A REVIEW ON TRADITIONAL HERBS USED IN PARKINSON’S DISEASE (NADUKKU VATHAM)

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ABSTRACT

Parkinson’s disease (PD) is a chronic neurodegenerative disorder of the central nervous system commonly found among the elderly. The disease is characterized by tremor, bradykinesia (lethargic movement), rigidity and postural instability. Medical research has yet found no complete cure for this disorder although many treatment options and surgical methods are prescribed depending on the severity of the disease. The ancient Siddha system of medicine describes the disease as Nadukkuvatham. Herbal medicines for Parkinsonism have been used worldwide. In conventional therapeutics, the symptoms of Parkinsonism can be ameliorated through the use of levodopa and dopamine agonists. In Siddha system of medicine, most of the diseases of the Vatham are degenerative diseases of the nervous system. The herbs in the present review have been selected for scientific evaluation based on their neuroprotective action indicated in the Siddha Materia medica. The current review focuses the efficacy of herbs such as Curcuma longa, Mucuna pruriens, Bacopa monnieri, Withania somnifera, Centella asiatica and Hyoscyamus niger for the management of Parkinsonism.

KEYWORDS: Siddha, Herbal Medicine, Traditional Medicine, Parkinsonism, Nadukkuvatham.
INTRODUCTION

Parkinsonism is the second most common neurodegenerative disease in the general population and it occurs due to loss of cells within the substantia nigra especially damaging the ventral component of the pars compacta. Approximately four million people worldwide are estimated to be living with Parkinson’s disease (PD). Adult onset of Parkinson’s disease is most common. Its prevalence in the general population is 0.1 – 0.3% and is most common in adult aged ≥65 years.\(^1\) An All India Institute of Medical Science (AIIMS) case study in Parkinsonism showed that women with higher number and longer duration of pregnancies had more immunity towards the disease due to protective role of oestrogen, the ‘feminine hormone’. Family history of Parkinsonism and previous history of depression are the risk factors of the disease.\(^2\)

In addition to synthetic drugs, herbal medicines can be used as adjacent or secondary medicines in treating the after effects of the synthetic conventional drug. In fact the medicinal herbs possess antiparkinson activity and also ameliorate the after effects produced by conventional drugs. This dual action helps in reducing the dose of dopaminergic drugs thereby reducing the adverse effects due to prolonged usage of dopaminergic agents and improving the quality of life in Parkinsonism patients. The hallmark findings in Parkinsonism include tremor, depression, anxiety, restless leg syndrome, parasthesia and visual disturbances. Insufficient production of dopamine leads to the disease progression and henceforth degeneration of the tissue of the brain. Ample of research on the pathology of the disease have pinpointed the important role of oxidative stress in the development of the disease. Antioxidants have assisted in reducing the oxidative burden in the blood vessels and cerebral tissues by scavenging the free radicals. The therapeutic flora often possesses varying amounts of antioxidants, which scavenges many free radicals thereby providing a natural resistance against some of the diseases.\(^3\)

**Curcuma longa**

*Curcuma longa* (turmeric) is a well known Indian spice most commonly used in all Indian cuisines. The plant is a rhizome belonging to the Zingiberaceae family. The active ingredient present in the spice is Curcumin which is a polyphenol responsible for the antioxidant\(^4\), anti-inflammatory, anti-cancer and neuroprotective properties.\(^5\) The perennial herb is well known for its medicinal properties for more than thousand years and is a key ingredient in Siddha system of medicine for treating skin diseases, pulmonary diseases, aches, pains,
wounds, sprains, hepatic diseases and gastrointestinal disorders.\textsuperscript{[6]} Ample of research studies have been conducted supporting the efficacy of curcumin in treating PD in different experimental models.\textsuperscript{[7]} The antimicrobial efficacy and anti-depressant potential of the plant also have been documented.\textsuperscript{[8]}

