International Journal of Biology, Pharmacy
and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

REVIEW ON NEUROPROTECTIVE ACTIVITY REPORTED IN VARIOUS MEDICINAL PLANTS

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ABSTRACT

Neurodegeneration refers to a condition of neuronal death occurring as a result of progressive disease of long-term and is becoming a major health problem in the 21st century. Neurons degenerated are not replaced resulting in a cognitive loss, many neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's disease (AD), dementia, cerebrovascular impairment, seizure disorders, head injury, parkinsonism. The common pathology of neurodegeneration includes deposition of misfolded proteins such as amyloid-β (Aβ) in Alzheimer's disease, α-synuclein in Parkinson's disease (PD), transactive response DNA-binding protein 43 (TDP-43) in dementia. Neuroprotection refers to the strategies and possible mechanisms that are able to protect the central nervous system (CNS) against neuronal injury and neurodegenerative disorders. The past decade has witnessed an intense interest in herbal plants having long-term health-promoting or medicinal qualities. Comprehensive research and discovery have demonstrated that natural products, medicinal herbs, plant extracts, and their metabolites, have great potential as the neuroprotective agent. Although the precise mechanisms of action of herbal drugs have yet to be determined, some of them have been shown to prevent formation of beta-amyloid plaques, promote nerve growth, some inhibit acetylcholinesterase (AChE) enzyme and malondialdehyde (MDA) formation in brain while other exhibits antioxidant activity by increasing the level of

superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx). Thus the herbal plants can be a valuable source of the drug against neurodegenerative disorders which will require high-throughput screening. This review will highlight the role of herbal plants and their phytoconstituents against neurodegenerative diseases and other related disorders, focusing on their mechanism of action and therapeutic potential.

Keywords: Alzheimer's disease, Amyloid-β, Antioxidant, Dementia, Herbal medicine, Neurodegenerative diseases, Neuroprotective

INTRODUCTION

Neurodegenerative diseases are characterized by progressive dysfunction and loss of neurons leading to the distinct involvement of functional systems defining clinical presentations [1].

Neurodegeneration is a process involved in both neuropathological conditions and brain aging. It is known that brain pathology in the form of the cerebrovascular and neurodegenerative disease is a leading cause of death all over the world, with an incidence of about 2/1000 and an 8% total death rate [2].

Studies have demonstrated that common pathology of neurodegeneration is deposition of proteins with altered physicochemical properties in the human brain. These pathological conformers are called as misfolded proteins such as accumulation and aggregation of amyloid-β (Aβ) in AD [3], α-synuclein in PD, huntingtin protein in Huntington's disease (HD), and TDP-43 in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) [4]. In addition, it has been recognized that protein elimination pathways, like the ubiquitin-proteasome system and the autophagy-lysosome pathway, stress response proteins and chaperones have a high impact on the pathogenesis [5].

Damage of neurons also contribute to progressive long-term neurodegenerative processes, for example, the role of L-glutamate (or L-aspartate) mediated acute excitotoxicity in cerebral ischemia or status epilepticus is well known. Microglia-mediated neuroinflammation is also one of the most striking hallmarks of various neurodegenerative diseases, including PD, AD, and ALS [6].

The presently available drugs for the treatment of AD are symptomatic only and do not alter the course or progression of the underlying disease and produce adverse reactions in patients thereby having limited scope for the treatment of patients with Alzheimer's syndrome. Research is also expanding at other substances and treatments that prevent the formation of beta-amyloid plaques, nerve growth factor to keep neurons healthy such as statins,

antioxidants (vitamins) and folic acid, anti-inflammatory drugs [7]. The past decade has also witnessed an intense interest in herbal medicines that have long-term health-promoting qualities. Herbal remedies for neurodegenerative disease is becoming more popular in the recent years as they show the possibility to slow down the brain's degeneration. The benefits derived from using herbal treatments have been very promising as they are not only as effective as prescription drugs but also have fewer side effects [8]. The use of some medicinal herbs has been touted to extend beyond that of modern prescription drugs and may be used as a substitute for pharmaceutical drugs or can be used in conjunction. In the present review, attempts have been made to present the mechanistic role of few herbal medicines in the treatment and management of neurodegenerative disease [9].

