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REVIEW ARTICLE

Therapeutic potential of culinary-medicinal mushrooms for the management of neurodegenerative diseases: diversity, metabolite, and mechanism

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Abstract

Mushrooms have long been used not only as food but also for the treatment of various ailments. Although at its infancy, accumulated evidence suggested that culinary-medicinal mushrooms may play an important role in the prevention of many age-associated neurological dysfunctions, including Alzheimer's and Parkinson's diseases. Therefore, efforts have been devoted to a search for more mushroom species that may improve memory and cognition functions. Such mushrooms include *Hericium erinaceus*, *Ganoderma lucidum*, *Sarcodon* spp., *Antrodia camphorata, Pleurotus giganteus, Lignosus rhinocerotis, Grifola frondosa*, and many more. Here, we review over 20 different brain-improving culinary-medicinal mushrooms and at least 80 different bioactive secondary metabolites isolated from them. The mushrooms (either extracts from basidiocarps/mycelia or isolated compounds) reduced beta amyloid-induced neurotoxicity and had anti-acetylcholinesterase, neurite outgrowth stimulation, nerve growth factor (NGF) synthesis, neuroprotective, antioxidant, and anti-(neuro)inflammatory effects. The *in vitro* and *in vivo* studies on the molecular mechanisms responsible for the bioactive effects of mushrooms are also discussed. Mushrooms can be considered as useful therapeutic agents in the management and/or treatment of neurodegeneration diseases. However, this review focuses on *in vitro* evidence and clinical trials with humans are needed.

Keywords

Alzheimer's disease, antioxidant, culinary-medicinal mushroom, neurite outgrowth, nerve regeneration, neurodegeneration, neuroprotection, secondary metabolite

History

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Introduction

Life expectancy of humankind had increased to 50–60 years at the beginning of the twentieth century due to improved medicinal, dietary, and sanitation conditions. It is, however, foreseen that society will witness an elevated life expectancy of 80–90 years by the twenty-first century (Candore et al., 2006). Nevertheless, ageing is inexorable with an age-associated decline in immune competence and the onset of chronic inflammation leading to neurodegenerative diseases including dementia, Alzheimer's disease (AD) and Parkinson's disease (PD); atherosclerosis and stroke; diabetes; sarcopenia; and cancer (Martorana et al., 2012). With the increased lifespan of the world's population, it is estimated that about 80 million people will suffer from dementia by 2040 whereby AD accounted for almost 60% of dementia cases (Bharadwaj et al., 2010).

The pathological hallmarks of AD are characterised by amyloidogenic processing of amyloid precursor protein (APP) and a subsequent β-amyloid cascade and tau hyperphosphorylation (Claeysen et al., 2012). Other hypotheses of AD pathogenesis include microglial activation associated with neuroinflammation, increased level of acetyl cholinesterase (AChE) activity, and free radical generation (Martorana et al., 2012). Drug therapies for AD include nicotine, melatonin, estrogens (Côté et al., 2012) cholinesterase inhibitors, and an *N*-methyl-D-aspartate receptor antagonist named memantine (Hong-Qi et al., 2012). However, the current AD drug therapy is ineffective and only provides a short-term delay progression of AD. Moreover, although there was a close association of the use of non-steroidal anti-inflammatory drugs (NSAIDs) and a lower incidence of AD, patients suffered from withdrawal syndrome as a result of gastrointestinal toxicity (Hong-Qi et al., 2012).

There has been a recent upsurge of interest in complementary and alternative medicine, especially dietary supplements and functional foods in delaying the onset of age-associated neurodegenerative diseases. As recently reviewed by Perry & Howes (2011), phyto-chemical approach for dementia and AD treatment includes galantamine from *Narcissus* sp., lemon balm (*Melissa officinalis*), and periwinkle (*Vinca minor*). Other edible ''brain food'' consists primarily of blueberry, grape seed, pomegranate, and walnut. The polyphenol entities found in the vegetables,

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fruits and nuts, inhibited neuro-inflammation by preventing APP signaling, and Aβ aggregation (Essa et al., 2012).

Mushrooms offer great potential as a polypharmaceutic drug because of the complexity of their chemical contents and different varieties of bioactivities. Available evidence suggests that mushrooms exhibit anti-oxidants, anti-tumor, anti-virus, anti-cancer, anti-inflammatory, immune modulating, anti-microbial, and anti-diabetic activities (Roupas et al., 2012). In contrast to plant herbal medicines, which are widely explored and relatively more advanced, the brain and cognition health effects of mushrooms are in the early stages of research. Palmitic, oleic, and linoleic acids dominate fatty acid profiles in mushrooms (Doğan & Akbaş, 2013). These fatty acids are important nutritionally, as oleic acid (C18:1 n-9) has been shown to promote axon generation in the striatum during brain development (Guest et al., 2013). Furthermore, *in vitro* toxicology assessment across different mushroom extracts on embryonic fibroblast and neuroblastoma cell lines suggested that the extracts are safe to be consumed even at high doses and they may be developed as a dietary supplement to improve brain and cognitive health. An elaborated discussion on the toxicity of various mushroom metabolites can be found in Phan et al. (2013).

Disease prevention is better than cure especially in neurodegenerative diseases as degeneration process is nearly impossible to be arrested or delayed once the process has commenced. In the present review, brain and cognition health effects of higher Basidiomycetes are analyzed with emphasis on dementia, AD, and PD. The review summarizes the biodiversity of brain-health promoting mushrooms, the chemical structure of the responsible bioactive metabolites, their biological actions, and molecular mechanisms, i.e. neurite outgrowth, cholinesterase inhibition, BACE1 inhibition, anti-neuroinflammation and neuroprotection. The positive, as well as negative, results of experimental testing (*in vitro* and *in vivo*) are also included.

Diversity of mushrooms with brain health promoting effects

In mushroom biology, species boundaries are always indistinct and many mushrooms are subsumed under erroneous names (Hallenberg et al., 2012). Therefore, common names and taxonomic descriptions of different culinary-medicinal mushrooms, which were found to promote brain and cognitive health, are included in Supplemental Table 1. Common names and a morphological description of the mushroom basidiocarps can also be found in Supplemental Table 1.

Inhibition of beta-amyloid, p-tau, and acetylcholinesterase

Beta-amyloid 1–42 (Aβ1–42), a 42-amino acid-length polypeptide, is a cleavage product of amyloid precursor protein (APP) by two secretase enzymes: beta (β-) and gamma (γ-) secretases. Aβ peptides self assemble into soluble oligomers and deposit as insoluble senile plaque in the hippocampus; causing impaired memory and cholinergic dysfunctions in the brains of Alzheimer's patients. Therefore, AD may be prevented by inhibiting the production of Aβ or preventing the aggregation of Aβ into amyloid plaques. Following this hypothesis, the potential of β-secretase (β-site APP cleaving enzyme, BACE1) inhibitor is promising (Sabotič & Kos, 2012). Some BACE1 (EC3.4.23.46) inhibitors such as KMI-429, GSK188909, and PMS777 have provided new insights for clinical application in the near future (Sathya et al., 2012). Apart from that, the level of acetylcholine, a neurotransmitter involved in the regulation of learning and memory functions, decreased dramatically in the neocortex and hippocampus in AD. Therefore, AChE inhibitors can be used to restore acetylcholine levels and therefore cholinergic brain activity.

