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Review

Agaricomycetes mushrooms (Basidiomycota) as potential neuroprotectants

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Abstract
The edible and medicinal agaricoid and polyporoid mushrooms (phylum Basidiomycota, order Agaricomycetes) have long been known by humans as valuable food and medicines. They are producers of different groups of high- and low-molecular weight bioactive compounds (alkaloids, phenolics, polysaccharides, proteins, terpenoids, vitamins etc.) with around 130 therapeutic effects, including neuroprotective. Mushroom-derived biotech products are reported as effective neuroprotectants, however their potential to prevent or mitigate several neurodegenerative pathologies, such as Alzheimer and Parkinson diseases, epilepsy, depression and others has not been fully explored. This review discusses the neuroprotective potential of Agaricomycetes fungi and possibilities for their application as natural neuroprotectants.

Keywords
Agaricomycetes, antioxidant, anti-inflammatory, bioactive compounds, neurodegenerative, neuroprotective

Introduction

Neurodegeneration is incurable pathological process of progressive loss of structure and function of nerve cells, which lead to their death. In recent years age-related neurodegenerative diseases (NDD), such as Alzheimer's, Parkinson's and Meniere's diseases, multiple sclerosis affecting more than 35 million people worldwide. Available scientific data support the theory that the oxidative stress-derived neuro-inflammation in the neuron-glia system, as well as mitochondrial dysfunction are early pathological conditions and key points in the pathogenesis of NDD (Lin and Beal, 2006; Kozarski et al., 2015; Chen et al., 2016b; Trovato Salinaro et al., 2018). The functional role of mitochondria and reactive oxygen species (ROS) formation are positively implicated in cellular stress response mechanisms and highly regulated process controlled by different intracellular signalling pathways, including vitagenes (Cornelius et al., 2013). The strategy to prevent the development of NDD is a stress-free lifestyle, physical activity, and healthy diet, enriched with different natural products, including mushroom supplements (Brandalise et al., 2017; Rossi et al., 2018; Bai et al., 2019; Fan et al., 2019).

Despite the advancement of pharmacological treatment of age-related NDD, their management remains largely ineffective. Moreover, available drugs have always been associated with several side effects, while natural products have gained recognition to prevent development of patho-neurological

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symptoms. Therefore, it is urgent to explore neuroprotectants with natural, including plant and mushroom origin.

Agaricomycetes mushrooms (phylum Basidiomycota) are widely distributed worldwide and have been appreciated in traditional medicine for thousands of years for nutritional and medicinal properties, as well as a part of human culture and religious attribute (Hobbs, 2004; Chang and Miles, 2004; Badalyan, 2012; Chang and Wasser, 2017; Badalyan and Zambonelli, 2019; Badalyan et al., 2019).

According to a large number of chemical and myco-pharmacological studies, mushrooms are producer of different bioactive compounds (BAC) with neuroprotective effect (NPE) (Friedman, 2015; Chen et al., 2018a,b; Gupta et al., 2018; Badalyan et al., 2019; Lee et al., 2019; Yadav et al., 2020; Badalyan and Rapior, 2021). Although the mechanism of neuroprotective action of mushroom-derived BAC has not been thoroughly investigated, recent literature and research reviews reveal their potential to prevent the development and mitigate the symptoms of NDD (Sabaratnam and Phan, 2018; Yadav et al., 2020; Badalyan and Rapior, 2021). Several mushroom-derived biotech products (pharmaceuticals, nutraceuticals and nutriceuticals) currently available in the market have been demonstrated to be effective as neuroprotectants (Wang et al., 2014; Friedman, 2015; Bandara et al., 2015; Phan et al., 2015; Thangthaeng et al., 2015; Brandalise et al., 2017; Rathore et al., 2017; Rossi et al., 2018; Yin et al., 2018; Ho et al., 2020).

The review discusses recent advances in research on the neuroprotective potential of Agaricomycetes mushrooms belonging to different ecological and taxonomic groups and perspectives of their biomedical application as neuroprotectants.

