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TREATMENT STRATEGIES FOR NEURODEGENERATIVE DISEASES THROUGH IMPORTANT MEDICINAL PLANTS USED IN UNANI MEDICINE

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ABSTRACT: Neurodegenerative diseases (NDs) that are characterized by progressive loss of functioning and structure of neurons are of great burden to the individuals and the society. With several hypotheses, the existent cause still remains a mystery for various NDs in healthcare. Protein degradation, inflammation, oxidative stress, environmental factor, mitochondrial defects, abnormal protein accumulation in neuron and familial history are amongst the commonly studied environmental causative factors for NDs. These disorders are a significant cause of disability and mortality, and consequently increasing life spans is one of the key challenges for medical research. The excessive treatment cost has led the world to move to alternative therapy with lower cost and minimal side effects compared to conventional treatments. Medicinal plants have been used for treating various diseases since ancient times in India. Medicinal plants used in Unani System of Medicine cover most of the NDs. It has defined a huge number of plants with multiple therapeutic benefits. In this review, the role of important medicinal plants, viz., *Prunella vulgaris* L., *Melissa officinalis* L., *Morinda citrifolia* L., *Hypericum perforatum* Linn., *Lycopodium serratum*, *Polygala tenuifolia* Willd., *Celastrus paniculatus* Willd., *Cyperus rotundus* L., *Ziziphus jujube* Mill., *Juglans regia* L., *Withania somnifera* (L.) Dunal, *Acorus calmus* L., *Centella asiatica* (L.) Urban, *Boswellia serrata* Roxb. ex Colebr., *Ferula asafoetida* L., and *Zingiber officinale* Rosc., on NDs has been discussed. This review highlights the studies carried out on medicinal plants having biological activity to treat several diseases with special reference to ND.

INTRODUCTION:

Neurodegenerative Diseases: Neurodegenerative disorders are a diversified group of diseases marked by escalating structural and functional degeneration of the central or peripheral nervous system.

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Neurodegenerative diseases (NDs) comprising of Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), vascular dementia (VD), frontotemporal dementia, Prion disease, Pick's disease, brain trauma, progressive supranuclear palsy and spinocerebellar ataxias are illnesses related with significant mortality and morbidity rates [1, 2].

In the course of past decade, substantial improvement has been achieved in understanding the phenomenon of cell death [3] which is a significant characteristic for most of the NDs [4].

Depending upon the pathways of cell death in these diseases their symptoms and the exacerbations varies and specific mechanisms of cell death requires novel therapeutic strategies. The underlying mechanisms associated with neurodegeneration are not fully understood and the effectiveness of current treatments for NDs is still narrow. Hence, attempts are being made to explore novel biological mechanism of ND models and develop their respective/suitable novel therapeutic strategies.

