ORIGINAL ARTICLE

Neuropharmacological properties of *Mikania scandens* (L.) Willd. (Asteraceae)

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ABSTRACT

Mikania scandens (L.) Willd. (Asteraceae), known as climbing hemp weed in English, is a herbaceous climbing vine grown as a weed throughout the plains of the Indian subcontinent. The present study evaluated some neuropharmacological properties of hydroalcoholic extract of aerial parts from *M. scandens* (HAMS) in experimental animal models. HAMS (at 250 and 500 mg/kg body weight, i.p.) was evaluated for central antinociceptive activity by tail flick method. Locomotor depressant activity was measured by means of an actophotometer. Skeletal muscle relaxant effect was evaluated by using rotarod apparatus and sedative potentiating property by phenobarbitone-induced sleep potentiation study. The results of the present study revealed significant ($P<0.001$) and dose-dependent central antinociceptive, locomotor depressant, muscle relaxant, and sedative potentiating effects of HAMS, demonstrating its depressant action on the central nervous system (CNS). From the present study, it can be concluded that the aerial parts of *M. scandens* possessed prominent depressant action on the CNS, as manifested by the important neuropharmacological properties in mice.

Key words: Central nervous system depressant, locomotor, muscle relaxant, phenobarbitone

INTRODUCTION

Natural products have contributed significantly towards the development of modern medicine. Recently traditional medicine worldwide is being re-evaluated by extensive research on different plant species and their active therapeutic principles. The rich wealth of plant kingdom can represent a novel source of newer compounds with significant therapeutic activities. The major merits of herbal medicine seem to be their perceived efficacy, low incidence of serious adverse effects, and low cost.

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Mikania scandens (L.) Willd. (Asteraceae), known as climbing hemp weed in English, is a twining herbaceous climbing vine with long-petioled, opposite leaves and small homogamous flower-heads grown as a common weed throughout the plains of India and Bangladesh. Traditionally, the plant has been used for some medicinal purposes in the Indian subcontinent. Aqueous leaf extracts of this plant have been used in folk medicine to treat stomach ulcers. The plant is thought to be efficacious in the treatment of gastric problems. Traditionally, its leaf juice is applied to the affected area of body in treatment of wounds and bruises. The plant is regarded as a rich source of vitamin A and C and also contains vitamin B, mikanin, friedelin, efifriedinol, and some sesquiterpene dilactones including mikanolide, dihydromikanolide, deoxymikanolide, and scandenolide. Three deterpenic acids known as kaurenic acid, butyryloxykaurenic acid, and benzoyloxykaurenic acid, stigmasterol, and betasitosterin have also been isolated from this plant.[1-3]

It has come to the author's notice that the rural people of Hooghly, Bardhaman, and Medinipur districts of West Bengal state of India use the young leaves of this plant in management of insect bites and stings. Previous workers reported analgesic and *in vitro* antioxidant activities of *M. scandens* leaf.[4] As very limited pharmacological work has been reported on this plant, the present study was aimed to

assess some neuropharmacological activities of *M. scandens* aerial parts in experimental rodent models.

MATERIALS AND METHODS

Plant Material and its Authentication

The aerial parts of *M. scandens* were collected during June-July, 2011 from Gotan region of Bardhaman district of West Bengal, India. The species was authenticated by Dr. P. Lakshminarasimhan, Scientist D, at the Central National Herbarium, Botanical Survey of India, Howrah, West Bengal, India, and a voucher specimen (CNH/44/2011/Tech.II/476) was deposited at the Pharmacognosy Research Laboratory, Bengal School of Technology, Delhi Road, Sugandha, Hooghly 712102, India. Just after collection, the plant material was washed thoroughly with running tap water and shade dried at room temperature (24-26°C) and ground mechanically into a coarse powder.

Drugs and Chemicals

Morphine sulfate, diazepam, chlorpromazine hydrochloride, and phenobarbitone sodium were from Sigma-Aldrich Corporation, St. Louis, MO, USA. All the other chemicals were of analytical grade obtained commercially. Doubled distilled water from all-glass still was employed throughout the study.

