

**REVIEW ON NEUROPROTECTIVE ACTIVITY OF HERBAL DRUGS**

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**ABSTRACT**

Neuroprotection is the preservation of the structure and function of neurons from insults arising from cellular injuries induced by a variety of agents or neurodegenerative diseases (NDs). The various NDs including Alzheimer's, Parkinson's, and Huntington's diseases as well as amyotrophic lateral sclerosis affect millions of people around the world with the main risk factor being advancing age. Neurodegeneration refers to a condition of neuronal death occurring as a result of progressive disease of long-term and is becoming a major health problem in the 21st century. Natural products play a very essential role in preventing and providing therapeutic effect to various neurodegenerative diseases, and neuronal dysfunctions. Plant secondary metabolites include an array of bioactive constituents' form both medicinal and food plants able to improve human health. In this review, we presented classical examples of plant-derived neuroprotective agents by highlighting their family, parts used, geographical location and their uses for the neuro protective activity.

**KEYWORDS:** Neurodegenerative Disease, Nervous Disorder, Ataxia, Ischemic Stroke, Alzheimer's disease, Dementia.

**INTRODUCTION**

Neuroprotection is generally concerned with the strategies and relative mechanisms able to struggle down the Central Nervous System (CNS) against neuronal damage caused by various neuropsychiatric which refers to the disorders of affect, cognition and complex conditions with poorly defined neurobiological bases and neurodegenerative disorders which affects the specific areas of the central and peripheral nervous system, leading to gradual and progressive cognitive or movement impairments such as Alzheimer's disease, anxiety, cerebrovascular impairment, seizures, Parkinson's disease, etc.<sup>[1,2]</sup> The World Health Organization (WHO) has stated that neurodegenerative diseases will be the second leading cause of natural death by 2040.<sup>[3]</sup> The WHO considers phytotherapy in its health programs and suggests basic procedures for the validation of drugs from plant origin in developing countries.<sup>[4]</sup> In recent times, focus on plant research has increased all over the world and a large body of evidence has been accumulated to highlight the immense potential of medicinal plants used in various traditional systems of medicine.<sup>[5]</sup> Nature remains to be a veritable source of medicines to mankind. Furthermore, traditional medicine remains a vital alternative source of medicine all over the world today.<sup>[6]</sup> Nowadays, these diseases, which are associated with different multifactorial etiologies, have created massive medical, social, and financial problems.

The general pathological signs of neurodegenerative disorders are aging, disability and mortality. The neurodegenerative diseases are including Alzheimer's Disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS) and etc. Irreversible memory impairment, cognitive and behavioral disturbances are prevalent AD symptoms.<sup>[7]</sup> A number of neurotoxic factors such as oxidative stress, inflammatory cytokines, abnormal protein dynamics and mitochondrial dysfunction are mainly responsible for neuronal dam. The most commonly used class of drug is stimulants, such as caffeine. These drugs are purportedly used primarily to treat cognitive or motor function difficulties attributable to disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and ADHD. Among them, reactive oxygen species (ROS)-induced oxidative stress is a major factor in neuronal cell death by causing oxidative damage to DNA, proteins, and lipids.<sup>[3]</sup> Oxidative stress is implicated in the neuronal damage associated with Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and cerebral ischemic stroke. The damage is thought to be mediated by reactive oxygen species (ROS) including superoxide anion ( $O_2^{\cdot-}$ ), hydrogen peroxide ( $H_2O_2$ ) and the hydroxyl radical ( $OH^{\cdot}$ ).<sup>[4]</sup> Further, oxidative stress is mainly related to secondary cell death in many central nervous system disorders. Apoptosis also plays an important role in neuronal cell






death.<sup>[3]</sup> Among the strategies for neuroprotection many categories of natural and synthetic neuroprotective agents have been reported, however, synthetic neuroprotective agents are believed to have certain side effects such as dry mouth, tiredness, drowsiness, sleepiness, anxiety or nervousness, difficulty with balance, etc. Herb based medicated products have drawn considerable awareness from research bases and industries in recent years at the national and international levels. Hence, there has been intense interest focussed on the part of potential phytochemicals to modulate neuronal function and protective mechanism against neurodegeneration. As complementary and alternative therapy, herbal medicine or phytotherapy, refers to the medical utilization of plant components (leaves, stems, roots, flowers, fruits and seeds) for their curative properties.<sup>[1]</sup> Recently, however, scientists have begun investigating the biological activities of medicinal plants, including their neuroprotective actions. For example: *Lycium Chinese Miller*, which is a traditional herbal medicine used in China, Korea, and Japan, has been shown to have hypotensive, hypoglycemic, and antipyretic effects in animal studies following treatment with the fruit and root bark of the plant. Furthermore, this plant has been used as an anti-aging therapy and a










