

**EFFECT OF MUCUNA PRURIENS ON HALOPERIDOL  
INDUCED SENSITIZATION OF CATALEPSY**

Urmila Aswar, Manoj Aswar, Subhash L. Bodhankar\* and Prasad A. Thakurdesai

Department of Pharmacology  
Bharati Vidyapeeth Deemed University,  
Erandawane, Paud Road, Pune-38, India

**Summary**

Current treatment of Parkinson's disease is based on Dopamine replacement therapy but this leads to long-term complications. Aim of present study was to examine the effect of alcoholic extract of *Mucuna pruriens* (MPE) on the induction or expression of context dependent augmentation (sensitization) of catalepsy in rats, which develops with repeated administration of haloperidol. Catalepsy induced by haloperidol (0.1-0.5 mg/kg, i.p.) was assessed by bar test periodically upto 3 h in rats. Haloperidol (0.2 mg/kg i.p) produced catalepsy, which increased day by day (sensitization of catalepsy). L-DOPA ((0.5. mg/kg, i.p.) showed antagonism of HAL catalepsy upto 5 days and sensitization was shown day-6 onwards. MPE (200 mg/kg, oral) exhibits antagonism of HAL induced catalepsy after day-2 onwards and persisted even after HAL challenge on day-8. combined treatment of L-DOPA with MPE showed significant antagonism of catalepsy from day-2 onwards which reached to maximum on day-3 and persisted till day-6 and sustained even after HAL challenge on day-8. In conclusion, MPE appears to be beneficial adjuvant treatment with L-DOPA in the management of Parkinson's disease.

**Keywords:** *Mucuna pruriens* (Linn) seed extract, haloperidol induced sensitization, catalepsy

Corresponding author  
Dr. Subhash L. Bodhankar,  
Professor and Head, Department of Pharmacology,  
Bharati Vidyapeeth Deemed University,  
Erandawane, Paud Road, Pune-38  
Tel: +91-20-25437237 Ext-29, Fax: +91-20-25439383,  
E-mail: [sbodh@yahoo.com](mailto:sbodh@yahoo.com)

*Mucuna pruriens* Linn (Fabaceae) is a annual twinning tropical legume that grows throughout Southern and South East Asian regions (1). It grows wildly in India and is cultivated as fodder crop; it is draught hardy species. In India and Srilanka, beans of *Mucuna pruriens* are consumed by tribals for restoring male potency (2). Its trichomes covering shells are used as vermifuge (2). In Ayurvedic system of medicine, the seeds of this plant are prescribed in the treatment of gonorrhoea, general debility and Parkinson's disease (3, 4).

The most effective and most commonly used symptomatic treatment for Parkinson's disease is 3,4-dihydroxy-L-phenylalanine (L-DOPA) combined with a peripheral DOPA decarboxylase inhibitor, such as carbidopa (5-7). L-DOPA is taken up by dopaminergic cell terminals and gets metabolized to the endogenous neurotransmitter dopamine. However, as the disease advances, the therapeutic index (ratio between therapeutic versus secondary effects) of L-DOPA decreases and its antiparkinsonian effect is very often associated with adverse effects, including progressive decline in symptomatic benefit (end-of-dose wearing-off and *on-off* phenomena) and dyskinesia (8)

The term dyskinesia implies excessive and abnormal purposeless movements, which interfere with physiological motor activity. L-DOPA -induced dyskinesia affects between 60 and 70% of all patients, although now this proportion has decreased to 20–30% due to the awareness of the dose of L-DOPA being a main factor involved in the appearance of dyskinesia (9, 10). Another main factor is the degree of striatal dopamine denervation, which lowers the threshold at which the dopamine agonist primes for the appearance of dyskinesia . (11-13). Once its appearance is “primed” by some not yet clearly defined striatal mechanism, L-DOPA-induced dyskinesia appears to be persistent or even permanent (14-16).