Preparation of Extract

The powdered plant material was first defatted by using petroleum ether (60-80°C). The defatted plant material (45 g) was extracted with 50% aqueous ethanol (400 ml) by boiling under reflux for 90 minutes. The extract was filtered and evaporated to dryness to yield the dry extract (HAMS, yield: 11.78%). The dry extract was kept in a refrigerator until use. Preliminary phytochemical studies were performed on HAMS as per reported method.[5]

Experimental Animals

Adult Swiss albino mice of either sex weighing 20 ± 2 g were used in the present study. The mice were grouped and housed in polyacrylic cages (38 × 23 × 10 cm) with not more than three animals per cage and maintained under standard laboratory conditions (temperature 25 ± 2°C, relative humidity 48%, with dark/light cycle 12/12 h). They were allowed free access to standard diet and water *ad libitum*. The mice were acclimatized to laboratory conditions for 7 days before commencement of the experiments. All experimental procedures were reviewed and approved by the Institutional Animal Ethics Committee, Bengal School of Technology (No. BST/11/SB/001).

Acute Toxicity

The acute oral toxicity of HAMS in Swiss albino mice was studied as per reported method.[6]

Assessment of Neuropharmacological Properties

Evaluation of antinociceptive activity (tail flick test)

Before treatment, the basal reaction time for each mouse to radiant heat (Analgesiometer, Techno) was determined by placing the tip of the tail on the radiant heat source (nichrome wire). The strength of the current passing through the naked nichrome wire was kept constant at 6 Amps. The tail withdrawal time in seconds from the heat (flicking response) was considered as nociceptive end point. Any mouse failing to withdraw its tail within 2 to 4 seconds was excluded from the study.

The prescreened animals (reaction time: 2-4 seconds) were divided into three groups (n=6). The first two groups received the HAMS at the doses of 250 and 500 mg/kg body weight i.p., respectively. The last group (which served as reference) received morphine sulfate at a dose of 5 mg/kg body weight s.c. The reactions of all groups of mice were determined after 5, 15, 30, 60, and 90 minutes of treatment by tail flick method, similarly as mentioned above, and the latency times (in seconds) were recorded. Each animal served as its own control. The mean reaction times for each group were calculated.[7]

Evaluation of locomotor activity

The central nervous system (CNS) depressant activity of HAMS was evaluated by studying locomotor activity of mice using an actophotometer (Techno, India). The mice were divided into three groups (n=6). The equipment was turned on and animals of each group were placed individually in the activity cage for 10 minutes and the basal activity score of all the animals were monitored and recorded. Then, the first group (which served as reference) received chlorpromazine hydrochloride at the dose of 3 mg/kg body weight i.p. The rest two groups received the HAMS at the doses of 250 and 500 mg/kg body weight i.p., respectively. The animals were again tested for activity scores similarly 30 and 60 minutes after these treatments. Each animal served as its own control.[8] Percent reduction in motor activity was calculated for each animal by using the following formula:-

$$\% \text{ reduction in motor activity} = (W_a - W_b/W_a) \times 100\%.$$

Where, W_a and W_b are the mean activity scores before and after treatment, respectively.

Evaluation of muscle relaxant activity

The muscle relaxant activity of HAMS was evaluated by studying neurological deficit of mice using rotarod apparatus (Techno, India). The mice were divided into three groups (n=6). The equipment was turned on and adjusted to appropriate speed (20 rpm). Animals of each group were placed individually on the rotating rod and the fall off time of all the animals were recorded when the mouse falls from the rotating rod. Then, the first two groups received the HAMS at

the doses of 250 and 500 mg/kg body weight i.p., respectively. The last group (which served as reference) received diazepam at the dose of 4 mg/kg body weight i.p. The animals were again tested for determination of fall off time similarly 30 and 60 minutes after these treatments. Each animal served as its own control.[9] Percent reduction in fall off time was calculated for each animal by using the following formula:-

% reduction in fall off time = $(W_a - W_b/W_a) \times 100\%$.

Where, W_a and W_b are the mean fall off times before and after treatment, respectively.

Evaluation of phenobarbitone-induced sleep potentiation

The animals were divided into four groups (n=6). The first group (which served as control) received normal saline 5 ml/kg body weight i.p. The second and third groups received the HAMS at the doses of 250 and 500 mg/kg body weight i.p., respectively. The last group (which served as reference) received chlorpromazine hydrochloride at the dose of 3 mg/kg body weight i.p. Thirty minutes after these treatments, all the animals received phenobarbitone sodium at the dose of 20 mg/kg i.p. Immediately after phenobarbitone administration, each animal was kept in an individual cage under observation. The latency to the loss of righting reflex (i.e., onset of action or induction time in minutes) and the time required to recover righting reflex or awakening (i.e., duration of action or sleeping time in minutes) for each group were recorded.[10]

Statistical Analysis

All results were expressed as the mean ± standard error of mean (SEM). The results were analyzed for statistical significance by Student's '*t*' test. P<0.001 was considered as statistically significant.

