Review Article

Application of phytochemicals for the treatment of neurodegenerative diseases

Kailash Kumar N, Greeshma John S, S. Sathesh Kumar*

ABSTRACT

Neurodegeneration is defined as the progressive loss of structure or function of neurons which includes amyotrophic sclerosis, Alzheimer's disease, and Huntington's disease. Many neurodegenerative diseases are caused by genetic mutations; however, multiple biological processes can cause neurodegeneration. Synthetic drugs are widely used for the treatment of most neurodegenerative disorders which are reported to cause side effects during the treatment. Researchers identified some naturally occurring chemical compounds in plants, i.e., phytochemical through various research programs, and these are used for the management of neurodegenerative diseases. Phytochemicals are generally accepted to be safe with minimal side effects. In this review, we comprehensively compiled the plant-derived compounds such as polyphenol, isothiocyanate, alkaloid, and cannabinoid, and other important phytochemicals reported possess beneficial effect in neurodegenerative disorders. These phytochemical compounds have various effects such as neuroprotective, antioxidant, and anti-inflammatory actions. In the case of phytochemical studies, different plants and plant parts containing many valuable constituents such as lignans, flavonoids, tannins, triterpenes, and sterols, and these constituents are exhibit neuroregeneration or neuroprotective effect. Many Ayurvedic formulations prepared from various plants are claimed to possess neurostimulant activity, thus improving the symptomatic conditions in patients with neurodegenerative disorders. The folklore medicine has also possessed a significant contribution identifying neurotonic and nerve stimulants. The systematic ethanopharmacological studies had yielded highly reliable results in exploring the phytochemical agents for the treatment of neurodegenerative disorders. This review article will provide the researchers comprehensive information about the plants and the mechanisms elucidated by them through *in vivo* or *in vitro* studies.

KEY WORDS: Neurodegenerative disorders, Neurotonic agents, Phytochemical agents

INTRODUCTION

Neurodegenerative diseases are a significant problem, and these are common symptomological features at different stages of disease progression. The main physiological symptoms include elevated oxidative/nitrosative stress, mitochondrial dysfunction, protein misfolding/aggregation, synapse loss, and decreased neuronal survival. Overabundance of protein aggregation affects cellular signaling and neuronal function and is a key cause of neuronal loss.[1]

Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration/death of nerve cell. This causes problems with movement or mental functioning called dementia. Dementias are responsible for the greatest burden of disease with Alzheimer's representing approximately 60–70% of cases.[2] The main neurodegenerative diseases are:

- Alzheimer's disease (AD) and other dementias
- Parkinson's disease (PD) and PD-related disorders
- Huntington's disease (HD)
- Prion disease
- Motor neuron diseases (MNDs)
- Spinocerebellar ataxia
- Spinal muscular atrophy
- Amyotrophic lateral sclerosis (ALS)
- Vascular dementia
- Frontotemporal dementia
- Multiple sclerosis
- Peripheral nerve disorders
- Genetic brain disorders.

Access this article online	
Website: jprsolutions.info	ISSN: 0975-7619

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai, Tamil Nadu, India

***Corresponding author:** S. Sathesh Kumar, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies, Pallavaram, Chennai, Tamil Nadu, India. Phone: +91-9551412737. E-mail: sathesh2000@gmail.com

Received on: 25-11-2017; Revised on: 26-12-2017; Accepted on: 04-03-2018

AD is one of the most complicated neurodegenerative diseases. Recently, we use some herbs and phytochemicals and their derivatives; they can delay the progression of the disease. Neurodegenerative diseases are affected by factors such as stimulating nuclear factor in the antioxidant system, sirtuin and transcription factors and chaperons and neurotrophic factors and by inhibiting acetylcholinesterase (AChE) activity.

In case of neurodegenerative diseases, neurotrophins are the important factors for the survival, maintenance, and regeneration of specific neuronal populations in the brain. The neurotrophins that are identified as neuronal survival-promoting proteins in mammals include brain-derived neurotrophic factor (BDNF), neurotrophin-3(NT-3), and nerve growth factor (NGF). Neurotrophic support is a significant factor in the pathogenesis of neurodegenerative diseases such as AD, PD, and ALS.

