Original Article

Neuropharmacological Effects of *Chassalia curviflora* (Rubiaceae) Leaves in Swiss Albino Mice Model

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Abstract
The current study aimed to investigate the neuropharmacological properties of ethanol, acetone, and ethyl acetate leaf extracts of *Chassalia curviflora* (*C. curviflora*) in mouse models. The neuropharmacological properties of this plant were studied on Swiss albino mice at dosages of 50, 100, and 200 mg/kg body weight in thiopental sodium-induced sleeping time test, and at dosages of 100 and 200 mg/kg body weight in other tests. The extracts caused a marked reduction in the initiation and sleep length ($P<0.05$) in studies on thiopental sodium-induced sleeping time at dosages of 100 and 200 mg/kg and a significant decrease ($P<0.05$) was found in terms of unconstrained locomotor and explorative activities in both hole crossing and open field tests at dosages of 100 and 200 mg/kg. Furthermore, the extracts increased sleeping time with a dosage-dependent onset of action. The hole-board test extracts also reduced the number of head dips at dosages of 100 and 200 mg/kg ($P<0.05$). It was found in this study that *C. curviflora* had the best neuropharmacological properties at a dosage of 200 ml/kg. Our findings also showed that all of the extracts from *C. curviflora* were experimentally active in an *in vivo* model. The study results suggested that the leaves had strong anti-depressant and hypnotic CNS properties that might be exploited for neuropharmacological adjuvant therapy in conventional medicine. However, pharmacological studies are warranted to explore the active substances and the mode of action.
Keywords: *Chassalia curviflora*, Gamma-aminobutyric acid, Latent period, Locomotor behavior, Neuropharmacological potential

1. Introduction

Nowadays, behavioral maladies are among the most concerning issues, and depression has become a common subject of neurocognitive science. It is typically less prevalent at an early age and affects around 10-30% of the world's population with monoamine neurotransmitter disorder (1). In the past two decades, the number of biological research has increased drastically, and in the case of diagnosis and treatment of these "brain and mind" diseases, they will come to rest on a paradigm that is equally essential for both "neurology and psychiatry" in the near future (2).

Stress plays a role in many psychiatric maladies, including autism, epilepsy, seizure, and migraines. Stress can lead to depression and anxiety, as well as endocrine and neurodegenerative disorders. Stress inhibits cognitive ability and results in a slowing down of the recall chart (3). Recent studies have shown that

some drugs used for the identification of brain neurotransmitters are sedative-hypnotics. The brain receptor gamma-aminobutyric acid (GABA) impacts these medicinal products. Some sedatives and hypnotic medications are used to treat anxiety, vertigo, and insomnia. Antidepressants are medications that treat major depressive disorders by altering the imbalance of the chemicals in the brain's neurotransmitters (4). Antidepressants are extensively approved for the management of depressive episodes, despite the fact that they are often ineffective and their common complications can be catastrophic in certain situations. Consequently, more efficacious antidepressants with fewer adverse effects are urgently needed. Anxiety is the most common psychiatric problem with prevalence rates ranging from 10% to 25% across the lifecycle. Sleeping problems affect more than 30% of adults as the second most prevalent symptom of depression (5, 6). According to the World Health Organization (WHO), diazepam is the most effective and safe drug for anxiety and sleep disorders. Despite its high effectiveness, diazepam has several negative health consequences, particularly including aggressive behavior, anger, and poor impulse control, owing to counterintuitive stimulation. Moreover, it can cause hypotension and respiratory impairment at larger concentrations, especially in parenteral dosages (7). The most effective antidepressants are selective serotonin reuptake inhibitors, which increase the serotonin level in the brain and lead to reduced anxiety, nervousness, panic, and post-traumatic stress disorder (PTSD). However, it causes some adverse effects, such as nausea, drowsiness, vertigo, tremors or limb shivering, and fatigue (8). Several conventional therapies, such as acupuncture, exercising, and the influence of natural ingredients on depressive-like symptoms are promising (9). More to the point, as previously stated, oxidative stress is linked to several neurological and mental illnesses, which are caused by an imbalance in the generation of reactive oxygen species (ROS) and antioxidants. With the increasing prevalence of neurological and psychiatric illnesses,

more antidepressant medications have been created, although only a few have been proven to be effective. In total, 70% of patients do not achieve complete remission and 30% do not make it to the medication treatment (10).

