A Mechanistic Review on Medicinal Mushrooms-Derived Bioactive Compounds: Potential Mycotherapy Candidates for Alleviating Neurological Disorders

Authors
Sonu Kumar Yadav[1*], Reshma Ir[1*], Rajesh Jeewon[2], Mukesh Doble[3], Kevin D. Hyde[4], Ilango Kaliappan[5], Ravindrian Jeyaraman[6], Rambabu N. Reddi[7], Jayalakshmi Krishnan[8], Min Li[9], Siva Sundara Kumar Durairajan[1*]

Affiliations
1 Division of Mycobiology and Neurodegenerative Disease Research, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu, Tiruvarur, India
2 Department of Health Sciences, Faculty of Science, University of Mauritius, Reduit, Mauritius
3 Department of Biotechnology, Indian Institute of Technology Madras, Chennai, India
4 Center of Excellence in Fungal Research, Mae Fah Luang University, Chiang Rai, Thailand
5 Interdisciplinary Institute of Indian System of Medicine, SRM Institute of Science and Technology, Kattankulathur, India
6 Corrosion and Materials Protection Division, CSIR-Central Electrochemical Research Institute, Karaikudi, India
7 Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel
8 Department of Life Sciences, School of Life Sciences, Central University of Tamil Nadu, Tiruvarur, India
9 Mr. & Mrs. Ko Chi-Ming Centre for Parkinson's Disease Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China

Correspondence
Dr. Siva Sundara Kumar Durairajan
Division of Mycobiology and Neurodegenerative Disease Research, Department of Microbiology, School of Life Sciences, Central University of Tamil Nadu
CUTN Bridge, Neelakudi, 610001 Tiruvarur, India
Phone: + 91 43 66 27 72 07, Fax: + 91 49 81 23 45 67 89
d.sivasundarakumar@cutn.ac.in

Correspondence
Min Li
Mr. & Mrs. Ko Chi-Ming Centre for Parkinson's Disease Research, School of Chinese Medicine, Hong Kong Baptist University
No. 5 Baptist University Road, Kowloon Tong, Hong Kong SAR, China
Phone: + 85 2 34 11 29 66, Fax: + 85 2 34 11 24 61
limin@hkbu.edu.hk

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ABSTRACT

According to the World Health Organization, neurological and neurodegenerative diseases are highly debilitating and pose the greatest threats to public health. Diseases of the nervous system are caused by a particular pathological process that negatively affects the central and peripheral nervous systems. These diseases also lead to the loss of neuronal cell function, which causes alterations in the nervous system structure, resulting in the degeneration or death of nerve cells throughout the body. This causes problems with movement (ataxia) and mental dysfunction (dementia), both of which are commonly observed symptoms in Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis. Medicinal mushrooms are higher fungi with nutraceutical properties and are low in calories and fat. They are also a rich source of nutrients and bioactive compounds such as carbohydrates, proteins, fibers, and vitamins that have been used in the treatment of many ailments. Medicinal mushrooms such as *Pleurotus giganteus*, *Ganoderma lucidium*, and *Hericium erinaceus* are commonly produced worldwide for use as health supplements and medicine. Medicinal mushrooms and their extracts

* These authors contributed equally to this work.

have a large number of bioactive compounds, such as polysaccharide β-glucan, or polysaccharide-protein complexes, like lectins, lactones, terpenoids, alkaloids, antibiotics, and metal-chelating agents. This review will focus on the role of the medicinal properties of different medicinal mushrooms that contain bioactive compounds with a protective effect against neuronal dysfunction. This information will facilitate the development of drugs against neurodegenerative diseases.

ABBREVIATIONS

A2A-R	adenosine-2A receptor
Aβ	amyloid-β
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
AP-1	activator protein-1
APP	amyloid-β precursor protein
ARE	antioxidant response element
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
CHOP	CCAAT-enhancer-binding protein homologous protein
CNS	central nervous system
CREB	cAMP response-binding protein
CTP	cytidine triphosphate
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
GDP	guanosine diphosphate
GTP	guanosine triphosphate
HD	Huntington's disease
HO-1	heme oxygenase-1
ICH	intracerebral hemorrhage
IKK	IκB kinase
IL	interleukin
iNOS	inducible nitric oxide synthase
JNK	c-Jun N-terminal kinase
Keap 1	Kelch-like ECH-associated protein
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein kinase kinase
MMP	mitochondrial membrane potential
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTOR	mammalian target of rapamycin
NF-κB	nuclear factor Kappa B
NGF	neuronal growth factor
Nrf2	nuclear transcription erythroid-2-related factor 2
PD	Parkinson's disease
PI3K/Akt	phosphatidylinositol-3-kinase/akt
PKC	protein kinase C
p-Tau	phosphorylated Tau
Rac1	Ras-related C1
RNS	reactive nitrogen species
ROS	reactive oxygen species
SG-ME	scabronine G methyl ester
SNCA	α-synuclein
SOD	superoxide dismutase
Trk	tyrosine kinase receptor
UTP	uridine triphosphate

Introduction

Neurological and neurodegenerative diseases are extremely detrimental to human health. Neurodegenerative diseases such as AD, PD, HD, ischemic stroke, epilepsy, ALS, and front temporal dementia exhibit different pathophysiological symptoms with some diseases causing the impairment of memory and cognitive skills, while others are responsible for weakening an individual's ability to move, speak, and breathe [1]. It is usually observed that the accumulation of abnormal misfolded proteins such as Aβ, neurofibrillary tangles, and p-Tau is associated with common neurodegenerative diseases [2], while the accumulation of SNCA is associated with PD [3], and Huntington's protein with HD [4]. Furthermore, there is a limited understanding of the mechanisms that are directly connected to the induction of disease pathology. *In vitro* studies have demonstrated that genetic mutations, such as those in the APP gene in Alzheimer's patients [5] and the SNCA gene in Parkinson individuals [3], represent another factor for the induction of neurodegenerative diseases. However, the progression of neurological diseases cannot be explained by a simple "Mendelian inheritance" pattern of genetic mutation [6, 7]. Brain injury and amnesia could be caused by lipid peroxidation, dysfunction of nuclear and mitochondrial DNA, and protein misfolding due to the imbalance between ROS production and antioxidant enzyme activities [8]. Neurons/glial cells mostly reside within a specific region of the brain and are destroyed and degraded in neurological disease conditions, resulting in severe symptoms in affected patients [9]. In several cases, multiple pathways are associated with disease progression. Conditions such as oxidative stress, neuroinflammation, mitochondrial dysfunction, ER stress, and axonal transport deficit are among the causal risk factors for nearly every neurodegenerative disease. The mechanisms of the inhibitory process of multiple-targeted therapy, such as the reversal of neurological damage via excitotoxicity, over-accumulation of Ca^{2+}, ROS, ER stress, and apoptosis, have been exploited in order to refine the potency of drugs for the treatment of neurological disorders [9]. The initiation of neuroinflammation in the CNS is triggered by multiple factors, such as the normal aging process, dementia, trauma, stroke, hypertension, depression, diabetes, tumor, infection, toxins, and even certain drugs [10]. The normal aging process is responsible for causing the degeneration of neurons, synaptic intoxication, metabolic stress, increased neuroinflammation, cognitive impairment, behavioral deficits, and a highly reactive immune response, and is also associated with an increase in the porosity of the BBB, abnormal glial signaling, and mild proinflammatory reactions in the CNS [10]. Neuroinflammation and neurodegeneration are interlinked; neuroinflammation causes neurodegeneration in the CNS, which causes further neuroinflammation [11]. Epidemiological studies have reported that

long-term use of nonsteroidal anti-inflammatory drugs reduces the risk of AD [12–15]. The research on the discovery of drugs for the nervous system has led to a shift in the focus on the identification of compounds affecting the growth of neurites [16]. The neuronal growth factor NGF is mainly targeted in therapeutic strategies for the mitigation of neurological disorders such as AD and PD. Although NGF is a high-molecular weight neuropeptide that helps in the regulation, proliferation, and extension of neurons, it cannot easily cross the BBB and is easily metabolized.

Until now, tremendous effort has been undertaken by the scientific community to ameliorate the progressive nerve dysfunction and neurodegenerative effects observed in patients with neurological disorders. Most medications have failed to target the underlying source of the disease but have rather focused on reducing the progressive symptomatic effect on brain function. Apparently, no medication available can treat neurodegenerative diseases. Tremendous research has shown evidence that the herbal medicine can be used to treat neurological disorders such as AD, PD, ALS, epilepsy, stroke, and neuropsychiatric diseases [17]. Hence, there has been a recent upsurge of interest in complementary and alternative medicine, especially dietary supplements and functional foods, for delaying the onset of age-associated neurodegenerative diseases. In this respect, natural alternatives with pleiotropic useful properties are needed to reduce the burden of neurological diseases and bioactive compounds from medicinal mushrooms may represent new hope.

