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Pharmacological Study

Dopamine mediated antidepressant effect of *Mucuna pruriens* seeds in various experimental models of depression

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Abstract

Background: The effects of antidepressant treatments have traditionally been discussed primarily in terms of effects on noradrenergic and serotonergic systems. Multiple lines of investigation have also explored the role of dopaminergic systems in mental depression. Seed of *Mucuna pruriens* Linn. (DC) (Leguminoseae) is well-known with dopaminergic action and has several therapeutic applications in folk medicine in curing or managing a wide range of diseases including Parkinsonism. **Aim:** To elucidate the anti-depressent profile and possible dopaminergic modulating action of *M. pruriens* seeds in various experimental models of depression. **Materials and Methods:** In the present study, antidepressant effect of the hydroalcoholic extract of the *M. pruriens* seeds (MPE) (100 and 200 mg/kg, p.o.) was investigated in the Forced Swimming Test (FST), Tail Suspension Test (TST), and Chronic Unpredictable Mild Stress (CUMS) test in mice. Further, dopaminergic interaction of same doses of MPE in the FST and TST were checked by the administration of a haloperidol (0.1 mg/kg, i.p.) and bromocriptine (2 mg/kg, i.p.) on the 7th day of MPE treatment. Effect of MPE on locomotor activity was also checked using actophotometer. **Results:** MPE produced a significant reduction of the immobility time in the FST and TST. Further, antidepressant action of MPE was significantly inhibited by haloperidol and potentiated by bromocriptine in the FST and TST. 21 days of MPE treatment produced protection in CUMS as indicated by a significant increase of sucrose intake of stressed mice. Locomotor activities of mice were not significantly changed after 1 h and 7th day of the MPE treatment. **Conclusion:** The results of this study indicate that hydroalcoholic extract of MPE have antidepressant action, which may be mediated by an interaction with the dopaminergic system.

Key words: Chronic mild stress test, forced swimming test, *Mucuna pruriens*, tail suspension test

Introduction

Depression is a disorder characterized by a broad range of symptoms, including altered mood and cognitive functions, and recurrent thoughts of death or suicide.[1] The World Health Organization (WHO) predicts that depression will become the second leading cause of premature death or disability worldwide by the year 2020.[2] The monoamine hypothesis of depression states that it is caused by functional deficit of monoamines (norepinephrine, serotonin and dopamine) at certain sites in the brain.[3] Previously study presented the first evidence for a dopaminergic dysfunction in depression.[4] Dopaminergic mesolimbic and mesocortical systems are involved in anhedonia and lack of motivation, two core symptoms of depression.[5] Because of the limitations of the antidepressant therapy, there has been renowned interest in medicinal plants, which have comparable efficacy to prescription medications with lesser side effects. *Mucuna pruriens* Linn. (DC) is a popular Indian medicinal plant commonly known as *Cowitch*, which has long been used in traditional Ayurvedic system of medicine for the management of a number of diseases. Roots are used in the treatment of nephropathy, strangury, dysmenorrhea, amenorrhea, elephantiasis, dropsy, neuropathy, ulcers, and fever and as febrifuge and tonic. Leaves are aphrodisiac, tonic, and are useful in ulcers, inflammation, helminthiasis, cephalalgia and general debility. Seeds are used in snakebite, sexual debility, cough, tuberculosis, impotence, rheumatic disorders, muscular pain, gonorrhea, sterility, gout, delirium, dysmenorrhea, diabetes, and cancer.[6,7] Several investigations have proposed that this plant possesses antiparkinsonian, antidiabetic, aphrodisiac, antioxidant, antineoplastic, antiepileptic, antimicrobial, anti-inflammatory, analgesic, and antipyretic activities.[8] A wide range of phytochemical constituents has been isolated from

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this plant. Presence of a large amount of L-dopa, alkaloids and a minor amount of 5-hydroxytryptamine have been reported in the seeds.[8] The powder of the seeds is clinically used for the management of hyperprolactinemia and Parkinson's disease, as it contains a high concentration of L-dopa a vital source of dopamine.[9,10] Also neuroprotective action of seeds of *M. pruriens* were showed to be due to restoration of the endogenous monoamine contents including dopamine in the substantia nigra[11] indicating dopaminergic action of *M. pruriens* seeds in the brain. In context to dopaminergic action of *M. pruriens* seeds and role of dopamine in the depression, the present study was designed to elucidate the anti-depressant profile and possible dopaminergic modulating action of *M. pruriens* seeds in various experimental models of depression.

