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Neurodegenerative disorders and herbal drugs: A review

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Abstract
Synthetic medications for human brain disorders are expensive and symptomatic. Long-term treatments that sometimes appear inevitable with serious side effects, with poor patient compliance. Hence herbal and Ayurvedic treatments are preferred over synthetic drugs for a number of human brain disorders including Alzheimer's disease, Parkinson's disease, depression, epilepsy, schizophrenia, anxiety etc., Herbal drugs and their formulations work mainly in different ways for example by increasing and replacing the neurotransmitter at high concentrations in the brain, antidepressant action, adaptation and stabilization of mood, better oxygenation, better concentration, resistance, improving memory and learning, stimulating growth and protecting brain cells. Herbs have memory enhancing properties due to their active chemical constituents. Since the allopathic medical system is yet to provide a radical cure, it is necessary to explore the usefulness of conventional medications. This article reviews common brain disorders and herbs used for their treatment.

Keywords: brain disorder, memory, neuro-protective

Introduction
It is a legitimate fact that nature provides the best response to any disease that affects the human body from time to time. When the synthetic drugs fail to be effective or show serious side effects, it is the plant medicine which brings relief. Herbal treatment is the natural form of healing therapy to cure the diseases of mankind [1].

Neuro-protection refers to the strategies and relative mechanisms able to struggle down the Central Nervous System (CNS) against neuronal damage caused by various neuropsychiatric and neurodegenerative disorders [2]. The true cause of various neurodegenerative diseases remains a mystery in healthcare. Some of the commonly studied environmental factors for neurodegenerative diseases are protein degradation, oxidative stress, inflammation, environmental factors, mitochondrial disorders, family history, and abnormal protein accumulation in the neurons. Aging is one of the main problems in neurodegenerative diseases. Examples of neurodegenerative diseases are Parkinson's, Alzheimer's, Huntington's diseases, motor neuron diseases, spinocerebellar ataxia (SCA), spinal cord atrophy (SMA) [3].

Neuro-protective agents act by reducing and preventing oxidative stress, mitochondrial dysfunction, inflammation, various forms of neurotoxicity (eg, excitotoxicity), protein deficiency etc [4]. Currently, the world is struggling for brain healing prescription of traditional medicines, including Ayurveda, which is a reliable cure with fewer side effects. Indian systems of medicine is very advanced in the treatment of the brain disorders and most important among the Indian drug systems is Ayurveda, which describes the use of hundreds of plants individually or in combination for the treatment of brain disorders [5].

Common Neurodegenerative Disorders
1. Dementia
Dementia refers to a clinical syndrome characterized by progressive cognitive decline that interferes the ability to function independently. The symptoms of dementia are gradual, continuous and progressive. People with dementia experience change in cognition, function and behaviour. The clinical manifestations of dementia vary greatly from one individual to another and the cognitive deficits they cause can manifest as memory loss, communication and language disorders, agnosia (inability to recognize objects), apraxia (inability to perform tasks previously learned) and decreased function (reasoning, judgment and planning) [6].

2. Alzheimer's disease
The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as Alzheimer's disease. It is a progressive neurodegenerative brain disorder causing a significant disruption to the normal brain structure and function. At the cellular level Alzheimer's disease is characterized by a progressive loss of cortical neurons especially pyramidal cells that mediate higher cognitive abilities. It causes synaptic dysfunction in the early stages of the disease process and interrupts communication in neural circuits important for memory and other cognitive functions [7].

3. Parkinson's disease
Parkinson disease is the second most common neurodegenerative disorder after Alzheimer disease. It is a neurodegenerative syndrome that involves multiple motor and non-motor neural circuits. Two major pathological processes involved are: premature selective loss of dopamine neurons and the accumulation of Lewy bodies, composed of α-synuclein which become misfolded and accumulate in multiple systems of patients with Parkinson disease [8].

4. Schizophrenia
Schizophrenia is a complex chronic mental health disorder characterized by many symptoms, including delusions,

hallucinations, speech or behavior disorders, and reduced cognitive abilities.
Abnormalities in neurotransmission is considered as the basic cause of schizophrenia [9].

5. Epilepsy
A "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain. "Epileptic seizure" is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. "Epilepsy" is the condition of recurrent, unprovoked seizures. Epilepsy has numerous causes, each reflecting underlying brain dysfunction [10].

6. Anxiety
Anxiety disorders (generalized anxiety disorders, panic / agoraphobia disorders, social anxiety disorders, and others) are the most common psychiatric disorders. Treatment is given only if the patient has significant complications due to the disorder. It should be treated with psychological therapy, pharmacotherapy, or a combination of both [11].