It is widely known that mushrooms have historically been used globally as food as well as in medicine. There are an estimated 2.2–3.8 million species of fungi, among which 10000 taxa are presently known [18]. A large number of bioactive compounds are present in the phylum Basidiomycotina, which makes them highly valuable [19–21]; they form an important component of valuable pharmaceutical products. Recently, numerous studies on traditional medicine have stated that mushrooms are commonly used in food as well as medicine [22]. Neural degeneration in AD can be prevented by using drugs with anti-inflammatory and antioxidant properties. Hence, mushrooms are attracting attention due to their antioxidant and neuroprotective properties, which may be suitable for various innovative research models [22]. Among the medicinal mushrooms, a few species of *Sarcodon, Cyathus, Hericium, Antrodia, Ganoderma*, and *Pleurotus* are well known for their use in traditional medicine and widely subjected to modern biomedical research in the fields of neurodegenerative disease and mycotherapy. All six genera are rich in bioactive compounds, such as polyphenols, polysaccharides, glucans, terpenoids, steroids, cerebrosides, and proteins. These compounds have tremendous potential in the inhibition of various neurodegenerative diseases. However, there is limited information on the underlying mechanism of action of the bioactive compounds from these genera. In this review, we report what is known about the bioactive potential of these genera and elucidate the mechanism of action for their underlying neuroprotective activity.

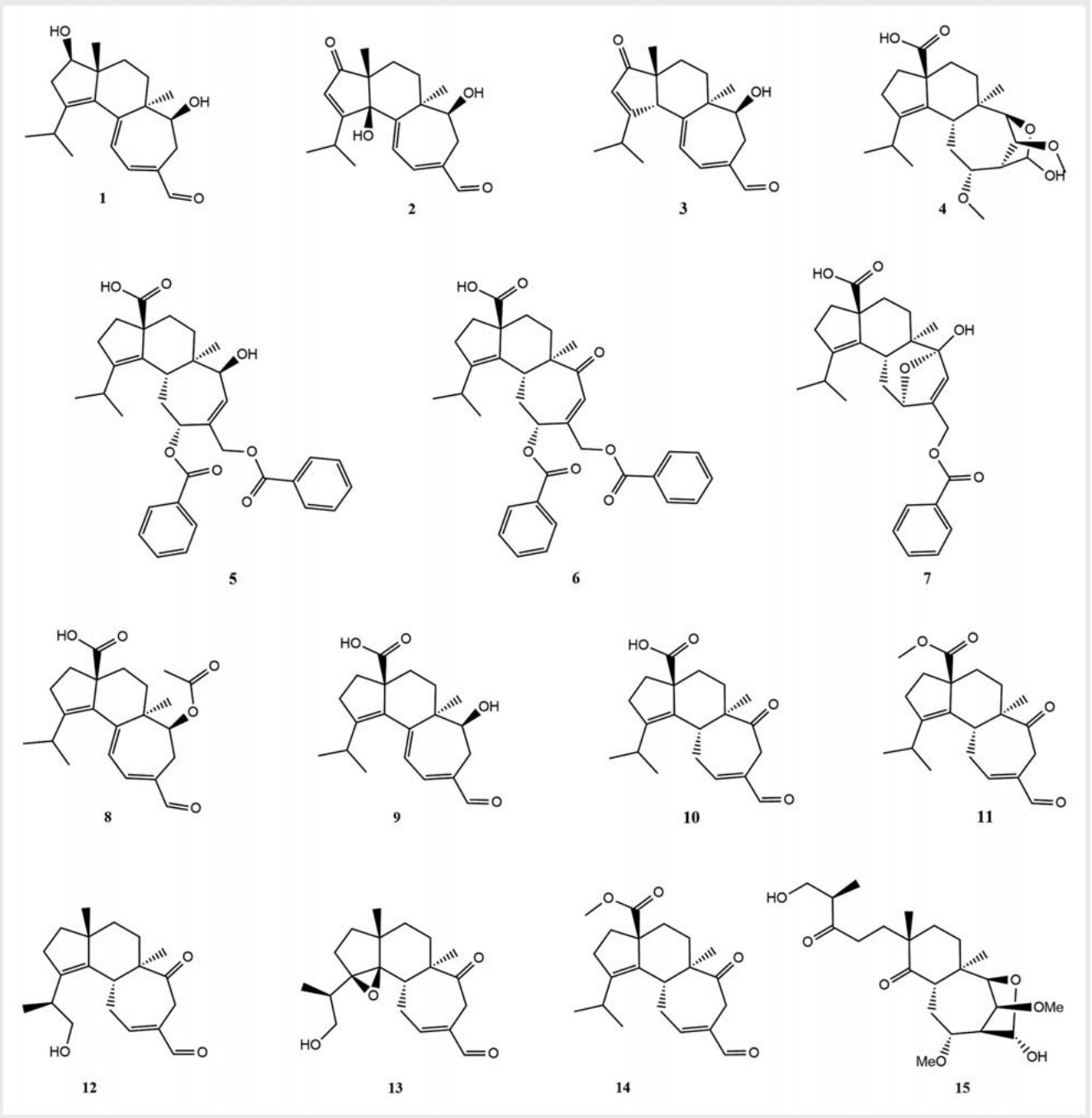
Search Strategy

A systemic search of electronic databases including the PubMed, Scopus, Embase, Web of Science, Medline, Ovid, Science Direct, and Google Scholar for papers reporting *in vivo* or *in vitro* studies, and which included clinical evidence of therapeutic effects of medicinal mushrooms supplements on neurodegenerative disorders was conducted. The data was collected for the years 1990–2019. This review included only published articles and did not consider unpublished works and non-peer reviewed articles. Language restrictions were implemented and only articles in English were included. Articles were evaluated for extracting data on dietary mushrooms supplement safety and efficacy, including study design, sample size, results, and mechanism of action.

Neuroprotective Mechanism of Medicinal Mushrooms

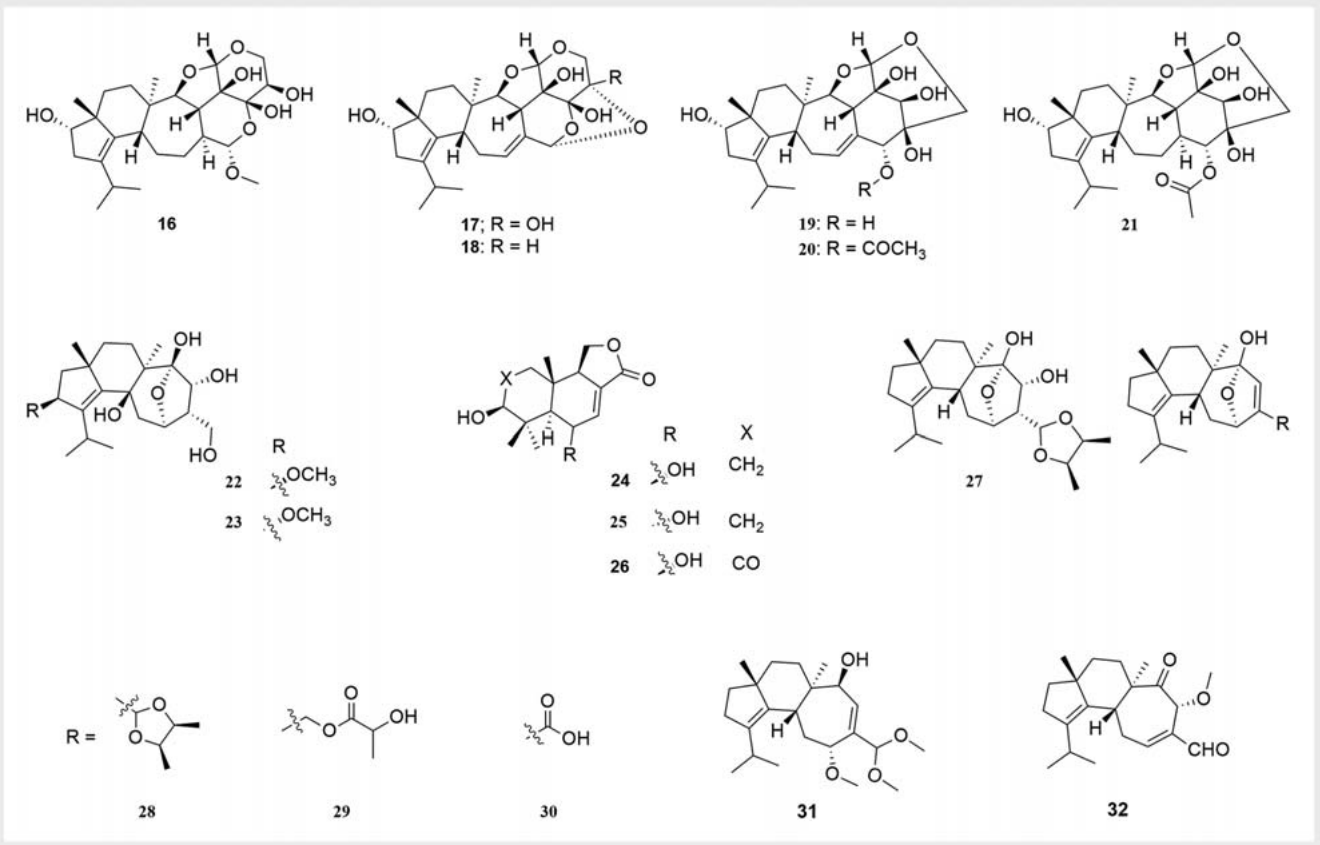
Sarcodon spp.