Materials and Methods

Plant material and preparation of the hydroalcoholic extract of seeds of *M. pruriens* (MPE)

The authenticated dried seeds of *M. pruriens* Linn. were obtained from the Medicinal and Aromatic Plant Department, Anand Agriculture University, Anand, Gujarat, India. The seed material was powdered to mesh size 60 and extracted exhaustively with 50% ethanol using soxhlet apparatus. Crude (hydroalcoholic) extract was filtered and dried under reduced pressure at 40°C (yield-13% w/w of dried powdered material). Freshly prepared aqueous solution of the dried extract (MPE) in doses of 100 mg/kg, and 200 mg/kg were used for pharmacological study.[8]

Preliminary phytochemical screening

The qualitative chemical investigation of hydroalcoholic extract was carried out to check the presence of various phytoconstituents.[12]

Animals

Swiss mice (20-25 g) of either sex (total 150) bred in 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. All experiments were conducted during the light period (08.00-16.00 h). All the protocols were approved by the Institutional Animal Ethics Committee (IAEC) and conducted according to the guidelines of Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA) (CPCSEA/IAEC/ARCP/09-10/07).

Drugs

Imipramine hydrochloride (standard drug) was obtained as gratis sample from Psychotropic India Ltd., Faridabad. Haloperidol (Seranace®, RPG Life science, India) was used as dopamine receptor (D_2) antagonist. Bromocriptine mesylate (Proctinal®, GlaxoSmithKline, India) was used as dopamine receptor (D_2) agonist. Haloperidol was diluted in distilled water which was used for a vehicle of injection. Bromocriptine mesylate was dissolved in one drop of glacial acetic acid and made up to volume in distilled water. Imipramine was dissolved in 0.9% normal saline. Haloperidol (0.1 mg/kg, i.p.) and bromocriptine mesylate (2 mg/kg, i.p.) were administered for 7 days in groups of mice in Forced Swimming Test (FST) and Tail Suspension Test (TST). Imipramine (10 mg/kg, p.o.) as a standard was administered in positive control groups for 7 days.

Forced swimming test (FST)

Mice were divided in to ten groups, each group consisting of six animals. Groupings and treatment protocol are shown in Table 1. On 7th day of the treatment, 1 h after MPE and imipramine or 30 min after haloperidol and bromocriptine administration, each animal was subjected to FST. Mice were made to swim individually in a polypropylene vessel (30 × 15 × 30 cm) with a water level of 15 cm at 25 ± 2°C. Two swim sessions were conducted, an initial 15 min pretest followed by a 5 min test 24 h later. The duration of immobility, characterized by complete cessation of swimming with the head just floating above water level was determined during the final 5 min period of test.[13] A decrease in the duration of immobility was indicative of an antidepressant effect.

Tail suspension test (TST)

TST was performed using another 10 groups of mice each consist of six animals. Groupings and treatment protocol are shown in Table 1. One hour after oral and 30 min after intraperitoneal administration, each animal was submitted to TST. Mice both acoustically and visually isolated were suspended on the edge of a table 50 cm above the floor by the adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 5 min period.[14] Animal was considered to be immobile when it did not show any movement of body and hung passively.

Table 1: Study groups for forced swimming test and tail suspension test

Groups	Drug and dose
I (control)	Normal saline (10 ml/kg, p.o.) for 7 days
II (positive control)	Imipramine (10 mg/kg, p.o.) as standard for 7 days
III (test)	MPE (100 mg/kg, p.o.) for 7 days
IV (test)	MPE (200 mg/kg, p.o.) for 7 days
V (dopamine antagonist)	Haloperidol (0.1 mg/kg, i.p.) for 7 days
VI (test+ dopamine antagonist)	MPE (100 mg/kg, p.o.) for 7 days and haloperidol (0.1 mg/kg, i.p.) 1 h after the last dose of MPE
VII (test+ dopamine antagonist)	MPE (200 mg/kg, p.o.) for 7 days and haloperidol (0.1 mg/kg, i.p.) 1 h after the last dose of MPE
VIII (dopamine agonist)	Bromocriptine mesylate (2 mg/kg, i.p.) for 7 days
IX (test+ dopamine agonist)	MPE (100 mg/kg, p.o.) for 7 days and bromocriptine mesylate (2 mg/kg, i.p.) 1 h after the last dose of MPE
X (test+ dopamine agonist)	MPE (200 mg/kg, p.o.) for 7 days and bromocriptine (2 mg/kg, i.p.) 1 h after the last dose of MPE