Aβ 1–40 causes oxidative stress and inflammation in the brain leading to the secretion of *p*-tau protein which is involved in neuron damage (Bharadwaj et al., 2010). In a study by Wang et al. (2012), the mycelium and/or fruiting body of *Antrodia camphorata* were able to reverse the damaging effects of *in vivo* Aβ-40 infusion and *in vitro* Aβ-40 treatment. A working memory test to evaluate short-term memory and learning abilities of Aβ brain infusion rats was carried out. The mushroom-supplemented group displayed better improvement in memory and learning abilities. Also, the expression of *p*-tau protein in rat pheochromocytoma (PC-12) cells was significantly decreased by the treatment of *A. camphorata.* However, *A. camphorata* did not have significant inhibitory effects on BACE expression. This result was interpreted to indicate that *p*-tau inhibition, rather than BACE modulation, played a vital role in AD prevention by *A. camphorata*.

The effects of *Hericium erinaceus* on Aβ25–35 peptide-induced cognitive dysfunction in mice was investigated by Mori et al. (2011). The powder of *H. erinaceus* was mixed with a normal powdered diet and the Aβ25–35 peptide was administered by intracerebroventricular injection. The results revealed that *H. erinaceus* prevented impairments of spatial short-term and visual recognition memory induced by Aβ25–35 in mice. Human trials with *H. erinaceum* derivatives also showed promising results in patients with dementia based on Revised Hasegawa Dementia Scale (HDS-R) (Mori et al., 2009).

Aqueous extract of *Ganoderma lucidum* significantly attenuated Aβ-induced synaptotoxicity and apoptosis by preserving the synaptic density protein called synaptophysin (Lai et al., 2008). Further, a study by Wang et al. (2004) concluded that senescence-accelerated mice (strain SAMP8) given a diet supplemented with *Ganoderma* extract exhibited significantly lower brain amyloid and higher antioxidation activities such as superoxide dismutase, glutathione peroxidase (GPx), and glutathione reductase when compared with the control mice. Moreover, a study by Pinweha et al. (2008) suggested that *G. lucidum* mycelium extract might possess nerve growth factor (NGF)-like properties for the processing of APP *via* an enhanced NGF signaling pathway. As a result, the increased APP expression promoted non-amyloidogenic protein secretion (sAPP).

The mushroom *Cortinarius infractus* has a strong bitter taste and an unpleasant odor due to the presence of indole alkaloids infractine, 6-hydroxyinfractine, and infractopicrine (Brondz, et al., 2007). Infractopicrin (**1**) and 10-hydroxy-infractopicrin (**2**) (Supplemental Figure 1) showed AChE-inhibiting activity with non-detectable cytotoxicity (Geissler et al., 2010). Topological polar surface area (TPSA) of below

70 Å^2 suggested that the compounds could pass through the blood–brain barrier. Aggregation of Aβ1–40 (fibril formation) was also inhibited by the two alkaloids as revealed by the thioflavin T fluorescence assay. In addition, *in vitro* AChE and butyrylcholinesterase-inhibiting activities of extracts of *Tricholoma* species (*T. fracticum*, *T. imbricatum,* and *T. terreum*) were tested. As a result, only the hexane extract of *T. imbricatum* (0.2 mg/mL) was confirmed to inhibit AChE and butyrylcholinesterase by 71.8 ± 0.3% and 52.6 ± 1.0%, respectively (Tel et al., 2011).

According to Dai et al. (2010), hispidin (**3**), a class of polyphenols is an important medicinal metabolite from *Phellinus* spp. Hispidin (Supplemental Figure 1) were isolated from the culture broth of *P. linteus*, and it has been shown to be a non-competitive inhibitor of BACE1 with an IC_{50} value of 4.9×10^{-6} M and a K_i value of 8.4×10^{-6} M (Park et al., 2004a). In addition, hispidin was shown to be an efficient reactive oxygen species (ROS) scavenger (Park et al., 2004b). *Agaricus bisporus* (button mushroom), *Flammulina velutipes* (enoki), and *Lentinula edodes* (shiitake) neither inhibited nor activated BACE1. The major polysaccharide of button mushroom, β-D-glucan, in contrast, did not cause BACE1 activation (Sheean et al., 2012). The results indicated that BACE1 activity behaved differently with different compound features. Nevertheless, the effects of button mushrooms, enoki, and shiitake together with β-D-glucan need to be tested further. Most recently, BACE1 activity was shown to be inhibited by extracts of fresh basidiocarps of *Auricularia polytricha* (wood ear mushroom). The BACE1 inhibitory activity was most likely due to the hispidin-derived polyphenolics (Bennett et al., 2013b).

Stimulation of neurite outgrowth and NGF synthesis

Neurotrophic factors (neurotrophins) such as NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and glia-derived neurotrophic factor (GDNF) play an important role in differentiation, survival, and maintenance of the neuronal cells. Insufficient neurotrophins is believed to result in dysfunction of the nervous system, causing dementia, AD, and PD. However, polypeptides such as NGF in therapy are unfavorable as they are unable to cross the blood–brain barrier. Therefore, finding small molecules that show neurotrophic properties and/or enhancing the action of endogenous neurotrophic factors is important (Shi et al., 2011).

Sarcodon spp., also called ''bitter tooth'', are widely distributed in Europe, North America, and Asia. *Sarcodon* mushrooms are considered inedible due to their bitter taste. On one hand, cyrneines A (**4**) and B (**5**) (Figure 1) isolated from *Sarcodon cyrneus* stimulated neurite outgrowth in PC12 at 100 μM with no cytotoxicity as indicated by lactate dehydrogenase (LDH) analysis (Marcotullio et al., 2006a) (Table 1). Later, it was shown that both cyrneines A and B promoted NGF production in 1321N1 cells (Marcotullio et al., 2007). Neurite outgrowth activity was also observed in NG108-15 cells, a hybrid neuronal cell line derived from mouse neuroblastoma and rat glioma (Obara et al., 2007). On the other hand, cyrneines C (**6**) and D (**7**) failed to induce neurite outgrowth. In addition, glaucopine C (**8**), isolated from the hexane extract of *Sarcodon glaucopus* (Marcotullio et al., 2006b), did not significantly promote neurite outgrowth in PC12 cells but induced NGF gene expression to a lesser extent when compared with cyrneines A and B. It seemed that the presence of the hydroxyl cycloheptadienyl carbaldehyde system in cyrneines could be important for neuritogenesis (Marcotullio et al., 2007). In other words, minor differences in functional groups on cyathane structures in cyrneines A, B, C, and D can influence the responses in neuronal cells. Figure 1 shows the chemical structure of different cyrneines.

Scabronine A (**9**) (Table 2), isolated from *Sarcodon scabrosus,* showed potent inductive activity of NGF synthesis in 1321N1 human astrocytoma cells (Ohta et al., 1998). Further investigation led to the isolation of novel cyathane diterpenoids named scabronines B–F (**10**–**14**) (Kita et al., 1998), G (**15**) (Obara et al., 1999), K (**16**), and L (**17**) (Shi et al., 2011). However, only scabronines B, C, E, and G showed NGF-synthesis stimulating activity. It appeared that the presence of the α,β-unsaturated aldehyde system in the seven-membered ring could be crucial for the bioactivity. Recently, the first synthesis of scabronine G in optically pure form has been reported, and the neurite outgrowth activity was comparable with NGF and natural scabronine G (Waters et al., 2005). Meanwhile, scabronine G-methyl-ester (**18**) synthesized from scabronine G also potently promoted the secretion of NGF and interleukin-6 (IL-6), another major neurotrophic factor released from astrocytes. Most recently, secoscabronine M (**19**), a hemiacetal cyathane diterpenoid was isolated from *S. scabrosus* but no neuritogenesis has been reported for this compound. Figure 1 shows the structures of scabronine A-G, K, L, scabronine G-methyl-ester, and secoscabronine M isolated from *S. scabrosus*.

