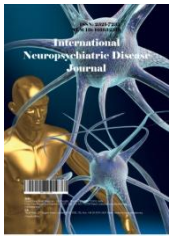

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Neurological and Molecular Interactions of Phytoconstituents from *Ricinus communis* Root Extract- A Pharmacological and Computational Approach

M. Ganga Raju [a*], V. Laxmi Prasanna [a], N. V. L. Suvarchala Reddy V [a] and Ch. Sneha [a]

[a] Department of Pharmacology, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, Telangana, India.

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

The majority of epileptic patients takes numerous anticonvulsant medications and is still not treated successfully. These medications' produce chronic side effects and drug interactions, which restrict their use, constitute their major drawback. On the other hand, the fact that nature has given us plants that can be used as safe, all-natural treatments for illnesses with little side effects and minimal drug interactions has prompted researchers to focus on herbal remedies with anticonvulsant potential. The antiepileptic potential of the methanolic root extract of *Ricinus communis* was investigated in rodent models. Molecular docking studies using Schrodinger software was employed to study interactions with active site using PDB ID: 4MS4 (GABA agonist's), 3WFG (glutamate antagonist), 5HCV (aspartate antagonist), 6J8G (sodium channel antagonist). At 30 and 60 minutes, MERC effectively diminished various convulsive phases and provided strong defence against the MES model. In PTZ, MERC extract treated groups at a dose (200 mg/kg and 400 mg/kg) showed significant antiepileptic activity with percentage protection of 24% and 33% respectively against seizures and significantly (* = p<0.0001) increased the latency of the seizures. Molecular docking studies confirmed the GABA agonist's effects, and the results revealed that quercetin. gallic acid, luteolic acid, gentixic acid, catechin, vanillic acid, ricinoilc acid

**Corresponding author: E-mail: mgrpharma@gmail.com;*

and standard phenytoin, clonazepam has highest Glide scores against all the selected proteins which indicates a stronger receptor -ligand binding affinity. From *in vivo* and molecular docking results it is clear that methanolic root extract of *Ricinus communis* possessed significant antiepileptic activity.

Keywords: Ricinus communis; anti-epileptic; GABA; docking; glide score.

1. INTRODUCTION

The most prevailing neuropsychiatric disorder, epilepsy is categorized by paroxysmal cerebral dysrhythmia. It conveys as brief episodes (seizures) of loss or disturbance of consciousness with or without identifiable body moments (convulsions), and it has a significant impact on one's ability to move around socially and medically. Convulsions, a kind of epilepsy that manifests as rapid, stereotyped episodes with concomitant alterations in motor activity, sensory, and behavior, are recurring, spontaneous seizure events or convulsions [1]. In most industrialized nations and in developed countries generally, the incidence of epilepsy ranges from 40 to 70 per 100,000 people. Thus, only emerging nations account for about 80% of all epilepsy cases worldwide. There are around 10 million epileptics in India, with an incidence of 1% [2]. Depending on the type of epilepsy, convulsions can also be accompanied by muscle spasms and a loss of consciousness. These are believed to be caused by an imbalance between the main excitatory and inhibitory systems in the brain, glutamate and g-amino-butyric acid (GABA), which leads in aberrant electrical discharges. Convulsions cause changes in membrane receptors and neurotransmitter uptake sites, both neurogenesis and apoptosis, astrocyte proliferation, and axonal sprouting in neurons, glia, and neuronal circuits [3]. Anticonvulsant therapy's emergence has made a big difference in how epilepsy is handled. With the use of conventional anti-epileptic drugs, 60–70% of epilepsy patients are able to control their seizures anti-epileptic drugs (AED). Even with the continued use of AED, seizure control is not achieved in nearly one-third of epileptic patients. Furthermore, the use of AEDs is linked to a wide range of adverse effects, including teratogenic effects, dose- related and chronic toxicity, and adverse effects from repeated exposure to the drug. As a result, there is a greater need to develop medications that are efficient in treating refractory epilepsy and cause fewer side effects. In underdeveloped nations, medicinal plant use is common and provides significant supplies of novel chemicals with potential therapeutic benefits [4].

