Article

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Bioactive Extracts from the Fruit Rind of *Limonia acidissima* L. Exhibit Neuro-Modulatory Properties in a Thiopental-Sodium Sleep Model in Swiss Albino Mice: Implications for Neuro-Pharmacological Interventions

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Background: Anxiety, stress, depression, and psychosis are conditions related to mental illnesses which interfere with the quality of life. Conventional interest in the preventive and therapeutic potential of natural products or nutraceuticals in disease management has escalated in recent years due to their relatively high safety index and affordability. Natural products with anxiolytic properties are essential central nervous system (CNS) modulators, which can reduce symptoms of anxiety and other associated psychological factors. This study investigated the neurotherapeutic effects of bioactive components of extracted in the methanol and acetone fractions of *Limonia acidissima* L. fruit rind in Swiss albino mice.

Methods: The bioactive properties reflecting neurotherapeutic activity were examined with standard protocols that included open field, hole board, hole cross, and sleeping time tests induced by thiopental sodium. The experimental design included 140 Swiss albino mice, randomly subdivided into twenty-eight groups ($n = 5$) and distributed into blocks for different *in vivo* protocols.

Results: Results of the thiopental sodium-mediated sleeping time test demonstrated that both extracts showed substantial ($p < 0.001$) reductions in sleep onset time while concomitantly increasing sleep duration time. The hole cross ($p < 0.001$) and open-field ($p < 0.05$, $p < 0.01$, $p < 0.001$) studies showed noteworthy reductions in spontaneous locomotor and experimental behaviours. The administration of the extracts significantly reduced the frequency of head dips during the hole-board testing ($p < 0.001$).

Conclusions: Our findings show that the methanol and acetone fruit rind extracts from *Limonia acidissima* (*L. acidissima*) are potentially active *in vivo*. The study indicates that the fruit's rind exhibits potent CNS functions regarding its hypnotic and anti-depressant effects.

Keywords: neuropharmacology; *Limonia acidissima*; fruit rind; sleeping time test; hole cross; hole board; open field test

Introduction

Modern lifestyles can often be stressful for miscellaneous reasons, sometimes leading to psychiatric or mental disorders, including anxiety and depression. Approximately 10–30% of people worldwide suffer from such issues at different stages of their lives [1]. Psychiatric disorders are common mental illnesses with behavioural or psychiatric symptoms that may influence many aspects of life [2,3]. They are characterised by a confused state of mind with abnormal thinking, altered emotions, and abuse of drugs [4]. Sedative-hypnotic drugs are a class of drugs that act as neurotransmitters in the brain, inhibiting the central nervous system (CNS) by acting on the brain's gamma-aminobutyric acid (GABA) A receptors [5]. Some sedative-hypnotic drugs reduce anxiety, maintaining calmness and

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an appropriate sleeping pattern [6]. Anti-depressants are a pharmacological category of medications that mitigate symptoms associated with depression illnesses via the modulation of brain neurotransmitter imbalances and can modulate mental status and behaviour. Serious adverse effects of anti-depressant medications include fatigue, dry mouth, agitation, vertigo, drowsiness, respiratory problems, gastrointestinal discomfort, and cardiac arrhythmias [7,8].

Anti-depressants have been widely authorised for treating depressive symptoms, regardless of their consistent lack of efficacy and the common occurrence of complications, which can be severe in certain circumstances. As a result, there is a need for more efficient anti-depressants with fewer side effects to achieve improved clinical outcomes. Anxiety is a prevalent mental disorder, with prevalence rates varying between 10 and 25% across an individual's lifespan. Sleep disturbance, characterised by a disrupted sleep-wake cycle, significantly impacts over 30% of the adult population, making it the second most common manifestation of depression [9,10]. According to the World Health Organization (WHO), diazepam has been identified as the most productive and secure pharmaceutical agent for treating anxiety and sleep problems. Despite its efficacy, diazepam has several adverse health effects, including higher aggression, rage, and impaired impulse control resulting from paradoxical stimulation. Furthermore, it should be noted that higher quantities of the substance may lead to hypotension and pulmonary impairment, mainly when administered parenterally [11].

The most commonly used anti-depressants are selective serotonin reuptake inhibitors (SSRIs), which relieve depression by improving serotonin levels in the brain. Serotonin is a chemical messenger that transmits impulses between brain cells. SSRIs obstruct the brain's reabsorption of serotonin to accumulate additional serotonin, which may cause severe side effects such as drowsiness, nervousness, and persistent headaches [12,13].