Search criteria

This review included articles from 2003 to 2017 that were found in various electronic databases: PubMed, Science Direct, Scopus, Web of Science, Scirus, and Google Scholar by using the search words: neurodegenerative diseases, neuroprotection, medicinal plants, antioxidant, Alzheimer's disease, Parkinsonism, dementia, amyloid-β, acetylcholinesterase. Only current articles that reported the effects of medicinal plants on neurodegenerative diseases were included in our study. Then, a comparison of the related vb mechanisms and evaluation of pharmacological effects in the treatment of disease was done.

Herbal neuroprotective agents and their mechanistic pathway

Neuroprotective agents refer to substances that are capable of preserving brain function and structure by reducing and preventing oxidative stress, mitochondrial dysfunction, inflammation, various forms of neurotoxicity (e. g. excitotoxicity), and protein deficiencies. Specific examples of things that can cause neurodegeneration include: traumatic brain injuries, drug abuse, pharmaceutical medications, schizophrenia, strokes, and dementia but the most common cause of neurodegeneration is oxidative stress and to prevent the effects of any neurodegeneration, considering neuroprotective agents may be beneficial for long-term brain health. Administration of a neuroprotective agent may help minimize the effects of chronic conditions that could: kill brain cells, decrease brain volume, and lead to long-term functional impairment. There are more than 120 traditional medicines that are being used for the therapy of CNS disorders in Asian countries [10]. In the Indian system of medicine the following medicinal plants

have shown promising activity in neuro-psycho-pharmacology:

Acorus calamus

Acorus calamus (Sweet flag) belonging to family Araceae, act as a rejuvenator for the brain and nervous system having beneficial memory enhancing the property, learning performance, and behavior modification. *Acorus calamus* contains a majority of α-and β-asarone, β-asarone has the capability of suppressing beta-amyloid-induced neuronal apoptosis in the hippocampus by reversal down-regulation of Bcl-2, Bcl-w, caspase-3 activation and c-Jun N-terminal kinase (JNK) phosphorylation [11]. Methanolic extracts of the roots containing α-asarone showed inhibitory effect on AChE with an IC50 value of 188µg/ml [12]. *Acorus calamus* has the potential of improving the function of dopaminergic nerve; by increasing striatal extracellular dopamine level and the expression of tyrosine hydroxylase in substanianigra therefore it can play role in PD. *Acorus calamus* also increases DJ-1 gene expression in the striatum and therefore acts as neuroprotective for PD [13].

Allium sativum

Allium sativum (family Amaryllidaceae), commonly known as garlic, is one of the most widely quoted herbs found in the old medical literatures mainly for its medicinal potentials in prevention and treatment of cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension, dementia, cancer and diabetes [14, 15]. Allicin (allyl 2-propene thiosulfinate or Diallylthiosulfinate) and alliin are the principal bioactive compounds of Allium sativum. S-allyl cysteine (SAC) is the major constituent of aged garlic extract (AGE) which is extensively studied [16, 17]. SAC has both direct and indirect antioxidant activity. Apart from decreasing lipid peroxidation and DNA fragmentation, it also reduces protein oxidation and nitration. In 1-methyl-4-phenyl pyridinium (MPP) and 6-hydroxydopamine (6-OHDA) models of Parkinsonism, SAC protected dopamine levels, oxidative damage and lipid peroxidation. In 3-nitro propionic acid and quinolinic acid animal models of HD, administration of SAC decreased lipid peroxidation and mitochondrial dysfunction. It also increased manganese and copper/zinc superoxide dismutase activity and prevented behavioural changes. AGE, directly and indirectly, activates expression of important genes needed for neuronal survival [18, 19]. Allyl-containing sulfides in garlic cause the upregulation of neuroprotective proteins such as mitochondrial uncoupling proteins. Allicin also activates transient receptor potential ion channels in the plasma membrane of neurons [20, 21].