Ricinus communis, commonly known as castor oil/amudham, is a perennial shrub with a small soft wooded tree that grows up to 6 meters with varying stem pigmentation, belonging to the family *Euphorbiaceae*. It is found not only in tropical and subtropical regions but also as a wild sprouting or ornamental plant essentially around the world. The plant has been evidenced to have important and desirable biological properties, which include antioxidant, antimicrobial, antihelmintic, insecticidal, diuretic, anti-inflammatory, and laxative; the above properties have been documented for use in the treatment of hypoglycemia, swelling, rheumatism, headache, asthma, dermatitis, and other conditions [5]. The present study aimed to evaluate the anti-epileptic activity of the methanolic root extract of *Ricinus communis* on Maximal electroshock (MES) induced convulsions and Pentylenetetrazole (PTZ) induced convulsion and an attempt is made to establish the *in silico* studies of active constituents of the extract using molecular docking and Ramchandran plot .

2. MATERIALS AND METHODS

2.1 Plant Collection and Drying

Roots of *Ricinus communis* were identified, collected, authenticated by botanist P. Suresh babu, government Degree College, Kukatpally, Medchal District. *Ricinus communis* roots were cleaned and dried under shade for about six days and powdered. The powdered material was stored.

2.2 Preparation of Methanolic Extract of *Ricinus communis* (Soxhlet)

300 gm powdered material of roots of *Ricinus communis* were dried and extracted with 1500 ml of methanol by soxhlation technique at a temperature of 45±5°C. As to get efficient extraction, this method allows a continuous extraction process; it is nothing but a series of short macerations. The organic extracts obtained were evaporated to dryness by keeping at room temperature. Large amounts of drug can

be extracted with a much smaller quantity of solvent. This process of extraction is economical in terms of time, energy and consequently financial investments [6].

2.3 Preliminary Phytochemical Analysis of the Extract

The extract was subjected to preliminary phytochemical investigations to identify various phytoconstituents present in the methanolic extract of roots of *Ricinus communis*.

2.4 Acute Toxicity Testing

The acute toxicity studies were carried out using OECD 425 guidelines. Present study was carried out in CPCSEA approved animal house of Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, India. (Reg. No. 1175/PO/ERe/S/08/CPCSEA).

2.5 Animal Housing

The animals (Rats and mice) were housed in poly acrylic cages with not more than six animals per cage, with 12 h light/12 h dark cycle. Animals have free access to standard diet and drinking water ad libitum. The animals were allowed to acclimatize the laboratory environment for a week before the start of the experiment. The care and maintenance of the animals were carried out as per the approved guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA).

2.6 *In vivo* Methods for Evaluation of Antiepileptic Activity

In vivo evaluation of antiepileptic activity of the methanolic extract of roots of *Ricinus communis* was carried out in following models.

a) Maximal electroshock Induced convulsions.
b) Pentylenetetrazole Induced convulsions.

2.7 Maximal Electroshock Induced Convulsions

24 healthy Albino rats of either sex weighing 200-250 gm were selected for the study. They are divided into 4 groups, each consisting of 6 animals (n=6).

Group I - (control) normal saline.
Group II - MERC at dose of 200 mg/kg, b. w. *p.o.*
Group III - MERC at dose of 400 mg/kg, b. w. *p.o.*
Group IV - standard phenytoin 25 mg/kg b. w. *i.p.*

All these drugs were administered 1-hour prior to induction of seizures by MES. After 1-hour, electric current of 150 mA for 0.2 seconds was administered through ear electrodes to induce convulsions in all the animals with the help of an electro convulsiometer. The different phases of convulsions were noted down along with the duration of each phase for recording various parameters. Rats were placed in a clear rectangular polypropylene cage with an open top permitting full view of the animal motor responses to seizure. Various phases of convulsions like tonic flexion, extension, stupor and mortality due to convulsions were observed. Abolition or reduction in the duration of hind limb tonic extensor (HLTE) phase will be taken as a measure of protection against MES induced seizures [7].

Fig. 1. Extension phase of Wistar Albino rat

2.8 Pentylenetetrazole Induced Convulsions

24 healthy Albino mice of either sex weighing 20-25 gm were selected for the study. They are divided into 4 groups, each consisting of 6 animals (n=6).

