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AGARICOMYCETES MEDICINAL MUSHROOMS WITH POTENTIAL NEUROPROTECTIVE ACTIVITY GROWING IN ARMENIA

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The Agaricomycetes mushrooms (phylum Basidiomycota) are recognised sources of valuable food and medicines. They are producers of bioactive compounds (phenolics, polysaccharides, proteins, steroids, terpenoids, etc.) possessing around 130 therapeutic effects (antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, etc.). Mushrooms are also reported as potential neurotrophic and neuroprotective agents. Seventeen edible and inedible agaricomycetous species from different taxonomic and ecological groups have been reported in Armenia to possess neuroprotective activity. Evaluation resource value and biotechnological potential of Armenian agaricomycetous mushrooms will assist further development of novel myco-pharmaceuticals to prevent and mitigate different disorders, including neurodegenerative.

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Introduction. Agaricomycetes mushrooms (phylum Basidiomycota) are rich sources of bioactive compounds (alkaloids, phenolics, polyketides, polysaccharides, proteins, ribosomal and non-ribosomal peptides, steroids, terpenoids, etc.) possessing more than 130 therapeutic effects (analgesic, antibacterial, antifungal, anti-inflammatory, antioxidant, cytotoxic, hepatoprotective, hypocholesterolemic, hypoglycemic, hypotensive, immunomodulatory, mitogenic/regenerative, etc.) [1–7]. They have also been reported as neuroprotective and anti-depressive agents [8–14]. New screening strategies based on innovative genetic approaches have identified novel mushroom metabolites-derived products widely applicable in biomedicine [15]. The evaluation of resource value and establishment of specialized culture collections of Agaricomycetes fungi will have an incredible impact on biomedical research that will assist to develop novel myco-pharmaceuticals [6, 16, 17].

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Neurodegenerative disorders (NDD) including age-related Alzheimer (AD) and Parkinson diseases (PD), dementia, autism, depression and epilepsy are affecting millions of people worldwide. Stress-less lifestyle and healthy diet prevent development of such pathological conditions [18]. Oxidative stress and neuroinflammation, protein aggregation and mitochondrial dysfunction are considered to play an important role in the etiopathogenesis of NDD [8, 18, 19]. Available therapies are associated with mild to severe side-effects, therefore, the search for novel approaches and natural resources of bioactive compounds that regulate pathways leading to neuronal death and dysfunction are warranted [6, 8, 20, 24, 33].

Recent studies focus on the pharmacology and feasibility of bioactive compounds of plant and fungal origin as a potential strategy to target a variety of human metabolic and brain disorders [37]. The mechanism and possible synergy of action of these compounds has not been studied yet, however mushrooms-derived products with potential neuroprotective and psychotropic activities can prevent and mitigate development of mental disorders, including depression, anxiety, sleep disturbances and cognitive alterations [1, 7, 8, 12–14, 20, 21–24]. According to recent myco-pharmacological research, Agaricomycetes mushrooms are producers of different neuroprotective compounds [8, 20, 25–27].

The current paper is directed to the evaluation of resource value of Agaricomycetes medicinal mushrooms growing in Armenia with potential neuroprotective activity (NPA) and discusses future perspectives of their usage in biomedicine.

Neuroprotective Compounds of Agaricomycetes Mushrooms. Mushrooms are widely distributed worldwide and have been appreciated in traditional medicine for their nutritional and medicinal properties [6, 7]. Edible and inedible mushrooms are industrially cultivated organisms however their biotechnological potential and perspectives of usage in biomedicine have not been fully exploited [15].

The polysaccharides (β-glucans) are considered one of the major bioactive compounds in mushrooms [6, 7]. The polysaccharides isolated from medicinal mushrooms *Agaricus bisporus, Cantharellus cibarius, Coprinellus truncorum, Coprinus comatus* and *Inonotus obliquus* (Chaga mushroom), distributed also in Armenia showed significant antioxidant, anti-inflammatory, anti-cholinesterase (AChE) and neuroprotective activities which may allow suggest them in the palliative treatment of NDD [11, 28–31].

