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Evaluation of Antiepileptic Effect of *Cleome viscosa* Linn. Leaves Extract in Experimental Animals

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The purpose of this study was to assess the antiepileptic effect of *Cleome viscosa Linn.* leaves extract in experimental animals.
Study Design: The extraction process, acute toxicity study was determined using OECD guidelines, Priliminary phytochemical screening, Antiepileptic pharmacological screening methods and statistical analysis.
Place and Duration of Study: The research work was conducted during 10 Jan. 2020 to 10 July 2020 at Dept. of Pharmacology, Rajiv academy for Pharmacy, Mathura (U.P), 281001, India.
Methodology: The fresh leaves were shade dried and reduced in size to powder and extracted by soxhlet apparatus. The MECV, CECV and AECV were prepared and subjected to comparative phytochemical profiling for *in-vitro* analysis. Further the *in-vivo* screening models like maximal electroshock induced seizures (MES), picrotoxin (PTX) and pentylenetetrazole (PTZ) induced models are used to assess the anti-epileptic effects of the methanol, chloroform and aqueous extracts of *Cleome viscosa*.
Results: The extracts were subjected to phytochemical tests and the carbohydrate, tannins, alkaloids, saponins, flavonoids, steroids and glycosides were found to be present. In the MES induced seizures, MECV (200 mg/kg) showed high significant inhibition on tonic hind limb extension (THLE) ($9.33\pm0.33^{***}$), decrease in duration of stupor period ($145.2 \pm 2.59^{***}$) and

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decreased mortality significantly. In PTX induced model, MECV (200 mg/kg) showed high significant delay on the onset of convulsions (18.00±0.63***), decreased duration of convulsion (3.50 ± 0.18***) and decreased mortality significantly. In PTZ induced model, MECV and AECV (200mg/kg) showed high significant delay on the onset of convulsions (2.55 ± 0.10***), (2.50 ± 0.18***), decreased duration of convulsion (3.67 ± 0.11***), (4.33 ± 0.17**) and decreased mortality significantly.

Conclusion: It is clear from the preceding that *Cleome viscosa* has antiepileptic properties.

Keywords: Cleome viscosa Linn; Anti-epileptic; seizures; phenytoin; Diazepam.

1. INTRODUCTION

Epilepsy is the third most typical neurological disorder after stroke and alzheimer's disease. It is a united term for a group of chronic seizure disorder having in common, sudden and transient episodes (seizure) of loss or interruption of consciousness, typically but not always with a characteristic body movements (convulsions) and sometimes with autonomic hyperactivity [1,2]. In developed countries, annual new cases are between 40 and 70 per 100,000 people in the general population. This figure is often close to twice as high due to the higher risk of experiencing conditions that can lead to permanent brain damage. At the present day, six antiepileptic drugs: Gabapentin, Lamotrigine, Topiramate, Tiagabine, Zonisamide and Vegabatrin has long been used to treat epilepsy. They have all proven to be highly effective in short-term add-on clinical trials in patients with uncontrolled epilepsy. Synthetic antiepileptic drugs are associated with side-effects, including chronic toxicity, teratogenicity and adverse effects, on cognition an behavior [3,4].

Cleome viscosa Linn. called as “Hurhur,” which is also referred to wild or dog mustard (Jhakhiya is a local term.) belongs to the family capparidaceae. It is a sticky annual herb with a strong odour, long slender pods containing seeds and yellow flowers found in plains of India, China, Pakistan and Africa etc. as a common weed [5].

Plant and its various parts like-leaves, seeds, roots, stem etc. are used traditionally to cure variety of diseases. In ayurvedic system of medicine, the plant is used in fever, inflammations, bronchitis, liver diseases, and diarrhea. The people of the countryside use crushed seed juice to treat infantile convulsions and in mental disorders. The plant juice diluted with water is given internally in small quantities in fever and the leaves are useful in healing the ulcer and wound [6,7,8].

A number of phytochemicals isolated from various parts of *Cleome viscosa* Linn. have been reported. Out of them terpenes, flavonoids, tannins, phenol carboxylic acid are major category for pharmacological activity. *Cleome viscosa* Linn. is extremely effective in a wide range of diseases and reported to possess antidiarrhoeal, analgesic, psychopharm-acological, antimicrobial properties, including in-vitro Helicobacter pylori and wound healing activity [9-14]. However, its antiepileptic activity has not yet been scientifically validated. As a result, the current study was carried out to test the antiepileptic activity of *Cleome viscosa* leaves in experimental animals.