7. Depression
Depression is a common affective disorder of mood rather than disturbances of thought or cognition. It is the most common affective disorder which is accompanied by delusions and hallucination. In this disease condition the neurotransmitters levels such as dopamine, acetylcholine, nor epinephrine etc., in the brain are increased. The symptoms of this disease are of two types (i) biological symptoms: retardation of thought, loss of libido, sleep disturbance and loss of appetite (ii) emotional symptoms: feelings of guilt, loss of motivation, ugliness etc [12].

8. Huntington's disease
Huntington disease (HD) is a rare neurodegenerative disorder of the central nervous system characterized by unwanted choreatic movements, behavioral and psychiatric disturbances and dementia. Mean age at onset of symptoms is 30-50 years. In some cases symptoms start before the age of 20 years with behavior disturbances and learning difficulties [13].

9. Attention Deficit Hyperactivity Disorder (ADHD)
Attention deficit/hyperactivity disorder (ADHD) is among the most common neurobehavioral disorders presenting for treatment in children and adolescents. ADHD is often chronic with prominent symptoms and impairment spanning into adulthood. ADHD is often associated with co-occurring disorders including disruptive mood, anxiety, and substance abuse [14].

Ayurvedic Plants for Neurodegenerative Disorder

1. Ginseng
Ginseng, a perennial plant belonging to the *Panax* genus of the Araliaceae family has been used in China, Korea and Japan as a traditional herbal medicine. Ginsenosides and other active ingredients in ginseng are known to exhibit neuroprotective properties and act as enhancers of cognitive performance and memory. The main active ingredients in ginseng are triterpenoid glycosides also known as ginsenosides found in roots, leaves, stems, buds and berries. Ginsenosides are considered as a part of the defense mechanism in ginseng plants.
One of the major pathological features of Alzheimer's disease is the presence of *β*-amyloid (A*β*) around arterioles or capillary wall in the brain. Administration of ginseng and its constituents may inhibit *β*-amyloid aggregation in cultured neurons. Hyperphosphorylated tau protein is also known to cause Alzheimer's disease. Ginsenosides Rd and Rb1 are also shown to reduce hyperphosphorylated tau whereas Ginsenoside Rg5 increases cholinergic neurons in the brain.
Rb1 and Rg1 decrease neurite length in Parkinson's disease [15].

2. Brahmi
Bacopa moniera belongs to family Scrophulariceae also known as *Herpestis monniera* locally known as Brahmi or Jalanimba in India. It has been used for centuries in Ayurveda. The plant has been utilized extensively as a nootropic, digestive aid and to improve learning, memory and respiratory function. The herb is from a family Scrophulariaceae and is a small creeping herb with numerous branches, small oblong leaves and light purple or small and white flowers, with four or five petals. Compounds responsible for the pharmacological effects of brahmi include alkaloids, saponins and sterols [16].
Studies have shown that brahmi promotes free radical scavenging mechanisms and protects cells in the prefrontal cortex, hippocampus and striatum from cytotoxicity and DNA damage associated with Alzheimer's disease. It reduced lipoxygenase activity and lipid peroxidation and increased glutathione peroxidase and forms chelates. Administration of Brahmi is believed to protect cholinergic neurons. It also reduces β-amyloid deposition in the hippocampus and stress-induced damage. The neuroprotective effect of Brahmi is also due to nitric oxide mediated cerebral vasodilation. Brahmi improved total memory score in logical memory and paired associate learning studies in humans [17].

3. Shankhupushpi
It is an Ayurvedic herb used for its action on central nervous system especially for boosting memory and intellect. It consist of whole plant of *Convolvulus pluricaulis* of family Convulvulaceae. Ethanolic extract of plant showed improvement in learning and memory and it significantly reversed amnesia induced by scopolamine. It also exhibited potent memory enhancing effect in the step-down and shuttle-box avoidance paradigms. Nootropic activity was assessed with passive and active avoidance paradigms using Cook and Weidley's pole climbing apparatus and elevated plus-maze model [18].

4. Amla
Phyllanthus Emblica Linn. (*Emblica officinalis*) commonly known Indian gooseberry or amla, family Euphorbiaceae, it is one of the main medicinal herbs of unani and ayurvedic systems of medicine. It contains tannins, alkaloids, phenolic compounds, higher amount of vitamin C, minerals, proteins and amino acids. Amla ameliorates alcohol- induced oxidative stress due to the combined effect of phyto-phenols such as tannins, flavanoid compounds and vitamin C present in it. It has the potency to modulate basal oxidative markers and enhance endogenous antioxidant defenses. Substantial reduction in the levels of lipid hydroperoxide and reactive

oxygen species (ROS) was observed in the study that incubated *Emblica officinalis*. Moreover it increased the levels of Glutathione, antioxidant capacity and activities of antioxidant enzymes like Superoxide dismutase, Catalase, Glutathione peroxidase, Glutathione reductase and Glutathione S-transferase. Additionally, when administered once daily for 7 days the active tannoids of *Emblica officinalis* induced a rise Superoxide dismutase, Catalase and Gluathione peroxidase activity with associated reduction in lipid peroxidation in these brain areas [19].