Mushroom-derived terpenoids, steroids, sterols and phenolics are also known by their diverse pharmacological effects, including anti-inflammatory, antioxidant and neuroprotective [1, 3–5, 32, 33]. The NPA of *Hericium erinaceus* (Lion's mane) has been attributed to cyathane diterpenoids as erinacinesthat can stimulate the production of brain-derived neurotrophic factor [34]. New lanostane triterpenes and aromatic meroterpenoids with antioxidant and neuroprotective activities were isolated from fruiting bodies of *Ganoderma lucidum* (Reishi ou Ling Zhi) [5]. Study of total phenolic content, as well as antioxidant, AChE, tyrosinase, α-amylase and α-glucosidase activities of polypore mushrooms as *Ganoderma applanatum, Trametes gibbosa* and *Trametes versicolor* suggest that they may be considered as a source of neuroprotective food supplements [3, 5, 32].

Agaricomycetous Mushrooms as a Source for Neuroprotective Biotech Products. The cultivated edible mushroom, *H. erinaceus* is an important medicinal fungus with immunomodulatory, anti-mutagenic, antioxidant, anti-inflammatory and antitumor properties. Myco-pharmacological studies have attracted considerable attention on *H. erinaceus* as a neuroprotector to prevent NDD, including dementia, anxiety or depression [7, 13, 20, 25, 35–38].

Scientific dada have reported antioxidant and neuroprotective activities of *Ganoderma* mushrooms [5, 9, 22, 39]. The ganoderic acid and lucidone A isolated from *G. lucidum* delay AD progression [22]. The inhibition of cholinesterase, tyrosinase, α-amylase and α-glucosidase enzyme activities, as well as antioxidant effect of extracts from medicinal mushrooms of *G. applanatum* and *Ganoderma resinaceum* allows suggesting them as a source to prepare new food supplements and develop new drug formulations with NPA [3].

Oyster mushrooms (*Pleurotus* spp.) possess a high quantity of antioxidants, including ergothioneine, adenosine, and polyphenol derivatives, which reduce oxidative stress-related aging. Consumption of edible medicinal mushroom *Pleurotus eryngii* (King Oyster mushroom) delayed the development of brain atrophy, ameliorated memory deficit in mice and significantly decreased the levels of brain phosphorylated τ-protein, Aβ plaque deposition and malondialdehyde [26]. The AChE activity was detected in *Pleurotus ostreatus* (Oyster mushroom), however the effect was weaker than the effect of galantamine [10].

Several white rot polypore *Trametes* (= *Coriolus*) species, such as *Trametes gibbosa, T. hirsute, T. pubescens* and *T. versicolor* have been used for centuries in traditional medicine [7]. *In vitro* antioxidant, anti-diabetes, anti-dementia and anti-inflammatory activities of *Trametes* species were evaluated. The importance of nutra- and nutriceuticals derived from these polypore mushrooms as neuroprotectores have been considered [19, 32].

The antioxidant power and NPA of edible mushroom *Amanita caesarea* (Caesar's mushroom) have been reported to alleviate the deposition of amyloid beta (Aβ) protein in the brain and improve the central cholinergic system function. *A. caesarea* as a potential food for treatment or prevention of NDD was reported [23]. Muscimol is the main compound found in toxic *Amanita muscaria* (Fly agaric or Fly amanita) with a suppressive effect on essential tremor, without impairing speech and coordination in Parkinson-affected patients. The extract of *A. muscaria* showed significant NPA on *in vitro* neurotoxicity models [40].

Mushrooms with Neuroprotective Potential Distributed in Armenia. The forest regions in Armenia rich with mushroom biodiversity are mainly distributed in North-Eastern (Ijevan and Lori floristic regions) and South-Eastern (Zangezur floristic region) parts of the country [41, 42].