_C. longa_ extract have shown to be effective against inflammation and Alzheimer's disease. Many studies have reported the efficacy of _C. longa_ in treating PD. Ma and Guo in 2017 investigated the neuroprotective potential and recovering ability of _C. longa_ extract against the toxicity induced by salsolinol in SH-SY5Y cells. _C. longa_ extract inhibited apoptosis with a substantial reduction in the gene expression levels of apoptotic markers, like p53, Bax and caspase 3. The toxicity of salsolinol was investigated in SH-SY5Y cells derived from human neuroblastoma cells.\textsuperscript{[9]} The _C. longa_ extract was able to partially ameliorate the toxicity induced by salsolinol in SH-SY5Y cells even at increased concentrations. The synergistic potential of the plant is more to be explored at for determining the therapeutic potential of the plant as a monotherapy and in combination with other counterparts. In addition many studies have warranted the potential of antioxidant and anti-inflammatory properties of the _C. longa_ extract in treating PD. Reasonable scientific evidence suggests a significant co-morbidity between depression and PD and so the mood regulating potential of the _C. longa_ extract would assist in treating PD.\textsuperscript{[10]}

**Mucuna pruriens:** _Mucuna pruriens_ is a tropical climber belonging to the legume family commonly found in India, Central and South America. This plant is also called “the cowhage” or “velvet” bean and “atmagupta” in India. The use of the plant in treating PD was practiced in Ancient system of medicine in China, India and Amazon. The plant is found in early Sanskrit incunabula for treating various ailments since 1500 BC. In Ayurveda Kampavata, a nervous malady similar to Parkinson’s syndrome, have been treated by atmagupta (_Mucuna_).\textsuperscript{[11]} The Mucuna seed preparations are employed for the treatment of PD in India.\textsuperscript{[12]} Parkinson’s disease occurs as a result of the substantial decrease of dopamine production, which is a neurotransmitter. Many studies have proved that the legume contains high levels of natural L. dopa, which is a precursor to dopamine, making the plant a potential drug for PD. The Ayurvedic system of medicine has linked Parkinson’s and _Mucuna pruriens_ as early as 300 BC. Contemporary research into the chemical composition of the plant has reported L. dopa concentrations of 4-6% in the plant.\textsuperscript{[13]} Like any other therapeutic plant _Mucuna pruriens_ also possess high anti oxidant activity which may be one of the reasons for
the increased efficacy against PD other than high L-dopa content. Levodopa (L-dopa) the key ingredient used in treating PD was first isolated from the seeds of *M pruriens* in 1937.\[^{14}\] Many Phase 2 and Phase 3 studies have been conducted to test the efficacy and safety of the drug. Three open label studies, with around 18 to 60 PD patients and mean dosages of 45 g/day of Mucuna seed powder extract containing about 1500 mg L-dopa were reported with significant changes for 12–20 weeks. Another study suggested better tolerability with Mucuna than with standard L-dopa preparations. A double blind study testing the efficacy of *M. pruriens* demonstrated that the *M pruriens* seed powder formulation possess a considerable quantity of L-dopa sufficient to induce a sustained on-period in fluctuating PD patients than with synthetic L-dopa response with short duration. On comparison *Mucuna pruriens* showed significant changes in terms of clinical development than synthetic L-dopa. In fact the latency to clinical onset was remarkably less than synthetic L-dopa. The on-period time span was significantly longer with mucuna (30 g) than with L- dopa with a mean difference of 37 min.\[^{15}\] Another double-blind randomized controlled trial of 8 Parkinson’s patients compared synthetic L-dopa with *Mucuna pruriens*. The study patients had dyskinesia for a short period following synthetic L-dopa. All patients exhibited a faster dopamine-stimulating response to mucuna seed powder without the regular side effects like dizziness upon standing, low blood pressure, nausea, vomiting, and uncontrollable muscle movement (dyskinesia) following conventional L-dopa administration.\[^{16}\] Similar studies warrant the anti-Parkinson’s activity of *Mucuna pruriens* with lesser side effects compared to synthetic drugs. L-dopa of the plant origin generated better results than synthetic.\[^{17}\] Further in-depth research is warranted to identify the distinctive interaction of *Mucuna pruriens* within the brain that may protect against treatment-induced dyskinesia.