RESULTS

Preliminary phytochemical analysis revealed the presence of flavonoids, steroids, alkaloids, tannins, saponins, and sugars in HAMS. The HAMS was found to be safe in Swiss albino mice up to the dose of 2 000 mg/kg body weight p.o. LD_{50} could not be determined because physical factors were limiting for administration of more amount of HAMS.

The results of antinociceptive activity, i.e., tail flick test are shown in Table 1. HAMS at the both doses exhibited significant (P<0.001, after 5 to 90 minutes) and dose-dependent steady increase in reaction time of mice up to 60 minutes of administration followed by minor decrease in activities, observed at both doses. Peak analgesic effect was observed at 30 to 60 minutes indicating maximum increase in reaction times.

In locomotor activity study, it was found that HAMS significantly (P<0.001) depressed the locomotor activity in mice in a dose and time-dependent fashion. The activities increased as time approached to 60 minutes. The results are summarized in Table 2.

In muscle relaxant study, the HAMS at both doses significantly (P<0.001) and dose dependently decreased the fall off time in mice demonstrating its skeletal muscle relaxant property. The effect was most prominent after 60 minutes of administration [Table 3].

The results of phenobarbitone sodium-induced sleeping time are presented in Table 4. Here, HAMS at all doses pretreatment exhibited significant (P<0.001) and potentiation of phenobarbitone-induced sleeping time in mice by hastening the onset of sleep (dose dependent) and delaying recovering the animals from sleep (non-dose dependent) as

Table 1: Effect of HAMS on tail flick test in mice

Treatment	Dose	Mean reaction time (seconds)					
		Before treatment	After treatment				
			5 min	15 min	30 min	60 min	90 min
HAMS	250 mg/kg	1.66 ± 0.14	4.73 ±0.45*	6.25 ± 1.05*	8.53 ± 1.25*	9.12 ± 0.66*	7.21 ± 0.38*
HAMS	500 mg/kg	1.94 ± 0.10	3.84 ± 0.40*	8.98 ± 1.13*	>10*¶	9.73 ± 1.15*	8.60 ± 0.80*
Morphine sulfate	5 mg/kg	1.60 ± 0.28	3.83 ± 0.30*	8.16±0.30*	9.67±0.33*	>10*¶	>10*¶

Data are expressed as mean ± SEM (n=6); *P<0.001 compared with control (mice before treatment), assessed by paired Student's '*t*' test. ¶A cut off time of 10 seconds was taken as maximum analgesic response to avoid tail damage due to heat

Table 2: Effect of HAMS on locomotor activity in mice

Treatment	Dose (mg/kg)	Mean motor activity scores (in 10 minutes)			% reduction in motor activity	
		Before treatment	After treatment			
			30 min	60 min	After 30 min	After 60 min
Chlorpromazine HCl	3	394.01 ± 22.08	102.37 ± 11.05*	71.14± 8.23*	74.02	81.94
HAMS	250	415.33 ± 33.80	120.0 ± 20.47*	95.66 ± 14.83*	71.11	76.97
HAMS	500	436.33 ± 24.96	126.33 ± 29.91*	33.0 ± 5.42*	71.05	92.44

Data are expressed as mean ± SEM (n=6); *P<0.001 compared with control (mice before treatment), assessed by paired Student's '*t*' test

Table 3: Effect of HAMS on muscle relaxant activity in mice

Treatment	Dose (mg/kg)	Mean fall off time (seconds)			% decrease in fall off time	
		Before treatment	After treatment			
			30 min	60 min	After 30 min	After 60 min
Diazepam	4	15.23 ± 2.14	4.01 ± 0.76*	2.83 ± 0.45*	73.67	81.42
HAMS	250	14.13 ± 3.88	4.13 ± 0.65*	7.76 ± 0.80*	70.77	45.08
HAMS	500	13.80 ± 1.34	4.26 ± 0.79*	5.80 ± 0.94*	69.13	57.97

Data are expressed as mean ± SEM (n=6); *P<0.001 compared with control (mice before treatment), assessed by paired Student's 't' test

Table 4: Effect of HAMS on phenobarbitone induced sleeping time in mice

Treatment	Onset of action (min)	Duration of action (min)
Normal saline (5 ml/kg)	57.50 ± 0.12	58.50 ± 0.12
HAMS (250 mg/kg)	20.33± 3.65*	108.0 ± 4.97*
HAMS (500 mg/kg)	11.33 ± 1.97*	107.0 ± 1.29*
Chlorpromazine HCl (3 mg/kg)	15.85 ± 2.05*	148.65 ± 2.83*

Data are expressed as mean ± SEM (n=6); *P<0.001 compared with saline control, assessed by unpaired Student's 't' test

compared with the vehicle control group.