Neuroprotective potential of Agaricomycetes mushrooms

Agaricomycetes mushrooms have been used by humans from ancient times as food and medicine (Chang and Miles, 2004; Hobbs, 2004; Badalyan, 2012; Chang and Wasser, 2017; Badalyan and Zambonelli, 2019; Badalyan et al., 2019; Badalyan and Rapior, 2021). They are a source of different BAC (β-glucans, lectins, phenolics, terpenoids, vitamins, etc.) possessing around 130 therapeutic effects (i.e., antitumor, anti-inflammatory, anti-oxidant, anti-microbial, hypocholesterolemic, hypoglycemic, etc.) (Badalyan, 2012; Gargano et al., 2017; Gupta et al., 2018; Morel et al., 2018; Badalyan et al., 2019; Hyde et al., 2019). Scientific data are documented the NPE of several mushrooms [i.e. *Agaricus bisporus* (J.E. Lange) Imbach, *Ganoderma lucidum* (Curtis) P. Karst., *Hericium erinaceus* (Bull.) Pers., *Pleurotus ostreatus* (Jacq.) P. Kumm., etc.] which could be highly efficient in complementary therapy of neurological disorders (Park et al., 2012; Phan et al., 2017; Sabaratnam and Phan, 2018; Chen et al., 2018a,b; Cui and Zhang, 2019; Lew et al., 2020; Badalyan and Rapior, 2021). However, further myco-pharmacological studies, pre-clinical and clinical trials are still required for the comprehensive evaluation of NPE of mushroom-derived products in the form of approved clinical drugs (Badalyan et al., 2019; Lucius, 2020).

Nowadays, dozens of mushroom species from different ecological (saprotrophs, xylotrophs, mycorrhizal) and taxonomic (agaricoid, polyporoid, russuloid, hymenochaetoid, and others) groups are biotechnologically cultivated and used as medicine however genetic mechanisms of their bioactivity and medicinal effect have not been fully exploited, yet (Kües and Badalyan, 2017). The recent advances in study of nutritional and medicinal values of Agaricomycetes, biotechnological production of mycelial biomass and mushrooms have been reported, innovative biological, biochemical and genetic approaches to produce health-enhancing mushroom-derived biotech products have been developed (Chang and Wasser, 2017; Gargano et al., 2017; Gupta et al., 2018; Badalyan and Zambonelli, 2019; Badalyan et al., 2019; Hyde et al., 2019; Badalyan and Rapior, 2021).

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Study of Agaricomycetes biodiversity, assessment of bioresources and creation of specialized culture collections will have an incredible impact on fundamental and applied myco-pharmacological and biotechnological research to develop novel mushrooms-derived products, including neuroprotectants (Badalyan and Gharibyan, 2016, 2017, 2020; Badalyan and Borhani, 2019a,b; Badalyan and Zambonelli, 2019; Badalyan, 2020).

Neuroprotective compounds of Agaricomycetes mushrooms

Agaricomycetes, particularly agaricoid (order Agaricales) and polyporoid (order Polyporales) species [*Flammulina velutipes* (Curtis) Singer*, Lentinula edodes* (Berk.) Pegler*, Pleurotus* (Fr.) P. Kumm., *Ganoderma* P. Karst., and *Trametes* Fr. species, etc.], as well as russuloid (order Russulales) species *Hericium erinaceus* (Bull.) Pers. are recognized as rich source of neuroprotective compounds, such as polysaccharides, terpenoids, phenolics, steroids, alkaloids, etc. (Badalyan, 2012; Phan et al., 2012; Zhang et al., 2016b; Chen et al., 2018a,b; Ćilerdžić et al., 2018, 2019; Lemieszek et al., 2018; Sabaratnam and Phan, 2018; Badalyan et al., 2019; Wang et al., 2019b; Badalyan and Rapior, 2021).

Polysaccharides or β-glucans are one of the major BAC in mushrooms. Except immunomodulating and antitumor activities they also possess significant antioxidant, anti-inflammatory, and neuroprotective activities allowing to use them as potential neuroprotectants (Wasser and Didukh, 2005; Khan et al., 2014; Kozarski et al., 2015; He et al., 2017; Wang et al., 2019a; Badalyan et al., 2019; Wu et al., 2019). The NPE of polysaccharides isolated from polyporoid chaga mushroom *Inonotus obliquus* (Fr.) Pilát (Ning et al., 2014), and agaricoid [*Agaricus bisporus*, *Coprinus comatus* (O. F. Müll.) Pers., *Coprinellus truncorum* (Scop.) Redhead, Vilgalys & Moncalvo and *Pleurotus eryngii* (DC.) Quél.] and cantharelloid (*Cantharellus cibarius* Fr.) species have also been reported (Mahmoud et al., 2014; Lemieszek et al., 2018; Pejin et al., 2019; Zhang et al., 2020). The NPE of bioactive polysaccharides from well-known edible medicinal mushroom *H. erinaceus* and new prospects for their usage as neuroprotectant is proposed (Friedman, 2015; Cheng et al., 2016; He et al., 2017; Wang et al., 2019a).

