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Neuropharmacological evaluation of different species of *Curcubitaceae* seeds extract in experimental animals

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Abstract: Major depressive disorders such as anxiety and depression is predominantly developed in the modern era due to stressful lifestyle and now become the second leading cause of disability. The purpose of the current investigation to evaluate and compared the neuropharmacological effects of three different varaities of Cucurbitaceae seeds including Cucumis Melo var. flexuosus, Cucumis melo var. reticulatus and Santa claus melons ethanol seed extract in experimental animals at three different doses, i.e. 25, 50 and 100mg/kg in animals after 60 days of oral administration. Afterward, various neuropharphamcological activities such as general behavior, phenobarbitone induced sleeping time and exploratory behavior (Elevated plus-maze and head dip test) and motor coordination by Rotarod test were assessed and compared with the control group. The extracts producing dose depended effects on central nervous system. The general behavior profile revealed significant depression at maximum doses. At maximum dose 100mg/kg of *Cucumis reticulatus* and *Santa Claus,* seed extracts significantly increases the number of entries in open arms. On the other hand, the *Cucumis flexuosus* seed extract significantly increases the frequency of numbers of head dips in mice. However, the lower doses of the extracts showed less significant results. The results suggested that all extracts at maximum doses produces anxiolytic effects without affecting the motor coordination in animals.

Keywords: Neuropharmacological effects, *Cucurbitaceae*, *Cucumis flexuosus*, *Cucumis reticulatus, Santa Claus* melon.

INTRODUCTION

Plants and herbs are the great source of medicine and were used to treat various infectious diseases from prehistoric times (Balunas and Kinghorn 2005). The demand of herbal medicine increases due to the natural origin and minimum side effects (Saeed 2015; Parmar *et al.,* 2022). The family *Cucurbitaceae* commonly known as Cucurbitis; comprises of a large group of crops such as melon and cucumbers which is medically essential. This family contains a large group of medicinally valuable plants, including 130 genera and around 800 species (Shetty *et al.,* 2012). Numerous edible plants of this family were extensively studied, including; *Cucumis melo, Cucurbita pepo, Citrullus colocynthia, Momordica charantia, Luffa echinata, Benincasa hispida, Cucrbita ficifolia, Cucumis sativus, Trichosanthes kirilowii etc.* Many researchers had been investigated and validated the medication and nutritional benefits of *Cucurbitaceae* plants(Gill *et al.,* 2011; de Melo, Narain and Bora 2000; Ibrahim *et al.,* 2018). These plants contain numbers of phytochemical constituents, including Alkaloids, Glycosides, Carotenoids, Resins, Steroids, Saponins, Tannins and Terpenoids. Many fruit and seeds of *Cucurbitaceae* family has been evaluated for many pharmacological activities including cytotoxic, antioxidant, anti-inflammatory, analgesic, antibacterial, antitumor, immunoregulatory cardiovascular and neuropharmacological activities (Vouldoukis *et al.,* 2004; Bidkar *et al.,* 2012; Neelamma *et al* 2018)

Several plants and their extract renowned for the medicinal effects by acting on the central nervous system and used for chronic anxiety and depression in which conventional therapeutic drugs not responding well (Verma and Singh 2008; Herrera-Ruiz *et al.,* 2006). The present investigation was designed to evaluate and compare the complete neuropharmacological profile of three seeds varieties including; *Cucumis melo var.flexuosus* (Snake melon), *Cucumis melo var. Reticulatus* (Galia melon) and *Santa Claus* (*Christmis melon)* belongs to the *Cucurbitaceae* family. The present study helps to conclude that which seed possess strong neuropharmacological effects in experimental models in mice.

MATERIAL AND METHODS

Collection of plant materials

The fruits of *Cucumis flexuosus*, *Cucumis reticulatus* and *Santa claus* was purchased from the local market, Imtiaz superstore, Karachi, Pakistan. Seeds were authenticated and recognized by *Dr. Muneeba Khan*, Taxonomist in Botany Department, Karachi University. The issued voucher specimens no (95600), (95607) and (956009) respectively was deposited in the Centre for Plant Conservation, Herbarium and Botanic Garden, University of Karachi.

