Role of Kaunch in Parkinsonism

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Abstract

"Velvet bean" is a common name for Mucuna pruriens, a legume native to eastern India and China that is grown as a vegetable crop. The seeds of this plant have been demonstrated to have significant therapeutic value. A member of the Fabaceae family, kapikacchu is utilized for aphrodisiac and Parkinsonian purposes. There were fewer dyskinesias and adverse events in MP-Ld than in MP-Hd at both the 90- and 180-minute time points; nevertheless, there were more dyskinesias in MP-Ld than in MP-Hd. LD1DDCI and LD2DDCI generated more AEs than MP-Hd. There were no variations in the heart's reaction. Noninferiority effectiveness and safety criteria compared to dispersible levodopa/benserazide were fulfilled by single dose MP consumption. The clinical effects of high-dose MP were comparable to levodopa alone at the same dosage, but the tolerance profile was better.

Keywords: Anti-Parkinsonism, aphrodisiac, Kapikacchu, Levo-dopa, Mucuna pruriens.

1. INTRODUCTION

Cowhage or Cowitch is known as Kaunch Beej in Hindi. It's a fantastic source of protein since it's a member of the legume family. A common name for the seeds is "Magic Velvet Beans," and they're a significant herbal remedy for treating mental health issues. Mucuna pruriens is the plant's genus name, according to the scientific literature.

Mucuna pruriens, a member of the Fabaceae family and the Papilionaceae subfamily, may be found all over the globe. Compared to other pulses, it is a particularly good source of protein. The tannins, flavonoids, alkaloids, and phenolic compounds found in Mucuna pruriens are among the numerous essential bioactive chemicals found in this plant. Because it is a legume, this plant takes atmospheric nitrogen gas and converts it into fertilizer, which enhances the condition of the soil. Diabetes mellitus, Rheumatoid Arthritis, Parkinsonism and atherosclerosis may all be alleviated by the seeds' multifaceted actions. Other uses include the treatment of constipation, oedema, fever and TB. In the hair of the seeds of Mucuna pruriens, a chemical called 5-hydroxytryptamine (serotonin) produces pruritus. Kapikacchu is well-known for its aphrodisiac properties because it raises the body's testosterone levels, which helps produce more sperm. Increased endurance and physical strength are two of the benefits of kapikacchu's use. Supplements are often used by athletes in order to improve their physical performance. It aids in the reduction of body fat as well as the growth of muscular mass. People who are depressed might also benefit from this herb since it encourages sexual activity, which raises desire. Many Ayurvedic literature refer to this plant.

There is a progressive loss of dopaminergic (DAergic) neurons in Substantia nigra pars compacta (SNpc), the presence of intra-neuronal inclusions called Lewy bodies (LB), and a subsequent decrease in striatal dopamine (DA) levels in Parkinson's disease (PD), which is second most common chronic neurodegenerative disorder after Alzheimer's disease (AD) (ST). The most common non-motor symptom in Parkinson's disease is cognitive impairment. However, environmental neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Paraquat (PQ), and others have been shown to exacerbate the symptoms of Parkinson's disease (PD). MPTP has been shown to be a strong inhibitor of mitochondrial complex-1 of the electron transport chain, according to a number of studies (ETC). To induce Parkinsonian symptoms in mice, it is one of the most often utilized neurotoxins, causing oxidative stress to result in DAergic degenerations in the nigrostriatal pathway. MPTP-intoxicated mouse models have also been utilized to investigate the molecular mechanisms that cause DAergic neuronal degeneration and to test the effectiveness of many neuroprotective drugs. In neurodegenerative illnesses, oxidative damage to macromolecules such as lipids, proteins, and DNA

results in the loss of membrane integrity, enzyme deactivation, and eventually cell death. Previous research has shown that persistent neuroinflammation contributes to neuronal degeneration. To put it another way, the inflammatory response to neurodegeneration is wide open for inquiry. Proinflammatory mediators like as cytokines/chemokines, enzymes like cyclooxygenase-2 (COX-2) and iNOS are created by glial cells (astroglia and microglia) when DAergic neurons are degraded.