MPE: Hydroalcoholic extract of *Mucuna pruriens* seeds

Chronic unpredictable mild stress (CUMS)

At the start of the experiment, mice were trained to consume 2% sucrose solution. Sucrose consumption was monitored throughout the experiment. After one week period of adaptation, sucrose solution intake baseline test was performed (two tests per 7 days) over a period of 18 days for all mice. This test involved a 3 h period of food and water deprivation, followed by offering of sucrose solution for 1 h. Intake was determined by weighing the bottles containing sucrose solution at the beginning and at the end of each test.[15] After this phase (18 days), one group of the 6 mice was housed under normal conditions (normal mice) and the other 24 mice were subjected to Chronic Unpredictable Mild Stress (CUMS). The stressor schedule was slightly modified from that used by Monleon *et al*.,[16] which include three 5 h periods of food and water deprivation, one 16 h period of water deprivation, three periods (3, 5, and 7 h) of intermittent illumination, three periods (5, 7, and 12 h) of 45° cage tilting, one 12 h period in a soiled cage (100 ml water in sawdust bedding) and three periods (7, 9, and 12 h) of low intensity stroboscopic illumination (150 flashes/min). The 14 stressors were scheduled in a semi-random order so that they were unpredictable for the animal. On average, two stressors were applied daily. The schedule was repeated weekly for 3 weeks. After 3 weeks of continuous exposure to the chronic mild stress, animals were divided into four matched subgroup. Group I served as stress control received normal saline (10 ml/kg, p.o.); groups II and III received oral treatment of MPE 100 and 200 mg/kg respectively; group IV served as a positive control received imipramine (10 mg/kg, p.o.) for 21 days. Sucrose intake was measured for each animal as mentioned above.

Locomotor activity

The locomotor activity of mice was measured using an actophotometer. The movement of the animal cuts off a beam of light falling on the photocell and a count was recorded and displayed digitally. Each mouse was placed individually in the actophotometer for 2 min for acclimatization and thereafter basal locomotor activity score was expressed in terms of total counts per 5 min. Mice were randomly divided into two group six mice in each group. One group was treated with MPE 100 mg/kg orally for 7 days. Other group was treated with MPE 200 mg/kg, orally for 7 days. Mice were individually placed again in the actophotometer after 1 h and 7 days of treatment for recording the locomotor activity score.[17]

Statistical analysis

Results were expressed as mean(s) ± SEM. 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. $P < 0.05$ or $P < 0.001$ was considered statistically significant as compared to control.

Results

Preliminary phytochemical screening

Phytochemical screening revealed the presence of alkaloid, carbohydrate, and aminoacid in the hydroalcoholic extract of MPE.

FST

As shown in Figure 1, significant ($P < 0.001$) and dose dependent reduction in the immobility time was observed with 7 days MPE (100 and 200 mg/kg, p.o.) treatment as compared to control. Similarly, positive control imipramine (10 mg/kg, p.o.) also produced antidepressant action as indicated by a significant reduction in the immobility time.

Results of action of haloperidol and modification of haloperidol immobility time by MPE in FST are shown in Figure 2. Haloperidol (a dopamine antagonist) treatment (0.1 mg/kg, i.p.) group showed a significant rise in the immobility time as compared to control. When haloperidol (0.1 mg/kg, i.p.) was administered 30 min after the last dose of 7 days MPE treatments (100 and 200 mg/kg, p.o.) and subjected to FST, this dopaminergic antagonist showed significant

