

Evaluation of Effectiveness of Bioactive Principles of *Mucuna pruriens* Seeds Using Experimental Models of Depression Associated with Parkinsonism and Associated Neurotransmitter Turnover

Galani Varsha J² and Talaviya Hetal K¹

- 1 Department of Pharmacology, AR College of Pharmacy and GH Patel Institute of Pharmacy, Vallabh Vidyanagar, Gujarat, India
- 2 Department of Pharmacology, Indukaka Ipcowala College of Pharmacy, New Vallabh Vidyanagar, Gujarat, India

Abstract

Background: *Mucuna pruriens* Linn. (DC) seeds are natural popular remedy, clinically used for the management of Parkinson's disease. Depression is most common non-motor symptom associated with Parkinsonism. Present study evaluates effect of bioactive constituents of the *M. pruriens* seeds in experimental models of depression associated with Parkinsonism.

Methods and Findings: Effect of 14 days treatment of isolated levodopa (ILD), alkaloid fraction (AF) and amino acid fraction (AAF) of the *M. pruriens* seeds were investigated in the catalepsy test, forced swim test, rotarod test and locomotor activity test after haloperidol challenge in mice. Further, the effects of Riboxtetine, Bromocriptine and Fluoxetine were also studied in all these tests. The level of mice brain noradrenaline, dopamine and serotonin were assessed after 14 days treatment of all groups of mice. 14 days treatment of ILD (100 mg/kg, 200 mg/kg, p.o.) AF (200 mg/kg, 400 mg/kg, p.o.) produced significant ($P < 0.001$) reversal of haloperidol induced catalepsy, depression and motor performance along with rise in brain noradrenaline, dopamine and serotonin in mice. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) also showed similar effect except action on serotonin level. However, AAF (200 mg/kg, 400 mg/kg, p.o.) and did not significantly modify haloperidol induced catalepsy, depression and motor performance in mice. Fluoxetine (20 mg/kg, i.p.) also failed to reverse any effect of haloperidol in experimental models except it was potentiated haloperidol induced catalepsy in mice. AAF and Fluoxetine caused significant ($P < 0.001$) reversal of haloperidol induced decrease in brain serotonin without modification of noradrenaline and dopamine level in mice.

Conclusion: The behavioral and biochemical results of the present study indicate that ILD and AF of *M. pruriens* seeds have noradrenergic, dopaminergic and serotonergic system mediated protective action in experimental models of depression associated with Parkinsonism. Further clinical study requires to validating these findings. In addition, this study also provides evidence of protective action of Bromocriptine and Reboxetine. This study also confirms controversy action of an antidepressant fluoxetine in cataleptic depression.

Keywords: Isolated levodopa; Haloperidol induced catalepsy; Forced swim test; Rotarod test; Locomotor activity; *Mucuna pruriens* L.; Depression associated with parkinsonism

Corresponding author: Galani Varsha J

✉ vrp173@yahoo.com

Department of Pharmacology, Indukaka Ipcowala College of Pharmacy, New Vallabh Vidyanagar-388 121, India.

Tel: +919429161203

Fax: 02692229700

Citation: Galani VJ, Talaviya HK. Evaluation of Effectiveness of Bioactive Principles of *Mucuna pruriens* Seeds Using Experimental Models of Depression Associated with Parkinsonism and Associated Neurotransmitter Turnover. *Herb Med.* 2016, 2:3.

Received: October 24, 2016; **Accepted:** September 02, 2016; **Published:** September 07, 2016

Introduction

Depression occurs in approximately 45% of all patients with Parkinson's disease. Serotonergic, noradrenergic and dopaminergic mechanisms play key roles in the etiology of depression in Parkinson's disease [1]. Various clinical studies show that antidepressants like tricyclic antidepressant, Pramipexole and serotonin uptake inhibitors improved depressive state associated with Parkinsonism but there are no uniformly accepted standards for treatment [2]. However, prediction of the effect of antidepressant on symptoms of Parkinson disease is limited due to lack of suitable animal model. The present study examines the possibility of using haloperidol induced catalepsy model in mice for this purpose [3].

