Review

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Posted Date: 26 September 2023

doi: 10.20944/preprints202309.1775.v1

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A Note on Mushroom Nutraceuticals in Ménière´s Disease

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Abstract: Nutraceuticals comprise dietary supplements, functional foods, medicinal foods, and pharmaceuticals. However, to date all these concepts are interpreted in different ways with the rapid increasing knowledge on nutrition, medicine, and plant biotechnology changing the concepts about food, health and agriculture. What matters are the bioactive elements conveyed by foodstuffs as nutrients or non-nutrients, which interfere with human metabolism and have impact on health, aging and well-being. Food, not nutrients, is the fundamental unit in nutrition and edible mushrooms, are fungi that supply unique biological compounds, different from plant or animal origin, which significantly impact on health status. Their influence on medicinal interventions has been known and studied for many years. The role on neurodegenerative disorders has been recently investigated and their significance on many other diseases has been well demonstrated. On this note it is synthesized the more recent knowledge of some edible mushrooms and preparations on Ménière's disease, a lifelong condition it can develop at any age, but most commonly appearing between 40 and 60 years of age.

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

1. Introduction

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 [1].

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 [2].

Mushrooms are edible fungus 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 supply of useful nutraceuticals.

Although some of nutraceuticals hold promising preventive and therapeutic opportunities, there is no universal definition and harmonised regulatory framework among countries [3].

There are many thousands of mushroom species but just a handful are edible or nutraceutical and there is as yet scarce clinical evidence for their efficacy, safety, and effectiveness [4].

We have recently reviewed how the enormous potential of the bioactive compounds 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 [5].

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Edible mushrooms represent not only a huge storehouse of vitamins, minerals, and dietary fibre, but they are also an important source of bioactive elements such as polysaccharides, terpenes, steroids, anthraquinone, phenolic acid, and benzoic acid, while primary metabolites contain proteins, oxalic acid, and peptides [6].

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 [7].

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 [8–10].

Mushrooms contain finest sources of poly- and oligosaccharides indigestible by human host enzymes, and ergothioneine, which humans are unable to synthesize, the later a unique sulphur-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 FDA and EFSA [11,12].

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. Mushroom contain bioactive proteins and peptides known to have antihypertensive, immunomodulatory, antifungal, antibiotic, antibacterial activities, anticancer, antiviral, and antioxidant properties [13,14].

Bioactive components reported in different edible mushrooms include β-glucans, lentinan, peptidoglycan, ergosterol, cordycepin, tocopherols, quercetin, catechin, lovastatin, eritadenine, hericenones, erinacines, among many other [15].

Furthermore, mushrooms bioactive elements include ribosome inactivating proteins, proteases, antifungal proteins, and lectins, present namely in *Ganoderma lucidum, Agaricus bisporus,* and *Boletus satanus* [16,17].

Fungi protein often differ from animal, vegetable, and microbial proteins, usually form cytotoxic enzymes, and include fungal immunomodulatory proteins (FIPs), Ribosome Inactivating Proteins (RIPs), nucleases, ubiquitin-like proteins, and proteins possessing enzymatic activity such as ribonucleases laccases [18–20].

Ergothioneine is a chief amino acid but under-recognised dietary nutrient known to avert several inflammatory and cardiovascular diseases, diabetes, liver and neurodegenerative diseases and has been suggested as a vitamin, and nutraceutical [21]. (**Figure 1**). It is also considered that 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 [22].

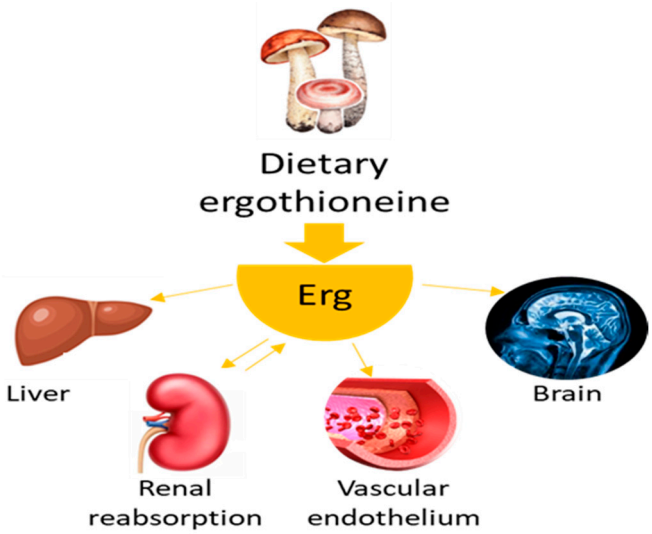

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Figure 1. Ergothioneine, an antioxidant present in significant amounts in mushrooms, is an essential amino acid for humans, capable of clearing up hydroxyl radicals, maintaining bioenergetic homeostasis.

Ergothioneine extracted from *Pleurotus ostreatus*, the second most cultivated edible mushroom worldwide, was shown to exhibit a strong antioxidant activity, hence to be a functional food for the prevention and treatment of ulcerative colitis [23].