Seventeen edible and inedible agaricoid, polyporoid, hymenochaetoid and cantharelloid Agaricomycetes medicinal species with potential NPA belonging to ecological groups of saprotrophes and xylotrophes have been recorded in Armenia. The antioxidative, anti-inflammatory and neuroprotective effects of these species have been reported (see Table) [1, 3, 5, 8–11, 17, 19, 27, 36, 37, 43, 44].

The Agaricomycetes mushrooms with potential neuroprotective activity growing in Armenia

	Species	Order	Edibility	Ecological group	Bioactive compound, medicinal activity	References
1.	*Agaricus bisporus* (J.E. Lange) Imbach	Agaricales	ED	Soil saprotrophe	Polysaccharide, against Alzheimer's disease	[28]
2.	*Amanita muscaria* (L.) Lam.	Agaricales	IE, toxic	Soil saprotrophe	Muscimol, neuroprotective	[40]
3.	*Cantharellus cibarius* Fr.	Cantharellales	ED	Soil saprotrophe	Polysaccharide, neuroprotective	[11]
4.	*Coprinellus truncorum* (Scop.) Redhead, Vilgalys & Moncalvo	Psathyrellales	IE	Soil saprotrophe/ xylotroph	Polysaccharide, antioxidant, anti-cholinesterase	[17, 31]
5.	*Coprinus comatus* (O.F. Müll.) Pers.	Agaricales	ED	Soil saprotrophe/ xylotroph	Polysaccharide, antioxidant, anti-cholinesterase	[17, 31]
6.	*Flammulina velutipes* (Curtis) Singer	Agaricales	ED	Xylotrophe	Polysaccharides, neuroprotective, mitigate neurodegeneration	[8, 20]
7.	*Ganoderma applanatum* (Pers.) Pat. [=*Ganoderma lipsiense) (Batsch) G.F.]*	Polyporales	IE	Xylotrophe	Triterpenes, aromatic meroterpenoids, neuroprotective, against Alzheimer's disease	[5]
8.	*Ganoderma lucidum* (Curtis) P.Karst.	Polyporales	IE	Xylotrophe	Triterpenes, aromatic meroterpenoids, antioxidant, anti-cholinesterase, neuroprotective, against Alzheimer's disease	[3, 5, 9, 22, 39]
9.	*Hericium erinaceus* (Bull.: Fr.) Pers.	Russulales	ED	Xylotrophe	Polysaccharides, cyathane diterpenoids, hericenones, erinacines, antioxidant, anti-depressant, memory enhancer, neuro-stimulating,	[4, 13, 21, 25, 30, 34–38]
10.	*Inonotus obliquus* (Ach. ex Pers.)	Hymeno-chaetales	IE	Xylotrophe	Polysaccharides, proliferate human neurogliocytoma cells	[29]
11.	*Laetiporus sulphureus* (Bull.) Murrill	Polyporales	ED	Xylotrophe	Polysaccharides, antioxidant, against Alzheimer and Parkinson diseases	[10]
12.	*Phellinus pini* (Brot.) A. Ames [=*Porodaedalea pini* (Brot.) Murrill]	Hymeno-chaetales	IE	Xylotrophe	Polysaccharides, phenolic compound hispidin, phenolic acids, polysaccharides, anti-cholinesterase, anti-inflammatory	[43]
13.	*Pleurotus eryngii* (DC.) Quél.	Agaricales	ED	Xylotrophe	Polysaccharides, phenolic compounds, ameliorate memory and learning deficit, against Alzheimer's disease	[14, 26]
14.	*Pleurotus ostreatus* (Jacq.) P. Kumm.	Agaricales	ED	Xylotrophe	Polysaccharides, antioxidant, against Alzheimer and Parkinson diseases	[10]
15.	*Trametes gibbosa* (Pers.) Fr.	Polyporales	IE	Xylotrophe	Polysaccharides, phenolics, antioxidative, anti-neurodegenerative	[27]
16.	*Trametes pubescens* (Schumach.) Pilát	Polyporales	IE	Xylotrophe	Polysaccharides, phenolics, antioxidative, anti-neurodegenerative	[27, 44]
17.	*Trametes versicolor* (L.) Lloyd	Polyporales	IE	Xylotrophe	Polysaccharides, phenolics, antioxidant, anti-dementia, anti-inflammatory	[27, 32]

ED – edible; IE – inedible.