Preparation of seeds extract

Seeds were carefully separated from the fruit of *Cucumis flexuosus, Cucumis reticulatus* and *Santa claus melon* by hand, cleaned and washed to remove any adhering residue. Afterward, the seeds were air-dried under the shade and

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pulverized to a coarse powder (particle size 500µm) by an electric blender (Moulinex, France). Seeds in the powder form were soaked in ethanol (powder to solvent ratio was 1:10w/v) at 37-40°C temperature for 24hr along with stirring at various time intervals. After that, the solvent was rinsed with a cotton cloth and further filtrated by filter paper (Whatman no.1). Later on, the ethanolic extract was vaporized under reduced pressure at (45-50°C) using a rotary evaporator. The final extracts yield was the semisolid dark brown residue of *Cucumis flexuosus* (CFE) 19.24%w/w, *Cucumis reticulatus* (CRE) 18.34%w/w and *Santa claus* (SCE) 19.34%w/w. Extracts were stored in amber brown colored airtight sterile bottles and kept at 4°C in the refrigerator until used.

Animal's selection

Healthy albino mice, rats and rabbits were purchased from the H.E.J International Center for Chemical & Biological Sciences and Herbal Sciences. All animals were housed in animal house under the standard environmental conditions for 1 week pre- experimental study. All animals were housed individually with free access to food and water ad libitum properly. All animals were kept under standard environmental conditions, i.e. temperature (25±2°C), 12h light and dark cycle and relative humidity (55±5%). The weight (g) of animals was noted on a regular basis. All the experimental activities and specification for handling were performed according to the Helsinki's Resolution, (1964). The study protocol was approved by the Board of Advanced studies and Research (BASR) Karachi University, resolution no. 10 (P) 07 dated 30-07-2019.

Neuro-pharmacological activities

The neuropharmacological activity was performed to evaluate the effects of ethanol extract of *Cucumis flexuosus* (CFE), *Cucumis reticulatus* (CRE) and *Santa claus* (SCE) melon seeds on the central nervous system. The following neuropharmacological activities were assessed.

General behavioral profiles

The general behavior profile was assessed according to the Srikanth & Muralidaran method. The experimental procedure was performed on albino mice (22-25g) of either sex. All animals were distributed into eleven groups separately each comprised of six animals (n=6). The control group received distilled water (10ml/kg p.o). The test group received an ethanol seeds extract of CFE, CRE, and SCE at different dosages (25, 50 and 100mg/kg body wt p.o.) for 60 days respectively. However, the standard group received diazepam (1mg/kg i.p.). Each animal was under observation for any change in its behavioral activities. The results were noted for 30 min intervals in the first hour. Subsequently, for the next 4 hours following activities were observed.

Awareness, alertness & spontaneous action

The animal awareness and alertness were assessed by the enclosure of the mouse in a bell jar and recorded their response visually. It normally shows a moderate degree of inquisitive behavior. The behavior of the animal was scored as (-) slight depression, (--) moderate depression, (---) strong depression, (----) very strong depression.

Sound response

The mice are usually soundless so any vocalization may point as a noxious stimulus.

Touch response

The mice were touched with the pencil or forceps on various body parts such as neck, abdomen and groin.

Pain response

Response of pain was evaluated when the small artery clamp attached with the base of a mouse's tail.

Righting reflex

The motor ability of mice was checked by righting reflex on which the mouse flips at feet from a supine position. Loss of righting reflex was considered if the animals persisted on their posterior side of the 30s.

Pinna reflex

This reflex was evaluated by touching the center of the mice pinna with the help of fine instrument.

Grip strength

The neuromuscular function was assessed by examining the animal grip strength. In this test, each animal was permitted to hold a pencil on the plane surface horizontally and their time taken to drop the pencil was noted.

Barbiturate induced sleeping time test

Animals were divided into eleven groups, each having six mice. Test groups received an ethanol seed extract of CFE, CRE & SCE at the dosage (25, 50, 100mg/kg p.o) respectively. However, normal saline (10ml/kg p.o) given to the control and diazepam (2mg/kg i.p) was administered to the standard group respectively. On the test day, 30 minutes after oral administration of test drugs all animals were treated with phenobarbitone (40mg/kg, i.p.) (Srikanth and Muralidharan 2009). The sleep latency period that is the time taken to loss the righting reflex after administration of phenobarbitone was noted.

Exploratory behavior

The exploratory behavior of animals was assessed by elevated plus maze and head dip test.

Elevated plus maze test

The test was performed on albino mice weighing between (18-25g). After administration of CFE, CRE, SCE ethanol seed extract at the dose of (25, 50, 100mg/kg, p.o.) respectively, for 60 days and diazepam (1mg/kg, i.p.) was injected on the test day. Each mouse was situated in a elevated plus maze and the number of entries in open and closed arms and time spent were recorded (Onaolapo *et al.*, 2020).

