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# Evaluation of CNS depressant activity of methanolic extract of *Brownlowia tersa* leaves in Swiss albino mice

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**Abstract**
*Brownlowia tersa* (Linn.) is called in Bangladesh as "Sundari lata." It's been used as a folk cure for diarrhea, dysentery, sores, and boils for centuries. The goal of this study was to see the methanolic extract of *Brownlowia tersa* (*B. tersa*) leaves might depress the central nervous system in Swiss albino mice. Open field, hole cross, force swimming, tail suspension, and thiopental sodium induced sleeping duration tests in mice were used to assess *B. tersa*'s central nervous system depressant activity. The mice were placed into five groups, each of which included five mice. In all behavioral animal models, the plant extract was administered orally at dosages of 50, 100, and 200 mg/kg body weight. All experiments used distilled water (0.1 mL/mouse, p.o.) as a control. The reference drug was diazepam (1 mg/kg, i.p.). In both the open field and hole cross tests, the plant extract significantly reduced locomotor and exploratory behaviors (*$p$<0.05). The extract caused a considerable increase in immobility time in the forced swimming and tail suspension tests. In addition, the crude extract resulted in a substantial reduction in latency time and an increase in sleeping time length (*$p$<0.05). The findings imply that the methanolic extract of *B. tersa* contains active principles that are responsible for the CNS depressing activity in mice. In order to produce novel drugs, more research into the mechanisms of action involved in these pharmacological effects is required.

**Keywords:** *Brownlowia tersa*, depressant, forced swimming, tail suspension, open field

## Introduction
In the human physiological system, the central nervous system (CNS) is extremely important. People in the modern society suffer from sadness, anxiety, epilepsy, and restlessness on a daily basis [1]. The most common and incapacitating neuropsychiatric disorder is depression [2]. According to the World Health Organization (WHO), depression is one of society's most debilitating disorders [3], with symptoms and signs such as low mood, lack of interest or pleasure, guilt or low self-worth, interrupted sleep or food, low energy, and poor concentration. It's also a complicated illness with a variety of pathologies [4]. The malfunction of the hypothalamic-pituitary-adrenal axis (HPA) and neural system, as well as discrepancies in neurochemicals, neurocytokine production, and other biochemicals, are all linked to stress [5-8]. Monoaminergic and neurotransmitter dysfunction are also known to have a role in the genesis of depression [9, 10]. While the majority of commercial medicines, such as diazepam, zolpidem, zopiclone, and zaleplon, were associated with negative side effects such as fatigue, weight gain, nausea, dry mouth, sexual dysfunction, forgetfulness, drowsiness, headache, and wooziness [11]. Herbal medications have been shown to have an important role in the treatment of central nervous system (CNS) diseases in previous studies [12]. There is a growing interest in medication derived from natural sources (mostly plant products), and there is great anticipation that pharmaceuticals derived from plants will have much fewer adverse effects than synthetic drugs while providing equivalent efficacy. A number of naturally occurring medicines were evaluated for psychopharmacological effects and shown to be beneficial in the treatment of CNS-related illnesses.

*Brownlowia tersa* (Linn.) Kosterm (Tiliaceae) is a 2–3 m tall, heavily branched shrub with brown-scaly juvenile twigs. In Bangladesh, it is referred to as "Sundari lata." It's found from India (Orissa) through Southeast Asia, including Myanmar, Cambodia, Thailand, Malaysia, Brunei, Indonesia, and the Bay of Bengal's coastal woods [13]. It's been used as a folk cure for diarrhea, dysentery, sores, and boils for centuries. The roots have been discovered to have potent antibacterial properties [13].

*Brownlowia tersa* leaves have antinociceptive and antidiarrheal properties in mouse models [14]. *Brownlowia tersa* has yielded the volatile phenolic chemical 2′- hydroxyl acetophenone as well as the lignan carinol for the first time [13]. *Brownlowia tersa* aerial portions have also been found to contain (4-nitrophenyl) propandiamide and (4-methylphenyl) propandiamide [15].

Because there is currently no literature to support the central nervous system (CNS) depressant properties of *Brownlowia tersa* leaves, the current study was designed to assess the CNS depressant activity of methanolic extract of *Brownlowia tersa* (MEBT) leaves in Swiss albino mice for use as a traditional folk remedy.

