ALZHEIMER'S DISEASE AND TREATMENT

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Phytopharmaceuticals in Neurodegenerative Disorders

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Abstract

Millions of individuals worldwide suffer from Neurodegenerative Diseases (NDs). Two of the most common neurodegenerative disorders, Parkinson's Disease (PD) and Alzheimer's Disease (AD), have a significant socioeconomic impact. People desire a cure for these disorders from the natural herbals since several centuries. Scientific literature has reported many medicinal plants and their secondary metabolites with their ability to relieve the symptoms. Medicinal plants represent a largely unexploited reservoir of natural medicines which have potential cure for Alzheimer's & Parkinson's diseases. The structural diversity of their phytocompounds make these plants a valuable source of novel lead compounds. On the basis of traditional literature and up-to-date research, several new therapeutically active compounds have been identified from herbal extracts, which may be valuable in the treatment of cognitive disorders. This chapter focuses on illnesses such as AD, PD, and trinucleotide disorders of repletion, as well as the significance of natural phytoconstituents/extracts and their possible mechanisms of neuroprotection.

Introduction

Alzheimer's Disease (AD) produces continuous and increasing cognitive decline, whereas Neurodegenerative Disorders (NDs) affect specific regions of the body, based on neuronal cells experiencing careful deterioration.

In the neurodegeneration of neurons, an important role is played by oxidative damage by highly reactive compounds. Different types of neurological disarrays influence advanced destruction of motor, sensory neurons, which can identify exterior objects as sensory information. [1]. Particularly in brain tissue sensitive to reactive oxygen species which damage cell, build up may lead to AD by lipid peroxidation.

Acetylcholine level ,which is neurotransmitter involved in memory and learning [2,3] is also affected**.** Most conventional dementia causes degradation of neurons apart from AD, PD, and Huntington's Disease(HD), [4,5]. Dementia is typified by chronic progressive mental disorder while AD distinctly distresses memory, intelligent, knowledge, design, and linguistic. Abundant in older population effecting 5% of people over 65 years and 50% of people above 85 years [6]. AD broadly affects all the ageing persons in world, characterized by universal cerebral malfunction, memory damage, change in behaviour personality, and performance injuries of activities of daily activities that leads the patient bedridden, incontinent, and reliant on supervisory care [7]. This devastating disease represents 22 million people globally developing in 3 years [8]. 20% of the occurrence is of Vascular dementia. It is estimated to increase more than 0.8 billion by 2040 [9]. Dementia affects millions of individuals worldwide, with two-thirds of them living in third-world nations.

Etiology

Alzheimer's Disease (AD)

Insulin resistance is linked to the development of Alzheimer's disease via promoting tau phosphorylation. [10], secretion of APPsα, which decreases the Amyloid beta intracellular pool [11]. Apart genomic, environmental abnormalities also cause AD. It is not understood by modified βAPP metabolism and amyloid β accumulation in sporic cases, but include age-dependant reasons in, compromised energy metabolism, oxidative stress, and disturbed ion homeostasis in cells.

Little education, history of AD trauma, with feeding of high-fat/ high-caloric and a lethargy life improve the risk of incidence of disease [12]. Ca^{2+} dysregulation, oxidative damage, and mitochondrial impairment, in Endoplasmic Reticulum (ER), apoptosis and ultimately death of neurons can be persuaded by

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beta amyloid [13,14]. AD pathogenesis of neurotoxic forms of amyloid beta from APP appear to be a critical step in the development of β and γ secretase inhibitors and blockers [15]. In the treatment for AD by drugs acetylcholinesterase inhibitors (AChE), which enhances the intensity of acetylcholine in the brain can be used. Aβ seems to be an important initiator [16].

Copper and iron chelators should also help neurons deal with oxidative stress that's why they are labeled as indirect antioxidants as accumulation of amyloid is reduced in brain [17]. Testosterone and Estrogen [18] are additional therapeutic approaches which are being examined including anti-inflammatory agents such as steroids and COX-2 inhibitors that naturally diminish with age.

Parkinson's Disease (PD)

PD is most widespread, after Alzheimer's that often impairs speech, motor skills, and other functions and detected pathologically by the loss of neurons in the nucleus basalis of Meynert additionally the septal forebrain areas [19] in connotation with the occurrence of inquinated protein in cytoplasm of neurons [20]. According to epidemiological research, the incidence of Parkinson's disease is around 1% among those aged 65-69, rising to 3% among people aged 80 and up around one million people, or 1% of those over the age of fifty-five, are affected by PD [21,22].

l-hydroxy phenylalanine (l-DOPA) enhancement of dopamine levels is enhanced by this monoamine oxidase inhibitors, which is precursor. Cholinesterase inhibitors enhance the cholinergic activity [23]. Alzheimer's, muscular rigidity, resting tremor, and an impairment of postural balance leading to disturbances of gait and falling is a clinical syndrome consisting of four cardinal features [24].

Causes of the Disease

It gets difficult for the cells to get the nutrients as brain and tangles in the nerve cells make it difficult for the cells to get the nutrients. Sixty percent to seventy percent of cases of dementia, Alzheimer's accounts for chronic neuro-degenerative disease which normally begins gradually and worsens with time.

Down's syndrome

Higher risk of developing AD is because of a genetic flaw that results in Down's syndrome can also lead to AD in some people because amyloid plaques builds up in the brain over time.

Genes

Genes that relate to causing Alzheimer's due to mutation in them are- Amyloid Protein Precursor (APP), PSEN1 (Presenilin 1) & PSEN 2 (Presenilin 2). Additional genes associated are- CLU, SORL1, PICALM, CR1 etc. Most of autosomal dominant family diseases like Alzheimer's attributable to mutations in either one of three genes: Those encoding amyloid precursor protein (APP) and presenilin's 1 and 2. At 65 years of age. Familial variants of autosomal dominant inheritance account for around 0.1 percent of cases before the age of 65.

APOE apolipoprotein E

Apolipoprotein C1 and C2 genes is present in chromosome 19. Mutations develop in type III hyper lipoproteinemia enhances blood plasma cholesterol and triglycerides in consequence of impaired clearance of chylomicron and VLDL remnants. Even though mutations reduce the overall quantity of Aβ generated, they can induce sickness and indicate to additional functions of presenilin or changes in the function of APP. Senile plaques are main components which increases Aβ42 production is increased by mutations in the presenilin genes and APP. The brain cells die in neurofibrillary tangles formed by the tau protein particles, and the signs and symptoms of AD.