Head dip test

The animal behavior, for example, curiosity and exploration have been evaluated by head dip test (Mallek-Ayadi, Bahloul and Kechaou 2018). Albino mice were divided into eleven groups, each having 6 animals. After administration of test drug (CFE, CRE and SCE) seed extract at various doses, i.e. (25, 50 and 100mg/kg p.o.) respectively and control received distilled water for 60 days, standard drug diazepam (1mg/kg, i.p.) was administered on test day. After 30min of treatment, each mouse was placed in a wooden box comprised of 16 holes which are equally positioned. The number of times each animal dipped their head into the holes were counted for 3 min (Murugesan *et al.,* 2001).

Rota rod test

The motor coordination of animals was evaluated by Rota rod test(Ghaderi, Rafieian and Nezhad 2020). The healthy albino rats (100-120g) were used for the rota rod test. Each animal was exercised to maintain balance on the Rota rod for 2min rotating at the speed (20r.m.p). The basal reading of each animal was recorded by placing each rat individually on the Rota rod, and their total number of falls recorded within 2min. Consequently, animals were divided into eleven groups, each having six animals. After administration of test drug CFE, CRE, SCE at three various doses (25, 50 and 100mg/kg, p.o) respectively, after 30, 60 and 90mins for 60 days. On test day, Diazepam (1mg/kg, i.p.) was administered to each rat and their number of falls on Rota rod was recorded

Histo-pathological examination

Once neuro-pharmacological observation and dosing were completed, after 60 days all experimental animals were euthanized via cervical decapitation under anesthesia by chloroform. The brain of each group of mice was cleansed with normal saline and fixed with 10% formalin. After standard processes of cleaning, dehydration and infiltration the tissue samples were paraffin-embedded. Afterward, a tissue sample was sent to the Laboratory of Dow International Medical College (DIMC) for pathological examination. Eosin and hematoxylin stained were used for the preparation of tissue slides. The Nikon Eclipse E-100 advanced Trinocular Microscope was used for some morphological differences as compared to the control group.

STATISTICAL ANALYSIS

All data were presented as the Mean±S.D (n=6). All values were statistically examined by using one-way ANOVA (Analysis of variance) and for the multiple comparison post hoc tukey's test were applied. All analysis was completed on software SPSS 23.0 version (SPSS, Inc Chicago, IL.USA).

RESULTS

The general behavioral profile effects were presented in table 1. The results revealed that all extracts produced slight to moderate type depression at higher doses (100mg/kg) as compared to the lower doses (25 and 50mg/kg). On the other hand, the standard reference drug diazepam produced highly significant result by cumulative depression of all behavioral responses as compared with the ethanol seed extract of CFE, CRE and SCE.

The dose depended effects of CFE, CRE, SCE extract were observed after administration of phenobarbitone sodium-induced sleeping as shown in table 2. The CFE extract at the dose of 100mg/kg showed a significant reduction in the sleeping time (47.34±1.48min) and sleep latency time (1.21±0.54min). Conversely, the lower dose 25mg/kg and 50mg/kg showed a significant increase in sleeping time. The most significant results ($p<0.001$) were produced by diazepam which considerably increased in the sleeping time (98.25±1.34min) and decreased in the onset of sleep (1.23±0.56min). Correspondingly, the ethanol extract of CRE and SCE at the lower doses of 25 and 50mg/kg showed significantly improved ($p<0.01$) sleeping time as compared to the diazepam treated group. However, at the doses of 100mg/kg showed moderate reduction in the sleeping time (53.21±1.19min), (67.34±1.33) respectively.

The results of CFE, CRE, SCE extract on in the Y - maze test shown in table 3. The results depict that CRE and SCE at the doses of 100mg/kg significantly ($p<0.001$) increases the time spent in open arms (210.34±2.34s), (215.56±2.14s) respectively, as compared to the diazepam (250.12±2.34s). The number of entries in open arms is significantly increased ($p<0.01$) by the Santa clause extracts at maximum dose (20.12±1.56). The ethanol extract of SCE and CRE at the doses of 100mg/kg produces more significant ($p<0.001$) results to increase time spent in open arms (215.56±2.14s), (210.34±2.34 s). However, the lower doses (25 and 50mg/kg) produced less significant results ($p<0.01$) as compared to diazepam (250.12±2.34s).

On the other hand, the frequency of open arm entries markedly increased at the higher doses as compared to the closed arms. Each extract showed more significant results at high doses 100mg/kg as compared to the lower doses (25, 50mg/kg).