Life and illnesses have been linked since the ancient periods. Every year, mankind is challenged by several new ailments, many of which are difficult to cure using conventional treatments. Thus, there is a strong desire to find a new potent but less hazardous alternative. Researchers are always on the lookout for potential drugs, both synthetic and natural, with minerals, plants, and animal sources (11). Plants are the primary source of medicinal products, which play a key role in global health. Human beings have been using plants for many years to cure and mitigate diseases (12). WHO recorded that more than 75% of people use herbal medicines to meet their everyday health needs (13, 14). The *C. curviflora* shrub is a medicinal plant that belongs to the Rubiaceae family. The genus also referred to as curved flower woody chassalia, has over 110 species (15). It is a small Rubiaceae tree that can grow to be two meters tall (16). The oil-boiled leaf juice is used in the treatment of ear, eye, ulcer, and sore throat conditions. The whole plant of Mananthavady tribes is used in the Wayanad district for skin conditions (17). Previous studies have demonstrated that the leaf extracts of this plant contained anti-inflammatory, analgesic, and hepatoprotective properties (18, 19). Many bioactive compounds have been isolated from leaves, roots, and whole plants, including alkaloids, triterpenoids, flavonoids, phenylpropanoids, and phenolic acids (20, 21). The current investigation focused on the neuro-pharmacological benefits of this plant in the *in vivo* mouse model to further explore the pharmacological properties of *C. curviflora*.

2. Materials and Methods

2.1 Chemicals and Plant Material

The standard drugs, thiopental sodium and diazepam were bought from Incepta Pharmaceuticals Ltd. and

Opsonin Pharma Ltd., Bangladesh, respectively. Different reagents and distilled water were purchased from the British drug house (BDH) Chemicals Ltd, Dhaka, Bangladesh. Plant material from *C. curviflora* (Rubiaceae) was collected from Sylhet, Bangladesh. The genus and family of the plant were identified by the National Herbarium in Bangladesh (DACB accession number: 40416) (22).

2.2 Extraction Procedure

The leaves of *C. curviflora* were washed with distilled water to remove undesirable materials. The leaves were shade-dried and ground into a coarse powder by a fitted processor. Quantities of 300, 350, and 350 g of granulated leaves of *C. curviflora* were soaked in 1000, 1500, and 1500 ml of ethanol, acetone, and ethyl acetate, respectively, in separate glass compartments for 10 days, followed by standard shaking and mixing in a room temperature. The entire blend was roughly filtered through a fine white cotton material and was further filtered by Whatman filter paper no. 1. To dissipate the solvent, the filtrate was placed in the open to obtain the dry extracts. The yield value of the ethanol, acetone and ethyl acetate extracts from the leaves was 2.11%, 1.99%, and 2.03% w/w, respectively (23).

2.3 Experimental Animals

Both sexes of Swiss albino mice (n=155), in the weight range of 22-25g, were obtained from Jahangirnagar University in Dhaka, Bangladesh, and housed in animal cages under standard natural conditions (22-25°C, moisture: 60-70%, 12:12-hour light/dark cycle). The mice were fed a standard pellet diet (22).

2.4 Qualitative Phytochemical Screening

The presence of some phytochemical groups was screened in the preliminary phytochemical study. These included alkaloids, flavonoids, saponins, tannins, steroids, gums, cardiac glycosides, and terpenoids that were identified by colorimetric methods (24).

2.5 Acute Toxicity Test

All preparations were administered orally to groups of mice (n=5) in dosages of 100, 200, 400, and 800 mg/kg, and the fatality rate was recorded from 24 hours to 7 days (25).