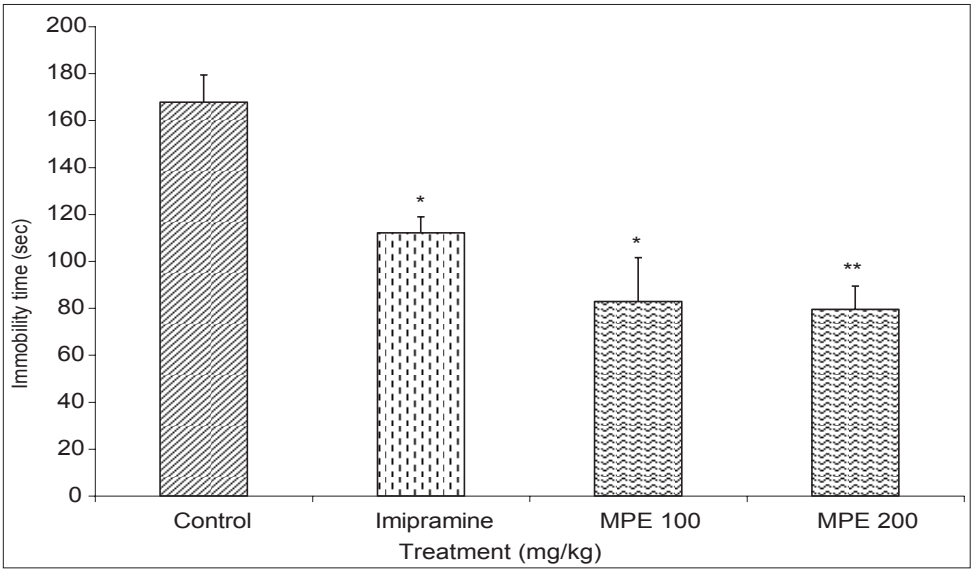

Figure 1: Effect of hydroalcoholic extract of *M. pruriens* seeds on immobility time in forced swimming test. Each bar expressed as mean±SEM (*n*=6). One-way analysis of variance followed by Tukey's test; **P*<0.05, ***P*<0.001 as compared to control

and dose dependent reversal of anti-immobility action of MPE (100 and 200 mg/kg, p.o.) as compared to MPE treatment alone [Figure 2].

As shown in Figure 3, bromocriptine (a dopamine agonist) treatment (2 mg/kg, i.p.) group showed significant anti-immobility action as compared to control. When bromocriptine administered 30 min after the last dose of 7 days MPE treatment and subjected to FST, this dopaminergic agonist produced significant and dose dependent potentiation of anti-immobility action of MPE (200 mg/kg, p.o.) as compared to MPE treatment alone [Figure 3].

TST

Results of TST are shown in Figure 4. There was significant ($P < 0.001$) and dose dependent reduction in the immobility time observed with 7 days MPE (100 and 200 mg/kg, p.o.) treatment as compared to control. Similarly, positive control imipramine (10 mg/kg, p.o.) showed anti-immobility activity, which further confirmed its antidepressant action.

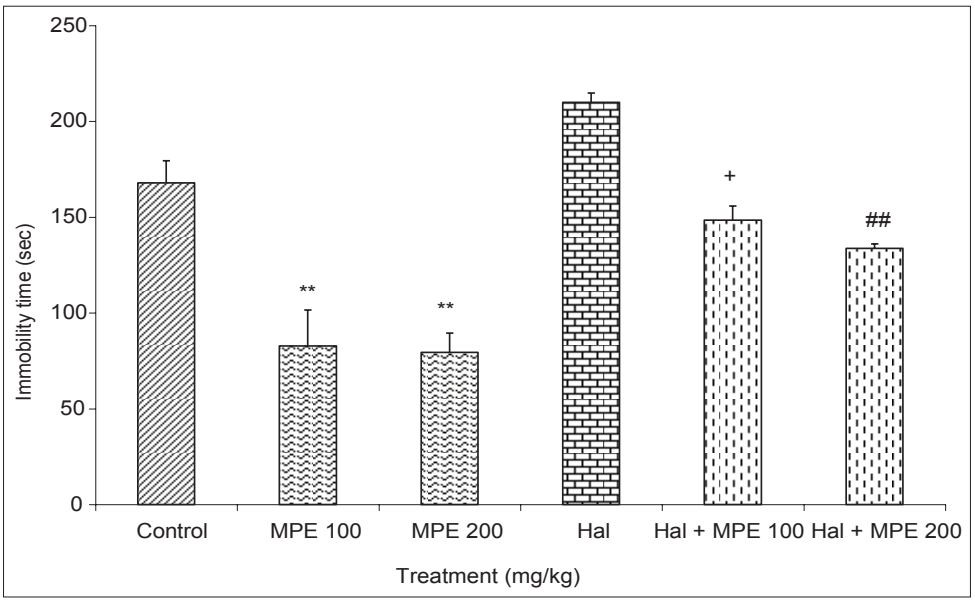

Figure 2: Effect of hydroalcoholic extract of *M. pruriens* seeds (MPE) and its modulation by haloperidol in forced swimming test. Each bar expressed as mean±SEM (*n*=6). One-way analysis of variance followed by Tukey's test, ***P*<0.001 as compared to control; +*P*<0.05 as compared to MPE 100 mg/kg; ##*P*<0.001 as compared to MPE 200 mg/kg