Mucuna pruriens Linn. (DC) seeds are natural popular remedy, clinically used for the management of Parkinson's disease, as it contains a high concentration of L-dopa a vital source of dopamine and it is proved superior to synthetic L-dopa for the treatment of Parkinsonism [4]. Also, neuroprotective action of seeds of *M. pruriens* was showed to be due to restoration of the endogenous monoamine contents including dopamine in the substantia nigra [5]. Dopamine, noradrenaline and serotonin mediated antidepressant activity of 50% ethanolic extract of *M. pruriens* seeds were reported from our laboratory using various experimental models of depression [6,7]. Based on this, seeds of *M. pruriens* are hypothesized to cure depression associated with Parkinsonism. Neuroleptic-induced catalepsy has long been used as an animal model for screening drugs for Parkinsonism [8]. Haloperidol induced catalepsy model is a suitable proposed model for evaluation of antidepressant drugs used in treatment of depression associated with Parkinsonism [3]. Haloperidol blocks dopaminergic action in the nigrostriatal pathway leading to a high frequency of extrapyramidal motor side effects [9]. In animal models, Haloperidol induces a behavioral state known as catalepsy in which the animals are unable to correct externally imposed postures [10]. Besides, dopamine receptor blockade and catecholamine depletion, other neurochemical hypotheses have been proposed for the development of catalepsy such as striatonigral GABAergic, cholinergic, glutamate and serotonergic etc. [11-13]. Present study evaluates antidepressant potential of major bioactive principles of *M. pruriens* seeds like levodopa, alkaloids and amino acids in experimental models of depression associated with Parkinsonism and associated neurotransmitter turnover in mice.

Materials and Methods

Animals

Swiss mice (20-25 g) of either sex bred in the central animal house facility of the institute were used. These animals were housed under standard conditions, maintained on a 12 h light/dark cycle and had free access to food and water up to the time of experimentation. The animals were acclimatized to the laboratory environment 1 h before the experiments. Animals were randomly distributed into groups of 6 animals each. The experiment was conducted during the light period (08.00-16.00 h). The protocol

was approved by the Institutional Animal Ethical Committee (IAEC) (Protocol No. CPCSEA/IAEC/ARCP/2011-2012/04) and conducted as per the guidelines of CPCSEA (Committee or the Purpose of Control and Supervision of Experiment on Animals).

Plant material and extraction

The authenticated dried seeds of *Mucuna pruriens* Linn were procured from the Medicinal and Aromatic Plant Department, Anand Agriculture University, Anand, Gujarat, India. Powdered seeds material was extracted with 0.5% acetic acid for isolation of levodopa (ILD) [14] and confirmation of levodopa was obtained by TLC method [15]. Other bioactive constituents such as alkaloids (AF) and aminoacids (AAF) were isolated [16] and confirmed by qualitative phytochemical testing [17].

Haloperidol-induced catalepsy

Mice were divided into eleven groups each group consisting of six animals. Grouping and treatment protocol are shown in **Table 1**. Drug treatment was given for 14 days and on 14th day, after 30 min of oral treatment (ILD, AAF and AF) and intraperitoneal treatment (Fluoxetine-selective serotonin reuptake inhibitor, Reboxetine-noradrenergic reuptake inhibitor, Bromocriptine-dopamine agonist), haloperidol (1 mg/kg, i.p) was injected to all groups of animals (except group 1) and were subjected to catalepsy test. Mice were tested for catalepsy by placing both front paws over an rod, 0.9 cm diameter adjusted at the height 2.5 cm from the table top [18]. The time elapsing between paw placement and the 1st movement of either paw (descent latency) measured in sec was catalepsy score. Animals were tested and evaluated for catalepsy 30 and 60 min after Haloperidol. Furthermore, the animals whose catalepsy score was more than 15 sec was considered to be cataleptic.

Forced swim test

Force swim test was performed using eleven groups of mice, each group consisting of six animals. Grouping and treatment protocol are shown in **Table 1**. Haloperidol (1 mg/kg, i.p) was injected to groups of mice as mentioned in haloperidol induced catalepsy model. All mice were subjected to forced swim test. Mice were individually made to swim individually in a polypropylene vessel (35 × 15 × 10) with a water level of 15 cm at 25 ± 2°C and observed for duration of 6 minutes [19]. The first 2 minutes was considered as vigorously active state and the duration of immobility was recorded during the last 4 minutes of the observation period. The mouse was considered immobile when it floated motionlessly or made only those moments necessary to keep its head above the water surface. A decrease in the duration of immobility was indicative of an antidepressant effect. Clean water was replaced after each test.

Rota rod test

Rota rod test was performed using another eleven groups of mice, each group consisting of six animals. Grouping and treatment protocol are shown in **Table 1**. Haloperidol (1 mg/kg, i.p) was injected to groups of mice as mentioned in haloperidol induced catalepsy model. All animals were subjected individually to Rotarod test using rotarod apparatus [19]. Fall off time indicate

skeletal muscle relaxant activity was recorded after 30 minutes and 60 minutes of haloperidol treatment.

