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【 ORIGINAL ARTICLE 】

# Japanese *Mucuna pruriens* (Hasshou beans) Showed Fast-acting and Long-lasting Effects in Parkinson's Disease

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**Abstract:**

**Objective** *Mucuna pruriens* (MP) is a legume whose seeds contain levodopa (LD), which has potential therapeutic effects against Parkinson's disease (PD). However, further research is needed to thoroughly evaluate its efficacy and safety for treating this condition. In this study, we analyzed the pharmacokinetics of MP grown in Japan and investigated its mechanism of action in PD.

**Methods** MP seeds ground after roasting (containing 4.02% LD per MP powder) were used as the reagent and compared with an equivalent LD/carbidopa (CD) preparation. This clinical trial was conducted using a crossover design among PD patients attending our institution. Each patient received a single dose of 100/10 mg LD/CD tablets and 11 g of MP reagent.

**Results** Among the seven patients with PD, MP prolonged the ON time 2-fold compared to LD/CD. The LD concentrations after MP intake were higher than those after LD/CD intake, whereas dyskinesia did not increase. An analysis of the LD metabolites showed that the 3-O-methyl-dopa/LD metabolic ratio was significantly lower after MP ingestion than after LD/CD ingestion, indicating that MP has a catechol-O-methyl transferase inhibitory effect.

**Conclusions** This is the first report of a pharmacokinetic analysis conducted on actual patients with PD showing that MP significantly prolongs the ON time. The advantages of MP as a treatment for PD have been confirmed: it is inexpensive, as effective as LD, works faster and longer than LD, and does not increase dyskinesia.

**Key words:** Mucuna pruriens, Parkinson's disease, levodopa, dyskinesia, COMT inhibition

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## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder treated with dopamine agonists. L-3,4-dihydroxyphenylalanine, also known as levodopa (LD), is the most effective drug for the standard treatment of PD. However, as the disease progresses, patients often experience motor complications, such as wearing-off and dyskinesia, making it challenging to manage symptoms with oral drugs alone. Furthermore, LD preparations are difficult to obtain in low-income countries, necessitating the development of inexpensive, effective, and safe alternatives.

*Mucuna pruriens* (MP) is a variety of velvet beans belonging to the genus *Mucuna*. It is found in India, Central America, and South America, along with other tropical regions, and was introduced to Japan from the Asian continent in the 1600s as a food source. MP spread throughout Japan and are often called Hasshou beans. "Hasshou" is a volume equivalent to approximately 14.4 liters and was used to represent a large quantity. MP cultivation in Japan was infrequent during the 1950s. However, in 2008, it was successfully cultivated at the Agricultural Experiment Station in Wakayama, which is the same location as our facility. The presence of LD in MP has long been a topic of global interest, drawing attention to its potential therapeutic effects.

Although LD was isolated from MP seeds in 1937 (1), MP has long been used to treat PD in Ayurvedic medi-

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cine (2). Therapeutic studies of MP in a small number of patients with PD have reported greater therapeutic effects of MP than LD/CD, including a prolonged ON time and reduced dyskinesia (3-5); however, the mechanism of action remains unclear. In addition, although MP is considered a potential alternative to LD owing to its low cost and easy availability, its efficacy and safety have not been fully investigated.

Previously, we reported that soybeans, a legume similar to MP, affect the pharmacokinetics and metabolism of LD. LD/CD plus soybeans significantly increased the ON time and suppressed dyskinesia in patients with PD (6). In the present study, we analyzed the pharmacokinetics and effects of MP grown in Japan in clinical and animal studies to verify its mechanism of action as a PD treatment.

## Materials and Methods

### *Pharmacokinetics of MP in rats*

**MP reagent**

The MP used in the present study was grown in Japan (Wakayama Prefectural Agriculture, Forestry and Fisheries Research Center, Wakayama, Japan). MP seeds were roasted at 170°C for 5 min and crushed to obtain a reagent that was confirmed to contain 4.02% LD by a chromatographic analysis.

**Animals**

Male Sprague-Dawley rats (250-300 g) (Kiwa Laboratory Animals, Wakayama, Japan) were housed in a room with controlled humidity (55% ±10%), temperature (23±1°C), and a 12-h light/dark cycle with free access to food and water. All animal experiments complied with institutional guidelines and were approved by the Institutional Animal Experimentation Facility Committee.

