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REVIEW ARTICLE

Neuroprotective Properties of Some Indian Medicinal Plants

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ABSTRACT

The study of antioxidants has gained great attraction recently due to their health implications. The central nervous system is vulnerable to oxidative stress as a consequence of high metabolic rate and deficient antioxidant system. The increasing amount of experimental evidence shows the involvement of reactive oxygen species in neurodegenerative diseases. Antioxidants neutralize free radicals and are effective in suppressing or preventing these disorders. Ayurveda, an ancient system of Indian medicine, has defined a number of plants with therapeutic benefits for the treatment of neurodegenerative disease, having antioxidant activities. Extracts of *Bacopa monniera* had proved to improve human cognitive function. *Bacopa* extract is claimed to have antioxidative function. *Ginkgo biloba* is reported to reduce free radical levels. Extracts of *Withania somnifera* improves antioxidant status in oxidative stress induced neurodegeneration. It has been proved that consumption of antioxidant rich diet may reduce lipid peroxide and increase antioxidant levels in plasma. There are still a large number of plants that need to be examined for their potential neuroprotective properties. Assays based on genomics and proteomics are expected to offer comprehensive information about molecular mechanism of neurological ailments and their protection by plant extracts. This will greatly help in identifying more potent compounds with potential applications in prevention of human ailments.

Key words: Antioxidants, Neurodegeneration, Neuroprotection, Oxidative Stress.

INTRODUCTION

Neurodegeneration refers to a condition of neuronal death occurring as a result of progressive disease of long term [1]. It involves degeneration of circumscribed group of neurons that may be functionally or neuroanatomically connected [2]. During neurodegeneration there is a deterioration of neurobiological tissue. Neurons degenerated are not replaced resulting in cognitive loss, dementia, Alzheimer's disease, Parkinson's disease Amyotrophic lateral sclerosis and cerebella degeneration. Thus any pathological process causing neuronal death generally has irreversible consequences [3]. It is possible to differentiate between acute and chronic neurodegeneration. Acute neurodegeneration is caused by a specific event whereas chronic neurodegeneration is normally a constant disease state with a multifactorial origin that has longer progression. The neurodegeneration field has attracted much attention in recent times, leading to several new insights in to cell biology.

Neurodegenerative diseases represent a large group of neurological disorders with heterogeneous clinical and pathological expressions affecting specific subsets of neurons in specific functional anatomical systems; they arise for unknown reasons and progress in a relentless manner. Neurodegenerative disorders are a major cause or mortality and disability and as result of increasing life spans represent one of the key medical research challenges. Among hundreds of different neurodegenerative disorders, so far lion's share of attention has been given Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD) and amyotrophic lateral sclerosis (ALS). The number of neurodegenerative diseases is currently estimated to a few hundred and among these many appear to overlap with one another clinically and pathologically rendering their practical classification quite challenging. Different neurodegenerative diseases are recognized by neuronal phenotypes that are primarily lost and neurological defects that accompany this loss. Neurodegenerative disorders of the Central Nervous System may be grouped into diseases of cortex, the basal ganglia, the brain stem, and the cerebellum or the spinal cord [4].

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Alzheimer's disease is a neurodegenerative disorder associated with a decline in cognitive impairments, progressive neurodegeneration and formation of amyloid-β (Aβ) containing plaques and neurofibrillary tangles. It is initially characterized by synaptic damage accompanied by neuronal loss [5]. It is the most common form of onset of adult dementia and attention deficit disorders [6]**.** Nootropic agents such are used primarily for improving memory, mood and behavior. Sporadic forms of AD generally afflict patients later in life, with onset of sporadic AD occurring usually between the ages of 60 and 70[7]. Parkinson's disease (PD) is a chronic progressive neurodegenerative movement disorder characterized by a profound and selective loss of nigrostriatal dopaminergic neurons. Clinical manifestations of this complex disease include motor impairments involving resting tremor, bradykinesia, postural instability, gait difficulty and rigidity [8]. A major hurdle in development of neuroprotective therapies are due to limited understanding of disease processes leading to death of dopaminergic neurons. The molecular pathways leading to this pathological condition and are obscure, but it is believed that it may result from an environmental factor, a genetic causation or a combination of the two.