treatment for neurodegenerative diseases, and recent research has confirmed neuroprotective effects of the fruit of the plant in a rat model of trimethyltin-induced learning and memory impairment.<sup>[8]</sup> Other plants have also shown neuroprotective effects. The most commonly used class of drug is stimulants, such as caffeine. These drugs are purportedly used primarily to treat cognitive or motor function difficulties attributable to disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease and ADHD.<sup>[9]</sup> This review will highlight the medicinal herbs from different plant species for the treatment of neurodegenerative disorders, specifying their family, their geographical location, the parts of the plant used for the particular treatment, and their neuroprotective function or their therapeutical use.

**Nervous Disorder:** Most of the population depends on traditional medicine for primary health care, however, neurological disorders are often not considered as common illness, as many people with mental illness are severely affected by health-related stigma and discrimination. Nervous disorder also affects the speaking, movement, breathing, mood and memory. The neurological disorder affects the brain and spinal cord.<sup>[10]</sup>

#### Medicinal plants against nervous disorder

**Table-1: Morphological benefits.**

Picture	Plant Species	Parts Used	Geographical Location	Uses	Family
	<i>Emblica officinalis L.</i>	Fruit	India	Epilepsy	<i>Euphorbiaceae</i>
	<i>Evolvulus alsinoides L.</i>	Whole Plant	East Asia	Psychotropic	<i>Convolvulaceae</i>
	<i>Ferula asafoetida L.</i>	Gum, Resin	Iran	Epilepsy	<i>Apiceae</i>
	<i>Valeriana</i>	Root	Europe	Sedative	<i>Caprifoliaceae</i>
	<i>Annona squamosa</i>	Fruit	America	Depression	<i>Annonaceae</i>

	<i>Cassia occidentalis L. (Link)</i>	Fruit Pulp	South East Asia	Hysteria	<i>Caesalpinaeaceae</i>
	<i>Cassia fistula L.</i>	Fruit Pulp	South East Asia	Epilepsy	<i>Caesalpinaeaceae</i>
	<i>Papaver somniferum L.</i>	Seed	Europe	Narcotic	<i>Papaverceae</i>
	<i>Strychnos nux vomica L.</i>	Seed	South East Asia	Paralysis	<i>Loganiaceae</i>
	<i>Hyoscyamus niger L.</i>	Leaves, Flower, Tops, Seeds	Europe	Hypnotic	<i>Solanaceae</i>
	<i>Aegle marmelos L.</i>	Fruit, Root, Seeds, Leaves	Sri Lanka, Thailand, Malaysia	Overcoming Sunstrokes	<i>Rutaceae</i>
	<i>Acorus calamus L.</i>	Root, Stem, Leaves	India, Japan, Indonesia, Phillipines	Gastrointestinal Problems	<i>Acoraceae</i>
	<i>Avina sativa L.</i>	Aerial Parts	South-Western Asia	Anxiety, Bladder weakness, Constipation	<i>Poaceae</i>
	<i>Datura metal L.</i>	Leaves, Seeds, Roots	India, East African	Increases intoxicating effect	<i>Solanaceae</i>