**Protocol**

Blood samples were obtained via a catheter placed in the right jugular vein of the rats under anesthesia for transcutaneous blood tests. Rats were fasted for 14-16 h. Following the fasting period, the rats were divided into 2 groups: one received MP reagent containing 15 mg/kg LD, while the other received 15 mg/kg LD (D9628; Sigma-Aldrich, St. Louis, MO, USA). Each group consisted of three rats. Each reagent was dissolved in 500 μL of 0.2 N HCl + 7% $NaHCO_3$ (4:1.5) solution and administered orally. Blood samples were collected before and 15, 30, 60, 120, 180, 240, 300, 360, 480, and 600 min after administration. Blood plasma was separated immediately after collection and stored at -80°C until analyses.

**Pharmacokinetic analyses**

Plasma concentrations of LD, dopamine (DA), 3-O-methyl-dopa (3-OMD), dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) were plotted to evaluate dose linearity. The area under the concentration-time curve (AUC) was calculated using the trapezoidal rule between 0-600 min. The peak plasma concentration (Cmax) and time to peak plasma concentration (Tmax) were determined by a visual inspection of the LD concentration profile over time. The metabolic ratio of 3-O-methyldopa (3-OMD) was calculated as follows: metabolic ratio (3-OMD) = (AUC 0-600 of 3-OMD) / (AUC 0-600 of LD); and metabolic ratio (DA) = (AUC 0-600 for DA) / (AUC 0-600 for L-DOPA).

### *Clinical trial*

**Patient selection**

Patients with PD who visited our institution were included in the study. Patients were selected if they met the diagnostic criteria of the Brain Bank of the Parkinson's Disease Society of the UK and met none of the exclusion criteria (7). The exclusion criteria were as follows: not using LD, changed anti-parkinsonism medication within 4 weeks, signs of active psychosis, cognitive impairment such as Hoehn and Yahr stage 5 during the off-state, Mini-Mental State Examination score <24, and a severe medical condition.

This study was approved by the institutional ethics committee.

**Study design**

This study used a crossover design in patients with PD. The primary endpoint was the difference in the ON time and dyskinesia scores after a single dose of the study drug. The observation period was from waking up to bedtime. Each patient received a single dose of 100/10 mg LD/CD tablets (Menesit®, MSD, Tokyo, Japan) and 11 g of MP reagent. As mentioned above, the 11 g MP reagent contained 442.2 mg of LD and was considered equivalent in potency to 100/10 mg LD/CD tablets. A previous paper reported that the LD content of MP needs to be at least 3.5 times higher than that of LD/CD to be equivalent to LD/CD (8).

The study protocol consisted of ingesting a single dose of 11 g MP reagent or LD/CD tablets under fasting conditions. During this administration, the participants were instructed to refrain from taking any anti-PD drugs that contained LD. The following week, the other drug (MP reagent or LD/CD tablets) was administered under the same conditions.

The motor function was assessed using the Japanese Unified Parkinson's Disease Rating Scale (UPDRS) III (9), modified Abnormal Involuntary Movements Scale (mAIMS) (10, 11), and patient diaries. Blood tests were performed before and at 15, 30, 45, 60, 90, 120, 150, and 180 min after administration, and plasma was separated immediately after blood collection and stored at -80°C until measurement.

**Pharmacokinetic analyses**

The plasma concentrations of LD, 3-OMD, DOPAC, and HVA were plotted according to the method described in the protocol, and the AUC, Cmax, Tmax, and metabolism ratio of 3-OMD and DA were calculated.

**Data analyses**

Statistical analyses were performed using the Mann-Whitney U test.