*Mucuna pruriens* has been reported to reverse neuroleptic induced catalepsy models in animals (17) and found to be clinically useful against parkinson's disease (3, 17-20). *Mucuna pruriens* endocarp has also been shown to be more effective compared to synthetic levodopa in an animal model of Parkinson's disease (21) Combination of *Mucuna pruriens* along with L-Dopa have been reported to show significant improvement in activities of daily living (ADL) and on motor examination (22) . Sensitization of neuroleptic induced catalepsy has been reported (23). Sensitization (day to day increase in catalepsy) resembles dyskinesia in the human. Sensitization refers to the increased effectiveness of a given drug with its repeated administration (24, 25). It is defined as the enhancement of directly elicited drug effect though adaptive appears and represents facilitation with in a system making effect easier to illicit on future occasions (26).

The aim of present study was to examine the effect of alcoholic extract of *Mucuna pruriens* (MPE) on the induction or expression of context dependent augmentation (sensitization) of catalepsy in rats, which develops, with repeated administration of haloperidol.

## **Materials and Methods**

### *Animals*

Swiss mice of either sex weighing 23-28 g divided into five groups (n=7) and were housed in a temperature (25 ± 2°C) and lights (12:12 light: dark cycle; lights on 7:00 h). The animals had free access to standard pellet diet and water.

Animals were handled and acclimatized to laboratory condition at least 12 h prior to experiments. All the experiments were conducted between 09.30 h and 15.00 h. The experiments described here in comply with ethical principles and guidelines provided by the committee for the purpose of control and supervision of experimental animals, Ministry of environment and forest. Government of India, New Delhi.

### Drugs

Levodopa (D<sub>2</sub> agonist) and haloperidol (D<sub>2</sub> antagonist) was obtained from Sun Pharmaceuticals Ltd. s gift sample. *Mucuna pruriens* Linn seeds were collected from forest areas of Bhopal (Madya Pradesh, India) in month of September 2004 and authenticated by expert taxonomist at University of Bhopal. Voucher specimen has been deposited in the pharmacy herbarium of the Bhopal University.

Alcoholic extract of *Mucuna pruriens* (MPE) was prepared by cold maceration process. Sun dried seeds of *Mucuna pruriens* were ground to a paste of uniform consistency. They were defatted with the help of petroleum ether to obtained uniform paste. Fifty grams of paste was soaked in 100 ml absolute ethanol and allowed to stand for 24 h at 4°C. The suspension was centrifuged at 10 000 X g for 20 min and the supernatant lyophilized to a powder (yield: 17 % w/w) which was stored at -4°C until use. The test solution was prepared in saline and used for the pharmacological activity experiments.

### Haloperidol induced catalepsy by bar test (27)

Catalepsy was induced by haloperidol (0.1-0.5 mg/kg, i.p.) and was assessed by bar test periodically upto 3 h in rats. The groups were treated either with vehicle (0.9 % saline) or MPE (200 mg/kg, oral) or L-Dopa (0.5. mg/kg, i.p.) or MPE+L-DOPA combination, one hour prior to haloperidol (0.2 mg/kg, i.p.) for 7 days. All the groups were challenged with haloperidol alone (0.2 mg/kg, i.p.) on day 8<sup>th</sup> and were observed for catalepsy (a condition characterized most often by rigidity of the extremities and by decreased sensitivity to pain).

### Results

Haloperidol (0.2 mg/kg i.p) produced catalepsy, which increased day by day (sensitization of catalepsy) as shown in Figure 1. Daily testing of animals treated with L-DOPA showed antagonism of HAL catalepsy upto 5 days. From day-6 onwards, sensitization was induced which was evident from day-to-day increase in catalepsy (Table 1). On challenging on day 8<sup>th</sup> with HAL (0.2 mg/kg, i.p.), L-DOPA treated animals showed augmentation of cataleptic behavior (from 1.4 to 1.6). MPE exhibits antagonism of HAL induced catalepsy (P < 0.05) after day-2 onwards (Table 1). This antagonism persisted even after HAL challenge on day-8. As shown in Table 1, combined treatment of L-Dopa with MPE showed significant antagonism of catalepsy from day-2 onwards which reached to maximum on day-3 and persisted till day-6 (P < 0.001). The strong antagonism shown by L-Dopa+MPE combination against HAL induced catalepsy (absence of sensitization) sustained when rats were challenged by HAL on day-8 (Table 1).