There is a possible use of *Hericium erinaceus* (Bull.: Fr.) Pers. in the treatment of neurological disorders and dementia as reported by Kawagishi & Zhuang (2008). In a study by Wong et al. (2007), the extracts of *H. erinaceus* fruiting body and mycelium induced neurite outgrowth of neuronal cells NG108-15 *in vitro* (Supplemental Figure 2). Also, ethanol extract of *H. erinaceus* promoted the neurite outgrowth of PC12 cells, enhanced NGF mRNA expression, and the secretion of NGF from 1321N1 human astrocytoma cells (Mori et al., 2008). Further, *in vivo* functional recovery of axonotmetic peroneal nerve injury in Sprague–Dawley rats was assessed by walking-track analysis and toe-spreading reflex (Wong et al., 2009) (Supplemental Figure 3). The peroneal functional index (PFI) and toe-spreading reflex improved more rapidly in the group treated with daily administration of *H. erinaceus* extract. These data suggested that *H. erinaceus* could promote the regeneration of nerve injury in the early stage of recovery (Wong et al., 2010). Although preliminary, it was demonstrated that the *H. erinaceus* extract exerted neurotrophic action and improved the myelination process in the rat brain without affecting nerve cell growth and toxicity (Moldavan et al., 2007). There was an attempt to isolate a polysaccharide from the mycelium of *H. erinaceus* and the polysaccharide (1 000 000 dalton; molar ratio of 1.5:1.7:1.2:0.6:0.9; glucose:galactose:xylose:mannose:fructose) promoted neurite outgrowth in PC12 cells *in vitro* (Park et al., 2002).

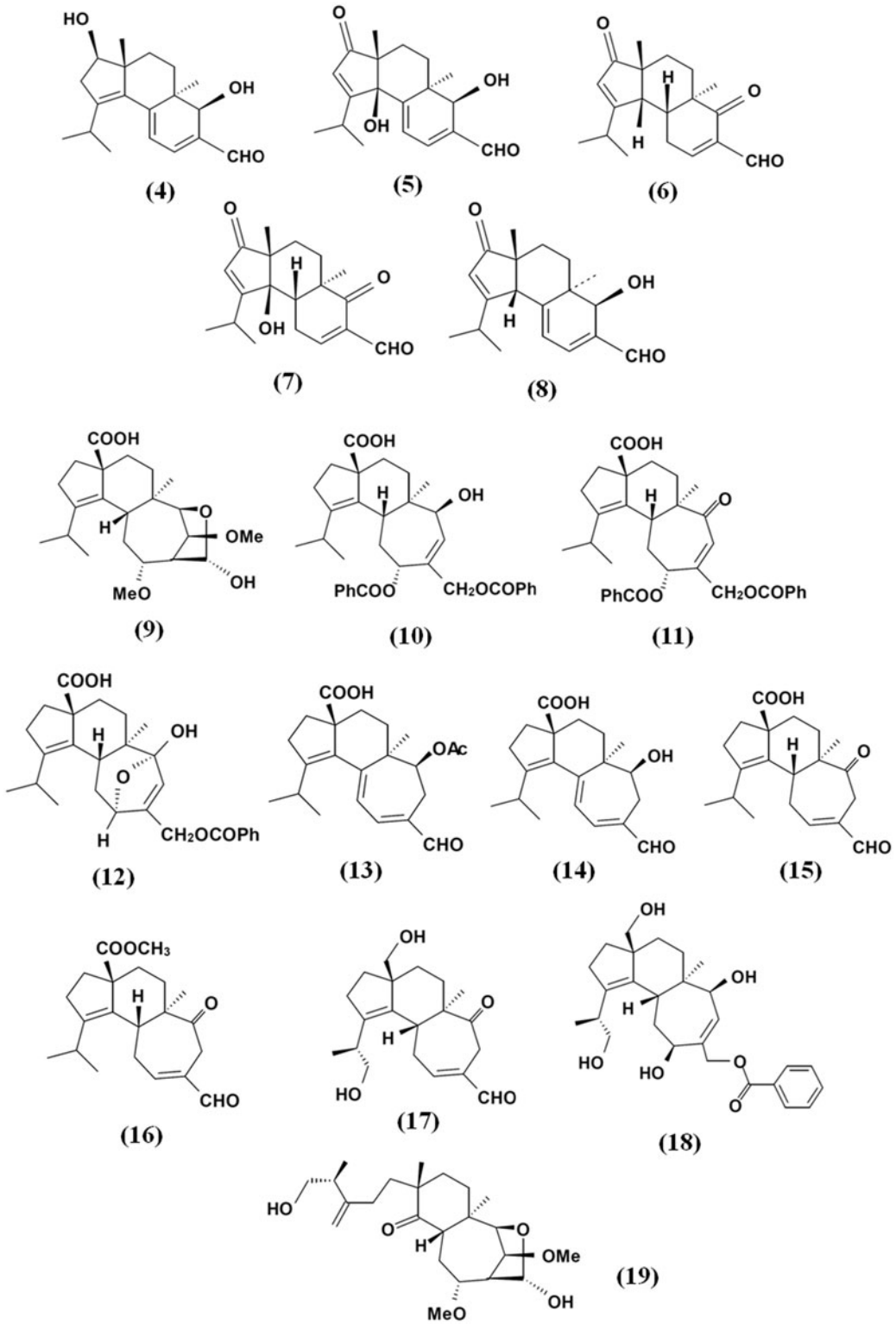


Figure 1. Cyrneines A (**4**), B (**5**), C (**6**), and D (**7**) from *Sarcodon cyrneus*; and glaucopine C (**8**), isolated from the hexane extract of *Sarcodon glaucopus*. Scabronine A–G (**9**–**15**), K (**16**), L (**17**), scabronine G-methyl-ester (**18**), and secoscabronine M (**19**), isolated from *Sarcodon scabrosus*.

However, it needs to be clarified that this *in vitro* evidence cannot be assumed to occur in *vivo* and that the *in vitro* activity of polysaccharides cannot be extrapolated to explain *in vivo* observations.

On one hand, hericenones (benzyl alcohol derivatives) were isolated from the fruiting bodies of *H. erinaceus* (Table 2). Hericenones A (**20**) and B (**21**) were first reported in 1990 but no neurite outgrowth activity was reported (Kawagishi et al., 1990). Hericenones C (**22**), D (**23**), E (**24**), F (**25**), G (**26**), and H (**27**) exhibited stimulating activity for the biosynthesis of NGF *in vitro* (Kawagishi & Ando, 1993; Kawagishi et al., 1991). On the other hand, diterpenoid derivatives (named erinacines) were isolated from the mycelium of *H. erinaceus*. Erinacines A–I (**28**–**36**) significantly induced the synthesis of NGF *in vitro* (Kawagishi et al., 1994, 1996a,b; Lee et al., 2000) and *in vivo* (Shimbo et al., 2005).

Table 1. Compounds isolated from mushroom *Sarcodon* spp. that were screened for neurite outgrowth activity.