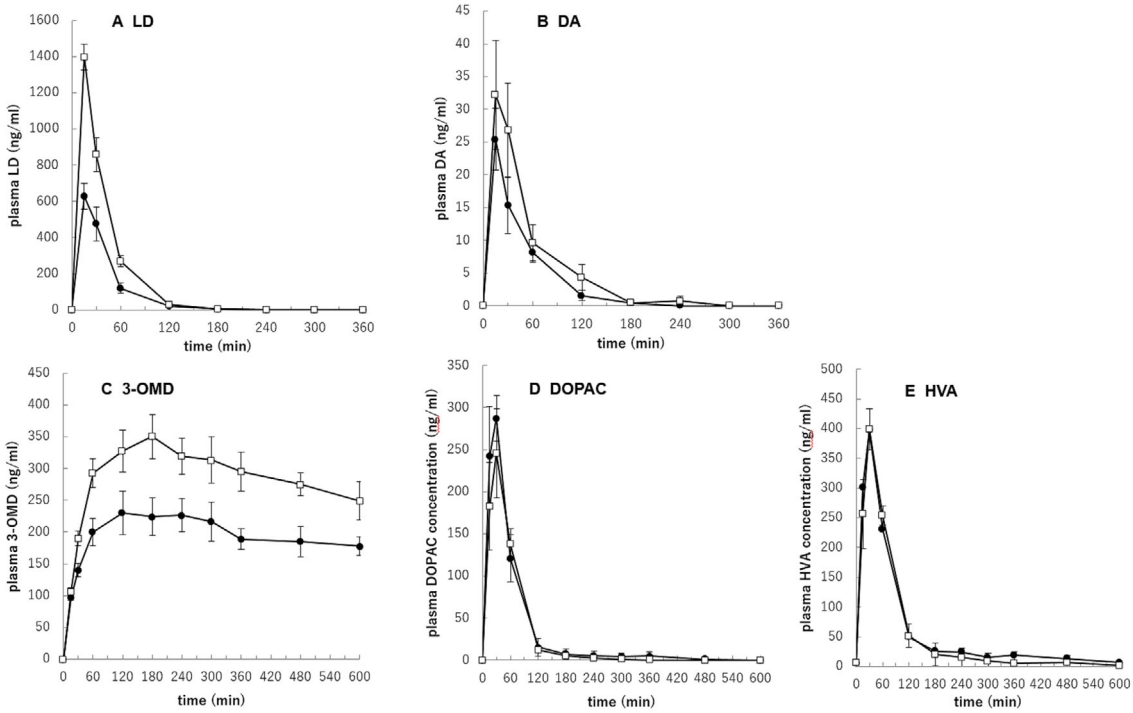


**Figure 1. Plasma concentrations over time profiles in rats. Plasma concentration over time profiles for (A) LD, (B) DA, (C) 3-OMD, (D) DOPAC, and (E) HVA following ingestion of LD (●) or MP (□). Data are presented as the mean ± SEM of three rats. DA: dopamine, DOPAC: 3,4-dihydroxyphenylacetic acid, HVA: homovanillic acid, LD: levodopa, MP: Mucuna pruriens, 3-OMD: 3-*O*-methyl-dopa, SEM: standard error of the mean**

**Table 1. Pharmacokinetic Parameters with LD and MP in Rats.**

| | LD | MP | p value |
|---|---|---|---|
| L-DOPA | | | |
| $AUC_{0\text{-}10}$ (ng·h/mL) | 453.1 (67.1) | 907.8 (72.4) | <0.05* |
| $C_{max}$ (ng/mL) | 626.4 (81.5) | 1,397.0 (120.7) | <0.05* |
| DA | | | |
| $AUC_{0\text{-}10}$ (ng·h/mL) | 20.3 (2.9) | 30.9 (0.2) | 0.83 |
| 3-OMD | | | |
| $AUC_{0\text{-}10}$ (ng·h/mL) | 1,955.0 (259.8) | 2,869.5 (306.0) | 0.13 |
| DOPAC | | | |
| $AUC_{0\text{-}10}$ (ng·h/mL) | 302.4 (75.9) | 262.8 (72.3) | 0.83 |
| HVA | | | |
| $AUC_{0\text{-}10}$ (ng·h/mL) | 563.3 (163.3) | 525.7 (56.6) | 0.51 |
| Metabolic ratio of $AUC_{0\text{-}10}$ | | | |
| $AUC_{DA}$ / $AUC_{L\text{-}DOPA}$ | 0.04 (0.01) | 0.03 (0.01) | 0.51 |
| $AUC_{3\text{-}OMD}$ / $AUC_{L\text{-}DOPA}$ | 4.33 (0.07) | 3.15 (0.15) | <0.05* |

The value represents the mean (SEM) of three rats. AUC: area under the concentration over time curve, $C_{max}$: peak plasma concentration, DA: dopamine, DOPAC: dihydroxyphenylacetic acid, HVA: homovanillic acid, LD: levodopa, MP: Mucuna pruriens, 3-OMD: 3-*O*-methyl-dopa, $T_{max}$: time to peak plasma concentration. Statistics were derived using Mann-Whiney U test.

