Indian Herbs for the Treatment of Neurodegenerative Disease

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Abstract Ayurveda, an ancient system of medicine that is indigenous to India, is believed to be the world's oldest comprehensive health-care system and is now one of the most recognized and widely practiced disciplines of alternative medicine in the world. Medicinal herbs have been in use for treating diseases since ancient times in India. Ayurvedic therapies with medicinal herbs and herbomineral products generally provide relief without much adverse effects even after prolonged administration. Neurodegenerative disorders are a major cause of mortality and disability, and increasing life spans represent one of the key challenges of medical research. Ayurvedic medicine describes most neurodegenerative diseases and has defined a number of plants with therapeutic benefits for the treatment of neurodegenerative diseases having antioxidant activities. In this chapter, the role of four important Ayurvedic medicinal plants, viz., *Withania somnifera* (ashwagandha), *Bacopa monnieri* (brahmi), *Centella asiatica* (gotu kola), and *Mucuna pruriens* (velvet bean), on neurodegenerative diseases are discussed.

Keywords Ayurveda • Neurodegenerative disorders • Withania somnifera • Bacopa monnieri • Centella asiatica • Mucuna pruriens

Ayurveda: The Indian System of Medicine

The practice of herbal medicine dates back to the very earliest periods of known human history. There is evidence of herbs having been used in the treatment of diseases and for revitalizing body systems in almost all ancient civilizations—the Indian, the Egyptian, the Chinese, and even the Greek and Roman civilizations. Plants were the mainstay of medicine and credited with mystical and almost supernatural powers of healing (Bakhru 2001). Ayurveda, "science of life," is believed to be the world's oldest comprehensive health-care system and is indigenous to India. It is now one of the most recognized and widely practiced disciplines of alternative medicine in the world.

In Ayurveda, substances of natural origin, including whole plants or their parts, animal parts, and minerals, are used as medicines, either alone or in combination.

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In addition, various other measures are used in an attempt to maintain health in a healthy person and alleviate disorders of the body and mind. The belief in Ayurvedic medicine is that a disease is the product of an imbalance in the body and mental elements that reduce the body's resistance to diseases. If the imbalance is corrected and the body's defense mechanisms are strengthened by herbal formulas, lifestyle changes, and diet, then the body will resist a disease with a goal of eliminating it (Mishra 2004).

Herbal and herbomineral products regularly used in Ayurveda are believed to strengthen the body's defenses. These substances act on the principles of *samanya* (homologous) and *visesha* (antagonistic) action. Substances possessing homologous properties and actions increase the relevant elemental properties or constituents of the body, while those having antagonistic properties or actions decrease those properties or constituents. In cases of disease or imbalance of *dosha* (humor), *dhatu* (seven body tissues, the lymph, blood, muscle, adipose tissue, bone, bone marrow, semen), and *mala* (feces, urine, and other waste products), the rational use of naturally available substances aims to restore normality (WHO 2010).

Ayurvedic medicine has benefited from the advances in science and technology. These advances facilitated the understanding of diseases, the development of better pharmaceutical products, and the implementation of diagnostic techniques. Ayurvedic therapies generally provide relief without much adverse effect even after prolonged administration. Ayurvedic herbs and formulas often have a wide spectrum of therapeutic activity. The pharmacological activities of herbs may not be confined to one specific chemical constituent. Ayurvedic therapies are known to be relatively economical, and the Ayurvedic formulas are time tested for safety (Mishra 2004).

Medicinal herbs have been in use for treating diseases since ancient times in India. Herbs are used in many different ways. However, the ultimate objective of their use is that they should interact directly with our body chemistry. They may be used in various forms like food, medicine, cosmetics, or fragrance, but in all cases, their active constituents must be absorbed into the body for deriving the required benefits. Once they are absorbed into the bloodstream, they circulate to influence our whole system. The active constituents of the herb can enter the body in several ways. These include consuming the herb orally or application on the skin or even smelling the aroma through the nose (Bakhru 2001). During the past 100 years, several hundred Ayurvedic herbs have been investigated with respect to plant chemistry, active chemical constituents, pharmacological effects, safety, and efficacy. A single herb is rarely administered to a patient in Ayurveda. Herbal formulas are favored because the founders of Ayurveda recognized the possible synergistic and counterbalancing effects of herbs.