No.	Compound	*Sarcodon spp.*	*In vitro* study	Neurite outgrowth activity	References
4	Cyrneine A	SC	PC12; NG108–15; 1321N1	Neurite outgrowth ↑, NGF ↑	Marcotullio et al. (2006a) and Obara et al. (2007)
5	Cyrneine B	SC	PC12	Neurite outgrowth ↑, NGF ↑	Marcotullio et al. (2006b, 2007)
6	Cyrneine C	SC	PC12	–	Marcotullio et al. (2007)
7	Cyrneine D	SC	PC12	–	Marcotullio et al. (2007)
8	Glaucopine C	SG	PC12	NGF gene expression ↑	Marcotullio et al. (2006a) and Marcotullio et al. (2007)
9	Scabronine A	SS	1321N1	Neurite outgrowth ↑	Ohta et al. (1998)
10	Scabronine B	SS	Rat astroglial cells	NGF ↑	Kita et al. (1998)
11	Scabronine C	SS	Rat astroglial cells	NGF ↑	Kita et al. (1998)
12	Scabronine D	SS	Rat astroglial cells	–	Kita et al. (1998)
13	Scabronine E	SS	Rat astroglial cells	NGF ↑	Kita et al. (1998)
14	Scabronine F	SS	Rat astroglial cells	–	Kita et al. (1998)
15	Scabronine G	SS	1321N1	Neurite outgrowth ↑	Obara et al. (1999) and Waters et al. (2005)
16	Scabronine G-Methyl ester	SS	PC12	NGF and IL-6 ↑	Obara et al. (2001)
17	Scabronine K	SS	PC12	–	Shi et al. (2011)
18	Scabronine L	SS	PC12	–	Shi et al. (2011)
19	Secoscabronine M	SS	–	–	Shi et al. (2012)

SC, *S. cyrneus*; SG, *S. glaucopus*; SS, *S. scabrosus*; –, no effect on neurite outgrowth; NGF, nerve growth factor; ↑, promoted/increased.

Table 2. List of hericenones and erinacines in *Hericium erinaceus*, some of which showed neurite outgrowth activity.

No.	Compound	Mushroom component	*In vitro* study	Neurite outgrowth activity	References
20	Hericenone A	F	–	–	Kawagishi et al. (1990)
21	Hericenone B	F	–	–	Kawagishi et al. (1990)
22	Hericenone C	F	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1991)
23	Hericenone D	F	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1991)
24	Hericenone E	F	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1991)
25	Hericenone F	F	Mouse astroglial cells	NGF ↑	Kawagishi & Ando (1993)
26	Hericenone G	F	Mouse astroglial cells	NGF ↑	Kawagishi & Ando, (1993)
27	Hericenone H	F	Mouse astroglial cells	NGF ↑	Kawagishi & Ando, (1993)
28	Erinacine A	M	Mouse astroglial cells Rat (*in vivo*)	NGF ↑; catecholamine ↑ in the CNS of rats	Kawagishi et al. (1994) Shimbo et al. (2005)
29	Erinacine B	M	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1994)
30	Erinacine C	M	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1994)
31	Erinacine D	M	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1996b)
32	Erinacine E	M	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1996a)
33	Erinacine F	M	Mouse astroglial cells	NGF↑	Kawagishi et al. (1996a)
34	Erinacine G	M	Mouse astroglial cells	NGF ↑	Kawagishi et al. (1996a)
35	Erinacine H	M	Rat astroglial cells	NGF ↑	Lee et al. (2000)
36	Erinacine I	M	Rat astroglial cells	NGF ↑	Lee et al. (2000)
37	Erinacine J	M	MRSA	–	Kawagishi et al. (2006)
38	Erinacine K	M	MRSA	–	Kawagishi et al. (2006)
39	Erinacine P	M	–	Biosynthesis of erinacines	Kenmoku et al. (2000)
40	Erinacine Q	M	–	Biosynthesis of erinacine C	Kenmoku et al. (2002)
41	Erinacine R	M	–	–	Ma et al. (2010, 2008)
42	Erinacol	M	–	Biosynthesis of erinacine Q	Kenmoku et al. (2004)

F, fruiting body; M, mycelium; –, none; NGF, nerve growth factor; CNS, central nervous system; MRSA, methicillin-resistant *Staphylococcus aureus*.

Isolation of new compounds from this mushroom continued with the discovery of erinacines J (**37**), K (**38**), P–R (**39**–**41**), as well as erinacol (**42**), a novel cyathadien-14β-ol (Kawagishi et al., 2006; Kenmoku et al., 2000; Kenmoku et al., 2002, 2004; Ma et al., 2010, 2008). Structures of hericenones and erinacines are given in Figure 2.

Cheung et al. (2000) reported that *G. lucidum* extract reduced PC12 cell proliferation and induced neuronal differentiation and neurite outgrowth *via* the activation of MAP kinases and cAMP-response element binding protein (CREB) signaling pathways. In addition, a lipophilic fraction of *G. lucidum* (125 and 500 mg/L) was also shown to induce neurite outgrowth of PC12 cells (Zhang et al., 2005).

Mycoleptodonoides aitchisonii is a rare mushroom that improves brain function in rats. The mycelium-containing cultivation medium was found to bear fragrant compounds of phenylpentane, which consists of 1-phenyl-3-pentanol and 1-phenyl-3-pentanone. The compounds improved dopamine liberation in the brains of rats fed with the mushroom powder or aqueous extracts (Okuyama et al., 2004a). Further, NGF synthesis in the cerebral cortex and hippocampus of newborn rats was also enhanced after the pregnant rats were fed

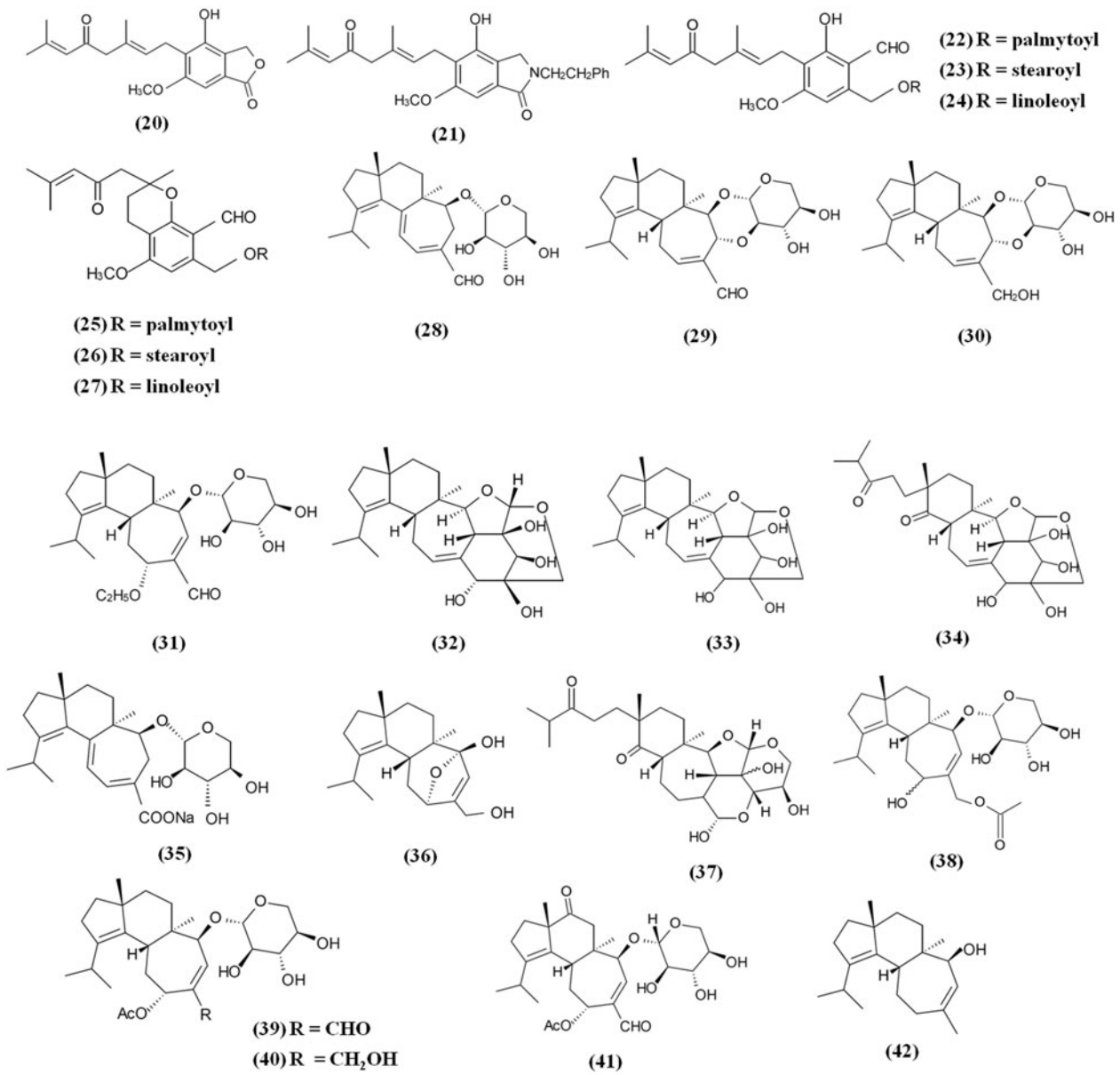


Figure 2. Hericenones A–H (**20**–**27**)**;** erinacine A–K (**28**–**38**), P–R (**39**–**41**), and erinacol (**42**).