## Results

### *Pharmacokinetics in rats*

The LD blood concentration was higher in the MP group than in the LD group from to 0-120 min (Fig. 1), and the AUC and Cmax were also significantly higher in the MP group than in the LD group. This indicated that MP had no inhibitory effect on CD (Table 1). In contrast, the metabolic ratio of 3-OMD was lower in the MP-treated group than in the LD group, whereas the trends of DOPAC and HVA were

not markedly different between the two groups. These results suggested that MP inhibits catechol-O-methyl transferase (COMT) (Fig. 2).

### Clinical trials

**Patients**

Seven patients (five women and two men) were enrolled in this study (Table 2). The mean age was 66.1 years old, mean disease duration was 11.7 years, and mean LD treatment was 10.4 years. The mean disease value was 3.2 according to the Hoehn and Yahr classification.

**Treatment effects**

The ON time was 356.4 minutes for the MP group and 162.1 minutes for the LD/CD group, more than twice as long as that for the MP group. The time to the onset of effects tended to be shorter in the MP group than in the LD group (40.0 minutes in the MP group and 53.6 minutes in the LD/CD group), but the difference was not significant (Table 3). The modified AIMs scores did not differ markedly between the two groups, and dyskinesia did not worsen with MP administration. No serious side effects were observed in either group.

**Pharmacokinetics and metabolite concentrations**

The plasma LD concentrations were higher after MP ingestion than after LD/CD ingestion (Table 4, Fig. 3). Consequently, the levels of LD, DOPAC, and HVA metabolites were also higher in the MP group than in the LD/CD group. The 3-OMD level was also higher in the MP group than in the LD group, but the mean metabolic ratio of AUC 0-180 (3-OMD/LD) was significantly lower than that with LD/CD intake. Thus, the inhibitory effect of MP on COMT was confirmed in patients with PD.

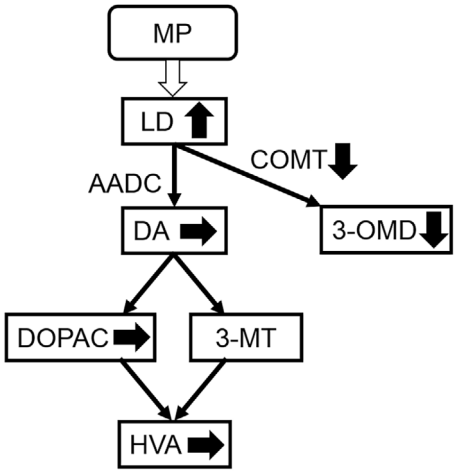


**Figure 2. Metabolic pathway of LD. The arrows indicate changes during MP administration. Compared to the same dose of LD, the LD concentration increased, the dopamine concentration did not increase, and the 3-OMD decreased, suggesting that AADC was not inhibited while COMT was inhibited. AADC: aromatic L-amino acid decarboxylase, DA: dopamine, DOPAC: 3,4-dihydroxyphenylacetic acid, HVA: homovanillic acid, LD: levodopa, MP: Mucuna pruriens, 3-MT: 3-Methoxytyramine, 3-OMD: 3-*O*-methyl-dopa**

## Discussion

The LD content of the Japanese MP (Hasshou beans) used was 4.02%. In a report analyzing a total of 25 MPs from Africa, Latin America, and Asia, the median LD content was 5.29% for dried seeds and 5.30% for roasted pow-

**Table 2. Demographic and Clinical Data in Patients.**

| Parameter | Value |
|---|---|
| Patients, n | 7 |
| Age (years), mean (SD) | 66.1 (7.2) |
| Male, n (%) | 2 (28.5) |
| Disease duration (years), mean (SD) | 11.7 (3.0) |
| Hoehn & Yahr stage (off state), mean (SD) | 3.2 (0.6) |
| LEDD (mg/day), mean (SD) | 500.0 (208.2) |
| Levodopa treatment duration (years), mean (SD) | 10.4 (3.7) |
| Other antiparkinsonian medication use, n (%) | |
| Dopamine receptor agonists | 6 (85.7) |
| MAO-B inhibitor | 5 (71.4) |
| Entacapone | 5 (71.4) |
| Amantadine | 4 (57.1) |
| Zonisamide | 4 (57.1) |
| Anti-cholinergic agents | 0 (0.0) |

COMT: catechol-O-methyl transferase, LEDD: levodopa equivalent daily dose, MAO-B: monoamine oxidase B, SD: standard deviation. Statistics were derived using Mann-Whitney U test.