Neurodegenerative Disorders

The progressive loss of structure and/or function of neurons, including their death, is referred to as neurodegeneration. This loss can be inherited and determined at birth or soon after birth or can even be due to an injury (Bredesen et al. 2006). The

number of neurodegenerative diseases is estimated to a few hundred, and among these, many appear to overlap with one another clinically and pathologically. Neurodegenerative disorders are a major cause of mortality and disability, and increasing life spans represent one of the key challenges of medical research. The mechanisms of neurodegeneration vary in nature, but in simpler terms, it could be due to (1) excitotoxicity, (2) apoptosis, (3) amyloid cascade, (4) oxidative stress, and (5) sodium nitrite-mediated neurodegeneration (Pandit 2011).

Reactive oxygen species (ROS) such as superoxide ($O_2^{\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2) produced endogenously play certain beneficial roles in cellular functions, but they also participate in harmful events such as in neurodegeneration. Much importance has been given to neurodegenerative diseases such as Alzheimer's, Huntington's, and Parkinson's diseases and amyotrophic lateral sclerosis, and these diseases have been shown to be tightly linked to mitochondrial dysfunction affected by ROS (Ahmad 2012). Any therapeutic strategy that prevents neurons from dying either a drug or treatment is termed as neuroprotection. 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 an undisturbed neural function. Antioxidants neutralize free radicals and are effective in suppressing or preventing these disorders.

The Ayurvedic Way of Treating Neurodegenerative Diseases

Ayurveda is practiced through its eight specialized branches: *Kayachikitsa* (internal medicine), *Shalya* (surgery), *Shalakya* (ophthalmology and ENT), *Kaumarbhritya* (pediatrics), *Aagada* (toxicology), *Bhuta Vidya* (psychology), *Rasayana* (rejuvenation), and *Bajikarana* (or *Vajikarana*, sexology). Among these disciplines, *Rasayana tantra* regards the treatments to improve longevity and memory, to attain youthful appearance, and to maintain cognitive performance and physical strength (Singh et al. 2008).

Ayurvedic medicine describes most neurodegenerative diseases as being due to significant Vata (the humor of space and air) imbalance in the body and mind, particularly in one of the seven tissues of the body known as majja, or marrow, and of the brain. Imbalance can occur in many different ways and to various different extents. How it occurs is what differentiates one neurodegenerative disease from the other and from one individual to another. The imbalance of Vata in the brain means that the brain "tissue" dries up due to lack of nourishment, whether from a physical or emotional perspective or both. Ayurveda has recognized the need for the brain to remain nourished and accomplishes this through preventative and responsive measures.

Ayurveda has defined a number of plants with therapeutic benefits for the treatment of neurodegenerative diseases having antioxidant activities. This chapter gives details about four important Ayurvedic medicinal plants, viz., *Withania somnifera* (ashwagandha), *Bacopa monnieri* (brahmi), *Centella asiatica* (gotu kola), and *Mucuna pruriens* (velvet bean), and their role in neurodegenerative diseases.

Withania somnifera

Withania somnifera Dunal, commonly known as ashwagandha, belongs to the Solanaceae family and is widely distributed in the drier parts of tropical and subtropical zones, ranging from the Canary Islands, the Mediterranean region, and Northern Africa to Southeast Asia (Warrier et al. 1996). It is an important medicinal plant used in Ayurvedic and indigenous medicine for over 3000 years. The whole plant as well as its specific parts such as roots, stems, and leaves and also the plant extract and its constituents have been used in the treatment of various ailments. The main constituents of ashwagandha are alkaloids and steroidal lactones. Withanine, somniferine, somnine, somniferinine, and withananine are some of the chemical constituents present in it (Rani et al. 2012).

Withania is widely claimed to have potent aphrodisiac, sedative, rejuvenating, and life-prolonging properties. It is also used as a general energy-enhancing tonic known as Medhya Rasayana, which means "that which promotes learning and a good memory," and in geriatric problems (Nadkarni 1976). The roots are also used in constipation, senile debility, rheumatism, general debility, nervous exhaustion, loss of memory, loss of muscular energy, and spermatorrhea (Singh and Kumar 1998).