with either *M. aitchisonii* powder or its aqueous extract for 7 d before delivery (Okuyama et al., 2004b). A recent study concluded that *M. aitchisonii* aqueous extract prevented the reduction of dopaminergic and serotoninergic neuronal activities following brain ischemia damage in the cerebral cortex (Okuyama et al. 2012). The concentrations of the neurotransmitters, dopamine, and its metabolites were increased after treatment with this mushroom. Moreover, *M. aitchisonii* was shown to activate NF-E2-related factor 2 (Nrf2) and might contribute to the prevention of oxidative stress-related diseases (e.g. Alzheimer's) by inducing anti-oxidative and phase II detoxifying enzyme series (Kokubo et al., 2011).

Dictyophora indusiata is a famous edible mushroom used in Chinese cuisine and medicine. Two eudesmane-type sesquiterpenes, dictyophorines A (**43**) and B (**44**) (Supplemental Figure 4), were isolated from the mushroom and were found to promote NGF synthesis by astroglial cells (Kawagishi et al., 1997). It was shown that NGF secreted into the medium in the presence of 3.3 mM of dictyophorines A was four times higher than the negative control. Meanwhile, lysophosphatidylethanolamine (LPE) isolated from *G. frondosa* (GLPE) was found to induce neurite outgrowth and it upregulated the neurofilament M expression in cultured PC12 cells (Nishina et al., 2006). This study also showed the suppressive effect of *G. frondosa* on serum deprivation-induced apoptosis of the PC12 cells.

The aqueous extract of *Tremella fuciformis* not only promoted neurite outgrowth of the PC12 cells but also significantly reversed the scopolamine- and trimethyltin-induced memory deficit in rats, as revealed by the Morris water maze test and choline acetyltransferase (ChAT) immunohistochemistry (Kim et al., 2007; Park et al., 2012). Besides, neuritogenic compounds named tricholomalides A–C (**45**–**47**) (Supplemental Figure 4) were also isolated from *Tricholoma* sp. and neurite outgrowth in PC-12 cells was significantly induced at concentrations of 100 μM (Tsukamoto et al., 2003). Whereas for *Termitomyces*

albuminosus, the cerebrosides named termitomycesphins A–D (**48**–**51**) (Qi et al., 2000), E–F (**52**–**53**) (Qi et al., 2001), and G–H (**54**–**55**) (Qu et al., 2012) (Supplemental Figure 4) were identified to potentiate neuritogenesis in PC12 cells. It is interesting that termitomycesphin with a 16-carbon-chain fatty acid (A, C, and G) showed higher neuritogenic activity than that of termitomycesphin with an 18-carbon-chain fatty acid (B, D, and H), suggesting that the chain length of the fatty acyl moiety played a determining role in neuritogenesis. A number of new mushrooms have been reported to possess neuritogenic effects (Sabaratnam et al., 2013). Aqueous extract of *L. rhinocerotis* sclerotium (Eik et al., 2012), *L. rhinocerotis* mycelium (John et al., 2013), *Ganoderma neo-japonicum* (Seow et al., 2013), and *Pleurotus giganteus* (Phan et al., 2012) were shown to induce neuronal differentiation and stimulate neurite outgrowth of PC12 and N2a cells. Meanwhile, a methanol extract of *Cordyceps militaris* (5–20 μg/mL) was able to increase primary neurite sprouting and ChAT expression in differentiated N2a cells (Lee et al., 2011). Administration of *C. militaris* also restored the scopolamine-induced memory deficit *in vivo*.

Neuroprotection, anti-inflammatory, and anti-oxidant activities

Accumulating evidence have indicated that oxidative stress and ROS play an important role in the progression of many chronic diseases including cardiovascular diseases, diabetes, and neurodegenerative disorders (Chu et al., 2012). Imbalance between ROS generation and antioxidant enzyme activities will cause lipid peroxidation, nuclear mitochondrial DNA damage and protein oxidation, resulting in brain damage and amnesia (Biasibetti et al., 2013). Therefore, a drug with antioxidant and anti-inflammatory activities may prevent neuronal degeneration in AD. Mushrooms, known for their potent antioxidant property, have attracted interest due to their potential in neuroprotection, antioxidant, and anti-inflammatory effects, in a variety of experimental models (Gunawardena et al., 2014).

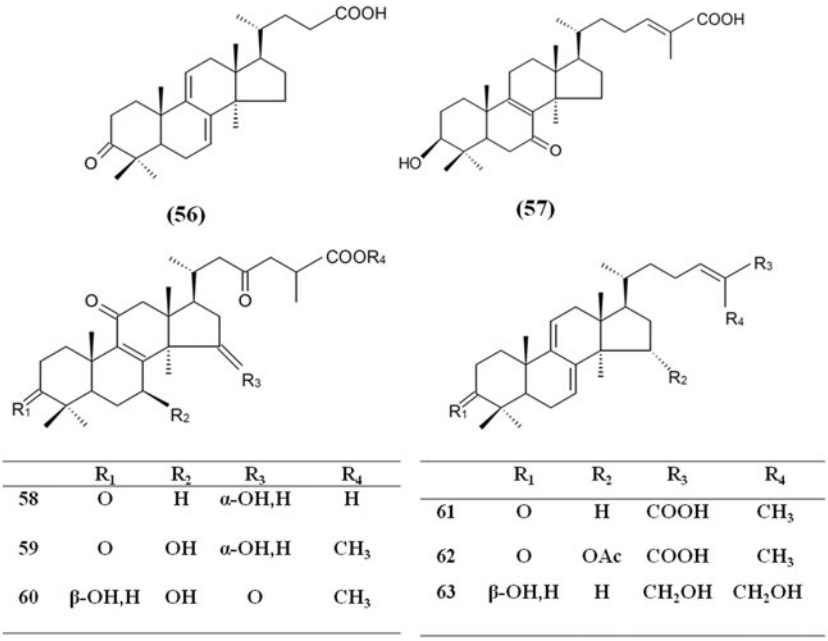
At least 140 different triterpenes have been identified in *G. lucidum* and they include ganoderic, lucidenic, ganodermic, ganoderenic, ganolucidic and applanoxidic acids, lucidones, ganoderals, and ganoderols (Connolly & Hill, 2003; Smina et al., 2011; Wu et al., 2001). The total triterpenes from *G. lucidum* scavenged 2,2-diphenyl-1-picryl hydrazyl ($DPPH^+$), 2,2′-azinobis-(3-ethylbenzothiazolin-6-sulphonic acid ($ABTS^+$) and superoxide radicals (Smina et al., 2011). Also, the administration of total triterpenes to mice enhanced the superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT), and GPx in the blood and liver tissues. Further, the aqueous extracts of *G. lucidum* fruiting bodies were shown to prevent H_2O_2-induced oxidative damage to cellular DNA (Shi et al., 2002). Dietary intake of natural or synthetic products with a putative antioxidant effect has been shown to delay the onset AD (Praticò, 2008). Therefore, the ability of the triterpenes of *G. lucidum* to scavenge free radicals may suppress reactive oxygen damage that leads to AD pathology.

