

Central Nervous System Depressant Effects of the Methanolic Leaves Extracts of *Tabernaemontana divaricata*

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Abstract: *Tabernaemontana divaricata* (TD) (family: Apocynaceae) has remarkable medicinal value. Traditionally the plant is used as an emmenagogue, aphrodisiac, tonic, purgative, tonic to the brain, the liver and spleen. Considering the important activities reported in traditional uses, aim of the present study was to assess the effect of methanolic extract of TD leaves on the central nervous system (CNS) in mice. The CNS depressant activity was assessed by open field and hole cross test while anti-depressant activity was evaluated by tail suspension and force swimming test. Two dose 200 and 400 mg/kg body weight were used for this purpose. A statically significantly decreases in locomotor activity at dose of 200 and 400 mg/kg was observed. The extracts, at the dose of 400 mg/kg body weight, were shown to have better effect than 200 mg/kg. The results demonstrated that, the extract of TD leaves had the potential phytomedicine value for its significant CNS depressant properties.

Keywords: open field, hole cross, tail suspension, force swimming, CNS depressant, *Tabernaemontana divaricata*.

1. INTRODUCTION

GABA is the chief inhibitory amino acid transmitter of central nervous system and it is present in some 25-50% of all neurones [1]. Different anxiolytic, muscle relaxant, sedative-hypnotic drugs are elucidated their action through GABA, therefore it is possible that extracts of *T. divaricata* may acts by potentiating GABAergic inhibition in the CNS via membrane hyperpolarization resulting in a decrease in the firing rate of critical neurons in the brain or may be due to direct activation of GABA receptor by the extracts[2].

The utilize of the medicinal plants is rising in many countries where 35% of drugs contain natural element. At present, thousands of plant metabolites are being successfully applied for the treatment of variety of ailments [3]. The study of the efficacy of plant-based drugs used in the traditional medicine have been paid great attention because they are cheap, have little side effects [4]. In Bangladesh thousands of species are known to have medicinal value and the use of different parts of several medicinal plants to cure specific ailments has been in vogue since ancient times. Obsession on modern medicinal system leads people to an alternative approach to improve and maintain good health is increased tremendously by using medicinal herb over the last centuries. Many of the modern days important drugs and processed medicines are of plant origin[5]. The beneficial medicinal effects of plant materials typically results from combinations of secondary product present in plant such as alkaloids, steroids, tannins, phenol compounds, resins, gums, flavonoids and fatty acids which are capable of producing definite physiological action on body [6].

Tabernaemontana divaricata belongs to the family of Apocynaceae, found in Asia, Africa, Australia, North and South America and a wide assortment of oceanic islands. Experimentally, *T. divaricata* are shown to possess reversible acetylcholinesterase inhibitory effect/roots part[7], anti fertility Activity/leaves[8], antioxidant and anti-Inflammatory/ flowers part [9,10,11], gastroprotective/ flowers[12], antidiabetic and cytotoxic/flowers[13,14], antinociceptive /leaves[15], anticonvulsant/ flowers [16], antibacterial [17], antiulcerogenic / flowers part [11], anthelmintic / leaves part. [18], anti-Obesity / leaves part [19], aemostatic potential/Latex Proteases [20], anticancer/flowers [21],

cardiovascular effects/roots [22], Inhibition of obsessive compulsive behavior/Leaves [23], antiproliferative/roots and barks [24] effects.

Previously it has been reported that various parts of plants such as leaves, stems, and roots contain chemical constituents such as alkaloids, terpenoids, steroids, flavonoids, phenyl propanoids, phenolic acids and enzymes [25,26,27,28]. Study of roots and stems of *T. divaricata* isolated six compounds: bis (2, 3-dihydroxypropyl) octacosanedioate, tetratriacontanol, palmitic acid, glycerol monopalmitate, β -sitosterol and β -daucosterol. [29]. At least 66 alkaloids have been isolated from *T. divaricata* [30]. Its folklore usage is as an emmenagogue, aphrodisiac, tonic, purgative, tonic to the brain, the liver and spleen. It is used in the treatment of paralysis, weakness of the limbs, cures scorpion-sting and epilepsy. The oil is beneficial for epilepsy (Yunani) [16].