2.6 Sleeping Time Test

The activity of the three extracts on the sleeping time triggered by thiopental sodium was investigated using the standard test described earlier (26). In this case, mice were divided into 11 groups of five animals, each. Group-I and II were used as a control and standard, respectively, and were provided with distilled water and diazepam orally. Groups III, IV, and V received ethanol leaf extracts orally at dosages of 50, 100, and 200 mg/kg body weight, respectively. Groups VI, VII, and VIII were given acetone-leaf extracts orally at dosages of 50, 100, and 200 mg/kg body weight. Ethyl acetate leaf extract was administered orally to groups IX, X, and XI at dosages of 50, 100, and 200 mg/kg body weight. After half an hour, intraperitoneally, thiopental sodium (20 mg/kg body weight) was administered to all groups for sleep-inducing purposes. Due to uncoordinated movements, individual mice were put on a table and registered. The animals were found to instantly inhibit their proper reflex after the injection of thiopental sodium, which induced sleep (the time between suppression and restoration of the reflex). The effect size was determined using the following formula:

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

2.7 Hole Cross Test

In the study conducted by Uddin, Shilpi (27), a cage was used at dimensions of 0.30×0.20×0.14 m. A partition was fixed in the center of the enclosure. A hole with a diameter of 0.03 m was created at a height of 0.075 m, situated in the middle of the frame. Experimental animals were treated with control, standard, or test samples and were positioned on one part of the compartment. After administration of the control, standard, and experimental extracts, the number of passages of the mouse through the hole from one chamber to another was counted for 3 min at minutes 0, 30, 60, 90, and 120 from the administration

of the extracts. Groups I and II were considered control and standard, respectively, and were provided with distilled water and diazepam orally. Groups III and IV received ethanol leaf extract orally at dosages of 100 and 200 mg/kg body weight. Groups V and VI were provided orally with extracts of acetone leaves at dosages of 100 and 200 mg/kg body weight, respectively. Groups VII and VIII were provided orally with extracts of ethyl acetate leaves at dosages of 100 and 100 mg/kg body weight, respectively.

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

2.8 Hole-Board Test

The formerly portrayed strategy was used according to that in the study conducted by Sheikh, Zihad (28)with minor changes. A level foundation of 0.90 m×0.90 m in radius with 16 equitably separated holes was utilized in the current study. Likewise, this stage had a frame of 0.05 m in height. Mice were assigned to eight groups of gatherings, Control (1 group), Standard (1 group), Test (6 groups), and each group included five mice (n=5). Group I and II were used as a control and standard, respectively, and were provided with distilled water and diazepam orally. Groups III, IV, V, VI, VII, and VIII were independently provided with ethanol, acetone, and ethyl acetate leaves extracts orally at the dosages of 100 and 200 mg/kg body weight; respectively. The number of head dips of individual mice into the holes was monitored for 10 minutes.

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

2.9 Open Field Test

This analysis has been performed according to Anisuzzman, Hasan (29). The test platform was a plane with a 0.5 m^2 field with a square progression. All the squares on the other side were painted black and white. The experimental board was identical to a chessboard. Likewise, the mechanical system had a compartment height of 0.1m. Mice were assigned to eight groups of five animals (n=5) each. Groups I and II were used as

control and standard, respectively, and were provided with distilled water and diazepam orally. Groups III, IV, V, VI, and VIII were independently provided with ethanol, acetone, and ethyl acetate leaf extracts orally in the dosages of 100 and 200 mg/kg body weight. Three minutes were initiated 0, 30, 60, 90, and 120 minutes after the oral administration of sample medications.

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

2.10 Statistical Analysis

The data analysis was conducted using SPSS software (version 20.0). The results were reported as the mean± standard error of the mean (SEM). A factual investigation was carried out using a one-way variance (ANOVA) followed by Dunnett's sleeping time test and hole-board test. A two-way ANOVA ("analysis of variance") is used to determine whether or not there is a statistically significant difference between the means of three or more independent groups.

The Bonferroni test is a statistical test used to reduce the instance of a false positive. In particular, Bonferroni designed an adjustment to prevent data from incorrectly appearing to be statistically significant. A p-value less than 0.05 ($P<0.05$) was considered statistically significant.

3. Results

3.1 Phytochemical Group Test

Phytochemical compounds of *C. curviflora* leaves extracts are presented in table 1.