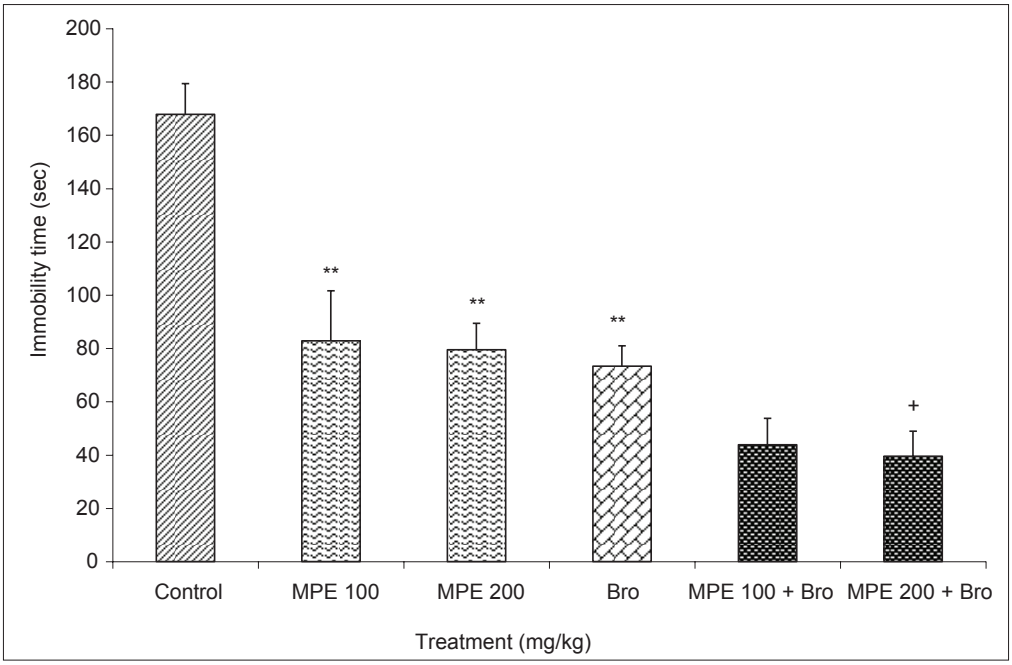

Figure 3: Effect of hydroalcoholic extract of *M. pruriens* seeds (MPE) and its modulation by bromocriptine in the forced swimming test. Each bar expressed as mean±SEM (*n*=6). One-way analysis of variance followed by Tukey's test, ***P*<0.001 as compared to control; +*P*<0.05 as compared to MPE 200 mg/kg

Results of action of haloperidol and modification of haloperidol immobility time by MPE in TST are shown in Figure 5. Haloperidol (a dopamine antagonist) treatment (0.1 mg/kg, i.p.) group caused a significant rise in the immobility time as compared to control. Haloperidol (0.1 mg/kg, i.p.) administration after 30 min of last dose of 7 days MPE treatments (100 and 200 mg/kg, p.o.) caused significant and dose dependent reversal of anti-immobility action of MPE.

As shown in Figure 6, bromocriptine (a dopamine agonist) treatment (2 mg/kg, i.p.) group showed a significant reduction of immobility time as compared to control. Bromocriptine administration after 7 days pretreatment with MPE (100 and 200 mg/kg, p.o.) showed significant and dose dependent potentiation of anti-immobility action of MPE as compared to MPE treatment alone.

CUMS

After the 1 week adaptation of sucrose solution, primary baseline value was determined by sucrose test. Then, mice were subjected to a chronic unpredictable stress schedule for 3 weeks. As shown in Table 2, there was a significant decrease in the sucrose intake relative to control animals. Primary baseline value for sucrose consumption observed in normal control was 1.40 ± 0.02 g/kg body weight of mice. In the control stressed animals, significant reduction of sucrose intake was observed (1.02 ± 0.09) and remained throughout the study period as compared to normal control. In MPE treated mice (100 mg/kg, p.o.) sucrose intake was significantly