Test for locomotor activity

Mice were divided in to eight groups each group consisting of six animals. Treatments are given as per group 1, 2, 3, 5, 7, 9, 10 and 11 of **Table 1**. Haloperidol (1 mg/kg, i.p.) was injected to groups of mice as mentioned in haloperidol induced catalepsy model. All mice were subjected individually to locomotor test using actophotometer [20]. The locomotor activity was expressed in terms of total photo beam interruption counts/5 min per animal. Increase in count was regarded as central nervous system stimulant activity and decrease in count was regarded as depressant activity.

Measurement of brain neurotransmitters

After haloperidol induced catalepsy test, mice were sacrificed and brains were isolated. Whole brain of each mouse was weighed without thawing and immediately homogenized in 5 ml ice cold acidified butanol. The homogenate was centrifuge at 500 rpm at 4°C for 10 min and the supernatant was collected. Noradrenaline (NA) and serotonin (5-HT) neurotransmitters were estimated by fluorimetric method of Jacobowitz and Richardson [21].

Statistical analysis: All statistical analysis was performed using SPSS software (Version 10.0, SPSS Inc., Chicago, IL, USA). The data were expressed as mean \pm S.E.M. The statistical significance of the difference between groups for the various treatments were determined by one way analysis of variance (ANOVA) followed by Tukey's multiple range test. $P < 0.001$ or $P < 0.05$ was considered statistically significant as compared to control.

Results

Haloperidol induced catalepsy

As shown in **Figure 1**, Haloperidol treatment produced significant catalepsy as compared to control animals. 14 days treatment of ILD (100 and 200 mg/kg, p.o.) and AF (200 mg/kg and 400 mg/kg, p.o.) from *M. pruriens* seeds showed significant ($p < 0.001$) and dose dependent reduction of haloperidol induced catalepsy. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) also showed significant ($p < 0.001$) reduction of haloperidol induced catalepsy. 14 days treatment of the AAF (200 mg/kg and 400 mg/kg, i.p.) from the seeds did not show significant change on

haloperidol induced catalepsy. However, Fluoxetine (20 mg/kg, i.p.) showed potentiation of haloperidol induced catalepsy in mice.

Forced swim test

Result of action of haloperidol and its modification by ILD, AF and AAF in forced swim test are shown in **Figure 2**. Haloperidol (1 mg/kg, i.p.) treatment caused significant ($p < 0.001$) increase in the immobility time as compared to control indicated that haloperidol can induce cataleptic depression. 14 days treatment of ILD (100 and 200 mg/kg, p.o.), AF (200 mg/kg and 400 mg/kg, p.o.) from *M. pruriens* seeds were showed significant ($p < 0.001$) and dose dependent inhibition of haloperidol induced depression in mice. However, 14 days treatment of AAF (200 mg/kg and 400 mg/kg, p.o.) from the seeds did not significantly reverse the haloperidol induced cataleptic depression. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) showed significant ($p < 0.001$) antagonism of haloperidol induced immobility in mice. Fluoxetine (20 mg/kg, i.p.) did not show any significant change in haloperidol induced cataleptic depression.

Rotarod test

Result of action of haloperidol and its modification by ILD, AF and AAF in rota rod test are shown in **Figure 3**. Haloperidol (1 mg/kg, i.p.) treatment caused significant decrease in the fall off time as compared to control. 14 days treatment of ILD (100 and 200 mg/kg, p.o.), AF fraction (200 mg/kg and 400 mg/kg, p.o.) from *M. pruriens* seeds were showed dose dependent reversal of haloperidol effect as indicated by significant ($p < 0.001$) increase in fall off time as compared to model control. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) also showed similar effect. However, the AAF (200 mg/kg and 400 mg/kg, p.o.) from the seeds and Fluoxetine (20 mg/kg, i.p.) did not show any significant effect as compared to model control.

Test for locomotor activity

Result of action of haloperidol and modification of haloperidol effect on locomotor activity by ILD, AF and AAF in actophotometer are shown in **Figure 4**. Haloperidol (1 mg/kg, i.p.) treatment caused significant ($p < 0.001$) decrease in the locomotor activity in mice as compared to control. 14 days treatment of ILD (200 mg/kg, p.o.), AF (400 mg/kg, p.o.) from *M. pruriens* seeds significantly ($p < 0.001$) reversed the haloperidol effect as indicated by

Table 1 Study protocol.