**Table 3. Measures of Parkinsonism and Dyskinesia after Ingestion of LD/CD and MP in Patients with Parkinson's Disease.**

| | LD/CD | MP | p value |
|---|---|---|---|
| Duration of on-period (min) , mean (SEM) | 162.1 (29.5) | 356.4 (57.6) | 0.03* |
| Time to beginning of on-period (min) , mean (SEM) | 53.6 (16.3) | 40.0 (9.8) | 0.30 |
| UPDRS-III total scores baseline, median (range) | 27.0 (24.0-31.5) | 21.0 (17.0-25.0) | 0.20 |
| Best UPDRS-III total score, median (range) | 8.0 (5.5-13.0) | 2.0 (1.0-9.0) | 0.02* |
| Change from baseline at best on time, UPDRS-III scores, median (range) | - 17.0 (13.5-20.0) | - 19.0 (12.0-19.5) | 0.90 |
| Worst mAIMs score, median (range) | 7.0 (2.5-9.0) | 6.0 (3.0-7.5) | 0.80 |

The value represents the mean or median of seven patients. LD/CD: L-DOPA/carbidopa, mAIMs: modified Abnormal Involuntary Movements Scale, MP: Mucuna pruriens, UPDRS-III: Japanese Unified Parkinson's Disease Rating Scale part III. Statistics were derived using Mann-Whitney U test.

**Table 4. Pharmacokinetic Parameters with LD/CD and MP in Patients with Parkinson's Disease.**

| | LD/CD | MP | p value |
|---|---|---|---|
| LD | | | |
| $AUC_{0\text{-}3}$ (ng·h/mL) | 4,744 (929) | 11,186 (1,528) | <0.05 |
| $C_{max}$ (ng/mL) | 3095 (700) | 7,607 (1,546) | <0.05 |
| $T_{max}$ (min) | 34.3 (4.3) | 25.7 (5.4) | 0.30 |
| 3-OMD | | | |
| $AUC_{0\text{-}3}$ (ng·h/mL) | 8,451 (1,427) | 9,947 (1,528) | <0.05 |
| DOPAC | | | |
| $AUC_{0\text{-}3}$ (ng·h/mL) | 161.2 (40.6) | 692.4 (147.8) | <0.05 |
| HVA | | | |
| $AUC_{0\text{-}3}$ (ng·h/mL) | 788.6 (114.1) | 2,013.4 (148.6) | <0.05 |
| Metabolic ratio of $AUC_{0\text{-}3}$ | | | |
| $AUC_{3\text{-OMD}}$ / $AUC_{L\text{-DOPA}}$ | 1.78 (1.54) | 0.89 (1.00) | <0.05 |

The value represents the mean (standard error of the mean; SEM). AUC: area under the concentration over time curve, $C_{max}$: peak plasma concentration, $T_{max}$: time to peak plasma concentration, LD: levodopa, LD/CD: levodopa/carbidopa, MP: Mucuna pruriens, 3-OMD: 3-*O*-methyl-dopa, DOPAC: 3,4-dihydroxyphenylacetic acid, HVA: homovanillic acid. Statistics were derived using Mann-Whiney U test.