NF-B also plays an important role in mediating the release of proinflammatory cytokines, as well as in generating the expression of tumor necrosis factor-alpha (TNF-) and interleukin-1beta (IL-1) via oxidative stress-mediated neurodegeneration, which contributes to neuronal death via cytotoxic mechanisms. There have been a number of recent studies showing that anti-inflammatory medications may protect against DAergic neuronal loss by suppressing the neuroinflammatory processes.

2. LITERATURE REVIEW

Olson and Gendelman (2016), Next to Alzheimer's disease, Parkinson's disease (PD) is the most frequent kind of progressive neurological illness (AD). Progressive loss of dopaminergic (DAergic) neurons in the nigrostriatum and the development of proteinaceous inclusions of alpha-synuclein are two features of Parkinson's disease (PD). Both motor and non-motor abilities diminish with time when DAergic neurons in the SNpc and their connections to the striatum (ST) are lost. When the dopamine (DA)-synthesizing neurons in the SNpc degenerate to some degree, it causes bradykinesia and other motor deficits such postural instability, stiffness, and resting tremors. Cognitive decline is the most common non-motor symptom in Parkinson's disease (PD). Among the non-motor symptoms of Parkinson's disease include sadness, constipation and discomfort. The disease's root origin is still a mystery to scientists. Factors that influence illness emergence and development include genetics, environment, age, and the interaction between the adaptive immune system and the innate immune system.

Hwang, Dias, and others (2013), DA, a neurotransmitter, may cause oxidative stress on its own. Toxic stress and quinone alteration, as well as DA's oxidation, have been linked to DAergic cell vulnerabilities. While the majority of DA is generally kept in vesicles, it may be converted to DA quinone by a variety of mechanisms, including spontaneous oxidation and enzyme catalysis. When the creation of ROS is out of balance with the antioxidant activity of cells, oxidative stress ensues. Due to the presence of ROS producing enzymes such as monoamine oxidase (MAO) and tyrosine hydroxylase (TH), DAergic neurons are especially vulnerable to oxidative stress (TH). Another source of oxidative stress in the brain is iron, which is found in nigral dopaminergic neurons and serves as a catalyst for the Fenton reaction, which generates hydrogen peroxide (H2O2) and superoxide radicals.

According to Salat and Tolosa, (2013), L-DOPA is a strong medicine used to treat Parkinsonian symptoms. Although L-DOPA has been the primary treatment choice for Parkinson's disease (PD) for many decades, its long-term usage is fraught with danger due to a variety of side effects that might occur. Long-term L-DOPA treatment for Parkinson's disease (PD) may induce motor difficulties, although no better treatment has yet been identified. When first-line dopamine agonists or MAO-B inhibitors are used as an alternative to L-DOPA treatment, they do not seem to have any permanent functional effects, and the symptomatic alleviation noticed by patients is only marginally better than when L-DOPA is initially administered. A patient's motor problems may be managed by switching to an alternate L-DOPA formulation or adding other medicines to their treatment if they develop dyskinesia or lose other clinical improvements as a result of various adverse effects of L-DOPA dosing.

'Muller' (2015), COMT inhibitors are often used in conjunction with L-DOPA treatment to help people with Parkinson's disease (PD) improve their symptoms. Chronic L-DOPA/DDI treatment for Parkinson's disease (PD) patients who have concurrent COMT inhibition enhances L-DOPA effectiveness, lowers L-DOPA plasma level fluctuations, and alleviates motor difficulties, notably wearing-off events. Entacapone and tolcapone, two COMT inhibitors, have been shown to be successful when taken regularly, whereas opicapone is still in the clinical trial stage. An increase in homocysteine, a biomarker for methylation insufficiency, is neutralized by COMT inhibitors by neutralizing the L-DOPA-associated rise in homocysteine.