NEURODEGENERATIVE DISEASES

AD

It is a chronic neurodegenerative disease that usually starts slowly and gets worse over time. It is the cause of 60–70% of cases of dementia. The most common early symptom is difficulty in remembering recent events (short-term memory). As the disease advances, symptoms can include problems with language, disorientation, mood swings, loss of motivation, not managing self-care, and behavioral issues.[3]

The disease process is associated with plaques and tangles in the brain. A probable diagnosis is based on the illness and cognitive testing with medical imaging and blood tests to rules out other possible causes.[4] The disease cause is divided into two stages, namely, early onset caused by mutation of genes and the late onset due to unknown reasons. About 70% of the risk believed to be genetic with many genes usually involved. Other risk factors include a history of head injuries, depression, or hypertension. It is an age-related disorder; the symptoms commonly occur in the age of 30–60 years.[5]

PD

It mainly affects the motor system in which is a long-term neurodegenerative disorder of the central nervous system. The symptoms generally come on slowly over time. Early in the disease, the most obvious are shaking, rigidity, slowness of movement, and difficulty with walking. Thinking and behavioral problems may also occur. Dementia becomes common in the advanced stages of the disease. Anxiety and depression are also common cause occurring in more than a third of people with PD. PD affects movement, producing motor symptoms. Non-motor symptoms, which include autonomic dysfunction and sensory and sleep difficulties, are also common. PD majorly occurs in people over the age of 60 years, of which about 1% is affected. Males are more than affected than females. When it is seen in people before the age of 40 or 50 years, it is called young-onset PD.[6]

HD

It is an inherited disorder that results in death of brain cells. A general lack of coordination and an unsteady movement of limbs often follow. Physical abilities gradually worsen until coordinated movements become difficult and the person is unable to talk. Mental abilities generally decline into dementia. Symptoms usually begin between 30 and 50 years of age but can start at any age. The disease may develop earlier in life in each successive generation. About 8% of cases start before the age of 20 years and typically present with symptoms similar to PD.[5,7]

HD generally inherited from a person's parents with 10% of cases due to a new mutation. The disease is caused by an autosomal dominant mutation in either of an individual's two copies of a gene called "Huntingtin." This means a child of an affected person typically has a 50% chance of inheriting the disease. Treatments can relieve some symptoms and

Table 1: Drugs currently used in the treatment of neurodegenerative disorders[10-20]

Diseases	Drugs	Route of administration	Dose
PD	Levodopa	Oral route	250–500 mg twice a day with meals
	Amantadine	Oral route	100 mg per day
AD	Tacrine	Oral	Initial dose - 20 mg–40 mg/day, final dose - 80 mg/day
	Donepezil	Oral route	5 mg once a day
	Rivastigmine	Oral route	1 mg twice a day
	Galantamine	Oral route	4 mg twice daily (8 mg–16 mg/day for 4 weeks)
HD	Tetrabenazine	Oral route	Initial dose - 12.5 mg twice a day. Final dose - 25 mg/week
	Olanzapine	Oral route	10–30 mg daily
MND	Riluzole	Oral route	100–200 mg/day for up to 12–21 months
	Baclofen	Oral	10–80 mg daily
Vascular dementia	Hydergine	Oral route	1.5–9 mg per day
	Nimodipine	Oral	30 mg for 3 times daily

Table 2: Plants reported to possess neuroprotective effect[21-42]