Withanamides are a novel class of compounds isolated from the fruit of *W. somnifera*. Jayaprakasam et al. (2004) have isolated the major withanamides A and C from *W. somnifera* fruit and tested their ability to inhibit lipid peroxidation. The free radical that initiated damage of the brain tissue is one of the major mechanisms considered in the pathology of AD. The withanamides were found to possess antioxidant activity. They also tested the ability of these withanamides in protecting the rat pheochromocytoma (PC-12) cells from β-amyloid peptide (BAP)-induced cytotoxicity as BAP plays a significant role in the development of AD. They found that withanamide A was the most active, and it completely neutralized the toxic effect of BAP on PC-12 cells. Withanamide C was found to protect the PC-12 cells from cell death due to the BAP (Jayaprakasam et al. 2010).

The active constituents of *W. somnifera* such as withanolide A, withanoside IV, and withanoside VI were shown to restore presynapses and postsynapses in addition to both axons and dendrites in cortical neurons after amyloid-β (Aβ)25–35-induced injury. Oral administration of withanolide A, withanoside IV, and withanoside VI (10 μmol/kg/day for 12 days) improved Aβ25–35-induced memory impairment, neurite atrophy, and synaptic loss in the cerebral cortex and hippocampus in mice. These observations by Tohda (2008) suggest the therapeutic potential of these *Withania* constituents in the treatment of neurodegenerative diseases.

The methanol extract of ashwagandha containing the active principles withanolide A, withanoside IV, and withanoside VI showed neurite outgrowth-promoting activity in human neuroblastoma SK-N-SH cells (Tohda et al. 2000). In an in vitro axonal atrophy model, withanolide A, withanoside IV, and withanoside VI were individually treated to the neurons, and each of these three compounds induced axonal growth in the presence of Aβ25–35 (Tohda et al. 2005; Kuboyama et al. 2005; 2006). Moreover, posttreatment with withanolide A, withanoside IV, or withanoside VI increased the synaptic densities in an in vitro synaptic degeneration

model established by the formation of synapses from rat cortical neurons and then treated with Aβ25–35 which resulted in losses of densities of presynapses and postsynapses (Kuboyama et al. 2005).

Scopolamine is a muscarinic receptor antagonist that induces amnesia in rodents (Klinkenberg and Blokland 2010). Scopolamine also influences the expression of genes related to muscarinic receptor signaling pathways, apoptosis, and cell differentiation in the rat brain (Hsieh et al. 2003). Konar et al. (2011) investigated the effects of the alcoholic extract of ashwagandha leaves on scopolamine-induced cell damages. Pretreatment with this alcoholic extract protected scopolamine-induced cell deaths in cultured human neuroblastoma IMR32 cells and cultured rat glioma C6 cells. Scopolamine treatment induced DNA damage and oxidative stress in C6 cells, but treatment with the alcoholic extract prevented the damage. Withaferin A and withanone were identified as the major constituents in this alcoholic extract. Withanone showed more preventive effects than withaferin A.

A study carried out by Sehgal et al. (2012) reports the reversal of Alzheimer's disease (AD) pathology in APP/PS1 mice by a partially purified *Withania somnifera* extract consisting of 75 % withanolides and 20 % withanosides by increasing the clearance of the toxic Aβ peptide from the brain, promoting its sequestration in plasma and ultimately its degradation in the periphery. These beneficial effects are associated with reversal of behavioral deficits and reduced AD pathology in very old AD-Tg mice (22–24 months old). The therapeutic benefits of *W. somnifera* on behavioral deficits and Aβ pathology are also confirmed in APPSwInd J20 mice, another AD mouse model. Oral administration of *W. somnifera* proved highly effective in reversing the behavioral deficits and pathological features in two mouse models of AD.

In a clinical trial involving chronically stressed humans, the effects of *W. somnifera* root and leaf extract were investigated. This extract contained withanolide glycosides, withaferin A, oligosaccharides, alkaloids, and polysaccharides with no scopolamine. It was reported that the consumption of this extract significantly reduced experiential and biochemical indicators of stress without adverse effects. The therapeutic activity of the extract was attributed to its effect on the hypothalamic-pituitary-adrenal axis, which regulates serum cortisol concentration (Auddy et al. 2008).