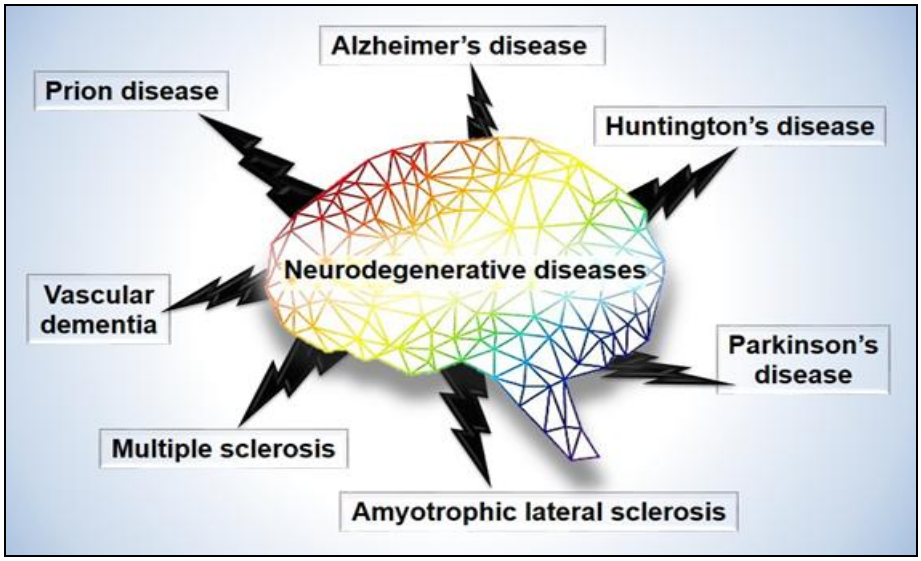

Fig. 1. Major Neurodegenerative diseases (NDs) comprising of Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), vascular dementia (VD), frontotemporal dementia, Prion disease. Use of natural plant products are being prescribed for treating various ailments. Large-scale researches are being carried out worldwide on different plants. Studies provide promising results of medicinal plants regarding its efficacy for treatment of several diseases such as cognitive problems, [5-7] gastrointestinal problems [8] stroke [9] and many others disease. Medicinal plants are rather more economical, have lesser side effects and more therapeutic benefits than allopathic medicine. Medicinal plants play an important role in the Unani system of medicine and have provided numerous Unani Single and Compound drugs. Plants with medicinal benefits are being used for neuroprotection, longevity promotion and cognitive improvement in traditional folklore since a long period of time.

Alzheimer's disease: NDs primarily includes Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), vascular dementia (VD), *etc*. AD is amongst the most common source of mental deterioration in healthy population and is a major ND [10]. Pathological signs of AD covers aggregation of beta-amyloid plaques in between the nerve cells and formation of neurofibrillary tangles inside nerve cells by Tau proteins, as the major events of AD [11-13]. Both acetyl cholinesterase enzymes (AChE) and butyrylcholinesterase (BChE) are accountable for the breakdown of neurotransmitter acetylcholine in synaptic region. Reduced levels of acetylcholine in brain have been related to age-related diseases leading to reduction of cognitive power. It is a genetic and sporadic ND that results in non-amnestic cognitive impairment in its less frequent variants and an amnestic cognitive impairment in prototypical presentation.

Medicinal plants used for the treatment of AD include *Hypericum perforatum, Prunella vulgaris, Lepidium meyenii, Cyperus rotundus, Lavandula officinalis, Zizyphus jujube, Salvia officinalis, Ginkgo biloba, Melissa officinalis, Panax ginseng* C.A. Mey., *Morinda citrifolia, Polygala tenuifolia, Lycopodium serratum, Celastrus paniculatus*. *Prunella vulgaris* L. is widely distributed over Europe, China, Japan and Korea. This traditional Korean and Chinese medicine has been employed

for treating inflammation, dizziness, headache and eye pain [14]. According to research studies *P. Vulgaris* has been found to possess various active compounds like ursolic acid, oleic acid, butyric acid, rosmarinic acid and flavonoids. Besides, it also has anti-inflammatory, anti-allergy, antioxidant, antiviral activity and antimicrobial [15, 16].

Melissa officinalis L. also called lemon balm is a lemon scented herb. M. officinalis (Lamiaceae) has been used for over 2000 years as traditional medicine. It has been acclaimed regarding the promotion of long life and memory restoration [17]. The plant leaves consist of phenol carboxylic acids (e.g. rosmarinic acid), showing antiamyloidogenic, antioxidative and antiapoptotic effects and monoterpenes (e.g. citral) having weak anti-AChE activity.

Morinda citrifolia L. is a popular herb. Juice of M. citrifolia is employed as substitute medicine for several diseases like cancer, heart disease, ulcers, arthritis, high blood pressure, diabetes, menstrual problems, atherosclerosis and depression [18]. The fruit and extract have antioxidant, anti-inflammatory and analgesic properties [19]. Ethyl acetate extract of this herb has been shown to prevent oxidative stress and memory deficit induced by amyloid β in mice [20]. Further, the treatment with its ethyl acetate, chloroform and butanol extracts reduced AChE activity in brain of scopolamine-treated mice models [19].

Hypericum perforatum Linn. (St. John's Wort) shows clinical effects via amelioration of neurological diseases, as antidepressant, wound healing, anti-inflammatory, anti-anxiety and analgesic effects [21]. *Lycopodium serratum* commonly called Club moss is a pteridophyte (Lycopodiaceae). This medicinal plant is an active participant of homeopathic preparations for raising memory and learning potential, for treatment of cancer [22], Alzheimer's disease [23] and oitis media in children [24]. The aforesaid medicinal plant has applications in the treatment of inflammation, fever, schizophrenia, and blood disorders [25]. Further, it is reversible, selective and effective inhibitor of AChE. Efficacy of AChE inhibition is comparable or higher than that of standard compounds Donepezil, Tacrine, Galanthamine and physostigmine [26]. Genus Lycopodium (Lycopodiaceae), produces a potent therapeutic agent known as huperzine A [27]. Huperzine A is a significant candidate for AD treatment. Additional protective effects related to AD involve decrease in glutamate-induced toxicity, mitochondrial dysfunction, protection against Amyloid β-induced oxidative damage and neuronal apoptosis, the regulation of nerve growth factor as well as anti-inflammation [28, 29]. Research data reveals Huperzine A significantly increases level of ACh in the rat brain [28].