Sarcodon spp. belong to ectomycorrhizal agaricomycetes in the family Bankeraceae and are characterized by stipitate, pileate basidiomata with colorless to brown basidiospores [23]. *Sarcodon* spp. are mainly distributed in Europe, North America, and Asia. Approximately 49 species of *Sarcodon* have been described in *Index Fungorum* [23], but Larsson et al. reassigned 12 species into the genus *Hydnellum* [24]. Among these species, only *Sarcodon imbricatus* (L.) P.Karst., *Sarcodon cyrneus* Maas Geest, *Sarcodon glaucopus* Maas Geest. & Nannf., *Sarcodon leucopus* (Pers.) Maas Geest. & Nannf., *Sarcodon laevigatus* (Sw.) P. Karst., Meddel., and *Sarcodon scabrosus* (Fr.) P. Karst. have been phytochemically and biologically studied [25]. These mushrooms are largely inedible due to their bitter taste. A variety of bioactive compounds have been isolated from these mushrooms that possess neurogenic properties under both *in vivo* and *in vitro* conditions [25]. Cyrneines A (**1**) and B (**2**) are the main bioactive compounds that were isolated from *S. cyrneus* (▶ **Fig. 1**) [25]. The chemical constituents of *S. cyrneus* are known to trigger the outgrowth of neurites in rat pheochromocytoma PC12 cells and astrocytoma cells 131N1, respectively, by mimicking NGF-mediated neurotrophic activity [25]. Neurite outgrowth was also observed in NG108–15 cells, which is a hybrid neuronal cell line obtained from the mouse neuroblastoma and rat glial cells. The process of neurogenesis could be induced by the presence of the hydroxyl cycloheptadienyl carbaldehyde side chain in cyrneines [26]. Glaucopine C (**3**), obtained from the hexane extract of *S. glaucopus*, has the ability to induce neuronal gene expression [27]. Furthermore, scabronine A (**4**), isolated from *S. scabrosus*, was also shown to significantly influence the synthesis of NGF in 1321N1 astrocytoma cells in humans [28–30]. This was followed by the further discovery of novel cyathane diterpenoid scabronines B–F (**5–9**) [30], scabronine G (**10**) [28], scabronine K (**11**), scabronine L (**12**) [31], and scabronine M (**13**) [32]. Scabronines A–M (**1–10**) have been shown to induce the secretion of NGF in 1321N1 human astrocytoma cell lines and differentiation of neurites in PC12 cells (rat pheochromocytoma cells) [28, 31, 32]. Similarly, SG-ME (**14**), derived from scabronine G and secoscabronine M (**15**), has the potent ability to enhance the secretion of NGF and IL-6, and also to release the major neurotropic factors (NGF/BDNF) from astrocytes. It has been shown that SG-ME-induced neurite growth is via the PKC



▶ **Fig. 1** Structures of cyrneines A (**1**) and B (**2**) isolated from *S. cyrneus*, and glaucopine C (**3**) isolated from *S. glaucopus* as well as scabronines A–G (**4**–**10**), K (**11**), L (**12**), M (**13**), scabronine G methyl ester (**14**), and secoscabronine M (**15**) isolated from *S. scabrosus*.

pathway because the SG-ME-induced neurite outgrowth was significantly reduced by the hydroxamate-based PKC inhibitor GF109203X [33]. In contrast, neurite promoting activity of cyrneine A in PC-12 was blocked by the ERK inhibitor PD98059 but not by the PI3K inhibitor wortmanninn or by the PKC inhibitor GF109203X, suggesting that only ERK but neither the PKC nor the PI3K/Akt signaling pathway was involved in the cyrneine A-induced neurite outgrowth [34]. Cyrneine A has also been shown to increase the activity of Rac1 (a GTPase protein) and regulates the actin dynamics [34]. Both SG-ME and cyrneine A have been shown to activate NF-κB but not phospho-CREB [33, 34]. Furthermore, the activation of three transcriptional factors (AP-1, NF-κB, and CREB) is required to regulate the neurite extension [35]. It has been demonstrated that cyrneine A enhances the activation of AP-1 and NF-κB [34]. Furthermore, the action of cyrneine A influences the dynamics of actin, followed by the assembly of F-actin at the tip of the neurites. The small GTPase Rac1 plays a crucial role in priming signals that regulate actin cytoskeleton dynamics,



▶ **Fig. 2** Structures of striatoids A–F (**16**–**21**) isolated from *C. striatus*, and neocyathin S (**22**), neocyathin T (**23**), 3*β*,6*β*-dihydroxycinnamolide (**24**), 3*β*,6*α*-dihydroxycinnamolide (**25**), and 2-keto-3*β*,6*β*-dihydroxycinnamolide (**26**) isolated from *C. africanus* as well as cyahookerins A–F (**27**–**32**) isolated from *C. hookeri*.

which promoted the preferential assembly of F-actin at the tip of the neurites [36]. Cyrneine A-induced actin dynamics was via the upregulation of Rac-1, which is, consequently, regulated by the expression of the dominant-negative Rac1 activity [34], suggesting cyrneine A influenced the outgrowth of neurites in a Rac1-dependent mechanism. ▶ **Fig. 1** shows the structures of cyrneines and scabronines isolated from *S. cyrneus* and *S. scabrosus*, respectively. The cellular and molecular mechanisms of cyrneines and scabroninin inducing NGF-induced neurite outgrowth in PC-12 cells are depicted in ▶ **Fig. 2**.

Cyathus spp.

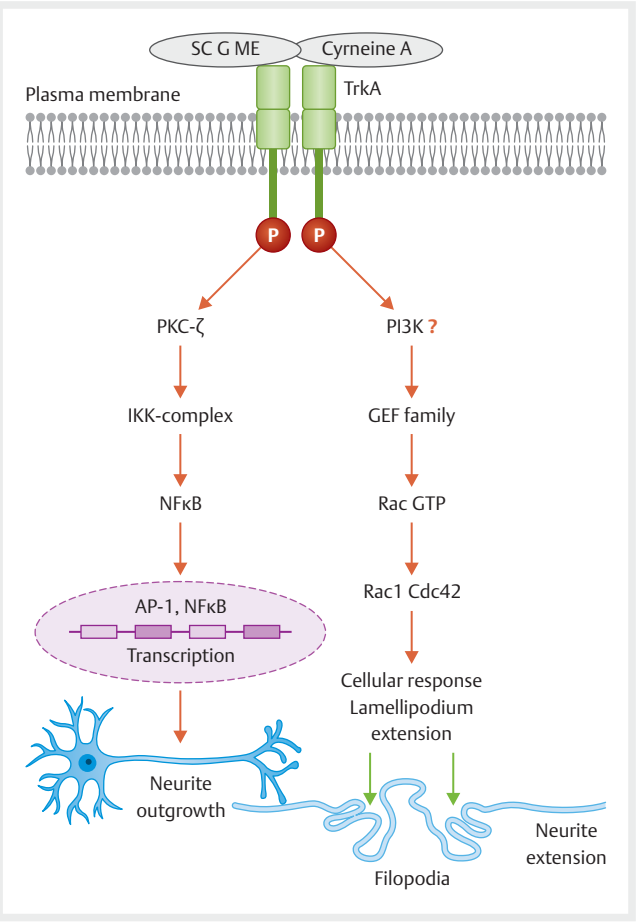
A number of cyathane diterpenoids were also isolated from the genera *Cyathus*, which belongs to the family Nidulariaceae in the phylum Basidiomycota [37]. Known as bird's nest fungi, several *Cyathus* species produce novel compounds with biological activities such as antibiotic, antifungal, anti-neurodegenerative, antioxidative, and anti-inflammatory activities [38], and some cyathanes are specific to this genus. Gao et al. isolated several cyathane diterpenoids with a contiguous 5/6/7 tricyclic skeleton from *Cyathus* species with neurotrophic activity [39–41]. Six highly oxygenated polycyclic cyathanexylosides, designated striatoids A–F (**16**–**21**), were shown to be isolated from the liquid cultures of *Cyathus striatus* (Huds.) Willd. for the first time [39]. Among the isolated striatoids, striatoids B (**17**) and C (**18**) borne a rare 15,4′-ether ring system with significant neurotrophic activity in PC12 cells [39]. In their continuing search of neuroprotrophic compounds from the *Cynathus* genus, two new cyathane diterpenoids named neocyathin S (**22**) and neocyathin T (**23**), along with three drimane sesquiterpenoids isolated from the solid culture of *Cyathus africanus* H. J. Brodie, including one known 3*β*,6*β*-dihydroxycinnamolide (**24**) and two new ones 3*β*,6*α*-dihydroxycinnamolide (**25**) and 2-keto-3*β*,6*β*-dihydroxycinnamolide (**26**), showed neurite outgrowth-promoting activity in PC12 cells [40]. From the liquid culture of *Cyathus hookeri* Berk., six new cyathane diterpenes, cyahookerins A–F (**27**–**32**), and nine known analogs were isolated, with cyahookerin C (**29**) showing significant neurotrophic activity amongst the nine screened cyathane diterpenoids [41]. ▶ **Fig. 3** shows the structures of striatoids, neocyathin, cinnamolide, and cyahookerins isolated from various species of *Cyathus*. These studies suggest that cyathane diterpenoids have potent NGF-inducing activity and thus can develop into potential therapeutic agents for treating neurodegenerative diseases such as, for instance, AD and PD.