In an experimentally validated Alzheimer's disease model, where the syndrome was induced by ibotenic acid (IA) lesioning of the nucleus basalis magnocellularis (NBM) in rats, glycowithanolides withaferin A and sitoindosides VII–X that were isolated from the roots of ashwagandha were tested by administering orally with equimolar amounts of sitoindosides VII–X and withaferin A. The authors found a significantly reversing effect of IA-induced cognitive deficits in these rats on treatment with sitoindosides VII–X and withaferin A (Bhattacharya et al. 1995).

Bacopa monnieri

Bacopa monnieri (L.), commonly known as brahmi, is found throughout the plains of India in damp marshy areas and also in Sri Lanka, Pakistan, and Bangladesh (Khare 2007). Brahmi is used in the Indian Ayurvedic system for its memory-enhancing,

anti-inflammatory, analgesic, antipyretic, sedative, and antiepileptic properties (Kirtikar and Basu 1935). Phytochemical studies on brahmi have shown that it contains many active constituents, including alkaloids, brahmine, herpestine, saponins (bacosides A, A3, and B and bacopasaponin A to F), D-mannitol, betulinic acid, β-sitosterol, and stigmasterols (Nathan et al. 2001). But the major constituents are the steroidal saponins, bacosides A and B (Chatterji et al. 1965). Research has been conducted on both animals and human volunteers to study the efficacy of *Bacopa monnieri*, especially on its neuroprotective and memory-enhancing effects.

The neuroprotective effects of brahmi were determined in normal and in β-amyloid protein (25–35) and glutamate-induced neurotoxicity in primary cortical cultured neurons. Brahmi extract was found to protect neurons from β-amyloid-induced cell death, but not in glutamate-induced excitotoxicity, and this neuroprotection was possible due to the extract's ability to suppress cellular acetylcholinesterase activity. This extract also promoted cell survival and exhibited both reducing and lipid peroxidation inhibitory activities (Limpeanchob et al. 2008). Brahmi was evaluated for its antioxidant activity in 3-month-old female Wistar rats for 10 days and found to protect the central and peripheral neuronal systems through its unique effects on the antioxidant enzyme activities and intracellular signaling pathways (Priyanka et al. 2013). A study was carried out to test the ability of brahmi leaf powder on neuronal oxidative stress in prepubertal mice. *Bacopa monnieri* modulated endogenous markers of oxidative stress in brain tissue of these animals (Shinomol and Muralidhara 2011).

Bacosides from the alcoholic extract of brahmi were tested on experimentally induced amnesia by scopolamine, sodium nitrite, and BN52021 in mice. The results showed that bacosides facilitate anterograde memory and attenuate anterograde experimental amnesia in mice (Kishore and Singh 2005). In a study involving human healthy volunteers and SDAT patients of 60–75 years, a poly-herbal formulation containing brahmi was given for a period of 12 months. The authors evaluated the cognitive functions, inflammatory markers, and oxidative stress in these healthy volunteers and SDAT patients and found an improvement in cognitive measures and a reduction in inflammation and oxidative stress levels (Sadhu et al. 2014). A standardized whole plant dry extract of *B. monnieri* was evaluated for its cognitive function and effect and its safety and tolerability in healthy elderly participants of 65 years or older. The results showed that the standardized extract has potential for enhancing cognitive performance in aging (Calabrese et al. 2008).

There is a significant correlation between paraquat exposure and increased risk for Parkinson's disease in humans. A standardized extract of brahmi was tested on acute paraquat-induced oxidative stress in different brain regions of prepubertal mice. In this study, brahmi supplementation restored the activities of cholinergic enzymes and also the striatal dopamine levels of paraquat-treated mice (Hosamani et al. 2014). These studies show that *B. monnieri* protects against oxidative damage, possibly by enhancing the activities of antioxidative enzymes and improving redox status. In an experiment by Jansen et al. (2014), fruit flies (*Drosophila melanogaster*) that served as a model of Parkinson's disease (based on loss of function of phosphatase and tensin-induced putative kinase 1 (PINK1)) were cultured for food

containing brahmi and a combination of herbs that included brahmi. They observed a significant improvement in the climbing ability of PD flies treated with brahmi alone and in combination with other herbs. Jadiya et al. (2011) tested the effects of *B. monnieri* on transgenic and pharmacological *Caenorhabditis elegans* models of Parkinson's disease. Their results showed that *B. monnieri* reduced α-synuclein aggregation, prevented dopaminergic neurodegeneration, and restored the lipid content in *C. elegans* proving *B. monnieri* as a possible antiparkinsonian agent.