2. MATERIALS AND METHODS

2.1 Plant Materials

New leaves of *Cleome viscosa* Linn. were collected from the valley of Pinder in chamoli district of Himalayan region in Uttarakhand in the month of July-August and shade dried. Dr. Anurag Chandra, Senior Scientist and Incharge, Systematic Botany Division, Forest Research Institute (F.R.I.), Dehradun has identified and authenticated the leaves of Cleome viscosa Linn. and for further documentation and voucher specimens were deposited in the Herbarium section (Voucher No.29/Dis/2019/Syst.Bot./Rev.Gen./4-5).

2.2 Preparation of Extracts

The leaves of *Cleome viscosa* L. were dried in the shade at room temperature and were subjected to size reduction in order to obtain coarse powder with the desired particle size. The powdered material (500gm) was exposed to successive extraction in a Soxhlet apparatus using with increasing polarity solvents-

methanol, chloroform and aqueous. The presence of a colourless solvent in the siphon tube was taken as the end point of extraction. The extracts were separately concentrated to dryness using rotary evaporator. The dried extracts were preserved in vacuum desiccators until further use. The yield was 6.7 % w/w, 5.1% w/w and 2.8 % w/w for methanol, chloroform and aqueous extract of *Cleome viscosa* L. respectively [15].

2.3 Preliminary Qualitative Phytochemical Screening

The various *Cleome viscosa* extracts namely methanol, chloroform and aqueous was then subjected to qualitative phytochemical screening for the identification of different constituents using standard methods [16,17].

2.4 Drugs and Chemicals

Pentylenetetrazole (PTZ), Diazepam hydrochloride, Picrotoxin (PTX), Phenytoin are purchased from S.D. Fine Chemicals, Mumbai, India were used in the present study. All of the other chemicals used in the study were purchased commercially and were of analytical grade.

2.5 Animal Selection

Healthy Swiss albino mice of either sex (18-20 gm) were obtained from National Institute of Biologicals (NIB), Noida. All animals were kept in a laboratory for one week. They were kept in cages made of polypropylene. and maintained at $27^0C \pm 2^0C$ under 12 hours dark / light cycle. They were provided with standard feed (Gold Mohur Lipton, India Ltd.) and water ad libitum.

2.6 Toxicity Studies

The acute toxicity of *Cleome viscosa* leaves extract was examined in albino mice of both genders, with body weights ranging from 22 to 26 g, kept under standard conditions. Prior to the experiments, the animals were fasted for 24 hours. Animals were given a single dose of methanol, chloroform, and aqueous leaves extract of *Cleome vicosa*, and their mortality was monitored for 48 hours (short term toxicity). The next dose was determined using OECD guidelines No 425 based on short-term toxicity profile. Since no mortality was observed upto dose 2000mg/kg from the LD50 dose, 200 mg/kg was selected of each extracts for screening dose for further studies.

2.7 Antiepileptic Screening Methods

2.7.1 Maximum electroshock (MES) - induced epileptic seizure method

The epileptic seizures induced by maximal electro shocks (MES) in animals represent the grand mal type of epilepsy. Electroshock is delivered through the corneal electrodes in MES-induced epilepsy. The mice were divided into five groups, each with six mice. Group I indicated as the epileptic control group, received only normal saline (5ml/kg, p.o.). Group II received the standard drug, Phenytoin (25 mg/kg, i.p). Group III -V received all three extracts of *Cleome viscosa* leaves (200mg/kg, p.o). Group I, III, IV and V animals were subjected to a dosage regimen with their respective drug for the time period of 14 days but standard group II received just single dose of Phenytoin on 14^{th} day. All the groups received maximal electro shock (150 mA, 50 Hz for 2 sec) on the 14th day, one hour after receiving normal saline and drug administration. For different phases of epileptic seizures, the animals were observed individually for 30 minutes after receiving an electric shock [18].