Antrodia camphorata

Antrodia camphorata, also called *Taiwanofungus camphoratus* (M. Zang & C. H. Su), is a unique basidiomycete belonging to the family Fomitopsidaceae. It is an endemic species that grows on plants of the family Lauraceae in Taiwan [42]. *A. camphorata*

grows on the camphor tree, which is rich in terpenoids, polyphenolics, and polysaccharides. *A. camphorata* has also been used in traditional Chinese herbal medicine and has several medicinal properties against a variety of diseases [42,43]. Antroquinonol (**33**) is among the major bioactive compounds present in *A. camphorata* [44]. It is a tetra-hydro-ubiquinone derivative and has various pharmacological activities. It is mainly extracted from the mycelium of *A. camphorata*. Seven kinds of antroquinonol and its related compounds are presently known. They include antroquinonol, antroquinonols B (**34**), C (**35**), D (**36**), L (**37**), and M (**38**), and 4-acetylantroquinonol-B (**39**) (▶ **Fig. 4**) [45]. Antroquinonol has been shown to alleviate oxidative stress and inflammatory cytokines by stimulating nuclear stimulating Nrf2 pathways in an APP mouse model [46]. In order to counteract oxidative stress and Aβ peptide-induced disruption, the activation of Nrf2 signaling is necessary [47]. In addition, the APP mouse study showed that oral intake of antroquinonol improved learning and memory by reducing the level of Aβ and glial fibrillary acidic protein-positive astrocytes (astrocytosis) in the cortex and hippocampus. The production of cytokines and ROS is usually due to astrocytosis. Antroquinonol exhibited anti-AD and antioxidative activities due to its ability to cross the BBB and its influence on multiple pathways, such as Nrf2 upregulation, astrocytosis reduction, and histone deacetylase 2 downregulation, in a transgenic APP mouse model [46]. The underlying mechanism of antroquinonol-mediated neuroprotection against Aβ-induced oxidative stress and neuroinflammation in the human brain is depicted in ▶ **Fig. 5**.

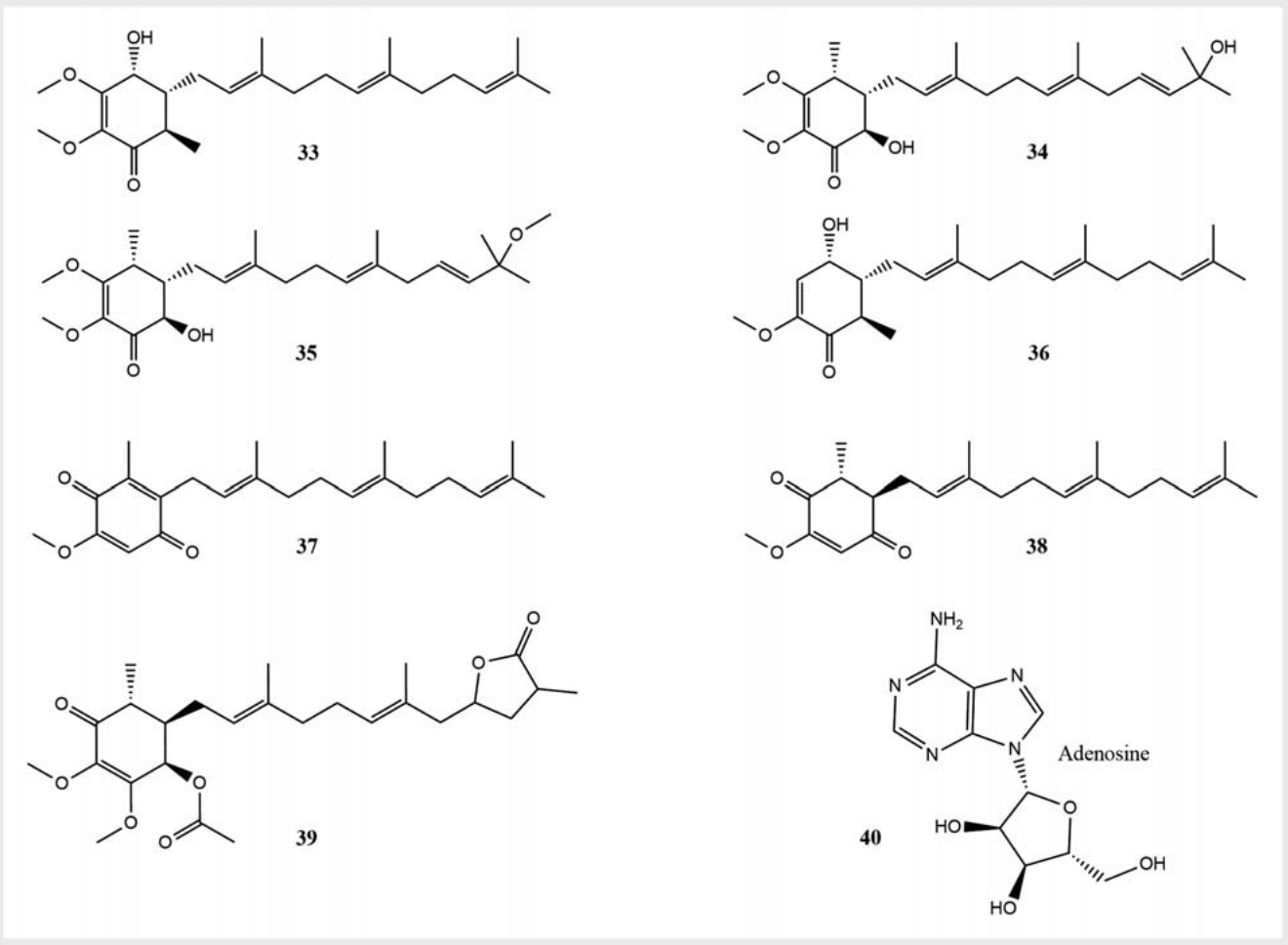
Lu et al. unraveled the neuritogenic effect of *A. camphorata* by isolating adenosine (**40**) from it [48]. A2A-R has been regarded as a potential therapeutic target site for neuroprotection, as it plays an important role in maintaining the CNS by regulating anxiety, aggression, seizures, epilepsy, motivation, reward, nociception, memory, and psychotic-like behaviors [49]. Adenosine is an active compound that acts through the A2A-R to delay apoptosis [49] (▶ **Fig. 5**). Since adenosine readily permeates the BBB and binds A2A-R, it promotes the release of neurotransmitters and post-synaptic depolarization, thereby delaying apoptosis [46]. Since *A. camphorata* contains large amounts of adenosine, it is able to modulate the neuronal and synaptic function through A2A-R, thereby aiding the development of drugs for the treatment of stroke-related injury in animal models for cerebral ischemia [50]. During hemoglobulin degradation, heme or hemin, which is derived from hemoglobin, accumulates in the ICH [51]. High levels of heme metabolites usually result in neuronal death and the affected neurons increase the levels of HO-1, a rate-limiting enzyme that catalyzes oxidative degradation of free heme. This enzyme has been found to be the mediator of neurotoxicity in ICH and is an attractive therapeutic target for ICH [51]. Several reports have suggested that a decrease in HO-1 expression by HO-1 inhibitors may provide a protective effect against stroke in various animal models [51].



▶ **Fig. 3** Proposed model on the underlying mechanism of action of cyrneine A (**1**) and scabromine G methyl ester (**14**) and induced neurite outgrowth. Treatment of cyrneine A (**1**)-induced neuronal differentiation through the formation of lamellipodia and filopodia at the growth cones as a result of actin polymerization via the Rac1-dependent pathway. Cynereine A (**1**) treatment may have enhanced the level of PI3K, which in turn activated the guanosine exchange factor, which not only converted the inactive Rac (Ras-related C protein)-GDP to Rac-GTP but also activated the Rac1 protein and cell division control protein 42, which are key molecules in promoting lamellipodia and filopodia, respectively. SG-ME (**14**) probably binds to TrkA and potently activated the IKK/NF-κB complex to release the NFκB from IKK via PKC-ζ activation. NFκB can then be translocated into the nucleus where it binds with a transcription factor (AP-1) to initiate further transcriptional expression of neurotrophic factors that promoted neurite outgrowth. NFκB is a key transcription factor involved in processes of synaptic plasticity and memory.

