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Neurotoxicity vs. Neuroprotection

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The Neurotrophic and Neuroprotective Potential of Macrofungi

Susanna M. Badalyan and Sylvie Rapior

Contents

Abstract Diversity of wild and cultivated macrofungi as edible and medicinal mushrooms has long been known by humans as a source of valuable food and medicines used by tradipraticians. In the fungal kingdom, macrofungi taxonomically belong to two phyla, the Basidiomycota (class Agaricomycetes) and Ascomycota

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(class Pezizomycetes). Macrofungi have been used in traditional Asian and European Medicines, and based on 90,000 known worldwide distributed mushroom species, are considered an important resource for modern clinical and pharmacological research. They are regarded as a source of high- and low-molecular-weight bioactive compounds (alkaloids, lipids, phenolics, polysaccharides, proteins, steroids, terpenoids, etc.) with more than 130 therapeutic effects (anti-inflammatory, antimicrobial, antioxidant, antitumor, antiviral, cytotoxic, hepatoprotective, hypocholesterolemic, hypoglycemic, hypotensive, immunomodulatory, etc.). There is also scientific evidence of using macrofungi as neuroprotectants, that is, *Agaricus blazei* (= *Agaricus subrufescens*), *Ganoderma lucidum*, *Grifola frondosa, Hericium erinaceus*, *Pleurotus ostreatus*, and *Trametes versicolor*. However, their neuroprotective effects have not been fully explored. This review discusses recent advances in research on the neuroprotective potential of macrofungi and perspectives for their application as neuroprotectants in biomedicine to prevent, support, or cure neurodegenerative disorders.

Keywords Anti-inflammatory · Antioxidant · Macrofungi · Neurodegenerative · Neuroprotective · Polysaccharides

Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AE	Aqueous extract
AIF	Apoptosis-inducing factor
AInA	Anti-inflammatory activity
ANDA	Anti-neurodegenerative activity
AOA	Antioxidant activity
APP	Amyloid precursor protein
ASD	Autism spectrum disorder
Aβ	Amyloid-β
BACE1	β-Site APP-cleaving enzyme 1
BDNF	Brain-derived neurotrophic factor
ChAT	Choline acetyltransferase
COX-2	Cyclooxygenase-2
CREB	C-AMP response element-binding protein
DA	Dopamine
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DRG	Dorsal root ganglia
EE	Ethanolic extract
ERK1/2	Extracellular signal-regulated kinase ½
FRAP	Ferric reducing power
GABA	γ-Aminobutyric acid

GFAP	Glial fibrillary acidic protein
GMI	*Ganoderma microsporum* immunomodulatory
hMAOB	Human monoamine oxidase B
Hsp	Heat shock proteins
HWE	Hot water extract
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LB	Lewy bodies
LPS	Lipopolysaccharide
LXA4	Lipoxin A4
MD	Meniere's disease
MDA	Malondialdehyde
ME	Methanolic extract
MM	Medicinal macrofungi
MMP	Mitochondrial membrane potential
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
N2a	Neuroblastoma-2a
NAC	Non-amyloid-β component
NDD	Neurodegenerative disease
NF-κB	Nuclear factor kappa B
NGF	Nerve growth factor
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NPE	Neuroprotective effect
NRA	Neuroregenerative activity
NRF2	Nuclear factor erythroid-2-related factor 2
NTA	Neurotrophic activity
NTF	Neurotrophic factor
PARP1	Poly (ADP-ribose) polymerase 1
PBS	Phosphate-buffered saline
PC12	Pheochromocytoma 12
PD	Parkinson's disease
PE	Pyrocatechol equivalent
PGE_2	Prostaglandin E_2
PhAC	Pharmacologically active compounds
PI3K-AKT	Phosphoinositide-3-kinase-AKT
PNI	Peripheral nerve injury
PNR	Peripheral nerve regeneration
PSAM	Protoilludane sesquiterpenoid aromatic
PSPC	Protein-bound polysaccharide complex
PUFA	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SE	Status epilepticus
SOD	Superoxide dismutase

TCM	Traditional Chinese medicine
TEAC	Trolox equivalent antioxidant
TNF	Tumor necrosis factor
VDM	Vitamin D_2-enriched mushrooms

1 Introduction

In recent years, neurodegenerative diseases (NDD), including age-related Alzheimer (AD), Parkinson (PD), and Meniere's diseases (MD), are affecting more than 36 million people worldwide. Understanding mechanisms of aging and determinants of life span will help to reduce age-associated diseases and morbidity and facilitate healthy cognitive aging (Gorman 2008; Deary et al. 2009). Mitochondria, as critical regulators of cell death, play important role in the development of aging-related NDD. Mutations in mitochondrial DNA and oxidative stress are contributed to the aging process—a risk factor for NDD (Lin and Beal 2006).

Recent literature data support the opinion that the oxidative stress-derived neuroinflammation is an early pathological feature in the development of NDD. An antistress lifestyle, healthy diet, and caloric restriction appear to extend healthy life by reducing reactive oxygen species (ROS)-mediated oxidative damage. The functional role of mitochondria and ROS formation are positively implicated in cellular stress response mechanisms, and in highly regulated processes controlled by several intracellular signaling pathways, including vitagenes, as an intracellular redox system involved in neuroprotection (Cornelius et al. 2013; Chen et al. 2016b; Uddin and Ashraf 2018). The vitagenes encode for cytoprotective heat shock proteins (Hsp) Hsp32 and Hsp70, heme oxygenase-1, sirtuin protein systems, thioredoxin, and lipoxin A4 (LXA4) and are involved in preserving cellular homeostasis during stress. Current research focuses on biomolecules that activate the vitagene system as novel targets to minimize processes associated with free radical-induced cell damage, such as neurodegeneration (Cornelius et al. 2013).

Within the kingdom of Fungi, macrofungi are a group of 90,000 known mushroom species that form visible cap-like structures (namely known as fruiting bodies or sporocarps). Based on a large number of chemical and myco-pharmacological studies, the macrofungi (fruiting bodies and mycelium) are producers of different pharmacologically active compounds (PhAC) with neuroprotective effect (NPE) to prevent the development of different neurodegenerative processes in the human brain (Kim et al. 2014; Mahmoud et al. 2014; Phan et al. 2015, 2017; Zengin et al. 2015; Cheng et al. 2016; Trovato et al. 2016a, b; Zhang et al. 2016a, b; Ahuja et al. 2017; He et al. 2017; Sabaratnam and Phan 2018; Knežević et al. 2018; Trovato Salinaro et al. 2018; Bai et al. 2019; Ćilerdžić et al. 2019; Lai et al. 2019; Varghese et al. 2019; Wang et al. 2019a, b; Liang et al. 2020; Lucius 2020; Yadav et al. 2020). Mushroom-derived LXA4 is an emerging endogenous eicosanoid (based on the enzymatic or nonenzymatic of polyunsaturated fatty acids, PUFA) able to prevent

an inflammatory process (Cornelius et al. 2013; Trovato et al. 2016a). Although the mechanism of neuroprotective action of macrofungi-derived PhAC has not been thoroughly investigated, recent studies have revealed their potential to develop novel myco-pharmaceuticals to prevent and mitigate the development of various NDD (Bennett et al. 2013b; Zajac et al. 2016; Cardwell et al. 2018; Sabaratnam and Phan 2018; Badalyan et al. 2019; Yadav et al. 2020). Mushrooms-based dietary biotech products with different formulation have also been demonstrated to be neuroprotective (Barros et al. 2008; Palacios et al. 2011; Phan et al. 2012, 2014a, b, 2015, 2017; Cornelius et al. 2013; Wang et al. 2014; Bandara et al. 2015; Friedman 2015; Zhang et al. 2016a, b, 2017; Brandalise et al. 2017; Solayman et al. 2017; Lemieszek et al. 2018; Rossi et al. 2018; Yin et al. 2018; Bell et al. 2019; Dhakal et al. 2019; Jang et al. 2019; Ho et al. 2020; Lucius 2020).

The current review discusses recent advances in research on the neuroprotective potential of macrofungi and the perspectives of their application in biomedicine to prevent or cure neurodegenerative disorders.

2 Etiopathogenesis of Neurodegenerative Diseases

2.1 Age-Related Alzheimer's, Parkinson's, and Meniere's Diseases

Aging is an inevitable biological process and the greatest risk factor for different neurodegenerative disorders, such as AD and Lewy body (LB) dementia (mental dysfunction), PD, MD, and Huntington's disease, and multiple sclerosis (Gorman 2008; Deary et al. 2009; Olanow and Brundin 2013; Theillet et al. 2016; Uddin and Ashraf 2018; Luryi et al. 2019). The process of aging is caused by changes in cells to loss of nutrient sensing, cellular homeostasis, and genomic instability, disrupted cellular functions, increased oxidative stress, accumulation of misfolded protein, impaired cellular defenses, and telomere shortening. The perturbation of cellular processes in neuronal cells can lead to life-threatening neurological disorders, which are the most frequent cause of death in elderly people (Uddin and Ashraf 2018).

Oxidative stress and antioxidant systems, as well as mitochondrial dysfunction and neuro-inflammation, are considered to play a very important role in the etiology and pathogenesis of major NDD (Lin and Beal 2006; Kim et al. 2014; Phan et al. 2015; Chen et al. 2016b; Sabaratnam and Phan 2018; Trovato Salinaro et al. 2018; Uddin and Ashraf 2018; Jiang et al. 2020; Yadav et al. 2020). Under oxidative and inflammatory pathological conditions, the development of different NDD, including ocular neural degeneration or neurosensory degeneration occurring in glaucoma and MD, is taking place, respectively (Chen et al. 2016b; Luryi et al. 2019). Reducing the level of stress that would produce protective responses against pathogenic processes is an innovative area of neurobiology to understand the basics of neurodegeneration and develop new approaches to treat different NDDs.

Alzheimer's disease (AD) is the most common neurodegenerative disorder, which annually affects the daily life of more than 5% of the population worldwide. This disease has a poor prognosis, and new therapeutic approaches are required to improve the quality of life of AD patients (Gorman 2008; Uddin and Ashraf 2018). As a potentially innovative approach in AD therapy associated with mitochondrial dysfunction and neuro-inflammation, the endogenous cellular defense mechanism modulation and neurohormesis were documented (Lin and Beal 2006; Chen et al. 2016b; Trovato Salinaro et al. 2018).