**Bacopa monneri:** *Bacopa monneri* is a perennial creeper found in the swampy lands of South and East India, Australia, North and South America. It is commonly known as the water hyssop and also Bramhi in Hindi, Neer bramhi in Tamil, Timare in Kannada. The plant has been long used as a memory supplement in various systems of traditional medicine throughout the globe. The plant has also been found to increase the generalized neurological and cognitive function and is a mood enhancer.\[^{18}\] Many studies have proved that the plant possess antioxidant, antiamnesic\[^{19}\], anxiolytic\[^{20}\], antistress and antiulcerogenic\[^{21}\] efficacy. The plant is rich in a special type of triterpenoid saponins called as bacoside A and B who claim the responsibility for the neurological efficacy of the plant.\[^{22}\] Many preclinical studies have proved that the plant extract assists in preventing dopaminergic neuronal death by
reducing the alpha synuclein aggregation.[23] Another study proved the efficacy of BM extract to regulate catecholamine system in different brain regions of RT induced rodent model of PD. The performance of the BM is superior to the LD drug. Recent research has been done using platinum nanoparticles (PtNPs) of the leaf extract of BM which offers ample of opportunities for future drug discoveries and novel treatment strategies in PD. These nanoparticles (BM-PtNPs) were then coated with varied phytochemicals present in the leaf extract to treat oxidative stress mediated disease like Parkinson's disease (PD) in 1-methyl 4-phenyl 1,2,3,6 tetrahydropyridine- (MPTP-) induced zebrafish model. BM-PtNPs pretreatment greatly reduced toxic effects of MPTP by increasing the levels of dopamine and metabolites, GSH and activities of GPx, catalase, SOD and complex I, and reducing levels of MDA along with enhanced locomotor activity. Similarly many works prove the efficacy of the plant in treating Parkinsonism and its adverse effects (Jayshree Nellore et al., 2013).[24]

**Withania somnifera:** Withania somnifera is a medicinal shrub geographically located in the Indian sub continent. It is a key ingredient in many ayurvedic and Siddha preparations. Also called as Ashwagandha or Indian ginseng, this traditional herbal medicine has been used since 4000 years in India. The plant has proven effect on neural growth and locomotor function. The shrub has been used in the alternative system of medicine to treat stress, sleeplessness, anxiety, arthritis and other neurological disorders such as PD and Alzheimer’s disease. The plant is also used in the prevention and management of drug addiction.[25] MPTP-induced PD mouse model was employed to study the antioxidant and free radical scavenging efficacy of the plant and was found to be very high by earlier researchers.[26]

Although catecholamines and oxidative stress resulting in neurodegeneration and locomotor disorder are the main events in Parkinson's disease (PD), efficacy of the drug on these molecules and physiological abnormality are not clear.

**Synergistic effect of Mucuna and Withania:** Both Mucuna pruriens (Mp) and *Withania somnifera* (Ws) are traditionally used together as neuro-protective agents as both the plants possess significant amount of L-DOPA which is a neuroprotective component. Mucuna seed powder and withanoloides present in Ws root extract have high concentrations of the active compound L-Dopa. Many preclinical animal studies have been conducted to study in depth the mechanism of the synergistic action of the two plants. In one such study, the synergistic effect of Mp and Ws in Parkinsonian mice induced by chronic exposure to paraquat was evaluated. The treatment which lasted for 9 weeks significantly decreased the elevated nitrite
levels and lipid peroxidation found in Parkinsonian mice. In addition the tyrosine hydroxylase expression was greatly enhanced in the substantia nigra region of the brain. These results suggest that the dual drug can be a better treatment option since the synergistic efficacy of the two plants are relatively high when given as a combined whole than a single drug.\textsuperscript{[27]}

\textbf{Centella asiatica:} \textit{Centella asiatica} is a renowned medicinal herb belonging to the family Umbellifere. It is known as Indian Pennywort, Jal Brahmi (Hindi) and Mandookaparni (Sanskrit). The plant has also been used in the Japanese (Tsubokusa) and Chinese (Gotu kola) system of medicine. The herb is tasteless, odorless and normally grows in swampy places.\textsuperscript{[28]} The leaves are fan shaped with light purple flowers. It is botanically and functionally synonymous to Bacopa monnieri, and the two are oft-times administered as a combined whole, since both have intertwined medicinal history.\textsuperscript{[29]} The medicinal herb has very low flavonoid and phenolic content, but high in tannin content (20-25\%).\textsuperscript{[30]} The plant is renowned for its cognitive enhancing, haem cleansing, and wound healing and anti-rheumatic properties with numerous preclinical evidence.