Yadav et al (2016), When it comes to male virility, Mp seeds have long been utilized in India as an aphrodisiac. The seeds and pods have antihelmintic and anti-inflammatory properties. A compound in the seeds known as LDOPA may be responsible for their anti-parkinsonism effects when ground into powder (a precursor of neurotransmitter dopamine). The fact that dopamine acts as a neurotransmitter is well-known. When the conversion of tyrosine to L-DOPA is prevented, the brain's DA level decreases. When L-DOPA (the DA precursor) crosses the BBB and undergoes conversion to DA, neurotransmission is restored. Polyphenol compound UA, which has anti-action, Parkinson's is also found in Mp seed.

Nirukti of Kapikacchu

It consists of two words—one is Kapi and another is kacchu. Kapi means monkey and kacchu means itching. It causes itching for monkeys if monkey sit on the trees where this creeper is twisted around the stem; the pods may produce itching (Kacchu) on the hip of monkeys [9].

Scientific Classification

Kingdom Plantae

Division Magnoliophyta

Class Magnoliopsida

Order Fabales

Family Fabaceae

Subfamily Faboideae

Tribe Phaseoleae

Genus Mucuna

Species pruriens

Vernacular Names

Sanskrit: Kapikacchu, Markati, Kandura, Sukasimbi, Kapiprabha

Bengali: Aalkushee, Alkusa

English: Cowhage, Cowitch

Gujrati: Kaucha, Kavach

Hindi: Kevanch, Kaunch, Khujanee

Properties and Action

Rasa: Tikta, Kasaya

Guna: Guru, Snigdha

Virya: Sita

Vipaka: Katu

Karma: Kaphahara, Pittahara, Vrisya, Brimhana, Balya, Yonisamkirnakara, Vajikarana

Botanical Description

From the Himalayas to Cape Comorin in the plains and up to 3000 ft. above sea level, wild Mucuna pruriens plants may be found across India's countryside. Assam, Bengal, the Khasi Hills, and the Deccan are the most common locations to find it. The hairs are present in the early stage, but go away as the plant ages. Leaflets are 2–3 mm long, and the flower heads range in length from 15–32 mm and feature 2–3 blooms in white and purple. The seed pods are 10 cm long [10] and coated with loose hairs that cause severe itching when they come into touch with skin. The husk is hairy and contains seven seeds (Figure 1).

Fig. 1: Mucuna pruriens.

3. RESULTS

The research comprised 18 people with severe Parkinson's disease (13 men and 5 women), all of whom showed motor fluctuations and dyskinesias (table 1). Levodopa/carbidepopa single-dose at home lasted around 160 minutes for patients with a mean disease duration of 10 years. Stable MP treatment was maintained by eight patients for an average of 3.5 years.

Efficacy: LD 1DDCI was shown to be noninferior to MP-Hd and MP-Ld in all main and secondary efficacy outcomes. Figure 2 depicts the final outcome.

A comparable improvement in motor symptoms was seen with MP-Hd at 90 and 180 minutes ($p=0.037$ and $p=0.002$, respectively) but not with MP-Ld or MP 1DDCI intake. UPDRS-III scores after 180 minutes were lowered (i.e., motor performance improved) by 32% on average after LD1DDCI, 16% after MP-Ld, and 50% after MP 1DDCI when compared to motor performance at 90 minutes. Similar motor responses were seen when levodopa was taken from either the MP (MP-Hd) or the pharmaceutical formulation (LD 2DDCI).

MP-Hd had a considerably lower mean latency to on than LD 1DDCI ($p = 0.008$), although LD 2DDCI, MPLd, and MP1DDCI were all closer to LD 1DDCI in latency.

With MP-Hd, the on state lasted an average of 221 minutes, while LD 1DDCI and MP-Ld had the same length of time in the on state (221 minutes, p 0.001). Similar dosages of levodopa pharmaceutical formulations with and without the DDCI (MP1DDCI and MP-Hd, respectively) were compared with MP and found to be 20% shorter on duration.