Group No.	Treatment
1	Normal saline (10 ml/kg, p.o.) for 14 days (control)
2	Normal saline (10 ml/kg, p.o.) for 14 days (model control)
3	Isolated levodopa (ILD 100 mg/kg, p.o.) for 14 days
4	Isolated levodopa (ILD 200 mg/kg, p.o.) for 14 days
5	Amino acid fraction (AAF 200 mg/kg, p.o.) for 14 days
6	Amino acid fraction (AAF 400 mg/kg, p.o.) for 14 days
7	Alkaloid Fraction (AF 200 mg/kg, p.o.) for 14 days
8	Alkaloid Fraction (AF 400 mg/kg, p.o.) for 14 days
9	Normal saline (10 ml/kg, p.o.) for 14 days and Fluoxetine (20 mg/kg, i.p.) 30 min after last dose of normal saline
10	Normal saline (10 ml/kg, p.o.) for 14 days and Reboxetine (1 mg/kg, i.p.) 30 min after last dose of normal saline
11	Normal saline (10 ml/kg, p.o.) 14 days and Bromocriptine (2 mg/kg, i.p.) 30 min after last dose of normal saline

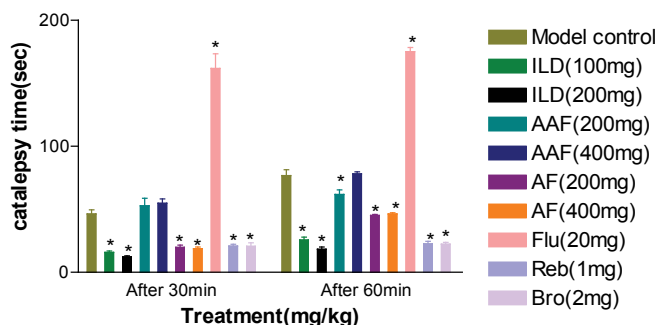


Figure 1 Effect of bioactive principles of *Mucuna pruriens* seeds on haloperidol induced catalepsy in mice. Each bar expressed as mean \pm S.E.M. Data were analysed by one way ANOVA followed by Tukey's test. *P<0.001 when compared with model control.

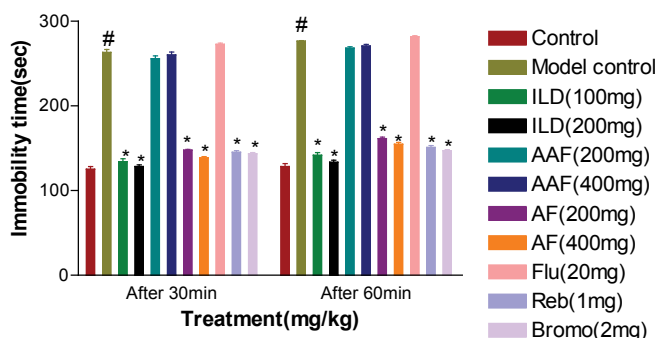


Figure 2 Effect of bioactive principles of *Mucuna pruriens* seeds on forced swim test in mice. Each bar expressed as mean \pm S.E.M. Data were analysed by one way ANOVA followed by Tukey's test. #P<0.001 when compared with control. *P<0.001 when compared with model control.

increase of locomotor activity counts. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) also showed similar effect. However, the AAF (200 mg/kg and 400 mg/kg, i.p.) from the seeds did not significantly modify the haloperidol effect. Fluoxetine (20 mg/kg, i.p.) did not show any significant change as compared to model control.

Measurement of brain neurotransmitters

Measurement of brain serotonin level: Result of action of haloperidol and its modification by IL, AF and AAF on brain serotonin level in mice are shown in **Figure 5**, Haloperidol (1 mg/kg, i.p.) treatment caused significant (p<0.001) reduction in mice brain serotonin level as compared to control. IL (200 mg/kg, p.o.), AF (400 mg/kg, p.o.) and AAF (400 mg/kg, p.o.) from *M. pruriens* seeds showed significant (p<0.001) reversal of the effect of haloperidol on brain serotonin level in mice. Reboxetine (1 mg/kg, i.p.) and Fluoxetine (20 mg/kg, i.p.) also showed similar effect on brain serotonin level in mice. Bromocriptine (2 mg/kg) did not significantly modify haloperidol effect on brain 5-HT level in mice.