Polygala tenuifolia Willd. is another plant of medicinal importance, the roots of which are used as a tonic, an expectorant, and a tranquilizer for the treatment and prevention of dementia [30, 31]. Its roots are the typical participant in formulae for cognition. This plant have multiplex neuroprotective potential with regard to Alzheimer's, such as anti-Tau protein,[32] anti-Amyloid β aggregation,[33] anti-inflammation,[34] antioxidant, anti-neuronal, apoptosis,[35] promote neuronal proliferation and improving central cholinergic system [36, 37].

Celastrus paniculatus Willd. (Black Oil Plant): is useful a stimulant nervine tonic, sedative, rejuvenant, diuretic and tranquilizer [38]. According to a study report the oral administration of seed oil in rat brain reduced levels of dopamine, noradrenaline and 5-hydroxytryptamine leading to improvement in memory and learning processes. Furthermore, the seed oil was not neurotoxic [39].

Cyperus rotundus L. (Nut Grass) belonging to Cyperaceae –family is also called purple nutgrass or nutsedge. It is a common perennial weed that is widely used as a traditional herbal medicine for analgesic, sedative, antimalarial, antispasmodic, stomach disorders and to alleviate diarrhoea [40]. *Cyperus rotundus* L. includes alkaloids, quercetin, flavonoids, kaempferol, tannins, glycosides, starch, chalcones, p-coumaric acid and gallic acid [41, 42].

According to scientific research *Cyperus rotundus* L. demonstrates acetylcholinesterase inhibitory (AChEI), antioxidant, memory-enhancing and neuroprotective activities [43-47]. *Ziziphus jujube* Mill. (Chinese Date) fruit is edible and sweet in taste tasting having medicinal properties like soothing effect and anti-grouch properties.

It has been employed for reduction in anxiety and strengthening of spleen, stomach and gastrointestinal system [48] in traditional Chinese and Korean medicine.

Inhibition of Cholinesterase Activity: Inducing release of neurotransmitter acetylcholine in brain is one of the treatment ways used for NDs such as AD that may control further decline in higher cognitive function and dementia. [10] Cholinesterase inhibition is the most accepted treatment strategy for AD that can inactivate the enzyme acetylcholinesterase (AChE) to raise levels of acetylcholine in the brain. Despite production of several synthetic drugs for the treatment of learning and memory disorders, the therapeutic effectiveness is low and is accompanied by undesirable side effects. This has led to an increase in the inclination of people toward traditional medicines. [49] Herbs like Juglans regia L., *Withania Somnifera* (L.) Dunal., Acorus calmus L., *Centella asiatica* (L.) Urban, *Boswellia serrata* Roxb. ex Colebr., are used in Unani medicine to enhance memory by clearing the Acetylcholinesterase and β-amyloid plaques, antioxidation and anti-inflammatory activity.

Juglans regia L. (Walnuts) posses a high amount (3.68 mmol/oz) of antioxidants, such as flavonoids, melatonin, phenolic acid (ellagic acid), gamma tocopherol (vitamin E), folate, juglone, selenium, and proanthocyanidins [50-51]. It has various constituents possessing anti-inflammatory and antioxidant effects. A diet with walnuts has been reported to show beneficial effects on memory, anxiety, coordination, learning, motor and locomotor activity gas [51]. Studies demonstrated reduction in oxidative stress both by decreasing free radical levels and by boosting antioxidant defence, thus reducing oxidative damage to lipids and proteins.

Withania somnifera (L.) Dunal. (Winter Cherry) is an evergreen shrub. The apparent properties of this medicinal plant include the potential to ameliorate concentration, mood, and memory, as well as furnish resilience against disease and pathogens [52]. Traditionally, formulations involving *Withania somnifera* (L.) Dunal. are used for asthma, ulcers, goiter, and arthritis, insomnia, anxiety and neurological disorders. *Acorus calamus* L. (Sweet Flag) is a wild plant referred to as a potent medication for enhancing memory in the popular sources of the Iranian traditional medicine 53 and has been suggested for treating AD [54, 55]. *Centella asiatica* (L.) Urban, (Indian pennywort) from the Apiaceae family is used in Ayurvedic medicine and traditional Chinese to enhance memory function [56]. Extracts of this medicinal plant have been widely known to show mitoprotective and neuronal antioxidant results *in-vitro* and *in-vivo* [57, 58].