2.7.2 Picrotoxin (PTX)-induced epileptic seizure method

Picrotoxin was injected into mice to induce epileptic seizures. The mice were divided into five groups, each with six mice. Group I received only normal saline (5 ml/kg, *p.o.*). Group II received the standard drug, Diazepam (4 mg/kg, i.p.). Group III -V received all three extracts of *Cleome viscosa* leaves (200mg/kg, p.o). Group I, III, IV and V animals were subjected to a dosage regimen with their respective drug for the time period of 14 days but standard group II received just single dose of Diazepam on 14^{th} day. On the 14^{th} day, all groups were given a convulsive dose of PTX (3.5 mg/kg, s.c.) 45 minutes after the vehicle or extracts and 30 minutes after the standard drug and are observed for (1) onset of convulsions (elapsed time between PTZ injection and convulsion), (2) duration of seizure (Total amount of time the animal is convulsing) and (3) mortality for the duration of 30 minutes [19].

2.7.3 Pentylenetetrazole (PTZ) induced epileptic seizure method

PTZ was injected into mice to induce tonic-clonic convulsions. The mice were divided into five groups, each with six mice. Group I received

only normal saline (5 ml/kg, *p.o.*). Group II received single dose of the standard drug Phenytoin (10 mg/kg, *i.p.*). Group III -V received all three extracts of *Cleome viscosa* leaves (200mg/kg, p.o). Group I, III, IV and V animals were subjected to a dosage regimen with their respective drug for the time period of 14 days but standard group II received just single dose of Phenytoin on 14th day. On the 14th day, A convulsive dose of PTZ (80 mg/kg, i.p.) was injected into mice 45 minutes after the vehicle or extracts and 30 minutes after the standard drug. Immediately after PTZ administration mice were observed for (1) onset of convulsions (elapsed time between PTZ injection and convulsion), (2) duration of seizure (Total amount of time the animal is convulsing) and (3) mortality for the duration of 30 minutes [20].

2.8. Statistical Analysis

The results are represented by the mean S.E.M. The current study's findings were analysed using one-way ANOVA, followed by Dunnett's multiple comparison test. Data was computed for statistical analysis by using Graph Pad PRISM 5 Software.

3. RESULTS

3.1 Preliminary Qualitative Phytochemical Screening

All the extracts of *Cleome viscosa* Linn. leaves had to go through preliminary qualitative phytochemical tests as per the standard guidelines to identify the presence of chemical constituents in the extract for various phytoconstituents were represented in Table 1.

3.2 Effect of *Cleome viscosa* Extracts on MES-induced Convulsion

The *Cleome viscosa* extracts significantly reduced the duration of THLE and the period of stupor caused by maximal electroshock, but they were unable to completely prevent its occurrence. All of the extracts demonstrated significant protection. MECV and AECV at 200 mg/kg high significantly ($p<0.001$) inhibited THLE in mice when compared to vehicle control, whereas CECV at 200 mg/kg significantly ($p<0.01$) inhibited THLE in mice when compared to vehicle control. MECV at a dose of 200 mg/kg significantly ($p<0.001$) reduced the duration of the stupor period whereas AECV showed the significance ($p<0.01$) and CECV showed less significantly ($p<0.05$) decreased duration of stupor at the dose of 200mg/kg were represented in Table 2, Fig. 1.

The standard drug Phenytoin has a high significance ($p<0.001$) in mortality protection, with no deaths recorded. and 200mg/kg dose of MECV and AECV showed 16.66%. The 200 mg/kg dose CECV showed 33.66% respectively and with four deaths out of six, the control group has a mortality rate of 66.66 percent.

3.3 Effect of *Cleome viscosa* Extracts on PTX Induced Seizure Model

The extract provided good protection against Picrotoxin-induced convulsions but was unable to completely inhibit them. The results of this model show that MECV at a dose of 200 mg/kg provided high significant ($p<0.001$) protection against the onset and duration of clonic convulsions caused by PTX. The CECV 200mg/kg showed less protection ($p<0.05$) in duration of clonic convulsions rather on onset ($p<0.01$) of convulsions. The AECV 200mg/kg showed less significant ($P<0.05$) in protection in onset of convulsions and not significant in duration of clonic convulsions in mice were represented in Table 3, Fig.2. In terms of mortality protection, the standard drug Diazepam treated group did not show any signs of convulsions, indicating a high significance ($p<0.001$) with no death recorded and 200mg/kg of MECV showed 16.67% mortality rate and 200 mg/kg of CECV, AECV showed 33.33% respectively.