Bacopa monnieri

Bacopa monnieri (Linn), commonly referred to as "Brahmi," from the plant family Scrophulariaceae is a creeping herb found in India and neighbouring tropical countries. Steroidal saponins and bacosides A and B are the active chemical constituents responsible for improving both learning and memory **[22]**. Other constituents include bacopa saponins D, E and F as well as alkaloids, flavonoids, and phytosterols **[23]**. Bacoside A increases the activities of superoxide SOD, CAT, GPx, and glutathione reductase (GSR). As a result, the levels of glutathione (primary endogenous antioxidant conjugate) in the brain are significantly increased. Bacoside A inhibits lipid peroxidation by modulating the effects of enzymes like Hsp 70 and cytochrome P450 in the brain. It also improves the activities of adenosine triphosphatases (ATPases), maintains ionic equilibrium and restores zinc and selenium levels in the brain. The researchers found *Bacopa monnieri* produce a reduction in alpha-synuclein protein aggregation. *Bacopa monnieri* also enable the body to better cope with the deleterious mental and physical consequences of stress by elevating levels of noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) in the cortex and NA and 5-HT in the hippocampus **[24]**. Jadiya *et al*. investigated the effect of *Bacopa monnieri* on pharmacologically induced 6-hydroxydopamine (6-OHDA) PD model in Caenorhabditiselegans which expressed human version of alpha-synuclein. The researchers found that the extract showed a significant 3.5-fold reduction in alpha-synuclein protein aggregation, which may be due to induction of the stress-buffer protein Hsp-70 **[25, 26]**.

Centella asiatica

Centella asiatica belonging to family Apiaceae (Umbelliferae) has been demonstrated to possess the neuroprotective property and is used as an alternative medicine for memory improvement in the Indian Ayurvedic system of medicine for a long time **[27]**. The primary active constituents of *Centella asiatica* are saponins (also called triterpenoids), which include asiaticosides, in which a trisaccharide moiety is linked to the aglyconeasiatic acid, madecassoside and madasiatic acid. Other components isolated are brahmoside and brahminoside, which may be responsible for CNS action **[28]**. *Centella asiatica* exhibits potent antioxidant activity, capable of scavenging free radical, reduces ferric ions, restores GSH levels by increasing the glutathione-S-transferase activity. *Centella asiatica* also decreases Aβ deposition in the brain. Chen et al. carried out a study which suggested that *Centella asiatica* ethanol extract can suppress Aβ-induced

neurotoxicity by enhancing the antioxidative defence system in differentiated PC12 and IMR32 cells [29, 30]. Amelioration of the colchicine-induced decrease in AChE activity and inhibition of nitric oxide induced neuronal damage by asiaticoside may also explain the neuroprotective effect of *Centella asiatica* [31, 32].

Curcuma longa

Turmeric, derived from the plant *Curcuma longa* belonging to the Zingeberacea family, is a gold-coloured Spice that has been used as a traditional medicine. Curcumin, the principal constituent of turmeric, has several known neuroprotective actions [33]. In Alzheimer's disease, it has been shown that curcumin has the ability to bind Aβ peptides, prevent aggregation of new amyloid deposits and promote disaggregation of existing amyloid deposits [34]. Scientific studies also reported that curcumin and its analogues demethoxy-curcumin and bis-demethoxy-curcumin can protect cells from Aβ-induced oxidative stress [35]. Curcumin has the ability to inhibit Aβ oligomerization and fibril formation, enhance Aβ uptake by macrophages and inhibits the peroxidase activity of A beta-heme complex [36]. Curcuminoids, polyphenol compounds from turmeric attenuate mitochondrial dysfunction induced oxidative stress and

inflammatory responses to inflammatory cytokines, COX-2, and iNOS. Curcuminoids also bind to Aβ plaques to inhibit amyloid accumulation and aggregation in the brain [37, 38].

Celastrus paniculatus Wild

Celastrus paniculatus Wild commonly known as Jyotishmati belongs to family Celastraceae. In the traditional system of medicine, it was administered as a powerful brain tonic, appetite stimulant, and emetic [39]. Phytochemical studies show the presence of evoninoate, a sesquiterpene, alkaloids paniculatine A, paniculatine B and wifornine F, celastrine, celapanine, celapanigine, celapagine, polyalcohol like malangunin, malkanginnol, malkanguniol and paniculatadiol, triterpenoids, sterols such as β-amyrin and β-sitosterol [40, 41]. The scientific studies suggested that *Celastrus paniculatus* water extract protected neuronal cells against glutamate-induced toxicity by modulating glutamate receptor function and showed an improvement in learning and memory. It also stimulates a significant decrease in the brain levels of MDA which is an important marker of oxidative damage, with simultaneous significant increases in levels of glutathione and CAT; two endogenous antioxidants in the brain [42]. Research carried out by Jakka AL also elucidated the neurotrophic potential of flavonoids present in Celastruspaniculata Wild whole plant

methanolic extract (CPPME) and treatment with CPPME demonstrated decrease in AChE and enhanced neurotrophic activity and thus, ultimately improving spatial memory formation in scopolamine-induced amnesia [43].