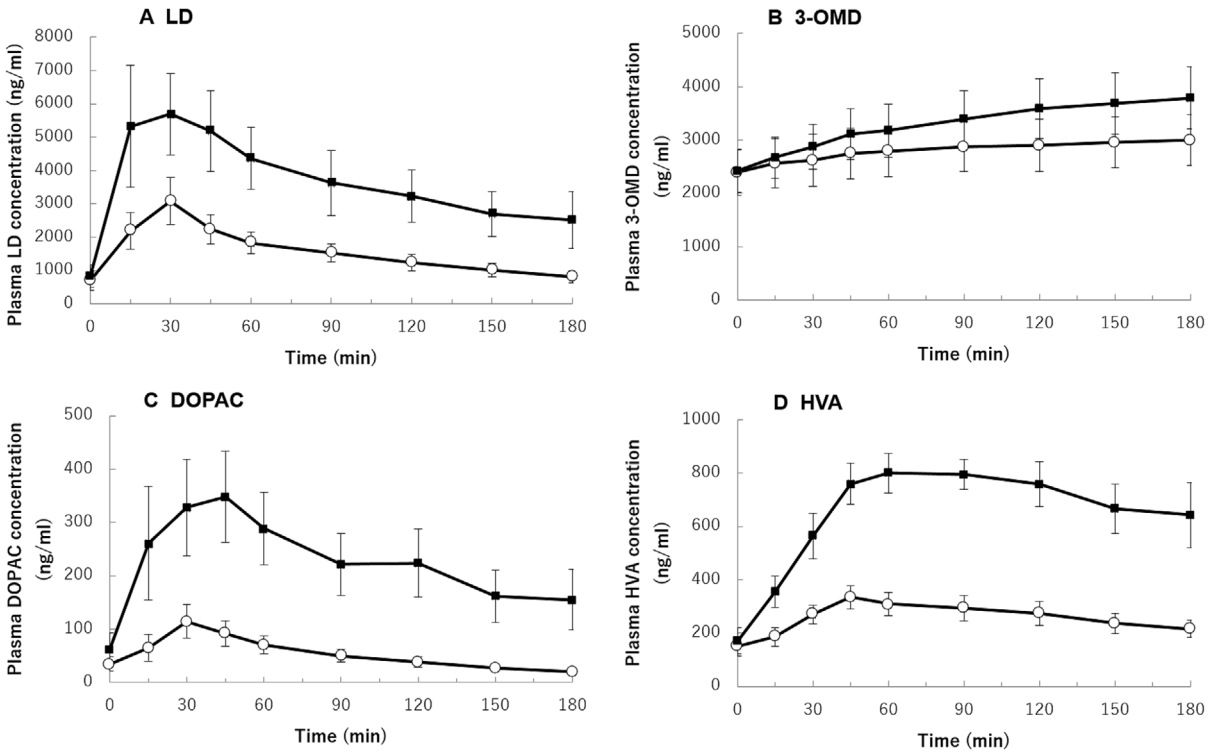


**Figure 3. Plasma concentration over time profiles in patients with Parkinson's disease. Plasma concentrations over time for (A) LD, (B) 3-OMD, (C) DOPAC, and (D) HVA following the ingestion of 100 mg LD/10 mg carbidopa (○) or 11 g MP (■). Data are presented as the mean ± SEM of seven patients. DOPAC: 3,4-dihydroxyphenylacetic acid, HVA: homovanillic acid, LD: levodopa, MP: Mucuna pruriens, 3-OMD: 3-*O*-methyl-dopa, SEM: standard error of the mean**

der (8). Other reports also found the LD content in MP to range from 4% to 6% (2, 12). Similar to the present results, previous studies have reported that MP significantly prolongs ON time in patients with PD compared to oral LD/CD formulations.

In a randomized, controlled, double-blind crossover study, 8 patients with PD received single doses of 200/50 mg LD/CD, 15 g MP formulation, and 30 g MP formulation, each administered 1 week apart. The results showed that the 30 g MP formulation had a significantly faster onset of effect than that of LD/CD (34.6 vs. 68.5 min) and a shorter time to peak plasma concentration. The mean ON time was

21.9% (37 min) longer, and the peak LD plasma concentration was 110% higher for the 30 g MP formulation than for LD/CD. There are no significant differences in dyskinesia expression or tolerability between these two agents (4).

In studies comparing a single dose of high-dose MP (17.5 mg/kg) or low-dose MP (12.5 mg/kg), it was found that low-dose MP was equally effective and resulted in less dyskinesia than a single dose of 3.5 mg/kg LD/CD. The high-dose MP group had substantial motor improvement at 90 and 180 min post-dose, longer ON time, and less dyskinesia than LD/CD group. This study demonstrated that a single dose of MP was not inferior to commercial LD preparation (5). These studies showed that the blood LD levels remained significantly higher after MP administration than LD/CD group, suggesting that the substances in MP had a delayed effect on LD metabolism. Our study also compared the therapeutic effects of MP and LD/CD, but it should be considered that MP of different origins may have different components.