The results of the head dip test after administration of ethanol extract of CFE, CRE, SCE at the doses of (25, 50 and 100mg/kg) revealed that there is a significant decline of head dip responses as compared to the control group.

The frequency of head dip prominently reduced in the diazepam treated group (32.32±2.21min) ($p<0.001$) as compared to the control group (85.37±1.45min). The ethanol extract of CFE and CRE at the dose of 100mg/kg produced similar significant results (41.34±3.12min), (42.34±4.23min) respectively. However, the ethanol extract of SCE exhibit less significant results (55.33±4.22 min) ($p<0.05$) as compared to the diazepam treated group.

Table 1: Comparison of different behavioral study of ethanol extract of CFE, CRE, SCE at various doses in mice

Behavioral Type	CFE (mg/kg)			CRE (mg/kg)			SCE (mg/kg)			Diazepam (mg/kg)	DW (ml/kg)
	25	50	100	25	50	100	25	50	100	5	10
Spontaneous activity	-	--	---	--	--	--	-	--	--	----	-
Alertness	-	--	--	--	--	--	-	--	--	---	-
Awareness	-	--	--	-	--	--	-	--	--	----	-
Sound response	--	--	-	-	--	---	-	--	--	----	-
Touch response	-	-	--	--	--	--	-	--	---	----	-
Pain response	-	--	--	-	--	--	--	--	---	----	-
Righting reflex	-	--	---	-	--	--	--	--	---	---	-
Pinna reflex	-	--	--	-	---	--	-	--	---	----	-
Grip strength	--	--	---	-	--	--	-	--	---	----	-

n=6, (-) slight depression, (--) moderate depression, (---) strong depression, (----) very strong depression.

Table 2: Effects of CFE, CRE, SCE on barbiturates induced sleeping time

Treatment	Dose(mg/kg)	Sleep Latency (min)	Sleeping Time (min)
Vehicle + PS	-	2.07±0.34	67.32±1.54
Diazepam+PS	1	1.23±0.56	98.25±1.34***
CFE+PS	25	1.67±0.65	76.34±1.44**
CFE +PS	50	1.45±0.47	67.34±2.17*
CFE+PS	100	1.21±0.54	47.34±1.48
CRE+PS	25	1.59±0.96	84.78±1.53**
CRE+PS	50	1.48±0.67	72.34±1.49**
CRF+PS	100	1.19±0.45	53.21±1.19*
SCE+PS	25	2.01±0.53	78.89±1.78**
SCE+PS	50	1.98±0.87	73.98±1.62**
SCE+PS	100	1.04±0.57	67.34±1.33*

Table 3: Effects of CFE, CRE, SCE on Elevated plus- maze test

Treatment Group	Dose mg/kg	Time spent in open arms (s)	Entries in open arms	Time spent in closed arms (s)	Entries in closed arms
Control	10 ml	120.12±1.23	9.45±3.41	185.34±2.45	15.34±3.21
Diazepam	1	250.12±2.34***	19.56±2.56**	51.31±3.33***	2.13±2.16*
CFE	25	145.45±1.56	5.78±2.45	112.45±2.56	4.43±1.55*
CFE	50	171.32±1.78	9.34±1.13	92.47±1.54*	3.42±3.14*
CFE	100	192.17±2.31**	13.67±1.23*	71.29±1.65*	2.11±1.37*
CRE	25	148.12±1.56	6.34±1.67	111.31±2.34	4.26±2.41*
CRE	50	182.6±1.98**	11.23±2.11*	89.45±2.12**	3.15±1.45*
CRE	100	210.34±2.34***	19.11±3.12**	59.47±2.44***	1.81±3.47*
SCE	25	143.21±1.31	5.48±2.10	104.2±1.79	4.21±1.67*
SCE	50	171.83±3.23**	10.43±3.22	85.31±2.29*	3.62±1.56
SCE	100	215.56±2.14***	20.12±1.56***	55.12±1.09***	1.79±1.43*

All values are presented as the mean ± S.D (Standard deviation) of three observations.

Table 4: Effects of CFE and CRE extract on locomotor activity

Treatment	Dose mg/kg	Head dip (min)
Control	-	85.37±1.45
Diazepam	1	32.32±2.21***
CFE	25	75.32±3.58
CFE	50	69.54±4.22*
CFE	100	41.34±3.12**
CRE	25	95.63±2.11
CRE	50	79.45±3.95
CRE	100	42.34±4.23**
SCE	25	93.45±3.33
SCE	50	62.79±2.31*
SCE	100	55.33±4.22*

All values are presented as the Mean ±S.D of three observations.