Agaricomycetes are also source of bioactive terpenoids, steroids, and sterols with neurotrophic and anti-neuroinflammatory activity. Hericenones, hericipins and erinacines have been isolated from *H. erinaceus* (Rupcic et al., 2018; Lee et al., 2020), cyathane diterpenes with from *Cyathus africanus* H.J. Brodie and *C. hookeri* Berk. (Tang et al., 2019; Yin et al., 2019), lanostane triterpenes, ganoderic acid, lucidone A, and aromatic meroterpenoids from *G. lucidum* (Wang et al., 2019b) and other *Ganoderma* species [*G. applanatum* (Pers.) Pat.*, G. leucocontextum* T. H. Li, W. Q. Deng, Sheng H. Wu, Dong M. Wang & H. P. Hu*, G. microsporum* R. S. Hseu*, G. resinaceum* Boud.] (Chen et al., 2018a; Ćilerdžić et al., 2018; Lai et al., 2019; Zhao et al., 2019). Anti-neuroinflammatory polyoxygenated lanostanoids from Chaga mushroom *I. obliquus* were recently reported (Kou et al., 2021).

Phenolics, such as hispidin and derivatives were isolated from *G. applanatum, Phellinus baumii* Pilát*, Trametes versicolor* (L.) Lloyd, and *T. gibbosa* (Pers.) Fr. They possess diverse pharmacological effects, including anti-inflammatory, antioxidant and neuroprotective (Palacios et al., 2011; Khatua et al., 2013; Kozarski et al., 2015; Pop et al., 2018; Jiang et al., 2020).

Agaricomycetes mushrooms as neuroprotectants

Medicinal Agaricomycetes species with protective effects against oxidation and inflammation can be used as neuroprotectants in treatment of various life-style and age-related chronic diseases, including NDD (Palacios et al., 2011; Thangthaeng et al., 2015; Phan et al., 2015, 2017; Badalyan et al. 2019; Yadav et al., 2020; Badalyan and Rapior, 2021). It was reported that mushroom-based daily diets can improve the cognitive abilities in ageing people and prevent the neurodegeneration (Rathore et al.,

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2017; Rossi et al., 2018; Sabaratnam and Phan, 2018; Yin et al., 2018; El Sayed and Ghoneum, 2020). However, scientific validation and further clinical trials are required to understand the molecular and biochemical mechanisms involved in the stimulation of neurite outgrowth and consider mushrooms as neuroprotectants (Badalyan et al., 2019; Cui and Zhang, 2019; Lucius, 2020; Badalyan and Rapior, 2021).

Several agaricoid, polyporoid, russuloid, cantharelloid and other groups of agaricomycetous mushrooms, such as *A. bisporus* (Kozarski et al., 2020), *Agaricus brasiliensis* Fr. (Qin and Han, 2014), *Auricularia polytricha* (Mont.) Sacc. (Bennett et al., 2013), *Amanita caesarea* (Scop.) Pers. (Li et al., 2017), *Cantharellus cibarius* (Lemieszek et al., 2018), *Laetiporus sulphureus* (Bull.) Murrill, and *P. ostreatus* (Ćilerdžić et al., 2018, 2019), *Fomitopsis betulina* (Bull.) B. K. Cui, M. L. Han & Y. C. Dai, and *Fomitopsis officinalis* (Vill.) Bondartsev & Singer (Pleszczyńska et al., 2017; Muszyńska et al., 2020), *G. lucidum* (Rahman et al., 2020), *H. erinaceus* (Ma et al., 2010), *Lignosus rhinocerotis* [= *L. rhinocerus* (Cooke) Ryvarden] (Farha et al., 2019), *Phellinus linteus* (Berk. & M. A. Curtis) Teng (Chen et al., 2016a), *Trametes* (= *Coriolus*) species (Knežević et al., 2018; Scuto et al., 2020), as well as *Flammulina velutipes* (Phan et al., 2017; Sabaratnam and Phan, 2018), *Grifola frondosa* (Dicks.) Gray (Fan et al., 2019), *Lentinus edodes* (Berg.) Singer (Diallo et al., 2020) and *Pleurotus giganteus* (Berk.) Karun. & K. D. Hyde (Phan et al., 2012, 2014) have been used in traditional medicine as neuroprotective and antidepressant agents against ageing-related NDD (Fig. 1). Among these, *H. erinaceus, G. lucidum, L. edodes* and *Polyporus umbellatus* (Pers.) Fr. are widely used as bio-ingredients in the formulation of cholesterol-free natural food products (Chang and Buswell, 1996; Ma et al., 2010; Bandara et al., 2015; Rossi et al., 2018; Sabaratnam and Phan, 2018; Yin et al., 2018; Ho et al., 2020).

Currently, around 80 different BAC from over 20 brain-improving culinary and medicinal mushrooms have been reported, molecular mechanisms of neuroprotection and possible clinical trials are discussed (Phan et al., 2015; Badalyan and Rapior, 2021). Nevertheless, before the clinical application of mushroom-derived neuroprotectants as preventive and therapeutic drugs the synergistic effects of isolated biocompounds and stabilization for their administration needs to be appropriately evaluated (Badalyan et al., 2019; Gründemann et al., 2020; Lucius, 2020; Badalyan and Rapior, 2021).