Pleurotus giganteus

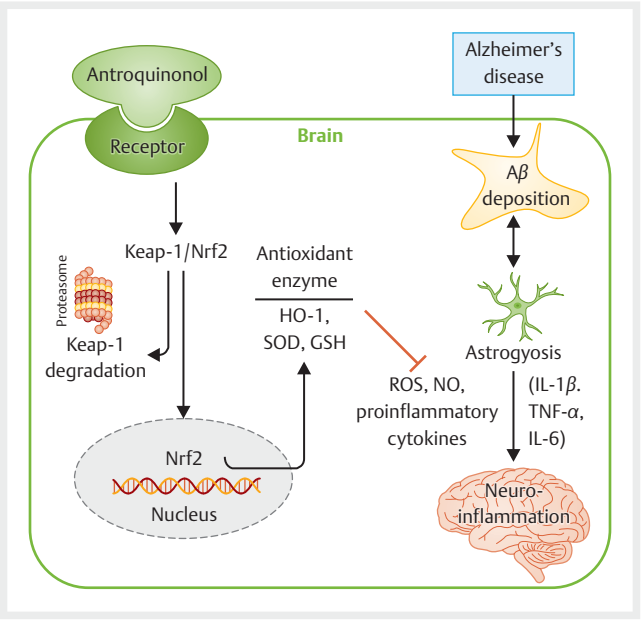
Pleurotus giganteus (Berk. Karunarathna and K. D. Hyde) is an edible mushroom that has been shown to exert significant neuritogenic properties [52,53]. The strong antioxidant and neuroprotective properties of this mushroom are associated with its nutritional composition. This has gained popularity for its culinary properties as well as commercial prospects. The wild mushrooms of this species were traditionally consumed in indigenous villages of Peninsular Malaysia [54]. The chemical compounds in the basidiocarp of the mushroom were tested for neurotrophic activity in N2a cells. Using LC-MS and GC-MS analysis, the neuritogenic compounds reported were uridine (**41**), linoleic acid, succinic acid, benzoic acid, cinnamic acid, caffeic acid, oleic acid, and *p*-coumaric acid, in the descending order of activity [55]. The secondary metabolites such as sterols and triterpenes from *P. giganteus* are



▶ **Fig. 4** Structure of antroquinonols A–D (**33**–**36**), L (**37**), M (**38**), 4-acetylantroquinonol (**39**), and adenosine (**40**) isolated from *A. camphorata*.

reported to possess NGF-like properties, which cause neurite outgrowth in PC12 cells [52]. They do so by either mimicking the NGF or triggering its production [52, 53]. Since the secondary metabolites from this mushroom have neuritogenic properties, there is a need to elucidate the underlying neuroprotective mechanism of these compounds. Neuronal survival, neurite outgrowth, precursor proliferation, and neuronal differentiation are the major events that take place in the promotion of neuritogenesis. CREB plays an important role in facilitating the stimulation of these events. Uridine in *P. giganteus* increased the phosphorylation of Akt and ERKs [56]. Finally, it also increased the phosphorylation of the mTOR, a protein kinase that regulates protein synthesis and cell growth. The ERKs and PI3K/Akt pathways were partly involved in crosstalk to promote uridine-induced neuritogenesis and activate the transcription factor CREB. As the kinases MAPK and PI3K/Akt are involved in the phosphorylation of CREB at Ser133, it is hypothesized that uridine in the *P. giganteus* extracts could influence the centralized cell survival and growth signaling pathway in N2a cells. Uridine binds to P2Y receptors, a class of G protein-coupled receptors, and activates PI3K/Akt and MAPK pathways and thereby phosphorylates the transcription factor CREB that can selectively activate various downstream genes (e.g., growth-associated protein 43) [56]. Treatment with uridine (**41**) significantly increased the levels of neuronal biomarkers in N2a cells. The uridine-mediated neurite outgrowth in PC12 cells via MEK/ERK or PI3K/Akt pathways is depicted in ▶ **Fig. 6**. The enhancement of neurite outgrowth and the formation of membrane synapses depends on the levels of three key nutrients in the brain, namely, uridine, docosahexaenoic acid, and choline. Hence, it is anticipated that uridine could be beneficial against AD, a disease characterized by the loss of neurites and brain synapses. Uridine directly penetrates the BBB and enters the brain through a high-affinity transporter, yielding UTP, which is then converted to CTP by CTP synthase [57]. Intracellular levels of UTP depend on the availability of free uridine and thus function accordingly.

Recent studies have revealed that ergothioneine (**42**), found in high levels in *Pleurotus* spp., has neuroprotective and neuritogenic activities [57]. Ergothioneine promotes the differentiation of neural progenitor cells into neurons by arresting cellular proliferation [57]. Ergothioneine significantly decreased the accumulation of Aβ peptide in the hippocampus of d-galactose-treated mice (0.5 mg/kg body weight), resulting in the enhancement of learning and memory in mice [58]. Ergothioneine can also protect against Aβ-induced memory impairment in mice by exhibiting

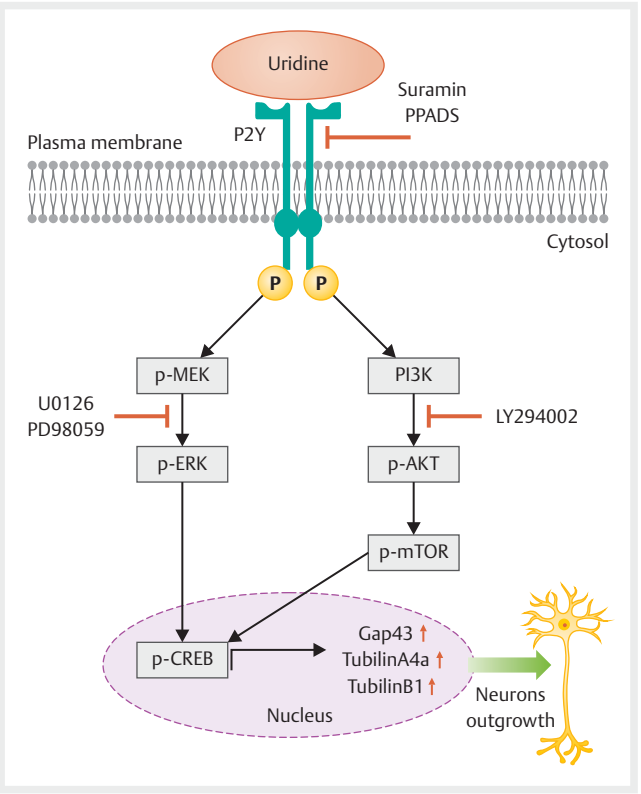


▶ **Fig. 5** Pictorial representation of antroquinonol (**33**)-mediated neuroprotection against Aβ- induced oxidative stress and neuro-inflammation in the human brain. Antroquinonol (**33**) upregulated the antioxidant genes via the Keap 1/Nrf2/ARE signaling pathway. Upon activation of Keap 1/Nrf2/ARE signaling, Nrf2 translocates to the nucleus and binds to the ARE. Nrf2-ARE binding regulates the expression of antioxidant and anti-inflammatory genes such as HO-1, SOD, glutathione, cyclooxygenase-2, and iNOS to suppress ROS and proinflammatory cytokines such as IL-1β, IL-6, and TNF-α.

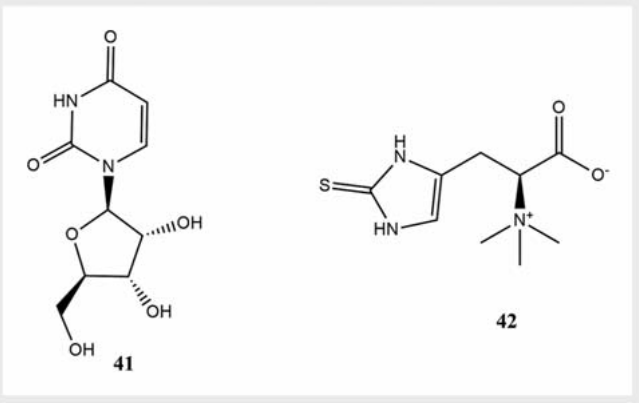
antioxidative, anti-acetylcholinesterase activities in the brain lysates of Aβ1–40-treated mice [59]. Orally ingested ergothioneine promoted neuronal differentiation and readily permeated the BBB, thus alleviating the symptoms of depression in mice [60]. The structures of uridine (**41**) and ergothioneine (**42**) are shown in ▶ **Fig. 7**.

