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Neuropharmacological potential of *Ceriscoides turgida* (Roxb.) leaf and root in mice

Wahid Hafiz[1], Md Nazmul Hasan Zilani[1*], Nazneen Ahmeda Sultana[1], Md Mahmodul Isalm[1], Md Anisuzzman[2] and Md Golam Hossain[2]

Abstract

Background: Recently, medicinal plants have grabbed attention worldwide in the field of neurosciences for therapeutic intervention. Traditionally, *Ceriscoides turgida* is used to treat scorpion string, epilepsy, stomachache etc. Present study was designed to peruse neuropharmacological properties of leaf and root extract of *C. turgida*.

Methods: The neuropharmacological activities were examined by thiopental sodium induced sleeping time, hole cross, hole board and open field tests in mice at the doses of 100 mg/kg and 200 mg/kg body weight.

Results: All the extracts exhibited significant reduction of onset and duration of sleep in thiopental sodium induced sleeping time test. Besides, significant reduction of spontaneous locomotor and exploratory activities was found in both hole cross and open field test. Furthermore, both extracts also decreased the number of head dips by mice in hole-board test.

Conclusion: Altogether, these results suggest that experimental extracts of *C. turgida* possesses potent CNS depressant and hypnotic properties, which support its use in traditional medicine.

Keywords: *Ceriscoides turgida*, CNS depressant, Sleeping time test, Hole cross test, Open field test

Background

Modern stressful life is linked with variety of psychiatric disorders. Among these disorders, depression is a pervasive psychiatric problem. It occurs usually in the early adult life of patients with decrease in monoamine neurotransmitters and about 10–30% of general population is suffering from these throughout the world [1]. Typically, sedative and hypnotics are used to reduce anxiety as its produce a calming effect by inducing the onset of sleep as well as maintaining sleeping duration [2]. Tricyclic antidepressants (TCAs), selective reversible inhibitors of monoamine oxidase A (RIMAs), selective serotonin reuptake inhibitors (SSRIs), and specific serotonin–noradrenaline reuptake inhibitors (SNRIs) are clinically recommended for drug therapy in psychiatric disorders. Nowadays, these drugs are extensively used in treatment of different psychiatric disorders. However, serious side effects ranging from respiratory, digestive, and immune system dysfunctions to decline of cognitive function, physical dependence, and tolerance have tend for incessant use of these currently available synthetic drugs [3]. Thus, development of new sedative-hypnotic drugs with fewer side effects has been suggested to be a promising approach to counter different psychiatric disorders. That's why the search for new anxiolytic agents with reduced adverse effects is still an area great interest for the researchers. Generally, natural products, specifically medicinal plants are considered to be a fundamental arsenal of chemical substances with therapeutic potentiality.*Ceriscoides turgida* (Roxb.) belongs to the *Rubiaceae* family. It is available in Lawasara forest, Shremangal, Sylhet, Bangladesh. *C. turgida* (Roxb) is an armed deciduous tree, up to 8 m tall, leaf-bearing spines. Leaves are opposite decussating, dimorphic and flowers are white that turn yellow with age. *C. turgida* has been described to be useful traditionally against leucorrhoea, scorpion string, epilepsy,

* Correspondence: mnhzilani09@gmail.com
[1]Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka 1207, Bangladesh
Full list of author information is available at the end of the article

stomachache, snake bite etc. in traditional medicine [4]. Traditionally, roots are used as a remedy for indigestion in children; fruits are used in affections of the mammary glands and pounded pulp is applied to forehead in fever [5]. To the best of our knowledge, very few pharmacological studies have been reported so far on *C. turgida,* the medicinal plant of the Lawasara forest. However, as a part of the continuation of our research on bioactivity screening of Bangladeshi medicinal plants, present study was design to estimate the role of this plant on neuropharmacological effect in mice.

Material and method

Chemicals and reagents

Standard drug thiopental sodium was purchased from Beximco Pharmaceuticals Ltd. and diazepam from Square Pharmaceuticals Ltd. Bangladesh.