Measurement of brain dopamine level: Result of action of haloperidol and its modification by IL, AF and AAF on brain dopamine level are shown in **Figure 6**, Haloperidol (1 mg/kg, i.p.) treatment produced significant (p<0.001) decrease in brain dopamine level as compared to control. IL (200 mg/kg, p.o.), AF (400 mg/kg, p.o.) from *M. pruriens* seeds were caused significant (p<0.001) reversal of the effect of haloperidol on brain dopamine level as compare to haloperidol. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) also showed similar effect on brain dopamine level in mice. However, AAF (400 mg/kg, i.p.) from the seeds did not modify haloperidol effect significantly. Fluoxetine (20 mg/kg, i.p.) did not significantly modify haloperidol effect on brain dopamine level in mice.

Measurement of brain noradrenaline level: Result of action of haloperidol and its modification by IL, AF and AAF on brain noradrenaline level are shown in **Figure 7**, Haloperidol (1 mg/kg, i.p.) treatment produced significant (p<0.001) decrease in brain noradrenaline level as compared to control. IL (200 mg/kg, p.o.), AF (400 mg/kg, p.o.) from *M. pruriens* seeds caused significant (p<0.001) reversal of the effect of haloperidol on brain

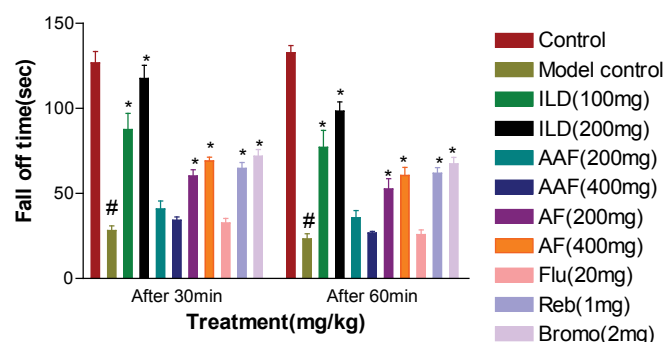


Figure 3 Effect of bioactive principles of *Mucuna pruriens* seeds on Rotarod test in mice. Each bar expressed as mean \pm S.E.M. Data were analysed by one way ANOVA followed by Tukey's test. #P<0.001 when compared with control. *P<0.001 when compared with model control.

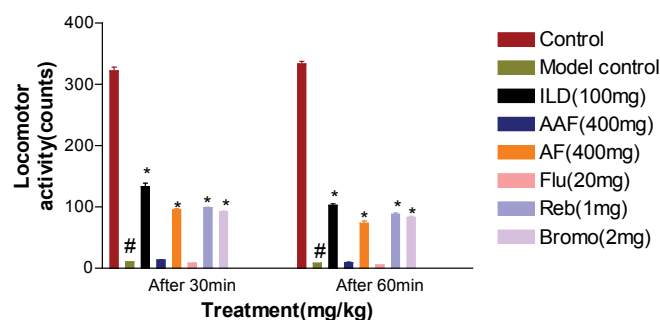


Figure 4 Effect of bioactive principles of *Mucuna pruriens* seeds on locomotor activity in mice. Each bar expressed as mean \pm S.E.M. Data were analyzed by one way ANOVA followed by Tukey's test. #P<0.001 when compared with control. *P<0.001 when compared with model control.

noradrenaline level. Reboxetine (1 mg/kg, i.p.) and Bromocriptine (2 mg/kg, i.p.) also showed similar effect on brain noradrenaline level in mice. However, AAF (400 mg/kg, i.p.) from the seeds did not modify haloperidol effect significantly. Fluoxetine (20 mg/kg, i.p.) did not significantly modify haloperidol effect on brain noradrenaline level in mice.

Discussion

Although Parkinsonism is well characterized by motor symptoms including akinesia, tremor, rigidity and postural instability, it is often accompanied by non-motor symptoms such as depression, anxiety and dementia. The presence of depression has a negative impact on the quality of life of Parkinson's disease patients and their families [22]. It is reported that depression in Parkinsonism is associated with disability, disease progression, decline of activities of daily living functions and reduced cognitive performance [23]. Thus, antidepressant drugs are likely to be included in the list of drugs prescribed for patients with Parkinson's disease. For many years, the tricyclic antidepressants and the monoamine oxidase inhibitors have dominated the pharmacological treatment of depressive disorders [24]. However, prediction of the effect of antidepressants on symptoms of Parkinson's disease is limited due to lack of suitable animal model. Haloperidol induced catalepsy in conjunction with force swim test is reported as a useful model for screening of drug useful in depression associated with Parkinsonism [3].