According to Aware *et al*. [14], plants have a crucial role as the primary source of biologically active substances that have preventative and curative effects. These molecules have made significant contributions to conventional and modern medical practice. Throughout history, individuals across the world have used botanical-derived substances extensively as a means of alleviating specific ailments [15]. The WHO has estimated that herbal medicines are used by more than 75% of people for their daily healthcare needs [16]. As sources of medicinal molecules, natural compounds are promoted as a possible therapeutic alternative for mental and neurological ailments. Several phytochemicals found in herbal remedies, fruits, and vegetables have been shown to reduce neurodegenerative lesions and increase cerebral retention and cognitive performance [17].

A good example is *Limonia acidissima* L., formulations of which have been used as a herbal therapy for several disorders [18]. Belonging to the monotypic genus *Limonia*, *Limonia acidissima* (*L. acidissima*) belongs to the Rutaceae (citrus family), which is endemic to the Indian subcontinent and southeast Asia [19]. Also known as kaitha, kath bel, elephant apple, curd fruit, or wood apple, it is an erect, slow-growing, deciduous tree. Its spherical fruit has a 5–12.5 cm diameter and a greyish-white rind approximately 6 mm thick, with a hardwood and tough outer shell that is difficult to break open (fruit rind). The plant's roots, fruit, bark, and leaves are used therapeutically [20]. It is commonly used as a liqueur for liver and heart disease, diarrhoea, and dysentery [21]. The fruit also has traditional uses in managing hepatitis, asthma, wounds, and cardiac debility [22].

In the current study, we examined the neuropharmacological properties of the acetone and methanol extracts of the fruit rind of *L. acidissima*. The findings of this research highlight the possible benefit of fruit rind in addressing mental disorders associated with anxiety and psychological stress.

Materials and Methods

Chemicals and Reagents

Thiopental sodium and diazepam, both considered to be industry standards, were procured, respectively, from Incepta and Opsonin Pharma Ltd. of Bangladesh. The British Drug House (BDH) Chemicals Ltd. in Leicestershire, UK supplied the laboratory with distilled water and the other required reagents.

Extraction Procedure

The fruits of the *L. acidissima* plant were obtained from the fields near Jahangirnagar University in Dhaka, Bangladesh, and verified from Bangladesh National Herbarium, Mirpur, Dhaka, Bangladesh. The fruit rind obtained from *L. acidissima* was washed in distillation water to remove unwanted substances. These were then dried in the shade and eventually crushed into a coarse powder using the appropriate processor. For future use in the research, the powder was sealed in an airtight container before being placed in a location that was also cold, dark, and dry. A quantity of 400 g and 450 g of granulated fruit rind of *L. acidissima* were each soaked for ten days in a separate glass compartment containing 1000 mL of methanol and 1500 mL of acetone, respectively. This was done in addition to the usual shaking and mixing. The mixture underwent a coarse filtering process using a fine, white cotton material and underwent further filtration using Whatman filter paper. The filtrate was left out in the air to obtain the dry extract so that the solvent may evaporate. The amount of methanol and acetone that could be extracted from the rind yielded 2.25% and 2.13% w/w, respectively.

Experimental Animals

The Swiss albino mice (Catalog no. 599) used in this study were obtained from Jahangirnagar University, Dhaka,

Bangladesh. The mice were aged between 6 and 7 weeks and weighed around 22–25 g. The experimental design included 140 Swiss albino mice from different batches, randomly divided into twenty-eight groups (n = 5). Accordingly, as described in each experimental section, it is distributed in Randomized Complete Block Design (RCBD) for other *in vivo* protocols. The experimental animals were placed in animal cages under standard conditions (22–25 °C, 60–70% moisture, 12-hour light: 12-hour dull cycle). The typical pellet diet for mice was obtained from Jahangirnagar University, Dhaka. All experimental protocols related to animal studies were approved by the Faculty of Allied Health Sciences Research Ethics Committee, Daffodil International University, Dhaka-1207, Bangladesh. (Reference number: FAHSREC/DIU/2020/1006).

Qualitative and Quantitative Phytochemical Analysis

Major phytochemical classes, for example, phenols, tannins, alkaloids, flavonoids, terpenoids, saponins, gum, and glycosides, were identified in the extracts by their characteristic qualitative tests, as reported previously [23]. Quantitative estimation of certain important phytochemicals was also performed, such as the determination of alkaloids by Harborne's method, tannins by Van-Burden and Robinson's method, and glycosides by Bohm and Kocipai Abyazan's procedure [24–26].