Plant materials and extraction

Ceriscoides turgida leave and roots were collected from Lawasara forest, Shremangal, Sylhet, Bangladesh and identified by experts at Bangladesh National Herbarium, Dhaka, Bangladesh. A voucher specimen (DACB 43316) has been submitted there for future reference. The collected plant parts were separated from undesirable materials. They were shade dried for one week after cutting into small pieces. The plant parts were ground into coarse powder with the help of a suitable grinder. The powder was stored in an airtight container and kept in a cool, dark and dry place until analysis commenced. About 190 g of powdered leaves and 200 mg roots were taken in separate clean, flat-bottomed glass container and soaked in 600 mL of 95% methanol. The container with its contents was sealed and kept for a period of 14 days accompanying occasional shaking and stirring. The whole mixture then underwent a coarse filtration by apiece of clean, white cotton material. Then it was filtered through Whatman No.1 filter paper. The filtrate was kept in an open space to evaporate the solvent thus crude extract was obtained. The yield percentage of the crude extract from leaves and root was 2.04 *w*/w and 1.5w/w respectively.

Experimental animals

Swiss-albino mice of 4–5 weeks age and, average weight of 18–25 g were used for the present experiment. The mice were purchased from Jahangirnagar University, Dhaka, Bangladesh. They were kept in standard environmental condition (24 ± 0 °C, 12 h light/dark cycle and relative humidity of 55–65%) for two weeks for adaptation and fed standard pellet diet and water ad libitum properly. The animals were fasted overnight before the experiments. All the experimental animals were treated following the Ethical Principles and Guidelines for Scientific Experiments on Animals (1995) formulated by The Swiss Academy of Medical Sciences and the Swiss Academy of Sciences.

Thiopental sodium-induced sleeping time test

The method described by Ali et al. (2015) [6] was adopted to study the effect of the extracts on thiopental sodium induced sleeping time test. For this intention, mice were divided into six groups each containing five in number. Group-I was considered as control and received distilled water (10 mL/b.w., p.o.) and group-II received diazepam (1 mg/kg, b.w., p.o.), which was considered as standard. Group III and IV received leaf extract at the dose of 100 and 200 mg/kg body weight respectively. And group V and VI were treated with root extract at the dose of 100 and 200 mg/kg body weight respectively. Thirty minutes later thiopental sodium (20 mg/kg b.w.) was administered intraperitonealy to all groups to induce sleep. Individual mice was placed on a table and recorded for the uncoordinated movements. Then the animals were observed for the time to lose their righting reflex, immediately after thiopental sodium injection (latent period) and the duration of sleep (time between the loss and recovery of reflex) induced by thiopental sodium. Percentage of effect was calculated using the following formula:

$$\text{Effect}\ (\%) = \frac{\text{Average duration of loss of righting reflex in the test group}}{\text{Average duration of loss of righting reflex in the control group}} \times 100$$

Hole cross test

This experiment was carried out as previously described method by Uddin et al. (2006) [7]. A cage was used which have a size of 30 × 20 × 14 cm. A partition was fixed in the middle of the cage. A hole of 3 cm diameter was made at a height of 7.5 cm in the center of the cage. Mice were treated with control, standard or extract and were placed in one side of the cage. The number of passage of a mouse through the hole from one chamber to other was then counted for a period of 3 min at 0, 30, 60, 90 and 120 min after the administration of the control, standard and test sample (p.o). Among six different groups of mice, group-I was considered as control and received distilled water (10 ml/b.w., p.o.) and group-II received diazepam (1 mg/kg, b.w., p.o.), which was considered as standard. Group III and IV received leaf extract at the dose of 100 and 200 mg/kg body weight respectively. And group V and VI were treated with root extract at the dose of 100 and 200 mg/kg body weight respectively.

$$\text{Movements Inhibition (\%)} = \frac{\text{Mean No.of movements (control)} - \text{Mean No.of movements (test)}}{\text{Mean No.of movements (control)}} \times 100$$

Hole board test

The hole-board test was carried out according to the formerly described method by Sheikh et al. (2016) [8] with slight modifications. For the present experiment, a flat platform of 45 cm × 45 cm in diameter with 16 evenly spaced holes was used. This platform also had a wall of 5 cm height. All animals were divided into six groups, control and standard and test groups. Each group was containing five mice. Group-1 was considered as control and received distilled water (10 ml/b.w., p.o.). Group-2 received diazepam (1 mg/kg, b.w., p.o.), which was considered as standard. Group III and IV received leaf extract at the dose of 100 and 200 mg/kg body weight respectively. And group V and VI were treated with root extract at the dose of 100 and 200 mg/kg body weight respectively. After 30 min oral administration of control, standard and extracts each animal was kept on the center of the platform and allowed to move on the platform. The number of head dips into the holes by individual mice was counted for 10 min.