3.4 Effect of *Cleome viscosa* Extracts on PTZ Induced Convulsion Model

The extract provided good protection against PTZ-induced convulsions but was unable to completely inhibit them. The results of this model show that MECV at a dose of 200 mg/kg provided significant ($p<0.001$) protection against the onset and duration of clonic convulsions caused by PTX. The AECV 200mg/kg had a significant effect ($p<0.01$) on the duration of clonic convulsions rather than the onset of convulsions ($p<0.001$). In Table 4, Fig. 3 shows that CECV 200mg/kg had a significant ($P<0.001$) effect on the onset of convulsions and a less significant ($P<0.05$)

effect on the duration of clonic convulsions in mice. In terms of mortality protection, the standard drug Diazepam treated group did not show any signs of convulsions, indicating a high significance ($p<0.001$) with no death recorded and 200mg/kg of MECV showed 0% mortality rate and 200 mg/kg of AECV showed 16.67% whereas CECV showed 33.33% mortality respectively.

4. DISCUSSION

A wide range of phytochemicals have been revealed to have CNS activities. Flavonoids have also been found to act as Benzodiazepine-like molecules in the central nervous system (CNS) and to adapt GABA-generated chloride currents in animal models of sedation, anxiety,

Table 1. Preliminary phytochemical analysis in different extracts of *Cleome viscosa* Linn. leaves obtained by successive soxhlet extraction

Sr. No.	Metabolites	Methanol extract	Chloroform extract	Aqueous extract
1	Carbohydrates	+	+	++
2	Tannin	++	+	+++
3	Proteins and amino acid	+	+	++
4	Flavonoids	+++	++	++
5	Steroids	+	+	-
6	Triterpinoids	+	++	+
7	Glycosides	+	-	-
8	Alkaloids	++	+	++
9	Saponins	++	+	+

'+'= present '-' = absent

Table 2. Effect of *Cleome viscosa* Linn. extracts on tonic seizures induced by maximal electroshock (MES) in mice

Experimental Group	Dose(mg/kg) b.w	Duration of Tonic hind Limb Extension (THLE) (sec)	Stupor (sec)	% Mortality
Control (saline)	5 ml/kg	13.17 ± 0.60	188.7 ± 2.19	4/6 (66.67%)
Standard (Phenytoin)	25 mg/kg	3.17 ± 0.75***	0.0 ± 0.0***	0/6 (0.0 %)
MECV	200 mg/kg	9.33±0.33***	145.2 ± 2.59***	1/6 (16.66 %)
CECV	200 mg/kg	10.83±0.40**	180 ± 2.24*	2/6 (33.33%)
AECV	200 mg/kg	10.17±0.48***	176.7 ± 2.47**	1/6 (16.66%)

All values are expressed as Mean ±S.E.M. (n=6 per group). p values:<0.05,**<0.01,***<0.001 as compared to vehicle control (saline) by one-way ANOVA followed by Dunnett multiple comparison test.*

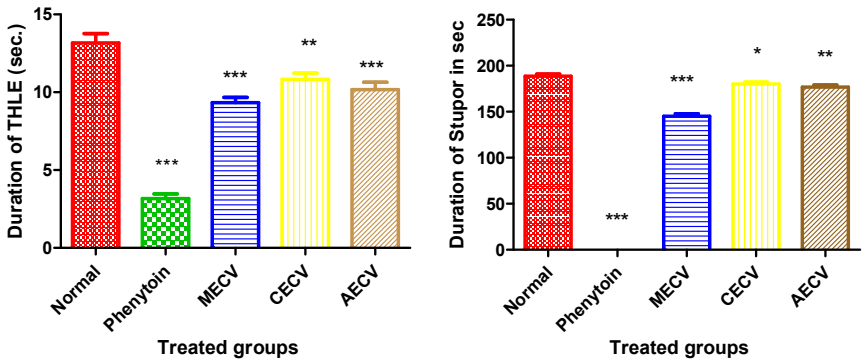

Fig. 1. Effect of *Cleome viscosa* Linn. extracts on duration of THLE and Stuper (sec.) in MES-induced convulsion in mice

and convulsions [21]. The presence of alkaloids,tannins, flavonoids, steroids, and saponin in methanol, chloroform, and aqueous extracts of *Cleome viscosa* was found to have antiepileptic activity in the current study.