Table 5: Effects of ethanol extract of CFE, CRE & SRE on Rota rod

Groups	Dose mg/kg	Time spent on Rota rod (sec)		
		30 min	60 min	90min
Control	10 ml	335.14±1.23	330.17±0.34	335.18±13.34
Diazepam	1	103.45±1.27***	127.34±1.34***	165.21±2.31***
CFE	25	220.32±1.44	225.67±1.34	289.12±4.32
CFE	50	267.34±2.12	261.31±3.21	258.34±10.13*
CFE	100	256.12±2.26	249.11±2.45	210.43±1.34**
CRE	25	362.32±1.56	354.32±2.87	341.45±3.34
CRE	50	333.21±1.76	326.28±2.56	311.67±3.89
CRE	100	284.34±3.12	278.43±2.32	273.45±1.41
SCE	25	325.12±1.78	320.12±1.44	319.89±3.41
SCE	50	315.21±2.68	303.16±2.67	297.60±2.89
SCE	100	319.44±3.11	307.13±2.45	289.87±2.65

All values are presented as Mean ± S.D (Standard deviation) of three observations.

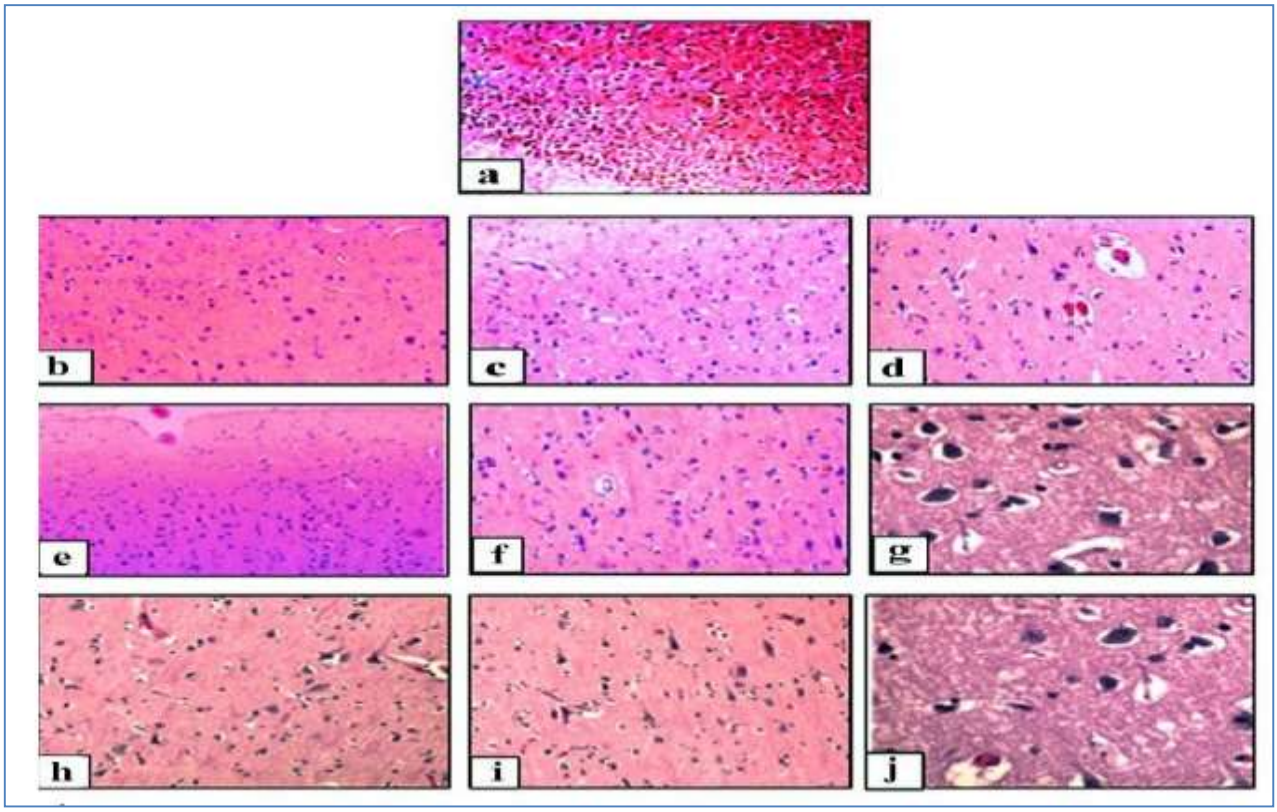

Fig. 1: Histopathalogical sections of mice brain with H & E stain after treatment presents (a) Control group (b) CFE 25mg/kg group, (c) CFE 50mg/kg group, (d) CFE 100mg/kg, (e) CRE 25mg/kg, (f) CRE 50mg/kg, (g) CRE 100mg/kg, (h) SCE 25mg/kg, (i) SCE 50mg/kg and (j) SCE 100mg/kg showing insignificant changes as compared to the control group.