## Methods

### Chemicals

Diazepam (Square Pharmaceutical Ltd, Bangladesh), Thiopental sodium (Gonoshastha Pharmaceuticals Ltd, Bangladesh), and Methanol were employed in this research (Sigma Chemicals Co., USA). In deionized water, MEBT was suspended. In open field, hole cross, force swimming, tail suspension, and thiopental sodium-induced sleeping duration tests, diazepam (1 mg/kg i.p.) was utilized. The medications were given 15 minutes before the experimental mice were given the drugs intraperitoneally (i.p.). The extract was given orally at dosages of 50, 100, and 200 mg/kg 30 minutes prior to the trials (excluding open field and hole cross tests), with the control group receiving deionized water (0.1 mL/mouse, p.o.). Gavage was used to provide the medication and samples to all of the groups. All other chemicals and reagents were analytical grade and highly purified.

### Collection of plant materials

Leaves of *B. tersa* were collected from Karamjal area of Sundarban forest, Bangladesh and were then identified by Bushra Khan, Principal Scientific Officer, Bangladesh National Herbarium, Mirpur, Dhaka, Bangladesh. A reference specimen has been deposited in the Herbarium for further reference.

### Preparation of extraction

*B. tersa* fresh leaves were dried at room temperature. The powder was made from the dried leaves. In a beaker, 300 g of powdered materials were steeped in 1000 mL methanol for 72 hours at 25±2º C, stirring every 18 hours with a sterile glass rod. With the aid of Whatman 102 filter paper and a sterilized cotton bed, the filtrate was collected three times. Solvent was extracted using a rotary evaporator, yielding 28.20 g extract (Yield 9.40 %). Acute toxicity, phytochemical screening, and CNS depressant-like action experiments were all conducted on the extract.

### Test animals

The Animal Research Branch of the International Center for Diarrheal Disease and Research in Bangladesh gathered 100 mature Swiss albino mice weighing 20-25 g. Mice were kept in regular settings (temperature: 25ºC, humidity: 55-65 %, and a 12 hour light/dark cycle). Prior to doing the studies, mice were acclimatized to the laboratory environment for 14 days. The Swiss Academy of Medical Sciences and the Swiss Academy of Sciences developed the Ethical Principles and Guidelines for Scientific Experiments on Animals (1995), which were followed by all of the experimental mice. All experimental rules were authorized by Stamford University Bangladesh's Institutional Animal Ethical Committee.

### Acute toxicity test

A total of 25 healthy adult mice were divided into four test groups and one control group (n=5). The control group received deionized water (0.1 mL/mouse). The test groups were given extract doses of 500, 1000, 2000, and 3000 mg/kg orally. The animal was observed for the first four hours following medication to see whether there were any behavioral changes. They were, however, maintained under monitoring for 72 hours following injection to see if there was any mortality [16].

### Phytochemical screening

Alkaloids, flavonoids, saponins, tannins, cardiac glycosides, carbohydrates, reducing sugars, proteins, terpenoids, and steroids were detected in a methanolic extract of *B. tersa* [17].

### CNS depressant activity tests

### Open field test

The experiment was conducted out according to Takagi *et al*. instructions [18]. A half-square-meter open area was split into a series of squares, each alternately colored black and white. The equipment has a 40-centimeter-high wall. The animals were then placed into three groups: test, control, and positive control, each consisting of five animals. The mice were then given leaves extract (50, 100, and 200 mg/kg; body weight, p.o.), control (0.1 mL/mouse, p.o.), and diazepam (1 mg/kg, i.p.). The number of squares visited by the animals was counted for 3 minutes, 0, 30, 60, 90, and 120 minutes following oral administration of test medicines.

### Hole cross test

Takagi *et al*. [18] outlined the procedure, which was followed exactly. In the centre of a cage measuring 30×20×14 cm3, a wood divider was installed. In the center of the cage, a 3 cm diameter hole was drilled at a height of 7.5 cm. Twenty-five animals were split into five groups, each with five mice. The mice were next given leaves extract (50, 100, and 200 mg/kg; body weight, p.o.), control (0.1 mL/mouse, p.o.), and diazepam (1 mg/kg, i.p.) in that order. In this test, the animals' spontaneous migration through the opening from one room to the other was timed for 3 minutes. The observations were made on 0, 30, 60, 90 and 120 min after oral administration of the test drugs.