Parkinson's disease (PD) is another neurodegenerative disorder with unknown origin. Progressive functional impairment of the nigral dopaminergic neurons, intraneuronal aggregation of amyloid protein α-synuclein—a principal component of Lewy pathology is linked to PD. Except for protein aggregation, mitochondrial dysfunction, iron accumulation, both neuro-inflammation, and oxidative stress also play an important role in the etiopathogenesis of the disease. Moreover, mutations in the α-synuclein gene cause rare familial forms of PD (Olanow and Brundin 2013; Theillet et al. 2016). The duplication/triplication of the wild type α-synuclein gene is also considered the etiology of PD, indicating that increased levels of normal α-synuclein protein are sufficient for the development of the disease. α-Synuclein protein can transfer from affected to unaffected nerve cells to promote misfolding of the host α-synuclein, which leads to the formation of larger aggregates, neuronal dysfunction, and neurodegeneration. This mechanism plays an important role in the pathogenesis of PD and allows to develop novel neuroprotective therapies (Olanow and Brundin 2013; Theillet et al. 2016).

The anti-Parkinson drugs, such as levodopa, carbidopa, dopamine (DA) agonists, monoamine oxidase type B inhibitors, and anticholinergics to replace DA, are associated with numerous side effects. Therefore, the search for new therapeutic approaches that regulate pathways leading to neuronal dysfunction and death is warranted.

Meniere's disease (MD) represents a clinical syndrome mainly characterized by episodes of spontaneous vertigo, associated with fluctuating sensorineural hearing loss and tinnitus, affecting one or both ears (Sajjadi and Paparella 2008; Luryi et al. 2019). The cause of MD is still unknown. Increasing evidence shows that oxidative stress and neuro-inflammation may be important causes of developing endolymphatic hydrops and consequent otolithic degeneration (Luryi et al. 2019).

Cellular pathways, such as vitagenes conferring protection against oxidative stress, are not sufficient to prevent full neuroprotection, which can be reinforced by exogenous nutritional approaches. The search for innovative approaches can promote the development of therapies able to enhance the intrinsic reserve of vulnerable neurons, such as ganglion cells to maximize anti-degenerative stress responses and neuroprotection (Trovato Salinaro et al. 2018; Scuto et al. 2020).

Various therapeutic molecules have been designed to overcome the social, economic, and healthcare problems caused by NDD; however, almost all compounds in clinical practice are being limited to palliative care. The antioxidant polyphenolics may potentially be the most effective preventative strategy against NDD (Dhakal et al. 2019).

The age-related diseases also involve epigenetic changes in the epigenome influenced by lifestyle and diet; therefore, dietary components could accelerate or prevent age-related NDD. Thus, the combined dietary and therapeutic approaches are required to treat these diseases. The research interest in new anti-neurodegenerative drugs is high. For many years, natural products derived from medicinal plants, fruits, and vegetables have been regarded as primary resources for the discovery of potential therapeutic agents. They have been effective as anti-PD agents due to their neuroprotective properties, antioxidative and anti-inflammatory activities, as well as inhibitory effects regarding iron accumulation, protein misfolding, maintenance of proteasomal degradation, and mitochondrial homeostasis (Solayman et al. 2017; Rossi et al. 2018; Yin et al. 2018; Bell et al. 2019; Dhakal et al. 2019; Jang et al. 2019; Ho et al. 2020).

2.2 Autism, Epilepsy, and Depression

Autism Spectrum Disorder (ASD) is a largely unknown neurological disease, including a condition related to brain development that impacts how a person leading to problems in social interaction and communication. ASD is an incurable systemic neurological disability in the pathogenesis of which inflammation plays an important role. Previous studies showed that gut microbiota may assist in the development of ASD symptoms. Autistic patients may benefit from a balanced diet rich with antioxidants, improvement of gut microbiota, and immunity. Mushroom-derived dietary supplementation may decrease gastrointestinal inflammation and improve health conditions in patients (Bell et al. 2019).

Status Epilepticus (SE) or epilepsy is accompanied by continuous or rapidly repeating seizures persisting for 20–30 min and cause injury to the neurons. SE can also be caused by penicillin and related compounds that antagonize the effects of γ-aminobutyric acid (GABA)—the main inhibitory neurotransmitter of the central nervous system. Although the danger of seizure activity has been recognized since ancient times, the pathophysiology of SE is not completely understood (Lowenstein and Alldredge 1998).

Depression is a common and severe neuropsychiatric disorder in humans. The symptoms of depression include feelings of intense sadness and hopelessness, which may occur after a specific event or in response to a gradual decline in health associated with aging. The treatments of depression include antidepressants and behavioral therapy. However, antidepressant drugs are associated with mild to severe side effects.

Recent studies focus on the pharmacology and feasibility of bioactive herbal and fungal compounds as a potential strategy to target a variety of human metabolic and brain disorders. Natural bioactive ingredients are reported to produce both neuroprotective and psychotropic activities and may help to combat mental disorders, including depression, anxiety, sleep disturbances, and cognitive alterations (Nagano et al. 2010; Zhang et al. 2019; Huang et al. 2020; Lew et al. 2020).

3 Neuroprotective and Psychotropic Compounds of Macrofungi

Macrofungi are ascomycetous and basidiomycetous mushrooms that fruit above or below the ground. Mushroom "any fungus with a distinctive fruiting body that is large enough to be ... picked by hand" (Chang and Wasser 2017). Macrofungi are taxonomically placed in two phyla, the Basidiomycota (class Agaricomycetes) and Ascomycota (class Pezizomycetes) of the subkingdom Dikarya (Hibbet and Taylor 2013). From an estimated 0.5–(1.5) – (5.1) million fungal species, about 140,000–160,000 are macrofungi from which around 10% (14,000–16,000) have been taxonomically identified (Hawksworth 2012). Macrofungi are widely distributed worldwide and have been appreciated for their nutritional and medicinal properties in traditional medicine for thousands of years (Chang and Miles 2004; Barros et al. 2008; Badalyan 2012; Chang and Wasser 2012; Gupta et al. 2018; Badalyan et al. 2019). Many species of macrofungi are industrially cultivated at a large scale, however, their medicinal and biotechnological potential and perspectives of usage in biomedicine and bio-industry have not been fully exploited, yet (Kües and Badalyan 2017; Pleszczyńska et al. 2017; Badalyan and Zambonelli 2019; Badalyan et al. 2019; Hyde et al. 2019; Diallo et al. 2020).

Macrofungi are increasingly recognized as rich sources of PhAC (alkaloids, fatty acids, lectins, lipids, phenolics, polyketides, polysaccharides, proteins, peptides, steroids, terpenoids, etc.) possessing more than 130 therapeutic effects, that is, antimicrobial, anti-inflammatory, antioxidant, antiviral, cytotoxic, hepatoprotective, hypocholesterolemic, hypoglycemic, hypotensive, immunomodulatory, mitogenic/regenerative, and so on (Mizuno 1999; Poucheret et al. 2006; Ma et al. 2010; Palacios et al. 2011; Badalyan 2012, 2016; De Silva et al. 2013; Friedman 2015; Zengin et al. 2015; Wang et al. 2017; Gupta et al. 2018; Morel et al. 2018; Badalyan et al. 2019; Akiba et al. 2020; Kosanić et al. 2020a, b). New screening strategies based on innovative biological, biochemical, and genetic approaches have identified novel macrofungi—metabolites-derived products widely applicable in biomedicine (Schueffler and Anke 2014; Kües and Badalyan 2017).

The evaluation of mushroom resources and establishment of specialized culture collections will have an incredible impact on myco-pharmacological and biotechnological research that will assist in developing novel mushroom-based health-enhancing biotech products (Badalyan 2012, 2016, 2020; Bandara et al. 2015; Badalyan and Gharibyan 2016, 2017, 2020; Badalyan and Borhani 2019a, b; Hyde et al. 2019; Badalyan and Zambonelli 2019; Badalyan and Rapior 2020; Diallo et al. 2020; Badalyan et al. 2021).

The mushrooms are widely used in Asian countries as antitumor, anti-inflammatory, antioxidative, and antimicrobial agents and are becoming popular in the Western hemisphere (Hobbs 2004; Grienke et al. 2014; Chen et al. 2016a). They have also been reported as antidepressant and neuroprotective agents (Park et al. 2007; Aguirre-Moreno et al. 2013; Sabaratnam and Phan 2018; Ćilerdžić et al. 2018; Chen et al. 2018a, b, 2019; Lemieszek et al. 2018; Chong et al. 2019; Yadav et al.

2020). However, further interdisciplinary collaboration and myco-pharmacological study with the involvement of new medicinal species, as well as valid clinical and preclinical trials are still required for the comprehensive evaluation of their therapeutic potential not only in the form of dietary supplements but also in the form of approved clinical drugs (Lew et al. 2020; Lucius 2020).

The recent advances, perspectives, and major challenges of medicinal macrofungi concerning their nutraceutical and pharmaceutical properties, as well as dietary value, the biotechnological production of fruiting bodies and mycelial biomass, isolation, purification, and characterization of various bioactive compounds have been recently reviewed (Gargano et al. 2017; Kües and Badalyan 2017; Badalyan and Zambonelli 2019; Badalyan et al. 2019; Hyde et al. 2019; Gründemann et al. 2020).

3.1 Polysaccharides

Indeed, polysaccharides and proteins from macrofungi are potential therapeutics for aging and age-related neurodegeneration. Previous myco-pharmacological studies have shown that polysaccharides are considered one of the major bioactive compounds with immunomodulatory and antitumor effects without any toxicity (Meng et al. 2016; Wang et al. 2017; Badalyan et al. 2019). Mushroom-derived β-glucans also possess significant antioxidant, anti-inflammatory, and neuroprotective activities (Wasser and Didukh 2005; Khan et al. 2014; Kozarski et al. 2014; He et al. 2017; Bandara et al. 2019).

Hericium erinaceus is among the most appraised edible medicinal agaricomycetous mushroom regarded as a producer of different bioactive metabolites with the potential to treat different pathological conditions, including NDD. The polysaccharides are supposed to be one of the major bioactive compounds of *H. erinaceus*. It possesses immunomodulating, antitumor, antioxidant, gastroprotective, neuroprotective, hepatoprotective, hypoglycemic, and hypolipidemic activities. The current advancements in extraction, purification, structural characteristics, and bioactivities of polysaccharides obtained from the fruiting bodies, mycelium, and culture broth of *H. erinaceus* have been reported, and new prospects for their biomedical usage has been proposed (He et al. 2017; Wang et al. 2019a).