The study was undertaken in order to determine the safety and antiepileptic activity of various extract of *Cleome viscosa*. The finding showed that extracts of *Cleome viscosa* had no lethal effect at doses up to 2000 mg/kg and dependent anticonvulsant activity against seizures induced by MES, PTX and PTZ. In MES induced model, the methanol, chloroform and aqueous extract has protected the animals from seizures and decrease the duration of hind leg extension in the doses of 200 mg/kg whereas the control did not shown any protection, indicating that the extracts is effective against seizures.

Table 3. Effect of *Cleome viscosa* Linn. extracts on PTX-induced convulsion in mice

Experimental group	Dose mg/kg b.w.	Onset of clonic convulsion(min.)	Duration of convulsion(min.)	Mortality/ used (%)
Normal (saline)	5ml/kg	12.58 ± 0.20	4.67 ± 0.17	3/6 (50%)
Standard (Diazepam)	5 mg/kg	0.00 ± 0.00***	0.00 ± 0.00***	0/6 (0%)
MECV	200 mg/kg	18.00±0.63***	3.50 ± 0.18***	1/6 (16.67%)
CECV	200 mg/kg	14.83±0.40**	4.00 ± 0.22*	2/6 (33.33%))
AECV	200 mg/kg	14.17±0.40*	4.17 ± 0.21ns	2/6 (33.33%)

All values are expressed as Mean ±S.E.M. (n=6 per group). p values:<0.05,**<0.01,***<0.001 as compared to vehicle control (saline) by one-way ANOVA followed by Dunnett multiple comparison test.*

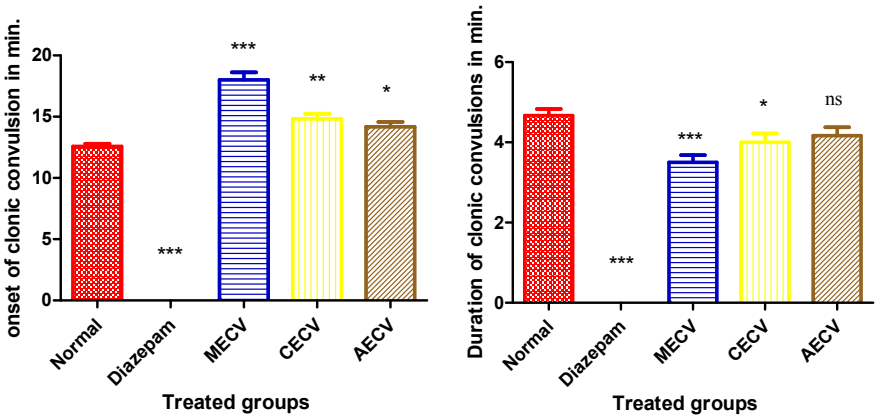

Fig. 2. Effect of *Cleome viscosa* Linn. extracts of onset and duration of clonic convulsion (min.) in PTX-induced convulsions in mice

Table 4. Effect of *Cleome viscosa* Linn. extracts on PTZ - induced convulsion in mice

Experimental group	Dose (mg/kg) b.w.	Onset of clonic convulsion(min.)	Duration of convulsion(min.)	Mortality/ used (%)
Normal (saline)	5ml/kg	1.33 ± 0.17	4.92 ± 0.15	4/6 (66%)
Standard (Diazepam)	5mg/kg	0.00 ± 0.00***	0.00 ± 0.00***	0/6 (0%)
MECV	200 mg/kg	2.55 ± 0.10***	3.67 ± 0.11***	0/6 (0 %)
CECV	200 mg/kg	2.08 ± 0.15**	4.42 ± 0.08*	2/6 (33.33 %)
AECV	200 mg/kg	2.50 ± 0.18***	4.33 ± 0.17**	1/6 (16.67%)