### Forced swimming test

The forced swimming test is one of the most widely used pharmacological models for determining antidepressant efficacy. It was carried out using Porsolt *et al*. [19] approach with certain changes. Twenty-five healthy mice were divided into five groups at random. Each group of mice was given an oral treatment once a day between 1-3 p.m. for 14 days. After 14 days of treatment, mice were placed individually in a glass cylinder (height 45 cm, diameter 20 cm) filled to a 17 cm depth with water at 25±1 °C for 15 minutes (pre-test session). Mice were subjected to the identical settings for 5 minutes after the pre-test session, and extract solution was provided orally three times between the pre-test and main sessions. Except for minor movements to maintain its head above water, a mouse was deemed inert. Observers conducted it for 5 minutes between 1 and 3 p.m.

### Tail suspension test

The tail suspension test [20] is a simple, quick, and accurate way to check for antidepressant effects. This approach is based on the observation that a mouse held by its tail agitates

and immobilizes alternately [21]. The tail suspension test was detailed with minor adjustments based on the approach of Steru *et al*. [22]. Twenty-five mice were separated into three groups: control, positive control, and test. There were five mice in each group. Two stands were set up with a 23-cm space between them, each with a clamp 22 cms from the floor. Mice were only considered motionless when they were passively suspended 5 cm from the end of their tail on a stand for 6 minutes. The exam was conducted during the hours of 1-3 p.m. Observers rated the duration of immobility.

**Thiopental sodium-induced sleeping time test**

Ferrini *et al*. [23] provided a procedure for conducting this test. The test groups received thiopental sodium (40 mg/kg; i.p.) 30 minutes after receiving the methanolic extract of *B. tersa*, and the sleeping duration was calculated as the time between losing and recovering the righting reflex. The control group received deionized water (0.1 mL/mouse; p.o.) while the standard group received diazepam (1 mg/kg; i.p.).

**Statistical analysis**

The data was provided as a mean ± standard error of the mean (SEM). Using SPSS 18.00 software, the statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test if needed. At a significance level of $*p<0.05$, differences between groups were judged significant.

## Results

**Phytochemical screening**

Alkaloids, flavonoids, saponins, tannins, cardiac glycosides, terpenoids, and steroids were found in the crude extract of *B. tersa*, according to phytochemical screens (Table 1).

**Table 1:** Preliminary qualitative phytochemical screening of methanolic extract of *B. tersa* (MEBT).

| Plant constituents | Inference |
|---|---|
| Alkaloids | + |
| Flavonoids | + |
| Saponins | + |
| Tannins | + |
| Cardiac glycosides | + |
| Carbohydrates | - |
| Reducing sugars | - |
| Proteins | - |
| Terpenoids | + |
| Steroids | + |

+: Presence; -: Absence.

**Acute toxicity test**

There was no mortality after oral administration of MEBT at dosages of 500-3000 mg/kg, however behavioral abnormalities were seen throughout a 72-hour period. As a result, MEBT is thought to have a low toxicity profile, with an $LD_{50}$ of more than 3000 mg/kg.

**Open field test**

At the dosage levels (50, 100, and 200 mg/kg body weight), the extract caused a substantial reduction in locomotion in the test animals from the second to the last observation period. In the open field test, test animals demonstrated a substantial reduction in movement when compared to the control group ($*p<0.05$). Diazepam (1 mg/kg; i.p.) exhibited dose-dependent CNS depressing actions that were statistically significant ($*p<0.05$) (Table 2).

**Table 2:** Effects of *B. tersa* extract and diazepam on the open field test in mice.

| Treatment | Dose (mg/kg) | Number of square crossed | | | | |
|---|---|---|---|---|---|---|
| | | 0 min | 30 min | 60 min | 90 min | 120 min |
| Control | 0.1 mL/mouse | 75.60±1.99 | 57.00±1.30 | 48.40±1.28 | 34.40±2.15 | 24.80±1.02 |
| Diazepam | 1 | 84.20±1.24 | 36.20±1.77* | 16.80±1.42* | 7.80±0.86* | 2.80±0.66* |
| MEBT | 50 | 73.60±1.36 | 51.40±1.91* | 36.20±1.53* | 18.20±1.53* | 9.40±0.67* |
| MEBT | 100 | 82.80±1.28 | 45.60±1.20* | 27.00±1.30* | 13.80±1.15* | 6.00±1.00* |
| MEBT | 200 | 84.20±1.24 | 39.60±1.32* | 19.40±1.28* | 10.00±1.30* | 4.20±0.86* |

Values are presented as mean ± SEM (n= 5). MEBT= Methanolic extract of *B. tersa*.
* $p< 0.05$, vs. control (Dunnett's test).

