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Management of Parkinson's disease in Ayurveda: Medicinal plants and adjuvant measures

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ABSTRACT

Ethnopharmacological relevance: Medicinal plants like Mucuna pruriens *L.*(DC) and Withania somnifera *L.* (Dunal) have been used in traditional Ayurvedic medicine to manage neurodegenerative diseases like Parkinson's disease.

Aim: The aim of this review is to share the role of Ayurveda's insights, traditional usage and contemporary investigations for translational, integrative applications to manage Idiopathic Parkinson's Disease.

Materials and methods: High impact journals for Parkinson's diseases, traditional textbooks from Ayurveda as well as relevant clinical and para clinical studies with botanicals are selectively incorporated to evolve the aforesaid translational application.

Results:

A. Contemporary understanding and existing therapeutic gaps: Parkinson's disease (PD) is a complex multisystem, neurodegenerative disease. Though predominantly perceived as a motor disease, it also has debilitating non- motor features, which are frequently missed and not treated. Major treatment goals are to increase striatal dopamine levels with precursor-substitution and/or reduce its breakdown. As the disease progresses, a steady increase in the dose of levodopa is inevitable. However, higher doses cause motor complications of dyskinesia and dystonia and compromise medical treatment.

B. Role of Mucuna pruriens L.DC), the most promising botanical from Ayurveda: Ayurveda offers a natural source of levodopa – the seeds of *Mucuna pruriens* L.(DC)– which have a long standing safe use in the condition. Its clinical studies have shown pharmacokinetic profile distinct from synthetic levodopa, which is likely to reduce the untoward motor complications. Additionally, its seed extracts have shown neuroprotective benefits which are unrelated to levodopa.

C. Ayurvedic regimens and medicinal plants for neuroprotective and symptomatic benefits: Other regimens (Panchakarma) and medicinal plants used in Ayurveda have been subjected to exploratory studies with promising early results in the condition. The debilitating non motor symptoms in patients have shown response with one of the regimens – medicated oil enema (*basti*). Effects of two medicinal plants *Withania somnifera*(L.)Dunal and *Curcuma longa* Linn in Parkinson's Disease related models have been discussed in detail. We have also shared a shortlist of medicinal plants most likely to be useful in management of specific features of the disease such as cognitive decline, mood disorders, risk of osteoporosis amongst others.

Conclusion: Ayurveda with its medicinal plants and treatment approaches, can strengthen the therapeutic armamentarium of PD to improve clinical outcomes, if these leads are systematically further investigated by well-designed longer term studies.

1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder, affects about 7–10 million people worldwide. (Parkinson's Disease Foundation website, 2015) Dopamine (DA) deficiency manifests its characteristic features: bradykinesia, tremors and rigidity. (Postuma et al., 2015). The main cause of

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PD- dopamine deficiency- results from the degeneration of the dopaminergic nigro-striatal neurones to the corpus striatum. The neuronal damage is ascribed to the fibrillar deposits of misfolded α-*syn*uclein (Ozansoy and Basak, 2013). These are considered similar to prions triggering apoptosis in the neurones. The intracytoplasmic Lewy bodies, formed from such tangles of 'prions', are pathognomic brain lesions of PD (Luc et al., 2013).

The conventional strategies of treatment are targeted towards increasing the level of the striatal DA; this is achieved either through an increase in the precursor (levodopa) supply or by an inhibition of DA breakdown by monoamine oxidase (MAO). However, as the neuronal degeneration progresses, a steady increase in the dose of levodopa is needed. With higher doses, the side-effects of dyskinesia and dystonia compromise the benefits and limit the medical treatment. Often, for such cases currently, the next option is surgical viz. deep brain stimulation by implanted electrodes (Gazewood, 2013). Simultaneously, there is a research quest to stall or delay the progression by an early diagnosis and amelioration of damage to the neurons, targeting the basic pathogenetic process. A specific druggable target has been identified from over 200,000 molecules which reduces α-*syn*uclein-induced toxicity (Daniel et al., 2013). Attempts are also being made to use mesenchymal stem cells and induced pluripotent stem cells to efficiently generate DA neurons (Yong-Hee et al., 2011; Takayu et al., 2012).

The focus of management is the relief of the clinically dominant motor symptoms of PD. But now, there is an increasing recognition of the non-motor features of PD, which also need attention (Sethi, 2008; Siderowf and Stern, 2008). These features are sleep disturbances, constipation, cognitive decline, depression, fear, anxiety, bladder problems, weight changes, fatigue, and loss of energy, autonomic dysfunction/hypotension, and sexual problems. These can be dominant and debilitating in a sizeable number of patients, affecting the quality of their life (Pfeiffer, 2016). PD also has predisease symptoms like constipation and loss of smell, reduced facial expressions, low voice, sleep changes, dizziness which precede months to decades before the clinical diagnosis of PD. There is a substantial scope to avail of the modalities of Ayurvedic management for both the non motor and predisease features of PD.