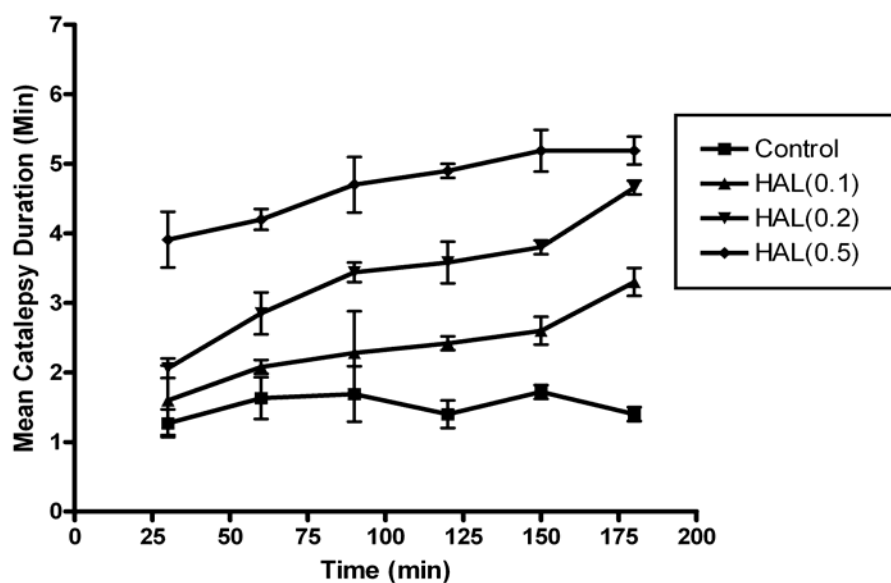


Figure 1: Dose dependant effect of haloperidol (HAL) on catalepsy duration in bar test. Data is presented as mean catalepsy duration (min) ± SEM. Number of animals per group (n) = 6

Table 1:

Effect of alcoholic extract of *Mucuna pruriens seeds* (MPE) on mean catalepsy scores after subacute treatment for 7 days and then challenged by haloperidol on 8th Day

Mean Catalepsy Duration (min) ± S.E.M.					
Day	Vehicle	HAL	L-DOPA + HAL	MPE + HAL	L-DOPA + MPE + HAL
1	0.80 ± 0.10	1.14 ± 0.20 <sup>ns</sup>	0.42 ± 0.20 <sup>ns</sup>	0.95 ± 0.11 <sup>ns</sup>	0.95 ± 0.20 <sup>ns</sup>
2	0.75 ± 0.09	1.70 ± 0.20 <sup>##</sup>	0.90 ± 0.09*	0.95 ± 0.09*	0.92 ± 0.21*
3	0.85 ± 0.08	1.98 ± 0.20 <sup>###</sup>	0.95 ± 0.07**	1.22 ± 0.07*	0.90 ± 0.12***
4	0.80 ± 0.05	2.02 ± 0.10 <sup>###</sup>	1.25 ± 0.10*	1.22 ± 0.12*	0.95 ± 0.14***
5	0.70 ± 0.10	2.02 ± 0.40 <sup>###</sup>	1.23 ± 0.22*	1.25 ± 0.23*	0.98 ± 0.16***
6	0.81 ± 0.06	2.04 ± 0.30 <sup>###</sup>	1.32 ± 0.21 <sup>ns</sup>	1.30 ± 0.21*	1.00 ± 0.23***
7	0.79 ± 0.05	2.11 ± 0.20 <sup>###</sup>	1.40 ± 0.13 <sup>ns</sup>	1.32 ± 0.12*	1.20 ± 0.22**
8	0.76 ± 0.10	2.13 ± 0.40 <sup>###</sup>	1.60 ± 0.22 <sup>ns</sup>	1.32 ± 0.21*	1.20 ± 0.21**

Data is presented as mean catalepsy duration (min) ± SEM. Number of animals per group (n) = 6, HAL-Haloperidol (0.2 mg/kg, i.p), L-Dopa (0.5 mg/kg, i.p), MPE-alcoholic extract of *Mucuna pruriens seeds* (200 mg/kg, oral), Data was analyzed by two-way ANOVA followed by Bonferroni posttests, # P < 0.05, ## P < 0.01 and ### P < 0.001, as compared with vehicle group, \* P < 0.05, \*\* P < 0.01 and \*\*\* P < 0.001 as compared with HAL group, ns - not significant, On Day 8, HAL (0.2 mg/kg) was administered alone in all group of animals.

