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[Fecha de consulta:]

Ayurveda Medicine for the Treatment of Parkinson's Disease

Review Article

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Abstract In most western countries, the symptomatic management of Parkinson's Disease (PD) is usually achieved with medicinal products including levodopa (LD), dopamine agonists, MAO-B inhibitors, COMT inhibitors, antimuscarinics and amantadine. The control of the quality of the production of such medications is strict and the assessment of the benefit-risk ratio of these interventions is regulated by official recommendations which follow an evidence-based approach. Ayurveda Indian medicine has used *Mucuna Pruriens* (MP) for the treatment of PD since ancient times. MP includes LD as an active moiety, among many others. A literature search was conducted between 1978-2012 with the keywords Parkinson's disease, ayurveda or *mucuna pruriens*. MP antagonized the effects of 6OHDA lesions in rats and when administered chronically it showed lower dyskinetic potential compared to L-DOPA. MP also reduced Parkinsonian symptoms in an MPTP treated monkey with less dyskinesias compared to L-DOPA. Four clinical trials of MP for PD treatment were found. Initially they were open-label, uncontrolled studies, suggesting that MP might reduce parkinsonism severity. One double-blind randomized crossover study was conducted in 8 PD patients, employing acute challenges of levodopa or MP. It showed that the effect of MP had a faster onset than LD,

with shorter latencies to peak and increased on-time. No other medium-term (i.e., 6 months) randomized-controlled trials (RCT) are available. According to the MDS EBM taskforce working procedures, an intervention is considered as "efficacious" when there is at least one high quality randomized controlled trial (RCT) showing a positive effect on studied outcomes with no conflicting data from other RCTs. Based on these premises, there is insufficient evidence to conclude the efficacy of MP in the treatment of PD. Thus its use in clinical practice remains open to investigation. It must also be emphasized that various MP formulations can be used, raising concerns about their quality, which is difficult to control, as regulation is limited. Impurities or variations in active moieties, can lead to unexpected adverse drug reactions. In conclusion, the use of MP in PD treatment remains open to investigation and thus cannot be recommended for clinical use.

Keywords Ayurveda Medicine, *Mucuna Pruriens*, Parkinson's Disease, Pharmacological Treatment

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition [1] affecting over 1 million people in Europe

and North America [2,3]. A systematic review of 25 incidence studies found that in eight studies, the mean age of symptom onset was 60–65 years, and >65 years in five studies [4].

Pharmacological treatment of PD can be accomplished with levodopa, dopamine agonists, Catechol-O-Methyl transferase (COMT) inhibitors, Monoaminoxidase-B (MAOB) inhibitors, antimuscarinics or amantadine. The Movements Disorders Society Evidence-based Medicine (MDS MBE) task force conducted a literature review in 2005 [5].

Levodopa dramatically improves the motor symptoms of PD and remains the “gold standard” anti-Parkinsonian treatment [6], but its chronic use is frequently associated with the development of motor complications, such as dyskinesias or motor fluctuations. When levodopa is administered with a decarboxylase inhibitor, such as carbidopa or benzeraside, the drug is metabolized primarily by the COMT enzyme. Thus, the administration of levodopa with a COMT inhibitor increases its elimination half-life (from about 90 minutes to about 3 hours) and increases its plasma area under the curve, which is a measure of total exposure to levodopa [7]. MAO-B inhibitors, such as selegiline or rasagiline have been used as symptomatic therapy for PD for approximately 20 years (selegiline), based on their capacity to block the MAO-B oxidation of dopamine and thereby increase dopamine levels in the synapses [7].

Dopamine agonists were developed for the treatment of PD because they act directly on the dopamine receptors and because they have the potential to provide anti-Parkinsonian effects with less motor complications than levodopa. They have been used in the treatment of PD since the early 1970s [8], initially as adjuncts to levodopa in patients who had begun to experience motor complications. Today, dopamine agonists are also used as an early symptomatic therapy to delay the risk of developing the motor complications associated with levodopa therapy. Antimuscarinic drugs are typically used in PD patients typically younger than 60 years of age with resting tremors as the dominant clinical feature and with intact cognitive function [7]. Its use is limited because of atropinic-like adverse reactions, such as confusion, psychosis, hyperthermia, etc. Finally, amantadine is an antiviral agent that was discovered by chance to improve parkinsonism and LD-induced dyskinesia [7].