Group I - (Disease control) normal saline + PTZ 90 mg/kg, b. w., *i.p*
Group II - MERC at dose of 200 mg/kg, b. w. *p.o.* + PTZ 90 mg/kg, b. w., *i.p*
Group III - MERC at dose of 400 mg/kg, b. w. *p.o.* + PTZ 90 mg/kg, b. w., *i.p*
Group IV - Standard Clonazepam 1 mg/kg b. w. *i.p.* + PTZ 90 mg/kg, b. w., *i.p*

30 minutes after treatment, mice in all the groups receive PTZ (90 mg/kg, b. w. *i.p*). Later the latency of convulsions, duration of the convulsions, and mortality protection (percentage

of deaths in 24h) will be recorded. Absence of an episode of clonic spasm of at least 5 seconds duration indicates the extract or a compounds ability to abolish the effect of PTZ on seizure threshold [8].

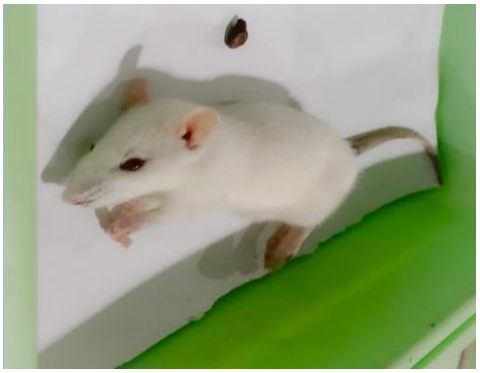

Fig. 2. Pentylenetetrazole induced convulsions in Swiss albino mice

2.9 *In-silico* Analysis

2.9.1 Molecular docking studies

2.9.1.1 Structure based drug design

Initially the protein downloaded from PDB was prepared by removing chain B. Water molecules present in both the chains are removed. Energy minimization was done. Later molecules drawn using chemdraw were converted to mol format and ligprep was created. Grid generation was done by removing crystal ligand and the structures were docked against protein 4MS4, 3WFG, 5HCV and 6J8G.

2.9.1.2 Schrodinger XP-docking results

XP docking indicates that some of our compounds have good binding ability with GABA agonists (PDB ID: 4MS4), Voltage gated sodium channel antagonist (PDB ID: 6J8G), Glutamate antagonist (PDB: 3WFG) and Aspartate antagonist (PDB ID: 5HCV).

Ramachandran Plot: Ramachandran plot has been generated from PROCHECK validation server which was used to access the quality of the model by looking into the allowed and disallowed regions of the plot [9].

2.10 Statistical Analysis

Values are expressed as Mean ± SEM, (n=6). All the groups were compared with control, negative control, and standard by using Dunnett's test. Significant values are expressed as control group (**=p<0.01, *=p<0.05), negative control (a=p<0.01, b=p<0.05) and standard (A=p< 0.01, B=p< 0.05), ns- non significant.

3. RESULTS

Maximal Electroshock (MES) and pentylenetetrazole-induced convulsions were used to test the *in vivo* antiepileptic activity of a methanolic extract of the roots of *Ricinus communis*. All the results obtained in the study were included below.

3.1 Preparation of Methanolic Extract of Roots of *Ricinus communis*

Using the soxhlation method, a methanolic extract of *Ricinus communis* roots was created. The formula below was used to determine the % yield of the methanolic extract.

% of yield obtained = Amount of extract obtained (gm)/ Total amount powder used × 100

% Yield of extract = 55.5/300 ×100=18.5 % w/w

3.2 Preliminary Phytochemical Analysis

The methanolic extract of *Ricinus communis* roots preliminary phytochemical analysis revealed the presence of alkaloids, flavonoids, glycosides, terpenoids, carbohydrates, tannins, and saponins (Table 1).

Table 1. Preliminary phytochemical analysis

Phytoconstituents	Results
Alkaloids	+
Flavonoids	+
Carbohydrates	+
Terpenoids	+
Fatty acids	+
Steroids	-

3.3 Acute Toxicity Studies

Swiss albino mice were examined with a methanolic extract of *Ricinus communis* roots up to a dose of 2000 mg/kg, b. w. Up to 2000 mg/kg body weight, the animal showed no symptoms of toxicity or fatality. Throughout the investigation, a variety of physical and behavioral characteristics were seen. Therefore, it was determined that the extract was safe up to 2000 mg/kg, b. w.