Cataleptic effects of haloperidol depend on the balance between the dopaminergic and serotonergic systems, and the serotonergic system exerts an inhibitory influence on the dopaminergic system [25]. D_1 and D_2 agonist reduced haloperidol induced catalepsy [25]. In the present study, similar result was obtained with ILD, AF of *M. pruriens* seeds, Bromocriptine, and Reboxetine treatments against haloperidol induced catalepsy in mice. While, serotonin reuptake inhibitor, Fluoxetine exacerbated haloperidol induced catalepsy [26]. AAF of *M. pruriens* seeds did not show significant protection against haloperidol induced catalepsy in mice.

Forced swim test are quite sensitive and widely employed in rodents to predict antidepressant potential by reduction of immobility period [27]. It is reported that haloperidol induced depression in forced swim test [3]. In the present study, ILD, AF of *M. pruriens* seeds, Bromocriptine, and Reboxetine treatments showed significant reversal of the haloperidol induced immobility in mice. While AAF of *M. pruriens* seeds and Fluoxetine did not show significant effect on haloperidol induced immobility in mice.

The most widely used animal models for CNS depressant screenings are the locomotion test and rotarod tests. These tests are quite sensitive and relatively specific to all major classes of central nervous system depressants. It is reported that haloperidol decreased locomotor activity and ethanolic extract of *M. pruriens* seeds significantly reversed the haloperidol induced decrease in locomotor activity [28]. In present study, effect of ILD and AF of *M. pruriens* seeds, Bromocriptine, and Reboxetine treatment on locomotor activity and motor co-ordination produced supportive evidence for their protective effect in catatonic depression in mice. While AAF of the seeds and Fluoxetine were not produced positive effect in these tests also.

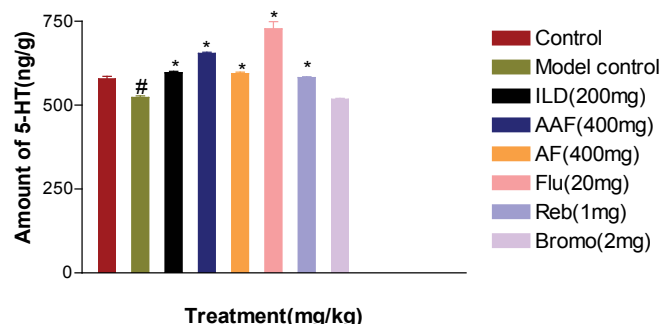


Figure 5 Effect of bioactive principles of *Mucuna pruriens* seeds on brain serotonin level in mice. Each bar expressed as mean \pm S.E.M. Data were analysed by one way ANOVA followed by Tukey's test. * $P < 0.001$ when compared with control. * $P < 0.001$ when compared with model control.

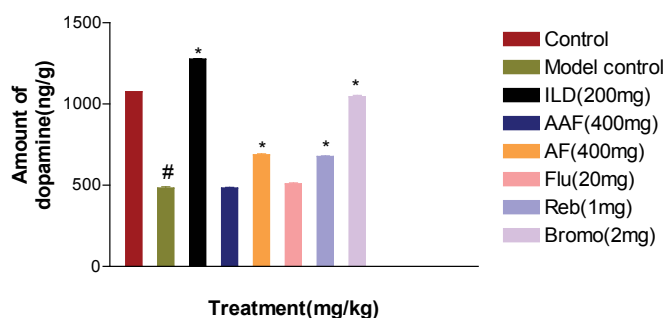


Figure 6 Effect of bioactive principles of *Mucuna pruriens* seeds on brain dopamine level in mice. Each bar expressed as mean \pm S.E.M. Data were analysed by one way ANOVA followed by Tukey's test. * $P < 0.001$ when compared with control. * $P < 0.001$ when compared with model control.

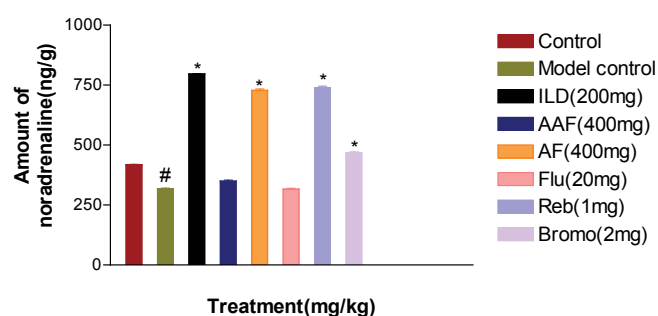


Figure 7 Effect of bioactive principles of *Mucuna pruriens* seeds on brain noradrenaline level in mice. Each bar expressed as mean \pm S.E.M. Data were analysed by one way ANOVA followed by Tukey's test. * $P < 0.001$ when compared with control. * $P < 0.001$ when compared with model control.