Coriandrum sativum L

Coriandrum sativum L. commonly known as dhanya belongs to family Apiaceae [44]. Major phytochemical present includes flavonoids like quercetin 3-glucoronide; polyphenolics like caffeic acid, protocatechinic acid, and glycitin. The flavonoid content of the seeds was reported to be 12.6 quercetin equivalents/kg and the polyphenolic content was reported to be 12.2 gallic acid equivalents/kg [45, 46]. A study showed that the extract of *Coriandrum sativum* increased enzyme levels of SOD, GSH, CAT and total protein levels, and reduces cerebral infarct size, lipid peroxidation (LPO) and calcium levels in the experimental rat. Memory deficits induced by scopolamine and diazepam was also reversed by leaves of *Coriandrum sativum* [47]. It also decreases reactive changes in brain histology like gliosis, lymphocytic infiltration and cellular edema which assist the protective role in cerebrovascular insufficiency states. The leaves also show antioxidant property having 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, lipoxygenase inhibition and phospholipid peroxidation inhibition activity, which may also contribute to its memory enhancement effect [48].

Galanthus nivalis

Galanthus nivalis commonly known as snowdrop belongs to family Amaryllidacea. The major constituent found in bulbs and flowers of *Galanthus nivalis* is galantamine which is a tertiary isoquinoline alkaloid. The neuroprotective effect of galantamine is associated with the dual action of this alkaloid. The drug is a competitive and selective AChE inhibitor. It is capable of stimulating nicotinic receptors which further enhance cognition and memory [49]. The drug also modulates allosterically nicotinic acetylcholine receptors, especially α7 and α3β4 subtypes, on cholinergic neurons to increase acetylcholine release [50].

Ginkgo biloba

This species, belonging to the Ginkgoaceae family, is considered as a 'living fossil' [51]. The extract contains 24% of flavonoids fraction which is mainly composed of three flavonols, quercetin, kaempferol and isorhamnetin and 6% of terpenic lactones that include diterpenic lactones-the ginkgolides A, B, C, J and M, and a sesquiterpene tri lactone-the bilobalide [52]. Extract exhibit the neuroprotection by several mechanisms that include inhibition of membrane lipid

peroxidation, anti-inflammatory effects, and direct inhibition of amyloid-b aggregation and anti-apoptotic activities. The flavonoid fraction of *Ginkgo biloba* (G. biloba) extract is responsible for the antioxidant and free-radical scavenging properties and bilobalide can reduce damage caused by global brain ischemia and excitotoxicity-induced neuronal death [53, 54]. G. biloba extract significantly inhibit the AChE activity in the brain that indicates an increase in the basal level of acetylcholine [55]. Flavonoids alter a number of a biological process like their interactions with neuronal and signalling pathways, expression of proteins required for synaptic plasticity and repair, changes in cerebral blood flow, inhibition of neuropathological process in certain brain regions. A study carried out by Dash SK showed that the extract of G. biloba inhibits the production of brain Aβ levels by lowering cholesterol, as free and circulating free cholesterols that affect amyloidogenesis. It may also influence the formation of Aβ fibrils by increasing gene expression of transthyretin that prevent Aβ aggregation in vitro [56].

Glycyrrhiza glabra

Glycyrrhiza glabra (G. glabrais) commonly known as Yashti-madhuh or liquorice, belongs to family Leguminosae. The major flavonoid of *G. glabra* is Glabridin that possesses multiple pharmacological activities like antiviral, anticancer, anti-ulcer, anti-diabetic, antioxidant, immunomodulatory activity, antimicrobial activity, anti-inflammatory activity, and anticonvulsant. Liquorice significantly improved learning and memory but the research have indicated that its consumption improves the general intelligence rather than short-term memory [57]. Glabridin significantly decreases the level of MDA and it elevates the level superoxide dismutase and reduced glutathione in the brain [58]. A study indicated that administration of G. glabra restored the decreased levels of brain enzymes such as glutamate and dopamine and decreased AChE activity [59].