Sodium nitrite mediated neurodegeneration

D-galactose and $NaNO_2$ in combination has been stated in medical conditions of Alzheimer's. Sodium Nitrite ($NaNO_2$) having capability to change haemoglobin into methaemoglobin, which lowers the blood's oxygen carrying ability [25,26].

Vascular dementia and Alzheimer's disease -Difference in symptoms

Clinical condition characterized by a steady decline in brain intellectual function, with the individual affected unable to carry out daily tasks adequately [27].

The extent of the lacunae dementia was shown to be more linked with the degree of hippocampal and cortical atrophy [28,29]. Most common in elderly persons have multi-infract dementia [30] where the brain has been damaged by frequent small strokes. In sum, Japan accounts for 50 percent of all dementias, 20-40 percent in Europe, and 15% in Latin America. Men than in women rate is found to be high and it increases with age [31]. High blood pressure, abnormal heart rhythms, and disorders that damage the arteries in the brain are all causes of vascular dementia. In patients with a mild degree of vascular dementia, memory impairment may be limited or non-existent [32]. Microvascular pathology, such as pallor, neuronal loss, and gliosis, has been discovered to play a causal role in dementia, with cholinergic impairments being seen in individuals in later stages.

The active form of Vitamin D, 1,25 dihydroxyvitamin D3, governs neurotrophin expression, including nerve growth factor, neurotrophin 3, and glial-derived neurotrophic factor, as well as neural cell survival, development, and function [33,34]. Reducing the cost of randomized controlled trials and improving the design, Vitamin D pills are being studied to see if they can help elderly people delay or prevent dementia and AD [35]. Vitamin D stimulates macrophages, which promotes phagocytic clearance of amyloid plaques under *in vitro* conditions [36,37]. All forms of dementia and Alzheimer's is associated with lower concentration of vitamin D [38,39].

Neuroprotection - possible ways

As revealed in literature there are numerous scientific studies and confirmations of AD, traditional literature claims herbal research has demonstrated its efficacy to prevent the neurodegeneration.

Herbal Neuroprotectives

Oxygen delivery to the brain is the main focus of all modalities. None of these approaches has shown to be optimal thereby demonstrating the demand of alternate medicine especially those mentioned in the various AD.

Conventional crude form to cure has appeared in the form of standardized herbal extract, its formulations, and composite preparations [40,41]. (Table 1) summarizes the potential phytochemicals and their studies for the management of AD, PD and HD used. Medicines give a safe alternative to traditional treat-

ment and well borne remedies for a persistent sickness with fewer adverse effects [42]. Few case studies of herbal extracts are discussed below:

Effect of *Bacopa monniera* on lipofuscin genesis and D-Galactose fluorescent product in the brain induced elderly mice was studied. D-Galactose, react with amino groups and protein AEGs which are ironic source of free radicals in AD causing chemical oxidation of AEGs causes oxidative stress. AGE receptor binding and activation of signalling pathways. *Bacopa monniera* is a tropical Ayurvedic herb used to treat many central nervous system disorders [43]. At physiological pH, free radicals cause increased oxidative stress and, as a result, damage to micromolecules, particularly mitochondria [44].

Withania somnifera therapy causes an increase in cAMP through superoxide dismutase, lipid peroxidation activity, and a decrease in total suphahydral levels, making it an antioxidant and antistress agent. *Withania somnifera* is used for several clinical condition like development of memory and cognition augmentation [45]. *Withania somnifera* root extract in mice shows, nootropic effects, and AchE is reversed. Indirect cholinergic spread facilitation, which could be very useful in NDs with cholinergic deficits [46,47]. indicated reduction of long term hypoperfusion caused anxiety and restlessness and memory shortage [48]. Moderate attenuation of histological abnormalities is seen in long-term reperfusion injury, such as partial reduction in inflammatory cell penetration, lympholytic infiltration and cell proliferation. Aptogenic properties of *Withania somnifera* is studied for neuroprotection [47].

The antioxidant mechanism of *Centella asiatica* was investigated by boosting endogenous antioxidant enzymes in the brain. When tested utilising a range of AD paradigms, aqueous extract of *Centella asiatica* at doses of 200mg/kg and 300 mg/kg showed improvement in memory and learning, with significant reductions in malondialdehyde and concurrently significant levels of glutathione [49].

When tested utilising a conditioned avoidance response paradigm, an extract of *Ocimum sanctum* in ethanol alleviated scopolamine (0.4mg/kg). Amelioration indicated possible mechanism of its action by cholinergic modulation and AD and age-related dementia benefit from its use.

Semecarpus anacardium documented its potential utility along with Methanolic extract of *Semecarpus anacardium* which demonstrated inhibition of AchE with *Nardostachys jatamansi*. *Semecarpus anacardium* prevents stress induced neurodegeneration.

AcE has close association and hence *Semecarpus anacardium* therapy could be of dual benefits. The effect of *Clitoria ternatea* roots in alcohol on scopolamine-persuaded memory impairment was seen by Vyawahare.

Caryocar brasiliense (Camb), a Caryocaraceae family member popularly known as “pique”. A decoction of the leaves and petals is used as an energetic, tonic, aphrodisiac, and treatment for liver disorders, while the fruit pulp is used as a stomachic and flu treatment. Flavonoids found in *C. brasiliense* have been shown to have leishmanicidal, antifungal, antioxidant, and vasorelaxant effects [50]. Antioxidant substances such as gallic acid, quinic acid, quercetin, and quercetin 3-o-arabinose were found in *C. brasiliense* leaves in studies [51,52]. Anticholinesterase actions and protection from *C. brasiliense* extract consumption are currently restricted [53].

Details of Phyto compounds

Table 1: Promising phytochemical and their studies for the management of AD, PD, HD.

Promising phytochemicals and their studies for the management of Parkinson’s diseases				
Phytochemicals	**Studied materials**	**Dose**	**Physiological effects**	**References**
Chrysin	C57BL/6Jmice (Male)	10 mg/kg	↑Behavioral functions↑TH-positive cells in the SN and ST↑DA, DOPAC, and HVA levels	[54]
	C57BL/6mice(Male)	50 and 100 mg/kg	↑DA and its metabolites↑AKT/GSK3β/MEF2D pathway↓MAO-B activity	[55]
	C57BL/6Jmice(Male)	50, 100, and 200 mg/kg	↑BDNF and GDNF protein expression↓IL-10, IL-6, TNF-α, and NF-κB proteinexpression	[56]
Vanillin	Wistar albino rats(Male)	5, 10, and 20 mg/kg	↓iNOS, COX-2, IL-1β, and IL-6 protein expression	[56]
			↓ERK1/2, p38, and NF-κB signaling↓Microglia activation	[57]
			↑Striatal DA and its metabolite levels↑Behavioral function	[57]
	Wistar albino rats(Male)	5, 10, and20 mg/kg	↓Cyto-C, Bax, and caspase protein expression↑Bcl-2 protein expressions	[58]
	C57BL/6mice(Male)	20, 40, and80 mg/kg	↑Striatal DA levels↑Striatal TH, TLR4, BDNF, and GFAP proteinexpression	[59]
			↓α-Synuclein and lowered AIF proteinexpression	[60]
Asiatic acid	Wistar albino rats(Male)	100 mg/kg(in vivo)and 0.1–10 nM(invitro)	↑Motor functions ↑PI3K, Akt, GSK-3β, and mTORphosphorylation	[60]
			↑TrKB protein expression ↓NLRP3 inflammasome expression inmicroglia cells	[61]
	Wistar albino rats(Male)	100 mg/kg	↓Mitochondrial Drp1 expression ↑PGC1αgene and protein expression ↑Mfn2 and mitochondrial dynamics	[62]