Plant species	Phytoconstituents	Pharmacological actions	Suggested mechanism
Zingiber officinale	6-shogaol	Stimulates TrK- mediated neurite outgrowth, inhibits the level of COX2, TNF-α, NF- Kb, IL-1β, NO, P^{38}, iNOS, PGE2,and RO, increases SOD, Bcl-2, and Bcl-XL levels	Neuritogenesis, neuroinflammation, and neuroprotection
Magnolia officinalis	Honokiol, magnolol	Increase the secretion of NGF and BDNF, inhibits TNF-α, NF-kB, IL-1β, IL-6, inhibits ROS levels, and increases Akt activity	Neuritogenesis, neuroinflammation, and neuroprotection
Melissa officinalis	Rosmarinic acid, neral/geraniol, citronellal, isomenthone	Mimetic to NGF, ERK ½-mediated neurite outgrowth activating capacity, increase cholinergic activity and NF-kB pathway, and inhibits the action of IL-1β, TNF-α	Antidepressant, cognitive disorder, neuritogenesis, neuroinflammation, and neuroprotection
Pimpinella brachycarpa	3,5-0-trans-diciffeolyl-quinic acid, methyl ester, 1-0-trans-p-coumaroyl-5-0-cis-p-coumaroyl quinic acid	Inhibition of NO, iNOS production, and induce antioxidant system	Neuroinflammation
Schisandra chinensis	α-iso-cubebene, dibenzocyclooctadiene lignans, schisanchinins A-D, nigranoic acid	PKA/B/Ca^{2+}-CaMKII/ERK ½-mediated CREB and Nrf_2 pathway activation, inhibits NO, and PGE_2 production	PD, neuroinflammation, and neuroprotection
Panax ginseng	Ginosenoside Rg3 panaxynol	Activates cAMP/MAPK and Trk-mediated neuritogenesis, neurotrophic mimetic action	Neuritogenesis, neuroinflammation, neurodegenerative diseases, and neuroprotection
Morus alba	Quercetin, cyaniding-3-O-β-glucopyranoside, gallic acid.	Induces P13k/ERK ½-mediated CREB activation, neurite outgrowth, and induce NGF secretion	Cognitive disorder, neuritogenesis, antiaging, and neuroprotection
Olea europaea	Oleuropein	Induces NGF and BDNF secretion and increase GSH level	Neuroinflammation and neuroprotection
Vitis vinifera	Resveratrol	Stimulates ERK-mediated CREB regulation, induces NGF, GDNF and BDNF secretion, and inhibits caspare-3-TNF-α, NF-Kb, IL-10, IL-1β, MPI, and MDA levels	Neuritogenesis, neuroinflammation, and neuroprotection
Aster scaber	(-)-3,5-Dicaffeoyl-muco-quinic acid	Shows neurotrophic mimetic action, Activates TrK/ERK ½/ P13K-mediated neuritogenesis, increase SOD, and decreases MDA activity	Neurodegenerative disease, neuroinflammation, neuritogenesis, and neuroprotection
Abies holophylla	Ligraminol E4-o-β-d-xyloside, juniperigiside	Inhibits NO production and activates Trk- mediated NGF production	Neurodegenerative diseases, neuropathy, neuritogenesis, and neuroinflammation
Ginkgo biloba	Ginkgolide B	Activates Trk/RaS/ MAPK-mediated neurite outgrowth, induces BDNF secretion and reduces ROS, LDH caspase3, and pro-apoptotic factors	Antidepressant dementia, neuroprotective, phosphor diesterase, antioxidant, neuritogenesis, and neuroinflammation
Huperzia serrata	Huperzine A	Activates Trk/MAPK/ ERK-mediated neurite outgrowth, induces NGF and BDNF secretion, reduces acetylcholinesterase (AChE)	Neuritogenesis, neuroinflammation, and neuroprotection
Liriope platyphylla	Spicatoside A	Activates Trk/ERK ½/ P13K-mediated neurite outgrowth, induces NGF and BDNF secretion	Neurodegenerative disease, neuritogenesis, and neuroprotection

(Contd...)

Table 2: ***(Continued)***

Plant species	Phytoconstituents	Pharmacological actions	Suggested mechanism
Dioscorea nipponica	Diosniposide B,3,7-dihydroxy-2,4, 6- trimethoxy-phenanthrene, sapogenin	Activates Trk signaling pathway-mediated neurite outgrowth and induces NGF secretion, inhibits NO	Neuritogenesis, neuroinflammation, and neuroprotection
Eucommia ulmoides	Geniposidic acid	Activates P13K/AKT/P^{38} MAPK/ ERK ½-mediated inhibition of LDH, BDNF expression, and AChE inhibition	Antiapoptotic, AD, neurodegenerative disease, and neuroprotection
Camellia sinensis	Epigallocatechin-3-galate	Activates Trk signaling pathway-mediated neurite outgrowth, P13K/AK7/GSK-3β, induces NGF, BDNF secretion, and inhibits Ca3 and ROS level	Neuritogenesis, neuroinflammation, neuroprotection, cognitive disorders
Coptis chinensis	Berberine	Activates AKT/GSK- 3β/ Nrf_2-mediated regulation, cholinergic activity- mediated neurite outgrowth, induces NGF and BDNF secretion, and inhibits COX2, TNF-α, and NF-KB levels	Neuritogenesis, neuroinflammation, and neuroprotection
Curcuma longa	Curcumin	AKT/GSK-3β-mediated regulation, induces BDNF secretion, and inhibits Cas3, TNF-α, and NF-KB levels	Neuritogenesis, neuroinflammation, and neuroprotection
Withania somnifera	Withanine, somniferine, somnine, withaferine A, pseudowithanine, withanone	Amyloid plaques trigger neuronal cell death and also blocked by withanamides	Treatment of HD, neurodegenerative disease, ability to support a healthy immune system and CNS