Thiopental Sodium-Induced Sleeping Time Test

The modulatory activity of the two extracts on the sleeping time induced by thiopental Na was investigated using the standard test described earlier [27]. The experimental mice were classified into ten groups with five animals. Group I was given distilled water was used as control. Diazepam administered group II (0.5 mg/kg, b.w., p.o.) was used as a standard. Groups III, IV, V, and VI obtained methanol fruit rind extracts at 25, 50, 125, and 200 mg/kg b.w, p.o. respectively.

Further groups VII, VIII, IX, and X were administered with acetone fruit rind extracts at 25, 50, 125, and 200 mg/kg b.w. After half an hour, intraperitoneally, thiopental Na (20 mg/kg b.w.) was injected into all groups to induce sleep. The animals were found to inhibit their right reflex instantly after injecting thiopental Na, which reflects the length of sleep. The following formula determined the effect:

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

Hole Cross Test

According to what had been reported previously by Uddin *et al.* [28], the research used an enclosure that was 0.30 meters in length, 0.20 meters in width, and 0.14 meters in height, with a partition in the middle. A circular opening of 0.03 meters in diameter and 0.75 millimeters in height was cut into the central portion of the framework. The animals used in the experiment were separated into their respective groups and placed on one side of the frame. After the administration of the control, standard, and test extracts (p.o.), the number of times the mouse moved from one chamber to another by moving through the hole was counted for three minutes at 0 minutes, 30, 60, 90, and 120 minutes after the administration of the extracts. The control group, group I, received just distilled water, whereas the standard group, group II, received diazepam at a dose of one milligram per kilogram of body weight orally. Groups III and IV got methanol fruit rind extract at levels of between 50 and 125 mg/kg b.w., p.o. Group V and Group VI were given acetone fruit rind extract at different doses: 50 and 125 mg/kg b.w., p.o., 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 test was performed according to the standard protocol with minor modifications [29]. The platform has a 0.90 m × 0.90 m radius with a frame of 0.05 m height and 16 equitably separated holes. There were six groups of mice, with five mice (n = 5) in each group, including control, standard, and test groups. Group I was set as a control and was given distilled water. Diazepam was standard in group II (1 mg/kg, b. w., p. o.). Group III, IV, and V, VI independently took methanol and acetone fruit rind extracts in the doses of 50 and 125 mg/kg b.w., p.o., respectively. The number of head dips into the holes was monitored for 10 minutes, and inhibition was recorded as follows:

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

Open Field Test

This analysis was performed using a test device of a plane of 0.5 m^2 field with a compartment height of 0.1 m, with a square progression. The experimental board had all the squares painted black and white like a chessboard [30]. Mice were grouped into six groups-five mice (n = 5) in each group. Group I was used as a control and provided with distilled water. Diazepam (1 mg/kg, b.w., p.o.), administered group II was set as a standard. Methanol fruit rind extract at doses of 50 and 125 mg/kg b.w., p.o. was given to groups III and IV, whereas acetone fruit rind extract at 50 and 125 mg/kg b.w., p.o. was given to groups V and VI. For three minutes initiated at 0, 30, 60, 90, and 120 minutes after the oral route of test medications, the number of squares moved at any pace by the animals was recorded.

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

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Statistical Analysis

The data was analyzed using the SPSS statistical program (version 20), IBM, Chicago, IL, USA. The findings are presented as the mean ± standard error of the mean (SEM). The study used a one-way analysis of variance (ANOVA) in conjunction with Dunnett's test to analyze the data obtained from the sleeping time and hole board tests. A repeated measurement one-way ANOVA was conducted for the hole cross test and open field test, followed by Dunnett's test. Statistical significance was given in all experimental setups, with $p < 0.05$, $p < 0.01$, and $p < 0.001$ denoting varying significance levels.

Results

Qualitative and Quantitative Phytochemical Analysis

As shown in Table 1, the extracts' phytochemical profile included several specific compound classes, such as tannins, phenols, flavonoids, saponins, terpenoids, gum, glycosides, and alkaloids. The methanol extract lacked saponins, gum, and alkaloids whereas phenols, flavonoids, terpenoids, and gum were absent in the acetone extract. Table 2 summarises the quantitative estimates of the extracts' major phyto-constituents and shows that tannins were the most prevalent compound class.

Table 1. Phytochemical screening of the fruit rind extracts.