The neuroprotective activity of polysaccharide-enriched aqueous extract (AE) from the mycelium of *H. erinaceus* was also reported (Zhang et al. 2016a). In the AD mouse model, AE administration enhanced the horizontal and vertical movements, improved the endurance time, and decreased the escape latency time, as well as enhanced the central cholinergic system function, demonstrated dose-dependent enhancement of acetylcholine (ACh), and choline acetyltransferase (ChAT) concentrations in the serum and hypothalamus in mice. Thus, the NPE of *H. erinaceus* is useful for the prevention and treatment of NDD (Zhang et al. 2016a).

The observed in vitro dose-dependent inhibitory effect of Chaga mushroom (*Inonotus obliquus)* polysaccharide extracts (25, 50, 100, 200, and 500 μg/mL) on U251 human neurogliocytoma cells was related to the downregulation of anti-apoptotic Bcl-2 and upregulation of caspase-3 proteins (Ning et al. 2014). The water-soluble polysaccharide extracted from *Agaricus bisporus*, composed of glucose and galactose, showed potent antioxidant and acetylcholinesterase (AChE) inhibitory activity (Mahmoud et al. 2014; Kozarski et al. 2020). The polysaccharide extracts of two medicinal coprini mushrooms *Coprinus comatus* and *Coprinellus truncorum* contain β-glucans, proteins, and polyphenolics and showed AChE inhibitory effect that may allow using these species in the palliative treatment of AD (Pejin et al. 2019; Badalyan 2020).

Study of NPE of 1 → 2, 3 and 1 → 3-glucans isolated from edible medicinal mushroom *Cantharellus cibarius* in different in vitro models of neurodegeneration revealed the beneficial effect of *C. cibarius* polysaccharide fractions CC2a and CC3 on neuron viability and neurite outgrowth under normal and stress conditions. Both fractions showed antioxidant activity (AOA) and effectively neutralized the negative changes induced by glutamatergic system activators. They can be suggested as an effective and safe therapeutic strategy to prevent or mitigate neurodegenerative pathologies (Lemieszek et al. 2018).

3.2 Terpenoids and Steroids

Mushrooms are considered sources of different bioactive terpenoids, steroids, and sterols with NPE (Rupcic et al. 2018; Tang et al. 2019; Wang et al. 2019a, b; Yin et al. 2019; Akiba et al. 2020; Lee et al. 2020; Yadav et al. 2020).

The NPE of *H. erinaceus* has been attributed to terpenoids that can stimulate the production of NGF or brain-derived neurotrophic factor (BDNF). Along with six previously identified cyathane diterpenes, the novel erinacines possess neurotrophin-inducing effects and act on NGF expression (Ma et al. 2010; Rupcic et al. 2018).

Erinacine A derived from ethanol extract (EE) of *H. erinaceus* mycelium shows effects on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity with posttreatment regimens (Lee et al. 2020). A novel mechanism for posttreatment with erinacine A to protect from neurotoxicity through regulating neuronal survival and cell death pathways was suggested by Lee and coauthors (Lee et al. 2020).

Evaluation of neurotrophic activity (NTA) of new cyathane diterpenoids cyafricanins and cyahookerins isolated from mycelia of two agaricoid mushrooms, *Cyathus africanus* and *Cyathus hookeri* in PC-12 cells and anti-neuroinflammatory activity in BV2 microglia cells have been reported (Tang et al. 2019; Yin et al. 2019; Yadav et al. 2020). These compounds showed NGF-induced neurite outgrowth-promoting activity and strong inhibitory effects on inducible iNOS and COX-2 expression (Yin et al. 2019). Cyahookerins and its known analogs showed differential NGF-induced neurite outgrowth-promoting activity in PC-12 cells, while

cyahookerin, cyathin, cyathin, and cyathin inhibitory effect on nitric oxide (NO) production in lipopolysaccharide (LPS)-activated BV-2 microglial cells (Tang et al. 2019).

Isolation and structure elucidation of ten meroterpenoids from chloroform extracts of russoloid fungus *Albatrellus yasudae* (Agaricomycetes) and their Aβ aggregation inhibitory activity has been reported (Akiba et al. 2020). Three compounds were novel whereas seven were previously identified as grifolin, grifolic acid, neogrifolin, confluentin, 2-hydroxyneogrifolin, daurichromenic acid, and a cerebroside derivative.

Seven secondary metabolites, that is, a new lanostane triterpene, four known triterpenes, and two known aromatic meroterpenoids were isolated from fruiting bodies of medicinal polypore mushroom *Ganoderma lucidum*; they showed in vitro AOA and NPE against H_2O_2 and aged Aβ-induced cell death in SH-SY5Y cells (Wang et al. 2019b).

Sixteen secondary metabolites, including 3 new lanostane triterpenes, 3 ganoleucoins, and 13 known compounds with NPE tested on PC12 cells, were isolated from *Ganoderma leucocontextum,* cultivated in China. Two ganoleucoins showed NPE against H_2O_2-induced damage of PC12 cells at 200 μM with a survival rate of 83.19% and 73.37%, respectively, and induced neurite outgrowth at 50–200 μM (Chen et al. 2018a). Thus, *G. lucidum* and *G. leucocontextum* metabolites, particularly meroterpenoids, may be suggested as potential antioxidants and neuroprotective functional food ingredients to prevent the development of NDD (Chen et al. 2018a; Wang et al. 2019b).

3.3 Phenolics and Other Compounds

Phenolics are a diverse group of PhAC, including a large number of subclasses, such as flavonoids, phenolic acids, quinones, tocopherols, tannins, and so on. Mushroom-derived phenolics are known for their diverse pharmacological effects, including anti-inflammatory, antioxidant, and neuroprotective (Palacios et al. 2011; Khatua et al. 2013; Kozarski et al. 2015; Zengin et al. 2015; Islam et al. 2016; Pop et al. 2018; Dhakal et al. 2019; Jiang et al. 2020; Yadav et al. 2020).

Polyphenols extracted from hymenochaetoid fungus *Phellinus baumii* showed strong DPPH-scavenging (78.76%) and Trolox equivalent antioxidant (TEAC) (32.28 μmol Trolox/g sample) activities. The phenolic compound hispidin was isolated and identified from the ethanolic extract (EE) of mycelia of *Ph. baumii*. Hispidin showed a strong ability to scavenge DPPH free radicals and TEAC, equivalent to positive (vitamin C) value of 89.41% and 75.98%, respectively. Furthermore, hispidin protected H_2O_2-induced PC12 cells injured by the decreased oxidative stress level. These results indicated that *Ph. baumii* is a potential source to develop new natural antioxidants for food or medicines (Jiang et al. 2020).

The total phenolic content of methanolic extract (ME) and AE from *Ganoderma applanatum,* as well as their antioxidant, antimicrobial, and inhibitory effects against

cholinesterase, tyrosinase, α-amylase, and α-glucosidase enzymes support to be considered this fungus as a source of new food supplements and represent a model for the development of new drug formulations (Zengin et al. 2015).

The total phenolic contents and AOA of wild polypore species *Trametes versicolor* and *T. gibbosa* were evaluated using ME and AE. The highest AOA was observed in ME, whereas the highest polyphenol and flavonoid contents were detected in AE of screened species (Pop et al. 2018).

High concentrations of tryptamine alkaloids psilocybin and psilocin (dephosphorylated psilocybin) as well as a small amount of baeocystin were detected in cultivated fruiting bodies of *Psilocybe samuiensis.* The psilocybin amount varied from 0.23% to 0.90% dry weight and was the highest in the caps. It was also found in the mycelium of *P. samuiensis* (0.24–0.32%). The relative content of psilocybin, psilocin, and baeocystin found in *P. samuiensis* was similar to that measured in many other psychoactive fungi but completely different from that found in *Psilocybe semilanceata* (Gartz et al. 1994).

A novel ergosterol conjunction-type alkaloid, hericirine, and ergosterol were isolated from the dried fruiting bodies of *H. erinaceum*. The hericirine significantly inhibited the protein expression of iNOS and COX-2 and reduced NO, PGE_2, TNF-α, IL-6, and IL-1β production in RAW264.7 cells exposed to LPS (Li et al. 2014).

Vitamin D deficiency, particularly in elderly people, plays an important role in the development of neurological and psychiatric disorders. However, interventional clinical evidence is lacking. Mushrooms are a nonanimal source of vitamin D and a rich source of ergosterol—the precursor of vitamin D_2. Vitamin D_2-enriched mushrooms (VDM) could prevent the cognitive and pathological abnormalities associated with dementia. However, randomized clinical trials to determine whether VDM consumption improves cognitive performance in the broader population are required (Bennett et al. 2013b; Zajac et al. 2016; Cardwell et al. 2018).

4 Macrofungi as Neuroprotectants

Mushrooms have been part of human culture for thousands of years as food, medicine, and religious attribute (Hobbs 2004; Badalyan 2012; Thongbai et al. 2015; Badalyan and Zambonelli 2019). Edible and medicinal mushrooms are an excellent source of polysaccharides (β-glucans), proteins (lectins), phenolics, unsaturated fatty acids, ergosterol (precursor of vitamin D_2), minerals, fiber, as well as bioactive metabolites (alkaloids, lectins, phenolics, polysaccharides, terpenoids, etc.). Possessing different medicinal properties, they may play an important role in the prevention, mitigation, and treatment of many diseases, including age-associated neurological dysfunctions, including AD and PD (Chang and Miles 2004; Cheung 2010; Chang and Wasser 2012; Thangthaeng et al. 2015; Valverde et al. 2015; Zengin et al. 2015; Gargano et al. 2017; Phan et al. 2015, 2017; Rathore et al. 2017; Badalyan and Zambonelli 2019; Badalyan et al. 2019; Chen et al. 2019; Hyde et al. 2019; Ho et al. 2020; Lucius 2020; Yadav et al. 2020) (Table 1).