Disturbed 5-HT metabolism may possibly play a role in Parkinson's disease as a predisposing factor in the development of depression [29]. PET study using [^{11}C] RTI-32, a dopamine and noradrenaline transporter ligand, showed significant loss in limbic structures including the locus coeruleus, ventral striatum and amygdale of PD patients, and this was associated with

depression [30]. A dysfunctional dopamine system might also contribute to depression in PD since data suggest that mood improves once levodopa treatment has been initiated [31]. Haloperidol administration decreased the dopamine levels [32] and increase noradrenaline and serotonin turnover [33].

It is reported that dopamine, noradrenaline and serotonin levels decrease in depression [34] and ILD and AF of *M. pruriens* seeds with haloperidol challenge significantly increased brain dopamine, noradrenaline and serotonin level in mice indicating antidepressant activity of these bioactive constituents. These would correlate with their behavioural effect in force swim test, actophotometer and rota rod test. In a clinical study, Reboxetine was reported to be effective and well tolerated in Parkinson's disease patients receiving 4 weeks of treatment of moderate-to-severe depression [35] and our study also showed effectiveness of Reboxetine in depression associated Parkinsonism animal models. Bromocriptine showed antidepressant effects possibly mediated through the noradrenergic system and dopaminergic

system [36]. AAF of the seeds and Fluoxetine treatments did not influence dopaminergic and noradrenergic system but affected serotonergic system. Hence, both are not seem to be effective in depression associated with Parkinsonism.

Conclusion

This study validates the use of haloperidol induced cataleptic depression model for the screening of drug used in depression associated with Parkinsonism. The behavioral and biochemical results of the present study indicate that ILD and AF of *M. pruriens* seeds have protective action in haloperidol induced catatonic depression, which may be mediated by the noradrenergic, dopaminergic and serotonergic mechanisms in mice brain. While AAF did not show protective effect but it may cause increase brain serotonin level. In addition, this study also provides evidence of protective action of Bromocriptine and Reboxetine. This study also confirms controversy action of an antidepressant Fluoxetine in cataleptic depression.