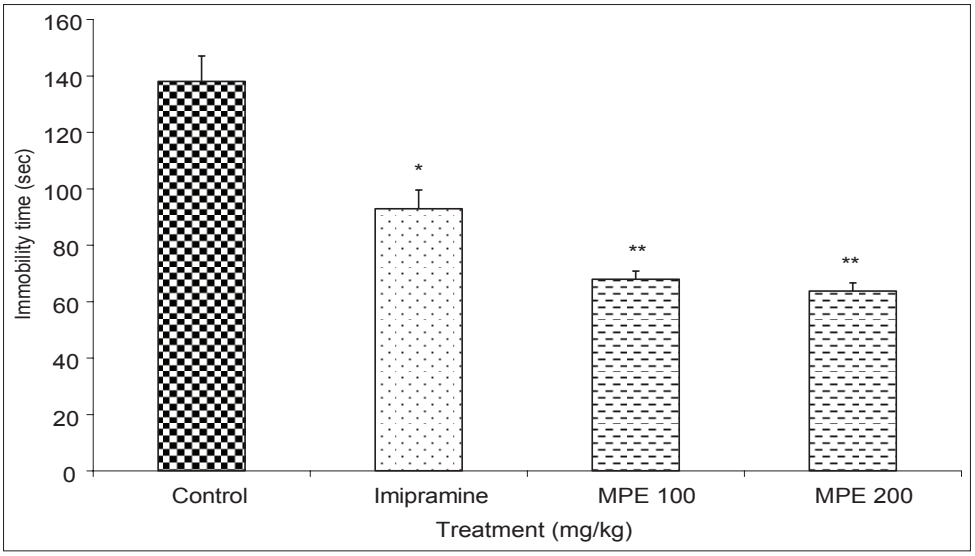

Figure 4: Effect of hydroalcoholic extract of *M. pruriens* seeds (MPE) on immobility time in the tail suspension test. Each bar expressed as mean±SEM (*n*=6). One-way analysis of variance followed by Tukey's test, **P*<0.05, ***P*<0.001 as compared to control

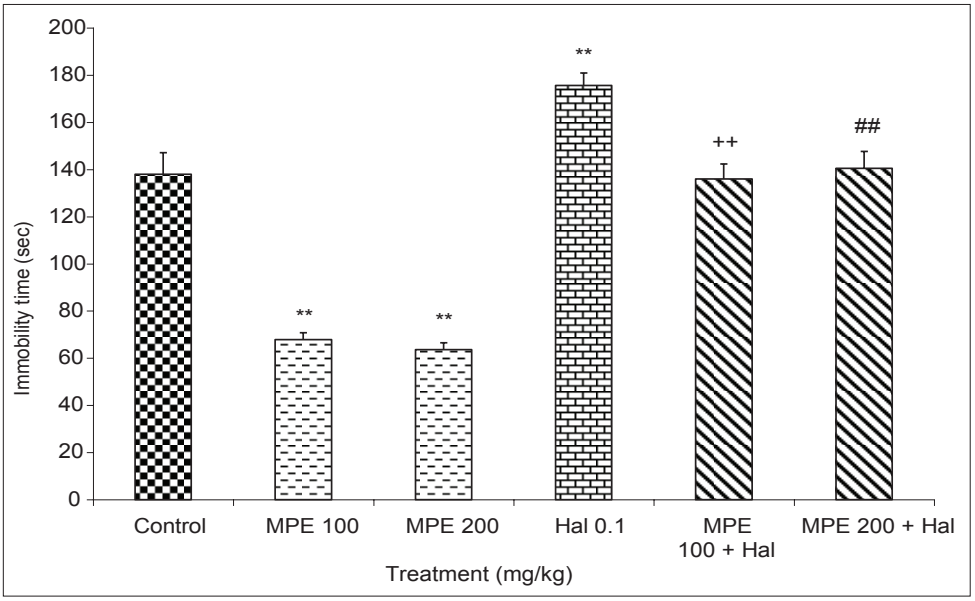

Figure 5: Effect of hydroalcoholic extract of *M. pruriens* seeds (MPE) and its modulation by haloperidol in tail suspension test. Each bar expressed as mean±SEM (*n*=6). One-way analysis of variance followed by Tukey's test, ***P*<0.001 as compared to control; ++*P*<0.001 as compared to MPE 100 mg/kg; ##*P*<0.001 as compared to MPE 200 mg/kg