DISCUSSION

Anxiety and depression are the conditions associated with the mental stress, which disturbs the performance of regular work. According to the Charles Darwin perceptions that animals specially rodents and humans having similar mechanism for emotions (Adolphs 2017). The assessment of neurological conditions and pharmacological action of several medicine has been recognized by the advancement of stress and anxiety model in animals (Onaolapo *et al.*, 2020).

The current study was carried out to compare and investigate the Neuro-pharmacological properties of *Cucurbitaceae* species, including *C. flexuosus*, *C. reticulatus* and *Santa claus* seed extract which has not been identified previously. In this study, we described the influence of ethanolic extract of each extract at different

doses on mouse behavior by employing various experimental models. The result of the current study discloses that all seed extract's effects on general behavioral profiles, including spontaneous activity, alertness, awareness, sound response, touch response, righting reflex, pinna reflex and grip strength. All extracts exhibit depressant effects on higher doses which indicate that these drug effects on the CNS.

Previous studies validate that *Cucurbitaceae* family species contain many phytoconstituents such as alkaloids, carotenoids, carbohydrates, ellagitannins, flavonoids, tannins, terpenoids, glycosides, resins, saponins, methionine, phenolic and phytosterols producing effects on CNS (Ibrahim *et al.,* 2018; Bidkar *et al.,* 2012; Mallek-Ayadi, Bahloul and Kechaou 2018). Our finding showed that lower doses of *Cucumis reticulatus* and *Santa cluas* extract showed hypnotic effects. As benzodiazepines have three subtypes BZ1, BZ2, and BZ3 (Bourin 2019). It might be possible that constituents of plant extract binds to these receptors for hypnotic effects. Additionally, these properties may possibly associate with permits specific inhibitory systems such as GABAergic. Previous studies reported that some plant constituents such as flavonoids having affinity for GABA/BDZ receptors (Aguirre-hernández *et al.,* 2016; Gazola *et al.,* 2018; Siddika *et al.,* 2015). However the increase in the number of of head dipping is the indication of anxiolytic behavior in animals.

The elevated-maze test is used for the recognition of spatial memory in rodents (Alikatte *et al.,* 2012). The reduction of locomotor activity in the elevated plus-maze test confirmed the sedative activity. Researchers suggested that flavonoids present in plants responsible for the sedation (Khatun *et al.,* 2016). The maximum dose of *Cucmis reticulatus* and *Santa claus* extract produces more significant results. Moreover, equivalent types of responses were observed in diazepam treat group.

The Rota rod test is a conventional animal model used to evaluate the peripheral neuromuscular blockage and motor coordination. Rotarod performance is affected by virtually any abnormality of the motor system. The discrepancy in motor coordination would possibly disturb the behavioral performance (Matias *et al.,* 2018). Our finding revealed that the all extracts produce insignificant results as compared to the diazepam. The benzodiazepine is the class of drug responsible for the blockage of neuromuscular coordination by reducing the time of animals to remain on the rotarod (Miyagawa *et al.,* 2014a; Vijayalakshmi 2020). The current results validate the anxiolytic effects of all extracts without blocking neuromuscular system. Previous researchers reported that plant phytochemicals such as alkaloids, flavonoids, terpenoids, sterols, saponins and tannins are responsible for CNS depressants and anxiolytic effects (Zahan *et al.,* 2020; Fedotova *et al.,* 2017; Miyagawa *et al.,* 2014b). The supposed anxiolytic action of CFE, CRE and SCE might be due to presence of phytoconstituents which binds to GABA and benzodiazepine complex. The histopathalogical examination showed insignifant changes in the brain of animals.

CONCLUSION

The current investigation suggested that CFE, CRE and SCE have significant medicinal property. The phytochemical constituents present in the seed extracts of these plant are commendable for further analysis and requisite structure elucidation for actual pharmacological mechanism.

CONFLICT OF INTREST

The author decleared no conflict of intrest. The autors are solely responsible for the content and writing of this paper.

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