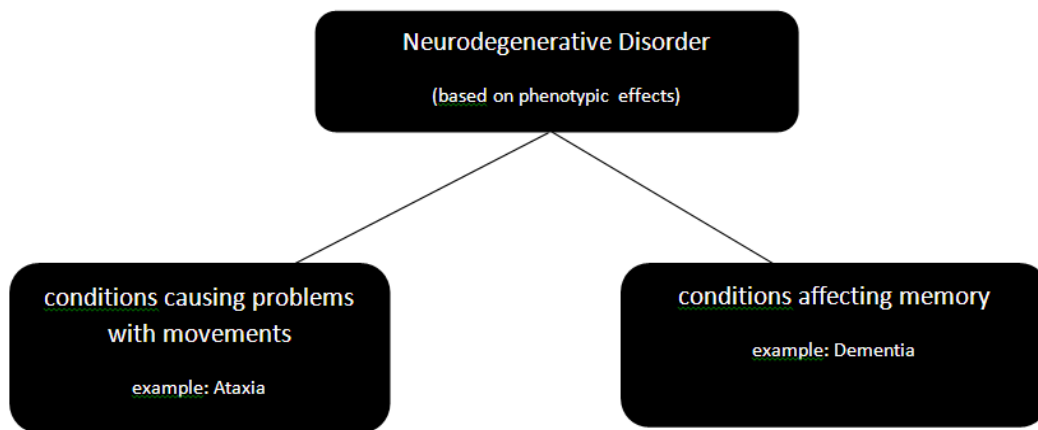
**Neurodegenerative Disorder:** Neurodegenerative disorder (Greek neuro – “nerval” and Latin degenerate, “to decline” or “to worsen”) is a heterogeneous group of degenerative conditions affecting specific areas of the central and peripheral nervous system, leading to gradual and progressive cognitive or movement impairments,

depending on the type of neuronal cells undergoing selective degeneration with this disease. It is a condition in which cells of the brain and spinal cord are lost. Some sources limit the term “degenerative” to conditions primarily affecting grey matter that are not associated with an obvious inciting event. This disorder,

characterized by progressive loss of motor, sensory neurons and the ability of the mind to refer sensory information to an external object, is affected in different kinds of neurological disorders. Neurodegenerative disorders are crudely divided into two groups according to phenotypic effects: 1) conditions causing problems with movements, such as ataxia, and 2) conditions affecting memory and related to dementia. The majority of neurodegenerative pathologies are age-related dementia, thus becoming an increasing health and socioeconomically problem in industrialized countries, where the frequency has increased in the last decades,

together with an increased life expectancy of the individuals. Neurodegenerative disorders may be inherited, sporadic or transmitted.<sup>[11]</sup> Although in the recent years much attention has been paid to traditional herbal medicines. Traditionally, various parts of the plant are used in the treatment of neurodegenerative disorder.<sup>[12]</sup> Neurodegeneration is the process, involved in both neuropathological conditions and brain ageing. It is known that brain pathology in the form of the cerebrovascular and neurodegenerative disease is a leading cause of death all over the world, with an incidence of 2/1000 and an 8% of total death rate.<sup>[13]</sup>

❖ Ataxia




Flowchart-1: Neurological disorders.

Ataxia is a rare degenerative neurological disease. Ataxia is basically a term for a group of disorders that affect co-ordination, balance and speech. Ataxia usually results from damage to a part of the brain called cerebellum, but it can also cause damage to other parts of the nervous system. This damage can be part of an underlying conditions such as MS, or can be head injury, lack of oxygen to the brain, or long term, excessive alcohol consumption, tumor, multiple sclerosis. The common symptoms of ataxia are lack of coordination, difficulty walking, tremors, etc.

**Ischemic Stroke:** Stroke, is regarded as the important problem in developing countries which is the major cause of death and disability. Frequent incidences of cerebral ischemia are observed in age-related disorders, hypoxic– ischemic brain injury, carotid artery pathologies, asphyxiation and shock etc.<sup>[14]</sup> This is an ischemia generally caused by thrombosis or haemorrhage

which blocks the blood flow to a specific brain region. In particular, the occlusion of a cerebral vessel due to a blood clot (thrombus) discharged from the surface of an atherosclerotic lesion may cause an ischemic stroke, whereas an intracranial or intracerebral haemorrhage, commonly caused by hypertension, may lead to a haemorrhagic stroke. It is a devastating event that is associated with great morbidity.<sup>[15]</sup> Despite the importance of stroke and the advances of technologies nowadays, the prophylactic protection against stroke with neuroprotective agents has gained much attention.<sup>[14]</sup> The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic principles. Herbal drugs have gained lot of acceptance in the recent years because they have a relatively higher therapeutic window, less serious side effects, and are economical. They have been extensively studied in in neurological disorders like stroke with promising results.<sup>[16]</sup>

Table-2: Natural plants Herbs & drug used as a neuroprotection in ischemic stroke.