Table 1. Phytochemical compounds of leaves extracts of *Chassalia curviflora*

Compounds	EE	AE	ETAE
Alkaloids	+	+	+
Flavonoids	+	+	+
Saponins	+	-	-
Tannins	+	+	+
Steroids	+	+	+
Gums	+	+	-
Cardiac glycosides	+	+	-
Terpenoids	-	+	+

EE: ethanol extract; AE: acetone extract; ETAE: ethyl acetate extract
Key (+) and (-) indicate presence and absence, respectively

3.2 Acute Toxicity

All extracts (100–800 mg/kg p.o) produced acceptable behavior in the mice. Apathy, repetitive behavior, or vocalization were not observed. They had typical motor behavior and secretory markers. No evidence of depression was observed in the mice. The mice's vigilance, cognitive function, limb tone, functional capacity, and gait were all normal. The extracts were considered to be safe in mice at dosages of up to 800 mg/kg.

3.3 Sleeping Time Test

In the thiopental-induced hypnosis procedure, extracts at dosages of 50, 100, and 200 mg/kg caused a great reduction in the sleep period, primarily after administration of ethanol, acetone, and ethyl acetate extracts of *C. curviflora* leaves (Table 2). The extracts produced effects that were comparable to those produced by the standard diazepam at the onset of sleep. The length of thiopental sodium-induced sleep time and its latency in experimental animals was effectively modulated by varying dosages of the extract relative to controls. The leaves extracts had a maximal effect at 200 mg/kg, while diazepam had a 506.15% effect at 0.50 mg/kg.

3.4 Hole Cross Test

In this procedure, mice were given ethanol, acetone, and ethyl acetate leaves extracts of *C. curviflora* at dosages of 100 and 200 mg/kg. From minutes 30 to 120, the number of holes crossed from one section to the next was nearly identical in the control group. From the second to the last observation, there was a consistent decrease in the development of the experimental animals (Table 3). Significant results were obtained in this study in a dosage-dependent manner. Both dosages caused a substantial decrease in mice's inactivity, compared to the standard and the control groups, and the experimental animals' movement continued to increase from the second to the last observation.

3.5 Hole Board Test

Leaf samples were given orally to mice in all the dosages in this study. Thus, the number of head plunging was greatly reduced, compared to the test sample. The results revealed that the ethanol, acetone, and ethyl acetate extracts of the leaves caused 39.11%, 40.59%, and 39.11% inhibition at the prescribed dosages, respectively, and the obtained 67.33% inhibition was higher in both dosages, compared to the standard diazepam (Table 4).

3.6 Open Field Test

Leaf extracts significantly reduced locomotor function in mice at all the dosages, and this activity was noticeable from the first inspection (0 min) and lasted until the final assessment (120 min). Diazepam caused a significant decrease in locomotor function of the mice from the second to the third inspection (Table 5).

Table 2. Sleeping time in mice was induced by the neuropharmacological activity of the extracts by seeping time test

Group	Dosage (mg/kg)	Latency period	Sleeping time	Effect (%)
Control	10ml/kg	10.0±0.71	35.8±1.98	0
Standard	0.5	3.2±0.37	181.2±14.52	506.15*
EE	50	6.2±0.80	73.4±4.63	205.03
EE	100	4.4±0.51	138.6±5.41	387.15*
EE	200	2.2±0.25	243.6±8.85	680.45*
AE	50	6.4±0.81	64.2±3.08	179.33
AE	100	4.8±0.58	118.0±6.40	329.61*
AE	200	2.6±0.43	215.6±8.01	602.23*
ETAE	50	7.4±0.67	66.4±2.46	185.47
ETAE	100	4.6±0.40	124.4±7.44	347.49*
ETAE	200	2.4±0.29	228.0±13.82	636.87*

EE: ethanol extract; AE: acetone extract; ETAE: ethyl acetate extract. Results are presented as Mean±SEM (n=5), *$P<0.05$, statistically significant in comparison with the control group (one-way ANOVA followed by Dunnett's test)