3.4 *In vivo* Anti-Epileptic Activity

The following models were used to investigate the methanolic extract of *Ricinus communis* roots for antiepileptic activity, and the findings are shown in Table 2.

3.4.1 Maximal electroshock induced convulsions

Table 2. Effect of MERC on Maximal Electro Shock (MES) induced convulsions

Groups	Flexion (seconds)	Extension (seconds)	Jerky movements (seconds)
Control	23±0.67	14±0.79	14.6±0.88
(MERC 200 mg/kg, b. w.)	8±0.57^{*A}	6.5±0.61^{*A}	7.83±0.54^{*A}
(MERC 400 mg/kg, b. w.)	4±0.36^{*B}	3.5±0.42^{*B}	4.66±0.21^{*B}
(Phenytoin 25 mg/kg, b. w.)	1.83±0.30*	1.33±0.21*	4±0.25*

Mean ± SEM (n=6) is used to express data. ANOVA was used for the statistical analysis, which was followed by Dunnett's test. Values that were significant were expressed as compared to the control group. (= p<0.0001) and when compared to standard group (A = p<0.0001, B = p<0.001)*

3.5 Pentylenetetrazole Induced Convulsions (PTZ)

Table 3. Effect of MERC on Pentylenetetrazole Induced Convulsions (PTZ)

Groups	Latency of Convulsions (secs)	Duration of Convulsions (secs)	% Protection
Disease control	91.1±0.86	166±0.87	
(MERC 200 mg/kg, b. w.)	128±0.89^{*A}	148.66±0.73^{*A}	24
(MERC 400 mg/kg, b. w.)	205.16±0.92^{*A}	128±0.99^{*A}	33
(Clonazepam 1 mg/kg, b. w.)	386±0.80*	118.16±0.79*	40

Mean ± SEM (n=6) is used to express values. ANOVA was used for the statistical analysis, which was followed by Dunnett's test. Significant data were denoted by the symbols when compared to control group (= p<0.0001) and when compared to standard group (A = p<0.0001)*

3.6 *In silico* Analysis

3.6.1 Molecular docking

Table 4. Schrodinger XP docking scores

Compounds	4MS4	3WFG	5HCV	6J8G
Catechin	-8.01	-7.92	-7.01	-7.43
Quercetin	-	-9.74	-10.03	-6.84
Gallic acid	-9.27	-7.25	-8.11	-6.60
Vitexin	-	-	-	-6.34
Luteolin	-8.47	-12.21	-9.92	-5.73
Gentisic acid	-8.22	-6.95	-7.83	-5.56
Vanillic acid	-3.79	-7.36	-6.77	-4.78
Ricinine	-	-6.19	-6.05	-
Ricinoleic acid	-8.91	-	-	-3.60
Quercetin-3-O-β-D-xylopyranoside	-	-	-	-7.81
Stigmasterol oleate	-	-	-	-5.22
Clonazepam	-2.40	-9.30	-10.25	-6.76
Phenytoin	-8.44	-7.96	-7.43	-5.16

G score = glide score, The more negative the Glide score, the more favorable the binding

3.6.2 Ramachandran plot analysis

Proteins 4MS4, 3WFG, 5HCV, and 6J8G were examined using a Ramachandran plot to determine the presence of amino acids in various sections of each protein. The results are shown in Table 5 and in the image below.

Table 5. Ramachandran plot status with protein with 4MS4, 3WFG, 5HCV and 6J8G

Residues	4MS4	3WFG	5HCV	6J8G
Most favorable region (%)	91.2	94.7	94.8	94.5
Additional allowed regions (%)	8.5	5.3	5.8	3.7
Generously allowed regions (%)	0.3	0.0	0.0	1.1
Disallowed regions (%)	0.0	0.0	0.0	0.7

