Journal of Young Pharmacists, 2023; 15(2):194-200.
https://www.jyoungpharm.org

Review Article

Medicinal Plants and Herbal Formulations Ameliorating Neurodegeneration: Remedies Combating Parkinson's and Alzheimer's Disease

Kumar Abhishek[1], Rai Saksham[2], Katiyar Deepti[3], Rao NGR[4], Prakash Surya[5], Kumar Vinay[1], Saxena Vidhu[1], Bansal Priya[1,*]

KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, Uttar Pradesh, INDIA.

ABSTRACT

Neuronal degeneration, characterized by progressive and irreversible loss of structure and function of neurons, could be a physiological age related or pathological intervention resulting in death of neuronal tissues. Neurodegenerative disease (ND) like Parkinson's Disease (PD) and Alziemer's Diseases (AD) aving molecular complexity in pathogenesis resulting in prominent loss of normal physiology of an individual. Practically, ND are incurable but by therapeutic approaches the loss of neurons and progress of disease is controlled but these drugs are associated with many unwanted effects. Herbals have been used from ancient times and referred to as conventional treatment methods to treat neurodegenerative disease having natural healing power and less side effects. Phytochemicals like Alkaloids, terpenes, saponins, phenols, flavonoids, etc. have major mechanisms behind management of most of the ND. In this review we briefly discussed some medicinal plants which have neuroprotective activities against ND specially AD and PD along with its mechanism of actions behind their pharmacological activities. Some herbal formulations used as traditional medicines to treat neurodegenerative disease worldwide are also briefly discussed.

Keywords: Neurodegenerative disease, Phytochemicals, Traditional Medicine, Herbals.

Correspondence:
Mrs. Priya Bansal
Assistant Professor, Division of Pharmacology, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad-201206, Uttar Pradesh, INDIA.
Email id: bansalpriya23@gmail.com

Received: 19-09-2022;
Revised: 29-11-2022;
Accepted: 20-12-2022.

INTRODUCTION

Neurodegenerartion comprises a group of diseases of major research interest but still is having increasing prevalence and mostly are practically incurable. Researchers revealed various complicated genetic and cellular mechanisms exploring the role of various protein and pathways involved like damage of dopaminergic neurons in Parkinson's Disease (PD), cellular pathophysiologies and cognitive changes in Alzheimer's Disease (AD), amyotrophic lateral sclerosis, Huntington's disease (HD), frontotemporal dementia and the spinocerebellar ataxias.[1] These insights proposed opportunities for development of more treatment approaches. Early origin with slow and non-symptomatic progression, involvement of different factors from exogenous (environmental) to endogenous (familial, genetic, mitochondrial, protein accumulation) in neurodegenerative diseases (ND) restricts their treatment approaches upto only palliative cares but none are capable enough to prevent or revert the neuronal degeneration.[2] Hence, the early therapeutic approaches should be intended to restrict the primary factors responsible for disease progression. The present therapeutic interventions are associated with limited symptomatic efficacy with major side effects.

Different ND affect variable functioning of individuals in mild to severe impairment of mobility, speech (dysarthria), cognition, memory (dementia) and even breath. Parkinsonism is symbolized by damage of neurons which release dopamine as a neurotransmitter which finally affects motor coordination. Molecular to cellular changes like oxidative strain, abnormal folding at some stage in synthesis of protein, defect in functioning of mitochondria, damage of neurons due to overexcitations by numerous biochemical biochemical reactions and mutilation of lysosome leads to progression of disease resulting in partial tremors and stiffness to severe impaired balance and coordination of muscles.[3] Similar to PD, AD is also an age related progressiveand irreversible neurodegenerative disorder that may lead to impaired intellectual skills and loss of memory. Changes in microRNA expression, mutation in precursor of amyloid protein, neurofibrillary tangle construction enclosing β-amyloid and phosphorylated tau proteins and plaque are few of the morbid circumstances involved in AD.[4] Furthermore, genetic mutation in chromosome 4 resulted in HD characterized by movement

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DOI: 10.5530/jyp.2023.15.28

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Table 1: Medicinal Plants against ND.