Table 1 Macrofungi with potential neuroprotective activity

Mushroom species	Bioactive compounds	Therapeutic effects	References
Agaricus bisporus (J.E. Lange) Imbach	Polysaccharides	Against AD, improves memory, AChE inhibitory	Bennett et al. (2013b), Mahmoud et al. (2014), Kozarski et al. (2020)
Agaricus blazei Murrill (= *Agaricus brasiliensis* Wasser, M. Didukh, Amazonas & Stamets (= *Agaricus subrufescens* Peck.)	Polysaccharide (WSP-AbM)	Antidepressant, anti-inflammatory, neuroprotective, against diabetic neuropathy	Ji et al. (2014), Qin and Han (2014)
Albatrellus yasudae (Lloyd) Pouzar	Meroterpenoids	Aβ-aggregation inhibitory activity	Akiba et al. (2020)
Amanita caesarea (Scop.) Pers.	Fatty acids, phenolics	Antioxidant, neuroprotective	Doğan and Akbaş (2013), Li et al. (2017)
Amanita muscaria (L.) Lam.	Muscimol	Neuroprotective	Kondeva-Burdina et al. (2019)
Antrodia cinnamomea T.T. Chang & W.N. Chou [= *Taiwanofungus camphoratus* (M. Zang & C.H. Su) Sheng H. Wu, Z.H. Yu, Y.C. Dai & C.H. Su]	Polysaccharides, terpenoids	Anti-inflammatory, antioxidant, neuroprotective	Lu et al. (2013), Hsiao and Weng (2019)
Armillaria mellea (Vahl) P. Kumm.	Protoilludane sesquiterpenoids, aromatic esters	Antidepressant-like activity	Zhang et al. (2019)
Calocybe indica Purkayastha & A. Chandra	Polyphenols	Antioxidant, neuroprotective	Cardoso et al. (2015), Rathore et al. (2018)
Cantharellus cibarius Fr.	Polysaccharides	Neuroprotective	Lemieszek et al. (2018)
Clitocybe geotropa (Bull. ex DC.) Quél. [= *Infundibulicybe geotropa* (Bull. Ex DC.) Harmaja]	Phenolics	Anti-AChE activity, antioxidant, strong neuroprotective	Kosanić et al. (2020a)
Clitocybe nebularis (Batsch) P. Kumm.	Phenolics	Antioxidant, anti-AChE activity, strong neuroprotective	Kosanić et al. (2020a)
Coprinellus truncorum (Scop.) Redhead, Vilgalys & Moncalvo	Polysaccharides	Antioxidant, anti-AChE activity	Pejin et al. (2019)
Coprinus comatus (O.F. Müll.) Pers.	Polysaccharides	Antioxidant, anti-AChE activity	Pejin et al. (2019)

(continued)

Table 1 (continued)

Mushroom species	Bioactive compounds	Therapeutic effects	References
Cyathus africanus H.J. Brodie	Cyathane diterpenoids cyafricanins	Anti-neuroinflammatory activity, NGF-induced neurite outgrowth-promoting activity	Yin et al. (2019), Yadav et al. (2020)
Cyathus hookeri Berkeley	Cyathane diterpenoids cyahookerins	Anti-neuroinflammatory NGF-induced neurite outgrowth-promoting and neutrophic activity	Tang et al. (2019), Yadav et al. (2020)
Dictyophora indusiata (Vent.) Desv. (= *Phallus indusiatus* Vent.)	Polysaccharides	Anti-inflammatory, antioxidant, neuroprotective	Zhang et al. (2016b)
Flammulina velutipes (Curtis) Singer	Polysaccharides	Neuroprotective, mitigate neurodegeneration	Phan et al. (2017), Sabaratnam and Phan (2018)
Fomitopsis officinalis (Vill.) Bondartsev & Singer	Polysaccharides, lanostane triterpenoids officimalonic and eburicoic acids, flavonoids, organic acids, coumarins, phenolic compounds	Antioxidant, anti-inflammatory, neuroprotective, neuroregenerative, antidepressant, anti-epileptic	Muszyńska et al. (2020)
Ganoderma applanatum (Pers.) Pat. [=*Ganoderma lipsiense* (Batsch) G.F.]	Polysaccharides, triterpenes, aromatic meroterpenoids, proteins, peptides, sterols	Neuroprotective, against AD and PD, modulation of neurogenesis, therapeutic effect on epilepsy, protective effect on neural cells in stroke injury	Zengin et al. (2015), Zhao et al. (2019)
Ganoderma leucocontextum T.H. Li, W.Q. Deng, Sheng H. Wu, D.M. Wang & H.P. Hu	Lanostane triterpenes, meroterpenoids, ganoleucoins	Antioxidant, neuroprotective	Chen et al. (2018a)
Ganoderma lucidum (Curtis) P. Karst.	Polysaccharides, triterpenes, aromatic meroterpenoids, proteins, peptides, sterols	Antioxidant, anti-AChE activity, neuroprotective against AD and PD, analgesic, antidepressant, antiepileptic, antinociceptive, hypnotic, neuroprotective, sedative	Qin and Han (2014), Zengin et al. (2015), Diling et al. (2017), Ćilerdžić et al. (2018), Cui and Zhang (2019), Lai et al. (2019), Wang et al. (2019b), Zhao et al. (2019), Yadav et al. (2020)
Ganoderma microsporum R.S. Hseu	Proteins	Inhibition of neuronal cell death	Chen et al. (2018b)

Ganoderma neo-japonicum Imazeki	Polysaccharides	Antidepressant, neuroprotective	Tan et al. (2015)
Grifola frondosa (Dicks.) Gray	Protein-bound polysaccharide (PGM)	Antidepressant, neuroprotective, ameliorates AD-like pathology and cognitive impairments by enhancing microglial amyloid-β clearance	Bai et al. (2019), Fan et al. (2019)
Hericium erinaceus (Bull.: Fr.) Pers.	Polysaccharides, cyathane diterpenoids, hericenones and erinacines	Antioxidant, antidepressant, memory enhancer, neuroprotective and neurostimulating	Ma et al. (2010), Nagano et al. (2010), Phan et al. (2014a), Zengin et al. (2015), Cheng et al. (2016), He et al. (2017), Rossi et al. (2018), Rupcic et al. (2018), Chong et al. (2019), Kushairi et al. (2019), Saitsu et al. (2019), Üstün and Ayhan (2019), Wang et al. (2019a), Limanaqi et al. (2020), Yadav et al. (2020)
Hygrophorus eburneus (Bull.) Fr.	Phenolics	Antioxidant, anti-AChE activity, strong NPE	Kosanić et al. (2020b)
Inonotus obliquus (Ach. ex Pers.) Pilát	Polysaccharides	Inhibitory effects on the proliferation of human neurogliocytoma cells	Ning et al. (2014)
Laetiporus sulphureus (Bull.) Murrill	Polysaccharides, phenolics	Antioxidant, neuroprotective, against AD and PD, AChE, and tyrosinase inhibitory activities	Ćilerdžić et al. (2019)
Lentinus edodes (Berk.) Pegler	Polysaccharides	Antioxidant, anti-inflammatory, antidepressant, neuroprotective	Badalyan et al. (2019), Diallo et al. (2020)
Lignosus rhinocerotis (Cooke) Ryvarden	Glucans, proteins, proteases, phenolics	Antidepressant, anti-inflammatory, antioxidant, enhances motor and sensory functional recovery after nerve injury and has no adverse effects on nervous tissues, stimulation of neurite outgrowth, neuroprotective, neuroregenerative	Phan et al. (2013), Nallathamby et al. (2018), Farha et al. (2019)

(continued)

Table 1 (continued)

Mushroom species	Bioactive compounds	Therapeutic effects	References
Phellinus linteus (Berk. & M.A. Curtis) Teng, Zhong Guo De Zhen Jun [= *Tropicoporus linteus* (Berk. & M.A. Curtis) L.W. Zhou & Y.C. Dai]	Aromatic acids, polysaccharides, flavones, phenolics, triterpenes	Antidepressant, anti-inflammatory, neuroprotective	Hsieh et al. (2013), Chen et al. (2016a), Chen et al. (2019)
Phellinus pini (Brot.) A. Ames [= *Porodaedalea pini* (Brot.) Murrill]	Polysaccharides, phenolic compound hispidin, phenolic acids	Anti-AChE activity, anti-inflammatory	Im et al. (2016a)
Pleurotus eryngii (DC.) Quél.	Polysaccharides, phenolic compounds	Ameliorates memory and learning deficit, against AD	Liang et al. (2020), Zhang et al. (2020)
Pleurotus giganteus (Berk.) S.C. Karunarathna & K.D. Hyde	Polysaccharides, phenolics, triterpenoids, proteins	Antioxidant, antidepressant, neuroprotective, neurite stimulation	Phan et al. (2012), Bennett et al. (2013a), Yadav et al. (2020)
Pleurotus ostreatus (Jacq.) P. Kumm.	Polysaccharides pleuran	Antioxidant, against AD and PD	Bobek and Galbavy (2001), Ćilerdžić et al. (2019)
Polyporus umbellatus (Pers.) Fr.	Exopolysaccharides	Antioxidant	Bandara et al. (2015)
Poria cocos F.A. Wolf [= *Wolfiporia cocos* (F.A. Wolf) Ryvarden & Gilb.]	*P. cocos* water extract (PCW)	Antidepressant-like, antioxidant, anti-inflammatory, sedative and tonic agent, regulation of monoaminergic neurotransmission	Huang et al. (2020)
Psilocybe samuiensis Guzmán, Bandala & J.W. Allen	Alkaloids psilocybin, psilocin and baeocystin	Psychoactive	Gartz et al. (1994)
Trametes gibbosa (Pers.) Fr.	Polysaccharides, phenolics	Antioxidative, anti-neurodegenerative	Knežević et al. (2018)
Trametes pubescens (Schumach.) Pilát	Polysaccharides, phenolics	Antioxidant, anti-neurodegenerative	Im et al. (2016b), Knežević et al. (2018)
Trametes versicolor (L.) Lloyd	Polysaccharides, phenolics	Antioxidant, anti-dementia, anti-inflammatory	Knežević et al. (2018), Pop et al. (2018)
Tremella fuciformis Berk.	Fatty acids, proteins, polysaccharides, enzymes, phenols, flavonoids, volatile oil	Antioxidant, antiaging, neuroprotective, neurotrophic, induces neurite outgrowth via activation of CREB transcription and cholinergic systems	Park et al. (2007), Park et al. (2012), Liu et al. (2019), Wu et al. (2019)

AChE acetylcholinesterase, *AD* Alzheimer's disease, *CREB* C-AMP response element-binding protein, *NGF* nerve growth factor, *NPE* neuroprotective effect, *PD* Parkinson's disease, *WSP-AbM* water-soluble polysaccharide of *Agaricus blazei* Murill

The NDD will continue to rise steadily and is expected to reach 42 million cases in 2020 worldwide. The oxidative stress and inflammation in the neuron–glia system are key factors in the pathogenesis of NDD, the main challenges to modern medicine (Uddin and Ashraf 2018). The general strategy to prevent the development of NDD is a stress-free lifestyle, physical activity, and a healthy diet, enriched with different natural supplements. Despite the advancement of pharmacological treatment, the management of these diseases remains largely ineffective. Moreover, available drugs have always been associated with several side effects; natural products have gained recognition for the prevention or management of diseases. Therefore, it is urgent to explore novel neuroprotective agents and myco-pharmaceuticals to mitigate the development of age-related neurodegenerative conditions.