At 90 minutes, there were less dyskinesias with MP-Hd and LD 2DDCI than LD 1DDCI. Only LD 1DDCI and MP-Ld were found to vary from one other.

There were no serious AEs and no participants withdrew from the trial. Our results showed that MP-Ld had a much lower rate of adverse events (AEs) than LD 1DDCI, and that MP-Hd had an even lower rate of adverse events (AEs). It is rare for AEs to remain more than a half-hour after therapy administration, although four individuals experienced AEs lasting more than 90 minutes after LD 2DDCI. While the levodopa doses were identical, LD 2DDCI caused more adverse events (AEs) than MP-Hd and was the only therapy linked to sustained AEs, the study concluded. Between the off and on states, there was no difference in blood pressure or heart rate between the active therapies. In

contrast to the other treatment groups, those who took the placebo experienced no change from their pre-treatment conditions.

We also investigated the connection between levodopa pharmacokinetics and motor responsiveness to therapy in four Italian individuals with PD (this analysis was not feasible in Bolivia due to the lack of adequate laboratory facilities and technical experience). In addition to the main text, there is supplemental information supplied.

4. DISCUSSION

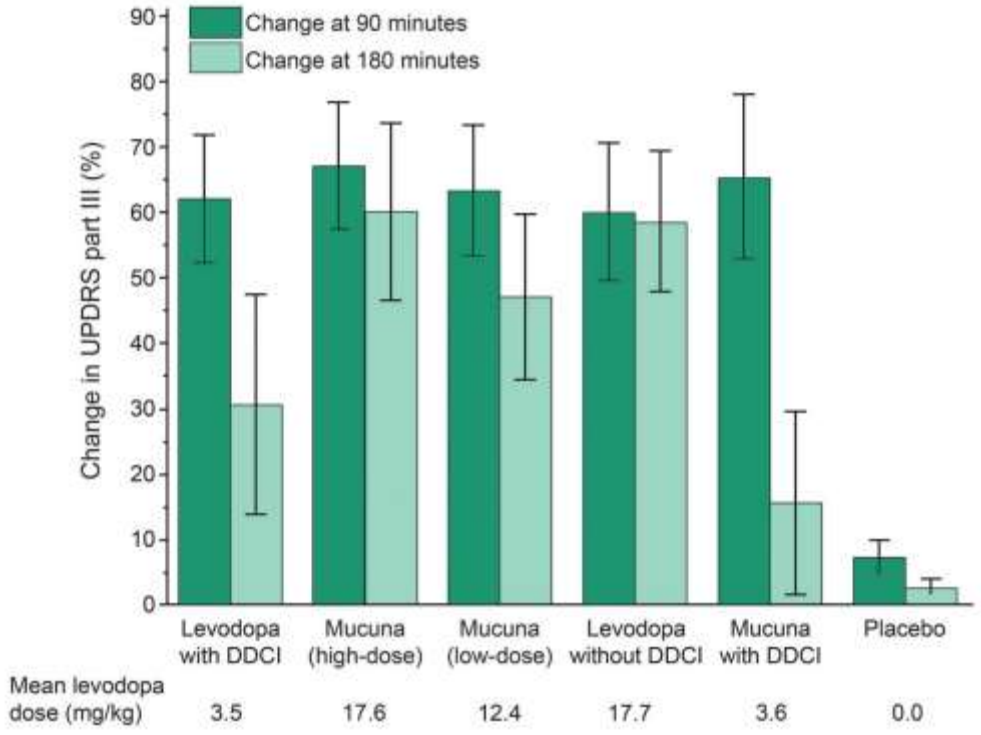
According to the findings of this trial, acute ingestion of MP powder at either a high or low dosage is as effective and safe as dispersible levodopa/benserazide.