Ganoderma lucidum

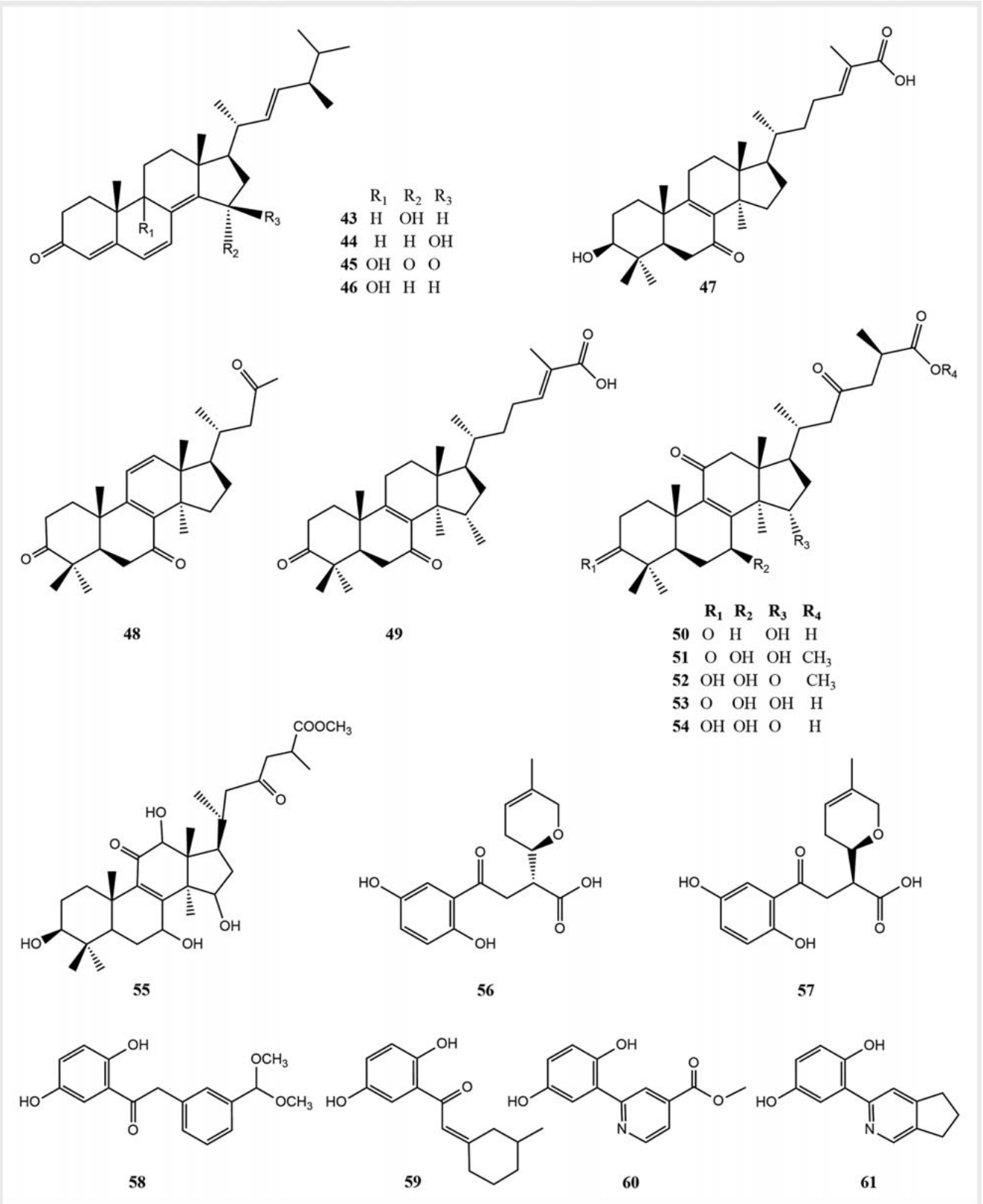
Ganoderma lucidum (Curtis) P.Karst. is a woody-inhabiting basidiomycetous fungus belonging to the family Ganodermataceae in the order Polyporales. It is commonly utilized in oriental medicine for long-term health promotion [61]. *G. lucidium* (also known as the "mushroom of immortality" or the "longevity mushroom") and its close relative *Ganoderma lingzhi* (Sheng H. Wu, Y. Cao, and Y. C. Dai), which has been used in traditional Chinese medicine, contains several bioactive compounds for the alleviation of diseases [62]. Because *G. lucidium* contains numerous bioactive compounds with alleged health benefits without obvious side effects, it has a reputation as an herbal medicine The bioactive compounds and extracts isolated from different parts of *G. lucidum* include polysaccharides, β-glucans, lectins, amino acids, lignin, mycin, and vitamins, which have potential antioxidant, anti-inflammatory, and neuroprotective effects [62, 63]. Ganodermasides A–D (**43–46**), the biologically active compounds obtained from different parts of *G. lucidum*, increase life span and show anti-aging properties [64–66]. Other bioactive triterpenoid compounds such as lucidenic acids, 7-oxo-ganoderic acid-Z (**47**),



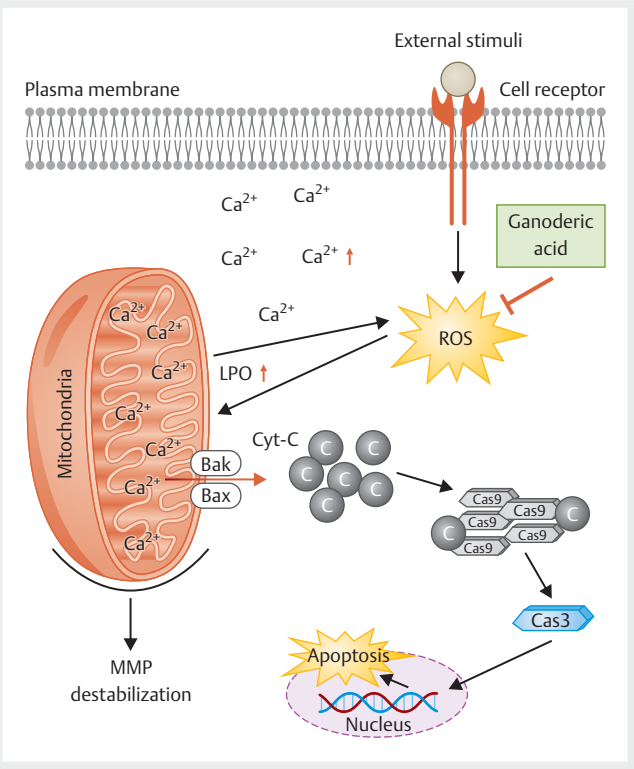
▶ **Fig. 6** Schematic depiction of neurite outgrowth by uridine (**41**) in PC12 cells via the MEK/ERK or PI3K/AKT pathway. Uridine, an isolated *P. giganteus* mushroom compound, activates nucleotide metabotropic receptor P2Y. The P2Y receptor was coupled to ERK1/2 activation through PI3K. Upon uridine-mediated activation of P2Y, the ERK1/2 is then activated, which primes the activation of the CREB transcription factor, an ERK1/2 direct target. Uridine (**41**) has also been shown to activate the PI3K/AKT signaling pathway, which further activated the mTOR, a kinase that regulates protein synthesis and cell growth in response to growth factors. The involvement of ERK and PI3K/AKT/pMTOR in uridine-mediated neuronal growth is confirmed because the treatment of MEK/ERK selective U0126 and PD98059 inhibitors and the PI3k/AKT signaling selective inhibitor LY294002 substantially decreased the percentage of neurite outgrowth in PC12 cells.



▶ **Fig. 7** Structures of uridine (**41**) and ergothioneine (**42**) isolated from *P. giganteus*.



▶ **Fig. 8** Structures of ganodermasides A–D (**43**–**46**), 7-oxo-ganoderic acid-Z (**47**), 4,4,1,4α-trimethyl-5α-chol-7,9 (11)-diene-3-oxo-24-oic acid (**48**), ganoderic acid-S1 (**49**), ganolucidic acid-A (**50**), methyl ganoderic acid-A (**51**), methyl ganoderic acid-B (**52**), ganoderic acid A (**53**), ganoderic acids B (**54**), methyl ganoderate (**55**), lingzhine E (**56**), lingzhine F (**57**), lucidumin B (**58**), lucidumin C (**59**), lucidimine E (**60**), and ganocochlearine A (**61**) isolated from *G. lucidium*.



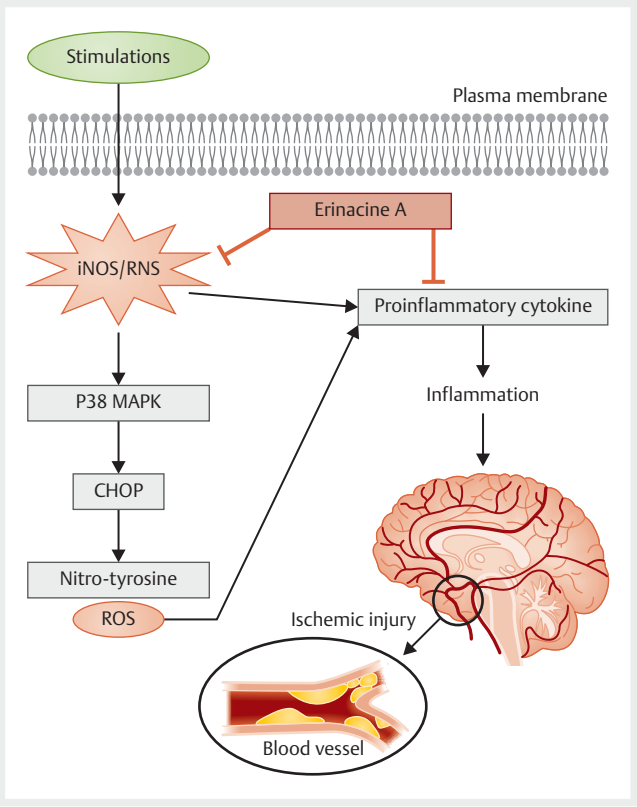
▶ **Fig. 9** Schematic representation of mitochondrial membrane stabilization via action of the antioxidative activity of ganoderic acid (**51**). The excessive accumulation of an excitotoxic insult such as glutamate and its binding on the cell receptor induces ROS generation, which in turn impairs the stabilization of the mitochondrial membrane and its functions in hippocampal neurons. Mitochondrial damage may also be caused by the results of lipid peroxidation of the membrane. Ganoderic acid A (**51**) increased the levels of SOD to inhibit the production of ROS, thereby preserving the integrity of the mitochondrial membranes by improving the MMP of the hippocampal neurons. Due to its mitochondrial membrane stabilizing activity, the release of cytochrome C from mitochondria may also be greatly reduced by ganoderic acid (**51**), and thus control the release of apoptotic proteases such as caspases 3 and 9 to protect the hippocampal neurons against epileptic insults.