In vivo and in vitro studies revealed a high nutritional value and nutraceutical properties of macrofungi and have provided evidence for their protective effects against oxidation and inflammation, as well as various lifestyle- and age-related chronic diseases, including AD, PD, arterial hypertension, cancer, and high risk of stroke (Chang and Buswell 1996; Poucheret et al. 2006; Barros et al. 2008; Palacios et al. 2011; Badalyan 2012; Phan et al. 2015, 2017).

The association between dietary patterns with cognitive function has not been thoroughly investigated (Nagano et al. 2010; Lucius 2020). A recent study in a population of elderly Japanese patients suggests that frequent mushroom consumption is associated with a lower risk of incident dementia (Zhang et al. 2017). It has been suggested that both "mushroom, vegetable, and fruits" and "meat and soybean products" patterns were associated with better cognitive function among adults aged more than 60 years old (Yin et al. 2018). Mushroom-derived bioactive compounds and mushroom-based daily diets can improve the cognitive abilities in aging people, inhibit AChE and tyrosinase activity, and prevent the development of NDD (Cardwell et al. 2018; Rossi et al. 2018; Yin et al. 2018; Dhakal et al. 2019). However, scientific validation is required to consider macrofungi as neuroprotective agents, to understand the molecular and biochemical mechanisms involved in the stimulation of neurite outgrowth in in vitro and in vivo studies (Sabaratnam et al. 2013; El Sayed and Ghoneum 2020).

Macrofungi, such as *Agaricus brasiliensis* (Ji et al. 2014; Qin and Han 2014), *Cantharellus cibarius* (Lemieszek et al. 2018), *Laetiporus sulphureus* and *Pleurotus ostreatus* (Bobek and Galbavy 2001; Ćilerdžić et al. 2019), *Fomitopsis betulina* (Pleszczyńska et al. 2017), *Fomitopsis officinalis* (Muszyńska et al. 2020), *Polyporus umbellatus* (Bandara et al. 2015), *Amanita caesarea* (Li et al. 2017), *Hericium erinaceus* (Ma et al. 2010; Üstün and Ayhan 2019), *Phellinus linteus* (Chen et al. 2016a), *Ganoderma lucidum* (Diling et al. 2017), *Ganoderma neo-japonicum* (Tan et al. 2015), *Trametes* (= *Coriolus*) species (Im et al. 2016b; Knežević et al. 2018), *Lignosus rhinocerotis* (Phan et al. 2013; Nallathamby et al. 2018; Farha et al. 2019) and others species, that is, *Agaricus bisporus, Auricularia polytricha*, *Flammulina velutipes, Grifola frondosa, Lentinus edodes* and *Pleurotus giganteus* (Phan et al. 2012, 2015; Bennett et al. 2013a; Fan et al. 2019; Kozarski et al. 2020) have been used in traditional medicine as neuroprotective and antidepressant agents against age-related NDD (Table 1**,** Figs. 1 and 2). Among these,

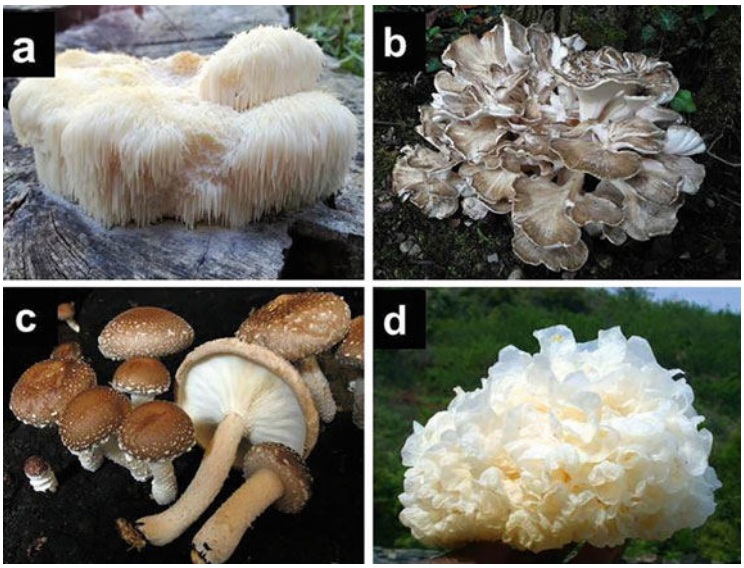

Fig. 1 Fruiting bodies of edible potential neuroprotective mushrooms: (**a**) *Hericium erinaceus* (Photo Courtesy of Angelini C), (**b**) *Grifola frondosa* (Photo Courtesy of Angelini C), (**c**) *Lentinus edodes* (Photo Courtesy of Angelini C), and (**d**) *Tremella fuciformis* (Photo Courtesy of Callac P)

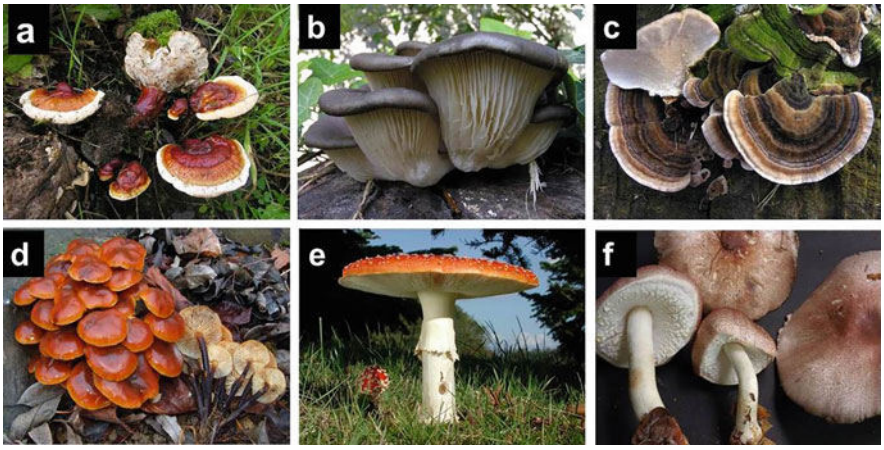

Fig. 2 Wild-growing fruiting bodies of agaricoid and polyporoid neuroprotective mushrooms: (**a**) *Ganoderma lucidum* (Photo Courtesy of Angelini C), (**b**) *Pleurotus ostreatus* (Photo Courtesy of Angelini C) (**c**) *Trametes versicolor* (Photo Courtesy of Angelini C), (**d**) *Flammulina velutipes* (Photo Courtesy of Moingeon JM, (**e**) *Amanita muscaria* (Photo Courtesy of Callac P and Guinberteau J), (**f**) wild specimen CA918 *Agaricus subrufescens* (Photo Courtesy of Callac P)

H. erinaceus, G. lucidum and *L. edodes* are widely used as bio-ingredients in the formulation of cholesterol-free functional food products which are of great interest to the modern dietary nutrition industry (Chang and Buswell 1996; Ma et al. 2010; Valverde et al. 2015; Ho et al. 2020; Lucius 2020; Yadav et al. 2020).

Recent literature data have provided information about neuroprotective, psychotropic, and antidepressant effects of macrofungi attributed to their antioxidant, anti-neuroinflammatory, and cholinesterase inhibitory properties (Grienke et al. 2014; Phan et al. 2015, 2017; Badalyan and Zambonelli 2019; Badalyan et al. 2019; Hyde et al. 2019; Zhang et al. 2020). More than 20 different brain-improving culinary–medicinal mushrooms and their around 80 bioactive compounds from basidiocarps and mycelia have been reported to reduce β-amyloid-induced neurotoxicity, to show anti-AChE and neurite outgrowth stimulatory effects, as well as to assist NGF synthesis. Moreover, the in vitro and in vivo studies on the molecular mechanisms of neuroprotection and possible clinical trials are also discussed (Phan et al. 2015). Nevertheless, there is a gap between traditional knowledge, experimental evidence, and clinical studies, which are restricted by the quality of trials and other important criteria that may affect their success to become clinically verified drugs. Moreover, before the clinical application of mushroom-derived neuroprotectants, the therapeutic potential and synergistic effects of bioactive ingredients and stabilization for the administration of the drug needs to be evaluated appropriately (Lindequist 2013; Money 2016; Badalyan et al. 2019; Lew et al. 2020; Lucius 2020).

4.1 Hericium erinaceus

The cultivated edible mushroom, *Hericium erinaceus* (Lion's mane or Monkey's head) known as "Houtou" or "Shishigashira" in Chinese and "Yamabushitake" in Japanese), has been frequently prescribed in TCM, as an important medicinal fungus with immunomodulatory, antioxidant, anti-inflammatory, antitumor, and neuroprotective properties (Thongbai et al. 2015; Badalyan et al. 2019; El Sayed and Ghoneum 2020).

The modern myco-pharmacological study has attracted considerable attention on *H. erinaceus* as a neuroprotector to prevent and mitigate NDD, including AD, PD, and other forms of dementia, anxiety, or depression (Mizuno 1999; Wong et al. 2007, 2011, 2012, 2014; Ma et al. 2010; Nagano et al. 2010; Mori et al. 2011; Kim et al. 2014; Phan et al. 2014a, b, 2019; Thongbai et al. 2015; Cheng et al. 2016; Kuo et al. 2016; Zhang et al. 2016a; Spelman et al. 2017; Chong et al. 2019; Jang et al. 2019; Kushairi et al. 2019; Saitsu et al. 2019; Üstün and Ayhan 2019; Limanaqi et al. 2020; Yadav et al. 2020).