Mechanism of neurodegeneration

Excitotoxicity: Olney (1969) coined the term 'excitotoxin' to describe the neurotoxic effects of excitatory amino acids which destroyed neurons in the area of injection [9]. Excitotoxicity refers to neuronal cell death caused by activation of excitatory amino acid receptors. Glutamate is the primary excitatory neurotransmitter in the central nervous system. Interaction of glutamate with specific membrane receptors is responsible for many neurological functions, including cognition, memory and sensation. It is believed that glutamate mediate most excitatory synaptic transmission in mammalian brain. In various neurodegenerative diseases, activation of glutamate receptors may mediate neuronal injury of death [10]. This form of injury appears to be mediated by excessive influx of calcium into neurons through ionic channels triggered by the activation of glutamate receptors. Although glutamate is necessary for normal functioning of brain, but, excessive amounts can lead to cell death via excitotoxic mechanism [11].

Apoptosis: Apoptosis, which is recognized by changes in nucleus viz. chromatin aggregation, DNA fragmentation and cell shrinkage; can be initiated by various cell signals. Often it is associated with excitotoxicity. The final process of apoptosis includes activation of proteases which in turn activates various inactive protein [12]

Amyloid cascade hypothesis: According to this hypothesis abnormal deposition of β amyloid leads to removal of the neuronal cells. It is reported in patients having abnormality of DNA coding Amyloid Precursor Protein (APP), lethal chemical cascade in neurons is initiated. Abnormal DNA causes formation of altered APP which in turn gets accumulated as β amyloid deposits [13].

Oxidative stress: Oxygen is a dangerous friend. Evidence indicates that oxidative stress can lead to cell and tissue injury. However the free radicals that are generated during oxidative are produced during normal metabolism and thus involve in both human health and disease. Oxygen radicals may be formed as a by-product of enzymatic reactions in vivo. Oxidative stress is a cytotoxic consequence of such by products observed during neurodegeneration and ageing process. During oxidative stress there is a shift towards the pro-oxidant in the pro-oxidant/antioxidant balance that can occur as a result of an increase in oxidative metabolism. Its increase at the cellular level can come as a consequence of several factors, including exposure to alcohol, cold, medications, trauma, toxins, radiation etc [14]. Oxidative stress occurs in a cellular system when the production of free radical moieties exceeds the antioxidant capacity of that system

Sodium nitrite mediated neurodegeneration: The nitrite salt of $NaNO_2$ (Sodium nitrite), has ability go convert hemoglobin to methemoglobin. This causes reduction in oxygen carrying capacity of blood, leading to memory impairment. Under clinical conditions of AD, the combination of $NaNO_2$ and D-galactose has also been reported [15].

Neuroprotection: Neuroprotection is a broad term to cover any therapeutic strategy to prevent nerve cells called neurons from dying, and it usually involves an intervention, either a drug or treatment. It is a mechanism used to protect neuronal injury or degeneration of CNS following acute disorders. The goal of neuroprotection is to limit neuronal dysfunction after injury and attempt to maintain the possible integrity of cellular interactions in the brain resulting in undisturbed neural function. There is a wide range of neuroprotection products available or undergoing research and some products can potentially be used in more than one disorder, as many of the

mechanism underlying are similar. These products may be of various kinds and can be classified as free radical scavengers, anti-excitotoxic agents, apoptosis inhibitors, neurotrophic factors etc.[16] Different aspects of neuroprotection are being examined, concentrating on different elements leading to loss of nerve cells.

Antioxidant Defense: An antioxidant is any substance that when present at low concentrations compared to oxidizeable substance, significantly delays or prevents oxidation of that substrate [17]. These antioxidants may be endogenous or exogenous in origin. Depending upon mode of action, antioxidants may be classified as chain breaking and preventive antioxidants. Among the most prominent defenses are the enzyme superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) which constitute the major intracellular antioxidant protection systems by removing superoxide anion and hydrogen peroxide. Evidence indicates that phytochemicals having antioxidant properties reduce the symptoms of Neurodegeneration. Some studies have indicated that phenolic substances such as flavonoids are considerably potent antioxidants [18]. Flavonoids have the property of scavenging free radical and preventing lipid peroxidation [19].