DISCUSSION

The present study examined some important neuropharmacological activities of hydroalcoholic extract from aerial parts of *M. scandens* (HAMS) in Swiss albino mice. The acute toxicity results revealed that this plant might be considered as non-toxic.

The antinociceptive activity of *M. scandens* extract (HAMS) was evaluated by tail flick method in mice to assess central (narcotic) analgesic activity.[11] The results of tail flick study clearly indicated that the HAMS had significant central antinociceptive action revealing the involvement of the CNS in antinociception. This implies that the HAMS exerted analgesic activity interfering the central mechanisms for the transmission of painful messages in mice.

The tail flick test is thermally induced nociception model where radiant heat is used as a source of pain. Here, radiant heat (through a hot nichrome wire) is applied to the tail of mice and the withdrawal of tail from the radiant heat source (hot nichrome wire) is considered as flicking response to thermally induced pain. The flicking reaction which is the end point of this test may be mediated as a spinal reflex. Analgesics of only narcotic (central) type, e.g., morphine, pethidine, pentazocine, etc., can increase the tail flick latency period indicating antinociception.[11,12]

Most of the centrally acting analgesics have certain CNS depressant effects. The locomotor activity was evaluated to assess the CNS-depressant property of HAMS on the motor activity in mice. Most of the centrally active analgesic agents influence the locomotor activities in human beings and rodents mainly by reducing the motor activity because of their CNS depressant property.[13] Locomotor activity is considered as an index of wakefulness or alertness of mental activity and a decrease may lead to calming and sedation as a result of reduced excitability of the CNS.[14] The results of the present study showed significant influence in locomotor activity of mice by HAMS treatment demonstrating decrease in locomotor activity and hence indicating its CNS depressant property in mice.

In muscle relaxant evaluation, the HAMS-induced decrease in fall off tine was due to the loss of muscle grip implying skeletal muscle relaxation.[11] Demonstration of marked muscle relaxant effect by the rotarod study indicated that HAMS induced neurological deficit accompanied with taming or calming effect in mice, thereby further supporting its CNS-depressant effect.

Barbiturates are putative sedatives inducing sleep in human beings and animals by depressing the CNS.[15] Phenobarbitone, although a long-acting barbiturate, at lower doses, it can serve as short to intermediate acting barbiturate.[10] In the present study, in the saline control group of mice, phenobarbitone (20 mg/kg) produced intermediate onset and duration of sleep as indicated by the loss of righting reflex (inability to maintain posture) and awakening or regaining righting reflex subsequently.[16] HAMS pretreatment remarkably reduced the sleep induction time in mice in a dose-dependent manner. It markedly and significantly prolonged the duration of sleep in phenobarbitone-induced mice; however, here the observed effect was not found dose dependent. Potentiation of phenobarbitone induced sleeping time by HAMS indicated the anxiolytic or sedative property of HAMS, thereby confirming its CNS depressant role in mice.

Polyphenolic compounds, like flavonoids, tannins, and phenolic acids, commonly found in higher plants have been reported to possess multiple biological effects.[17] Previous research showed that plants containing flavonoids, saponins, and tannins are useful in many CNS disorders.[18] Many flavonoids and neuroactive steroids were found to be ligands for the $GABA_A$ receptors in the CNS, which led to the assumption that they may act as benzodiazepine-like molecules (which act through $GABA_A$ receptor).[19] In the

present study, phytochemical investigations revealed the presence of alkaloids, flavonoids, saponins, and tannins in the HAMS; therefore, presence of these phytoconstituents may be responsible for its CNS depressant properties.

From the present preliminary study, it can be concluded that the aerial parts of *M. scandens* possessed promising centrally mediated antinociceptive, locomotor depressant, skeletal muscle relaxant, and sedative potentiating effects in the experimental rodent models demonstrating its prominent depressant action on the CNS, as manifested by these important neuropharmacological properties in Swiss mice. Purification of the plant extract and further studies may reveal the exact mechanisms and constituents behind the observed neuropharmacological activities of *M. scandens*.

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