H. erinaceus contains high amounts of antioxidants and polysaccharides (β-glucans); in addition, a potent catalyst for brain tissue regeneration helps to improve memory and cognitive functions. The fruiting bodies and mycelium of *H. erinaceus* possess immunomodulating, antitumor, hypoglycemic, and antiaging properties. This fungus can be considered as useful therapeutic agents in the

management and/or treatment of NDD (Ma et al. 2010; Wong et al. 2012; Kim et al. 2014; Cheng et al. 2016; Zhang et al. 2016a; Diling et al. 2017; Chong et al. 2019).

The fruiting bodies and fermented mycelia of *H. erinaceus* have been reported to produce different groups of bioactive compounds (polysaccharides, proteins, lectins, phenolic derivatives, and terpenoids) among which two classes of terpenoids—hericenones and erinacines stimulate the synthesis of nerve growth factor (NGF)—a neurotrophic factor and neuropeptide primarily involved in the regulation of growth, maintenance, proliferation, and survival of certain target neurons (Kim et al. 2014; Thongbai et al. 2015). Isolation, structural elucidation, and bioactivity of hericenones and erinacines from the fruiting body and mycelium of *H. erinaceus* have been reviewed (Kawagishi et al. 1991; Ma et al. 2010; Phan et al. 2014a; Li et al. 2018). Hericenones and erinacines have been found to promote the expression of the neurotrophic factor (NTF) associated with cell proliferation. However, only erinacine A has revealed therapeutic properties in the central nervous system of experimental rats (Li et al. 2018). The screening of 58 biomolecules isolated from *H. erinaceus* and their neurotropic activity was recently reported (Aparicio-Razo 2020). Four benzyl alcohol derivatives of hericenones B–E exerts NTA in PC12 cells by extracellular signal-regulated 21 kinase 1/2 (ERK1/2) and phosphoinositide-3-kinase/AKT or protein kinase B (PI3K/AKT) signaling pathways (Phan et al. 2014a). The hericenones, an inhibitor of the β-secretase enzyme improved mitochondrial dysfunction, intracellular Ca^{2+} levels, inhibition of the production of ROS, increase in the mitochondrial membrane potential (MMP) and ATP levels, as well as regulation of the expression of genes encoding for p21, COX I, COX II, PARP1, and NF-κB proteins can be suggested as neuroprotectants for the treatment of various NDD (Diling et al. 2017).

The hericipins A, B, C, E, F and hericenones C, D, E, and Y-A-8-c, promoted the induction of NGF synthesis. The NGF could prolong neuronal axons and regulate the formation of neurons, as well as promote their regeneration in animals. The activity of hericipins was suspected to be more potent compared to the activity of adrenaline. This finding should have opened a new perspective in the treatment of Alzheimer-type dementia and neurasthenia (Kawagishi et al. 1990, 1991; Mizuno 1999; Ma et al. 2010). Bioactive compounds erinaceolactones with plant-growth regulatory activity were isolated from the culture broth of *H. erinaceus* (Wu et al. 2014).

Although antidepressant effects of *H. erinaceus* have not been scientifically validated and compared to conventional antidepressants, based on the neurotrophic and neurogenic pathophysiology of depression, the medicinal properties of this fungus may allow developing a potential alternative drug for prevention and treatment of depression (Nagano et al. 2010; Chong et al. 2019).

Although *H. erinaceus* has shown therapeutic potential in many neurological diseases, its role in SE-mediated neuronal death remains unclear. The NPE of crude extracts obtained from *H. erinaceus* before and after SE was observed. At 7 d after SE, animals treated with 60 mg/kg and 120 mg/kg of *H. erinaceus* revealed improved hippocampal neuronal survival, whereas those treated with 300 mg/kg showed similar neuronal death to that of vehicle-treated controls. Thus,

H. erinaceus, as a neuroprotectant can be used for preventing neuronal death after epileptic seizures (Jang et al. 2019).

The neurobiological activities of *H. erinaceus,* such as its effect on neurite outgrowth and differentiation in PC12 cells, have been revealed. The NPE of two high molecular weight of polysaccharides (1.7 × 10(5)Da, 1.1 × 10(5)Da) obtained from EE of *H. erinaceus* showed that 250 μg/mL of polysaccharide prevented Aβ-induced shrinkage and nuclear degradation of PC12 cells. The polysaccharides, except NPE, also showed AOA (Cheng et al. 2016).

H. erinaceus has been extensively tested in vivo and in vitro as a stimulator of neurite outgrowth in cultured cells of the neural hybrid clone NG108–15 and rat PC12 cells (Phan et al. 2014a; Wong et al. 2007, 2011, 2012, 2014, 2016). The enhancement of peripheral neuro-regenerative activity (NRA) by AE from cultivated *H. erinaceus* after crush injury in vivo, as well as the physiological mechanisms of its effect on growth and development of neuronal cell cultures, improvement of functional recovery after nerve injury, together with its neurotropic and neurotrophic effects, have been previously reported (Wong et al. 2011, 2012, 2014, 2016). *H. erinaceus* did not cause neuron damage, toxic effect, or suppression of cellular respiration, improving the myelination process in the mature myelinating fibers. However, further studies are warranted to elucidate molecular mechanisms to promote the growth and regeneration of axons by this fungus. The development of *H. erinaceus* in alternative therapies is in progress (Wang et al. 2014; Wong et al. 2014, 2016).

HWE and EE from fruiting bodies of *H. erinaceus* were investigated for their NPE. The EE showed potent NPE leading to a significant increase in the viability of H_2O_2-treated neurons accompanied by a reduction in ROS and improvement of the catalase (CAT) and glutathione (GSH) content. It also increased the production of MMP and ATP, while reducing mitochondrial toxicity, Bcl-2-associated X (Bax) gene expression, and nuclear apoptosis, as well as reduced NO level in LPS-treated BV2, indicating anti-inflammatory activity (AInA) in microglia. Thus, the EE of *H. erinaceus* may be considered as a potential neuroprotective and anti-inflammatory agent (Phan et al. 2019; Kushairi et al. 2019).

The oral administration of mycelial biomass of *H. erinaceus* during 3 months showed NPE in an experimental animal model. The upregulation of LXA4 was associated with increased content of redox-sensitive proteins. The maximal induction of LXA4 was observed in the cortex, and hippocampus followed by substantia nigra, striatum, and cerebellum (Trovato et al. 2016b).

Peripheral nerve injury (PNI) is an important health problem. Insights into this process are important for the development of novel effective therapies**.** NGF plays a significant role in the survival, growth, and maintenance of various neurons in the nervous system. The study of NPE of *H. erinaceus* and NGF on a mouse PNI model showed that *H. erinaceus* exhibits a higher NPE compared to the NGF. The combination of both increases the axonal regeneration ability of axotomized neurons in mice. Moreover, *H. erinaceus* prevents the death of neurons and regenerates their axons, therefore, may serve as a neuroprotective and neuro-regenerative agent for

treating PNI. Further studies of *H. erinaceus* as a potential source of biocompounds to cure PNI are warranted (Üstün and Ayhan 2019).

The neuroprotective properties of *H. erinaceus* mycelia enriched with erinacines may contribute to further research on the therapeutic role of this fungus. Preclinical studies have shown that daily consumption of *H. erinaceus* enriched with erinacines can prevent the occurrence of ischemic stroke, AD, PD, and depression (Li et al. 2018). Oral supplementation with *H. erinaceus* results in specific and selective improvements in novelty-seeking behavior and object recognition in mice (Rossi et al. 2018). Studies related to the impact of *H. erinaceus* dietary oral supplementation on brain function are few; however, the effect on cognitive skills and hippocampal neurotransmission in wild-type mice has been reported (Nagano et al. 2010; Brandalise et al. 2017; Lucius 2020).

Several bioactive compounds of *H. erinaceus* have been developed into food supplements and alternative medicines (Kawagishi et al. 1990, 1991; Hobbs 2004; Jiang et al. 2014; Wang et al. 2014, 2019a, b; Friedman 2015; Thongbai et al. 2015; He et al. 2017; Li et al. 2018; Rossi et al. 2018; Trovato Salinaro et al. 2018). A new mushroom product available in the market for the treatment of AD and dementia has been developed on standardized extracts, containing hericinones and amiloban from *H. erinaceus*. However, the correspondence of active mushroom components that cause the observed effects is often not clear (Chang and Wasser 2012**;** Lindequist 2013; Wang et al. 2014; Money 2016).

Since NDD is associated with oxidative stress, antioxidant therapy has been suggested for its prevention and treatment. The antioxidant product *Antia* developed from *H. erinaceus* and several plants (*Centella asiatica, Dioscorea villosa, Salacia reticulata* and *Phyllanthus emblica*) showed a NPE in AD-induced mice. Moreover, the treatment with *Antia* showed a protective effect on malondialdehyde (MDA), NF-κB, IL-6, TNF-α, and amyloid-β and other compounds (El Sayed and Ghoneum 2020).

A recent study has also explored *H. erinaceus* as potential fortified foods enriched with lithium. Co-cultivation of *H. erinaceus* with lithium chloride results in a concentration-dependent uptake of lithium and its accumulation in *H. erinaceus* fruiting bodies, to be useful as supplementation for daily dietary intake of lithium underlying the beneficial effects in the brain (Limanaqi et al. 2020). However, further investigation should be carried out in psychiatric disorders.

4.2 Ganoderma *Species*

The age-related oxidative damage and DNA methylation generated in the human body can cause different neuropathological disorders, including dementia. Therefore, the modulation of these conditions may be an effective strategy to delay the progression of NDD (Cornelius et al. 2013; Uddin and Ashraf 2018; Lai et al. 2019).

Numerous studies have reported AOA and NPE of *Ganoderma* mushrooms during stroke injury, modulation of neurogenesis, as well as treatment of AD,

dementia and epilepsy (Chen et al. 2018a; Ćilerdžić et al. 2018; Lai et al. 2019; Wang et al. 2019b; Zhao et al. 2019; Rahman et al. 2020; Yadav et al. 2020).

The ganoderic acid and lucidone A isolated from alcoholic extracts of *Ganoderma lucidum* delay AD progression, improve learning and memory function, ameliorate neuronal apoptosis, and brain atrophy, and downregulate the expression of AD intracellular marker, Ab1–42, in animals (Lai et al. 2019). It has been shown that the biotechnological cultivation of *G. lucidum* is promising, and the cultivation substrate greatly affects not only the chemical profile but also the neuroprotective capacity of basidiocarps (Ćilerdžić et al. 2018). The meroterpenoids isolated from *G. lucidum* have been suggested as potential antioxidant and neuroprotective functional food ingredients (Wang et al. 2019b). Hypercholesterolemia is a risk factor in the development of AD. HWE from *G. lucidum* showed spatial learning and memory-related behavioral amelioration and has an important role in the pathogenesis of AD in hypercholesterolemic rats (Rahman et al. 2020).