Table 3. Neuropharmacological activity of the extracts by hole cross method

Group	Dosage	Quantity of movement (percentage of movements inhibition)				
		0 min	30 min	60 min	90 min	120 min
Control	10 ml/kg	3.8±0.86	3.8±0.37	4.8±0.86	4.8±0.80	4.6±0.40
Standard	1	2.2±0.58*	2.0±0.32*	1.4±0.51*	1.8±0.58*	1.6±0.60*
EE	100	3.0±0.45*	3.6±0.60	3.8±1.46	3.4±1.91	3.4±0.68
EE	200	2.8±0.49*	3.0±1.00	2.8±0.86*	1.6±0.51*	2.6±0.24*
AE	100	2.6±1.08*	3.8±0.58	4.4±1.16	4.2±1.83	3.0±0.71
AE	200	4.0±0.32	3.4±0.75	3.4±0.60	3.2±1.07*	2.8±0.58*
ETAE	100	3.6±0.81	3.2±0.58*	3.8±1.46	2.8±1.71*	3.0±0.71
ETAE	200	4.2±0.73	4.2±0.66	3.6±0.51	3.2±0.86*	3.0±0.55

EE: ethanol extract; AE: acetone extract; ETAE: ethyl acetate extract. Results are presented as Mean±SEM (n=5), *$P<0.05$, statistically significant in comparison with the control group (one-way ANOVA followed by Dunnett's test)

Table 4. Neuropharmacological activity of the extracts by hole board test

Group	Dosage (mg/kg)	Quantity of Head dips	Inhibition (%)
Control	10 ml/kg	40.4±2.87	0
Standard	1	14.8±1.24	63.37*
EE	100	27.2±2.37	32.67
EE	200	24.6±1.72	39.11*
AE	100	25.8±2.82	36.14*
AE	200	24.0±2.39	40.59*
ETAE	100	28.4±2.79	29.70
ETAE	200	24.6±1.63	39.11*

EE: ethanol extract; AE: acetone extract; ETAE: ethyl acetate extract. Results are presented as Mean±SEM (n=5), *$P<0.05$, statistically significant in comparison with the control group (two-way ANOVA followed by Bonferroni's test)

Table 5. Neuropharmacological activity of the extracts by open field test

Group	Dosage	Movement Quantity (percentage of movements inhibition)				
		0 min	30 min	60 min	90 min	120 min
Control	10 ml/kg	36.2±5.54	37.6±3.85	35.8±6.11	39.6±4.11	40.2±3.28
Standard	1	14.8±3.47*	15.2±4.02*	18.8±4.55*	20.2±4.14*	18.8±4.12*
EE	100	34.8±2.65	28.2±2.85	30.4±1.66	29.8±2.48*	27.0±2.76*
EE	200	24.6±3.44	26.8±2.92	26.8±2.11	23.4±1.66*	26.6±1.50*
AE	100	32.0±3.19	27.2±2.35	28.4±2.11	28.6±2.04*	35.2±4.61
AE	200	27.4±2.30	28.2±2.76	28.4±4.85	25.6±1.29*	28.6±3.19*
ETAE	100	35.2±3.77	30.4±3.17	24.2±3.31*	23.0±2.61*	28.4±1.83*
ETAE	200	16.6±2.20*	28.6±2.52	25.4±4.30*	26.8±1.46*	27.2±2.20*

EE: ethanol extract; AE: acetone extract; ETAE: ethyl acetate. Results are presented as Mean± SEM (n=5), *$P<0.05$, statistically significant in comparison with the control group (two-way ANOVA followed by Bonferroni's test)