References

- 1 Lemke MR (2008) Depressive symptoms in Parkinson's disease. *Eur J Neurol* 15: 21-25.
- 2 Poewe W, Seppi K (2001) Treatment options for depression and psychosis in Parkinson's disease. *J Neurol* 248: 12-21.
- 3 Khisti RT, Mandhane SN, Chopde CT (1997) Haloperidol-induced catalepsy: a model for screening antidepressants effective in treatment of depression with Parkinson's disease. *Indian J Exp Biol* 35: 1297-1301.
- 4 Hussain G, Manyam BV (1997) *Mucuna pruriens* proves more effective than L- DOPA in Parkinson's disease animal model. *Phytother Res* 11: 419-423.
- 5 Manyam BV, Dhanasekaran M, Hare TA (2004) Neuroprotective effects of the antiparkinson drug *Mucuna pruriens*. *Phytother Res* 18: 706-712.
- 6 Rana DG, Galani VJ (2014) Dopamine mediated antidepressant effect of *Mucuna pruriens* seeds in various experimental models of depression. *Ayu (An international Quarterly published journal)* 35: 90-97.
- 7 Patel JS, Galani VJ (2013) Investigation of noradrenaline and serotonin mediated antidepressant action of *Mucuna pruriens* (L) D.C seeds using various experimental models. *Oriental Pharmacy and Experimental Medicine* 13: 143-148.
- 8 Anil K, Kulkarni SK (2006) Effect of BR-16A (Mentat), a polyherbal formulation on drug induced catalepsy in mice. *Indian J Exp Biol* 44: 45-48.
- 9 Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, et al. (1992) Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: Relation to extra-pyramidal side effects. *Arch Gen Psychiatry* 49: 538-544.
- 10 Sanberg PR (1980) Haloperidol-induced catalepsy is mediated by postsynaptic dopamine receptors. *Nature* 284: 472-473.
- 11 Bazian AS (2001) Divergent and convergent mechanism of integrative activity of mammalian brain. *Zh Vyssh Nerv Deiat Im I P Pavlova* 51: 514-528.
- 12 Okuyama S (1999) Atypical antipsychotic profile of sigma receptor ligands. *Nippon Yakurigaku Zasshi* 114: 13-23.
- 13 Neal Belveau BS, Joyce JN, Lucki I (1993) Serotonergic involvement in haloperidol-induced catalepsy. *J Pharmacol Exp Ther* 265: 207-217.
- 14 Manayath D, Raghaviah R (1937) Isolation of l-3:4-dihydroxyphenylamine from the seeds of *Mucuna pruriens*. *Biochem J* 31: 2149-2152.
- 15 Behera A, Sankar DG, Si SC (2010) Development and validation of an HPTLC - densitometric method for determination of levodopa in seeds of *Mucuna pruriens* and its dosage form. *Eurasian Journal of Analytical Chemistry* 5: 126-136.
- 16 Misra L, Wagner H (2006) Lipid derivatives from *Mucuna pruriens* seeds. *Indian J Chem (Section B)* 45: 801-804.
- 17 Kokate CK, Purohit AP, Gokhale SB (2006) Practical in pharmacognosy. Nirali Prakashan, pp: 105-114.
- 18 Mhetre NA, Ambavade SD (2005) Neuroleptic activity of extracts of *Sphaeranthus indicus* flowers in mice. *Indian J Nat Prod* 22: 24-27.
- 19 Joy HH, Krishna VG (2011) CNS depressant activity of extract from *Flaveria trinervia* spring C. Mohr. *Phytopharmacol* 1: 101-104.
- 20 Dhanasekaran S, Ratheesh KS, Palayan M (2010) Effect of ethanolic seed extract of *Mucuna pruriens* on haloperidol induced tardive dyskinesia in rats. *International J of Pharma sci review and Res* 3: 106-113.
- 21 Jacobowitz DM, Richardson JS (1977) Method for the rapid determination of norepinephrine, dopamine, and serotonin in the same brain region. *Pharmacol Biochem & Behav* 8: 515-519.
- 22 Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 69: 308-312.
- 23 Aarsland D, Bronnick K, Alves G (2009) The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Psychi* 80: 928-930.
- 24 Meco G, Bernardi S (2007) Antidepressant use in treatment of psychosis with comorbid depression in Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychia* 31: 311-313.
- 25 Kaori H, Kiyomi I, Hajime K, Yasufumi S, Tatsuji I (1997) Prediction of drug induced catalepsy based on dopamine D1, D2, and muscarinic acetylcholine receptor occupancies. *Drug metabolism and disposition* 25: 675-684.
- 26 Neal-belveau B, Joyce J (1993) Serotonergic involvement in haloperidol induced catalepsy. *J Pharmacol* 265: 207-217.
- 27 Kulkarni SK, Bhutani MK, Bishnoi M (2008) Antidepressant activity of curcumin: involvement of serotonin and dopamine system. *Psychopharmacology* 201: 435-442.
- 28 Mayeux R, Stern Y, Williams JB, Cote L, Frantz A, et al. (1986) Clinical and biochemical features of depression in Parkinson's disease. *Am J Psychia* 143: 756-759.
- 29 Mayeux R, Stern Y, Cote L, Williams JB (1984) Altered serotonin metabolism in depressed patients with parkinson's disease. *Neurology* 34: 642-646.
- 30 Remy P, Doder M, Lees A, Turjanski N, Brooks D (2005) Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 128: 1314-1322.
- 31 Fetoni V, Soliveri P, Monza D, Testa D, Girotti F (1999) Affective symptoms in multiple system atrophy and Parkinson's disease: response to levodopa therapy. *J Neurol Neurosurg Psychia* 66: 541-544.
- 32 Ali O, Haleem DJ, Obaid R, Kamil N (2003) Effect of co administration of haloperidol and large neutral amino acids (tryptophan and valine) on rats striatal dopamine, serotonin and their metabolism. *Pak J Pharm Sci* 16: 13-25.
- 33 Hall LM, Anderson GM, Cohen DJ (1995) Acute and chronic effects of fluoxetine and haloperidol on mouse brain serotonin and norepinephrine turnover. *Life sci* 57: 791-801.
- 34 Nutt DJ (2008) Relationship of neurotransmitters to the symptoms of major depressive disorder. *J Clin Psychia* 69: 4-7.
- 35 Lemke MR (2002) Effect of reboxetine on depression in Parkinson's disease patients. *J Clin Psychiatr* 63: 300-304.
- 36 Nordin C, Siwers B (1981) Bromocriptine treatment of depressive disorders: Clinical and biochemical effects. *Acta Psychiatr Scand* 64: 25-33.