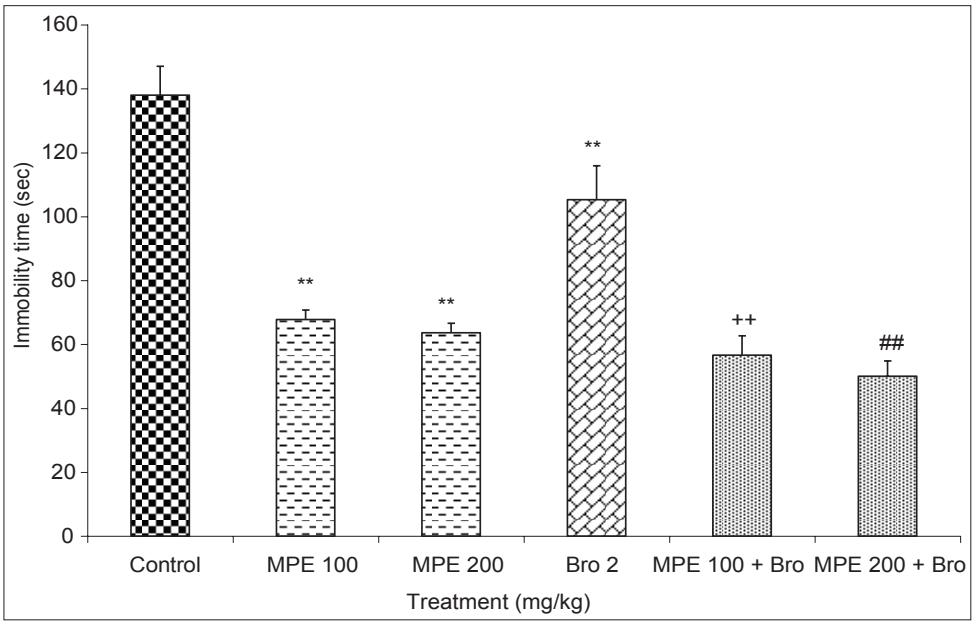

Figure 6: Effect of hydroalcoholic extract of *M. pruriens* seeds (MPE) and its modulation by bromocriptine in the tail suspension test. Each bar expressed as mean±SEM (*n*=6). One-way analysis of variance followed by Tukey's test, ***P*<0.001 as compared to control; ++*P*<0.001 as compared to MPE 100 mg/kg; ##*P*<0.001 as compared to MPE 200 mg/kg

Table 2: Effects of MPE on sucrose intakes in mice exposed to CUMS test

Days of treatment	Treatment and sucrose intake (g/kg b.w. of mice)				
	Normal control	Stress control	MPE (100 mg/kg)	MPE (200 mg/kg)	Imipramine (10 mg/kg)
0 day	1.40±0.02	1.02±0.09*	1.02±0.08	1.05±0.04	1.13±0.07
3rd day	1.33±0.04	0.93±0.07*	1.05±0.09	1.08±0.05	1.09±0.06
6th day	1.40±0.03	1.01±0.116*	1.12±0.09	1.20±0.07	1.09±0.05
9th day	1.36±0.04	0.93±0.14*	1.29±0.07	1.29±0.14	1.14±0.08
12th day	1.43±0.03	1.06±0.07*	1.13±0.09	1.22±0.08	1.14±0.08
15th day	1.41±0.03	0.88±0.05*	1.06±0.04	1.20±0.08#	1.25±0.10#
18th day	1.41±0.06	0.81±0.05*	1.33±0.14#	1.29±0.11#	1.23±0.13
21st day	1.42±0.03	0.79±0.05*	1.25±0.10#	1.23±0.14#	1.22±0.09

Values are expressed as mean±SEM (*n*=6). One-way ANOVA followed by Tukey's test, **P*<0.05 as compared to normal control, #*P*<0.05 as compared to stress control.
MPE: Hydroalcoholic extract of *Mucuna pruriens* seeds, CUMS: Chronic unpredictable mild stress, ANOVA: Analysis of variance

increased (1.06 ± 0.04) after 17 days of treatment as compared to stress control (0.88 ± 0.05) mice and remained elevated for further 4 days of the test period. Similarly, higher dose of MPE treatment (200 mg/kg, p.o.) also, significantly increased sucrose consumption after 14 days (1.20 ± 0.08) as compared to stress control (0.88 ± 0.05). Positive control imipramine (10 mg/kg, p.o.) treated group also showed an increase in sucrose consumption after 14 days of treatment (1.25 ± 0.10) as compared to stress control (0.88 ± 0.05) group.

Locomotor activity

Acute oral administration of hydroalcoholic extract of MPE at the dose of 100 mg/kg did not show any significant changes in the locomotor activity of mice after 1 h (658.66 ± 7.38) as compared to baseline control (661.00 ± 7.01). While, 7 days treatment of MPE (100 mg/kg, p.o.) did not significantly change (657.33 ± 7.58) the locomotor activity of mice as compared to baseline control (661.00 ± 7.01). Similarly, higher tested dose of MPE (200 mg/kg, p.o.) did not show any significant changes in the locomotor activity after 1 h (570.5 ± 6.13) or after 7 days of treatment (569.33 ± 5.96) as compared to baseline control (572.33 ± 5.77).