In an animal model of Alzheimer's disease induced by ethylcholine aziridinium, the effect of the alcoholic extract of *B. monnieri* was analyzed. This extract mitigated the memory impairment and the degeneration of neurons in the hippocampus in this animal model by improving acetylcholine levels and cerebral blood flow, suggesting the cognitive enhancing and neuroprotection of brahmi in Alzheimer's disease (Uabundit et al. 2010). Another study by Saini et al. (2012) evaluated the neuroprotective potential of *B. monnieri* against cognitive impairment in colchicine-induced dementia in rats as this is an accepted model of sporadic dementia of Alzheimer's disease. *B. monnieri* administration attenuated the oxidative damage by colchicine by decreasing lipid peroxidation and protein carbonyl levels and restoring the antioxidant enzymes along with the membrane-bound enzymes in the brain suggesting the therapeutic potential of *B. monnieri* in the treatment of AD-associated cognitive decline. In a study by Zhang et al. (2013), the role of *B. monnieri* in improving memory performance and protection against AD by increasing expression or activity of Na^+/K^+-ATPase was highlighted. The effect of bacosides, the active saponins of *B. monnieri*, was investigated against age-associated neurodegeneration in aged female Wistar rat brain and was found to act as a potential therapeutic intervention in forestalling the deleterious effects of aging and preventing the age-associated pathologies like senile dementia of Alzheimer's type (SDAT) (Rastogi et al. 2012a). These authors (Rastogi et al. 2012b) further tested backsides against age-related chronic neuroinflammation in the Wistar rat brain for 3 months as neuroinflammation finds importance in age-associated neurodegeneration and SDAT. The results of this study demonstrated a significant attenuation of age-dependent elevation of pro-inflammatory cytokines, iNOS protein expression, and total nitrite and lipofuscin content in middle-aged and aged rat brain cortex on long-term administration of bacosides.

Centella asiatica

Centella asiatica (L.), commonly known as Indian pennywort, belongs to the family Apiaceae. It is a perennial creeper and a valuable medicinal herb. It is distributed throughout the tropical and subtropical regions of India, China, Nepal, Madagascar, Sri Lanka, and Indonesia. It has been used as a medicinal herb for thousands of years in India, China, Sri Lanka, Nepal, and Madagascar. *C. asiatica* is one of the chief herbs used for treating skin problems, to heal wounds, for revitalizing the nerves and brain cells, to increase attention span and concentration,

and to combat aging (Brinkhaus et al. 2000). In India, *C. asiatica* is valued as an ethnomedicine in Ayurveda and Unani, for treating different ailments like asthma, skin disorders, ulcers, and body aches and for improving memory, and also as a nervine tonic (Singh et al. 2010). *C. asiatica* contains a broad spectrum of phytochemicals that include triterpenoids, volatile fatty acids, glycosides, flavonoids, alkaloids, and tannins (Das 2011).

Fresh leaf extracts of *C. asiatica* were found to facilitate the dendritic growth in the hippocampal CA3 neurons. The active components of *C. asiatica*, asiatic acid, asiaticoside, and SM2, exhibited neuroprotective property and inhibited β-amyloid and free radical-induced cell death in B103 cell cultures and hippocampal slices (Rao et al. 2006). *Centella asiatica* were effective in preventing the cognitive deficits, as well as the oxidative stress caused by the intracerebroventricular administration of streptozotocin, indicating that *the C. asiatica* can act as a free radical scavenger (Kumar and Gupta 2003).

Glutamate treatment for rats can lead to excitation and oxidative stress resulting in neurodegeneration (Mates et al. 2002). Glutamate-administered rats were treated with a standardized extract of *C. asiatica* containing asiaticosides and found to attenuate the glutamate-induced excitation and oxidative stress (Ramanathan et al. 2007). Xu et al. (2012) investigated the neuroprotective effect of asiatic acid both in vitro (human neuroblastoma SH-SY5Y cells) and in vivo (neonatal mice) of glutamate toxicity. Pretreatment of the cells with asiatic acid attenuated glutamate toxicity by decreasing apoptotic cell death and reducing reactive oxygen species and stabilizing mitochondrial membrane potential. In mice, asiatic acid administration attenuated cognitive deficits and lipid peroxidation and glutathione in the hippocampus and cortex. It also attenuates neuronal damage of the pyramidal layer in the CA1 and CA3 regions.