Ferulic acid	C57BL/6mice(Male)	100 mg/kg	↑HSP-70 protein expression ↑TH-positive fibers in corpus striatum	[63]
	C57BL/6mice(Male)	20 mg/kg and muscle exercise	↑Motor behavior ↑CAT, SOD, GPx, and GSH activity ↓TBARS activity ↑Activation of the Nrf2 signaling	[64]
	C57BL/6mice(Male)	40 mg/kg	↓iNOS, COX-2, IL-1β, and IL-6 protein expression	[65]
Thymoquinone	Wistar albino rats(Male)	7.5 and15 mg/kg	↑Parkin, Drp1, TH-positive cells in the SN and ST ↑DA, DOPAC, and HVA levels	[66]
	Wistar albino rats(Male)	5 and 10 mg/kg	↑Behavioral functions ↑DA level in the SN↓MDA level	[67]
	Wistar albino rats(Male)	50 mg/kg	↑Motor function and electrophysiological performance ↑CAT, SOD, GPx, and GSH cerebral activity	[67]
	Wistar albino rats(Male)	50 mg/kg	↓MAO-B activity ↑ERβ/Nrf2/HO-1 signaling cascade	[68]
	Drosophila melanogaster	0.5, 1, and 2 mg/g	↑CAT, SOD, GPx, and GSH cerebral activity ↓TBARS activity	[69]
	A53T transgenic mice	5 mg/kg	A53T α-synuclein ↑Bcl-2-mediated autophagy pathway ↑Behavioral functions	[70]
Caffeic acid	C57BL/6 mice(Male)	0.5, 1, and 2 g/kg	↑DA synthesis ↑TH-positive cells ↑BDNF and GDNF protein expression, maintained loss ↓IL-1β, IL-6, TNF-α, iNOS, and COX-2 expression ↓GFAP protein expression	[71]
	C57BL/6 mice(Male)	50 mg/kg	↑Iron-export protein ferroportin in SN ↑CAT, SOD, GPx, and GSH cerebral activity ↓TBARS activity ↑DA synthesis	[72]
Epigallocatechin-3-gallate	C57BL/6J mice (Male)	25 mg/kg	↑Movement behavior ↑TH-positive cells in the SN region ↑$CD3^+CD4^+$ to $CD3^+CD8^+$ T-cell lymphocyte ratio in the peripheral blood ↓TNF-α and IL-6 cytokine expression in serum	[73]
	Postmortem PDtissue	100 nM	↓α-Synuclein aggregates	[74]
	C57BL/6mice (Male)	10 mg/kg	↑Movement behavior ↓Microglial activation	[75]
	C57BL/6mice (Male)	10 mg/kg	↑HVA, DOPAC, 5-HIAA levels ↑TH-positive cells in the ST region ↓JNK and p-JNK expression ↑Bcl-2 protein expression	[76]
α- and β-Asarone	Sprague Dawley rats	15 mg/kg	↑CAT, SOD, GPx, and GSH cerebral activity ↓TBARS activity ↑PERK/CHOP/Bcl-2/Beclin-1 pathway ↓GRP78 levels	[77]
	C57BL/6mice (Male)	10 mg/kg	↑DAT and VMAT-2 expression ↑Behavioral functions ↑CAT, SOD, GPx, and GSH cerebral activity ↓TBARS activity	[78]
Theaflavin	C57BL/6mice (Male)	10 mg/kg	↑Behavioral characterization ↑TH-positive cells in the ST region	[79]
	C57BL/6mice (Male)	10 mg/kg	↓Caspase-3, caspase-8, and caspase-9 activity ↓Bax expression ↑Bcl-2 protein expressions ↑Behavioral characterization ↓IL-4 and IL-10 protein expressions	[80]

Promising phytochemicals and their physiological effects for the management of Alzheimer's disease (AD)

Phytochemicals	Experimental Model	Dose	Physiological effects	References
Apigenin	In vitro induced neurogenesis in vivo mouse model of AD	-	↓inflammatory cytokines, ↓cortical hyperexcitation ↓Aβ burden, ↓oxidative stress, ↑ERK/CREB/BDNF pathway ↓β-amyloid neurotoxicity, ↑mitochondrion protection	[81-83]