### Discussion

Blockade of sensitization of haloperidol catalepsy in haloperidol induced sensitization of catalepsy by MPE suggests antiparkinson's activity. These findings are in line with the reports of effectiveness of *Mucuna pruriens* cotyledon powder against 6-hydroxydopamine (6-OHDA) induced lesions (a model of Parkinson's disease) in animals (17) and restoration of endogenous levels of neurotransmitters (like levodopa, dopamine, norepinephrine, and serotonin) in substantia nigra (17).

The blockade of sensitization shown by MPE with L-DOPA against HAL induced catalepsy might be due to several reasons. Presence of L-DOPA is reported to be one of the constituents of *Mucuna pruriens* seeds (3). There is significant evidence of involvement of the generation of reactive oxygen species in pathogenesis of Parkinson's disease (28) and antioxidant activity of *Mucuna pruriens* seeds has been demonstrated in various in vitro tests (29). However, *Mucuna pruriens* endocarp was shown to have significant effect on dopamine content in the cortex but not on L-DOPA, norepinephrine, dopamine, serotonin, and their metabolites in the nigrostriatal tract, which supports the possibility of synergistic effects of some constituents in *Mucuna pruriens* seeds other than L-DOPA (21). NADH (Nicotinamide Adenine Dinucleotide) and coenzyme Q-10 are shown to have beneficial effects in Parkinson's disease, are also found to be present in *Mucuna* seed powder (17, 21) supports blockade of sensitization of L-DOPA against HAL catalepsy. In conclusion, adjuvant treatment with MPE appears to be beneficial in the management of Parkinson's disease to avoid long-term complications of L-DOPA.

### References

1. Duke JA. Legume species. Handbook of Legumes of World Economic Importance. Jodhpur: Scientific Publishers; 2003. p. 170-3.
2. Vasudev Rao MK, Shanpru R. Some plants in the life of garos of Meghalaya. In: Jain SK, editor. Glimpses of Indian ethnobotany. New Delhi: Oxford and LBH Publishing Co; 1981. p. 153-60.
3. Katzenschlager R, Evans A, Manson A, Patsalos PN, Ratnaraj N, Watt H, et al. *Mucuna pruriens* in Parkinson's disease: a double blind clinical and pharmacological study. J Neurol Neurosurg Psychiatry. 2004 Dec;75(12):1672-7.
4. Kirtikar KR, Basu BD. Indian medicinal plants. In: Blatter E, Caius JF, Mhaskar KS, editors. 3rd ed. Dehra Dun: International Book Distributor; 1988. p. 1126-7.
5. Rajput A, Rajput AH. Parkinson's disease management strategies. Expert Rev Neurother. 2006 Jan;6(1):91-9.
6. Romrell J, Fernandez HH, Okun MS. Rationale for current therapies in Parkinson's disease. Expert Opin Pharmacother. 2003 Oct;4(10):1747-61.
7. Suchowersky O. Parkinson's disease: medical treatment of moderate to advanced disease. Curr Neurol Neurosci Rep. 2002 Jul;2(4):310-6.