**Hole cross test**

At doses of 50, 100, and 200 mg/kg body weight, the extract reduced locomotor activity in mice in a dose-dependent manner. In comparison to the control group, it was comparable. Diazepam (1 mg/kg; i.p.) was employed as a control medication in the experimental animals to assess the plant extract's CNS depressing impact. ($*p<0.05$) The results were statistically significant (Table 3).

**Table 3:** Effects of *B. tersa* extract and diazepam on hole cross test in mice.

| Treatment | Dose (mg/kg) | Number of hole crossed | | | | |
|---|---|---|---|---|---|---|
| | | 0 min | 30 min | 60 min | 90 min | 120 min |
| **Control** | **0.1 mL/mouse** | **30.20±1.15** | **18.8±0.80** | **17.60±0.51** | **14.40±1.07** | **13.20±0.86** |
| Diazepam | 1 | 28.00±1.41 | 7.20±0.80* | 3.60±0.51* | 1.80±0.37* | 0.80±0.37* |
| MEBT | 50 | 26.00±1.22 | 14.0±1.30 | 9.20±0.86 | 5.80±0.86* | 3.20±0.37* |
| MEBT | 100 | 27.00±1.58 | 11.60±1.20* | 6.80±0.86* | 3.80±0.66* | 1.80±0.37* |
| MEBT | 200 | 27.80±1.15 | 9.20±0.97* | 5.00±0.70* | 2.60±0.74* | 1.20±0.37* |

Values are presented as mean ± SEM (n= 5). MEBT= Methanolic extract of *B. tersa*.
* $p< 0.05$, vs. control (Dunnett's test).

**Forced swimming test**

When compared to the control, the extract of *B. tersa* at 50, 100, and 200 mg/kg substantially extended the duration of immobility time ($*p<0.05$). In the mouse model, the conventional medication diazepam (1 mg/kg, i.p.) significantly enhanced the immobility time ($*p<0.05$). The maximum depressing effect of *B. tersa* was recorded at a dosage of 200 mg/kg (Table 4).

**Table 4:** Effects of *B. tersa* extract and diazepam on forced swimming test in mice.

| Treatment | Dose (mg/kg) | Immobility time (s) |
|---|---|---|
| Control | 0.1 mL/mouse | 26.60±1.20 |
| Diazepam | 1 | 92.60±1.77* |
| MEBT | 50 | 34.40±1.47 |
| MEBT | 100 | 58.00±1.30* |
| MEBT | 200 | 86.40±2.13* |

Values are presented as mean ± SEM (n= 5). MEBT= Methanolic extract of *B. tersa*.
* $p< 0.05$, vs. control (Dunnett's test).

### Tail suspension test

Table 5 shows the impact of *B. tersa* (50, 100, and 200 mg/kg) in the tail suspension test. When compared to the control group, the results showed a substantial increase in immobility time (*$p<0.05$). The usual medication diazepam (1 mg/kg, i.p.) similarly increased immobility time considerably (*$p<0.05$).

**Table 5:** Effects of *B. tersa* extract and diazepam on tail suspension test in mice.

| Treatment | Dose (mg/kg) | Immobility time(s) |
|---|---|---|
| Control | 0.1 mL/mouse | 55.40±2.06 |
| Diazepam | 1 | 118.80±2.55* |
| MEBT | 50 | 53.40±1.20 |
| MEBT | 100 | 80.20±1.59* |
| MEBT | 200 | 103.40±1.72* |

Values are presented as mean ± SEM (n= 5). MEBT= Methanolic extract of *B. tersa.*
* $p< 0.05$, vs. control (Dunnett's test).

### Thiopental sodium induced sleeping time test

The extract of *B. tersa* at dosages of 100 and 200 mg/kg lowered sleep at an earlier stage in the thiopental sodium induced hypnosis test, and the same extract at doses of 100 and 200 mg/kg also had a dose dependent influence on the sleeping period of thiopental sodium induced sleep. Furthermore, as compared to control, both dosages increased the duration of sleeping time in test animals (Table 6).