Ayurveda Medicine is an ancient system of Indian medicine (Ayu= life and Veda= science) which described PD before 2500 BC, naming it Kampavata (kampa= tremors) [9]. Ayurveda usually uses a concoction of several spices, herbs and minerals for the treatment of diseases. In the case of Kampavata several herbal

formulations are available, of which nearly 18 contain *Mucuna Pruriens* (MP). The MP leguminosae plant is a twiner with trifoliate leaves with purple flowers and turgid pods covered with hairs. In 1937 by Damodaran and colleagues managed to isolate Levodopa from MP [10]. Other studies have shown that MP also significantly inhibits the oxidation of lipids and deoxyribose sugar, exhibits divalent iron chelating activity and does not have any genotoxic/mutagenic effects on the plasmid’s DNA [11,12]. It was thus suggested that MP could have neuroprotective and neurorestorative properties, related to its antioxidant activity and independent of its symptomatic effects [13,14].

Evidence about its efficacy in PD treatment will be discussed in this review.

2. Literature search methods

A Pubmed literature search was conducted between 1978 and 2012. Keywords were Parkinson’s Disease, ayurveda or *mucuna pruriens*. Thirteen papers were found: 6 reviews [9,15-19], 3 papers on the effect of MP on PD animal models [20-22] and 4 clinical trials [23-26]. A search of the reference sections of these papers did not yield any extra references. Only clinical trials in PD patients or studies addressing anti-Parkinsonian effects in PD animal models were included in this review.

Effects of Mucuna Pruriens on PD animal models

The effects of MP were studied in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of PD [20]. Two weeks before the 6-OHDA lesion, the rats were handled by the experimenter for the first 3 days to allow the animals to familiarize themselves with the experimenter’s grip. Over the following 2 days the rats were trained to run spontaneously up the ramp (1 m long) toward the home cage. Rats were then lesioned with 6-OHDA and at the fourth week, the rats were divided into four groups and treated with benserazide (6 mg/kg i.p.) plus L-DOPA (2 or 6 mg/kg i.p.) or MP extract (16 or 48 mg/kg i.p. which contained 2 or 6 mg/kg L-DOPA, respectively). The initiation time of the stepping test and the adjusting step test with the right and left forelimbs were assessed before (first week) and after (second and third weeks) nigrostriatal lesion with 6-OHDA with no drugs. The fourth week after the 6-OHDA lesion, drug (L-DOPA and MP extract) tests were performed. After the drug test, the rats were tested without drugs in the same week (fourth week) to evaluate the possibility of spontaneous recovery. The results obtained revealed that an acute administration of MP extract at a dose of 16 mg/kg (LD: 2 mg/kg) consistently antagonized the deficit in latency of step initiation and adjusting step induced by lesions. MP significantly improved the placement of the forelimb in vibrissae-evoked forelimb placing, suggesting a significant

antagonistic activity on both the motor and sensory-motor deficits.

One week after priming, the rats were injected twice a day for 19 days with benserazide (6 mg/kg i.p.) plus L-DOPA (6 mg/kg i.p) or MP extract (48 mg/kg i.p. containing 6 mg/kg of L-DOPA). Contralateral rotational behaviour and Abnormal Involuntary Movements (AIMs) were evaluated on alternate days for 19 days. MP extract acutely induced a significantly higher contralateral turning behaviour than L-DOPA (6 mg/kg) when administered at a dose of 48 mg/kg (LD: 6 mg/kg). When subchronic administration was used, both the MP extract (48 mg/kg) and L-DOPA (6 mg/kg) induced a sensitization of contralateral turning behaviour; however, L-DOPA alone induced a concomitant sensitization in AIMs suggesting that the dyskinesic potential of MP is lower than that of L-DOPA.