For PD, a neuroprotective approach to salvage dopamine neurons from progressive death in the brain (substantia nigra region) is currently being explored. A study by Zhu et al. (2005) has shown that rats fed with *G. lucidum* spores oil ameliorated Parkinsonism induced by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The number of surviving dopamine neurons in the substantia nigra and the level of dopamine in the striatum of MPTP-induced mice has increased after treatment with the oil of *Ganoderma* spores. Furthermore, involuntary movement of mice was also significantly reduced. Microglia is the resident innate immune cells of central nervous system (CNS) and it plays a major role in the neuroinflammatory process. Activation of microglia can trigger neurotoxicity *via* the production of pro-inflammatory and cytotoxic factors including tumor necrosis factor-(TNF)-α, nitric oxide (NO), superoxide radicals, interleukin- β (IL-β), and cyclooxygenase 2 (COX2) (Liu et al., 2006). The over-activation of microglia in the CNS contributes to neurodegenerative processes (Brown & Neher, 2010). To test for the potential neuroprotective effect of *G. lucidum*, co-cultures of 1-methyl-4-phenylpyridinium-(MPP^+)-treated dopaminergic neuronal cell line MES23.5 and LPS-activated microglia were used (Zhang et al., 2011a). MPP^+ is a metabolite of the neurotoxin MPTP. The *G. lucidum* extracts significantly inhibited the production of microglia-derived proinflammatory and cytotoxic factors (NO, TNF-α, and IL-1β) suggesting that *G. lucidum* is a promising agent in deterring inflammation-induced Parkinson's disease.

Ganoderic acid is a member of highly oxygenated C_{30} lanostane-type triterpenoids. However, its biological activity on the nervous system is still unknown. Recently, a new lanostanoid, 4,4,14-trimethyl-5-chol-7,9(11)-dien-3-oxo-24-oic acid (**56**) was isolated from an ethyl acetate extract of the dried fruiting bodies of *G. lucidum*. The triterpenoids, together with seven other known triterpenoids, i.e. 7-oxo-ganoderic acid Z (**57**), ganolucidic acid A (**58**), methyl ganoderic acid A (**59**), methyl ganoderic acid B (**60**), ganoderic acid S1 (**61**), ganodermic acid TQ (**62**) and ganodermatriol (**63**) (Figure 3), have shown NGF- and brain-derived neurotrophic factor-like neuronal survival-promoting effects (Table 3).

The role of vitamin D2-enriched button mushrooms (*Agaricus bisporus*) was studied especially for their memory improving effects in rats (Bennett et al., 2013a). Fungi, especially the members of Basidiomycetes, are rich in ergosterol. The ergosterol in mushrooms can be converted to vitamin D2 following exposure to ultra violet (UV) light. Recent research suggested that higher vitamin D dietary intake was associated with a lower risk of developing AD among older women (Annweiler et al., 2012). Compound (**56**) has a steroidal feature resembling cholesterol that can be converted to vitamin D by enzymatic pathways, in response to UV irradiation. Therefore, there is a potential for this class of compounds to interact with vitamin D receptors and exert bioactivity *via* vitamin D mimicry.

The endoplasmic reticulum (ER) is an organelle within fungal cells in which protein folding, lipid biosynthesis, and calcium storage takes place (Brown & Naidoo, 2012). The ER, by serving as quality control machinery, suppresses protein aggregation in the cells under normal physiological



	R_1	R_2	R_3	R_4
58	O	H	α-OH,H	H
59	O	OH	α-OH,H	CH_3
60	β-OH,H	OH	O	CH_3

	R_1	R_2	R_3	R_4
61	O	H	COOH	CH_3
62	O	OAc	COOH	CH_3
63	β-OH,H	H	CH_2OH	CH_2OH

Figure 3. New lanostanoid (**56**), 7-oxo-ganoderic acid Z (**57**), ganolucidic acid A (**58**), methyl ganoderic acid A (**59**), methyl ganoderic acid B (**60**), ganoderic acid S1 (**61**), ganodermic acid TQ (**62**), and ganodermatriol (**63**), isolated from *Ganoderma lucidum*.

Table 3. List of ganoderic acids in *Ganoderma lucidum* which showed neuroprotection effects in *in vitro* studies using NIH-3T3/TrkA and NIH-3T3/TrkB cells.

No.	Compound	Neuronal surviving effect	References
56	4,4,14-Trimethyl-5-chol-7,9(11)-dien-3-oxo-24-oic acid	NGF ↑	Zhang et al. (2011b)
57	7-Oxo-ganoderic acid Z	BDNF ↑	Li et al. (2006) and Zhang et al. (2011b)
58	Ganolucidic acid A	BDNF ↑	Zhang et al. (2011b)
59	Methyl ganoderic acid A	BDNF ↑	Zhang et al. (2011b)
60	Methyl ganoderic acid B	NGF ↑	Zhang et al. (2011b)
61	Ganoderic acid S1	BDNF ↑	Zhang et al. (2011b)
62	Ganodermic acid TQ	BDNF ↑	Zhang et al. (2011b)
63	Ganodermatriol	BDNF ↑	Zhang et al. (2011b)

NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor.

Table 4. Protective effects of mushrooms from endoplasmic reticulum stress-induced neuronal cell death.

No.	Mushroom	Compound	References
64	*Hericium erinaceum*	3-Hydroxyhericenone F	Ueda et al. (2008)
		Dilinoleoyl-phosphatidylethanolamine	Nagai et al. (2006)
65	*Stropharia rugosoannulata*	Strophasterol	Wu et al. (2011, 2012)
66	*Leccinum extremiorientale*	Ethyl 2-(*N*-phene-thylformamido)acetate; also Leccinine A	Choi et al. (2011)
67–71	*Termitomyces titanicus*	Termitomycamides A–E	Choi et al. (2010)
72	*Mycoleptodonoides aitchisonii*	3-(Hydroxymethyl)-4-methylfuran-2(5*H*)-one	Choi et al. (2009)
73		3-(10-Hydroxyethyl)-4-methyldihydrofuran-2(3*H*)-one	
74		3-Hydroxyethyl-4-methyldihydrofuran-2(3*H*)-one	
75		1-Hydroxy-3-pentanone	

conditions. However, with age and under stress, ER homeostasis will be interrupted and brings about the ER-stress response or the activation of the unfolded protein response, followed by programmed cell death (apoptosis) in the brain and/or insoluble protein fibrils formation. ER stress accompanies and contributes to several neurological disorders including PD. Due to that, the demand for new protective substances against the ER-stress-dependent cell death is high. In this review, the protective effects of medicinal mushrooms, namely *H. erinaceus*, *Stropharia rugosoannulata*, *Leccinum extremiorientale*, *Termitomyces titanicus*, and *Mycoleptodonoides aitchisonii* against age-implicated ER stress are discussed (Table 4).