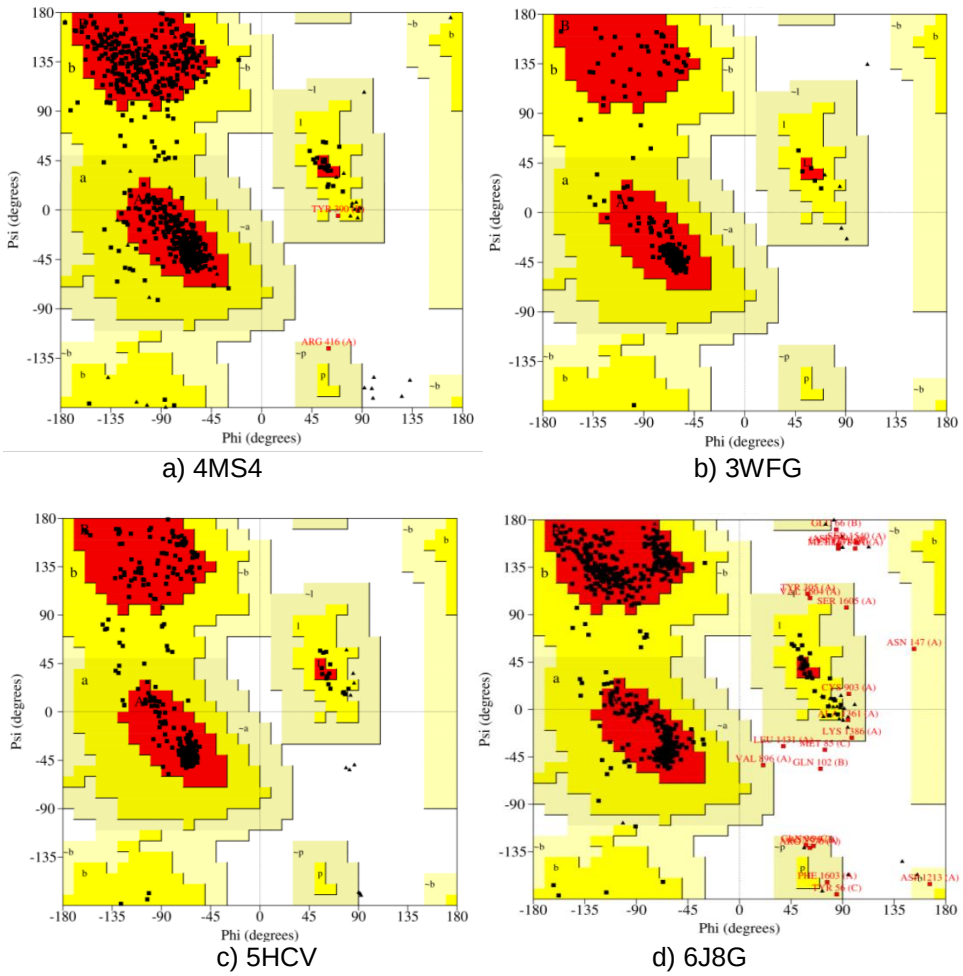

Fig. 3. Ramachandran plot of protein 4MS4, 3WFG, 5HCV and 6J8G

4. DISCUSSION

Alkaloids, flavonoids, glycosides, terpenoids, carbohydrates, tannins, and saponins were identified in the methanolic extract of the roots of *Ricinus communis*, according to a preliminary chemical screening. The phytochemical research approach is considered to be successful in identifying the bioactive profile of plants with therapeutic value. According to the acute toxicity study, these phytochemical constituents were found to be non-toxic. These had no mortality or pre-terminal death-inducing effects. Salivation, lacrimation, sweating, piloerection, micturition, and faeces did not change. No abnormalities were found in any of the treated animals when they were tested for ptosis, sleepiness, stereotypy, aggression, tremors, convulsions,

Straub's test, motor incoordination, and writhing. The corneal reflex, righting reflex, and gait were all normal. The animals' bodies, skin, fur, eyes, and weight were all normal. During the course of the trial, no tremors, lethargy, diarrhoea, or comas were noticed.