The effects of MP were also studied in the MPTP-treated monkey PD model [21]. In this study, 14 adult (6–9 kg) rhesus (*Macaca mulatta*) and two cynomolgus (*Macaca fascicularis*) monkeys received intracarotid 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injections. Clinical assessments were taken after MPTP to ensure the stability of parkinsonism and at subsequent treatment exposure using the modified version of the Unified Parkinson's Disease Rating scale for primates (mUPDRS). Electrophysiological recordings before and after treatments were performed on awake, behaving Parkinsonian animals. Monkeys were treated with LD or MP after the MPTP lesion. Animals were first tested to find the optimal MP dose. MP was titrated in these studies from 6 g/day to the highest dose of 18 g/day (N = 11) to evaluate gastrointestinal effects, drug-induced dyskinesias, or behavioural correlates of psychiatric symptoms. A blood draw was performed 90 minutes after the administration and consumption of the medications (placebo, LD+CD (250 mg/62.5mg) and MP+CD (4.5 g/25 mg)) to test the bioavailability of orally administered LD and MP at approximately equivalent doses for the pharmacological estimation of dopamine levels.

In these initial studies, mean mUPDRS scores improved by 4% (change from 35 to 33.5), 24.2% (35 to 26.5), and 27.1% (35 to 25.5), respectively, with 3 g, 6 g, and 9 g (total daily dose) of MP alone. The optimal dose for MP+CD was determined to be 9 g of MP + 50 mg of CD/day.

Results showed that mUPDRS scores for the placebo were 15.6 ± 2.6 and decreased to 8.0 ± 1.6 with MP alone, 7.7 ± 1.5 with MP+CD, and 4.5 ± 1.1 with LD+CD, optimal doses (all $p < 0.05$ vs placebo). LD+CD treatments produced significant drug-induced dyskinesias (AIMS score = 7.3 ± 1.3) in two bilaterally Parkinsonian animals, whereas no apparent dyskinesias were observed with MP treatments (AIMS score = 0).

Similar results were found in a study assessing MPTP treated rats [22]. In the first set of experiments, animals that received LD+BZ or MP+BZ at high (6 mg/kg) and medium (4 mg/kg) equivalent doses demonstrated a significant alleviation of parkinsonism, but developed severe dose-dependent DID. LD + BZ at low doses (2 mg/kg) did not provide a significant alleviation of parkinsonism. In contrast, MP+BZ at an equivalent low dose significantly ameliorated parkinsonism. In the 2nd set of experiments, MP without any additives (12 mg/kg and 20 mg/kg LD equivalent dose) alleviated parkinsonism with significantly less drug-induced dyskinesia compared to LD+BZ or MP+BZ. MP without additives administered chronically provided long-term anti-Parkinsonian benefits without causing dyskinesias. MP alone also provided significantly more behavioural benefits when compared to the equivalent dose of synthetic LD alone without BZ. Finally, MP alone reduced the severity of dyskinesias in animals initially primed with LD+BZ.

Mucuna Pruriens efficacy in PD treatment

Vaidya et al. reported the beneficial effects of MP in patients with PD in an open clinical trial in 1978 [26], but no further information was available.

Author (year)	Design	Duration	Sample size	Outcomes	Results
HP-200 in PD study group (1995)	Open-label, uncontrolled trial	12-w	60	UPDRS score	Reduction
Nagashayana (2000)	Open-label, uncontrolled trial	12-w	18	UPDRS score	Reduction
Katzenschlager (2004)	DB, cross-over RCT (MP 15 or 30 mg vs SLC)	Acute	8	duration of on periods, LIDs	Longer levodopa effect duration. No differences in LIDs

DB= Double-blind, RCT= Randomized-controlled trial, MP= *Mucuna Pruriens*, SLC= Standard Levodopa/Carbidopa preparation, LIDs= Levodopa-induced Dyskinesias.

Table 1. Clinical trials with *Mucuna Pruriens*.

The HP-200 PD Study Group assessed the efficacy and tolerability of HP-200, a product derived from *Mucuna Pruriens*, in 60 PD patients (Table 1) [23]. Sixty patients with Parkinson's disease (46 male) with a mean age of 59 years, 26 of whom were on levodopa/carbidopa, were treated in an open uncontrolled manner for 12 weeks. HP-200, a powder (supplied as a 7.5 g sachet), was mixed with water and administered orally. The Unified Parkinson's Disease Rating Scale (UPDRS) was used as a baseline and then periodically during the 12-week evaluation. Statistically significant reductions at the Hoehn and Yahr (H&Y) stage and UPDRS scores were seen from the baseline to the end of the 12-week treatment ($p < 0.0001$, t-test). The group mean \pm SD dose for the optimal control of symptoms was 6 ± 3 sachets.