Picture of the herb	Parts Used	Plant Species	Family	Geographical Location	Uses
	Leaves, Stem	<i>Leonurus heterophyllus</i>	<i>Lamiaceae</i>	China, Japan	Menstrual disturbance, dysmenorrhoea

	Leaves, Seeds	<i>Ginkgo biloba</i>	<i>Ginkgoaceae</i>	China	To treat dementia, memory loss, premenstrual syndrome,
	Fruit	<i>Fructus chebulae</i>	<i>Combretaceae</i>	India, Nepal, Sri Lanka, Malaysia	Asthma, Vomiting, Ulcer, Bleeding piles
	Fruits, Seeds	<i>P.granatum</i>	<i>Lythraceae</i>	India, Iran, America	Cancer, Osteoarthritis, Urinary infection, Skin disorder
	Flower	<i>R.laevigata</i>	<i>Rosaceae</i>	China, Taiwan, Vietnam, United States	Anti-uretic and astringent
	Fruits	<i>A.sativum</i>	<i>Amaryllidaceae</i>	India, China, Iran	Artherosclerosis, High cholesterol, Heart attack, hypertension
	Roots, Bulb, Leaves, Seed	<i>Allium cepa</i>	<i>Amaryllidaceae</i>	South western Asia	Joint disorder, High blood pressure, Blood pressure
	Fruit, Leaves	<i>Grape</i>	<i>Vitaceae</i>	North-America	Diarrhoea, Hepatitis
	Fruit, Leaves	<i>O.europaea</i>	<i>Oleaceae</i>	China, Australia	High cholesterol, heart disease

**Conditions affecting memory:** The majority of neurodegenerative pathologies are age-related dementia, thus becoming an increasing health and socio economical problem in industrialized countries, where the frequency has increased in the last decades.<sup>[17]</sup> Alzheimer's disease is a neurodegenerative disorder, which is characterized by deficit, learning and memory loss followed by cognitive disorders like depression, agitation and psychosis.<sup>[10]</sup>

**Alzheimer's disease:** The AD is the most prevalent and devastating disorder of the NDs. It is an incurable disease of cognition and behavioral impairment. It affects the social and occupational activities to a great extent and is also a leading cause of institutionalization in the elderly.<sup>[6]</sup> The pathogenesis or the progression of



the variety of acute and chronic neurological and neurodegenerative disorders including Alzheimer's disease has been implicated by neuroinflammation<sup>[18]</sup>. Alzheimer's disease is caused basically due to aggregation of mis-folded proteins which accumulate fibrillary amyloid deposits in selective regions of central nervous system. Alzheimer's disease results in memory loss, personality changes, unusual behaviour, and loss of the ability to thinking. Early disease shows short term memory loss, fail to remember names and addresses, failure to learn new information, mood swings, as the condition develops, changes become more prominent and individuals even fail to remember way to home. Frustration, irritability and hostility are usual emotional features showed by AD patients. Medicinal plants contain various phytochemicals which



are extractable and utilized as raw material for different scientific survey. Various secondary metabolites from plants are commercially essential and utilized in pharmaceutical industries. Recently, medicinal plants have gained wide acceptance because of their fewer side effects compared to the synthetic medicines and necessity to meet the requirement of medicine for increasing human population. Several investigations reported that medicinal plants are utilized in the

Alzheimer's disease treatment which includes *Centella asiatica*, *Ginkgo biloba*, *Withania somnifera*, *Bacopa monnieri*, *Salvia officinalis*, *Melissa officinalis*, *Tinospora cordifolia*, *Glycyrrhiza glabra* etc.<sup>[19]</sup> Galantamine plays a very important role to treat the symptoms of Alzheimer's disease.<sup>[20]</sup> The consequence of these diseases are also very significant in terms of the cost of caring for patients.<sup>[15]</sup>