4. Discussion

Natural remedies derived from various medicinal plants were used for their therapeutic properties since ancient times. Natural substances are frequently used in pharmaceutical, nutritional, and food additive enterprises to produce herbal medications, minerals, nutritional supplements, and ailment medications (30). The plants are economical sources of archaic medicine. As a complementary approach to traditional medicine, many ethnomedical plants identified can enhance neuro conductance. The sedating effects of *C. curviflora* were studied for the random locomotor behavior of mice in hole crossing and open field analysis. Each sedative agent decreases the rate and magnitude of the movement in these experiments. The data showed a substantial decrease in hole crossing numbers (*P<0.05) caused by the oral administration of experimental ethanol, acetone, and ethyl acetate plant leaf extract (Table 3). The repressive activity was detected in 0-120 minutes and continued until 120 minutes after the extract administration. Meanwhile, the experimental extracts induced substantial locomotion inhibition at tested dosages in open field tests (*P<0.05), which increased from 0 to 120 min (Table 5). A sharp decrease was observed in the locomotor behaviors of the mice in both the hole-cross and open field tests. Several physiological and emotional pathways suggest that GABA is the most critical inhibitory intravenous neuro transmitting agent of the CNS (31). By altering the GABA receptor synthesis, eclectic medicinal products could alter the mechanism of GABA through the potential inhibition of postsynaptic GABA (32, 33). It raised chloride conductivity in GABA while simultaneously lowering Ca^{2+} channel voltage (34, 35). These findings may indicate that anxiety in animals increases head-dip behavior, despite the decrease in the amount of head-dip associated with the depressant effect (36, 37). The study results indicated that extracts at dosages of 100 and 2000 mg/kg caused a clear enhancement in the acquisition and retention of cognition for the acquired task, as evidenced by an enhancement in the evasion behaviors, indicating nootropic function. This is most likely due to the interaction of neurotransmitters, as memory enhancement occurs only when neurotransmitter levels are reduced after concurrent administration of the extracts. There is a great deal of evidence suggesting that the central cholinergic system, serotonergic transmission, and noradrenaline activity are all important for the brain's cognitive performance (38).

The extract doses (50, 100, and 200 mg/kg) prolong the sleep period, The extract doses (50, 100, and 200 mg/kg) prolong the sleep period, meaning that thiopental sodium sleep has a strong sedative effect on sleep duration. Sodium thiobarbiturate is an ingredient observed in the biopsy that helps humans and mice sleep. It is linked to the GABA receptor complex and displays the hyperpolarization of GABA-mediated postsynaptic neurons (39). Moreover, it encourages GABA function and can impede exciting glutamate receptors as well. This molecular action causes a reduction in all neuronal outputs. The medicinal effects of traditional remedies may rely on a mixture of components. In some studies, alkaloids, glucose, terpenoids, and flavonoids were found to have anxious and sedative effects. The non-specific CNS depression of tannin may be attributed to sedative effects (40-42). The psychosomatic effects of flavonoid, steroid, and protein kinase C (PKC) activation are caused by genes expressing transcriptional factors. They were also described as protecting neurons against a series of metabolic and oxidant insults (43). In studies, photochemical measurements of the *C. curviflora* extracts revealed alkaloids, flavonoids, saponins, tannins, steroids, gums, and cardiac glycosides. Several studies have shown that alkaloids, glycosides, and flavonoids have potent anti-anxiety and anti-epileptic properties (44, 45).

Several laboratory research studies have shown that the plant extracts with the above secondary metabolites have anxiolytic and sedative effects induced by their affinity for the GABAergic complex system (46). The findings showed that *C. curviflora* extracts significantly

lower mouse locomotive activity. The analysis also supports the usual epilepsy and anxiety treatment of the plant (47). Therefore, the leaf extracts demonstrate the activity of neuropharmacology.

5. Conclusion

The current study provided evidence for the pharmacological properties of *C. curviflora* leaves extracts in complementing the effects of thiopental sodium by restricting the locomotor activity in the mice model. This study revealed that *C. curviflora* leaves extract had the highest neuropharmacological effects at the dosage of 200 ml/kg. However, further studies are required to investigate the plausible modes of action responsible for the neuropharmacological effects of *C. curviflora* leaves extracts. The study introduced *C. curviflora* as a nutraceutical or functional food with neuro-modulatory pharmacological properties

Authors' Contribution

Study concept and design: F. I. and T. B. E.
Acquisition of data: F. I., A. K., U. R., and M. M. R.
Analysis and interpretation of data: F. I., A. A. M., M. R. I., and A. A. M.
Drafting of the manuscript: F. I.
Critical revision of the manuscript for important intellectual content: K. D. and T. B. E.
Intellectual content: K. D. and T. B. E.
Statistical analysis: M. S. R., and M. M. R.
Administrative, technical, and material support: A. K.

Ethics

The measures undertaken in our study, including those related to animals, were confirmed by the Faculty of Allied Health Sciences Research Ethics Committee, Daffodil International University, Dhaka, Bangladesh (Ref. No.: FAHSREC/DIU/2020/1007(5)).

Conflict of Interest

The authors declare that they have no conflict of interest.

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