Berberine	In vitro model of AD in vivo rodent model of AD	-	↓AChE, ↓MAO-B, ↓BACE1, ↑IκB-α, ↑Akt,↑p38 kinase ERK1/2 ↓NF-κB, ↓TNF-α,↓IL-6 production, ↓MCP-1, ↓COX 2,↓iNOS ↓Aβ plaque, ↓ CTF-α, ↓CTF-β (which reflects α- and β-secretase processing of APP)	[84-86]
Crocin	In vivo mouse model of AD in vivo rat model of AD	-	↓oxidative stress, ↑SOD, ↓MDA ↓AChE, ↑ACh activity ↓neuroinflammation, ↓TNF-α, ↓PGE, ↓iNOS, ↓COX2 ↓Tau hyperphosphorylation	[87,88]
Genistein	In vitro model of AD	-	↓MAO ↓inflammation, ↓NF-κB ↓Aβ toxicity, ↑apoptosis	[89]
Ginsenoside	In vitro cell model of AD	-	↓β- and γ-secretases, ↓NO, ↓ROS, ↓lipid peroxidation, ↓IL-1,↓IL-8, ↓TNF-α, ↓Aβ plaque, ↓caspase-9, ↓caspase-3	[86]
Isoquercitrin	In vivo rat model of AD		↓BACE1, ↓γ-secretase, ↓Aβ fibrillogenesis, ↓caspase-3, ↓caspase-9, ↓apoptosis, ↓amyloid plaque, ↓tau hyperphosphorylation	[90]
Linalool	In vivo mouse model of AD	-	Anti-inflammatory ↓p38, ↓MAPK, ↓Nos2, ↓COX2, ↓IL-1β↓ Aβ in the hippocampus ↓tauopathy, inhibition of T-type Ca2+ channels	[91,92]
Morin	In vivo rat models of AD	-	↓BACE1, ↓γ-secretase, ↓Aβ fibrillogenesis ↓apoptosis, ↑caspase-3, ↑caspase-9 ↓amyloid plaque, ↓tau hyperphosphorylation	[90]
Naringenin	In vitro models of AD	-	↓inflammatory cytokines, ↓NF-κB signalling, ↑Nrf2/ARE signaling ↓NO	[91]
Naringin	In vivo rat model of AD	-	↓AChE, ↓cognitive deficit, ↓GFAP, ↑neurotrophic factors	[92]
Quercetin	In vivo mouse model of AD		↓TNF-α, ↓IL-6, ↓GFAP, ↓MDA, ↑glutathione peroxidase, ↑AMPK activity ↓apoptosis, ↓GSK3β, ↓tau	[93,94]
Rutin	In vivo rodent model of AD	-	↑SOD, ↑CAT, ↑GPx, ↓iNOS ↑MAPK, ↑apoptosis, ↑JNK, ↑p38 MAPK ↓ IL-1, ↓IL-6, ↑BDNP expression	[95,96]
Silibinin	In vivo rat model of AD	-	↓AChE, ↓ROS ↓Aβ aggregation, ↓hypoxic/ischemic	[97]
Withanamides A and C	In vivo rat model of AD	-	↓Aβ fibril formation	[81]
Withanolide A	In vivo rat model of AD	-	↑axonal/dendritic regeneration exhibited neurotrophic activity	[98]
Withanone	In vivo rat model of AD	-	Protect neurons and glial cells	[99]
Promising phytochemicals and their physiological effcets for the management of Huntington's disease (HD)				
Phytochemicals	**Experimental Model**	**Dose**	**Physiological effects**	**References**
α-Mangostin	3-NP-induced CGNs		Cell death inhibition Mitochondrial reductant capacity	[100]
Astragalan	Ischemic male Wistar rats		Hemeoxygenase-1expression	[101]
Berberine	Ischemic middle cerebral artery occlusion model, oxygen–glucose-deprived PC12cell line		Blocking of the mitochondrial apoptotic pathway	[102]
Celastrol	G93A SOD1transgenic mouse model		HSP70 immunoreactivity	[103]
Sesamol	3-NP-induced rats		Oxidative defense	[104]
(−) Schisandrin B	3-NP-treated neuronal PC12 cells		Pyruvate dehydrogenase activation	[105]
Quercetin	3-NP-treated rats		Neuromodulation	[106]
Naringin	3-NP-treated rats		Neuromodulation	[107]
Lycopene	3-NP-treated rats		Oxidative defense	[108]
Kaempferol	3-NP-inducedrats		Oxidative damage reversal	[109]
Ginsenosides	Glutamate-induced YAC128 medium spiny neurons		Ca (2 +) response inhibition	[110]
Curcumin	3-NP-inducedrats		Nrf2 and HO-1expression	[111]

Diet Management

Nutritional support can help patients with AD decrease the progression of dementia and possibly enhance their quality of life not affecting their survival chances. Folic acid increases the concentration of omega-3 PUFAs such as Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), which is beneficial in the impediment and treatment of AD and dementia.

Fruits, fish, nuts, vegetables and even Indian spices have been shown to reduce AD risk by leading to 45 percent. Fructose for example should be consumed at less than 25 g/day.

Antioxidants such as beta-carotene, vitamin A, vitamins E and C, and others are found in small amounts and can be increased to normal levels to cure disease [112,113].

Astrocytes transplantation

The hippocampus of AD mice was implanted with astrocytes. The role of astrocytes as active A clearance cells in the brain, which could have crucial ramifications for the future development of AD therapy was studied [114].

Stem-cells transplantation

BDNF-mediated hippocampus synaptic density increases significantly after stem cell transplantation. It improves spatial learning and memory in Alzheimer's patients without affecting Aβ deposits [115-117].

Sternlyaffectedareasin AD brainarewithinthetemporal lobes, especially in hippocampus. cognitivedeficitsandpathogenesisof Alzheimer's is caused by degeneration of BFCN's suggesting, BFCNs may be an ideal form of donor cell for treating Alzheimer's-related cognitive impairments.

Exogenous cholinergic neurons displayed cholinergic projection in the basal forebrain. and migratory patterns, as well as morphological and functional integration into the endogenous projection system. The feasibility of developing stem cell treatment utilizing ESC-derived cells was in a behaviour test was performed to demonstrate HuCNS-SC cells which are human neural stem cells that have been produced according to cGMP standards under controlled conditions. HuCNS-SC cells can engraft, migrate, and develop into neurons, astrocytes, and oligodendrocytes over time with no evidence of tumour formation or AD side effects.

Induced pluripotent stem cells

Pluripotent stem cells are found in the early stages of development and serve as the basis for all cell types in the body. Because induced pluripotent stem cells can develop all types of cells in the body, they could provide cells that would otherwise be difficult to obtain, such as brain neurons.

Technology that allows scientists to create neurons in the lab that exhibit some of the hallmarks of AD. The development of a method for generating neurons from these IPS cells in a dish lab, where the beta amyloid protein that forms plaques in patients' brains is released.

Future aspects

AD, for example, necessitates early detection to receive successful treatment. The number of AD patients is increasing at an alarming rate, making it critical to employ modern Alzheimer's technology to treat the condition. Much research has been conducted and still going on the biomarkers, proteomics, and genomics level. There are numerous challenges that must be conquered. Technology alone will not be enough to treat the disease; standardization of processes and techniques is critical for preserving consistency and achieving an elevated level of reliability.

Intracellular neurofibrillary tangles, extracellular amyloid plaques, synaptic deterioration and neuronal death are all implicated in the metabolic processes that lead to AD as a neurodegenerative disorder, according to numerous research. Genetics accounts for about 70% of the risk of AD at any given age. The epsilon 4 allele of the apolipoprotein E gene is a genetic risk factor for AD (ApoE). Apart from the genetic and biochemical aspects of AD , a diet deficient in vitamin D modulates nerve growth factor in its active form, appears to be another culprit. In conclusion biomarkers and stem cell therapy may be promising strategies for early diagnosis and treatment of AD and other NDs.