Discussion

In the present investigation, antidepressant activity of the MPE was evaluated using various experimental models of depression. In the present study, 7 days treatment of hydroalcoholic extract of MPE in the dose of 100 mg/kg and 200 mg/kg (p.o.) in mice showed significant antidepressant activity in FST and TST, respectively. FST and TST are widely used to screen new antidepressant drugs.[13,14] Characteristic behavior scored in these tests is termed immobility, reflecting behavioral despair as seen in human depression.[14,18] It has been seen that TST is less stressful and has higher pharmacological sensitivity than FST.[19]

According to our result, the antidepressant like effect of MPE was significantly potentiated by bromocriptine (a dopamine D_2 receptor agonist) and reversed

by haloperidol (a dopamine D_2 receptor antagonist) suggesting that antidepressant action of MPE mediated via interaction with dopaminergic system. Moreover, it should be pointed out that the antidepressant-like effect of MPE in the FST and TST do not seem to be associated with any stimulating locomotor activity, as at doses similar to that causing a marked antidepressant-like action did not affect spontaneous motor activity. MPE at the tested dose level did not produce any behavioral changes or motor dysfunction in the locomotor activity test after either the acute or repeated treatment. This result confirms the assumption that the antidepressant like effect of the MPE at the tested doses in the FST and TST are specific. Furthermore, the results observed with MPE treatment were largely comparable to imipramine, which suggests that MPE may produce a selective antidepressant effect.

In recent years, a number of lines of evidence have begun to shed light on the mechanisms of antidepressant drugs. One research work suggested that monoamine dopamine and especially the D_2-like family of dopamine receptors might play a crucial role in mediating the action of antidepressant treatments.[20] There is also a report that dopamine D_2 receptor activation could reduce immobility time.[21] In the present study, the obtained results suggest the involvement of dopamine D_2 receptor agonistic nature of MPE in mediating its antidepressant action.

CUMS appears more suitable for studying the neurobiological basis of depression and the mechanisms of action of antidepressant drugs compared to acute stress models.[22] This paradigm has the advantage of excluding false positive effects caused by psycho-stimulant agents in acute stress based models.[23] The CUMS model of depression involves the presentation of a series of varied and unpredictable environmental stressors, such as food and water deprivation, wet cage and light-dark reversal. Following such exposure, animals have been reported to exhibit a persistent reduction in responsiveness to pleasurable stimuli, measured by a stress lead to decrease in consumption of sucrose solution in the test animals.[22] Chronic administration (21 days) of MPE could reverse the decrease in sucrose intake. Various studies indicated that of dopamine agonists[24,17] and antidepressants[16,25] produce similar effect. Taken together, the findings of the current study show that MPE displays a behavioral profile consistent with an antidepressant-like action. The efficacy of most herbal remedies is attributed to various active principles in combination. Results of phytochemical screening showed the presence of alkaloid, carbohydrate and aminoacids in the seeds. L-dopa is reported to be the main constituent mainly in seeds.[8] Therefore, the antidepressant activity can be attributed to dopaminergic action; however, the fact that MPE are more effective than L-dopa in Parkinson's disease in an animal model indicates a role for other active principles.[26] Therefore, present results suggest that intermittent administration of MPE as a dopamine agonist may merit clinical investigation as a novel strategy for the treatment of depression, particularly in patients with Parkinsonism.

In conclusion, the present study provides scientific evidence that hydroalcoholic extract of MPE produces a specific antidepressant-like effect in acute and chronic models of depression which may be mediated by an interaction with the dopaminergic system.

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हिन्दी सारांश

कपिकच्छु बीज के अवसादहर प्रभाव का प्रायोगिक अध्ययन

दिग्विजय जी. राणा, वर्षा जे. गलानी

प्रस्तुत अध्ययन मे केवाँच के बीज के अवसादहर प्रभाव का प्रायोगिक अध्ययन किया गया है । इस के मुल्यांकन हेतु फोर्स स्वीम टेस्ट, टेइल सस्पेन्सन टेस्ट और क्रोनिक माइल्ड स्ट्रेस टेस्ट के माध्यम से स्वीस आल्बिनो चूहों में अवसाद नाशक प्रतिक्रिया का अध्ययन किया गया । प्राप्त परिणाम दर्शाते हैं कि केवाँच के बीजों के अवसाद नाशक प्रभाव में डोपामीन न्युरोट्रान्समीटर की गतिविधियाँ सम्मिलित है ।