$$\text{Inhibition (\%)} = \frac{\text{Mean No.of head dips (control)} - \text{Mean No.of head dips (test)}}{\text{Mean No.of head dips (control)}} \times 100$$

Open field test

This experiment was carried out as described by Anisuzzman et al. (2017) [9]. The open field device consisted of a smooth field of half square meter with a series of squares. All squares alternatively painted in black and white. This test board is looks like a chess board. The apparatus also had a wall of 10 cm height. The animals were divided into 6 groups namely control, standard and test groups. Each group was containing 5 mice. Group-I was considered as control and received distilled water (10 ml/b.w., p.o.). Group-II received diazepam (1 mg/kg, b.w., p.o.), which was considered as standard. Group III and IV received leaf extract at the dose of 100 and 200 mg/kg body weight respectively. And group V and VI were treated with root extract at the dose of 100 and 200 mg/kg body weight respectively.. The number of squares passed anyway by the animals was counted for 3 min started at 0, 30, 60, 90 and 120 min after oral administration of the test drugs.

$$\text{Movements Inhibition (\%)} = \frac{\text{Mean No.of movements (control)} - \text{Mean No.of movements (test)}}{\text{Mean No.of movements (control)}} \times 100$$

Statistical analysis

The results are presented as Mean ± SEM. The statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's test for sleeping time test and hole board test. For the hole cross test and open field test two-way ANOVA followed by Bonferroni's tests was adopted. $P < 0.05$ was considered to be statistically significant.

Result

In the thiopental induced hypnosis test, the extract at 100 and 200 mg/kg doses showed significant lessening in the time of onset of sleep and boost the duration of sleep in a dose-dependent manner. The results were found to be statistically significant ($p < 0.05$) (Table 1). Both doses of the extract heightened the duration of thiopental sodium induced sleeping time in test animals compared to controls. In this test, both leaf and root extract at 200 mg/kg showed maximum 156.65% and 197.71% effect in duration of loss of righting reflex respectively, whereas the standard drug Diazepam (1 mg/kg) produced 325.10% effect (Table 1).

In the hole cross technique, the number of hole crossed from one chamber to another by mice of the control group was about to similar from 30 to 120 min. The leaf and root extracts at 100 mg/kg and 200 mg/kg dose showed continuous decrease of movement in the experimental animals from the second observation to last observation. Here, significant ($p < 0.05$) results were obtained in dose depending manner (Table 2). In this test, maximum 74% and 86% suppression of locomotor activity

Table 1 Effect of *C. turgida* extracts on thiopental-Na induced sleeping time on mice

Group	Dose (mg/kg)	Latent period (mins)	Duration of sleep (mins)	% Effect
Control	10 ml/kg	19.2 ± 3.44	44.11 ± 2.13	0
Standard	1	3.8 ± 0.66	143.4 ± 13.19*	325.1
Leave extract	100	8.6 ± 0.93	57.8 ± 2.13	131.04
Leave extract	200	6 ± 0.71	69.1 ± 5.39*	156.65
Root extract	100	13.2 ± 2.69	58.4 ± 3.87	132.4
Root extract	200	6 ± 2.07	87.21 ± 7.40*	197.71

Values are presented as Mean ± SEM (n = 5), *$P < 0.05$, which is significant compared with the control group (One-way ANOVA followed by Dunnett's test)

Table 2 CNS depressant activity test result of *C. turgida* extracts by hole cross method