To the best of our knowledge, no scientific data regarding the neuropharmacological effect on Hole cross method, Tail suspension test, and Forced swimming test of *T. divaricata* leaves have been found. Thus the present study was undertaken to evaluate the neuropharmacological effect of methanolic extract of *T. divaricata* leaves.

2. MATERIALS AND METHODS

2.1. Plant Materials and Extraction

Tabernaemontana divaricata (TD) were collected from the adjacent area Feni, Bangladesh during October 2017. The plant material was taxonomically identified by the National Herbarium of Bangladesh. Its voucher specimen no 45254. maintained in our laboratory for future reference.

Powdered plant materials (Flowers) having a weight of 350 gm were taken in an amber colored reagent bottle and soaked in methanol. The bottle with its contents were sealed and kept for a period of about 7 days with occasional shaking and stirring. The whole mixture was then filtered through cotton and then through what man No.1 filters paper and was concentrated with a rotary evaporator under reduced pressure at 55°C temperature to afford crude extract.

2.2. Animals

Swiss albino mice (25-30g) were used for assessing biological activity. The animals were maintained under standard laboratory conditions. The animals were allowed to adjust to the environment for 10 days prior to experimental session. The animals were divided into different groups, each consisting of five animals which were fasted overnight prior to the experiments. Experiments on animals were performed in accordance with guidelines of the Institutional Animal Ethics Committee, Southeast University, Dhaka, Bangladesh. Animal treatment and maintenance for analgesic effects were conducted in accordance with the Principle of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) and apply Guidelines of Southeast University, Dhaka, Bangladesh.

2.3. Drugs and Chemicals

Diazepam and Diclofenac Sodium were obtained from Square Pharmaceuticals Company Ltd, Bangladesh. Nortriptyline was obtained from Navana Pharmaceuticals Limited, Bangladesh. Acetic acid was purchased from Merck, Germany. Normal saline water (0.9% NaCl), a creation of Beximco Infusion Company Ltd., Bangladesh was purchased from local market.

2.4. Neuropharmacological Test

2.4.1. Open Field Test

The experiment was carried out following the methods described by Wash and Cummins [31]. This experiment evaluates a range of anxiety-induced, locomotor activity and exploratory actions of rodents [32]. The animals were divided into four groups with five mice in each group. Group I animals received vehicle (saline water, 10 ml/kg body weight), animals of Group II received Diazepam at 1 mg/kg body weight while animals of Group III, IV were treated with 200 and 400 mg/kg body weight (p.o.) of the TD leaves extract. The floor of an open field of half square meter was separated into a series of squares. Every squares alternatively colored black and white. The tools had 40 cm height a wall. Total number of squares visited by mice was computed for 3 min on 30, 60, 90 and 120 min after oral administration of test samples.

2.4.2. Hole Cross Test

It was described by Takagi [33]. A cage having a size of 30×20×14 cm with a steel partition fixed at the middle. A hole of 3 cm diameter was made at a height of 7.5 cm in the middle of the cage. The animals were segregated into different group and each group contain 5 animals. The control group received vehicle (saline water) whereas the test group received *T. divaricata* extracts (at the doses of 200 and 400 mg/kg p.o.) and standard group received diazepam at the dose of 1mg/kg body weight orally. Each mice was then placed on one side of the chamber and the number of passages of each mice through the hole from one chamber to other was recorded for 3 min on 30, 60, 90 and 120 min during the study period.

2.4.3. Tail Suspension Test

The tail suspension test is commonly used to measure the effects of psychotropic drugs, such as antidepressants, in mice [34]. Briefly, mice both acoustically and visually isolated were hold 30 cm above the floor by adhesive tape placed approximately 1-2 cm from the tip of the tail. During a 5 min period, Immobility time was recorded. Mice were considered immobile only when they hung passively or stayed completely motionless. Conventional antidepressant drugs decrease the immobility time in this test. The animals were treated with the plant extract (200 and 400 mg/kg), nortriptyline or vehicle, 45 min before the test.