Sl. No.	Name of Plant	Family	Animal/ Cell Line used	Possible MOA	References
1	*Rosmarinus officinalis*	Lamiaceae	SH-SY5Y (human dopaminergic cell line)	Inhibition of apoptotic genes (Bax, Bak, Caspase-3 and -9) Increase Bcl-2 expression, and catecholamines [tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC)] expressions in human dopaminergiccells, SH-SY5Y.	9
				Carnosic acid acts through upregulation of Parkin protein.	10
				Modulation of PI3K / Akt Pathway, Activation of Nrf2,	11
			Rat	Improve long term memory by inhibition of AChE activity in brain.	12
			Rat	Anti-apoptotic and Anti-oxidative action.	13
2	*Baccopa monnieri*	Scrophulariaceae	Mice	Modulation of oxidation stress and apoptotic machinery (reduced apoptotic genes (Bax and caspase-3) and increased levels of anti-apoptotic (Bcl2) protein expression).	14
			Rat	Anti-apoptotic and Anti-oxidative action.	15
3	*Mucuna pruriens* (L.)	Fabaceae	Mice	Modulation of NF-kB and Akt pathway.	16
4	*Glycyrrhiza glabra*	Leguminosae	Mice	Facilitation of cholinergic-transmission in mouse brain.	20
			B65 neuroblastoma cells	Increasing the protein expression level of glucose-6 phosphate dehydrogenase.	21
5	*Withania somnifera*	Solanaceae	Mice	Antioxidant properties.	22
			Mice	Reduce the level of oxidative stress and protect dopaminergic neurodegeneration which is exhibited by increase in TH positive cells in SN region of brain.	23
			Rat	Inhibition of AChE, modification of Aβ processing, protection against oxidative stress and anti-inflammatory effects.	25
6	*Zingiber officinale*	Zingeberaceae	Mice	Nerve growth factor (NGF) – induced ERK/ SERB activation.	26
			Mice	Increasing systemic superoxide dismutase activity.	27
			Primary microglial cell cultures.	Antioxidant and Anti-inflammatory activity.	28-30
7	*Hypericum perforatum*	Hypericaceae	Rat	Antioxidant and Anti-inflammatory activity.	29
			Rat	Antioxidant, anti-inflammatory activity, antiapoptotic and potentiation of antioxiadantdefence system.	30-31

Sl. No.	Name of Plant	Family	Animal/ Cell Line used	Possible MOA	References
8	*Centella asiatica*	Apiaceae	Rat	Protection of mitochondrial complex I activity, antioxidants activity and increase in antioxidant enzyme expression.	32
			PC12 and IMR32 cells	Modulation of the antioxidative defense system in cells, including the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and levels of glutathione and glutathione disulfide by CAE.	33-34
9	*Polygala tenuifolia*	Polygalaceae	5xFAD (Tg) mice	Alleviating cognitive impairment and Reduces amyloid plaque deposition.	35-36
10	*Crocus sativus*	Iridaceae	Merioneshawi	Antioxidant power, particularly an anti-radical activity and a metal reducing activity.	37
			Mice	Antioxidant Property and improve reminiscence activity.	38
11	*Nardostachysa jatamansi*	Valerianaceae	Mice	Anti-oxidant property.	39
			Drasophilla	Anti-oxidant, Anti-inflammatory property and Inhibitory action against extracellular signal regulated kinase (ERK) signaling.	40
12	*Ginkgo biloba*	Ginkgoaceae	Sprague-Dawley Rats	Anti-oxidant property.	41
			Wistar rats	Anti-oxidant and Anti-apoptosis property.	42
			Wistar rats	Reduction in oxidative damage and increase in BDNF level.	43
13	*Curcuma longa*	Zingiberaceae	Swiss albino male mice	Anti-oxidant property.	44
			5XFAD Mice	Anti-oxidant, Anti-inflammatory property.	45
14	*Cassia obtusifolia*	Leguminosae	Acute mouse hippochampal cells	Anti-inflammatory and it weekend Aβ –induced microglia, cyclooxygenase activation and inducible NO synthase.	46
			Mice	Anti-oxidant and Anti-apoptosis.	48
			Human SK-N-SH cells	Inhibition of ROS production, lipid peroxidation, paraquat- induced apoptosis and DNA damage.	49
15	*Magnolia officinalis*	Magnoliaceae	Rats PC12 Cells	Reduced ROS production, intracellular Calcium level and inhibition of caspase-3 activity.	50
			C57BL/6N mice and human SH-SY5Y cells	Decreased ROS production in human SH-SY5Y cells and prevented the lipid peroxidation in striatum in mice.	51

Table 2: Polyherbal Formulations against ND.