Conclusion. Given the aging of the population, finding natural resources with a potential effect to prevent or support the treatment of neurodegenerative diseases is a crucial societal issue. Indeed, further evaluation of resource value and biotechnological potential of Armenian medicinal Agaricomycetes mushrooms will assist to use them as potential natural source to formulate novel potential neuro-protective myco-pharmaceuticals and functional foods without adverse side effects for preventingor mitigating different diseases, including neurodegenerative.

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Ս. Մ. ԲԱԴԱԼՅԱՆ, ՍԻԼՎԻ ՌԱՊԻՈՐ

ՀԱՅԱՍՏԱՆՈՒՄ ԱՃՈՂ ԱԳԱՐԻԿՈՄԻՑԵՏԱՅԻՆ ԴԵՂԱՍՆԿԵՐԻ ՆԵՅՐՈՊԱՇՏՊԱՆ ՆԵՐՈՒԺԸ

Ագարիկոմիցետային սնկերը (բաժին Basidiomycota) հայտնի են որպես արժեքավոր սննդի և դեղամիջոցների աղբյուր: Դրանք կենսաակտիվ միացությունների (ֆենոլներ, պոլիսախարիդներ, ստերոիդներ, տերպենոիդներ և այլն) արտադրողներ են, որոնք ունեն շուրջ 130 բուժական ազդեցություն (հակամանրէային, հակաբորբոքային, հակաօքսիդիչ, իմունոմոդուլյատոր և այլն): Սնկերը հանդիսանում են նաև որպես նեյրոտրոֆիկ և նեյրոպաշտպան գործոններ: Հոդվածում բերվում է Հայաստանում աճող տարբեր կարգաբանական և էկոլագիական խմբերին պատկանող ուտելիևոչ ուտելի ագարիկոմիցետային սնկերի 18 տեսակներ, որոնք օժտված են նյարդապաշտպան ազդեցությամբ: Նրանց ռեսուրսային արժեքի և կենսատեխնոլոգիական ներուժի գնահատումը կնպաստի սնկային ծագման դեղապատրաստուկների ստացմանն ու կիրառմանը տարբեր նեյրոդեգեներատիվ խանգարումները կանխելու և մեղմելու նպատակով:

С. М. БАДАЛЯН, С. РАПИОР

РАСТУЩИЕ В АРМЕНИИ АГАРИКОМИЦЕТНЫЕ ЛЕКАРСТВЕННЫЕ ГРИБЫ С НЕЙРОПРОТЕКТОРНЫМ ПОТЕНЦИАЛОМ

Грибы Agaricomycetes (отдел Basidiomycota) являются источниками ценных пищевых и лекарственных продуктов. Они являются производителями биоактивных соединений (фенолов, полисахаридов, стероидов, терпеноидов и т.д.), обладающих около 130 терапевтическими эффектами (противомикробным, противовоспалительным, антиоксидантным, иммуномодулирующим и др.). Грибы также известны как потенциальные нейротрофические и нейропротекторные агенты. Было обнаружено, что восемнадцать видов растущих в Армении съедобных и несъедобных агарикомицетных грибов обладают нейропротекторной активностью. Оценка их ресурсной ценности и биотехнологического потенциала поможет в разработке новых микопрепаратов для предотвращения и смягчения симптомов различных нейродегенеративных нарушений.