Group	Dose (mg/kg)	Number of movement (% of movements Inhibition)				
		0 min	30 min	60 min	90 min	120 min
Control	10 ml/kg	7.8 ± 1.24	10 ± 0.95	11.2 ± 1.24	10 ± 1.30	10 ± 0.51
Standard	1	7.8 ± 0.58	5.2 ± 0.58 (48%)	3.4 ± 0.51 (69.6%)	2.2 ± 0.58 (78%)	0.8 ± 0.37 (92%)
Leaf extract	100	8.2 ± 0.58	5.4 ± 0.51 (46%)	4.2 ± 0.37 (62.5%)	3.8 ± 0.37* (62%)	2.8 ± 0.37* (72%)
Leaf extract	200	8.2 ± 0.86	5.6 ± 0.51 (44%)	4.2 ± 0.66* (62.5%)	3.2 ± 0.49* (68%)	2.6 ± 0.24* (74%)
Root extract	100	7 ± 0.71	5.2 ± 0.58 (48%)	3.8 ± 0.58* (66%)	3.6 ± 0.51 (64%)	2.2 ± 0.37* (72%)
Root extract	200	8.2 ± 0.97	5.4 ± 0.81 (46%)	3.8 ± 0.66* (66%)	2.6 ± 0.68* (74%)	1.4 ± 0.51* (86%)

Values are presented as Mean ± SEM (n = 5), $P < 0.05$, which is significant compared with the control group (two-way ANOVA followed by Bonferroni's test)
*Indicates the significance of the result

were exhibited with the leaf and root extract at 200 mg/kg at 5th observation period respectively. In this study diazepam exhibited 92% suppression in activity.

In hole board test both extracts caused a dose-dependent and significant ($p < 0.05$) reduction in head-dip response in the animals (Table 3). The inhibition of movement by root extract at 200mg/kg was greater than that standard.

Both the experimental extracts significantly decreased the locomotor activity in mice at the doses of 100 and 200 mg/kg body weight ($p < 0.05$) and this effect was evident from the initial observation (0 min) period and continued up to 5th observation period (120 min) (Table 4). Diazepam (1 mg/kg) showed a noticeable dwindle in locomotion in mice from the 2nd observation period to 5th observation period. In this test, maximum 87.9% inhibition of locomotor activity was revealed with the root extract at 200 mg/kg, whereas the standard drug Diazepam displayed 85.5% suppression.

Discussion

The medicinal plants offer as a source of well accessible, economical and competent medicine from antique time. Various ethnomedicinal plants have been instigated to equip neurobehavioral state and act as an alternative option of modern medicine.

Table 3 CNS depressant activity test of *C. turgida* extracts by hole board method

Group	Dose (mg/kg)	Number of head dips	% inhibition
Control	10 ml/kg	36 ± 2.14	0
Standard	1	21.8 ± 2.06	39.44
Leave extract	100	32.4 ± 1.91	10
Leave extract	200	24.8 ± 2.33	31.11*
Root extract	100	27 ± 2.30	25*
Root extract	200	20 ± 3.46	44.44*

Values are presented as Mean ± SEM ($n = 5$), $*P < 0.05$, which is significant compared with the control group (one-way ANOVA followed by Dunnett's test)

Sedative effects of *C. turgida* was evaluated by recording spontaneous locomotor activity of mice in hole cross and open field tests. In these tests, any agents with sedative properties will reduce the frequency and amplitude of movements, interpreted as a decrease in curiosity of the new environment. Our result demonstrated that the oral administration of both leaf and root extract of experimental plant in all doses (100 and 200 mg/kg) caused a significant ($P < 0.05$) reduction in number of hole crossed (Table 2). The suppressive action was found at 30 min and continued up to 120 min after administration of extracts. Meanwhile, in open field test, experimental extracts at tested doses produced significant ($P < 0.05$) inhibition of locomotion that was brought up from 30 min to 120 min of observation period (Table 4). The results of the present study (Tables 2 and 4) revealed that the extract condensed locomotor activity corroborating CNS depressant effects of the experimental plant extract. Both tests significantly decreased locomotion in mice. Gamma amino butyric acid (GABA) is the key inhibitory neurotransmitter in the central nervous system, which is implicated in the physiological functions allied to different psychological and neurological disorders [10]. Eclectic drugs might amend the GABA system, at the level of the synthesis of it by potentiating the GABA-mediated postsynaptic inhibition through an allosteric modification of GABA receptors [11, 12]. It can either increase chloride conductance or potentiate GABA-induced chloride conductance with concurrent depression of voltage activated Ca^{2+} channel [13, 14]. Consequently, it is anticipated that the extract may potentiate GABAergic inhibition in the CNS via membrane hyper polarization of critical neurons in the brain or it may directly activate GABA receptors. It may enhance affinity for GABA or an increase in the duration of the GABA-gated channel opening [15].