The antioxidant, antimicrobial, and cholinesterase, tyrosinase, α-amylase, and α-glucosidase inhibitory activities of ME and AE from other medicinal *Ganoderma* mushrooms, such as *G. applanatum,* and *G. resinaceum* have been reported. The highest AOA and enzyme inhibitory effects were detected in ME of tested species with the highest amount of phenolics. These macrofungi can be potentially used to develop new food supplements and drug formulations (Zengin et al. 2015). Furthermore, anti-inflammatory and neuroprotective effects of *Ganoderma microsporum* immunomodulatory protein (GMI) involving microglial inhibition are reported (Chen et al. 2018b).

According to Cui and Zhang (2019), *Ganoderma* species, and mainly *G. lucidum* have a broad spectrum of neuropharmacological effects as an analgesic, antidepressant, antiepileptic, antinociceptive, hypnotic, neuroprotective, and sedative. The authors summarize among other things rare preclinical and clinical trials of *Ganoderma* and its ingredients in the patients with these disorders.

4.3 Pleurotus *Species*

One of the major etiological factors of AD is oxidative stress, which accelerates Aβ peptide plaque and neurofibrillary tangle accumulation in the brain. Oyster mushrooms (*Pleurotus* spp.) possess a high quantity of antioxidants, including ergothioneine, adenosine, and polyphenol, which reduce oxidative stress-related aging (Badalyan 2012; Phan et al. 2014b; Liang et al. 2020).

A recent study has shown that consumption of edible medicinal mushroom *Pleurotus eryngii* delayed the development of brain atrophy, ameliorated memory deficit in mice, and significantly decreased the levels of brain phosphorylated τ-protein, Aβ plaque deposition, MDA, and protein carbonyl therefore may improve memory and learning capacity in an Aβ-induced AD mouse model (Zhang et al. 2020).

In vitro and in vivo studies of neuroprotective and antidepressant properties of polysaccharides isolated from *P. eryngii* on Aβ-induced neurotoxicity in PC12 cells showed, that 28-weeks treatment by polysaccharides resulted in the significant elevation of cell viability, decreased in the levels of intracellular calcium, and attenuation of the Aβ-mediated cell apoptosis. In aging rats, *P. eryngii* polysaccharides may decrease the production of amyloid precursor protein (APP) in the brain by a mechanism associated with the lowering of iNOS and COX-2 levels showing neuroprotective and antidepressant effects (Zhang et al. 2020).

Pleurotus (= *Panus*) *giganteus* contain a high number of polysaccharides, phenolics, triterpenoids, proteins, dietary fiber, potassium as well as vitamins B_1, B_2, and B_3. Both AE and EE of *P. giganteus* induced neurite outgrowth in rat PC12 and mouse N2a cells, as well as stimulates neuronal differentiation and elongation. Linoleic acid present in the EE promoted NGF biosynthesis, whereas the phenolics positively correlated to the AOA. Thus, *P. giganteus* contains bioactive compounds that mimic NGF and are responsible for neurite stimulation. They can be used in a well-balanced diet as a source of antioxidants to promote neuronal health (Phan et al. 2014a, b; Yadav et al. 2020). The AChE inhibitory activity was detected in HWE from fruiting bodies of *Pleurotus ostreatus*, however, the effect was weaker than the effect of the commercial anti-AD preparation, galantamine (Ćilerdžić et al. 2019).

4.4 Trametes (= Coriolus) *Species*

Several white-rot polypore *Trametes* (= *Coriolus*) species, such as *Trametes versicolor, T. hirsute, T. gibbosa,* and *T. pubescens* have been used for centuries in the traditional medicine of East Asian cultures, however, only *T. versicolor* has been comprehensively studied (Hobbs 2004; Im et al. 2016b; Knežević et al. 2018; Pop et al. 2018; Kıvrak et al. 2020). The high-molecular-weight fractions, especially polysaccharide Krestin (PSK) derived from mycelium, have been studied in human clinical trials in Japan with several chemotherapy protocols. Numerous in vitro and in vivo studies and clinical trials of bioproducts obtained from *T. versicolor* have shown enhancement of immune response and improvement of the quality of life (Wasser 2017; Badalyan et al. 2019).

T. versicolor mycelium extract was the most effective inhibitor of AChE activity, but twice weaker than galantamine. The mycelium extract of *T. gibbosa* more significantly inhibited tyrosinase activity than kojic acid. The chemical screening revealed strong synergistic action of the content of bioactive compounds, such as triterpenes, sugars, and polyphenols produced by studied *Trametes* species (Knežević et al. 2018).

Basidiocarp extracts from *Trametes* species (*T. gibbosa*, *T. hirsuta*, *T. versicolor*) were more effective ABTS+ scavengers and Fe^{2+} reducers in comparison with mycelium extract, however, they were less effective than L-ascorbic acid (Knežević et al. 2018).

The LXA4 upregulation was associated with increased content of redox-sensitive proteins involved in cellular stress response (Trovato et al. 2016a). The maximum induction of LXA4 by *Coriolus* (= *Trametes*) *versicolor* was observed in the cortex and hippocampus of the brain in experimental rats. The supplementation with *C. versicolor* maintained a response to counteract intracellular pro-oxidant status in MD patients (Scuto et al. 2020).

The emerging role of the inflammasome and the importance of *Coriolus* and *Hericium* medicinal mushroom-based nutra- and nutriceuticals in neuroprotection have recently been considered (Trovato Salinaro et al. 2018).

In vitro evaluation of ME and HWE from fruiting bodies of *Trametes pubescens* revealed antioxidant related antidiabetes, anti-dementia, and anti-inflammatory activities (Im et al. 2016b). Eleven phenolic compounds were detected in tested extracts. The ME showed NPE against glutamate-induced PC-12 cell cytotoxicity at 2–40 μg/mL. The AChE and BChE inhibitory effects by both tested extracts at 2.0 mg/mL were moderate and comparable with galanthamine (CAS 357–70-0), the standard drug to treat AD. The extracts also possess AInA and significantly suppressed the carrageenan-induced rat paw edema.

4.5 Amanita *Species*

The bioactivity, chemical composition, as well as AOA and NPE of edible mushroom *Amanita caesarea* (Caesar's mushroom) have been reported (Doğan and Akbaş 2013; Li et al. 2017). The AE of *A. caesarea* improve cell viability, restored mitochondrial function, inhibited the overproduction of intracellular ROS and Ca^{2+}, and suppressed the high expression levels of cleaved-caspase-3 and calpain 1 enzymes, apoptosis-inducing factor (AIF) in the AD–mouse model, as well as alleviated the deposition of Aβ in the brain. The extract improved the central cholinergic system function, as indicated by an increase in ACh and ChAT concentrations and a reduction in AChE levels, as well as reduced ROS and increased SOD levels in the brain of experimental mice. The results provide evidence that *A. caesarea* may be used as a potential neuroprotectant to prevent or mitigate different neurodegenerative disorders (Li et al. 2017).

Muscimol (known also as agarin or pantherine) is one of the principal psychoactive constituents of *Amanita* mushrooms. Muscimol is a potent, selective agonist for the $GABA_A$ receptors and possesses neurotropic, sedative, and hallucinogenic activity. Muscimol is the main hallucinogenic compound found in toxic *Amanita muscaria* mushroom (Kupka and Wieczorek 2016; Kupka et al. 2020). Several studies have described the suppressive effect of muscimol on tremor, without impairing speech and coordination in Parkinson-affected patients. The extract of *A. muscaria* containing high amounts of muscimol showed statistically significant in vitro neuroprotective and antioxidant effects on different neurotoxicity models tested at subcellular and cellular levels in rat brain microsomes, mitochondria, synaptosomes, as well as on neuroblastoma cell line SH-SY5Y (Kondeva-Burdina et al. 2019).

4.6 Agaricus blazei (= Agaricus subrufescens)

Well-known medicinal mushroom *Agaricus blazei* (= *Agaricus subrufescens*) contains several bioactive compounds with various pharmacological effects (Val et al. 2015; Badalyan et al. 2019; Rahmani-Nezhad et al. 2019). For taxonomy and synonymy of that species we recommend the following report as mentioned in Badalyan et al. (2019): the main synonyms of *A. subrufescens* are *Agaricus blazei* Murrill sensu Heinemann, *A. rufotegulis* Nauta, *A. brasiliensis* Wasser, M. Didukh, Amazonas and Stamets, *A. albopersistens* Zuccher, and *A. bambusae* Beeli var. *bambusae*.

The severe clinical presentation of cerebral malaria has been associated with poor treatment access, therapeutic complexity, and drug resistance; therefore, alternative therapies are required. Mice treated with AE or fraction C from *A. blazei* (= *A. subrufescens*) showed AOA, lower parasitemia, increased survival, reduction in weight loss, decrease in brain lesions, and protection against cerebral malaria caused by *Plasmodium berghei*. Thus, *A. blazei* was effective in improving the consequences of cerebral malaria in mice and may provide bases for the development of novel therapeutic strategies (Val et al. 2015).

Different extracts of *A. subrufescens* obtained from Iranian and French strains showed selective AChE inhibitory activity with IC_{50} values of 154.63 and 145.43 μg/mL, respectively. However, the extracts were not demonstrated BChE inhibitory activity whereas its anti-Aβ aggregation activity was comparable to donepezil, as a reference drug. Thus, the extracts induced moderate AOA by DPPH-radical scavenging activity and weak neuroprotective activity against A-β-induced damage (Rahmani-Nezhad et al. 2019).

4.7 Grifola frondosa

Maitake mushroom, *Grifola frondosa,* possesses nutritional and medicinal value and contains a high amount of health-enhancing bioactive compounds (Badalyan and Zambonelli 2019; Badalyan et al. 2019; Bai et al. 2019; Fan et al. 2019). It has been reported that proteoglucan isolated from *G. frondosa* (PGM) possesses strong immunomodulatory effects and can improve learning and memory, decrease the loss of neurons and histopathological abnormalities in mice (Bai et al. 2019; Fan et al. 2019) Moreover, PGM treatment could activate microglia, astrocytes, promote microglial recruitment to the Aβ plaques, and enhance Aβ phagocytosis, thereby alleviating Aβ burden and pathological changes in the cortex and hippocampus. The administration of PGM as a dietary supplement may provide potential benefits on brain aging-related memory dysfunction (Bai et al. 2019; Fan et al. 2019).