5. Gingko

The Chinese tree *Ginkgo biloba* or maiden hair tree is extensively cultivated due to the medicinal properties of its leaves. From this, a well-defined extract designated "EGb 761" has been developed which is used in the treatment of cerebral disorders, neurosensory problems and peripheral circulatory disturbances. The major therapeutic components of "EGb 761" are flavonoids, terpenoids, ginkgolides and bilobalide. It significantly improved memory of healthy volunteers in an evaluation meta-analysis of 40 clinical trials. It was reported that gingko was able to improve twelve different symptoms associated with cerebral insufficiency [20].

6. Hypericum

Hypericum perforatum is a perennial plant commonly known as St. John's wort. It has been used in traditional medicine for centuries to treat many disorders such as minor burns, anxiety, and mild to moderate depression. Neuroprotection can be achieved through one or more mechanisms such as anti-apoptotic effects or indirectly through direct antioxidant properties. Structure-activity relationships chemically suggest that the sugar side chain of flavonoids may be important for neuroprotective activity, and various hydroxyl groups give these compounds significant antioxidant properties. Therefore it was concluded that *Hypericum perforatum* was used in various neurodegenerative disorder such as Alzheimer's disease, Parkinsons disease etc., [21].

3. Patha

Patha is a widely used drug in Ayurveda botanical source of the Laghupatha and Rajpatha are *Cissampelos pareira* and *Cyclea peltata* which belongs to the Menispermaceae family. They contain many alkaloids like hayatine, hayatinine, hayatidine and other bisbenzylisoquinoline alkaloids, berberines etc., which are found to be responsible for its various activities [22].

The effects of *Cissampelos pariera* on learning and memory in mice was evaluated by elevated plus maze and passive avoidance methods. [23].

8. Ashwagandha

Ashwagandha (*Withania somnifera*, family: Solanaceae) commonly known as Indian winter cherry or Indian ginseng. It is one of the most important herbs in Ayurveda which has been used as Rasayana (tonic) for thousands of years for its extensive health benefits. The biologically active chemical constituents of *Withania somnifera* include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins (Sitoindosides and acylsterylglucosides) in Ashwagandha are anti-stress agents. Active principles of Ashwagandha such as sitoindosides VII-X and Withaferin-A have significant anti-stress activity. Ashwagandha slows neurotic atrophy and synaptic loss. Therefore Ashwagandha can be used to treat Alzheimer's, Parkinson's, Huntington's and other neurodegenerative diseases at any stage of the disease. Glycowithanolides withaferin- A and sitoindosides VII–X isolated from the roots of Ashwagandha significantly reversed ibotenic acid induced cognitive defects in Alzheimer's disease model [24].

9. Lemon Balm

Lemon balm (*Melissa officinalis* L.) belongs to the mint family and it is indigenous of Southern Europe, Mediterranean region, Western Asia, and North Africa. Lemon balm is now cultivated worldwide. The main constituent of the essential oil of the plant is citral (geranial and neral), citronellal and geraniol. Lemon balm has been traditionally used for different medical purposes as tonic, antispasmodic, carminative, diaphoretic, surgical dressing for wounds, sedative, hypnotic, strengthening the memory and headache. Lemon balm has psychoneurological activity. Treatment with lemon balm had shown to improve cognitive performance [25].

Conclusion

In the future, phytochemicals from plants can be used as promising therapeutic agents for neurodegenerative disorders due their anti-inflammatory and antioxidant and anticholinesterase activity. Neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Huntington, and others share common characteristics at both the cellular and subcellular level and generally use common molecular signaling pathways that can lead to apoptosis, necroptosis, and inflammation. The present review clearly explains that the ayurvedic system of medicine is very well developed for treating most of the brain related disorders and included some of the important plants which have been described for mental disorders and are currently part of the ayurvedic prescriptions. Thus it could be concluded that the ayurvedic system of herbal medicine is certainly a treasury of plant drugs which brings back the much sought after hope for the complete and permanent treatment of mental disorders through natural means with minimum side effects as compared to the allopathic drugs.

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