Sl. No.	Formulation Name	Composition	References
1	KCHO-1	Roots of *Nardostachys jatamansi, Crocus sativus* L, Selenium.	52
2	TRASINA	*Withania somnifera, Ocimum sanctum, Eclipta alba, Tinospora cordifolia, Picrorrhiza kurroa*, and shilajit.	53
3	BR-16A (Mentat)	Brahmi, Ashvagandha, Vacha, Shatavari, Amla, Shankhapushpi and Triphala.	54
4	NCSe	*Nardosatchys jatamansi*, crocetin and selenium as sodium selenite.	55
5	Saraswatharishtam	*Acorus calamus, Operculina ipomoea, Saussurea lappa, Bacopa moniera, Anethum sowa, Piper longum, Zingiber officinale, Syzygium aromaticum, Terminalia chebula, Terminalia embelica, Asparagus racemosus, Terminalia belerica, Pueraria tuberosa, Elettaria cardmomum, Cinamomum zeylanicum, Withania somnifera, Tinospora cordifolia*, Pure metallic gold.	56
6	Polyherbal Vati	*Commiphora wightii, Aloe barbadensis, Boswellia serrata, Hemidesmus indicus, Zingiber officinale, Withania somnifera*,*Berberis aristata* and *Cucurma longa*.	57
7	Abana	*Withania somnifera, Tinospora cordifolia, Terminalia arjuna, Phyllanthus emblica, Nepeta hindostana*, Dashamoola, *Terminalia chebula, Nardostachys jatamansi.*	58
8	Polyherbal formulation	Mucuna pruriens, *Withania somnifera, Evolvulus alsinoides, Rauwolfia serpentena, Hyoscyamus niger, Emblica officinalis, Mineral resin*, pearl, *Asparagus racemosus, Nardostachys jatamansi* and coral calcium.	59
9	US7,273,626 B2 Polyherbal formulations	*Hippophae rhamnoides, Dioscorea bulbifera* and *Bacopa monnieri.*	60

disorder, regular failure of nerve cells, dystonia and chorea, motor ataxia, psychiatric diseases and cognitive decline.[5,6]

In the last few decades, usage of herbal-based medicine againstND has attracted considerable attention from researchers and clinicians. The Conventional medication which finds its basis in the ancient practice and principles has become very famous because of the fewer adverse reactions, potency in opposition to various human ailments, less expensive and effortless accessibility. Herbal drugs have for eternity offered imperative leads alongside numerous ailments such as AD, malaria and Acquired Immunodeficiency Syndrome. Quite a lot of herbal drugs are available commercially and are under the final stage of clinical trial.[5,7] Herbals and herbal formulations evident to be effective but less potent therapeutic options. Many natural products with promising antioxidant potentials are reported to have neuroprotective efficacy as well as few are reported to stimulate neuronal regeneration.[8] Identifying the key role of reactive oxygen species (ROS) and other free radicals, herbal secondary metabolites like flavonoids and other polyphenolic molecules effectively scavenge the neuronal damage and promote regeneration.[2] Challenges in efficacy, extraction, safety, administration, toxicity, tolerability etc. discourage the use of these effective herbals and their formulations and need further investigations. Table 1 summarizes and explains various herbals and their formulations which are studied extensively to be used against detrimental neuronal disorders like PD and AD. Various medicinal plants, mono- and polyherbal formulations investigated earlier with promising neuroprotective efficacy against different ND are discussed in this review. This will give an insight towards the use of herbals for ND.

Medicinal plants against neurodegeneration

From literature the authors have identified several herbs which showed protective effects in various research studies for neurodegenerative diseases. The authors tried to summarize the details of the research studies on the basis of possible mechanisms and animals used in experiments in tabular form (Table 2).

Polyherbal formulations for neurodegeneration

KCHO-1

A polyherbal formulation containing *Curcuma longa*, *Gastrodia elata, Salvia miltiorrhiza*, *Chaenomeles sinensis*, *Paeonia japonica, Polygala tenuifolia, Glycyrrhiza uralensis*, *Aconitum carmichaeli* and *Atractylodes japonica*is reported to reduce glutamate and hydrogen peroxide induced cell damage, increase mRNA and protein expression levels of heme oxygenase (HO)-. KCHO-1 remarkably upregulates nuclear factor erythroid-derived 2-related factor-2 (Nrf2) nuclear translocation. The possible

mechanism behind the KCHO-1 effect may be Nrf2/ERK mitogen-activated protein kinase-dependent HO-1 expression. So it may be concluded that KCHO-1 may be beneficial for the management of neurodegenerative disorders.[52]