8. Waters CH. Managing the late complications of Parkinson's disease. *Neurology*. 1997 Jul;49(1 Suppl 1):S49-57.
9. Carta M, Lindgren HS, Lundblad M, Stancampiano R, Fadda F, Cenci MA. Role of striatal L-DOPA in the production of dyskinesia in 6-hydroxydopamine lesioned rats. *J Neurochem*. 2006 Mar;96(6):1718-27.
10. Scott L. Identifying poor symptom control in Parkinson's disease. *Nurs Times*. 2006 Mar 21-27;102(12):30-2.
11. Calon F, Birdi S, Rajput AH, Hornykiewicz O, Bedard PJ, Di Paolo T. Increase of preproenkephalin mRNA levels in the putamen of Parkinson disease patients with levodopa-induced dyskinesias. *J Neuropathol Exp Neurol*. 2002 Feb;61(2):186-96.
12. Calon F, Grondin R, Morissette M, Goulet M, Blanchet PJ, Di Paolo T, et al. Molecular basis of levodopa-induced dyskinesias. *Ann Neurol*. 2000;47(4 Suppl 1):S70-8.
13. Camp DM, Loeffler DA, LeWitt PA. L-DOPA does not enhance hydroxyl radical formation in the nigrostriatal dopamine system of rats with a unilateral 6-hydroxydopamine lesion. *J Neurochem*. 2000 Mar;74(3):1229-40.
14. Ludatscher JI. Stable remission of tardive dyskinesia by L-dopa. *J Clin Psychopharmacol*. 1989 Feb;9(1):39-41.
15. Miller R, Chouinard G. Loss of striatal cholinergic neurons as a basis for tardive and L-dopa-induced dyskinesias, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia. *Biol Psychiatry*. 1993 Nov 15;34(10):713-38.
16. Sgambato-Faure V, Buggia V, Gilbert F, Levesque D, Benabid AL, Berger F. Coordinated and spatial upregulation of arc in striatonigral neurons correlates with L-dopa-induced behavioral sensitization in dyskinetic rats. *J Neuropathol Exp Neurol*. 2005 Nov;64(11):936-47.
17. Manyam BV, Dhanasekaran M, Hare TA. Neuroprotective effects of the antiparkinson drug *Mucuna pruriens*. *Phytother Res*. 2004 Sep;18(9):706-12.
18. Pugalenti M, Vadivel V, Siddhuraju P. Alternative food/feed perspectives of an underutilized legume *Mucuna pruriens* var. utilis--a review. *Plant Foods Hum Nutr*. 2005 Dec;60(4):201-18.
19. Singhal B, Lalkaka J, Sankhla C. Epidemiology and treatment of Parkinson's disease in India. *Parkinsonism Relat Disord*. 2003 Aug;9 Suppl 2:S105-9.
20. Manyam BV, Sanchez-Ramos JR. Traditional and complementary therapies in Parkinson's disease. *Adv Neurol*. 1999;80:565-74.
21. Manyam BV, Dhanasekaran M, Hare TA. Effect of antiparkinson drug HP-200 (*Mucuna pruriens*) on the central monoaminergic neurotransmitters. *Phytother Res*. 2004 Feb;18(2):97-101.

22. Nagashayana N, Sankarankutty P, Nampoothiri MR, Mohan PK, Mohanakumar KP. Association of L-DOPA with recovery following Ayurveda medication in Parkinson's disease. *J Neurol Sci.* 2000 Jun 15;176(2):124-7.
23. Schmidt WJ, Tzschentke TM, Kretschmer BD. State-dependent blockade of haloperidol-induced sensitization of catalepsy by MK-801. *Eur J Neurosci.* 1999 Sep;11(9):3365-8.
24. Phillips TJ, Roberts AJ, Lessov CN. Behavioral sensitization to ethanol: genetics and the effects of stress. *Pharmacol Biochem Behav.* 1997 Jul;57(3):487-93.
25. Ujike H. [Advanced findings on the molecular mechanisms for behavioral sensitization to psychostimulants]. *Nippon Yakurigaku Zasshi.* 2001 Jan;117(1):5-12.
26. Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol.* 1993;4(4):289-312.
27. Iwata S, Izumi K, Shimizu T, Fukuda T. Effects of repeated testing on the incidence of haloperidol-induced catalepsy in mice. *Pharmacol Biochem Behav.* 1989 Jul;33(3):705-7.
28. Schulz JB, Lindenau J, Seyfried J, Dichgans J. Glutathione, oxidative stress and neurodegeneration. *Eur J Biochem.* 2000;267(16):4904-11.
29. Tripathi YB, Upadhyay AK. Effect of the alcohol extract of the seeds of *Mucuna pruriens* on free radicals and oxidative stress in albino rats. *Phytother Res.* 2002;16(6):534-8.