In the protection assay against ER stress-dependent cell death, a popular cell line Neuro2a (N2a) cell is widely used. In general, the ER stress was either induced by addition of tunicamycin or thapsigargin. Tunicamycin is a protein glycosylation inhibitor that induces accumulation of misfolded protein in the ER and ultimately causes cell death. Thapsigargin is a non-competitive inhibitor of Ca^{2+} ATPase in ER that causes Ca^{2+} reduction. 3-hydroxyhericenone F (**64**) (Supplemental Figure 5), which was isolated from the fresh fruiting bodies of *H. erinaceus,* was found to protect N2a cells against both tunicamycin and thapsigargin toxicities (Ueda et al., 2008). Another ER stress attenuating compound, dilinoleoyl-phosphatidylethanolamine, was also isolated and

identified from the dried fruiting bodies of *H. erinaceum* (Nagai et al., 2006). A compound from *S. rugosoannulata* attenuated the ER stress caused by thapsigargin, but not by tunicamycin (Wu et al., 2011). The compound was later found to be strophasterol (**65**) with a new steroid skeleton not previously reported (Wu et al., 2012) (Supplemental Figure 5). Similarly, leccinine A (**66**) (Supplemental Figure 5) from *L. extremiorientale* also showed significant protective activity against thapsigargin toxicity but not tunicamycin (Choi et al., 2011). Meanwhile, five fatty acid amides, termitomycamides A–E (**67–71**) isolated from *T. titanicus* (Supplemental Figure 5), were screened for their protective effects against tunicamycin toxicity. Only termitomycamides B and E showed significant protective effects, suggesting that these compounds blocked the inhibitory action of tunicamycin and N-linked glycosylation in ER was not repressed. Another four compounds (**72–75**) (Supplemental Figure 5) were also successfully isolated from the mushroom *M. aitchisonii* and they have shown attenuating effects on ER stress-dependant neuronal cell death (Choi et al., 2009).

Inonotus obliquus is another mushroom popular for its antioxidative effects in neuronal cells (Jung et al., 2008). An acid protein-bound polysaccharide from *I. obliquus* exhibited notable quenching of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and hydroxyl radicals (Chen et al., 2010). Enzymatically hydrolyzed *I. obliquus* by carbohydrase (Celluclast) and protease (Protamex) showed the highest DPPH radical-scavenging activities (Kim et al., 2011). Pepsin extracts of *I. obliquus* managed to decrease generation of ROS and cell death in PC12 cells against H_2O_2-induced oxidative damage. In another study using the peroxide-treated human fibroblasts, *I. obliquus* showed cytoprotective effects by scavenging intracellular ROS and preventing lipid peroxidation and ultimately stopping premature senescence. Most recently, a significant cognitive enhancement was observed in amnesic mice after orally administration of methanolic extracts of *I. obliquus* (Giridharan et al., 2011). The critical metabolites responsible for the neuroprotection were thought to be the phenolic ingredients namely 3,4-dihydroxybenzalacetone (**76**) and caffeic acid (**77**) (Nakajima et al., 2009) (Supplemental Figure 6).

Armillaria mellea produces an array of different metabolites, including carbohydrates, sterols, sphingolipids, fatty acids, sesquiterpenes, non-hallucinogenic indole compounds, peptides, enzymes, and adenosine derivatives (Muszyńska et al., 2011). N6-(5-hydroxy-2-pyridyl)-methyl-adenosine (**78**) (Supplemental Figure 6) from the mycelia of *A. mellea* displayed an adenosine-like cerebral protecting activity (Gao et al., 2009; Watanabe et al., 1990). Compounds of *Daldinia concentric*, 1-(3,4,5-trimethoxyphenyl) ethanol (**79**) and caruilignan C (**80**) (Supplemental Figure 6) showed neuroprotective effects against iron-induced neurotoxicity in mouse cortical cell cultures (Lee et al., 2002).

Five compounds were isolated from the fruiting bodies of *Antrodia camphorata* (Chen et al., 2006) (Supplemental Figure 6). The compounds, 19-hydroxylabda-8(17)-en-16,15-olide (**81**), 3β,19-dihydroxylabda-8(17),11*E*-dien-16,15-olide (**82**), 13-*epi*-3β,19-dihydroxylabda-8(17),11*E*-dien-16,15-olide (**83**), 19-hydroxylabda-8(17),13-dien-16,15-olide (**84**), and 14-deoxy-11,12-didehydroandrographolide (**85**), were shown to protect neurons from $A\beta_{25–35}$ damage. In the study, primary cultures of neonatal cortical neurons from the cerebral cortex of Harlan Sprague–Dawley rat pups at postnatal day 1 were used. The cell stress model for this particular study was serum-deprived PC12 cells (Huang et al., 2005; Lu et al., 2008). Lu et al. (2006) unraveled that the protective effect of *A. camphorata* was due to adenosine (**86**) (Supplemental Figure 6). The protective effect of adenosine was found to be mediated through Adenosin-$_{2A}$ receptor (A_{2A}-R) activation on PC12 cells. A_{2A}-R has been regarded as a potential therapeutic target in protecting against neuronal injury and it has been reported that A_{2A}-R activation delayed apoptosis in human neutrophils (Lu et al., 2006).

Mechanisms and signaling pathways of bioactivity of mushrooms secondary metabolites in neurodegenerative diseases

Signal transduction cascades like the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase-Akt (PI3K-Akt), and protein kinase C (PKC) pathways play important roles in neurons downstream of multiple signals including neurotrophins and neurotransmitters (Martin & Arthur, 2012). Certain mushrooms have shown NGF-like neuritogenic effects. Therefore, it is of utmost importance to elucidate the molecular mechanism responsible for the activity. Essentially, the process where a cell translates an external signal into cellular response is ''signal transduction'' (Martin & Arthur, 2012). Signal transduction begins with the binding of an external ligand (NGF, neurotransmitter, or mushroom compound in this case) to a specific receptor on a cell. This ultimately causes a systematic signalling cascade that initiates a response in a cell, for instance cell differentiation and extension of neurite.

The MAPK signal cascade is known to regulate cell growth and differentiation (Zhang & Liu, 2002). Three MAPK families have been characterized namely extracellular signal-regulated kinase (ERK), C-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 kinase. Small and selective molecule protein kinase inhibitor is a powerful tool to study kinase function. Since NGF induces the activation of MEK and phosphorylation of ERK1/2, MEK inhibitors (U0126 and PD98059) were widely used as one of the checkpoints to assess the MAPK cascade. As reported by Phan et al. (2012), the induction of activation of ERK1/2 by both NGF and *P. giganteus* extracts was inhibited by U0126 and PD98059. Therefore, the mushroom extracts (as well as NGF) induced the activation of MEK1/2, resulting in neurite outgrowth. Similar observations were reported by Cheung et al. (2000) for *G. lucidium* extracts and Nishina et al. (2006), for lysophosphatidylethanolamine from *Grifola frondosa*. Interestingly, there was no direct involvement of the Trk family of receptor tyrosine kinase, (TrkA) for the above mushroom-potentiated neuritogenesis, as opposed by the classical NGF. It is thus predicted that activation of TrKA may not be necessary for NGF-independent neuritogenic effects by mushrooms. It is widely accepted that PI3K/Akt regulates neuritogenesis (Kimura et al., 1994). Akt is a serine/threonine kinase essential for neurotrophin-induced cell survival and the activation of Akt by neurotrophins is