Hypericum perforatum

Hypericum perforatum (H. perforatum), is also known as hypericum or millepertuis is a member of the family Hypericaceae. Although it has a worldwide distribution, it is mainly native to Europe, western Asia, and northern Africa. Hyperoside is the main active component of H. perforatum. Hypericin, Kaempferol, Biapigenin and quercetin are its other constituents [60]. H. perforatum extract has also been reported to protect against enzymatic (NADPH-dependent) and non-enzymatic (Fe^{2+}/ascorbate dependent) lipid peroxidation in the cerebral cortex [61]. The extract also protects brain cells from glutamate-induced cytotoxicity by reducing glutathione loss,

calcium overload and ROS-mediated cell death [62]. H. perforatum ethanolic extract may improve microglial viability by reducing amyloid-beta mediated toxicity in Alzheimer's disease [63]. Hypericumperforatum inhibits acetylcholineesterase enzyme [64] and MDA formation in the brain and increases the level of SOD, CAT, GPx. According to these findings, H. perforatum also act as an antioxidant and have the ability to bind iron ions and have scavenging action for hydroxyl radical [65].

Lycopodium serratum

Lycopodiumis is a genus of club mosses, also known as ground pines or creeping cedar, in the family Lycopodiaceae, a family of fern-allies. The leaves contain a single, unbranched vascular strand and are microphylls by definition. The genus Lycopodium (Lycopodiaceae), which produces a potential therapeutic agent, huperzine A, for the treatment of AD, has been extensively studied in recent years [66]. Huperzine A is an alkaloid extracted from *Lycopodium serratum* and has been used for centuries to treat fever, inflammation, blood disorders and schizophrenia [67]. It is a highly selective, reversible, and potent AChE inhibitor, and potency of AChE inhibition is similar or superior to that of physostigmine, galanthamine, donepezil and tacrine [68]. The huperzine A is a strong candidate for treatment of AD. Other potentially beneficial effects, as far as AD is concerned, include protection against Aβ-induced oxidative injury and neuronal apoptosis, regulation of nerve growth factor and reduction in glutamate-induced toxicity. Huperzine A caused a significant increase in ACh levels in rat brain [69]. Huperzine A has several protective effects such as regulating amyloid precursor protein metabolism, protecting against Aβ mediated oxidative stress, apoptosis and mitochondrial dysfunction, as well as anti-inflammation [70].

Melissa officinalis

The leaves of *Melissa officinali*s L. (Lamiaceae), also known as lemon balm, are used in traditional medicine for its nerve calming and spasmolytic effects. The leaves produce calming and soothing effects through $GABA_A$ benzodiazepine receptor [71]. Its extracts contain some compounds such as flavonoids such as quercitrin as well as apigenin, luteolin and phenolic acids. These derivatives inhibit enzymes monoamine oxidases (MAO) and AChE, scavenge these free radicals and prevent apoptosis. The inhibition of these enzyme leads to alleviation of depression symptoms [72]. Research also suggests that *Melissa officinali*s exert protective activities in the PC12 cell line and might protect neurons from oxidative stress [73].

Ocimum sanctum

Ocimum sanctum, also known as 'Tulsi' in Hindi and 'Holy Basil' in English belongs to family Labiatae. The plant is also reported to contain alkaloids, glycosides, saponins, and tannins, vitamin C, and maleic acid, citric and tartaric acid [74]. A research conducted by Kusindarta et al. indicated that an ethanolic extract derived from leaves of *Ocimum sanctum* may stimulate and restores the expression of choline acetyltransferase in ageing human cerebral microvascular endothelial cells and could provide nerve protection and increased production of Ach may enhance the memory and cognitive ability [75]. Scientific studies reveal that the hydroalcoholic extract of *Ocimum sanctum* exhibits strong antioxidant activity against DPPH and hydroxyl radicals which may be due to the high amount of polyphenols and flavonoids. It inhibits lipid peroxidation, ROS generation, DNA damage, and membrane depolarization. It also decreases the lactate dehydrogenase leakage and preserved the cellular morphology, restored superoxide dismutase and catalase enzyme levels thereby preventing neuronal damage [76].