Ayurveda has an individualized approach in the management of Parkinson's disease, based on the *agni-dosha-dhatu-mala* factors specific to pathogenesis as well as the dominant imbalance in that person. The reluctance to adopt and adapt such remedial measures is often due to trans-cultural resistance, unawareness of Ayurveda and the demand of the type of evidence that often negates a vast and long use experience. The present article is an attempt to address these concerns and needs.

Thus, there are at least three clinical benefits to be gained from Ayurveda for a better management for PD (a) reducing the incidence and severity of the side effects of the conventional therapy (b) improving non-motor symptoms (c) affecting the neurodegenerative process from the prodromal stage onward. In this chapter we share the role of medicinal plants and Ayurvedic treatment modalities to possibly bridge this gap.

2. *Mucuna pruriens* L.(DC): Therapeutic activity and safety

An important Ayurvedic medicinal plant for PD is *Mucuna pruriens* L.(DC). (*M.pruriens*), named as cowhedge plant as its prickly trichomes prevented stray cows from entering farms. Many formulations containing *M.pruriens* exist as dietary substances and Ayurvedic drugs. Besides being a natural source of levodopa, the seeds of *M.pruriens* have additional advantages in cognitive improvement, a reduction in dyskinesia, mood enhancement and an increase in libido. Its safety has been established in humans even at very high doses of 15–30 g over the course of 12–20 weeks (Katzenschlager et al., 2004).

2.1. Clinical studies

Levodopa was isolated from the seeds of *M.pruriens* as early as in 1937 (Damodaran and Ramaswamy, 1937). However it was only in 1960, that dopamine deficiency in the corpus striatum was found in the brains of patients with PD (Ehringer and Hornykiewicz, 1960). One of the authors (ADBV) had participated in the early trials of levodopa, with Van Woert, at Yale Medical School in the late sixties. On his return to India, an open clinical trial with the seed powder of *M.pruriens* (taxonomically identified with details available in reference) in 23 patients PD showed clinical improvement and safety of levodopa (Vaidya et al., 1978). This first clinical trial has been followed up by several experimental, bioavailability and clinical studies as described below.

The promising results had enthused an Ayurvedic pharmaceutical company (Zandu) to develop and manufacture a standardized standardized product- HP-200- from the plant seeds, with $\pm$4% L-dopa (Mahajani et al., 1996). A multi-centric, open clinical study of HP-200 was carried out in sixty patients with PD, for 12 weeks (Manyam et al., 1995). There was significant improvement ($p < 0.001$) on both the comprehensive Unified Parkinson's Disease Rating Scale and Hoehn & Yahr staging. The formulation was well tolerated. With the preclinical and clinical data an investigational new drug was submitted to the US FDA for a Phase 1 trial. This was approved but not pursued in the US.

Much later, in 2004, these carefully conducted open-labelled studies were followed by a randomized, controlled, double-blind, cross-over design clinical trial at London, UK. The objective was to study whether *M.pruriens* as a substitution therapy was better tolerated and equi-effective in patients who had only briefly responded to conventional levodopa, with an increase in dyskinesia. Patients were randomized into three groups: a) levodopa/carbidopa 200 mg/50 mg, b) 15 g *M.pruriens*, (equivalent to 100 mg levodopa/carbidopa or 500 mg levodopa) and c) 30 g (equivalent to 200 mg levodopa/carbidopa or 1000 mg pure levodopa). It was found *M.pruriens* had a more rapid onset of action, longer on-time without a concomitant increase in dyskinesias as compared with levodopa (Katzenschlager et al., 2004).

2.2. Pharmacokinetics of levodopa after the administration of M. pruriens

The rapid peripheral decarboxylation of levodopa to DA reduces the availability of levodopa across the blood brain barrier. Large doses of levodopa can induce nausea too. Hence, decarboxylase inhibitor either carbidopa or benserazide was added to levodopa in 1975. It has been suggested that dyskinesias result not as much due to levodopa, but so much due to the inhibitor of dopa decarboxylase– carbidopa (Hinz et al., 2014). It is postulated that the dyskinesias observed clinically are in fact caused by the irreversible inactivation of vitamin B6 by carbidopa.

The effects of different dosages and combinations of levodopa, benserazide and water extract of were studied systematically in five different types of experiments in rats. (Lieu et al., 2010) *M. pruriens* without benserazide alleviated parkinsonism, with significantly reduced dyskinesias. In a long term administration, it did not cause dyskinesias. In animals with dyskinesias, due to LD/benserazide combinations, it reduces their intensity. *M.pruriens* can have a specific advantage of efficacy with a reduction in dyskinesias.

The variability of the ingredients, including levodopa, in many marketed formulations of *M.pruriens* is a challenge to optimally integrate and translate their clinical use in PD. There is a need for