2.4.4. Forced Swimming Test

Forced swimming test is important for showing of antidepressant activity. It is the most widely used pharmacological model for measuring antidepressant activity. This method is based on the observation of animals exposed to a situation of forced swimming. In this test, animals become passive and immobile after a period of forceful activity, producing only the movements required to keep their heads above the water. This test was carried out on mice according to the method of Porsolt [35].Swimming sessions were performed by placing the animals in individual Plexiglas's cylinders (40 cm high, 24 cm diameter) containing 20 cm of water. The animals were treated with the extract (200 and 400 mg/kg), nortriptyline (1 mg/kg) or vehicle. Treatments were occurred before 45 minute of the test. All animals were forced to swim for 6 min, and the time spent in immobility during the last 5 min of a 6 min observation period was traced. A decrease in the duration of immobility in the forced swimming test indicates antidepressant activity. The period between when the mouse was immersed and when no further attempts to escape were made (apart from the movements necessary to keep its head above the water) was recorded as the immobility time.

3. RESULTS

3.1. CNS Test

3.1.1. Open Field Test

In the Open field test, *T.divaricata* extracts exhibited a decrease in the movements of the test animals at all dose levels tested. They were statistically significant ($P<0.05$) for all dose levels and followed a dose-dependent response (Table1).

Table1. Effect of methanolic extract of the *Tabernaemontana divaricata* leaves extract on open field test in mice

Group	Dose	Number of Movements			
		30 min	60 min	90 min	120 min
Group-I	Vehicle	136.6 ± 3.91	115.25 ± 5.52	86.2 ± 6.92	90.25 ± 7.43
Group-II	1 mg/kg	88.75 ± 4.5	54.25 ± 6.53	19.5 ± 4.5*	6.5 ± 1.10*
Group-III	200 mg/kg	118 ± 5.25	65.25 ± 6.13	45 ± 8.81*	33.25 ± 3.99*
Group-IV	400 mg/kg	75.75 ± 6.60	62 ± 3.25	37.25 ± 3.83*	30 ± 2.16*

Values are mean ± SD, (n = 5). Dunnet test as compared to vehicle control. Group I animals received vehicle (saline water), Group II received diazepam 1 mg/kg body weight, Group III and Group IV were treated with 200 and 400 mg/kg body weight (p.o.) of the the methanolic extract of *Tabernaemontana divaricata* leaves.

3.1.2. Hole-Cross Test

In the Hole-cross test, the effect of methanolic extract of *T. divaricata* on mice has been shown in (Table-2). *T. divaricata* extracts showed a drop off in the movements of the test animals at all dose levels tested. They were statistically significant ($P < 0.05$) for all dose levels and followed a dose-dependent response. The depressing effect was most intense during the 90 min and 120 min observation periods.

Table2. Effect of methanolic extract of the *Tabernaemontana divaricata* on hole cross test in mice

Group	Dose	Number of Movements			
		30 min	60 min	90 min	120 min
Group- I	Vehicle	13.5 ± 1.2	14.25 ± 1.2	15 ± 1.5	14.25 ± 1
Group- II	1 mg/kg	0.25 ± 0.5*	1 ± 0*	0.75 ± 0.9*	0.75 ± 0.95*
Group- III	200 mg/kg	8.25 ± 1.54	5.5 ± 0.5*	5 ± 1.08*	3.75 ± 0.44*
Group- IV	400 mg/kg	7.75 ± 1.7	5.5 ± 1.29*	4.5 ± 0.4*	3.6 ± 0.5*

Values are mean ± SD, (n = 5); * $p < .05$, Dunnet test as compared to vehicle control. Group I animals received vehicle (saline water), Group II received diazepam 1 mg/kg body weight, Group III and Group IV were treated with 200 and 400 mg/kg body weight (p.o.) of the METD.

3.1.3. Tail Suspension Test

In the tail suspension test, the methanol extract of *T. divaricata* leaves showed no significant result in comparison with the positive control, nortriptyline & that's why it can be assumed that extract has depressive effect (Table 3).