Phytochemicals	Methanol extract	Acetone extract
Tannins	+	+
Phenols	+	-
Flavonoids	+	-
Saponins	-	+
Terpenoids	+	-
Gum	-	-
Alkaloids	-	+
Glycosides	+	+

(+) indicates positive; (-) indicates negative.

Table 2. Quantitative estimation of tannins, alkaloids, and glycosides in the fruit rind extracts.

Phytochemical class	Quantity (%)	
	Methanol Extract	Acetone Extract
	(Mean ± SEM)	(Mean ± SEM)
Tannins	0.31 ± 0.27	0.22 ± 0.19
Alkaloids	0.25 ± 0.11	0.19 ± 0.11
Glycosides	0.19 ± 0.07	0.26 ± 0.14

Data are expressed as the mean ± SEM; SEM, standard error of the mean.

Thiopental Sodium-Induced Sleeping Time Test

Across 25, 50, 100, and 200 mg/kg b.w., p.o. doses, the methanol and acetone rind extracts demonstrated substantially increased sleep duration in a dose-dependent manner. Statistically significant results were obtained in the test model ($p < 0.001$). This analysis used methanol and acetone extract at 200 mg/kg b.w., p.o. There was a maximum dose-dependent effect of methanol and acetone rind of 701.06% and 706.42%, respectively, throughout losing the right reflex, while the standard drug (diazepam) showed a 529.95% effect (Table 3).

Hole Cross Test

In the hole cross test, the number of holes through the chambers passed by mice in the control group was compared with the test groups. At the 50 mg/kg b.w., p.o. dose, both extracts elevated the activity of the mice. However, at 125 mg/kg b.w., p.o. both extracts reduced activity levels between the second and final examination. Significant effects ($p < 0.001$) were shown in a dose-dependent manner (Table 4). At 125 mg/kg b.w., p.o. during the 5th observation period, methanol and acetone extracts demonstrated a maximum suppression of 81% and 79% of locomotor activity, respectively, while diazepam demonstrated 98% suppression.

Hole-Board Test

In the hole-board test, the results revealed a dose-dependent inhibition of head dips in the treated animals. The test is a simple method to measure treated animals' exploratory behaviour, and the frequency of head-dipping is directly related to their emotional state. This test model used the methanol fruit rind extracts at 125 mg/kg b.w., p.o. inducing 70.09% suppression of head dipping behaviour, higher than the 67.29% inhibition recorded for diazepam. The activity of acetone extract at the same dose was inferior to methanol, demonstrating 64.49% inhibition in the behaviour (Table 5).

Open Field Test

In the open field test, at doses of 50 and 125 mg/kg b.w., p.o. both experimental extracts substantially diminished locomotor function in mice ($p < 0.05$, $p < 0.01$, $p < 0.001$) and this effect persisted from the second (30 min) until the final inspection (120 min) (Table 6). When treated with diazepam, we found fluctuating locomotion in mice between the second and final inspection. The methanol extract showed a maximum of 54.1% inhibition of locomotor activity at 50 mg/kg.b.w., p.o. (120 min), which was comparable to 41.6% for acetone extract at 125 mg/kg.b.w., p.o. (120 min), while diazepam showed 47.7% suppression at 120 min. The results based on these sensorimotor tests, which quantitatively analyse the exploratory be-

Table 3. Effect of fruit rind extracts on thiopental-Na-induced sleep time in mice.

Group	Dose (mg/kg)	Latent period	Sleeping time	% Effect
Control	10 mL/kg	9.4 ± 0.92	37.4 ± 1.44	0
Standard	0.5	2.6 ± 0.24***	198.2 ± 4.71***	529.95
Methanol Extract	25	8.4 ± 0.50	39.4 ± 2.87	105.35
Methanol Extract	50	6.0 ± 0.71***	74.6 ± 3.72***	199.47
Methanol Extract	100	4.1 ± 0.24***	143 ± 5.89***	382.35
Methanol Extract	200	2.3 ± 0.11***	262.2 ± 4.16***	701.06
Acetone Extract	25	8.1 ± 0.43	39.8 ± 1.59	106.42
Acetone Extract	50	6.5 ± 0.47***	73.8 ± 3.07***	197.33
Acetone Extract	100	4.6 ± 0.33***	143.0 ± 5.65***	382.46
Acetone Extract	200	2.6 ± 0.17***	264.2 ± 3.26***	706.42

Data are expressed as mean ± SEM (n = 5), ***$p < 0.001$, compared to the control group, which is significant (one-way ANOVA followed by Dunnett's test). Control group (distilled water); Standard (Diazepam). SEM, standard error of the mean; ANOVA, analysis of variance.