Trasina

A polyherbal formulation known as Medhyarasayanas or drugs used to ameliorate remembrance and intelligence mainly consist of *Withania somnifera, Ocimum sanctum, Eclipta alba, Tinospora cordifolia, Picrorrhiza kurroa* and Shilajit. The study revealed that after 14 and 21 days treatment with 200 and 500 mg/kg dose of Trasina, it increases Ach concentration in frontal cortical and hippocampal region, ChAT activity and MCR (Muscarinic cholinergic receptor) binding which was decreased due to colchicine treatment. The formulation mainly produces memory improvement by altering the deficient cholinergic function.[53]

BR-16A (Mentat)

A polyherbal composition consists of various indigenous herbs important for improvement of various intellect based disorders and also important herbs of Ayurvedic system of medicines. It is composed of 7 herbs that mainly include-Brahmi (*Hydrocotyl asiatica*), Vacha (*Acoruscalamus*), Ashvagandha (*Withania somnifera*), Shatavari (*Asparagus racemosus*), Shankhapushpi (*Evolvulus alsinoides*), Amla (*Emblica officinalis*) and Triphala. Kulkarni *et al*., concluded that inverse colchicine and ibotenic acid induced cognitive impairment and scopolamine induced memory declension in Alzheimer animal models.[54]

NCSe

The study revealed that combined pretreatment with extracts of *Nardosatchysj atamansi* (N), crocetin (C) and selenium (Se) as sodium selenite ((N, 200 mg/kg + C, 25 µg/kg + Se, 0.05 mg/kg body weight) for 15 days show amended behavioural changes in streptozotocin (STZ)-induced cognitive mutilation in rats. The possible mechanism of action behind the neuroprotective effect may be by remarkably decreasing the TBARS levels and raise the concentration of glutathione and by improving the action of antioxidant enzyme like glutathione peroxidase, catalase and glutathione-S-transferase.[55]

Saraswatharishtam

An ayurvedic formulation named as Saraswatharishtam (SWRT) mainly used to treat neuropsychiatric and neurodegenerative diseases like slurred speech, partial memory loss, Alzheimer's disease, Parkinson disease etc. It contains *Acorus calamus*, *Operculina ipomoea*, *Saussurea lappa*, *Bacopa monnieri*, *Anethum sowa*, *Piper longum*, *Zingiber officinale*, *Syzygium aromaticum, Terminalia chebula, Terminalia emblica*, *Asparagus racemosus*, *Terminalia belerica*, *Pueraria tuberosa*, *Elettaria cardamomum*, *Cinnamomum zeylanicum*, *Withania somnifera*, *Tinospora cordifolia*, pure metallic gold. SWRT significantly reversed the loss of memory in Adult Wistar Swiss albino mice observed by elevated rectangular maze, plus maze and radial maze experiments. The protective effect of SWRT is based on antioxidant property.[56]

Polyherbal formulation (Vati)

Vati is a polyherbal formulation consisting of various herbs having proved anti-inflammatory and antioxidant activities. It mainly includes *Commiphora wightii*, *Boswellia serrata*, *Aloe barbadensis*, *Zingiber officinale*, *Hemidesmus indicus*, *Berberis aristata*, *Withania sominifera* and *Cucurma longa*. Vati at a dose of 3.125 µg/mL of Vaati shows good for anti-inflammatory activity on RAW264.7 cell lines. Numerous processes like DPPH, ABTS, cell culture and various protein assays were performed to assess anti-inflammatory and antioxidant activity of formulation and the positive result confirms that it can be used for inflammation and free radical scavenging activity.[57]

Abana

Abana, an ayurvedic herbomineral formulation (mainly include *Withania somnifera*, *Tinospora cordifolia*, *Terminalia arjuna*, *Phyllanthus emblica*, *Nepeta hindostana*, Dashamoola, *Terminalia chebula*, *Nardostachys jatamansi*e) significantly improve remembrance in youthful and elderly mice in a dose dependent manner (50, 100 and 200 mg/kg, orally). The mechanism of action behind memory enhancing activity of Abana formulation might be an increase in the level of acetylcholine via significant reduction in acetyl cholinesterase activity.[58]

Poly herbal formulation

An Indian polyherbal formulation (PHF) consist of *Mucuna pruriens*, *Withania somnifera*, *Evolvulus alsinoides*, *Rauwolfia serpentina*, *Hyoscyamus niger*, *Emblica officinalis*, Mineral resin, pearl, *Asparagus racemosus*, *Nardostachys jatamansi* and coral calcium have been reported to have neuropsychopharmacological effect on the memory and learning process in rats. The formulations treated animals exhibits significant diminution in transfer latency contrasted to control group in elevated plus maze model (EPM). The significant recovery in passive avoidance acquisition as well as memory retrieval in animals (rats) was produced by PHF. The effect may be due to involvement of a cholinergic mechanism or due to inhibition of GABA receptors which improves short memory in rats.[59]