**Table 6:** Effects of *B. tersa* extract and diazepam on thiopental sodium-induced sleeping time test in mice.

| Treatment | Dose (mg/kg) | Onset of action (min) | Duration of sleeping time (min) |
|---|---|---|---|
| Control | 0.1mL/mouse | 8.46±0.56 | 34.20±3.68 |
| Diazepam | 1 | 2.77±0.22* | 134.80±3.00* |
| MEBT | 50 | 7.27±0.64 | 41.00±3.86* |
| MEBT | 100 | 5.08±0.30* | 73.20±2.81* |
| MEBT | 200 | 3.67±0.27* | 117.20±2.78* |

Values are presented as mean ± SEM (n= 5). MEBT= Methanolic extract of *B. tersa*.
* $p< 0.05$, vs. control (Dunnett's test).

## Discussion

The open field, hole cross, force swimming, tail suspension, and thiopental sodium induced sleeping duration tests were used in this work to assess the CNS depressant action of the methanolic extract of *B. tersa* in mice. The extract was observed to generate considerable reductions in the treated mice's movement activities. In force swimming and tail suspension tests, the extract considerably increased the immobility time of the mice, whereas in the thiopental sodium induced sleeping time test, the extract significantly enhanced the duration of sleeping time at all dosages.

An increase in alertness and a decrease in sedative impact is referred to as locomotor activity. Locomotor activity was assessed in mice using open field and hole cross tests, and the extract significantly reduced locomotor activity. Both experiments show that the plant depresses the central nervous system. The common sedative diazepam also showed a considerable reduction in locomotor activity. When compared to the control group, locomotor activity reduced dramatically as time passed. Tables 2 and 3 describe the effects of methanolic extract *B. tersa* and standard medication on spontaneous locomotor activity. The benzodiazepine diazepam, which was employed to induce sleep in this study, is thought to function at particular binding sites that are intimately connected to -aminobutyric acid (GABA) receptors, with benzodiazepine binding boosting GABA-ergic transmission. Many flavonoids and neuroactive steroids have been discovered to be GABA receptor ligands in the central nervous system, which can perform as benzodiazepine-like compounds [24]. In a methanolic extract of *B. tersa* leaves, preliminary phytochemical analyses indicated the presence of flavonoids, tannin, and glycosides. As a result, these chemicals are most likely to blame for their CNS depressive properties.

Antidepressant screening and assessment relies heavily on animal models of depression [25]. In the condition of immobility, the forced swimming test is a useful screening tool with high reliability and predictive validity [26]. This test is said to mirror the symptoms of depression in humans [27]. It is very sensitive and specific to all main antidepressant medication groups [28]. The methanolic extract of *B. tersa* had a considerable depressing effect in mice in this investigation. In this test, the usual medication diazepam considerably enhanced the immobility time. Mice are confined to a small space from which they are unable to escape. This causes animals to go into a state of behavioral despair, which is said to replicate a condition comparable to human depression [29]. In a forced swimming test, our findings suggest that *B. tersa* extract can enhance immobility time.

The tail suspension test is based on the fact that animals that are hung by their tail for a short period of time will adopt an immobile posture. Various antidepressants can help people overcome their immobility and engage in escape-related activity. This depression model is commonly used to test novel medicines [30, 31]. Clinically effective benzodiazepines (such as diazepam) are widely recognized for lengthening the duration of immobility time in the tail suspension test. In mice, the extract increased immobility time in a similar way. During a tail suspension test, this was noticed. Increased pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-, and interferon (IFN)-, have recently been reported to have a role in the progression of depression [32, 33]. Stress-induced changes in the cytokine system have been connected to genetic anomalies, mRNA expression, intracellular, serum, or saliva cytokine levels, and neurotransmitter concentrations in the course of depression [34-37]. Depression, on the other hand, can cause the body's immune system to malfunction. The monoamine theory of depression states that depletion of serotonin, norepinephrine, and dopamine levels in the central nervous system is the underlying pathophysiological foundation of depression. The mechanism of action of depressants that raise the levels of these neurotransmitters in the brain appears to support this predicted pathophysiology. These have been demonstrated to be helpful in reducing depression symptoms [38]. In this investigation, the mechanism of action remains unclear.