In another clinical prospective study, Nagashayana and colleagues assessed the efficacy of Ayurveda treatment (as a concoction in cow's milk of powdered *Mucuna pruriens*, *Hyoscyamus reticulatus* seeds, *Withania somnifera* and *Sida cordifolia* roots) in 18 clinically diagnosed PD patients (Table 1) [25]. The study design was uncontrolled and open-label. As a baseline, the mean age of the patients was 60 years, mean H&Y stage in OFF was 2.22, mean disease duration was 3 years and the male:female ratio was 5:4. All medications, including herbal preparations, were discontinued 15 days prior to the initiation of the study. PD symptoms and signs were evaluated and then "converted" to UPDRS for better representation and interpretation. A positive response was determined when more than 50% of the patients showed improvements in stiffness, tremor, bradykinesia and cramp-like pain in lower limbs and in the objective tests. As per Ayurveda principles, 13 patients underwent both cleansing (i.e., oleation, sudation, purgation, enema and errhines) for 28 days and palliative therapy with MP for 56 days whereas 5 patients underwent palliative therapy alone (84 days).

Biochemical tests showed that single doses of the medication as administered in milk contained a total of 200 ± 5 mg of levodopa. Only the group given cleansing and palliative therapy showed significant improvements in the activities in their daily lives and in the motor examination, as per the UPDRS rating, of between 5-50%, but reasons for this were not provided. Total UPDRS (Mean score 59 ± 12) also showed significant ($p < 0.05$, Student t-test) improvement in 62% of these patients.

In the last study that we could identify, the clinical effects and pharmacokinetics of levodopa following two different doses of mucuna preparation were compared with the effects of the standard levodopa/carbidopa treatment (LD/CD) (Table 1) [24]. Eight Parkinson's disease patients with a short-duration levodopa response and "ON" period dyskinesias were included in this

randomised, controlled, double-blind crossover trial. Patients were administered with single doses of 200/50 mg LD/CD, and 15 and 30 g of mucuna preparation in a randomised order at weekly intervals. The main outcome measures were differences in the duration of "ON" episodes and in dyskinesia scores following single doses of levodopa. Plasma sampling allowed for pharmacokinetics determination, while patients were assessed with the UPDRS and tapping speed as a baseline and then repeatedly during the 4 h following drug ingestion. Dyskinesias were assessed using the modified AIMS and Goetz scales. The mucuna seed powder preparation was a light, yellowish powder, manufactured in Germany (Wiewelhove, Ibbenbueren, Germany) from raw materials obtained in India.

The patients' mean age was 62.2 years (range 50–72); mean disease duration was 12.4 years (range 7–17); and mean Hoehn and Yahr stage (when "off") was 3.5 (range 2.5–4). Patients took a mean daily L-dopa dose of 572 mg (range 200–1000 mg) prior to the trial. Other anti-Parkinsonian medications taken were amantadine in two (200 mg), pergolide in three (mean, 3.2 mg), and ropinirole (18 mg), cabergoline (6 mg), and pramipexole (1.4 mg) in one patient each. Compared with standard LD/CD, the 30 g mucuna preparation led to a considerably faster onset of the anti-Parkinsonian effects (34.6 v 68.5 min; $p = 0.021$), reflected in shorter latencies to peak L-dopa plasma concentrations. Mean on time was 21.9% (37 min) longer with 30 g mucuna than with LD/CD ($p = 0.021$); peak L-dopa plasma concentrations were 110% higher and the area under the plasma concentration v time curve (area under curve) was 165.3% larger ($p = 0.012$). No significant differences in dyskinesias or tolerability occurred.

Safety and medicinal product quality issues

The HP-200 PD study group reported that adverse effects were mild and mainly gastrointestinal in their study [23]. No adverse effects were seen in clinical laboratory reports. In the paper by Nagashayana and colleagues, no adverse events were reported [25]. Finally, in the study by Katzenschlager and colleagues, one patient dropped out due to short-lasting vomiting on 30 g MP [24]. Other adverse events were mild (short-lasting nausea, mild gastric pain and mild dizziness). No clinically relevant changes in haematology or biochemistry parameters were observed.