It was found that the head-dipping behavior of the animals is directly linked to their emotional state and this test is performed to explore anxiety-related activity [16]. Based on this observation, it was suggested that the expression of an anxiolytic state in animals might be

Table 4 Data of CNS depressant activity test of *C. turgida* extracts by open field method

Group	Dose (mg/kg)	Number of movement (% of Inhibition)				
		0 min	30 min	60 min	90 min	120 min
Control	10 ml/kg	61 ± 4.32	60.2 ± 4.41	66.6 ± 5.88	60.2 ± 6.06	51.2 ± 3.46
Standard	1	55.8 ± 5.17	21 ± 1.87 (74.1%)	15.6 ± 1.67 (76.6%)	11.2 ± 1.46 (81.4%)	7.4 ± 0.51 (85.5%)
Leave extract	100	54 ± 6.47	38 ± 3.49 (36.4%)	32 ± 1.73 (51.9%)	23.4 ± 1.29 (61.1%)	16.2 ± 0.86* (68.4%)
Leave extract	200	52.8 ± 3.43	33.4 ± 4.48 (44.5%)	22.4 ± 3.36 (66.4%)	13 ± 1.41* (78.7%)	8.2 ± 1.16* (84%)
Root extract	100	57.8 ± 2.99	35.6 ± 5.06 (40.9%)	24.6 ± 2.99 (63.1%)	15.2 ± 1.39* (74.8%)	9 ± 0.95* (82.4%)
Root extract	200	58.2 ± 2.85	29.2 ± 2.82 (51.5%)	15.8 ± 1.02* (76.2%)	9.4 ± 1.60* (84.4%)	6.2 ± 0.97* (87.9%)

Values are presented as Mean ± SEM (n = 5), $P < 0.05$, which is significant compared with the control group (two-way ANOVA followed by Bonferroni's test)
*Indicates the significance of the result

reflected by an augment in head-dipping behavior, while dwindle in the number of head dips was found to be associated with the depressant effect.

In the thiopental sodium induced sleeping time test both the doses (100 and 200 mg/kg body weight) of the extracts subside sleep latency and extend sleep duration in a dose dependent manner, thus suggesting a profound sedative activity. Thiopental sodium belongs to the thiobarbiturateand induces sleep in both humans and rodents. It binds with GABA receptor complex and shows GABA mediated hyperpolarization of postsynaptic neurons [17]. It potentiates GABA activity and also can hinder excitatory glutamate receptors. All of these molecular action lead to abate neuronal activity.

The therapeutic benefits of traditional remedies might hinge on a combination of constituents. Several reports confirmed that the alkaloids, glycosides, terpenoids and flavonoids are responsible for anxiolytic and sedative effects [18, 19]. Besides, nonspecific CNS depression can also be ascribed by tannin [20]. Alkaloids, flavonoids, steroids and terpenoids were quoted to have psychoactive effect by activation of protein kinase C (PKC) and transcription factors that induce the expression of cell-survival genes; protecting neurons against a range of oxidative and metabolic insults; stimulating nicotinic receptors which further enhance cognition and memory; revitalizing and strengthening the nervous function; activating transient receptor potential calcium channels in the nerve cell membrane etc. [21, 22] In a previous study, the presence of alkaloid, tannin, glycosides, flavonoid and saponins in both extracts of *C. turgida* was revealed by phytochemical tests [23]. Both the experimental extracts possess good amount of phenol, flavonoids and tannin contents. The presence of these phytochemical compounds can be correlated to the biological activities of *C. turgida*.

Conclusion

The result indicated that the *C. turgeda* extract significantly decreased the locomotor activity of mice. Therefore, the traditional use of the plant in the treatment of epilepsy can be avowed by this study. However, further investigation is suggested to explore the exact phytoconstituents and precise mechanism of action that are accountable for the neuropharmacological activities of the *C. turgeda* extract.

Abbreviations

CNS: Central nervous system; GABA: Gamma amino butyric acid

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Authors' contributions

MNHZ and MGH conceived and designed the experiments; WH and NAS performed the experiments; MNHZ, MMI and MA analyzed the data; MNHZ, WH, NAS wrote the paper. All authors read and approved the final manuscript.

Ethics approval

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85–23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Publisher's Note

Author details

[1]Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka 1207, Bangladesh. [2]Pharmacy Discipline, Life Science School, Khulna University, Khulna 9208, Bangladesh.

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