The methanolic extract of *B. tersa* had a sedative-hypnotic

effect when treated with thiopental. It binds to the gamma amino butyric acid (GABA) A receptors, increasing GAB Aergic transmission. GABA is the primary inhibitory amino acid transmitter in the central nervous system, with 25-50 % of all neurons containing it [39]. It increases GABA activity, allowing chloride to enter the cell by lengthening the time the chloride channel is open. Thiopental has the potential to inhibit excitatory glutamate receptors. These chemical processes result in lower neuronal activity, which is consistent with the results obtained with the reference medication diazepam, a CNS depressant that slows the onset of sleep or extends the duration of sleep [40].

## Conclusions

The results of this study reveal that the methanolic extract of *B. tersa* has depressive effects on the central nervous system (CNS) in behavioral models. However, more comprehensive study is needed to isolate the plant's active ingredients and comprehend the underlying mechanism behind its pharmacological effect.

## Declarations

### Ethics approval and consent to participate

The document does not contain any personal information about any individual. As a result, this information is irrelevant.

The Swiss Academy of Medical Sciences and the Swiss Academy of Sciences developed the Ethical Principles and Guidelines for Scientific Experiments on Animals (1995), which were followed by all of the experimental mice. All experimental rules were authorized by Stamford University Bangladesh's Institutional Animal Ethical Committee.

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## Competing interests

There are no conflicts of interest reported by the authors. The paper's content and writing are solely the responsibility of the writers.

## References

1. Moreno LCGAI, Oliveira GZ, Cavalcanti IMF, Santos-Magalhaes NS, Rolim HML, de Freitas RM. Development and evaluation of liposomal formulation containing nimodipine on anxiolytic activity in mice. Pharmacol Biochem Behav. 2014;116:64-68.
2. Liao JC, Tsai JC, Liu CY, Huang HC, Wu LY. Antidepressant-like activity of turmerone in behavioral despair tests in mice. BMC Complement Altern Med. 2013;13:299.
3. Dang H, Chen Y, Liu X, Wang Q, Wang L. Antidepressant effects of ginseng total saponins in the forced swimming test and chronic mild stress models of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33:1417-1424.
4. Yi LT, Xu HL, Feng J, Zhan X, Zhou LP. Involvement of monoaminergic systems in the antidepressant-like effect of nobiletin. Physiol Behav. 2011;102:1-6.
5. Esch T, Stefano GB, Fricchione GL, Benson H. The role of stress in neurodegenerative diseases and mental disorders. Neuro Endocrinol Lett. 2002;23:199-208.
6. Alfonso J, Frasch AC, Flugge G. Chronic stress, depression and antidepressants: Effects on gene transcription in the hippocampus. Rev Neurosci. 2005;16:43-56.
7. Sartori SB, Whittle N, Hetzenauer A, Singewald N. Magnesium deficiency induces anxiety and HPA axis dysregulation: Modulation by therapeutic drug treatment. Neuropharmacology. 2012;62:304-312.
8. Chen Y, Andres AL, Frotscher M, Baram TZ. Tuning synaptic transmission in the hippocampus by stress: The CRH system. Front Cell Neurosci. 2012;6:13.
9. Delgado PL. Depression: The case for a monoamine deficiency. J Clin Psychiatry. 2000;61(6):7-11.
10. Chuang CY, Shi YC, You HP, Lo YH, Pan TM. Antidepressant effect of GABA-rich monascus-fermented product on forced swimming rat model. J Agric Food Chem. 2011;59:3027-3034.
11. Dhingra D, Sharma A. A review on antidepressant plants. Nat. Prod. Radiance. 2006;5:144-152.
12. Carlini EA. Plants and the central nervous system. Pharmacol Biochem Behav. 2003;75:501-512.
13. Hettiarachchi DS, Locher C, Longmore RB. Antibacterial compounds from the root of the indigenous Australian medicinal plants. Nat Prod Res. 2009;15:1-8
14. Sariful IH, Jamil AS, Shubhra KD, Arpona H, Ferdoushi J, Hemayet H. Antinociceptive and antidiarrhoeal properties of the ethanolic extract of Brownlowia tersa leaves. Int J Pharm Phytopharmacol Res. 2012;1(5):292-296.
15. Shehata AB, Hassan MA, Nour MA. Two propandiamides from aerial part of *Brownlowia tersa* (L.) Kosterm. J Hazard Mater. 2003;102(2-3):121-36.
16. Seth UK, Dadkar NK, Kamat UG. Selected Topics in Experimental Pharmacology, 1st Ed. Kothari Book Depot, Bombay, India, 1972, 126.
17. Ghani A. Medicinal Plants of Bangladesh with Chemical Constituents and Uses. 2nd Ed. The Asiatic Society of Bangladesh, Dhaka, 2003, 331-332.
18. Takagi K, Watanabe M, Saito H. Studies on the spontaneous movement of animals by the hole cross test: Effect of 2-dimethylaminoethane, its acylesters on the central nervous system. JPN J Pharmacology. 1971;21:797-810.
19. Porsolt RD, Bertin A, Jalfre M. Behavioural despair in mice: a primary screening test for antidepressants. Archives Internationals de Pharmacodynamie et de Therapie. 1977;229:327-336.
20. Wesołowska A, Nikiforuk A, Stachowicz K, Tatarczyńska E. Effect of `the selective 5-HT7 receptor antagonist SB 269970 in animal models of anxiety and depression. Neuropharmacol. 2006;51:578-86.
21. Nanjappa K, Shalam M, Harish M, Prabhu Rao S, Kutty B. Pharmacological and neurobiochemical evidence for antidepressant-like effect of Sumind, A herbal product in animals. Int J. Nut, 2006, 4.
22. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacol. 1985;85:367-370.
23. Ferrini R, Miragoli G, Taccardi B. Neuropharmacological studies on SB 5833, a new psychotherapeutic agent of the benzodiazepine class. Arzneimittel-Forsch (Drug Res). 1974;24(12):2029-2032.
24. Dal Molin MM, Silva S, Alves DR, Quintão NL, Delle Monache F, Cechinel Filho V. Phytochemical analysis