Table 4. Neuro-pharmacological potential activity test using the hole-cross procedure for fruit rind extracts.

Group	Dose	Number of movement				
		0 min	30 min	60 min	90 min	120 min
Control	10 mL/kg	5.0 ± 0.70	6.2 ± 0.37	6.2 ± 0.48	6.6 ± 0.40	8.6 ± 0.24
Standard	1	1.6 ± 0.51***	1.2 ± 0.37***	1.6 ± 0.40***	1.2 ± 0.58***	0.2 ± 0.20***
Methanol Extract	50	0.8 ± 0.37***	1.6 ± 0.51***	1.0 ± 0.71***	1.4 ± 0.40***	1.8 ± 0.37***
Methanol Extract	125	1.6 ± 0.51***	1.8 ± 0.37***	1.6 ± 0.40***	0.6 ± 0.24***	1.6 ± 0.24***
Acetone Extract	50	1.8 ± 0.37***	1.6 ± 0.60***	1.4 ± 0.24***	1.6 ± 0.24***	2.0 ± 0.32***
Acetone Extract	125	1.6 ± 0.51***	2.0 ± 0.32***	1.8 ± 0.37***	1.0 ± 0.32***	1.8 ± 0.37***

Data are expressed as mean ± SEM (n = 5), ***$p < 0.001$, compared to the control group, which is significant (repeated measurement one-way ANOVA followed by Dunnett's test). Control group (distilled water); Standard (Diazepam).

haviour and gross locomotor activity in treated animals, suggest active neuro-modulatory properties of the fruit rind of the *L. acidissima* plant.

Discussion

The therapeutic capabilities of natural medicines generated from plants with medicinal properties have been exploited throughout history. Herbal drugs, minerals, nutritional supplements, and illness treatments often use natural compounds in the nutrition, pharmaceutical, and food additive industries [31].

The sedation properties of *L. acidissima* were evaluated by observing the spontaneous locomotor activity of mice in hole-crossing and open-field experiments. In our trials, medications with sedation characteristics decreased the length and frequency of motion. Spontaneous locomotor activity represents the state of excitability of the CNS, and the reduction in such activity by administering these extracts demonstrates a soothing effect. For example, decreased movement in the hole cross test suggested a lack of curiosity when the animals were placed in a new environment. Moreover, the hole-board test evaluated mice's response to a novel environment, specifically examining anxiolytic-like behaviour. However, further study has discovered that the dipping movement of an animal's head is associated with its cognitive state.

The presence of anxiolytic qualities in mice was shown to be associated with an anxiolytic state, which subsequently led to an increase in head-poking behaviour. Ebert *et al*. [32] showed that, when administered orally at 125 mg/kg bw., p.o. dosages, fruit rind extracts elicited a more pronounced inclination for head dipping in mice. The effects of fruit rind extract on the time that mice slept after being given thiopental-sodium demonstrated that the extract has considerable sleep-modulating characteristics. The results also showed that oral administration of the fruit rind extracts at doses of 50 and 125 mg/kg b.w., p.o. reduced the number of holes crossed and the amount of movement across the hole board. After extract administration, suppressive activity was consistently visible from 30–120 min.

The most frequent approach for measuring anxiolytic efficacy is the open field test, intended to evaluate the potency of clinically used drugs. Previous research has consistently shown that spending more time in brightly lit environments influences anxiety [33]. At the doses tested, both extracts also yielded a significant inhibition of loco-

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Table 5. Neuro-pharmacological potential activity test using the hole-board procedure for fruit rind extracts.

Group	Dose (mg/kg)	Number of Head dips	% inhibition
Control	10 mL/kg	21.4 ± 2.97	0
Standard	1	7.0 ± 0.70***	67.29
Methanol Extract	50	9.8 ± 0.73***	54.20
Methanol Extract	125	6.4 ± 0.51***	70.09
Acetone Extract	50	10.0 ± 0.84***	53.27
Acetone Extract	125	7.6 ± 0.51***	64.49

Data are expressed as Mean ± SEM (n = 5), ***$p < 0.001$, compared to the control group, which is significant (one-way ANOVA followed by Dunnett's test). Control group (distilled water); Standard (Diazepam).

Table 6. Neuro-pharmacological potential activity test using the open-field procedure for fruit rind extracts.