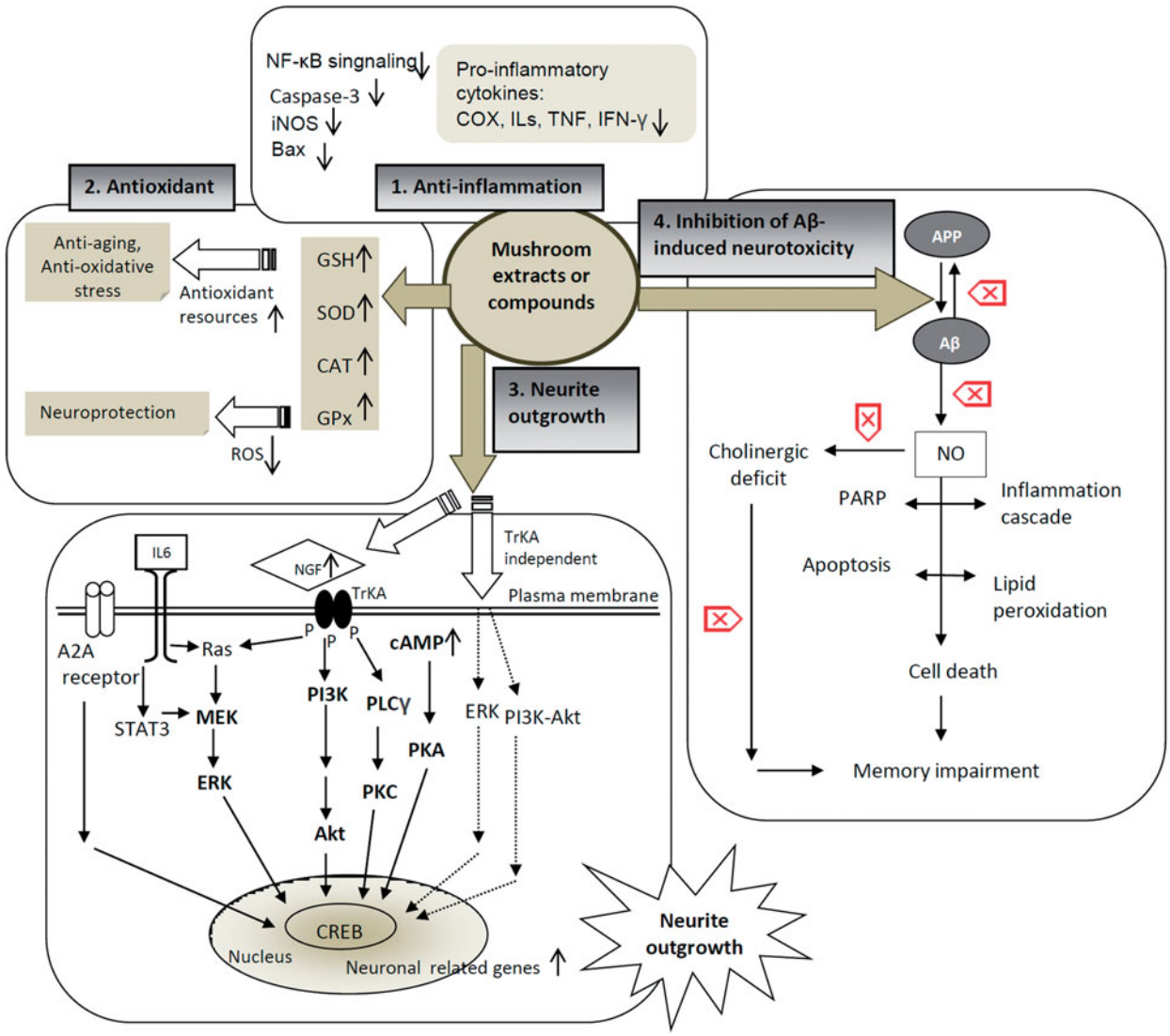


Figure 4. Schematic model of the antioxidative, anti-inflammatory, neurite outgrowth, and neuroprotective effects of mushroom extracts/compounds. ↑, increased; ↓, decreased; ⊠, inhibited; COX, cyclooxygenase; ILs, interleukins; TNF, tumor necrosis factor; IFN-γ, interferon-γ; NF-κB, nuclear factor-κB; iNOS, inducible nitric oxide synthase; Bax, BCL2-associated X; GSH, glutathione; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; ROS, reactive oxygen species; cAMP, cyclic adenosine monophosphate; STAT3, signal transducers and activators of transcription 3: CREB, cAMP response element-binding; PLC-γ, phosphoinositide phospholipase C-γ; NO, nitric oxide; APP, amyloid precursor protein; PARP, poly (ADP-ribose) polymerase.

mediated by phosphatidylinositol-3 kinase (PI3K). Inhibition of PI3K/Akt by inhibitor LY294002 negatively affected neurite outgrowth of PC12 potentiated by *P. giganteus*. This finding suggested that *P. giganteus* induced-neurite outgrowth is also regulated by PI3K/Akt cascade.

As for the inhibitory mechanism of *G. lucidum* on Aβ25–35 neurotoxicity, the levels of stress kinases, namely phosphorylated JNK, phosphorylated c-Jun, and phosphorylated p38 were markedly attenuated (Lai et al., 2008). Meanwhile, the phosphorylation levels of ERK, JNK, and p38 were found to increase in microglia after lipopolysaccharide (LPS) and/or interferon gamma treatment. The methanol extracts of *A. camphorata* significantly inhibited the phosphorylation of ERK and JNK, slightly inhibited the activator of transcription (STAT-1) phosphorylation, in the course of anti-inflammatory activity in microglia. Another study also agreed that *A. camphorata* prevented serum deprivation-induced PC12 cell apoptosis through a PKA-dependent pathway and by suppression of JNK and p38 activities (Lu et al., 2008). 3,4-Dihydroxybenzalacetone (DBL) isolated from *I. obliquus*, inhibited H_2O_2-induced apoptosis of neurons by suppressing the intracellular ROS levels and inhibited Bax and caspase-3 activation. Treatment of DBL significantly inhibited the H_2O_2-dependent phosphorylation of p38-MAPK, but not the ERK and JNK, since p38 was responsible for phosphorylate p53, which ultimately lead to apoptosis.

IL-6 is an important interleukin to promote neuronal survival and neuronal differentiation. Scabronine G-ME-induced neuritogenesis was mediated by PKC cascades, since a selective inhibitor of PKC, GF109203X inhibited the process (Obara et al., 2001). In contrast, GF109203X, as well as the wortmannin (another inhibitor of PI3K), did not inhibit neurite outgrowth of PC12 in response to cyrneine A from the mushroom *Sarcodon cyrneus*. This indicated that PKC and PI3K/Akt were not

involved. However, the neurite outgrowth process was blocked by PD98059, indicating that ERK1/2 is required for cyrneine A-induced neuritogenesis. The activity of Rac1, which is a GTPase protein that regulates actin, was also increased by cyrneine A. Both scabronine G-methylester and cyrneine A enhanced the activation of nuclear factor-κB, but not phospho-cAMP-response element-binding protein (CREB). In contrast to this, *Tremella fuciformis* (Park et al., 2012) and *G. lucidum* (Cheung et al., 2000) enhanced the neurite outgrowth of PC12 cells *via* activation of CREB transcription. *A. camphorata* was also found to prevent serum deprivation-induced PC12 cell apoptosis through CREB-dependent protein kinase A (PKA) pathway (Huang et al., 2005). The coordinated events involved in the mechanisms of antioxidant, anti-inflammation, neurite outgrowth, and inhibition of neurotoxicity are presented in Figure 4.

Conclusions

In this review, we have summarized mushrooms that have been reported to show beneficial effects in neuronal health, with particular emphasis on either crude extracts or isolated metabolites. Taken as a whole, these medicinal mushrooms have shown neurological properties such as neuronal survival and neurite outgrowth activities, including improvement in recovery and function in both *in vitro* and *in vivo* mammalian nervous systems. Therefore, based on the studies discussed in this review, including our own research over the last decade, we propose that these medicinal mushrooms may have therapeutic values to treat human neurological diseases. However, any such endeavor, involving human models, must be carried out with great care and caution as the pharmacological and negative effects of these mushrooms are not well established even though many of these mushrooms are edible. We hope this review will promote interest in medicinal mushroom research in the experimental clinical neurology area with a long-term objective of developing effective therapies for neurological diseases.

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Declaration of interest

The authors report no conflicts of interest.

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Supplementary material available online
Supplemental Table 1
Supplemental Figures 1–6.