Conclusion

Neuroprotective agents which are synthetically manufactured and are used in various neurodegenerative diseases like PD, AD and HD have own sluggishness, drowsiness, dry mouth, weariness, tension or apprehension, difficulties with balance, and other side effects which have been reported during treatment. Plant based natural phytomedicines are therefore being explored showing cognitive functions in humans. Numerous classes of plant based natural medicines have been mentioned in literature which stimulate cell stress -reaction pathways and thus contribute to imparting neuroprotective excellence. Medicinal plants are having numerous phytochemicals with different secondary metabolites like poly phenols (phenolic acids, anthocyanins, proanthocyanidins, flavonols, tannins), isoprenoids (sesqiterpenes, diterpenes, triterpenes, steroids, saponins), alkaloids (indole alkaloids, lysergic acid diethylamide, tropane alkaloids, ergot group) and fatty acid they show their effect by inhibiting or even scavenging the excess free radicals produced by oxidative and neurotoxin-induced stressors in brain nerve cells. However more exploratory research is needed to demonstrate the exact molecular processes involved in neuroprotection by these phytocompounds which can lead to effective formulation development.

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Abbreviations

AD: Alzheimer's disease; PD: Parkinson's disease; HD: Huntington's disease; ND: Neurodegenerative disease.

References

1. Coppede F, Mancuso M, Siciliano G, Migliore L, Murri L. Genes and the environment in neurodegeneration. Biosci Rep. 2006; 26: 341-367.
2. Cheignon C, M Tomas, D Bonnefont-Rousselot, P Faller, C Hureau, et al. "Oxidative stress and the amyloid beta peptide in Alzheimer's disease," Redox Biology. 2018; 14: 450-464.
3. Tang F, S Nag, SYW Shiu, SF Pang. "The effects of melatonin and Ginkgo biloba extract on memory loss and cho- line acetyltransferase activities in the brain of rats infused intracerebroventricularly with β-amyloid 1-40," Life Sciences. 2002; 71: 2625-2631.
4. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: an overview of environmental risk factors. Environ Health Perspect. 2005; 113: 1250-1256.
5. Mayeux R. Epidemiology of neurodegeneration. Annu Rev Neurosci. 2003; 26: 81-104.
6. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, et al. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA. 1989; 262: 2551-2556.
7. Sisodia SS. Alzheimer's disease: Perspectives for the new millennium. J Clin Invest. 1999; 104: 1169-1170.
8. Sleegers K, Van Duijn CM. Alzheimer's disease: Genes, pathogenesis and risk. 2001.
9. Smith MA, Tabaton M, Perry G. Neuroscience. 1996; 217: 210-211.
10. Melzer D, Ely M, Brayne C. Cognitive impairment in elderly people: Population based estimate of the future in England, Scotland, and Wales. BMJ. 1997; 315: 462.
11. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. CNS Drugs. 2003; 17: 27-45.

12. Tanzi RE, Bertram L. New frontiers in Alzheimer's disease genetics. Neuron. 2001; 32: 181-184.

13. Mattson MP. 2003. Gene-diet interactions in brain aging and neurodegenerative disorders. Ann Intern Med. 2003; 139: 441-444.

14. Miranda S, Opazo C, Larrondo LF, Muñoz FJ, Ruiz F, et al. The role of oxidative stress in the toxicity induced by amyloid beta-peptide in Alzheimer's disease. Prog Neurobiol. 2000; 62: 633-648.

15. Chauhan V, Chauhan A. Oxidative stress in Alzheimer's disease. Pathophysiology. 2006; 13: 195-208.

16. Dewachter I, Van Leuven F. Secretases as targets for the treatment of Alzheimer's disease: The prospects. Lancet Neurol. 2002; 1: 409-416.

17. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004; 430: 631-639.

18. Ritchie CW, Bush AI, Mackinnon A, Macfarlane S, Mastwyk M, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: A pilot phase 2 clinical trial. Arch Neurol. 2003; 60: 1685-1691.

19. Hoozemans JJ, Veerhuis R, Rozemuller AJ, Eikelenboom P. Non-steroidal anti-inflammatory drugs and cyclooxygenase in Alzheimer's disease. Curr Drug Targets. 2003; 4: 461-468.

20. Whitehouse PJ, JC Hedreen, White CL 3rd, Price DL. Basal forebrain neurons in the dementia of Parkinson disease. Ann Neurol. 1983; 13: 243-248.

21. Pollanen MS, DW Dickson, Bergeron C. Pathology and biology of the Lewy body. J Neuropathol Exp Neurol. 1993; 52: 183-191.

22. Zigmond JM, ER Burke. Pathophysiology of Parkinson's disease. In: Fifth Generation of Progress. Davis KL, Coyle J, Charney D, editors. In: Philadelphia: Lippincott, Williams and Wilkens. 2002; 1781-1794.

23. Perry EK, M Curtis, Dick DJ, Candy JM, Atack JR, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: Comparisons with Alzheimer's disease. J Neurol Neurosurg Psychiatr. 1985; 48: 413-421.

24. Kidd PM. Parkinson's disease as multifactorial oxidative neurodegeneration: implications for integrative management. Altern Med Rev. 2000; 5: 502-529.

25. Lang AE, Lozano. New Engl. J Med. 1998; 339: 1044-1053.

26. Steller H. Science. 1995; 267: 1445-1449.

27. Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology, Churchill, Livingstone. 2003.

28. Gilman S. Oxford American handbook of neurology. Oxford University Press, Oxford, UK. 2010.

29. Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology. 2000; 55: 1626-1635.

30. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR. Prevalence of dementia in the United States: The aging, demographics, and memory study. Neu- roepidemiology. 2007; 29: 125-132.

31. Brown MM. Vascular dementia. Alzheimer's Rev. 1993; 3: 57-62.

32. Hagnell O, Franck A, Grasbeck A, Ohman R, Otterbeck L, et al. Vascular dementia in the Lundby study. 1. A prospective, epidemiological study of incidence and risk from 1957 to 1972. Neuropsychobiology. 1992; 26: 43-49.

33. Roman GC. Vascular dementia: distinguishing characteristics, treatment, and prevention. J Am Geriatr Soc. 2003; 51: S296-S304.

34. Annweiler C, Montero-Odasso M, Hachinski V, Seshadri S, Bartha R. Vitamin D concentration and lateral cerebral ventricle volume in older adults. Mol Nutr Food Res. 2013; 57: 267-276.

35. Fernandes de Abreu DA, Eyles D, Féron F. Vitamin D, a neuroimmunomodulator: Implications for neurode-generative and autoimmune diseases. Psychoneuroendo- crinology. 2009: 34: S265-S277.

36. Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Vitamin D and the risk of dementia and alz- heimer disease. Neurology. 2014; 83: 920-928.