Regardless of dosage, both low- and high-dose MP outperformed placebo in the study. At low doses of MP, the motor response was comparable to that of levodopa/benserazide, however at high doses, the motor response was superior to that of LD1DDCI, with a 45-minute on state duration and less dyskinesias. High-dose MP had a shorter time to activate than LD1DDCI (as also reflected by the shorter average tmax values obtained in the independent sample). As our findings on the mean latency to on with levodopa/benserazide are similar with prior publications, this is likely to represent a shorter latency with MP rather than a delayed one with LD1DDCI. This data is consistent with previous preclinical/clinical studies that have used pharmacological processing of MP extract, all reporting shorter latency to on7 and longer on duration with reduced dyskinesias in comparison to the standard treatment, which is currently used in the treatment of Parkinson's disease. Because of its substantially shorter latency to on, it is doubtful that MP will operate as an extended-release levodopa preparation, even if the longer duration of the motor response may be related to the larger dosage of levodopa delivered. Taking levodopa alone has no impact on these positive clinical outcomes of MP. Is this due to some inherent features of MP that are not connected to levodopa? The clinical response to LD2DDCI was similar to that of high-dose MP in terms of a longer on state with fewer dyskinesias compared to LD1DDCI, making the latter theory the most likely. In 1967, the first peripheral DDCI was developed, and subsequent clinical studies showed that the administration of levodopa alone or in combination with DDCIs had an overall equivalent effect on motor symptoms.

Table 1 Demographic and general clinical features of patients with Parkinsondisease (PD) at baseline

Patients with PD (n 5 18)	
Features	
Male sex, n (%)	13 (72.2)
Age, y	61.8 (9.1)
Age at onset, y	52.1 (9.5)
Body weight, kg	75.1 (16.7)
Disease duration, y	9.8 (3.0)
Disease duration at initiation oflevodopa therapy, y	1.9 (1.4)
Disease duration at initiation ofchronic MP therapy, y[a]	7.8 (4.0)
Patients presenting tremor-dominant phenotype	10 (55.6)
UPDRS part I	2.3 (2.0)
UPDRS part II: off	16.1 (6.5)
UPDRS part III: off	37.8 (11.1)
UPDRS part IV: dyskinesias (items 32-34)	1.4 (1.2)
UPDRS part IV: off (items 36-39)	4.2 (2.2)

Hoehn & Yahr stage: off	2.6 (0.6)
Motor complications	
Duration of motor fluctuations, y	5.4 (3.1)
Duration of on time on current home therapy, min[b]	158 (58)
Disease duration at onset of motor fluctuations, y	5.4 (2.0)
Levodopa duration at onset of motor fluctuations, y	3.6 (2.1)
Disease duration at onset of dyskinesias, y	6.7 (1.9)
Levodopa duration at onset of dyskinesias, y	5.1 (2.3)
Therapy	
Total LEDD, mg/d[c]	1,457 (858)
Duration of levodopa therapy, y	7.9 (3.6)
Levodopa dose, mg/d	897 (331)
Levodopa dose including MP, mg/d[d]	1,343 (917)
Levodopa dose weight-adjusted, mg$kg21$day21d	19.3 (11.2)
Patients on stable MP therapy, n (%)	8 (44.4)
Patients on dopamine agonists, n (%)	11 (61.1)
Dopamine agonist dose, LEDD/d, mg	279 (57)
Duration of dopamine agonisttherapy, y	5.6 (2.0)
Patients on iMAO-B, n (%)	0 (0)
Patients on iCOMT, n (%)	1 (5.6)
Patients on amantadine, n (%)	8 (44.4)
Patients on anticholinergics, n (%)	1 (5.6)



DDCI = dopa-decarboxylase inhibitor

Figure 2: Changes (mean 6 standard error) in Unified Parkinson's Disease Rating Scale part III (motor score) at 90 and 180 minutes after treatment intake

