 MD patients, it was evaluated the neurotoxic insult as a critical primary mediator operating in MD pathogenesis, exhibited by quantitative changes in biomarkers of oxidative stress and cellular stress response in the peripheral blood of MD patients (Figure 5) [130].

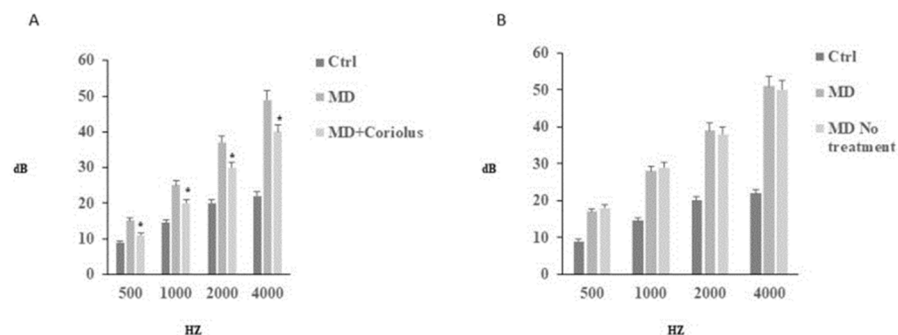


Figure 5. Tonal audiometry analysis. Tonal interest was centered on medium–high frequencies, with an average intensity of 55 dB loss. All subjects reported in both T0 (B) and T1 (A) phases no significant changes, either in the frequency range, or in the average loss in dB. Speech audiometry analysis, revealed in subjects of group A, who received mushrooms, a significant improvement of intellection threshold [130]. * Significantly different vs. untreated MD patients.

Comprehensive oxidative stress and a wide range of molecular changes in the cells of MD patients were investigated in the absence or in the presence of oral administration with a mushroom (*Coriolus versicolor*) biomass of commercial preparation (Manufactured by Mycology Research Laboratories Ltd., Luton, UK. *Coriolus versicolor* containing both mycelium and primordia biomass).

In a controlled study in 40 individuals with Meniere's disease (MD), the effects of 2 months of supplementation with 3 g/day of a biomass of commercial preparation from *Coriolus versicolor* (3 tablets of 500 mg every 12 h) on their peripheral blood antioxidant levels were measured to evaluate systemic oxidative stress and cellular stress response. This study has been replicated for a longer period (6 months) of administration with auspicious outcomes, but is presently still under publication [131].

With *Coriolus versicolor* treatment, it was observed in the plasma a significant stimulation of vitagenes (e.g., lipoxin A4, heat shock proteins 70, heme oxygenase-1, sirtuin-1, thioredoxin, and γ -GC ligase) and a significant increase in ratio-reduced glutathione vs. oxidized glutathione. This ratio is used as an indicator of cellular health [132,133].

This study also underlined the advantage of researching MD as a suitable facsimile of cochlear neuropathy spectrum disorder. Auditory neuropathy spectrum disorder (ANSD), designated as a spectrum since it affects each person in different ways, with symptoms ranging from mild to severe, a relatively rare form of sensorineural impairments and deafness, is characterized by a range of hearing impairments, namely compromised acoustic transmission from the inner ear to the brain due to defective synaptic function or neural conduction [134,135].

ANSD, a possible consequence of cranial nerve VIII degeneration with clinical profiles that are largely heterogeneous, can result from syndromic and non-syndromic (a partial or total loss of hearing) genetic abnormalities, as well as environmental causes (e.g., lack of oxygen, noise-pollution, chemotherapy drugs) and aging [136]. A rare degenerative ANSD familial disorder is caused by a riboflavin transporter deficiency, reflecting the need for high-dose oral supplementation of riboflavin (vitamin B₂) between 10 mg and 50 mg/kg/day, thus indicating the importance of diets [137,138].

Sensorineural hearing rehabilitation depends on the many varieties of etiologies and is currently being treated by genetic therapies which are in development. By looking for state-of-the-art activators of the vitagene system, the development of new pharmacological strategies will be possible, resulting in enhanced defense against energy and stress-resistant homeostasis disruption [139].

By incrementing the inherent pool of sensitive neurons, such as retinal ganglion cells, boosting anti-degenerative feedback, and through the study of major neurological biomarkers of brain disorders, it will be possible to deliver neurohealing, neurorescue, neuroregeneration, and neurorestoration [140].

Therefore, patients affected by Ménière's disease are considered as being under conditions of systemic oxidative stress, and the induction of vitagenes by mushroom supplementation indicates a sustained response to counteract intracellular compounds that initiate, facilitate, or accelerate lipid oxidation [130].

9. Conclusions

The benefits and risks of different lifestyles and dietary changes for Ménière's disease are currently unclear and the efficacy of different dietary interventions for preventing vertigo attacks and their associated symptoms is still vague. However, it is clear from a study in 40 human MD patients that oral consumption of a biomass preparation, with 3 g/day from mushroom *Coriolus versicolor* for 2 or 6 months, reduced systemic oxidative stress and cellular stress response, decreasing the number of crises and their duration and the frequency of symptoms.

Novel techniques are being explored for the extraction of bioactive components from edible mushrooms and/or the use of complete biomass, and the nutraceutical potential of mushrooms needs to be investigated in clinical trials. Only a limited number of clinical trials have been carried out so far, mainly due to ethical reasons.

An understanding of the key drivers of the functional food market alongside a consistent and well-defined regulatory framework will provide further opportunities for growth, expansion, and segmentation of different applications of mushrooms.

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