37. Masoumi A, Goldenson B, Ghirmai S, Avagyan H, Zaghi J. 1alpha, 25- dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of alzheimer's disease patients. J Alzheimers Dis. 2009; 17: 703-717.

38. Mizwicki MT, Menegaz D, Zhang J, Barrientos-Durán A, Tse S. Genomic and non genomic signaling in- duced by 1a, 25 (OH) 2-vitamins D3 promotes the recovery of amyloid-b phagocytosis by alzheimer's disease macro- phages. J Alzheimers Dis. 2012; 29: 51-62.

39. Sommer I, Griebler U, Kien C, Auer S, Klerings I. Vitamin D deficiency as a risk factor for dementia: A systematic review and meta-analysis. BMC Geriatr. 2017; 17: 16.

40. Gezen-Ak D, Yilmazer S, Dursun E. Why vitamin D in alzheimer's disease? The hypothesis. J Alzheimers Dis. 2014; 40: 257-269.

41. Prajapati, Purohit, Sharma, Kumar N. A Handbook of medicinal plants complete source book, Agrobios Publication .prediction. Community Genet. 2003; 4: 197-203.

42. Wasik, J. Consumer's digest. 1999; 75-79.

43. Song CM, Vandewoude W, Stevens L, De Clerck, M Planken, et al. Psychiatry Res. 1999; 85: 71-80.

44. Chatterji N, RP Rastorgi, Dhar ML. Indian J. Chem. 1963; 1: 212.

45. Deshmukh AA, Gajare KA, Pillai MM. J. Cell Tissue Res. 2006; 6: 647-650.

46. Vinutha B, D Prashanth, Salma K, Sreeja SL, Pratiti D, et al. J. Ethnopharmacol. 2007; 109: 359-363.

47. Dhuley JN. Phytotherapy Res. 2001, 15: 524-528.

48. Trigunayat A, M Raghavendra, Singh RK, Bhattacharya AK, Acharya SB. J. Nat. Rem. 2007; 7: 234-246.

49. Schliebs R, A Libemann, Bhttacharya SK, Kumar A, Ghosal S. Neuro Chem. Int. 1997; 30: 181-190 .

50. Veerendra Kumar MH, YK Gupta. J. Ethnopha- rmacol. 2002; 79: 253-260.

51. Geőcze KC, LC A Barbosa, PH Fidêncio. "Essential oils from pequi fruits from the Brazilian Cerrado ecosystem," Food Research International. 2013; 54: 1-8.

52. CA Breda, AM Gasperini, VL Garcia, KM Maia Monteiro, GA Bataglion, et al., "Phytochemical analysis and antifungal activity of extracts from leaves and fruit residues of Brazilian savanna plants aiming its use as safe fungicides," Natural Products and Bioprospecting. 2016; 6: 195-204.

53. Oliveira LM, de AG Rodrigues, EF da Silva. "Endo- thelium-dependent vasorelaxant effect of butanolic fraction from Caryocar brasiliense Camb. leaves in rat thoracic aorta," Evidence-based Complementary and Alternative Medicine. 2012; 2012: 9.

54. Leão DP, AS Franca, LS Oliveira, R Bastos, MA Coimbra. "Physico-chemical characterization, antioxi- dant capacity, total phenolic and proanthocyanidin content of flours prepared from pequi (Caryocar brasilense Camb.) fruit by-products," Food Chemistry. 2017; 225: 146-153.

55. Goes A, Jesse CR, Antunes MS, Lobo Ladd FV, Lobo Ladd A, et al. Protective role of chrysin on 6-hydroxydopamine-induced neurodegeneration a mouse model of Parkinson's disease: Involvement of neuroinflammation and neurotrophins. Chemico-biological interactions. 2018; 279: 111-120.

56. Guo B, Zheng C, Cai W, Cheng J, Wang H, et al. Multifunction of Chrysin in Parkinson's Model: Anti-Neuronal Apoptosis, Neuroprotection via Activation of MEF2D, and Inhibition of Monoamine Oxidase-B. Journal of agricultural and food chemistry. 2016; 64: 5324-5333.

57. Krishnamoorthy A, Sevanan M, Mani S, Balu M, Balaji S, PR 2019. Chrysin restores MPTP induced neuroinflammation, oxidative stress and neurotrophic factors in an acute Parkinson's disease mouse model. Neuroscience letters. 2019; 709: 134382.

58. Yan X, Liu DF, Zhang XY, Liu D, Xu SY, et al. Vanillin Protects Dopaminergic Neurons against Inflammation-Mediated Cell Death by Inhibiting ERK1/2, P38 and the NF-κB Signaling Pathway. International journal of molecular sciences. 2017; 18: 389.

59. Dhanalakshmi C, Janakiraman U, Manivasagam T, Justin Thenmozhi A, Essa MM, et al. Vanillin Attenuated Behavioural Impairments, Neurochemical Deficts, Oxidative Stress and Apoptosis Against Rotenone Induced Rat Model of Parkinson's Disease. Neurochemical research. 2016; 41: 1899-1910.

60. Chao PC, Lee HL, Yin MC. Asiatic acid attenuated apoptotic and inflammatory stress in the striatum of MPTP-treated mice. Food & function. 2016; 7: 1999-2005.

61. Nataraj J, Manivasagam T, Justin Thenmozhi A, Essa MM. Neurotrophic Effect of Asiatic acid, a Triterpene of Centella asiatica Against Chronic 1-Methyl 4-Phenyl 1, 2, 3, 6-Tetrahydropyridine Hydrochloride/Probenecid Mouse Model of Parkinson's disease: The Role of MAPK, PI3K-Akt-GSK3β and mTOR Signalling Pathways. Neurochemical research. 2017; 42: 1354-1365.

62. Anis E, Zafeer MF, Firdaus F, Islam SN, Anees Khan A, et al. Ferulic acid reinstates mitochondrial dynamics through PGC1α expression modulation in 6-hydroxydopamine lesioned rats. Phytotherapy research: PTR. 2020; 34: 214-226.

63. Askar MH, Hussein AM, Al-Basiony SF, Meseha RK, Metias EF, et al. Effects of Exercise and Ferulic Acid on Alpha Synuclein and Neuroprotective Heat Shock Protein 70 in An Experimental Model of Parkinsonism Disease. CNS & neurological disorders drug targets. 2019; 18: 156-169.

64. Li X, Zhang J, Rong H, Zhang X, Dong M. Ferulic Acid Ameliorates MPP+/MPTP-Induced Oxidative Stress via ERK1/2-Dependent Nrf2 Activation: Translational Implications for Parkinson Disease Treatment. Molecular neurobiology. 2020; 57: 2981-2995.