The origin of the MP used in the HP-200 PD Study group trial was Zandu Pharmaceutical (Zandopa). Nagashayana and colleagues obtained the MP from the Government Ayurveda College Pharmacy. For the Katzenschlager and colleagues trial, MP was prepared by a German pharmaceutical facility according to a proprietary formula. Quality control was performed by an independent laboratory.

3. Discussion

MP has shown anti-Parkinsonian activity with less dyskinesia potency in PD animal models [20-22]. Anecdotal evidence also suggested that MP could be useful in PD treatment [26]. This issue was further explored in 2 open-label, uncontrolled clinical trials involving 78 heterogeneous PD patients in total [23,25]. These studies showed that the effect of MP on parkinsonism could be confounded by many factors. Indeed, up to 16% of PD patients undergoing clinical trials can show a 50% improvement in parkinsonism while on a placebo [27]. Uncontrolled trials cannot exclude placebo effects, thus offering a potentially biased result. Moreover, these studies lacked a number of other important key methodological issues that make the results of a trial reliable, including blinding and they lacked validated clinical outcomes. Double-blind, controlled trials, such as the one conducted by Katzenschlager and colleagues should be able to monitor the placebo effect [24]. These authors were able to show significant improvements of MP on levodopa pharmacokinetics and validated the outcome measures of parkinsonism. Nonetheless, it must be emphasized that the study included only a very small number of PD patients (eight) who have been simply exposed to an acute dose of the tested medication, with no chronic follow-up and assessment of their response to MP. Official recommendations emphasize the fact that clinical trials aimed at evaluating treatment efficacy should use a double-blind, parallel, controlled design, should include a homogeneous population, should last no less than 6 months and should utilize standardized effect measures and validated outcomes [28]. No such trials are available for MP.

Therefore, although potentially promising, the evidence currently available for the efficacy of MP for the treatment of PD can only be considered as insufficient for establishing the efficacy of the compound for the prevention of PD progression, the symptomatic treatment of PD and the prevention or treatment of motor complications. Thus, using MP in clinic practice remains o, at least according to the usual modern standards and regulatory recommendations which currently apply for any medications marketed in the western world.

The same caution should apply to the safety conclusions related to MP. Although the evidence available from the 4 published studies that we could identify did not disclose any safety problems, the size of this sample is clearly insufficient for any thoughtful evaluation. At this point, one must emphasize that as far as we know, MP is not included in any pharmacopeia in Europe or in the Americas. Therefore manufacturing the processes, purity and other physicochemical characteristics of MP are not standardized, thus making quality control difficult.

Moreover, the use of complementary and alternative medicine is largely unregulated [29]. As with many other medicinal products derived from plants, MP contains many more than one active moiety, which in this case would be levodopa, many of which may not be known. Indeed, the putative neuroprotective effects that have been claimed for MP are probably not related to levodopa, but to other uncharacterized actives principles [13,14]. Quantitative variations in the content of active moieties or in impurities from one MP batch to another, could also lead to unexpected adverse drug reactions, either by itself or through interactions with other drugs. There are indeed examples of dramatic Serious Adverse Reactions that have been caused by presumed "safe" herbal medicines, including for example cases of terminal nephrotoxicity with aristolochic acid, a Chinese herb used by young women to lose weight, and herbal medicine-induced hepatitis caused by Germander (*teucrium chamaedrys*), a plant traditionally used for the treatment of gout [30-32]. In these examples, unexpected Serious Adverse Reactions were found with herbal preparations, which were previously held as "inoffensive" [31].

4. Conclusions

MP may display anti-Parkinsonian efficacy, due to its levodopa contents, but there is insufficient evidence, according to modern western standards, to allow for any reliable conclusion and recommend it for clinical use. Also interesting results on neuroprotection have been claimed but none of these have been tested in the clinical field. Finally, herbal medicine regulation is scarce, which means that the quality control of such medicinal products is almost impossible. This in turn poses a number of questions regarding the safety approach of the product. Therefore, caution is advised when utilizing MP for the treatment of PD. In light of the current evidence, utilization of MP may expose patients to unexpected toxicity while its efficacy has been insufficiently studied. Further studies are needed to explore the potential usefulness of MP in PD.

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