Herbal neuroprotection: The Indian system of medicine, Ayurveda, is gaining greater attention these days. The disease preventive and health promotive approach of Ayurveda is now gaining increasing acceptability. The revitalization and rejuvenation treatment therapy in Ayurveda is known as the 'Rasyana chikitsa'**.** *Rasayana* drugs act inside the human body by modulating the nuero-endocrino-immune systems and have been found to be a rich source of antioxidants [20,21]**..** These medicinal plants represent a great deal of untapped reservoir of drugs and the structural diversity of their component molecules makes a valuable source of novel lead compounds [22]. Researches had proved that certain non-nutritive chemicals in plants viz terpenoids and flavonoids possess antioxidant properties. The lack of effective and widely applicable pharmacological treatments in the modern therapy for neurodegenerative disorders may explain a growing interest in the traditional medicines [23]. According to estimation of WHO, 70-80% of the world population relies on traditional medicine, mostly plant drug for their primary healthcare need [24]. The traditional crude form of remedy has emerged as standardized herbal extract, its formulations and even composite preparations. Moreover particular component responsible for activity have also been isolated and some of which have been synthesised [25,26]. Some available scientific literature revealing neuroprotective action of such plants are described below in this article.

According to ayurveda, Alzheimer's disease is an imbalance of *vata, pitta* and *kapha.* Medhya (intellectual promoting) herbs such as, *Convolvulus microphyllus (C. pluricaulis), Centella asiatica, Bacopa monnieri, Acorus calamus* and *Celastrus paniculatus* are beneficial in cognitive disorders [27,28,29]

Hemidesmus indicus (HI), commonly known as Indian sarsaparilla or Anantmool is a slender, laticiferous and twining shrub, occurs over the greater part of India and some costal districts of Orissa [14]. It is widely recognized in folk medicine and as ingredient in Ayurvedic and Unani preparations against various diseases. The root is said to be having antioxidant properties and studies have reported the nootropic (memory enhancer) potential in mice.). *n-butanol fraction of Hemidesmus indicus* root extracts is proved to enhance memory [57].

Trapa bispinosa a floating herb is one of the medicinal plant that have been used as nerve tonic from time immemorial [30]. It is proved to be neuroprotective via reducing oxidative stress induced by D- galactose in the way of activating glutathione peroxidase and catalase consequently reducing lipid peroxide [31] *Bacopa monniera* (BM) is a reputed nootropic plant mentioned in ayurveda for various disorder of CNS [32]. Gajare et al have reported neuroprotective effect of BM on lipofuscinogenesis and fluorescence product in brain of D-Galactose induced aging accelerated mice. The study demonstrated that D-Galactose, react with amino groups side chains of protein and leads to formation of amadori products which finally result in to advanced glycation end product (AEGs) [33], which are rich source of free radicals [34] and cause oxidative stress by chemical oxidation of AEGs (35). Also the glycated protein produce fifty times more free radicals than non glycated protein at physiological pH [36,37,38], resulting in increased oxidative stress and thereby damage to the micromolecules and cell organelles particularly mitochondria, which is one of the sites of reactive oxygen species (ROS) formation. In another study, BM has documented for prevention of aluminum neurotoxicity in the cerebral cortex of rat brain [39]. Proteins and lipid are vital macromolecules when damaged by aluminum results in interference with functioning

of cell organelles like mitochondria and lysosomes making them less efficient [40]. The BM protected these macromolecules and thereby exhibited neuroprotection. The conservation of endogenous antioxidant with the treatment of BM enzymes further indicated the neuroprotection from the free radical induced toxicity.

Withania somnifera (WS) has been in use for more than 2500 years for diverse clinical condition especially for improvement of memory and cognition enhancement [41]. WS root extract was shown to exhibit nootropic effects in mice and caused inhibition of AchE, this inhibition suggested indirect facilitation of cholinergic transmission which may be of great value in neurodegeneration states associated with cholinergic deficiencies [42,43].

Trigunayat et al reported attenuation of long term hypoperfusion induced anxiety and restlessness accompanied by deficit in learning and memory. Biochemical investigation reflected significant increase in the lipid peroxidation, superoxide dismutase activity and fall in total suphahydral (T-SH) levels, suggesting antioxidant properties of WS in neuroprotection [44].