4,4,1,4α-trimethyl-5α-chol-7,9 (11)-diene-3-oxo-24-oic acid (**48**), ganoderic acid-S1 (**49**), ganolucidic acid-A (**50**), methyl ganoderic acid-A (**51**), and methyl ganoderic acid-B (**52**) from *G. lucidum* are capable of inducing neurite outgrowth [64–66]. These promising properties have made it important to further investigate more bioactive compounds for future applications. The isolated small molecules of *G. lucidum* are shown in ▶ **Fig. 8**.

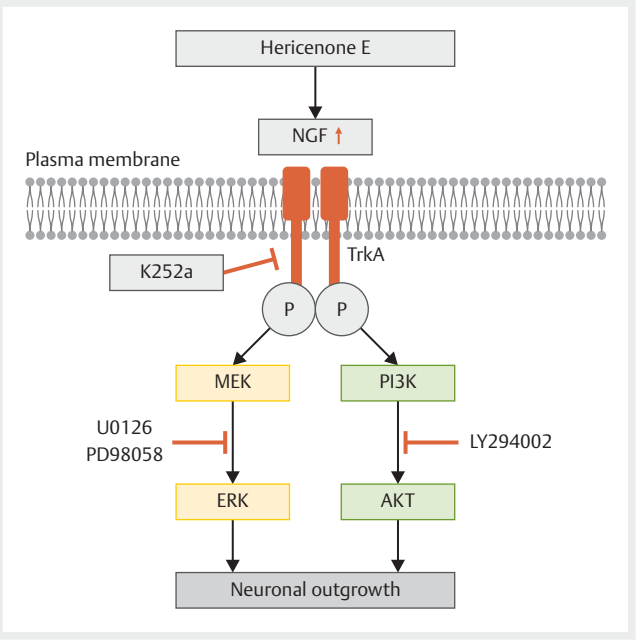
Epilepsy is a major neurological disorder with frequent seizures due to abnormal neuronal firing and synaptotoxicity and apoptosis of neurons in the cortico-hippocampal region [67]. Several factors such as apoptotic proteins (Bax/Bad) and cytoplasmic organoids are associated with apoptosis in the hippocampal neurons [67]. In the mitochondria of epileptiform hippocampal neurons, the damage is caused by the peroxidation of lipids after the induction of free radicals [67]. It has been experimentally demonstrated that ganodermic acids A (**53**) and B (**54**) play an important role in the regulation of lipid peroxidation and stabilization of the MMP (ψ), thus maintaining the mitochondrial structure [64]. Similarly, apoptosis is associated with SOD activity and MMP; thus, apoptosis in epileptic hippocampus neurons is caused via mitochondrial apoptosis pathways. Finally, as ganoderic acids A and B significantly improve SOD activity and maintain the MMP in hippocampus neurons, they protect the hippocampus neurons by inhibiting apoptosis [68, 69]. The ganodermic acid-mediated stabilization of mitochondrial membranes via its antioxidative activity is represented in ▶ **Fig. 9**. A newly isolated lanostane triterpene named methyl ganoderate (**55**) and two known aromatic meroterpenoids, namely, lingzhine E (**56**) and lingzhine F (**57**), have been documented to possess neuroprotective activities against H_2O_2 and aged Aβ-induced cell death in neuroblastoma SHSY5Y cells, an Alzheimer's cell model [70]. Two new benzendiols, designated as lucidumins B and C (**58, 59**), along with two new alkaloids, namely, lucidimine E (**60**) and ganocochlearine A (**61**), have shown remarkable neuroprotective activity against corticosteroid-induced cytotoxicity in PC12 cells [71]. In patients with depressive disorders, glucocorticoids such as corticosterone and cortisol are secreted at a high level due to the dysfunction and hyperactivity of the hypothalamic-pituitary-adrenal axis, which further leads to damage to hippocampal neurons, followed by depressive symptoms [72–74]. Hence, the neuroprotective effect of lucidumins and lucidimines against glucocorticoids-induced hippocampus dysfunction may play a protective role in fighting depression. The above studies indicate that *G. lucidum* may have potential for the treatment of neurodegenerative diseases and other neurological disorders.

Hericium erinaceus

Hericium erinaceus (Bull.) Persoon, commonly known as the "lion's mane mushroom" or "hedgehog mushroom", is a culinary mushroom. It is classified in the class Agaricomycetes and phylum Basidiomycota [75]. *H. erinaceus* and *Hericium coralloides* (Scop.) Pers. have also been traditionally used to improve memory and health in China [71]. Earlier studies have reported that *Hericium* has numerous bioactive compounds that have various strong activities, such as neuroprotective anti-(neuro)-inflammatory, antioxidant, immunomodulatory, and antiaging activities [76–79]. Numerous studies have reported that the bioactive compounds of *H. erinaceus*, such as hericenones C–H (**62–67**) [80] and erinacines A–I (**68–77**) [81, 82], play a significant role in the *in vitro* synthesis of NGF. ER stress is also a causative factor for neurodegenerative diseases and could be attenuated by dilinoleoyl phosphatidylethanolamine, which is obtained from the dried fruiting bodies of *Hericium* [83]. Ischemic stroke is among the major causes of death worldwide. Ischemic abnormality is responsible for producing free radicals in the hippocampus neurons, which leads to ER stress, resulting in neuronal cell death. Ischemic injury is caused by the accumulation of free radicals, ER stress, protein misfolding, ROS, oxidative stress, and protein nitrosylation [84]. ROS and RNS, the major factors that cause ischemic reperfusion, are related to ER stress signaling pathways, which are responsible for the death or survival of neuronal cells [84]. Neuronal cell death in ER stress-mediated apoptosis is mediated via p38 MAPK and CHOP signaling pathways [85]. Finally, iNOS/RNS and p38 MAPK/CHOP have been acknowledged to play a key role in neuronal cell death in ischemic



▶ **Fig. 10** Schematic description of erinacine A (**68**)-mediated antioxidative and anti-inflammatory activity in the intermittent ischemic brain injury. An ischemic injury or stroke produces oxidative stress (ROS) that leads to the generation of nitric oxide, a mediator of protein nitrosylation, that leads to the phosphorylation of p38 MAPK and CHOP and the phosphorylated p38 MAPK/CHOP involved in the ER stress signaling pathway-mediated neuronal death. The oxidative damage of the brain also upregulates proinflammatory cytokines. Erinacine A (**68**) treatment reduced the levels of iNOS/RNS, phosphorylated p38 MAPK, CHOP, nitrotyrosine protein, and proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in a stroke animal model.