Asiaticoside isolated from *C. asiatica* was investigated on memory impairment and inflammatory cytokine expression induced by transient cerebral ischemia and reperfusion in mice. Asiaticoside was found to be neuroprotective in these mice, and this effect could be associated with the anti-inflammatory effect of asiaticoside via inhibiting overactivation of p38 MAPK pathway (Chen et al. 2014). The derivatives of asiaticoside were tested for their potential protective effects against Aβ-induced cell death of B103 cells. Three of such derivatives, asiatic acid, asiaticoside 6, and SM2, showed strong inhibition of Aβ-induced death of B103 cells. Further, these three derivatives reduced H_2O_2-induced cell death and lowered intracellular free radical concentration (Mook-Jung et al. 1999). Lee et al. (2000) attempted to prepare neuroprotective compounds that were more efficacious than asiatic acid by modifying the chemical structure of asiatic acid. In an in vitro study using primary cultures of rat cortical neurons treated with glutamate, three of those asiatic acid derivatives were found to protect neurons from the oxidative damage caused by exposure to excess glutamate.

Tabassum et al. (2013) evaluated the preventive role of the ethanolic extract of *C. asiatica* in middle cerebral artery occlusion (MCAO) in rats. The administration of this extract revealed improved neurobehavioral activity and diminished infarction volume along with restored histological morphology of the brain in these rats.

Further, this extract reduced the levels of free radicals and improved the antioxidant status in MCAO rats. The authors attribute this antioxidant activity of *C. asiatica* extract to the presence of bioactive triterpenes, asiatic acid, asiaticoside, madecassic acid, and madecassoside. A water extract of *C. asiatica* was examined in a murine model of AD with high amyloid burden and found to attenuate the β-amyloid-associated behavioral abnormalities in these mice. In an in vitro study, this extract protected the SH-SY5Y cells and MC65 human neuroblastoma cells from β-amyloid toxicity (Soumyanath et al. 2012).

The prevention of aggregation of α-synuclein is a potential therapeutic intervention for preventing PD. In a study by Ruben et al. (2014), an aqueous leaf extract of *C. asiatica* was tested for amyloid-β (Aβ) levels in the brain and Aβ aggregation. In this in vitro study, *C. asiatica* extract inhibited α-synuclein aggregation and inhibited the formation of oligomer to aggregates indicating the therapeutic potential of *C. asiatica* in PD. In a rat model of the early phase of parkinsonism, madecassoside isolated from *C. asiatica* was tested by Xu et al. (2013). Treatment with madecassoside was found to improve locomotor dysfunction and to protect dopaminergic neuron by antagonizing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity. Madecassoside was effective in recovering MPTP-induced early signs of parkinsonism via its neuroprotective effects, including reversing the depletion of dopamine, antioxidant activity, increasing ratio of Bcl-2/Bax, and increasing protein expression of brain-derived neurotropic factor (BDNF). In another study, *C. asiatica* extract was administered to MPTP-induced neurotoxicity in aged Sprague-Dawley rats. The authors (Haleagrahara and Ponnusamy 2010) found that this extract significantly increased total antioxidants and antioxidant enzymes in the corpus striatum and hippocampus showing the neuroprotective effect of *C. asiatica*.

Mucuna pruriens

Mucuna pruriens L. (velvet bean), belonging to the family Fabaceae, is a vigorous annual climbing legume originally from eastern India and southern China (Duke 1981). It is widely distributed in tropical and subtropical regions of the world and was once widely cultivated as a green vegetable crop due to its high protein concentration (Pugalenthi et al. 2005). The plant has long been used in Ayurveda as a powerful aphrodisiac (Amin et al. 1996), to treat nervous disorders and arthritis (Jeyaweera 1981), and also for treating parkinsonism (Sathiyanarayanan and Arulmozhi 2007). The seed, root, and stem of *M. pruriens* possess valuable medicinal properties (Suresh et al. 2012).