Panax ginseng

Ginseng belongs to the family of Araliaceae growing in north-eastern Asia. It is one of the most widely used herbs for boosting energy [77] Ginseng root is characterized by the presence of ginsenosides. Ginseng may provide protection against neurodegeneration by multiple mechanisms. The ginsenosides improve performance in a passive avoidance learning paradigm and the neuroprotection was possibly, due to its ability to suppress cellular AChE activity and enhancement of cholinergic metabolism [78]. It also produces a dose-dependent reduction in the β-amyloid deposition or glutamate-induced excitotoxicity; thereby prevent apoptosis and neuronal death. In different experimental models against PD it suppresses nitric oxide (NO) production and tissue necrotic factor-alpha (TNF-α) secretion, inhibits the mRNA expressions of inducible nitric oxide synthase (iNOS), TNF-α, interleukin (IL-1β), cyclooxygenase-2 (COX-2) and reduces the generation of ROS [79].

Rosmarinus officinalis

Rosemary commonly known as Satapatrika, belongs to the family Lamiaceae. It contains several essential oils like carvacrol, eugenol, oleanolic acid, thymol, and ursolic acid; antioxidant constituents such as carnosic acid and ferulic acid [80]. Carnosic acid, which was first isolated from the plant by Wenkert et al. has also shown to have neuroprotective effects on cyanide-induced brain damage in cultured rodent and human-induced

pluripotent stem cell-derived neurons in vitro and in vivo in various brain areas of a non-Swiss albino mouse model. Lian et al. have also shown that carnosol and rosemary essential oils inhibit the adhesion of tumour necrosis factor-α-(TNF-α-) induced monocytes to endothelial cells and suppress the expression of intercellular adhesion molecule (ICAM-1) at the transcriptional level in vitro. Meng et al. reported the inhibitory effect of rosemary diterpenes on α-secretase which is one of the major proteolytic enzymes that process amyloid precursor protein. The mechanism behind its neuroprotective actions involves not only inhibition of AChE and β-amyloid deposits as well as anti-BuChE (butyrylcholinesterase) activity [81]. Apart from above activities, it possesses cytoprotective, anti-apoptotic and anti-inflammatory activities that also add on to its neuroprotective mechanism [82].

Salvia officinalis

Salvia is an important genus in the Lamiaceae family reputed for improving memory and has a long history of use as memory enhancing agents [83, 84]. The Rosmarinic acid and carnosic acid are the main active ingredient of S. officinalis having potential pharmacological effects that include anti-inflammatory and antioxidant properties as well as weak AChE inhibitory effect [85, 86]. It inhibits reactive oxygen species formation, lipid peroxidation, DNA fragmentation, caspase-3 activation and tau protein hyperphosphorylation [87]. All these clinical evidence may help to prevent or reduce the symptoms of dementia. One small pilot trial showed that oral administration of S. officinalis essential oil to 11 patients showing mild-to-moderate symptoms of AD significantly improved cognitive function [88].

Terminalia chebula

Terminalia chebula (*T. chebula*), called the "King of Medicines" in Tibet, belongs to the family Combretaceae and is one of the most important medicinal plants used in medicines of Ayurveda, Siddha, Unani and Homeopathy [89]. It contains compounds such as triterpene sarjunglucoside 1, arjungenin and the chebulosides 1 and 2, tannins, chebulic acid, chebulinic acid, tannic acid, ellagic acid, 2,4-chebulyi–β-D-glucopyranose, gallic acid, ethyl gallate, punicalaginterflavin A, terchebin. Some flavonoids like luteolin, rutins, and quercetinetc are also present. A study reported that *T. chebula* exhibit anxiolytic activity that is comparable to standard drug diazepam [90, 91]. *T. chebula* has good pharmacological activities relevant to dementia therapy. Sancheti *et al.* extracted 1, 2, 3, 4, 6-penta-O-galloyl-β-D-glucose extracted from *T. chebula* by chromatographic methods that were reported to be the potent AChE and

Butyrylcholinesterase inhibitor. Sulaiman *et al*. showed that ethyl acetate extract with doses of 0.001, 0.005, 0.015, and 0.025 g/ml inhibited AChE by 29.36%, 32.44%, 45.82%, and 62.32%, respectively. Gallic acid derived from *T. chebula* exerts anti-inflammatory activity via the down-regulation of the nuclear factor-κB(NF-κB) pathway in the development of inflammatory diseases, both in vitro and in vivo **[92]**. *T. chebula* also acts as an antioxidant and its activity is comparable with reference radical scavengers such as quercetin, showing 95% activity with inhibitory concentration (IC$_{50}$) value 2.2 μg/ml **[93]**. *T. chebula* fruit extract may also protect neuronal cells against ischemia, reduces NO production and death rate of microglia cells stimulated by lipopolysaccharide **[94]**.