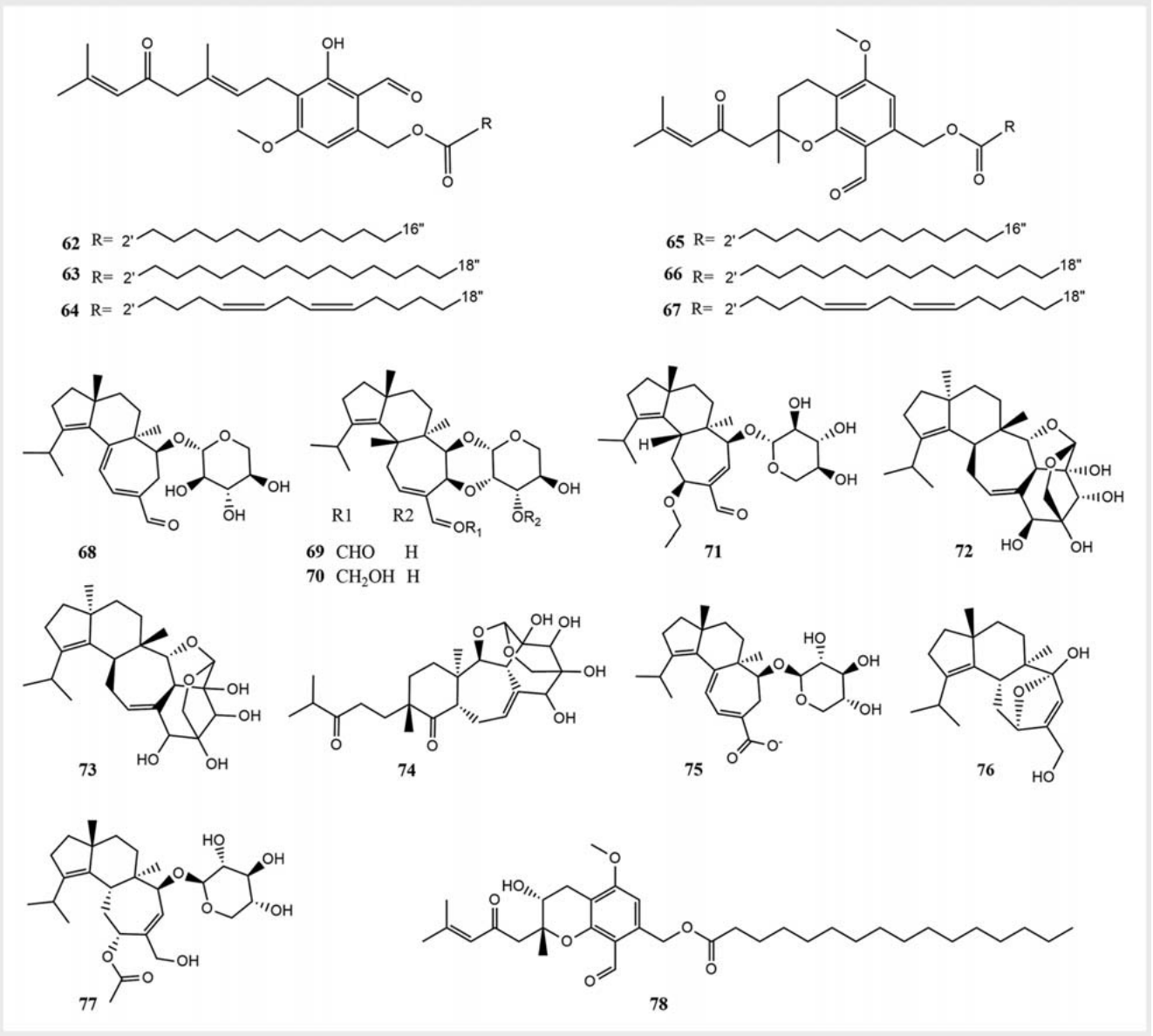


▶ **Fig. 11** The involvement of the PI3K/Akt and Erk1/2 signaling pathways in hericeone E (**64**)-induced neuronal outgrowth. The neuroprotective activity of hericenone E may mimic the action of the endogenous synthesized nerve growth factor that induced neuronal outgrowth by binding with the TrkA receptor, thereby either activating the ERK or PI3K/AKT signaling pathway. The involvement of PI3K/AKT or ERK in hericeone E (**64**)-induced neurite outgrowth was elucidated by use of a specific ERK (U0126 or PD98059) or PI3K class I inhibitor (LY294002), respectively, which abrogated the hericeone E (**64**)-induced neurite growth or neuritogenesis.

reperfusion brain injury [85]. Erinacine A is a biologically active compound that decreases the extent of ischemic injury to the brain [86]. *In vitro* studies have demonstrated that the active compound of *H. erinaceus*, erinacine A, has the capacity to decelerate cerebral ischemic brain injuries through the inactivation of iNOS/RNS and p38 MAPK/CHOP pathways [86]. Erinacine A-mediated antioxidative and anti-inflammatory activity in an intermittent ischemic brain injury is shown in ▶ **Fig. 10**. Therefore, biologically active compounds of *Hericium* such as erinacine A have a strong ability to enhance the synthesis of NGF and induce neuroprotection, while their polysaccharides have to scavenge the ROS.

H. erinaceus has been comprehensively studied for its neurite outgrowth-promoting activity. The expression of NGF mRNA is promoted by *Hericium* compounds through the activation of phosphorylated JNK signaling pathways [87]. Mori et al. reported that *H. erinaceus* had increased the expression of the mRNA level of NGF in 1321N1 human astrocytoma cells [87]. A new cyanthane derivative cyatha-3, 12-diene-14β-olnamederinacol, along with 11-O-acetylcythin A3 and erinacine Q (**73**), isolated from *H. erinaceus*, have been shown to induce the synthesis of NGF [88]. Hericenone E (**63**) showed significant neuroprotective activity by activating the PI3K/Akt and MEK signaling pathways [89]. It is hypothesized that hericenone E acts by binding to TrkA, which leads to the phosphorylation of Akt and ERK1/2, resulting in neuronal outgrowth [90]. The involvement of the Akt and ERK1/2 signaling pathways in hericenone E-induced neuronal outgrowth is depicted in ▶ **Fig. 11**. Peripheral nerve injury is associated with changes in axonal injury and dorsal root ganglia [91]. In a double-blinded clinical trial performed on senior patients diagnosed with AD, oral administration of 96% dry powder of *H. erinaceus* at 750 mg per day for 16 weeks improved the condition of dementia patients without any side effects [92]. Diling et al. reported that 3-hydroxyhericenone F (**78**) can downregulate the β-site of APP cleaving enzyme 1 (BACE1) and can also decrease the level of serum cytokines (IFN-γ, IL-1β, IL-17α, and TNF-α) as well as ROS production [93]. Thus, it was confirmed that hericenones-enriched mushrooms may ameliorate Aβ pathology and oxidative stress in AD. ▶ **Fig. 12** shows the structures of hericenones C–H (**62**–**67**), erinacines A–I (**68**–**77**), and hydroxyhericenone-F (**78**).

In the context of PD, mycelia of *H. erinaceus* and its pure compound erinacine A boosts the survival and protection of neuronal cells against MPTP-induced parkinsonism in mice [94]. MPTP is a neurotoxin that was found to be responsible for causing a myste-



▶ **Fig. 12** Structures of hericenones C–H (**62**–**67**), erinacines A–K (**68**–**77**), and hydroxyhericenone F (**78**) isolated from *H. erinaceus*.

rious parkinsonian epidemic that led to the development of MPTP-induced Parkinson models in primates and mice [95]. The neurotoxic property is mediated by the metabolites of MPTP, such as 1-methyl-4-phenylpyridinium ion and monoamine oxidase-B in the neuronal cells, which have harmful effects on cellular function, such as damage to the dopaminergic neurons, free radical generation from mitochondria, and neuroinflammation, resulting in chronic neurological disabilities [95]. Therefore, this demonstrates that *H. erinaceus* and erinacine A have the potential ability to protect neurons against MPTP-induced brain injury and the potential to be anti-Parkinson agents. In addition, *H. erinaceus* has been shown to be an antidepressant in a stress-induced mouse model of depression. Treatment with erinacine A not only reverted the depressive symptoms of stressed mice but it also induced the BDNF/TrkB/PI3K/Akt/GSK-3β pathways and stopped the NF-κB signals in brain lysates of stressed mice [96]. Overall, all these findings suggest that *Hericium* has several neuroprotective activities that could pave the way for treatment of AD, PD, epilepsy major depressive disorder, stroke, and other neurological disorders.

Conclusion

In this review, we summarize information regarding the therapeutic potential of culinary mushrooms with respect to their bioactive compounds. Selected edible and therapeutic mushrooms can effectively increase the development of neuritis in the brain by increasing NGF output, mimicking NGF reactivity, or by preventing neurons from cell death triggered by neurotoxicants. Such mushrooms may exhibit neuroprotective effects towards neurodege-

nerative disease, including AD and PD, through the basic mechanisms of the neurotrophic compounds of the mushroom. Regular mushroom intake may minimize or postpone age-related neurodegeneration. Although many mushrooms are edible, they should be verified carefully when it comes to human trials since their adverse effects are not clearly defined. In particular, there has been concern about consuming *Ganoderma* mushrooms, as they reduced the viability of peripheral blood mononuclear cells from patients administered extracts of *Ganoderma* and *G. lucidum* spore powder [97]. However, several preclinical and clinical studies have reported that there is no evidence on the systematic toxicity attributed to the oral administration of *Ganoderma* extracts [98–100]. With this review, we hope that the interest in exploring new compounds from medicinal mushrooms, which can help in neurological diseases, will develop, and that these developments in clinical neurology will lead to a long-term objective of developing effective therapies. In summary, these mushrooms exert neurological properties either by enhancing neuronal survival or by helping neurite outgrowth activity with the help of NGFs. Though many of these mushrooms are edible, using them in human trials should be done with great care since their negative effects are not well established.

Contributors' Statement

Conceptualized the study: S. S. K. Durairajan; preparation of manuscript: S. S. K. Durairajan, M. Li, S. K. Yadhav, R. Ir, R. Reddi; critical revision and edition of the manuscript: S. S. K. Durairajan, M. Li, S. K. Yadhav, R. Jeewon, K. D. Hyde, I. Kaliappan, R. Jeyaraman, J. Krishnan; principal investigators of the grants: S. S. K. Durairajan, M. Li.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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