Table 3: Traditionally used plants for the treatment of brain disorders[43]

Plant name	Chemical constituents	Traditional use
Adhatoda zeylanica	Vasicine, vasicinone	Treatment of epilepsy, stiffness
Cannabis sativa	Tetrahydrocannabinoids	Treat epilepsy in women, treatment for sleeplessness
Brassica nigra	Gallic acid, quercetin	It helps to relieve migraine and reduces laziness and fatigue
Coriandrum sativum	Coriandrol, limonene, geranyl acetate, and linalool	It is used to strengthen brain and memory and relieves vertigo
Cassia occidentalis	Flavonoid glycosides	Used to treat epilepsy and hysteria
Convolvulus microphyllus	Convoline, convolamine	To improve the memory, cures psychosis
Cuscuta reflexa	Cuscutoside A and B	It improves brain disorders
Ficus benghalensis	Bengalenosides	It enhances memory power
Anacyclus pyrethrum	Pyrethrin	It improves mental inability
Albizia lebbeck	Budmunchiamine alkaloids, saponins	Used to treat psychosis, anxiety, and cures unconsciousness

in some improve quality of life. Symptoms of HD most commonly occur in the age of 35 and 45 years, but they can begin at any age from infancy to old age. In the early stages, there are changes in personality, cognition, and physical skills. The most characteristic initial physical symptoms are jerky, random, and unsteady movements called "Chorea." Seizures are also common symptom of this form of HD.[7]

ALS

It is a specific disease that causes the death of neurons which control voluntary muscles. ALS is characterized by stiff muscles, muscles twitching, and gradually worsening weakness due to muscles decreasing in size. This results in difficulty in speaking, swallowing, and eventually breathing.

The cause is not known in 90% and 95% of cases. About 5–10% of cases are inherited from a person's parents. The diagnosis is based on a person's signs and symptoms with testing done to rule out other potential courses.[8]

ALS is an MND, which is a group of neurological disorders that selectively affect motor neurons, the cells that control voluntary muscles of the body, including ALS, primary lateral sclerosis, and progressive muscular atrophy. Most commonly the limb is affected, first. In this case, neurons in the

brain and the spinal cord are affected and this form is called "limb onset." About 25% of cases muscles in the face, mouth, and throat are affected because motor neurons in the part of the brain stem called "the medulla oblongata" (formerly called the bulb). The progressive death of lower motor neurons is referred as "bulbar onset [Table 1].[9]"

PHYTOCHEMICALS AGENTS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

Phytochemicals provide an effective way of halting neurodegenerative diseases. Phytochemicals and derivatives such as diosniposide B, lignin derivatives, 3,7-hydroxy-2,4,6-trimethoxy-phenanthrene, ginkgolide B, and clerodane diterpenoids induces neuronal cell differentiation and upregulate neurotrophic factors such as NGF and BDNF. These compounds may have the potential to prevent and arrest neurodegeneration by inducing neurotrophic factors and by boosting the activity of certain components of the antioxidant system. The list of phytochemical agents that are reported to possess the potential to act against the neurodegenerative diseases is listed in Table 2.

TRADITIONALLY USED PLANTS FOR BRAIN-RELATED DISORDERS

A wide range of plants are used in the treatment of brain-related disorders, traditionally. The ancient literature also refers many plants for stimulation of brain activity. The ethanopharmacological uses of some of the plants are explored by various researchers, and the phytochemicals present was also isolated. The details of the ethnopharmacological uses and the phytoconstituents are listed in Table 3.

CONCLUSION

The development of new drugs for neurodegenerative disorders, very specifically to make them to reach the brain is most complicated. The isolation of specific phytoconstituents from ethanopharmacologically important plants may lead to identification of novel neuroprotective agents or neurotonic agents. The least number of drugs currently available for the treatment of neurodegenerative disorders and their adverse drug reactions accelerates the need for exploitation of alternative molecules from plant sources.