In addition the plant is used to treat leprosy, ulcers, varicose veins and mental retardation. The plant is said to enhance the growth of neurons in a few weeks by activating Mitogen-activated protein kinases (MAPKs) proteins which catalyses the release of neuronic growth factor called Brain-derived Neurotrophic Factor (BDNF). One study points the increase in BDNF to CREB (cAMP response element binding protein) phosphorylation, and the CREB phosphorylation to the activation of MAPKs.\textsuperscript{[31]} \textit{Centella asiatica} activates BDNF expression after oral, because of the phosphorylation of CREB from MAPKs in neurons. This specific neurological activity is similar in mechanism to \textit{Bacopa monnieri} but more clear scientific evidence is obligatory. \textit{Centella asiatica} possess free radical scavenging activity in par with grape seed extract, Vitamin C, and bacopa monnieri.\textsuperscript{[30]} The saponins of \textit{Centella asiatica} have been found to promote neuronal growth. Many studies have proved that the oral intake of \textit{Centella asiatica} extract augments dendritic arborization in apical, basal, and branching points of young mice and in hippocampuses rat pups within four weeks.\textsuperscript{[32]} The same effect was observed in adult rats with delayed timings (requiring six weeks for a dosage that is effective in four for young animals).\textsuperscript{[33]}

\textbf{Hyoscyamus niger:} \textit{Hyoscyamus niger} (L), is one of the medicinal herbs used traditionally in the Indian subcontinent for various neurological disorders. This plant belongs to the
Solanaceae family and commonly known as henbane. The active constituents of henbane are hyoscyamine (present in larger proportion), scopolamine and atropine which are all toxic tropane alkaloids. Hyoscyamine and hyoscine are also found in other members of nightshade family such as jimsonweed (Datura stamonium) and belladonna (Atropa bella-donna). Other substances that are found in the plant are flavonoids, tannins, amines, albumin, calcium and potassium nitrate.\[34\] One preclinical study on the neuroprotective potential of Hyoscyamus niger (MHN) seeds in stereotaxically induced rotenone model of PD was studied in rat models. The methanolic extract had high concentration of L-dopa which greatly inhibited DPPH, ABTS and monoamine oxidase activity. The neurobehavioural activity and antioxidant status of the rotenone infused rats were tested after treating them with Hyoscyamus niger extract. Administration of the plant extract (containing L-DOPA) significantly reduced the levels of thiobarbituric acid reactive substance (TBARS) and increased GSH content and antioxidants enzymes activities (GPX, SOD and CAT) in addition to restoring the motor function in the extract treated PD rat. These findings support the potency of the drug in treating oxidative damage and physiological abnormalities which arise as after effects of PD in study animals.\[34\] Although the traditional systems of medicine claim the neuroprotective activity of the plant, scientific evidences are still prospective and more clinical trials are warranted to prove the potentiality of the plant.

CONCLUSION
Parkinson’s disease is a chronic neurological syndrome with many pathological complications like oxidative stress, mitochondrial dysfunction, neurotransmitter imbalance and apoptosis leading to neuronal degeneration. In such a case, any drug with a mono therapeutic approach targeting a single pathological process becomes ineffective. So drug combinations with a wide pharmacological efficacy are likely to be more effective. Synthetic drugs exhibit diverse adverse reactions when administered for a chronic disease like Parkinson, where complete cure of the disease does not take place. Prolonged exposure to these conventional drugs eventually lead to deterioration of vital parts of the body like kidneys, liver, pancreas and gastrointestinal tract. The plant kingdom is richly endowed with vital antioxidants and therapeutically efficient phytochemical constituents like terpenoids, saponins, flavonoids and alkaloids which both protect and heal the internal organs. The medicinal plants mentioned in the present review attenuate the disease advent to a greater extent and offers multiple protection against a variety of pathological conditions observed in Parkinson’s disease. But further more in-depth research of the molecular mechanism of the
plants in the central nervous system, synergistic effects of the herbs in the human system and chronic effects of the herbs as a single drug or in combination is highly warranted.

ACKNOWLEDGEMENT
The author wishes to acknowledge Dr.K.kanakavalli, M.D.(S),Principal, Government Siddha Medical College, Arumbakkam, Chennai – 600106 for their valuable guidance and support.

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