The therapeutic effects of aqueous extract of *Mucuna pruriens* seed were evaluated in paraquat-exposed parkinsonian mouse model. Treatment of these mice with *M. pruriens* seed extract reduced paraquat-induced neurotoxicity by decreasing oxidative damage, physiological abnormalities, and immunohistochemical changes in this mouse model (Yadav et al. 2013). The neuroprotective effect of an

ethanolic extract of *M. pruriens* seed was evaluated in the MPTP model of PD. The extract recovered the number of tyrosine hydroxylase-positive cells in the substantia nigra and striatum and reduced the expression of iNOS and glial fibrillary acidic protein (GFAP) in the substantia nigra and increased the levels of dopamine. The extract also downregulated nitric oxide production, neuroinflammation, and microglial activation which can be contributed to its neuroprotective activity (Yadav et al. 2014).

Manyam et al. (2004a) evaluated the neurorestorative effect of *Mucuna pruriens* cotyledon powder on the nigrostriatal tract of 6-hydroxydopamine (6-OHDA)-lesioned rats, a model of PD. The cotyledon powder significantly restored the endogenous levodopa, dopamine, norepinephrine, and serotonin content in the substantia nigra. In a series of tests conducted by Kasture et al. (2009) in a subchronic mouse model of MPTP-induced dopamine neuron degeneration, *M. pruriens* seed extract was found to be antiparkinsonian but not neuroprotective. They attributed this effect to the presence of L-DOPA (dihydroxyphenylalanine) in the seed extract.

In a study involving eight Parkinson's disease patients, the seed powder of *Mucuna* and standard L-dopa/carbidopa (LD/CD) were administered. The authors conclude that *Mucuna* seed powder is better on tests performed than the standard LD/CD (Katzenschlager et al. 2004). Nagashayana and coworkers (2000) evaluated the efficacy of Ayurveda treatment (a concoction in cow's milk of powdered *Mucuna pruriens* and *Hyoscyamus reticulatus* seeds and *Withania somnifera* and *Sida cordifolia* roots) in 18 clinically diagnosed parkinsonian patients for a period of 84 days. They underline the importance of cleansing therapy in Ayurveda medication prior to palliative therapy based on their results. *M. pruriens* in the form of a powder (HP-200) was mixed with water and given orally to 60 patients with Parkinson's disease for a period of 12 weeks and found to be an effective treatment for these patients (HP-200 in Parkinson's Disease Study Group 1995). In a long-term study (52 weeks) in rats, HP-200 was administered to elucidate the levels of monoaminergic neurotransmitters and its metabolite in various regions of the brain. Oral administration of HP-200 had a significant effect on dopamine content in the cortex, but no significant effect on the other neurotransmitters and their metabolites in the nigrostriatal tract (Manyam et al. 2004b).

Mucuna pruriens was co-treated with *Withania somnifera* to parkinsonian mice induced by chronic exposure to paraquat. This co-treatment was effective in behavioral and antioxidant recovery, which is an indicator of the neuroprotective effects of both these plants (Prakash et al. 2013). *M. pruriens* is reputed to provide antiparkinsonian benefits without inducing drug-induced dyskinesias. Lieu et al. (2010) studied the effects of *M. pruriens* seed extract alone or in combination with dopa-decarboxylase inhibitors in the hemiparkinsonian rat model of PD. They found that the seed extract administered chronically provided long-term antiparkinsonian benefits without causing drug-induced dyskinesias. These authors (Lieu et al. 2012) further tested the *M. pruriens* endocarp powder in rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) hemiparkinsonian monkeys. They observed that the seed powder significantly ameliorates behavioral deficits in these animals, and this action could be attributed not only to the presence of L-dopa but to several other constituents in this extract.

Other Important Ayurvedic Medicinal Plants on Neuroprotection

The active component of *Curcuma longa*, curcumin, is a polyphenolic compound, and it has been reported to have protective effects in neurodegenerative disease by either reducing inflammation or oxidative damage in AD (Begum et al. 2008). Curcumin provided protection against α-synuclein-induced cytotoxicity in SH-SY5Y neuroblastoma cells by decreasing cytotoxicity, reducing intracellular ROS, inhibiting caspase-3 activation, and ameliorating signs of apoptosis (Wang et al. 2010). Other plants such as *Acorus calamus* (Zanoli et al. 1998) and *Glycyrrhiza glabra* (Dhingra et al. 2004) are also reported to have neuroprotective activity.

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