4.1 Anti-Epileptic Activity

The most pervasive neuropsychiatric disorder, epilepsy is categorized by paroxysmal cerebral dysrhythmia and causes severe medical and social morbidity. It demonstrates as brief episodes (seizures) of loss or disturbance of consciousness, with or without the characteristic body movements (convulsions), sensory or psychiatric phenomena. Many neuropsychiatric illnesses' pathogenesis appears to be heavily influenced by GABA. Anxiety and epilepsy have both been successfully treated with medications that enhance brain GABA content and by administering centrally active GABA mimic drugs [10]. In the current study, gamma-amino butyric acid (GABA) ergic neurotransmission was modelled using MES in rats and PTZ-induced convulsions in mice to assess in-vivo anti-epileptic activity. It's possible that MES and PTZ models cause convulsions by preventing gamma amino butyric acid (GABA) from acting on GABA-A receptors. The main inhibitory neurotransmitter associated with epilepsy is GABA. [11]. The methanolic extract of Ricinus communis roots was shown to contain a variety of phytochemically active substances, including alkaloids, flavonoids, terpenoids, tannins, steroids, carbohydrates, and saponins. Alkaloid ricinine has the ability to prevent MES and PTZ-induced seizures, possibly via interfering with GABA, glutaminergic mechanisms, Na+, and Ca2+ channels [12]. By influencing certain protein kinases and lipid kinases signalling cascades, such as the phosphatidylinositol 3-kinase (PI3K)/Akt, tyrosine kinase, protein kinase C (PKC), and mitogen-activated protein kinase (MAP kinase) signalling pathways, quercetin (Flavonoid) may also modulate intracellular signal [13]. These processes alter the central nervous system's capabilities, including its vulnerability to seizures, as well as the excitability of neurons. Gallic acid (Phenolic acid) has anticonvulsant properties, which may be brought about by GABAergic neurotransmission potentiation or an increase in seizure threshold in neurons caused by decreased Na+ channel activity [14]. The anticonvulsant action of vanillic acid (Phenol) is not entirely known. However, the most obvious mechanism is an increase in GABAergic transmission. In both MES and PTZ models of seizures, ellagic acid exhibits neuroprotective effects. Its anticonvulsant effects may be mediated by a decrease in oxidative stress and an increase in GABAA transmission in the brain [15].

4.2 Molecular Docking

In the area of computer-based drug creation, where tiny compounds are screened by positioning and scoring them in a protein's binding site, molecular docking still shows a lot of potential. Using Schrödinger software, identified chemicals from a methanolic root extract of *Ricinus communis* and common medications like phenytoin and clonazepam were docked. The different components found in the plant extract are Catechin, Quercetin, Gallic acid, Vitexin, Luteolin, Gentisic acid, Vanillic acid, Ricinine, Ricinoleic acid, Quercetin-3-O- β-D-Xylopyranoside, Stigmasterol oleate and standard drugs phenytoin, clonazepam was subjected to docking against PDB ID: 4MS4, 3WFG, 5HCV, 6J8G. The glide testing with the highest results were Catechin, Quercetin, Gallic acid, Vitexin, Luteolin, Gentisic acid, Vanillic acid, Ricinine, Ricinoleic acid, phenytoin and clonazepam against all the selected PDB ID: 4MS4, 3WFG, 5HCV, 6J8G. The glide scores of clonazepam, phenytoin, catechin, quercetin, and gallic acid were found to be less than those of these chemicals, indicating that they may not have the same affinity for binding to proteins [16]. These results clearly show that the chemical constituents listed above may have demonstrated a mechanism comparable to that of the common medication clonazepam and the anti-epileptic drug phenytoin.

The identified proteins, PDB ID: 4MS4, 3WFG, 5HCV, and 6J8G, are modeled, and the 3D model's attributes are assessed using the PROCHECK tool and the Ramachandran plot. The Ramachandran plot makes it clear that predicted models have the most favorable regions, as well as additional allowed regions, usually allowed regions, and disallowed regions. A Ramachandran map showing such a percentage distribution of the protein residues demonstrates the high calibre of the predicted models. A high-quality model would be predicted by the Ramachandran plot to have a majority of over 90% in the most favoured area. Proteins such PDB ID: 4MS4, 3WFG, 5HCV, and 6J8G exhibited 90 percent favoured a region, which amply demonstrates the high

quality of the models chosen for the current investigation [17].

5. CONCLUSION

According to *in vivo* and *in silico* investigations the methanolic root extract of *Ricinus communis clearly* possessed antiepileptic activity in rodent models. But more research is required to identify specific phytochemical components of the extract and determine precise mechanism underlying its antiepileptic effect.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The Institutional Animal Ethics Committee of GRCP approved the research entitled “Neurological and molecular interactions of phytoconstituents from *Ricinus communis* root extract- A pharmacological and computational approach" with Regd number. 1175/PO/Re/S/08/CPCSEA. All animal experiments were carried out in accordance with CPCSEA guidelines.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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