4.8 Other Mushroom Species as Potential Neuroprotectants

In addition to species as mentioned earlier, other Agaricomycetes mushrooms, such as *Antrodia cinnamomea, Armillaria mellea, Calocybe indica, Clitocybe geotropa, Cyathus hookeri, Dictyophora indusiata, Fomitopsis betulina, Hygrophorus eburneus, Laetiporus sulphurous, Lignosus rhinocerotis, Paxillus panuoides, Phellinus linteus, Poria cocos,* and *Tremella fuciformis* have also been reported to possess NPE (Park et al. 2007; Hsieh et al. 2013; Lu et al. 2013; Phan et al. 2013; Bandara et al. 2015; Chen et al. 2016a; Zhang et al. 2016b; Nallathamby et al. 2018; Rathore et al. 2018; Ćilerdžić et al. 2019; Farha et al. 2019; Hsiao and Weng 2019; Lee et al. 2019; Wu et al. 2019; Kosanić et al. 2020a, b; Yadav et al. 2020).

The NPE of mushrooms acts by several biological pathways, including inhibiting β-site APP-cleaving enzyme (BACE1), responsible for releasing toxic Aβ peptide from the brain. Several medicinal mushrooms, such as *Agaricus bisporus, Auricularia polytricha*, *Flammulina velutipes,* and *Lentinus edodes* have been tested for the regulation of BACE1. Both BACE1 inhibitory and stimulatory effects were observed. The inhibitory effect was detected in *A. polytricha*, whereas *A. bisporus, F. velutipes*, and *L. edodes* were activators of BACE1. The inhibitory effect was attributed to lipophilic hispidin-derived polyphenols with possible brain bioavailability, whereas the stimulatory effect—to polysaccharides (Bennett et al. 2013a).

Protoilludane sesquiterpenoid aromatic (PSAM) esters isolated from edible medicinal mushroom *A. mellea* are the main active components with antibacterial and anticancer activities. However, 1 mg/kg intraperitoneal injection of PSAM esters showed also significant antidepressant-like activity, which could be reversed by pretreatment with haloperidol (a nonselective D_2 dopamine receptor antagonist), bicuculline—a competitive GABA antagonist and N-methyl-D-aspartate (NMDA)—an agonist at the glutamate site. PSAM esters also effectively increased the hippocampus DA and GABA and decreased the hippocampus glutamate (Glu) levels of mice, indicating that the antidepressant-like effect of PSAM ester might be mediated by the DAergic, GABAergic, and Gluergic systems (Zhang et al. 2019).

The medicinal mushroom *Dictyophora indusiata (= Phallus indusiata)* has been traditionally used in China to cure different inflammatory and neurological diseases. *D. indusiata* polysaccharides are shown to possess in vitro and in vivo antioxidant-related NPE in *Caenorhabditis elegans* nematode. The fungus was shown not only to increase survival rate and reduce stress level but also to decrease ROS and MDA levels and to increase SOD activity. Moreover, *D. indusiata* has restored the functional parameters of mitochondria in the nematode. These findings demonstrate AOA and NPE of *D. indusiata* polysaccharide and suggest further pharmacological usage of this mushroom in the treatment of NDD (Zhang et al. 2016b).

The hymenochaetoid medicinal mushroom *Phellinus linteus* contains polysaccharides, flavones, triterpenes, aromatic acids, phenylpropanoids, furans, amino acids and has been widely used in Asian countries to treat hemorrhage and blood coagulation disorders. Antitumor, hypoglycemic, anti-inflammatory, anti-obesity,

and neuroprotective activities of *Ph. linteus* have also been reported (Hsieh et al. 2013; Chen et al. 2016a, 2019).

The highest potency to induce neurite outgrowth in PC12 cells compared to other previously reported natural substances of HWE derived from *Tremella fuciformis* was reported (Park et al. 2007). The *T. fuciformis*-treated PC12 cells before β-amyloid peptide treatment have significantly diminished toxicity. Therefore, *T. fuciformis* may potentially be used as a neuroprotectant in the therapy of NDD. Park et al. (2012) also reported that on the one hand, *T. fuciformis* enhances the neurite outgrowth of PC12 cells and, on the other hand, restores trimethyltin-induced impairment of memory in rats via activation of CREB transcription and cholinergic systems. Strong AOA (IC_{50} = 0.176 mg/mL) detected in *T. fuciformis* was positively correlated with the concentration of volatile oil extracted from this fungus (Liu et al. 2019).

The neuroprotective, hepatoprotective, anti-inflammatory, antioxidant, and anti-neoplastic activities were reported in a medicinal polypore mushroom, *A. cinnamomea* (Lu et al. 2013; Hsiao and Weng 2019). It was shown that the oral administration of a low dosage of AE from another polypore species *L. rhinocerotis* has improved motor and functional sensory recovery after nerve injury and had no adverse effect on nervous tissues, unlike mecobalamin, used for the treatment of peripheral neuropathies (Phan et al. 2013; Nallathamby et al. 2018; Farha et al. 2019).

A medicinal polypore mushroom *Poria cocos* (= *Wolfiporia cocos*) possesses antioxidant and anti-inflammatory activities and was used as a sedative, diuretic, and tonic agent in traditional medicine. A potent antidepressant-like effect of AE of *P. cocos* via regulation of monoaminergic neurotransmission and inactivation of inflammation in a rodent animal model have been reported (Huang et al. 2020).

The study of neuroprotective, antioxidant, antimicrobial, and cytotoxic activities of acetone extracts from agaricoid mushrooms *Hygrophorus eburneus, Clitocybe geotropa,* and *Clitocybe nebularis* showed dose-dependent AChE inhibitory activity and a strong NPE. Estimated as pyrocatechol equivalent (PE), total phenolic content of *H. eburneus* was 9.27 μg PE/mg, of *C. geotropa*—95.71 μg PE/mg, and of *C. nebularis*—93.94 μg PE/mg. These mushrooms can be regarded as a source of nutraceuticals and neuroprotective functional food (Kosanić et al. 2020a, b).

In vitro study of antioxidant and neuroprotective properties of extracts from *P. ostreatus* and *Laetiporus sulphureus* showed the highest reducing power in *L. sulphureus*. In comparison to α-kojic acid, the tested extracts showed a weaker tyrosinase inhibitory activity. Fungal extracts were rich in phenolics, which were in positive correlation with AOA, AChE, and tyrosinase inhibition. Thus, mushroom-derived phenolic compounds are the potential carriers of NPE possessing significant antioxidant and anti-neurodegenerative capacity and can be suggested as novel nutraceuticals and myco-pharmaceuticals (Ćilerdžić et al. 2019).

The study of a neuroprotective mechanism by *p*-terphenyl leucomentins derived from *Paxillus panuoides* showed potent inhibition of lipid peroxidation and H_2O_2-induced neurotoxicity, but free from any role as ROS scavengers. The leucomentins can chelate iron when DNA is present with iron and H_2O_2, thereby inhibiting DNA

single-strand breakage. These results suggest that the NPE of leucomentins is dependent on their ability to chelate iron (Lee et al. 2003).

The bracket fungus *Fomitopsis betulina* has been traditionally used in folk medicine as antimicrobial, anticancer, and anti-inflammatory agents. Due to its therapeutic properties, the pieces of its fruiting body were carried by Ötzi the Iceman (Pöder 2005). Modern myco-pharmacological studies confirm the health-enhancing effects of *F. betulina* and provided evidence supporting the antibacterial, antiparasitic, antiviral, anti-inflammatory, anticancer, and immunomodulatory activities, as well as NPE. *F. betulina* is a source of bioactive triterpenoids, valuable enzymes, (1 → 3)-α-D-glucan, and can be considered as a promising source for the development of new healthcare bioproducts (Pleszczyńska et al. 2017).

The qualities of medicinal preparations obtained from the *Fomitopsis officinalis* fruiting bodies are determined by the unique composition of its bioactive compounds, such as triterpenoids, polysaccharides, organic acids, coumarins, and phenolic compounds. It has been proved that both crude extracts and the compounds isolated from *F. officinalis* have a wide spectrum of therapeutic effects, including anti-inflammatory, cytotoxic, and antimicrobial effects. The potential mechanism of action of bioactive compounds, such as flavonoids of *F. officinalis* on the central nervous system has been discussed. Dietary products originated from *F. officinalis*, such as *Agarikon* capsules, and powdered *F. officinalis* mycelium are already available in the market (Muszyńska et al. 2020).

The total phenolic content, free radical DPPH-scavenging activity, and ferric reducing power (FRAP) of ME from Se-enriched fruiting bodies of *Calocybe indica* have almost doubled. The correlations amongst the biomass yield, polyphenols, and AOA at 5 mg/mL concentrations of the Se was demonstrated (Rathore et al. 2018). Indeed, further investigation should be carried out on Se-enriched *C. indica* biomass, as a potential novel food supplement with improved Se bioavailability in neurological disorders (Cardoso et al. 2015).

The hypogeal sclerotia of edible medicinal fungus *Polyporus umbellatus* contain antitumor, anticancer, immune-modulating, antimicrobial, and antioxidant compounds and currently used as an ingredient in many healthcare products and food supplements (Bandara et al. 2015). Further investigation could be carried out on antioxidant capacity, and free radical scavenging activity of *P. umbellatus* to develop natural health food from mycelium and sclerotia and exopolysaccharides-based food supplement to prevent, support, or cure neurodegenerative diseases.

5 Conclusion and Future Prospects

Presently, human neurodegenerative and neurological diseases, such as Alzheimer's, Parkinson's, Meniere diseases, as well as epilepsy and depression, are affecting the adult population worldwide. Therefore, scientists have been attempting for more than 20 years to discover new resources of medicines, including mushrooms-derived neuroactive compounds, to delay the progression of these diseases.

This review discusses the current state of knowledge and the findings of recent studies on the neuroprotective potential of macrofungi. It offers a preliminary roadmap for both physicians and researchers interested in expanding their knowledge about neurodegenerative disorders. However, the investigated list of macrofungi is far from being complete.

Future research should be carried out using an interdisciplinary approach involving physicians, biologists, chemists, pharmacologists, and mycologists partnering with social scientists to create a scientific framework that incorporates traditional knowledge, biochemical, and biomedical data.

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