65. Ardah MT, Merghani MM, Haque ME. Thymoquinone prevents neurodegeneration against MPTP in vivo and modulates α-synuclein aggregation in vitro. Neurochemistry international. 2019; 128, 115-126.

66. Ebrahimi SS, Oryan S, Izadpanah E, Hassanzadeh K. Thymoquinone exerts neuroprotective effect in animal model of Parkinson's disease. Toxicology letters. 2017; 276, 108-114.

67. Sedaghat R, Roghani M, Khalili M. Neuroprotective effect of thymoquinone, the nigella sativa bioactive compound, in 6-hydroxydopamine-induced hemi-parkinsonian rat model. Iranian journal of pharmaceutical research: IJPR. 2014; 13: 227-234.

68. Sarkaki A, Farbood Y, Dolatshahi M, Mansouri SM, Khodadadi A. Neuroprotective Effects of Ellagic Acid in a Rat Model of Parkinson's Disease. Acta medica Iranica. 2016; 54: 494-502.

69. Baluchnejadmojarad T, Rabiee N, Zabihnejad S, Roghani M. Ellagic acid exerts protective effect in intrastriatal 6-hydroxydopamine rat model of Parkinson's disease: Possible involvement of ERβ/Nrf2/HO-1 signaling. Brain research. 2017; 1662: 23-30.

70. Dos Santos Nunes RG, Pereira PS, Elekofehinti OO, Fidelis KR, et al. Possible involvement of transcriptional activation of nuclear factor erythroid 2-related factor 2 (Nrf2) in the protective effect of caffeic acid on paraquat-induced oxidative damage in Drosophila melanogaster. Pesticide biochemistry and physiology. 2019; 157: 161-168.

71. Zhang Y, Wu Q, Zhang L, Wang Q, Yang Z, et al. Caffeic acid reduces A53T α-synuclein by activating JNK/Bcl-2-mediated autophagy in vitro and improves behaviour and protects dopaminergic neurons in a mouse model of Parkinson's disease. Pharmacological research. 2019; 150, 104538.

72. Tsai SJ, Chao CY, Yin MC. Preventive and therapeutic effects of caffeic acid against inflammatory injury in striatum of MPTP-treated mice. European journal of pharmacology. 2011; 670: 441-447.

73. Xu Q, Langley M, Kanthasamy AG, Reddy MB. Epigallocatechin Gallate Has a Neurorescue Effect in a Mouse Model of Parkinson Disease. The Journal of nutrition. 2017; 147: 1926-1931.

74. Zhou T, Zhu M, Liang Z. 2018. (-)-Epigallocatechin-3-gallate modulates peripheral immunity in the MPTP-induced mouse model of Parkinson's disease. Molecular medicine reports. 2018; 17: 4883-4888.

75. Xu Y, Zhang Y, Quan Z, Wong W, Guo J, et al. Epigallocatechin Gallate (EGCG) Inhibits Alpha-Synuclein Aggregation: A Potential Agent for Parkinson's Disease. Neurochemical research. 2016; 41: 2788-2796.

76. Kim BW, Koppula S, Kumar H, Park JY, Kim IW, et al. α-Asarone attenuates microglia-mediated neuroinflammation by inhibiting NF kappa B activation and mitigates MPTP-induced behavioral deficits in a mouse model of Parkinson's disease. Neuropharmacology. 2015; 97: 46-57.

77. Zhang S, Gui XH, Huang LP, Deng MZ, Fang RM, et al. Neuroprotective Effects of β-Asarone Against 6-Hydroxy Dopamine-Induced Parkinsonism via JNK/Bcl-2/Beclin-1 Pathway. Molecular neurobiology. 2016; 53: 83-94.

78. Ning B, Deng M, Zhang Q, Wang N, Fang Y. β-Asarone Inhibits IRE1/XBP1 Endoplasmic Reticulum Stress Pathway in 6-OHDA-Induced Parkinsonian Rats. Neurochemical research. 2016; 41: 2097-2101.

79. Anandhan A, Janakiraman U, Manivasagam T. Theaflavin ameliorates behavioral deficits, biochemical indices and monoamine transporters expression against subacute 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP)-induced mouse model of Parkinson's disease. Neuroscience. 2012; 218: 257-267.

80. Anandhan A, Tamilselvam K, Radhiga T, Rao S, Essa MM, et al. Theaflavin, a black tea polyphenol, protects nigral dopaminergic neurons against chronic MPTP/probenecid induced Parkinson's disease. Brain research. 2012; 1433: 104-113.

81. Anandhan A, Essa MM, Manivasagam T. Therapeutic attenuation of neuroinflammation and apoptosis by black tea theaflavin in chronic MPTP/probenecid model of Parkinson's disease. Neurotoxicity research. 2013. 23: 166-173.

82. Dey A, Bhattacharya R, Mukherjee A, Pandey DK. Natural products against Alzheimer's disease: Pharmaco-therapeutics and

biotechnological interventions. Biotechnology advances. 2017; 35: 178-216.

83. Dey A, Bhattacharya R, Mukherjee A, Pandey DK. Natural products against Alzheimer's disease: Pharmaco-therapeutics and biotechnological interventions. Biotechnology advances. 2017; 35: 178-216.

84. Santos G, Giraldez-Alvarez LD, Ávila-Rodriguez M, Capani F, Galembeck E, et al. SUR1 Receptor Interaction with Hesperidin and Linarin Predicts Possible Mechanisms of Action of Valeriana officinalis in Parkinson. Frontiers in aging neuroscience. 2016; 8: 97.

85. Kaufmann D, Kaur Dogra A, Tahrani A, Herrmann F, Wink M. Extracts from Traditional Chinese Medicinal Plants Inhibit Acetylcholinesterase, a Known Alzheimer's Disease Target. Molecules (Basel, Switzerland). 2016; 21: 1161.

86. Zanforlin E, Zagotto G, Ribaudo G. The Medicinal Chemistry of Natural and Semisynthetic Compounds against Parkinson's and Huntington's Diseases. ACS chemical neuroscience. 2017; 8: 2356-2368.

87. Kim MH, Kim SH, Yang WM. Mechanisms of action of phytochemicals from medicinal herbs in the treatment of Alzheimer's disease. Planta medica. 2014; 80: 1249-1258.

88. Zang CX, Bao XQ, Li L, Yang HY, Wang L, et al. The Protective Effects of Gardenia jasminoides (Fructus Gardenia) on Amyloid-β-Induced Mouse Cognitive Impairment and Neurotoxicity. The American journal of Chinese medicine. 2018; 46: 389-405.