Group	Dose	Number of movement				
		0 min	30 min	60 min	90 min	120 min
Control	10 mL/kg	25.9 ± 1.60	27.9 ± 2.29	27.8 ± 2.34	29.7 ± 2.17	37.7 ± 2.01
Standard (Diazepam)	1	14.3 ± 2.33*	14.7 ± 3.91*	16.5 ± 2.99**	18.1 ± 2.96***	19.7 ± 3.56***
Methanol Extract	50	16.99 ± 1.63	17.5 ± 4.01*	16.5 ± 2.33**	16.1 ± 1.81***	17.3 ± 3.01***
Methanol Extract	125	14.9 ± 0.84*	18.0 ± 1.44*	17.2 ± 1.11**	19.2 ± 1.62**	21.2 ± 2.42***
Acetone Extract	50	17.2 ± 1.16	16.8 ± 1.32*	17.2 ± 1.83**	19.8 ± 1.83**	19.8 ± 2.42***
Acetone Extract	125	15.4 ± 1.03*	17.4 ± 1.21*	18.0 ± 1.34**	19.8 ± 1.91**	22. 0 ± 2.12**

Data are expressed as mean ± SEM (n = 5), *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared to the control group, which is significant (repeated measurement one-way ANOVA followed by Dunnett's test). Control group (distilled water); Standard (Diazepam).

motion that rose from 30 to 120 min in the evaluation time. These findings showed that the extracts from the tested fruit rind suppressed locomotor activity, demonstrating a soothing effect. Administration of the two extracts to mice also reduced motor skills.

GABA is implicated in biochemical functioning and has been associated with various psychiatric and neurological disorders, including epilepsy, depression, Alzheimer's disease, and Parkinson's disease [34]. Eclectic drugs can alter the GABA mechanism by triggering post-synaptic inhibition through allosteric modulation of the GABA receptors during its synthesis [35,36]. This would either raise or intensify chloride conductance caused by GABA with voltage-activated Ca^{2+} channels with concurrent depression [37,38]. Both the extracts' doses decreased sleep latency and increased sleep duration in the daily dosage pattern of the thiopental sodium-mediated sleep time test, showing a deep sedative operation. Thiopental sodium is a barbiturate general anaesthetic that also affects sleep. It connects to the GABA receptor complex and shows post-synaptic neuron hyperpolarisation mediated by GABA [39].

As a result, it might be assumed that the plant extract works by stimulating GABAergic suppression *via* membrane hyperpolarisation, reducing the firing rate of the brain's essential neurons. Therefore, the CNS sedative function could be due to the increased length of the GABA-gated ion channel opening and increased affinity for GABA [40].

Bioactive molecules derived from natural sources or human diets serve as an armamentarium of drug candidates for the chemoprevention of chronic diseases [41]. Hydrolysable tannins from plant sources have been reported to interfere with multiple molecular mechanisms to suppress stress-induced depression [42]. Phytochemicals derived from natural sources are considered to be of broad neuro-pharmacological significance as lead compounds for drugs with anti-depressant and anxiolytic activities [43].

Conclusions

The present study presented empirical support for the neuropharmacological insights of *L. acidissima* fruit rind extracts in intensifying the effects of thiopental sodium by inhibiting locomotor activity in a mouse model. Nevertheless, additional research is necessary to explore the potential mechanisms by which the neuropharmacological effects of *L. acidissima* fruit rind extracts are mediated. The study presented *L. acidissima* as a nutraceutical or functional food with neuro-modulatory pharmacological effects.

Availability of Data and Materials

This published paper comprises the data acquired or researched during this project. Information will be supplied upon proper request.

Author Contributions

All authors contributed to the study conception and design. FI, MAKA, and TBE designed the study. FI, MAKA, BP, JKG, RD, PAL and TM help in data curation. MAKA, CM, KTKR, HAA-M, SFA, and TBE help in formal analysis. FI, MAKA, and TBE perform the initial drafting. FI, MAKA, HAA-M, SFA, and TBE help in review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All experimental protocols related to animal studies were approved by the Faculty of Allied Health Sciences Research Ethics Committee, Daffodil International University, Dhaka 1207, Bangladesh (Reference number: FAHSREC/DIU/2020/1006).

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Conflict of Interest

The authors declare no conflict of interest. Talha Bin Emran is serving as the Guest editor of this journal. We declare that Talha Bin Emran had no involvement in the peer review of this article and have no access to information regarding its peer review.

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