Another study with methanolic extract of WS reported significant inhibition ofAchE activity and thereby suggested its role in AD prominently associated with cholinergic depletion. The collective data supports the use of WS as a neuroprotective with putative mechanism of action [41].

The aqueous extract of *Centella asiatica* (CA) in the dose of 200 and 300 mg/kg showed significant improvement in learning and memory The study further reported significant decrease in the levels of malondialdehyde (MDA), with simultaneous significant level of glutathione [45]. MDA is end product of lipid peroxidation and is a measure of a free radical generation which is prime reason for neurodegeneration caused by oxidative stress. In addition, glutathione is major anti oxidant and free radical scavenging enzyme. The increased levels of it further support the potential of CA towards involvement of antioxidant mechanism by augmenting the endogenous antioxidant enzymes in the brain [45].

Ethanolic extract of *Ocimum sanctum* (OS) ameliorated scopolamine (0.4mg/kg) as well as aging induced memory deficit. This amelioration suggested possible cholinergic modulation as mechanism of its action and thereby indicated possible utility in the management of AD and age associated dementias [47].

Similar inhibition of AchE was also observed with methanolic extract of *Semecarpus anacardium* (SA) and *Nardostachys jatamansi* (NJ). The SA was especially effective to prevent stress induced neurodegeneration [48, 49].

*Clitoria ternatea (*CT) is a reputed drug in Indian traditional system of ayurvedic medicine [50]. Vyawahare et al reported the effect of alcoholic extract of roots of CT on scopolamine induced memory disruption using radial arm maze and condition avoidance response test. The study reported significant prevention of scopolamine induced memory disruption, and thereby validated traditional claim.

Shukla et al studied neuroprotective effect of Hydroalcoholic extract of rhizomes of *Acorus calamus* AC against middle cerebral artery occlusion (MCAO) induced ischemia and thereby neuronal damage. The investigation found significant improvement in neurobehavioral performance associated with significant reduction in malonaldehyde levels in cortex and increased in glutathione as well as superoxide dismutase activity in cortex and corpus striatum in rats [51].

Panax ginseng (PG) is another plant that has been used since ancient time to treat ailments including neurodegeneration associated with aging [52].Animals treated with either ginseng extract or composite preparations containing ginseng is claimed to improve learning and memory [53]. The Wang et al documented the dose dependent reduction in the βamyloid deposition or glutamate induced excitotoxicity, thereby neuronal death, a majorcause of AD [40].

Study had demonstrated that Brahmi extracts protected neurons from the beta-amyloid induced cell death, but not glutamate induced exitoxicity. This neuroprotection was possibly, due to its ability to suppress cellular acetyl-cholinestrase activity but not the inhibition of glutamate-mediated toxicity [54]. Coriander (Coriandrum sativum) is a plant among others which improve blood circulation to the head, impart mental concentration and memory capabilities. It has free radical scavenging and lipid peroxidation activities [55]. Coriander seed aqueous extract has shown protection and an improvement in therapeutic action on pyramidal cells in cerebral cortex against neurodegenerative disorders and Alzheimer's disease [56]

CONCLUSION

Ayurveda emphasizes use of herbs, nutraceuticals or lifestyle changes for controlling age related neurodegenerative disorders. In traditional practice of medicines, various plants have been

used for neuroprotection. An ethnopharmacological approach has provided which leads to identify potential of new drugs from plant sources, including those for neurodegenerative disorders. It is apparent from the manuscript that a variety of plant shows or has potential to show activities relevant to use in the neurodegenerative disorder. The majority of studies found on cholinergic. Certain plant like *Clitoria ternatea, Acorus calamus* etc. has shown beneficial effects on cognitive function. However further studies regarding the compounds responsible for exact mechanism involved are necessary. The typical scientific approach for selecting plants to investigate for the treatment of a neurodegenerative disease is relatively rational method to develop more acceptable and better substitute to the present pharmacotherapy. Research is required to explore active components involved in antioxidant activity. The revealed antioxidant property of extracts may provide potential therapeutic intervention against oxidative threats and neurodegenerative disorders.

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