The *Pleurotus ostreatus* and *Ganoderma lucidum* bioactive compounds have antimicrobial and prebiotic properties, distributed in the mushroom mycelium and fruiting body. These mushrooms are rich in non-digestible carbohydrates (e.g. chitin and glucan), which act as prebiotics and support the growth and activity of beneficial gut microbiota, thereby maintaining a healthy balance of gut microbiome and reducing the risk of antibiotic resistance [24].

In general, mushrooms contain large amounts of chitin, mannans, galactans, xylans, glucans, krestin, lentinan, and hemicelluloses, therefore they perform as foods with potential candidate for prebiotics [25].The prebiotic activity of mushrooms beneficially affects gut homeostasis performance and the balance of gut microbiota is enhanced [26].

Presently it is well established 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 [5].

2. Ménière's Disease

The Ménière's disease (MD) was first described by Prosper Ménière in 1861 when investigating migraine headaches [27]. MD represents a non-communicable disorder of the inner ear with a high clinical heterogeneity but characterized by episodes of spontaneous vertigo, tinnitus, associated with fluctuating, low to medium frequencies sensorineural hearing loss, and a sensation of ear being full affecting one or both ears [28].

Thus far, the aetiology of MD remains largely unknown, despite 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 [29]. (**Figure 2**).

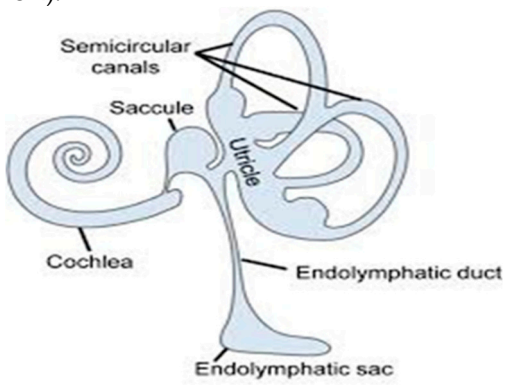

Figure 2. Diagram of the inner ear anatomy showing the endolymphatic sac where the hydrostatic pressure and endolymph homeostasis is maintained.

Due to aging, otholitic degeneration and displacement in the reuniting duct and stockpile of debris in the semicircular canals may cause an otolithic crisis [30].

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 [31].

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 [32,33].

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Many authors using different methodologies have been investigating candidate genes related to MD and the prevalence of autoimmune diseases diagnosed with MD among different populations [34–37].

As our understanding concerning the aetiology 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 mushroom nutrition on MD and few other neurodegenerative diseases.

Further to the ongoing genetic research, multiple studies have been concentrated on the pharmacology and usefulness of bioactive elements and metabolites as a novel relevant procedure to address a number of human diseases mainly those related to neurological degeneration [38].

3. Mushroom Nutrition in Neurodegenerative Diseases

The pivotal role of mitochondria in redox regulation and the 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 [39].

The brain and nervous tissues have a large potential oxidative capacity but a limited ability to counteract oxidative stress [40]. 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 [41].

Mushroom supplementation represent a valid ally in health-promoting strategies and showed an effective prophylactic and therapeutic antioxidant intervention to keep the wholeness and persistence of neurons and to oppose the age-related neurodegenerative pathologies [42,43].

Still undisclosed the possible mechanisms of action of edible mushrooms on preventing several age-based neuronal diseases, it is advanced the reduction of oxidative stress, the neuroinflammation, and the modulation of acetylcholinesterase activity, protecting neurons or stimulation, and regulating neurotrophins synthesis on the rough endoplasmic reticulum [44,45].

The tripeptide gluthatione, 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, Parkinson's diseases. Many edible mushroom species (e.g. *Hericium erinaceus*, *Ganoderma lucidum*, *Agaricus bisporus*, *Grifola frondosa*, *Pleurotus ostreatus*, *Lentinula edodes*) are reliable sources of glutathione, thus good nutritional supporters of the regulation of homeostasis and metabolism in the nervous system [46].

The 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 [47].

These vitagenes encode for heat shock proteins, the small ubiquitous redox proteins and the sirtuin family of signalling protein systems, significant on longevity processes [48]. Dietary antioxidants from exogenous nutritional approaches, such as mushrooms, have recently been demonstrated to be neuroprotective through the activation of hormetic pathways, including vitagenes [49].

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 ageing [48].

To overcome stress, organisms, including mushrooms, expresses heat-shock proteins (Hsps) or chaperons to stabilize client proteins involved in various cell functions in fungi [50]. Heat shock proteins [51] mushroom-derived lipoxin A4 (LXA4) is a short-lived endogenous bioactive lipid eicosanoid (oxidised derivatives of arachidonic acid) able to promote resolution of inflammation, acting as an endogenous ''braking signal'' in the inflammatory process [52].

Lipoxin A4 may serve as biomarker and play a significant role in several auto-immune diseases [53]. *Hericium erinaceus* and *Coriolus versicolor* mushrooms administered to mice were found to be

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neuroprotectors through their ability to increase levels of the anti-inflammatory mediator lipoxin A4 (LXA4) [52,54].