Table3. Effect of methanolic extract of the *Tabernaemontana divaricata* leaves on tail suspension test in mice

Group	Dose(mg/kg)	Immobility time(S)
Group-I	Vehicle	132.5 ± 8
Group-II	1	64.25 ± 10*
Group-III	200	126.5 ± 14
Group-IV	400	135.5 ± 8

Values are mean ± SEM, (n = 5); * $p < .05$ Dunnet test as compared to vehicle control. Group I animals received vehicle (saline water), Group II received Nortriptylene 1 mg/kg body weight, Group III and IV were treated with 200 and 400 mg/kg body weight (p.o.) of *Tabernaemontana divaricata* leaves extract.

3.1.4. Forced Swimming Test

In the forced swimming test, *T. divaricata* extracts exhibited a decrease in the movements of the test animals at all dose levels tested. That's why it can be said that extract has depressive effect (Table 4).

Table4. Effect on methanolic extract of the *Tabernaemontana divaricata* on forced swimming test

Group	Dose(mg/kg)	Immobility time(sec)
Group I	Vehicle	118.5±4.33
Group II	1	70.5±10.34 *
Group III	200	95,75±5.67
Group IV	400	158.5±8.08 *

Values are mean ± SD, (n =5); * $p < .05$ as compared to vehicle control. Group I animals received vehicle (saline water), Group II received Nortriptylene 1 mg/kg body weight, Group III and IV were treated with 200 and 400 mg/kg body weight (p.o.) of *Tabernaemontana divaricata* leaves extract. METD=Methanolic extract of *Tabernaemontana divaricata*

4. DISCUSSION

The present study investigated the behavioral effects of the methanolic leaves extracts of TD in mice. For anxiolytic test we used two methods- open field test and hole cross test. From both methods we observed that TD extracts produced significant depressant-like effects. In open field method, the extract showed a decrease in locomotion in the test animals at both dose levels (200 and 400mg/kg

body weight). The depressant activity was most prominent during third (90 min) and fourth period (120 min) and statistically significant.

In the hole cross test, the extract also showed a decrease in locomotion in the test animals at both dose levels (200 and 400mg/kg body weight) and was statistically significant(0.05).

We also used forced swimming test and Tail emulsion test to check anti depressant-like effects. But both doses of TD extracts did not produce significant anti depressant effect.

When assessed in Tail Suspension Test (TST), we noticed that after oral administration of varying doses (200 and 400 mg/kg) of TD methanolic extracts immobility time was increased compared to standard nortriptylene (antidepressant) drugs .Even at 400 mg/kg dose of our extracts immobility time was increased higher than control group. Similar result happened on forced swimming test. At both doses of 200 and 400 mg/kg, the extract showed higher immobility time than the standard. Based on the these findings, it can be suggested that the extracts have depressant effect which supports the earlier report had been done by another method. The report said that TD has depressive effects on both peripheral and central nervous systems [36].Previously it was also reported that TD (ethanolic and aqueous extracts) showed anticonvulsant activity against maximal electroshock (MES)-induced convulsion which also supports our findings [22].

Locomotor activity considered as an increase in alertness and decrease in locomotor activity indicated sedative effect [37]. Extracts of *T.divaricata* decreased locomotor activity indicates its CNS depressant activity. Many research showed that plant containing flavonoids, saponins and tannins are useful in many CNS disorders [38]. Earlier investigation on phytoconstituents and plants suggests that many flavonoids and neuroactive steroids were found to be ligands for the GABA_A receptors in the central nervous system; which led to assume that they can act as benzodiazepine like molecules [37]. Phytochemical investigations also showed the presence of alkaloids, flavonoids, steroid and tannins in the extracts, so might be this phytoconstituents are responsible for its CNS depressant activity.

5. CONCLUSION

Our findings confirmed the depressant activity of *Tabernaemontana divaricata* .From the study it may be concluded that the test drug can be replaced as an alternative agent in preventing and treating the anxiety. However, further studies are needed to evaluate the safety profile of the plant as safe and therapeutic depressant agent.

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