Although levodopa dosages were reduced by 60% to 80%, DDCIs were shown to result in earlier and more severe dyskinesias. Levodopa alone (MP-HD and LD2DDCI) was shown to have lower rates of dyskinesias than the combination levodopa and DDCI (LD1DDC and MP-1DDC) despite the larger levodopa dosage. Levodopa treatment prior to the emergence of DDCIs may educate us how to employ MP-based therapy in low-income nations to break out of their prelevodopa period. In comparison to the safety profiles of LD1DDCI and LD2DDCI, the acute ingestion of MP powder was shown to be more beneficial. Both low and high doses of MP were linked with fewer adverse effects than LD1DDCI. Although the daily levodopa dosage was reduced, our results reveal that the addition of DDCIs had either no impact or even worsened hypotension, mental disorders, and dyskinesias in comparison with levodopa alone.

It was discovered that there were no variations in cardiovascular profile between the active groups, with systolic and diastolic values dropping by 20–25 mm Hg and 10–15 mm Hg each, respectively (highest drops with LD1DDCI, albeit not significant). Studies on levodopa alone found that 15–20 mm Hg drops were frequent and that they were typically asymptomatic and transitory. 16,28 Secondly, high-dose MP caused fewer AEs than a comparable dosage of levodopa pharmaceutical preparation alone. Only long-lasting AEs lasting more than 90 minutes were seen in the LD2DDCI group, whereas the few AEs caused by MP were moderate and temporary. Regardless of the presence or absence of DDCIs, these findings support the idea that MP powder has a more favorable safety profile than pharmaceutical formulations of levodopa.

Despite the fact that these patients had access to regular levodopa/carbidopa medication, this group did not completely reflect the target demographic in low-income locations. After 12 to 14 hours, we can't rule out the possibility of a residual DDCI effect, which is around 4–4.5 half-lives, after the last intake of LD1DDCI, which typically happened 12 to 14 hours before the challenge. High-dose levodopa alone would have considerably enhanced dyskinesia severity had such an effect been observed. A residual DDCI impact is unlikely to have affected this data, given we obtained the opposite reaction. The inclusion of only individuals with motor fluctuations and dyskinesias ensured that the effectiveness and safety objectives could be clearly defined. Practice recommendations for MP monotherapy will need to be derived from research including many centers and long-term follow-up of de novo individuals with PD.

What may we anticipate to face in the long run as a result of the long-term use of MP powder? Tolerability is the solution. More than 2,000 people were studied for almost a decade to determine the long-term safety of levodopa alone at high daily dosages (up to 16 g/d). Due to its short half-life and relatively low toxicity profile, levodopa was able to be used at high doses without encountering serious adverse events (AEs). As it is impossible to predict the amount of levodopa in individual MP samples in low-income locations, delayed titration schemes are inevitable in any MP-based treatment. Levodopa concentrations (about 4% to 6% in most samples), length of Parkinson's disease (PD), and body weight all need to be taken into account while developing these plans. The long-term advantages of MP-based treatment may outweigh the short-term difficulties of making levodopa accessible and affordable to patients who otherwise would not have access to medication, especially in low-income nations. Low-dose LD1DDCI and MP may be useful for individuals whose levodopa supply have been disrupted by the discontinuation of commercial levodopa formulations (as is currently the case in Santa Cruz, Bolivia).

Overall, MP was not inferior to levodopa/benserazide in terms of all outcomes. Identical to the effects of levodopa alone at similar dosages, the clinical response to MP was similar, with fewer adverse effects. Patients in low-income nations with Parkinson's disease (PD) may be able to use MP as an alternative to commercially available levodopa in the long run.

5. CONCLUSION

One of the most potent Ayurvedic herbs is kapikacchu. It offers a wide range of advantages. Improved reproductive function and aphrodisiac benefits may be achieved by using this supplement. It also

promotes the enhancement of stamina and potency by raising testosterone levels. Levodopa (L-DOPA) is a crucial precursor of the neurotransmitter dopamine, which is utilized in Parkinson's disease, and it's a good treatment for vata-dominant condition. As a result, this plant should be employed in a variety of illness conditions, and extensive human study is needed to develop this plant in many disease models.

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