Tinospora cordifolia

Tinospora cordifolia (T. cordifolia) belongs to the family Menispermaceae, is commonly known as giloe. Chemical constituents derived from the plant are alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides **[95]**. *T. cordifolia* possesses a memory enhancing property which is due immune-stimulation and increased synthesis of acetylcholine **[96]**. T. cordifolia exhibits strong free radical scavenging properties against ROS and reactive nitrogen species as studied by electron paramagnetic resonance spectroscopy. It also increases the level of reduced glutathione, expression of the gamma-glutamyl-cysteine ligase and copper-zinc superoxide dismutase genes, which plays a major role in neuronal injury during hypoxia/ischemia **[97]**. In addition, *T. cordifolia* significantly decreases the mRNA expressions of iNOS. *T. cordifolia* also increases the level of dopamine in the brain. Thus, T. cordifolia has shown to prevent the neurodegenerative changes and enhance cognition, learning and memory **[98]**.

Withania somnifera

Withania somnifera belongs to the family Solanaceae, popularly known as Ashwagandha is considered as the Indian ginseng. The major constituents of Ashwaganda root are two withanolides, withaferin A and withanolide D. Active glyco-withanolides of *Withania somnifera* have a significant antioxidant function, which is accomplished by increasing the activities of SOD, CAT, and GPx. Ashwagandha is also reported as a Nervine tonic that rejuvenates the cells and boosts energy **[99]**. According to Rajasankara, oral treatment of PD mice with *Withania somnifera* root extract (0.1 g/kg body weight) for 7 d or 28 d elevated dopamine, 3,4-dihydroxy phenyl acetic acid and homovanillic acid levels in the corpus striatum. Furthermore, it was reported that *Withania somnifera* treatment

increased the level of anti-apoptotic (Bcl-2) proteins and decreased the level of the pro-apoptotic (Bax) proteins in the Maneb-Paraquat-induced dopaminergic neurodegeneration model of PD **[100]**. Ashwagandha extract has shown to prevent the lipid peroxidation and increase the antioxidant activity by increasing the free-radical scavenging enzymes levels in the brain. Sitoindosides VII-X and withaferin, other constituents isolated from the aqueous methanol extract of roots of *Withania somnifera* tend to decreased AChE activity in the brain **[101]**.

Zizyphus jujube

Jujube fruits are used in traditional Korean and Chinese medicine to reduce anxiety and strengthen the stomach and gastrointestinal system. Jujube seeds contain large amounts of terpenoid, flavonoid, phenyl glycosides and alkaloid compounds mucilage, malic acid, citric acid, sugar, protein, organic minerals and vitamin C **[102]**. The herb exerts inhibitory activity against histamine release and AChE and cyclooxygenase I and II inhibitory activity. Flavonoids present exert antioxidant properties **[103]** Cis-9-octadecenamide (oleamide), a compound extracted from jujube is reported to have high effect on the activation of acetylcholine transferase (34.1%) in the in vitro which leads to the increase in acetylcholine level and improves mild to moderate cognitive functions, learning and memory, motor coordination and behavioral disorders **[104]**.

CONCLUSION

The management of neurodegenerative diseases remains a challenge in the modern medicine because of their complicated pathogenesis. Protein misfolding and their accumulation inside or outside of neurons is the key pathological feature in several neurodegenerative diseases including Alzheimer's, Parkinson's Huntington's disease. Herbal medicines are regarded as effective and promising sources of potential neuroprotective agents because of their cognitive benefits and more significantly, their mechanisms of action with respect to the fundamental pathophysiology of the diseases. Our review has acknowledged several herbal medicines such as such as *Allium sativum*, *Ginkgo biloba*, panaxginseng, *Terminalia chebula* with potential therapeutic effects for neurodegenerative diseases. It is anticipated that the information provided through this review should help the researcher to provide some evidence and conceptual detail of the benefit of a wide range of herbs as neuroprotective agents.

share their knowledge on the use of herbal medicinal plants as neuroprotective agents.

CONFLICTS OF INTERESTS

All authors have none to declare

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