We previously examined the effects of soy consumption on LD metabolism. The AUC of LD increased significantly when soybeans and LD were consumed simultaneously, suggesting 3-OMD inhibition in soybeans. It has been hypothesized that the polyphenols contained in soybeans produce this effect (6). It is possible that a similar substance acts on MP, which belongs to the same legume family as soybeans.

In animal studies, MP components have been shown to inhibit COMT. To investigate this further, the compound (1 R, 3 S ) -6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquino line-1,3-dicarboxylic acid contained in MP was synthesized, and its pharmacological effects were evaluated *in vitro* and *in vivo* using an animal model of PD. The results indicated that this compound inhibited COMT, making it an effective peripheral COMT inhibitor. Its inability to penetrate the blood-brain barrier further supports its role as a peripheral inhibitor. This compound has been suggested to play a significant role in the mechanism of action of MP in the treatment of PD (13).

It was recently reported that MP may have neuroprotective effects. A pharmacological analysis showed that MP contains phenolic compounds, flavonoids, tannins, alkaloids, terpenoids, and saponins, which exhibit iron-reducing antioxidant properties and free-radical scavenging activity (12). *In vitro* studies using MP extracts have also reported that MP exhibits significant neuroprotective activity and acetylcholinesterase inhibitory activity and enhances LD activity (14).

In the present study, the MP-treated group showed higher blood LD levels than the LD-treated group; however, dyskinesia was not exacerbated. Similar results have been reported previously (10, 11), and experiments using animal models of PD have also suggested that MP may have antidyskinesia effects (15, 16). MP reduces dyskinesia via several mechanisms. First, it serves as LD monotherapy without the inclusion of CD. In addition, MP significantly decreases the bioavailability of LD (17). There is also the possibility that MP may contain unidentified substances that exert antidyskinesia effects. These combined mechanisms contribute to the reduction in dyskinesia observed with MP.

Furthermore, in our study, no adverse events were associated with MP ingestion, confirming its safety at a single dose. MP is more readily available than LD/CD preparations and can serve as a valuable PD treatment option in low-income countries (18). Therefore, it is imperative to confirm the safety of long-term administration of MP.

In a study of 14 PD patients treated with MP or LD/CD for 16 weeks in a crossover design, half (7 patients) discontinued medication during the MP treatment period because of gastrointestinal side effects (n = 4) or disease progression (n = 3) (19). Patients who continued to take MP enjoyed a clinical efficacy comparable to that of LD. Dispensing and dosing methods to reduce side effects should be considered for long-term administration of MP.

As MP ingestion increases the blood LD concentration, ingestion of MP with CD-containing LD preparations may significantly increase blood LD concentration and cause adverse events. Since MP has traditionally been consumed as food, it is dangerous for PD patients to consume MP without understanding its risks. It is necessary to conduct educational activities to inform patients of the risks and promote research on the safe use of MP in combination with anti-PD drugs.

Several limitations associated with the present study warrant mention. First, the sample size of patients included in the study was small, which may limit the generalizability of the findings. Second, it is important to note that this study was not a double-blind study, introducing the possibility of bias in the results. Another limitation was that the drug was administered as a single dose, potentially overlooking any cumulative or long-term effects. Finally, the observation period was relatively short, which might not capture the full extent of the drug's effects over a more extended period.

## Conclusion

MP has several advantages as a treatment option for PD patients. It is inexpensive, as effective as L-DOPA, faster- and longer-acting than L-DOPA, and does not increase dyskinesia. However, information on the persistence of efficacy and side effects of long-term use is lacking, and a safe method of MP administration in combination with anti-PD drugs has not yet been established.

**The authors state that they have no Conflict of Interest (COI).**

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**Competing Interests:** Nothing to report

**Ethics approval:** This study was approved by the institutional ethics committee (registration number: 1100). Consent was ob-

tained prior to participation in the study.

**Availability of data:** dataset is available upon reasonable request from the corresponding author.

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