5. Targeting Neurogenisis with Mushroom Neutraceuticals

Neurogenesis, or formation of neurons *de novo*, is the process by which new neurons are formed in the brain even late throughout lifespan. The mature brain has many specialised areas of function, and neurons that differ in structure and connections. The hippocampus, which is a brain region that plays an important role in memory function and spatial navigation, alone has at least 122 different types of neurons [55,56].

We have previously reviewed this subject showing that ongoing neurogenesis does decline with growing mature with age, possibly linked to compromised neurocognitive-psychological human resilience. Hippocampal neurogenesis drops sharply during early stages of Alzheimer's disease, while older individuals have less angiogenesis and neuroplasticity and a smaller quiescent neural stem cell pool [57,58].

We have previously evaluated in mice the safety and toxicity of *Coriolus versicolor* based on EU guidelines [59]. In 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) (63).

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 reserve essential for learning and memory [60].

Although mushroom active bio-compounds elicits health benefit outcomes, exercised via numerous approaches [61], late consideration is given on how their elements may generate internal mechanisms of safeguard immunity by modulating cellular signalling processes such as key transcription factors regulating the pathways and cellular response against reactive electrophilic and oxygen species stresses [62].

6. Mushroom Nutrition on 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 about dizziness and vertigo can also indicate B12 deficiency [63].

Immune system dysregulation is increasingly being attributed to the development of a multitude of neurodegenerative diseases [64]. 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 [65].

Many studies have reported that *Coriolus versicolor* has several well researched effects namely antioxidant, hypoglycemic, and immune-enhancing outcomes. (**Figure 3**).

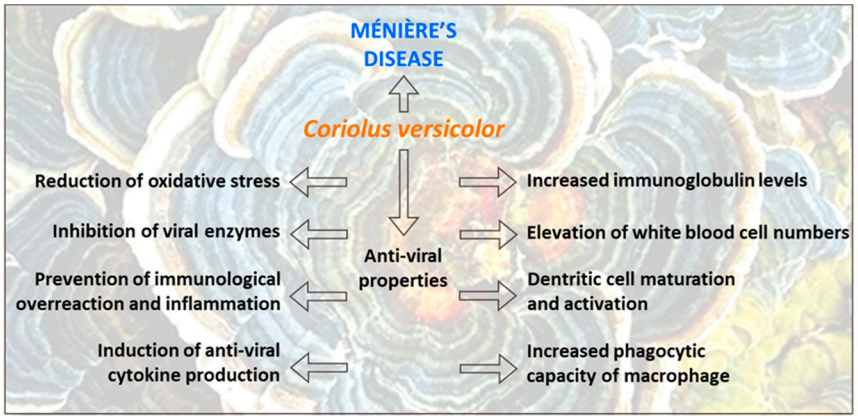

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Figure 3. Some of the multiple roles of *Coriolus versicolor*.

One emerging and complementary strategy tackling MD is nutritional supplementation with mushrooms. On a specific and pioneer human trial, conducted by the Italian team of Professor V. Calabrese on 40 MD patients, where all experimental protocols were approved by the appropriate boards, it was evaluated the hypothesis that neurotoxic insult represents a critical primary mediator operating in MD pathogenesis, exhibited by quantitative changes of biomarkers of oxidative stress and cellular stress response in the peripheral blood of MD patients [66].

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

In a controlled study the effects of 2 months of supplementation with 3 g/d of a biomass commercial preparation from *Coriolus versicolor* (3 tablets of 500 mg every 12 h) on 40 individuals with Meniere's disease (MD) peripheral blood antioxidant levels were measured to evaluate systemic oxidative stress and cellular stress response.

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 ratio-reduced glutathione vs. oxidized glutathione. This ratio is used as an indicator of cellular health [67,68].

This study also underlined the advantage of researching MD as a suitable facsimile of cochlear neuropathy spectrum disorder. By looking for state-of-the-art activators of the vitagene system, the development of new pharmacological strategies will be possible [69].

By the increment of the inherent pool of sensitive neurons, such as retinal ganglion cells, and boost the anti-degenerative feedback, and through the study of major neurological biomarkers of brain disorders, it will be possible to deliver neurohealing, neurorescue, neuroregeneration, and neurorestauration [70].

In conclusion, patients affected by Ménière´s disease are considered being under conditions of systemic oxidative stress, and the induction of vitagenes by mushroom supplementation indicate a sustained response to counteract intracellular compounds that initiate, facilitate, or accelerate lipid oxidation [66].

7. Conclusions

The emerging field of digital public health, future research will outline not just the absence of disease, but the state of complete physical, mental, and social well-being, setting the basis of a scientific rationale interpretation and mode of action of different bioactive metabolites.

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 need to be investigated in pre-clinical trials.

The bulk collected evidence underlies the urgent need to carry out further clinical trials to prove the safety and specific efficacy of mushroom supplementation. Only a limited number of clinical trials have been carried out so far in different disease conditions, mainly due to ethical reasons.

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

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, T.H.F. and V.B.; investigation, T.H.F.; writing—original draft preparation, T.H.F.; writing—review and editing, T.H.F and V.B.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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