Oleo-gum resin of *Boswellia serrata* Roxb. ex Colebr. also called Kundur is popularly used in the Unani system of medicine for various ailments especially skin diseases, rheumatism, dyspepsia, dysentery, haemorrhoids, lung diseases, corneal ulcer and urinary disorders [59]. Also it is considered as a promising substitute to nonsteroidal anti-inflammatory drug [60]. Kundur has been used for treating inflammatory diseases in traditional medicine [60].

Anti-Inflammatory and Antioxidative Activities: Many medicinal plants are available that exhibit anti-inflammatory activity inhibiting cyclooxygenase-1 (COX-1) that is present around amyloids plaque in microglia. The collection of this enzyme in AD patients in microglia cells may be the cause of local growth in oxidative stress and synthesis of prostaglandin [61]. Plants *Ferula assafoetida* L., *Zingiber officinale* Rosc. *and Syzygium aromaticum* Merr. & L.M. Perry have been shown to possess anti-COX-1 activity. [61] *Ferula assafoetida* L. (Asafoetida) has previously been used in traditional medicines for treating diseases like asthma, bronchitis, epilepsy, ulcer, intestinal parasites, antihelminthic influenza, whooping cough, and as a memory enhancer [62-65].

Further, it possesses neuroprotective, [66] antioxidant, [67] cancer chemopreventive, [68] anticarcinogenesis, [68, 69] anti-diabetic, [70] relaxant effect, [71] antimicrobial, [72] antifungal, [73] antiviral, [74] antispasmodic and hypotensive [75] activities. Outcomes of *F. asafoetida* extract were investigated on learning and memory in rat models by Vijayalakshmi *et al*. [76] Marked improvements of memory score and transfer latency in elevated plus maze model was shown by the extract. Also, increased antioxidant levels and inhibition of cholinesterase levels in the brain were observed.

Hence, the ability of *F. asafoetida* as memory enhancer may be accredited to acetylcholinesterase inhibition and antioxidation characteristics. *Zingiber officinale* Rosc. (Dry Ginger) contains gingerol, shogaol, and paradols [77]. Data from scientific research have shown *Z. officinale* to possess antioxidant, neuroprotective, acetylcholinesterase inhibitory (AChEI), and memory-improving effects. It displayed anti-COX-1 and free radical scavenging activities that may be due to the presence of prominent phytochemicals: shogaols and gingerols [78].

Syzygium aromaticum Merr. & L.M. Perry (Clove) has been used in the traditional medicinal systems owing to its various pharmacological activities. Its antioxidant and antimicrobial properties have led to its use as preservative in many foods [79]. There are various formulations containing this plant that imparts cognitive improvement. A study was conducted by Hossein M. et al that indicates that clove extract improves mice's learning and memory recall ability in an inverse dose-dependent manner [80].

CONCLUSION: Neuronal death and degeneration is the underlying process accountable for clinical manifestations of plenty of different neurological disorders of aging. AD is a chronic ND, considered amongst the most intractable medical problems with large economic and social costs. AD has no proper treatment to cure the disease till date. Medicinal plants depict promise in ND treatment due to active phyto-constituents and their biological activities with cognitive benefits and mechanisms of action. The application of medicinal plants has gained much interest for their therapeutic efficacy for numerous decades. Clinical evidence shows medicinal plants can ameliorate memory and learn in patients with mild-to-moderate AD. Biological and pharmacological studies have been seen for several medicinal plants, such as *Prunella vulgaris* L., *Melissa officinalis* L., *Morinda citrifolia* L., *Hypericum perforatum* Linn., *Lycopodium serratum, Polygala tenuifolia* Willd., *Celastrus paniculatus* Willd., *Cyperus rotundus* L., *Ziziphus jujube* Mill., *Juglans regia* L., *Withania somnifera* (L.) Dunal, *Acorus calmus* L., *Centella asiatica* (L.) Urban, *Boswellia serrata* Roxb. ex Colebr., *Ferula asafoetida* L., and *Zingiber officinale* Rosc. The active components of these plants exhibit one or more properties amongst inhibition of AChE, alteration of Aβ processing, oxidative stress, protection against apoptosis, anti-inflammatory effects, cognitive improvement and neuroprotection. Ultimately the application of medicinal plants for treating ND, specifically AD, and the pharmacological treatment currently used need to be compared for further advancement.

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