One of the major etiological factors of Alzheimer's disease is oxidative stress, which accelerates β - amyloid peptide plaque accumulation in the brain. Edible medicinal agaricoid oyster mushrooms (*P. eryngii, P. giganteus, P.* ostreatus) contain a high level of antioxidants, including ergothioneine, adenosine, and polyphenol, which reduce the age-related oxidative stress (Badalyan, 2012; Phan et al., 2014; Ćilerdžić et al., 2019; Liang et al., 2020; Zhang et al., 2020).

Several white-rot polyporoid fungi, such as *Trametes* (= *Coriolus*) species, have been used for centuries in the traditional medicine, however only *T. versicolor* has been comprehensively studied (Knežević et al., 2018; Pop et al., 2018; Kıvrak et al., 2020). The mycelial extract of *T. versicolor* was the most effective inhibitor of acetylcholinesterase activity, while extract of *T. gibbosa* significantly inhibited tyrosinase activity. The chemical screening revealed strong synergistic action of content of BAC produced by studied *Trametes* species (Knežević et al., 2018). According to research data the role of the inflammasome and the importance of *Coriolus* (= *Trametes*) and *Hericium* derived nutra- and nutriceuticals in neuroprotection have been considered (Trovato Salinaro et al., 2018).

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Legend

Fig. 1. Agaricoid and polyporoid mushrooms with neuroprotectant potential: (**a**) *Flammulina velutipes* (Photo Courtesy of PM Marty); (**b**) *Laetiporus sulphureus* (Photo Courtesy of PM Marty; (**c**) *Auricularia polytricha* (Photo Courtesy of JC Malaval); (**d**) *Ganoderma lucidum* (Photo Courtesy of JC Malaval); (**e**) *Trametes versicolor* (Photo Courtesy of JC Malaval); (**f**) *Clitocybe geotropa* (Photo Courtesy of JC Malaval); (**g**) *Lentinus edodes* (Photo Courtesy of AR Bandara, (**h**) *Cantharellus cibarius* (Photo Courtesy of AR Bandara; (**i**) *Pleurotus ostreatus* (Photo Courtesy of C Angelini); (**j**) *Grifola frondosa* (Photo Courtesy of C Angelini); (**k**) *Amanita caesarea* (Photo Courtesy of JC Malaval) and (**l**) russuloid species *Hericium erinaceus* (Photo Courtesy of AR Bandara).

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Well-known maitake mushroom, *G. frondosa,* contains a high amount of health-enhancing BAC and possesses nutritional and medicinal values (Badalyan and Zambonelli, 2019; Badalyan et al., 2019; Bai et al., 2019; Fan et al., 2019). It has been reported that proteoglucan from *G. frondosa* (PGM) can improve learning and memory; decrease the loss of neurons and histopathological abnormalities in mice. Moreover, PGM treatment could activate microglia, astrocytes, promote microglial recruitment to the β-amyloid plaques and enhance their phagocytosis, thereby alleviating pathological changes in the cortex and hippocampus. The administration of PGM as a dietary supplement may provide potential benefits on brain age-related memory dysfunction (Bai et al., 2019; Fan et al., 2019).

Several other Agaricomycetes species [*Antrodia cinnamomea* T. T. Chang & W. N. Chou*, Armillaria mellea* (Vahl.) P. Kumm.*, Calocybe indica* Purkay. & A. Chandra*, Clitocybe geotropa* (Bull.) Quél.*, Dictyophora indusiata* (Vent.) Desv.*, Hygrophorus eburneus* (Bull.) Fr.*, Paxillus panuoides* (Fr.) Fr., *Polyporus umbellatus*, *Poria cocos* F. A. Wolf, *Tremella fuciformis* Berk.*,* etc.] have also been reported as potential neuroprotectants (Lee et al., 2003; Park et al., 2012; Hsieh et al., 2013; Lu et al., 2013; Bandara et al., 2015, 2019; Zhang et al., 2016b; Rathore et al., 2017; Lee et al., 2019, 2020; Wu et al., 2019; Huang et al., 2020; Kosanić et al., 2020a,b; Badalyan and Rapior, 2021) (Fig. 1**).**

Further studies of biomedical potential of Agaricomycetes mushrooms will assist development and formulation of novel mushrooms-derived neuroprotectants.

Conclusion

Presently, human age-related neurodegenerative and psychotropic diseases are affecting the adult population worldwide. Therefore, discovering new resources of natural medicines, including plant- and mushrooms-derived biotech products is topical. This review discusses the current state of knowledge and the findings of recent studies on the neuroprotective potential of Agaricomycetes mushrooms. However, the list of studied species is far from being completed.

Future interdisciplinary research involving physicians, biologists, chemists, pharmacologists and mycologists collaborating with social scientists is required to create a scientific framework that incorporates traditional and clinical knowledge and experience to assist in the use of mushroom resources for human welfare.

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