### Role of medicinal plants against Alzheimer's disease

**Table-3: Holistic medicines as neuroprotective.**

Herbs	Plant Species	Parts Used	Geographical location	Uses	Family
	<i>Centella asiatica</i> (Gotu kola)	Leaves	India, Srilanka, Bangladesh	Neuromuscular disorder, skin disorder	<i>Apiaceae</i>
	<i>Glycyrrhiza gabra</i>	Roots & Rizome	South-Western Asia	Cold, Cough, Asthma	<i>Fabaceae</i>
	<i>Curcuma longa</i> (Turmeric)	Tuberous rhizome, underground stem	South –East Asia	Respiratory problems, Arthritis	<i>Zingiberaceae</i>
	<i>Bacopa monnieri</i> (Brahmi)	Whole Plant	Europe, Asia	Alzeimer's disease, improving memory	<i>Srophulariaceae</i>
	<i>Ginkgo biloba</i>	Leaves	China	Memory Loss, Dementia	<i>Ginkgoaceae</i>
	<i>Withania somnifera</i> (Ashwagandha)	Whole plant	Afganisthan, North America, Sri Lanka	Asthma, Arthritis disease, depression	<i>Solanaceae</i>
	<i>Magnolia officinalis</i>	Bark	China	Digestive system	<i>Magnoliaceae</i>
	<i>Lepidium meyenii</i>	Roots	South America	Reducing erectile dysfunction, Depression	<i>Brassicaceae</i>






	<i>Tinospora cordifolia</i>	Stem, Root, Leaves, Whole plant	India	High cholesterol	<i>Menispermaceae</i>
	<i>Convolvulus pluricaulis</i> (shankhpushpi)	Whole plant, Roots, seeds	India	Hypertension, Prevent Memory loss, Anxiety neurosis	<i>Convolvulaceae</i>




**Age-related brain disorders (dementia):** Dementia is the most common form of neurodegenerative disorder affecting several million people world wide. Dementia is not a disease itself, but rather a group of symptoms that might accompany certain diseases or conditions. It is characterized by chronic progressive mental disorder,

which adversely affects memory, thinking, comprehension and language. Dementia is alarmingly prevalent in the elderly population, affecting 5% of people over the age of 65 and up to 50% of people over the age of 85.<sup>[11]</sup>

### Natural medicines against dementia

**Table-4: Flora for neuroprotective.**

Class of the compound	Name of the compound	Source	Plant Family	Uses	Picture
Steroidal alkaloid	Galantamine	<i>Galanthus nivalis</i>	<i>Amaryllidaceae</i>	50% inhibition at $1.077 \pm 0.18 \mu\text{M}$	
Steroidal alkaloid	Assoanine	<i>Narcissus assoanus</i>	<i>Amaryllidaceae</i>	50% inhibition at $3.877 \pm 0.24 \mu\text{M}$	
Quinolizidine alkaloid	(-)-Huperzine A	<i>Huperzia serrata</i>	<i>Lycopodiaceae</i>	50% inhibition at $10-4 \mu\text{M}$	
Indole alkaloid	Physostigmine	<i>Physostigma venenosum</i>	<i>Leguminosae</i>	50% inhibition $6 \times 10-4 \mu\text{M}$	
Cynatroside A	Pregnane glycoside	<i>Cynanchum atratum</i>	<i>Asclepiadaceae</i>	50% inhibition at $6.4 \mu\text{M}$	

Isoquinoline alkaloid	Corynoline	<i>Corydalis incisa</i>	<i>Papaveraceae</i>	50% inhibition at 30.6 $\mu$ M	
Glycoalkaloid	$\alpha$ -Solanine	<i>Solanum tuberosum</i>	<i>Solanaceae</i>	44.3% inhibition at 10 $\mu$ M	
Stilbene oligomer	(+)- $\alpha$ -Viniferin	<i>Caragana chamlague</i>	<i>Leguminosae</i>	50% inhibition at 2.0 $\mu$ M	

## CONCLUSION

Many lifestyle factors endorse health of the nervous system in trouble by imposing a mild stress on neural cells. Although demand for phytotherapeutic agents is growing, there is a need for their scientific validation before plant derived extracts gain wider acceptance and use. Hence “natural” products may provide a new source of beneficial neuropsychotropic drugs. The management of neurodegenerative diseases remains a challenge in the modern medicine because of their complicated pathogenesis. This review has acknowledged many herbal medicines such as *Allium Sativum*, *Ginkgo biloba*, etc with potential therapeutic effect for neurodegenerative disease.

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