89. Finley JW, Gao S. A Perspective on Crocus sativus L. (Saffron) Constituent Crocin: A Potent Water-Soluble Antioxidant and Potential Therapy for Alzheimer's Disease. Journal of agricultural and food chemistry. 2017; 65: 1005-1020.

90. Larit F, Elokely KM, Chaurasiya ND, Benyahia S, Nael MA, et al. Inhibition of human monoamine oxidase A and B by flavonoids isolated from two Algerian medicinal plants. Phytomedicine: international journal of phytotherapy and phytopharmacology. 2018; 40: 27-36.

91. Carmona V, Martín-Aragón S, Goldberg J, Schubert D, Bermejo-Bescós P. Several targets involved in Alzheimer's disease amyloidogenesis are affected by morin and isoquercitrin. Nutritional neuroscience. 2020; 23: 575-590.

92. Sabogal-Guáqueta AM, Osorio E, Cardona-Gómez GP. Linalool reverses neuropathological and behavioral impairments in old triple transgenic Alzheimer's mice. Neuropharmacology. 2016; 102: 111-120.

93. El Alaoui C, Chemin J, Fechtali T, Lory P. Modulation of T-type Ca2+ channels by Lavender and Rosemary extracts. PloS one. 2017; 12: e0186864.

94. Shal B, Ding W, Ali H, Kim YS, Khan S. Anti-neuroinflammatory Potential of Natural Products in Attenuation of Alzheimer's Disease. Frontiers in pharmacology. 2018; 9: 548.

95. Hussain G, Zhang L, Rasul A, Anwar H, Sohail MU, et al. Role of Plant-Derived Flavonoids and Their Mechanism in Attenuation of Alzheimer's and Parkinson's Diseases: An Update of Recent Data. Molecules (Basel, Switzerland). 2018; 23: 814.

96. Elufioye TO, Berida TI, Habtemariam S. Plants-Derived Neuroprotective Agents: Cutting the Cycle of Cell Death through Multiple Mechanisms. Evidence-based complementary and alternative medicine: eCAM. 2017; 3574012.

97. Zhang J, Zhang R, Zhan Z, Li X, Zhou F, et al. Beneficial Effects of Sulforaphane Treatment in Alzheimer's Disease May Be Mediated through Reduced HDAC1/3 and Increased P75NTR Expression. Frontiers in aging neuroscience. 2017; 9: 121.

98. Ngoungoure VL, Schluesener J, Moundipa PF, Schluesener H. Natural polyphenols binding to amyloid: a broad class of compounds to treat different human amyloid diseases. Molecular nutrition & food research. 2015; 59: 8-20.

99. Xu J, Lacoske MH, Theodorakis EA. Neurotrophic natural products: chemistry and biology. Angewandte Chemie (International ed. in English). 2014; 53: 956-987.

100. Dar NJ, Hamid A, Ahmad M. Pharmacologic overview of Withania somnifera, the Indian Ginseng. Cellular and molecular life sciences: CMLS. 2015; 72: 4445-4460.

101. Janhom P, Dharmasaroja P. Neuroprotective Effects of Alpha-Mangostin on MPP (+)-Induced Apoptotic Cell Death in Neuroblastoma SH-SY5Y Cells. Journal of toxicology. 2015; 919058.

102. Yan L, Zhou QH. 2012. Study on neuroprotective effects of astragalan in rats with ischemic brain injury and its mechanisms. Chinese journal of applied physiology. 2012; 28: 373-377.

103. Jiang W, Wei W, Gaertig MA, Li S, Li XJ. Therapeutic Effect of Berberine on Huntington's Disease Transgenic Mouse Model. PloS one. 2015; 10: e0134142.

104. Cleren C, Calingasan NY, Chen J, Beal MF. Celastrol protects against MPTP- and 3-nitropropionic acid-induced neurotoxicity. Journal of neurochemistry. 2005; 94: 995-1004.

105. Chopra K, Tiwari V, Arora V, Kuhad A. Sesamol suppresses neuroinflammatory cascade in experimental model of diabetic neuropathy. The journal of pain. 2010; 11: 950-957.

106. Lam PY, Ko KM. Beneficial effect of (-)schisandrin B against 3-nitropropionic acid-induced cell death in PC12 cells. BioFactors (Oxford, England). 2012; 38: 219-225.

107. PA Senyah. 2018. Anti-hyperglycaemic and anti-oxidant effect of Synedrella nodiflora (L) gaertn in streptozotocin-induced diabetes in rats, World J. Gastroenterol. 19, 6416.

108. Rong W, Wang J, Liu X, Jiang L, Wei F, et al. Naringin treatment improves functional recovery by increasing BDNF and VEGF expression, inhibiting neuronal apoptosis after spinal cord injury. Neurochemical research. 2012; 37: 1615-1623.

109. Sandhir R, Mehrotra A. Quercetin supplementation is effective in improving mitochondrial dysfunctions induced by 3-nitropropionic acid: implications in Huntington's disease. Biochimica et biophysica acta. 2013; 1832: 421-430.

110. Lagoa R, Lopez-Sanchez C, Samhan-Arias AK, Gañan CM, Garcia-Martinez V, et al. Kaempferol protects against rat striatal degeneration induced by 3-nitropropionic acid. Journal of neurochemistry. 2009; 111: 473-487.

111. Lian XY, Zhang Z, Stringer JL. Protective effects of ginseng components in a rodent model of neurodegeneration. Annals of neurology. 2005; 57: 642-648.

112. Verma S, Sinha R, Kumar P, Amin F, Jain J, Tanwar S. Study of Convolvulus pluricaulis for antioxidant and anticonvulsant activity. Central nervous system agents in medicinal chemistry. 2012; 12: 55-59.

113. Biessels GJ, F Despa. Cognitive decline and demen- tia in diabetes mellitus: Mechanisms and clinical implica- tions. Nat Rev Endocrinol. 2018; 14: 591-604.

114. Nield D. Controlling brain inflammation could slow down the progress of alzheimer's, scientists find. Science alert. 2016.

115. Pihlaja RJ, Koistinaho Malm T, Sikkila H, Vainio S. Transplanted astrocytes internalize deposited beta-amyloid peptides in a transgenic mouse model of alzheimer's disease. Glia. 2008; 56: 154-163.

116. Blurton-Jones MM, Kitazawa Martinez-Coria H, Castello NA, Muller FJ. Neural stem cells improve cognition via BDNF in a transgenic model of alzheimer disease. Proc Natl Acad Sci USA. 2009; 106: 13594-13599.

117. Stahl SM. Essential Psychopharmacology, Cambridge University Press. 1998.