US7,273,626 B2 polyherbal formulations

The U.S patented polyherbal formulation US7,273,626 B2 consists of *Hippophae rhamnoides, Dioscorea bulbifera* and *Bacopa monnieri* extracts. Following quotidian administration of formulation along with scopolamine for 14 days in rats, it was observed that the formulation is effective in reducing the effect of scopolamine in AD. Moreover, formulation was found to be effective in restraining scopolamine produced reduction

in acetylcholine level, augmented AChE level and reduced antioxidant enzymes activity.[60]

Future aspects

Neuroactive potentials have been found in plants from the Fabaceae, Apocynaceae, Solanaceae, Euphorbiaceae and Asteraceae families. These plant groups have the potential to be a major natural supply for future anti-neurodegenerative medication development, as well as their metabolites, should be focused. These medicinal plant's neuroprotective actions may have the capacity to suppress NO synthesis and overexpression. The expression of reactive oxygen species (ROS) in neuronal cells makes them prone to harm from oxygen free radicals. Hydroxyl groups, Peroxides and reactive oxygen and nitrogen clusters, for example, might rise substantially in cerebral ischemia or even neurotoxicity. Moreover hyper-dopaminergic stimulation may have a role in the pathophysiology and mechanism of psychotic episodes. The reported therapeutic characteristics are generally the consequence of synergistic actions of numerous chemicals, making it difficult to link the pharmacological properties of a plant/or plant extract to a single component or class of chemicals. On a variety of objectives Apigenin, curcumin, crocin, and EGCG are only a few of these chemicals. Hesperidin, Ginsenosides, resveratrol, linalool, rosmarinic acid, quercetin, and with anolides are all either ginsenosides, linalool, hesperidin, resveratrol, quercetin, rosmarinic acid, or with anolides. Prevalent in many species of plants, present in indigenous herbal species, and/or found in herbs, fruits and spices are examples of food sources. A key factor that limits the treatment potential of these natural substances for NDD is their toxicity. Their low absorption makes therapy difficult. Curcumin, for example, is a polyphenol that has been shown to have health benefits. Effects in the treatment of Alzheimer's disease, but with limited absorption and bioavailability. To make it bigger bioavailability, tolerance to metabolic processes, and transit through the blood-brain barrier are all factors to consider. New pharmaceutical techniques, such as liposomal microencapsulation and polymeric delivery, are required. Nanoparticles (nanocurcumin), cyclodextrins, nano-suspensions, and nano-emulsions are all examples of micelles. Furthermore, secondary metabolites have additional features, such as metabolism and the potential to traverse the blood-brain barrier. the blood-brain barrier, the dose needed for favourable benefits in people without causing toxicity, and There are additional crucial considerations to consider, such as combinations with existing drugs. Long-term studies are required. It can be inferred that plant secondary metabolites provide a beneficial effect.

CONCLUSION

Neurodegenerative diseases are chronic and incurable conditions that mainly result in loss of neurons characterized by severe oxidative stress and inflammation. The pervasiveness of ND, mainly PD&AD continues to revolt worldwide. Till date no cure is available for ND and the drugs which are used for symptomatic treatment cause various side effects and high monetary value to the patients. Nowadays, scientists are having an eye on herbal drugs as an alternative treatment option for ND to reduce side effects. The major drawback in the use of herbs are limited information available on metabolism, pharmacokinetics, low bioavailability in brain and any other effect which can cause change in the brain central region. This paper mainly summarizes some important medicinal plants and their formulations which are pharmacologically proven effective in the treatment of ND mainly PD&AD. These plants are evident to delay the progression of disease as well as ameliorate the symptoms. However more research is necessary to comprehend the mechanism of numerous herbal drugs and their formulations.

ACKNOWLEDGEMENT

The authors would like to convey thanks to KIET (KIET School of Pharmacy, Ghaziabad) for providing the infrastructure for carrying out the present study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Abhishek K, Saksham R, Deepti K, Rao NGR, Surya P, Vinay K, *et al*. Medicinal Plants and Herbal Formulations Ameliorating Neurodegeneration: Remedies Combating Parkinson's and Alzheimer's Disease. J Young Pharm. 2023;15(2):194-200.