All values are expressed as Mean S.E.M. (n=6 per group). p values:<0.05,**<0.01,***<0.001 as compared to vehicle control (saline) by one-way ANOVA followed by Dunnett multiple comparison test.*

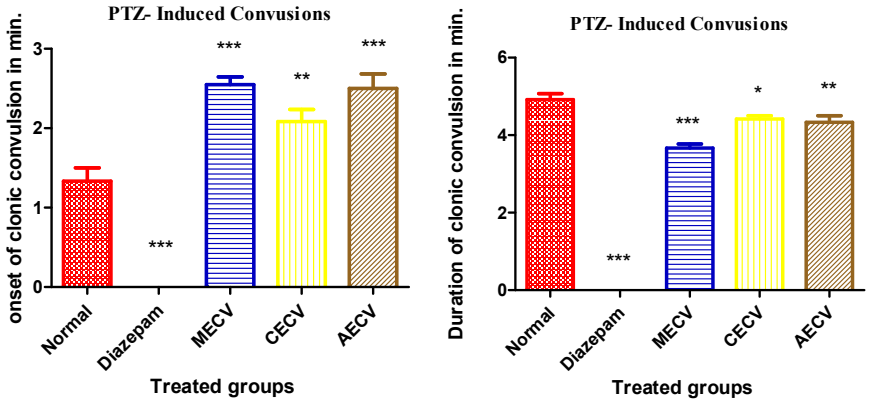

Fig. 3. Effect of *Cleome viscosa* Linn. extracts of onset and duration of clonic convulsion (min.) in PTZ-induced convulsions in mice

The mechanism of inhibition of seizures may be due to enhancement of GABA activity or inhibition of sodium channels. Comparison of control and test group by one way ANOVA, where P<0.001, P<0.01 and P<0.05 indicating the activity is significant. It is thought that a compound's ability to prevent maximal electroshock seizures correlates with its ability to prevent the spread of seizures discharge through neural tissue. Activity against maximal electroshock seizures is thought to indicate potential efficacy in the treatment of major motor (grandma) seizures. Phenytoin is the antiepileptic drug best known for its selective action in preventing maximal seizures.

Picrotoxin, a selective noncompetitive antagonist of GABA-A-receptors, causes seizures by blocking chloride-ion channels associated with GABA-A-receptors, preventing chloride ions from entering the brain. This, in turn, will inhibit GABA neurotransmission and activity in the brain [22], which has been widely linked to epilepsy [23]. On the other hand, Pentylenetetrazole is a chemoconvulsant, which induces seizures by the inhibition of GABA-A receptors and it is broadly accepted experimental model for absence seizure [24].

In the current study, various extracts and diazepam were shown to inhibit seizures caused by pentylenetetrazole and picrotoxin. All extracts at 200mg/kg were also shown to delay the latency and duration of pentylenetetrazole and picrotoxin-induced seizures, implying that the extracts exhibit anticonvulsant effects when compared to the vehicle group, most likely by opening chloride channels associated with GABA receptors. As the test group is compared with control group P<0.001, P<0.01 and P<0.05 indicating the results are significant.

Our current study has evaluated anti epileptic activity by maximal electro shock, Picrotoxin and Pentylenetetrazole methods, the MES method is applicable for tonic-clonic seizures, and PTZ test is a model for absence seizure Standard drugs like Phenytoin and Carbamazepine acts on voltage gated sodium channels in MES induced seizures. and drugs like Diazepam, Clonazepam, increases opening of GABA-Chloride channels prevents MES, PTX, PTZ induced convulsions [25]. A detailed reports on phytochemical and Pharmacological studies on *Cleome viscosa* for the proves antiepileptic activity [26,27]. It may be due to the presence of flavonoids and sterols in various extracts.

5. CONCLUSION

It was found that methanolic, chloroform and aqueous extract of *Cleome viscosa* leaves at the dose of 200mg/kg body weight showed significant effect against MES, PTX and PTZ induced convulsions when compared to control groups.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors andproducers of the products because we do not intend to use these products as an avenue forany litigation but for the advancement

of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable

ETHICAL APPROVAL

The experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) constituted under Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA) (Regd. No. 882/Po/Re/S/05/CPCSEA). The written approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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