REFERENCES

1. Venkatesan R, Ji E, Kim SY. Phytochemicals that regulate neurodegenerative disease by targeting neurotrophins: A comprehensive review. Biomed Res Int 2015;2015:814068.
2. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of alzheimer's disease: A review of progress. J Neurol Neurosurg Psychiatry 1999;66:137-47.
3. Singhal AK, Naithani V, Bangar OP. Medicinal plants with a potential to treat Alzheimer and associated symptoms. Int J Nutr Pharmacol Neurol 2012;2:84-91.
4. Agarwal P, Alok S, Fatima A, Singh PP. Herbal remedies for neurodegenrative disorder (alzheimer disease): A review. Int J Pharm Sci Res 2013;4:3328-40.
5. Natarajan S, Shunmugiah KP, Kasi PD. Plants traditionally used in age-related brain disorders (dementia): An ethanopharmacological survey. Pharm Biol 2013;51:492-523.
6. DeMaagd G, Philip A. Parkinson's disease and its management: Part 1: Disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. P T 2015;40:504-32.
7. Huntington's Disease Information Page: National Institute of Neurological Disorders and Stroke (NINDS)" NINDS. 28 January 2016. Archived from the Original on 27 July 2016.
8. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano PF, *et al.* A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int 2015;6:171.
9. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, *et al.* Amyotrophic lateral sclerosis. Lancet 2011;377:942-55.
10. Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE, *et al.* Pathological gambling caused by drugs used to treat Parkinson disease. Arch Neurol 2005;62:1377-81.
11. Scott LJ, Goa KL. Galantamine: A review of its use in Alzheimer's disease. Drugs 2000;60:1095-122.
12. Farlow MR, Hake A, Messina J, Hartman R, Veach J, Anand R, *et al.* Response of patients with alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. Arch Neurol 2001;58:417-22.
13. Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J, *et al.* A controlled trial of tacrine in Alzheimer's disease. The tacrine study group. JAMA 1992;268:2523-9.
14. Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, *et al*. Efficacy of Donepezil in early stage AD. Arch Neurol 2004;6:1852-6.
15. Diana P. Tetrabenzine in the treatment of Huntington's disease. Neuropsychiatr Dis Treat 2007;3:545-51.
16. Tyagi SN, Tyagi LK, Shekhar R, Singh M, Kori ML. Symptomatic treatment and management of HD; An overview. Glob J Pharmacol 2010;4:6-12.
17. Turner MR, Al-Chalabi A, Shaw CE, Lergh PN. Riluzole and motor neurone disease. Pract Neurol 2003;3:160-9.
18. Leigh PN, Abrahams S, Al-Chalabi A, Ampong MA, Goldstein LH, Johnson J, *et al.* The management of motor neurone disease. J Neurol Neurosurg Psychiatry 2003;74 Suppl 4:iv32-iv47.
19. Schneider LS, Olin JT. Overview of clinical trials of hydergine in dementia. Arch Neurol 1994;51:787-98.
20. Zhong XY, Su XX, Liu J, Zhu GQ. Clinical effects of acupuncture combined with nimodipine for treatment of vascular dementia in 30 cases. J Tradit Chin Med 2009;29:174-6.
21. Palatty PL, Haniadka R, Valder B, Arora R, Baliga MS. Ginger in the prevention of nausea and vomiting: A review. Crit Rev Food Sci Nutr 2013;53:659-69.
22. Hoi CP, Ho YP, Baum L, Chow AH. Neuroprotective effect of honokiol and magnolol, compounds from *Magnolia officinalis*, on beta-amyloid-induced toxicity in PC12 cells. Phytother Res 2010;24:1538-42.
23. Yoo DY, Choi JH, Kim W, Yoo KY, Lee CH, Yoon YS, *et al.* Effects of *Melissa officinalis* L. (lemon balm) extract on neurogenesis associated with serum corticosterone and GABA in the mouse dentate gyrus. Neurochem Res 2011;36:250-7.
24. Soh Y, Kim JA, Sohn NW, Lee KR, Kim SY. Protective effects of quinic acid derivatives on tetrahydropapaveroline-induced cell death in C6 glioma cells. Biol Pharm Bull 2003;26:803-7.
25. Yuan XX, Yang LP, Yang ZL, Xiao WL, Sun HD, Wu GS, *et al.* Effect of nigranoic acid on ca^{2+} influx and its downstream signal mechanism in NGF-differentiated PC12 cells. J Ethnopharmacol 2014;153:725-31.
26. Joo SS, Yoo YM, Ahn BW, Nam SY, Kim YB, Hwang KW, *et al.* Prevention of inflammation-mediated neurotoxicity