and antinociceptive properties of the seeds of *Garcinia achachairu*. Arch Pharm Res. 2012;35:623-631.
25. McArthur R, Borsini F. Animal models of depression in drug discovery: a historical perspective. Pharmacol Biochem Behav. 2006;84:436-452.
26. Petit-Demouliere B, Chenu F, Bourin M. Forced swimming test in mice: a review of antidepressant activity. Psychopharmacology. 2005;177:245-255.
27. Renard CE, Dailly E, David DJ, Hascoet M. Monoamine metabolism changes following the mouse forced swimming test but not the tail suspension test. Fundam Clin Pharmacol. 2003;17:449-455.
28. Detke MJ. Active Behavior in the rat forced swim test differentially produced by Serotonergic and noradrenergic antidepressants. Psychopharmacology. 1995;121:66.
29. Willner P. The validity of animal models of depression. Psychopharmacology. 1984;83:1-16.
30. Porsolt R, Bertin A, Jalfre M. Behavioral despair in mice: A primary screening test for antidepressants. Arch Int Pharmacodyn Ther. 1977;229(2):327-36.
31. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: A new method for screening antidepressants in mice. J Psychophar. 1985;85(3):367-70.
32. Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A. Cytokine production and serum proteins in depression. Scand J Immunol. 1995;41:534-538.
33. Lichtblau N, Schmidt FM, Schumann R, Kirkby KC, Himmerich H. Cytokines as biomarkers in depressive disorder: Current standing and prospects. Int Rev Psychiatry. 2013;25:592-603.
34. Himmerich H, Fulda S, Linseisen J, Seiler H, Wolfram G. Depression, comorbidities and the TNF-alpha system. Eur Psychiatry. 2008;23:421-429.
35. Himmerich H, Milenovi ÄS, Fulda S, PlÃ¼mÃ¤kers B, Sheldrick AJ. Regulatory T cells increased while IL-1Î² decreased during antidepressant therapy. J Psychiatr Res. 2010;44:1052-1057.
36. Bernberg E, Ulleryd MA, Johansson ME, Bergström GM. Social disruption stress increases IL-6 levels and accelerates atherosclerosis in ApoE-/-mice. Atherosclerosis. 2012;221:359-365.
37. Jaremka LM, Lindgren ME, Kiecolt-Glaser JK. Synergistic relationships among stress, depression and troubled relationships: Insights from psychoneuroimmunology. Depress Anxiety. 2013;30:288-296.
38. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med. 2008;358:55-68.
39. Fagg GE, Foster AC. Amino acid neurotransmitters and their pathways in the mammalian central nervous system. Neuroscience. 1983;9:701-719.
40. Nyeem MAB, Alam MA, Awal MA, Mostofa M, Uddin SJ, Islam N. CNS depressant effect of the crude ethanolic extract of the flowering tops of Rosa damascena. Iranian J Pharmacol Ther. 2006;5(2):171-174.