by rg3 and its role in microglial activation. Biol Pharm Bull 2008;31:1392-6.
27. Ercisli S, Orhan E. Chemical composition of white (*Morus alba*), red (*Morus rubra*) and black (*Morus nigra*) mulberry fruits. Food Chem 2007;103:1380-4.
28. Peng CH, Liu LK, Chuang CM, Chyau CC, Huang CN, Wang CJ, *et al*. Mulberry water extracts possess an anti-obesity effect and ability to inhibit hepatic lipogenesis and promote lipolysis. J Agric Food Chem 2011;59:2663-71.
29. Carito V, Venditti A, Bianco A, Ceccanti M, Serrilli AM, Chaldakov G, *et al*. Effects of olive leaf polyphenols on male mouse brain NGF, BDNF and their receptors trkA, trkB and p75. Nat Prod Res 2014;28:1970-84.
30. Anastácio JR, Netto CA, Castro CC, Sanches EF, Ferreira DC, Noschang C, *et al*. Resveratrol treatment has neuroprotective effects and prevents cognitive impairment after chronic cerebral hypoperfusion. Neurol Res 2014;36:627-33.
31. Yang YJ, Yao J, Jin XJ, Shi ZN, Shen TF, Fang JG, *et al*. Sesquiterpenoids and tirucallane triterpenoids from the roots of *Scorzonera divaricata*. Phytochemistry 2016;124:86-98.
32. Zhang C, Tian X, Luo Y, Meng X. Ginkgolide B attenuates ethanol-induced neurotoxicity through regulating NADPH oxidases. Toxicology 2011;287:124-30.
33. Zhang HY, Tang XC. Neuroprotective effects of huperzine A: New therapeutic targets for neurodegenerative disease. Trends Pharmacol Sci 2006;27:619-25.
34. Hur J, Lee P, Moon E, Kang I, Kim SH, Oh MS, *et al.* Neurite outgrowth induced by spicatoside A, a steroidal saponin, via the tyrosine kinase A receptor pathway. Eur J Pharmacol 2009;620:9-15.
35. Woo KW, Kwon OW, Kim SY, Choi SZ, Son MW, Kim KH, *et al.* Phenolic derivatives from the rhizomes of *Dioscorea nipponica* and their anti-neuroinflammatory and neuroprotective activities. J Ethnopharmacol 2014;155:1164-70.
36. Kwon SH, Kim MJ, Ma SX, You IJ, Hwang JY, Oh JH, *et al.* *Eucommia ulmoides* oliv. Bark. Protects against hydrogen peroxide-induced neuronal cell death in SH-SY5Y cells. J Ethnopharmacol 2012;142:337-45.
37. Liu M, Chen F, Sha L, Wang S, Tao L, Yao L, *et al.* (−)-Epigallocatechin-3-gallate ameliorates learning and memory deficits by adjusting the balance of TrkA/p75NTR signaling in APP/PS1 transgenic mice. Mol Neurobiol 2014;49:1350-63.
38. Hsu YY, Tseng YT, Lo YC. Berberine, a natural antidiabetes drug, attenuates glucose neurotoxicity and promotes nrf2-related neurite outgrowth. Toxicol Appl Pharmacol 2013;272:787-96.
39. Liao KK, Wu MJ, Chen PY, Huang SW, Chiu SJ, Ho CT, *et al.* Curcuminoids promote neurite outgrowth in PC12 cells through MAPK/ERK- and PKC-dependent pathways. J Agric Food Chem 2012;60:433-43.
40. Matsuda H, Murakami T, Kishi A, Yoshikawa M. Structures of withanosides I, II, III, IV, V, VI, and VII, new withanolide glycosides, from the roots of indian *Withania somnifera* DUNAL. And inhibitory activity for tachyphylaxis to clonidine in isolated guinea-pig ileum. Bioorg Med Chem 2001;9:1499-507.
41. Jayaprakasam B, Padmanabhan K, Nair MG. Withanamides in *Withania somnifera* fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease. Phytother Res 2010;24:859-63.
42. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): A review. Altern Med Rev 2000;5:334-46.
43. Balakrishnan A, Misea LN. Ayurvedic Plants for Brain Disorders; The Herbal Hope. Vol. 6. Varanasi: Chaukhambha Orientalia; 2017.

Source of support: Nil; Conflict of interest: None Declared